Evidence evaluation report — Chlamydia

Consultation draft — October 2017



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1 Key messages

Sensitivity and specificity of urine samples for chlamydia relative to endocervical samples were 96.5% (95%CI 90.1 to 99.3%) and 100% (99.8 to 100%), respectively. The positive and negative predictive values were 100% (95%CI 95.6 to 100%) and 99.8% (95%CI 99.5 to 100%), respectively.

The prevalence of chlamydia is highest among women aged <30 years. Early treatment reduces the risk of preterm birth among young women.

An Australian cost-effectiveness study found that, from an Australian government perspective, chlamydia testing of all women aged 16–25 years old during an antenatal visit was likely to be cost-effective compared with no testing or selective testing, especially with increasing chlamydia prevalence.

2 Process of the review

2.1 Research questions

2.1.1 Testing for chlamydia

- Q1 Compared to a reference test, what is the diagnostic accuracy of the following methods of identifying genital chlamydia among pregnant women: age, urine testing, endocervical swabs, serum antibody testing, history?
- Q2 What are the harms and benefits of routine testing for chlamydia in pregnancy compared to targeted/no testing?
- Q3 What are the harms and benefits of point-of-care testing compared to a reference test for chlamydia among pregnant women in remote communities?

2.1.2 Additional considerations

- Q4 What are the additional needs of Aboriginal and Torres Strait Islander women?
- Q5 What are the additional considerations for migrant and refugee women

2.1.3 PICO criteria used to inform the literature search

PICO criteria used to inform the literature search

Population	Intervention	Comparator	Outcomes
Pregnant women	Routine chlamydia testing	Targeted chlamydia testing	Perinatal mortality Preterm birth
	Routine chlamydia testing	No testing	Low birth weight Premature rupture of the membranes
	Point of care testing	Reference testing	Miscarriage

2.2 Search strategy

To be included.

2.3 Exclusion criteria

Full texts of 60 papers were reviewed and the exclusion criteria outlined below applied.

- Background information
- Duplicate or included in another study
- Not specific to target population (eg specific to non-pregnant women or high-risk women)
- Does not answer research question
- Does not meet criteria for grading (eg no outcomes reported or reporting too limited to establish risk of bias, abstract)
- Narrative review or opinion paper (editorial, letter, comment)
- Not in English

Following application of the exclusion criteria, eight studies were included in the analysis. PRISMA diagram to be included.

2.4 Assigning level of evidence

Levels of evidence were assigned using the NHMRC levels and the study design definitions given in Section 2.5.

Level	Screening
I	A systematic review of level II studies
II	A randomised controlled trial
III-1	Pseudo-randomised controlled trial
III-2	A comparative study with concurrent controls: • Non-randomised, experimental trial • Cohort study • Case-control study
III-3	A comparative study without concurrent controls: Historical control study Two or more single arm study
IV	Case series

2.5 Study design definitions

- Case series a single group of people exposed to the intervention (factor under study). Post-test only outcomes after the intervention (factor under study) are recorded in the series of people, so no comparisons can be made. Pre-test/post-test measures on an outcome are taken before and after the intervention is introduced to a series of people and are then compared (also known as a 'before- and-after study').
- **Case-control study** people with the outcome or disease (cases) and an appropriate group of controls without the outcome or disease (controls) are selected and information obtained about their previous exposure/non-exposure to the intervention or factor under study.
- **Cross-sectional study** a group of people are assessed at a particular point (or cross-section) in time and the data collected on outcomes relate to that point in time ie proportion of people with asthma in October 2004. This type of study is useful for hypothesis-generation, to identify whether a risk factor is associated with a certain type of outcome, but more often than not (except when the exposure and outcome are stable eg genetic mutation and certain clinical symptoms) the causal link cannot be proven unless a time dimension is included.
- Historical control study outcomes for a prospectively collected group of people exposed to the intervention (factor under study) are compared with either (1) the outcomes of people treated at the same institution prior to the introduction of the intervention (ie. control group/usual care), or (2) the outcomes of a previously published series of people undergoing the alternate or control intervention.
- Non-randomised, experimental trial the unit of experimentation (eg. people, a cluster of people) is allocated to either an intervention group or a control group, using a non-random method (such as patient or clinician preference/availability) and the outcomes from each group are compared. This can include:
 - a controlled before-and-after study, where outcome measurements are taken before and after the intervention is introduced, and compared at the same time point to outcome measures in the (control) group.
 - an adjusted indirect comparison, where two randomised controlled trials compare different interventions to the same comparator ie. the placebo or control condition. The outcomes from the two interventions are then compared indirectly.
- **Prospective cohort study** where groups of people (cohorts) are observed at a point in time to be *exposed or not exposed* to an intervention (or the factor under study) and then are followed prospectively with further outcomes recorded as they happen.
- **Pseudo-randomised controlled trial** the unit of experimentation (eg. people, a cluster of people) is allocated to either an intervention (the factor under study) group or a control group, using a pseudo-random method (such as alternate allocation, allocation by days of the week or odd-even study numbers) and the outcomes from each group are compared.

- Randomised controlled trial the unit of experimentation (eg. people, or a cluster of people4) is allocated to either an intervention (the factor under study) group or a control group, using a random mechanism (such as a coin toss, random number table, computer-generated random numbers) and the outcomes from each group are compared.
- **Retrospective cohort study** where the cohorts (groups of people exposed and not exposed) are defined at a point of time in the past and information collected on subsequent outcomes, eg. the use of medical records to identify a group of women using oral contraceptives five years ago, and a group of women not using oral contraceptives, and then contacting these women or identifying in subsequent medical records the development of deep vein thrombosis.
- Systematic literature review systematic location, appraisal and synthesis of evidence from scientific studies.
- **Two or more single arm study** the outcomes of a single series of people receiving an intervention (case series) from two or more studies are compared.

Source: NHMRC (2009) NHMRC levels of evidence and grades of recommendations for developers of guidelines.

