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Antibiotic treatment for newborns with congenital syphilis (Review)

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[Intervention Review]

Antibiotic treatment for newborns with congenital syphilis

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ABSTRACT

Background

Congenital syphilis continues to be a substantial public health problem in many parts of the world. Since the first use of penicillin for the treatment of syphilis in 1943, which was a notable early success, it has remained the preferred and standard treatment including for congenital syphilis. However, the treatment of congenital syphilis is largely based on clinical experience and there is extremely limited evidence on the optimal dose or duration of administration of penicillin or the use of other antibiotics.

Objectives

To assess the effectiveness and safety of antibiotic treatment for newborns with confirmed, highly probable and possible congenital syphilis.

Search methods

We searched the Cochrane STI Group Specialized Register, CENTRAL, MEDLINE, Embase, LILACS, WHO ICTRP, ClinicalTrials.gov and Web of Science to 23 May 2018. We also handsearched conference proceedings, contacted trial authors and reviewed the reference lists of retrieved studies.

Selection criteria

Randomised controlled trials (RCTs) comparing antibiotic treatment (any concentration, frequency, duration and route) with no intervention or any other antibiotic treatment for neonates with confirmed, highly probable or possible congenital syphilis.

Data collection and analysis

All review authors independently assessed trials for inclusion, extracted data and assessed the risk of bias in the included studies. We resolved any disagreements through consensus. We assessed the quality of the evidence using the GRADE approach.

Main results

Two RCTs (191 participants) met our inclusion criteria and none of these trials was funded by the industry. One trial (22 participants) compared benzathine penicillin with no intervention for infants with possible congenital syphilis. Low-quality evidence suggested that benzathine penicillin administration may not have decreased the rate of neonatal death due to any cause (risk ratio (RR) 0.83, 95% confidence interval (CI) 0.06 to 11.70), and showed a possible reduction into the proportion of neonates with clinical manifestations of congenital syphilis (RR 0.12, 95% CI 0.01 to 2.09). Penicillin administration increased the serological cure at the third month (RR 2.13, 95% CI 1.06 to 4.27). These results should be taken with caution, because the trial was stopped early because there were four cases with clinical congenital syphilis in the no treatment group and none in the treatment group. Interim analysis suggested this difference was significant. This study did not report neonatal death due to congenital syphilis or the frequency of serious or minor adverse events after therapy. We downgraded the quality of evidence because of imprecision and risk of bias.

One trial (169 participants) compared benzathine penicillin versus procaine benzylpenicillin. High- and moderate-quality evidence suggested that there were probably no differences between benzathine penicillin and procaine benzylpenicillin for the outcomes: absence of clinical manifestations of congenital syphilis (RR 1.00, 95% CI 0.97 to 1.03) and serological cure (RR 1.00, 95% CI 0.97 to 1.03). There were no cases of neonatal death due congenital syphilis; all 152 babies who followed up survived. This study did not report on the frequency of serious or minor adverse events after therapy. We downgraded the quality of evidence because of serious risk of bias.

Authors' conclusions

At present, the evidence on the effectiveness and safety of antibiotic treatment for newborns with confirmed, highly probable or possible congenital syphilis is sparse, implying that we are uncertain about the estimated effect. One trial compared benzathine penicillin with no intervention for infants with possible congenital syphilis. Low-quality evidence suggested penicillin administration possibly reduce the proportion of neonates with clinical manifestations of congenital syphilis, penicillin administration increased the serological cure at the third month. These findings support the clinical use of penicillin in neonates with confirmed, highly probable or possible congenital syphilis. High- and moderate-quality evidence suggests that there are probably no differences between benzathine penicillin and procaine benzylpenicillin administration for the outcomes of absence of clinical manifestations of syphilis or serological cure.

PLAIN LANGUAGE SUMMARY

Which antibiotic are useful to treat newborns with congenital syphilis?

Review question

To assess the effectiveness and safety of antibiotic treatment for newborns with congenital syphilis.

Background

Pregnant women with syphilis can transmit it through the placenta to the fetus or at birth to the neonate; in such cases the baby is said to have congenital syphilis. This continues to be a substantial public health problem in many countries. In 2007, the World Health Organization launched a global initiative for the elimination of mother-to-child transmission of syphilis.

Trial characteristics

We identified only two clinical trials following extensive searches of medical databases carried out up to 23 May 2018 and involved two main formulations of penicillin, long-acting benzathine penicillin and procaine benzylpenicillin. Both trials recruited infants with asymptomatic (no symptoms) congenital syphilis. The first with 22 newborns was undertaken in South Africa and compared benzathine penicillin with no treatment. The second trial was carried out in USA and recruited 169 infants and compared the effectiveness of benzathine penicillin and procaine benzylpenicillin.

Key results

The first study showed there was not difference in the rate of neonatal death due to any cause, moreover results suggested a possible reduction into the proportion of neonates with clinical manifestations of congenital syphilis. Also penicillin administration increase the number of patients who experience a favourable response in terms of the test used to monitor disease activity (serological cure). This trial was stopped early after there were four cases of congenital syphilis found in the no-treatment group and none in the penicillin group.

The second trial showed that both benzathine penicillin and procaine benzylpenicillin were probably equally effective in treating congenital syphilis for the outcomes absence of clinical manifestations of congenital syphilis and serological cure. None of the studies assessed the side effects of treatment.

Quality of the evidence

The quality of the evidence for the first trial was low due to poor reporting of study methods. For the second trial, there was high-quality evidence for the absence of clinical manifestations of congenital syphilis on neonates, but moderate-quality evidence for serological cure due to few data.

Conclusions

Compared with no intervention, treatment with benzathine penicillin may increase rates of serological cure by the age of three months and possibly reduce the the clinical manifestation of congenital syphilis. There is probably no difference between long-acting benzathine penicillin and procaine benzylpenicillin for treating newborns with congenital syphilis.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Antibiotic treatment compared to no intervention for newborns with congenital syphilis

Patient or population: newborns with congenital syphilis
Setting: inpatient clinic
Intervention: antibiotic treatment
Comparison: no intervention

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with no intervention	Risk with antibiotic treatment			
Neonatal death rate due congenital syphilis	Not reported				
Neonatal death rate due any cause	100 per 1000	83 per 1000 (6 to 1000)	**RR 0.83** (0.06 to 11.70)	22 (1 RCT)	⊕⊕◯◯ **Low**[a,b]
Absence of clinical manifestations of congenital syphilis during follow-up	300 per 1000	36 per 1000 (3 to 627)	**RR 0.12** (0.01 to 2.09)	22 (1 RCT)	⊕⊕◯◯ **Low**[a,b]
Serious adverse events	Not reported				
Serological cure (≥ 4-fold decrease in non-treponemal tests titre)	444 per 1000	947 per 1000 (471 to 1000)	**RR 2.13** (1.06 to 4.27)	20 (1 RCT)	⊕⊕◯◯ **Low**[a,b]
Minor adverse events of therapy	Not reported				

*__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 quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: 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 quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a]Downgraded one level for serious limitations on other bias domain (stopped early rule due to apparent benefit).
[b]Downgraded one level for imprecision.

BACKGROUND

Description of the condition

Congenital syphilis continues to be a substantial public health problem in many parts of the world (Walker 2002; Conway 2007; Mabey 2011; Newman 2013). Subsequent perinatal mortality and morbidity associated with maternal infection with syphilis exceeds that from other infections (Follett 2011). It has received less attention than mother-to-child transmission of HIV, and the prospect of avoiding infection with HIV and dying from syphilis has been raised as a disastrous possibility (Peeling 2004; Taylor 2017a). In 2012, the World Health Organization (WHO) estimated that 930,000 pregnant women experience 350,000 adverse pregnancy outcomes annually due to syphilis. However, while countries frequently have well-resourced programmes for HIV prevention and care, syphilis control is seldom centralised and often falls within the responsibilities, but outside the priorities, of HIV programmes or antenatal care (Taylor 2017b). Not only is the disease burden from congenital syphilis substantial on individuals and families, but also the management of the sequelae of the infection can place appreciable costs on health services (Bateman 1997; Owusu-Edusei 2013).

Congenital syphilis is a systemic infection in which a baby might have been delivered prematurely. The classic description of the congenital syphilitic baby is a severely infected premature infant with marasmus, a pot belly, an 'old man face' and withered skin. Congenital syphilis is a serious condition which, if not fatal at a young age, can cause permanent impairment, debilitation and disfigurement from the stigmata associated with this condition (Chakraborty 2008; Richens 2008; Sparling 2008). A wide spectrum of severity exists, from inapparent infection to severe cases that are clinically present at birth. An infant or child (aged less than two years) may have signs such as hepatosplenomegaly, rash, condyloma lata, snuffles, jaundice (non-viral hepatitis), pseudoparalysis, anaemia or oedema (nephrotic syndrome or malnutrition, or both). An older child may have stigmata (e.g. interstitial keratitis, nerve deafness, anterior bowing of shins, frontal bossing, mulberry molars, Hutchinson teeth, saddle nose, rhagades or Clutton joints) (see Centers for Disease Control (CDC) Congenital Syphilis Definitions - Revised January 2015 www.cdc.gov/std/stats/congenitalsyphilisdef-rev-jan-2015.pdf).

Syphilis is caused by the spirochete, *Treponema pallidum* (*T pallidum*). Most cases of congenital syphilis arise from in utero infection, although a mother can rarely transmit syphilis to her baby at the time of delivery (Shafii 2008). Syphilis can be transmitted transplacentally at all stages during the course of untreated maternal disease, from incubation, through primary, secondary, latent and tertiary syphilis (Doroshenko 2006). The risk to the foetus or baby varies considerably according to the stage of untreated syphilis of the mother, and decreases as maternal disease progresses (Chakraborty 2008). Infectivity and severity of untreated syphilis in pregnant women becomes less with each successive pregnancy (Chakraborty 2008; Gomez 2013).

In most middle- and low-income countries syphilis is endemic and congenital syphilis continues to be a serious public health problem (Gichangi 2004; Beltrami 2006; Walker 2007; Gomez 2013; Newman 2013). It is a major cause of perinatal mortality and morbidity, particularly in sub-Saharan Africa, and remains the leading cause of perinatal mortality, resulting in an estimated 21% of all perinatal deaths and about a third of stillbirths (Shafii 2008). The WHO estimated in 2006 that the global annual incidence of congenital syphilis (including miscarriages, perinatal deaths, premature births/low birthweight babies and neonatal infections) was between 713,600 and 1,575,000 (WHO 2007). Estimates for 2008 based on modelling have produced lower figures, with a mid-case scenario of 520,000 perinatal adverse outcomes due to maternal syphilis infection (215,000 stillbirths, 90,000 neonatal deaths, 65,000 preterm or low birthweight infants and 150,000 newborns infected with congenital syphilis) (Newman 2013). Whatever the correct figures, there is no doubt that syphilis adversely affects more perinates than any other major neonatal infection including HIV infection and tetanus (Follett 2011).

In many 'affluent' countries since the late 1990s, there have been, from very low levels, increases in the numbers of congenital syphilis cases. This has been associated with the near epidemic increase during the late 20th and early 21st centuries in the incidence of primary and secondary syphilis among young females, particularly among inner-city minorities, and often associated with the use of crack cocaine and the exchange of illegal drugs for sex among multiple sex partners and men who have sex with men, as an infectious focus for women (McFarlin 1994; Shafii 2008). In middle- and low-income countries, lack and poor quality of antenatal care appear to be the most important risk factors for increasing numbers of mothers giving birth to babies with congenital syphilis (Gloyd 2001; Walker 2002; Desperthes 2004; Rodrigues 2008; WHO, UNAIDS, UNICEF 2012; Cifuentes-Cifuentes 2013; Cruz 2013).

A mainstay of the prevention of congenital syphilis has been, and continues to be, screening of pregnant women to identify those who have syphilis, followed by treatment (Walker 2002; Hawkes 2009; Munkhuu 2009; Peeling 2012; Peeling 2013). Although there have been concerns about its cost-effectiveness (Terris-Prestholt 2003), this approach has been shown to be generally cost-effective (Walker 2002; Rydzak 2008; Hong 2010; Blencowe 2011; WHO 2012; Kuznik 2013; Sweeney 2014). However, antenatal screening and treatment can remain unaffordable in certain low income countrieswhere there are extremely limited resources available for health care (Schackman 2007; Lomotey 2009; Wiwanitkit 2010). A major innovation in the antenatal testing and on-the-spot treatment of women found to be infected with syphilis has been the development of point-of-care tests (POCTs) (Tucker 2010a; Mabey 2012; Peeling 2012; Tucker 2013). For some years, POCTs have been available as an alternative to rapid plasma reagin

(RPR) or Venereal Disease Research Laboratory (VDRL) testing for syphilis. Unlike RPR, POCTs do not require specialist training or laboratory equipment, and results are available immediately. This allows swift treatment and ends the need for people to return to the clinic to obtain test results (Tucker 2010b; Jafari 2013).

Diagnosis of congenital syphilis

Diagnosis of congenital syphilis is not straightforward (Walker 2007; Shafii 2008; Winscott 2009; Woods 2009; Herremans 2010; Singh 2013; Wright 2013), principally because of the transplacental transfer of non-treponemal/treponemal immunoglobulin (Ig)G antibodies and asymptomatic or non-specific presentation of congenital syphilis (Stoll 1994; Liu 2010; CDC 2015). The diagnosis of congenital syphilis is recognised to be problematic, with more than half of babies asymptomatic at birth and the signs in symptomatic infants often being subtle and non-specific (Arnold 2000; Herremans 2010; Murali 2012; Basu 2013; Introcaso 2013).

The most recent CDC Sexually Transmitted Diseases Treatment Guidelines (June 2015) define the following four categories of babies who are more or less likely to have congenital syphilis (CDC 2015).

A. Confirmed or highly probable congenital syphilis

Any neonate with:

- an abnormal physical examination that is consistent with congenital syphilis; or
- a serum quantitative non-treponemal serologic titre that is four-fold higher than the mother's titre; or
- a positive darkfield test or polymerase chain reaction of lesions or body fluid(s).

B. Possible congenital syphilis

Any neonate who has a normal physical examination and a serum quantitative non-treponemal serological titre of four-fold or less of the maternal titre, and one of the following:

- mother was not treated, inadequately treated or has no documentation of having received treatment; or
- mother was treated with erythromycin or a regimen other than those recommended (i.e. a non-penicillin G regimen); or
- mother received recommended treatment less than four weeks before delivery.

