World Health Organization

WHO GUIDELINES FOR THE

Treatment of *Treponema pallidum* (syphilis)

Web annex D: Evidence profiles and evidence-to-decision frameworks

The full guidelines are available at:
www.who.int/reproductivehealth/publications/rtis/syphilis-treatment-guidelines/en/

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WHO Library Cataloguing-in-Publication Data

WHO guidelines for the treatment of Treponema pallidum (syphilis).

Contents: Web annex D: Evidence profiles and evidence-to-decision frameworks - Web annex E: Systematic reviews for syphilis guidelines - Web annex F: Summary of conflicts of interest

1.Syphilis – drug therapy. 2.Treponema pallidum. 3.Sexually Transmitted Diseases. 4.Guideline. I.World Health Organization.

ISBN 978 92 4 154980 6 (NLM classification: WC 170)

Printed by the WHO Document Production Services, Geneva, Switzerland

CONTENTS

RECOMMENDATIONS 1 AND 2:
EARLY SYPHILIS – ADULTS AND ADOLESCENTS

Treatments for adults with early syphilis (primary, secondary, or early latent syphilis of not more than 2 years' duration)	
Population:	Adults with early syphilis
Intervention:	Ceftriaxone, azithromycin, doxycycline, erythromycin
Comparison:	Benzathine penicillin G 2.4 MU × 1
Main outcomes:	Critical: serological response, clinical cure Important: transmission to partner, antimicrobial resistance, compliance, side-effects (including allergy, toxicity), HIV transmission or acquisition, STI complications
Setting:	All settings
Perspective:	Population level
Background:	Syphilis is a systemic disease from the outset and is caused by the spirochaete *Treponema pallidum*. The infection can be classified as congenital (transmitted from mother to child in utero) or acquired (through sex or blood transfusion). Acquired syphilis is divided into early and late syphilis. Early syphilis comprises the primary, secondary and early latent stages. Late syphilis refers to late latent syphilis, gummatous, neurological and cardiovascular syphilis. Primary syphilis is characterized by an ulcer or chancre at the site of infection or inoculation. Secondary syphilis manifestations include a skin rash, condylomata lata, mucocutaneous lesions and generalized lymphadenopathy. The 2003 World Health Organization (WHO) STI guidelines recommend treatment of early syphilis in adults with benzathine benzyl penicillin, 2.4 million IU by intramuscular injection, at a single session. Because of the volume involved, this dose is usually given as two injections at separate sites. An alternative regimen for penicillin-allergic pregnant patients is erythromycin, 500 mg orally, four times daily for 14 days.

ASSESSMENT

<table>
<tr><th></th><th>Judgement</th><th>Research evidence</th></tr>
<tr><td>Problem</td><td>Is the problem a priority?
• No
• Probably no
• Probably yes
• Yes
• Varies
• Don't know</td><td>Research evidence:
WHO estimates that 5.6 million new cases of syphilis occurred among adolescents and adults aged 15–49 years worldwide in 2012 and there are an estimated 18 million prevalent cases of syphilis.

Untreated, up to one third of patients progress to later stages of disease. Late syphilis can cause irreversible damage to the cardiovascular and central nervous systems, resulting in profound morbidity and even death.

Additional considerations:
None</td></tr>
<tr><td>Desirable Effects</td><td>How substantial are the desirable anticipated effects?
• Trivial
• Small
• Moderate
• Large
• Varies
• Don't know</td><td rowspan="2">Research evidence:
We included 7 randomized and 18 non-randomized studies with one or two groups. Many studies did not indicate whether people had early or late syphilis. When indicated, we included studies when over 90% of patients were defined as "early".

Serological cures: when compared to single dose benzathine penicillin G, the evidence suggested little to no difference for a double dose of benzathine penicillin G, but fewer cures for a triple dose; similar cure rates with ceftriaxone, azithromycin and doxycycline; fewer cures with doxycycline and tetracycline together.

Transmission to partners, HIV transmission and acquisition, and STI complications were not measured.

Few studies provided data for adverse events. Azithromycin may increase gastrointestinal side-effects and dizziness or headache, but may reduce rash, fever and serious adverse events. Ceftriaxone may lead to fewer people with diarrhoea and rash, but this evidence is uncertain.

A systematic review (Blank, 2011) reported on the effects in people living with HIV. This review was updated. Results suggest that there is little to no difference in the effects in treatments in people living or not living with HIV.

See Evidence profiles for the detailed summary of the findings.

Additional considerations:
The Guideline Development Group (GDG) noted that there are few studies conducted and most treatment is based on historical use of benzathine penicillin G and procaine penicillin.

Data were not available for resistance to azithromycin for syphilis in specific settings and will probably be unknown in many places. Resistance to azithromycin for other conditions is spreading, therefore there was concern for the risk of azithromycin resistance to syphilis.</td></tr>
<tr><td>Undesirable Effects</td><td>How substantial are the undesirable anticipated effects?
• Large
• Moderate
• Small
• Trivial
• Varies
• Don't know</td></tr>
</table>

Certainty of evidence	**What is the overall certainty of the evidence of effects?** • **Very low** • Low • Moderate • High • No included studies	
Values	**Is there important uncertainty about or variability in how much people value the main outcomes?** • Important uncertainty or variability • **Possibly important uncertainty or variability** • Probably no important uncertainty or variability • No important uncertainty or variability • No known undesirable outcomes	**Research evidence:** According to economic evaluation studies, the disability weights due to syphilis (utility loss due to the disease) are as follows: early syphilis: 0.0072–0.015 secondary syphilis: 0.041 tertiary (neurological): 0.094–0.283 death: 1 **Additional considerations:** The GDG noted that there may be variability in outcome values depending on stages of syphilis.
Balance of effects	**Does the balance between desirable and undesirable effects favour the intervention or the comparison?** • Favours the comparison • **Probably favours the comparison** • Does not favour either the intervention or the comparison • Probably favours the intervention • Favours the intervention • Varies • Don't know	**Research evidence:** No research evidence **Additional considerations:** The GDG decided that there was little agreement with the evidence for higher doses (given two or three times) providing greater benefit (probably due to study methodology). When compared with azithromycin, benzathine penicillin G was probably favoured due to side-effects. Because there was little evidence for the effects and side-effects for ceftriaxone and doxycycline, benzathine penicillin G was favoured.
Resources required	**How large are the resource requirements (costs)?** • Large costs • Moderate costs • Negligible costs and savings • Moderate savings • Large savings • **Varies** • Don't know	**Research evidence:** No research evidence **Additional considerations:** Benzathine penicillin G requires local preparation, making cost heavily dependent on local labour costs. Benzathine penicillin G without preparation costs $0.28 per dose. For three doses, $3.72 was the average price. Azithromycin cost $1.56. Ceftriaxone has greater costs (data not available).

Certainty of evidence of required resources	**What is the certainty of the evidence of resource requirements (costs)?** • Very low • Low • Moderate • High • **No included studies**	**Research evidence:** No research evidence **Additional considerations:** None
Cost–effectiveness	**Does the cost-effectiveness of the intervention favour the intervention or the comparison?** • Favours the comparison • **Probably favours the comparison** • Does not favour either the intervention or the comparison • Probably favours the intervention • Favours the intervention • Varies • No included studies	**Research evidence:** No research evidence available published since 2005. **Additional considerations:** The benefits are similar between the different medicines, but costs are probably higher with ceftriaxone and azithromycin compared to benzathine penicillin.
Equity	**What would be the impact on health equity?** • Reduced • Probably reduced • **Probably no impact** • Probably increased • Increased • Varies • Don't know	**Research evidence:** No research evidence **Additional considerations:** The GDG considered that health equity could be reduced, if benzathine penicillin is not available, but other medicines should be included in the recommendations.