2.6 Selection of outcomes for GRADE analysis

Outcomes were selected on the basis of clinical impact.

Outcome	Importance	Inclusion
Perinatal mortality	9	\checkmark
Preterm birth	9	\checkmark
Low birth weight	8	\checkmark
Premature rupture of the membranes	8	\checkmark
Miscarriage	8	\checkmark

Key: 1 - 3 less important; 4 - 6 important but not critical for making a decision; 7 - 9 critical for making a decision

2.7 Quality assessment

Quality of included studies was assessed using adapted NHMRC criteria for quality assessment of systematic reviews and GRADE criteria for quality assessment of randomised controlled trials and observational studies.

Assessment of quality of systematic literature reviews

Considerations in assessing quality of systematic reviews
Questions and methods clearly stated
Search procedure sufficiently rigorous to identify all relevant studies
Review includes all the potential benefits and harms of the intervention
Review only includes randomised controlled trials
Methodological quality of primary studies assessed
Data summarised to give a point estimate of effect and confidence intervals
Differences in individual study results are adequately explained
Examination of which study population characteristics (disease subtypes, age/sex groups) determine the magnitude of effect of the intervention is included
Reviewers' conclusions are supported by data cited
Sources of heterogeneity are explored
Source: Adapted from (NHMRC 2000a; NHMRC 2000b; SIGN 2004).

Assessment of limitations of randomised controlled trials

Study limitation	Explanation
Lack of allocation concealment	Those enrolling patients are aware of the group (or period in a crossover trial) to which the next enrolled patient will be allocated (a major problem in "pseudo" or "quasi" randomised trials with allocation by day of week, birth date, chart number, etc.).
Lack of blinding	Patient, caregivers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which patients are allocated (or the medication currently being received in a crossover trial).
Incomplete accounting of patients and outcome events	Loss to follow-up and failure to adhere to the intention-to-treat principle in superiority trials; or in noninferiority trials, loss to follow-up, and failure to conduct both analyses considering only those who adhered to treatment, and all patients for whom outcome data are available. The significance of particular rates of loss to follow-up, however, varies widely and is dependent on the relation between loss to follow-up and number of events. The higher the proportion lost to follow-up in relation to intervention and control group event rates, and differences between intervention and control groups, the greater the threat of bias.
Selective outcome reporting	Incomplete or absent reporting of some outcomes and not others on the basis of the results.
Other limitations	Stopping trial early for benefit. Substantial overestimates are likely in trials with fewer than 500 events and large overestimates are likely in trials with fewer than 200 events. Empirical evidence suggests that formal stopping rules do not reduce this bias. Use of unvalidated outcome measures (e.g. patient-reported outcomes) Carryover effects in crossover trial Recruitment bias in cluster-randomised trials

Source: (Schünemann et al 2013).

Assessment of limitations of observational studies

Study limitation	Explanation
Failure to develop and apply appropriate eligibility criteria (inclusion of control population)	Under- or over-matching in case-control studies Selection of exposed and unexposed in cohort studies from different populations
Flawed measurement of both exposure and outcome	Differences in measurement of exposure (e.g. recall bias in case-control studies) Differential surveillance for outcome in exposed and unexposed in cohort studies
Failure to adequately control confounding	Failure of accurate measurement of all known prognostic factors Failure to match for prognostic factors and/or adjustment in statistical analysis
Incomplete or inadequately short follow-up	Especially within prospective cohort studies, both groups should be followed for the same amount of time.

Source: (Schünemann et al 2013).

Quality criteria of diagnostic accuracy studies derived from QUADAS-2

Domain	Patient Selection	Index Test	Reference Standard	Flow and Timing
Description	Describe methods of patient selection Describe included patients (previous testing, presentation, intended use of index	Describe the index test and how it was conducted and interpreted	Describe the reference standard and how it was conducted and interpreted	Describe any patients who did not receive the index tests or reference standard or who were excluded from the 2 X 2 table
	test, and setting)			Describe the interval and any interventions between index tests and the reference standard

Domain	Patient Selection	Index Test	Reference Standard	Flow and Timing
Signaling questions	Was a consecutive or random sample of patients enrolled? Was a case-control design avoided? Did the study avoid inappropriate exclusions?	Were the index test results interpreted without knowledge of the results of the reference standard? If a threshold was used, was it pre- specified?	Is the reference standard likely to correctly classify the target condition? Were the reference standard results interpreted without knowledge of the results of the index test?	Was there an appropriate interval between index tests and reference standard? Did all patients receive a reference standard? Did all patients receive the same reference standard? Were all patients
				included in the analysis?
Risk of bias	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct, or its interpretation have introduced bias?	Could the patient flow have introduced bias?
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Source: (Schünemann et al 2013).

2.8 Assessing clinical utility of tests

- *Risks*: what is the extent of the risks associated with the condition?
- *Diagnostic accuracy*: how does the test compare to a reference test?
- Prevalence: at what prevalence does testing make a difference?
- Treatment: is effective treatment available and does it improve maternal/fetal outcomes?
- Cost-effectiveness: is the test cost-effective for the target population in the Australian context?

2.9 Grading of the certainty of the body of evidence

Assessing the certainty of a body of evidence using GRADE involves consideration of the following five domains: risk of bias, inconsistency, indirectness, imprecision and publication bias.

For an evidence base drawn from RCTs, the grading of the certainty of the body of evidence starts at 'high'. An evidence base drawn from observational studies starts as 'low'. In both cases, the evidence can be downgraded for each of the five domains depending on whether the limitation is considered serious (downgrade one level) or very serious (downgrade two levels). Evidence can also be upgraded when the effect is large (upgrade one level) or very large (upgrade two levels), where confounders would reduce the effect or where there is a dose-response effect.

Diagnostic accuracy studies start as high quality evidence. However, these studies are vulnerable to limitations and often lead to low quality evidence, mostly owing to indirectness of evidence associated with diagnostic accuracy being only a surrogate for patient outcomes.

