UK National Screening Committee

Chlamydia Screening in Pregnancy

External Review against Programme Appraisal Criteria for the UK National Screening Committee

Version: Final

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The UK National Screening Committee secretariat is hosted by Public Health England.

About the UK National Screening Committee (UK NSC)

The UK NSC advises ministers and the NHS in the 4 UK countries about all aspects of population screening and supports implementation of screening programmes.
Conditions are reviewed against evidence review criteria according to the UK NSC's evidence review process.

Read a complete list of UK NSC recommendations.

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Plain English Summary

Genital chlamydia trachomatis is the most common sexually transmitted infection (STI) in the UK. Most people who have chlamydia do not have any obvious signs or symptoms, or the infection may be mild and go undetected. It is unclear, so far, what effects an untreated chlamydia infection has on pregnant women or on pregnancy and baby outcomes. Yet, there are some reports that the infection may be the cause of premature rupture of membranes and chorioamnionitis.

Newborns can become infected with chlamydia during vaginal birth if the mother has the infection. If a baby is born with the infection, the most common symptoms are conjunctivitis and respiratory infections. In this case, the baby can be treated with antibiotics.

To treat chlamydia during pregnancy, pregnant women can take antibiotics. But, treatment options in pregnancy are limited because there are fewer antibiotics that can be used safely.

The current UK NSC recommendation is that a population screening programme for chlamydia in pregnancy should not be introduced in the UK. This evidence summary updates this recommendation by evaluating published evidence.

This evidence summary looks at the evidence to see if there are any consequences of chlamydial infection on the pregnancy outcomes or on the newborn baby. It also searched for evidence about the possible harms to babies born to women who received antibiotics for chlamydia in pregnancy.

Currently, the NHS recommends that pregnant women under 25 years old should be given information about screening, but does not recommend screening all women in pregnancy.

The conclusion of this evidence summary is that there is not sufficient evidence to definitely say that untreated chlamydia infection during pregnancy will result in some women going on to have serious problems, such as premature rupture of membranes (PROM) or stillbirth..

This evidence summary found no evidence that screening during pregnancy had benefits for the pregnancy or the baby outcomes. Also, it identified no evidence on the effects of chlamydia treatment (antibiotics) during pregnancy.

For these reasons, this review concludes that the 2010 UK NSC recommendation should be reconfirmed, and a population screening programme for chlamydia in pregnancy should not be introduced at this time in the UK.

Executive Summary

Background

Genital *Chlamydia trachomatis* is the most common sexually transmitted infection (STI) in the UK. In 2016, over 1.4 million chlamydia tests were carried out in England among young people aged 15 to 24 covering an estimated 30% of females and 12% of males within this age range [1]. In women, chlamydia initially infects the cervix and urethra and can lead to abnormal vaginal discharge and dysuria. If left untreated, the infection can progress to pelvic inflammatory disease [2] [3, 4]. Approximately 75% of females and 50% of males who have chlamydia have no obvious signs or symptoms, so the infection may go undetected.

UK NSC screening recommendations are updated every three years and screening for chlamydia in pregnancy is currently due for review as part of this cycle.

Screening for chlamydia during pregnancy would have two aims:

1. To reduce adverse pregnancy outcomes like low birth weight, prematurity, stillbirth, intrauterine growth retardation
2. To reduce neonatal morbidities, for example, conjunctivitis or respiratory tract infections

The current recommendation of the UK National Screening Committee (UK NSC) is that screening for chlamydia in pregnancy should not be offered.

The National Institute for Health and Care Excellence (NICE) currently recommends that information on the National Chlamydia Screening Programme (NCSP) should be provided to pregnant women who are 25 years or younger.

Focus of the Review

One systematic review and four rapid reviews focused on issues around pregnancy and chlamydia infection. The objectives of the reviews are to:

- assess the consequences of chlamydial infection on pregnancy outcomes and on neonatal outcomes in the UK (Screening criterion 1);
- evaluate screening pathways of chlamydia infection during pregnancy, in particular effect on pregnancy outcomes, the timing of the test and the need for a test of cure following treatment (Screening criterion 11);
- investigate the potential harms associated with *in utero* exposure to antibiotics (Screening criterion 9); and
- evaluate screening pathways of chlamydia infection during pregnancy, in particular effect on neonatal outcomes, the timing of the test and the need for a test of cure following treatment (Screening criterion 11).

Database searches yielded 10,860 records, from which 305 documents were obtained as full text for further assessment. Five studies were eligible. The searches to inform the systematic review were not limited by date. The searches for the rapid reviews were limited to studies conducted from 2009 onwards.

Key questions included:

1. Key question one (systematic review): What is the impact of untreated chlamydial infection, during pregnancy, on pregnancy outcomes in the UK?
2. Key question two (rapid review): What is the impact on neonatal outcomes, of untreated chlamydial infection in pregnancy in the UK?
3. Key question three (rapid review): What is the optimal screening strategy for chlamydia infection in pregnancy to avoid adverse pregnancy outcomes?
4. Key question four (rapid review): Are there any known side effects from antibiotic treatment of chlamydial infection during pregnancy on the newborn?
5. Key question five (rapid review): What is the optimal screening strategy for chlamydia infection in pregnancy to avoid adverse neonatal outcomes?

Findings in the Evidence of this Review

An overview of the findings from the systematic review include the following:

Pre-term birth

One RCT and one prospective cohort study reported data on pre-term birth in women with a current chlamydia infection identified prior to 32 weeks, from 32 to 36 weeks and prior to 37 weeks of pregnancy. The RCT reported no significant differences in the incidence of pre-term birth between women who were treated and women who were untreated or who received placebo. The prospective cohort did not compare groups statistically.

Premature rupture of membranes

One prospective cohort study comparing untreated pregnant women with chlamydia to pregnant women without chlamydia reported that women with untreated chlamydia were more than twice as likely to have premature rupture of membranes (PROM) than women without chlamydia (OR 2.12 (95%CI: 1.57, 2.86) $p<0.001$).

The studies comparing treated and untreated women reported conflicting results. The largest RCT showed no significant differences between 196 women treated with erythromycin and 193 women treated with placebo at less than 37 weeks, ≥ 37 weeks, or both. A second RCT reported that erythromycin was beneficial, however study numbers were small with 13 women in the erythromycin group and 12 in the placebo group.

A large prospective cohort study, with over 1000 participants in the erythromycin and untreated groups, showed that erythromycin significantly reduced PROM compared to untreated women who had PROM using multiple logistic regression to account for age, ethnicity, parity, birth weight, urinary tract infections, smoking, hypertension and diabetes. A smaller prospective cohort study showed no differences in PROM between 23 women who received erythromycin and 58 untreated women.

It is important to note that the NCSP reported that 10-15% of people who test positive and cure are re-infected within 3 months. If partners are not treated or the partner's treatment is not effective, any intervention provided to the pregnant women will suffer from reduced effect size.

Low birth weight

The studies reporting low birth weight reported conflicting results. The largest RCT showed no significant differences between 201 women treated with erythromycin and 199 women treated with placebo in newborns weighing less than 1,500g, 1,500 to 2,000g, or all newborns under 2,500g.

Two comparative observational studies also showed conflicting results. The largest study, with over 1000 participants in erythromycin and untreated groups, showed that erythromycin significantly reduced low birth weight compared to untreated women using multiple logistic regression to account for age, ethnicity, parity, birth weight, urinary tract infections, smoking, hypertension and diabetes. A smaller study did not report statistical analyses, but showed that 23 patients receiving erythromycin had a greater incidence of low birth weight newborns than those who did not receive treatment (n=52).

Meta-analysis was not possible because the studies were too dissimilar. It is unclear whether antibiotic treatment, specifically erythromycin, reduces the incidence of low birth weight newborns in women with chlamydia.

Pre-eclampsia

None of the eligible studies reported this outcome.

Miscarriage

One study comparing the treatment of women with chlamydia with erythromycin with untreated patients reported miscarriage (occurring before 24 completed weeks of pregnancy) outcomes. There are insufficient data to draw conclusions about whether treating chlamydia in pregnancy results in fewer miscarriage events.

Re-infection rates

One RCT provided data on re-infection rates but did not report statistical analyses. It appears that there are no significant differences between re-infection rates in women who were treated with either clindamycin or erythromycin. However, women who received erythromycin had a much higher incidence of chlamydia positivity at the first and second test of cure (in the second trimester) and at birth or rupture of membranes.

Stillbirth/neonatal death

Two studies reported outcomes for stillbirth (occurring after 24 completed weeks of pregnancy) and for neonatal death. One RCT reported no differences for either outcome (separately) and a large prospective cohort study reported no differences for a combined outcome (including both stillbirth and neonatal death). A second prospective cohort study reported no differences between erythromycin treated and untreated groups, or for women with chlamydia who were untreated compared to women who were chlamydia negative.

Intrauterine growth restriction

None of the eligible studies reported this outcome.

Summary

There is conflicting evidence from the RCTs and prospective comparative studies included in this review that untreated chlamydia results in poorer outcomes for pregnant women. For outcomes reported by two or more studies, results were often contradictory.

We did not identify any comparative studies reporting neonatal outcomes.

The findings from the systematic review do not provide sufficient evidence upon which to base a decision about whether screening should be recommended in pregnant women.

No new evidence was found for the questions looking at:

- the burden of untreated chlamydial infection in pregnancy on neonatal outcomes in the UK;
- information on the optimal screening strategy in pregnancy for chlamydia infection to avoid adverse pregnancy and neonatal outcomes; and,
- the side effects from antibiotic treatment of chlamydial infection during pregnancy on the newborn.

Recommendations on Screening

This review shows that the highest quality evidence available from RCTs and comparative observational studies is not able to inform a decision about chlamydia screening in pregnancy.

Evidence uncertainties

There is still conflicting evidence linking maternal chlamydia infection to adverse outcomes of pregnancy. This review found that studies looking at this issue were poorly reported, often contradictory, and, in the largest trial with the least methodological bias, the authors claimed that their data should not be used as a basis for decision-making. Therefore, more research is needed in this area to clarify if the infection has any effects on pregnancy outcomes.

No new evidence was found since the 2010 UK NSC review on the burden of chlamydial infection on neonatal outcomes in the UK, and the consequences of untreated maternal chlamydial infection on newborns. Thus, it is still not possible to determine whether neonatal chlamydia infection is an important public health problem in the UK.

Similarly, no evidence was found on the impact that antibiotic treatment of chlamydia during pregnancy might have on the unborn baby. Considering that the implementation of a screening programme in pregnancy would increase the use of antibiotic treatment during pregnancy, it is, therefore, important to understand the consequences that such treatment might have on newborns.

Unsurprisingly, given the above, the review found no evidence on the optimal screening strategy for chlamydia infection in pregnancy to avoid adverse pregnancy and neonatal outcomes. Therefore, research is still needed on the effectiveness of chlamydia screening and treatment in pregnancy with respect to prevention of adverse pregnancy outcomes and infant complications, particularly regarding optimal timing in pregnancy and repeat testing.

Introduction and Approach

Health problem

Genital *Chlamydia trachomatis* is the most common sexually transmitted infection (STI) in the UK. In women, chlamydia initially infects the cervix and urethra and can lead to abnormal vaginal discharge and dysuria. However, approximately 70% of women who have chlamydia do not have any obvious symptoms, or the infection may be mild and go undetected, therefore remaining untreated. Chlamydia in general populations can be treated with high microbial cure rates (over 95%) with antibiotics*[5], though reinfection rates appear to be high, particularly among young women [6-8].

If untreated, in women the infection can ascend to the upper genital tract [2] and may persist for months or years [9]. This can lead to pelvic inflammatory disease (PID) in 10% to 40% of affected women, which can result in infertility, ectopic pregnancy and chronic pelvic pain [10, 11] [3].

To date, studies have reported conflicting results regarding the effects of antenatal chlamydia infection on pregnancy outcomes, but these may include ascending infection in pregnancy resulting in premature rupture of membranes and chorioamnionitis. Moreover, there is a limited understanding of the potential mechanisms by which chlamydia might lead to such outcomes [12].

The infection can be treated in pregnancy by antibiotics with an estimated 64-95% success rate after the first course [13] [14]. However, treatment of chlamydia in pregnancy is less straightforward than treatment outside pregnancy because the range of antibiotics is more limited. Another factor requiring consideration when treating pregnant women is the impact of the drug on the developing fetus, particularly as erythromycin, amoxicillin and azithromycin all cross the placental barrier [15].

* The recommended treatment is Doxycycline 100mg bd for 7 days (contraindicated in pregnancy) or Azithromycin 1g orally in a single dose; 2015 UK national guideline for the management of infection with Chlamydia trachomatis http://psnc.org.uk/communitypharmacyss/wp-content/uploads/sites/121/2017/10/uk-chlamydia-guidelines-2015.pdf

The infection can be transmitted to newborns during vaginal birth. In neonates it is difficult to estimate the burden of infection because infected infants are usually asymptomatic. The most common symptoms (conjunctivitis and respiratory infections) are non-specific and treatable on the basis of symptomatic presentation. Additionally, there is a lack of clear evidence about the number of infants who have conjunctivitis because many are managed in primary care [13].

The main justification for the introduction of an antenatal screening programme for an infection is to prevent any adverse pregnancy outcomes caused by the infection and to reduce the risk of infants becoming infected and developing associated morbidities. The 2010 UK NSC review concluded that the impact that a possible screening programme would have on such outcomes is closely related to the timing of the screening test in such a screening pathway. This is because the issues relating to the screening and treatment of chlamydia infection during pregnancy differ significantly to the non-pregnancy context in terms of the timing of the test and the need for a test of cure following treatment. For example, the earlier in pregnancy that screening takes place, the greater the potential for a sexually active pregnant woman to acquire infection after screening [16-18]. Thus screening and treatment of women late in pregnancy would seem the more appropriate hypothetical approach for prevention of infection and reducing morbidities in infants of mothers with chlamydia. However, if screening were to take place in the third trimester the opportunity to avert any adverse pregnancy outcomes potentially resulting from chlamydia infection in pregnancy, such as preterm labour or premature rupture of membranes (PROM), would be lost as these would hypothetically require early detection and treatment.

The 2010 UK NSC review noted also that an important aspect that a screening programme would have to take into account is the possibility of re-infection, although very limited information is available on the impact of recurrent infection during pregnancy on pregnancy and neonatal outcomes.

Current Policy

The current recommendation of the UK National Screening Committee (UK NSC) is that screening for chlamydia in pregnancy should not be offered.

The National Institute for Health and Care Excellence (NICE) currently recommends that information on the National Chlamydia Screening Programme (NCSP) should be provided for pregnant women who are 25 years old or younger.

Previous review

In 2009 the UK NSC commissioned a review [13] that sought to answer the following questions:

1. Is chlamydia trachomatis an important health problem?
2. Is the natural history understood?
3. Does early detection and treatment have benefit over later detection and treatment? Are treatments or interventions effective?
4. Is the screening test valid and reliable? Is there a safe and acceptable screening test? Are there adequate facilities for confirming test results and resources for treatment?
5. Organisational considerations.
6. Would the objectives of screening justify the costs?

The review concluded that:

1. There was insufficient evidence to recommend chlamydia screening during pregnancy.
2. The evidence linking maternal chlamydia infection to adverse pregnancy and neonatal outcomes was limited and conflicting.
3. The available antibiotics are not tolerated well and many women do not complete the course. The balance of benefit and harm is uncertain.

Current review and approach taken

UK NSC screening recommendations are updated every three years and screening for chlamydia in pregnancy is currently due for review as part of this cycle.

The current review addresses questions generated by the previous review. However, the methodology used in the current review differs from that used in the previous one. The current review comprises one systematic review, using methodologies developed by York CRD and Cochrane, and four rapid reviews undertaken according to the UK NSC's recommendations for the development of evidence summaries.

Objectives

The systematic review (key question 1) and four rapid reviews (key questions 2 to 5) focus on:

- assessing the consequences of chlamydial infection on pregnancy outcomes and on neonatal outcomes in the UK (key questions 1 and 2);
- evaluating screening pathways to identify chlamydia infection during pregnancy and the effect that screening has on pregnancy outcomes, the timing of the test and the need for a test of cure following treatment (key question 3);
- the potential harms associated with *in utero* exposure to antibiotics (key question 4); and
- evaluating screening pathways to identify chlamydia infection during pregnancy in particular the effect on neonatal outcomes, the timing of the test and the need for a test of cure following treatment (key question 5).

This report describes the methods and results of the reviews carried out by York Health Economics Consortium (YHEC) to meet UK NSC's requirements.

Table 1. Key questions for the evidence summary, and relationship to UK NSC screening criteria

UK NSC screening criterion number	Criterion	Key questions	Studies included
1	The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease.	1. What is the impact of untreated chlamydial infection, during pregnancy, on pregnancy outcomes in the UK? 2. What is the impact on neonatal outcomes, of untreated chlamydial infection in pregnancy in the UK?	Question 1 Alger 1991 [19] Martin 1997 [20] McGregor 1990 [21] Rivlin 1997 [22] Ryan 1990 [23] Question 2 No studies identified
9	There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme shouldn't be further considered.	4. Are there any known side effects from antibiotic treatment of chlamydial infection during pregnancy on the newborn?	No studies identified
11	There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (e.g. Down's syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.	3. What is the optimal screening strategy for chlamydia infection in pregnancy to avoid adverse pregnancy outcomes? 5. What is the optimal screening strategy for chlamydia infection in pregnancy to avoid adverse neonatal outcomes?	Question 3 No studies identified Question 5 No studies identified

Methods

This review was conducted by YHEC, in keeping with the UK National Screening Committee (UK NSC) evidence review process. Following agreement of a protocol, database searches were conducted to identify studies relevant to the following key questions:

1. Key question one (systematic review): What is the impact of untreated chlamydial infection, during pregnancy, on pregnancy outcomes in the UK?
2. Key question two (rapid review): What is the impact on neonatal outcomes, of untreated chlamydial infection in pregnancy in the UK?
3. Key question three (rapid review): What is the optimal screening strategy for chlamydia infection in pregnancy to avoid adverse pregnancy outcomes?
4. Key question four (rapid review): Are there any known side effects from antibiotic treatment of chlamydial infection during pregnancy on the newborn?
5. Key question five (rapid review): What is the optimal screening strategy for chlamydia infection in pregnancy to avoid adverse neonatal outcomes?

Question one was undertaken using systematic review methodology, and questions two to five were undertaken using rapid review methodology. See Appendix 2 for further details about the record selection process (PRISMA).

Eligibility for inclusion in the review

To identify relevant evidence to answer the review question, clear definitions of the eligible study participants, interventions, comparators, outcomes and study types of interest (PICOS) were required. These are described in detail below and are summarised, by key question, in Table 16 to Table 20 in Appendix 2.

The main comparison of interest in this review was pregnant women with confirmed chlamydia infection who were untreated (as well as newborns born to these women) compared with pregnant women without confirmed chlamydia. Because chlamydia is resolved with antibiotics in most cases, we also compared untreated women with women who received antibiotic treatment (as well as newborns born to these women).

Eligible maternal outcomes included:

- miscarriage (defined as pregnancy loss before 24 weeks gestation)[†];
- stillbirth (defined as pregnancy loss after 24 weeks gestation);
- preterm birth;
- premature rupture of the membrane;
- intrauterine growth restriction;
- small for gestational age / low birth weight;
- pre-eclampsia;
- reinfection rates.

Eligible neonatal outcomes included:

- conjunctivitis;
- pneumonia;
- respiratory tract infections;
- ear infections;
- congenital abnormalities;
- infant microbiome development;
- persistent wheezing or asthma;
- development of allergy in early infancy;
- long term adverse outcome from in utero antimicrobial treatment.

We included comparative studies (RCTs, cohort studies and case-controls studies) with no date limit for the systematic review, and studies published since 2009 (the search date of the previous review) for the rapid reviews. Studies conducted in the UK were prioritised, but studies conducted in Western countries analogous to the UK were also eligible. Western countries, and those analogous to the UK, included countries of Western Europe, Central Europe (Hungary, Poland, Slovakia, the Czech Republic, and Slovenia), North America, Australia and New Zealand.

Searches were conducted in 9 databases as well as the websites of relevant regulatory bodies and recent conferences. Relevant studies were selected, extracted and quality assessed by two independent reviewers. Any differences

[†] We understand that clinicians use the term ‘abortion’ and ‘miscarriage’ synonymously. We have used the term ‘miscarriage’ throughout this report.

in decisions were resolved through discussion and/or by consulting another reviewer. Results from the key questions were reported in tables and in the text.

Results

Search Strategy and Results

The search strategy for MEDLINE is shown in Table 2. The full strategies are provided in Appendix 2.

Table 2. Search strategy for Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present> (URL/Interface: OvidSP)

Set	Search terms (number of records)
1	Chlamydia/ (2719)
2	Chlamydia trachomatis/ (11262)
3	Chlamydia Infections/ (14607)
4	chlamydia$.ti,ab,kf. (25702)
5	or/1-4 (28931)
6	Pregnancy/ (813112)
7	exp Pregnancy outcome/ (49607)
8	Pregnancy complications/ (84616)
9	Pregnancy complications, infectious/ (34504)
10	Prenatal care/ (23828)
11	exp Infant, newborn/ (560299)
12	(pregnanc$ or pregnant or gestat$ or newborn$ or neonate$ or neonatal or ante-natal or pre-natal or antenatal or prenatal or infant$1 or infancy or baby or babies).ti,ab,kf. (1124384)
13	(miscarriage$1 or miscarry or miscarried or spontaneous abortion$1).ti,ab,kf. (20408)
14	Abortion, Spontaneous/ (18586)
15	exp Obstetric Labor, Premature/ (22532)
16	exp fetal membranes, premature rupture/ (6627)
17	(preterm birth$1 or premature).ti,ab,kf. (117602)
18	(premature$ adj4 rupture$).ti,ab,kf. (5474)
19	(membrane$1 adj4 rupture$).ti,ab,kf. (10716)
20	fetal growth retardation/ (14740) exp
21	((fetal or foetal or intrauterine) adj3 growth).ti,ab,kf. (25779)
22	(small adj4 gestational age).ti,ab,kf. (8632)
23	low birth weight.ti,ab,kf. (23971)
24	underweight.ti,ab,kf. (8288)
25	(congenital adj4 abnormalit$).ti,ab,kf. (9929)
26	exp congenital abnormalities/ (543270)
27	(microbiome adj4 develop$).ti,ab,kf. (334)
28	in utero.ti,ab,kf. (24590)
29	exp microbiota/ (11724)
30	microbiota.ti,ab,kf. (22487)
31	or/6-30 (2136152)
32	5 and 31 (4715)
33	exp animals/ not humans/ (4386446)

34	**32 not 33 (4228)**
35	**(news or comment or editorial or letter or case reports).pt. or case report.ti. (3469022)**
36	**34 not 35 (3815)**
37	**limit 36 to english language (3125)**
38	**remove duplicates from 37 (3024)**

Database searches yielded 10854 results and 6 records were identified from other sources. 5 studies were judged to be relevant to the review question 1.

Included Studies - Systematic Review

Figure 1 (in Appendix 1) provides a full PRISMA flow diagram for the record selection process. For the systematic review, some trials were reported in more than one publication. All of the publications related to each study are reported in Table 3, with the main publication shown in grey.

Table 3. Included studies – systematic review

Study identifier	Reference(s)
Alger 1991 [24]	Alger LS, Lovchik JC. Comparative efficacy of clindamycin versus erythromycin in eradication of antenatal Chlamydia trachomatis. Am J Obstet Gynecol 1991;165(2):375-81.
Martin 1997 [20]	Martin DH, Eschenbach DA, Cotch MF, Nugent RP, Rao AV, Klebanoff MA, et al. Double-blind placebo-controlled treatment trial of Chlamydia trachomatis endocervical infections in pregnant women. Infect Dis Obstet Gynecol 1997;5(1):10-7. Eschenbach DA, Nugent RP, Rao AV, et al. A randomized placebo-controlled trial of erythromycin for the treatment of U. urealyticum to prevent premature delivery. The Vaginal Infections and Prematurity Study Group. Am J Obstet Gynecol 1991;164:734-42. Klebanoff MA, Regan JA, Rao AV, et al. Outcome of the Vaginal Infections and Prematurity Study: Results of a clinical trial of erythromycin among pregnant women colonized with group B streptococci. Am J Obstet Gynecol 1995;172:1540-5.
McGregor 1990 [21]	McGregor JA, French JI, Richter R, Vuchetich M, Bachus V, Seo K, et al. Cervicovaginal microflora and pregnancy outcome: Results of a double-blind placebo-controlled trial of erythromycin treatment. Am J Obstet Gynecol 1990;163(5):1580-91.
Rivlin 1997 [22]	Rivlin ME, Morrison JC, Grossman III JH. Comparison of pregnancy outcome between treated and untreated women with chlamydial cervicitis. J Miss State Med Assoc 1997;38(11):404-8.
Ryan 1990 [23]	Ryan GM Jr, Abdella TN, McNeeley G, Baselski VS, Drummond DE. Chlamydia trachomatis infection in pregnancy and effect of treatment on outcome. Am J Obstet Gynecol 1990;162(1):34-39.

Included Studies - Rapid Reviews

No studies published from 2009 onwards were identified that reported outcomes for rapid review questions 2 to 5.

Systematic Review – Key Question 1

What is the impact of untreated chlamydial infection, during pregnancy, on pregnancy outcomes in the UK?

This question relates to NSC criterion 1: The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease.

UK NSC evidence summaries are usually developed using rapid review methodologies. They provide an evaluation of the 'volume and direction' of the literature on a single question or set of questions on a given screening topic. However, for this evidence summary the decision was made to use a systematic review approach for the question looking at the impact of untreated chlamydial infection, during pregnancy, on pregnancy outcomes. The rationale for this decision was based on the conclusion reached by the 2011 UK NSC review. The impact of chlamydia infection on pregnancy outcomes is a key issue for the evaluation of antenatal screening. The previous review reported conflicting evidence on a range of pregnancy outcomes making it difficult to evaluate the impact of the infection. A systematic review including an attempt to develop a meta-analysis was therefore identified as the best method to generate point estimates of the outcomes of interest and to evaluate the quality of the evidence base.

The search resulted in 10860 unique references. After screening titles and abstracts, 310 full text articles were assessed for further screening. 305 publications were subsequently excluded using the pre-defined inclusion/exclusion criteria (see Appendix 3 for excluded studies with reason). Five articles met the inclusion criteria, and these were included in the synthesis. Appendix 2 provides the PRISMA diagram showing the study selection process.

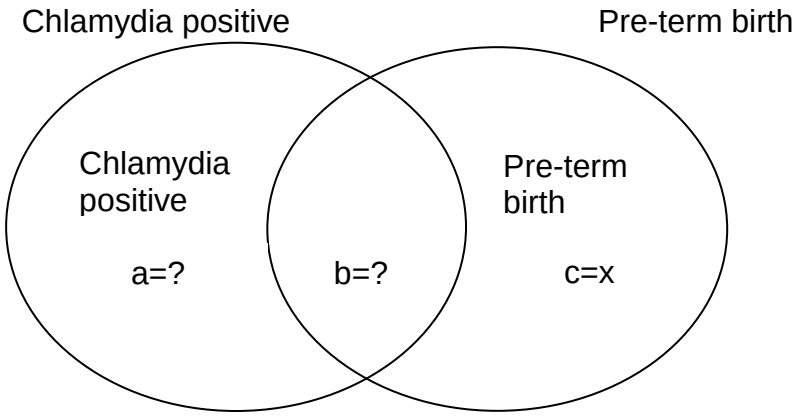
Study design and inclusion in this review

We note that there are a number of studies reporting risk factors for chlamydia in pregnancy where the study populations were selected based on one of the

outcomes of interest in this report, and chlamydia was retrospectively investigated. For example, there are studies of women who had pre-term birth where investigators retrospectively assess the potential reasons for this, of which chlamydia was one of the proposed reasons. These studies are interesting, but limited methodologically because they are inherently confounded by attempting to verify chlamydia retrospectively. We know that it is good practice to offer chlamydia testing to women under 25 in the UK, but the testing is not carried out uniformly and there are a variety of reasons a pregnant woman may choose not to undergo a test.

Figure 1 represents the data from such studies graphically. In a hypothetical study, we know the number of women selected for the study had a pre-term birth; these are c+b in the diagram. However, we cannot be sure how many women in the greater population had chlamydia when the study was undertaken (this is a + b in the diagram) or how many women had both chlamydia and pre-term birth (this is b in the diagram) in the study population.

Figure 1: Venn diagram representing a risk factor study



There may be cases where studies are able to be vigilant on verifying tests for chlamydia, for example if the study was conducted in a small town and primary services (who may have tested for chlamydia) were linked to secondary services (who would have recorded pre-term births), however this is unlikely to be the case for the majority of studies.

There are additional factors that make reliance on these studies difficult. For example, we do not know what happened to the women over the course of their pregnancy, and whether chlamydia was eradicated in early or late pregnancy, or both. We may not know how many partners were offered antibiotic therapy and

we may not know if any of the women required antibiotics for an unrelated condition that also had an effect on chlamydia. Moreover, NCSP reported that 10-15% of people who test positive and cure are re-infected within 3 months. If partners are not treated or the partner's treatment is not effective, any intervention provided to the pregnant women will suffer from reduced effect size [25].

These risk factor studies were not included in this review because the judgement was made that relying on their results could either over- or under-estimate the degree to which chlamydia contributed to pre-term birth. There is some benefit to be gained from these uncontrolled studies, primarily for hypothesis generating as a basis for further prospective studies, but they are not reliable enough for decision-making about whether screening is a worthwhile decision for the NHS.

Study characteristics

Table 4 presents the main characteristics of the five included studies. Further details can be found in Appendix 3. Three studies were RCTs and two were prospective cohort studies.

Alger 1991 [24] and colleagues conducted their trial between October 1985 and April 1998 at one site in the USA. The trial aimed to determine the comparative efficacy of clindamycin and erythromycin in eradicating *C. trachomatis* from the lower genital tract in pregnant women and to investigate whether clindamycin was better tolerated (promoting patient compliance) and had superior cure rates to erythromycin. 135 eligible patients with a cervical specimen that was culture-positive for *C. trachomatis* before 24 weeks' gestation were enrolled and were randomized to one of three treatment groups; clindamycin, erythromycin or placebo. Partners of pregnant women were treated with doxycycline 200mg (100mg BID) for seven days. The study received funding from the Upjohn Company.

Martin 1997 [20] and colleagues conducted a RCT, the Vaginal Infection and Prematurity (VIP) study, between November 1984 and March 1989 at seven sites in the USA. The trial aimed to determine if treatment of pregnant women with *C. trachomatis* infection would lower the incidence of preterm delivery and/or low birth weight. The trial enrolled 13,914 women aged over 16 years, seeking prenatal care between the 23rd and 26th weeks of pregnancy. Of these 13,750 (99%) were tested for *C. trachomatis* and had results available and a positive chlamydia result was isolated from 1,239 (9.0%). Of these 1239

women, 204 were ineligible for the trial due to *N. gonorrhoea* infection (n=59), asymptomatic bacteriuria (n=60), or other exclusion criteria. Of the 1,035 eligible women 933 could be contacted, of whom 218 women (23%) did not keep their enrolment appointment, 121 (13%) refused to participate, and 594 were entered into the placebo run-in. Eligible women entered a 1-week placebo run-in prior to randomization. One hundred and eighty women who did not comply with the run-in were not randomized, resulting in 414 women who were randomized to receive either erythromycin (n=205) or placebo (n=209) for ten weeks, or until the end of the 35th week of pregnancy, whichever came first. Treatment of partners was recommended, but it was not clear if they received the same drug/dose nor how many partners were treated. The study was supported by grants from the National Institute of Child Health and Human Development and the National Institute of Allergy and Infectious Diseases.

McGregor (1990) [21] and colleagues conducted a RCT from October 1985 to August 1998 among women between 26 and 30 weeks' gestation who attended publicly supported antenatal clinics in the USA. The number of clinics was unclear. The trial aimed to evaluate associations of cervicovaginal microflora and selected lower genital tract microbe-associated factors with pregnancy outcomes in women receiving a short-course erythromycin treatment at 26 to 30 weeks' gestation to prevent preterm birth. Following an initial clinical evaluation during which vaginal and endocervical swabs were taken, 235 patients were randomized to treatment with either erythromycin or placebo. The total evaluated sample included 229 women (and their newborns), of whom 119 received erythromycin and 110 received placebo. Partners of pregnant women were not referred for treatment for chlamydia.

Rivlin 1997 [22] and colleagues conducted supplementary data analysis from a prospective cohort study among women registering for obstetric care at a university medical centre in the USA. The dates of data collection and details about the study funding were not reported. The original study compared two different types of antigen test. The supplementary study, using the same data, aimed to compare maternal, foetal, neonatal and infant outcomes among women with positive endocervical cultures for *C. trachomatis* who were correctly diagnosed during pregnancy and treated, and women who were incorrectly diagnosed during pregnancy (false negatives) and did not receive antibiotics. Endocervical samples were obtained from 1350 enrolled women. Of the 81 patients with positive Chlamydia cultures, 23 had a positive direct antigen test and were treated with erythromycin. The remaining 58 patients had either a false-negative direct antigen test or a non-evaluable test, or the test results were

unknown. These patients were untreated. It was not reported whether partners of the pregnant women were treated.

Ryan (1990) [23] and colleagues conducted a prospective cohort study between September 1982 and August 1985 among women attending their first prenatal visit at a single centre in the USA. Details about funding were not reported. The study aimed to evaluate the effects of *C. trachomatis* on pregnancy outcomes, and to discover whether treatment of chlamydial infections during pregnancy could reduce the impact of the infections on pregnancy outcome. Endocervical cultures for chlamydia were obtained from 11,544 new patients, of which 9111 were negative and 2433 were positive. Of the 2433 chlamydia-positive patients, 1110 received no treatment and 1323 were treated with erythromycin. It was not reported whether partners of the pregnant women were treated.

