

Evidence evaluation report — Syphilis

Draft — October 2017



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Australian Government Department of Health

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1 Key messages

Outcomes associated with syphilis during pregnancy

Untreated syphilis during pregnancy is associated with stillbirth and fetal loss, neonatal death, preterm birth, low birthweight and congenital syphilis.

Routine versus no testing

An historical cohort study from the United States that compared routine testing for syphilis to no testing concluded that the results provide strong support for universal testing, particularly in countries with high prevalence.

No studies into the cost-effectiveness of routine testing in the Australian context were identified.

Testing in the third trimester

Studies conducted in the United States found that universal testing in the third trimester would require a seroconversion incidence of 0.017% (compared to the assumed base case incidence of 0.012%) or a prevalence of 3.5% to be cost-effective. A third study (also from the United States) in an area of high prevalence found that testing and treatment early in the third trimester prevented 78% of cases of congenital syphilis.

Point-of-care testing

There is currently only one syphilis point of care test registered by the Therapeutic Goods Administration in Australia, the Determine Syphilis TP™ manufactured by Alere. The CDNA notes the following limitations with current syphilis point-of-care tests:

- currently tests cannot distinguish current from previous syphilis infection, due to either the absence or non-quantified nature of a non-treponemal component
- even in ideal use, sensitivity is slightly lower than laboratory based assays
- the tests are moderately complicated and require staff to be specifically trained in their use
- the results may not be captured by current notification and testing registries.

Intervention

Treatment for syphilis with benzathine penicillin in the first or second trimester reduces rates of congenital syphilis (moderate quality evidence) and may reduce rates of other adverse outcomes (low quality evidence). Risks from treatment among pregnant women are likely to be low (very low quality evidence).

Treatment for syphilis in the first or second trimester is more effective in reducing risk of congenital syphilis than treatment in the third trimester (low quality evidence).

2 Process of the review

2.1 Research questions

2.1.1 Background question

Q1 What is the prevalence of syphilis in pregnant women in Australia?

2.1.2 Testing for syphilis

Q2 What are the harms and benefits of routine antenatal testing for syphilis compared to targeted/no testing?

Q3 What is the diagnostic accuracy of tests available for detection of syphilis infection in pregnancy?

Q4 What are the harms and benefits of point of care testing for syphilis among pregnant women in remote communities?

2.1.3 Interventions

Q5 What interventions are safe and effective in the management of syphilis infection in pregnant women?

2.1.4 Additional considerations

Q6 What are the additional considerations for Aboriginal and Torres Strait Islander women?

Q7 What are the additional considerations for migrant and refugee women?

2.1.5 PICO criteria used to inform the literature search

PICO criteria used to inform the literature search

Population	Intervention	Comparator	Outcomes
Pregnant women	Routine syphilis testing	Targeted syphilis testing	Perinatal mortality Incidence of congenital syphilis
	Routine syphilis testing	No testing	Proportion of women tested and treated
	Point-of-care testing	Reference testing	Adequate treatment Partner treatment
	Outreach point of care testing	Centralised testing	Syphilis prevalence (post intervention)

2.2 Search strategy

To be included

2.3 Exclusion criteria

Full texts of 204 papers were reviewed and the exclusion criteria outlined below applied.

- Background information
- Not relevant to the Australian context (prevalence studies)
- 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
- Not a systematic review (for outcomes associated with syphilis during pregnancy)
- Industry study
- Relevant to research not practice
- Not applicable to the Australian context (cost-effectiveness studies)
- Superseded by more recent data (prevalence studies)

Following application of exclusion criteria, 35 studies were included in the analysis.

Figure 1: PRISMA diagram

2.4 Assigning level of evidence

Levels of evidence were assigned using the NHMRC levels and the following definitions.

Level	Screening	Intervention
I	A systematic review of level II studies	Systematic review of level II studies
II	A randomised controlled trial	A randomised controlled trial
III-1	Pseudo-randomised controlled trial (ie alternate allocation or some other method)	Pseudo-randomised trial
III-2	A comparative study with concurrent controls: <ul style="list-style-type: none"> ▪ Non-randomised, experimental trial ▪ Cohort study ▪ Case-control study 	A comparative study with concurrent controls: <ul style="list-style-type: none"> • Non-randomised experimental trial • Cohort study • Case-control study • Interrupted time series with control group
III-3	A comparative study without concurrent controls: Historical control study Two or more single arm study	A comparative study without concurrent controls: <ul style="list-style-type: none"> ▪ Historical control study ▪ Two or more single arm study ▪ Interrupted time series without parallel control
IV	Case series	Case series with either post-test or pre-test/post-test outcomes

2.5 Study design definitions

- **All or none** – all or none of a series of people (case series) with the risk factor(s) experience the outcome. The data should relate to an unselected or representative case series, which provides an unbiased representation of the prognostic effect. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination. This is a rare situation.
- **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.
- **Interrupted time series with a control group** - trends in an outcome or disease are measured over multiple time points before and after the intervention (factor under study) is introduced to a group of people, and then compared to the outcomes at the same time points for a group of people that do not receive the intervention (factor under study).

- **Interrupted time series without a parallel control group** - trends in an outcome or disease are measured over multiple time points before and after the intervention (factor under study) is introduced to a group of people, and compared (as opposed to being compared to an external control group).
- **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 considered for inclusion comprised conditions associated with syphilis in pregnancy. Outcomes were selected on the basis of clinical impact.

Outcome	Importance	Inclusion
Perinatal mortality	9	<input checked="" type="checkbox"/>
Incidence of congenital syphilis	9	<input checked="" type="checkbox"/>
Proportion of women tested and treated	9	<input checked="" type="checkbox"/>
Adequate treatment	9	<input checked="" type="checkbox"/>
Partner treatment	9	<input checked="" type="checkbox"/>
Syphilis prevalence	8	<input checked="" type="checkbox"/>

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 test, and setting)	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 Describe the interval and any interventions between index tests and the reference standard
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?

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 Background question

3.1 Q1: What is the prevalence of syphilis in pregnant women in Australia?

3.1.1 Evidence summary

No national evidence specific to prevalence of syphilis in Australian pregnant women was identified through the systematic review. Narrative review identified the following.

Rates of diagnosis of syphilis

Between 2012 and 2016, the notification rate of infectious syphilis increased 107% from 6.9 per 100,000 in 2012 to 14.3 per 100,000 in 2016, with an increase in both men (103%) and women (157%) (Kirby Institute 2017b).¹ Rates among women in 2016 were highest in the 15-19 year (11.5 per 100,000), 20-24 year (9.5 per 100,000) and 25-29 year (9.9 per 100,000) age groups. The rate of notification for infectious syphilis among Aboriginal and Torres Strait Islander women was 39 times that among non-Indigenous women (57.1 vs 1.5 per 100,000) (Kirby Institute 2017a).

Geographical distribution

In 2016, infectious syphilis notification rates were highest in remote and very remote areas of residence (49.4 per 100,000) (Kirby Institute 2017b). Increases in notification rates occurred in all regions of residence between 2012 and 2017, with the sharpest increase in regional areas (209%) followed by remote areas (176%). Rates of notification among Aboriginal and Torres Strait Islander people were highest in the Northern Territory (229.6 per 100,000) and Queensland (99.3 per 100,000) (Kirby Institute 2017a), corresponding with regions in which there has been an outbreak of infectious syphilis (see Section 6.1).

Congenital syphilis

Australia is a country of low prevalence for congenital syphilis. However, coinciding with peaks in infectious syphilis notifications, there have been peaks in cases of congenital syphilis (see below).

Risk factors

Syphilis in Australia largely continues to be an infection primarily of men having male-to-male sex in urban settings, and of young heterosexual Aboriginal and Torres Strait Islander people in remote communities (The Kirby Institute 2016). A pregnant woman is at high risk of syphilis infection or reinfection when:

- she is a sexual contact of a person with infectious syphilis
- she or her partner(s) reside in a declared outbreak area (see below)
- she has late, limited or no antenatal care
- she is aged 19 years or younger
- she and/or her partner(s) have sexual partners from high prevalence countries
- she has a male sexual partner who has sex with men
- she engages in intravenous substance use during pregnancy – particularly methamphetamine ('ice')
- she has a sexually transmitted infection in the current pregnancy or within the previous 12 months
- she has unprotected vaginal, oral or anal sex with a male partner at high risk of having syphilis
- she has previously had infectious syphilis in pregnancy.

Syphilis outbreak among Aboriginal and Torres Strait Islander people in remote Australia

In January 2011, an increase of infectious syphilis notifications among young Aboriginal and Torres Strait Islander people was identified in the North-West region of Queensland, which subsequently spread to other regions in north Queensland (Bright & Dups 2016). Subsequent increases in notifications were reported in the Northern Territory and Western Australia in July 2013 and June 2014 respectively, following sustained periods of low notification rates. In March 2017, South Australia declared an outbreak in the Western and Eyre and Far North regions from November 2016 (MJSO 2018). By 30 June 2018, there had been seven confirmed cases of congenital syphilis, six probable cases and six deaths from congenital syphilis (three confirmed and three

¹ An expanded infectious syphilis national case definition was implemented in July 2015 in all jurisdictions except for New South Wales, where it was implemented in July 2016. The new case definition includes a new subcategory of 'probable' infectious syphilis to capture infectious syphilis cases in people without a prior testing history, particularly young people aged 15–19 years. The probable infectious syphilis cases are included in the number of infectious syphilis notifications in 2015 and 2016.

probable) associated with the outbreak (MJSO 2018). Surveillance reports on the outbreak are published online regularly by the [Multijurisdictional Syphilis Outbreak Working Group](#).

Notification

Syphilis is a notifiable disease under the public health acts of all states and territories, and nationally. Cases of reactive serology are reported by pathology laboratories to public health authorities (CDNA 2018). In some jurisdictions, the health professional who diagnoses syphilis is also required to notify the jurisdictional public health authority. Probable or confirmed congenital syphilis must also be notified, including syphilis-related stillbirth (CDNA 2018).

3.1.2 Excluded studies

Reference	Reason for exclusions
Borges-Costa J, Matos C, Pereira F. Sexually transmitted infections in pregnant adolescents: prevalence and association with maternal and foetal morbidity. <i>J Eur Acad Dermatol Venereol</i> . 2012 Aug;26(8):972-5.	Not relevant to the Australian context
Bowen V, Su J, Torrone E, Kidd S, Weinstock H. Increase in incidence of congenital syphilis - United States, 2012-2014. <i>MMWR Morb Mortal Wkly Rep</i> . 2015 Nov 13;64(44):1241-5	Not relevant to the Australian context
Chopra S, Garg A, Chopra M, Ghosh A, Sreenivas V, Sood S, Kapil A, Das BK. Declining trends of Syphilis seroprevalence among antenatal clinic cases and STD clinic cases in a tertiary care centre: from January 2002 to December 2012. <i>Indian J Med Microbiol</i> . 2015 Feb;33 Suppl:126-8	Not relevant to the Australian context
De Paschale M, Ceriani C, Cerulli T, Cagnin D, Cavallari S, Cianflone A, Diombo K, Ndayaké J, Aouanou G, Zaongo D, Priuli G, Viganò P, Clerici P. Antenatal screening for <i>Toxoplasma gondii</i> , Cytomegalovirus, rubella and <i>Treponema pallidum</i> infections in northern Benin. <i>Trop Med Int Health</i> . 2014 Jun;19(6):743-746	Not relevant to the Australian context
Forrest CE, Ward A. Clinical diagnosis of syphilis: a ten-year retrospective analysis in a South Australian urban sexual health clinic. <i>Int J STD AIDS</i> . 2016 Dec;27(14):1334-1337	Not specific to target population
Ham DC, Lin C, Newman L, Wijesooriya NS, Kamb M. Improving global estimates of syphilis in pregnancy by diagnostic test type: A systematic review and meta-analysis. <i>Int J Gynaecol Obstet</i> . 2015 Jun;130 Suppl 1:S10-4	Does not answer research question
Kang SH, Lee JH, Choi SH, Lee J, Yoon HS, Cha SH, Choi YS. Recent change in congenital syphilis in Korea: Retrospective 10 year study. <i>Pediatr Int</i> . 2015 Dec;57(6):1112-5.	Not relevant to the Australian context
Kenyon CR, Osbak K, Buyze J, Chico RM. The changing relationship between bacterial STIs and HIV prevalence in South Africa - an ecological study. <i>Int J STD AIDS</i> . 2015 Jul;26(8):556-64	Does not answer research question
Kenyon CR, Osbak K, Tsoumanis A. The Global Epidemiology of Syphilis in the Past Century - A Systematic Review Based on Antenatal Syphilis Prevalence. <i>PLoS Negl Trop Dis</i> . 2016 May 11;10(5):e0004711.	Does not answer research question
Kirkcaldy RD, Su JR, Taylor MM, Koumans E, Mickey T, Winscott M, Kenney K, Weinstock HS. Epidemiology of syphilis among Hispanic women and associations with congenital syphilis, Maricopa county, Arizona. <i>Sex Transm Dis</i> . 2011 Jul;38(7):598-602	Not relevant to the Australian context
Kuo M, Money DM, Alvarez M, Buxton JA, Krajden M, Lester RT, Ogilvie G, Gilbert M. Test uptake and case detection of syphilis, HIV, and hepatitis C among women undergoing prenatal screening in British Columbia, 2007 to 2011. <i>J Obstet Gynaecol Can</i> . 2014 Jun;36(6):482-490	Does not answer research question
Lutomski JE, Shiely F, Molloy EJ. The prevalence of syphilis at childbirth in Ireland: a six-year review. <i>J Matern Fetal Neonatal Med</i> . 2014 Nov;27(17):1823-5.	Not relevant to the Australian context

Reference	Reason for exclusions
Marrazzo JM. What's new in sexually transmitted infections in the HIV care setting: focus on syphilis and gonorrhoea. <i>Top Antivir Med.</i> 2014 Dec-2015 Jan;22(5):698-701	Not specific to target population
McGettrick P, Ferguson W, Jackson V, Eogan M, Lawless M, Cipriki V, Varughese A, Coulter-Smith S, Lambert JS. Syphilis serology in pregnancy: an eight-year study (2005-2012) in a large teaching maternity hospital in Dublin, Ireland. <i>Int J STD AIDS.</i> 2016 Mar;27(3):226-30	Not relevant to the Australian context
Mulhall BP, Wright S, Allen D, Brown K, Dickson B, Grotowski M, Jackson E, Petoumenos K, Read P, Read T, Russell D, Smith DJ, Templeton DJ, Fairley CK, Law MG. High rates of sexually transmissible infections in HIV-positive patients in the Australian HIV Observational Database: a prospective cohort study. <i>Sex Health.</i> 2014 Sep;11(4):291-7.	Not specific to target population
Newman L, Kamb M, Hawkes S, Gomez G, Say L, Seuc A, Broutet N. Global estimates of syphilis in pregnancy and associated adverse outcomes: analysis of multinational antenatal surveillance data. <i>PLoS Med.</i> 2013;10(2):e1001396.	Background information
Preston-Thomas A, Ryder N, Harmen S, Fagan P. Was infectious syphilis being misclassified in remote Australian outbreaks? Evidence that informed modification of the national case definition. <i>Commun Dis Intell Q Rep.</i> 2015 Dec 31;39(4):E571-7	Does not answer research question
Read P, Tagg KA, Jeoffreys N, Guy RJ, Gilbert GL, Donovan B. <i>Treponema pallidum</i> Strain Types and Association with Macrolide Resistance in Sydney, Australia: New TP0548 Gene Types Identified. <i>J Clin Microbiol.</i> 2016 Aug;54(8):2172-4	Does not answer research question
Rodríguez-Cerdeira C, Silami-Lopes VG. Congenital syphilis in the 21st century. <i>Actas Dermosifiliogr.</i> 2012 Oct;103(8):679-9	Narrative review
Shaw SY, Ross C, Nowicki DL, Marshall S, Stephen S, Davies C, Riddell J, Bailey K, Elliott LJ, Reimer JN, Plourde PJ. Infectious syphilis in women: what's old is new again? <i>Int J STD AIDS.</i> 2017 Jan;28(1):77-87.	Does not answer research question
Soeiro CM, Miranda AE, Saraceni V, Santos MC, Talhari S, Ferreira LC. Syphilis in pregnancy and congenital syphilis in Amazonas State, Brazil: an evaluation using database linkage. <i>Cad Saude Publica.</i> 2014 Apr;30(4):715-23	Not relevant to the Australian context
Su JR, Brooks LC, Davis DW, Torrone EA, Weinstock HS, Kamb ML. Congenital syphilis: trends in mortality and morbidity in the United States, 1999 through 2013. <i>Am J Obstet Gynecol.</i> 2016 Mar;214(3):381.e1-9	Not relevant to the Australian context
Vallely LM, Toliman P, Ryan C, Rai G, Wapling J, Tomado C, Huliafi S, Munnall G, Rarau P, Phuanukoonnon S, Wand H, Siba P, Mola GDL, Kaldor JM, Vallely AJ. Prevalence and risk factors of <i>Chlamydia trachomatis</i> , <i>Neisseria gonorrhoeae</i> , <i>Trichomonas vaginalis</i> and other sexually transmissible infections among women attending antenatal clinics in three provinces in Papua New Guinea: a cross-sectional survey. <i>Sex Health.</i> 2016 Oct;13(5):420-427	Not relevant to the Australian context
Wijesooriya NS, Rochat RW, Kamb ML, Turlapati P, Temmerman M, Broutet N, Newman LM. Global burden of maternal and congenital syphilis in 2008 and 2012: a health systems modelling study. <i>Lancet Glob Health.</i> 2016 Aug;4(8):e525-33	Does not answer research question

Reference	Reason for exclusions
<p>Yáñez-Alvarez I, Conde-González CJ, Uribe-Salas FJ, Olamendi-Portugal ML, García-Cisneros S, Sánchez-Alemán MA. Maternal/child seroprevalence of antibodies against <i>Treponema pallidum</i> at four general hospitals in the state of Morelos, Mexico. Arch Med Res. 2012 Oct;43(7):571-7</p>	<p>Not relevant to the Australian context</p>
<p>Yeganeh N, Watts HD, Camarca M, Soares G, Joao E, Pilotto JH, Gray G, Theron G, Santos B, Fonseca R, Kreitchmann R, Pinto J, Mussi-Pinhata M, Ceriotto M, Machado DM, Grinzstejn B, Veloso VG, Morgado MG, Bryson Y, Mofenson LM, Nielsen-Saines K; NICHD HPTN 040P1043 Study Team. Syphilis in HIV-infected mothers and infants: results from the NICHD/HPTN 040 study. Pediatr Infect Dis J. 2015 Mar;34(3):e52-7</p>	<p>Does not answer research question</p>

4 Testing for syphilis

4.1 Q2: What are the harms and benefits of routine antenatal testing for syphilis compared to targeted/no testing?

4.1.1 Evidence summary

Outcomes associated with syphilis during pregnancy

Three systematic reviews of the risks associated with syphilis during pregnancy were identified (observational studies were excluded). The reviews were consistent in finding that untreated syphilis during pregnancy is associated with stillbirth (Arnesen et al 2015; Gomez et al 2013; Qin et al 2014) and fetal loss, neonatal death, preterm birth, low birthweight and congenital syphilis (Gomez et al 2013; Qin et al 2014).