C. Congenital syphilis less likely

Any neonate who has a normal physical examination and a serum quantitative non-treponemal serological titre of fourfold or less of the maternal titre, and both of the following are true:

- mother was treated during pregnancy, treatment was appropriate for the stage of infection and treatment was administered more than four weeks before delivery, and
- mother had no evidence of reinfection or relapse.

D. Congenital syphilis unlikely

Any neonate who has a normal physical examination and a serum quantitative non-treponemal serological titre of four-fold or less of the maternal titre and both of the following are true:

- mother's treatment was adequate before pregnancy and
- mother's non-treponemal serological titre remained low and stable (i.e. serofast) before and during pregnancy and at delivery (VDRL less than 1:2; RPR less than 1:4).

Description of the intervention

Since the first use of penicillin for the treatment of syphilis by Mahoney in 1943 (Thomas 1949; Idsoe 1972; McCracken 1974), its introduction was a notable early success and has remained the preferred treatment of all types of syphilis. This applies to the treatment of congenital syphilis, with penicillin establishing itself as the standard treatment shortly after its discovery. However, the treatment of congenital syphilis is largely based on clinical experience and there is limited evidence on the optimal dose or duration of administration of penicillin (Zenker 1990).

Different countries and organisations recommend slightly different regimens of penicillin to treat babies with congenital syphilis (AGUM and MSSVD 2002; WHO Euro 2003; Saloojee 2004; Kingston 2008; French 2009; CDC 2015). Treatment schedules vary between clinicians and different units (Finelli 1998), but there are said to be advantages to using standard guidelines for the management of congenital syphilis (Lago 2013).

Although well-documented foetal and infant treatment failures with penicillin are rare (Conover 1998), there have been reservations raised about the occasional inadequacy of maternal treatment with penicillin of gestational syphilis in preventing congenital syphilis (Rawstron 1991; Zenker 1991; Monif 1994; Stoll 1994; Richardson 2002; Wendel 2002; Saloojee 2004) and of treating congenital syphilis (Beck-Sague 1987; Ikeda 1990). Concerns have also been raised about the adequacy of concentrations in cerebrospinal fluid of penicillin when babies with congenital syphilis are treated with procaine and aqueous penicillin and benzathine penicillin (Speer 1977).

Although antibiotics other than penicillin (e.g. azithromycin, doxycycline and tetracycline) are occasionally used to treat syphilis in adults, given the effectiveness of penicillin in the treatment of majority of cases of congenital syphilis it is extremely rare for other antibiotics to be used. Azithromycin has been used for the treatment of syphilis in adults since the late 1990s with occasional resistance being reported. The most frequent problem with the use of macrolides is the increased percentage of strains with genetic mutations with more likely resistance and therapeutic failure (Katz 2008). This example, with macrolide resistance of *T pallidum* shows the capacity of the micro-organism for change in the

genetic code and a mechanism for the development of resistance for other antibiotics (Stamm 2015). Occasionally, the third-generation cephalosporin ceftriaxone has been used to treat congenital syphilis (CDC 2015). Even when infants and children who require treatment for syphilis have a history of penicillin allergy or develop an allergic reaction presumed secondary to penicillin they are usually, if necessary, desensitised, and then treated with penicillin (CDC 2015).

The US CDC in its latest guidelines recommends three alternative regimens for the treatment of babies with congenital syphilis (CDC 2015):

- aqueous crystalline penicillin G 100,000 units/kg/day to 150,000 units/kg/day, administered as 50,000 units/kg/dose intravenously every 12 hours during the first seven days of life and every eight hours thereafter for a total of 10 days; OR
- procaine penicillin G 50,000 units/kg/dose intramuscularly in a single daily dose for 10 days OR
- benzathine penicillin G 50,000 units/kg/dose intramuscularly in a single dose.

The WHO in 2016 made the following specific recommendations for the treatment of congenital syphilis (WHO 2016).

- In infants with confirmed congenital syphilis or infants who are clinically normal, but whose mothers had untreated syphilis, inadequately treated syphilis (including treatment within 30 days of delivery) or syphilis that was treated with non-penicillin regimens, the WHO sexually transmitted infections (STI) guideline suggests aqueous benzyl penicillin or procaine penicillin. Either:
    - aqueous benzyl penicillin 100,000 units/kg/day to 150,000 units/kg/day intravenously for 10 to 15 days or
    - procaine penicillin 50,000 units/kg/day single dose intramuscularly for 10 to 15 days.
- In infants who have no clinical signs of infection with syphilis and whose mothers had syphilis that was adequately treated with no signs of reinfection, the WHO guideline suggests close monitoring of the infants. If decided to treat:
    - benzathine penicillin G 50,000 units/kg/day single dose intramuscularly.

It was noted that both recommendations were conditional and based on very low-quality evidence.

How the intervention might work

Treatment with antibiotics could decrease the risk of neonatal death, improve quality of life and reduce risk of neurological impairment or the sequelae of congenital syphilis. Penicillin is a β-lactam antibiotic that functions at the level of the cell wall via binding to penicillin-binding proteins (PBPs) and when bound, the β-lactam (penicillin) is able to interfere with the production of specific peptidoglycans critical for cell wall structure. Once these peptides are eliminated, the cell wall ruptures and the bacteria dies (Rougas 2012)

Ceftriaxone is a third-generation cephalosporin antibiotic. Like other third-generation cephalosporins, it has broad-spectrum activity. It inhibits bacterial cell wall synthesis by means of binding to the PBPs. Inhibition of PBPs in turn inhibit the transpeptidation step in peptidoglycan synthesis which is required for bacterial cell wall formation. The half-life of ceftriaxone is about seven hours. A range of adverse effects have been reported for ceftriaxone, particularly in neonates (see Ceftriaxone - safety in neonates. Second Meeting of the Subcommittee of the WHO Expert Committee on the Selection and Use of Essential Medicines, Geneva, 29 September to 3 October 2008, www.who.int/selection_medicines/committees/subcommittee/2/Ceftriaxone.pdf).

While there has not yet been resistance of the spirochete to penicillin, caution should be maintained. Cases of syphilis have been increasing worldwide, and so does the potential for antibiotic resistance. A mutation in a PBP (e.g. Tp47) may alter the protective byproducts upon which the sensitivity of syphilis to penicillin depends. Such a mutation would likely result in profound problems in the efficacious treatment of syphilis.

Why it is important to do this review

While the mainstay of treatment of congenital syphilis has been (and remains) penicillin and not other antibiotics such as azithromycin and ceftriaxone, there is some uncertainty about the most appropriate dose and length of treatment. In addition, there is concern about the most appropriate treatment in babies born to mothers also infected with HIV. It is likely that many babies will continue to be born with congenital syphilis and consequently there continues to be a need to clarify issues related to the treatment of this condition (Goode 2013).

As made clear earlier, congenital syphilis is a tragedy for families, accounts for a substantial burden of disease (Murray 2012), and has significant implications for health services (Bateman 1997; Owusu-Edusei 2013). This would be appreciably increased if resistance to penicillin were to occur and would present even greater challenges and result in increased costs to individuals and health services. Now is an opportune time to clarify which antibiotics are effective in treating congenital syphilis, and avoid increased rates of resistance to antibiotics that can offer the same degree of effectiveness to that of penicillin

OBJECTIVES

To assess the effectiveness and safety of antibiotic treatment for newborns with confirmed, highly probable and possible congenital syphilis.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs), published and unpublished, that compared the use of antibiotic treatment (any concentration, frequency, duration and route) with no intervention or any other antibiotic treatment (any concentration, frequency, duration and route) for the treatment of neonates with confirmed, highly probable and possible congenital syphilis.
We excluded quasi-randomised trials because this approach produces effect estimates that indicate more extreme benefits compared with those generated by RCTs (Higgins 2011). We also excluded cross-over trials and cluster-randomised trials because of the nature of the condition (Higgins 2011).

Types of participants

Newborns with confirmed, highly probable or possible congenital syphilis according to CDC definition (CDC 2015). Neonates were included regardless of the mother's HIV status.

Types of interventions

Antibiotic treatment (at any concentration, frequency, duration and route) versus one of the following:

- no intervention;
- any other antibiotic treatment (any concentration, frequency, duration and route).

Types of outcome measures

Primary outcomes

- Neonatal death rate due to congenital syphilis.
- Neonatal death rate due to any cause.
- Absence of clinical manifestations of congenital syphilis during follow-up (defined as proportion of newborns without hepatosplenomegaly, lymphadenopathy, organ involvement or any other clinical manifestation after treatment).
- Serious adverse events (proportion of neonates who experience any adverse effect that was life-threatening or required discontinuation of therapy or intervention to prevent permanent impairment or damage).

Secondary outcomes

- Serological cure (defined as four-fold decrease or greater in non-treponemal tests titre by the third month of age).
- Minor adverse events of therapy (e.g. fever, diarrhoea, vomiting or allergic reactions).

Search methods for identification of studies

We followed the recommendations suggested by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and we published our protocol before conducting the literature search (Walker 2016). We attempted to identify RCTs of "antibiotics" for "congenital syphilis," irrespective of language of publication, publication date and publication status (published, unpublished, in press and in progress). We used both electronic searching in bibliographic databases and handsearching, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Electronic searches

We contacted the Information Specialist of the Cochrane Sexually Transmitted Infections Group to implement a comprehensive search strategy to capture as many relevant studies as possible in electronic databases. For this purpose, we used a combination of exploded controlled vocabulary (MeSH, Emtree, DeCS) and free-text terms (considering spelling variants, plurals, synonyms, acronyms and abbreviations) for "antibiotics" and "congenital syphilis," with field labels, truncation, proximity operators and Boolean operators. The sensitivity of the search strategies was improved by including keywords from relevant studies detected by earlier searches. The search strategies can be found in Appendix 1.
Specifically, we searched the following electronic databases:

- Cochrane Central Register of Controlled Trials (CENTRAL), Ovid: inception to 23 May 2018;
- MEDLINE, Ovid: inception to 23 May 2018;
- MEDLINE In-Process & Other Non-Indexed Citations, Ovid: inception to 23 May 2018;
- MEDLINE Daily Update, Ovid: inception to 23 May 2018;
- Embase.com: inception to 23 May 2018;
- LILACS, iAHx interface: inception to 23 May 2018;

For MEDLINE, we used the Cochrane highly-sensitive search strategy for identifying RCTs: sensitivity and precision maximising version (2008 revision), Ovid format (Higgins 2011). The LILACS search strategy was combined with the RCT filter of the iAHx interface.

Searching other resources

We searched the following resources for additional trials.

- The STI Cochrane Review Group's Specialized Register, which includes RCTs and controlled clinical trials, from 1944 to 23 May 2018, located through:
  - electronic searching in CENTRAL, MEDLINE and Embase;
  - online handsearching in those journals not indexed in MEDLINE or Embase, according to the Journals' Master List of the STI Cochrane Review Group.
- Trials registers:
  - WHO International Clinical Trials Registry Platform ICTRP portal (apps.who.int/trialsearch/): inception to 23 May 2018;
  - ClinicalTrials.gov (clinicaltrials.gov/): inception to 23 May 2018.

- Grey literature in System for Information on Grey Literature in Europe "OpenGrey" (www.opengrey.eu/): inception to 23 May 2018.
- We contacted the trial authors of all RCTs we identified by other methods. A list of RCTs included in the review along with the criteria for considering studies was sent to one of the authors of each included study, asking for any additional studies, published or unpublished, that might be relevant.
- We handsearched conference proceeding abstracts of the following events:
  - International Society for Sexually Transmitted Diseases Research (ISSTDR; www.isstdr.org/): 2007, 2009, 2011, 2013 and 2015;
  - British Association for Sexual Health and HIV (BASHH; www.bashh.org/): 2004, 2006, 2007 and 2009;
  - International Congress on Infectious Diseases (ICID; www.isid.org/): 2010 and 2012;
  - International Union against Sexually Transmitted Infections (IUSTI; www.iusti.org/): 2011 and 2012;
  - International Society for Infectious Diseases (ISID; www.isid.org/): 2011;
  - International Meeting on Emerging Diseases and Surveillance (IMED; www.isid.org/): 2007, 2009 and 2011;
  - Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC; www.icaac.org/): 2011 and 2012;
  - International Federation of Gynecology and Obstetrics (FIGO; www.figo2012.org/home/): 2009, 2012 and 2015.
- We handsearched relevant publications on congenital syphilis. This included online searching of certain journals from the early part of the 20th century including the *American Journal of Diseases of Childhood*, *Journal of Pediatics*, *Archives of Dermatology and Syphilology*, *Lancet*, *BMJ*, *Acta Dermato-Venereologica* and *Journal of Venereal Disease Information*.
- Handsearching the reference lists of all relevant RCTs identified by other methods.

Data collection and analysis

Selection of studies

We downloaded and managed the results of all searches using Endnote bibliographic software. We removed duplicate records of the same study and obtained the full texts of possibly relevant studies. The review authors (GW, DW, DF and CFG-A) independently assessed for inclusion all the titles, abstracts and full texts of records retrieved from the search strategy. The review authors (GW, DW, DF and CFG-A) independently undertook the final selection of studies included in the review and resolved disagreements through discussion.

Data extraction and management

One review author (GW) designed a form to extract data. This was based on a form used by the Cochrane STI Group. The review authors (GW, DW, DF and CFG-A) independently extracted the data from eligible studies using the data extract form. We discussed any disagreements regarding extracted data until we reached consensus.

We extracted the following data.

- Methods:
  - location of the study and setting;
  - trial design;
  - power calculation performed;
  - methods used to generate and maintain allocation;
  - use of any method of blinding of the researchers or participants (i.e. their parents) in order to evaluate outcomes.
- Participants:
  - inclusion and exclusion criteria;
  - total number of intervention groups;
  - baseline information on the participants in order to have comparable intervention groups at entry;
  - number of participants enrolled, randomised, excluded after randomisation and analysed;
  - number of participants lost to follow-up in the groups.
- Intervention and comparison:
  - types of interventions: antibiotics (any concentration, frequency and duration of therapy);
  - adherence to the planned intervention and other interventions in the groups under evaluation;
  - types of comparison: no intervention or any antibiotic treatment.
- Outcomes:
  - how outcomes were defined;
  - time of follow-up of participants to measure outcomes;
  - differences between groups for outcome assessment;
  - outcomes stated in methods versus outcomes reported in results.
- Others:
  - funding sources, reported;

- ethical issues: use of signed informed consent and ethics approval.