3 Testing for chlamydia

3.1 **Q1**: Compared to a reference test, what is the diagnostic accuracy of the following methods of identifying genital chlamydia among pregnant women: age, urine testing, endocervical swabs, serum antibody testing, history?

3.1.1 Background information

The Australian STI Management Guidelines recommend nucleic acid amplification testing of endocervical, vaginal or anorectal swabs (if the woman has anal sex or anorectal symptoms) and advise consideration of self-collection of samples by pregnant women (ASHA 2018).

3.1.2 Evidence summary

No studies were identified that explicitly compared a diagnostic test to a reference test among pregnant women with uncomplicated pregnancies.

One study (Roberts et al 2011) compared nucleic acid amplification testing of urine and cervical secretion samples. Sensitivity and specificity of the urine sample for chlamydia relative to the endocervical sample were 96.5% (95%CI 90.1 to 99.3%) and 100% (99.8 to 100%), respectively. The positive and negative predictive values were 100% (95%CI 95.6 to 100%) and 99.8% (95%CI 99.5 to 100%), respectively.

There was insufficient evidence to develop an evidence statement for this research question.

3.1.3 Advice to the Expert Working Group

Suggest including a consensus-based recommendation that the use of urine samples or self-collected vaginal samples be considered if testing for chlamydia is undertaken.

3.1.4	Evidence table:	Diagnostic	accuracy
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Study ref	Design	LoE	N	Aim, setting, methods	Results	Comments
(Roberts et al 2011)	Cohort	111-2	2,018	Aim: To compare the rates of Chlamydia trachomatis detection using urine and cervical secretions from pregnant women. Methods: A sample of pregnant women at 35-37 weeks of gestation were tested for chlamydia with both endocervical and urine sampling using the Aptima Combo 2 Assay.	A prevalence of 4.3% and 4.1% were found for Chlamydia endocervical and urine samples, respectively. There was no clear difference between the two tests by McNemar's test (0.02%, 0.32%; P=0.083). There was excellent correlation between the tests found by the kappa statistic (0.982 [0.961-1.000]). Sensitivity and specificity of the urine sample for chlamydia relative to the endocervical sample were 96.5% (95%CI 90.1 to 99.3%) and 100% (99.8 to 100%), respectively. The positive and negative predictive values were 100% (95%CI 95.6 to 100%) and 99.8% (95%CI 99.5 to 100%), respectively.	

3.1.5 Excluded studies

Reference	Reason for exclusion
Baud D, Zufferey J, Hohlfeld P, Greub G. Performance of an automated multiplex immunofluorescence assay for detection of Chlamydia trachomatis immunoglobulin G. <i>Diagn Microbiol Infect Dis</i> . 2014 Mar;78(3):217-9	Does not answer research question
Chan PA, Janvier M, Alexander NE, Kojic EM, Chapin K. Recommendations for the diagnosis of Neisseria gonorrhoeae and Chlamydia trachomatis, including extra-genital sites. <i>Med Health R I</i> . 2012 Aug;95(8):252-4	Narrative review
Daponte A, Pournaras S, Deligeoroglou E, Skentou H, Messinis IE. Serum interleukin-1B, interleukin-8 and anti-heat shock 60 Chlamydia trachomatis antibodies as markers of ectopic pregnancy. <i>J Reprod Immunol</i> . 2012 Mar;93(2):102-8	Does not answer research question
de Lima Freitas NS, Borborema-Santos CM, Barroso Serrão das Neves D, Costa de Oliveira CM, Dutra Ferreira JR, Astolfi-Filho S. High prevalence detection of Chlamydia trachomatis by polymerase chain reaction in endocervical samples of infertile women attending university hospital in Manaus-Amazonas, Brazil. <i>Gynecol Obstet Invest</i> . 2011;72(4):220-6.	Not specific to target population
Krõlov K, Frolova J, Tudoran O, Suhorutsenko J, Lehto T, Sibul H, Mäger I, Laanpere M, Tulp I, Langel Ü. Sensitive and rapid detection of Chlamydia trachomatis by recombinase polymerase amplification directly from urine samples. J Mol Diagn. 2014 Jan;16(1):127-35.	Relevant to research not practice

Reference	Reason for exclusion
Martens MG, Fine P, Fuller D, Ginde SY, Hook EW 3rd, Lebed J, Mena L, Taylor SN, Van Der Pol B. Clinical evaluation of a new Pap test-based method for screening of Chlamydia trachomatis and Neisseria gonorrhoeae using liquid-based cytology media. South Med J. 2013 Sep;106(9):506-1	Industry-funded study
Piso B, Reinsperger I, Winkler R. Recommendations from international clinical guidelines for routine antenatal infection screening: does evidence matter? <i>Int J Evid Based Healthc</i> . 2014 Mar;12(1):50-61	Background information
Raychaudhuri M. False positive chlamydia results in pregnancy: should we retest them? Sex Transm Infect. 2013 Dec;89(8):665	Opinion paper
Scholes D, Satterwhite CL, Yu O, Fine D, Weinstock H, Berman S. Long-term trends in Chlamydia trachomatis infections and related outcomes in a U.S. managed care population. Sex Transm Dis. 2012 Feb;39(2):81-8.	Does not answer research question
Su WH, Tsou TS, Chen CS, Ho TY, Lee WL, Yu YY, Chen TJ, Tan CH, Wang PH. Diagnosis of Chlamydia infection in women. <i>Taiwan J Obstet Gynecol</i> . 2011 Sep;50(3):261-7.	Not specific to target population
Sulaiman S, Chong PP, Mokhtarudin R, Lye MS, Wan Hassan WH. Comparison of nested and ELISA based polymerase chain reaction assays for detecting Chlamydia trachomatis in pregnant women with preterm complications. <i>Trop Biomed</i> . 2014 Mar;31(1):36-45	Not specific to target population
Wilson SP, Vohra T, Knych M, Goldberg J, Price C, Calo S, Mahan M, Miller J. Gonorrhea and chlamydia in the emergency department: Continued need for more focused treatment for men, women and pregnant women. <i>Am J Emerg Med</i> . 2017 May;35(5):701-703	Not specific to target population

3.2 **Q2**: What are the harms and benefits of routine testing for chlamydia in pregnancy compared to targeted/no testing?