Routine versus no testing

Only one historical cohort study from the United States compared routine testing for syphilis to no testing (Fung & Robles 2016). This study found that introduction of mandatory antenatal testing for syphilis decreased neonatal mortality rates by 8.6% among babies of non-Caucasian women, while having no discernible effect on babies of Caucasian women (probably due to higher prevalence and lower rates of testing among non-white women). The study concluded that the results provide strong support for universal testing, particularly in countries with high prevalence.

No studies into the cost-effectiveness of routine testing in the Australian context were identified.

Testing in the third trimester

Studies conducted in the United States found that universal testing in the third trimester would require a seroconversion incidence of 0.017% (compared to the assumed base case incidence of 0.012%) (Albright et al 2015) or a prevalence of 3.5% (Shiber & Todia 2014) to be cost-effective. A third study (also from the United States) in an area of high prevalence found that testing and treatment early in the third trimester prevented 78% of cases of congenital syphilis (Matthias et al 2017).

4.1.2 Advice to the EWG

Given the severity of outcomes associated with syphilis during pregnancy and the availability of effective treatment (see Section 5.1.1), the advice to routinely test for syphilis at the first antenatal visit remains current.

Suggest including a consensus-based recommendation on repeat testing early in the third trimester (28 weeks) for women at high risk of infection or re-infection.

Based on the advice of the Office of Public Health, suggest including a separate consensus-based recommendation on testing five times around pregnancy for women who are at risk of syphilis infection or reinfection.

4.1.3 Evidence table: Outcomes associated with syphilis during pregnancy

Study ref	Design	LoE	N	Aim, setting, methods	Results	Comments
(Arnesen et al 2015)	SLR	IV	8 studies	<p>Aim: To perform a systematic review and meta-analysis of reported estimates of the association between gestational syphilis (GS) and stillbirth.</p> <p>Setting: the Americas</p> <p>Methods: Cochrane Library, Embase, LILACS, MEDLINE/PubMed, PLOS, and ScienceDirect were searched for original research studies quantifying the relationship between GS and stillbirth in the region. A cumulative meta-analysis plus four subgroup meta-analyses of study data on the association between maternal syphilis during pregnancy and stillbirth were conducted. The four meta-analyses were based on 1) definition of cases and the control; 2) syphilis treatment (presence or absence, effective or ineffective); 3) definition of stillbirth as “showing no signs of life at birth”; and 4) definition of stillbirth based on low birth weight and gestational age. Random-effects meta-analyses were used to calculate pooled estimates of stillbirth with exposure to GS, and each subgroup analysis was tested for heterogeneity.</p>	<p>Women with GS had increased odds of stillbirth (pooled OR 6.87; 95%CI 2.93 to 16.08). There was considerable heterogeneity across the studies ($I^2= 95$). The funnel plot was not statistically significant, pointing to a lack of publication bias. Increased odds of stillbirth among pregnant women with syphilis were also seen in all four subgroup meta-analyses.</p>	<p>Review includes observational studies and is of low to moderate methodological quality (see Section 4.1.6)</p>

Study ref	Design	LoE	N	Aim, setting, methods	Results	Comments
(Gomez et al 2013)	SLR	IV	6 case-control studies	<p>Aim: To perform a systematic review and meta-analysis of reported estimates of adverse pregnancy outcomes among untreated women with syphilis and women without syphilis.</p> <p>Settings: Malawi, Tanzania, United Kingdom, United States, Zambia</p> <p>Methods: PubMed, EMBASE and Cochrane Libraries were searched for literature assessing adverse pregnancy outcomes among untreated women with seroreactivity for <i>Treponema pallidum</i> infection and non-seroreactive women. Adverse pregnancy outcomes were fetal loss or stillbirth, neonatal death, prematurity or low birth weight, clinical evidence of syphilis and infant death. Random-effects meta-analyses were used to calculate pooled estimates of adverse pregnancy outcomes and, where appropriate, heterogeneity was explored in group-specific analyses.</p>	<p>Pooled estimates showed that among untreated pregnant women with syphilis, fetal loss and stillbirth were 21% more frequent, neonatal deaths were 9.3% more frequent and prematurity or low birth weight were 5.8% more frequent than among women without syphilis. Of the infants of mothers with untreated syphilis, 15% had clinical evidence of congenital syphilis. The single study that estimated infant death showed a 10% higher frequency among infants of mothers with syphilis. Substantial heterogeneity was found across studies in the estimates of all adverse outcomes for both women with syphilis (66.5%; 95%CI 58.0 to 74.1; $I^2 = 91.8\%$; $P < 0.001$) and women without syphilis (14.3%; 95%CI 11.8 to 17.2]; $I^2 = 95.9\%$; $P < 0.001$).</p>	<p>Review includes observational studies and is of low to moderate methodological quality (see Section 4.1.6)</p>

Study ref	Design	LoE	N	Aim, setting, methods	Results	Comments
(Qin et al 2014)	SLR	IV	54 studies 11,398 women with syphilis 43,342 women without syphilis	<p>Aim: To estimate probability of adverse pregnancy outcomes (APOs) among women with and without syphilis through a systematic review of published literature.</p> <p>Settings: China, Kenya, Malawi, Russia, Tanzania, United Kingdom, United States, Zambia</p> <p>Methods: Chinese and English literature were searched for studies assessing pregnancy outcomes in the presence of maternal syphilis through August 2013. The prevalence estimates were summarised and analysed by meta-analysis.</p>	<p>Among mothers with untreated syphilis, pooled estimates were 76.8% for all APOs, 36.0% for congenital syphilis, 23.2% for preterm, 23.4% for low birth weight, 26.4% for stillbirth or fetal loss, 14.9% for miscarriage and 16.2% for neonatal deaths.</p> <p>Among mothers receiving treatment only in the late trimester (>28 weeks), pooled estimates were 64.4% for APOs, 40.6% for congenital syphilis, 17.6% for preterm, 12.4% for low birth weight, and 21.3% for stillbirth or fetal loss. Among mothers with high titers ($\geq 1:8$), pooled estimates were 42.8% for all APOs, 25.8% for congenital syphilis, 15.1% for preterm, 9.4% for low birth weight, 14.6% for stillbirth or fetal loss and 16.0% for neonatal deaths.</p> <p>Among mothers without syphilis, the pooled estimates were 13.7% for all APOs, 7.2% for preterm birth, 4.5% for low birth weight, 3.7% for stillbirth or fetal loss, 2.3% for miscarriage and 2.0% for neonatal death. Begg's rank correlation test indicated little evidence of publication bias ($P > 0.10$). Substantial heterogeneity was found across studies in the estimates of all adverse outcomes for both women with syphilis ($I^2 = 93.9\%$; $P < 0.0001$) and women without syphilis ($I^2 = 94.8\%$; $P < 0.0001$).</p>	Review includes observational studies and is of low to moderate methodological quality (see Section 4.1.6)

4.1.4 Evidence table: Routine testing

Study ref	Design	LoE	N	Aim, setting, intervention, comparator, methods	Results	Comments
(Fung & Robles 2016)	Cohort	III-2	—	<p>Aim: to study antenatal testing laws initiated in the U.S. in 1938-1947 which mandated physicians and other persons permitted by law to attend to a pregnant woman to test her for syphilis.</p> <p>Setting: United States</p> <p>Intervention: States where the testing laws had been enacted.</p> <p>Comparator: States where the testing laws had not been enacted.</p> <p>Method: We used the variation in the timing of state antenatal testing laws to estimate the laws' effect on neonatal mortality rates and deaths due to preterm birth.</p>	<p>Using 1931-47 Vital Statistics data, we find that these laws decreased neonatal mortality rates of non-whites by 3.15 per 1000 live births (a 8.6% reduction) while having no discernible impact on whites. The laws contributed to an 18% narrowing of the white vs non-white neonatal mortality gap by 1947. Using 1950 U.S. Census data, we find that mandatory antenatal testing led to a 7% increase in the cohort size of non-white poor, which is consistent with the neonatal mortality results. We find universal antenatal testing to be very cost-effective, with an estimated \$7600 cost (in 2013 dollars) per life-year saved.</p>	

4.1.5 Evidence table: Third trimester testing

Study ref	Design	LoE	N	Aim, setting, methods	Results	Comments
(Albright et al 2015)	Modelling study	—	—	<p>Aim: To estimate the cost to prevent one case of congenital syphilis or fetal or neonatal death with universal third-trimester syphilis rescreening and to estimate the incidence of syphilis seroconversion at which rescreening becomes cost-effective.</p> <p>Setting: United States</p> <p>Method: We created a decision model comparing universal third-trimester syphilis rescreening in women who screened negative in the first trimester with no rescreening. The assumed base case incidence of seroconversion was 0.012%. The primary outcome was the cost to prevent one case of congenital syphilis. Secondary outcomes included the cost to prevent one fetal or neonatal death and the number needed to rescreen to prevent one adverse outcome. A strategy was considered cost-effective if it cost less than \$285,000 to prevent one case of congenital syphilis (the estimated long-term care cost).</p>	<p>Under our assumptions, universal third trimester rescreening would cost an additional \$419,842 for each case of congenital syphilis prevented and \$3,621,144 and \$6,052,534, respectively, for each fetal and neonatal death prevented. Rescreening 4,000,000 women would prevent 60 cases of congenital syphilis and 7 fetal and 4 neonatal deaths. Prevention of one case of congenital syphilis would require 65,790 women to be rescreened. Seroconversion incidence of 0.017% would make third-trimester rescreening cost-effective.</p>	

Study ref	Design	LoE	N	Aim, setting, methods	Results	Comments
(Matthias et al 2017)	Cohort	III-2	710	<p>Aim: to evaluate the effectiveness of early (first or second) and third trimester syphilis screening for the prevention of congenital syphilis in high-morbidity states.</p> <p>Setting: United States</p> <p>Methods: Reported syphilis cases among pregnant women in Louisiana and Florida during January 1, 2013, to December 31, 2014, were reviewed for documented screening for syphilis in the first two trimesters and third trimester. Pregnant women with syphilis were linked to congenital syphilis records and stratified by whether the pregnancy led to a reported congenital syphilis case.</p>	<p>Screening in the first two trimesters identified 513 pregnant women who tested positive for syphilis and 470 (92%) potential congenital syphilis cases were averted.</p> <p>In the third trimester, 109 pregnant women tested positive for syphilis (of whom 36 tested negative in the first two trimesters and 73 had not been previously tested) and 85 (78%) had babies without congenital syphilis.</p> <p>During their pregnancy, 85 (12%) women tested negative at least once, and 55 (65%) had babies with congenital syphilis. Thirty-nine women had no reported syphilis screening 30 days or longer before birth.</p>	

Study ref	Design	LoE	N	Aim, setting, methods	Results	Comments
(Shiber & Todia 2014)	Cohort	III-2	58,569	<p>Aim: to determine the clinical utility and cost of repeating syphilis testing in the third trimester of pregnancy in a high-risk urban population.</p> <p>Setting: United States</p> <p>Methods: A retrospective cohort analysis was performed for patients delivering from January 1993 through December 2009 with at least 1 venereal disease research laboratory (VDRL) test sent during pregnancy. Chart review was performed for patients with confirmed syphilis to determine the temporal relationship of syphilis diagnosis to the pregnancy. For patients who seroconverted during pregnancy (no antecedent history or treatment for syphilis), newborn charts were reviewed. The costs of treating seropositive neonates and the costs of implementing additional third-trimester syphilis screening were then compared.</p>	<p>In all, 113 new cases of syphilis occurred (192.9/100,000 deliveries). There were 17 detected seroconversions; 10 were not rescreened in the third trimester and tested positive at delivery. These 10 patients may have benefitted from implementing uniform VDRL testing at 28-32 weeks' gestation. All newborns were asymptomatic with a negative workup and received empiric penicillin therapy. Based on 2011 hospital charges, the cost of evaluating and treating a neonate for syphilis is \$11,079. Implementing an additional VDRL screen at 28-32 weeks' gestation for each pregnant patient during the 17 years studied would cost \$1,991,346.</p> <p>An 18-fold increase in syphilis prevalence (3500/100,000 [3.5%] deliveries) would be required for the cost of implementation of universal early third-trimester screening to be equal to the potential health care charges saved by detecting maternal seroconversion and obviating the need for neonatal therapy.</p>	

4.1.6 Evaluation of quality of systematic reviews

(Arnesen et al 2015)	Comment
Questions and methods clearly stated	The review question is not stated but eligibility criteria are clearly articulated. Methods used are clearly stated.
Search procedure sufficiently rigorous to identify all relevant studies	<p>Using text search strings, a search was conducted for studies that examined the association between GS and stillbirth for all years covered in the following databases up to 6 October 2013: Cochrane Library, Embase, LILACS, MEDLINE/ PubMed, PLOS (all journals), and ScienceDirect (journals only). Publications found in the search were included in the analysis if they contained at least one term from each of the five categories (“syphilis,” “mother-to-child transmission,” “pregnancy,” “stillbirth,” and “Americas region”)</p> <p>Studies in English, French, Portuguese, and Spanish were considered. Reports published only as abstracts were excluded if all necessary data were not available in the abstract. Reference lists were then manually searched for other potential studies of relevance to the analysis.</p>
Review includes all the potential benefits and harms of the intervention	Not applicable (review assessed outcomes associated with syphilis in pregnancy)
Review only includes randomised controlled trials	Review included only observational studies.
Methodological quality of primary studies assessed	Assessment of study quality not described.
Data summarised to give a point estimate of effect and confidence intervals	The unadjusted odds ratio (OR) estimates and corresponding 95% confidence intervals (CIs) were calculated from the data extracted from each study. A cumulative meta-analysis was used to assess the overall relationship between GS and stillbirth. Random-effects models were used to estimate the pooled ORs and the respective 95% CIs. The I2 statistic was used to test for heterogeneity (percentage of variance) due to differences in the studies beyond random chance. Publication bias was addressed with visual inspection of a funnel plot.
Differences in individual study results are adequately explained	Studies varied in terms of focus (which included efficacy of syphilis treatment and the effect of syphilis on stillbirth) and by whether syphilis treatment was given to all mothers, some mothers, or no mothers.
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	Four subgroup meta-analyses were carried out to examine potential sources of heterogeneity. The I2 statistic was used to test for heterogeneity in each subgroup after controlling for the respective identifying covariate.

(Gomez et al 2013)	Comment
Questions and methods clearly stated	The review question is not stated but eligibility criteria are clearly articulated. Methods used are clearly stated.
Search procedure sufficiently rigorous to identify all relevant studies	We used combinations of the following terms to search PubMed, EMBASE and Cochrane Libraries: syphilis/congenital syphilis, pregnancy, antenatal/prenatal, neonate/newborn, infant, birth/pregnancy outcome, mortality, death, stillbirth/fetal death, neonatal death, infant death, preterm/low birth weight and perinatal death/mortality. The last search was performed in December 2011. We included literature published in any language and on any date. We reviewed references in seminal papers, review articles and medical textbooks. We canvassed experts in the field to identify additional studies, particularly older studies that may have been published before the availability of online databases. The grey literature and conference abstracts were not searched.
Review includes all the potential benefits and harms of the intervention	Not applicable (review assessed outcomes associated with syphilis in pregnancy)
Review only includes randomised controlled trials	Review included only observational studies.
Methodological quality of primary studies assessed	Assessment of study quality not described.
Data summarised to give a point estimate of effect and confidence intervals	Random-effects meta-analyses were used to calculate pooled estimates of adverse pregnancy outcomes.
Differences in individual study results are adequately explained	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	Not applicable
Reviewers' conclusions are supported by data cited	Reviewers' conclusions are supported by data cited.
Sources of heterogeneity are explored	Where appropriate, heterogeneity was explored in group-specific analyses.

(Qin et al 2014)	Comment
Questions and methods clearly stated	The review question is not stated but eligibility criteria are clearly articulated. Methods used are clearly stated.
Search procedure sufficiently rigorous to identify all relevant studies	PubMed, Cochrane Libraries, China Biology Medicine disc (CBMdisc), Chinese Scientific Journals Fulltext Database (CQVIP), China National Knowledge Infrastructure (CNKI) and Wanfang Data were searched through August 2013 with no restrictions to identify published peer-reviewed research articles assessing pregnancy outcomes in the presence of maternal syphilis by the following search terms: syphilis, pregnancy, adverse birth or pregnancy outcomes, congenital syphilis, preterm, low birth weight, stillbirth, fetal loss or death, abortion or miscarriage, neonatal death, and perinatal death or morbidity or mortality. We also performed a manual search on the reference lists of published articles. The grey literature and conference abstracts were not searched.
Review includes all the potential benefits and harms of the intervention	Not applicable (review assessed outcomes associated with syphilis in pregnancy)
Review only includes randomised controlled trials	Review included only observational studies.
Methodological quality of primary studies assessed	Assessment of study quality not described.
Data summarised to give a point estimate of effect and confidence intervals	We calculated the combined incidence and the corresponding 95% confidence intervals (CI) for all APOs in women with syphilis and women without syphilis. We then also calculated the summary incidence and the corresponding 95%CI for the following selected pregnancy loss.
Differences in individual study results are adequately explained	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	Not applicable
Reviewers' conclusions are supported by data cited	Reviewers' conclusions are supported by data cited.
Sources of heterogeneity are explored	The subgroup analysis for all APOs and specific APOs was performed based on whether women were infected with syphilis, whether syphilitic women were treated during pregnancy (i.e. syphilitic women receiving at least one injection of 2.4 million units of penicillin before delivery), gestational week at treatment (i.e. <12 or 12 to 28 or ≥28 weeks), and maternal baseline titers (i.e. ≥1:8 or <1:8) to explore the sources of heterogeneity.