We entered data into Review Manager 5 (Review Manager 2014), and checked them for ensuring data accuracy. When information regarding any of the above was unclear, we attempted to obtain clarification by contacting authors of the original reports to ask for further details. For a single RCT report, we extracted data directly onto a data collection form and in case of multiple reports, we extracted data from each report separately, and then combined information across data collection forms. We cross checked to ensure there were no duplicated data.

Assessment of risk of bias in included studies

All review authors (GW, DW, DF and CFG-A) independently assessed the risk of bias for each included study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved disagreements by discussion. The review authors assessing risk of bias were content and methodology experts. When we needed to obtain missing information, we contacted the study investigators using open-ended questions. We assessed risk of bias in the included trials and collected information in data extraction forms. We then added the information to Review Manager 5 (Review Manager 2014).
We evaluated the following topics proposed in the *Cochrane Handbook for Systematic Reviews of Interventions* to assess the risk of bias in the included studies (Higgins 2011).

- Random sequence generation: it refers to the method of randomisation.
- Allocation concealment: to assess the risk of selection bias.
- Blinding of participants and personnel: to evaluate the possible performance bias.
- Blinding of outcome assessment: to evaluate the possible detection bias.
- Incomplete outcome data: to determine attrition bias due to withdrawals, dropouts and protocol deviations.
- Selective outcome reporting: to evaluate possible selective reporting of outcomes.
- Other sources of bias.

Overall risk of bias

To summarise the quality of the evidence, we considered sequence generation, blinding of outcome assessor, incomplete outcome data and selective reporting domains to classify each study as:

- low risk of bias when we judged all four criteria at low risk of bias;
- high risk of bias when we judged at least one criterion at high risk of bias;
- unclear risk of bias when we judged all four criteria at unclear risk of bias and moderate risk of bias in the remaining cases (Romero 2017).

We explored the impact of the level of bias through undertaking sensitivity analyses (see Sensitivity analysis).

Measures of treatment effect

For dichotomous data, we presented results as summary risk ratio (RR) with 95% confidence intervals (CI). The RR as a relative effect measure has consistency, works well with a low or high rate of events, and it is easy to interpret and use in clinical practice.

Unit of analysis issues

The unit of analysis was infants with confirmed, highly probable or possible congenital syphilis who were treated. In updates of this review, if we identify a clinical trial in which participants were randomised to several intervention groups, we will determine which intervention groups were relevant and to avoid confusion for the reader, we will report all intervention groups of the study in the Characteristics of included studies table, and will provide a detailed description of the intervention groups relevant to the review and only use these groups in our analyses. To avoid a unit-of-analysis error for a study that could contribute multiple, correlated, comparisons, we will combine groups to create a single pairwise comparison.

Dealing with missing data

For included studies, we noted levels of attrition. We explored the impact of including studies with high levels of missing data in the overall assessment of treatment effects by using sensitivity analysis. For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis (i.e. we attempted to include all participants randomised to each group in the analyses, and all participants were analysed in the group to which they were allocated), regardless of whether or not they received the allocated intervention. We contacted the study investigators to request the missing data.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the I^2 statistic and Chi^2 test values (Higgins 2011). We regarded heterogeneity as substantial if the I^2 statistic was greater than 40% and if we found a low P value less than 0.10 in the Chi^2 test for heterogeneity, which we plotted in a forest plot (Review Manager 2014).
We planned to quantify statistical heterogeneity with the I^2 statistic, using the following cut-off values for interpretation:

- 0% to 39%: statistical heterogeneity may be negligible;
- 40% to 60%: statistical heterogeneity may be moderate;
- greater than 60%: statistical heterogeneity may be substantial.

Assessment of reporting biases

We planned to explore publication bias through assessment of funnel plot asymmetry and formal tests. For dichotomous outcomes, we planned to use the test proposed by Harbord 2006. However, we included fewer than 10 trials in the meta-analysis, so we did not perform these analyses.

Data synthesis

We performed statistical analyses using Review Manager 5 (Review Manager 2014). We used a fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect (i.e. where trials were examining the same intervention, and the trial populations and methods were judged sufficiently similar). If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if we detected moderate or substantial statistical heterogeneity, we used a random-effects meta-analysis to produce an overall summary if a mean treatment effect across trials was considered clinically meaningful. We treated the random-effects summary as the mean range of possible treatment effects and we discussed the clinical implications of treatment effects differing between trials. If the mean treatment effect was not clinically meaningful, we did not combine trials.
If we used random-effects analyses, we presented the results as the mean treatment effect with 95% CIs, and the estimates of the Tau ^{2} and I^2 statistics.

Subgroup analysis and investigation of heterogeneity

We planned to undertake the following subgroup analyses:

- according to congenital syphilis CDC definition (confirmed, highly probable or possible);
- comparison of different maternal HIV serostatus (positive or negative);
- comparison of different antibiotic type;
- setting (high-income versus middle- and low-income countries).

We planned to restricted subgroup analyses to the outcomes: neonatal death rate due congenital syphilis, neonatal death rate due any causes, absence of clinical manifestations of congenital syphilis during follow-up and serious adverse events.

Sensitivity analysis

We planned to perform sensitivity analyses for aspects of the review that might have affected the results, for example, where there was risk of bias associated with the quality of some of the included trials (low versus unclear or high risk of bias).

'Summary of findings' table

We prepared 'Summary of findings' tables using GRADEpro (GRADEpro GDT 2015) and Cochrane methods (Higgins 2011). These tables evaluate the overall quality of the body of evidence for the review outcomes (neonatal death rate due to congenital syphilis, neonatal death rate due to any cause, absence of clinical manifestations of congenital syphilis during follow-up, serious adverse events, serological cure and minor adverse events) for the main review comparisons (antibiotic treatment versus no intervention and antibiotic treatment versus any other antibiotic). We assessed the quality of the evidence using GRADE criteria: risk of bias, consistency of effect, imprecision, indirectness and publication bias). All review authors (GW, DW, DF and CFG-A) independently made judgements about evidence quality (high, moderate, low or very low), with disagreements resolved by discussion. We justified, documented and incorporated judgements into reporting of results for each outcome.
We planned to extract study data, format our comparisons in data tables and prepare 'Summary of findings' tables before writing the results and conclusions of our review.

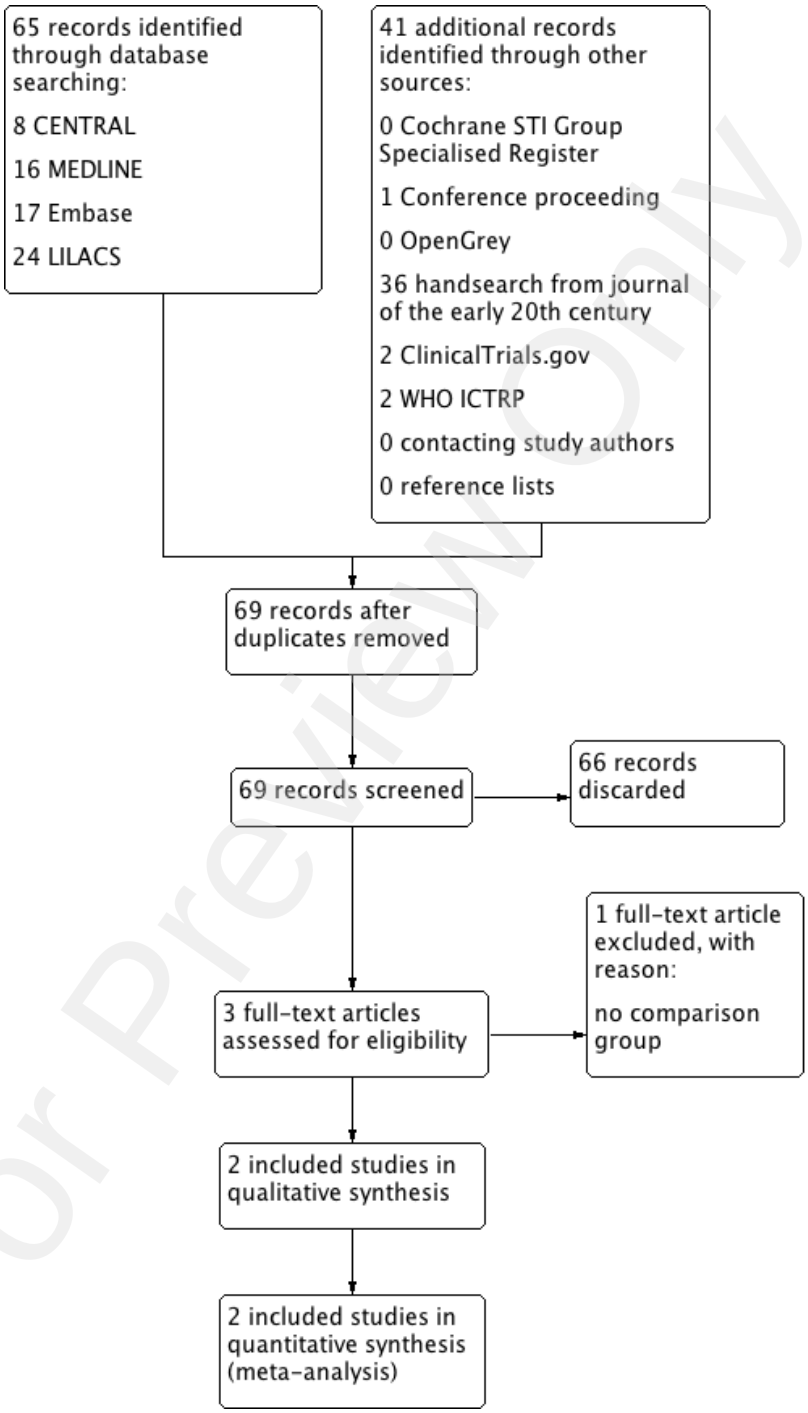
RESULTS

Description of studies

Results of the search

We searched the available literature up to 23 May 2018. We retrieved 106 references, of which we screened 69 after we removed duplicates. Of these, we retrieved the full-text of three references. Two published trials (Paryani 1994; Radcliffe 1997) meet our eligibility criteria for inclusion. We excluded one study (see the Characteristics of excluded studies). We presented a PRISMA diagram in Figure 1 to illustrate the study selection process.

Figure 1. Study flow diagram.



Included studies

The two included trials had 174 participants with a sample size of 22 (Radcliffe 1997) and 152 (Paryani 1994). One was from South Africa (Radcliffe 1997), and the other from the USA (Paryani 1994). None were multicentric, and, despite that, one of them used a method for sample size calculation (Radcliffe 1997), this target for recruitment was not achieved because the study was stopped early after there were several cases of congenital syphilis in the no treatment group. The Included trials recruited their participants from public and private specialist hospital units and received ethics and research committee approval. One was sponsored by an academic institution (Paryani 1994), and it was not clear if the other received any outside financial support (Radcliffe 1997). The reports of both trials were published in English.

Population

The two trials included newborns with possible congenital syphilis. Mothers were diagnosed with gestational syphilis during their antenatal care using the combination of treponemal and non-treponemal test and were interviewed soon after birth. Infants of mothers who had not received treatment, or whose treatment for syphilis during pregnancy was inadequate, were eligible for inclusion. Only infants who could be followed up were included and infants were recruited regardless of the presence of comorbidities or maternal risk behaviour (e.g. HIV status, drug users) or their gestational age, birthweight, race or sex. All newborns received a complete physical examination after birth and before their inclusion in the trials.

For the first trial, infants were eligible for the study if they met the following criteria were met:

- neonate born to a mother with positive RPR and microhaemagglutination assay for *T pallidum* antibodies (MHA-TP) results at time of delivery;
- no or inadequate treatment of syphilis in the mother;
- no systemic antibiotics given to the infant before enrolment;
- no signs of congenital syphilis on physical examination, cerebrospinal fluid cell count or VDRL test, x-ray study of long bones and platelet count or liver function tests.

Infants were not eligible for the study if cerebrospinal fluid was not obtained for the VDRL test and cell count. Enrolled infants were considered to be at high risk of acquiring congenital syphilis if they had any of the following: no maternal treatment of syphilis, positive fluorescent treponemal antibody immunoglobulin M (FTA-IgM) results, infant's RPR titre at least four-fold higher at birth than the mother's or serum HIV antibody (Paryani 1994).

The second study recruited asymptomatic infants with congenital syphilis (Radcliffe 1997). This category was defined as those born to mothers with untreated syphilis (i.e. positive VDRL and treponema pallidum haemagglutination (TPHA) tests), with a VDRL titre of 32 or more. Infants were regarded as asymptomatic at birth if: there were no clinical signs of congenital syphilis; the x-rays of the long bones were normal and the rheumatoid factor latex test was negative at birth.

Intervention and comparison

The intervention was similar for both trials, being the antibiotic benzathine penicillin 50,000 units/kg in a single intramuscular injection (Paryani 1994; Radcliffe 1997). One trial compared the intervention with no treatment (Radcliffe 1997); while the other trial used procaine benzylpenicillin 50,000 units/kg given daily intramuscularly for 10 days (Paryani 1994).

Outcomes

Included trials reported at least one prespecified primary outcome of this review. The largest trial was scheduled to follow-up babies at two to three months, five to six months and 12 months of age (Paryani 1994). The trial comparing benzathine penicillin with no treatment included reporting the proportion of neonates with abnormal physical examination suggestive of congenital syphilis at the third month of age, follow-up was planned at six-weekly intervals after birth but the trial was stopped early after there were several cases of congenital syphilis found within 12 weeks of entry into the trial in the no treatment group (Radcliffe 1997).

The included studies assessed serological cure defined as a four-fold (or greater) decrease in the non-treponemal titre within 12 weeks of entry into the trial. One study reported the neonatal death rate due any cause at the end of follow-up (Radcliffe 1997), and the other trial reported the neonatal death rate due congenital syphilis at 12 months of age (Paryani 1994). Finally, included studies reported the proportion of neonates with abnormal physical examination suggestive of congenital syphilis at the third month of age. We obtained no data for the primary outcome of serious adverse events or for the secondary outcome of minor adverse events.