Table 4. Study Characteristics

Study identifier	Chlamydia status	Design	Location and number of countries	Date of trial	Number of participants analysed	Intervention/ comparator	Dosing regimen
Randomised controlled trials							
Alger 1990 [24]	Chlamydia positive	RCT	One site, USA	Between October 1985 and April 1988	40	Erythromycin (+ clindamycin placebo)	Total dose: 1332mg/day Regimen 333mg QID for 14 days
					42	Clindamycin (+erythromycin placebo)	Total dose: 1800mg/day Regimen: 450mg QID for 14 days
					44	Placebo	Regimen: 1 capsule + 1 tablet, QID for 14 days
Martin 1997 [20]	Chlamydia positive	RCT	Seven sites, USA	Between November 1984 and March 1989	205	Erythromycin	Total dose: 1000mg/day Regimen: 333mg TID for 10 weeks or until 35 weeks gestation
					205	Placebo	Regimen: TID for 10 weeks or until 35 weeks gestation
McGregor 1990 [21]	Chlamydia positive	RCT	Unspecified sites, USA	Between October 1985 and August 1988	13	Erythromycin	Total dose: 1000mg/day Regimen: 333mg TID for 7 days
					12	Placebo	Regimen: 1 tablet TID for 7 days
Comparative, observational studies							
Rivlin 1997 [22]	Chlamydia positive	Prospective cohort	One site, USA	NR	23	Erythromycin	Total dose: 3200mg/day Regimen: 800mg QID for 7 days
					58	No treatment	NA
Ryan 1990 [23]	Chlamydia positive	Prospective cohort	One site, USA	Between September 1982 and August 1985	1323	Erythromycin	Total dose: 2000mg/day Regimen: 500mg QID for 7 days
					1110	No treatment	NA
	Chlamydia negative				9111	NA	NA

NA – not applicable; NR – not reported; QID – 4 times per day; TID – three times per day.

Participant Characteristics

All of the included studies diagnosed chlamydia using direct immunofluorescence of endocervical swabs in women with a mean age between 20 and 25 years. In most included studies the majority of women were described as black, except in McGregor 1990 [21] where the number of black, white and Hispanic women ranged from 20% to 40% in each group.

The three RCTs (Alger 1991 [24]; Martin 1997 [20]; McGregor 1990 [21]) evaluated women in their third trimester whereas the two prospective cohort studies (Ryan 1990 [23]; Rivlin 1997 [22]) evaluated women at any stage of pregnancy.

Participant characteristics are reported in Table 5. The inclusion and exclusion criteria used by each study are reported in detail in Appendix 3.

Table 5. Participant characteristics

Study identifier	Intervention	Diagnostic procedure	Age of mothers (years)	Ethnicity	Gestational age at assessment (weeks)	Concurrent infections
Randomised controlled trials						
Alger 1991 [24]	Erythromycin Clindamycin Placebo	Endocervical swabs: Epifluorescence detection of cycloheximide-treated McCoy cells stained with fluorescein-conjugated *C. trachomatis*-specific monoclonal antibody.	21.7 (SD 4.2) 20.3 (SD 3.2) 21.3 (SD 4.0)	Black: 97% Black: 93% Black: 91%	20.1 (SD 2.0) 19.8 (SD 1.8) 20.1 (SD 2.0)	No specific details reported, but women found positive for *N. gonorrhoea* prior to enrolment were treated, as were women with other infectious conditions that required treatment.
Martin 1997 [20]	Erythromycin Placebo	Endocervical swabs: Fluorescence detection of McCoy cells stained with fluorescein isothiocyanate-conjugated C. trachomatis-specific monoclonal antibody.	21.5 (SD 4.2) 21.1 (SD 4.3)	White, Asian and Native American: 34 (17%) Black: 126 (61%) New York Hispanic: 34 (17%) Non-New York Hispanic: 11 (5%) White, Asian and Native American: 33 (16%) Black: 123 (59%) New York Hispanic: 47 (22%) Non-New York Hispanic: 6 (3%)	Screening: 24.5 (SD 1.1) Randomization: 29.4 (SD 1.8) Screening: 24.5 (SD 1.1) Randomization: 29.4 (SD 1.5)	Genital infections (group B streptococci, *U. urealyticum*, Trichomonas vaginalis, bacterial vaginosis, or endocervical mucopus); no further details reported. 6/85 (7%) of the women who had positive *C.*

Study identifier	Intervention	Diagnostic procedure	Age of mothers (years)	Ethnicity	Gestational age at assessment (weeks)	Concurrent infections
						trachomatis cultures also had positive cultures for *N. gonorrhoea*.
McGregor 1990 [21]	Erythromycin	Endocervical swabs: inoculation followed by standard techniques for group A and group B streptococci, *S. aureus, G. vaginalis* and yeast organisms, microscopic examination of cycloheximide-treated McCoy cells treated with fluorescence-conjugated anti-chlamydia monoclonal antibody for *C. trachomatis*, and Mycotrim GU Triphasic culture System for identification of cultured *M. hominis* and *U. urealyticum* microorganisms. Negative cultures of *C. trachomatis* were blind passaged once and reprocessed.	23.0 (SD 4.3) (range: 13 - 37)	White: 45 (37.8%) Black: 42 (35.3%) Hispanic: 30 (25.2%) Other: 2 (1.6%)	26 - 30	Pre-treatment organisms and virulence factors were: *N. gonorrhoea, C. trachomatis, U. urealyticum, M. hominis*, bacterial vaginosis, Mobiluncus species, *G. vaginalis, T. vaginalis, S. aureus*, group A and group B streptococci, yeast species, proline aminopeptidase, phospholipase C, nonspecific protease.
	Placebo		23.2 (SD 4.2) (range: 16 - 34)	White: 43 (39.1%) Black: 42 (38.2%) Hispanic: 21 (19.1%) Other: 4 (3.6%)	26 - 30	
Comparative, observational studies						
Rivlin 1997 [22]	Erythromycin	Endocervical swabs: Direct fluorescent chlamydial antigen test. Tissue culture	20 (range: 13-30)	African-American: 70(86.4%) Caucasian: 11 (13.6%)	Diagnosis: mean 21 (range : 4 - 42)	NR

Study identifier	Intervention	Diagnostic procedure	Age of mothers (years)	Ethnicity	Gestational age at assessment (weeks)	Concurrent infections
	No treatment	isolation for *C. trachomatis*; further details reported in previous publications.	22 (range: NR)			
Ryan 1990 [23]	Chlamydia positive (erythromycin + untreated patients)	Endocervical swabs: Microscopic examination of cycloheximide-treated McCoy cells stained with iodine or a monoclonal fluorescent antibody.	Overall for chlamydia positive patients (treated + untreated) 11 - 17: 652 (32.1%) 18 - 19: 606 (29.0%) 20 - 24: 854 (20.0%) 25 - 29: 238 (11.6%) 30 - 45: 83 (7.5%)	Overall for chlamydia-positive patients (treated + untreated): n=2433 Non-white: 2290 (94.1%) White: 143 (5.9%)	NR	Not specifically reported, although maternal discharge diagnoses were used to examine associations between positive chlamydia culture and urinary tract infection, chronic hypertension, superimposed toxaemia, pre-eclampsia, diabetes, fever of unknown origin, pneumonia, asthma, seizures (other than pre-eclampsia), haemoglobin As, or abnormal Papanicolaou smears.
	Chlamydia negative		11 - 17: 1379 (15.1%) 18 - 19: 1481 (16.3%) 20 - 24: 3419 (37.5%) 25 - 29: 1810 (19.9%) 30 - 45: 1022 (11.2%)	Non-white: 7706 (84.6%) White: 1405 (15.4%)		

NR – not reported; SD – standard deviation

Outcomes Assessed

The mechanisms by which chlamydia might lead to adverse pregnancy outcomes is not well understood and the 2011 UK NSC review was not able to clearly identify whether or not chlamydia directly causes adverse pregnancy outcomes. Evidence was limited and conflicting with some studies reporting an association between untreated chlamydia infection and greater risk of developing complications during pregnancy (such as PROM, miscarriage, preterm birth, intrauterine growth restriction and low birth weight) [26-28], and others not finding such associations [29, 30]. Therefore, this review aims to both re-evaluate the previous evidence and include newer evidence by using a narrower scope of higher quality studies. There previous review reported evidence that the infection can be transmitted from the mother to the baby during vaginal birth, but there was very limited evidence of in utero transmission. However, it was difficult to estimate the burden of neonatal infection with chlamydia as infected infants are usually asymptomatic and the most common manifestations of neonatal chlamydia (conjunctivitis and pneumonia) are non-specific and treatable on the basis of symptomatic presentation.

Recent, although conflicting, evidence has suggested that women who were previously infected by chlamydia could be at increased risk of adverse birth outcomes such as preeclampsia, spontaneous preterm birth or stillbirth [31-33].

Most studies included in this review were more than two decades old and did not report whether outcomes were primary or secondary (Table 6). The studies were different, particularly in terms of the dose of erythromycin given and the length of treatment duration and for this reason, meta-analysis has not been undertaken in this review.

Alger 1991 [24] aimed to report the eradication of chlamydia, cure rates and antibiotic compliance. Martin 1997 [20] reported birth weight, neonatal death and stillbirth, premature delivery and PROM. McGregor 1990 [21] reported PROM. Ryan 1990 [23] reported birth weight, neonatal death and PROM and Rivlin 1997 [22] reported abortion, premature delivery, birth weight, stillbirth and PROM.

Table 6. Outcomes assessed

Outcome	Intervention vs. comparator	Studies
Pre term birth	Erythromycin vs. placebo	Martin 1997 [20]
	Erythromycin vs. untreated	Rivlin 1997 [22]
Premature rupture of membranes	Erythromycin vs. placebo	Martin 1997 [20]
		McGregor 1990 [21]
	Erythromycin vs. untreated	Rivlin 1997 [22]
		Ryan 1990 [23]
	Erythromycin vs no chlamydia	Ryan 1990 [23]
	Untreated vs. chlamydia negative	Ryan 1990 [23]
Low birth weight	Erythromycin vs. placebo	Martin 1997 [20]
	Erythromycin vs. no treatment	Rivlin 1997 [22]
		Ryan 1990 [23]
	Erythromycin vs no chlamydia	Ryan 1990 [23]
	Untreated vs. chlamydia negative	Ryan 1990 [23]
Pre-eclampsia	None	None
Miscarriage	Erythromycin vs. untreated	Rivlin 1997 [22]
Test of cure/Reinfection	Erythromycin vs clindamycin vs placebo	Alger 1991 [24]
Intrauterine grown restriction	None	None
Stillbirth	Erythromycin vs. placebo	Martin 1997 [20]
	Erythromycin vs. untreated	Rivlin 1997 [22]
Neonatal death	Erythromycin vs. placebo	Martin 1997 [20]
	Erythromycin vs. untreated	Ryan 1990 [23]
	Erythromycin vs no chlamydia	Ryan 1990 [23]
	Untreated vs no chlamydia	Ryan 1990 [23]

Statistical Analysis

None of the included studies reported conducting a power calculation. All of the included studies reported descriptive statistics, using chi-squared tests and Fisher's exact test, and studies that described continuous variables used analysis of variance (ANOVA). Logistic regression was used by some studies to account for confounding variables.

For most studies it was unclear whether an intention to treat (ITT) analysis or a per protocol analysis had been undertaken. Among the

RCTs, Alger 1991 [24] analysed only the patients with relevant outcomes, Martin 1997 [20] was unclear because although the authors stated that analyses had been conducted on the ITT population, some analyses were conducted on assessed patients only and with no explanation about missing data. McGregor 1990 [21] reported that the study sample comprised 229 of the 235 women enrolled, but it is unclear whether the six excluded women had been randomized and treated. The analyses in the two observational studies appear to have been conducted for all included patients.

All of the three RCTs reported losses to follow up. Alger 1991 [24] described 135 participants enrolled, but outcome data were available for 126. It was unclear whether the number who were not analysed was balanced across the groups, because the group to which the missing participants belonged was not reported. Overall, 9 patients were lost to follow-up because they delivered their babies elsewhere. One participant discontinued clindamycin treatment (due to side effects) without discussing this with the investigator. Martin 1997 [20] reported that after starting medication, 25 erythromycin-treated and 23 placebo-treated women withdrew from the trial, but were included in the ITT analysis. In McGregor 1990 [21], six enrolled women were excluded from the analyses: 4 were lost to follow-up, one was treated for premature labour on the day of enrolment, and one experienced intrauterine foetal death at 30 weeks' gestation.

Neither observational study reported losses to follow up.

The statistical analyses and loss to follow up details are reported in Table 7.

Table 7. Statistical analyses

Study identifier	Statistical analysis	Type of analysis	Loss to follow up and discontinuations
Randomised controlled trials			
Alger 1991 [24]	Categorical variables were compared using chi-squared tests, or Fisher's exact tests when categories contained fewer than 5 patients.	Per protocol analysis. Patients with data on delivery outcomes were included in the analysis.	135 patients enrolled, but outcome data available for 126. Unclear whether the number who were not analysed was balanced across the groups. Overall: 9 patients lost to follow-up (delivered elsewhere); losses /discontinuations not reported by treatment group. One patient discontinued clindamycin treatment (due to side effects) without discussing this with the investigator.
Martin 1997[20]	The data were analysed using ANOVA for continuous variables and contingency table methods for categorical variables. Categorical variables were compared using chi-square tests or Fisher's exact test. A Mantel-Haenszel test was conducted when treatment group comparisons were adjusted for a single categorical factor (in this related publication, p-values in the tables were for tests of differences between treatment groups for patients in specific strata and were not based on Mantel-Haenszel statistics). Further analyses were conducted using a logistic regression model which included stratification factors. The efficacy of the trial was periodically monitored by conditional power techniques. Significance was defined as a two-tailed $p<0.05$.	Reported to be ITT analysis but some analyses appear to have been conducted on assessed patients and methods used to account for missing data were not reported.	After starting medication, 25 erythromycin-treated and 23 placebo-treated women withdrew from the trial but were included in the ITT analysis.
McGregor 1990 [21]	Descriptive statistics were used to summarize the data, with chi-squared tests and Fisher's exact test (two-tailed) used to test the statistical significance of differences between treatment groups and other univariate associations. Student's t test was used to analyse continuous	Type of analysis undertaken was unclear. Total evaluated sample comprised 229/235 women enrolled, but it is unclear whether the six excluded women had been randomized and treated.	Losses to follow-up reported overall and not according to treatment group. Six enrolled women were excluded from the analyses: 4 lost to follow-up, one treated for premature labour on day of enrolment, and one

	data. Relative risks with 95% CIs were calculated, where appropriate. Logistic regression analyses were performed to control the effects of multiple independent variables on preterm birth, PROM, and low birth weight. Multivariate analysis was not attempted for the dependent variables PROM or preterm birth without PROM because of the small number of women with these outcomes. Univariate and multivariate analyses were conducted using an alpha-value of 0.05. The Breslow-Day test for homogeneity of results of odds ratios was used to confirm significance, where appropriate.		experienced intrauterine foetal death at 30 weeks' gestation.
Comparative, observational studies			
Rivlin 1997 [22]	Statistical analyses were conducted using chi-squared tests, Fisher's exact test and ANOVA, as appropriate. A p-value of ≥0.05 was considered significant.	Analyses appear to have been conducted according to ITT for maternal outcomes.	NR
Ryan 1990 [23]	Statistical methods included descriptive statistics, chi-squared tests, Fisher's exact test, and stepwise multiple logistic regression (reported as odds ratios with 95% CIs and p-values). A probability of <0.05 was considered significant (type I error) for all statistical comparisons.	Analyses appear to have been conducted according to ITT.	NR

ANOVA – analysis of variance; CI – confidence interval; ITT – intention to treat; NR – not reported; PROM – premature rupture of membranes

Risk of Bias

Table 8 presents an overview of the quality of methodological reporting in the three included RCTs and further details are provided in Appendix 3. The main quality assessment criteria (randomisation, allocation concealment and blinding) were well reported across two of the included trials (Martin 1997 [20] and McGregor 1990 [21]) and were unclear in one trial (Alger 1991 [24]).

Random sequence generation was considered to be low risk in two trials and of unclear risk in one. Martin 1997 [20] and McGregor 1990 [21] used computer generation randomisation, and in Martin 1997 [20] this was conducted according to a permuted block procedure and was stratified by study site, whereas in McGregor 1990 [21] the randomisation list was generated by an external company. In Alger 1991 [24] the risk of bias was unclear since participants were reported to have been randomised, but no details were reported.

Allocation concealment was considered to be low risk in two trials (Martin 1997 [20]; McGregor 1990 [21]) and of unclear risk in one trial (Alger 1991 [24]). In Martin 1997 [20], numbers corresponding to packets of either erythromycin or placebo were individually assigned to participants using central telephone allocation by an external company. Placebo tablets were identical in appearance to erythromycin tablets. In McGregor 1990 [21], treatments were prepared and randomized by an external pharmaceutical company. Women were given sealed identical-appearing treatment bottles and tablets, which either contained erythromycin or placebo. In Alger 1991 [24], the authors stated that medications were provided in blister packs, but it seems this was more to enable measures of compliance rather than to conceal allocation. No details were reported about whether treatments were identically packaged or sequentially numbered.

Blinding of participants and personnel was considered to be low risk in two trials (Martin 1997 [20], McGregor 1990 [21]). Both trials used study drug and placebos with an identical appearance, provided by external companies. In one trial (Alger 1990 [24]), which was reported to be double-blind, patients received their assigned treatment plus a placebo, such that each dose comprised a tablet and a capsule, but there was no indication that the capsules/tablets were of similar appearance. It was

unclear whether study personnel were blinded to the assigned intervention. Hence, this trial was considered to have unclear risk of bias.

Blinding of outcome assessors was considered to be low risk in all of the included trials. In two trials (Alger 1991 [24]; McGregor 1990 [21]), culture results were not available to study staff and in one trial, quality control measures were put in place to ensure blinding of study staff including each site sending five specimens to other centres and a random sample of women undergoing duplicate cultures (Martin 1997 [20]).

The risk of bias was unclear in terms of whether incomplete outcome data has been adequately addressed. In Alger 1991 [24], only participants with available data for each specific outcome appear to have been included in the analyses. In Martin 1997 [20], 25 erythromycin-treated and 23 placebo-treated women withdrew from the trial after starting medication, but were included in the ITT analysis. However, tabulated data reflect the numbers assessed for each outcome. In McGregor 1990 [21], the total evaluated sample comprised 229 of the 235 women enrolled, but it was unclear whether all six excluded patients had been randomized and treated. If maternal/outcome records were unavailable for review, private physicians and patients were contacted for data. There were no details of how missing data were accounted for in the analysis.

Selective outcome reporting was considered to be low risk in one trial McGregor 1990 [21]) and of unclear risk in two trials (Alger 1991 [24]; Martin 1997 [20]). In McGregor 1990 [21], all pre-specified outcomes were reported. In both Alger 1991 [24] and Martin 1997[20], outcomes were not pre-specified.

In terms of other problems that could put individual studies at risk of bias, two studies were assessed as unclear (Alger 1991 [24]; Martin 1997 [20]) and one trial was assessed as high risk (McGregor 1990 [21]). In Alger 1991 [24], nine (20%) placebo patients had no subsequent positive cultures for the remainder of their pregnancy. Eight of these women had three successive negative cultures. All participants were confirmed to be culture positive initially and all denied taking any antibiotics other than the study drug. By delivery, an even higher number (23 (58%)) of the placebo participants had negative cultures. The authors stated: “The placebo-control group, resulted from the participation of these patients in

a separate investigation to determine whether antenatal treatment of chlamydia improves pregnancy outcome, which required a placebo arm". The authors did not provide a study reference for this investigation so it is unclear what it means and whether it had any bearing on the randomisation process. In Martin 1997 [20], the authors reported that at three study sites which contributed 46% of the cases to the trial, high clearance of *C. trachomatis* occurred in the placebo group. In McGregor 1990 [21], participants with various micro-organisms were recruited of which only a small number of participants in each group (13 in each) were found to be positive for chlamydia infection; these were reported separately, so met the inclusion criteria for this review. It was also unclear how many participants with chlamydia had concurrent cervicovaginal infections. Sixty six per cent of the erythromycin group and 69% of the placebo group received non-protocol antimicrobial therapy during their antenatal care, however it is unclear how many of these had chlamydia.

Table 9 presents an overview of the quality of methodological reporting in the two included observational studies. Further details are provided in Appendix 3. Overall, both observational studies were poorly reported.

Both studies were at high risk of bias due to a lack of reported data about participants' baseline characteristics. It was not possible to ascertain whether groups were comparable at baseline in either study. Gestational age at diagnosis was reported overall in Rivlin 1997 [22], rather than by group, and was not reported at all in Ryan 1990 [23]. No confounding variables were reported by either study, but analyses in one study (Ryan 1990 [23]) were conducted to assess the contribution of clinical factors known to be associated with low birth weight. One study (Rivlin 1991 [22]) had antigen testing and tissue sampling conducted at an external reference laboratory with results not available to clinic physicians. It was unclear whether follow up was long enough for the outcomes to occur because neither study reported follow up duration, and it is unclear what proportion of the cohort was followed up in each study. Losses to follow up were not reported in either study.

Table 8. Summary of the risk of bias in RCTs

	Study identifier		
Risk of bias dimension	**Alger 1991 [24]**	**Martin 1997 [20]**	**McGregor 1990 [21]**
Was the allocation sequence adequately generated?	Unclear risk	Low risk	Low risk
Was the concealment of treatment allocation adequate?	Unclear risk	Low risk	Low risk
Was knowledge of the allocated interventions adequately prevented from participants and personnel	Unclear risk	Low risk	Low risk
Was knowledge of the allocated interventions adequately prevented from outcome assessors	Low risk	Low risk	Low risk
Were incomplete outcome data adequately addressed?	Unclear risk	Unclear risk	Unclear risk
Are reports of the study free of suggestion of selective outcome reporting?	Unclear risk	Unclear risk	Low risk
Was the study apparently free of other problems that could put it at a high risk of bias?	Unclear risk	Unclear risk	High risk
Baseline characteristics comparable?	Low risk	Low risk	Unclear risk
Intention to treat (ITT) analysis?	High risk	Unclear risk	Unclear risk

Table 9. Summary of the risk of bias in observational studies

	Study identifier	
Risk of bias dimension	**Rivlin 1997 [22]**	**Ryan 1990 [23]**
Is there sufficient description of the groups and the distribution of prognostic factors?	High risk	High risk
Are the groups assembled at a similar point in their disease progression?	High risk	Unclear
As the intervention/treatment reliable ascertained?	Unclear	Unclear
Were the groups comparable on all important confounding variables?	Unclear	Unclear
Was there adequate adjustment for the effect of these confounding variables?	Unclear	Low risk
Was outcome assessment blind to exposure status?	Low risk	Unclear
Was follow-up long enough for the outcomes to occur?	Unclear	Unclear
What proportion of the cohort was followed up?	Unclear	Unclear
Were drop-out rates and reasons for dropout similar across intervention and unexposed groups?	Unclear	Unclear

Pre-term birth

Two studies reported outcomes for pre-term birth; one RCT (Martin 1997 [20]) and one prospective cohort study (Rivlin 1997 [22]). Details are provided in Table 10.

The trial reported subgroups for pre-term birth prior to 32 weeks, from 32 to 36 weeks and prior to 37 weeks. Statistical comparisons were not reported for the first two subgroups. The third subgroup (pre-term birth prior to 37 weeks) showed no differences between erythromycin and placebo groups (p=0.7) (Martin 1997 [20]).

The prospective cohort study reported three pregnancies that resulted in pre-term birth in the erythromycin group; one at 28 weeks, twins born at 34 weeks and one at 35 weeks. In the untreated group, seven women delivered prematurely; three with PROM, one induced for pre-eclampsia, and three with no clear reason for premature delivery. The data were not statistically compared (Rivlin 1997 [22]).

Table 10. Pre-term birth

Identifier	Intervention/ comparator	Subgroup	Number experiencing outcome	Statistical comparison
Chlamydia positive women untreated vs chlamydia negative women				
Martin 1997 [20]	Erythromycin	<32 weeks	1/202 (0.5%)	NR
	Placebo	<32 weeks	1/203 (0.5%)	NR
	Erythromycin	32-36 weeks	26/202 (13%)	NR
	Placebo	32-36 weeks	29/203 (14%)	NR
	Erythromycin	<37 weeks	27/202 (13%)	No statistically significant difference in the number of pre-term deliveries (p=0.7)
	Placebo	<37 weeks	30/203 (15%)	
Rivlin 1997 [22]	Erythromycin	1 at 28 weeks, twins at 34 weeks, 1 at 35 weeks	3/23 (15%)	NR
	Untreated	3 with PROM, one induced for pre-eclampsia, 3 with no clear reason	7/58 (12%)	NR

NR - Not reported; PROM - Premature rupture of membranes

Premature Rupture of Membranes

Four studies reported outcomes for premature rupture of membranes (or prelabour rupture of membranes) (PROM); two RCTs (Martin 1997 [20], McGregor 1990 [21]) and two prospective cohort studies (Ryan 1990 [23], Rivlin 1997 [22]). We have reported the definitions used in the included studies in the results below. Details are provided in Table 11.

One RCT investigated the incidence of PROM at less than 37 weeks and at ≥37 weeks, defined as membrane rupture before the onset of regular uterine contractions (Martin 1997 [20]). There were no significant differences (p-values not reported) between women receiving erythromycin or placebo for either of these subgroups, or for both subgroups combined.

A second RCT investigated the incidence of PROM, defined as rupture of membranes ≥1 hour before onset of uterine contractions (McGregor 1990 [21]). Erythromycin significantly reduced the number of women who had PROM compared to placebo (RR 0.4, 95% CI: 0.2, 0.8, p=0.03), but the study numbers were small, with 13 participants in the erythromycin group and 12 in the placebo group.

One prospective cohort study investigated the incidence of PROM defined as rupture of membranes ≥1 hour before onset of labour (Ryan 1990 [23]). Three groups were compared; women with chlamydia who were treated with erythromycin; women with chlamydia who were untreated; and women without chlamydia. Women with untreated chlamydia were more than twice as likely to have PROM as women without chlamydia (OR 2.12, 95% CI: 1.57, 2.86, p<0.001). Erythromycin significantly reduced the number of women with chlamydia who had PROM compared to women who were untreated (OR 0.56, 95% CI: 0.37, 0.85, p<0.01). There were no significant differences between women with chlamydia who were treated and women without chlamydia (p=0.556).

A second prospective cohort study found no differences between women with chlamydia who were treated with erythromycin and women with chlamydia who were untreated (Rivlin 1997 [22]).

Although PROM was investigated in two RCTs, meta-analysis was not undertaken because the treatment periods in the studies were quite different. Martin 1997 [20] prescribed erythromycin for ten weeks or until 35 weeks gestation, whichever came first, while McGregor 1990 [21] prescribed erythromycin for seven days. The trial by (McGregor 1990 [21]) had very few patients (25 in total) while the trial (Martin 1997 [20]) had almost 200 patients in each arm. Although the smaller trial showed a significant effect for erythromycin compared with the placebo, the addition (pooling in a meta-analysis) of the very small trial to the larger trial would likely show no differences between the erythromycin and placebo groups; an indicative point estimate was calculated by YHEC (OR: 1.51, 95% CI: 0.84, 2.71, p=0.1719). The small numbers combined with the differences in treatment duration mean that undertaking meta-analysis for this outcome would be of no additional benefit.

One prospective cohort study comparing untreated women with chlamydia to women without chlamydia reported that women with untreated chlamydia were more than twice as likely to have PROM than women without chlamydia (OR 2.12 (95%CI: 1.57, 2.86) p<0.001).

The studies comparing treated and untreated women reported conflicting results. The largest RCT showed no significant differences between 196 women treated with erythromycin and 193 women treated with placebo at less than 37 weeks, ≥ 37 weeks, or both. A second RCT reported that erythromycin was beneficial, however study numbers were small with 13 women in the erythromycin group and 12 in the placebo group.

A large prospective cohort study, with over 1000 participants in the erythromycin and untreated groups, showed that erythromycin significantly reduced PROM compared to untreated women who had PROM using multiple logistic regression to account for age, ethnicity, parity, birth weight, urinary tract infections, smoking, hypertension and diabetes. A smaller prospective cohort study showed no differences in PROM between 23 women who received erythromycin and 58 untreated women.

It is unclear whether antibiotic treatment, specifically erythromycin, reduces the incidence of PROM in women with chlamydia.

Table 11. Premature Rupture of Membranes

Study identifier	Intervention	Outcome definition and measure (if details are provided)	Number experiencing event	Statistical comparison
Chlamydia positive women untreated vs chlamydia negative women				
Ryan 1990 [23] Prospective cohort	Erythromycin	PROM	39/1323 (2.9%)	Erythromycin significantly reduced the number of women with chlamydia who had PROM Untreated vs. treated**: OR 0.56 (95%CI: 0.37, 0.85) p<0.01
	Untreated			Women with untreated chlamydia were more than twice as likely to have PROM than women without chlamydia Untreated vs chlamydia negative: OR 2.12 (95%CI: 1.57, 2.86) p<0.001
	Chlamydia negative			Treated vs chlamydia negative: NS (p=0.556)
Chlamydia positive women treated vs chlamydia positive women untreated				
Martin 1997 [20] RCT	Erythromycin	<37 weeks	5/196 (3%)	NR
	Placebo		7/193 (4%)	
	Erythromycin	≥37 weeks	16/196 (8%)	NR
	Placebo		18/193 (9%)	
	Erythromycin	PROM total	21/196 (11%)	No significant difference in the proportion of women experiencing PROM (p value not reported).
	Placebo		25/193 (13%)	
McGregor 1990 [21] RCT	Erythromycin	PROM	0/13 (0%)	Erythromycin significantly reduced the number of women who had PROM: RR 0.4 (95%CI: 0.2, 0.8) p=0.03
	Placebo		6/12 (50%)	
Rivlin 1997 [22]	Erythromycin	NR	1/23 (5%)*	NR

Prospective cohort	Untreated	3/58 (5%)
	Untreated	58/1110 (5%)
	Chlamydia negative	243/9111 (3%)

CI - confidence interval; N - number of patients; NA - not applicable; NR - not reported; NS - not significant; PROM - premature rupture of membranes; OR - odds ratio; RR - relative risk.
** In Rivlin 1997, 1/23 was reported to be 5%, however YHEC calculate this to be 4.3%
* In Ryan 1990 two sets of results were presented for the untreated vs. treated comparison; one set of results reported in a table with a different version in the text. We have reported the results from the table in this report because it was the most complete (contained 95% confidence intervals).

Low Birth Weight

Three studies reported outcomes for low birth weight; one RCT (Martin 1997 [20]) and two prospective cohort studies (Ryan 1990 [23], Rivlin 1997 [22]). Details are provided in Table 12.

The RCT investigated the incidence of low birth weight in newborns weighing less than 1,500g, between 1,500 and 2,000g and in infants under 2,500g (Martin 1997 [20]). At delivery 13% of erythromycin treated women were <37 weeks gestation, while 15% of women who received placebo were <37 weeks gestation. No statistical analysis was reported for newborns weighing less than 1,500g or between 1,500 to 2,000g, however, the incidence of low birth weight in these subgroups does not appear to be different between the erythromycin and placebo groups. In all infants weighing less than 2,500g, there were no significant differences in the incidence of low birth weight between women who were randomised to erythromycin or women who were randomised to placebo (p=0.4).

One prospective cohort study did not report any statistical analyses comparing low birth weight; 20% of women receiving erythromycin and 14% of women receiving no treatment had low birth weight newborns. The gestational age at delivery was not reported (Rivlin 1997 [22]).

One prospective cohort study investigated low birth weight in newborns weighing less than 2,500g (Ryan 1990 [23]). Three groups were compared; women with chlamydia who were treated with erythromycin, women with chlamydia who were untreated and women without chlamydia. Women with untreated chlamydia were more likely to have a low birth weight baby (under 2,500g) than women without chlamydia (p<0.001, no further details reported). Erythromycin significantly reduced the number of women with chlamydia who had a low birth weight baby (under 2,500g) compared to untreated women (p<0.0001, no further details reported). There were no significant differences between women with chlamydia who were treated and women without chlamydia (p=0.4190). The gestational age at delivery was not reported.

There was only one RCT reporting results for low birth weight. Because of the number of participants in the larger cohort (n=1000) a meta-analysis would weight this study higher than the RCT (n=201) which would

disregard the fact that the RCT is the better quality study. Meta-analysis should only really be considered in studies that we know are similar because otherwise any point estimates generated will not be reliable. Studies were not considered similar enough to combine in a meta-analysis to obtain a reliable point estimate.

Table 12. Low birth weight

Identifier	Intervention	Outcome	Outcome definition	Number experiencing event	Statistical analysis
Chlamydia positive women untreated vs chlamydia negative women					
Ryan 1990[23]	No treatment	Low birth weight	<2,500 g	7/52 (14%)*	Women with untreated chlamydia were more likely to have a low birth weight baby under 2,500g than women without chlamydia Untreated vs chlamydia negative: p<0.001 (no further details reported)
	Erythromycin			145/1323 (11%)	
	Untreated			218/1110 (20%)	Erythromycin significantly reduced the number of women with chlamydia who had a low birth weight baby under 2,500g compared to untreated women Untreated vs. treated**: p<0.0001 (no further details reported) Treated vs chlamydia negative: NS (p=0.4190)
	Chlamydia negative			1068/9111 (12%)	
Chlamydia positive women treated vs chlamydia positive women untreated					
Martin 1997 [20]	Erythromycin	Low birth weight	<1,500 g	0/201 (0%)	NR
	Placebo			2/199 (1%)	
	Erythromycin	Low birth weight	1,500 - 2,000 g	17/201 (8%)	NR
	Placebo			20/199 (10%)	
	Erythromycin	Low birth weight	<2,500 g	17/201 (8%)	There were no significant differences in the number of low birth weight newborns between women who took erythromycin or placebo: p=0.4 (no further details reported
	Placebo			22/199 (11%)	
Rivlin 1997 [22]	Erythromycin	Low birth weight	<2,500g	4/23 (20%)	NR

NR - not reported; NA - not applicable; NS - not significant

* In Rivlin 1997 7/52 is reported as being 14%. YHEC calculate this to be 13%

**In Ryan 1990 two sets of results were presented for the untreated vs. treated comparison; one set of results reported in a table with a different version in the text. We have reported the results from the table in this report because it was the most complete (contained 95% confidence intervals).