4.1.7 Excluded studies

Outcomes associated with syphilis during pregnancy

Reference	Reason for exclusion
Baidya A, Ghosh A, Chopra S, Garg A, Sood S, Kapil A, Das BK. Congenital syphilis in the era of decreasing seroprevalence. Indian J Med Microbiol. 2016 Jan-Mar;34(1):111-2.	Opinion paper

Reference	Reason for exclusion
Bradley H, Tapia V, Kamb ML, Newman LM, Garcia PJ, Serruya SJ, Fort AL, Broutet N, Nelson R, Kirkcaldy RD, Gonzales GF. Can the Perinatal Information System in Peru be used to measure the proportion of adverse birth outcomes attributable to maternal syphilis infection? <i>Rev Panam Salud Publica</i> . 2014 Aug;36(2):73-9	Does not answer research question
Bristow CC, Klausner JD. Cuba: defeating mother-to-child transmission of syphilis. <i>Lancet</i> . 2015 Oct 17;386(10003):1533	Opinion paper
Caddy SC, Lee BE, Sutherland K, Robinson JL, Plitt SS, Read R, Singh AE. Pregnancy and neonatal outcomes of women with reactive syphilis serology in Alberta, 2002 to 2006. <i>J Obstet Gynaecol Can</i> . 2011 May;33(5):453-9	Does not answer research question
Casal C, Araújo Eda C, Corvelo TC. Risk factors and pregnancy outcomes in women with syphilis diagnosed using a molecular approach. <i>Sex Transm Infect</i> . 2013 May;89(3):257-61	Not a systematic review
Casal CA, Silva MO, Costa IB, Araújo Eda C, Corvelo TC. Molecular detection of <i>Treponema pallidum</i> sp. <i>pallidum</i> in blood samples of VDRL-seroreactive women with lethal pregnancy outcomes: a retrospective observational study in northern Brazil. <i>Rev Soc Bras Med Trop</i> . 2011 Jul-Aug;44(4):451-6.	Not a systematic review
Chen XS, Yin YP. Syphilis: still a major cause of infant mortality. <i>Lancet Infect Dis</i> . 2012 Apr;12(4):269-70; author reply 270-1.	Opinion paper
Domingues RM, Saracen V, Hartz ZM, Leal Mdo C. Congenital syphilis: a sentinel event in antenatal care quality. <i>Rev Saude Publica</i> . 2013 Feb;47(1):147-56; discussion 157.	Does not answer research question
Domingues RM, Szwarcwald CL, Souza PR Jr, Leal Mdo C. Prenatal testing and prevalence of HIV infection during pregnancy: data from the "Birth in Brazil" study, a national hospital-based study. <i>BMC Infect Dis</i> . 2015 Feb 26;15:100	Does not answer research question
Hebmuller MG, Fiori HH, Lago EG. Subsequent pregnancies in women with previous gestational syphilis. <i>Cien Saude Colet</i> . 2015 Sep;20(9):2867-78	Not a systematic review
Krakauer Y, Pariente G, Sergienko R, Wiznitzer A, Sheiner E. Perinatal outcome in cases of latent syphilis during pregnancy. <i>Int J Gynaecol Obstet</i> . 2012 Jul;118(1):15-7.	Not a systematic review
Lago EG, Vaccari A, Fiori RM. Clinical features and follow-up of congenital syphilis. <i>Sex Transm Dis</i> . 2013 Feb;40(2):85-94	Does not answer research question
Mabey D, Peeling RW. Syphilis, still a major cause of infant mortality. <i>Lancet Infect Dis</i> . 2011 Sep;11(9):654-5	Opinion paper
Qin JB, Feng TJ, Yang TB, Hong FC, Lan LN, Zhang CL, Yang F, Mamady K, Dong W. Risk factors for congenital syphilis and adverse pregnancy outcomes in offspring of women with syphilis in Shenzhen, China: a prospective nested case-control study. <i>Sex Transm Dis</i> . 2014 Jan;41(1):13-23	Not a systematic review
Qin JB, Feng TJ, Yang TB, Hong FC, Lan LN, Zhang CL. Maternal and paternal factors associated with congenital syphilis in Shenzhen, China: a prospective cohort study. <i>Eur J Clin Microbiol Infect Dis</i> . 2014 Feb;33(2):221-32	Does not answer research question

Reference	Reason for exclusion
Sampath A, Maduro G, Schillinger JA. Infant Deaths Due To Herpes Simplex Virus, Congenital Syphilis, and HIV in New York City. <i>Pediatrics</i> . 2016 Apr;137(4).	Does not answer research question
Zhou Q, Wang L, Chen C, Cao Y, Yan W, Zhou W. A case series of 130 neonates with congenital syphilis: preterm neonates had more clinical evidences of infection than term neonates. <i>Neonatology</i> . 2012;102(2):152-6	Does not answer research question
<i>Approach to testing</i>	
Reference	Reason for exclusion
[No authors listed] Testing for syphilis during pregnancy. <i>Lancet Infect Dis</i> . 2012 Apr;12(4):255	Opinion paper
Aebi-Popp K, Kahlert C, Rauch A, Mosimann B, Baud D, Low N, Surbek D. Heterogeneity in testing practices for infections during pregnancy: national survey across Switzerland. <i>Swiss Med Wkly</i> . 2016 Jul 11;146:w14325	Does not answer research question
Cantor AG, Pappas M, Daeges M, Nelson HD. Screening for Syphilis: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. <i>JAMA</i> . 2016 Jun 7;315(21):2328-37. doi: 10.1001/jama.2016.4114.	Narrative review
Cha S, Malik T, Abara WE, DeSimone MS, Schumann B, Mallada E, Klemme M, Aguon V, Santos AM, Peterman TA, Bolan G, Kamb ML. Screening for Syphilis and Other Sexually Transmitted Infections in Pregnant Women - Guam, 2014. <i>MMWR Morb Mortal Wkly Rep</i> . 2017 Jun 23;66(24):644-648.	Narrative review
Desai M, Woodhall SC, Nardone A, Burns F, Mercey D, Gilson R. Active recall to increase HIV and STI testing: a systematic review. <i>Sex Transm Infect</i> . 2015 Aug;91(5):314-23.	Not specific to target population
Dinh TH, Kamb ML, Msimang V, Likibi M, Molebatsi T, Goldman T, Lewis DA. Integration of preventing mother-to-child transmission of HIV and syphilis testing and treatment in antenatal care services in the Northern Cape and Gauteng provinces, South Africa. <i>Sex Transm Dis</i> . 2013 Nov;40(11):846-51	Does not answer research question
Drago F, Ciccarese G, Javor S, Parodi A. Syphilis screening, treatment and follow-up: strengths and weaknesses of the international guidelines. <i>J Eur Acad Dermatol Venereol</i> . 2016 Oct;30(10):e77-e78	Opinion paper
Ensari T, Kirbas A, Ozgu-Erdinc AS, Gokay Saygan S, Erkaya S, Uygur D, Danisman N. An eight-year retrospective analysis of antenatal screening results for syphilis: is it still cost effective? <i>J Infect Dev Ctries</i> . 2015 Sep 27;9(9):1011-	Does not answer research question
Freyne B, Stafford A, Knowles S, Hora AO, Molloy EJ. Universal perinatal screening for <i>Treponema pallidum</i> : the role of a dedicated infectious diseases team for prevention of mother-to-child transmission. <i>Sex Transm Infect</i> . 2013 Nov;89(7):582	Opinion paper
Hawkes S, Matin N, Broutet N et al (2011) Effectiveness of interventions to improve screening for syphilis in pregnancy: a systematic review and meta-analysis. <i>The Lancet Infectious Diseases</i> 11(9): 684-91.	Does not answer research question

Reference	Reason for exclusion
Hong FC, Yang YZ, Liu XL, Feng TJ, Liu JB, Zhang CL, Lan LN, Yao MZ, Zhou H. Reduction in mother-to-child transmission of syphilis for 10 years in Shenzhen, China. <i>Sex Transm Dis</i> . 2014 Mar;41(3):188-93	Does not answer research question
Kahn JG, Jiwani A, Gomez GB, Hawkes SJ, Chesson HW, Broutet N, Kamb ML, Newman LM. The cost and cost-effectiveness of scaling up screening and treatment of syphilis in pregnancy: a model. <i>PLoS One</i> . 2014 Jan 29;9(1):e87510.	Not applicable to the Australian context
Kingston M, Goold P, Radcliffe K. Amendment and correction to the 2008 UK national guideline on the management of syphilis. <i>Int J STD AIDS</i> . 2011 Oct;22(10):613-4	Opinion paper
Kwan KS, Giele CM, Greville HS, Reeve CA, Lyttle PH, Mak DB. Syphilis epidemiology and public health interventions in Western Australia from 1991 to 2009. <i>Sex Health</i> . 2012 Jul;9(3):272-9	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. <i>Am Fam Physician</i> . 2016 Dec 1;94(11):907-915.	Background information
Low N, Hawkes SJ. Trials of antenatal syphilis screening urgently needed. <i>Lancet</i> . 2011 Sep 3;378(9794):877; author reply 877-8	Opinion paper
Luu M, Ham C, Kamb ML, Caffè S, Hoover KW, Perez F. Syphilis testing in antenatal care: Policies and practices among laboratories in the Americas. <i>Int J Gynaecol Obstet</i> . 2015 Jun;130 Suppl 1:S37-42	Does not answer research question
Marseille E, Larson B, Kazi DS, Kahn JG, Rosen S. Thresholds for the cost-effectiveness of interventions: alternative approaches. <i>Bull World Health Organ</i> . 2015 Feb 1;93(2):118-24	Does not answer research question
Mattei PL, Beachkofsky TM, Gilson RT, Wisco OJ. Syphilis: a reemerging infection. <i>Am Fam Physician</i> . 2012 Sep 1;86(5):433-40.	Narrative review
Milanez H. Syphilis in Pregnancy and Congenital Syphilis: Why Can We not yet Face This Problem? <i>Rev Bras Ginecol Obstet</i> . 2016 Sep;38(9):425-427	Does not answer research question
Moline HR, Smith JF Jr. The continuing threat of syphilis in pregnancy. <i>Curr Opin Obstet Gynecol</i> . 2016 Apr;28(2):101-4.	Narrative review
Murali MV, Nirmala C, Rao JV. Symptomatic early congenital syphilis: a common but forgotten disease. <i>Case Rep Pediatr</i> . 2012;2012:934634	Narrative review
Nkamba D, Mwenechanya M, Kilonga AM, Cafferata ML, Berrueta AM, Mazzoni A, Althabe F, Garcia-Elorrio E, Tshefu AK, Chomba E, Buekens PM, Belizan M. Barriers and facilitators to the implementation of antenatal syphilis screening and treatment for the prevention of congenital syphilis in the Democratic Republic of Congo and Zambia: results of qualitative formative research. <i>BMC Health Serv Res</i> . 2017 Aug 14;17(1):55	Does not answer research question
Oomeer S, Alagaratnam J, Lyall H, Gurtin D, Goldmeier D. Seven years of undiagnosed syphilis: a missed opportunity for mother and child. <i>Int J STD AIDS</i> . 2015 Nov;26(13):982-4	Opinion paper

Reference	Reason for exclusion
Op de Coul EL, Hahne S, van Weert YW et al (2011) Antenatal screening for HIV, hepatitis B and syphilis in the Netherlands is effective. <i>BMC Infect Dis</i> 11: 185.	Does not answer research question
Owusu-Edusei K Jr, Introcaso CE, Chesson HW. Hospitalization cost of congenital syphilis diagnosis from insurance claims data in the United States. <i>Sex Transm Dis</i> . 2013 Mar;40(3):226-9	Opinion paper
Owusu-Edusei K Jr, Tao G, Gift TL, Wang A, Wang L, Tun Y, Wei X, Wang L, Fuller S, Kamb ML, Bulterys M. Cost-effectiveness of integrated routine offering of prenatal HIV and syphilis screening in China. <i>Sex Transm Dis</i> . 2014 Feb;41(2):103-10.	Not applicable to the Australian context
Patel NU, Oussedik E, Landis ET, Strowd LC. Early Congenital Syphilis: Recognising Symptoms of an Increasingly Prevalent Disease. <i>J Cutan Med Surg</i> . 2017 Aug 1:12034754	Opinion paper
Peeling RW, Mabey D. Celebrating the decline in syphilis in pregnancy: a sobering reminder of what's left to do. <i>Lancet Glob Health</i> . 2016 Aug;4(8):e503-4. doi: 10.1016/S2214-109X(16)30154-1	Opinion paper
Rac MW, Revell PA, Eppes CS. Syphilis during pregnancy: a preventable threat to maternal-fetal health. <i>Am J Obstet Gynecol</i> . 2017 Apr;216(4):352-363	Narrative review
Reed D, Stiller R. Challenges in the diagnosis and treatment of congenital syphilis. <i>Conn Med</i> . 2012 Aug;76(7):397-400.	Does not answer research question
Reif LK, Rivera V, Louis B, Bertrand R, Peck M, Anglade B, Seo G, Abrams EJ, Pape JW, Fitzgerald DW, McNairy ML. Community-Based HIV and Health Testing for High-Risk Adolescents and Youth. <i>AIDS Patient Care STDS</i> . 2016 Aug;30(8):371-8.	Not specific to target population
Ross CE, Tao G, Patton M, Hoover KW. Screening for human immunodeficiency virus and other sexually transmitted diseases among U.S. women with prenatal care. <i>Obstet Gynecol</i> . 2015 May;125(5):1211-6	Does not answer research question
Silva S, Henriques R, Gomes JP, Borrego MJ, Afonso E. Could we miss congenital neurosyphilis? <i>Lancet Infect Dis</i> . 2012 Oct;12(10):816	Not specific to target population
Singh AE, Chernesky MA, Morshed M, Wong T. Canadian Public Health Laboratory Network laboratory guidelines for the use of point-of-care tests for the diagnosis of syphilis in Canada. <i>Can J Infect Dis Med Microbiol</i> . 2015 Jan-Feb;26 Suppl A:29A-32A	Background information
Trope LA, Wijesooriya NS, Broutet N, Temmerman M, Newman L. Reaching beyond pregnant women to eliminate mother-to-child transmission of syphilis in Africa. <i>Expert Rev Anti Infect Ther</i> . 2014 Jun;12(6):705-14.	Narrative review
Wallace HE, Broomhall HM, Isitt CE, Miall LS, Wilson JD. Serological follow-up of infants born to mothers with positive syphilis serology - real-world experiences. <i>Int J STD AIDS</i> . 2016 Nov;27(13):1213-121	Does not answer research question

Repeat testing

Reference	Reason for exclusion
Plitt SS, Osman M, Sahni V, Lee BE, Charlton C, Simmonds K. Examination of a prenatal syphilis screening program, Alberta, Canada: 2010-2011. Can J Public Health. 2016 Oct 20;107(3):e285-e29	Does not answer research question

4.2 Q3: What is the diagnostic accuracy of tests available for detection of syphilis infection in pregnancy?

4.2.1 Background information

There are two main classifications of serological tests for syphilis (*T. pallidum*) performed in medical testing laboratories (CDNA 2018):

- treponemal tests, which detect specific treponemal antibodies and can be run on high throughput random access instruments – commonly used assays include enzyme immunoassays (EIAs) and particle agglutination assays (eg *T. pallidum* particle agglutination [TPPA])
- non-treponemal tests, which detect non-specific antibodies and are performed manually – the assay most commonly used is the rapid plasma reagin (RPR).

In Australia, serum from blood specimens is usually screened with a treponemal assay and confirmed with an alternative treponemal assay using a different platform (ie screening with an EIA and confirmation with a TPPA). In people with prior treated syphilis, because the treponemal assays remain reactive for life, an RPR alone is sometimes used to detect reinfection or treatment success (ASHA 2018).

Due to intralaboratory and interlaboratory variation, when a person has a changing non-treponemal antibody result, the current specimen should be tested in parallel with previous specimens.

Point-of-care tests are now available that present results within 15-20 minutes (see Section 4.3).

4.2.2 Evidence summary

Most diagnostic accuracy studies identified were specific to point of care testing (see Section 4.3.1).

Of the remaining included diagnostic accuracy studies:

- one compared the accuracy of dried blood spot on filter paper samples with venepuncture screening methods and found it to be highly accurate (100%; 95%CI 99.25 to 100)
- one found lower concordance between IgG EIA testing and TPPA (ie false positives) among pregnant women (Henrich & Yawetz 2011)
- three found high levels of false positives for chemiluminescent immunoassay among pregnant women (Boonchaoy et al 2016; Mmeje et al 2015; Wang et al 2016).

4.2.3 Advice to the EWG

The identified evidence does not provide information that is useful in the context of testing in Australia. Include the background information on testing in the narrative.

4.2.4 Evidence table

Study ref	Design	LoE	N	Aim, setting, intervention, comparator, methods	Results	Comments
(Boa-Sorte et al 2014)	Cross-section		692	<p>Aim: to compare the accuracy of dried blood spot and venepuncture screening methods for HIV, HTLV, VHB, VHC, <i>Treponema pallidum</i>, and <i>Toxoplasma gondii</i> during the prenatal period.</p> <p>Setting: Brazil</p> <p>Intervention: dried blood spot in filter paper</p> <p>Comparator: venepuncture serological screening</p> <p>Methods: A cross-sectional study was conducted between November 2009 and March 2010.</p>	<p>The dried blood spot accuracy for syphilis and was 100% (95%CI 99.25 to 100). The average time (SD) between blood collection and recording of the sample in the reference laboratory was 4.93 (3.82) days and between dried blood spot processing and active search for pregnant women was 3.44 (4.27) days.</p>	
(Henrich & Yawetz 2011)	Cohort		34,251	<p>Aim: to determine the performance of IgG EIA screening in specific populations, such as pregnant women</p> <p>Setting: United States</p> <p>Intervention: treponemal-specific enzyme immunoassays (EIA)</p> <p>Comparator: confirmatory tests such as the Treponemal pallidum particle agglutination (TPPA) assay.</p> <p>Methods: We reviewed laboratory results of 34,251 samples from individuals who underwent IgG EIA screening at a large academic medical center, so as to calculate positive concordance of these screening tests with a confirmatory TPPA or subsequent rapid plasma reagin (RPR) test by age, gender, pregnancy, and obstetric or gynecologic (Ob/Gyn) service.</p> <p>Binary regression modeling was used to identify independent associations between demographic variables and positive concordance of EIA screening with RPR and confirmatory TPPA tests.</p>	<p>Samples from younger women, from an Ob/Gyn service, and from pregnant women had significantly lower concordance by univariate analysis, and therefore higher false positive rates of the IgG EIA screening assay.</p>	

Study ref	Design	LoE	N	Aim, setting, intervention, comparator, methods	Results	Comments
(Boonchaoy et al 2016)	Cohort		11,640	<p>Aim: to evaluate the diagnostic performance of chemiluminescent microparticle immunoassay (CMIA) in screening for syphilis in pregnant women.</p> <p>Setting: Thailand</p> <p>Intervention: CMIA</p> <p>Comparator: Samples were also tested by rapid plasma reagin (RPR) and Treponema pallidum particle agglutination assay (TPPA).</p> <p>Methods: This study retrospectively reviewed the CMIA results of pregnant women attending an antenatal care clinic. Women with reactive CMIA results were extracted from the laboratory database and further analysed. A reactive/positive result for Treponema pallidum was defined as having a sample/cut-off absorbance ratio of >1.0.</p>	<p>Among 65 women (0.56%) with reactive CMIA results, 58 women (89.2%) had non-reactive RPR results. TPPA were non-reactive in 35 women (60.3%) who had non-reactive RPR results. A total of 23 women (39.7%) with RPR non-reactive and TPPA reactive results; therefore, the prevalence rate of syphilis in this population was estimated as 1.98 per 1,000 pregnant women. Among this, 7 cases had a history of past, partial treatment for syphilis and 16 cases were considered as untreated, late, latent syphilis. If RPR tests were used as the screening test, 16/23 cases (69.6%) cases with untreated syphilis would be missed.</p> <p>Even though CMIA has high false positive results, it is still recommended that this reverse sequence screening be used instead of the traditional algorithm. The rate of false positive results can be decreased by adjusting the sample/cut-off absorbance ratio of CMIA.</p>	