Excluded studies

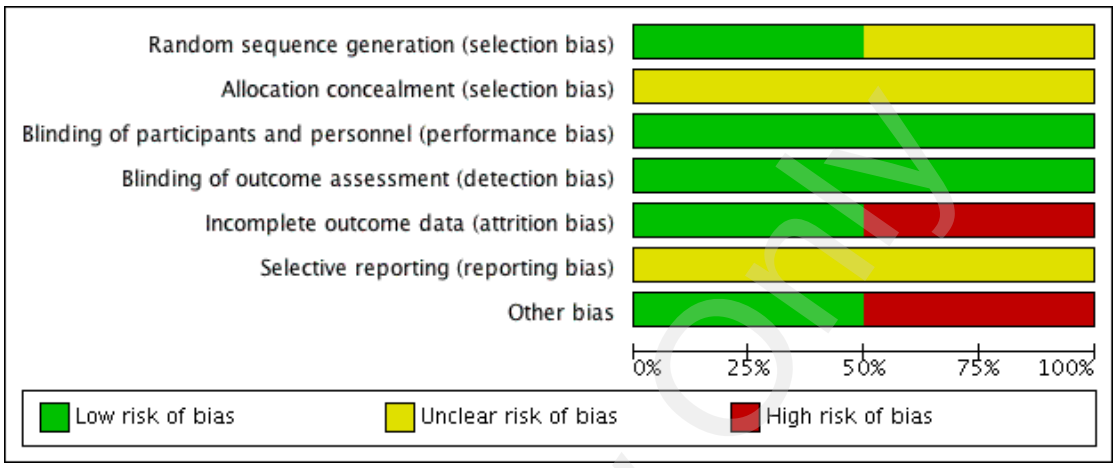
The one excluded trial (Venter 1986) was designed with the objective to determine if penicillin therapy caused a deterioration in liver function. Infants were randomly assigned into two groups: penicillin therapy only and penicillin plus prednisone as an adjunct. We excluded this trial because it did not compare the use of antibiotic treatment with no intervention or any other antibiotic treatment (see Characteristics of excluded studies table).

Risk of bias in included studies

We summarised the risk of bias assessment in Figure 2 and Figure 3, and included additional details in the Characteristics of included studies table.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Random sequence generation (selection bias)

One trial adequately reported the random sequence generation method by using a computer-generated randomisation list, making selection bias at entry unlikely (Paryani 1994). The remaining included trial did not report the random sequence generation method, making the risk of selection bias at entry unclear (Radcliffe 1997).

Allocation concealment (selection bias)

Neither trial described the method used to conceal allocation to interventions prior to assignment and we could not assess whether intervention allocation could have been foreseen in advance of, or during, recruitment or changed after assignment (Paryani 1994; Radcliffe 1997). We judged them at unclear risk of selection bias.

Blinding

One study did not report the method used to blind outcome assessors and personnel regarding which intervention a baby received (Paryani 1994). The second RCT was an open-label trial; participants were assigned to the intervention (single injection of benzathine penicillin) or no treatment arm (Radcliffe 1997). However, we considered both studies were at low risk for performance and detection bias because the outcomes of neonatal death due to congenital syphilis or any cause, absence of clinical manifestations of congenital syphilis and serological cure were objectively assessed, so the lack of blinding was unlikely to affect the results.

Incomplete outcome data

One trial appropriately stated the attrition and exclusions at each stage and the level of missing data was not over 20% (Radcliffe 1997). In the no treatment arm of 10 participants, two infants were lost to follow-up, one after four months who was considered not to be infected because the VDRL had declined to one by four months. The second infant died of diarrhoea aged two months and had no follow-up VDRL but the study authors considered this infant was not infected. In the treatment arm of 12 infants, one was lost to follow-up. For this study, the overall assessment of was of low risk because the level of missing data was not over 20% for this outcome.

The other study had a low attrition rate for the outcomes of neonatal death rate due congenital syphilis and absence of clinical manifestations of congenital syphilis but an extremely high attrition level for serological cure (Paryani 1994). Initially, this study randomly assigned 169 infants to receive either benzathine penicillin (92 infants) or procaine benzylpenicillin (77 infants). Three infants were excluded from the benzathine penicillin group and five from the procaine benzylpenicillin group because of maternal false-positive RPR results and positive x-rays results not recognised before enrolment. Five were lost to follow-up in the benzathine penicillin group and four in the procaine benzylpenicillin group. Overall, excluded or lost to follow-up was 8.7% in the benzathine penicillin group and 11.7% in the procaine benzylpenicillin group for the outcomes of neonatal death rate due congenital syphilis and absence of clinical manifestations of congenital syphilis. However, only 129 infants were assessed by four month of follow-up with RPR titre (68 in the benzathine penicillin arm and 61 in the procaine benzylpenicillin arm). For this study, the overall assessment was of high risk because the level of missing data was over 20%

for the outcome of serological cure.

Selective reporting

The trial protocols were not available for either of the included trials and it was unclear if the published reports included all the expected outcomes, including those that were prespecified. The published reports had insufficient information to permit a judgement of 'yes' or 'no' and consequently were rated at unclear risk of reporting bias.

Other potential sources of bias

One study had a potential source of bias related to a formal 'stopped early' rule due to apparent benefit (Radcliffe 1997). The remaining retrieved trial was sponsored by an academic institution (Paryani 1994). This study appeared to be free from other sources of bias and was at low risk of other bias.

Effects of interventions

See: **Summary of findings for the main comparison** Antibiotic treatment compared to no intervention for newborns with congenital syphilis; **Summary of findings 2** Antibiotic treatment (benzathine penicillin) compared to any other antibiotic (procaine benzylpenicillin) for newborns with congenital syphilis

See: Summary of findings for the main comparison for the main comparison antibiotic treatment versus no intervention; This trial was stopped early because there were four cases with clinical congenital syphilis in the no treatment group and none in the treatment group. Summary of findings 2 for antibiotic treatment compared to any other antibiotic treatment. The sources of all data presented in the review were published literature.

1. Antibiotic treatment compared to no intervention

Only one trial including 22 participants compared benzathine penicillin versus no intervention for infants with possible congenital syphilis (Radcliffe 1997). This study had intended to recruit 60 infants but the trial was terminated early following an interim analysis when 22 babies had been recruited.

1.1. Neonatal death rate due to congenital syphilis

The trial did not report neonatal death due to congenital syphilis.

1.2. Neonatal death rate due to any cause

In the benzathine penicillin group of 12 babies, one died at two weeks of a congenital heart defect (hypoplastic left heart disease); and in the no treatment group of 10 newborns, nine survived and one died of diarrhoeal disease at age two months. There was little or no difference between antibiotic treatment and no intervention in terms of neonatal death rate due to any cause (RR 0.83, 95% CI 0.06 to 11.70; 1 study, 22 infants; Analysis 1.1). The quality of the evidence was low due to limitations on risk of bias and imprecision.

1.3. Absence of clinical manifestations of congenital syphilis during follow-up

In the benzathine penicillin group, no infants developed physical signs suggestive of congenital syphilis. However, four participants assigned to the no intervention group had clinical manifestations of congenital syphilis but results showed little or no difference between the groups (RR 0.12, 95% CI 0.01 to 2.09; 1 study, 22 infants; Analysis 1.2). The quality of the evidence was low due to limitations of precision and risk of bias.

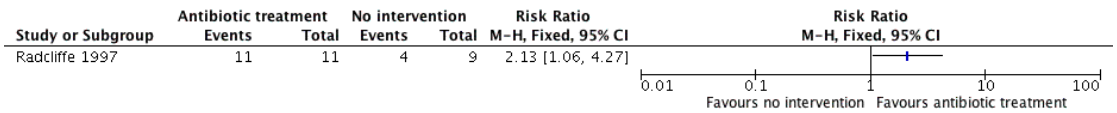
1.4. Serious adverse events

The trial did not report serious adverse events.

1.5. Serological cure

In the group treated with benzathine penicillin of 11 babies with follow-up, VDRL titres of all newborns declined to zero in the absence of any signs of congenital syphilis; and in the no treatment group of nine infants with complete follow-up, there were only four with a four-fold decrease or greater in non-treponemal tests titre by the third month. Antibiotic treatment may have increased the proportion of infants experiencing a four-fold decrease or greater in non-treponemal tests titre by the third month (RR 2.13, 95% CI 1.06 to 4.27; 1 study, 20 infants; Analysis 1.3; Figure 4). The quality of the evidence was low due to limitations of imprecision and risk of bias.

Figure 4. Forest plot of comparison: 1 Antibiotic treatment compared to no intervention for congenital syphilis, outcome: 1.3 Serological cure (four-fold decrease or greater in non-treponemal tests titre).



1.6. Minor adverse events of therapy

The trial did not report minor adverse events of therapy.

2. Antibiotic treatment compared to any other antibiotic treatment

One trial including 152 infants compared benzathine penicillin versus procaine benzylpenicillin for the treatment of newborns with possible congenital syphilis (Paryani 1994).

2.1. Neonatal death rate due to congenital syphilis

Of 152 babies followed up (84 in the benzathine penicillin group and 68 in the procaine benzylpenicillin group), all survived. There were no cases of neonatal death due to congenital syphilis.

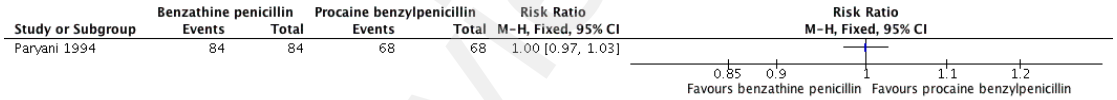
2.2. Neonatal death rate due to any cause

The trial did not report neonatal death due to any cause.

2.3. Absence of clinical manifestations of congenital syphilis during follow-up

No infants developed physical signs suggestive of congenital syphilis during follow-up. There was no evidence of a difference between benzathine penicillin and procaine benzylpenicillin (RR 1.00, 95% CI 0.97 to 1.03; 1 study, 152 infants; Analysis 2.1; Figure 5). The quality of the evidence was high.

Figure 5. Forest plot of comparison: 2 Any antibiotic treatment (benzathine penicillin) compared to any other antibiotic (procaine benzylpenicillin) for congenital syphilis, outcome: 2.1 Absence of clinical manifestations of congenital syphilis during follow-up.



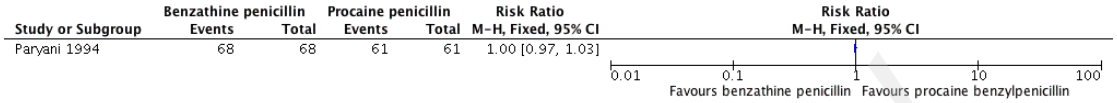
2.4. Serious adverse events

The trial did not report serious adverse events.

2.5. Serological cure

All babies who were tested in both groups had at least a four-fold decrease or greater in non-treponemal tests titre by three months of age. There were probably no differences between benzathine penicillin and procaine benzylpenicillin in terms of serological cure (RR 1.00, 95% CI 0.97 to 1.03; 1 study 129 infants; Analysis 2.2; Figure 6). The quality of the evidence was moderate due to attrition bias risk.

Figure 6. Forest plot of comparison: 2 Any antibiotic treatment (benzathine penicillin) compared to any other antibiotic (procaine benzylpenicillin) for congenital syphilis, outcome: 2.2 Serological cure (four-fold decreased or greater in non-treponemal tests titre).



2.6. Minor adverse events of therapy

The trial did not report minor adverse events of therapy.

Subgroup analysis and investigation of heterogeneity

We could not analyse potential sources of heterogeneity using subgroup analysis by congenital syphilis CDC definition, maternal HIV serostatus, antibiotic type or setting (high-income versus middle- and low-income countries), because of lack of information.

Sensitivity analysis

We could not carry out the planned sensitivity analyses based on the quality of the included trials because all of the included studies were assessed at unclear or high risk of bias.

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

Antibiotic treatment (benzathine penicillin) compared to any other antibiotic (procaine benzylpenicillin) for newborns with congenital syphilis

Patient or population: newborns with congenital syphilis
Setting: inpatient clinic
Intervention: antibiotic treatment (benzathine penicillin)
Comparison: any other antibiotic (procaine benzylpenicillin)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with any other antibiotic (procaine benzylpenicillin)	Risk with antibiotic treatment (benzathine penicillin)			
Neonatal death rate due congenital syphilis	There were 0 cases of neonatal death due congenital syphilis				
Neonatal death rate due to any cause	Not reported				
Absence of clinical manifestations of congenital syphilis during follow-up	1000 per 1000	1000 per 1000 (970 to 1000)	**RR 1.00** (0.97 to 1.03)	152 (1 RCT)	⊕⊕⊕⊕ **High**
Serological cure (4-fold decrease or greater in non-treponemal tests titre)	1000 per 1000	1000 per 1000 (970 to 1000)	**RR 1.00** (0.97 to 1.03)	129 (1 RCT)	⊕⊕⊕◯ **Moderate**[1]
Minor adverse events of therapy	Not reported				

*__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 quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: 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 quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a]Downgraded one level for serious limitations on incomplete outcome data domain.

DISCUSSION

Summary of main results

Two RCTs (191 participants) met our inclusion criteria; neither were funded by the pharmaceutical industry (Paryani 1994; Radcliffe 1997).

One trial (22 participants) compared benzathine penicillin administration with no intervention for infants with possible congenital syphilis (Radcliffe 1997). Low-quality evidence suggested there was no difference in the rate of neonatal death due to any cause (RR 0.83, 95% CI 0.06 to 11.70; on average, 83 infants per 1000 population with benzathine penicillin versus 100 per 1000 population with no intervention), but there was a possible difference with penicillin on the proportion of neonates with clinical manifestations of congenital syphilis during follow-up (RR 0.12, 95% CI 0.01 to 2.09; on average, 36 infants per 1000 population with benzathine penicillin versus 300 per 1000 population with no intervention) but the results were imprecise because the trial was stopped early because there were four cases with clinical congenital syphilis in the no treatment group and none in the treatment group. Benzathine penicillin administration increased the serological cure at three months of age (RR 2.13, 95% CI 1.06 to 4.27; on average, 947 infants per 1000 population with benzathine penicillin versus 444 infants per 1000 population with no intervention). These results should be taken with caution, because were mainly driven by one trial. This study did not report neonatal death due to congenital syphilis or the frequency of serious or minor adverse events after therapy. We downgraded the quality of evidence because of imprecision and risk of bias.