3.2.1 Evidence summary

No studies were identified that directly compared outcomes associated with routine antenatal testing with those associated with targeted or no testing.

Outcomes associated with chlamydia during pregnancy

A systematic review of cohort studies (Silva et al 2011) found that chlamydia infection during pregnancy increased the risk of preterm birth (n=845; RR 1.35; 95%CI 1.11 to 1.63), low birth weight (n=703; RR 1.52; 95%CI 1.24 to 1.87) and perinatal mortality (n=173; RR 1.84; 95%CI 1.15 to 2.94). There was no clear evidence of an increased risk of premature rupture of membranes (n=1,465; RR 1.13; 95%CI 0.95 to 1.34), miscarriage (n=397; RR 1.20; 95%CI 0.65 to 2.20) or postpartum endometritis (n=68; RR 0.89; 95%CI 0.49 to 1.61).

A cohort study found that, compared to women whose chlamydia infection was detected after 20 weeks or persisted during pregnancy, women whose chlamydia was detected and treated before 20 weeks gestation had a reduced risk of preterm birth in the less than 20 year age group (RR 0.54; 95%CI 0.37 to 0.80) but no difference in risk for women in other age groups was seen (Folger 2014).

A cross-sectional study that compared outcomes among women with or without gonorrheal or chlamydial cervicitis found no significant statistical difference for any outcome (Hill et al 2015).

Prevalence

Narrative review identified data on prevalence of chlamydia among specific population groups in Australia, which may inform recommendations on testing.

- *Rates of diagnosis:* Chlamydia is the most frequently reported sexually transmitted infection in Australia. The notification rate for chlamydia increased steadily between 2007 and 2011, remained relatively stable between 2011 and 2015 and increased by 8% in 2016 (Kirby Institute 2017b). Notifications have been higher in women than in men in all years (457.6 vs 364.3 per 100,000 in 2016). The rate of notification in the Aboriginal and Torres Strait Islander population has remained relatively stable since 2012 but in 2016 was more than three times that in the non-Indigenous population (1,193 vs 419 per 100,000) (Kirby Institute 2017a).
- *Age*: The trends in notification rates vary by age group. Among women, rates in the 15-19 year age group have declined (from 2,425 in 2011 to 1,932 per 100,000 in 2016), rates in the 20-24 year age group have remained stable (2,248 in 2011 and 2,399 in 2016) and rates in the 25-29 year age group have increased (from 892 in 2011 to 1,086 per 100,000 in 2016) (Kirby Institute 2017b). The chlamydia notification rate in Aboriginal and Torres Strait Islander women aged 15-19 and 20-29 years in 2016 was four times and three times higher, respectively, than in the non-Indigenous population (Kirby Institute 2017a).
- *Geographical distribution:* After a steady increase in notifications between 2007 and 2011 in all jurisdictions, between 2012 and 2016 chlamydia notification rates were more stable, except in Queensland, where there was a steady increase (from 410.7 to 480.4 per 100,000). Chlamydia notification rates rose between 2015 and 2016 in New South Wales (by 14%) and Western Australia (by 7%) (Kirby Institute 2017b). Between 2012 and 2016, notification rates were highest and remained stable in remote and very remote regions (806.6 per 100 000 in 2016). Notification rates also remained stable in major cities in the same period (327.0 per 100 000 in 2016) but declined by 13% in inner and outer regional areas (419.5 to 367.2 per 100 000) (Kirby Institute 2017b). A similar pattern was seen in both males and females but in females there was a larger decline in inner and outer regional areas (16%) and rates also declined (11%) in the major cities.

Data on diagnoses of chlamydia are incomplete and may provide a distorted view of population rates in Australia. Differences in rates of diagnosis between areas and populations may reflect a range of factors, including variations in approaches to offering testing, access to services, and recording of Indigenous status.

Clinical uptake of recommendations on testing

An Australian study that assessed clinical uptake of the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) recommendation to test pregnant women aged younger than 25 years, found that in 2010 only about one-fifth of participants routinely tested women in this population group (Li et al 2013). The study highlighted the need for national clinical leadership regarding screening for chlamydia among pregnant women aged younger than 25 years.

Cost-effectiveness

An Australian cost-effectiveness study (Ong et al 2016) found that, from an Australian government perspective, chlamydia testing of all women aged 16–25 years old during an antenatal visit was likely to be cost-effective compared with no testing or selective testing, especially with increasing chlamydia prevalence (the study assumed a prevalence of 3%; in 2016 prevalence was 1.9% among women aged 15-19 years and 2.4% among women aged 20-24 years).

International cost-effectiveness studies found that:

- universal antenatal testing for chlamydia was cost-saving in the Netherlands (estimated overall prevalence 3.9%), with further increases in savings when testing was targeted to pregnant women younger than 30 years of age (Rours et al 2016)
- cost and benefit of universal testing in the United States was reliant on the prevalence of chlamydia when prevalence was above 16.9% there were net cost savings; at a prevalence of 8%, expenses were \$124.65 million (\$19.34/individual); and at a prevalence of 6.7%, net expenditure for screening was \$249.08 million (\$38.65/individual) (Ditkowsky et al 2017).

There was insufficient evidence to inform an evidence statement for this research question.

3.2.2 Advice to the Expert Working Group

Suggest including a consensus-based recommendation to consider testing for chlamydia in women younger than 30 years based on:

- the high prevalence of chlamydia in young people in Australia
- treatment before 20 weeks reducing the risk of preterm birth among young women
- the cost-effectiveness of antenatal screening among women aged 16-25 years
- the benefits of consistency between recommendations in national guidelines (eg (ASHA 2018; RACGP 2016)).