Pre-Eclampsia

None of the included studies reported this outcome.

Miscarriage

One prospective cohort study reported results for miscarriage (Rivlin 1997 [22]) (**Table 13**). The study describes three miscarriages in the untreated group: one missed miscarriage, one at 22 weeks associated with pyelonephritis and one therapeutic for foetal anomaly. No further details are reported.

Table 13. Miscarriage rates

Study	Intervention/comparator	Number experiencing outcome	Statistical comparison
Chlamydia positive women treated vs chlamydia positive women untreated			
Rivlin 1997 [22]	Erythromycin	0/23 (0%)	NR
	Untreated	3/58 (5%)	NR

NR – not reported

Because only one study comparing erythromycin with untreated patients reported miscarriage, insufficient data are available to draw conclusions about whether treating chlamydia in pregnancy results in fewer miscarriage events.

Test of Cure/Re-Infection

One RCT reported outcomes for re-infection rates and test of cure (Alger 1991 [24]). Details are in Table 14.**Error! Reference source not found.**

Patients were recruited and screened between 16 and 24 weeks gestation. Tests of cure were conducted on completion of therapy (14 days after the first dose of medication), approximately 4 weeks after screening, and on admission for labour or ruptured membranes (at term, or preterm). Although there were more patients remaining chlamydia positive in the erythromycin group than the clindamycin group after the first and second test of cure, there were no statistically significant differences between the groups. No statistical analyses were reported comparing either intervention group with placebo, however there were

many more women who remained chlamydia positive in the placebo group.

Table 14. Re-infection rates

Identifier	Intervention	Outcome	Time point of assessment	Number analysed	Statistical analysis
Chlamydia positive women treated vs chlamydia positive women untreated					
Alger 1991 [24]	Erythromycin	Number remaining chlamydia positive at completion of therapy (14 days)	2nd trimester	4/34 (12%)	No significant differences in the number remaining chlamydia positive at the first test of cure between patients randomised to erythromycin or clindamycin. No other comparisons were reported.
	Clindamycin			2/40 (5%)	
	Placebo			30/40 (75%)	
	Erythromycin	Number remaining chlamydia positive 4 weeks following therapy	2nd trimester	5/32 (16%)	No significant differences in the number remaining chlamydia positive at the second test of cure between patients randomised to erythromycin or clindamycin. No other comparisons were reported.
	Clindamycin			2/36 (6%)	
	Placebo			30/42 (71%)	
	Erythromycin	Number remaining chlamydia positive during labour and delivery	3rd trimester	8/38 (21%)	Not reported
	Clindamycin			4/34 (12%)	
	Placebo			17/40 (43%)	

Stillbirth/Neonatal Death

Three studies reported outcomes for stillbirth and/or neonatal death; one RCT (Martin 1997 [20]) and two prospective cohort studies (Rivlin 1997 [22]; Ryan 1990 [23]). Details are provided in Table 15. Stillbirth and neonatal death were defined differently across the studies. The study by Martin 1997 [20] did not define either term, but reported outcomes for stillbirth and neonatal death separately. The first prospective cohort study by Rivlin (1997) [22] reported outcomes for stillbirth but also did not report a definition. A second prospective cohort study investigated the incidence of newborn survival defined as newborns who left the hospital alive (Ryan 1990 [23]). Non-survivors included stillbirths, neonatal deaths

and infants who died after 28 days if they had been continuously hospitalised from birth.

The trial reported subgroups for stillbirth and neonatal death and although statistical analyses were not conducted, there appear to be no significant differences between erythromycin and placebo groups (Martin 1997 [20]).

One prospective cohort study reported one stillbirth in an erythromycin treated group and none in a placebo group (Rivlin 1997 [22]). Statistical analyses were not conducted, however an odds ratio calculation conducted by YHEC shows no significant differences (OR 0.14 (95% CI: 0.0059, 3.8) p=0.2494).

Three groups were compared; women with chlamydia who were treated with erythromycin, women with chlamydia who were untreated, and women without chlamydia. Multiple logistic regression was undertaken to correct for age race, parity, PROM, birth weight, urinary tract infection, smoking, hypertension and diabetes (Ryan 1990 [23]). There were no statistically significant differences between women with untreated chlamydia and women without chlamydia (results were not reported). There were no statistically significant differences between women with chlamydia who received erythromycin and women with chlamydia who were untreated (OR 2.21 (95% CI: 0.89, 5.49) p<0.08). Infants born to mothers with chlamydia who were treated were more likely to survive than infants born to mothers who did not have chlamydia (OR 1.65 (95% CI: 1.13, 2.42) p<0.01). The authors did not explain this finding further, although one potential explanation is that antibiotics prescribed for chlamydia may have eradicated other infections. The number of participants in this study was of sufficient size (more than 1000) that further research may be warranted to confirm or clarify this finding.

Table 15. Stillbirth/neonatal death

Study identifier	Intervention	Outcome definition	Number of participants experiencing event	Statistical analysis
Chlamydia positive women untreated vs chlamydia negative women				
Ryan 1990 [23]	Erythromycin	Newborn survival (Newborns who left hospital alive)	1315/1323 (99.4%)	There were no differences in newborn survival between women with untreated chlamydia and women without chlamydia Untreated vs chlamydia negative: p<0.05 (no further details reported)
	Untreated (with chlamydia)		1083/1110 (97.6%)	There were no significant differences between women with chlamydia who were treated with erythromycin compared with untreated women with chlamydia. Untreated vs. treated: OR 2.21 (95%CI: 0.89, 5.49) p<0.08
	Untreated (without chlamydia)		8793/9111 (98.5%)	Infants born to mothers with chlamydia who were treated were more likely to survive than infants born to mothers who did not have chlamydia Treated vs chlamydia negative: OR 1.65 (95%CI: 1.13, 2.42) p<0.01
Chlamydia positive women treated vs chlamydia positive women untreated				
Martin 1997 [20]	Erythromycin	Stillbirth	2/202 (1%)	NR
	Placebo		1/203 (0.5%)	
	Erythromycin	Neonatal death	1/202 (0.5%)	NR
	Placebo		0/203 (0%)	
Rivlin 1997 [22]	Erythromycin	Stillbirth	1/23 (4.3%)	NR
	Untreated		0/52 (0%)	

NR – not reported

Intrauterine Growth Restriction

None of the included studies reported this outcome.

Summary of Findings

Summary of Findings Relevant to Systematic Review Question 1

Pre-term birth

The data reporting pre-term birth is limited to one RCT and one prospective cohort. The RCT reported no significant differences in the incidence of pre-term birth between women who are treated for chlamydia and women who are untreated or who receive placebo. The prospective cohort did not compare studies statistically.

Premature rupture of membranes

Studies reporting PROM had conflicting results. The largest RCT showed no significant differences between 196 women treated with erythromycin and 193 women treated with placebo at less than 37 weeks, ≥ 37 weeks, or both. A second RCT reported that erythromycin was beneficial, but study numbers were small (totalling 25).

Two comparative observational studies also showed conflicting results. The largest study (over 1000 participants in the erythromycin and untreated groups) showed that erythromycin significantly reduced PROM compared to untreated women who had PROM using multiple logistic regression to account for age, ethnicity, parity, birth weight, urinary tract infections, smoking, hypertension and diabetes. A smaller study showed no differences in PROM between 23 women treated with erythromycin and 58 untreated women.

It is unclear whether the incidence of PROM in untreated women is different from the incidence in treated women with chlamydia. It is also unclear whether antibiotic treatment, specifically erythromycin, reduces the incidence of PROM in women with chlamydia.

Low birth weight

Studies reporting low birth weight infants had conflicting results. The largest RCT showed no significant differences between 201 women

treated with erythromycin and 199 women treated with placebo in newborns weighing less than 1,500g, 1,500 to 2,000g, or all newborns under 2,500g.

Two comparative observational studies also showed conflicting results. The largest study (over 1000 participants in erythromycin and untreated groups) showed that erythromycin significantly reduced low birth weight compared to untreated women using multiple logistic regression to account for age, ethnicity, parity, birth weight, urinary tract infections, smoking, hypertension and diabetes. A smaller study did not report statistical analyses, but showed that 23 patients receiving erythromycin had a greater incidence of low birth weight newborns than those who did not receive treatment (n=52).

It is unclear whether the incidence of low birth weight babies in untreated women is different from the incidence in treated women with chlamydia. It is also unclear whether antibiotic treatment, specifically erythromycin, reduces the incidence of low birth weight newborns in women with chlamydia.

Pre-eclampsia

None of the included studies reported this outcome.

Miscarriage

Only one study comparing erythromycin with untreated patients reported miscarriage outcome. There are insufficient data available to draw conclusions about whether treating chlamydia in pregnancy results in fewer miscarriage events.

Re-infection rates

One RCT reported re-infection rates, without statistical analyses. It appears that there were no significant differences between re-infection rates in women who were treated with either clindamycin or erythromycin. However, women who received erythromycin had a much higher incidence of chlamydia positivity at the first and second test of cure (in the second trimester) and at birth or rupture of membranes.

Stillbirth/neonatal death

Two studies reported outcomes for stillbirth and for neonatal death. A RCT reported no differences for either outcome (separately). A large prospective cohort study reported no differences for a combined outcome (including both stillbirth and neonatal death). A second prospective cohort study reported no differences between erythromycin treated and untreated groups, or for women with chlamydia who were untreated compared to women who were chlamydia negative.

Intrauterine growth restriction

None of the included studies reported this outcome.

Overall Summary

Criterion 1: Not met

There is very little evidence from the RCTs and prospective comparative studies included in this review that untreated chlamydia results in poorer outcomes for pregnant women. For outcomes reported by two or more studies, results were often contradictory.

We did not identify any comparative studies reporting neonatal outcomes.

Methodological Limitations

Defining the population in this review was both a methodological limitation and a strength. UK NCS were primarily interested in the outcomes for untreated women who have chlamydia during pregnancy compared with women who do not have chlamydia. There was only one study reporting this comparison. Of lesser importance was the comparison between untreated women with chlamydia and treated women with chlamydia and, as such, eligible studies were required to include women with confirmed chlamydia. This has resulted is a very small set of eligible studies, because no recent studies have chosen not to treat pregnant women with known chlamydia. There are many studies that investigate risk factors for particular outcomes in pregnancy (of which chlamydia is one), but assessing risk was not the focus of this review. Such studies have included participants based on the outcome of interest rather than specifically including participants who have chlamydia. The challenge in identifying such studies is that the search strategy would result in very large numbers of records since the population would be pregnant women. These studies also have limitations because they are not designed specifically with chlamydia in mind, and thus they are likely to be underpowered to detect differences between women with chlamydia who were treated or untreated. It is unclear how reliable the results from these types of retrospective studies would be given the analysis would have been conducted on an ad hoc basis depending on whether stored samples (which may or may not have been available for all women) showed that participants had chlamydia or not.

A considerable number of comparative studies were excluded from this review because they were not conducted in the UK or analogous Western countries. We considered Western countries and those analogous to the UK to include the UK, Western Europe, Central Europe (Hungary, Poland, Slovakia, the Czech Republic, and Slovenia), North America, Australia and New Zealand. This means that studies from Asian, South American, African, Middle Eastern and Eastern European countries were excluded. This limitation on included studies is justified because analogous countries with similar availability of health care, particularly in terms of screening services, will be more generalisable to the UK. However, this then limits the key questions where generalisability is less of an issue. For example, key questions one and two are essentially about the natural history of chlamydia. These questions may have benefitted from

additional evidence about the impact of chlamydia in pregnancy. It is unclear whether the outcomes experienced by pregnancy women with chlamydia are based on race/ethnicity. Future reviews regarding the impact of chlamydia could consider evidence from a wider number of countries.

The previous NSC review conducted in 2009 appears to have been conducted with broader study eligibility criteria compared to this review, which answered five specific key questions with tightly defined PICO criteria. This is evident in the included studies of both reviews: there is very little overlap.

Limitations in the Included Studies

There are limitations in the studies included in this review that could hinder the reliability of the results reported. Only limitations related to the three included RCTs are reported here. Further details about the risk of bias in all of the included studies (including the two additional prospective cohort studies) are reported in Appendix 3.

Overall there are inherent limitations in the trials that may mean the results are inaccurate. Testing sensitivity is likely to be low because all of the studies were conducted using outdated test methods that we know have low sensitivity; this means that there is a high likelihood that at least some women with chlamydia were in the control arm of these studies. The current method, using NAAT tests, is more likely to diagnose women with chlamydia accurately. Treating partners with chlamydia to reduce reinfection rates is also a limitation. In this review, two studies did not report whether the partners were treated. One study reported that partners were not treated and the other recommended that partners were treated but did not directly offer treatment. Only one study offered doxycycline to partners. Any intervention that is expected to work for women with chlamydia must have effective partner notification built in.

Martin 1997 [20] included patients from seven study sites. At three study sites, which contributed almost half of the cases to the trial, high clearance of *C. trachomatis* occurred in the placebo group (37%). The study investigators examined the quality control data separately by site in order to ensure laboratories had correctly identified positive and negative

C. trachomatis specimens. For the most part, these were accurate. Data were then investigated regarding the use of antibiotics prescribed outside of the trial. Results in the placebo group were found to be, in part, due to a significantly greater number of placebo patients receiving non-trial antibiotics effective against chlamydia, but this did not explain all of the differences. Further analysis, subgrouping women by high and low clearance, did not report any further differences. Despite a thorough investigation of the possible causes of the high clearance in the placebo group, only some of the discrepancies could be explained. The authors concluded that "Due to the high clearance of *C.trachomatis* in the placebo group, these data do not provide unequivocal evidence that erythromycin use in *C.trachomatis* infected women prevents low birth weight."

The study population in the McGregor 1990 [21] trial comprised pregnant women with various microflora and bacterial conditions. It was unclear how many participants were infected with more than one microorganism. Results were presented overall for erythromycin vs placebo groups with more than 100 patients in each arm, but only a small number had chlamydia (n=13 and n=12 respectively). There was some stratification of the data according to the presence of susceptible microorganisms or abnormal vaginal conditions, but results appear only to have been reported when significant differences/effects were observed. Baseline characteristics were not reported separately for chlamydia positive women, so it is unclear whether groups were comparable. *C. trachomatis* was significantly associated with increased risk of PROM (p=0.03; RR 3, 95% CI: 1.2, 8.1), but other associations failed to reach significance. Similarly to Martin 1997 [20], patients in both the treated and untreated groups of McGregor 1990 received non-protocol antibiotic therapy during their antenatal care. Sixty six per cent of the erythromycin group and 69% of the placebo group received such antibiotics, although they were reported not to have received antibiotics within two weeks of the study treatment (McGregor 1990 [21]).

In Alger 1991 [24], women in the placebo group resulted from the participation of these patients in a separate investigation to determine whether antenatal treatment of chlamydia improves pregnancy outcome, which required a placebo arm. No study reference was given for this investigation and it is unclear whether using a placebo group from another study had any effect on the randomisation process for the current study, the details of which are not reported. Nine of the placebo patients

(20%) had no subsequent positive cultures for the remainder of their pregnancy. Eight of these women had three successive negative cultures. All patients were confirmed to be culture positive initially and all denied taking any antibiotics other than the study drug. By delivery, 23 (58%) of the placebo women had negative cultures. The authors did not investigate potential reasons for this, apart from checking the women notes for indications of antibiotic use.

Although it appears concerning that 37% of placebo patients in Martin 1997 [20] and 58% of placebo patients in Alger 1991 [24] appeared to undergo spontaneous clearance of chlamydia infection by delivery, a recent review, conducted by the Centers for Disease Control and Prevention, indicates that there may be reason to believe that this is common in women with chlamydia [34]. In a recent five-country trial, the determination of sample size to identify the necessary number of participants to demonstrate a reduction in bacterial sexually transmitted infection (STI) was based primarily on chlamydia (65.8% of the bacterial infections observed at recruitment; 10.3% prevalence). One year later, the rates of chlamydia were 60% lower suggesting that half of the new chlamydia infections may have spontaneously resolved [35]. Further studies investigating chlamydia during pregnancy should be carefully designed to ensure multiple follow up periods in order to adequately capture spontaneous remission.

Conclusions and Implications for Policy

The findings from the systematic review do not provide sufficient evidence upon which to base a decision about whether screening should be recommended in pregnant women. Studies were poorly reported, often contradictory, and in the largest trial with the least methodological bias, the authors claimed that their data should not be used as a basis for decision making.

This review shows that the highest quality evidence available from RCTs and comparative observational studies is not able to inform a decision about chlamydia screening in pregnancy. Further research on this subject will need to be carefully designed to ensure that confounding factors are taken into account, for example, whether partners of women with chlamydia were also treated and that methods to test for chlamydia are sufficiently sensitive. Consideration should also be given to study

design and the type of evidence (e.g. RCT, observational study) that would be regarded as sufficient upon which to base changes in practice.

Rapid Reviews – Key Questions 2 to 5

Key Question 2

What is the impact of untreated chlamydial infection, during pregnancy, on neonatal outcomes in the UK?

This question relates to NSC criterion 1: The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease.

This question aimed to assess the burden of chlamydial infection on neonatal outcomes in the UK, and the consequences of untreated maternal chlamydial infection on the newborns. The previous UK NSC review concluded that there was a lack of evidence that clearly estimated the burden of symptomatic chlamydial infection in neonates in the UK. Therefore, it was not possible to determine whether or not neonatal chlamydia infection was an important public health problem in the UK. It also concluded that a minority of infants born to women with chlamydia develop a symptomatic disease (conjunctivitis and/or pneumonia), however, these symptoms are usually not severe and are treatable.

Criterion: Not met.
No studies published since 2009 were identified. Ideally, high quality RCTs or prospective comparative studies the follow women throughout their pregnancies would be needed to determine whether there are benefits of screening pregnant women for chlamydia. (For more information see section ‘Study design and inclusion in this review’)

Key Question 3

What is the optimal screening strategy for Chlamydia infection in pregnancy to avoid adverse pregnancy outcomes?

This question relates to NSC criterion 11: There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (e.g. Down's syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.

The aim of this question is to evaluate whether an optimal approach to screening during pregnancy has been identified, and the effect that such a screening programme has on pregnancy outcomes. The 2010 review found that there was no evidence of the effectiveness of a systematic approach to screening for chlamydia in pregnancy.

Criterion: Not met.

No studies published from 2009 were identified.

Key Question 4

Are there any known side effects from antibiotic treatment of chlamydial infection during pregnancy on the newborn?

This question relates to NSC criteria 9: There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme should not be further considered.

The 2010 review concluded that the range of antibiotics available for use in pregnancy is limited and pregnancy is associated with exacerbated gastro-intestinal intolerance and non-completion of treatment. Following the ORACLE study [36], there were also concerns about the long term effect of antibiotics in pregnancy and the potential harms associated with in utero exposure to antibiotics was not clearly defined making difficult to

evaluate the balance of benefit and harm. Considering that the implementation of a screening programme in pregnancy would increase the use of antibiotic treatment during pregnancy, it is, therefore, essential to understand the consequences that such treatment might have on newborns.

Criterion: Not met.

No studies published from 2009 were identified.

Key Question 5

What is the optimal screening strategy for Chlamydia infection in pregnancy to avoid adverse neonatal outcomes?

This question relates to NSC criteria 11: There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an “informed choice” (e.g. Down’s syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.

The aim of this question is to evaluate whether an optimal approach to screening for chlamydia infection during pregnancy has been identified and the effect that such a screening programme has on neonatal outcomes. The 2010 review concluded that more research was needed to understand the effectiveness of chlamydia screening and treatment in pregnancy with respect to prevention of newborn complications, particularly regarding optimal timing in pregnancy and repeat testing. At the time, there was insufficient evidence of benefit from screening for chlamydia in pregnancy over the clinical management of infants with symptomatic infection.

Criterion: Not met.

No studies published from 2009 were identified.

Appendix 1 – Search Strategy

Electronic Databases

The search strategies and the conduct of searches reflect the PHE guidance on conducting literature searches to inform evidence summaries [37]. The search approach for key questions 2-5 reflects the rapid review context as described in PHE guidance [38], where the rapid review "aims to provide an evaluation of the 'volume and direction' of the literature on a single question or set of questions on a given screening topic". Search methods were designed to target those studies most likely to be relevant to the rapid review context, rather than aiming to be 'exhaustive'.

Searches for the systematic review for key question 1 reflect a systematic review approach involving a sensitive search without a date limit, and conducted in databases additional to those searched for the rapid reviews.

The search strategy involved searches of the databases shown in Table 1.1.

Table 1.1: Summary of electronic database searches and dates

Database	Platform	Searched on date	Date range of search
Medline	OvidSP	18 April 2017	1946 to 18 April 2017
Embase	OvidSP	18 April 2017	1974 to April 17 2017
Maternity & Infant Care Database (MIDIRS)	OvidSP	18 April 2017	1971 to March 2017
HMIC Health Management Information Consortium	OvidSP	18 April 2017	1979 to January 2017
Cochrane Database of Systematic Reviews	Cochrane Library, Wiley	18 April 2017	All content in Issue 4 (April 2017)
Health Technology Assessment HTA	Cochrane Library, Wiley	18 April 2017	All content in Issue 4 (October 2016)
Database of Abstracts of Reviews of Effects DARE	Cochrane Library, Wiley	18 April 2017	All content in Issue 2 (April 2015)
Cochrane Central Register of Controlled Trials	Cochrane Library, Wiley	18 April 2017	All content in Issue 3 (March 2017)

NHS Economic Evaluations Database NHS EED	Cochrane Library, Wiley	18 April 2017	All content in Issue 2 (April 2015)
Science Citation Index Expanded	Web of Science	19 April 2017	1900 to 18 April 2017
ClinicalTrials.gov	https://www.clinicaltrials.gov/ct	19 April 2017	All content on 19 April 2017
WHO International Clinical Trials Registry Platform (WHO ICTRP)	http://www.who.int/ictrp/en/	19 April 2017	All content on 19 April 2017
National Institute for Health and Care Excellence (NICE) website	www.nice.org.uk	19 April 2017	All content on 19 April 2017
Canadian Agency for Drugs and Technologies in Health (CADTH) website	https://www.cadth.ca/	19 April 2017	All content on 19 April 2017
Agency for Healthcare Research and Quality (ARHQ) website	https://www.ahrq.gov/	19 April 2017	All content on 19 April 2017
National Services Division website	http://www.nsd.scot.nhs.uk/services/screening/	19 April 2017	All content on 19 April 2017
Wales Screening Committee website	http://gov.wales/topics/health/professionals/committees/screening/?lang=en	19 April 2017	All content on 19 April 2017
Public Health Agency website	http://www.publichealth.hscni.net/directorate-public-health/service-development-and-screening/screening	19 April 2017	All content on 19 April 2017
Royal College of Obstetricians and Gynaecologists website	https://www.rcog.org.uk/	19 April 2017	All content on 19 April 2017
British Association for Sexual Health and HIV website	https://www.bashh.org/	19 April 2017	All content on 19 April 2017
Royal College of Midwives website	https://www.rcm.org.uk/	19 April 2017	All content on 19 April 2017
National Health Service websites	via Google	20 April 2017	No date limits
Government websites	via Google	20 April 2017	No date limits

For the rapid reviews, the MEDLINE search strategy was adapted to perform efficiently in Embase and the Cochrane Library, the minimum databases recommended in the PHE search methods guidance [37].

For the systematic review for key question 1 the following additional databases were searched:

- Maternity and Infant Care (Ovid);
- HMIC;
- Science Citation Index;
- ClinicalTrials.gov;
- ICTRP;
- Web pages of key healthcare organisations and health technology assessment agencies;
- Google searches limited to NHS and government sites using the site limit;
- Citation searches of eligible studies.

The reference lists of any included studies and relevant systematic reviews were checked for any eligible studies that might have been missed by the database searches for both rapid and systematic reviews.

Search Terms

The literature search aimed to identify the relevant published and unpublished studies on chlamydia screening in pregnancy.

The strategy has two concept groups:

- Chlamydia (search lines 1 – 4);
- Pregnancy or infants or selected outcomes that might have been missed despite the pregnancy and infants terms (search lines 6 – 30).

Reflecting PHE search methods guidance, animal studies were excluded from MEDLINE using a standard algorithm (search line 33) and case reports were excluded (search line 35). The strategy also excluded other publication types which are unlikely to yield relevant study reports: editorials, news items, comments and letters (search line 35). No date limits were applied so that the search could serve for both the systematic review and the rapid reviews. An English language limit was applied.

Table 1.2: Search strategy for Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present> (URL/Interface: OvidSP)
Records retrieved: 3024

Set	Search terms (number of records)
1	Chlamydia/ (2719)
2	Chlamydia trachomatis/ (11262)
3	Chlamydia Infections/ (14607)
4	chlamydia$.ti,ab,kf. (25702)
5	or/1-4 (28931)
6	Pregnancy/ (813112)
7	exp Pregnancy outcome/ (49607)
8	Pregnancy complications/ (84616)
9	Pregnancy complications, infectious/ (34504)
10	Prenatal care/ (23828)
11	exp Infant, newborn/ (560299)
12	(pregnanc$ or pregnant or gestat$ or newborn$ or neonate$ or neonatal or ante-natal or pre-natal or antenatal or prenatal or infant$1 or infancy or baby or babies).ti,ab,kf. (1124384)
13	(miscarriage$1 or miscarry or miscarried or spontaneous abortion$1).ti,ab,kf. (20408)
14	Abortion, Spontaneous/ (18586)
15	exp Obstetric Labor, Premature/ (22532)
16	exp fetal membranes, premature rupture/ (6627)
17	(preterm birth$1 or premature).ti,ab,kf. (117602)
18	(premature$ adj4 rupture$).ti,ab,kf. (5474)
19	(membrane$1 adj4 rupture$).ti,ab,kf. (10716)
20	fetal growth retardation/ (14740) exp
21	((fetal or foetal or intrauterine) adj3 growth).ti,ab,kf. (25779)
22	(small adj4 gestational age).ti,ab,kf. (8632)
23	low birth weight.ti,ab,kf. (23971)
24	underweight.ti,ab,kf. (8288)
25	(congenital adj4 abnormalit$).ti,ab,kf. (9929)
26	exp congenital abnormalities/ (543270)
27	(microbiome adj4 develop$).ti,ab,kf. (334)
28	in utero.ti,ab,kf. (24590)
29	exp microbiota/ (11724)
30	microbiota.ti,ab,kf. (22487)
31	or/6-30 (2136152)
32	5 and 31 (4715)
33	exp animals/ not humans/ (4386446)
34	32 not 33 (4228)
35	(news or comment or editorial or letter or case reports).pt. or case report.ti. (3469022)
36	34 not 35 (3815)
37	limit 36 to english language (3125)
38	remove duplicates from 37 (3024)

Table 1.3: Search Strategy for Embase <1974 to 2017 April 17> (URL/Interface: OvidSP) Search date: 18 April 2017 Records retrieved: 4355

Set	Search terms (number of records)
1	Chlamydia/ (9024)
2	Chlamydia trachomatis/ (17752)
3	chlamydiasis/ (15140)
4	chlamydia$.ti,ab,kw. (30916)
5	or/1-4 (38056)
6	Pregnancy/ (687096)
7	pregnancy outcome/ (48778)
8	pregnancy complication/ (73201)
9	Pregnancy complications, infectious/ (46185)
10	Prenatal care/ (34757)
11	newborn/ (552742)
12	(pregnanc$ or pregnant or gestat$ or newborn$ or neonate$ or neonatal or ante-natal or pre-natal or antenatal or prenatal or infant$1 or infancy or baby or babies).ti,ab,kw. (1289609)
13	(miscarriage$1 or miscarry or miscarried or spontaneous abortion$1).ti,ab,kw. (29939)
14	spontaneous abortion/ (37351)
15	exp premature labor/ (42290)
16	premature fetus membrane rupture/ (8154)
17	(preterm birth$1 or premature).ti,ab,kw. (150553)
18	(premature$ adj4 rupture$).ti,ab,kw. (7372)
19	(membrane$1 adj4 rupture$).ti,ab,kw. (13874)
20	exp intrauterine growth retardation/ (36018)
21	((fetal or foetal or intrauterine) adj3 growth).ti,ab,kw. (35258)
22	(small adj4 gestational age).ti,ab,kw. (11503)
23	low birth weight.ti,ab,kw. (30414)
24	underweight.ti,ab,kw. (11885)
25	(congenital adj4 abnormalit$).ti,ab,kw. (12641)
26	exp congenital disorder/ (1234247)
27	(microbiome adj4 develop$).ti,ab,kw. (441)
28	in utero.ti,ab,kw. (30966)
29	exp microflora/ (82606)
30	microbiota.ti,ab,kw. (28618)
31	or/6-30 (2844357)
32	5 and 31 (6152)
33	(animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/ (5466470)
34	32 not 33 (5698)
35	(conference abstract or conference paper or conference proceeding or conference review or editorial or letter).pt. or case report.ti. (1767720)
36	34 not 35 (5421)
37	limit 36 to english language (4500)
38	remove duplicates from 37 (4355)

Table 1.4: Search Strategy for Maternity & Infant Care Database (MIDIRS) <1971 to March 2017> (URL/Interface: OvidSP) Records retrieved: 443

Set	search terms (number of records)
1	chlamydia$.af. (493)
2	(pregnanc$ or pregnant or gestat$ or newborn$ or neonate$ or neonatal or ante-natal or pre-natal or antenatal or prenatal or infant$1 or infancy or baby or babies).af. (182349)
3	(miscarriage$1 or miscarry or miscarried or spontaneous abortion$1).af. (5551)
4	(preterm birth$1 or premature).af. (23284)
5	(premature$ adj4 rupture$).af. (2399)
6	(membrane$1 adj4 rupture$).af. (3535)
7	((fetal or foetal or intrauterine) adj3 growth).af. (7366)
8	(small adj4 gestational age).af. (3752)
9	low birth weight.af. (11804)
10	underweight.af. (574)
11	(congenital adj4 abnormalit$).af. (1066)
12	(microbiome adj4 develop$).af. (15)
13	in utero.af. (2824)
14	(microbiota or microflora).af. (300)
15	or/2-14 (183544)
16	1 and 15 (445)
17	(news or comment or editorial or letter or case reports).pt. or case report.ti. (4680)
18	16 not 17 (444)
19	remove duplicates from 18 (443)

Table 1.5: Search Strategy for HMIC Health Management Information Consortium <1979 to January 2017> (URL/Interface: OvidSP) Records retrieved: 63

Set	search terms (number of records)
1	chlamydia$.af. (358)
2	(pregnanc$ or pregnant or gestat$ or newborn$ or neonate$ or neonatal or ante-natal or pre-natal or antenatal or prenatal or infant$1 or infancy or baby or babies).af. (11811)
3	(miscarriage$1 or miscarry or miscarried or spontaneous abortion$1).af. (316)
4	(preterm birth$1 or premature).af. (1245)
5	(premature$ adj4 rupture$).af. (11)
6	(membrane$1 adj4 rupture$).af. (47)
7	((fetal or foetal or intrauterine) adj3 growth).af. (108)
8	(small adj4 gestational age).af. (102)
9	low birth weight.af. (400)
10	underweight.af. (164)
11	(congenital adj4 abnormalit$).af. (98)
12	(microbiome adj4 develop$).af. (0)
13	in utero.af. (165)
14	(microbiota or microflora).af. (23)
15	or/2-14 (12881)
16	1 and 15 (63)
17	remove duplicates from 16 (63)

Table 1.6: Search Strategy for Cochrane Database of Systematic Reviews (Issue 4 of 12, April 2017) (URL/Interface: Cochrane Library, Wiley) Records retrieved: 6

Set	search terms (number of results)
#1	[mh ^Chlamydia] 33
#2	[mh ^"Chlamydia trachomatis"] 372
#3	[mh ^"Chlamydia Infections"] 517
#4	chlamydia*:ti,ab,kw 1413
#5	{or #1-#4} 1413
#6	[mh ^Pregnancy] 60
#7	[mh "Pregnancy outcome"] 3156
#8	[mh ^"Pregnancy complications"] 1458
#9	[mh ^"Pregnancy complications, infectious"] 928
#10	[mh ^"Prenatal care"] 1288
#11	[mh "Infant, newborn"] 14959
#12	(pregnanc* or pregnant or gestat* or newborn* or neonate* or neonatal or ante-natal or pre-natal or antenatal or prenatal or infant* or infancy or baby or babies):ti,ab,kw 77676
#13	(miscarriage* or miscarry or miscarried or spontaneous next abortion*):ti,ab,kw 1481
#14	[mh ^"Abortion, Spontaneous"] 400
#15	[mh "Obstetric Labor, Premature"] 1286
#16	[mh "fetal membranes, premature rupture"] 410
#17	(preterm next birth* or premature):ti,ab,kw 11883
#18	(premature* near/4 rupture*):ti,ab,kw 713
#19	(membrane* near/4 rupture*):ti,ab,kw 1126
#20	[mh ^"fetal growth retardation"] 298
#21	((fetal or foetal or intrauterine) near/3 growth):ti,ab,kw 973
#22	(small near/4 gestational next age):ti,ab,kw 646
#23	"low birth weight":ti,ab,kw 3692
#24	underweight:ti,ab,kw 446
#25	(congenital near/4 abnormalit*):ti,ab,kw 254
#26	[mh "congenital abnormalities"] 4504
#27	(microbiome near/4 develop*):ti,ab,kw 7
#28	"in utero":ti,ab,kw 406
#29	[mh microbiota] 172
#30	microbiota:ti,ab,kw 1142
#31	[39-#30] 85240
#32	#5 and #31 in Cochrane Reviews (Reviews and Protocols) 6