One trial (169 participants) compared benzathine penicillin versus procaine benzylpenicillin (Paryani 1994). High- and moderate-quality evidence suggested that there were probably no differences between benzathine penicillin and procaine benzylpenicillin for absence of clinical manifestations of congenital syphilis during follow-up (RR 1.00, 95% CI 0.97 to 1.03; on average, 1000 infants per 1000 population with benzathine penicillin versus 1000 infants per 1000 population with procaine benzylpenicillin) and serological cure (RR 1.00, 95% CI 0.97 to 1.03; on average, 1000 infants per 1000 population with benzathine penicillin versus 1000 infants per 1000 population with procaine benzylpenicillin). There were no cases of neonatal death due congenital syphilis; all 152 babies who were followed up survived. This study did not report on neonatal death rate due to any cause, or frequency of serious or minor adverse events after therapy. We downgraded the quality of evidence because of serious risk of bias.

Overall completeness and applicability of evidence

Although we conducted comprehensive searches to retrieve all published and unpublished RCTs, this systematic review only identified two trials. Evidence from RCTs suggested that, compared with no intervention, benzathine penicillin administration may have increased serological cure at three months of age (on average, 947 infants per 1000 population with benzathine penicillin versus 444 infants per 1000 population with no intervention). These findings support the current practice, regarding the treatment of babies born with confirmed, highly probable or possible congenital syphilis established over many years of clinical experience. The lack of apparent effect of penicillin for reduction on the frequency of neonates with clinical manifestations of congenital syphilis during follow-up could be the consequence of low precision results rather than the absence of effect. We were unable to evaluate the primary outcomes: serious adverse events and the secondary outcome of minor adverse events after therapy as neither trial reported these outcomes.

It is surprising that so few RCTs have been carried out concerned with the treatment of congenital syphilis and no trials including antibiotics other than different formulations of penicillin. Despite limitations of the completeness of evidence, the results of this systematic review have broad applicability. The review's conclusions can be extrapolated to infants born to mothers diagnosed with gestational syphilis during their antenatal care and who did not receive treatment or whose treatment was inadequate, resulting in the birth of an asymptomatic infant with confirmed, highly probable or possible congenital syphilis. Finally, because the included studies only assessed the effectiveness of the intervention (penicillin), the wider safety of the penicillin therapy and that of any alternative antibiotic, continue to be issues requiring research.

Quality of the evidence

We used the GRADE approach to assess the quality of the evidence and produce 'Summary of findings' tables (Higgins 2011). We attempted to clarify details related to design and execution of the two identified trials by contacting the authors of the papers. However in both cases, the authors were unable to provide additional information. Consequently, the included studies showed flaws related to risk of bias (unclear for selection and reporting bias and high risk for attrition or other potential sources of bias), while for one of the trials, the reviewed evidence showed additional, serious precision limitations (outcome events with wide CIs and some regarding limited numbers included in the trial) (Radcliffe 1997). We could not evaluate publication bias because there were too few included trials for comparisons. The results of the comparison antibiotic treatment versus non-intervention should be viewed with caution, as they were based on one small study with low-quality evidence (see Summary of findings for the main comparison; Summary of findings 2).

Potential biases in the review process

This systematic review has several weaknesses: the limited number of studies undertaken and small numbers involved; both identified RCTs had limitations regarding possible bias. However, the review adhered to a predefined protocol; the search strategy for this review was extensive and included extended methods to identify eligible studies; all review authors independently assessed trials for inclusion, extracted data and assessed the risk of bias in the included studies; we described the included and excluded studies in sufficient detail, providing an explanation for excluded studies and finally, all authors declared no potential conflict of interest.

One of the problems in identifying potentially eligible studies is that they are likely to have been conducted in low- and middle-income countries, where congenital syphilis is more common. If such studies are published in journals that are not easy to access, or are unpublished, they may not have been identified by our search strategy. In this sense, we have some concerns about publication bias and related small-study effects. Due to the low quality of evidence for some outcomes, we have uncertainty for some conclusions of this systematic review. We would welcome information about any potentially eligible studies for this review (please send information to godfrey.walker64@alumni.imperial.ac.uk).

Agreements and disagreements with other studies or reviews

To the best of our knowledge, there are no previous systematic reviews published on this topic. The results of this systematic review showed that compared with no intervention, treatment with benzathine penicillin increased neonatal serological cure at three months of age. This review also found no differences between benzathine penicillin and procaine benzylpenicillin for the treatment of infants with possible or highly probable congenital syphilis. Penicillin for the treatment of congenital syphilis was established shortly after it became available in the 1940s and is based on early case series of its success (Barker 1948, Enkvist 1948, Goodwin 1950, Platou 1945, Platou 1946, Platou 1947, Platou 1949, Rose 1949). The findings of this review support the recommendations from guideline development groups (CDC 2015; WHO 2016), who proposed these therapeutic alternatives for the treatment of babies with asymptomatic congenital syphilis.

AUTHORS' CONCLUSIONS

Implications for practice

At present, althougth the evidence from randomised controlled trials (RCTs) on the effectiveness and safety of antibiotic treatment for newborns with confirmed, highly probable or possible congenital syphilis is sparse, and was qualified as low-quality evidence. Pencillin administration suggests there is possibly effect into reduction of the proportion of neonates with clinical manifestations of congenital syphilis and increasing the serological cure at the third month. These results support the current clinical practice of treating with penicillin those newborns diagnosed with confirmed, highly probable or possible congenital syphilis. High- and moderate-quality evidence, suggests that there are probably no differences between benzathine penicillin and procaine benzylpenicillin treatment for the outcomes of absence of clinical manifestations of congenital syphilis or serological cure. The findings of this review support the recommendations from guideline development groups, which propose these therapeutic alternatives for the treatment of babies born with confirmed, highly probable or possible congenital syphilis (CDC 2015; WHO 2016).

Implications for research

Althougth evidence about the effectivennes of penicillin against no treatment because were mainly driven by one trial, it would be very difficult to make another clinical tral comaring those alternatives because ethical concerns. Studies are needed to evaluate treatment failure cases with currently recommended regimens and this should include an assessment of the role of HIV infection in cases of congenital syphilis treatment failure. Uncertainty remains regarding serious adverse effects of treatment and these should be documented in future studies. There are few data on the use of antibiotics other than penicillin such as ceftriaxone for treatment of infants with confirmed or highly probable congenital syphilis and research is needed in comparing other antibiotics to procaine benzylpenicillin and benzathine penicillin.

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REFERENCES

References to studies included in this review

Paryani 1994 ***{published data only (unpublished sought but not used)}***
Paryani SG, Vaughn AJ, Crosby M, Lawrence S. Treatment of asymptomatic congenital syphilis: benzathine versus procaine penicillin G therapy. *Journal of Pediatrics* 1994; **125**(3):471–5.

Radcliffe 1997 ***{published data only (unpublished sought but not used)}***
Radcliffe M, Meyer M, Roditi D, Malan A. Single-dose benzathine penicillin in infants at risk of congenital syphilis - results of a randomised study. *South African Medical Journal* 1997;**87**(1):62–5.

References to studies excluded from this review

Venter 1986 ***{published data only (unpublished sought but not used)}***
Venter A, Pettifor JM, Duursma J, Pudifin DJ, Smyth A, Becker PJ. Liver function in early congenital syphilis: does penicillin cause a deterioration?. *Journal of Pediatric Gastroenterology and Nutrition* 1991;**12**(3):310–4.
Venter A, Pettifor JM, Ninin DT, Pudifin DJ, Duursma J. Steroid therapy - does it have a role to play in the treatment of congenital syphilis?. Proceedings of the Seventh Conference on the Priorities in Perinatal Care in South Africa, Ceres, , Cape Province. March 8–11, 1988:70–73.

Additional references

AGUM and MSSVD 2002
Association for Genitourinary Medicine (AGUM), Medical Society for the Study of Venereal Disease (MSSVD). *2002 National Guidelines on the Management of Early Syphilis*. London: Association for Genitourinary Medicine (AGUM), Medical Society for the Study of Venereal Disease (MSSVD), 2002.

Arnold 2000
Arnold SR, Ford-Jones EL. Congenital syphilis: a guide to diagnosis and management. *Paediatrics & Child Health* 2000;**5**(8):463–9.

Barker 1948
Barker LP. An evaluation of the penicillin treatment in early congenital syphilis. *The Journal of Pediatrics* 1948;**32**(5): 516–521.

Basu 2013
Basu S, Kumar A. Case report. varied presentations of early congenital syphilis. *Journal of Tropical Pediatrics* 2013;**59** (3):246–9.

Bateman 1997
Bateman DA, Phibbs CS, Joyce T, Heagarty MC. The hospital cost of congenital syphilis. *Journal of Pediatrics* 1997;**130**(5):752–8.

Beck-Sague 1987
Beck-Sague C, Alexander ER. Failure of benzathine penicillin G treatment in early congenital syphilis. *Pediatric Infectious Disease Journal* 1987;**6**:1061–4.

Beltrami 2006
Beltrami J, Berman S. Congenital syphilis: a persisting sentinel public health event. *Sexually Transmitted Diseases* 2006;**33**(11):675–6.

Blencowe 2011
Blencowe H, Cousens S, Kamb M, Berman S, Lawn JE. Lives Saved Tool supplement detection and treatment of syphilis in pregnancy to reduce syphilis related stillbirths and neonatal mortality. *BMC Public Health* 2011;**11**(Suppl 3):S9.

CDC 2015
Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2015. *MMWR. Morbidity and Mortality Weekly Report* 2015;**64** (3):1–140.

Chakraborty 2008
Chakraborty R, Luck S. Syphilis is on the increase: the implications for child health. *Archives of Disease in Childhood* 2008;**93**(2):105–9.

Cifuentes-Cifuentes 2013
Cifuentes-Cifuentes MY, Ojeda-Enríquez CV. The congenital syphilis protocol used at the Instituto Materno Infantil-Hospital la Victoria, Bogotá [Sífilis congénita en el Instituto Materno Infantil–Hospital la Victoria, Bogotá]. *Revista de Saude Publica* 2013;**15**(3):434–45.

Conover 1998
Conover CS, Rend CA, Miller GB Jr, Schmid GP. Congenital syphilis after treatment of maternal syphilis with a penicillin regimen exceeding CDC guidelines. *Infectious Diseases in Obstetrics and Gynecology* 1998;**6**(3):134–7.

Conway 2007
Conway JH. Recognizing and reducing the global burden of congenital syphilis: the time is now. *Sexually Transmitted Diseases* 2007;**34**(7 Suppl):S2–4.

Cruz 2013
Cruz AR, Castrillon MA, Minotta AY, Rubiano LC, Castano MC, Salazar JC. Gestational and congenital syphilis epidemic in the Colombian Pacific Coast. *Sexually Transmitted Diseases* 2013;**40**(10):813–9.

Desperthes 2004
Desperthes BD, Meheus A, O'Reilly K, Broutet N. Maternal and congenital syphilis programmes: case studies in Bolivia, Kenya and South Africa. *Bulletin of the World Health Organization* 2004;**82**(6):410–6.

Doroshenko 2006
Doroshenko A, Sherrard J, Pollard AJ. Syphilis in pregnancy and the neonatal period. *International Journal of STD & AIDS* 2006;**17**(4):221–7.

Enkvist 1948
Enkvist O. Penicillin combined with other treatment in congenital syphilis. *Acta Dermato-Venereologica* 1948;**28**(2): 104–115.

Finelli 1998
Finelli L, Crayne EM, Spitalny KC. Treatment of infants with reactive syphilis serology, New Jersey: 1992 to 1996. *Pediatrics* 1998;**102**(2):e27.

Follett 2011
Follett T, Clarke DF. Resurgence of congenital syphilis: diagnosis and treatment. *Neonatal Network* 2011;**30**(5): 320–8.

French 2009
French P, Gomberg M, Janier M, Schmidt B, van Voorst Vader P, Young H. IUSTI: 2008 European guidelines on the management of syphilis. *International Journal of STD & AIDS* 2009;**20**(5):300–9.

Gichangi 2004
Gichangi P, Renterghem LV, Karanja J, Bwayo J, Kiragu D, Temmerman M. Congenital syphilis in a Nairobi hospital. *East African Medical Journal* 2004;**81**(11):589–93.

Gloyd 2001
Gloyd S, Chai S, Mercer MA. Antenatal syphilis in sub-Saharan Africa: missed opportunities for mortality reduction. *Health Policy and Planning* 2001;**16**(1):29–34.

Gomez 2013
Gomez GB, Kamb ML, Newman LM, Mark J, Broutet N, Hawkes SJ. Untreated maternal syphilis and adverse outcomes of pregnancy: a systematic review and meta-analysis. *Bulletin of the World Health Organization* 2013;**91**: 217–26.

Goode 2013
Goode L. Blogmaster. Are point-of-care tests the answer to meeting WHO target for congenital syphilis? 2013 March. blogs.bmj.com/sti/2013/04/03/are-point-of-care-tests-the-answer-to-meeting-who-target-for-congenital-syphilis/ (accessed prior to 18 November 2018).

Goodwin 1950
Goodwin MS. Status of Treatment of Syphilitic Pregnant Women and of Children who have Congenital Syphilis. *Journal of Venereal Disease Information* 1950;**31**(7):178–84.

GRADEpro GDT 2015 [Computer program]
GRADE Working Group, McMaster University. GRADEpro GDT. Version accessed 26 March 2018. Hamilton (ON): GRADE Working Group, McMaster University, 2015. Available at gradepro.org.

Harbord 2006
Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analysis of controlled trials with binary endpoints. *Statistics in Medicine* 2006;**25**(20):3443–57.

Hawkes 2009
Hawkes S. Eliminating congenital syphilis - if not now then when?. *Sexually Transmitted Diseases* 2009;**36**(11):721–3.

Herremans 2010
Herremans T, Kortbeek L, Notermans DW. A review of diagnostic tests for congenital syphilis in newborns. *European Journal of Clinical Microbiology & Infectious Diseases* 2010;**29**:495–501.

Higgins 2011
Higgins JPT, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011)*. Chichester (UK): John Wiley & Sons, 2011.

Hong 2010
Hong FC, Liu JB, Feng TJ, Liu XL, Pan P, Zhou H, et al. Congenital syphilis: an economic evaluation of a prevention program in China. *Sexually Transmitted Diseases* 2010;**37** (1):26–31.

Idsoe 1972
Idsoe O, Guthe T, Willcox RR. Penicillin in the treatment of syphilis: the experience of three decades. *Bulletin of the World Health Organization* 1972;**47**(Suppl):S1–S68.

Ikeda 1990
Ikeda MK, Jenson HB. Evaluation and treatment of congenital syphilis. *Journal of Pediatrics* 1990;**117**:843–52.

Introcaso 2013
Introcaso CE, Bradley H, Gruber D, Markowitz LE. Missed opportunities for preventing congenital syphilis infection. *Sexually Transmitted Diseases* 2013;**40**(5):431.