Study ref	Design	LoE	N	Aim, setting, intervention, comparator, methods	Results	Comments
(Mmeje et al 2015)	Cohort		194	<p>Aim: To determine the clinical significance of discordant serology for maternal and neonatal outcomes.</p> <p>Setting: United States</p> <p>Intervention: chemiluminescence immunoassay (CIA)</p> <p>Comparator: rapid plasma reagin test (RPR)</p> <p>Methods: From August 2007 to August 2010, all pregnant women at Kaiser Permanente Northern California with discordant treponemal serology underwent reflexive testing with Treponema pallidum particle agglutination assay (TP-PA) and were categorised as “TP-PA confirmed” (CIA-/RPR-/TP-PA-) or “isolated CIA positive” (CIA-/RPR-/TP-PA-). Demographic variables and clinical data were abstracted from the medical record and compared by TP-PA status.</p>	<p>Of 194 pregnant women, 156 (80%) were CIA+/RPR-/TP-PA- and 38 (20%) were CIA+/RPR-/TP-PA+. Among the 77 (49%) CIA+/RPR-/TP-PA- women who were retested, 53% became CIA-. CIA+/RPR-/TP-PA+ (n=38) women were more likely to be older, have a prior history of sexually transmitted infections, and receive treatment for syphilis during pregnancy than women who were CIA-/RPR-/TP-PA- (all P<0.005).</p> <p>CIA-/RPR-/TP-PA- serology in pregnancy is likely to be falsely positive. Reflexive testing of discordant specimens with TP-PA is important to stratify risk given the likelihood of false-positive results in this population.</p>	
(Wang et al 2016)	Cross-section		3,962	<p>Aim: to verify whether chemiluminescent micro-particle immunoassay (CLIA) is feasible for syphilis screening</p> <p>Setting: China</p> <p>Intervention: automated CLIA</p> <p>Comparator: conventional methods</p> <p>Methods: Serum samples were tested by CLIA, rapid plasma reagin test (RPR), and Treponema pallidum particle agglutination (TPPA). Meanwhile, another 36 000 sera were screened for syphilis using CLIA and the positive samples were confirmed using TPPA, RPR or Western blotting.</p>	<p>The sensitivity and specificity were 100% and 99.8% for CLIA, and 65% and 99.6% for RPR. With the elevation of the optical density value of samples to cut-off ratio (S/CO) value, the true-positive rate of CLIA increased significantly, and when the S/CO value exceeded 10, the true-positive rate of CLIA reached 100%. The false-positive rate of CLIA was 0.22%; pregnant women had the most false-positive results.</p>	

4.2.5 Excluded studies

Reference	Reason for exclusion
Binnicker MJ. Which algorithm should be used to screen for syphilis? <i>Curr Opin Infect Dis.</i> 2012 Feb;25(1):79-85	Narrative review
Bosshard PP (2013) Usefulness of IgM-specific enzyme immunoassays for serodiagnosis of syphilis: comparative evaluation of three different assays. <i>J Infect</i> 67(1): 35-42.	Industry study
Donkers A, Levy HR, Letens-van Vliet A (2014) Syphilis detection using the Siemens ADVIA Centaur Syphilis treponemal assay. <i>Clin Chim Acta</i> 433: 84-7.	Relevant to research not practice
Harding AS, Ghanem KG. The performance of cerebrospinal fluid treponemal-specific antibody tests in neurosyphilis: a systematic review. <i>Sex Transm Dis.</i> 2012 Apr;39(4):291-7.	Not specific to target population
Hunter MG, Robertson PW, Post JJ. Significance of isolated reactive treponemal chemiluminescence immunoassay results. <i>J Infect Dis.</i> 2013 May 1;207(9):1416-23	Does not answer research question
Kubanov A, Runina A, Deryabin D. Novel Treponema pallidum Recombinant Antigens for Syphilis Diagnostics: Current Status and Future Prospects. <i>Biomed Res Int.</i> 2017;2017:1436080.	Relevant to research not practice
Levett PN, Fonseca K, Tsang RS, Kadkhoda K, Serhir B, Radons SM, Morshed M. Canadian Public Health Laboratory Network laboratory guidelines for the use of serological tests (excluding point-of-care tests) for the diagnosis of syphilis in Canada. <i>Can J Infect Dis Med Microbiol.</i> 2015 Jan-Feb;26 Suppl A:6A-12A	Background information
Loeffelholz MJ, Wen T, Patel JA. Analysis of bioplex syphilis IgG quantitative results in different patient populations. <i>Clin Vaccine Immunol.</i> 2011 Nov;18(11):2005-	Narrative review
Marangoni A, Foschi C, Capretti MG, Nardini P, Compri M, Corvaglia LT, Faldella G, Cevenini R. Contribution of a Comparative Western Blot Method to Early Postnatal Diagnosis of Congenital Syphilis. <i>Clin Vaccine Immunol.</i> 2016 May 6;23(5):410-416.	Not specific to target population
Marangoni A, Nardini P, Foschi C, Moroni A, D'Antuono A, Bacchi Reggiani L, Cevenini R. Evaluation of the BioPlex 2200 syphilis system as a first-line method of reverse-sequence screening for syphilis diagnosis. <i>Clin Vaccine Immunol.</i> 2013 Jul;20(7):1084-8.	Relevant to research not practice
Nemes-Nikodém E, Vörös E, Pónyai K, Párducz L, Kárpáti S, Rozgonyi F, Ostorházi E. The importance of IgM positivity in laboratory diagnosis of gestational and congenital syphilis. <i>Eur J Microbiol Immunol (Bp).</i> 2012 Jun;2(2):157-60.	Does not answer research question
Peng RR, Wang AL, Li J, Tucker JD, Yin YP, Chen XS. Molecular typing of Treponema pallidum: a systematic review and meta-analysis. <i>PLoS Negl Trop Dis.</i> 2011 Nov;5(11):e1273	Does not answer research question
Peterman TA, Newman DR, Davis D, Su JR. Do women with persistently negative nontreponemal test results transmit syphilis during pregnancy? <i>Sex Transm Dis.</i> 2013 Apr;40(4):311-5.	Does not answer research question

Reference	Reason for exclusion
Taylor MM, Ebrahim S, Abiola N, Kinkodi DK, Mpingulu M, Kabuayi JP, Ekofo F, Newman DR, Peterman TA, Kamb ML, Sidibe K. Correlates of syphilis seropositivity and risk for syphilis-associated adverse pregnancy outcomes among women attending antenatal care clinics in the Democratic Republic of Congo. <i>Int J STD AIDS</i> . 2014 Sep;25(10):716-25	Does not answer research question
Tsang RS, Morshed M, Chernesky MA, Jayaraman GC, Kadkhoda K. Canadian Public Health Laboratory Network laboratory guidelines for the use of direct tests to detect syphilis in Canada. <i>Can J Infect Dis Med Microbiol</i> . 2015 Jan-Feb;26 Suppl A:13A-7A	Background information
Wellinghausen N, Dietenberger H. Evaluation of two automated chemiluminescence immunoassays, the LIAISON Treponema Screen and the ARCHITECT Syphilis TP, and the Treponema pallidum particle agglutination test for laboratory diagnosis of syphilis. <i>Clin Chem Lab Med</i> . 2011 Aug;49(8):1375-7	Relevant to research not practice
Wong T, Fonseca K, Chernesky MA, Garceau R, Levett PN, Serhir B. Canadian Public Health Laboratory Network laboratory guidelines for the diagnosis of neurosyphilis in Canada. <i>Can J Infect Dis Med Microbiol</i> . 2015 Jan-Feb;26 Suppl A:18A-22A	Background information

4.3 Q4: What are the harms and benefits of point-of-care testing for syphilis among pregnant women in remote communities?

4.3.1 Background information

The CDNA notes the following limitations with current syphilis point-of-care tests (CDNA 2018):

- currently tests cannot distinguish current from previous syphilis infection, due to either the absence or non-quantified nature of a non-treponemal component
- even in ideal use, sensitivity is slightly lower than laboratory based assays
- the tests are moderately complicated and require staff to be specifically trained in their use
- the results may not be captured by current notification and testing registries.

4.3.2 Evidence summary

Diagnostic accuracy

One systematic review (Rogozinska et al 2017) and four observational studies (Bristow et al 2016b; Omoding et al 2014; Shakya et al 2016; Smit et al 2013) examined the diagnostic accuracy of point of care (POC) tests for syphilis (also referred to as rapid syphilis tests). The observational studies were all conducted in developing countries with high prevalence of syphilis and HIV. The findings of these studies may be applicable to some remote areas of Australia, although median prevalence in the studies was much higher than prevalence even in those parts of Australia where an outbreak has been identified (see Section 6.1.1).

There is currently only one syphilis point of care test registered by the Therapeutic Goods Administration in Australia, the Determine Syphilis TP™ manufactured by Alere (CDNA 2018). The Determine Syphilis TP™ is a treponemal-specific test. The Determine™ and SD Bioline Syphilis 3.0™ tests are commercially available in Australia (CDNA 2015). SD Bioline HIV/Syphilis Duo kit is also included in the analysis below as it had the highest sensitivity and specificity of the tests.

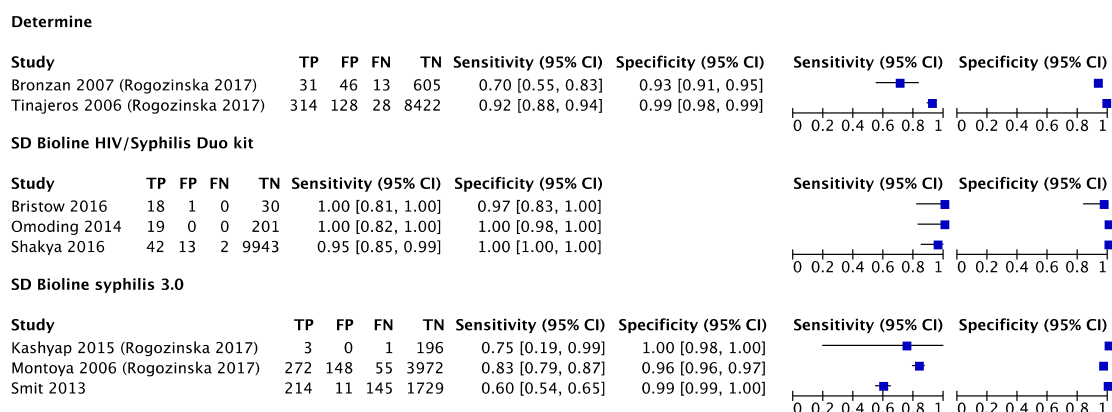


Figure 2: Forest plot of tests: Determine, SD Bioline HIV/Syphilis Duo kit, SD Bioline syphilis 3.0

Summary of findings: SD Bioline Syphilis 3.0 for detection of syphilis in pregnant women

Population : Pregnant women

Setting: India, Mozambique, Tanzania

New test: SD Bioline Syphilis 3.0

Reference test: THPA/TPPA

Range of sensitivities : 0.60 to 0.83 | **Range of specificities :** 0.96 to 1.00

Test result	Number of results per 1,000 patients tested (95% CI)			Number of participants (studies)	Certainty of the Evidence (GRADE)
	Prevalence 0.01% (2016 prevalence among Australian women aged 15 to 29 years)	Prevalence 0.2% (2016 prevalence among Aboriginal and Torres Strait Islander people in the Northern Territory)	Prevalence 7.4% (Median prevalence in studies; range= 2.0 to 17.1%)		
True positives	0 to 0	1 to 2	44 to 61	6746 (3)	⊕⊕⊕○ MODERATE ^a
False negatives	0 to 0	0 to 1	13 to 30		
True negatives	960 to 1000	958 to 998	889 to 926	6746 (3)	⊕⊕⊕⊕ HIGH
False positives	0 to 40	0 to 40	0 to 37		

CI: Confidence interval

a. Downgraded due to heterogeneity of results for sensitivity.

Summary of findings: Determine™ for detection of syphilis in pregnant women

Patient or population: Pregnant women

Setting: Bolivia, South Africa

New test: Determine

Reference test: THPA/TPPA

Range of sensitivities: 0.70 to 0.92 | **Range of specificities:** 0.93 to 0.99

Test result	Number of results per 1,000 patients tested (95% CI)			Number of participants (studies)	Certainty of the Evidence (GRADE)
	Prevalence 0.01% (2016 prevalence among Australian women aged 15 to 29 years)	Prevalence 0.2% (2016 prevalence among Aboriginal and Torres Strait Islander people in the NT)	Prevalence 5% (Mean prevalence in studies)		
True positives	0 to 0	1 to 2	35 to 46	9587 (2)	⊕⊕⊕○ MODERATE ^a
False negatives	0 to 0	0 to 1	4 to 15		
True negatives	930 to 990	928 to 988	884 to 941	9587 (2)	⊕⊕⊕⊕ HIGH
False positives	10 to 70	10 to 70	9 to 66		

CI: Confidence interval

a. Downgraded due to heterogeneity of results for sensitivity.

Summary of findings: SD Bioline HIV/Syphilis 3.0 duo kit for detection of syphilis in pregnant women

Population: Pregnant women

Settings: China, Haiti, Nepal, Nigeria, Uganda

New test: SD Bioline HIV/Syphilis Duo kit

Reference test: TPHA/TPPA

Range of sensitivities: 0.95 to 1.00 | **Range of specificities:** 0.97 to 1.00

Test result	Number of results per 1,000 patients tested (95% CI)			Number of participants (studies)	Certainty of the Evidence (GRADE)
	Prevalence 0.01% (2016 prevalence among Australian women aged 15 to 29 years)	Prevalence 0.2% (2016 prevalence among Aboriginal and Torres Strait Islander people in the NT)	Prevalence 7.4% (Median prevalence in studies; range= 6.3 to 38.7%)		
True positives	0 to 0	2 to 2	70 to 74	10269 (3)	⊕⊕⊕⊕ HIGH
False negatives	0 to 0	0 to 0	0 to 4		
True negatives	970 to 1000	968 to 998	898 to 926	10269 (3)	⊕⊕⊕⊕ HIGH
False positives	0 to 30	0 to 30	0 to 28		

CI: Confidence interval

Uptake and treatment

One systematic review (Swartzendruber et al 2015), a cluster randomised controlled trial (RCT) (Gaitan-Duarte et al 2016) and five historical control studies (Bonawitz et al 2015; Dassah et al 2015; De Schacht et al 2015; Severe et al 2013; Smith et al 2015) examined uptake of point-of-care testing and rates of treatment.

All studies in the systematic review reported substantial increases in antenatal syphilis testing following introduction of rapid syphilis testing in low and middle income countries. Qualitative data revealed that women were highly satisfied with rapid syphilis testing. Adequate training for health care workers and supplies of commodities were cited as key implementation barriers. The requirement for health professional training was also noted in an historical control study (Smith et al 2015).

The RCT (Gaitan-Duarte et al 2016) compared single POC tests for syphilis and HIV (Arm A) with a dual POC test for the two conditions (Arm B) and found high acceptability among women (>99%) for both approaches. There were no significant differences in rates of testing and timely treatment between the two approaches.

Historical control studies comparing uptake of syphilis testing before and after introduction of POC testing were inconsistent regarding changes in the proportion of women tested, with findings including:

- significant increases – from 10.6 to 67.5% at 6 months and to 56.3% at 12 months (P<0.001) (Bonawitz et al 2015) and from 91.5 to 95.9% (P<0.001), with further increases to 96.8% (P<0.001) following a quality improvement intervention (Severe et al 2013)
- no significant change – from 80.8 to 87.0% (P=0.282) (De Schacht et al 2015) and from 49.6 to 50.3% at 12 months (P=0.87) (Smith et al 2015)
- a decrease from 50 to 33.6% at 16 months (Dassah et al 2015).

Variables that may explain the heterogeneity of findings include levels of testing at baseline, prevalence and length of follow-up.

Cost-effectiveness

While the cost-effectiveness studies were all conducted in developing countries and may not be applicable to the Australian context, they highlighted that:

- use of dual HIV and syphilis tests resulted in lower levels of adverse outcomes, lower costs and fewer disability-adjusted life years (DALYs) compared with HIV rapid test alone, single tests for HIV and syphilis, or HIV and syphilis laboratory tests (Bristow et al 2016a)
- rapid tests were more cost-effective than RPR both in the field (Sweeney et al 2014) and laboratory-based (Mallma et al 2016)

- rapid tests for treponemal antibodies were more cost-effective than tests for both treponemal and non-treponemal antibodies (Owusu-Edusei et al 2011; Terris-Prestholt et al 2015).

4.3.3 Evidence statements

Point-of-care tests for syphilis have sensitivity and specificity in the ranges of 0.70 to 0.92 and 0.93 to 0.99 for Determine™ (Rogozinska et al 2017), 0.60 to 0.83 and 0.96 to 1.00 for SD Bioline Syphilis 3.0 (Smit et al 2013; Rogozinska et al 2017), and 0.95 to 1.00 and 0.97 to 1.00 for SD Bioline HIV/Syphilis Duo Kit (Omoding et al 2014; Bristow et al 2016b; Shakya et al 2016) (moderate to high quality evidence).

Point-of-care testing appears to increase uptake of testing in low and middle income countries (moderate quality) but this effect may not be sustained in the longer term (low quality).

Point-of-care testing appears to be cost-effective in developing countries (low quality).

4.3.4 Advice to EWG

Include the above information in the narrative.