Table 1.7: Search Strategy for Health Technology Assessment Database (Issue 4 of 4, October 2016) (URL/Interface: Cochrane Library, Wiley) Records retrieved: 4

Set	Search terms (number of records)
#1	[mh ^Chlamydia] 33
#2	[mh ^"Chlamydia trachomatis"] 372
#3	[mh ^"Chlamydia Infections"] 517
#4	chlamydia* 1566
#5	{or #1-#4} 1566
#6	[mh ^Pregnancy] 60
#7	[mh "Pregnancy outcome"] 3156
#8	[mh ^"Pregnancy complications"] 1458
#9	[mh ^"Pregnancy complications, infectious"] 928
#10	[mh ^"Prenatal care"] 1288
#11	[mh "Infant, newborn"] 14959
#12	(pregnanc* or pregnant or gestat* or newborn* or neonate* or neonatal or ante-natal or pre-natal or antenatal or prenatal or infant* or infancy or baby or babies) 83947
#13	(miscarriage* or miscarry or miscarried or spontaneous next abortion*) 1939
#14	[mh ^"Abortion, Spontaneous"] 400
#15	[mh "Obstetric Labor, Premature"] 1286
#16	[mh "fetal membranes, premature rupture"] 410
#17	(preterm next birth* or premature) 13322
#18	(premature* near/4 rupture*) 851
#19	(membrane* near/4 rupture*) 1463
#20	[mh ^"fetal growth retardation"] 298
#21	((fetal or foetal or intrauterine) near/3 growth) 1301
#22	(small near/4 gestational next age) 888
#23	"low birth weight" 4091
#24	underweight 563
#25	(congenital near/4 abnormalit*) 606
#26	[mh "congenital abnormalities"] 4504
#27	(microbiome near/4 develop*) 7
#28	"in utero" 631
#29	[mh microbiota] 172
#30	microbiota 1206
#31	[39-#30] 91892
#32	#5 and #31 in Technology Assessments 4

Table 1.8: Search Strategy for Database of Abstracts of Reviews of Effect (DARE): Issue 2 of 4, April 2015 (URL/Interface: Cochrane Library, Wiley) Records retrieved: 15

Set	search terms (number of records)
#1	[mh ^Chlamydia] 33
#2	[mh ^"Chlamydia trachomatis"] 372
#3	[mh ^"Chlamydia Infections"] 517
#4	chlamydia* 1566
#5	{or #1-#4} 1566
#6	[mh ^Pregnancy] 60
#7	[mh "Pregnancy outcome"] 3156
#8	[mh ^"Pregnancy complications"] 1458
#9	[mh ^"Pregnancy complications, infectious"] 928
#10	[mh ^"Prenatal care"] 1288
#11	[mh "Infant, newborn"] 14959
#12	(pregnanc* or pregnant or gestat* or newborn* or neonate* or neonatal or ante-natal or pre-natal or antenatal or prenatal or infant* or infancy or baby or babies) 83947
#13	(miscarriage* or miscarry or miscarried or spontaneous next abortion*) 1939
#14	[mh ^"Abortion, Spontaneous"] 400
#15	[mh "Obstetric Labor, Premature"] 1286
#16	[mh "fetal membranes, premature rupture"] 410
#17	(preterm next birth* or premature) 13322
#18	(premature* near/4 rupture*) 851
#19	(membrane* near/4 rupture*) 1463
#20	[mh ^"fetal growth retardation"] 298
#21	((fetal or foetal or intrauterine) near/3 growth) 1301
#22	(small near/4 gestational next age) 888
#23	"low birth weight" 4091
#24	underweight 563
#25	(congenital near/4 abnormalit*) 606
#26	[mh "congenital abnormalities"] 4504
#27	(microbiome near/4 develop*) 7
#28	"in utero" 631
#29	[mh microbiota] 172
#30	microbiota 1206
#31	[39-#30] 91892
#32	#5 and #31 in Other Reviews 15

Table 1.9: Search Strategy for Cochrane Central Register of Controlled Trials: Issue 3 of 12, March 2017 (URL/Interface: Cochrane Library, Wiley) Records retrieved: 227

Set	search terms (number of records)
#1	[mh ^Chlamydia] 33
#2	[mh ^"Chlamydia trachomatis"] 372
#3	[mh ^"Chlamydia Infections"] 517
#4	chlamydia* 1566
#5	{or #1-#4} 1566
#6	[mh ^Pregnancy] 60
#7	[mh "Pregnancy outcome"] 3156
#8	[mh ^"Pregnancy complications"] 1458
#9	[mh ^"Pregnancy complications, infectious"] 928
#10	[mh ^"Prenatal care"] 1288
#11	[mh "Infant, newborn"] 14959
#12	(pregnanc* or pregnant or gestat* or newborn* or neonate* or neonatal or ante-natal or pre-natal or antenatal or prenatal or infant* or infancy or baby or babies) 83947
#13	(miscarriage* or miscarry or miscarried or spontaneous next abortion*) 1939
#14	[mh ^"Abortion, Spontaneous"] 400
#15	[mh "Obstetric Labor, Premature"] 1286
#16	[mh "fetal membranes, premature rupture"] 410
#17	(preterm next birth* or premature) 13322
#18	(premature* near/4 rupture*) 851
#19	(membrane* near/4 rupture*) 1463
#20	[mh ^"fetal growth retardation"] 298
#21	((fetal or foetal or intrauterine) near/3 growth) 1301
#22	(small near/4 gestational next age) 888
#23	"low birth weight" 4091
#24	underweight 563
#25	(congenital near/4 abnormalit*) 606
#26	[mh "congenital abnormalities"] 4504
#27	(microbiome near/4 develop*) 7
#28	"in utero" 631
#29	[mh microbiota] 172
#30	microbiota 1206
#31	[39-#30] 91892
#32	#5 and #31 in Trials 227

Table 1.10: Search Strategy for NHS Economic Evaluation Database: Issue 2 of 4, April 2015 (URL/Interface: Cochrane Library, Wiley)
Records retrieved: 57

Set	search terms (number of records)
#1	[mh ^Chlamydia] 33
#2	[mh ^"Chlamydia trachomatis"] 372
#3	[mh ^"Chlamydia Infections"] 517
#4	chlamydia* 1566
#5	{or #1-#4} 1566
#6	[mh ^Pregnancy] 60
#7	[mh "Pregnancy outcome"] 3156
#8	[mh ^"Pregnancy complications"] 1458
#9	[mh ^"Pregnancy complications, infectious"] 928
#10	[mh ^"Prenatal care"] 1288
#11	[mh "Infant, newborn"] 14959
#12	(pregnanc* or pregnant or gestat* or newborn* or neonate* or neonatal or ante-natal or pre-natal or antenatal or prenatal or infant* or infancy or baby or babies) 83947
#13	(miscarriage* or miscarry or miscarried or spontaneous next abortion*) 1939
#14	[mh ^"Abortion, Spontaneous"] 400
#15	[mh "Obstetric Labor, Premature"] 1286
#16	[mh "fetal membranes, premature rupture"] 410
#17	(preterm next birth* or premature) 13322
#18	(premature* near/4 rupture*) 851
#19	(membrane* near/4 rupture*) 1463
#20	[mh ^"fetal growth retardation"] 298
#21	((fetal or foetal or intrauterine) near/3 growth) 1301
#22	(small near/4 gestational next age) 888
#23	"low birth weight" 4091
#24	underweight 563
#25	(congenital near/4 abnormalit*) 606
#26	[mh "congenital abnormalities"] 4504
#27	(microbiome near/4 develop*) 7
#28	"in utero" 631
#29	[mh microbiota] 172
#30	microbiota 1206
#31	[39-#30] 91892
#32	#5 and #31 in Economic Evaluations 57

Table 1.11: Search Strategy for Science Citation Index Expanded (SCI-EXPANDED, 1900-present, Data last updated: 2017-04-18) (URL/Interface: Web of Science)
Records retrieved: 2624

Set	Number of records	Search terms	Limits
# 21	2,624	(#1 AND #19) AND LANGUAGE: (English)	Refined by: [excluding] DOCUMENT TYPES: (NEWS ITEM OR LETTER OR EDITORIAL MATERIAL)
# 20	2,766	(#1 AND #19) AND LANGUAGE: (English)	
# 19	1,047,882	#18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2	
# 18	29,323	TS="microbiota"	
# 17	23,894	TS=”in utero”	
# 16	347	TS=("microbiome" NEAR/4 develop*)	
# 15	7,102	TS=("congenital" NEAR/4 abnormalit*)	
# 14	6,303	TS=”underweight”	
# 13	28,408	TS=”low birth weight”	
# 12	7,506	TS=("small" NEAR/4 "gestational age")	
# 11	30,874	TS=((“fetal” OR “foetal” OR “intrauterine”) NEAR/3 “growth”)	
# 10	8,130	TS= (membrane$ NEAR/4 rupture$)	
# 9	5,315	TS=(premature$ NEAR/4 rupture$)	
# 8	112,255	TS=(“preterm birth$” OR “premature”)	
# 7	18,801	TS=(miscarriage$ OR “miscarry” OR “miscarried” OR “spontaneous abortion$”)	
# 6	920,558	TS=(pregnanc$ OR "pregnant" OR gestat$ OR newborn$ OR neonate$ OR "neonatal" OR "ante-natal" OR "pre-natal" OR "antenatal" OR "prenatal" OR infant$ OR "infancy" OR "baby" OR "babies")	
# 5	5,596	TS=”Prenatal care”	
# 4	5,183	TS="Pregnancy complication*"	
# 3	10,082	TS=”Pregnancy outcome”	
# 2	304,333	TS=”Pregnancy”	
# 1	27,924	TS=chlamydia*	

Table 1.12: Search Strategy for ClinicalTrials.gov (URL: www.clinicaltrials.gov/ct)
Records retrieved: 29

Advanced search screen was used. Terms were entered into the "Search Terms:" box. It is not possible to use wildcards. The database maps terms to other relevant words and phrases, adding them to the search. Search terms: chlamydia AND pregnancy

Table 1.13: Search Strategy for WHO International Clinical Trials Registry Platform (ICTRP) (URL: http://www.who.int/ictrp/en/)
Records retrieved: 7 records for 7 trials

Search terms: chlamydia* AND pregnan*

Table 1.14: Search Strategy for National Institute for Health and Care Excellence (NICE) (URL: www.nice.org.uk)
Records retrieved: 2

Search terms were entered into the search box on the initial screen. Results were screened by an information specialist for inclusion. Search terms: chlamydia pregnancy

Table 1.15: Search Strategy for Canadian Agency for Drugs and Technologies in Health (CADTH) (URL: https://www.cadth.ca/)
Records retrieved: no records retrieved

Search terms were entered into the search box on the initial screen. Results were screened by an information specialist for inclusion. Search terms: chlamydia pregnancy

Table 1.16: Search Strategy for Agency for Healthcare Research and Quality (ARHQ) (URL: https://www.ahrq.gov/)
Records retrieved: 2

Search terms were entered into the search box at "Search research & data" section. Results were screened by an information specialist for inclusion. Search terms: chlamydia pregnancy

Table 1.17: Search Strategy for National Services Division (URL: http://www.nsd.scot.nhs.uk/services/screening/)
Records retrieved: no records retrieved

Search terms were entered into the search box. Results were screened by an information specialist for inclusion. Search terms: chlamydia pregnancy

Table 1.18: Search Strategy for Wales Screening Committee (URL: http://gov.wales/topics/health/professionals/committees/screening/?lang=en and http://www.antenatalscreening.wales.nhs.uk/professional/home)
Records retrieved: no records retrieved

The web pages were browsed for relevant documents. Search terms were entered into the search box and results were screened by an information specialist for inclusion. Search terms: chlamydia pregnancy

Table 1.19: Search Strategy for Public Health Agency (URL: http://www.publichealth.hscni.net/directorate-public-health/service-development-and-screening/screening)
Records retrieved: no records retrieved

The web pages were browsed for relevant documents. Search terms were entered into the search box and results were screened by an information specialist for inclusion. Search terms: chlamydia pregnancy

Table 1.20: Search Strategy for Royal College of Obstetricians and Gynaecologists (URL: https://www.rcog.org.uk/)
Records retrieved: 1

RCOG guidelines were searched (Guidelines & Research services → Guidelines) by entering the search terms into the “By keyword” search box. Results were screened by an information specialist for inclusion. Search terms were entered into the search box on the initial screen. Results were screened by an information specialist for inclusion. Search terms: chlamydia pregnancy

Table 1.21: Search Strategy for British Association for Sexual Health and HIV
(URL: https://www.bashh.org/)
Records retrieved: no records retrieved

Search terms were entered into the search box on the initial screen. Results were screened by an information specialist for inclusion.

BASHH guidelines were searched (BASHH Guidelines → Search) by entering the search terms into the search box. Results were screened by an information specialist for inclusion.

Search terms:
chlamydia pregnancy

Table 1.22: Search Strategy for Royal College of Midwives
(URL: https://www.rcm.org.uk/)
Records retrieved: no records retrieved

Search terms were entered into the search box on the initial screen. Results were screened by an information specialist for inclusion.

Search terms:
chlamydia pregnancy

Table 1.23: Search Strategy for National Health Service websites via Google
Records retrieved: no records retrieved

Search terms were entered into the Google search box and a site limit option was used. Results were screened by an information specialist for inclusion.

Search terms:
site:www.nhs.uk chlamydia pregnancy screening

Table 1.24: Search Strategy for Government sites via Google
Records retrieved: 1

Search terms were entered into the Google search box and a site limit option was used. Results were screened by an information specialist for inclusion.

Search terms:
site:https://www.gov.uk chlamydia pregnancy screening

Appendix 2 – Methods

Eligibility for Inclusion in the Review

Population

Studies assessing pregnant women with confirmed chlamydia infection, or newborns born to mothers with confirmed chlamydia infection were eligible for inclusion. Women with *C. trachomatis* only were eligible; studies reporting *C. pneumoniae* and *C. psittaci* were excluded.

Studies of women with confirmed chlamydia who were not pregnant and newborns born to mothers without confirmed chlamydia infection were excluded. Studies of women with confirmed concurrent chlamydia and gonorrhoea infections were excluded, as well as studies of women with HIV.

Intervention

Studies reporting the following interventions were eligible for inclusion:

- Screening strategies using nucleic acid amplification test (NAAT);
- Antibiotic treatment strategies.

Comparators

Eligible comparator populations included:

- Pregnant women without confirmed chlamydia;
- Newborns without symptomatic infection.

Eligible comparator interventions included:

- No screening;
- No antibiotic treatment;
- Placebo.

Outcomes

Eligible maternal outcomes included:

- Miscarriage (defined as pregnancy loss before 24 weeks gestation)[3];
- Stillbirth (defined as pregnancy loss after 24 weeks gestation);
- Preterm birth;
- Premature rupture of the membrane;
- Intrauterine growth restriction;
- Small for gestational age / low birth weight;
- Pre-eclampsia;
- Reinfection rates.

Because outcomes were not limited to a specific time point during pregnancy (for example, chlamydia in early pregnancy) the distinction between miscarriage and stillbirth was necessary. The NHS defines stillbirth as occurring after 24 completed weeks of pregnancy and miscarriage as occurring before 24 completed weeks. In other countries it is different, for example, the USA considers before 20 weeks a miscarriage and after 20 weeks a stillbirth. This review follows the NHS definition.

Studies of women with ectopic pregnancy were not eligible.

Eligible neonatal outcomes included:

- Conjunctivitis;
- Pneumonia;
- Respiratory tract infections;
- Ear infections;
- Congenital abnormalities;
- Infant microbiome development;
- Persistent wheezing or asthma;
- Development of allergy in early infancy;
- Long term adverse outcome from in utero antimicrobial treatment.

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[3] We understand that clinicians use the term ‘abortion’ and ‘miscarriage’ synonymously. We have used the term ‘miscarriage’ throughout this report.

Study Design

We took a pragmatic approach to the inclusion of studies by their design. Well conducted systematic reviews and/or randomised controlled trials (RCTs) were prioritised over prospective and retrospective comparative observational studies (cohorts and case-control studies).

Systematic reviews were eligible for inclusion in the rapid reviews and were defined as reviews with the following characteristics:

- A stated and clear research question;
- A statement of the eligibility criteria which have guided the selection of studies for the systematic review, including a statement about eligible study designs;
- Indications of an extensive search for relevant studies, i.e. searches beyond MEDLINE. Searches beyond MEDLINE could include searches of additional databases, reference checking, web searches, and hand-searching;
- A description of study selection methods;
- A synthesis of the included studies, either narrative or statistical;
- A list or table of included studies.

Non-systematic reviews, non-comparative observational studies (cross-sectional studies, case series studies), case reports and editorials were not eligible for any of the reviews.

Limits

The search included in the most recent UK review of this topic was conducted in 2009. For the four rapid reviews studies published from 2009 until the present were eligible. For the systematic review no date limit was applied.

Only English language studies were eligible for inclusion in the reviews.

Studies conducted in the UK were prioritised, but studies conducted in Western countries analogous to the UK were also eligible. Western countries, and those analogous to the UK, included countries of Western Europe, Central Europe (Hungary, Poland, Slovakia, the Czech Republic, and Slovenia), North America, Australia and New Zealand.

Inclusion and exclusion criteria for the key questions

Table 16. Key question one – systematic review

Question 1	**What is the impact of untreated chlamydial infection, during pregnancy, on pregnancy outcomes in the UK?**
Criterion	**Inclusion criteria**
Population and subgroups	Women with untreated chlamydia infection during pregnancy. Subgroup by infection and reinfection; Subgroup by gestational age.
Comparator	Women with chlamydia during pregnancy who are treated. Women without chlamydia during pregnancy.
Outcomes	Miscarriage; Stillbirth Preterm birth; Premature rupture of the membrane; Intrauterine growth restriction; Small for gestational age / low birth weight; Pre-eclampsia; Reinfection rates.
Study design	Systematic reviews (will be included only for reference checking to identify studies which may have been missed by the searches); RCTs; Prospective and retrospective comparative observational studies (cohorts and case-control studies).
Geographic focus	UK. Western countries analogous to the UK.
Date focus	No date limit
Other limits	English language only. Where studies did not report sufficient data to confirm whether women were treated or untreated, the study was excluded.

Table 17. Key question two – rapid review

Question 2	**What is the impact on neonatal outcomes, of untreated chlamydial infection in pregnancy in the UK?**
Criterion	**Inclusion criteria**
Population and subgroups	Women with untreated chlamydia infection during pregnancy and newborns with symptomatic chlamydia infection: Subgroup by infection and reinfection; Subgroup by gestational age.
Comparison Population	Women with chlamydia infection during pregnancy who are treated. Women without chlamydia infection during pregnancy.
Outcomes	Conjunctivitis; Pneumonia; Respiratory tract infections; Ear infections.
Study design	Systematic reviews (SR); RCTs; Prospective and retrospective comparative observational studies (cohorts and case-control studies).
Geographic focus	UK. Western countries analogous to the UK.
Date focus	Studies published since January 2009
Other limits	English language only. SRs that score moderately to highly on the AMSTAR checklist will be reported in the rapid review; SRs scoring poorly on AMSTAR will not be reported, instead their primary studies will be assessed.

Table 18. Key question three – rapid review

Question 3	**What is the optimal screening strategy for chlamydia infection in pregnancy to avoid adverse pregnancy outcomes?**
Criterion	Inclusion criteria
Additional questions	What is the best time to carry out the screening test? What is the best strategy for test of cure following treatment?
Population	Women with chlamydia during pregnancy Subgroup by trimester.
Intervention	Screening strategies using NAATs followed by antibiotic treatment of the mother.
Comparators	No screening; No screening/treatment; Screening and placebo treatment.
Outcomes	Change (reduction) in rates of adverse outcomes: Miscarriage; Preterm birth; Premature rupture of the membrane; Intrauterine growth restriction; Small for gestational age / low birth weight; Pre-eclampsia.
Study design	Systematic reviews. RCTs; Prospective and retrospective comparative observational studies if RCTs are not available.
Geographic focus	UK Western countries or regions within Western countries analogous to the UK.
Date focus	Studies published since January 2009
Other limits	English language only. SRs that score moderately to highly on the AMSTAR checklist will be reported in the rapid review; SRs scoring poorly on AMSTAR will not be reported, instead their primary studies will be assessed.

Table 19. Key question four – rapid review

Question 4	**Are there any known side effects from antibiotic treatment of chlamydial infection during pregnancy on the newborn?**
Criterion	**Inclusion criteria**
Population and subgroups	Newborn babies of women with confirmed chlamydia infection (using NAATs) in pregnancy. • Subgroup of newborns by gestational age.
Intervention	Antibiotic treatment licensed for use in pregnancy in the UK.
Comparator	• No treatment; • Other antibiotic treatment; • Placebo.
Outcomes	• Congenital abnormalities; • Infant microbiome development; • Persistent wheezing or asthma; • Development of allergy in early infancy; • Long term adverse outcome from in utero antimicrobial treatment.
Study design	• Systematic reviews; • RCTs; • Prospective and retrospective comparative observational studies included if RCTs not available.
Geographic focus	UK. Western countries or regions within Western countries analogous to the UK.
Date focus	Studies published since January 2009
Other limits	English language only. SRs that score moderately to highly on the AMSTAR checklist will be reported in the rapid review; SRs scoring poorly on AMSTAR will not be reported, instead their primary studies will be assessed.

Table 20. Key question five – rapid review

Question 5	**What is the optimal screening strategy for chlamydia infection in pregnancy to avoid adverse neonatal outcomes?**
Criterion	**Inclusion criteria**
Additional Questions	What is the best timing for the test? What is the best strategy for test of cure following treatment?
Population	Pregnant women with chlamydia • Subgroup by trimester.
Intervention	Screening strategies using NAATs and consequent antibiotic treatment of the mother.
Comparator	• No screening; • No screening/treatment; • Screening and placebo.
Outcomes	Adverse neonatal outcomes • Conjunctivitis; • Pneumonia; • Respiratory tract infections; • Ear infections.
Study design	• Systematic reviews; • RCTs; • Prospective and retrospective observational studies (cohort studies and case-control studies).
Geographic focus	UK Western countries or regions within Western countries analogous to the UK.
Date focus	Studies published since January 2009
Other limits	English language only. SRs that score moderately to highly on the AMSTAR checklist will be reported in the rapid review; SRs scoring poorly on AMSTAR will not be reported, instead their primary studies will be assessed.

Study Selection

The search results were loaded into bibliographic software (EndNote) [40]. The results were deduplicated using several algorithms.

We rapidly assessed the search results according to their relevance in providing information on the five key questions. The eligibility criteria for each question are presented in Tables 1 to 5 in this appendix. We removed the obviously irrelevant records, such as animal studies, commentaries and news items, and records on issues unrelated to the topic of interest. The number of records included and removed at each stage is reported in Appendix 3.

The systematic review was conducted using double independent reviewer selection with disagreements mediated by a third reviewer. The rapid reviews were based on a single reviewer selecting studies.

We obtained electronic or paper copies of potentially relevant full papers meeting the reviews' eligibility criteria and assessed them in detail for relevance to the reviews' eligibility criteria. Studies excluded at this stage are listed in the excluded studies table in Appendix 3 with reasons for exclusion.

The eligibility criteria were assessed in the following order so that the first 'no' response was used as the primary reason for exclusion of the study and the remaining criteria were not assessed:

- Study design;
- Population;
- Intervention/comparator;
- Outcomes.

Where results for one study were reported in more than one document, all related documents were identified and grouped together to ensure that participants in individual studies were only included once. Details of these papers and the included studies to which they relate can be found in Table 9.

Data Extraction

Two reviewers independently extracted data from each of the included studies for the systematic review. A single reviewer would have extracted data for documents for the rapid reviews, with a second reviewer checking the data. Any discrepancies were resolved through discussion or by consulting a third reviewer.

Information on the following elements was extracted:

- Bibliographic data (i.e. publication identification, author and year of publication);
- Country/countries in which study was conducted;
- Study objectives;
- Study design;
- Patient characteristics (e.g. age, gestation, sample type taken);
- Details of prior and concomitant therapy;
- Treatment;
- Type;
- Scheduling;
- Dosage;
- Inclusion criteria;
- Exclusion criteria;
- Follow-up duration;
- Outcomes;
- Quality assessment.

A data extraction sheet was developed as an Excel spreadsheet. Because all included studies were conducted more than 20 years ago, we did not attempt to write to study authors where key data were not identifiable in a paper or where we identified discrepancies.

Appraisal of Quality/Risk of Bias Tool

Two reviewers independently extracted data for quality assessment from each of the included studies for the systematic review. A single reviewer would have extracted quality assessment information from documents for the rapid reviews, with a second reviewer checking the information. Any discrepancies were resolved through discussion or by consulting a third reviewer.

Table 21 details the risk of bias assessment tools used for each type of study design. Risk of bias was discussed according to study design.

Table 21. Risk of bias assessment tools

Study design	Tool
Systematic reviews	AMSTAR [41]
RCTs	Cochrane Risk of Bias tool [42]
Case control studies	CRD Case Control Checklist [43]
Cohort studies	CRD Cohort Study Checklist [43]

Databases/Sources Searched

Table 22. Summary of electronic database searches and dates

Database	Platform	Searched on date	Date range of search
Medline	OvidSP	18 April 2017	1946 to 18 April 2017
Embase	OvidSP	18 April 2017	1974 to April 17 2017
Maternity & Infant Care Database (MIDIRS)	OvidSP	18 April 2017	1971 to March 2017
HMIC Health Management Information Consortium	OvidSP	18 April 2017	1979 to January 2017
Cochrane Database of Systematic Reviews	Cochrane Library, Wiley	18 April 2017	All content in Issue 4 (April 2017)
Health Technology Assessment HTA	Cochrane Library, Wiley	18 April 2017	All content in Issue 4 (October 2016)
Database of Abstracts of Reviews of Effects DARE	Cochrane Library, Wiley	18 April 2017	All content in Issue 2 (April 2015)
Cochrane Central Register of Controlled Trials	Cochrane Library, Wiley	18 April 2017	All content in Issue 3 (March 2017)
NHS Economic Evaluations Database NHS EED	Cochrane Library, Wiley	18 April 2017	All content in Issue 2 (April 2015)
Science Citation Index Expanded	Web of Science	19 April 2017	1900 to 18 April 2017
ClinicalTrials.gov	https://www.clinicaltrials.gov/ct	19 April 2017	All content on 19 April 2017
WHO International Clinical Trials Registry Platform (WHO ICTRP)	http://www.who.int/ictrp/en/	19 April 2017	All content on 19 April 2017
National Institute for Health and Care Excellence (NICE) website	www.nice.org.uk	19 April 2017	All content on 19 April 2017
Canadian Agency for Drugs and Technologies in Health (CADTH) website	https://www.cadth.ca/	19 April 2017	All content on 19 April 2017

Agency for Healthcare Research and Quality (ARHQ) website	https://www.ahrq.gov/	19 April 2017	All content on 19 April 2017
National Services Division website	http://www.nsd.scot.nhs.uk/services/screening/	19 April 2017	All content on 19 April 2017
Wales Screening Committee website	http://gov.wales/topics/health/professionals/committees/screening/?lang=en	19 April 2017	All content on 19 April 2017
Public Health Agency website	http://www.publichealth.hscni.net/directorate-public-health/service-development-and-screening/screening	19 April 2017	All content on 19 April 2017
Royal College of Obstetricians and Gynaecologists website	https://www.rcog.org.uk/	19 April 2017	All content on 19 April 2017
British Association for Sexual Health and HIV website	https://www.bashh.org/	19 April 2017	All content on 19 April 2017
Royal College of Midwives website	https://www.rcm.org.uk/	19 April 2017	All content on 19 April 2017
National Health Service websites	via Google	20 April 2017	No date limits
Government websites	via Google	20 April 2017	No date limits

Question Level Synthesis

For the systematic review (key question one), the studies are summarised in tables providing data on their methods and results. We assessed the similarity of studies and availability of data, but studies were not similar enough to pool in a meta-analysis.

No studies met the eligibility criteria for the rapid reviews.

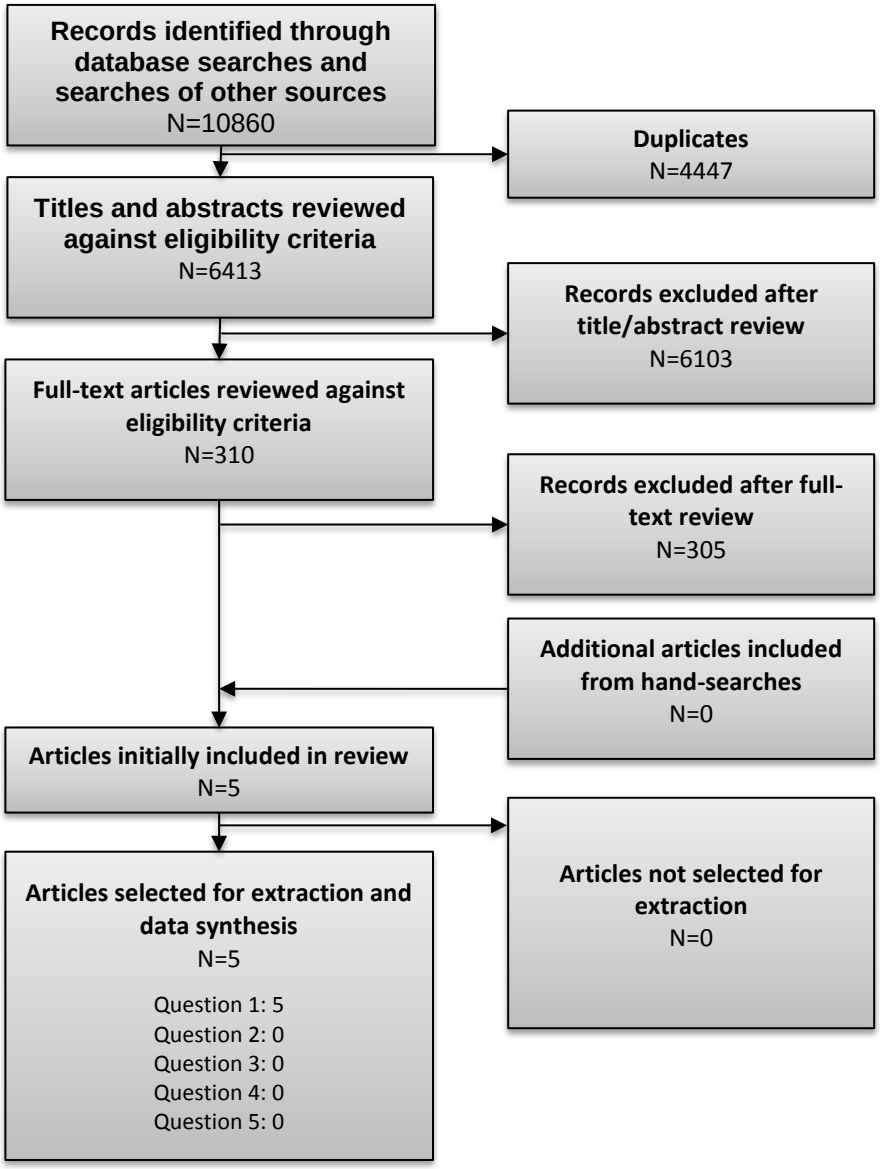
An overall assessment of the strength of the research evidence in relation to each research question is provided (Summary of findings section). The analysis was conducted by one reviewer and checked by a second reviewer.

Appendix 3 – Included and Excluded Studies

PRISMA Flowchart

Figure 3.1 summarises the volume of publications included and excluded at each stage of the review. Five publications were ultimately judged to be relevant to one or more review questions and were considered for extraction. Publications that were included or excluded after the review of full-text articles are detailed below.

Figure 3.1: Summary of publications included and excluded at each stage of the review



Publications Included after Review of Full-Text Articles

The five publications included after review of full-texts are summarised in the body of the report.

Publications Excluded after Review of Full-Text Articles

Of the 310 publications included after the review of titles and abstracts, 305 were ultimately judged not to be relevant to this review. These publications, along with the reasons for exclusion, are listed in Table 3.1.