Acceptability	**Is the intervention acceptable to key stakeholders?** • No • Probably no • **Probably yes** • Yes • Varies • Don't know	**Research evidence:** We found four studies that addressed acceptability of injections (daily or weekly) versus oral medicines in people with various stages of syphilis. Studies were from 1997 to 2006 and indicated that ~80% or more people accepted injections, but weekly injections were preferred. The others refused injections and took oral medicines. **Additional considerations:** The GDG reported that in practice, there seemed to be variation in acceptability to key stakeholders. In different countries, health workers were averse to giving injections for this infection, and in others they wanted to give the injections (instead of giving oral treatment). Regarding acceptability to patients, some were averse to injections, and in other settings patients preferred injections. Some suggested that part of this variability could be explained by the varying fear of allergic reaction among both patients and health workers.
Feasibility	**Is the intervention feasible to implement?** • No • Probably no • **Probably yes** • Yes • Varies • Don't know	**Research evidence:** No research evidence **Additional considerations:** Currently, azithromycin and doxycycline are considered more widely available than benzathine penicillin G.

SUMMARY OF JUDGEMENTS

	Judgement						
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies
Cost–effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

CONCLUSIONS

Treatments for adults with early syphilis

Type of recommendation	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	•	•	•	●	•
Recommendation	**Recommendation 1** In adults and adolescents with early syphilis, the WHO STI guideline recommends benzathine penicillin G 2.4 million units (MU) once intramuscularly over no treatment. *Strong recommendation, very low quality evidence* **Recommendation 2** In adults and adolescents with early syphilis, the WHO STI guideline suggests using benzathine penicillin G 2.4 MU once intramuscularly over procaine penicillin G 1.2 MU 10–14 days intramuscularly. *Conditional recommendation, very low quality evidence* When benzathine or procaine penicillin cannot be used (e.g. due to penicillin allergy) or is not available, the WHO STI guideline suggests using doxycycline 100 mg twice daily orally for 14 days or ceftriaxone, 1 g intramuscularly once daily for 10–14 days, or in special circumstances azithromycin 2 g once orally. *Conditional recommendation, very low quality evidence* Remarks: Doxycycline is preferred over ceftriaxone due to its lower cost and oral administration. Doxycycline should not be used in pregnant women (see recommendations for pregnant women). Azithromycin is an option in special circumstances only when local susceptibility to azithromycin is likely. If the stage of syphilis is unknown, follow recommendations for people with late syphilis.				
Justification	Overall, there was very low quality evidence for outcomes from treatment of early syphilis. Evidence was from seven randomized and 18 non-randomized studies including one or two groups evaluating benzathine penicillin G, procaine penicillin, ceftriaxone, azithromycin and doxycycline (with or without tetracycline). Although not captured in published studies, most treatments today are based on historical and successful use of benzathine penicillin G and procaine penicillin. Serological cure with benzathine penicillin G 2.4 MU provided once intramuscularly was estimated on average as 840 per 1000 people with early syphilis. When compared to single dose benzathine penicillin G, the evidence suggested little to no difference in serological cures with a double dose of benzathine penicillin G, but fewer cures for a triple dose; similar cure rates with ceftriaxone, azithromycin and doxycycline; and slightly fewer cures with doxycycline and tetracycline together. A systematic review that was updated in the course of preparations for these guidelines (Blank, 2011) suggests that there may be little to no difference in the effects of different medicines in people living with HIV and those not living with HIV. Transmission to partners, HIV transmission and acquisition, and STI complications were not measured. Few studies provided data for adverse events. Azithromycin may increase gastrointestinal side-effects and dizziness or headache (3–4 times greater than with benzathine penicillin G), but it may reduce rash (65% reduction), fever (50–65% reduction) and serious adverse events (30% reduction). Ceftriaxone may lead to fewer people with diarrhoea and rash, but this evidence is uncertain. Data were not available on resistance to azithromycin for treating syphilis in specific settings, and this will likely remain unknown in many places as the capacity to monitor antimicrobial resistance (AMR) in *T. pallidum* is not available in many settings. Resistance to azithromycin for other conditions is spreading, and therefore there was concern for the risk of azithromycin resistance to syphilis.				

Justification	There was some research evidence for overall acceptability of injections versus oral medicines in people with syphilis, but approximately 10–20% of people refused injections. The GDG noted that in practice, some health-care providers are averse to providing injections, and there are additional staff time and equipment costs with intramuscular administration. The GDG raised concerns about the impending global shortage of benzathine penicillin; a shortage would reduce health equity and it would not be feasible to apply the treatment recommendation. The GDG judged the benefits of treatment with benzathine penicillin G versus no treatment as large based on the historical successful treatment of syphilis over the past 70 years. It was also judged that the differences in benefits between medicines are likely trivial. There were inconsistent results for greater benefit with higher doses of benzathine penicillin G. The differences in the undesirable anticipated effects (side-effects) were judged as small. Because the benefits probably outweigh the harms, and because of the potential for resistance to azithromycin and greater cost, benzathine penicillin G was suggested. Benzathine penicillin G was also suggested over ceftriaxone and doxycycline due to the unknown side-effects and benefits of the latter two medicines, and the higher costs of ceftriaxone. The GDG also judged the administration benzathine and procaine penicillins by injection as being acceptable to most people.
Subgroup considerations	The recommendation for adults and adolescents with early syphilis applies to people living with HIV, people who are immunocompromised, or people at high risk of transmitting and acquiring STIs. If the stage of syphilis is unknown, follow recommendations for people with late syphilis.
Implementation considerations	
Monitoring and evaluation	Resistance to azithromycin should be monitored.
Research priorities	Trials investigating appropriate dosages and effectiveness of ceftriaxone use for early and late syphilis should be conducted. The trials should compare ceftriaxone with benzathine penicillin G and doxycycline. More research should also be conducted into medicines that are taken orally for a few days, such as cephalosporins. Since benzathine penicillin G and other penicillins require injection by health workers, it was suggested that the safety of self-injection be investigated.

EVIDENCE PROFILE

Other treatments compared to benzathine penicillin G 2.4 MU × 1 for treatment of adults and adolescents with early syphilis							
Outcomes	**Benzathine penicillin 2.4 MU × 2 doses**	**Benzathine penicillin 2.4 MU × 3 doses**	**Ceftriaxone 1 g IM qd × 10–14 days**	**Azithromycin 1-2 g × 1 dose**	**Doxycycline 100 mg po bid × 14 days**	**Doxycycline 100 mg po bid × 14 days/tetracycline 500 mg po qid × 14 days**	**Benzathine penicillin G 2.4 MU × 1 dose**
Serological cure	**RR 1.02** (0.96–1.08) **17 more per 1000** (58 fewer to 391 more) 1654 participants, 3 non-RCT ⨁⊖⊖⊖ **very low** Imprecision[1]	**RR 0.92** (0.65–1.30) **67 fewer per 1000** (from 252 more to 294 fewer) 287 participants, 2 non-RCT ⨁⊖⊖⊖ **very low** Imprecision[3]	**RR 1.01** (0.91–1.11) **8 more per 1000** (from 76 fewer to 92 more) 155 participants, 2 RCTs and 1 non-RCT[4] ⨁⊖⊖⊖ **very low** Imprecision[1,3]	**RR 1.00** (0.95–1.06) **0 fewer per 1000** (from 42 fewer to 50 more) 1742 participants, 3 RCTs and 2 non-RCT 4 ⨁⊖⊖⊖ **very low** Imprecision[1]	**RR 1.02** (0.99–1.05) **17 more per 1000** (from 8 fewer to 42 more) 125 participants, 3 non-RCT ⨁⊖⊖⊖ **very low** Imprecision[1,3]	**RR 0.96** (0.81–1.14) **34 fewer per 1000** (from 118 more to 160 fewer) 1086 participants, 2 non-RCT ⨁⊖⊖⊖ **very low** Imprecision[1,3]	**Overall/average risk** 840 serological cures per 1000[2] patients
Serological cure *HIV-positive adults*		**RR 1.04** (0.88–1.23) **29 more per 1000** (from 86 fewer to 165 more) 1138 participants, 3 non-RCT ⨁⊖⊖⊖ **very low** Inconsistency[5] and imprecision[1]			**RR 0.96** (0.88–1.05) **38 fewer per 1000** (from 48 more to 115 fewer) 125 participants, 1 non-RCT ⨁⊖⊖⊖ **very low** Imprecision[1,3]		**Overall/average risk** 948 serological cures per 1000[6] patients
Clinical cure			RR 1.00 (0.90 to 1.12) 0 fewer per 1000 (from 55 fewer to 807 more) 34 participants, 1 RCT ⨁⊖⊖⊖ **very low** Imprecision[1,3]	**Not estimable**[7] 642 participants, 2 RCTs ⨁⨁⨁⨁ **high**			**Overall risk** 1000 clinical cures per 1000 patients