4.3.5 Evidence table: Diagnostic accuracy of point-of-care tests

Study ref	Design	LoE	N	Aim, setting, intervention, comparator, methods	Results	Comments
(Rogozinska et al 2017)	SLR	IV	7 studies 17,546	<p>Aim: To assess the accuracy of on-site tests to detect infection with <i>Treponema pallidum</i> in pregnant women.</p> <p>Settings: Brazil, South Africa, India, Mozambique, Bolivia, Senegal</p> <p>Interventions: Determine™, SD BioLine Syphilis 3.0, VisiTect Syphilis and Rapid Plasma Reagin</p> <p>Comparator: Dual reference standard (non-treponemal and treponemal tests)</p> <p>Methods: Major databases were searched from inception to January 2016 using terms: ‘pregnancy’, ‘antenatal’, ‘syphilis’, ‘<i>Treponema pallidum</i>’ with their variations, and the search limit for the relevant study design. Extracted accuracy data were tabulated and pooled using hierarchical, bivariate random effects model.</p>	<p>On average, Determine™ (2 studies) and SD BioLine Syphilis 3.0 (2 studies) had the highest pooled sensitivity of all the evaluated tests: 0.83 (95%CI 0.58 to 0.98) and 0.86 (95%CI 0.82 to 0.89), respectively, with a pooled specificity 0.96 (95%CI 0.89 to 1.00) and 0.99 (95%CI 0.94 to 1.00), respectively. The sensitivity of VisiTect (1 study) was 0.63 (95% CI 0.31, 0.86) and specificity 0.98 (95% CI 0.97, 0.99).</p> <p>The Qualitative Rapid Plasma Reagin card commonly used in clinical practice had a pooled sensitivity of 0.70 (95% CI 0.54, 0.88) and specificity of 0.97 (95% CI 0.96, 0.99).</p>	<p>The review included only observational studies and is of moderate methodological quality (see Section 4.3.8).</p>

Study ref	Design	LoE	N	Aim, setting, intervention, comparator, methods	Results	Comments
(Shakya et al 2016)	Cross-section	IV	10,000	<p>Aim: To assess the performance and operational characteristics of point-of-care testing for syphilis and HIV among pregnant women.</p> <p>Setting: Nepal</p> <p>Intervention: SD Bioline HIV/Syphilis Duo kit</p> <p>Comparator: RPR test with all test positive samples were reconfirmed by TPHA method and national HIV algorithm</p> <p>Method: A prospective laboratory-based cross sectional study was conducted at a large Women's Hospital. Women visiting the Hospital for antenatal care or for childbirth were enrolled in study. Sensitivity, Specificity, positive predictive value and negative predictive value along with kappa coefficient were calculated for the kit under evaluation.</p>	<p>The sensitivity of the kit for syphilis diagnosis was found to be 95.45% (95%CI 84.86 to 98.74) and specificity was 99.87% (95%CI 99.78 to 99.92). Positive predictive value was 76.36% (95%CI 63.65 to 85.63) and Negative predictive value was 99.89% (95%CI 99.39 to 99.99). Kappa value was found to be 0.85.</p>	

Study ref	Design	LoE	N	Aim, setting, intervention, comparator, methods	Results	Comments
(Omoding et al 2014)	Cross-section	IV	220	<p>Aim: To evaluate the performance of the SD Biotest Syphilis/HIV Duo (Duo) assay among pregnant women attending a healthcare centre.</p> <p>Setting: Uganda.</p> <p>Intervention: SD Biotest Syphilis/HIV Duo (Duo) assay using venous blood samples</p> <p>Comparator: T pallidum haemagglutination assay (TPHA) and the Uganda HIV screening algorithm</p> <p>Methods: A convenience sample of pregnant women attending Kinoni Health Centre IV from March to May, 2013 was enrolled. Venous blood was collected and centrifuged for plasma isolation. Samples were tested with the Duo assay and compared with the Treponema pallidum hemagglutination assay and paired HIV rapid antibody tests as the reference standards. The ease of use and time required for the Duo assay were also assessed by laboratory technicians.</p>	<p>The sensitivity and specificity of the Duo assay were 100% (95%CI 79.0 to 100%) and 100% (95%CI 97.6 to 100.0) respectively, for syphilis, and, 100% (95%CI 75.9 to 100%) and 99.5% (95%CI 96.8 to 99.9%) respectively, for HIV.</p> <p>The PPV and NPV for syphilis were 100.0% (95%CI 79.1 to 100.0%) and 100.0% (95%CI 97.7 to 100.0%), respectively.</p> <p>The duo kit was found to be faster and easier to use than the current HIV and syphilis testing techniques.</p> <p>The Duo assay should be further evaluated in alternate populations and with point-of-care specimens (e.g. whole blood from finger stick specimens), but shows promise as a tool for improved HIV and syphilis surveillance, diagnosis, and treatment in field settings.</p>	

Study ref	Design	LoE	N	Aim, setting, intervention, comparator, methods	Results	Comments
(Bristow et al 2016b)	Cohort study	III-2	298 total 237 women 49 pregnant women	<p>Aim: To evaluate dual rapid tests for HIV and syphilis infections in the field.</p> <p>Setting: Haiti</p> <p>Intervention: SD BIOLINE HIV/Syphilis Duo test using whole blood fingerprick specimens</p> <p>Comparator: Venepuncture blood specimens were used for reference testing with standard tests commercially available for HIV and syphilis (TPHA) in Haiti</p> <p>Methods: GHESKIO (Haitian Study Group for Kaposi's Sarcoma and Opportunistic Infections) clinic attendees 18 years of age or older were invited to participate. The sensitivity and specificity of the Duo test compared to the reference standard were calculated. The exact binomial method was used to determine 95% confidence intervals (CI).</p>	In pregnant women, the sensitivity and specificity of the syphilis component were 100 % (95%CI 81.5 to 100%) and 96.8 % (95%CI 83.3 to 99.9 %), respectively.	2x2 table requested from study author.

Study ref	Design	LoE	N	Aim, setting, intervention, comparator, methods	Results	Comments
(Smit et al 2013)	Cohort	III-2	POCT 2,099 EIA 1,041	<p>Aim: To evaluate two methods to diagnose syphilis in pregnant women.</p> <p>Setting: Tanzania</p> <p>Intervention: SD bionline syphilis 3.0.</p> <p>Comparator: syphilis enzyme immunoassay (EIA)</p> <p>Reference test: Treponema pallidum particle agglutination assay (TPPA)</p> <p>Methods: The POCT was performed in the clinic on whole blood (finger prick), while the other assays were performed on plasma in the laboratory.</p>	<p>With TPPA as reference assay:</p> <ul style="list-style-type: none"> POCT had 11 false positive and 145 false negative results, giving a sensitivity of 59.6% (95%CI 54.3 to 64.7%) and specificity of 99.4% (95%CI 98.9-99.7%). There was a 92.6% agreement between POCT and TPPA. POCT detected 41 of 50 active cases, giving a sensitivity of 82% (69.2%-90.2%) and specificity of 100%. EIA had 20 false positive and 9 false negative results, giving a sensitivity of 95.2% (95%CI 91.1 to 97.8%) and specificity of 97.7% (95%CI 96.4 to 98.6%). There was 97.3% agreement between TPPA and EIA. The EIA showed a sensitivity and specificity of 100% to detect active syphilis cases <p>Only 15% of antenatal clinic attenders in this district visited a health facility with a laboratory capable of performing the EIA. Although it is less sensitive than EIA, its greater accessibility, and the fact that treatment can be given on the same day, means that the use of POCT would result in a higher proportion of women with syphilis receiving treatment than with the EIA in this district of Tanzania.</p>	

Study ref	Design	LoE	N	Aim, setting, intervention, comparator, methods	Results	Comments
(Yin et al 2015)	Cross-section	IV	1,514 serum samples	<p>Aim: To determine the laboratory-based performance and operational characteristics of three dual rapid diagnostic tests (RDTs) for testing HIV and syphilis.</p> <p>Setting: China and Nigeria</p> <p>Intervention: SD Bioline, Chembio, and MedMira</p> <p>Comparator: TTPA (China), TPHA (Nigeria)</p> <p>Methods: Three dual RDTs were evaluated using 1,514 serum specimens archived at laboratories or collected from clinics in China and Nigeria to determine sensitivity and specificity, with 95% confidence intervals. Concordance of testing results read by two technicians, stability of testing results read at two time points, and test operation characteristics were also assessed.</p>	<p>All three of the evaluated RDTs gave excellent performance with a combined sensitivity ranging from 99.0%–99.6% for HIV and 98.3%–99.0% for syphilis, and a combined specificity ranging from 97.9%–99.0% for HIV and 97.2%–99.6% for syphilis.</p> <p>The sensitivity and specificity for SD Bioline Duo were 96.6% (95%CI 95.0 to 97.7%) and 99.1% (95%CI 98.2 to 99.6%)</p> <p>Concordance of testing results between two technicians and stability of testing results read within and one hour past the recommended reading period showed excellent agreement, with Kappa greater than or equal to 0.98.</p>	Data on false negatives and positives not reported.

4.3.6 Evidence table: Uptake of testing and treatment

Study ref	Design	LoE	N	Aim, setting, intervention, comparator, methods	Results	Comments
(Swartzendru ber et al 2015)	SLR	IV	6 studies	<p>Aim: To examine the impact of rapid syphilis testing (RST) on syphilis and HIV screening among pregnant women.</p> <p>Settings: Asia, Africa, and Latin America</p> <p>Population: Pregnant women</p> <p>Methods: We searched MEDLINE for English and non-English language articles published through November, 2014. We included studies that used a comparative design and reported on syphilis and HIV test uptake among pregnant women in low and middle-income countries (LMICs) following introduction of RST.</p>	<p>All studies reported substantial increases in antenatal syphilis testing following introduction of RST; the latter did not appear to adversely impact antenatal HIV screening levels at sites already offering rapid HIV testing and may increase HIV screening among pregnant women in some settings.</p> <p>Qualitative data revealed that women were highly satisfied with RST. Nevertheless, ensuring adequate training for healthcare workers and supplies of commodities were cited as key implementation barriers.</p>	<p>The review included only observational studies and meta-analysis could not be conducted due to reporting differences.</p> <p>The review is of high methodological quality (see Section 4.3.8).</p>

Study ref	Design	LoE	N	Aim, setting, intervention, comparator, methods	Results	Comments
(Gaitan-Duarte et al 2016)	Cluster RCT	II	Arm A: 1,048 Arm B: 1,166	<p>Aim: To compare the effectiveness of a dual and single rapid tests for syphilis and HIV screening.</p> <p>Setting: Colombia</p> <p>Intervention: SD BIOLINE syphilis 3.0 and the SD BIOLINE HIV 3.0 (Arm A)</p> <p>Comparator: SD BIOLINE HIV/Syphilis Duo (Arm B)</p> <p>Methods: Pregnant women aged >14 years at their first antenatal visit and who had not been previously tested for HIV and syphilis during the current pregnancy were included. Women were randomized to Arm A or Arm B. The main outcomes measured were: (1) acceptability of the test, (2) uptake of testing, (3) treatment on the same day (that is, timely treatment), and (4) treatment at any time for positive rapid test cases.</p> <p>Bivariate and multivariate analyses were calculated to adjust for the clustering effect and the period.</p>	<p>Acceptability of the rapid tests was 99.8% in Arm A and 99.6% in Arm B. The prevalence of positive rapid tests was 2.21% for syphilis and 0.36% for HIV. Timely treatment was provided to 20 of 29 patients (69%) in Arm A and 16 of 20 patients (80%) in Arm B (RR 1.10; 95%CI 1.00 to 1.20). Treatment at any time was given to 24 of 29 patients (83%) in Arm A and to 20 of 20 (100%) in Arm B (RR, 1.11; 95% CI: 1.01–1.22).</p> <p>Testing for syphilis and HIV in the intervention period was 100% in both arms of the study. In comparison to the period prior to the intervention, syphilis testing showed an increase of 9.7% in Arm A and of 6.6% in Arm B</p>	High risk of bias; see Section 4.3.9.
(Bonawitz et al 2015)	Historical control study	III-3	4,154	<p>Aim: To evaluate the impact of rapid syphilis tests (RSTs) on syphilis testing and treatment in pregnant women.</p> <p>Intervention: Test not specified.</p> <p>Comparator: Testing before RST introduction</p> <p>Methods: In March 2012, health workers at 35 health facilities were trained in RST use and penicillin treatment. In March 2013, data were retrospectively abstracted from 18 randomly selected health facilities and stratified into three time intervals: baseline (6 months prior to RST introduction), midline (0–6 months after RST introduction), and endline (7–12 months after RST introduction).</p>	<p>The proportion of women screened improved from baseline (140/1,365, 10.6%) to midline (976/1,446, 67.5%), finally decreasing at endline (752/1,337, 56.3%) (P<0.001).</p> <p>There was no significant difference in the proportion of syphilis-seroreactive pregnant women who received 1 dose of penicillin before (1/2, 50%) or after (5/48, 10.4%; P = 0.199) RST introduction, with low treatment rates throughout.</p>	Syphilis-reactive seroprevalence was 2.7%.

Study ref	Design	LoE	N	Aim, setting, intervention, comparator, methods	Results	Comments
(Dassah et al 2015)	Historical control study	III-3	8,282	<p>Aim: To compare the uptake of maternal syphilis and HIV screening before and after roll-out of point-of-care testing (POCT).</p> <p>Setting: Ghana</p> <p>Intervention: rollout of syphilis POCTs (test not specified)</p> <p>Comparator: period before rollout of POCT</p> <p>Methods: Antenatal register records were reviewed in 15 selected health facilities over an eight-month period, 16 months apart. Register records had been evaluated using the maternal record booklets (MBR) as a gold standard in a separate prior survey.</p>	Use of POCTs for syphilis did not result in increased uptake. When adjusted for under-recording, syphilis screening uptake was 50% before and 33.6% after the introduction of POCTs.	
(De Schacht et al 2015)	Historical control study	III-3	Pre-POCT: 865 Post-POCT: 808	<p>Aim: to evaluate the effect of point-of-care testing (POCT) for hemoglobin quantification, syphilis testing and CD4+ T-cell enumeration performed within maternal and child health services on testing and treatment coverage, and assess acceptability by health workers.</p> <p>Setting: Mozambique</p> <p>Intervention: SD Bioline 3.0 syphilis</p> <p>Comparator: Rapid Plasma Reagin</p> <p>Methods: Demographic and testing data on women attending first antenatal care services were extracted from existing records, before (2011) and after (2012) introduction of POCT. Study outcomes per health facility were compared using z-tests (categorical variables) and Wilcoxon rank-sum test (continuous variables), while inverse variance weights were used to adjust for possible cluster effects in the pooled analysis. A structured acceptability-assessment interview was conducted with health workers before (n=22) and after (n=19).</p>	<p>After implementation of POCT, there was no significant change in uptake of overall hemoglobin screening (67.9 to 83.0%; p=0.229), syphilis screening (80.8 to 87.0%; p=0.282) and CD4+ T-cell testing (84.9 to 83.5%; p=0.930).</p> <p>Initiation of antiretroviral therapy for treatment eligible women was similar in the weighted analysis before and after, with variability among the sites. Time from HIV diagnosis to treatment initiation decreased (median of 44 days to 17 days; p<0.0001).</p> <p>A generally good acceptability for point-of-care testing was seen among health workers.</p>	

Study ref	Design	LoE	N	Aim, setting, intervention, comparator, methods	Results	Comments
(Severe et al 2013)	Historical control study	III-3	Pre-POCT: 34,776 Post-POCT: 16,025 Pre-QI: 14,137 Post-QI: 16,435	<p>Aim: To evaluate interventions to improve syphilis testing and treatment in pregnancy.</p> <p>Setting: Haiti</p> <p>Intervention: point-of-care testing (POCT) (SD bioline syphilis 3.0) plus quality improvement (QI)</p> <p>Comparator: period before intervention</p> <p>Method: POCT and a systems-based improvement intervention were introduced sequentially to 14 clinics over 51 months from 2007 to 2011. Between January 2008 and April 2009, POCT was introduced to 14 clinical study sites. In October 2010, a QI intervention was introduced to all study sites simultaneously. A time series analysis was utilized to understand the effects of these interventions occurring sequentially over the study period.</p>	<p>Syphilis testing increased from 91.5% prior to POCT to 95.9% after ($P < 0.001$) and further increased to 96.8% ($P < 0.001$) after the QI intervention.</p> <p>Despite high rates of testing across all time periods, syphilis treatment lagged behind and only increased from 70.3% to 74.7% after the introduction of POCT ($P = 0.27$), but it improved significantly from 70.2% to 84.3% ($P < 0.001$) after the systems strengthening QI intervention.</p>	
(Smith et al 2015)	Historical control study	III-3	901	<p>Aim: to describe the key lessons learned following one year's implementation of triple point-of-care (POC) screening for HIV, syphilis, and HBV through outreach teams</p> <p>Setting: Guatemala</p> <p>Intervention: SD Bioline Syphilis 3.0, Determine HIV-1/2, and Determine HBsAg offered by outreach teams</p> <p>Comparator: Centralised testing using the same tests</p> <p>Methods: Nurses or nurse practitioners collected offered pre-test counselling and collected a single fingerprick sample to perform. Women received their results within 15 minutes and those with a reactive test result were referred for confirmatory testing and treatment following national guidelines</p>	<p>One year following program implementation, antenatal care coverage increased from 73.7 to 99.6% (32.5% increase, $P < 0.001$), testing uptake increased from 49.6 to 50.3% for syphilis (1.3% increase; $P = 0.87$).</p> <p>Despite the expansion of triple antenatal POC testing, a shortage of healthcare workers and poor supply chain management limited screening uptake. Moreover, training is essential to help health workers overcome their fear of communicating positive results and improve partner notification. Engagement of community health workers was essential to build local capacity and facilitate community acceptance.</p>	

4.3.7 Evidence table: Cost-effectiveness

Study ref	N	Aim, setting, methods	Results	Comments
(Bristow et al 2016a)	100,000	<p>Aim: to assess the health and economic outcomes of a dual testing strategy in a simulated cohort of 100,000 antenatal care patients.</p> <p>Setting: Malawi</p> <p>Methods: We compared four screening algorithms: (1) HIV rapid test only, (2) dual HIV and syphilis rapid tests, (3) single rapid tests for HIV and syphilis and (4) HIV rapid and syphilis laboratory tests. We calculated the expected number of adverse pregnancy outcomes, the expected costs and the expected newborn disability-adjusted life years (DALYs) for each screening algorithm. The estimated costs and DALYs for each screening algorithm were assessed from a societal perspective using Markov progression models. Additionally, we conducted a Monte Carlo multiway sensitivity analysis, allowing for ranges of inputs.</p>	<p>Our cohort decision model predicted the lowest number of adverse pregnancy outcomes in the dual HIV and syphilis rapid test strategy. Additionally, from the societal perspective, the costs of prevention and care using a dual HIV and syphilis rapid testing strategy was both the least costly (\$226.92 per pregnancy) and resulted in the fewest DALYs (116 639) per 100,000 pregnancies.</p> <p>In the Monte Carlo simulation the dual HIV and syphilis algorithm was always cost saving and almost always reduced DALYs compared with HIV testing alone.</p>	
(Terris-Prestholt et al 2015)	—	<p>Aim: To assess the cost-effectiveness of rapid syphilis immunochromatographic strip tests detecting only <i>Treponema pallidum</i> antibodies (single RSTs) or both treponemal and non-treponemal antibodies (dual RSTs) in pregnant women.</p> <p>Setting: Peru, Tanzania, and Zambia</p> <p>Methods: Observed costs of maternal syphilis screening and treatment using clinic-based rapid plasma reagin (RPR) and single RSTs in 20 clinics were used to model the cost-effectiveness of algorithms using combinations of RPR, single, and dual RSTs, and no and mass treatment. Sensitivity analyses determined drivers of key results.</p>	<p>Although this analysis found screening using RPR to be relatively cheap, most (70%) true cases went untreated. Algorithms using single RSTs were the most cost-effective in all observed settings, followed by dual RSTs, which became the most cost-effective if dual RST costs were halved. Single test algorithms dominated most sequential testing algorithms, although sequential algorithms reduced overtreatment. Mass treatment was relatively cheap and effective in the absence of screening supplies, though treated many uninfected women.</p>	