Table 3.1: Publications excluded after review of full-text articles

Full reference	Exclusion reason	Notes on exclusion reasons + tags
Abdu N, Al-Inizi S, Harrop A, Bapir M, Hoh J. Grading of tubal disease in association with raised chlamydia serology total and specific titre: a retrospective controlled study. Human Fertility. Conference: FERTILITY. 2015;18(4)	Ineligible patient population	Women with C. trachomatis positive vs C. trachomatis negative titres. Population subfertile women not specifically pregnant.
Abel E, Vonunwerth L. The incidence of asymptomatic chlamydia and gonorrhea in pregnant-women. Clin Res. 1987;35(1):A94-A94.	Abstract only	No full text version identified.
Adair CD, Gunter M, Stovall TG, et al. Chlamydia in pregnancy: a randomized trial of azithromycin and eryhthromycin. Obstet Gynecol. 1998;91(2):165-68.	Ineligible outcomes	Head-to-head trial; reports no adverse neonatal outcomes;
Akande V, Turner C, Horner P, Horne A, Pacey A. Impact of chlamydia trachomatis in the reproductive setting: British fertility society guidelines for practice. Hum Fertil. 2010;13(3):115-25.	Ineligible study design	Non-systematic review
Alary M, Joly JR, Moutquin JM, Labrecque M. Strategy for screening pregnant women for chlamydial infection in a low-prevalence area. Obstet Gynecol. 1993;82(3):399-404.	Ineligible outcomes	Comparative, but risk factor analysis. No pregnancy or neonatal outcomes reported. Reports how many cases were picked up by screening women identified as at-risk but doesn't meet screening vs no screening criteria.
Alary M, Joly JR, Moutquin JM, Mondor M, Boucher M, Fortier A, et al. Randomised comparison of amoxycillin and erythromycin in treatment of genital chlamydial infection in pregnancy. Lancet. 1994;344(8935):1461-5.	Ineligible outcomes	Head-to-head trial; no relevant neonatal outcomes.
Alawattegama AB. Gonococcal and chlamydial antibodies in ectopic and intrauterine pregnancy. Br J Obstet Gynaecol. 1989;96(2):251-52.	Ineligible study design	Letter to editor
Alexander ER, Harrison HR, Lewis M. Strategies for prevention of infant chlamydial disease. Ferns Found	Ineligible study	Non-systematic overview of chlamydial infections. Article also reports findings from a selection of the authors' studies on

Series. 1982;2:225-28.	design	neonatal infections, but no references per se - just a list of 'Selected reading' - so it's unclear to what extent the studies have been published.
Alexander ER. Chlamydia: the organism and neonatal infection. Hosp Pract. 1979;14(7):63-9.	Ineligible study design	Non-systematic review; review of mainly the authors' studies;
Alger LS, Lovchik JC, Hebel JR, Blackmon LR, Crenshaw MC. The association of chlamydia trachomatis, neisseria gonorrhoeae, and group B streptococci with preterm rupture of the membranes and pregnancy outcome. Am J Obstet Gynecol. 1988;159(2):397-404.	Study protocol	Meeting abstract for Alger 1991 (included study)
Alger LS, Lovchik JC. Comparative efficacy of clindamycin versus erythromycin in eradication of antenatal chlamydia trachomatis Genitourin Med. 1992(1):68.	Ineligible patient population	Patients with PROM enrolled; controls without PROM; Ineligible study population.
Allaire AD, Huddleston JF, Graves WL, et al. Initial and repeat screening for chlamydia trachomatis during pregnancy. Infect Dis Obstet Gynecol. 1998;6(3):116-22.	Ineligible comparator	Patients found to have chlamydia were treated with erythromycin. Data presented is not comparative.
Andersen B, van Valkengoed I, Sokolowski I, Moller JK, Ostergaard L, Olesen F. Impact of intensified testing for urogenital chlamydia trachomatis infections: a randomised study with 9-year follow-up. Sex Transm Infect. 2011;87(2):156-61.	Ineligible patient population	Comparison of two screening strategies and no screening in a randomly selected sample of men and women. Not specifically pregnant women.
Andrews WW, Goldenberg RI, Mercer B, et al. The preterm prediction study: association of second-trimester genitourinary chlamydia infection with subsequent spontaneous preterm birth. Am J Obstet Gynecol. 2000;183(3):662-68.	Ineligible study design	In this study, case patients had preterm birth and were matched to controls who did not and were investigated (retrospectively) for the presence of chlamydia; Ineligible study population.
Andrews WW, Klebanoff MA, Thom EA, Hauth JC, Carey JC, Meis PJ, et al. Midpregnancy genitourinary tract infection with chlamydia trachomatis: association with subsequent preterm delivery in women with bacterial vaginosis and trichomonas vaginalis. Am J Obstet Gynecol. 2006;194(2):493-500.	Ineligible study design	This is an ancillary study pooling data from two RCTs that randomised women with bacterial vaginosis or trichomonas vaginalis infection. The objective of the 2 parent studies was to estimate whether treatment for asymptomatic bacterial vaginosis or T. vaginalis infection would reduce the risk of preterm delivery. They checked for chlamydia at the randomisation visit. There is a small section in the results that reports data for women with and without chlamydia who received metronidazole or placebo, however metronidazole is not a first-line treatment for chlamydia, rather it treats anaerobic protozoa of bacterial

		vaginosis or trichomonas vaginalis infections.
Angelova M, Kovachev E, Tsankova V, Koleva I, Mangarova S. Role and importance of chlamydia trachomatis in pregnant patients. OA Maced J Med Sci. 2016;4(3):410-12.	Ineligible patient population	Women with positive cultures were treated with Sumamed (500mg BID) and then again ten days later.
Anonymous [Editorial]. Erythromycin for chlamydial infections in pregnancy. S Afr Med J. 1986;69(13):789.	Ineligible setting	South Africa - not considered analogous to the UK
Arkoulis T, Decavalas G, Papapetropoulou M, Detorakis J, Kondakis X, Tzigounis V. Prevalence of asymptomatic carriers of chlamydia trachomatis among pregnant and non-pregnant women in south-western Greece. Eur J Epidemiol. 1989;5(4):526-8.	Ineligible comparator	Comparison between pregnant and non-pregnant women;
Auger P, Desilets J, Bernard D, Roussin ML, Poliquin J, Robert J, et al. Screening pregnant women for chlamydia--Quebec. Can Dis Wkly Rep. 1990;16(10):45-6.	Ineligible patient population	Comparison of screening results - prevalence of C. trachomatis - in pregnant and non-pregnant women.
Avasthi K, Garg T, Gupta S, Grewal RK, Ram S. A study of prevalence of chlamydia trachomatis infection in women with first trimester pregnancy losses. Indian J Pathol Microbiol. 2003;46(1):133-6.	Ineligible setting	India not analogous to the UK
Baboonian C, Smith DA, Shapland D, Arno G, Zal B, Akiyu J, et al. Placental infection with chlamydia pneumoniae and intrauterine growth restriction. Cardiovasc Res. 2003;60(1):165-9.	Ineligible indication	Chlamydia pneumoniae is excluded
Bakken IJ, Skjeldestad FE, Lydersen S, et al. Births and ectopic pregnancies in a large cohort of women tested for chlamydia trachomatis. Sex Transm Dis. 2007;34(10):739-43.	Ineligible outcomes	Only reports data for ectopic pregnancy; this outcome is excluded.
Banniettis N, Szigeti A, Sharma S, Chotikanatis K, Hammerschlag MR, Kohlhoff S. The impact of universal chlamydia trachomatis (CT) screening during pregnancy on seroepidemiology of chlamydial infection in american children, 1991-2013. Sex Transm Infect. 2015;91(Suppl 2):A87.	Ineligible patient population	Abstract only; children not specifically neonates;
Barry WC, Teare EL, Uttley AH, Wilson SA, McManus TJ, Lim KS, et al. Chlamydia trachomatis as a cause of neonatal conjunctivitis. Arch Dis Child. 1986;61(8):797-9.	Ineligible patient population	Neonates with or without conjunctivitis tested for chlamydia infection. Not specifically neonates born to mothers with chlamydia; Ineligible study population.
Baud D, Goy G, Jaton K, Osterheld MC, Blumer S, Borel N, et al. Role of chlamydia trachomatis in miscarriage. Emerg	Ineligible patient	Women with/without miscarriage enrolled; Ineligible study population

Infect Dis. 2011;17(9):1630-35.	population	
Baud D, Goy G, Jaton-Ogay K, Osterheld M, Blumer S, Borel N, et al. Molecular and serological evidence of the role of chlamydia trachomatis in miscarriage. Clin Microbiol Infect. 2010;16(Suppl 2):S627.	Ineligible patient population	Women with/without miscarriage enrolled; Ineligible study population.
Baud D, Vial Y, Hohlfeld P, Greub G, Goy G, Jaton K, et al. Molecular and serological evidence of the role of chlamydia trachomatis in miscarriage. Am J Obstet Gynecol. 2011;204:S329-S29.	Ineligible patient population	Duplicate of study above: Baud D, Goy G, Jaton-Ogay K, Osterheld M, Blumer S, Borel N, et al. Molecular and serological evidence of the role of chlamydia trachomatis in miscarriage. Clin Microbiol Infect. 2010;16(Suppl 2):S627.
Baumgardner DJ, Christopherson A, Momont S. Chlamydia in pregnant women: southeastern Wisconsin. Wis Med J. 1989;88(9):12-5.	Ineligible outcomes	Appears to measure associations between social/obstetrical factors in women with/without positive chlamydial smears
Beem MO, Saxon E, Tipple MA. Treatment of chlamydial pneumonia of infancy. Pediatrics. 1979;63(2):198-203.	Study protocol	Same study as Beem 1977
Beem MO, Saxon EA. Pneumonia in infants infected with chlamydia trachomatis. Pediatr Res. 1976;10(4):395-95.	Ineligible study design	Non-comparative study.
Beem MO, Saxon EM. Respiratory tract colonization and a distinctive pneumonia syndrome in infants infected with chlamydia trachomatis. N Engl J Med. 1977;296(6):306-10.	Ineligible patient population	Neonates with chlamydial pneumonia who were treated; Ineligible study population.
Bekler C, Kultursay N, Ozacar T, Sayiner A, Yalaz M, Akisu M. Chlamydial infections in term and preterm neonates. Jpn J Infect Dis. 2012;65(1):1-6.	Ineligible patient population	Preterm and healthy infants enrolled and followed up; not specifically neonates born to mothers with chlamydia; Women with positive cultures were treated with Clarithromycin
Bell TA, Sandstrom IK, Eschenbach DA. Treatment of chlamydia trachomatis in pregnancy with amoxicillin. Ferns Found Series. 1982;2:221-24.	Pre 2009	No relevant maternal outcomes. Reports some neonatal outcomes but study pre 2009
Berggren EK, Patchen L. Prevalence of chlamydia trachomatis and neisseria gonorrhoeae and repeat infection among pregnant urban adolescents. Sex Transm Dis. 2011;38(3):172-4.	Ineligible study design	Original study was a prospective cohort study; this paper is a secondary analysis with data evaluated through retrospective chart review of medical records. In original study, any comparison should initially be patients with STD (C. trachomatis and/or N. gonorrhoea) (n=32) vs without STD (n=93) . Thus, for chlamydia positive patients only, the comparator group would comprise patients with no STD + those with N. gonorrhoea only. Outcomes not reported for those without STD, and available outcomes only for the 95 patients who were re-tested. Also, all patients with STD were treated.

Binns B, Williams T, McDowell J, Brunham RC. Screening for chlamydia-trachomatis infection in a pregnancy Counseling Clinic. Am J Obstet Gynecol. 1988;159(5):1144-49.	Ineligible study design	Diagnostic accuracy study
Black-Payne C, Ahrabi MM, Bocchini JA, Jr., Ridenour CR, Brouillette RM. Treatment of chlamydia trachomatis identified with chlamydiazyme during pregnancy. Impact on perinatal complications and infants. J Reprod Med. 1990;35(4):362-7.	Ineligible patient population	In both chlamydia-positive and chlamydia-negative groups there were patients with N. gonorrhoea;
Black-Payne C, Bocchini JA, Jr., Cedotal C. Failure of erythromycin ointment for postnatal ocular prophylaxis of chlamydial conjunctivitis. Pediatr Infect Dis J. 1989;8(8):491-5.	Ineligible study design	Infants who had ophthalmic specimens tested, not all infants had chlamydia. Ineligible study population.
Blas MM, Canchihuaman FA, Alva IE, et al. Pregnancy outcomes in women infected with chlamydia trachomatis: a population-based cohort study in Washington State. Sex Transm Infect. 2007;83(4):314-18.	Ineligible patient population	The comparison in this study is women with known chlamydia vs women without chlamydia. The authors state: In the present study, we were unable to assess whether women diagnosed with C trachomatis were successfully treated for the infection. This study is excluded because we do not know whether the women were treated or not and to be included in our review they must be untreated.
Blatt AJ, Lieberman JM, Hoover DR, et al. Chlamydial and gonococcal testing during pregnancy in the United States. Am J Obstet Gynecol. 2012;207(1):55-56.	Ineligible study design	This study is not comparative. Its reports rates of testing positivity and re-test positivity and compared chlamydia with gonorrhea
Bogdonoff MD. Pregnancy outcome following chlamydial infection. Drug Therapy. 1990;20(9):78.	Ineligible study design	Letter to editor
Borborema-Alfaia APBd, Freitas NSdL, Astolfi Filho S, Borborema-Santos CM. Chlamydia trachomatis infection in a sample of northern Brazilian pregnant women: prevalence and prenatal importance. Braz J Infect Dis. 2013;17(5):545-50.	Ineligible study design	Not comparative study. 1st phase cross-sectional; 2nd phase case series. Cohort study of newborns: not all from mothers with C. trachomatis. Setting is Brazil.
Borges-Costa J, Matos C, Pereira F. Sexually transmitted infections in pregnant adolescents: prevalence and association with maternal and foetal morbidity. J Eur Acad Dermatol Venereol. 2012;26(8):972-5.	Ineligible study design	Case series study, no comparator group.
Bradshaw N, Floodshaffer K, Rodriguez E, Johnson-Rubio A, Porter K, Prien S. Early outcomes from the West Texas	Ineligible study	Reports prevalence only. Not a comparative study.

early pregnancy and chlamydia project: potential impact on future fertility. Fertil Steril. 2004;82(Suppl 2):S15.	design	
Brewster DR, De Silva LM, Henry RL. Chlamydia trachomatis and respiratory disease in infants. Med J Aust. 1981;2(7):328-30.	Ineligible study design	Small case series of 11 infants. Not a comparative study. Not specifically neonates/neonates born to mothers with C trachomatis.
Brewster DR, Desilva LM, Ng KM, Henry RL. Chlamydia trachomatis and respiratory illness in infants. Aust Paediatr J. 1981;17(2):146-46.	Abstract only, no full text identified	Conference abstract of study above (Brewster 1981).
Brocklehurst P, Rooney G. Interventions for treating genital chlamydia trachomatis infection in pregnancy. Cochrane Database Syst Rev. 2009(4):1-33.	Relevant SR; individual studies have been included in YHEC review	Two studies identified in this SR are relevant to our review - Martin 1997 and Edwards 1996. Both have been included at full text selection stage.
Burchfield DJ, Reuman PD, Bucciarelli RL, Ayoub EM. Chlamydia trachomatis (Ct) pneumonitis in premature-infants. Pediatr Res. 1985;19(4):A336-A36.	Ineligible study design	Small case series. Not a comparative study.
Bush MR, Rosa C. Azithromycin and erythromycin in the treatment of cervical chlamydial infection during pregnancy. Obstet Gynecol. 1994;84(1):61-3.	Ineligible outcomes	Head-to-head study of antibiotics for chlamydial infection. No neonatal outcomes.
Carlini L, Somigliana E, Rossi G, Veglia F, Busacca M, Vignali M. Risk factors for spontaneous preterm birth: a northern Italian multicenter case-control study. Gynecol Obstet Invest. 2002;53(3):174-80.	Ineligible patient population	Women who had a pre-term birth were recruited and chlamydia was one of the variables investigated. Ineligible study population.
Carroll JC. Chlamydia trachomatis during pregnancy. To screen or not to screen? Can Fam Physician. 1993;39:97-102.	Ineligible study design	Non-systematic review
Carver A, Taft W, Borowski K, Turner H, Mullins BC, Sharma M, et al. Efficacy of azithromycin for treatment of chlamydia cervicitis in pregnancy. Am J Obstet Gynecol. 2004;191(6):S61.	Ineligible study design	Retrospective case series study. Not comparative;
Chandler JW, Alexander ER, Pheiffer TA, Wang SP, Holmes KK, English M. Ophthalmia neonatorum associated with maternal chlamydial infections. Trans Sect Ophthalmol.	Ineligible study design	Case series study. Not comparative.

1977;83(2):302-8.		
Chavalitdhamrong P, Siritantikorn S, Wasi C, Boonyaprakob U, Jirapaet K, Kolatat T. Neonatal chlamydial conjunctivitis. J Med Assoc Thai. 1986;69(8):400-6.	Ineligible setting	Thailand not analogous to the UK.
Chen MY, Fairley CK, De Guingand D, Hocking J, Tabrizi S, Wallace EM, et al. Screening pregnant women for chlamydia: what are the predictors of infection? Sex Transm Infect. 2009;85(1):31-5.	Ineligible study design	Risk factor analysis only, not comparative.
Chiba S, Chiba Y, Numazaki K, Mito K, Suga K, Moroboshi T, et al. Pulmonary infections with respiratory syncytial virus and chlamydia trachomatis in early infancy. Acta Paediatr Jpn. 1988;30(3):225-30.	Ineligible study design	Two case reports. Not comparative.
Choi SJ, Park SD, Jang IH, Uh Y, Lee A. The prevalence of vaginal microorganisms in pregnant women with preterm labor and preterm birth. Ann Lab Med. 2012;32(3):194-200.	Ineligible patient population	Korea not analogous to the UK
Chokephaibulkit K, Patamasucon P, List M, Moore B, Rodriguez H. Genital chlamydia trachomatis infection in pregnant adolescents in East Tennessee: a 7-year case-control study. J Pediatr Adolesc Gynecol. 1997;10(2):95-100.	Ineligible patient population	All women who had chlamydia were treated.
Chrysostomou M, Karafyllidi P, Papadimitriou V, Bassiotou V, Mayakos G. Serum antibodies to chlamydia trachomatis in women with ectopic pregnancy, normal pregnancy or salpingitis. Eur J Obstet Gynecol Reprod Biol. 1992;44(2):101-5.	Ineligible patient population	Comparative study of 3 groups of women: ectopic pregnancy, normal first trimester pregnancy, and salpingitis (infection/inflammation of fallopian tubes), i.e. Ineligible study population. Reports association between C. trachomatis and ectopic pregnancy; not an included outcome.
Cohen I, Tenenbaum E, Fejgin M, Michaeli G, Beyth Y, Sarov I. Serum-specific antibodies for chlamydia trachomatis in preterm premature rupture of the membranes. Gynecol Obstet Invest. 1990;30(3):155-58.	Ineligible study design	Not comparative: all patients appear to have been treated.
Cohen I, Veille JC, Calkins BM. Improved pregnancy outcome following successful treatment of chlamydial infection. JAMA. 1990;263(23):3160-3.	Ineligible patient population	Study in patients with PROM. Ineligible study population.
Cohen I. Efficacy of erythromycin in the treatment of inner city pregnant women with cervical Chlamydia trachomatis infection. Clin Ther. 1992;14(2):185-91.	Ineligible study design	Study of pregnant women with C. trachomatis (2 groups - successfully treated and chlamydia positive at end of pregnancy) and pregnant women without C. trachomatis. No untreated women included.
Colarizi P, Chiesa C, Pacifico L, Adorisio E, Rossi N,	Ineligible	Not a comparative study: only reported results for neonates who

Ranucci A, et al. Chlamydia trachomatis-associated respiratory disease in the very early neonatal period. Acta Paediatr. 1996;85(8):991-4.	study design	were found positive for C. trachomatis; Ineligible study population.
Cooper R, Tien HC, Baldomero A, Sun S. Nasopharyngeal colonization of chlamydia and mycoplasma in infants admitted to neonatal intensive-care unit - a preliminary-report. Pediatr Res. 1985;19(4):A290-A90.	Ineligible patient population	Abstract only. Preterm infants and neonates with respiratory distress enrolled; not specifically born to mothers with chlamydia. Reports neonatal colonization rates and risk factor analysis of whether maternal chlamydia associated with premature birth or neonatal respiratory distress. Ineligible study population.
Corina Nicola T, Dragos N, Mircea O, Mihaela Camelia T. Assessment of the association of urinary chlamydia trachomatis infection and pregnancy outcome. J Perinat Med. 2015;43(Suppl 1):P-0258.	Ineligible setting	Romania not analogous to the UK. Abstract only. Patients testing positive for chlamydia received treatment.
Crombleholme WR, Schachter J, Grossman M, et al. Amoxicillin therapy for chlamydia trachomatis in pregnancy. Obstet Gynecol. 1990;75(5):752-56.	Ineligible outcomes	Head to head trial but does not report neonatal outcomes of interest.
Curran G. Universal antenatal chlamydia screening by rural midwives. Aust Nurs J. 2012;19(7):30-2.	Ineligible study design	Non-systematic review/news type review article. Reports a 'reflective narrative study' of a universal antenatal chlamydia screening programme. Not a comparative study or a systematic review
da Costa JB, Domingues D, Louren I, Alves M, Palma F, Martins I, et al. Pregnant adolescents and chlamydia trachomatis infection: prevalence and diagnostic challenges. Int J STD AIDS. 2006;17(1):45-45.	Abstract only	No full text identified
Dannevig L, Schive B, Straume BK, Melby K. Perinatal transmission of chlamydia trachomatis. The use of serological tests in detecting infectec women. Infection. 1991;19(3):135-37.	Pre 2009	Pre 2009
Dannevig L, Straume B, Melby K. Ophthalmia neonatorum in northern Norway. II. Microbiology with emphasis on chlamydia trachomatis. Acta Ophthalmol. 1992;70(1):19-25.	Ineligible patient population	Ineligible study population.
Darling E. Prenatal screening for chlamydia and gonorrhea: an evidence based approach. CJMRP. 2009;8(2):6-14.	Ineligible study design	Insufficient methodology to be considered an SR: vague/broad question and adequate search only.
Darougar S. Prevalence of chlamydia trachomatis infections in pregnant women and neonates. Ann N Y Acad Sci. 1988;549:24-30.	Ineligible study design	Discussion paper.

Davies B, Turner KME, Frolund M, Ward H, May MT, Rasmussen S, et al. Risk of reproductive complications following chlamydia testing: a population-based retrospective cohort study in Denmark. Lancet Infect Dis. 2016;16(9):1057-64.	Unknown treatment	Data from a national data set so unclear whether women were treated. Authors state: "In this cohort, women with a diagnosed (and presumably treated) chlamydia infection..."
de Attayde Silva MJPM, Dantas Florencio GL, Erbolato Gabiatti JR, do Amaral RL, Junior JE, da Silveira Goncalves AK. Perinatal morbidity and mortality associated with chlamydial infection: a meta-analysis study. Braz J Infect Dis. 2011;15(6):533-39.	Ineligible patient population	Although SR included pregnant women, individual studies included in the meta-analysis have various exclusion criteria relating to pregnancy; All relevant studies have been identified by YHEC review.
de Carvalho Gomes H, Velasco-Garrido M, Busse R. Screening on urogenital chlamydia trachomatis. GMS Health Technol Assess. 2005;1:1-9.	Non English language paper	Executive summary only, in German
De Guingand DL, Fairley CK, Garland S, Tabrizi S, Grover S, Wallace E, et al. Chlamydia screening of antenatal women in Melbourne between 16-25 years. Sexual Health. 2007;4(4):307-07.	Study protocol	Abstract only
Delgadillo RA, Muylaert LD, Vanden Berghe DA, Neetens A. Chlamydia conjunctivitis. Bull Soc Belge Ophtalmol. 1983;207:97-107.	Non English language paper	French
Ditkowsky J, Shah KH, Hammerschlag MR, Kohlhoff S, Smith-Norowitz TA. Cost-benefit analysis of chlamydia trachomatis screening in pregnant women in a high burden setting in the United States. BMC Infect Dis. 2017;17(1):155.	Ineligible study design	Cost benefit model with assumptions based on published data; studies have been identified by YHEC searches. No use of SR to populate model.
Divers MJ, Lilford RJ. Infection and preterm labour: a meta-analysis. Contemp Rev Obstet Gynaecol. 1993;5(2):71-84.	Ineligible study design	Meta-analysis but no systematic review methodology.
Donders GG, Moerman P, De Wet GH, Hooft P, Goubau P. The association between chlamydia cervicitis, chorioamnionitis and neonatal complications. Arch Gynecol Obstet. 1991;249(2):79-85.	Ineligible patient population	Black patients in South Africa; not analogous to the UK.
Dunlow SG, Duff P. Microbiology of the lower genital tract and amniotic fluid in asymptomatic preterm patients with intact membranes and moderate to advanced degrees of cervical effacement and dilation. Am J Perinatol. 1990;7(3):235-8.	Ineligible patient population	Women with pre-term labour included, i.e. Ineligible study population; Full text also states that it isn't a comparative study but a descriptive one.
Edwards MS, Newman RB, Carter SG, Leboeuf FW, Menard	Pre 2009	Head to head antibiotic trial reporting neonatal outcomes - but

MK, Rainwater KP. Randomized clinical trial ofazithromycin vs. arythromycin for the treatment of chlamydia cervicitis in pregnancy. Infect Dis Obstet Gynecol. 1996;4(6):333-7.		pre 2009.
Edwards R, Bennett M, Langstraat C, Greene D. Does one need to repeat screening for gonorrhea, chlamydia, and syphilis in the third trimester of pregnancy? Am J Obstet Gynecol. 2005;193(6):S187-S87.	Ineligible study design	Abstract only.
Eggert-Kruse W, Scholz S, Klopsch I, Michel T, Strowitzki T. Is the determination of chlamydial heat shock protein (HSP) antibodies clinically useful in patients with recurrent pregnancy loss? Arch Gynecol Obstet. 2012;286(Suppl 1):S192.	Ineligible patient population	Abstract only. Prospective comparative study of women with/without miscarriage and association with presence of Chlamydial heat shock protein. Ineligible study population.
Eschenbach D. Significance for the fetus of sexually acquired maternal infection with mycoplasma, chlamydia, and neisseria gonorrhoeae. Semin Perinatol. 1977;1(1):11-24.	Ineligible study design	Non-systematic review
Feingold M, Sbarra A, Newton ER, Thomas GB, Selvaraj RJ, Cetrulo CL. Significance of chlamydia trachomatis infection during pregnancy. Isr J Med Sci. 1988;24(2):109-11.	Ineligible study design	Population based on various outcomes (preterm labour, PROM, vaginal bleeding, abruption placentae).
FitzSimmons J, Callahan C, Shanahan B, Jungkind D. Chlamydial infections in pregnancy. J Reprod Med. 1986;31(1):19-22.	Ineligible patient population	Women with positive cultures were treated at 36 weeks with erythromycin (500mg QID).
Folger AT. Maternal chlamydia trachomatis infections and preterm birth: the impact of early detection and eradication during pregnancy. Matern Child Health J. 2014;18(8):1795-802.	Ineligible patient population	17% of women had concurrent gonorrhoea.
Frommell GT, Rothenberg R, Wang S, McIntosh K. Chlamydial infection of mothers and their infants. J Pediatr. 1979;95(1):28-32.	Ineligible outcomes	There are no relevant results reported - no results for maternal outcomes of interest and the neonatal outcomes are outside the 2009 date cut-off.
Gabel HD, Bacon J, Dowda H, Shearin EE, Arvelo M. Chlamydia trachomatis in a high risk pregnant population. J S C Med Assoc. 1985;81(5):273-4.	Ineligible study design	Animal study
Genc MR. Treatment of genital chlamydia trachomatis infection in pregnancy. Best Pract Res Clin Obstet Gynaecol. 2002;16(6):913-22.	Ineligible study design	Non-systematic review
Gencay M, Koskiniemi M, Fellman V, Ammala P, Vaheri A, Puolakkainen M. Chlamydia trachomatis infection in	Ineligible patient	Prospective comparative study of women with/without preterm birth. Ineligible study population.

mothers with preterm delivery and in their newborn infants. APMIS. 2001;109(9):636-40.	population	
Gencay M, Koskiniemi M, Saikku P, Puolakkainen M, Raivio K, Koskela P, et al. Chlamydia trachomatis seropositivity during pregnancy is associated with perinatal complications. Clin Infect Dis. 1995;21(2):424-26.	Duplicate record	Duplicate of study above
Gerard HC, Branigan PJ, Balsara GR, Heath C, Minassian SS, Hudson AP. Viability of chlamydia trachomatis in fallopian tubes of patients with ectopic pregnancy. Fertil Steril. 1998;70(5):945-8.	Ineligible patient population	Women with ectopic pregnancy. Ineligible study population.
Gillespie P, O'Neill C, Adams E, Turner K, O'Donovan D, Brugha R, et al. The cost and cost-effectiveness of opportunistic screening for chlamydia trachomatis in Ireland. Sex Transm Infect. 2012;88(3):222-8.	Ineligible patient population	Cost-effectiveness analysis of screening vs no screening alongside prospective study of opportunistic screening programme. Doesn't report effectiveness outcomes in main text; modelled various maternal/neonatal complications avoided. Not specifically pregnant women: people attending general practices, family planning and student health clinics;
Goscienski PJ. Inclusion conjunctivitis in the newborn infant. J Pediatr. 1970;77(1):19-26.	Ineligible study design	Case report of 5 infants.
Govender S, Theron GB, Odendaal HJ, Chalkley LJ. Prevalence of genital mycoplasmas, ureaplasmas and chlamydia in pregnancy. J Obstet Gynecol. 2009;29(8):698-701.	Ineligible outcomes	Focuses on prevalence of specific infections - not eligible outcomes. Note also that population seems to be based on 'outcomes': women attending their first prenatal visit, in conjunction with pre-term labour or HIV status.
Gravett MG, Nelson HP, DeRouen T. Independent associations of bacterial vaginosis and chlamydia trachomatis infection with adverse pregnancy outcome. JAMA. 1986;256(14):1899-903.	Ineligible patient population	Comparison between women with/without bacterial vaginosis, not specifically C. trachomatis. Ineligible study population.
Gribble RK, Ricci-Goodman JM, Berg RL. Screening for chlamydia trachomatis in low-risk obstetric patients. Infect Dis Obstet Gynecol. 1994;1(4):177-81.	Ineligible outcomes	Prospective comparative study of pregnant women with low/high risk factor for C. trachomatis. Prevalence and risk factor analysis reported. No relevant outcomes.
Gronroos M, Honkonen E. Cervical and serum IgA and serum IgG antibodies to chlamydia trachomatis and herpes simplex virus in threatened abortion: a prospective study. Br J Obstet Gynaecol. 1983;90(2):167-70.	Ineligible patient population	Comparative study of women with normal birth and those with miscarriage (with further subgroups of type of miscarriage). Ineligible study population.
Grossman M, Schachter J, Sweet R. Prospective studies in chlamydia in newborns. Ferns Found Series. 1982; 2:213-16.	Pre 2009	pre 2009

Haggerty CL, Klebanoff MA, Panum I, Uldum SA, Bass DC, Olsen J, et al. Prenatal Chlamydia trachomatis infection increases the risk of preeclampsia. Pregnancy Hypertens. 2013;3(3):151-54.	Ineligible study design	Secondary analysis of longitudinal study conducted in subset of women with pre-eclamptic and normotensive pregnancies; Ineligible study population.
Haggerty CL, Panum I, Uldum SA, Bass DC, Olsen J, Darville T, et al. Chlamydia trachomatis infection may increase the risk of preeclampsia. Pregnancy Hypertens. 2013;3(1):28-33.	Ineligible study design	Nested case-control study among a longitudinal-based population study. Conducted on subset of women with pre-eclampsia or normotensive pregnancy. Ineligible study population.
Hammerschlag MR, Anderka M, McComb D, Semine D, McCormack WM. Prospective-study of maternal and infant infection with chlamydia trachomatis. Pediatr Res. 1978;12(4):493-93.	Ineligible study design	Brief overview covers inclusion conjunctivitis, pneumonia and infections at other sites. Non-systematic review.
Hammerschlag MR, Anderka M, Semine DZ, McComb D, McCormack WM. Prospective study of maternal and infantile infection with chlamydia trachomatis. Pediatrics. 1979;64(2):142-8.	Abstract only, no full text identified	Abstract only.
Hammerschlag MR. Chlamydia trachomatis infection in infants. Report on Pediatric Infectious Diseases. 1994;4(3):10-11.	Pre 2009	pre 2009
Handsfield HH, Jasman LL, Roberts PL, Hanson VW, Kothenbeutel RL, Stamm WE. Criteria for selective screening for chlamydia trachomatis infection in women attending family planning clinics. JAMA. 1986;255(13):1730-4.	Ineligible patient population	Population is women attending family planning clinics for various reasons, not specifically pregnant women.
Hardy PH, Hardy JB, Nell EE, Graham DA, Spence MR, Rosenbaum RC. Prevalence of six sexually transmitted disease agents among pregnant inner-city adolescents and pregnancy outcome. Lancet. 1984;2(8398):333-7.	Ineligible study design	Case series study, not comparative.
Harrison HR, Alexander ER, Weinstein L, Lewis M, Nash M, Sim DA. Cervical chlamydia trachomatis and mycoplasmal infections in pregnancy. Epidemiology and outcomes. JAMA. 1983;250(13):1721-7.	Ineligible study design	Prospective observational study but not comparative. Study does not specifically state whether patients were treated or not. However, details about "antibiotic therapy during pregnancy" were collected and the discussion states "we have observed a preventative effect (of premature deliver) with ampicillin" so have assumed that women in this study were treated and is excluded on that basis.
Harrison HR, Alexander ER, Weinstein L. Epidemiologic correlations of genital infections and outcomes in	Ineligible patient	Chlamydia positive (treated) vs chlamydia negative.

pregnancy. Ferns Found Series. 1982;Vol. 2:159-62.	population	
Harrison HR, English MG, Lee CK, Alexander ER. Chlamydia trachomatis infant pneumonitis: comparison with matched controls and other infant pneumonitis. N Engl J Med. 1978;298(13):702-08.	Ineligible patient population	Hospitalised infants; Ineligible study population.
Helin I, Mardh PA. Mother-to-infant transmission of chlamydia trachomatis and its consequences for the baby. Scand J Infect Dis [Suppl]. 1982;32:135-40.	Ineligible study design	Discussion paper - non-systematic review.
Herieka E, Dhar J. Acute neonatal respiratory failure and chlamydia trachomatis. Sex Transm Infect. 2001;77(2):135-36.	Ineligible study design	Case report.
Hillman LS, Gardner M. Chlamydia trachomatis seropositivity in sudden infant death syndrome cases (SIDS) and controls. Pediatr Res. 1981;15(4):613-13.	Ineligible patient population	Abstract only. Comparison of incidence of C. trachomatis seropositivity in SIDs cases and living infants aged 13 weeks (i.e. not neonates);
Hobson D, Rees E, Viswalingam ND. Chlamydial infections in neonates and older children. Br Med Bull. 1983;39(2):128-32.	Ineligible study design	Case series, not comparative
Hobson D, Rees E. Maternal genital chlamydial infection as a cause of neonatal conjunctivitis. Postgrad Med J. 1977;53(624):595-7.	Ineligible study design	General discussion paper;
Howell MR, Quinn TC, Brathwaite W, Gaydos CA. Screening women for chlamydia trachomatis in family planning clinics: the cost-effectiveness of DNA amplification assays. Sex Transm Dis. 1998;25(2):108-17.	Ineligible patient population	Considers number of prevented neonatal infections by screening for C. trachomatis. Cost-effectiveness of screening vs no screening. Not specifically pregnant women.
Hu D, Hook EW, Goldie SJ. The impact of natural history parameters on the cost-effectiveness of chlamydia trachomatis screening strategies. Sex Transm Dis. 2006;33(7):428-36.	Ineligible patient population	Cost-effectiveness analysis employs model based on cohort of non-pregnant, disease-free teenagers.
Hueston WJ, Lenhart JG. A decision analysis to guide antibiotic selection for chlamydia infection during pregnancy. Arch Fam Med. 1997;6(6):551-5.	Ineligible study design	Cost and effectiveness of different antibiotic combinations for treating C. trachomatis in pregnant women, not a screening programme/strategy. Has literature search but not SR methodology.
Humphreys JT, Henneberry JF, Rickard RS, Beebe JL. Cost-benefit analysis of selective screening criteria for chlamydia trachomatis infection in women attending Colorado family planning clinics. Sex Transm Dis. 1992;19(1):47-53.	Ineligible outcomes	Financial benefit of screening methods vs no screening. Not comparative.