Adverse events			**See supplementary table**				
Transmission to partner	Not measured						
Antimicrobial resistance	Not measured						
HIV transmission or acquisition	Not measured						
STI complications	Not measured						

IM: intramuscular; MU: million units; po: by mouth (orally); qd: daily; qid: 4 times daily

1. The 95% CI is inconclusive, suggesting "other treatment" as more effective treatment in one extreme, and benzathine penicillin G × 1 dose in the other extreme.
2. The baseline risk represents the average risk (range 65.4–99.4%) of the control group patients (treated with benzathine penicillin G × 1 dose) through all the different comparisons.
3. The total number of events does not meet the optimal information size (OIS).
4. 50% of studies RCT and 50% non-RCT.
5. The point estimates of the included studies suggest different magnitude of effects; I2 > 70%.
6. Baseline risk represents the average risk (range 93.8–94.7%) of the control groups in studies on HIV patients.
7. All patients were clinically cured in both benzathine penicillin G × 1 dose and azithromycin treatment groups.

SUPPLEMENTARY TABLE OF ADVERSE EVENTS

Azithromycin 2 g × 1 dose compared to benzathine penicillin G 2.4 MU × 1 for treatment of adults with early syphilis[3]					
Outcomes	**Number of participants (studies)**	**Quality of the evidence (GRADE)**	**Relative effect (95% CI)**	**Anticipated absolute effects**	
				Risk with benzathine penicillin G 2.4 MU × 1	**Risk difference with azithromycin 2 g × 1**
Jarisch–Herxheimer reaction	74 (1 RCT)	⨁⨁◯◯ LOW [1,2]	**RR 0.71** (0.27–1.88)	238 per 1000	**69 fewer per 1000** (174 fewer to 210 more)
Nausea	74 (1 RCT)	⨁⨁◯◯ LOW [1,2]	**RR 2.77** (0.36–21.19)	48 per 1000	**84 more per 1000** (30 fewer to 961 more)
Vomiting < 2 h after administration	642 (2 RCT s)	⨁⨁◯◯ LOW [1,2]	**RR 3.11** (0.36–26.99)	1 per 1000	**2 more per 1000** (1 fewer to 26 more)
Diarrhoea	74 (1 RCT)	⨁⨁◯◯ LOW [1,2]	**RR 4.48** (0.26–77.65)	1 per 1000	**3 more per 1000** (1 fewer to 77 more)
Serious adverse events (excluding deaths)	568 (1 RCT)	⨁⨁◯◯ LOW [1,2]	**RR 0.72** (0.23–2.24)	25 per 1000	**7 fewer per 1000** (19 fewer to 30 more)
Cutaneous (rash, fever)	568 (1 RCT)	⨁⨁◯◯ LOW [1,2]	**RR 0.34** (0.11–1.03)	42 per 1000	**28 fewer per 1000** (37 fewer to 1 more)
Administration-related (pain, fever)	568 (1 RCT)	⨁⨁◯◯ LOW [1,2]	**RR 0.50** (0.27–0.94)	98 per 1000	**49 fewer per 1000** (72 fewer to 6 fewer)
Central nervous system (dizziness, headache)	568 (1 RCT)	⨁⨁◯◯ LOW [1,2]	**RR 2.73** (1.17–6.40)	25 per 1000	**42 more per 1000** (4 more to 133 more)
Gastrointestinal (diarrhoea, nausea)	568 (1 RCT)	⨁⨁◯◯ LOW [1,2]	**RR 3.31** (2.09–5.24)	74 per 1000	**170 more per 1000** (80 more to 312 more)

Ceftriaxone 1 g IM or IV × 10–14 days vs benzathine penicillin 4 MU × 1 in adults with early syphilis					
Outcomes	**Number of participants (studies)**	**Quality of the evidence (GRADE)**	**Relative effect (95% CI)**	**Anticipated absolute effects**	
				Risk with benzathine penicillin G 2.4 MU × 1 dose	**Risk difference with ceftriaxone 1 g IM or IV × 10–14 days**
Jarisch–Herxheimer reaction	34 (1 RCT)	⨁◯◯◯ VERY LOW [1,2]	**RR 1.00** (0.07–14.72)	59 per 1000	**0 fewer per 1000** (55 fewer to 807 more)
Mild transient macular rash	34 (1 RCT)	⨁◯◯◯ VERY LOW [1,2]	**RR 0.33** (0.01–7.65)	59 per 1000	**39 fewer per 1000** (58 fewer to 391 more)
Mild diarrhoea	34 (1 RCT)	⨁◯◯◯ VERY LOW [1,2]	**RR 0.33** (0.01–7.65)	59 per 1000	**39 fewer per 1000** (58 fewer to 391 more)

1. 95% CI includes potential for fewer or greater "adverse events"
2. The total number of events does not meet the optimal information size (OIS).
3. None of the patients treated with benzathine penicillin × 1 had vomiting or diarrhoea events.

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Penicillin allergy
Systematic review

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RECOMMENDATIONS 3 AND 4:
EARLY SYPHILIS – PREGNANT WOMEN

Treatments for pregnant women with early syphilis (primary, secondary or early latent syphilis of not more than 2 years' duration)	
Population:	Pregnant with early syphilis
Intervention:	Ceftriaxone, azithromycin, erythromycin
Comparison:	Benzathine penicillin G 2.4 MU × 1
Main outcomes:	Critical: mother-to-child transmission, serological response, low birth weight/preterm, stillbirth/neonatal death, clinical cure, congenital deformities, side-effects (including allergy, toxicity) Important: compliance, antimicrobial resistance, STI complications, transmission to partner, HIV transmission or acquisition
Setting:	All settings
Perspective:	Population level
Background:	Syphilis is a systemic disease from the outset and is caused by the spirochaete *Treponema pallidum*. The infection can be classified as congenital (transmitted from mother to child in utero) or acquired (through sex or blood transfusion). Acquired syphilis is divided into early and late syphilis. Early syphilis comprises the primary, secondary and early latent stages. Late syphilis refers to late latent syphilis, gummatous, neurological and cardiovascular syphilis. Primary syphilis is characterized by an ulcer or chancre at the site of infection or inoculation. Secondary syphilis manifestations include a skin rash, condylomata lata, mucocutaneous lesions and generalized lymphadenopathy. The 2003 WHO STI guidelines recommended treatment of early syphilis in adults is benzathine benzyl penicillin, 2.4 MU by intramuscular injection, at a single session. Because of the volume involved, this dose is usually given as two injections at separate sites. An alternative regimen for penicillin-allergic pregnant patients is erythromycin, 500 mg orally, four times daily for 14 days.