Study ref	Design	LoE	N	Aim, methods	Results	Comments
(Silva et al 2011)	SLR	IV	12 studies	 Aim: To evaluate the effect of Chlamydia trachomatis infection during pregnancy on perinatal morbidity and mortality. Methods: Systematic review and meta-analysis in an electronic database and manual, combining high sensitivity specific descriptors seeking to answer the research objective. The articles considered to be of high methodological quality (score above 6 on the Newcastle-Ottawa Scale) were assessed by meta-analysis. Summary estimates were calculated by means of Mantel-Haenszel test with 95% confidence interval. 	It was observed that Chlamydia infection during pregnancy increased risk of preterm labour (RR 1.35; 95%CI 1.11 to 1.63), low birth weight (RR 1.52; 95%CI 1.24 to 1.87) and perinatal mortality (RR 1.84; 95%CI 1.15 to 2.94). No evidence of increased risk was associated with Chlamydia infection in regard to premature rupture of membranes (RR 1.13; 95%CI 0.95 to 1.34), abortion and postpartum endometritis (RR 1.20; 95%CI 0.65 to 2.20] and 0.89; 95%CI 0.49 to 1.61 respectively).	Although it includes only observational studies, the review is of moderate methodological quality (see Section 3.2.6)
(Folger 2014)	Cohort	111-2	3,354	Aim: to evaluate the risk of preterm birth among women with maternal chlamydia infection. Methods: the intervention group comprised women with chlamydia detected and eradicated at or before 20 weeks gestation. Women with syphilis whose infections were detected after 20 weeks gestation or persistent during the pregnancy represented the reference group.	The risk ratio for moderate to late spontaneous preterm birth (32-36 weeks gestation) was 0.54 (95 % Cl 0.37 to 0.80) for women in the intervention group who aged <20 years. The relative risk did not reach significance for women aged 20-29 years (0.98; 95%Cl 0.73 to 1.32) or >29 years (1.15; 95%Cl 0.42 to 3.10).	

3.2.3 Evidence table: Risks associated with chlamydia during pregnancy

Study ref	Design	LoE	N	Aim, methods	Results	Comments
(Hill et al 2015)	Cross- section	IV	1,120	Aim: To evaluate the effect of gonorrheal and chlamydial cervicitis (GCC) on the risk of preterm labour (PTL) and preterm premature rupture of membranes (PPROM). Methods: Data on samples for GCC and pregnancy outcome were entered into a database from a retrospective chart review.	Among women with GGC (n=187), rates of preterm birth were 17.79% and 16.58% for GCC-negative and GCC- positive pregnancies, respectively. PPROM occurred in 3.97% and 2.67% of GCC-negative and GCC-positive pregnancies, respectively. PTL occurred in 8.25% and 8.02% of GCC-negative and GCC-positive pregnancies, respectively. No outcomes met statistical significance. When pregnancy outcomes were analysed by trimester of infection, there was a higher risk of preterm birth but not preterm labour with earlier infection. This did meet statistical significance. There was a trend towards lower rate of caesarean section in the infected group of patients, which did not meet statistical significance.	

Study ref	Design	N	Aim, methods	Results	Comments
(Li et al 2013)	Survey	1,644	 Aim: To assess clinical uptake and policy integration of the 2006 RANZCOG recommendation on chlamydia testing in pregnant women aged <25 years. Method: A mixed method approach was used involving a literature review, a survey of obstetricians and gynaecologists, and survey of hospital managers from April 2010 to May 2010. 	Among participating RANZCOG Fellows, Trainees, and Diplomates, 21.2% reported universal screening for pregnant women <25 years (25% of primary care clinicians, 23% of those working in the public hospital sector, 16% of those working in both public and private hospitals, and 13% of those in private hospitals or private practice). There was a strong association between members who agreed with the guideline and offering universal screening to pregnant women aged <25 years (adjusted OR 17.1, 95%CI 6.0 to 49.2, P<0.01). There were two national and four state/local policy documents recommending chlamydia screening in pregnancy. This study highlights the need for national clinical leadership regarding screening for chlamydia among pregnant women aged <25 years.	

3.2.4 Evidence table: Clinical uptake of recommendations on testing

Study ref	Design	Aim, setting, methods	Results	Comments
(Ong et al 2016)	Cost- effectiveness study	 Aim: To determine the cost-effectiveness of screening all pregnant women aged 16–25 years for chlamydia compared with selective screening or no screening. Setting: Antenatal clinics in Australia. Methods: Using clinical data from a previous study, and outcomes data from the literature, the authors modelled the short-term perinatal (12-month time horizon) incremental direct costs and outcomes from a government (as the primary third-party funder) perspective for chlamydia screening. Costs were derived from the Medicare Benefits Schedule, Pharmaceutical Benefits Scheme, and average cost-weights reported for hospitalisations classified according to the Australian refined diagnosis-related groups. Main outcome measures: Direct costs of screening and managing chlamydia complications, number of chlamydia cases detected and treated, and the incremental cost-effectiveness ratios were estimated and subjected to sensitivity analyses. 	Assuming a chlamydia prevalence rate of 3%, screening all antenatal women aged 16–25 years at their first antenatal visit compared with no screening was \$34,931 per quality-adjusted life years gained. Screening all women could result in cost savings when chlamydia prevalence was higher than 11%. The incremental cost-effectiveness ratios were most sensitive to the assumed prevalence of chlamydia, the probability of pelvic inflammatory disease, the utility weight of a positive chlamydia test and the cost of the chlamydia test and doctor's appointment. From an Australian government perspective, chlamydia screening of all women aged 16–25 years old during one antenatal visit was likely to be cost-effective compared with no screening or selective screening, especially with increasing chlamydia prevalence.	