Ismail MA, Chandler AE, Beem MO, Moawad AH. Chlamydial colonization of the cervix in pregnant adolescents. J Reprod Med. 1985;30(7):549-53.	Ineligible patient population	Comparison of adolescents with/without C. trachomatis, but some patients in each group also had N. gonorrhoea'. Reports intrauterine growth retardation. Study states that not all neonates followed closely prospectively. Text reports some neonatal outcomes overall but table mentioned appears to be missing. Pre-2009
Ismail MA, Pridjian G, Hibbard JU, et al. Significance of positive cervical cultures for chlamydia trachomatis in patients with preterm premature rupture of membranes. Am J Perinatol. 1992;9(5-6):368-70.	Ineligible patient population	Women with PROM; Ineligible study population.
Jacobson GF, Autry AM, Kirby RS, et al. A randomized controlled trial comparing amoxicillin and azithromycin for the treatment of chlamydia trachomatis in pregnancy. Am J Obstet Gynecol. 2001;184(7):1352-56.	Ineligible outcomes	Head to head trial but no neonatal outcomes reported.
Jain A, Nag VL, Goel MM, Chandrawati, Chaturvedi UC. Adverse foetal outcome in specific IgM positive chlamydia trachomatis infection in pregnancy. Indian J Med Res. 1991;94:420-3.	Ineligible setting	Non-pregnant controls. India not analogous to the UK.
Juhl C, Christensen M, Bor P. Should chlamydia screening be offered to women with miscarriages? Acta Obstet Gynecol Scand. 2012;91(159):95.	Ineligible patient population	Abstract only. Women with /without miscarriage; Ineligible study population.
Kacmar J, Cheh E, Montagno A, Peipert JF. A randomized trial of azithromycin versus amoxicillin for the treatment of chlamydia trachomatis in pregnancy. Infect Dis Obstet Gynecol. 2001;9(4):197-202.	Ineligible outcomes	Small (n=39) head-to-head trial of antibiotics. Neonatal outcomes not reported.
Kaddam LA, Mohager MO, Adam AA, Tahan MA. Immunological and molecular detection of chlamydia trachomatis among women at reproductive age attending omdurman maternity hospital. IJPSR. 2014;5(9):3664-68.	Ineligible setting	Saudi Arabia not analogous to the UK. Comparison of pregnant vs non-pregnant women;
Kadzhaia D, Merabishvili N. Prevalence and risk factors for chlamydia trachomatis infection in pregnant women. Georgian Med. 2005;129(12):33-6.	Ineligible setting	Georgia not analogous to the UK
Kajaia D, Merabishvili N, Burkadze G. Pap testing and direct immunofluorescence for chlamydia trachomatis infection in pregnant women. Georgian Med. 2006;131(2):27-30.	Ineligible study design	Women with C. trachomatis with/without other infections. Not a comparative study of women with chlamydia vs women without chlamydia or treated vs untreated women. NB. Authors appear to use term 'chlamydiosis', which is possibly a related infection in birds/animals, as a substitute for C. trachomatis.;

Kalwij S, Macintosh M, Baraitser P. Screening and treatment of chlamydia trachomatis infections. BMJ. 2010;340:c1915.	Ineligible study design	Most women with chlamydia were treated.
Katz Y, Mundel G, Lahat E, Ghinsberg R. Pneumonia in infants due to chlamydia trachomatis. Isr J Med Sci. 1983;19(7):670-70.	Ineligible setting	Israel not analogous to the UK
Keegan MB, Diedrich JT, Peipert JF. Chlamydia trachomatis infection: screening and management. J Clin Outcomes Manag. 2014;21(1):30-38.	Ineligible study design	Non-systematic review
Keskey TS, Suarez M, Gleicher N. Chlamydia trachomatis infections in infants. Mt Sinai J Med. 1986;53(2):77-79.	Ineligible study design	Infants with conjunctivitis or suspected respiratory symptoms. Ineligible study population.
Khurana CM, Deddish PA. Incidence of chlamydial infection in pregnant-women and the effectiveness of treatment in prevention of neonatal disease. Clin Res. 1982;30(2):A371-A71.	Abstract only, no full text identified	Abstract only
Kirk E, Bora S, Van Calster B, Condous G, Van Huffel S, Timmerman D, et al. Chlamydia trachomatis infection in patients attending an early pregnancy unit: prevalence, symptoms, pregnancy location and viability. Acta Obstet Gynecol Scand. 2008;87(6):601-7.	Ineligible study design	Cross-sectional study. Maternal outcomes are on 'final early pregnancy' outcomes rather than final (end of pregnancy/birth) outcomes.
Kirkham C, Harris S, Grzybowski S. Evidence-based prenatal care: part II. Third-trimester care and prevention of infectious diseases. Am Fam Physician. 2005;71(8):1555-60.	Ineligible study design	Non-systematic review
Kirschbaum T. Antibiotics in the treatment of preterm labor. Am J Obstet Gynecol. 1993;168(4):1239-46.	Ineligible study design	Non-systematic review: has search but no clear research question, eligibility criteria or other SR methodology.
Klapsa D, Skentou H, Stavropoulou M, Damani A, Anastassiadou F, Messinis I, et al. Prevalence of chlamydia trachomatis, neisseria gonorrhoeae, herpes simplex virus type 1,2 and papilloma virus in pregnant women in central Greece. Clin Microbiol Infect. 2009;15(Suppl 4):S639.	Ineligible study design	Not comparative.
Kovacs L, Nagy E, Berbik I, Meszaros G, Deak J, Nyari T. The frequency and the role of chlamydia trachomatis infection in premature labor. Int J Gynaecol Obstet. 1998;62(1):47-54.	Ineligible patient population	Chlamydia positive (treated) vs chlamydia negative. Three of seven sites treated women who were found to have chlamydia. Results are not stratified by treated/untreated.
Kuzmin V. The infections and other factors in development	Study	Abstract only

of preterm birth. Int J Gynaecol Obstet. 2012;119:S729-S30.	protocol	
LeFevre ML. Screening for chlamydia and gonorrhea: U.S. preventive services task force recommendation statement. Ann Intern Med. 2014;161(12):902-10.	Ineligible study design	Screening recommendations
Leszczynska-Gorzelak B, Darmochwal-Kolarz D, Borowiec-Blinowska A, Oleszczuk J. The prevalence of chlamydia trachomatis infection in pregnant women. Med Wieku Rozwoj. 2005;9(1):27-35.	Non English language paper	Polish
Liu B, Roberts CL, Clarke M, et al. Chlamydia and gonorrhoea infections and the risk of adverse obstetric outcomes: a retrospective cohort study. Sex Transm Infect. 2013;89(8):672-78.	Ineligible study design	Compares single cohort of patients according to birth outcome. Reports association between infections and adverse obstetric outcomes. Not comparative.
Lovchik JC, Alger LS. Early versus late screening for chlamydia trachomatis in pregnancy. Ann N Y Acad Sci. 1989;549:228-29.	Ineligible patient population	Prospective comparative study of women with/without PROM. Reports prevalence of C. trachomatis and other pathogens; Ineligible study population.
Low N, Bender N, Nartey L, Shang A, Stephenson JM. Effectiveness of chlamydia screening: systematic review. Int J Epidemiol. 2009;38(2):435-48.	Ineligible patient population	SR about chlamydia screening in men and non-pregnant and pregnant women. 2 relevant SRs identified (Nelson 2001 and Meyers 2007), both identified by YHEC.
Lunenfeld E, Shapiro B, Sarov B, Sarov I, Insler V, Decherney AH. The association between chlamydial-specific IgG and IgA antibodies and pregnancy outcome in an in vitro fertilization program. J In Vitro Fert Embryo Transf. 1989;6(4):222-7.	Ineligible patient population	Comparison between three groups of patients who had undergone IVF and embryo transfer: pregnancy loss, non-conception and term pregnancy. Patients who are receiving IVF are unlikely to undergo publically funded screening while they are pregnant.
Magat AH, Alger LS, Nagey DA, Hatch V, Lovchik JC. Double-blind randomized study comparing amoxicillin and erythromycin for the treatment of chlamydia trachomatis in pregnancy. Obstet Gynecol. 1993;81(5 (Pt 1)):745-9.	Ineligible outcomes	Head-to-head RCT of two antibiotics. No neonatal outcomes.
Magri V, Montanari E, Skerk V, Markotic A, Marras E, Restelli A, et al. Fluoroquinolone-macrolide combination therapy for chronic bacterial prostatitis: retrospective analysis of pathogen eradication rates, inflammatory findings and sexual dysfunction. Asian Journal of Andrology. 2011;13(6):819-27.	Ineligible patient population	Retrospective comparison of antibiotic treatments for prostatitis.
Maguire NC, Jordan AG, Ehya H. Detection of chlamydia-trachomatis in cervical smears from pregnant population. Arch Pathol Lab Med. 1990;114(2):204-07.	Ineligible study design	Diagnostic accuracy study
Mardh PA, Helin I, Bobeck S, Laurin J, Nilsson T.	Ineligible	A set of three case series studies.

Colonisation of pregnant and puerperal women and neonates with chlamydia trachomatis. Br J Vener Dis. 1980;56(2):96-100.	study design	
Mardh PA, Novikova N. Impact of chlamydial infections on pregnancy outcome, perinatal health and long-term sequelae of offsprings - A review of novel studies and reappraisal of earlier data. Italian Journal of Gynaecology and Obstetrics. 2000;12(4):145-53.	Ineligible study design	Non-systematic review. Searches in Medline but no systematic review methodology.
Marrazzo JM, Celum CL, Hillis SD, Fine D, Delisle S, Handsfield H. Performance and cost-effectiveness of selective screening criteria for chlamydia trachomatis infection in women: implications for a national chlamydia control strategy. Sex Transm Dis. 1997;24(3):131-41.	Ineligible study design	Cost-effectiveness analysis of screening strategies (universal, selective, none). Retrospective study to develop criteria (based on risk factors) for selective screening. Comparison of women attending family planning clinics and STD clinics, but not specifically pregnant women.
Martin DH, Alexander ER, Eschenbach DA, Kuo CC, Chiang WT, Maclurg BJ, et al. Prospective-study of chlamydia infection in pregnancy. Clin Res. 1979;27(2):A479-A79.	Abstract only, no full text identified	Abstract only
Martin DH, Koutsky L, Eschenbach DA. Prematurity and perinatal mortality in pregnancies complicated by maternal chlamydia trachomatis infections. JAMA. 1982;247(11):1585-88.	Unknown treatment	The study doesn't report whether women were treated or untreated. PHE decided that studies where there is not enough data reported to decide whether women were treated with antibiotics or not should be excluded.
Mathur M, Robertson C, Caird L, et al. Chlamydia infection among pregnant women and those seeking termination. J Obstet Gynecol. 2007;27(4):409-12.	Ineligible study design	Retrospective comparison between women seeking termination and antenatal group.
Matson SC, Pomeranz AJ, Kamps KA. Early detection and treatment of sexually transmitted disease in pregnant adolescents of low socioeconomic status. Clin Pediatr. 1993;32(10):609-12.	Ineligible study design	Retrospective cohort study comparing screening vs no screening for various STD, including C. trachomatis and N. gonorrhoea. Risk factor analysis and prevalence only.
Matthew Chico R, Hack BB, Newport MJ, Ngulube E, Chandramohan D. On the pathway to better birth outcomes? A systematic review of azithromycin and curable sexually transmitted infections. Expert Rev Anti Infect Ther. 2013;11(12):1303-32.	Ineligible outcomes	The birth outcomes reported are perinatal outcomes, rather than the neonatal outcomes specified in the protocol.
McKay A. Chlamydia screening programs: a review of the literature. Part 1: issues in the promotion of chlamydia testing of youth by primary care physicians. Can J Hum Sex. 2006;15(1):1-11.	Ineligible study design	Non-systematic review.

McMillan HM, O'Carroll H, Lambert JS, et al. Screening for chlamydia trachomatis in asymptomatic women attending outpatient clinics in a large maternity hospital in Dublin, Ireland. Sex Transm Infect. 2006;82(6):503-05.	Ineligible outcomes	Prospective comparative study. Reports risk factor analysis and prevalence only.
McMillan JA, Weiner LB, Lamberson HV. Efficacy of maternal screening and therapy in the prevention of chlamydia infection of the newborn. Infection. 1985;13(6):263-66.	Pre 2009	Prospective comparative study of treated vs untreated mothers; maternal and neonatal outcomes. Some women had both C. trachomatis and N gonorrhoea; pre 2009.
McNeeley Jr SG, Ryan Jr GM, Baselski V. Treatment of chlamydial infections of the cervix during pregnancy. Sex Transm Dis. 1989;16(2):60-62.	Ineligible outcomes	Head-to-head study of antibiotics to treat C. trachomatis; no neonatal outcomes reported;
Melzer-Lange M, Good L, Hennes H. Chlamydia trachomatis infections: implications for pregnant adolescents and their infants. Infect Dis Obstet Gynecol. 1994;2(1):10-5.	Ineligible patient population	Adolescents with positive cultures were treated within week of testing with erythromycin (500 mg TID) and retested within month. If chlamydia was detected at any time during pregnancy were also treated with erythromycin at the same dose.
Meyers DS, Halvorson H, Luckhaupt S. Screening for chlamydial infection: an evidence update for the U.S. preventive services task force. Ann Intern Med. 2007;147(2):135-42.	Ineligible patient population	Only one new study identified and this related to screening of non-pregnant women.
Miller JM, Jr., Schuth CR, Gottschalk SK, Martin DH. Considerations in the prevention of perinatally acquired group B streptococcal and chlamydial infections in the newborn. Semin Perinatol. 1988;12(4):336-47.	Ineligible study design	Non-systematic review/discussion article
Milteer RM, Nunleebland GI, Young MA. The impact of prenatal chlamydia infection on infant morbidity. Ann N Y Acad Sci. 1988;549:246-47.	Ineligible study design	Described as retrospective-prospective study. Infants with chlamydia pneumonia and/or conjunctivitis were identified over the two observation periods. Prenatal histories were obtained on all mothers of infants with a chlamydia infection. No comparisons between infants of mothers with/without chlamydia. Ineligible study population.
Mitsui Y. Relations between trachoma and inclusion conjunctivitis. Rev Int Trach. 1964;41:252-61.	Non English language paper	French
Molgaard IL, Nielsen PB, Kaern J. A study of the incidence of neonatal conjunctivitis and of its bacterial causes including chlamydia trachomatis. Clinical examination, culture and cytology of tear fluid. Acta Ophthalmol.	Ineligible patient population	Case series study, not comparative. Although states that mothers positive for C. trachomatis and their infants were called back for repeat testing, results appear to be presented for overall population (i.e. culture positive & negative mothers).

1984;62(3):461-71.		
Monif GR. The impact of chlamydia trachomatis on mother and infant. Ann N Y Acad Sci. 1988;549:31-8.	Ineligible study design	Non-systematic review.
Much DH, Yeh S. Prevalence of chlamydia trachomatis infection in pregnant patients. Public Health Rep. 1991;106(5):490-93.	Ineligible patient population	Women with positive cultures between 37 and 30 weeks were treated with oral erythromycin. Chlamydia positive (treated) vs chlamydia negative
Nadafi M, Abdali KH, Parsanejad ME, et al. A comparison of amoxicillin and erythromycin for asymptomatic chlamydia trachomatis infection in pregnancy. Int J Gynaecol Obstet. 2005;90(2):142-43.	Ineligible comparator	This study is said to be three arms (amoxicillin, erythromycin and placebo) but results for the placebo group are not reported. Only reports eradication of chlamydia and AEs in women. No neonatal outcomes.
Nadeau HCG, Subramaniam A, Andrews WW. Infection and preterm birth. Semin Fetal Neonatal Med. 2016;21(2):100-05.	Ineligible study design	Non-systematic review
Nadisauskiene R, Bergstrom S, Stankeviciene I, Spukaite T. Endocervical pathogens in women with preterm and term labour. Gynecol Obstet Invest. 1995;40(3):179-82.	Ineligible setting	Lithuania not analogous to the UK
Naprstkova J. Chlamydia trachomatis in pathological pregnancy. Pathology Research and Practice. 1987;182(4):532-32.	Abstract only, no full text identified	Abstract only.
National Institute for Health and Care Excellence. Chlamydia screening should not be offered as part of routine antenatal care [webpage]. London: NICE; 2016. [cited 01 June 2017]. Available from: https://www.nice.org.uk/donotdo/chlamydia-screening-should-not-be-offered-as-part-of-routine-antenatal-care.	Ineligible study design	Guideline
National Institute for Health and Care Excellence. Antenatal care for uncomplicated pregnancies (CG62). London: NICE; 2008. Available from: https://www.nice.org.uk/guidance/cg62/resources/antenatal-care-for-uncomplicated-pregnancies-pdf-975564597445.	Ineligible study design	Guideline
University of Aarhus. Randomized population-based study on chlamydia trachomatis screening. In: ClinicalTrials.gov [internet]. Bethesda. US National Library of Medicine. 2009. Available from http://clinicaltrials.gov/show/NCT00827970. Identifier: NCT00827970	Ineligible outcomes	NCT (trial protocol) record.

Nelson HD, Helfand M. Screening for chlamydial infection. Am J Prev Med. 2001;20(3 Suppl):95-107.	Relevant SR	SR only identified two relevant studies of pregnant women (Cohen 1990 & Ryan 1990), both already identified by YHEC.
Nelson HD, Saha S, Helfand M. Screening for chlamydial infection. Rockville (MD): Agency for Healthcare Research and Quality (AHRQ); 2001. Available from: https://www.ncbi.nlm.nih.gov/books/NBK42604/.	Ineligible study design	Structured abstract on HTA database. Most likely relates to #1467 Nelson 2001: Screening for Chlamydial infection Am J Prev Med 2001;20(3 Suppl):95-107;
Nesbakken T. Chlamydial inclusion conjunctivitis of the newborn. J Oslo City Hosp. 1983;33(1):3-8.	Ineligible study design	Case report
Nettleman MD, Bell TA. Cost-effectiveness of prenatal testing for chlamydia trachomatis. Am J Obstet Gynecol. 1991;164(5 Pt 1):1289-94.	Abstract only, no full text identified	Abstract only
Nettleman MD. Cost-effectiveness of pre-natal screening for chlamydia trachomatis. Clin Res. 1988;36(6):A874-A74.	Ineligible outcomes	Cost-effectiveness analysis of different screening strategies involving antigen or culture testing. The analysis was not informed by a systematic review of the literature. Reports positive and negative predictive values vs the strategy of neither test nor treat but not maternal or neonatal outcomes.
Norman JE, Logan S, McMillan L, Templeton A, Reid M, McKenzie H, et al. Prevalence of chlamydia trachomatis amongst women attending antenatal, colposcopy and termination of pregnancy clinics - A two centre study with analysis of acceptability of screening and cost effectiveness. J Soc Gynecol Investig. 2004;11(Suppl 2):342A-43A.	Abstract only, no full text identified	Abstract only
Norman JE, Wu O, Twaddle S, et al. An evaluation of economics and acceptability of screening for Chlamydia trachomatis infection, in women attending antenatal, abortion, colposcopy and family planning clinics in Scotland, UK. BJOG. 2004;111(11):1261-68.	Ineligible study design	Cost-effectiveness of universal screening of women for C. trachomatis, and of selective screening according to age group and clinical setting. Reports sequelae averted according to clinical setting, e.g. antenatal clinic. Baseline probabilities obtained from the cohort study and from the literature; no mention of a systematic review being conducted.
Novikova N, Cluver C. Interventions for treating genital chlamydia trachomatis infection in pregnancy. Cochrane Database Syst Rev. 2013(4):Art. No.: CD010485.	Study protocol	Protocol for Cochrane review (now published http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010485.pub2/full)
Numazaki K, Wainberg MA, McDonald J. Chlamydia trachomatis infections in infants. Can Med Assoc J. 1989;140(6):615-22.	Ineligible study design	Non-systematic review

Nyari T, Deak J, Nagy E, Vereb I, Kovacs L, Meszaros G, et al. Epidemiological study of Chlamydia trachomatis infection in pregnant women in Hungary. Sex Transm Infect. 1998;74(3):213-5.	Ineligible patient population	Chlamydia positive (treated) vs chlamydia negative
Nyari T, Nyari C, Woodward M, Meszaros G, Deak J, Nagy E, et al. Screening for chlamydia trachomatis in asymptomatic women in Hungary. An epidemiological and cost-effectiveness analysis. Acta Obstet Gynecol Scand. 2001;80(4):300-6.	Ineligible study design	Cost-effectiveness analysis of different screening strategies/tests.
Nyari T, Woodward M, Kovacs L. Should all sexually active young women in Hungary be screened for chlamydia trachomatis? Eur J Obstet Gynecol Reprod Biol. 2003;106(1):55-9.	Ineligible patient population	Women with positive cultures were treated with
Nyari T, Woodward M, Meszaaros G, Karsai J, Kovacs L. Chlamydia trachomatis infection and the risk of perinatal mortality in Hungary. J Perinat Med. 2001;29(1):55-59.	Ineligible study design	Cost-effectiveness model.
Oakeshott P, Hay P, Hay S, et al. Association between bacterial vaginosis or chlamydial infection and miscarriage before 16 weeks' gestation: prospective community based cohort study. BMJ. 2002;325(7376):1334-36.	Ineligible outcomes	Prospective cohort study but comparison of women with/without bacterial vaginosis. Focus of study was relationship between bacterial vaginosis and miscarriage. Prevalence of C. trachomatis reported but no comparative data;
Odendaal HJ, Schoeman J, Grove D, de Jager M, Theron GB, Orth H, et al. The association between chlamydia trachomatis genital infection and spontaneous preterm labour. SAJOG. 2006;12(3):146-49.	Ineligible setting	South Africa not analogous to the UK
Oh MK, Cloud GA, Baker SL, Pass MA, Mulchahey K, Pass RF. Chlamydial infection and sexual behavior in young pregnant teenagers. Sex Transm Dis. 1993;20(1):45-50.	Ineligible study design	Case series study
O'Higgins AC, Jackson V, Lawless M, Le Blanc D, Connolly G, Drew R, et al. Screening for asymptomatic urogenital chlamydia trachomatis infection at a large Dublin maternity hospital: results of a pilot study. Ir J Med Sci. 2017;186(2):393-97.	Ineligible study design	Study of pregnant women invited to participate in screening programme. Only reports data for those screened. No comparison between screened and not screened.
Olliaro P, Regazzetti A, Gorini G, Milano F, Marchetti A, Rondanelli EG. Chlamydia trachomatis infection in "sine causa" recurrent abortion. Bollettino dell Istituto Sieroterapico Milanese. 1991;70(1-2):467-70.	Ineligible patient population	Women with "sine causa" recurrent abortion were included; Ineligible study population.
Ong JJ, Chen M, Hocking J, Fairley CK, Carter R, Bulfone L,	Ineligible	Cost-effectiveness of screening all pregnant women vs selective

et al. Chlamydia screening for pregnant women aged 16-25 years attending an antenatal service: a cost-effectiveness study. BJOG. 2016;123(7):1194-202.	study design	screening or no screening. Clinical data from 2 studies already included by YHEC (Chen 2009 & Bilardi 2010).
Osser S, Persson K. Chlamydial antibodies in women who suffer miscarriage. Br J Obstet Gynaecol. 1996;103(2):137-41.	Ineligible patient population	Prospective comparison of women with/without miscarriage; Ineligible study population.
Paavonen J. Chlamydia trachomatis--a major threat to reproduction. Eur J Obstet Gynecol Reprod Biol. 1993;49(1-2):23-7.	Ineligible study design	Non-systematic review
Pamel GJ, Feldman ST. Chlamydial conjunctivitis and genital gonorrhea in pregnancy. Arch Ophthalmol. 1990;108(3):327.	Ineligible study design	Case report
Parker SE, Werler MM, Gissler M, Surcel H-M. Maternal antibodies to chlamydia trachomatis and risk of gastroschisis. Birth Defects Res. 2017;24:24.	Ineligible study design	Nested case-control of infants with gastroschisis vs nonmalformed matched controls. Reports risk factor analysis, in particular association between maternal antibodies (chlamydia exposure) and risk of gastroschisis. No relevant outcomes.
Paukku M, Tulppala M, Puolakkainen M, Anttila T, Paavonen J. Lack of association between serum antibodies to chlamydia trachomatis and a history of recurrent pregnancy loss. Fertil Steril. 1999;72(3):427-30.	Ineligible patient population	Prospective comparative study but doesn't appear to be of pregnant women.
Paul VK, Singh M, Gupta U, Buckshee K, Bhargava VL, Takkar D, et al. Chlamydia trachomatis infection among pregnant women: prevalence and prenatal importance. Natl Med J India. 1999;12(1):11-4.	Ineligible setting	India not analogous to the UK
Pawlowska A, Niemiec KT, Filipp E, El Midaoui A, Scholz A, Marianowska S, et al. Chlamydia trachomatis infection in pregnant women hospitalised in the Institute of Mother and Child in Warsaw, Poland. Med Wieku Rozwoj. 2005;9(1):21-6.	Non English language paper	Polish
Persson K, Ronnerstam R, Svanberg L, et al. Neonatal chlamydial conjunctivitis. Arch Dis Child. 1986;61:565-68.	Ineligible patient population	Comparison of infants who did/did not developed neonatal chlamydial conjunctivitis, and control group of newborns with suspected neonatal septicaemia. No relevant outcomes: reports antibody profile, antibody response in chlamydial conjunctivitis, and prevalence of maternal chlamydial antibodies; Ineligible study population.
Persson K, Ronnerstam R, Svanberg L, Holmberg L. Maternal and infantile infection with chlamydia in a Swedish	Ineligible study	Prospective study doesn't appear to be comparative; results reported for separate groups of patients, studied at different

population. Acta Paediatr Scand. 1981;70(1):101-5.	design	times. Retrospective comparative study of respiratory tract infection and chlamydia in infants with chlamydia infection (or chlamydia-positive mother) vs controls taken from same groups.
Persson K, Ronnerstam R, Svanberg L, Pohla MA. Neonatal chlamydial eye infection: an epidemiological and clinical-study. Br J Ophthalmol. 1983;67(10):700-04.	Ineligible patient population	Population selected based on presence of eye infection; Ineligible study population.
Peuchant O, Le Roy C, Desvaux C, Paris A, Asselineau J, Maldonado C, et al. Prevalence and risk factors associated with chlamydia trachomatis, neisseria gonorrhoeae and mycoplasma genitalium infections in French pregnant women. Clin Microbiol Infect. 2012;18(Suppl 3):236.	Ineligible study design	Not a comparative study.
Peuchant O, Le Roy C, Desveaux C, Paris A, Asselineau J, Maldonado C, et al. Screening for chlamydia trachomatis, neisseria gonorrhoeae, and mycoplasma genitalium should it be integrated into routine pregnancy care in French young pregnant women? Diagn Microbiol Infect Dis. 2015;82(1):14-9.	Ineligible study design	Not a comparative study.
Phelps G, Cruse KL, Hentz CS. Chlamydia trachomatis in a rural obstetrical population. J S C Med Assoc. 1984;80(9):441-2.	Ineligible study design	Not a comparative study.
Pirogova VI, Vinograd NA, Zhemela EM, Chegrinec NA. Immune status of newborns in perinatal chlamydial infection. Am J Reprod Immunol. 1995;33(1):94-6.	Ineligible outcomes	The study compares neonates with chlamydia to neonates without chlamydia but focuses on antibody titres - there don't appear to be any numbers reported for the outcomes of interest.
Piso B, Reinsperger I, Winkler R. Recommendations from international clinical guidelines for routine antenatal infection screening: does evidence matter? Int J Evid Based Healthc. 2014;12(1):50-61.	Ineligible study design	Systematic review but inclusion criteria specify guidelines not experimental studies, so included 'studies' would not be relevant for reference checking.
Pitegoff JG, Cathro DM. Chlamydial infections and other sexually transmitted diseases in adolescent pregnancy. Semin Adolesc Med. 1986;2(3):215-29.	Ineligible study design	Non-systematic review
Pitsouni E, Iavazzo C, Athanasiou S, Falagas ME. Single-dose azithromycin versus erythromycin or amoxicillin for chlamydia trachomatis infection during pregnancy: a meta-analysis of randomised controlled trials. Int J Antimicrob Agents. 2007;30(3):213-21.	Relevant SR; individual studies have been included in YHEC	SR and meta-analysis of head-to-head trials. Included studies seem to report perinatal, neonatal and AE outcomes but pre-2009.

	review	
Postma MJ, Bakker A, Welte R, Bergen JE, Hoek JA, Jong-van dBLT, et al. Screening for asymptomatic chlamydia trachomatis infection in pregnancy: cost-effectiveness favorable at a minimum prevalence rate of 3% or more. Ned Tijdschr Geneeskd. 2000;144(49):2350-54.	Non English language paper	Dutch
Powell K, Middleton GW, Forster GE. Chlamydia trachomatis in infants: a prospective study. Arch Dis Child. 1990;65(3):336.	Ineligible study design	Letter to editor
Preece PM, Ades A, Thompson RG, Brooks JH. Chlamydia trachomatis infection in late pregnancy: a prospective study. Paediatr Perinat Epidemiol. 1989;3(3):268-77.	Ineligible comparator	Pregnancy outcomes only reported for chlamydia-positive group therefore non-comparative.
Preece PM, Anderson JM, Thompson RG. Chlamydia trachomatis infection in infants: a prospective study. Arch Dis Child. 1989;64(4):525-29.	Ineligible patient population	Women positive for chlamydial antigen were offered treatment (erythromycin) for themselves and their partners.
Preece PM, Brooks JH, Anderson JM, Thompson R. The prevalence of chlamydia-trachomatis infection in infants following maternal infection. Arch Dis Child. 1986;61(6):627-27.	Study protocol	Abstract only
Price MJ, Ades AE, Soldan K, Welton NJ, Macleod J, Simms I, et al. The natural history of chlamydia trachomatis infection in women: a multi-parameter evidence synthesis. Health Technol Assess. 2016;20(22):1-250.	Ineligible study design	Reported to be review of all the available evidence about Chlamydia trachomatis in the UK and its sequelae but no SR methodology described and no specific mention of pregnant women/neonates.
Price MJ, Ades AE, Soldan K, Welton NJ, Macleod J, Simms I, et al. The natural history of chlamydia trachomatis infection in women: A multi-parameter evidence synthesis. Sex Transm Infect. 2015;91(Suppl 2):A59-A60.	Ineligible patient population	Not pregnant women and no eligible outcomes (seems to focus on pelvic inflammatory disease, tubal infertility and salpingitis).
Prien S, Flood-Shaffer K, Johnson-Rubio A, Rodriguez E, Porter K, Brice L. Early testing and treatment of chlamydia during pregnancy appears to have little effect on pre-term delivery rates. J Soc Gynecol Investig. 2006;13(2):326A-26A.	Abstract only, no full text identified	Abstract only
Pungetti D, Calderara MA, Cantiero D, Selleri MC, Travisani D, Lenzi M, et al. Epidemiological evaluation of the incidence of Chlamydia trachomatis infection in pregnancy. Acta Eur Fertil. 1989;20(2):97-8.	Ineligible patient population	Abstract only
Quinlivan JA, Petersen RW, Davy M, Evans SF. Abnormal pap smears in teenage mothers and the association with	Ineligible study	Comparison is universal screening vs selected screening - which is not a relevant comparison according to protocol.