ASSESSMENT

	Judgement	Research evidence
Problem	**Is the problem a priority?** • No • Probably no • Probably yes • **Yes** • Varies • Don't know	**Research evidence:** WHO estimates that 5.6 million new cases of syphilis occurred among adolescents and adults aged 15–49 years worldwide in 2012 and there are an estimated 18 million prevalent cases of syphilis. Mother-to-child transmission of syphilis is declining globally due to increased efforts to screen and treat pregnant women for syphilis. However, the burden of morbidity and mortality due to congenital syphilis remains high. In 2012, there were an estimated 350 000 adverse pregnancy outcomes worldwide attributed to syphilis, including 143 000 early fetal deaths/stillbirths, 62 000 neonatal deaths, 44 000 preterm/low weight births, and 102 000 infected infants. **Additional considerations:** None
Desirable Effects	**How substantial are the desirable anticipated effects?** • Trivial • Small • Moderate • **Large** • Varies • Don't know	**Research evidence:** We found 10 non-randomized studies including pregnant women with early and/or late syphilis, and with or without allergy to penicillin. The data suggested that a single dose of penicillin was better than a triple dose for achieving serological cure, but the evidence is uncertain. Mother-to-child transmission was greater with two doses than one dose of benzathine penicillin G, although this again was uncertain. Evidence was also used from adults and adolescents to inform judgements about the benefits of treatments. The benefits were large for benzathine penicillin compared to no treatment, but differences between medicines for benefits and harms were trivial. **Additional considerations:** In the studies it was often unclear if pregnant women had early or late syphilis. The GDG reported that this is common in practice. The GDG decided that there should be a recommendation in pregnancy generally (similar recommendations for early or late), and also a recommendation if early syphilis was suspected. The GDG noted that azithromycin is also ineffective for reducing mother-to-child transmission as it does not cross the placental barrier. Procaine penicillin crosses the placental barrier (and additionally the blood–brain barrier, thus treating neurosyphilis); it was proposed that should be the second-line treatment in pregnant women, not azithromycin.
Undesirable Effects	**How substantial are the undesirable anticipated effects?** • Large • Moderate • Small • **Trivial** • Varies • Don't know	
Certainty of evidence	**What is the overall certainty of the evidence of effects?** • ***Very low*** • Low • Moderate • High • No included studies	**Research evidence:** No research evidence was identified. **Additional considerations:** None

Values	**Is there important uncertainty about or variability in how much people value the main outcomes?** • Important uncertainty or variability • Possibly important uncertainty or variability • Probably no important uncertainty or variability • **No important uncertainty or variability** • No known undesirable outcomes	**Research evidence:** According to economic evaluation studies, the disability weights due to syphilis (utility loss due to the disease) are as follows: early syphilis: 0.0072–0.015 secondary syphilis: 0.041 tertiary (neurological): 0.094–0.283 death: 1 For neonatal, the disutilities are as follows: congenital syphilis: 0.315 low birth weight: 0.106 neonatal death: 1 stillbirth: 1 miscarriage: 1 **Additional considerations:** None
Balance of effects	**Does the balance between desirable and undesirable effects favour the intervention or the comparison?** • **Favours the comparison** • Probably favours the comparison • Does not favour either the intervention or the comparison • Probably favours the intervention • Favours the intervention • Varies • Don't know	**Research evidence:** The benefits of benzathine penicillin and procaine penicillin were large and outweighed undesirable effects. When comparing these medicines (Ceftriaxone, azithromycin and erythromycin to benzathine penicillin and procaine penicillin (in pregnant women and non-pregnant adults) by the desirable and undesirable effects, these medicines were not favoured over others. **Additional considerations:** None
Resources required	**How large are the resource requirements (costs)?** • Large costs • Moderate costs • **Negligible costs and savings** • Moderate savings • Large savings • Varies • Don't know	**Research evidence:** No research evidence. Benzathine penicillin G requires local preparation, making cost heavily dependent on local labour costs. Benzathine penicillin G without preparation costs $0.28 per dose. For three doses, $3.72 was the average price. Azithromycin cost $1.56. Ceftriaxone has greater costs (data not available). **Additional considerations:** None
Certainty of evidence of required resources	**What is the certainty of the evidence of resource requirements (costs)?** • Very low • Low • Moderate • High • **No included studies**	**Research evidence:** No research evidence was identified. **Additional considerations:** None

Cost–effectiveness	**Does the cost-effectiveness of the intervention favour the intervention or the comparison?** • **Favours the comparison** • Probably favours the comparison • Does not favour either the intervention or the comparison • Probably favours the intervention • Favours the intervention • Varies • No included studies	**Research evidence:** Cost–effectiveness studies assessed costs of screening and treatment, and data could not be separated for treatment. Most comments in published literature addressed the usefulness of screening only if treatment is provided. **Additional considerations:** The GDG indicated that treatment versus no treatment was favoured. The benefits are similar between the different medicines, but costs are probably higher with ceftriaxone and azithromycin compared to benzathine penicillin.
Equity	**What would be the impact on health equity?** • Reduced • Probably reduced • **Probably no impact** • Probably increased • Increased • Varies • Don't know	**Research evidence:** No research evidence. **Additional considerations:** The GDG considered that health equity could be reduced if benzathine penicillin is not available, but other medicines should be included in the recommendations.
Acceptability	**Is the intervention acceptable to key stakeholders?** • No • Probably no • **Probably yes** • Yes • Varies • Don't know	**Research evidence:** We found four studies that addressed acceptability of injections (daily or weekly) versus oral medicines in people with various stages of syphilis. Studies were from 1997 to 2006 and indicated that ~80% or more people accepted injections, but weekly injections were preferred. The others refused injections and took oral medicines. **Additional considerations:** The GDG reported that in practice there seemed to be variation in acceptability to key stakeholders. In different countries, health workers were averse to giving injections for this infection, and in others they wanted to give the injections (instead of giving oral treatment). Regarding acceptability to patients, some were averse to injections, and in other settings patients preferred injections. Some suggested that part of this variability could be explained by the varying fear of allergic reaction among both patients and health workers.
Feasibility	**Is the intervention feasible to implement?** • No • Probably no • **Probably yes** • Yes • Varies • Don't know	**Research evidence:** No research evidence. **Additional considerations:** Currently azithromycin and doxycycline are considered more widely available than benzathine penicillin G.

SUMMARY OF JUDGEMENTS

	Judgement						
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies
Cost–effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

CONCLUSIONS

Treatments for pregnant women with early syphilis

Type of recommendation	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	•	•	•	●	•
Recommendation	**Recommendation 3** In pregnant women with early syphilis, the WHO STI guideline recommends benzathine penicillin G 2.4 MU once intramuscularly over no treatment. *Strong recommendation, very low quality evidence* **Recommendation 4** In pregnant women with early syphilis, the WHO STI guideline suggests using benzathine penicillin G 2.4 MU once intramuscularly over procaine penicillin 1.2 MU intramuscularly once a day for 10 days. *Conditional recommendation, very low quality evidence* When benzathine or procaine penicillin cannot be used (e.g. due to penicillin allergy where penicillin desensitization is not possible) or is not available (e.g. due to stock-outs), the WHO STI guideline suggests using, with caution, erythromycin 500 mg orally four times daily for 14 days, or ceftriaxone 1 g intramuscularly once daily for 10–14 days, or azithromycin 2 g once orally. *Conditional recommendation, very low quality evidence* Remarks: Although erythromycin and azithromycin treat pregnant women, they do not cross the placental barrier completely and as a result the fetus is not treated. It is therefore necessary to treat the newborn infant soon after delivery (see recommendations for congenital syphilis). Ceftriaxone is an expensive option and is injectable. Doxycycline should not be used in pregnant women. Because syphilis during pregnancy can lead to severe adverse complications to the fetus or newborn, stock-outs of benzathine penicillin for use in antenatal care should be avoided.				
Justification	The overall quality of the evidence for treatments used for pregnant women was very low. There were few studies (10 non-randomized studies) and very few pregnant women were included in the studies. In most studies, the stage of syphilis (early or late) was unknown. The evidence in adults and adolescents was used to inform judgements about the benefits of different medicines. Similar to that evidence, the benefits were large for the use of benzathine penicillin compared to no treatment, and based on successful historical use of benzathine and procaine penicillins, and erythromycin. The differences in medicines for benefits and harms were trivial. Prevention of mother-to-child transmission was a critical outcome. The penicillins cross the placental barrier; however, azithromycin and erythromycin do not. Therefore there is an increased chance of transmission with the use of these latter medicines. There was no evidence for adverse effects, transmission to partner, antimicrobial resistance, HIV transmission or acquisition, or STI complications. Research evidence for the other factors (acceptability, feasibility, equity and costs) was not specific to pregnant women. Therefore evidence for non-pregnant adults was used to inform this recommendation. Overall, the recommendations for non-pregnant women with early syphilis were used to inform the recommendations for pregnant women with early syphilis, with the exception of the use of doxycycline, which cannot be used in pregnant women. Erythromycin was added as an alternative based on successful historical use.				

