Effectiveness of antenatal syphilis screening: systematic review

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Background

The World Health Organization (WHO) estimates that annually there are over 2 million women with active syphilis (i.e. test positive using both reaginic and non-reaginic tests) in pregnancy, the vast majority of whom live in low and middle income countries [1]. Active syphilis infection in pregnancy, when untreated or inadequately treated, is estimated to result in adverse pregnancy outcomes in up to 69% of infected women [2–4]. Historical and current data suggest that untreated syphilis in pregnancy can cause late abortion (after 16 weeks) or stillbirth in 25%, prematurity or low birth weight in 13%, neonatal death in 11%, and classic symptoms and signs of an infected syphilitic infant in 20% [1–3,5].

Adverse pregnancy outcomes due to syphilis are avoidable [6]. The WHO global initiative to eliminate congenital syphilis recommends a number of preventive strategies, including a) reducing the overall prevalence of syphilis in the adult population; b) delivering integrated sexual and reproductive health programmes (which, for example, meet the unmet need for family planning services); c) promoting and ensuring access to high quality antenatal care for all pregnant women; d) provision of syphilis screening and treatment within antenatal care services [7]. Two reviews have shown that the majority of countries have antenatal syphilis screening policies in place and have often had these policies for decades, but implementation of the policy is often poor [8,9]. As a result, fewer than one in eight of all pregnant women is estimated to get screened for syphilis at any point in their pregnancy [10], despite the known low costs of both screening and treatment [11].

Evidence about the optimal components and the size of the potential beneficial and harmful effects of antenatal syphilis screening programmes is needed to improve delivery and outcomes. Previous reviews of syphilis screening and treatment have concluded that there are no intervention studies showing an effect on preterm birth [12], that available studies provide only low grade evidence [13], and that further randomised trials would be unethical [12,13]. Whilst placebo-controlled trials of the efficacy of penicillin or other antibiotics are unethical, important information can be obtained from studies that compare the effectiveness of interventions to improve the delivery of antenatal syphilis screening with usual care.

Objectives

The overall aim is to determine the effectiveness of antenatal syphilis screening.

The primary objective is to:

1. Determine the effectiveness antenatal interventions to reduce the incidence of congenital syphilis or reduce adverse birth outcomes;

Secondary objectives are to:

2. Determine the effectiveness of antenatal interventions to increase successful treatment of syphilis in pregnancy;

3. Determine the effectiveness of effectiveness of antenatal interventions to increase the uptake of syphilis testing in pregnant women.

Search strategy

We will search the following electronic databases: (Amed), Medline, Embase, Cinahl, and the Cochrane Library from 1970-2010.

We will search the reference lists of manuscripts included in the review and ask experts in the field to identify additional articles.

We will restrict the search results to articles published in English.

We will use Medical Subject Headings (MeSH terms) for Medline and Cinahl searches, Emtree thesaurus terms for Embase, and free text terms for the Cochrane Library. We will supplement these with free text terms where necessary.

The search strategies for each database will be documented in appendices to this protocol.

Selection criteria

Two independent reviewers will screen the results of the electronic database searches. If there is disagreement, we will reach consensus by discussion. If the discrepancy cannot be resolved a third reviewer will adjudicate.

If there are more than 2000 unique hits, we will screen titles first to select references for further evaluation. If there are fewer than 2000 unique hits we will screen abstracts and titles at the same time to select full text manuscripts for further assessment.

We will obtain full text manuscripts for all potentially relevant articles and for articles where there is insufficient information in the title and abstract to decide whether it should be excluded.

At each stage we will document whether articles should be retained for further evaluation or excluded. If excluded we will document the reason as, a) topic of article not relevant to the review or b) study design ineligible.

Study design

We will include randomised and quasi-randomised study designs, non-randomised controlled trials that use either historical or parallel control groups. This includes ‘demonstration projects’ describing the implementation of antenatal syphilis screening interventions if data about relevant outcomes before and during or after implementation of the demonstration project are provided.

Types of participants

Pregnant women in any country who present for antenatal care and are eligible for antenatal syphilis screening according to national guidelines, or according to a trial protocol.

Types of interventions

We will include any intervention that examines the delivery of antenatal syphilis testing and management of syphilis infection. Potential interventions include: rapid point of care tests, on-site treatment, or improvement of health service infrastructure.

Types of comparison group

We will consider any existing antenatal syphilis screening intervention or no intervention as a comparison group.

Types of outcome measures

The primary outcome is congenital syphilis, as defined by the authors of individual studies.

Secondary outcomes are:

- Adverse birth outcomes including stillbirth;
- Perinatal death;
- Treatment for antenatal syphilis;
    - Complete course of treatment;
    - Received first dose;
    - Uninfected at delivery;
    - Partners treated;
- Uptake of antenatal syphilis testing;
    - in first trimester;
    - in third trimester;
    - at any time in pregnancy;

    - received result;

- Uptake of antenatal care in first trimester

Exclusion criteria

We will exclude economic evaluations and modelling studies that do not provide original empirical data, and studies that only examine the effectiveness of antibiotic treatment or diagnostic test performance.