Jafari 2013
Jafari Y, Peeling RW, Shivkumar S, Claessens C, Joseph L, Pai MP. Are Treponema pallidum specific rapid and point-of-care tests for syphilis accurate enough for screening in resource limited settings? Evidence from a meta-analysis. *PloS One* 2013;**8**(2):e54695.

Katz 2008
Katz KA, Klausner JD. Azithromycin resistance in *Treponema pallidum*. *Current Opinion in Infectious Diseases* 2008;**21**:83–91.

Kingston 2008
Kingston M, French P, Goh B, Goold P, Higgins S, Sukthankar A, et al. Syphilis Guidelines Revision Group 2008, Clinical Effectiveness Group. UK national guidelines on the management of syphilis 2008. *International Journal of STD & AIDS* 2008;**19**(11):729–40.

Kuznik 2013
Kuznik A, Lamorde M, Nyabigambo A, Manabe YC. Antenatal syphilis screening using point-of-care testing in sub-Saharan African countries: a cost-effectiveness analysis. *PLoS Medicine* 2013;**10**(11):e1001545. DOI: 10.1371/journal.pmed.1001545

Lago 2013
Lago EG, Vaccari A, Fiori RM. Clinical features and follow-up of congenital syphilis. *Sexually Transmitted Diseases* 2013;**40**(2):85–94.

Liu 2010
Liu JB, Hong FC, Pan P, Zhou H, Yang F, Cai YM, et al. A risk model for congenital syphilis in infants born to mothers with syphilis treated in gestation: a prospective cohort study. *Sexually Transmitted Infections* 2010;**86**(4):292–6.

Lomotey 2009
Lomotey CJ, Lewis J, Gebrian B, Bourdeau R, Dieckhaus K, Salazar JC. Maternal and congenital syphilis in rural

Haiti. *Revista Panamericana de Salud Publica [Pan American Journal of Public Health]* 2009;**26**(3):197–202.

Mabey 2011
Mabey D, Peeling RW. Syphilis, still a major cause of infant mortality. *Lancet Infectious Diseases* 2011;**11**(9):684–91.

Mabey 2012
Mabey DC, Sollis KA, Kelly HA, Benzaken AS, Bitarakwate E, Changalucha J, et al. Point-of-care tests to strengthen health systems and save newborn lives: the case of syphilis. *PLoS Medicine* 2012;**9**(6):e1001233. DOI: 10.1371/journal.pmed.1001233

McCracken 1974
McCracken GH, Kaplan JM. Penicillin treatment for congenital syphilis: a critical appraisal. *Journal of the American Medical Association* 1974;**228**:855–8.

McFarlin 1994
McFarlin BL, Bottoms SF, Dock BS, Isada NB. Epidemic syphilis: maternal factors associated with congenital infection. *American Journal of Obstetrics and Gynecology* 1994;**150**(2):535–40.

Monif 1994
Monif GR. Is current therapy for maternal syphilis inadequate for established fetal infection?. *American Journal of Obstetrics and Gynecology* 1994;**170**(2):705.

Munkhuu 2009
Munkhuu B, Liabsuetrakul T, Chongsuvivatwong V, McNeil E, Janchiv R. One-stop service for antenatal syphilis screening and prevention of congenital syphilis in Ulaanbaatar, Mongolia: a cluster randomized trial. *Sexually Transmitted Diseases* 2009;**36**(11):714–20.

Murali 2012
Murali MA, Nirmala C, Rao JV. Symptomatic early congenital syphilis: a common but forgotten disease. *Case Reports in Pediatrics* 2012;**2012**:934634.

Murray 2012
Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;**380**:2197–223.

Newman 2013
Newman L, Kamb M, Hawkes S, Gomez G, Say L, Seuc A. Global estimates of syphilis in pregnancy and associated adverse outcomes: analysis of multinational antenatal surveillance data. *PLoS Medicine* 2013;**10**(2):1–9.

Owusu-Edusei 2013
Owusu-Edusei KJ, Introcaso CE, Chesson HW. Hospitalization cost of congenital syphilis diagnosis from insurance claims data in the United States. *Sexually Transmitted Diseases* 2013;**40**(3):226–9.

Peeling 2004
Peeling RW, Mabey D, Fitzgerald DW, Watson-Jones D. Avoiding HIV and dying of syphilis. *Lancet* 2004;**364**: 1561–3.

Peeling 2012
Peeling R, Mabey D, Ballard RC. Introducing new diagnostics into STI control programmes: the importance of programme science. *Sexually Transmitted Infections* 2012; **89**(2):115–9. DOI: 10.1136/sextrans-2012-050617

Peeling 2013
Peeling R. Breaking the silence on syphilis, 2013. www.trust.org/item/20130228145900-1dik0/?source=search (accessed prior to 19 November 2018).

Platou 1945
Platou RV, Hill AJ, Ingraham NR, Goodwin MS, Wilkinson EE, Hansen AE. Penicillin in the treatment of infantile congenital syphilis. A brief preliminary note. *JAMA* 1945; **127**(10):582.

Platou 1946
Platou RV, Hill AI, Ingraham NR, Goodwin MS, Wilkinson EE, Hansen AE. Effect of penicillin in the treatment of infantile congenital syphilis, Further observations. *The American Journal of Diseases of Children* 1946;**72**(6): 635–648.

Platou 1947
Platou RV, Hill AJ, Ingraham NR, Goodwin MS, Wilkinson EE, Hansen AE, Heyman A. Early congenital syphilis treatment of two hundred and fifty-two patients with penicillin.. *JAMA* 1947;**133**(1):10–16.

Platou 1949
Platou RV. Treatment of congenital syphilis with penicillin. *Advances in Pediatrics 4 (1949): 39-86.* 1949;**4**:39–86.

Rawstron 1991
Rawstron SA, Bromberg K. Failure of recommended maternal therapy to prevent congenital syphilis. *Sexually Transmitted Diseases* 1991;**18**:102–6.

Review Manager 2014 [Computer program]
Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Richardson 2002
Richardson MP, Palfreeman A, Nielsen PB, Fenton KA. Congenital syphilis following negative antenatal screening. *Communicable Disease and Public Health / PHLS* 2002;**5**: 72–3.

Richens 2008
Richens J, Mabey CW. Sexually transmitted infections (excluding HIV). In: Cook G, Zumla A editor(s). *Manson's Tropical Diseases*. 22nd Edition. London: Saunders Elsevier, 2008.

Rodrigues 2008
Rodrigues CS, Guimarães MD, César CC. Missed opportunities for congenital syphilis and HIV perinatal transmission prevention. *Revista de Saude Publica* 2008;**42** (6):851–8.

Romero 2017
Romero L, Huerfano C, Grillo-Ardila CF. Macrolides for treatment of Haemophilus ducreyi infection in sexually

active adults. *Cochrane Database of Systematic Reviews* 2017, Issue 12. DOI: 10.1002/14651858.CD012492.pub2

Rose 1949
Rose EK, Gyorgy P, Ingraham NR. Treattment of infantile congenital syphilis. Results with aqueous penicillin alone in sixty Infants followed for an average of two years after treatment. *The American Journal of Diseases of Children* 1949;**77**(6):729–735.

Rougas 2012
Rougas S. From the archives: why is syphilis still sensitive to penicillin? 2012. www.clinicalcorrelations.org/?p=5134 (accessed prior to 19 November 2018).

Rydzak 2008
Rydzak CE, Goldie SJ. Cost-effectiveness of rapid point-of-care prenatal syphilis screening in sub-Saharan Africa. *Sexually Transmitted Diseases* 2008;**35**(9):775–84.

Saloojee 2004
Saloojee H, Velaphi S, Goga Y, Afadapa N, Steen R, Lincetto O. The prevention and management of congenital syphilis: an overview and recommendations. *Bulletin of the World Health Organization* 2004;**82**(6):424–30.

Schackman 2007
Schackman BR, Neukermans CP, Fontain SN, Nolte C, Joseph P, Pape JW, et al. Cost-effectiveness of rapid syphilis screening in prenatal HIV testing programs in Haiti. *PLoS Medicine* 2007;**4**(5):937–47.

Shafii 2008
Shafii T, Radolf JD, Sanchez PJ, Schulz KF, Murphy FK. Congenital syphilis. In: Holmes KK, Sparling PF, Stamm WE, Piot P, Wasserheit JN, Corey L, et al. editor(s). *Sexually Transmitted Diseases*. 4th Edition. New York (NY): McGraw Hill Medical, 2008.

Singh 2013
Singh AE, Guenette T, Gratrix J, Bergman J, Parker P, Anderson B, et al. Seroreversion of treponemal tests in infants meeting Canadian surveillance criteria for confirmed early congenital syphilis. *Pediatric Infectious Disease Journal* 2013;**32**(3):199–202.

Sparling 2008
Sparling PF, Swartz MN, Musher DM, Healy BP. Clinical manifestations of syphilis. In: Holmes KK, Sparling PF, Stamm WE, Piot P, Wasserheit JN, Corey L, et al. editor(s). *Sexually Transmitted Diseases*. 4th Edition. New York (NY): McGraw Hill Medical, 2008.

Speer 1977
Speer ME, Taber LH, Clark DB, Rudolph AJ. Cerebrospinal fluid levels of benzathine penicillin G in the neonate. *Journal of Pediatrics* 1977;**91**(6):996–7.

Stamm 2015
Stamm LV. Syphilis: antibiotic treatment and resistance. *Epidemiology and Infection* 2015;**143**:1567–74.

Stoll 1994
Stoll BJ. Congenital syphilis: evaluation and management of neonates born to mothers with reactive serologic tests for syphilis. *Pediatric Infectious Disease Journal* 1994;**13**: 845–53.

Sweeney 2014
Sweeney S, Mosha JF, Terris-Prestholt F, Sollis KA, Kelly H, Changalucha J, Peeling RW. The costs of accessible quality assured syphilis diagnostics: informing quality systems for rapid syphilis tests in a Tanzanian setting. *Health Policy and Planning* 2014;**29**(5):633–41. DOI: 10.1093/heapol/czt049

Taylor 2017a
Taylor M, Alonso-González, M, Gomez B, Korenromp E, Broutet N. World Health Organization global health sector strategy on sexually transmitted infections: an evidence-to-action summary for Colombia [Estrategia global de la Organización Mundial de la Salud contra infecciones de transmisión sexual: de la evidencia a la acción]. *Revista Colombiana de Obstetricia y Ginecologia* 2017;**68**(3): 193–201.

Taylor 2017b
Taylor MM, Kam M, Wu D, Hawkes S. Syphilis screening and treatment: integration with HIV services. *Bulletin of the World Health Organization* 2017;**95**:610–610A.

Terris-Prestholt 2003
Terris-Prestholt F, Watson-Jones D, Mugeye K, Kumaranayake L, Ndeki L, Weiss H, et al. Is antenatal syphilis screening still cost effective in sub-Saharan Africa?. *Sexually Transmitted Infections* 2003;**79**(5):375–8.

Thomas 1949
Thomas EW. Rapid treatment of syphilis with penicillin. II Penicillin in prenatal and infantile syphilis. *Bulletin of the World Health Organization* 1949;**2**:249–55.

Tucker 2010a
Tucker JD, Bu J, Brown LB, Yin Y-P, Chen X-S, Cohen MS. Accelerating worldwide syphilis screening through rapid testing: a systematic review. *Lancet Infectious Diseases* 2010;**10**:381–6.

Tucker 2010b
Tucker JD, Chen XS, Peeling RW. Syphilis and social upheaval in China. *New England Journal of Medicine* 2010; **362**(18):1658–61.

Tucker 2013
Tucker JD, Bien CH, Peeling RW. Point-of-care testing for sexually transmitted infections: recent advances and implications for disease control. *Current Opinion in Infectious Diseases* 2013;**26**(1):73–9.

Walker 2002
Walker DG, Walker GJA. Forgotten but not gone: the continuing scourge of congenital syphilis. *Lancet Infectious Diseases* 2002;**2**:432–6.

Walker 2007
Walker GJ, Walker DG. Congenital syphilis: a continuing but neglected problem. *Seminars in Fetal & Neonatal Medicine* 2007;**12**(3):198–206.

Wendel 2002
Wendel GDJ, Sheffield JS, Hollier LM, Hill JB, Ramsey PS, Sanchez PJ. Treatment of syphilis in pregnancy and

prevention of congenital syphilis. *Clinical Infectious Diseases* 2002;**35**(Suppl 2):S200–9.

WHO 2007
World Health Organization. *The Global Elimination of Congenital Syphilis: Rationale and Strategy for Action*. Geneva: WHO, 2007.

WHO 2012
World Health Organization. *Investment case for eliminating mother-to-child transmission of syphilis: promoting better maternal and child health and stronger health systems*. Geneva: Initiative for the Global Elimination of Congenital Syphilis, CDC, WHO and UCL, 2012.

WHO 2016
World Health Organization. *WHO guidelines for the treatment of Treponema pallidum (syphilis)*. Geneva: WHO, 2016.

WHO Euro 2003
World Health Organization. *Review of current evidence and comparison of guidelines for effective syphilis treatment in Europe*. Copenhagen: WHO Euro, 2003.

WHO, UNAIDS, UNICEF 2012
World Health Organization, United Nations Programme on HIV/AIDS, UNICEF. *Global HIV/AIDS Response - Epidemic Update and Health Sector Progress towards Universal Access - Progress Report 2011*. Geneva: WHO, 2012.

Winscott 2009
Winscott M, Taylor MM, Kenney K. Identifying unreported and undiagnosed cases of congenital syphilis in Arizona. Using live birth and fetal death registries. *Sexually Transmitted Diseases* 2009;**37.**(4):244–7.

Wiwanitkit 2010
Wiwanitkit V. Maternal and congenital syphilis in Haiti: a big problem. *Revista Panamericana de Salud Publica [Pan American Journal of Public Health]* 2010;**27**(6):471.

Woods 2009
Woods CR. Congenital syphilis? Persisting pestilence. *Pediatric Infectious Disease Journal* 2009;**28**(6):536–7.

Wright 2013
Wright DJM. Congenital neurosyphilis. *Lancet Infectious Diseases* 2013;**13**:475.

Zenker 1990
Zenker PN, Rolfs RT. Treatment of syphilis, 1989. *Reviews of Infectious Diseases* 1990;**12 Suppl 6**:S590–609.