Type of recommendation	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	•	•	•	●	•
Subgroup considerations					
Implementation considerations					
Monitoring and evaluation					
Research priorities	The GDG discussed the possibility of developing a new treatment. An oral therapy is needed that can treat syphilis in pregnant women, cross the blood–brain and placental barriers, and involve only a short course of therapy. Cephalosporins could be potential options. Trials investigating appropriate dosages and effectiveness of ceftriaxone use for early and late syphilis should be established. The trials should compare ceftriaxone with benzathine penicillin G. The extent to which the medicines cross the blood–brain and placental barriers should also be investigated.				

EVIDENCE PROFILE

Other treatments compared to benzathine penicillin G 2.4 MU × 1 dose for treatment of pregnant women with early syphilis				
Outcomes (IMPORTANCE)	**Benzathine penicillin 2.4 MU × 2 doses**	**Benzathine penicillin 2.4 MU × 3 doses**	**No treatment**	**Benzathine penicillin G 2.4 MU × 1 dose**
Serological cure CRITICAL)		**810 people per 1000** (0.7–0.87)		**1000 people per 1000** (0.99–1.01)
		197 participants, 1 non-RCT (one arm) ⨁⊖⊖⊖ **very low** Risk of bias[1]		204 participants, one-arm observational study ⨁⨁⊖⊖ **low** Risk of bias[1] and strong association
Compliance (IMPORTANT)		**890 people per 1000** (0.86–0.87)		
		383 participants, 2 non-RCT (one arm) ⨁⊖⊖⊖ **very low** Risk of bias[1], inconsistency[2]		
Prevention of mother-to-child transmission (CRITICAL)	**1000 people per 1000** (0.99–1.01)			**970 people per 1000** (0.95–1.00)
	250 participants, 2 non-RCT (one arm) ⨁⊖⊖⊖ **very low** Risk of bias[1] and strong association			204 participants, one-arm observational study ⨁⨁⊖⊖ **low** Risk of bias[1] and strong association
Stillbirth/neonatal death (CRITICAL)	**OR 0.42** (0.20–0.80) **34 fewer per 1000** (7 fewer to 48 fewer)	**OR 0.72** (0.28–1.82) **16 fewer per 1000** (43 fewer to 44 more)	**OR 0.19** (0.62–2.31) **11 more per 1000** (22 fewer to 69 more)	**Overall risk** 60 stillbirth/neonatal death per 1000 patients
	785 participants, 2 non-RCT ⨁⊖⊖⊖ **very low** Imprecision[3]	507 participants, 2 non-RCT ⨁⊖⊖⊖ **very low** Imprecision[3]	593 participants, 2 observational studies ⨁⊖⊖⊖ **very low** Imprecision[3]	

Other treatments compared to benzathine penicillin G 2.4 MU × 1 dose for treatment of pregnant women with early syphilis				
Outcomes (IMPORTANCE)	**Benzathine penicillin 2.4 MU × 2 doses**	**Benzathine penicillin 2.4 MU × 3 doses**	**No treatment**	**Benzathine penicillin G 2.4 MU × 1 dose**
Preterm delivery/low birth weight (CRITICAL)	**OR 0.13** (0.02–0.69) **335 fewer per 1000** (87 fewer to 407 fewer)	**OR 0.13** (0.04–0.42) **335 fewer per 1000** (187 fewer to 393 more)	**OR 0.73** (0.25–2.11) **74 fewer per 1000** (184 more to 267 fewer)	**Overall risk** 421 preterm delivery/low birth weight per 1000 patients
	63 participants, 1 non-RCT ⨁⊖⊖⊖ **very low** Imprecision[3]	101 participants, 1 non-RCT ⨁⊖⊖⊖ **very low** Imprecision[3]	74 participants, 1 non-RCT ⨁⊖⊖⊖ **very low** Imprecision[3]	
Clinical cure	**Not measured**			
Adverse events	**Not measured**			
Transmission to partner	**Not measured**			
Antimicrobial resistance	**Not measured**			
HIV transmission or acquisition	**Not measured**			
STI complications	**Not measured**			

MU: million units; OR: odds ratio; RCT: randomized controlled trial

1. One-arm study; authors did not mention any information related to the use of an appropriate analysis method that adjusted for all the critically important confounding domains.
2. Small sample size, the total number of events does not meet the optimal information size (OIS) and/or the 95% confidence interval is inconclusive.

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Patient values and preferences, acceptability and cost: Specific to syphilis infections

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3. Kingston MA, Higgins SP. Audit of the management of early syphilis at North Manchester General Hospital. Int J STD AIDS. 2004;15(5):352-4.
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RECOMMENDATIONS 5, 6, 7 AND 8: LATE SYPHILIS – ADULTS, ADOLESCENTS AND PREGNANT WOMEN

Treatments for adults and adolescents, and pregnant women with late syphilis (infection of more than 2 years' duration without evidence of treponemal infection)	
Population:	Adults and adolescents, and pregnant women with late syphilis
Intervention:	Azithromycin, ceftriaxone, doxycycline, erythromycin
Comparison:	Benzathine penicillin G 2.4 MU × 1
Main outcomes:	**Critical:** Serological response, compliance **Important:** Transmission to partner, antimicrobial resistance, side-effects (including allergy, toxicity), HIV transmission or acquisition, STI complications
Setting:	All settings
Perspective:	Population
Background:	Syphilis is a systemic disease from the outset and is caused by the spirochaete *Treponema pallidum*. The infection can be classified as congenital (transmitted from mother to child in utero) or acquired (through sex or blood transfusion). Acquired syphilis is divided into early and late syphilis. Early syphilis comprises the primary, secondary and early latent stages. Late syphilis refers to late latent syphilis, gummatous, neurological and cardiovascular syphilis. Primary syphilis is characterized by an ulcer or chancre at the site of infection or inoculation. Secondary syphilis manifestations include a skin rash, condylomata lata, mucocutaneous lesions and generalized lymphadenopathy. The 2003 WHO STI guidelines recommended treatment of late syphilis in adults was benzathine penicillin G 2.4 MU by intramuscular injection, once weekly for 3 consecutive weeks. An alternative regimen is procaine penicillin 1.2 MU by intramuscular injection, once daily for 20 consecutive days. Alternative regimen for penicillin-allergic non-pregnant patients is doxycycline 100 mg orally twice daily for 30 days, or tetracycline 500 mg orally four times daily for 30 days.