Data collection

Data will be extracted by two independent reviewers onto a pre-piloted structured form (Appendix 1). The items collected will relate to: study design; diagnostic tests; treatment; enrolment and retention; outcomes.

We will extract data about study characteristics that could bias the results of the study. These include completeness of reporting of: randomisation allocation and concealment (where relevant); blinding of assessment of outcomes; withdrawals from analysis.

Data analysis and synthesis

The main analysis will be descriptive. Results from trials will be described and examined, taking into account characteristics of the intervention and study design. Study results and characteristics will be tabulated.

If there are sufficient data that can be analysed statistically across studies we will conduct meta-analysis, if there is no strong evidence of heterogeneity between study results. If appropriate, we will use meta-analysis to estimate summary odds ratios and 95% confidence intervals. We will test for heterogeneity between pooled results using the I squared test [14]. In the presence of high (75-100%) or moderate (50-75%) inconsistency across studies, we will perform a sensitivity analysis based on the methodological quality and design features of the trials.

To examine evidence for publication and small study biases we will draw funnel plots of log odds ratio against trial size (measured by standard error of the log odds ratio) and perform a statistical test for asymmetry [15].

References

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Appendix 1: Effectiveness of syphilis screening in pregnancy: Data extraction

Study description and objectives

Study Identification

Reference Manager ID	
Database –change to databases used (necessary?)	Select
First author	
Journal Year/Volume Startpage-Endpage	 / -
Link to other publication reporting methods more detailed	Select Specify if yes (A.5.1):
Funding of the study	☐ Government (including university) (1) ☐ Voluntary sector (2) ☐ Industry (3) ☐ Unclear/not reported (4)

Overview

Checklist completed by	Select Date:
Include Report	Select If No ⇒ reasons (B.2.1.):
Link to multiple publication	Select Specify if yes (A.5.1):
Reference list checked	Select
Consensus done	Select Persons: 1. Select 2. Select 3. Select Date: Select
Consensus typed in	Select Person: Select Date:

General research question

Type of report:	Select If Other ⇒ specify (C.1.1.):
Type of study	Select If Other ⇒ specify (C.2.1.):
Objectives of the study as described by authors	
Inclusion and exclusion criteria specified	Select
Describe inclusion criteria	
Describe exclusion criteria	
Describe the intervention **C.5.1. How well has the method been described?**	Select
What does the intervention include	☐ Community level recruitment to ANC ☐ Point of care test used ☐ Test done on site? ☐ Same day treatment ☐ Laboratory support ☐ Supply chain management for tests ☐ Supply chain management for drugs ☐ Training of staff ☐ Repeat screening in third trimester ☐ Counselling/provision of information ☐ Partner notification ☐ Supervision and monitoring ☐ Other (12) ⇒ please specify (C.6.1.):
Country	Select Specify Other (C.7.1.):
City	Specify City (C.8.1.):
Any comments	

Methods

Setting

Setting	☐ Hospital antenatal clinic ☐ Primary health care antenatal clinic ☐ Antenatal clinics, unspecified ☐ Other (4) ☐ Not reported/unclear (9)
The date of this study ***(recruitment: MM/YYYY-MM/YYYY)***	- not reported ☐

Sampling

Describe the sampling method	Select Describe Other (E.3.1.):

Syphilis tests

Syphilis tests used in the intervention	☐ RPR test alone on serum ☐ RPR test alone - unspecified ☐ Rapid point of care treponemal test alone ☐ Other treponemal test alone ☐ RPR plus a confirmatory treponemal test ☐ Other – specify
Syphilis tests used in the control	☐ RPR test alone on serum ☐ RPR test alone - unspecified ☐ Rapid point of care treponemal test alone ☐ Other treponemal test alone ☐ RPR plus a confirmatory treponemal test ☐ Other – specify

Treatment used

Treatment used	☐ One dose of penicillin ☐ Three doses of penicillin ☐ Other - specify ☐ Unspecified

Outcomes overview

Outcomes reported in the study	☐ How many pregnant women received ANC (1) ☐ How many pregnant women accessed ANC in early pregnancy (1st trimester) (2) ☐ How many women had a syphilis test (3) ☐ How many women received a test result (4) ☐ How many women received a test result promptly (5) ☐ How many women received first dose of treatment (6) ☐ How many women received adequate treatment (7) ☐ How many women re-tested in third trimester (8) ☐ How many women uninfected at delivery (9) ☐ How many partners treated (10) ☐ How many cases of congenital syphilis (11) ☐ Other relevant outcomes (12) Specify (H.1.1.):
Was this reported as a number or a proportion?	Select Describe Other (H.2.1.):
Method of data collection	Select Describe Other (H.3.1.):
Is ethical committee approval reported?	Select