3.2.5 Evidence table: Cost-effectiveness

Study ref	Design	Aim, setting, methods	Results	Comments
(Rours et al 2016)	Cost- effectiveness study	 Aim: to estimate the cost-effectiveness of Chlamydia trachomatis screening during pregnancy. Setting: The Netherlands Methods: The authors used a health-economic decision analysis model, which included potential health outcomes of C. trachomatis infection for women, partners and infants, and premature delivery. We estimated the cost-effectiveness from a societal perspective using recent prevalence data from a population-based prospective cohort study among pregnant women in the Netherlands. We calculated the averted costs by linking health outcomes with health care costs and productivity losses. Cost-effectiveness was expressed as net costs per major outcome prevented and was estimated in base-case analysis, sensitivity, and scenario analysis. 	In the base-case analysis, the costs to detect 1,000 pregnant women with chlamydia were estimated at \notin 527,900. Prevention of adverse health outcomes averted \notin 626,800 in medical costs, resulting in net cost savings. Sensitivity analysis showed that net cost savings remained with test costs up to \notin 22 (test price \notin 19) for a broad range of variation in underlying assumptions. Scenario analysis showed even more cost savings with targeted screening for women less than 30 years of age or with first pregnancies only.	Age-specific prevalences were 13.5% in women <21 years (n=251), 6.7% between 21-25 years (n=794), 3.3% between 26-30 years (n=1235), and 1.6% in women over 30 years of age (n=1775) May not be applicable to the Australian context

Study ref	Design	Aim, setting, methods	Results	Comments
(Ditkowsky et al 2017)	6,444,686	Aim: To determine the cost-benefit of screening all pregnant women aged 15-24 for Chlamydia trachomatis infection compared with no screening. Setting: United States Methods: The authors developed a decision analysis model to estimate costs and health- related effects of screening pregnant women for chlamydia in a high burden setting. Outcome data were from literature for pregnant women in the 2015 US population. Using outcomes data from the literature, the authors predicted the number of chlamydia cases, associated morbidity, and related costs. Two comparison arms were developed: pregnant women who received chlamydia screening, and those who did not. Costs and morbidity of a pregnant woman-infant pair with chlamydia were calculated and compared.	Cost and benefit of screening relied on the prevalence of Chlamydia trachomatis; when rates are above 16.9%, screening was proven to offer net cost savings. At a pre-screening era prevalence of 8%, a screening program has an increased expense of \$124.65 million (\$19.34/individual), with 328,000 more cases of chlamydia treated, and significant reduction in morbidity. At a current estimate of prevalence, 6.7%, net expenditure for screening is \$249.08 million (\$38.65/individual), with 204.63 thousand cases of treated chlamydia and reduced morbidity.	May not be applicable to the Australian context

3.2.6 Evaluation of quality of systematic reviews

(Silva et al 2011)	Comment
Questions and methods clearly stated	The review question is stated as the objective of the review. Methods used are clearly stated.
Search procedure sufficiently rigorous to identify all relevant studies	Searches were conducted on electronic databases such as PubMed, Embase, Lilacs, Cochrane, and Google Scholar. Manual searches were also conducted through gynaecology journals and the bibliographies of reviewed articles. Search terms are not described.
Review includes all the potential benefits and harms of the intervention	Studies were selected through systematic review to determine the risk of perinatal morbidity and mortality associated with chlamydia infection, and classified according to the outcomes: preterm labour (labor occurring before 37 weeks gestation), premature rupture of membranes, low birth weight (full term newborn weighing less than 2500 grams), perinatal mortality (mortality occurring between 20 weeks of gestation until 28 days after birth), endometritis (infection of the endometrium or decidua) and abortion (expulsion or fetal death before 20 weeks gestation).
Review only includes randomised controlled trials	Review included only observational studies.
Methodological quality of primary studies assessed	The Newcastle-Ottawa scale was used to assess the methodological quality of studies. This scale varies between zero and nine points: studies with a score equal to or higher than six were considered methodologically sound.
Data summarised to give a point estimate of effect and confidence intervals	Summary estimates of 12 studies were calculated by means of Mantel-Haenszel test with 95% confidence interval.
Differences in individual study results are adequately explained	No significant differences in study results.
Examination of which study population characteristics (disease subtypes, age/sex groups) determine the magnitude of effect of the intervention is included	Not applicable
Reviewers' conclusions are supported by data cited	Reviewers' conclusions are supported by data cited.
Sources of heterogeneity are explored	The test for heterogeneity for preterm labour was found to be significant when all items were considered in the evaluation. The analysis of funnel plot items from three studies were removed for statistical re-evaluation, and as a result heterogeneity lost its significance (p=0.07).