domestic violence, homelessness, and chlamydia. J Low Genit Tract Dis. 2004;8(2):112-7.	design	
Quinlivan JA, Petersen RW, Gurrin LC. High prevalence of chlamydia and pap-smear abnormalities in pregnant adolescents warrants routine screening. Aust N Z J Obstet Gynaecol. 1998;38(3):254-7.	Ineligible patient population	Study is about normal vs abnormal pap smears and whether these are associated with other factors - population not chlamydia.
Rae R, Smith IW, Liston WA, Kilpatrick DC. Chlamydial serologic studies and recurrent spontaneous abortion. Am J Obstet Gynecol. 1994;170(3):782-5.	Ineligible patient population	Idiopathic recurrent spontaneous aborters; Ineligible study population.
Rantsi T, Joki-Korpela P, Wikstrom E, Ohman H, Bloigu A, Lehtinen M, et al. Population-based study of prediagnostic antibodies to chlamydia trachomatis in relation to adverse pregnancy outcome. Sex Transm Dis. 2016;43(6):382-7.	Ineligible patient population	PROM, ectopic pregnancy, miscarriage; Ineligible study population.
Rastogi S, Das B, Salhan S, et al. Effect of treatment for chlamydia trachomatis during pregnancy. Int J Gynaecol Obstet. 2003;80(2):129-37.	Ineligible setting	India not analogous to the UK
Reid F, Oakeshott P, Kerry SR, Hay PE, Jensen JS. Chlamydia related bacteria (Chlamydiales) in early pregnancy: community-based cohort study. Clin Microbiol Infect. 2017;23(2):119.e9-19.e14.	Ineligible study design	Seriolgocial case-control study comparing infected vs non-infected women. Maternal outcomes reported for overall Chlamydiales and also separately for Waddlia chondrophila,Chlamydia abortus and Chlamydia trachomatis.
Riggs MA, Klebanoff MA. Treatment of vaginal infections to prevent preterm birth: a meta-analysis. Clin Obstet Gynecol. 2004;47(4):796-807.	Relevant SR; individual studies have been included in YHEC review	Appears to be systematic review of antibiotics vs placebo for treating various infections, including C. trachomatis. Inclusion criteria specified studies reporting maternal outcomes; no mention of neonatal outcomes in either the eligibility criteria or the summary of main results. One trial of chlamydia (Martin 1997) is already included.
Rosenn M, Macones GA, Silverman N. A randomized trial of erythromycin and azithromycin for the treatment of chlamydia infection in pregnancy. Am J Obstet Gynecol. 1996;174:410.	Ineligible outcomes	Head-to-head trial, does not report neonatal AEs.
Rosenn MF. Randomized trial of erythromycin and azithromycin for treatment of chlamydial infection in pregnancy. Infect Dis Obstet Gynecol. 1996;3(6):241-44.	Study protocol	Study protocol only
Ross C, Hoover K, Tao GY. Prenatal screening for chlamydia and gonorrhea and the association with	Ineligible study	Retrospective study of screening rates for chlamydia and gonorrhea pregnant and non-pregnant women.

papanicolaou testing among medicaid-insured women United States, 2009-2010. Sex Transm Dis. 2014;41:S12-S12.	design	
Rours G, de Krijger RR, Ott A, Willemse HFM, de Groot R, Zimmermann LJI, et al. Chlamydia trachomatis and placental inflammation in early preterm delivery. Eur J Epidemiol. 2011;26(5):421-28.	Ineligible study design	Economic study. Not a comparison of screening strategies.
Rours G, Verkooijen RP, Verbrugh HA, Postma MJ. Cost-effectiveness of screening for chlamydia trachomatis in Dutch pregnant women. Sex Transm Infect. 2011;87(Suppl 1):A61-A61.	Ineligible study design	Sub-study of C. trachomatis embedded in the Generation R Study - population-based, noninterventional, prospective cohort study. Comparison of women positive/negative for C. trachomatis.
Rours GIJG, Duijts L, Moll HA, Arends LR, de Groot R, Jaddoe VW, et al. Chlamydia trachomatis infection during pregnancy associated with preterm delivery: a population-based prospective cohort study. Eur J Epidemiol. 2011;26(6):493-502.	Ineligible patient population	Pre-term birth. Ineligible study population.
Rours GIJG, Smith-Norowitz TA, Ditkowsky J, Hammerschlag MR, Verkooyen RP, de Groot R, et al. Cost-effectiveness analysis of chlamydia trachomatis screening in Dutch pregnant women. Pathog Glob Health. 2016;110(7-8):292-302.	Ineligible study design	Abstract only. Cost-effectiveness analysis. No comparator screening programme. No clinical outcomes.
Rowe DS, Aicardi EZ, Dawson CR, Schachter J. Purulent ocular discharge in neonates: significance of chlamydia trachomatis. Curr Ther. 1980;21(2):107-08.	Ineligible study design	Not a comparative study.
Rustveld LO, Kelsey SF, Sharma R. Association between maternal infections and preeclampsia: a systematic review of epidemiologic studies. Matern Child Health J. 2008;12(2):223-42.	Ineligible patient population	SR methodology. Inclusion criteria specified well-defined pre-eclampsia diagnosis but nothing specifically related to types of maternal infection. None of the included studies appear to have been conducted in women with C. trachomatis.
Sagy M, Barzilay Z, Yahav J, Ginsberg R, Sompolinsky D. Severe neonatal chlamydial pneumonitis. Am J Dis Child. 1980;134(1):89-91.	Ineligible study design	Case report
Sagy M, Yahav J, Ginsberg R, Sompolinsky D, Barzilay Z. Severe neonatal chlamydial pneumonitis. Isr J Med Sci. 1980;16(1):72-72.	Study protocol	Abstract only
Samson LM, MacDonald NE. Neonatal infection with chlamydia trachomatis. Report on Pediatric Infectious Diseases. 1996;6(2):8.	Ineligible study design	Non-systematic overview

Sangkomkamhang US, Lumbiganon P, Prasertcharoensook W, Laopaiboon M. Antenatal lower genital tract infection screening and treatment programs for preventing preterm delivery. Cochrane Database Syst Rev. 2009;4:CD006178.	Ineligible patient population	Cochrane review. Only one trial identified (Kiss 2004) included by YHEC.
Sangkomkamhang US, Lumbiganon P, Prasertcharoensuk W, Laopaiboon M. Antenatal lower genital tract infection screening and treatment programs for preventing preterm delivery. Cochrane Database Syst Rev. 2015(2):CD006178.	Ineligible patient population	Cochrane review – as above but update, no changes.
Sarin U, Bhalla P, Jyoti B. Genital infection with chlamydia trachomatis in pregnancy - maternal and fetal outcome. J Matern Fetal Neonatal Med. 1992;5(4):225-32.	Ineligible setting	India not analogous to the UK
Schachter J, Grossman M, Holt J, Sweet R, Goodner E, Mills J. Prospective study of chlamydial infection in neonates. Lancet. 1979;2(8139):377-80.	Ineligible study design	Duplicate
Schachter J, Grossman M, Holt J, Sweet RL, Goodner EK, Mills J. Prospective-study on chlamydial infections in the newborn. Pediatr Res. 1979;13(4):468-68.	Pre 2009	Prospective study of infants born to chlamydia positive women (cases) vs chlamydia positive women (control); neonatal outcomes; Mothers and their partners received antichlamydial therapy after the birth of their child or after breastfeeding was stopped. Pre 2009.
Schachter J, Grossman M, Sweet RL. Prospective study of perinatal transmission of chlamydia trachomatis. JAMA. 1986;255(24):3374-77.	Pre 2009	Associated with Schachter 1979. pre 2009.
Schachter J, Sweet RL, Grossman M. Experience with the routine use of erythromycin for chlamydial infections in pregnancy. N Engl J Med. 1986;314(5):276-79.	Ineligible study design	This study reports one outcome of interest - re-infection, however no results are reported for the untreated group, therefore not comparative.
Schaefer C, Harrison HR, Boyce WT, Lewis M. Illnesses in infants born to women with chlamydia trachomatis infection. A prospective study. Am J Dis Child. 1985;139(2):127-33.	Pre 2009	pre 2009
Sellors JW, Pickard L, Gafni A, Goldsmith CH, Jang D, Mahony JB, et al. Effectiveness and efficiency of selective vs universal screening for chlamydial infection in sexually active young-women. Arch Intern Med. 1992;152(9):1837-44.	Ineligible patient population	Pregnant women were excluded
Shao R, Feng Y, Zou S, Billig H. Systemic immune responses in women with chlamydia trachomatis infection: the difference between tubal ectopic pregnancy and early intrauterine pregnancy. Hum Reprod. 2014;29(Suppl 1):i135-	Ineligible patient population	Comparison between non-pregnant women, women with ectopic pregnancy (not eligible outcome) and women with early intrauterine pregnancy. Ineligible study population.

i36.		
Sharara FI, Queenan Jr JT, Scott Springer R, Marut EL, Scoccia B, Scommegna A. Elevated serum chlamydia trachomatis IgG antibodies: what do they mean for IVF pregnancy rates and loss? J Reprod Med Obstet Gynaecol. 1997;42(5):281-86.	Ineligible patient population	Population is women undergoing IVF. All women were found to be C. trachomatis negative prior to initiating IVF. Compares women with subsequent elevated Chlamydia antibody levels (not actual presence C. trachomatis) to those negative for Chlamydia antibodies. Outcome is result of IVF.
Silveira MFd, Sclowitz IKT, Entiauspe LG, Mesenburg MA, Stauffert D, Bicca GLdO, et al. Chlamydia trachomatis infection in young pregnant women in Southern Brazil: a cross-sectional study. Cad Saude Publica. 2017;33(1):e00067415.	Ineligible setting	Brazil not analogous to the UK
Silverman N, Hochman M, Sullivan M, Womack M. A randomized, prospective trial of amoxicillin vs erythromcycin for the treatment of chlamydia in pregnancy. Am J Obstet Gynecol. 1993;168:420.	Ineligible outcomes	Head-to-head RCT of antibiotic treatments. Reports maternal cure rates and side effects, but not neonatal outcomes.
Silverman NS, Sullivan M, Hochman M, et al. A randomized, prospective trial comparing amoxicillin and erythromycin for the treatment of chlamydia trachomatis in pregnancy. Am J Obstet Gynecol. 1994;170(3):829-32.	Study protocol	Abstract only
Siritantikorn S, Kantang R, Puthavathana P, Chavalitdhamrong P, Boonyaprakob U, Wasi C, et al. Chlamydia trachomatis infection in the newborns. J Med Assoc Thai. 1986;69(6):312-7.	Ineligible setting	Thailand not analogous to the UK
Skjeldestad FE, Johansen OJ, Dalen A. A comparative neonatal study of infants born by mothers with chlamydia trachomatis in cervix uteri. Acta Paediatr Scand. 1987;76(2):359-60.	Ineligible comparator	Although reported to be comparative study of infants born to chlamydia-positive (cases) vs chlamydia-negative(controls) mothers, only results for cases reported.
Skrablin S, Goluza T, Kuvaci I, Kalafatic D, Plavec A, Gorajscan V, et al. First trimester microbiology of the cervix and the outcome of pregnancies at high risk for prematurity. Gynaecologia et Perinatologia. 2002;11(4):143-49.	Ineligible patient population	Women with positive cultures were treated with erythromycin (2g daily) or azithromycin (500mg daily). Chlamydia positive (treated) vs chlamydia negative.
Smith JB, Gerdes JS, Hadley CB, Harris MC, Ludomirski A, Nachamkin I, et al. Prospective-study of chlamydia trachomatis (Ct) infections in premature-infants. Pediatr Res. 1987;21(4):A420-A20.	Study protocol	Abstract only
Soltz S, Schneider, Niebauer, Knobler, R M, Lindmaier.	Non English	German

Significance of the dose of josamycin in the treatment of chlamydia infected pregnant patients [German]. Zeitschrift fur Hautkrankheiten. 1989;64(2):129-31.	language paper	
Sozio J, Ness RB. Chlamydial lower genital tract infection and spontaneous abortion. Infect Dis Obstet Gynecol. 1998;6(1):8-12.	Ineligible patient population	Ineligible study population.compared a random sample of women who experienced a spontaneous abortion (cases) with a random sample of women with uncomplicated pregnancies (controls).
Stagno S, Brasfield DM, Brown MB, Cassell GH, Pifer LL, Whitley RJ, et al. Infant pneumonitis associated with cytomegalovirus, chlamydia, pneumocystis, and ureaplasma: a prospective study. Pediatrics. 1981;68(3):322-29.	Ineligible study design	Pneumonitis. Ineligible study population.
Stears S. Best evidence topic reports. BET 4. Treating chlamydia in pregnancy. Emerg Med J. 2009;26(2):120-2.	Ineligible study design	Non-systematic review
Steiner A, Geisler WM, Eisenberg E, Diamond M, Legro RS. Chlamydia trachomatis serostatus is an independent predictor of pregnancy and pregnancy outcome. Hum Reprod. 2015;30:i28-i29.	Ineligible patient population	Secondary analysis of women enrolled in PPCOS II and AMIGOS studies investigating anti-C.trachomatis as predictor of reproductive outcomes in infertile women. No relevant outcomes.
Steiner AZ, Diamond MP, Legro RS, Schlaff WD, Barnhart KT, Casson PR, et al. Chlamydia trachomatis immunoglobulin G3 seropositivity is a predictor of reproductive outcomes in infertile women with patent fallopian tubes. Fertil Steril. 2015;104(6):1522-26.	Ineligible study design	Secondary analysis of 2 RCTs: NCT00719186 and NCT01044862 (PPCOS II - clomiphene citrate and letrozole for treatment of PCOS; AMIGOS - gonadotropins, clomiphene citrate, and letrozole along with intrauterine insemination in the treatment of unexplained infertility.
Sterner G, Enocksson E, Brihmer-Wallde C, Kallings I. Chlamydia trachomatis infection in late pregnancy and in neonates. Scand J Infect Dis [Suppl]. 1990;Suppl 71:95-8.	Ineligible study design	Non-systematic review.
Stewart HE, Gold MA, Parker AM. The impact of using emergency contraception on reproductive health outcomes: a retrospective review in an urban adolescent clinic. J Pediatr Adolesc Gynecol. 2003;16(5):313-8.	Ineligible patient population	Retrospective chart review of girls who were prescribed emergency contraception and those seeking other reproductive health care. Reports pregnancy and incidence of chlamydia as outcomes.
Sugiura-Ogasawara M, Ozaki Y, Nakanishi T, Kumamoto Y, Suzumori K. Pregnancy outcome in recurrent aborters is not influenced by chlamydia IgA and/or G. Am J Reprod Immunol. 2005;53(1):50-3.	Ineligible setting	Japan not analogous to the UK
Sweet RL, Landers DV, Walker C, et al. Chlamydia trachomatis infection and pregnancy outcome. Am J Obstet	Unknown treatment	Unclear whether women were treated or not. PHE decided to exclude

Gynecol. 1987;156(4):824-33.		
Sziller I, Fedorcsak P, Csapo Z, Szirmai K, Linhares IM, Papp Z, et al. Circulating antibodies to a conserved epitope of the chlamydia trachomatis 60-kDa heat shock protein is associated with decreased spontaneous fertility rate in ectopic pregnant women treated by salpingectomy. Am J Reprod Immunol. 2008;59(2):99-104.	Ineligible patient population	Ineligible study population - ectopic pregnancy. Not comparison of relevance: desire to conceive/no desire to conceive/ lost to follow-up. Measured associations with C. trachomatis antibodies.
Taylor BD, Haggerty CL. Management of chlamydia trachomatis genital tract infection: screening and treatment challenges. Infect Drug Resist. 2011;4:19-29.	Ineligible study design	Non-systematic review. MEDLINE search but no SR methodology. Citations limited to non-pregnant women.
Thejls H, Gnarpe J, Gnarpe H, Larsson G. Age-related decrease in prevalence of chlamydia trachomatis among pregnant women. Sex Transm Dis. 1991;18(3):137.	Ineligible study design	Not a comparative study.
Thejls H, Rahm VA, Gnarpe J, et al. Diagnostic efficacy of chlamydial antibodies in cervical secretions from pregnant women and adolescent girls. Genitourin Med. 1995;71(6):370-74.	Ineligible outcomes	Outcomes are prevalence and test accuracy - not pregnancy and neonatal outcomes.
Thomason JL, Kellett AV, Gelbart SM, James JA, Broekhuizen FF. Short-course erythromycin therapy for endocervical chlamydia during pregnancy. J Fam Pract. 1990;30(6):711-2.	Ineligible outcomes	Exclude, does not report neonatal outcomes.
Thompson S, Lopez B, Wong KH. A prospective study of chlamydia and mycoplasma infections during pregnancy: relation to pregnancy outcome and maternal morbidity. Ferns Found Series. 1982;2:155-58.	Study protocol	Abstract only
Thompson SE, Dretler RH. Epidemiology and Treatment of Chlamydial Infections in Pregnant-Women and Infants. Rev Infect Dis. 1982;4:S747-S57.	Ineligible comparator	Prospective comparative study but non-infected group comprises women with neither chlamydia nor mycoplasia so not possible to compare pregnancy outcomes (prematurity) for women with/without chlamydia.
Thorne C. Chlamydia screening in pregnancy: an evidence review. London: UK National Screening Committee Policy Review; 2010. Available from: https://legacyscreening.phe.org.uk/policydb_download.php?doc=106.	Ineligible study design	Policy review
Townshend JRP, Turner HS. Analysing the effectiveness of chlamydia screening. J Oper Res Soc. 2000;51(7):812-24.	Ineligible study design	Modelling approach to analysing the cost-effectiveness of screening programmes. Undertook brief literature review but not a systematic review

Turrentine MA, Troyer L, Gonik B. Randomized prospective study comparing erythromycin, amoxicillin, and clindamycin for the treatment of chlamydia trachomatis in pregnancy. Infect Dis Obstet Gynecol. 1995;2(5):205-9.	Ineligible outcomes	Head-to-head trial but does not neonatal adverse effects.
Van den Borre C, Dab I, Malfroot A, Naessens A. Subclinical infantile chlamydia trachomatis pulmonary infection. Pediatr Pulmonol. 1993;15(4):263-65.	Ineligible study design	Case report
Anonymous. Study examines chlamydia and family planning methods. IPPF Open File. 1988;81:17-18.	Ineligible study design	South Africa not analogous to the UK
van Valkengoed IG, Postma MJ, Morre SA, van den Brule AJ, Meijer CJ, Bouter LM, et al. Cost effectiveness analysis of a population based screening programme for asymptomatic chlamydia trachomatis infections in women by means of home obtained urine specimens. Sex Transm Infect. 2001;77(4):276-82.	Relevant SR	Relevant individual studies were identified by YHEC and have been included.
van Valkengoed IGM, Morre SA, van den Brule AJC, Meijer CJLM, Bouter LM, Boeke AJP. Overestimation of complication rates in evaluations of chlamydia trachomatis screening programmes - implications for cost-effectiveness analyses. Int J Epidemiol. 2004;33(2):416-25.	Ineligible study design	Screening programme but not compared with no screening;
Vile Y, Carroll SG, Watts P, Ward M, Nicolaides KH. Chlamydia trachomatis infection in prelabour amniorrhexis. Br J Obstet Gynaecol. 1997;104(9):1091-3.	Ineligible patient population	Prospective comparative study of women with PROM; reports data for women with positive/negative chlamydia cultures but no relevant outcomes. Ineligible study population.
Vonsee HJ, Stobberingh EE, Bouckaert PX, de Haan J, van Boven CP. Detection of chlamydia trachomatis, mycoplasma hominis and ureaplasma urealyticum in pregnant Dutch women. Eur J Obstet Gynecol Reprod Biol. 1989;32(2):149-56.	Ineligible study design	Not a comparative study. Reports isolation rates of specific micro-organisms in pregnant women;
Vonsee HJ, Stobberingh EE, Bouckaert PX, Van den Bogaard AE. Frequency of chlamydia trachomatis, mycoplasma hominis and ureaplasma urealyticum infections in pregnant women. J Chemother. 1989;1(4 Suppl):904-5.	Ineligible study design	Non-comparative study reporting prevalence of selected microorganisms, including C. trachomatis.
Voskakis I, Keramitsoglou T, Avdeliodi K, Deligeoroglou E, Creatsas G, Varla-Leftherioti M. Chlamydia trachomatis (CT) infection and V gamma 9V delta 2 T cells in women with	Ineligible patient population	Prospective comparative study in women with miscarriage who were chlamydia positive/negative. No relevant outcomes. Ineligible study population.

recurrent spontaneous abortions. J Reprod Immunol. 2016;115:58-58.		
Vries R, Bergen JE, Jong-van dBLT, Postma MJ. Systematic screening for chlamydia trachomatis: estimating cost-effectiveness using dynamic modeling and Dutch data. Value Health. 2006;9(1):1-11.	Ineligible patient population	Cost-effectiveness analysis of a screening programme for men and women, not specifically pregnant women.
Wager GP, Martin DH, Koutsky L, Eschenbach DA, Daling JR, Chiang WT, et al. Puerperal infectious morbidity: relationship to route of delivery and to antepartum Chlamydia trachomatis infection. Am J Obstet Gynecol. 1980;138(7 Pt 2):1028-33.	Ineligible outcomes	Case-control study reporting associations between C. trachomatis and maternal puerperal infectious morbidity. Relevant comparator but does not report outcomes of interest.
Ward B, Rodger AJ, Jackson TJ. Modelling the impact of opportunistic screening on the sequelae and public healthcare costs of infection with chlamydia trachomatis in Australian women. Public Health. 2006;120(1):42-49.	Ineligible patient population	Comparison of a single opportunistic screening examination with no screening at differing prevalence rates of C. trachomatis in all women (not specifically pregnant women). Clinical outcomes from literature but not SR, and health costs.
Webb DA, Mathew L, Culhane JF. Lessons learned from the Philadelphia collaborative preterm prevention project: the prevalence of risk factors and program participation rates among women in the intervention group. BMC Pregnancy Childbirth. 2014;14:368.	Ineligible patient population	RCT of effect of a preventive service & treatment programme in women with previous preterm birth. Reports prevalence of various risk factors, most relevant being urogenital tract infections (chlamydia one of the named bacterial pathogens). Ineligible study population.
Wehbeh H, Ruggiero R, Ali Y, Lopez G, Shahem S, Zarou D. A randomized clinical trial of a single dose of zithromycin in treatment of chlamydia amongst pregnant women. Am J Obstet Gynecol. 1996(1 Pt 2):361.	Ineligible outcomes	Head-to-head trial of antibiotics in women and their partners. Reports cure rates, culture rates and side effects. No neonatal outcomes.
Wehbeh HA, Ruggeirio RM, Shahem S, et al. Single-dose azithromycin for chlamydia in pregnant women. J Reprod Med. 1998;43(6):509-14.	Study protocol	Abstract only
Weissenbacher TM, Kupka MS, Kainer F, et al. Screening for chlamydia trachomatis in pregnancy: a retrospective analysis in a German urban area. Arch Gynecol Obstet. 2011;283(6):1343-47.	Ineligible study design	Not comparative. Reports screening prevalence and mode of delivery with/without chlamydia.
Welte R, Jager H, Postma MJ. Cost-effectiveness of screening for genital chlamydia trachomatis. Expert Rev Pharmacoecon Outcomes Res. 2001;1(2):145-56.	Ineligible study design	SR excluded - cost-effectiveness. All relevant included studies checked and picked up by YHEC search.
Wilfert CM, Gutman LT. Chlamydia trachomatis infections of infants and children. Adv Pediatr. 1986;33:49-75.	Ineligible study design	Non-systematic review.

Witwer M. Chlamydia implicated in ectopic pregnancy, poor birth outcomes. Fam Plann Perspect. 1990;22(6):280.	Ineligible study design	Overview of two studies; Ineligible study population (women with ectopic pregnancy).
Wood PL, Hobson D, Rees E. Genital infections with chlamydia trachomatis in women attending an antenatal clinic. Br J Obstet Gynaecol. 1984;91(12):1171-6.	Ineligible outcomes	Comparative study but no relevant maternal outcomes for women with/without chlamydia;
Xia H, Li X, Li X, Liang H, Xu H. The clinical management and outcome of term premature rupture of membrane in East China: results from a retrospective multicenter study. Int J Clin Exp Med. 2015;8(4):6212-7.	Ineligible setting	China not analogous to the UK. Retrospective comparative study of population-based outcome: women with/without PROM.
Yang YS, Lee TY, Chang FM, Ko TM. Chlamydia trachomatis infection in pregnant women. J Formos Med Assoc. 1988;87(12):1177-81.	Ineligible setting	China not analogous to the UK
Zakher B, Cantor AG, Pappas M, Daeges M, Nelson HD. Screening for gonorrhea and chlamydia: a systematic review for the U.S. preventive services task force. Ann Intern Med. 2014;161(12):884-93.	Ineligible study design	SR of screening strategies vs no screening but no studies included in pregnant women.
L'Agence Nationale d'Accreditation d'Evaluation en Sante. Assessment of screening for chlamydia trachomatis infection of the lower genitourinary tract in France. Saint-Denis La Plaine, France: ANAES; 2003.	French	French
Anonymous. When is chlamydia screening necessary in family planning? Contracept Technol Update. 1989;10(4):45-8.	Ineligible study design	Overview/discussion article
Anonymous [News article]. Screening at risk groups for chlamydia trachomatis. Practitioner. 1989;233(1479):1518.	Ineligible study design	News item
Health and Welfare Canada - Health Protection Branch. 1989 Canadian guidelines for screening for chlamydia trachomatis infection. Can Dis Wkly Rep. 1989;15(Suppl 5):1-13.	Ineligible study design	Guidelines weren't informed by any form of literature review;
Anonymous [News article]. Chlamydia screening can prevent harm to newborns. Aust Nurs Midwifery J. 2015;23(4):26.	Ineligible study design	News item

Appendix 4 – Summary and Appraisal of Individual Studies

Data Extraction

Below are a series of tables of extracted data for studies included in this review. Most tables in the body of the report show condensed versions of these full data extraction tables. Blue text in the following tables denotes places where the YHEC has calculated outcomes. Please note that all extracted data relates to question one – the systematic review reporting the impact of untreated chlamydial infection, during pregnancy, on pregnancy outcomes in the UK. No studies were identified for key questions 2 to 5 (rapid reviews).

Table 4.1: Study characteristics

Study	Trial design	Objective	Location (sites/countries)	Date of Trial	Duration of trial/treatment	Details of funding
Randomised controlled trials						
Alger 1991 [24]	Double-blind, placebo controlled RCT	To determine the comparative efficacy of clindamycin and erythromycin in eradication of Chlamydia trachomatis from the lower genital tract in pregnant women and whether clindamycin is better tolerated and, hence, promotes patient compliance and cure rates superior to erythromycin.	One site in the USA; University of Maryland Hospital Obstetrical Clinic, Baltimore/USA	Between October 1985 and April 1988	Duration of study: approx. 2.5 years. Duration of treatment: 14 days.	The Upjohn Company.
Martin 1997 [20]	Double-blind RCT	To determine if treatment of pregnant women with Chlamydia trachomatis infection would lower the incidence of preterm delivery and/or low birth weight.	Seven sites in the USA (Harlem Hospital and Columbia University, New York, NY; Louisiana State University and Tulane University, New Orleans; University of Oklahoma, Oklahoma City; University of Texas Health Science Center, San Antonio; and University of Washington, Seattle)	Enrolment in Vaginal Infection and Prematurity (VIP) study was between November 1, 1984, and March 31, 1989.	Eligible women entered a 1-week placebo run-in prior to randomization. Duration of trial: until the end of the 35th week of pregnancy. Duration of treatment: 10 weeks or until the end of the 35th week of pregnancy, whichever came first.	National Institute of Child Health and Human Development (contract grants: HD-3-2832 through HD-3-2836). National Institute of Allergy and Infectious Diseases (contract grant AI-4-2532).
McGregor 1990 [21]	Double-blind RCT	To prospectively evaluate associations of cervicovaginal microflora and selected lower genital tract microbe-associated factors with pregnancy outcomes in women enrolled in a double-blind placebo-controlled trial of short-	Antenatal clinics in Denver/USA	From October 1985 to August 1988	Study duration: 35 months	NR

		course erythromycin treatment at 26 to 30 weeks' gestation to prevent preterm birth.				
Comparative, observational studies						
Rivlin 1997 [22]	Prospective cohort	To compare maternal, foetal, neonatal, and infant outcomes in treated versus untreated pregnant women with positive endocervical cultures for Chlamydia trachomatis. The study originally intended to compare two different types of antigen test. This is a supplementary study comparing women who were correctly diagnosed and treated and women who were incorrectly diagnosed (false negatives) and did not receive antibiotics.	One centre in the USA; University of Mississippi Medical Center/USA	NR	Study duration: NR Treatment duration: 7 days. Infants were followed up for between six weeks and two years	NR
Ryan 1990 [23]	Prospective cohort	To study the effect of Chlamydia trachomatis on pregnancy outcomes, and to discover whether treatment of chlamydial infections during pregnancy could reduce the impact of the infections on pregnancy outcome.	Single centre in the USA; regional medical centre, Memphis/USA	Patients were enrolled from September 1, 1982 through August 31, 1985.	Study duration: 36 months. Treatment duration: 7 days erythromycin, or 7 weeks oral sulfisoxazole (for patients allergic to erythromycin).	NR

NR: Not reported; RCT: randomised controlled trial; USA: United States of America

Table 4.2: Study methods

Study	Inclusion criteria	Exclusion criteria	Outcomes reported	Data collection time points	Duration of follow-up	Loss to follow up and discontinuations
Randomised controlled trials						
Alger 1991 [24]	Women with a cervical specimen that was culture-positive for C. trachomatis before 24 weeks' gestation.	- Sensitivity to study medication; - Significantly impaired hepatic function; - Persistent gastrointestinal symptoms or history of colitis; - Antibiotic therapy after screening and before enrolment; - Current treatment with insulin, steroids, carbamazepine, or warfarin.	Eradication of C. trachomatis, cure rates and antibiotic compliance.	Patients were screened for N. gonorrhoea and C. trachomatis before enrolment, at which time demographic characteristics were subsequently recorded (16-24 weeks) Tests of cure for C. trachomatis were conducted on completion of therapy (14 days after the first dose of medication), approximately 4 weeks later, and on admission for labour or ruptured membrane (term of preterm).	Patients: up to and including admission to delivery suite. Infants: 3 months	The study describes 135 patients enrolled, but outcome data only available for 126. The groups that the missing patients were assigned to are not reported, so it is not clear whether the number who were not analysed was balanced across the groups. Overall: 9 patients lost to follow-up (delivered elsewhere); losses /discontinuations not reported by treatment group. One patient discontinued clindamycin treatment (due to side effects) without discussing this with the investigator.
Martin 1997 [20]	Women seeking prenatal care between the 23rd and 26th completed weeks of pregnancy were eligible for inclusion if they	- Women who received antibiotics between the study screening period and the initiation of study medication;	Incidence of preterm delivery and low birth weight. Study also measured gestational age at delivery, other	Treatment compliance and side effects were recorded at each regular antenatal visit. Repeat cultures were obtained 2-4 weeks after enrolment from the first 100 women enrolled into the clinical trial at each study site. Repeat cultures were also taken from a random sample of 12% of	Patients: NR, although those with C. trachomatis were retreated immediately postpartum. Infants:	After starting medication, 25 erythromycin-treated and 23 placebo-treated women withdrew from the trial but were included in the intent-to-treat analysis.

	were: - Found to be positive for C. trachomatis in the observational phase of the study; - ≥16 years old; - Free of medical complications (hypertension, severe renal or cardiac disease requiring medication, diabetes requiring insulin) and obstetric conditions (erythroblastosis, multiple gestation, cervical cerclage) related to premature delivery; - Not taking selected medications (antibiotics within the previous 2weeks or current tocolytic or steroid use).	- Women who were allergic to erythromycin; - Women who were receiving theophylline; - Women with positive cultures for N gonorrhoeae or 105 microorganisms/ml of urine; - History of jaundice or liver disease within the past 3 years.	pregnancy outcomes, treatment compliance and side effects.	all study participants at 31-33 and 34-36 weeks gestation (6% each), from women admitted for pregnancy complications at <37 weeks gestation (premature labour, rupture of membranes), and from all women admitted to the hospital in term labour during weekday daytime hours. Patients admitted to the hospital for pregnancy complications or in labour had pertinent pregnancy, labour and delivery information collected on standardized forms.	those not treated empirically after delivery were followed until their first postnatal visit, at which time they were cultured and treated with antibiotics if necessary.	
McGregor 1990 [21]	Women between 26 and 30	- Recognised cause for	Obstetric and neonatal	Vaginal and cervical swabs were obtained at initial examination,	Patients: NR (records	Losses to follow-up reported overall and

	weeks' gestation who attended publicly supported antenatal clinics in the Denver metropolitan area.	prematurity (multiple gestation, placenta previa, or cervical incompetence; - Severe cardiac, renal, respiratory, or immunologic diseases; - Allergy to erythromycin.	outcomes including PROM, gestational length, birth weight, and newborn infection.	along with demographic, social, behavioural, sexual, medical, and obstetric information and specifics about urogenital symptoms. Follow-up examination was conducted 2 to 4 weeks after enrolment (including repeat vaginal sampling), in addition to other routine prenatal visits. Women were asked about side effects, sexual activity, and signs and symptoms of vaginitis before repeat vaginal sampling. Maternal and newborn medical records were reviewed for information on antenatal, intrapartum, and postpartum maternal course and the newborn course through 3 months of age.	were reviewed for antenatal, intrapartum and postpartum information) Newborns: through 3 months of age	not according to treatment group. Six enrolled women were excluded from the analyses: 4 lost to follow-up, one treated for premature labour on day of enrolment, and one experienced intrauterine foetal death at 30 weeks' gestation.
Comparative observational studies						
Rivlin 1997[22]	Women registering for obstetric care on the staff clinic service at the university medical centre were enrolled.	Patients undergoing antibiotic therapy.	Maternal, foetal, neonatal and infant outcomes.	Cervical samples were taken during the Initial clinical evaluation at pregnancy registration and a test of cure was conducted after treatment completed. No specific intermediate or post-delivery time points, but infant follow-up data was recorded variously from 6 weeks to 2 years.	Patients: NR; Infants: 6 weeks to 2 years	NR
Ryan 1990 [23]	New obstetric patients entering clinic from Sept	NR	Prenatal, intrapartum and postpartum	Cervical cultures were determined at first prenatal visit, along with demographic, clinical	NR. Only treated chlamydia-	NR

	1, 1982 through Aug 31, 1985 for their first prenatal visit.	complications, and clinical diagnoses.	and laboratory data. Prospectively collected clinical data included prenatal, intrapartum and postpartum complications, clinical diagnoses and procedures. During the first 16 months of the study, patients with positive chlamydia cultures were not treated and no subsequent cultures were performed. For the following 20 months, patients with a positive culture at their next prenatal visit after diagnosis were treated and had a second culture performed on completion of treatment, with repeat testing until the culture was negative.	positive women were seen for a follow-up visit prior to delivery/birth.