ASSESSMENT

	Judgement	Research evidence
Problem	**Is the problem a priority?** • No • Probably no • Probably yes • **Yes** • Varies • Don't know	**Research evidence:** WHO estimates that 5.6 million new cases of syphilis occurred among adolescents and adults aged 15–49 years worldwide in 2012 with a global incidence rate of 1.5 cases per 1000 females (regional range: 0.9–4.4) and 1.5 per 1000 males (regional range: 0.9–4.4). The estimated 18 million prevalent cases of syphilis in 2012 translates to a global prevalence of 0.5% (0.4–0.6%) among females and 0.5% (0.3–0.7%) among males aged 15–49 years, with the highest prevalence in the African region. Mother-to-child transmission of syphilis is declining globally due to increased efforts to screen and treat pregnant women for syphilis. However, the burden of morbidity and mortality due to congenital syphilis remains high. In 2012 there were an estimated 350 000 adverse pregnancy outcomes worldwide attributed to syphilis, including 143 000 early fetal deaths/stillbirths, 62 000 neonatal deaths, 44 000 preterm/low weight births, and 102 000 infected infants. The burden of disease is highest in low- and middle-income countries, particularly in the African region. Untreated, up to one-third of patients progress to later stages of disease. Late syphilis can cause irreversible damage to the cardiovascular and central nervous systems, resulting in profound morbidity and even death. **Additional considerations:** None
Desirable Effects	**How substantial are the desirable anticipated effects?** • Trivial • Small • Moderate • **Large** • Varies • Don't know	**Research evidence:** Two non-randomized studies were found which assessed treatment for late syphilis: one comparative study in adults (non-pregnant) and one single-arm (non-comparative) study in pregnant women. In non-pregnant adults, benzathine penicillin G 2.4 MU given once intramuscularly and azithromycin 2 g given once were evaluated. The study in pregnant women evaluated benzathine penicillin G 2.4 MU given once a week intramuscularly for 2 weeks. Serological cure rates were low in non-pregnant adults for both medicines (33–39%), but higher for the double dose in pregnant women (99%). **Additional considerations:** The GDG noted that there are few studies conducted in people with late syphilis and most treatment is based on historical use of benzathine penicillin G and procaine penicillin, and in addition, some use of doxycycline at higher and longer doses than treatments for early syphilis. Data were not available for resistance to azithromycin for syphilis in specific settings and will probably be unknown in many places. Resistance to azithromycin for other conditions is spreading, and therefore there was concern for the risk of azithromycin resistance to syphilis.
Undesirable Effects	**How substantial are the undesirable anticipated effects?** • Large • Moderate • **Small** • Trivial • Varies • Don't know	
Certainty of evidence	**What is the overall certainty of the evidence of effects?** • **Very low** • Low • Moderate • High • No included studies	**Research evidence:** No research evidence was identified. **Additional considerations:** None

Values	**Is there important uncertainty about or variability in how much people value the main outcomes?** • Important uncertainty or variability • **Possibly important uncertainty or variability** • Probably no important uncertainty or variability • No important uncertainty or variability • No known undesirable outcomes	**Research evidence:** According to economic evaluation studies, the disability weights due to syphilis (utility loss due to the disease) are as follows: early syphilis: 0.0072–0.015 secondary syphilis: 0.041 tertiary (neurological): 0.094–0.283 death: 1 **Additional considerations:** The GDG noted that there may be variability in outcome values depending on stages of syphilis.
Balance of effects	**Does the balance between desirable and undesirable effects favour the intervention or the comparison?** • Favours the comparison • **Probably favours the comparison** • Does not favour either the intervention or the comparison • Probably favours the intervention • Favours the intervention • Varies • Don't know	**Research evidence:** No research evidence. **Additional considerations:** The GDG agreed that the benefits with penicillins seen historically are large and favour their use. These benefits are similar for pregnant women. However, although there are limited historical data for doxycycline and erythromycin (for pregnant women), the benefits probably favour the use of these medicines.
Resources required	**How large are the resource requirements (costs)?** • Large costs • Moderate costs • **Negligible costs and savings** • Moderate savings • Large savings • Varies • Don't know	**Research evidence:** Benzathine penicillin G requires local preparation, making cost heavily dependent on local labour costs. Benzathine penicillin G without preparation costs $0.28 per dose. For three doses, $3.72 was the average price. Azithromycin cost $1.56. Ceftriaxone has greater costs (data not available). **Additional considerations:** None
Certainty of evidence of required resources	**What is the certainty of the evidence of resource requirements (costs)?** • Very low • Low • Moderate • High • **No included studies**	**Research evidence:** No research evidence was identified. **Additional considerations:** None

Cost–effectiveness	**Does the cost-effectiveness of the intervention favour the intervention or the comparison?** • Favours the comparison • **Probably favours the comparison** • Does not favour either the intervention or the comparison • Probably favours the intervention • Favours the intervention • Varies • No included studies	**Research evidence:** No research evidence available published since 2005. **Additional considerations:** The benefits are similar between the different medicines, but costs are probably higher with ceftriaxone and azithromycin compared to benzathine penicillin.
Equity	**What would be the impact on health equity?** • Reduced • Probably reduced • **Probably no impact** • Probably increased • Increased • Varies • Don't know	**Research evidence:** No research evidence. **Additional considerations:** The GDG considered that health equity could be reduced if benzathine penicillin is not available, but other medicines should be included in the recommendations.
Acceptability	**Is the intervention acceptable to key stakeholders?** • No • Probably no • **Probably yes** • Yes • Varies • Don't know	**Research evidence:** We found four studies that addressed the acceptability of injections (daily versus weekly) versus oral treatments in people with various stages of syphilis. Studies were from 1997 to 2006. Results indicated that approximately 80% or more of people accepted injections, but that weekly injections were preferred. The other people had refused injections and took oral medicines. **Additional considerations:** The GDG reported that in practice, there seemed to be variation in acceptability to key stakeholders. In different countries, health workers were averse to giving injections for this infection, and in others they wanted to give the injections (instead of giving oral treatment). Regarding acceptability to patients, some were averse to injections, and in other settings patients preferred injections. Some suggested that part of this variability could be explained by the varying fear of allergic reaction among both patients and health workers.
Feasibility	**Is the intervention feasible to implement?** • No • Probably no • **Probably yes** • Yes • Varies • Don't know	**Research evidence:** No research evidence. **Additional considerations:** Currently, azithromycin and doxycycline are considered more widely available than benzathine penicillin G.

SUMMARY OF JUDGEMENTS

	Judgement						
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies
Cost–effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

CONCLUSIONS

Treatments for adults and adolescents, and pregnant women with late syphilis

Type of recommendation	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	•	•	•	●	•
Recommendation	**Adults and adolescents** **Recommendation 5** In adults and adolescents with late syphilis or unknown stage of syphilis, the WHO STI guideline recommends benzathine penicillin G 2.4 MU intramuscularly once weekly for three consecutive weeks over no treatment. *Strong recommendation, very low quality evidence* Remarks: The interval between consecutive doses of benzathine penicillin should not exceed 14 days. **Recommendation 6** In adults and adolescents with late syphilis or unknown stage of syphilis, the WHO STI guideline suggests benzathine penicillin G 2.4 MU intramuscularly once weekly for three consecutive weeks over procaine penicillin 1.2 MU once a day for 20 days. *Conditional recommendation, very low quality evidence* When benzathine or procaine penicillin cannot be used (e.g. due to penicillin allergy where penicillin desensitization is not possible) or are not available (due to stock-outs), the WHO STI guideline suggests using doxycycline 100 mg twice daily orally for 30 days. *Conditional recommendation, very low quality evidence* Remarks: Doxycycline should not be used in pregnant women (see recommendation for pregnant women). **Pregnant women** **Recommendation 7** In pregnant women with late syphilis or unknown stage of syphilis, the WHO STI guideline recommends benzathine penicillin G 2.4 MU intramuscularly once weekly for three consecutive weeks over no treatment. *Strong recommendation, very low quality evidence* Remarks: The interval between consecutive doses of benzathine penicillin should not exceed 14 days.				