Zenker 1991
Zenker PN, Berman SM. Congenital syphilis: trends and recommendations for evaluation and management. *Pediatric Infectious Disease Journal* 1991;**10**:516–22.

References to other published versions of this review

Walker 2016
Walker GJA, Walker D, Molano Franco D. Antibiotics for congenital syphilis. *Cochrane Database of Systematic Reviews* 2016, Issue 2. DOI: 10.1002/14651858.CD012071

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Paryani 1994

Methods	**Setting:** University of Florida Health Science Center, Jacksonville, FL, USA, June 1989 to July 1991 **Trial design:** randomised clinical trial, 2 parallel arms **Funding sources:** supported in part by the Dean's Research fund, University of Florida, Health Science Center, Jacksonville, FL **Ethical issues:** whether ethical permission obtained not mentioned. Informed consent of mothers obtained
Participants	**Inclusion criteria:** neonate born to a mother with positive RPR and MHA-TP results at time of delivery; no or inadequate treatment of syphilis in the mother; no systemic antibiotics given to the infant before enrolment or during the treatment for syphilis, and no signs of congenital syphilis on physical examination, cerebrospinal fluid cell count or VDRL test, x-ray study of long bones, platelet count or liver function tests **Exclusion criteria:** cerebrospinal fluid was not obtained for the VDRL test and cell count **Population, number of participants:** 169; 92 in benzathine group, 77 in procaine benzylpenicillin group **Baseline characteristics:** babies in the 2 groups (benzpen vs procpen) compared with regard to: mothers with no antenatal care: benzpen 10/84 vs procpen 16/64; those with HIV-infected mother: benzpen 2/84 vs procpen 2/68; cocaine use in mother: benzpen 28/84 vs procpen 24/68; positive FTA-IgM test result in infant: benzpen 2/84 vs procpen 1/68. Mean and median RPR titres for infants at birth and mother at delivery were similar as also were maternal treatment for syphilis, before during pregnancy and during pregnancy at < 20 weeks, 20-36 weeks and < 4 weeks before delivery
Interventions	**Total number of intervention groups:** 2 **Intervention and comparison:** either benzathine penicillin G suspension 50,000 units/kg once intramuscularly or procaine benzylpenicillin G suspension 50,000 units/kg daily intramuscularly for 10 days
Outcomes	Follow-up visits were scheduled at 2-3 months, 5-6 months and 12 months of age. At follow-up examinations, the infants underwent a complete physical examination, a Denver Development Screening Test and a determination of RPR titre. If the infant repeatedly was not brought to follow-up appointments, the assigned research nurse practitioner did home for performance of the evaluations described above. Treatment failure defined as the presence of any of the following: clinical manifestations of congenital syphilis, < 4-fold decrease in RPR titre 3 months after treatment and reactive RPR finding 1 year after treatment
Notes	Trial authors provided us with limited additional information

Risk of bias

Bias	Authors' judgement	Support for judgement

Paryani 1994 (*Continued*)

Random sequence generation (selection bias)	Low risk	Quote: "Randomization list obtained with a computer generated system." Comment: this was probably done.
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information to enable judgement.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Absence of clinical manifestations of congenital syphilis and serological cure were objectively assessed and lack of blinding could have not affected results
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding or incomplete blinding, and the outcome or outcome measurement was unlikely to be influenced by a lack of blinding. Absence of clinical manifestations of congenital syphilis and serological cure were objectively assessed and lack of blinding could not have affected results
Incomplete outcome data (attrition bias) All outcomes	High risk	Risk of bias was high according to the level of missing data (> 20%) for the outcome clinical cure
Selective reporting (reporting bias)	Unclear risk	Comment: insufficient information to enable judgement.
Other bias	Low risk	Trial supported by grants from a research committee. Trial appeared free from other sources of bias

Radcliffe 1997

Methods	**Setting:** Peninsular Maternal and Neonatal Service in the Western Cape, Cape Town, South Africa. When carried out not stated but clearly before 1997 **Trial design:** randomised clinical trial, 2 parallel arms **Funding sources:** not mentioned **Ethical issues:** permission obtained from the Ethics and Research Committee of the University of Cape Town and informed consent was obtained from the mothers
Participants	**Inclusion criteria:** asymptomatic infants at high risk of congenital syphilis. This included babies born to mothers with untreated syphilis, i.e. positive VDRL and TPHA tests, with a VDRL titre $\geq$ 32. Infants were regarded as asymptomatic at birth if: there were no clinical signs of congenital syphilis; x-rays of long bones were normal and rheumatoid factor latex test was negative at birth. Mothers were interviewed soon after birth. Only infants who could be followed up were included in the study, which commenced within 72 hours of birth **Exclusion criteria:** infants could not be followed up.

Radcliffe 1997 (*Continued*)

	Population, number of participants: 22; 10 in no treatment group, 12 in treatment group **Baseline characteristics:** authors stated no statistically differences between groups with regard to birthweight (combined mean 2941 g), gestational age (combined 39.8 weeks) , maternal VDRL titre at delivery (median 128 in both groups) and infant VDRL titre at birth (median 8 in both groups)
Interventions	**Total number of intervention groups:** 1 **Comparisons:** single-dose injection of benzathine penicillin 50,000 units/kg compared with no treatment
Outcomes	Diagnosis of congenital syphilis was based on 4-fold rise in VDRL titre (and positive TPHA) during follow-up or a persistently positive VDRL and TPHA after 6 months. Participants with a positive Western blot for IgM antibody to pallidum were regarded as having congenital syphilis. In addition a diagnosis of congenital syphilis was made by means of a clinical assessment and serological testing (VDRL and IgM Western blotting) at birth and follow-up
Notes	Additional information was requested independently from 2 of the trial authors. A reply was received from 1 of them saying he could not add any further information to that contained in the paper. It was published in 1997

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Infants were randomised to receive either no treatment or a single injection." Comment: insufficient information to enable judgement.
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information to enable judgement.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Neonatal death rate due any cause, absence of clinical manifestations of congenital syphilis and serological cure were objectively assessed and lack of blinding could have not affected results
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding or incomplete blinding, and the outcome or outcome measurement was unlikely to be influenced by a lack of blinding. Neonatal death rate due any cause, absence of clinical manifestations of congenital syphilis and serological cure were objectively assessed and lack of blinding could not have affected results

Radcliffe 1997 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	≤ 20% participants excluded and intention-to-treat analyses were reported
Selective reporting (reporting bias)	Unclear risk	Comment: insufficient information to enable judgement.
Other bias	High risk	Stopped early rule due to apparent benefit.

benzpen: benzathine penicillin: FTA-IgM: fluorescent treponemal antibody immunoglobulin M; IgM: immunoglobulin M; MHA-TP: microhaemagglutination assay for *T pallidum* antibodies; procpen: procaine penicillin; RPR: rapid plasma reagin; TPHA: *Treponema pallidum* haemagglutination; VDRL: Venereal Disease Research Laboratory.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Venter 1986	This trial was designed with the objective to determine if penicillin therapy caused a deterioration in liver function. Infants were randomly assigned into two groups: penicillin therapy only and penicillin plus prednisone as an adjunct. We excluded this trial because it did not compare the use of antibiotic treatment with no intervention or any other antibiotic treatment

DATA AND ANALYSES

Comparison 1. Antibiotic treatment compared to no intervention for congenital syphilis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Neonatal death rate due to any cause	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Absence of clinical manifestations of congenital syphilis during follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Serological cure (≥ 4-fold decrease or greater in non-treponemal tests titre)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 2. Any antibiotic treatment (benzathine penicillin) compared to any other antibiotic (procaine benzylpenicillin) for congenital syphilis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Absence of clinical manifestations of congenital syphilis during follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Serological cure (≥ 4-fold decrease or greater in non-treponemal tests titre)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

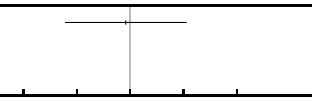
Analysis 1.1. Comparison 1 Antibiotic treatment compared to no intervention for congenital syphilis, Outcome 1 Neonatal death rate due to any cause.

Review: Antibiotic treatment for newborns with congenital syphilis

Comparison: 1 Antibiotic treatment compared to no intervention for congenital syphilis

Outcome: 1 Neonatal death rate due to any cause

Study or subgroup	Antibiotic treatment n/N	No intervention n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Radcliffe 1997	1/12	1/10		0.83 [0.06, 11.70]



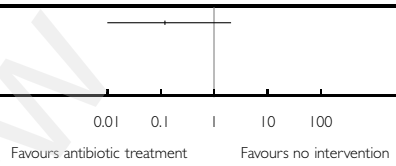
Analysis 1.2. Comparison 1 Antibiotic treatment compared to no intervention for congenital syphilis, Outcome 2 Absence of clinical manifestations of congenital syphilis during follow-up.

Review: Antibiotic treatment for newborns with congenital syphilis

Comparison: 1 Antibiotic treatment compared to no intervention for congenital syphilis

Outcome: 2 Absence of clinical manifestations of congenital syphilis during follow-up

Study or subgroup	Antibiotic treatment n/N	No intervention n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Radcliffe 1997	0/12	3/10		0.12 [0.01, 2.09]



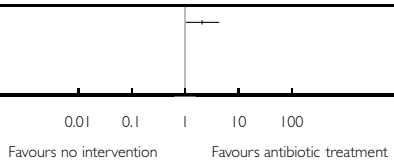
Analysis 1.3. Comparison 1 Antibiotic treatment compared to no intervention for congenital syphilis, Outcome 3 Serological cure (≥ 4-fold decrease or greater in non-treponemal tests titre).

Review: Antibiotic treatment for newborns with congenital syphilis

Comparison: 1 Antibiotic treatment compared to no intervention for congenital syphilis

Outcome: 3 Serological cure (≥ 4-fold decrease or greater in non-treponemal tests titre)

Study or subgroup	Antibiotic treatment n/N	No intervention n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Radcliffe 1997	11/11	4/9		2.13 [1.06, 4.27]

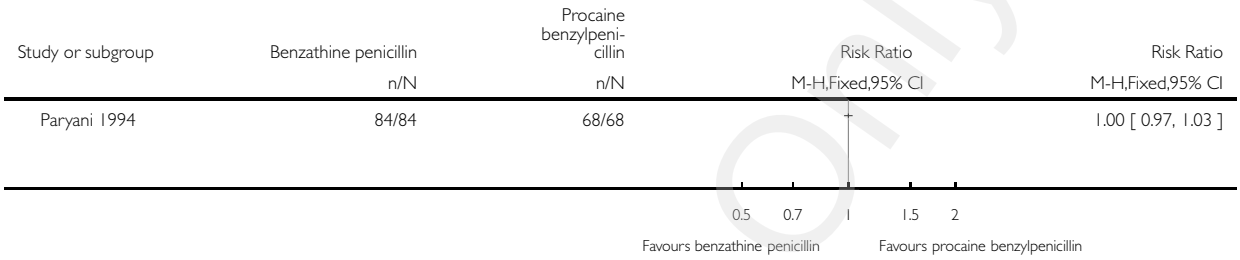


Analysis 2.1. Comparison 2 Any antibiotic treatment (benzathine penicillin) compared to any other antibiotic (procaine benzylpenicillin) for congenital syphilis, Outcome 1 Absence of clinical manifestations of congenital syphilis during follow-up.

Review: Antibiotic treatment for newborns with congenital syphilis

Comparison: 2 Any antibiotic treatment (benzathine penicillin) compared to any other antibiotic (procaine benzylpenicillin) for congenital syphilis

Outcome: 1 Absence of clinical manifestations of congenital syphilis during follow-up

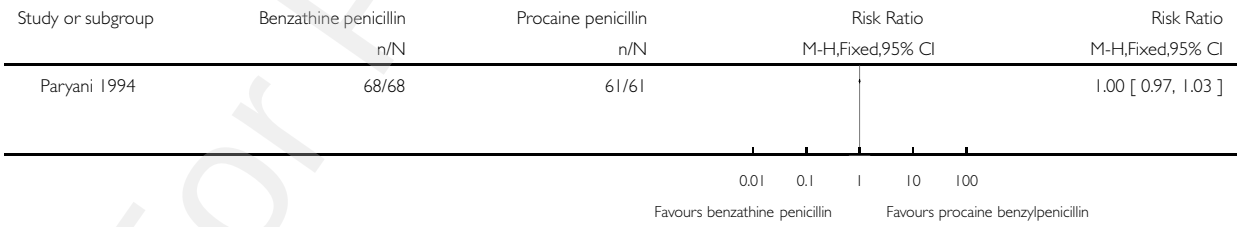


Analysis 2.2. Comparison 2 Any antibiotic treatment (benzathine penicillin) compared to any other antibiotic (procaine benzylpenicillin) for congenital syphilis, Outcome 2 Serological cure (≥ 4-fold decrease or greater in non-treponemal tests titre).

Review: Antibiotic treatment for newborns with congenital syphilis

Comparison: 2 Any antibiotic treatment (benzathine penicillin) compared to any other antibiotic (procaine benzylpenicillin) for congenital syphilis

Outcome: 2 Serological cure (≥ 4-fold decrease or greater in non-treponemal tests titre)



APPENDICES

Appendix 1. Electronic search strategies

MEDLINE and CENTRAL (Ovid platform)

1 exp Syphilis, Congenital/
2 (congenita$ adj5 syphilis).tw.
3 (hutchinson$ adj5 teeth).tw.
4 (congenital adj5 lues).tw.
5 or/1-4
6 exp Anti-Bacterial Agents/
7 anti bacterial$.tw.
8 antibacterial$.tw.
9 antibiotic$.tw.
10 bacteriocid$.tw.
11 bactericid$.tw.
12 exp Anti-Infective Agents/
13 anti infective$.tw.
14 antiinfective$.tw.
15 microbicid$.tw.
16 antimicrobial$.tw.
17 anti microbial$.tw.
18 exp Penicillins/
19 penicilli$.tw.
20 exp Macrolides/
21 macrolide$.tw.
22 exp Azithromycin/
23 azithromycin.tw.
24 exp Tetracyclines/
25 tetracyclin$.tw.
26 exp Doxycycline/
27 doxycycline.tw.
28 exp Cephalosporins/
29 cephalosporin$.tw.
30 exp Ceftriaxone/
31 ceftriaxon$.tw.
32 or/6-31
33 randomised controlled trial.pt.
34 controlled clinical trial.pt.
35 randomized.ab.
36 placebo.ab.
37 clinical trials as topic.sh.
38 randomly.ab.
39 trial.ti.
40 or/33-39
41 exp animals/ not humans.sh.
42 40 not 41
43 5 and 32 and 42

Note: the CENTRAL search strategy does not include the terms #33 - #42.