Study ref	N	Aim, setting, methods	Results	Comments
(Sweeney et al 2014)	6,362	<p>Aim: To determine the costs of Rapid Syphilis Test (RSTs) as compared with rapid plasma reagin (RPR) when implemented in a Tanzanian setting, and to determine the relative impact of a quality assurance (QA) system on the cost of RST implementation.</p> <p>Setting: Tanzania</p> <p>Methods: The incremental costs for RPR and RST screening programmes in existing antenatal care settings in Geita District, Tanzania were collected for 9 months in subsequent years from nine health facilities that varied in size, remoteness and scope of antenatal services. The costs per woman tested and treated were estimated for each facility. A sensitivity analysis was constructed to determine the impact of parameter and model uncertainty.</p>	<p>The average unit cost at the health facility level for routine screening with RSTs to be \$1.92 per woman screened. This was lower than the estimated unit cost for RPR (\$2.32 per woman screened), although direct comparisons varied by health facility. Our results suggest that rapid syphilis diagnostics are very inexpensive in a Tanzanian setting, and less expensive than RPR, even where RPR is feasible.</p> <p>QA has a small additional cost to rapid syphilis screening, but potentially improves quality of diagnosis considerably.</p>	
(Owusu-Edusei et al 2011)	1,000	<p>Aim: To compare the health and economic outcomes of dual nontreponemal/treponemal point-of-care test (Dual-POC) with existing syphilis tests/testing algorithms in a high prevalence setting.</p> <p>Setting: Sub-Saharan Africa</p> <p>Methods: We used a cohort decision analysis model to examine 4 testing/screening algorithms; the Dual-POC test, the laboratory-based rapid plasma reagin and <i>Treponema pallidum</i> haemagglutination assay (RPRTPHA) algorithm, an onsite RPR testing, and point-of-care treponemal immunochromatographic strip (ICS) testing. Outcomes included miscarriage, stillbirth, congenital syphilis, low birth weight, and neonatal death. Disability-adjusted life-years were estimated for all health outcomes. The analytic horizon was the life expectancy for the mother and child.</p>	<p>For a cohort of 1,000 pregnant women in a historically high syphilis prevalence population (10% infected and 15% previously infected), the model predicted a total of 39 adverse pregnancy outcomes if no serologic screening were performed; 13 for the laboratory-based RPRTPHA; 11 for the on-site RPR strategy; 5 for the Dual-POC strategy; and 2 for the ICS strategy.</p> <p>On the basis of assumption that the cost of ICS and the Dual-POC tests were the same, the ICS strategy was the most cost saving (saved \$30,000) followed by the Dual-POC strategy (saved \$27,000).</p>	

Study ref	N	Aim, setting, methods	Results	Comments
(Mallma et al 2016)	–	<p>Aim: to compare costs of rapid syphilis testing (RST) with laboratory- based rapid plasma reagin (RPR) tests in low-prevalence settings</p> <p>Setting: Peru</p> <p>Methods: The RST was introduced in a tertiary-level maternity hospital and in the Ventanilla Network of primary health centers, where syphilis prevalence is approximately 1%.</p>	The costs per woman tested and treated with RST at the hospital were \$2.70 and \$369 respectively compared with \$3.60 and \$740 for RPR. For the Ventanilla Network the costs per woman tested and treated with RST were \$3.19 and \$295 respectively compared with \$5.55 and \$1454 for RPR. The cost per DALY averted using RST was \$46 vs. \$109 for RPR. RST showed lower costs compared to the WHO standard costs per DALY (\$64).	Findings suggest syphilis screening with RST is cost-effective in low-prevalence settings.

4.3.8 Evaluation of methodological quality of systematic reviews

(Swartzendruber et al 2015)	Comment
Questions and methods clearly stated	The review question is not stated but eligibility criteria are clearly articulated. Methods used are clearly stated.
Search procedure sufficiently rigorous to identify all relevant studies	PubMed (MEDLINE) was searched using the following keyword combinations: "rapid syphilis" AND "HIV," "point-of-care" AND "syphilis" AND "HIV," "immunochromatographic" AND "syphilis" AND "HIV," and "infectious disease transmission, vertical/prevention and control" [MeSH Terms] AND "HIV" AND "syphilis." There were no language restrictions. Searches were limited to studies published after 1999. The last search was performed in November 2014. References in seminal papers and review articles were reviewed, reference lists of included articles manually searched, and potential studies upon experts' suggestions identified.
Review includes all the potential benefits and harms of the intervention	Not applicable (review assessed uptake of testing)
Review only includes randomised controlled trials	Review included only observational studies.
Methodological quality of primary studies assessed	Assessment of study quality not described.
Data summarised to give a point estimate of effect and confidence intervals	Due to differences in reporting between studies, meta-analysis could not be conducted.
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	Studies were not heterogeneous.

(Rogozinska et al 2017)	Comment
Questions and methods clearly stated	The review question is not stated but PICO criteria are clearly articulated. Methods used are clearly stated.
Search procedure sufficiently rigorous to identify all relevant studies	Medline, Embase, Web of Science, Scopus and Lilacs were searched with no language restrictions. The original search run from inception to February 2015 was updated in January 2016. The literature search strategy combined clinical terms such as 'Pregnancy', 'Antenatal', 'Gestation', 'Treponema pallidum' and 'Syphilis' with a filter for test accuracy studies. The detailed search strategy is available in Supporting Information Appendix S1.
Review includes all the potential benefits and harms of the intervention	Review assessed diagnostic accuracy.
Review only includes randomised controlled trials	Review included only observational studies.
Methodological quality of primary studies assessed	Included studies were assessed using the QUADAS-2 tool.
Data summarised to give a point estimate of effect and confidence intervals	Pooled estimates of sensitivity, specificity, positive and negative likelihood ratios and confidence intervals included.
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	Between-study heterogeneity of studies was assessed using Forest plots for sensitivity and specificity.

4.3.9 Evaluation of methodological quality of RCTs

Study limitation	Judgement	Support for judgement
(Gaitan-Duarte et al 2016)		
Random sequence generation	Low risk	Clusters were randomly allocated to Arm A or to Arm B with a 1:1 allocation ratio, using SAS software.
Allocation concealment	Unclear risk	Allocation of clusters was concealed until the cluster was ready to recruit patients.
Blinding	High risk	Open label
Incomplete outcome data	Low risk	Six women were excluded from Arm A and five from Arm B (reasons reported). Analysis does not include women lost to follow-up.
Selective reporting	Low risk	Pre-specified outcomes reported.
Other limitations	High risk	Baseline characteristics between groups varied in terms of number of sexual partners in the previous 6 months

4.3.10 Excluded studies

Reference	Reason for exclusion
Ansbro ÉM, Gill MM, Reynolds J, Shelley KD, Strasser S, Sripipatana T, Tshaka Ncube A, Tembo Mumba G, Terris-Prestholt F, Peeling RW, Mabey D. Introduction of Syphilis Point-of-Care Tests, from Pilot Study to National Programme Implementation in Zambia: A Qualitative Study of Healthcare Workers' Perspectives on Testing, Training and Quality Assurance. <i>PLoS One</i> . 2015 Jun 1;10(6):e0127728	Does not answer research question
Benzaken AS, Sabidó M, Galban E, Pedroza V, Araújo AJ, Peeling RW, Mabey D. Field performance of a rapid point-of-care diagnostic test for antenatal syphilis screening in the Amazon region, Brazil. <i>Int J STD AIDS</i> . 2011 Jan;22(1):15-8	Included in (Rogozinska et al 2017)
Bocoum FY, Kouanda S, Zarowsky C. Barriers to antenatal syphilis screening in Burkina Faso. <i>Pan Afr Med J</i> . 2014 Jan 18;17 Suppl 1:12	Does not answer research question
Bocoum FY, Ouédraogo H, Tarnagda G, Kiba A, Tiendrebeogo S, Bationo F, Liestman B, Diagbouga S, Zarowsky C, Traoré RO, Kouanda S. Evaluation of the diagnostic performance and operational characteristics of four rapid immunochromatographic syphilis tests in Burkina Faso. <i>Afr Health Sci</i> . 2015 Jun;15(2):360-7.	Relevant to research not practice
Bristow CC, Larson E, Javanbakht M, Huang E, Causer L, Klausner JD. A review of recent advances in rapid point-of-care tests for syphilis. <i>Sex Health</i> . 2015 Apr;12(2):119-25	Narrative review
Causer LM, Kaldor JM, Conway DP, Leslie DE, Denham I, Karapanagiotidis T, Ryan C, Wand H, Anderson DA, Robertson PW, McNulty AM, Donovan B, Fairley CK, Guy RJ. An evaluation of a novel dual treponemal/nontreponemal point-of-care test for syphilis as a tool to distinguish active from past treated infection. <i>Clin Infect Dis</i> . 2015 Jul 15;61(2):184-91	Relevant to research not practice
Dlamini NR, Phili R, Connolly C. Evaluation of rapid syphilis tests in KwaZulu-Natal. <i>J Clin Lab Anal</i> . 2014 Jan;28(1):77-81.	Relevant to research not practice
García PJ, Cárcamo CP, Chiappe M, Valderrama M, La Rosa S, Holmes KK, Mabey DC, Peeling RW. Rapid Syphilis Tests as Catalysts for Health Systems Strengthening: A Case Study from Peru. <i>PLoS One</i> . 2013 Jun 26;8(6):e66905	Does not answer research question
Gliddon HD, Peeling RW, Kamb ML, Toskin I, Wi TE, Taylor MM. A systematic review and meta-analysis of studies evaluating the performance and operational characteristics of dual point-of-care tests for HIV and syphilis. <i>Sex Transm Infect</i> . 2017 Jul 26	Not specific to target population
Jafari Y, Johri M, Joseph L, Vadnais C, Pant Pai N. Poor Reporting of Outcomes Beyond Accuracy in Point-of-Care Tests for Syphilis: A Call for a Framework. <i>AIDS Res Treat</i> . 2014;2014:465932	Relevant to research not practice
Kashyap B, Sagar T, Kaur IR. Utility of immunochromatographic assay as a rapid point of care test for screening of antenatal syphilis. <i>Indian J Sex Transm Dis</i> . 2015 Jul-Dec;36(2):162-5.	Included in (Rogozinska et al 2017)
Kay NS, Peeling RW, Mabey DC. State of the art syphilis diagnostics: rapid point-of-care tests. <i>Expert Rev Anti Infect Ther</i> . 2014 Jan;12(1):63-73.	Narrative review

Reference	Reason for exclusion
Kuznik A, Lamorde M, Nyabigambo A et al (2013) Antenatal syphilis screening using point-of-care testing in Sub-Saharan African countries: a cost-effectiveness analysis. <i>PLoS Med</i> 10(11): e1001545.	Does not answer research question
Kuznik A, Muhumuza C, Komakech H et al (2015) Antenatal syphilis screening using point-of-care testing in low- and middle-income countries in Asia and Latin America: a cost-effectiveness analysis. <i>PLoS One</i> 10(5): e0127379.	Does not answer research question
Lee JH, Lim CS, Lee MG, Kim HS. Evaluation of a Rapid Immunochromatographic Treponemal Antibody Test Comparing the Treponema Pallidum Particle Agglutination Assay. <i>J Clin Lab Anal.</i> 2015 Sep;29(5):383-6.	Relevant to research not practice
Marks M, Mabey DC. The introduction of syphilis point of care tests in resource limited settings. <i>Expert Rev Mol Diagn.</i> 2017 Apr;17(4):321-325	Narrative review
Pai NP, Kurji J, Singam A, Barick R, Jafari Y, Klein MB, Chhabra S, Shivkumar P. Simultaneous triple point-of-care testing for HIV, syphilis and hepatitis B virus to prevent mother-to-child transmission in India. <i>Int J STD AIDS.</i> 2012 May;23(5):319-24.	Included in (Swartzendruber et al 2015)
Perry M, Iveson H, White J. Assessment of the performance of a rapid point of care syphilis test in a London genitourinary medicine clinic. <i>Int J STD AIDS.</i> 2014 Nov;25(13):967-8	Opinion paper
Ruffinen CZ, Sabidó M, Díaz-Bermúdez XP, Lacerda M, Mabey D, Peeling RW, Benzaken AS. Point-of-care screening for syphilis and HIV in the borderlands: challenges in implementation in the Brazilian Amazon. <i>BMC Health Serv Res.</i> 2015 Nov 5;15:495	Not specific to target population
Shahrook S, Mori R, Ochirbat T, Gomi H. Strategies of testing for syphilis during pregnancy. <i>Cochrane Database Syst Rev.</i> 2014 Oct 29;(10):CD010385.	Studies included in (Rogozinska et al 2017)
Shelley KD, Ansbro ÉM, Ncube AT, Sweeney S, Fleischer C, Tembo Mumba G, Gill MM, Strasser S, Peeling RW, Terris-Prestholt F. Scaling Down to Scale Up: A Health Economic Analysis of Integrating Point-of-Care Syphilis Testing into Antenatal Care in Zambia during Pilot and National Rollout Implementation. <i>PLoS One.</i> 2015 May 13;10(5):e0125675	Does not answer research question
Singh AE, Levett PN, Fonseca K, Jayaraman GC, Lee BE. Canadian Public Health Laboratory Network laboratory guidelines for congenital syphilis and syphilis screening in pregnant women in Canada. <i>Can J Infect Dis Med Microbiol.</i> 2015 Jan-Feb;26 Suppl A:23A-8A	Background information
Skinner L, Robertson G, Norton R. Evaluation of the Dual Path Platform syphilis point of care test in North Queensland. <i>Pathology.</i> 2015 Dec;47(7):718-20	Background information
Smit PW, van der Vlis T, Mabey D, Changalucha J, Mngara J, Clark BD, Andreasen A, Todd J, Urassa M, Zaba B, Peeling RW. The development and validation of dried blood spots for external quality assurance of syphilis serology. <i>BMC Infect Dis.</i> 2013 Feb 26;13:102	Relevant to research not practice

Reference	Reason for exclusion
Strasser S, Bitarakwate E, Gill M, Hoffman HJ, Musana O, Phiri A, Shelley KD, Sripipatana T, Ncube AT, Chintu N. Introduction of rapid syphilis testing within prevention of mother-to-child transmission of HIV programs in Uganda and Zambia: a field acceptability and feasibility study. <i>J Acquir Immune Defic Syndr</i> . 2012 Nov 1;61(3):e40-6	Included in (Swartzendruber et al 2015)
Taylor MM, Peeling RW, Toskin I, Ghinidelli M. Role of dual HIV/syphilis test kits in expanding syphilis screening. <i>Sex Transm Infect</i> . 2017 Aug 4	Opinion paper
Wedderburn CJ, Murtagh M, Toskin I, Peeling RW. Using electronic readers to monitor progress toward elimination of mother-to-child transmission of HIV and syphilis: An opinion piece. <i>Int J Gynaecol Obstet</i> . 2015 Jun;130 Suppl 1:S81-3	Narrative review
Yang LG, Tucker JD, Liu FY, Ren XQ, Hong X, Wang C, McLaughlin MM, Bien CH, Chen XS, Yang B. Syphilis screening among 27,150 pregnant women in South Chinese rural areas using point-of-care tests. <i>PLoS One</i> . 2013 Aug 29;8(8):e72149	Does not answer research question

5 Interventions

5.1 Q5: What interventions are safe and effective in the management of syphilis infection in pregnant women?

5.1.1 Background information

Due to the extreme risk of vertical transmission of syphilis particular care is required to ensure adequate treatment in pregnancy, all case of syphilis in pregnancy should be discussed with a clinician with expertise in the area (CDNA 2018). Treatment of syphilis in pregnancy is according to disease stage and is usually the same as in the non-pregnant state. Contact tracing and treatment for the woman's partner/s are critical to minimise the potential for re-infection as this represents a particular threat to the unborn baby. The culture and gender of the interviewer and whether or not they are known to and trusted by the women are relevant considerations (CDNA 2018).

Women with infectious syphilis need to be informed of the infectious nature of the condition, even in the absence of visible lesions or symptoms, and to abstain from sexual activity for 5 days post-treatment or until symptoms have completely resolved (whichever is the longer) (CDNA 2018). The importance of follow up and repeat syphilis serology testing to monitor the response to treatment should be emphasised. The woman should be informed that she is likely to continue to have positive treponemal specific tests for life, even after successful treatment.

In areas affected by an outbreak, women who present with symptoms consistent with infectious syphilis should be treated at the time of first presentation (CDNA 2018). Women with infectious syphilis diagnosed on serology should be treated as soon as possible (and ideally within 2 days) of diagnosis.

Further details on management of syphilis in pregnancy are given in the CDNA *Syphilis National Guidelines for Public Health Units* (CDNA 2018).

5.1.2 Evidence summary

Systematic reviews found that:

- treatment of syphilis in pregnancy with at least 2.4 MU (1.8 g) benzathine penicillin intramuscularly as a single dose reduces the incidence of congenital syphilis by 97% (95%CI 93 to 98%; 3 studies; moderate quality evidence), stillbirth by 82% (95%CI 67 to 90%; 8 studies; low quality evidence), preterm birth by 64% (95%CI 53 to 73%; 7 studies; low quality evidence) and neonatal deaths by 80% (95%CI 68 to 87%; 5 studies; low quality evidence) (Blencowe et al 2011)
- rates of syphilis-related adverse outcomes were higher among women receiving treatment in the third trimester compared to those treated in the first or second trimester (OR 2.24; 95%CI 1.28 to 3.93), although there was considerable heterogeneity ($I^2=78.3$ to 81.7%) for outcomes other than congenital syphilis (OR 2.92, 95%CI 0.66 to 12.87; $I^2=48.2\%$, $p=0.165$) (low quality evidence) (Hawkes et al 2013)
- based on the risk of adverse reactions to benzathine penicillin in the general population (pooled absolute risk 0.169%; 95%CI 0.073 to 0.265% $I^2 = 97\%$), risks from treatment among pregnant women are likely to be low (very low quality evidence) (Galvao et al 2013)

Observational studies in settings of very high prevalence reported:

- higher incidence of congenital syphilis among infants of women treated with benzathine penicillin after 28 weeks compared to those treated before 28 weeks (aOR 8.06; 95%CI 2.93 to 22.21; $P < 0.001$) and among infants of mother who received one course of benzathine penicillin compared to those who received two courses of treatment (aOR 1.74; 95%CI 0.37 to 8.26) (Hong et al 2017)
- significantly higher rates of adverse pregnancy outcomes among women treated during pregnancy compared to those adequately treated before pregnancy (21 vs 0%; $p=0.02$) (Wallace et al 2016)
- higher risks of asphyxia (OR=2.7; 95%CI 1.3 to 5.8), congenital syphilis (OR=3.1; 95%CI 1.6 to 6.2), preterm birth (OR=1.5; 95%CI 1.2 to 2.1), low birth weight (OR=1.9; 95%CI 1.3 to 2.6) and perinatal death (OR=3.1; 95%CI 1.5 to 6.5) among infants born to mothers treated who received fewer than two courses of penicillin (2.4 MU benzathine penicillin weekly for 3 weeks) or non-penicillin treatment compared to those who received two courses of penicillin (Zhang et al 2016)

- higher risk of asphyxia (OR=3.0; 95%CI 1.0 to 8.5), congenital syphilis (OR=6.0; 95%CI 2.0 to 17.7) and low birth weight (OR=1.7; 95%CI 1.1 to 2.6) among infants whose mothers were treated in the third trimester compared to those treated in the first trimester (outcomes did not differ significantly between first and second trimester treatment) (Zhang et al 2016).