Type of recommendation	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	•	•	•	●	•
Recommendation	**Recommendation 8** In pregnant women with late syphilis or unknown stage of syphilis, the WHO STI guideline suggests benzathine penicillin G 2.4 MU intramuscularly once weekly for three consecutive weeks over procaine penicillin 1.2 MU intramuscularly once a day for 20 days. *Conditional recommendation, very low quality evidence* When benzathine or procaine penicillin cannot be used (e.g. due to penicillin allergy where penicillin desensitization is not possible) or are not available (due to stock-outs), the WHO STI guideline suggests using erythromycin 500 mg orally four times daily for 30 days. *Conditional recommendation, very low quality evidence* Remarks: Although erythromycin treats the pregnant women, it does not cross the placental barrier completely and as a result the fetus is not treated. It is therefore necessary to treat the newborn infant soon after delivery (see recommendations for congenital syphilis). Doxycycline should not be used in pregnant women. Erythromycin treats the mother but is not known to be effective for preventing mother-to-child transmission of syphilis. Because syphilis during pregnancy can lead to severe adverse complications to the fetus or newborn, stock-outs of benzathine penicillin for use in antenatal care should be avoided.				
Justification	Overall, the quality of the evidence was very low. Most studies typically report results for people with late or early syphilis and do not distinguish between the stage of syphilis in the results. However, one study included over 300 people identified with late syphilis. It evaluated benzathine penicillin G 2.4 MU given once intramuscularly and azithromycin 2 g given once. Serological cure was low with these doses, which are typically provided for early syphilis (33–39%). One study was also found for treatment for pregnant women with late syphilis. This study found a cure rate of 99% in 135 women with the double dose of benzathine penicillin G. Historically, multiple doses of benzathine penicillin G provided once a week for 3 weeks and procaine penicillin 1.2 MU provided once daily for 20 days, have been successful for serological and clinical cure of syphilis. For pregnant women, prevention of mother-to-child transmission is a critical outcome. The penicillins cross the placental barrier; however, azithromycin and erythromycin do not. Therefore there is an increased chance of transmission with the use of the latter medicines. There is some historical use of doxycycline 100 mg twice daily for 30 days with success (but not in pregnant women). There were no data for adverse events, transmission to partners, HIV transmission and acquisition, and STI complications. There are no reported data available on resistance to azithromycin for treating syphilis in specific settings, and this will likely remain unknown in many places as the capacity to monitor antimicrobial resistance (AMR) in *T. pallidum* is not available in many settings. Resistance to azithromycin for other conditions is spreading, and therefore the GDG was concerned about the risk of azithromycin resistance in *T. pallidum*. Evidence used for making recommendations in early syphilis was used to inform this recommendation for late syphilis. There was some research evidence for overall acceptability of injections versus oral medicines in people with syphilis, but approximately 10–20% of people refused injections. The GDG noted that in practice, some health-care providers are averse to providing injections, and there is additional staff time and equipment costs with intramuscular administration. The GDG raised concern about the impending global shortage of benzathine penicillin; a shortage would reduce health equity and it would not be feasible to apply the treatment recommendation.				

Justification	The GDG judged the benefits of treatment with benzathine penicillin G versus no treatment as large, based on the historically successful treatment of syphilis over the past 70 years. It was also judged that the differences in benefits between medicines used for treatment are likely to be trivial. The differences in the undesirable anticipated effects (side-effects) were judged to be small. Because the benefits probably outweigh the harms, and because of the potential for resistance to azithromycin, greater cost and lack of historical data for azithromycin, benzathine penicillin G and procaine penicillin were suggested. The penicillins were suggested over doxycycline due to the lack of historical data in late syphilis and unknown side-effects and benefits of doxycycline. For pregnant women, the penicillins were also suggested over erythromycin since erythromycin does not cross the placental barrier. The GDG also judged administration of benzathine and procaine penicillins by injection as being acceptable to most people.
Subgroup considerations	
Implementation considerations	
Monitoring and evaluation	
Research priorities	More clinical research is needed into the treatment of adults and HIV-positive patients with late syphilis with benzathine penicillin G (including different dosing regimens) and other treatments such as doxycycline and azithromycin.

EVIDENCE PROFILE

Benzathine penicillin G 2.4 MU weekly × 3 or azithromycin 2 grams for treatment of adults and adolescents, including HIV-positive patients, with late syphilis												
Quality assessment							**Number of patients**		**Effect with azithromycin**		**Quality of evidence (GRADE)**	**Importance**
Number of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Azithromycin 2 g × 1 dose**	**Benzathine penicillin G 2.4 MU ×1**	**Relative (95% CI)**	**Absolute (95% CI)**		
Serological cure												
1	Observational studies	Not serious	Not serious	Serious[1]	Serious[2]	None	55/165 (33.3%)	66/168 (39.3%)	**OR 0.77** (0.49–1.21)	60 fewer per 1000 (from 46 more to 152 fewer)	⨁⊖⊖⊖ VERY LOW[1]	CRITICAL

CI: confidence interval; MU: million units; OR: odds ratio

1. The data compare benzathine penicillin G given once, not three times.
2. The 95% CI is inconclusive, suggesting azithromycin as more effective treatment in one extreme, and benzathine penicillin G × 1 dose in the other extreme.

EVIDENCE PROFILE

Benzathine penicillin G 2.4 MU × 3 for treatment of pregnant women with late syphilis	
Effects and quality of the evidence	
Outcomes (IMPORTANCE)	**Benzathine penicillin 2.4 MU × 2 doses**
Serological cure (CRITICAL)	**990 people per 1000** (970 to 1010)
	135 participants, 1 non-RCT ⨁⊖⊖⊖ **Very low** Risk of bias and indirectness[1]
Prevention of mother-to-child transmission (CRITICAL)	**1000 people per 1000** (1 to 1)
	136 participants, 1 non-RCT ⨁⊖⊖⊖ **Very low** Risk of Bias and indirectness[1]
Stillbirth/neonatal death (CRITICAL)	**1 people per 1000** (–0.0137 to 0.0157)
	136 participants, 1 non-RCT ⨁⊖⊖⊖ **Very low** Risk of bias and indirectness[1]
Clinical cure	Not measured
Compliance	Not measured
Adverse events	Not measured
Transmission to partner	Not measured
Antimicrobial resistance	Not measured
HIV transmission or acquisition	Not measured
STI complications	Not measured

1. Results from single-arm non-randomized studies evaluating 1 dose for 2 weeks, not 3 weeks.

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RECOMMENDATION 5 AND 6

Systematic reviews

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Included studies

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2. Crowe G, Theodore C, Forster GE, Goh BT. Acceptability and compliance with daily injections of procaine penicillin in the outpatient treatment of syphilis-treponemal infection. Sex Transm Dis. 1997;24(3):127-30.
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5. Tayal S, Ahmed MS, Hanif U. Audit of early syphilis: Teesside experience 2005–2007. Int J STD AIDS. 2009;20(9):647-9.

RECOMMENDATION 7 AND 8

Systematic review

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2. Newman L, Rowley J, Vander Hoorn S, Wijesooriya NS, Unemo M, Low N et al. Global estimates of the prevalence and incidence of four curable sexually transmitted infections in 2012 based on systematic review and global reporting. PLoS One. 2015;10(12):e0143304. doi:10.1371/journal.pone.0143304.

RECOMMENDATIONS 9 AND 10: CONGENITAL SYPHILIS – INFANTS

Treatments for infants with confirmed congenital syphilis or infants who are clinically normal, but whose mothers had untreated syphilis, inadequately treated syphilis or syphilis that was treated with non-penicillin regimens

Treatments for infants who are clinically normal and whose mothers had syphilis that was adequately treated with no signs of reinfection

Population:	Infants with confirmed congenital syphilis or infants who are clinically normal, but whose mothers had untreated syphilis, inadequately treated syphilis or syphilis that was treated with non-penicillin regimens Infants who are clinically normal and whose mothers had syphilis that was adequately treated with no signs of reinfection
Intervention:	Aqueous crystalline/procaine penicillin
Comparison:	Ceftriaxone
Main outcomes:	Critical: – clinical cure – serological response – congenital syphilis manifestation
Setting:	All settings
Perspective:	Population
Background:	WHO definition of confirmed congenital syphilis: Microbiological evidence of congenital syphilis includes any one of the following: • demonstration by dark-field microscopy or fluorescent antibody detection of *T. pallidum* in the umbilical cord, the placenta, a nasal discharge or skin lesion material • detection of *T. pallidum*-specific IgM • infant with a positive non-treponemal serology titre ≥ fourfold above that of the mother Also defined as live birth to a syphilis seropositive mother without adequate syphilis treatment (from *Global guidance on criteria and processes for validation: elimination of mother-to-child transmission (EMTCT) of HIV and syphilis*)[1]. The GDG identified the following for review: Aqueous crystalline penicillin 100 000–150 000 U/kg IM single dose OR procaine penicillin 50 000 U/kg/day IM × 10–15 days OR ceftriaxone in infants (< 30 days) 75 mg/kg BW IM/IV single dose × 1 day, infants (≥ 30 days) 100 mg/kg BW IM/IV single dose × 1 day.