EMBASE.com

1 'congenital syphilis'/exp
2 (congenita* NEAR/5 syphilis):ab,ti
3 (hutchinson* NEAR/5 teeth):ab,ti

4 (congenital NEAR/5 lues):ab,ti
5 or/1-4
6 'antiinfective agent'/exp
7 antiinfective*:ab,ti
8 (anti NEAR/5 infective*):ab,ti
9 antibacterial*:ab,ti
10 (anti NEAR/5 bacterial*):ab,ti
11 antimicrobial*:ab,ti
12 (anti NEAR/5 microbial*):ab,ti
13 'antimicrobial therapy'/exp
14 'antibiotic agent'/exp
15 antibiotic*:ab,ti
16 'bactericide'/exp
17 bactericid*:ab,ti
18 bacteriocid*:ab,ti
19 'microbicide'/exp
20 microbicid*:ab,ti
21 'penicillin derivative'/exp
22 penicilli*:ab,ti
23 'macrolide'/exp
24 macrolide*:ab,ti
25 'azithromycin'/exp
26 azithromycin:ab,ti
27 'tetracycline derivative'
28 tetracyclin*:ab,ti
29'doxycycline'/exp
30 doxycycline:ab,ti
31 'cephalosporin derivative'/exp
32 cephalosporin*:ab,ti
33 'ceftriaxone'/exp
34 ceftriaxon*:ab,ti
35 or/6-34
36.'randomized controlled trial'/de
37.'controlled clinical study'/de
38.random*:ti,ab
39.'randomization'/de
40.'intermethod comparison'/de
41.placebo:ti,ab
42.compare:ti OR compared:ti OR comparison:ti
43.(evaluated:ab OR evaluate:ab OR evaluating:ab OR assessed:ab OR assess:ab) AND (compare:ab OR compared:ab OR comparing:ab OR comparison:ab)
44.(open NEAR/1 label):ti,ab
45.((double OR single OR doubly OR singly) NEAR/1 (blind OR blinded OR blindly)):ti,ab
46.'double blind procedure'/de
47.(parallel NEXT/1 group*):ti,ab
48.crossover:ti,ab OR 'cross over':ti,ab
49.((assign* OR match OR matched OR allocation) NEAR/5 (alternate OR group* OR intervention* OR patient* OR subject* OR participant*)):ti,ab
50.assigned:ti,ab OR allocated:ti,ab
51.(controlled NEAR/7 (study OR design OR trial)):ti,ab
52.volunteer:ti,ab OR volunteers:ti,ab
53.trial:ti
54.'human experiment'/de

55.#36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53OR #54
56.#5 AND #35 AND #55 AND [embase]/lim

LILACS (iAHx interface)

(mh:("Syphilis, Congenital")) OR (ti:("congenital syphilis")) OR (ab:("congenital syphilis")) AND db:("LILACS") AND type˙of˙study:("clinical˙trials")

RCTs filter:

((PT:"ensayo clinico controlado aleatorio" OR PT:"ensayo clinico controlado" OR PT:"estudio multicéntrico" OR MH:"ensayos clinicos controlados aleatorios como asunto" OR MH:"ensayos clinicos controlados como asunto" OR MH:"estudios multicéntricos como asunto" OR MH:"distribución aleatoria" OR MH:"método doble ciego" OR MH:"metodo simple-ciego") OR ((ensaio$ OR ensayo$ OR trial$) AND (azar OR acaso OR placebo OR control$ OR aleat$ OR random$ OR enmascarado$ OR simpleciego OR ((simple$ OR single OR duplo$ OR doble$ OR double$) AND (cego OR ciego OR blind OR mask))) AND clinic$)) AND NOT (MH:animales OR MH:conejos OR MH:ratones OR MH:ratas OR MH:primates OR MH:perros OR MH:gatos OR MH:porcinos OR PT:"in vitro")

WHO International Clinical Trials Registry Platform ICTRP portal

congenital syphilis

ClinicalTrials.gov

congenital syphilis

Appendix 2. Search strategies update (2017-2018)

Type of search	Update
Database	• MEDLINE • MEDLINE In-Process & Other Non-Indexed Citations • MEDLINE Daily Update
Platform	Ovid
Search date	22 May 2018
Range of search date	2017-2018
Language Restrictions	None
Other Limits	Randomized Clinical Trials
Search strategy (results)	1 exp Syphilis, Congenital/ (2708) 2 (congenita$ adj5 syphilis).tw. (2052) 3 (hutchinson$ adj5 teeth).tw. (13) 4 (congenital adj5 lues).tw. (26) 5 1 or 2 or 3 or 4 (3267) 6 exp Anti-Bacterial Agents/ (651462) 7 anti bacterial$.tw. (2654) 8 antibacterial$.tw. (61681) 9 antibiotic$.tw. (291432) 10 bacteriocid$.tw. (561) 11 bactericid$.tw. (27979) 12 exp Anti-Infective Agents/ (1494711)

(*Continued*)

	13 anti infective$.tw. (3609) 14 antiinfective$.tw. (455) 15 microbicid$.tw. (5780) 16 antimicrobial$.tw. (133056) 17 anti microbial$.tw. (3370) 18 exp Penicillins/ (77798) 19 penicilli$.tw. (63037) 20 exp Macrolides/ (101521) 21 macrolide$.tw. (14341) 22 exp Azithromycin/ (4532) 23 azithromycin.tw. (7035) 24 exp Tetracyclines/ (45575) 25 tetracyclin$.tw. (33410) 26 exp Doxycycline/ (8859) 27 doxycycline.tw. (11925) 28 exp Cephalosporins/ (40203) 29 cephalosporin$.tw. (20415) 30 exp Ceftriaxone/ (5446) 31 ceftriaxon$.tw. (9533) 32 or/6-31 (1720743) 33 controlled clinical trial.pt. (92438) 34 randomized controlled trial.pt. (462300) 35 randomized.ab. (413454) 36 placebo.ab. (189570) 37 clinical trials as topic.sh. (183855) 38 randomly.ab. (291342) 39 trial.ti. (183315) 40 or/33-39 (1154616) 41 exp animals/ not humans.sh. (4463161) 42 40 not 41 (1063407) 43 5 and 32 and 42 (16) 44 limit 43 to yr="2017 -Current" (1)
Number of references identified	1
Number of references without duplicates	1

Type of search	Update
Database	Embase
Platform	EMBASE.com
Search date	23 May 2018
Range of search date	2017-2018

(*Continued*)

Language Restrictions	None
Other Limits	Randomized Clinical Trials
Search strategy (results)	1. 'congenital syphilis'/exp (3237) 2. (congenita* NEAR/5 syphilis):ab,ti (2273) 3. (hutchinson* NEAR/5 teeth):ab,ti (15) 4. (congenital NEAR/5 lues):ab,ti (29) 5. #1 OR #2 OR #3 OR #4 (3645) 6. 'antiinfective agent'/exp (2927977) 7. antiinfective*:ab,ti (936) 8. (anti NEAR/5 infective*):ab,ti (5023) 9. antibacterial*:ab,ti (82700) 10. (anti NEAR/5 bacterial*):ab,ti (5485) 11. antimicrobial*:ab,ti (174266) 12. (anti NEAR/5 microbial*):ab,ti (5777) 13. 'antimicrobial therapy'/exp (182555) 14. 'antibiotic agent'/exp (1278115) 15. antibiotic*:ab,ti (384772) 16. 'bactericide'/exp (2426) 17. bactericid*:ab,ti (32167) 18. bacteriocid*:ab,ti (676) 19. 'microbicide'/exp (1776) 20. microbicid*:ab,ti (6600) 21. 'penicillin derivative'/exp (290757) 22. penicilli*:ab,ti (75614) 23. 'macrolide'/exp (203288) 24. macrolide*:ab,ti (18741) 25. 'azithromycin'/exp (30079) 26. azithromycin:ab,ti (10432) 27. 'tetracycline derivative'/exp (158716) 28. tetracyclin*:ab,ti (38755) 29. 'doxycycline'/exp (46493) 30. doxycycline:ab,ti (16649) 31. 'cephalosporin derivative'/exp (205963) 32. cephalosporin*:ab,ti (27244) 33. 'ceftriaxone'/exp (51588) 34. ceftriaxon*:ab,ti (14264) 35. #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR # 25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 (3112262) 36. 'randomized controlled trial'/de (497851) 37. 'controlled clinical study'/de (426369) 38. random*:ti,ab (1288799) 39. 'randomization'/de (77741) 40. 'intermethod comparison'/de (234226) 41. placebo:ti,ab (269265)

(*Continued*)

	42. compare:ti OR compared:ti OR comparison:ti (472043) 43. (evaluated:ab OR evaluate:ab OR evaluating:ab OR assessed:ab OR assess:ab) AND (compare:ab OR compared:ab OR comparing:ab OR comparison:ab) (1726872) 44. (open NEAR/1 label):ti,ab (63503) 45. ((double OR single OR doubly OR singly) NEAR/1 (blind OR blinded OR blindly)):ti,ab (207173) 46. 'double blind procedure'/de (148746) 47. (parallel NEXT/1 group*):ti,ab (21432) 48. crossover:ti,ab OR 'cross over':ti,ab (91765) 49. ((assign* OR match OR matched OR allocation) NEAR/5 (alternate OR group* OR intervention* OR patient* OR subject* OR participant*)):ti,ab (279205) 50. assigned:ti,ab OR allocated:ti,ab (327361) 51. (controlled NEAR/7 (study OR design OR trial)):ti,ab (291068) 52. volunteer:ti,ab OR volunteers:ti,ab (222766) 53. trial:ti (249242) 54. 'human experiment'/de (404507) 55. #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53OR #54 (4260415) 56. #5 AND #35 AND #55 (44) 57. #5 AND #35 AND #55 AND [embase]/lim AND [2017-2018]/py (4)
Number of references identified	4
Number of references without duplicates	4

Type of search	Update
Database	Cochrane Central Register of Controlled Trials (CENTRAL)
Platform	Ovid
Search date	23 May 2018
Range of search date	2017-2018
Language Restrictions	None
Other Limits	None
Search strategy (results)	1 exp Syphilis, Congenital/ (10) 2 (congenita$ adj5 syphilis).tw. (16) 3 (hutchinson$ adj5 teeth).tw. (0) 4 (congenital adj5 lues).tw. (0) 5 1 or 2 or 3 or 4 (19)

(*Continued*)

	6 exp Anti-Bacterial Agents/ (21919) 7 anti bacterial$.tw. (86) 8 antibacterial$.tw. (1816) 9 antibiotic$.tw. (16622) 10 bacteriocid$.tw. (14) 11 bactericid$.tw. (1051) 12 exp Anti-Infective Agents/ (51810) 13 anti infective$.tw. (171) 14 antiinfective$.tw. (26) 15 microbicid$.tw. (299) 16 antimicrobial$.tw. (4490) 17 anti microbial$.tw. (115) 18 exp Penicillins/ (4752) 19 penicilli$.tw. (1974) 20 exp Macrolides/ (6274) 21 macrolide$.tw. (685) 22 exp Azithromycin/ (764) 23 azithromycin.tw. (1536) 24 exp Tetracyclines/ (1915) 25 tetracyclin$.tw. (1460) 26 exp Doxycycline/ (776) 27 doxycycline.tw. (1259) 28 exp Cephalosporins/ (3765) 29 cephalosporin$.tw. (1079) 30 exp Ceftriaxone/ (585) 31 ceftriaxon$.tw. (1081) 32 or/6-31 (67246) 33 5 and 32 (8) 34 limit 33 to yr="2017 -Current" (0)
Number of references identified	0
Number of references without duplicates	N/A

Search type	Update
Database	LILACS lilacs.bvsalud.org/es/
Platform	Biblioteca Virtual en Salud (BVS), interfaz iAHx
Search date	5 February 2018
Range of search date	2016-2017
Language restrictions	None

(*Continued*)

Other limits	RCT
Search strategy	(mh:("Syphilis, Congenital")) OR (ti:("congenital syphilis")) OR (ab:("congenital syphilis")) AND db:("LILACS") AND type_of_study:("clinical_trials") AND (year_cluster:("2016" OR "2017")) RCTs filter: ((PT:"ensayo clinico controlado aleatorio" OR PT:"ensayo clinico controlado" OR PT:"estudio multicéntrico" OR MH:"ensayos clinicos controlados aleatorios como asunto" OR MH:"ensayos clinicos controlados como asunto" OR MH:"estudios multicéntricos como asunto" OR MH:"distribución aleatoria" OR MH:"método doble ciego" OR MH:"metodo simple-ciego") OR ((ensaio$ OR ensayo$ OR trial$) AND (azar OR acaso OR placebo OR control$ OR aleat$ OR random$ OR enmascarado$ OR simpleciego OR ((simple$ OR single OR duplo$ OR doble$ OR double$) AND (cego OR ciego OR blind OR mask))) AND clinic$)) AND NOT (MH:animales OR MH:conejos OR MH:ratones OR MH:ratas OR MH:primates OR MH:perros OR MH:gatos OR MH:porcinos OR PT:"in vitro")
# of records identified	0
# of records without duplicates	N/A

CONTRIBUTIONS OF AUTHORS

GW drafted the protocol.

GW, DW, DM and CFG-A reviewed and edited the review.

DECLARATIONS OF INTEREST

GW: none known.

DW: none known.

DM: none known.

CFG-A: none known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National University of Colombia, Colombia.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The outcomes have been clarified from:

- survival rate;
- adverse events: (fever, diarrhoea, vomiting and allergic reactions);
- absence of any clinical manifestations of congenital syphilis at follow-up three and six months and one year after treatment and non-reactive serology testing (i.e. a nontreponemal test) at these times. (CDC 2015);
- neurosyphilis.

to:

- neonatal death rate due congenital syphilis;
- neonatal death rate due any cause;
- absence of clinical manifestations of congenital syphilis during follow-up (defined as proportion of newborns without hepatosplenomegaly, lymphadenopathy, organ involvement or any other clinical manifestation after treatment);
- serious adverse events (proportion of neonates who experience any adverse effect life-threatening or requires discontinuation of therapy or intervention to prevent permanent impairment or damage);
- serological cure (defined as fourfold decreased or greater in non-treponemal tests titre by third month);
- minor adverse events of therapy (e.g. fever, diarrhoea, vomiting or allergic reactions).