5.1.3 Evidence statements

Treatment for syphilis with benzathine penicillin in the first or second trimester reduces rates of congenital syphilis (moderate quality evidence) and may reduce rates of other adverse outcomes (low quality evidence).

Risks from treatment among pregnant women are likely to be low (very low quality evidence).

Treatment for syphilis in the first or second trimester is more effective in reducing risk of congenital syphilis than treatment in the third trimester (low quality evidence).

5.1.4 Advice to the EWG

Suggest including a recommendation on treatment in the first or second trimester or at least 30 days before the estimated date of birth.

On the advice of the Office of Public Health, suggest including a consensus-based recommendation on treating women in areas affected by an outbreak without waiting for confirmatory testing, particularly if there is a risk of loss to follow-up.

5.1.5 Summary of findings

At least 2.4 MU benzathine penicillin compared to no treatment for syphilis in pregnancy

Patient or population: Pregnant women with syphilis

Setting: China, Kenya, Russian Federation, South Africa, Tanzania, United States, Zimbabwe

Intervention: At least 2.4 MU benzathine penicillin

Comparison: No treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no treatment	Risk with at least 2.4 MU penicillin				
Congenital syphilis	194 per 1,000	6 per 1,000 (4 to 14)	RR 0.03 (0.02 to 0.07)	3,460 (3 observational studies)	⊕⊕⊕○ MODERATE ¹	
Stillbirth	120 per 1,000	22 per 1,000 (12 to 40)	RR 0.18 (0.10 to 0.33)	4,186 (8 observational studies)	⊕⊕○○○ ² LOW	
Neonatal mortality (all cause)	64 per 1,000	13 per 1,000 (8 to 20)	RR 0.20 (0.13 to 0.32)	3,040 (5 observational studies)	⊕⊕○○○ ² LOW	
Preterm birth	247 per 1,000	89 per 1,000 (67 to 116)	RR 0.36 (0.27 to 0.47)	1,959 (7 observational studies)	⊕⊕○○○ ² LOW	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1 Observational studies, upgraded due to large effect size.

2 Observational studies.

5.1.6 Evidence table

Study ref	Design	LoE	N	Aim, setting, methods	Results	Comments
(Blencowe et al 2011)	SLR	I	13 studies	<p>Aim: to estimate the effect of detection and treatment of active syphilis in pregnancy with at least 2.4MU benzathine penicillin (or equivalent) on syphilis-related stillbirths and neonatal mortality.</p> <p>Settings: China, Kenya, Russian Federation, South Africa, Tanzania, United States, Zimbabwe</p> <p>Methods: We conducted a systematic literature review of multiple databases to identify relevant studies. Data were abstracted into standardised tables and the quality of evidence was assessed using adapted GRADE criteria. Where appropriate, meta-analyses were undertaken.</p>	<p>Moderate quality evidence (3 studies) supports a reduction in the incidence of clinical congenital syphilis of 97% (95%CI 93 to 98%) with detection and treatment of women with active syphilis in pregnancy with at least 2.4MU penicillin. The results of meta-analyses suggest that treatment with penicillin is associated with an 82% reduction in stillbirth (95%CI 67 to 90%) (8 studies), a 64% reduction in preterm delivery (95%CI 53 to 73%) (7 studies) and an 80% reduction in neonatal deaths (95%CI 68 to 87%) (5 studies).</p> <p>Although these effect estimates were large and remarkably consistent across studies, few of the studies adjusted for potential confounding factors and thus the overall quality of the evidence was considered low. However, given these large observed effects and a clear biological mechanism for effectiveness the GRADE recommendation is strong.</p>	<p>The review only included observational studies but is of high methodological quality (see Section 5.1.7.</p> <p>Two studies overlap with (Hawkes et al 2013); one study overlaps with (Galvao et al 2013)</p>

Study ref	Design	LoE	N	Aim, setting, methods	Results	Comments
(Galvao et al 2013)	SLR	I	13 studies; 5 specific to pregnancy	<p>Aim: To estimate the risk of serious adverse reactions to benzathine penicillin in pregnant women for preventing congenital syphilis.</p> <p>Setting: French Guiana, Kenya, South Africa, Tanzania, Thailand</p> <p>Methods: We searched for clinical trials or cohorts that assessed the incidence of serious adverse reactions to benzathine penicillin in pregnant women and the general population (indirect evidence). MEDLINE, EMBASE, Scopus and other databases were searched up to December 2012. The GRADE approach was used to assess quality of evidence. Absolute risks of each study were calculated along with their 95% confidence intervals (95% CI). We employed the DerSimonian and Laird random effects model in the meta-analyses.</p>	<p>In the studies that included pregnant women no serious adverse reactions were reported among the 1,244 pregnant women included. In the general population, among 2,028,982 patients treated, 4 died from an adverse reaction. The pooled risk of death was virtually zero. Fifty-four cases of anaphylaxis were reported (pooled absolute risk = 0.002%; 95% CI: 0%-0.003% I₂= 12%). From that estimate, penicillin treatment would be expected to result in an incidence of 0 to 3 cases of anaphylaxis per 100,000 treated. Any adverse reactions were reported in 6,377 patients among 3,465,322 treated with penicillin (pooled absolute risk = 0.169%; 95% CI: 0.073%-0.265% I₂= 97%). The quality of evidence was very low.</p>	<p>The review only included observational studies is of moderate methodological quality (see Section 5.1.7. Two studies overlap with (Hawkes et al 2013); one study overlaps with (Blencowe et al 2011)</p>
(Hawkes et al 2013)	SLR	I	5 studies	<p>Aim: to review evidence on the optimal timing of antenatal interventions to prevent mother-to-child transmission of syphilis and its associated adverse outcomes.</p> <p>Setting: China, French Guiana, Tanzania, United States</p> <p>Methods: Systematic review and meta-analysis of published literature. English-language articles were included if they (1) reported the gestational age at which the mother was screened or tested for syphilis; (2) reported on pregnancy outcome. No publication date limits were set.</p>	<p>All studies showed a lower prevalence of any adverse outcome among women who received an intervention (screening and treatment) in the first and second trimesters of pregnancy compared to the third trimester. The overall odds ratio for any adverse outcome was 2.24 (95%CI 1.28 to 3.93). All sub-analyses by type of outcome presented important heterogeneity between studies, except for those studies reporting an infected infant (OR 2.92, 95%CI 0.66 to 12.87; I₂= 48.2%, p=0.165).</p>	<p>The review only included observational studies is of high methodological quality (see Section 5.1.7. Two studies overlap with (Blencowe et al 2011); two studies overlap with (Galvao et al 2013)</p>

Study ref	Design	LoE	N	Aim, setting, methods	Results	Comments
(Hong et al 2017)	Cohort	III-2	4,746 mother infant pairs	<p>Aim: To compare incidence of congenital syphilis following different treatment regimens or no treatment.</p> <p>Setting: China</p> <p>Methods: We obtained data from the Shenzhen Program for Prevention of Congenital Syphilis (SPPCS) and estimated incidence rates of congenital syphilis among infants born to syphilis-seropositive women treated with different regimens or untreated for maternal syphilis.</p>	<p>The incidence of congenital syphilis was 1.82-11.90% lower among infants born to the women treated with early (<28 wks) benzathine penicillin G (BPG) compared with those treated with late (\geq28 wks) BPG (aOR 8.06; 95%CI 2.93 to 22.21; P <0.001), other antibiotics (aOR 7.71; 95%CI 0.86 to 69.28; P=0.068), or those untreated (aOR 68.28; 95%CI 29.64 to 157.28; P < 0.001). The incidence rates were 0.22% (95%CI 0.06 to 0.80%) and 0.59% (95%CI 0.35 to 1.02%) in infants born to women treated with 2 courses and 1 course of BPG, respectively, corresponding to a risk difference of 0.37% (aOR 1.74; 95%CI 0.37 to 8.26).</p>	<p>Confidence intervals are very wide and, for other antibiotics, cross the line of no effect.</p> <p>Stillbirths attributable to maternal syphilis were absent from the criteria of congenital syphilis, potentially resulting in an underestimation of risk</p>

Study ref	Design	LoE	N	Aim, setting, methods	Results	Comments
(Wallace et al 2016)	Cohort	III-2	57	<p>Aim: To assess pregnancy outcomes among women with positive syphilis serology.</p> <p>Setting: United Kingdom</p> <p>Methods: A retrospective review of women with positive syphilis serology and a pregnancy outcome between 2005 and 2012 in Leeds, UK, was performed.</p>	<p>In all, 57 cases of positive syphilis serology in pregnancy were identified: 24 with untreated syphilis treated in the current pregnancy (Group 1); seven with reported but unconfirmed prior treatment who were retreated (Group 2); and 26 adequately treated prior to pregnancy (Group 3). The rate of severe adverse pregnancy outcomes in Group 1 at 21% was significantly higher than the 0% outcome of Group 3 (p. 0.02). The severe adverse pregnancy outcomes were two second-trimester miscarriages, two pre-term births at 25 and 28 weeks and one stillbirth at 32 weeks. There were no cases of term congenital syphilis or term neonatal death, but we observed high rates of other adverse pregnancy outcomes despite treatment during pregnancy.</p>	

Study ref	Design	LoE	N	Aim, setting, methods	Results	Comments
(Zhang et al 2016)	Cohort	III-2	3,767	<p>Aim: To determine the effectiveness of treatment in improving pregnancy outcomes among women with syphilis.</p> <p>Setting: China</p> <p>Methods This is a retrospective study based on the provincial prevention of mother-to-child transmission of syphilis database. All women with syphilis with singleton pregnancies were recruited. We evaluated their pregnancy outcomes by group-specific analyses according to their treatment time and adequacy.</p>	<p>Of 745 infants born to untreated pregnant women with syphilis, 1.2% manifested pneumonia, 2.7% asphyxia, 1.6% birth defects, 3.8% congenital syphilis (CS), 14.2% were preterm, 10.1% had low birth weight (LBW) and 3.1% experienced perinatal death. The risks of asphyxia (OR=2.7), CS (OR=3.1), preterm birth (OR=1.5), LBW (OR=1.9) and perinatal death (OR=3.1) were much higher in infants born to mothers treated inadequately than those treated adequately. Moreover, mothers with syphilis who initiated treatment in the third trimester suffered an increased risk for asphyxia (OR=3.0), CS (OR=6.0) and LBW (OR=1.7) compared with those who initiated treatment in the first trimester.</p>	

5.1.7 Evaluation of quality of systematic reviews

(Blencowe et al 2011)	Comment
Questions and methods clearly stated	The review question is not included but PICO criteria are clearly articulated and methods used are clearly stated.
Search procedure sufficiently rigorous to identify all relevant studies	PubMed, EMBASE, Cochrane Libraries, and all World Health Organisation Regional Databases were searched and publications in any language included. Snowball searching was used whereby literature referenced in key papers was included. Combinations of the following search terms were used: “congenital syphilis/ syphilis” “pregnancy” “neonate/ newborn” “mortality” “screening” “syphilis/ drug therapy” “antibiotics” “preterm” “stillbirth/ foetal death” “perinatal mortality”.
Review includes all the potential benefits and harms of the intervention	The outcomes of interest were adverse pregnancy outcomes including stillbirth, preterm delivery, congenital syphilis and neonatal mortality associated with congenital syphilis.
Review only includes randomised controlled trials	Review included only observational studies as no randomised controlled trial were identified.
Methodological quality of primary studies assessed	Each study was assessed for limitations and graded according to the CHERG adaptation of the GRADE technique. The evidence was summarised by outcome including a qualitative assessment of study quality and sources of bias adapted from the Cochrane review handbook.
Data summarised to give a point estimate of effect and confidence intervals	Summary risk ratios and corresponding 95% confidence intervals were reported.
Differences in individual study results are adequately explained	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	Not applicable
Reviewers’ conclusions are supported by data cited	Reviewers’ conclusions are strongly supported by data cited.
Sources of heterogeneity are explored	For each outcome, sources of heterogeneity were explicitly explored.

(Galvao et al 2013)	Comment
Questions and methods clearly stated	The review question is not included but eligibility criteria are included and adverse outcomes defined. Methods used are clearly stated.
Search procedure sufficiently rigorous to identify all relevant studies	Searches were conducted to identify clinical trials or cohorts that assessed the incidence of serious adverse reactions to benzathine penicillin in pregnant women and the general population (indirect evidence). MEDLINE, EMBASE, Scopus and other databases were searched up to December 2012.
Review includes all the potential benefits and harms of the intervention	The primary outcome measured was the incidence of serious adverse reactions in pregnant women due to treatment with benzathine penicillin for preventing congenital syphilis. As serious adverse reactions we considered anaphylaxis and death, but these were not summarised as a composite outcome.
Review only includes randomised controlled trials	All studies included in the review had a cohort design, either prospective or retrospective.
Methodological quality of primary studies assessed	The GRADE approach was used to assess quality of evidence. The quality assessment was considered when interpreting the findings.
Data summarised to give a point estimate of effect and confidence intervals	Absolute risks of each study were calculated along with their 95% confidence intervals (95% CI). We employed the DerSimonian and Laird random effects model in the meta-analyses.
Differences in individual study results are adequately explained	It is clear that studies were performed in different decades and settings, and this may be the main causes of the heterogeneity we found, but we could not identify the statistical sources of heterogeneity, nor could we derive more homogeneous results from the sensitivity analysis.
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 strongly supported by data cited.
Sources of heterogeneity are explored	The statistical heterogeneity was very high. In the sensitivity analysis, we investigated the effect of older studies, the level of country economic development where the studies were conducted, the stage of disease, and the dosing regimens.

(Hawkes et al 2013)	Comment
Questions and methods clearly stated	The review question and methods used are clearly stated.
Search procedure sufficiently rigorous to identify all relevant studies	PubMed was searched for articles with no date limitations using a search strategy combining the MESH terms: “syphilis” and “screening” and “pregnancy”. When relevant articles were located and reviewed, their reference lists were searched for additional articles. Expert opinion was also sought on any additional articles which may fit the search criteria for the review.
Review includes all the potential benefits and harms of the intervention	Major adverse outcomes associated with syphilis in pregnancy were reported.
Review only includes randomised controlled trials	Review included only observational studies.
Methodological quality of primary studies assessed	Quality assessment of primary studies is not described.
Data summarised to give a point estimate of effect and confidence intervals	Odds ratios and confidence intervals provided for all outcomes.
Differences in individual study results are adequately explained	Differences in results are not discussed.
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	Possible sources of heterogeneity due to characteristics of both recording of the outcome and treatment in sub-group meta-analyses were explored.

5.1.8 Excluded studies

Reference	Reason for exclusion
Braccio S, Sharland M, Ladhani SN. Prevention and treatment of mother-to-child transmission of syphilis. <i>Curr Opin Infect Dis.</i> 2016 Jun;29(3):268-74.	Narrative review
Bradley H, Gruber D, Introcaso CE, Foxhood J, Wendell D, Rahman M, Ewell J, Kirkcaldy RD, Weinstock HS. Congenital syphilis investigation processes and timing in Louisiana. <i>Sex Transm Dis.</i> 2014 Sep;41(9):560-3	Does not answer research question
Chen XS, Peeling RW, Yin YP, Mabey D. Improving antenatal care to prevent adverse pregnancy outcomes caused by syphilis. <i>Future Microbiol.</i> 2011 Oct;6(10):1131-4.	Opinion paper
Clement ME, Okeke NL, Hicks CB. Treatment of late-stage syphilis--reply. <i>JAMA.</i> 2015 Mar 3;313(9):969-70	Opinion paper

Reference	Reason for exclusion
Clement ME, Okeke NL, Hicks CB. Treatment of syphilis: a systematic review. <i>JAMA</i> . 2014 Nov 12;312(18):1905-17.	Included studies specific to the target population were either reviews included here or studies included in those reviews
Dallé J, Baumgarten VZ, Ramos MC, Jimenez MF, Acosta L, Bumaguin DB, Antonello VS. Maternal syphilis and accomplishing sexual partner treatment: still a huge gap. <i>Int J STD AIDS</i> . 2017 Aug;28(9):876-880	Opinion paper
Davies O, Jayakody C, Issa R, White J, Sethi C. A reaudit of the management of syphilis in pregnancy in a large inner London hospital. <i>Sex Transm Infect</i> . 2014 Aug;90(5):381.	Opinion paper
de Oliveira LR, Costa Mda C, Barreto FR, Pereira SM, Dourado I, Teixeira MG. Evaluation of preventative and control measures for congenital syphilis in State of Mato Grosso. <i>Rev Soc Bras Med Trop</i> . 2014 May-Jun;47(3):334-40	Does not answer research question
De Santis M, De Luca C, Mappa I, Spagnuolo T, Licameli A, Straface G, Scambia G. Syphilis Infection during pregnancy: fetal risks and clinical management. <i>Infect Dis Obstet Gynecol</i> . 2012;2012:43058	Narrative review
de Souza Campos Fernandes RC, Medina-Acosta E. Congenital neurosyphilis. <i>Lancet Infect Dis</i> . 2013 Jun;13(6):474-5	Opinion paper
Díaz Olavarrieta C, Valencia J, Wilson K, García SG, Tinajeros F, Sanchez T. Assessing the effectiveness of a patient-driven partner notification strategy among pregnant women infected with syphilis in Bolivia. <i>Sex Transm Infect</i> . 2011 Aug;87(5):415-9	Does not answer research question
Drago F, Ciccarese G, Reborá A. Treatment of late-stage syphilis. <i>JAMA</i> . 2015 Mar 3;313(9):969	Opinion paper
Ferreira A, Young T, Mathews C, Zunza M, Low N. Strategies for partner notification for sexually transmitted infections, including HIV. <i>Cochrane Database Syst Rev</i> . 2013 Oct 3;(10):CD002843.	Does not answer research question
Follett T, Clarke DF. Resurgence of congenital syphilis: diagnosis and treatment. <i>Neonatal Netw</i> . 2011 Sep-Oct;30(5):320-8	Narrative review
Freyne B, Stafford A, Knowles S, O'Hora A, Molloy E. Perinatal <i>Treponema pallidum</i> : evidence based guidelines to reduce mother to child transmission. <i>Ir Med J</i> . 2014 Jan;107(1):14-6.	Background information
Hawkes SJ, Gomez GB, Broutet N. Early antenatal care: does it make a difference to outcomes of pregnancy associated with syphilis? A systematic review and meta-analysis. <i>PLoS One</i> . 2013;8(2):e56713.	Duplicate
Holman KM, Hook EW 3rd. Clinical management of early syphilis. <i>Expert Rev Anti Infect Ther</i> . 2013 Aug;11(8):839-43	Narrative review
Hussey J, Mitchell L, Hew Y, Foster K, Waldram A. Preventing congenital syphilis - a regional audit of syphilis in pregnant women seen in Genitourinary Medicine services. <i>Int J STD AIDS</i> . 2014 May;25(6):448-51	Does not answer research question