3.2.7 Excluded studies

Reference	Reason for exclusion
Andersen B, van Valkengoed I, Sokolowski I, Møller JK, Østergaard L, Olesen F. Impact of intensified testing for urogenital Chlamydia trachomatis infections: a randomised study with 9-year follow-up. <i>Sex Transm Infect</i> . 2011 87(2):156-61	Not specific to antenatal care
Balendra A, Oakeshott P, Hayes K, Planche T, Hay PE. Chlamydia screening in an early pregnancy unit. Sex Transm Infect. 2016 May;92(3):231	Opinion paper
Blatt AJ, Lieberman JM, Hoover DR, Kaufman HW. Chlamydial and gonococcal testing during pregnancy in the United States. <i>Am</i> J Obstet Gynecol. 2012 Jul;207(1):55.e1-8	Does not answer research question
Campbell S, Lynch J, Esterman A, McDermott R. Pre-pregnancy predictors linked to miscarriage among Aboriginal and Torres Strait Islander women in North Queensland. <i>Aust N Z J Public Health</i> . 2011 Aug;35(4):343-51	Not specific to target population
Chavez JM, Vicetti Miguel RD, Cherpes TL. Chlamydia trachomatis infection control programs: lessons learned and implications for vaccine development. <i>Infect Dis Obstet Gynecol</i> . 2011;2011:754060	Narrative review
Christianson M, Boman J, Essén B. 'Let men into the pregnancy'men's perceptions about being tested for chlamydia and HIV during pregnancy. <i>Midwifery</i> . 2013 Apr;29(4):351-8.	Does not answer research question
Curran G. Universal antenatal chlamydia screening by rural midwives. Aust Nurs J. 2012 Feb;19(7):30-2	Narrative review
Dhairyawan R, Creighton S, Sivyour L, Anderson J. Testing the fathers: carrying out HIV and STI tests on partners of pregnant women. <i>Sex Transm Infect</i> . 2012 Apr;88(3):184-6.	Does not answer research question
Ekeroma AJ, Pandit L, Bartley C, Ikenasio-Thorpe B, Thompson JM. Screening for sexually transmitted infections in pregnancy at Middlemore Hospital, 2009. N Z Med J. 2012 Aug 10;125(1359):23-9	Does not answer research question
Geisler WM. Diagnosis and Management of Uncomplicated Chlamydia trachomatis Infections in Adolescents and Adults: Summary of Evidence Reviewed for the 2015 Centers for Disease Control and Prevention Sexually Transmitted Diseases Treatment Guidelines. <i>Clin Infect Dis</i> . 2015 Dec 15;61 Suppl 8:S774-84	Background information
Gillespie P, O'Neill C, Adams E, Turner K, O'Donovan D, Brugha R , Vaughan D, O'Connell E, Cormican M, Balfe M, Coleman C, Fitzgerald M, Fleming C. The cost and cost-effectiveness of opportunistic screening for Chlamydia trachomatis in Ireland. <i>Sex</i> <i>Transm Infect</i> 2012;88:222e228.	Not specific to target population
Grandcolin S, Lioni M, Jourdain M, Albouy-Llaty M. [In Poitou-Charentes family planning centers, Chlamydia trachomatis infection in women is more frequently detected through the presence or absence of risk factors than in accordance with official guidelines]. <i>Rev Epidemiol Sante Publique</i> . 2016 Dec;64(6):397-403	Not in English

Reference	Reason for exclusion
Hocking JS, Garland SM. Low chlamydia testing uptake among young pregnant women in Australia highlights the need for national leadership in this area. <i>Aust N Z J Obstet Gynaecol</i> . 2013 Aug;53(4):329-30	Opinion paper
Jackson JA, McNair TS, Coleman JS. Over-screening for chlamydia and gonorrhea among urban women age ≥25 years. <i>Am J</i> Obstet Gynecol. 2015 Jan;212(1):40.e1-6.	Does not answer research question
Kalwij SA. Opportunistic chlamydia screening in a general practice consultation. <i>BMJ</i> . 2011 Aug 15;343:d5108. doi: 10.1136/bmj.d5108.	Not specific to target population
Kwan KS, Giele CM, Combs B, Mak DB. Improvement in antenatal testing for sexually transmissible infections and blood-borne viruses in Western Australian hospitals, 2007 to 2010. Sex Health. 2012 Sep;9(4):349-54.	Does not answer research question
Lavoué V, Vandenbroucke L, Lorand S, Pincemin P, Bauville E, Boyer L, Martin-Meriadec D, Minet J, Poulain P, Morcel K. Screening for Chlamydia trachomatis using self-collected vaginal swabs at a public pregnancytermination clinic in France: results of a screen-and-treat policy. <i>Sex Transm Dis</i> . 2012 Aug;39(8):622-7	Does not answer research question
Lee KC, Ngo-Metzger Q, Wolff T, Chowdhury J, LeFevre ML, Meyers DS. Sexually Transmitted Infections: Recommendations from the U.S. Preventive Services Task Force. Am Fam Physician. 2016 Dec 1;94(11):907-915	Background information
LeFevre ML; U.S. Preventive Services Task Force. Screening for Chlamydia and gonorrhea: U.S. Preventive Services Task Force recommendation statement. <i>Ann Intern Me</i> d. 2014 Dec 16;161(12):902-10	Background information
Mahmud NU, Hossain MA, Nahar K, Ahmed GS, Mahmud C, Paul SK, Khan SI, Amin SR, Nasreen SA, Ahmed S, Kabir MR, Hoque N. Non-culture diagnosis of Chlamydia trachomatis genital infection in sexually active women. <i>Mymensingh Med J</i> . 2012 Jan;21(1):8-12	Does not answer research question
Mishori R, McClaskey EL, WinklerPrins VJ. Chlamydia trachomatis infections: screening, diagnosis, and management. <i>Am Fam</i> Physician. 2012 Dec 15;86(12):1127-32	Narrative review
[No authors listed] Chlamydia screening can prevent harm to newborns. Aust Nurs Midwifery J. 2015 Oct;23(4):26	Summary of (Ong et al 2016)
Ong KJ, Soldan K, Jit M, Dunbar JK, Woodhall SC. Chlamydia sequelae cost estimates used in current economic evaluations: does one-size-fit-all? Sex Transm Infect. 2017 Feb;93(1):18-24	Does not answer research question
Paavonen J. Chlamydia trachomatis infections of the female genital tract: state of the art. Ann Med. 2012 Feb;44(1):18-28.	Narrative review
Parker RM, Bell A, Currie MJ, Deeks LS, Cooper G, Martin SJ, Del Rosario R, Hocking JS, Bowden FJ. 'Catching chlamydia': combining cash incentives and community pharmacy access for increased chlamydia screening, the view of young people. <i>Aust J Prim Health</i> . 2015;21(1):79-83	Does not answer research question