NR: not reported; PROM: premature rupture of the membrane

Table 4.3: Intervention details

Study identifier	Chlamydia status	Intervention	Total dose	Scheduling	Duration of treatment	Number of women analysed	Partner treated
Randomised controlled trials							
Alger 1991 [3]	Chlamydia positive	Erythromycin (+ clindamycin placebo)	1332 mg/day	333 mg tablet QID	14 days	40	Doxycycline 200mg (100mg BID) for 7 days
	Chlamydia positive	Clindamycin (+ erythromycin placebo)	1800 mg/day	450 mg capsule QID	14 days	42	
	Chlamydia positive	Placebo (erythromycin + clindamycin placebos)	NA	1 capsule + 1 tablet, QID	14 days	44	
Martin 1997 [4]	Chlamydia positive	Erythromycin	1000 mg/day	333 mg TID	10 weeks or until completion of 35 weeks' pregnancy, whichever came first.	205	Treatment of partners was recommended. Unclear whether they received the same drug/dose or how many were treated.
	Chlamydia positive	Placebo	NA	TID		209	
McGregor 1990 [5]	Chlamydia	Erythromycin	1000 mg	333 mg TID	7 days	13	With the exception of

	positive		/day				one patient with N. gonorrhoea, sexual partners were not referred for evaluation and treatment.
	Chlamydia positive	Placebo	NA	1 tablet TID	7 days	12	
Comparative, observational studies							
Rivlin 1997[6]	Chlamydia positive	Erythromycin	3,200 mg/day	800 mg QID	7 days	23	NR
	Chlamydia positive	No treatment	NA	NA	NA	58	NR
Ryan 1990 [7]	Chlamydia positive	Erythromycin	2000 mg/day	500 mg QID	7 days	1323	NR
	Chlamydia positive	No treatment	NA	NA		1110	NR
	Chlamydia negative	NA	NA	NA		9111	NR

NR: Not reported; NA: Not applicable; mg: milligrams; BID: twice daily; TID: three times daily; QID: four times daily

Table 4.4: Participant details

Study identifier	Intervention	Diagnostic procedure	Age of mothers	Ethnicity	Mean Gestation*	Concurrent infections
Randomised controlled trials						
Alger 1991 [24]	Erythromycin	Endocervical swabs: Epifluorescence detection of cycloheximide-treated McCoy cells stained with fluorescein-conjugated C. trachomatis-specific monoclonal antibody.	21.7 (SD 4.2) years	Black: 97%	20.1 (SD 2.0) weeks	No specific details reported, but women found positive for N. gonorrhoea prior to enrolment were treated, as were women with other infectious conditions that required treatment.
	Clindamycin		20.3 (SD 3.2) years	Black: 93%	19.8 (SD 1.8) weeks	
	Placebo		21.3 (SD 4.0) years	Black: 91%	20.1 (SD 2.0) weeks	
Martin 1997 [20]	Erythromycin	Endocervical swabs: Fluorescence detection of McCoy cells stained with fluorescein isothiocyanate-conjugated C. trachomatis-specific monoclonal antibody .	21.5 (SD 4.2) years	White, Asian and Native American: 34 (17%) Black: 126 (61%) New York Hispanic: 34 (17%) Non-New York Hispanic: 11 (5%)	Screening: 24.5 (SD 1.1) Randomization: 29.4 (SD 1.8) weeks	Genital infections (group B streptococci, U. urealyticum, Trichomonas vaginalis, bacterial vaginosis, or endocervical mucopus); no further details reported. Six of 85 (7%) of the women who had positive *C. trachomatis* cultures also
	Placebo		21.1 (SD 4.3) years	White, Asian and Native American: 33 (16%) Black: 123 (59%) New York Hispanic: 47 (22%) Non-New York Hispanic: 6 (3%)	Screening: 24.5 (SD 1.1) Randomization: 29.4 (SD 1.5) weeks	

						had positive cultures for N. gonorrhoea.
McGregor 1990 [21]	Erythromycin	Endocervical swabs: inoculation followed by standard techniques for group A and group B streptococci, S. aureus, G. vaginalis and yeast organisms, microscopic examination of cycloheximide-treated McCoy cells treated with fluorescence-conjugated anti-chlamydia monoclonal antibody for C. trachomatis, and Mycotrim GU Triphasic culture System for identification of cultured M. hominis and U. urealyticum microorganisms. Negative cultures of C. trachomatis were blind passaged once and reprocessed.	23.0 (SD 4.3) years (range: 13-37)	White: 45 (37.8%) Black: 42 (35.3%) Hispanic: 30 (25.2%) Other: 2 (1.6%)	26-30 weeks	Pretreatment organisms and virulence factors were: N. gonorrhoea, C. trachomatis, U. urealyticum, M. hominis, bacterial vaginosis, Mobiluncus species, G. vaginalis, T. vaginalis, S. aureus, group A and group B streptococci, yeast species, proline aminopeptidase, phospholipase C, nonspecific protease.
	Placebo		23.2 (SD 4.2) years (range: 16-34)	White: 43 (39.1%) Black: 42 (38.2%) Hispanic: 21 (19.1%) Other: 4 (3.6%)	26-30 weeks	
Comparative, observational studies						
Rivlin 1997 [22]	Erythromycin	Endocervical swabs: Direct fluorescent chlamydial antigen test. Tissue culture isolation for C. trachomatis; further details reported in previous publications.	20 years (range: 13-30)	African-American: 70 (86.4%) Caucasian: 11 (13.6%)	Diagnosis: mean 21 weeks (range : 4-42)	NR
	No treatment		22 years (range: NR)			

Ryan 1990 [23]	Chlamydia positive (erythromycin + untreated patients)	Endocervical swabs: Microscopic examination of cycloheximide-treated McCoy cells stained with iodine or a monoclonal fluorescent antibody.	Overall for chlamydia positive patients (treated + untreated) 11-17 years: 652 (32.1%) 18-19 years: 606 (29.0%) 20-24 years: 854 (20.0%) 25-29 years: 238 (11.6%) 30-45 years: 83 (7.5%)	Overall for chlamydia-positive patients (treated + untreated: n=2433): Non-white: 2290 (94.1%) White: 143 (5.9%)	NR	Not specifically reported, although maternal discharge diagnoses were used to examine associations between positive chlamydia culture and urinary tract infection, chronic hypertension, superimposed toxaemia, pre-eclampsia, diabetes, fever of unknown origin, pneumonia, asthma, seizures (other than pre-eclampsia), haemoglobin As, or abnormal Papanicolaou smears.
	Chlamydia negative		11-17 years: 1379 (15.1%) 18-19 years: 1481 (16.3%) 20-24 years: 3419 (37.5%) 25-29 years: 1810 (19.9%) 30-45 years: 1022 (11.2%)	Non-white: 7706 (84.6%) White: 1405 (15.4%)		

NR: not reported; SD: standard deviation

Table 4.5: Statistical analysis

Study identifier	Statistical analysis	Type of analysis	Loss to follow up and discontinuations
Randomised controlled trials			
Alger 1991 [24]	Categorical variables were compared using chi-squared tests, or Fisher's exact tests when categories contained fewer than 5 patients.	Per protocol analysis. Patients with data on delivery outcomes were included in the analysis.	The study describes 135 patients enrolled, but outcome data available for 126, unclear whether the number who were not analysed was balanced across the groups. Overall: 9 patients lost to follow-up (delivered elsewhere); losses /discontinuations not reported by treatment group. One patient discontinued clindamycin treatment (due to side effects) without discussing this with the investigator.
Martin 1997 [20]	The data were analysed using ANOVA for continuous variables and contingency table methods for categoric variables. Categorical variables were compared using chi-square tests or Fisher's exact test. A Mantel-Haenszel test was conducted when treatment group comparisons were adjusted for a single categoric factor (in this related publication, p-values in the tables were for tests of differences between treatment groups for patients in specific strata and were not based on Mantel-Haenszel statistics). Further analyses were conducted using a logistic regression model which included stratification factors. The efficacy of the trial was periodically monitored by conditional power techniques. Significance was defined as a two-tailed $p<0.05$.	Reported to be ITT analysis but some analyses appear to have been conducted on assessed patients and methods used to account for missing data were not reported.	After starting medication, 25 erythromycin-treated and 23 placebo-treated women withdrew from the trial but were included in the ITT analysis.
McGregor 1990 [21]	Descriptive statistics were used to summarize the data, with chi-squared tests and Fisher's exact test (two-tailed) used to test the statistical significance of differences between treatment groups and other univariate associations. Student's t test was used to analyse continuous data. Relative risks with 95% CIs were calculated, where appropriate. Logistic regression analyses were performed to control the effects of multiple independent variables on preterm	The type of analysis undertaken was unclear. The total evaluated sample comprised 229 of	Losses to follow-up reported overall and not according to treatment group. Six enrolled women were excluded from the analyses: 4 lost to follow-up, one

	birth, PROM, and low birth weight. Multivariate analysis was not attempted for the dependent variables PROM or preterm birth without PROM because of the small number of women with these outcomes. Univariate and multivariate analyses were conducted using an alpha-value of 0.05. The Breslow-Day test for homogeneity of results of odds ratios was used to confirm significance, where appropriate.	the 235 women enrolled, however it is unclear whether the six excluded women had been randomized and treated.	treated for premature labour on the day of enrolment, and one experienced intrauterine foetal death at 30 weeks' gestation.
Comparative, observational studies			
Rivlin 1997[22]	Statistical analyses were conducted using chi-squared tests, Fisher's exact test and ANOVA, as appropriate. A p-value of ≥0.05 was considered significant.	Analyses appear to have been conducted according to ITT for maternal outcomes.	NR
Ryan 1990 [23]	Statistical methods included descriptive statistics, chi-squared tests, Fisher's exact test, and stepwise multiple logistic regression (reported as odds ratios with 95% CIs and p-values). A probability of <0.05 was considered significant (type I error) for all statistical comparisons.	Analyses appear to have been conducted according to ITT.	NR

NR: not reported; ITT: intention to treat; ANOVA: analysis of variance; CI: confidence interval; PROM: premature rupture of membranes

Table 4.6: Miscarriage

Study identifier	Chlamydia status	Intervention	Subgroups analysed	Trimester of treatment	Outcome definition and measure	Timepoint of assessment	Number analysed	Number experiencing event	% experiencing event	Statistical comparison
Rivlin 1997	Chlamydia positive	Erythromycin	NA	1st, 2nd, or 3rd	NR	Antepartum	23	0	0%	NR
Rivlin 1997	Chlamydia positive	Untreated	NA	NA	NR	Antepartum	58	3	5%	NR

NA: Not applicable; NR: Not reported; N: Number of participants

Table 4.7: Stillbirth/neonatal death

Study identifier	Intervention	Trimester of treatment	Outcome definition and measure (if details are provided)	Time point of assessment	Number analysed	Number experiencing event	% experiencing event	Statistical analysis
Martin 1997	Erythromycin Placebo	3rd trimester	Stillbirth	3rd trimester	202 203	2 1	1% 0.5%	NR
	Erythromycin Placebo		Neonatal death		202 203	1 0	0.5% 0%	NR
Rivlin 1997	Erythromycin	1st, 2nd, or 3rd	NR	Birth	23	1	4.3%	NR
	Untreated	NA			52	0	0.0%	
Ryan 1990	Erythromycin	1st, 2nd, or 3rd	Newborn survival (Newborns who left hospital alive)	NR	1323	1315	99.4%	There were no differences in newborn survival between women with untreated chlamydia and women without chlamydia Untreated vs chlamydia negative: p<0.05 (no further details reported) There were no significant differences between women with chlamydia who were treated with erythromycin compared with untreated women
	Untreated (with chlamydia)	NA			1110	1083	97.6%	
	Untreated (without chlamydia)	NA			9111	8793	98.5%	

						with chlamydia. Untreated vs. treated: OR 2.21 (95%CI: 0.89, 5.49) p<0.08 Infants born to mothers with chlamydia who were treated were more likely to survive than infants born to mothers who did not have chlamydia Treated vs chlamydia negative: OR 1.65 (95%CI: 1.13, 2.42) p<0.01

Table 4.8: Pre-term birth

Study identifier	Chlamydia status	Intervention	Trimester of treatment	Outcome	Outcome definition and measure (if details are provided)	Time point of assessment	Number analysed	Number experiencing event	% experiencing event	Statistical comparison
Randomised controlled trials										
Martin 1997	Chlamydia positive	Erythromycin	3rd trimester	Premature delivery	<32 weeks	3rd trimester	202	1	0.5%	NR
	Chlamydia positive	Placebo	3rd trimester	Premature delivery	<32 weeks	3rd trimester	203	1	0.5%	NR
	Chlamydia positive	Erythromycin	3rd trimester	Premature delivery	32-36 weeks	3rd trimester	202	26	13%	NR
	Chlamydia positive	Placebo	3rd trimester	Premature delivery	32-36 weeks	3rd trimester	203	29	14%	NR
	Chlamydia positive	Erythromycin	3rd trimester	Premature delivery	<37 weeks	3rd trimester	202	27	13%	No statistically significant difference in the number of pre-term deliveries in the erythromycin vs placebo groups (p=0.7)
	Chlamydia positive	Placebo	3rd trimester	Premature delivery	<37 weeks	3rd trimester	203	30	15%	
Comparative, observational studies										
Rivlin 1997	Chlamydia positive	Erythromycin	1st, 2nd, or 3rd	Premature delivery	1 at 28 weeks, twins at 34 weeks, 1 at 35 weeks	Antepartum	23	3	15.0%	NR

	Chlamydia positive	Untreated	NA	Premature delivery	3 with PROM, one induced for pre-eclampsia, 3 with no clear reason	Antepartum	58	7	12.0%	NR

Table 4.9: Premature rupture of membranes

Study identifier	Chlamydia status	Intervention	Trimester of treatment	Outcome definition and measure (if details are provided)	Time point of assessment	Number analysed	Number experiencing event	% experiencing event	Statistical comparison
Randomised controlled trials									
Martin 1997	Chlamydia positive	Erythromycin	3rd trimester	<37 weeks (defined as membrane rupture before the onset of regular uterine contractions)	3rd trimester	196	5	3%	NR
	Chlamydia positive	Placebo				193	7	4%	
	Chlamydia positive	Erythromycin	3rd trimester	≥37 weeks (defined as membrane rupture before the onset of regular uterine	3rd trimester	196	16	8%	NR
	Chlamydia positive	Placebo				193	18	9%	

				contractions)					
	Chlamydia positive	Erythromycin	3rd trimester	PROM total (defined as membrane rupture before the onset of regular uterine contractions)	3rd trimester	196	21	11%	No significant difference in the proportion of women experiencing PROM (p value not reported).
	Chlamydia positive	Placebo				193	25	13%	
McGregor 1990	Chlamydia positive	Erythromycin	3rd trimester	Rupture of membranes ≥1 hour before onset of uterine contractions.	NR	13	0	0	Erythromycin significantly reduced the number of women who had PROM: RR 0.4 (95%CI: 0.2, 0.8) p=0.03
	Chlamydia positive	Placebo				12	6	50%	
Comparative, observational studies									
Ryan 1990	Chlamydia positive	Erythromycin	1st, 2nd, or 3rd	Rupture of membranes ≥1 hour before onset of labour	NR	1323	39	2.9%	Women with untreated chlamydia were more than twice as likely to have PROM than women without chlamydia Untreated vs chlamydia negative: OR 2.12 (95%CI:
	Chlamydia positive	Untreated				1110	58	5.2%	
	Chlamydia negative	NA				9111	243	2.7%	

									1.57, 2.86) p<0.001 Erythromycin significantly reduced the number of women with chlamydia who had PROM Untreated vs. treated*: OR 0.56 (95%CI: 0.37, 0.85) p<0.01 Treated vs chlamydia negative: NS (p=0.556)
Rivlin 1997	Chlamydia positive	Erythromycin	1st, 2nd, or 3rd	NR NR	Antepartum	23	1	5.0%	NR
	Chlamydia positive	Untreated				58	3	5.0%	

NR: not reported; NA: not applicable; NS: not significant; N: number of patients; PROM: premature rupture of membranes; OR: odds ratio; CI: confidence interval

*** In Ryan 1990 two sets of results were presented for the untreated vs. treated comparison; one set of results reported in a table with a different version in the text. We have reported the results from the table in this report because it was the most complete (contained 95% confidence intervals)**

Table 4.10: Low birth weight

Study identifier	Chlamydia status	Intervention	Trimester of treatment	Outcome	Outcome definition	Number analysed	Number experiencing event	% experiencing event	Statistical analysis
Randomised controlled trials									
Martin 1997	Chlamydia positive	Erythromycin	3rd trimester	Low birth weight	<1,500 g	201	0	0%	NR
Martin 1997	Chlamydia positive	Placebo	3rd trimester	Low birth weight	<1,500 g	199	2	1%	
Martin 1997	Chlamydia positive	Erythromycin	3rd trimester	Low birth weight	1,500 - 2,000 g	201	17	8%	NR
Martin 1997	Chlamydia positive	Placebo	3rd trimester	Low birth weight	1,500 - 2,000 g	199	20	10%	
Martin 1997	Chlamydia positive	Erythromycin	3rd trimester	Low birth weight	<2,500 g	201	17	8%	There were no significant differences in the number of low birth weight newborns between women who took erythromycin or placebo: p=0.4 (no further details reported
Martin 1997	Chlamydia positive	Placebo	3rd trimester	Low birth weight	<2,500 g	199	22	11%	
Comparative, observational studies									
Rivlin 1997	Chlamydia positive	Erythromycin	1st, 2nd, or 3rd	Low birth weight	<2,500g	23	4	20%	None reported
Rivlin 1997	Chlamydia positive	No treatment	NA	Low birth weight	<2,500g	52	7	14%	

Ryan 1990	Chlamydia positive	Erythromycin	1st, 2nd, or 3rd	Low birth weight	<2,500 g	1323	145	11.0%	Women with untreated chlamydia were more likely to have a low birth weight baby under 2,500g than women without chlamydia Untreated vs chlamydia negative: p<0.001 (no further details reported) Erythromycin significantly reduced the number of women with chlamydia who had a low birth weight baby under 2,500g compared to untreated women Untreated vs. treated*: p<0.0001 (no further details reported) Treated vs chlamydia negative: NS (p=0.4190)
Ryan 1990	Chlamydia positive	Untreated	NA	Low birth weight	<2,500 g	1110	218	19.6%	
Ryan 1990	Chlamydia negative	NA	NA	Low birth weight	<2,500 g	9111	1068	11.7%	

NR: not reported; NA: not applicable; N: number of patients

Table 4.11: Test of cure/re-infection

Study identifier	Intervention	Trimester of treatment	Outcome definition and measure (if details are provided)	Time point of assessment	Number analysed	Number experiencing event	% experiencing event	Statistical analysis
Alger 1991	Erythromycin	2nd trimester	Number remaining chlamydia positive at completion of therapy (14 days)	2nd trimester	34	4	12%	There were no significant differences in the number remaining chlamydia positive at the first test of cure between patients randomised to erythromycin or clindamycin. No other comparisons were reported.
	Clindamycin				40	2	5%	
	Placebo				40	30	75%	
Alger 1991	Erythromycin	2nd trimester	Number remaining chlamydia positive 4 weeks following therapy	2nd trimester	32	5	16%	There were no significant differences in the number remaining chlamydia positive at the second test of cure between patients randomised to erythromycin or clindamycin. No other comparisons were reported.
	Clindamycin				36	2	6%	
	Placebo				42	30	71%	
Alger 1991	Erythromycin	2nd trimester	Number remaining chlamydia positive during labour and delivery	3rd trimester	38	8	21%	NR
	Clindamycin				34	4	12%	
	Placebo				40	17	43%	

Appraisal for Quality and Risk of Bias

Quality assessments of included studies are reported below.

Table 4.12: Detailed risk of bias for RCTs

	Studies		
	Alger 1991 [24]	**Martin 1997 [20]**	**McGregor 1990 [21]**
Was the allocation sequence adequately generated?	Unclear risk: Patients were reported to have been randomized to one of three treatment groups; no other details reported.	Low risk: Patients were randomized to treatment with either erythromycin or placebo by computer according to a permuted-block procedure with random block sizes (randomly selected between two, four and six). The randomization scheme was stratified by study site and micro-organism combination to allow subgroup analyses.	Low risk: Randomization was conducted using a computer-generated random number list by an external pharmaceutical company.
Was the concealment of treatment allocation adequate?	Unclear risk: Study states that medications were provided in blister packs, but it seems this was more to enable measures of compliance rather than to conceal allocation. No details about whether treatments were identically packaged or sequentially numbered.	Low risk: Numbers corresponding to packets of either erythromycin or placebo were individually assigned to patients by Research Triangle Institute, using a balanced randomization scheme, by telephone. Placebo tablets were identical in appearance to erythromycin tablets and were supplied by an external company.	Low risk: Treatments were prepared and randomized by an external pharmaceutical company. After the initial examination, women were given sealed identical-appearing treatment bottles and tablets, which either contained erythromycin or placebo. It was unclear how treatments were allocated (e.g. central allocation, sequentially numbered sealed envelopes).
Was knowledge of the allocated interventions adequately prevented from participants and personnel	Unclear risk: Reported to be double-blind. Patients received their assigned treatment plus a placebo, such that each dose comprised a tablet and a capsule; no indication of whether capsules/tablets were of similar appearance. Unclear whether study personnel were blinded to the assigned intervention.	Low risk: Reported to be double-blind. Placebo tablets and erythromycin tablets were identical in appearance and were supplied by an external company.	Low risk: Reported to be double-blind. Placebo and erythromycin tablets were identical in appearance, as were the bottles they were supplied in, and were prepared by an external pharmaceutical company.
Was	Low risk: Culture results were not	Low risk: Quality control measures were	Low risk: Negative cultures were blind

knowledge of the allocated interventions adequately prevented from outcome assessors	available to members of the clinical medical staff and were only reported to the investigators by study number.	in place. Each study site in turn sent 5 "unknowns" that included both positive and negative specimens to the other centres. In addition, a random sample of women had duplicate C. trachomatis specimens obtained and submitted to the laboratories for culture. Different study numbers were assigned to blind laboratory personnel to the duplicate specimens. The coded questionnaires on history, physical examination, and laboratory results were sent to Research Triangle Institute, where the data were keyed, verified and edited.	passaged once and reprocessed. Only positive N. gonorrhoea cultures were reported to health care providers
Were incomplete outcome data adequately addressed?	Unclear risk: Only patients with available data for each specific outcome appear to have been included in the analyses.	Unclear risk: After starting medication, 25 erythromycin-treated and 23 placebo-treated women withdrew from the trial but were included in the ITT analysis. However, tabulated data reflects the numbers assessed for each outcome.	Unclear risk: The total evaluated sample comprised 229 of the 235 women enrolled (unclear whether all six excluded patients had been randomized and treated). If maternal/outcome records were unavailable for review, private physicians and patients were contacted for data. There were no details of how missing data were accounted for in the analysis.
Are reports of the study free of suggestion of selective outcome reporting?	Unclear risk: Outcomes were not pre-specified. All outcomes measured (according to the study Methods) were reported, although there were no outcome data for infants despite them being followed up for 3 months. Side effects, which were not considered in the study methods, were reported.	Unclear risk: Outcomes were not pre-specified. All outcomes measured (according to the study Methods) were reported.	Low risk: All pre-specified outcomes were reported.
Was the study apparently free of other problems that could put it at a	Unclear risk: Of the placebo patients in this trial, 9 (20%) had no subsequent positive cultures for the remainder of their pregnancy. Eight of these women had three successive negative cultures.	Unclear risk: The authors reported that at three study sites which contributed 46% of the cases to the trial, high clearance of C. trachomatis occurred in the placebo group.	High risk: Only a small number of patients in each group (13 in each) were found to be positive for chlamydia infection. It was also unclear how many of these had concurrent cervicovaginal

high risk of bias?	All patients were confirmed to be culture positive initially and all denied taking any antibiotics other than the study drug. By delivery, 23 (58%) of the placebo patients had negative cultures. The authors stated: 'The placebo-control group, resulted from the participation of these patients in a separate investigation to determine whether antenatal treatment of chlamydia improves pregnancy outcome, which required a placebo arm'; no study reference given for this investigation so unsure what it means and whether it had any bearing on the randomization process.		infections.
Baseline characteristics comparable?	Low risk: Baseline characteristics were statistically compared. The authors reported there were no significant differences between groups in terms of demographic characteristics (p-value not reported), but these were limited to age, race, gestational age, parity and some social factors.	Low risk: Demographic, behavioural, and obstetrical characteristics were statistically compared. There were no significant differences in baseline characteristics between the groups.	Unclear risk: The authors reported that there were no differences between women in the erythromycin and placebo groups in terms of demographic, historical, or behavioural characteristics, but did not report this in terms of statistical significance
ITT analysis?	High risk: 135 patients were randomized to treatment but only 126 patients with delivery outcome data were subsequently included; 9 patients were lost to follow-up. Analyses were only conducted on patients with available data for each specific outcome.	Unclear risk: Reported to be ITT analysis. Baseline characteristics reported for all randomized patients but some analyses appear to have been conducted on patients assessed for each outcome.	Unclear risk: Six of the 235 women enrolled/randomized were excluded from the analysis. Thus, the total evaluated sample included 229 women (and their newborns).
ITT: intention to treat			

Table 4.13: Detailed risk of bias table for observational studies

	Studies	
	Rivlin 1997 [22]	**Ryan 1990 [23]**
Is there sufficient description of the groups and the distribution of prognostic factors?	High risk: Limited baseline description. Means and ranges provided for overall study, but not by groups, so unclear whether groups were comparable at baseline.	High risk: Baseline characteristics were sorely lacking and were reported according to culture results, i.e. positive and negative, so details of chlamydia-positive women were presented for treated and untreated women combined. Although analyses were conducted on clinical factors known to be associated with low birth weight (socioeconomic levels, incidence of pre-eclampsia, urinary tract infections, smoking), only race, parity and age range categories were reported.
Are the groups assembled at a similar point in their disease progression?	High risk: Gestational age at diagnosis was reported overall and not by study groups, but no further details relating to the pregnancy were reported. Only patients with both a culture and direct antigen test positive for chlamydia were treated; those with only a positive culture for chlamydia were left untreated.	Unclear risk: New obstetric patients were included in the study and tested for chlamydia, but were not described further in terms of their pregnancy. Chlamydia-positive women were either treated or untreated.
As the intervention/treatment reliable ascertained?	Unclear risk: Pregnancy outcomes were compared between treated and untreated women with chlamydia-positive cultures. Erythromycin is/was standard treatment at the time of the study	Unclear risk: Pregnancy outcomes were compared between treated and untreated women with chlamydia-positive cultures and women with chlamydia-negative cultures.
Were the groups comparable on all important confounding variables?	Unclear risk: No confounding variables were reported.	Unclear risk: No confounding variables were reported.
Was there adequate adjustment for the effect of these confounding variables?	Unclear risk: No confounding variables were reported.	Low risk: Analyses were conducted to assess the contribution on clinical factors known to be associated with low birth weight (socioeconomic levels, incidence of pre-eclampsia, urinary tract infections, smoking), and multiple logistic regression was used to correct for confounding factors when investigating the relationship between C. trachomatis infections and the outcomes of perinatal survival and PROM.
Was a dose response relationship between	Study was not designed to measure dose response relationship.	Study was not designed to measure dose response relationship.

intervention and outcome demonstrated?		
Was outcome assessment blind to exposure status?	Low risk: Direct antigen tests were performed in clinical laboratories at the medical centre and results were supplied to the physician for on-going care. Tissue samples were sent to an external reference laboratory for tissue culture isolation, but the results were not available to the clinic physicians.	Unclear risk: Blinding of the outcome assessment was not reported.
Was follow-up long enough for the outcomes to occur?	Unclear risk: Duration of follow-up for the women was not reported; For women in earlier stages of pregnancy follow up was long enough, but there appear to be some women who were beyond full term (i.e., more than 40 weeks). It is unclear how many women were in late stages of pregnancy and whether there was sufficient time for antibiotics to work in these women. The duration of follow-up in infants with recorded data ranged from 6 weeks to 2 years.	Unclear risk: Duration of follow-up was not reported. Only chlamydia-positive patients who received treatment were seen for a follow-up visit prior to delivery/birth.
What proportion of the cohort was followed up?	Unclear risk: Not specifically reported for women or neonates/infants. Maternal outcomes were reported for all chlamydia-positive women. Newborn charts were only available for 23 newborns of treated mothers and 52 of untreated mothers, and follow-up records for only 14 and 32, respectively.	Unclear risk: Follow-up was not specifically reported. Only treated chlamydia-positive women were seen for a follow-up visit, although all women appear to have been included in the analyses.
Were drop-out rates and reasons for dropout similar across intervention and unexposed groups?	Unclear risk: Loss to follow-up was not reported. Of newborns with available charts, follow-up data appears to be missing for 9 patients in the 'treated' group and 20 in the 'untreated' group.	Unclear risk: Loss to follow-up and study discontinuations were not reported. All patients appear to have been included in the analyses.
PROM: premature rupture of membranes		

Appendix 5 – UK NSC Reporting Checklist for Evidence Summaries

All items on the UK NSC Reporting Checklist for Evidence Summaries have been addressed in this report. A summary of the checklist, along with the page or pages where each item can be found in this report, is presented in Table 5.1.

Table 5.1: UK NSC reporting checklist for evidence summaries

	Section	Item	Page no.
1.	TITLE AND SUMMARIES		
1.1	Title sheet	Identify the review as a UK NSC evidence summary.	Title page
1.2	Plain English summary	Plain English description of the executive summary.	5
1.3	Executive summary	Structured overview of the whole report. To include: the purpose/aim of the review; background; previous recommendations; findings and gaps in the evidence; recommendations on the screening that can or cannot be made on the basis of the review.	6
2.	INTRODUCTION AND APPROACH		
2.1	Background and objectives	Background – Current policy context and rationale for the current review – for example, reference to details of previous reviews, basis for current recommendation, recommendations made, gaps identified, drivers for new reviews Objectives – What are the questions the current evidence summary intends to answer? – statement of the key questions for the current evidence summary, criteria they address, and number of studies included per question, description of the overall results of the literature search.	11

		Method – briefly outline the rapid review methods used.	
2.2	Eligibility for inclusion in the review	State all criteria for inclusion and exclusion of studies to the review clearly (PICO, dates, language, study type, publication type, publication status etc.) To be decided a priori.	15
2.3	Appraisal for quality/risk of bias tool	Details of tool/checklist used to assess quality, e.g. QUADAS 2, CASP, SIGN, AMSTAR.	24
3.	SEARCH STRATEGY AND STUDY SELECTION (FOR EACH KEY QUESTION)		25
3.1	Databases/ sources searched	Give details of all databases searched (including platform/interface and coverage dates) and date of final search.	25
3.2	Search strategy and results	Present the full search strategy for at least one database (usually a version of Medline), including limits and search filters if used. Provide details of the total number of (results from each database searched), number of duplicates removed, and the final number of unique records to consider for inclusion.	27
3.3	Study selection	State the process for selecting studies – inclusion and exclusion criteria, number of studies screened by title/abstract and full text, number of reviewers, any cross checking carried out.	23
4.	STUDY LEVEL REPORTING OF RESULTS (FOR EACH KEY QUESTION)		
4.1	Study level reporting, results and risk of bias assessment	For each study, produce a table that includes the full citation and a summary of the data relevant to the question (for example, study size, PICO, follow-up period, outcomes reported, statistical analyses etc.). Provide a simple summary of key measures, effect estimates and confidence	Study level reporting: p.30 Quality

		intervals for each study where available. For each study, present the results of any assessment of quality/risk of bias.	assessment: p.42
4.2	Additional analyses	Describe additional analyses (for example, sensitivity, specificity, PPV, etc.) carried out by the reviewer.	Not applicable
5.	QUESTION LEVEL SYNTHESIS		
5.1	Description of the evidence	For each question, give numbers of studies screened, assessed for eligibility, and included in the review, with summary reasons for exclusion.	Q1: p28 Q2-Q5: p29
5.2	Combining and presenting the findings	Provide a balanced discussion of the body of evidence which avoids over reliance on one study or set of studies. Consideration of four components should inform the reviewer's judgement on whether the criterion is 'met', 'not met' or 'uncertain': quantity; quality; applicability and consistency.	Q1: 59-65 Q2-Q5: 65-67
5.3	Summary of findings	Provide a description of the evidence reviewed and included for each question, with reference to their eligibility for inclusion. Summarise the main findings including the quality/risk of bias issues for each question. Have the criteria addressed been 'met', 'not met' or 'uncertain'?	Q1: 59-65 Q2-Q5: 65-67
6.	REVIEW SUMMARY		
6.1	Conclusions and implications for policy	Do findings indicate whether screening should be recommended? Is further work warranted? Are there gaps in the evidence highlighted by the review?	Q1: 65 Q2-Q5 - not applicable
6.2	Limitations	Discuss limitations of the available evidence and of the review methodology if relevant.	61-64

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