Reference	Reason for exclusion
Introcaso CE, Bradley H, Gruber D, Markowitz LE. Missed opportunities for preventing congenital syphilis infection. <i>Sex Transm Dis.</i> 2013 May;40(5):431	Opinion paper
Janier M, Hegyi V, Dupin N, Unemo M, Tiplica GS, Potočník M, French P, Patel R. 2014 European guideline on the management of syphilis. <i>J Eur Acad Dermatol Venereol.</i> 2014 Dec;28(12):1581-93. doi: 10.1111/jdv.12734. Epub 2014 Oct 27. Erratum in: <i>J Eur Acad Dermatol Venereol.</i> 2015 Jun;29(6):1248	Background information
Janier M, Unemo M, Dupin N, Tiplica GS, Patel R. 2014 European guideline on the management of syphilis: giving evidence priority. <i>J Eur Acad Dermatol Venereol.</i> 2016 Oct;30(10):e78-e79	Opinion paper
Kiarie J, Mishra CK, Temmerman M, Newman L. Accelerating the dual elimination of mother-to-child transmission of syphilis and HIV: Why now? <i>Int J Gynaecol Obstet.</i> 2015 Jun;130 Suppl 1:S1-3.	Narrative review
Kingston M, French P, Higgins S, McQuillan O, Sukthankar A, Stott C, McBrien B, Tipple C, Turner A, Sullivan AK; Members of the Syphilis guidelines revision group 2015, Radcliffe K, Cousins D, FitzGerald M, Fisher M, Grover D, Higgins S, Kingston M, Rayment M, Sullivan A. UK national guidelines on the management of syphilis 2015. <i>Int J STD AIDS.</i> 2016 May;27(6):421-46	Background information
Knapper C, Furness L, Collett M, Lomax N, Browning M. Effective use of an audit tool devised to optimize the management of syphilis in an integrated sexual health clinic. <i>Int J STD AIDS.</i> 2011 May;22(5):290-1	Not specific to target population
Knight V, Ryder N, Bourne C, McNulty A. A cross sectional study of how people diagnosed with a bacterial sexually transmitted infection inform their partners. <i>Sex Transm Infect.</i> 2014 Dec;90(8):588-91	Does not answer research question
Koumans EH, Rosen J, van Dyke MK, Zell E, Phares CR, Taylor A, Loft J, Schrag S; ABC and DHAP/RTI teams. Prevention of mother-to-child transmission of infections during pregnancy: implementation of recommended interventions, United States, 2003-2004. <i>Am J Obstet Gynecol.</i> 2012 Feb;206(2):158.e1-158.e11	Does not answer research question
Kwak J, Lamprecht C. A review of the guidelines for the evaluation and treatment of congenital syphilis. <i>Pediatr Ann.</i> 2015 May;44(5):e108-14	Narrative review
Lago EG. Current Perspectives on Prevention of Mother-to-Child Transmission of Syphilis. <i>Cureus.</i> 2016 Mar 9;8(3):e525	Narrative review
Le Doaré K, Gannon H, Handforth J. Missed opportunities to treat: syphilis in pregnancy. <i>Sex Transm Infect.</i> 2012 Dec;88(8):594.	Opinion paper
Lenzer J. How Cuba eliminated mother-to-child transmission of HIV and syphilis. <i>BMJ.</i> 2016 Mar 21;352:11619	Narrative review
Mason-Jones AJ, Sinclair D, Mathews C, Kagee A, Hillman A, Lombard C. School-based interventions for preventing HIV, sexually transmitted infections, and pregnancy in adolescents. <i>Cochrane Database Syst Rev.</i> 2016 Nov 8;11:CD006417	Not specific to target population

Reference	Reason for exclusion
Newman Owiredo M, Newman L, Nzomo T, Conombo Kafando G, Sanni S, Shaffer N, Bucagu M, Peeling R, Mark J, Diop Toure I. Elimination of mother-to-child transmission of HIV and syphilis: A dual approach in the African Region to improve quality of antenatal care and integrated disease control. <i>Int J Gynaecol Obstet.</i> 2015 Jun;130 Suppl 1:S27-31	Does not answer research question
Oboho IK, Ghanem KG. Blissful ignorance when managing pregnant women with syphilis and nonreactive nontreponemal tests? <i>Sex Transm Dis.</i> 2013 Apr;40(4):316-7	Opinion paper
Pastuszczak M, Wojas-Pelc A. Current standards for diagnosis and treatment of syphilis: selection of some practical issues, based on the European (IUSTI) and U.S. (CDC) guidelines. <i>Postepy Dermatol Alergol.</i> 2013 Aug;30(4):203-10	Narrative review
Patel CG, Huppert JS, Tao G. Provider Adherence to Syphilis Testing Recommendations for Women Delivering a Stillbirth. <i>Sex Transm Dis.</i> 2017 Jun 16	Does not answer research question
Patel SJ, Klinger EJ, O'Toole D, Schillinger JA. Missed opportunities for preventing congenital syphilis infection in New York City. <i>Obstet Gynecol.</i> 2012 Oct;120(4):882-8.	Does not answer research question
Pham MN, Ho HE, Desai M. Penicillin desensitization: Treatment of syphilis in pregnancy in penicillin-allergic patients. <i>Ann Allergy Asthma Immunol.</i> 2017 May;118(5):537-541	Narrative review
Qin JB, Feng TJ, Yang TB, Hong FC, Lan LN, Zhang CL, Liu XL, Yang YZ, Xiao SY, Tan HZ. Synthesized prevention and control of one decade for mother-to-child transmission of syphilis and determinants associated with congenital syphilis and adverse pregnancy outcomes in Shenzhen, South China. <i>Eur J Clin Microbiol Infect Dis.</i> 2014 Dec;33(12):2183-98	Does not answer research question
Rac MW, Bryant SN, McIntire DD, Cantej JB, Twickler DM, Wendel GD Jr, Sheffield JS. Progression of ultrasound findings of fetal syphilis after maternal treatment. <i>Am J Obstet Gynecol.</i> 2014 Oct;211(4):426.e1-6	Does not answer research question
Read PJ, Donovan B. Clinical aspects of adult syphilis. <i>Intern Med J.</i> 2012 Jun;42(6):614-20	Narrative review
Santella AJ, Pollack A, Harrison C, Sawleshwarkar SN, Britt HC, Hillman RJ. Management rates of sexually transmissible infections by Australian general practitioners, 2000-2012. <i>Sex Health.</i> 2014 Mar;11(1):52-7	Not specific to target population
Stamm LV. Syphilis: antibiotic treatment and resistance. <i>Epidemiol Infect.</i> 2015 Jun;143(8):1567-7	Narrative review
Taylor MM, Nurse-Findlay S, Zhang X, Hedman L, Kamb ML, Broutet N, Kiarie J. Estimating Benzathine Penicillin Need for the Treatment of Pregnant Women Diagnosed with Syphilis during Antenatal Care in High-Morbidity Countries. <i>PLoS One.</i> 2016 Jul 19;11(7):e0159483.	Does not answer research question
Townsend CL, Francis K, Peckham CS, Tookey PA. Syphilis screening in pregnancy in the United Kingdom, 2010-2011: a national surveillance study. <i>BJOG.</i> 2017 Jan;124(1):79-86	Does not answer research question
Tsimis ME, Sheffield JS. Update on syphilis and pregnancy. <i>Birth Defects Res.</i> 2017 Mar 15;109(5):347-352.	Narrative review

Reference	Reason for exclusion
Tuddenham S, Ghanem KG. Penicillin is the drug of choice to treat all stages of syphilis despite a paucity of clinical trials data for the treatment of some stages, pregnant women and HIV-infected people. <i>Evid Based Med</i> . 2015 Apr;20(2):63.	Narrative review
van Brussel AS, Landman GW. Treatment of late-stage syphilis. <i>JAMA</i> . 2015 Mar 3;313(9):968-9	Opinion paper
Wahab AA, Ali UK, Mohammad M, Md Monoto EM, Rahman MM. Syphilis in pregnancy. <i>Pak J Med Sci</i> . 2015 Jan-Feb;31(1):217-	Opinion paper
Wang AL, Qiao YP, Wang LH, Fang LW, Wang F, Jin X, Qiu J, Wang XY, Wang Q, Wu JL, Vermund SH, Song L. Integrated prevention of mother-to-child transmission for human immunodeficiency virus, syphilis and hepatitis B virus in China. <i>Bull World Health Organ</i> . 2015 Jan 1;93(1):52-6	Does not answer research question
WHO Guidelines for the Treatment of <i>Treponema pallidum</i> (Syphilis). Geneva: World Health Organization; 2016	Background information
Wu D, Hawkes S, Buse K. Prevention of mother-to-child transmission of syphilis and HIV in China: What drives political prioritization and what can this tell us about promoting dual elimination? <i>Int J Gynaecol Obstet</i> . 2015 Jun;130 Suppl 1:S32-6	Does not answer research question

6 Additional considerations

6.1 Q6: What are the additional considerations for Aboriginal and Torres Strait Islander women?

6.1.1 Evidence summary

Syphilis outbreak in Northern Australia

The outbreak of infectious syphilis among young Aboriginal and Torres Strait Islander people in remote Australia is discussed in Section 3.1.1 (based on narrative review).

Notification of congenital syphilis

One study found that 95% of babies in the Northern Territory meeting Communicable Disease Network Australia (CDNA) criteria for probable congenital syphilis were not notified between 2009 and 2014 and that improved education regarding CDNA criteria for notification of congenital syphilis is necessary for clinicians and public health staff (McLeod et al 2015). This study, while conducted in the Northern Territory only, contributed to the release of new national case definitions for congenital syphilis on 1 July 2015.

6.1.2 Advice to EWG

Suggest including information on the outbreak and notification of probable congenital syphilis in the narrative.

6.1.3 Evidence table

Study ref	Design	LoE	N	Aim, setting, methods	Results	Comments
(McLeod et al 2015)	Cohort		31	<p>Aim: To determine whether cases of congenital syphilis in the Northern Territory between 2009 and 2014 were correctly notified based on probable or confirmed case criteria stipulated by the Communicable Diseases Network Australia (CDNA).</p> <p>Methods: Pregnant women with positive syphilis serology defined as reactive treponemal test and rapid plasma reagin titre $\geq 1:8$ were identified from the Northern Territory Syphilis Register Information System. Risk classification was performed based on local guidelines, and CDNA criteria for probable/confirmed cases of congenital syphilis were applied to determine whether cases were appropriately notified.</p>	<p>Thirty-four cases of positive maternal syphilis serology in pregnancy were identified from 31 women; all were Indigenous. Twenty-one cases fulfilled criteria for probable congenital syphilis; 1 case was formally notified to the Centre for Disease Control. Twenty cases (95%) fulfilling CDNA criteria for probable congenital syphilis were not notified over the study period.</p> <p>Application of standard case definitions significantly increases the rate of congenital syphilis cases in the Northern Territory. Improved education regarding CDNA criteria for notification of congenital syphilis is necessary for clinicians and public health staff. Emerging evidence has supported the recent simplification of CDNA criteria for notification of congenital syphilis, effective 1 July 2015.</p>	This study contributed to the release of new national case definitions for congenital syphilis in July 2015.

6.1.4 Excluded studies

Reference	Reason for exclusion
Bowden FJ. Eliminating syphilis in remote Aboriginal and Torres Strait Islander communities. Comment. <i>Med J Aust</i> . 2011 Aug 1;195(3):15 Comment	Opinion paper
Bright A (2015) National Notifiable Diseases Surveillance System surveillance report: Sexually transmissible infections in Aboriginal and Torres Strait Islander people. <i>Commun Dis Intell Q Rep</i> 39(4): E584-9.	Superseded by more recent data (Kirby Institute 2017a)
Bright A & Dups J (2016) Infectious and congenital syphilis notifications associated with an ongoing outbreak in northern Australia. <i>Commun Dis Intell Q Rep</i> 40(1): E7-10.	Superseded by more recent data (MJSO 2018)

Reference	Reason for exclusion
Graham S, Smith LW, Fairley CK et al (2016) Prevalence of chlamydia, gonorrhoea, syphilis and trichomonas in Aboriginal and Torres Strait Islander Australians: a systematic review and meta-analysis. <i>Sex Health</i> 13(2): 99-113.	Not specific to target population
Nattabi B, Matthews V, Bailie J et al (2017) Wide variation in sexually transmitted infection testing and counselling at Aboriginal primary health care centres in Australia: analysis of longitudinal continuous quality improvement data. <i>BMC Infect Dis</i> 17(1): 148.	Not specific to target population
Ward J, Wand H, Bryant J, Delaney-Thiele D, Worth H, Pitts M, Byron K, Moore E, Donovan B, Kaldor JM. Prevalence and Correlates of a Diagnosis of Sexually Transmitted Infection Among Young Aboriginal and Torres Strait Islander People: A National Survey. <i>Sex Transm Dis.</i> 2016 Mar;43(3):177-84	Does not answer research question
Ward JS, Dyda A, McGregor S, Rumbold A, Garton L, Donovan B, Kaldor JM, Guy RJ. Low HIV testing rates among people with a sexually transmissible infection diagnosis in remote Aboriginal communities. <i>Med J Aust.</i> 2016 Aug 15;205(4):168-71.	Does not answer research question
Ward JS, Guy RJ, Akre SP et al (2011) Epidemiology of syphilis in Australia: moving toward elimination of infectious syphilis from remote Aboriginal and Torres Strait Islander communities? <i>Med J Aust</i> 194(10): 525-9.	Superseded by more recent data (Kirby Institute 2017a)

6.2 Q7: What are the additional considerations for migrant and refugee women?

6.2.1 Evidence summary

An Australian cohort study reported on maternal health among migrant women from Africa (Gibson-Helm et al 2014) and among migrant women from Africa and Asia (Gibson-Helm et al 2015) and compared (among other things) prevalence of syphilis between women from humanitarian and non-humanitarian source countries.

The study found higher prevalence among women from humanitarian source countries in Africa (0-0.3% vs 1.2-7.5%) and Africa and Asia (0.4 vs 2.5% $p < 0.001$).

6.2.2 Advice to EWG

Include point in the narrative on higher prevalence among women from humanitarian source countries.

6.2.3 Evidence table

Study ref	Design	LoE	N	Aim, setting, methods	Results	Comments
(Gibson-Helm et al 2014)	Cohort		1,361 North Africa 706 Middle and Eastern Africa 106 West Africa	Aim: To compare maternal health, pregnancy care attendance and pregnancy outcomes among migrant women from Africa with or without a refugee background. Setting: a metropolitan, maternity service in Australia 2002-2011 Methods: Retrospective, observational study of singleton births at a single, , to women born in humanitarian source countries (HSC) and non-HSC from North Africa (n = 1361), Middle and East Africa (n = 706) and West Africa (n = 106).	Compared to non-HSC groups, syphilis was generally more common among the HSC groups (0-0.3% vs 1.2-7.5%).	
(Gibson-Helm et al 2015)	Cohort		2,713 HSC 10,606 non-HSC	Aim: to describe maternal health, pregnancy care, and pregnancy outcomes among migrant women from humanitarian and nonhumanitarian source countries. Setting: a maternity service in Australia 2002-2011 Methods: Retrospective, observational study of singleton births, at a single maternity service in Australia 2002–2011, to migrant women born in humanitarian source countries (HSCs, n = 2,713) and non-HSCs (n = 10,606). Multivariable regression analysis assessed associations between maternal HSC-birth and pregnancy outcomes.	Compared to women from non-HSCs groups, syphilis (0.4 vs 2.5% p < 0.001) was more common in women from HSCs.	

6.2.4 Excluded studies

Reference	Reason for exclusion
McGready R, Kang J, Watts I, Tyrosvoutis ME, Torchinsky MB, Htut AM, Tun NW, Keereecharoen L, Wangsing C, Hanboonkunupakarn B, Nosten FH. Audit of antenatal screening for syphilis and HIV in migrant and refugee women on the Thai-Myanmar border: a descriptive study. Version 2. F1000Res. 2014 Jun 10 [revised 2015 Jan 1];3:123.	Does not answer research question
Paxton GA, Sangster KJ, Maxwell EL, McBride CR, Drewe RH. Post-arrival health screening in Karen refugees in Australia. PLoS One. 2012;7(5):e38194	Does not answer research question

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- Boa-Sorte N, Purificacao A, Amorim T et al (2014) Dried blood spot testing for the antenatal screening of HTLV, HIV, syphilis, toxoplasmosis and hepatitis B and C: prevalence, accuracy and operational aspects. *Braz J Infect Dis* 18(6): 618-24.
- Bonawitz RE, Duncan J, Hammond E et al (2015) Assessment of the impact of rapid syphilis tests on syphilis screening and treatment of pregnant women in Zambia. *Int J Gynaecol Obstet* 130 Suppl 1: S58-62.
- Boonchaoy A, Wongchampa P, Hirankarn N et al (2016) Performance of Chemiluminescent Microparticle Immunoassay in Screening for Syphilis in Pregnant Women from Low-Prevalence, Resource-Limited Setting. *J Med Assoc Thai* 99(2): 119-24.
- Bright A & Dups J (2016) Infectious and congenital syphilis notifications associated with an ongoing outbreak in northern Australia. *Commun Dis Intell Q Rep* 40(1): E7-10.
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- Kirby Institute (2017b) [Bloodborne Viral and Sexually Transmissible Infections in Aboriginal and Torres Strait Islander People: Annual Surveillance Report 2017](#). Sydney: The Kirby Institute, UNSW Australia.

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