Results

Baseline characteristics

	Intervention	**Control**
Total number of eligible pregnant women in community	Select If yes, give number (I.1.1.):	Select If yes, give number (I.1.2.):
Total number of eligible pregnant women coming to clinic	Select If yes, give number (I.2.1.):	Select If yes, give number (I.2.2.):
Total number of women invited to participate	Select If yes, give number (I.3.1.):	Select If yes, give number (I.3.2.):
Total number of women agreeing to participate	Select If yes, give number (I.4.1.):	Select If yes, give number (I.4.2.):
Total number of women tested	Select If yes, give number (I.5.1.):	Select If yes, give number (I.5.2.):

Total number of persons included in analysis mentioned (main analysis)	Select If yes, give **total number of intervention index cases (I.6.1.):**	Select If yes, give **total number of control index cases (I.6.2.):**
Do these numbers reported above add up logically?	Select	Select
Gestational age at first test		
Any comments		

Outcomes and results – general questions

Is it possible to calculate outcomes from raw data?	Select
Has any multivariate analysis been done?	Select
If yes, describe characteristics analysed	
If yes, describe results reported	
Any comments	

Numerical Outcomes

Outcome 1	**Intervention**	**Control**
Outcome concerned	Select Describe Other:	
Was this reported as a number or a proportion ?	Select Describe Other (K1.2.1.):	
Raw data: Total number of women in this analysis (or partners or babies = denominator) Number with outcome (= numerator)	Number in intervention group	Number in control group
Outcome : Proportion / 95%CI (please convert percentage into a number between 0.000 and 1)	Proportion with outcome lower limit CI upper limit CI	Proportion with outcome lower limit CI upper limit CI
Outcome 2	**Intervention**	**Control**
Outcome concerned	Select Describe Other:	
Was this reported as a number or a proportion?	Select Describe Other (K1.2.1.):	
Raw data: Total number of women in this analysis (or partners or babies = denominator) Number with outcome (= numerator)	Number in intervention group	Number in control group
Outcome : Proportion / 95%CI (please convert percentage into a number between 0.000 and 1)	Proportion with outcome lower limit CI upper limit CI	Proportion with outcome lower limit CI upper limit CI

Outcome 3	**Intervention**	**Control**
Outcome concerned	Select Describe Other:	
Was this reported as a number or a proportion?	Select Describe Other (K1.2.1.):	
Raw data: Total number of women in this analysis (or partners or babies = denominator) Number with outcome (= numerator)	Number in intervention group	Number in control group
Outcome : Proportion / 95%CI (please convert percentage into a number between 0.000 and 1)	Proportion with outcome lower limit CI upper limit CI	Proportion with outcome lower limit CI upper limit CI
Outcome 4	**Intervention**	**Control**
Outcome concerned	Select Describe Other:	
Was this reported as a number or a proportion?	Select Describe Other (K1.2.1.):	
Raw data: Total number of women in this analysis (or partners or babies = denominator) Number with outcome (= numerator)	Number in intervention group	Number in control group
Outcome : Proportion / 95%CI (please convert percentage into a number between 0.000 and 1)	Proportion with outcome lower limit CI upper limit CI	Proportion with outcome lower limit CI upper limit CI

Outcome 5	**Intervention**	**Control**
Outcome concerned	Select Describe Other:	
Was this reported as a number or a proportion?	Select Describe Other (K1.2.1.):	
Raw data: Total number of women in this analysis (or partners or babies = denominator) Number with outcome (= numerator)	Number in intervention group	Number in control group
Outcome : Proportion / 95%CI (please convert percentage into a number between 0.000 and 1)	Proportion with outcome lower limit CI upper limit CI	Proportion with outcome lower limit CI upper limit CI
Outcome 6	**Intervention**	**Control**
Outcome concerned	Select Describe Other:	
Was this reported as a number or a proportion?	Select Describe Other (K1.2.1.):	
Raw data: Total number of women in this analysis (or partners or babies = denominator) Number with outcome (= numerator)	Number in intervention group	Number in control group
Outcome : Proportion / 95%CI (please convert percentage into a number between 0.000 and 1)	Proportion with outcome lower limit CI upper limit CI	Proportion with outcome lower limit CI upper limit CI

Outcome 7	**Intervention**	**Control**
Outcome concerned	Select Describe Other:	
Was this reported as a number or a proportion?	Select Describe Other (K1.2.1.):	
Raw data: Total number of women in this analysis (or partners or babies = denominator) Number with outcome (= numerator)	Number in intervention group	Number in control group
Outcome : Proportion / 95%CI (please convert percentage into a number between 0.000 and 1)	Proportion with outcome lower limit CI upper limit CI	Proportion with outcome lower limit CI upper limit CI
Outcome 8	**Intervention**	**Control**
Outcome concerned	Select Describe Other:	
Was this reported as a number or a proportion?	Select Describe Other (K1.2.1.):	
Raw data: Total number of women in this analysis (or partners or babies = denominator) Number with outcome (= numerator)	Number in intervention group	Number in control group
Outcome : Proportion / 95%CI (please convert percentage into a number between 0.000 and 1)	Proportion with outcome lower limit CI upper limit CI	Proportion with outcome lower limit CI upper limit CI