Reference	Reason for exclusion
Pereboom MT, Spelten ER, Manniën J, Rours GI, Morré SA, Schellevis FG, Hutton EK. Knowledge and acceptability of Chlamydia trachomatis screening among pregnant women and their partners; a cross-sectional study. <i>BMC Public Health</i> . 2014 Jul 9;14:704.	Does not answer research question
Plavchan J. Testing options for the detection of gonorrhea and Chlamydia. Am Fam Physician. 2013 Sep 1;88(5):290-1.	Opinion paper
Satterwhite CL, Gray AM, Berman S, Weinstock H, Kleinbaum D, Howards PP. Chlamydia trachomatis infections among women attending prenatal clinics: United States, 2004-2009. Sex Transm Dis. 2012 Jun;39(6):416-20.	Does not answer research question
Tao G, Hoover KW, Nye MB, Body BA. Age-specific chlamydial infection among pregnant women in the United States: evidence for updated recommendations. <i>Sex Transm Dis</i> . 2014 Sep;41(9):556-9.	Does not answer research question
Tao G, Hoover KW, Kent CK. Chlamydia testing patterns for commercially insured women, 2008. <i>Am J Prev Med</i> . 2012 Apr;42(4):337-41	Does not answer research question
Taylor MM, Reilley B, Tulloch S, Winscott M, Dunnigan A, Russell M, Redd JT. Identifying opportunities for chlamydia screening among American Indian women. <i>Sex Transm Dis</i> . 2011 Oct;38(10):947-8	Does not answer research question
Weissenbacher TM, Kupka MS, Kainer F, Friese K, Mylonas I. Screening for Chlamydia trachomatis in pregnancy: a retrospective analysis in a German urban area. <i>Arch Gynecol Obstet</i> . 2011 Jun;283(6):1343-7	Does not answer research question
WHO Guidelines for the Treatment of Chlamydia trachomatis. Geneva: World Health Organization; 2016.	Background information
Wiehe SE, Rosenman MB, Wang J, Katz BP, Fortenberry JD. Chlamydia screening among young women: individual- and provider- level differences in testing. <i>Pediatrics</i> . 2011 Feb;127(2):e336-44	Does not answer research question
Wiesenfeld HC. Screening for Chlamydia trachomatis Infections in Women. N Engl J Med. 23;376(8):765-773.	Narrative review
Wise MR, Sadler L, Ekeroma A. Chlamydia trachomatis screening in pregnancy in New Zealand: translation of national guidelines into practice. <i>J Prim Health Care</i> . 2015 Mar 1;7(1):65-70	Does not answer research question
Yeung A, Bush M, Cummings R, Bradshaw CS, Chen M, Williams H, Denham I, Fairley CK. Use of computerized medical records to determine the feasibility of testing for chlamydia without patients seeing a practitioner. Int J STD AIDS. 2010 Nov;21(11):755-7	Not specific to target population

3.3 **Q3**: What are the harms and benefits of point-of-care testing compared to a reference test for chlamydia among pregnant women in remote communities?

3.3.1 Evidence summary

No studies were identified that explicitly compared outcomes from point-of-care testing with a reference test for chlamydia among pregnant women.

A systematic review (which was excluded as it was not specific to the target population) (Herbst de Cortina et al 2016) noted that, while pregnant women specifically have not been studied, the results available in non-pregnant populations are encouraging for the ability to test and treat women in antenatal care using point-of-care tests to prevent adverse pregnancy and neonatal outcomes.

3.3.2 Excluded studies

Reference	Reason for exclusion
Herbst de Cortina S, Bristow CC, Joseph Davey D et al (2016) A Systematic Review of Point of Care Testing for Chlamydia trachomatis, Neisseria gonorrhoeae, and Trichomonas vaginalis. <i>Infect Dis Obstet Gynecol</i> 2016: 4386127.	Not specific to target population
Howick J, Cals JW, Jones C, Price CP, Plüddemann A, Heneghan C, Berger MY, Buntinx F, Hickner J, Pace W, Badrick T, Van den Bruel A, Laurence C, van Weert HC, van Severen E, Parrella A, Thompson M. Current and future use of point-of- care tests in primary care: an international survey in Australia, Belgium, The Netherlands, the UK and the USA. <i>BMJ Open</i> . 2014 Aug 8;4(8):e005611	Does not answer research question

4 Additional considerations

4.1 **Q4**: What are the additional needs of Aboriginal and Torres Strait Islander women?

4.1.1 Evidence summary

A single study (n=57) found a prevalence of chlamydia of 14% among Aboriginal and/or Torres Strait Islander women attending their first antenatal visit in an Indigenous Health Service in Brisbane, with lower prevalence (5%) among women aged 16-20 years (Maher et al 2014).

Information on national prevalence among Aboriginal and Torres Strait Islander women is included in Section 3.2.1.

4.1.2 Evidence table

Study ref	Design	LoE	N	Aim, setting, methods	Results	Comments
(Maher et al 2014)	Cross- section	IV	64	Aim: to address the gap in knowledge about the health and well-being of urban Aboriginal and Torres Strait Islander women by investigating the timing of their first antenatal visit and determining their health status and lifestyle characteristics. Setting: Inala Indigenous Health Service, Brisbane Methods: We recruited a consecutive sample of pregnant Aboriginal and/or Torres Strait Islander women aged ≥ 16 years presenting for their first antenatal visit at the IIHS between September 2010 and September 2011 into this cross-sectional study. antenatal check information was entered directly into computerised templates by the treating medical and nursing staff. Data from the first antenatal visit were imported into the specialist statistical software Stata, version 10.0 (StataCorp, College Station, Tex, USA), for analysis. ⁷	Overall, 57 participants (90%) were screened for chlamydia and 52 for gonorrhoea. For chlamydia, positive tests were returned by 14% (8) of participants and 5% of women aged younger than 20 years of age.	

4.2 **Q5**: What are the additional considerations for migrant and refugee women? No studies were identified to answer this question.

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- Herbst de Cortina S, Bristow CC, Joseph Davey D et al (2016) A Systematic Review of Point of Care Testing for Chlamydia trachomatis, Neisseria gonorrhoeae, and Trichomonas vaginalis. *Infect Dis Obstet Gynecol* 2016: 4386127.
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- Kirby Institute (2017b) <u>HIV, Viral Hepatitis and Sexually Transmissible Infections in Australia. Annual Surveillance Report</u> <u>2017</u>. Sydney: The Kirby Institute, UNSW.
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