BW: body weight; IgM: immunoglobulin M; IM: intramuscular; IV: intravenous

1. Global guidance on criteria and processes for validation: elimination of mother-to-child transmission (EMTCT) of HIV and syphilis. Geneva: World Health Organization; 2014 (http://www.who.int/reproductivehealth/publications/rtis/9789241505888/en/).

ASSESSMENT

	Judgement	Research evidence
Problem	**Is the problem a priority?** • No • Probably no • **Probably yes** • Yes • Varies • Don't know	**Research evidence:** Global estimates published in 2013 (Newman) indicated that there were 217 678 live births with syphilis per 1 360 485 women with syphilis not treated. This would mean approximately 16 live births with syphilis per 100 women with syphilis not treated, therefore there would have been other stillbirths or neonatal deaths, or premature births. A systematic review found that when mothers are treated, the risk of congenital syphilis is 0.03 times the risk in infants born to untreated mothers; from this it can be roughly estimated that there would be 4.8 births with congenital syphilis per 1000 treated mothers. Only half of these infants (2.4 per 1000) would be expected to show signs or symptoms of congenital syphilis. Therefore in 1000 treated mothers there would be a risk of 2–3 infants born with congenital syphilis who are clinically normal. The resource implications of hospitalization for infants with congenital syphilis is > 3 times higher versus infants without the disease. At one South African hospital, 57% of symptomatic infants required neonatal intensive care unit (NICU) admission, and 52% of those infants died. On average, almost one NICU bed (in a 12-bed unit with 600 admissions annually) was always occupied by an infant with syphilis (Bateman, 1997). Also, it has been reported that in developed countries neonates with congenital syphilis are more likely to be admitted to the NICU and stay longer in hospital. **Additional considerations:** None
Desirable Effects	**How substantial are the desirable anticipated effects?** • Trivial • Small • Moderate • **Large** • Varies • Don't know	**Research evidence:** We found nine non-randomized studies. Most studies included very few babies and there was very low follow-up of babies after treatment was provided. When there was follow-up, it ranged from 6 months to 1 year. Treatments provided included aqueous benzyl penicillin and procaine penicillin; ceftriaxone was not assessed. In most studies, treatment resulted in 100% cures with no adverse effects. However, ceftriaxone was known to interact with calcium in neonates and is contraindicated in infants before 41 weeks. Historical experience is available. Historically, benzathine penicillin dosing consists of scaling down doses by body weight, and there is little data obtained about success. **Additional considerations:** None
Undesirable Effects	**How substantial are the undesirable anticipated effects?** • Large • Moderate • **Small** • Trivial • Varies • Don't know	

Certainty of evidence	**What is the overall certainty of the evidence of effects?** • **Very low** • Low • Moderate • High • No included studies	**Research evidence:** No research evidence was identified. **Additional considerations:** None
Values	**Is there important uncertainty about or variability in how much people value the main outcomes?** • Important uncertainty or variability • Possibly important uncertainty or variability • Probably no important uncertainty or variability • **No important uncertainty or variability** • No known undesirable outcomes	**Research evidence:** According to economic evaluation studies, the disability weights due to syphilis (utility loss due to the disease) are as follows: congenital syphilis: 0.315 low birth weight: 0.106 neonatal death: 1 stillbirth: 1 miscarriage: 1 **Additional considerations:** A high value was placed on treatment and avoidance of congenital syphilis.
Balance of effects	**Does the balance between desirable and undesirable effects favour the intervention or the comparison?** • Favours the comparison • **Probably favours the comparison** • Does not favour either the intervention or the comparison • Probably favours the intervention • Favours the intervention • Varies • Don't know	**Research evidence:** Aqueous benzyl penicillin or procaine penicillin was favoured over ceftriaxone, for which there was little to no data and potential for side-effects and contraindications. **Additional considerations:** None

Resources required

How large are the resource requirements (costs)?

- Large costs
- Moderate costs
- **Negligible costs and savings**
- Moderate savings
- Large savings
- Varies
- Don't know

Treatment	Administer in dose(s) across day	Treatment duration (days)	Cost, per dose ($) *	Cost per full-course treatment ($)	25% procurement ($)
Aqueous crystalline penicillin G, benzyl 100 000-150 000 U/kg (5 MU INJ IV) ~10 kg	2	10–15	0.23	2.30–3.45	2.88–4.31
Procaine penicillin 50 000 U/kg (1 MU powder INJ) ~10 kg	1	10–15	0.18	1.80–2.70	2.25–3.38
Ceftriaxone 75 mg/kg (250 mg vial INJ) ~4 kg	1	10–14	0.52	5.20–7.28	6.50–9.10
Ceftriaxone 100 mg/kg (1 g vial INJ) ~12 kg	1	10–14	0.75	7.50–10.50	9.38–13.13

* Sources: International drug price indicator guide, 2014 editions (Management Sciences for Health, 2015) and www.drugs.com

Additional considerations:
Costs for therapy would be increased if the infant had to stay in hospital. The GDG agreed that there was little cost difference between aqueous benzyl penicillin or procaine penicillin, but that ceftriaxone was more expensive.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

- Very low
- Low
- Moderate
- High
- **No included studies**

Research evidence:
No research evidence was identified.

Additional considerations:
None

Cost–effectiveness	**Does the cost-effectiveness of the intervention favour the intervention or the comparison?** • Favours the comparison • **Probably favours the comparison** • Does not favour either the intervention or the comparison • Probably favours the intervention • Favours the intervention • Varies • No included studies	**Research evidence:** No research evidence was identified. **Additional considerations:** None
Equity	**What would be the impact on health equity?** • Reduced • Probably reduced • **Probably no impact** • Probably increased • Increased • Varies • Don't know	**Research evidence:** No research evidence **Additional considerations:** The GDG agreed that the medicines are available and probably would not have an impact on equity. However, for people who need to travel for treatment, health equity may be reduced.
Acceptability	**Is the intervention acceptable to key stakeholders?** • No • Probably no • **Probably yes** • Yes • Varies • Don't know	**Research evidence:** No research evidence. **Additional considerations:** There were concerns that 10–15 days of injections would not be acceptable or feasible if patients had to travel, but for infants born in hospital this regimen was deemed appropriate. The GDG agreed that intramuscular injections would be acceptable, given that finding a vein for intravenous administration is often very difficult for infants. However, if an experienced venipuncturist is present and willing, intravenous benzyl penicillin could be administered.
Feasibility	**Is the intervention feasible to implement?** • No • Probably no • **Probably yes** • Yes • Varies • Don't know	**Research evidence:** The infant will already be hospitalized in a confirmed case so implementing a strategy in this population is likely to be feasible. All medicines are feasible to acquire in various settings. In addition to these considerations, it was noted that opened containers of benzathine penicillin G need to be refrigerated. **Additional considerations:** None

SUMMARY OF JUDGEMENTS

	Judgement						
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies
Cost–effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

CONCLUSIONS

Treatments for infants with confirmed or suspected congenital syphilis

Type of recommendation	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	•	•	•	●	•
Recommendation	**Infants** **Recommendation 9** 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 STI guideline suggests aqueous benzyl penicillin or procaine penicillin. *Conditional recommendation, very low quality evidence* Dosages: · Aqueous benzyl penicillin 100 000–150 000 U/kg/day intravenously for 10–15 days · Procaine penicillin 50 000 U/kg/day single dose intramuscularly for 10–15 days Remarks: If an experienced venipuncturist is available, aqueous benzyl penicillin may be preferred instead of intramuscular injections of procaine penicillin. **Recommendation 10** In infants who are clinically normal and whose mothers had syphilis that was adequately treated with no signs of reinfection, the WHO STI guideline suggests close monitoring of the infants. *Conditional recommendation, very low quality evidence* Remarks: The risk of transmission of syphilis to the fetus depends on a number of factors, including maternal titres from non-treponemal tests (e.g. rapid plasma reagin, RPR), timing of maternal treatment and stage of maternal infection, and therefore this recommendation is conditional. If treatment is provided, benzathine penicillin G 50 000 U/kg/day single dose intramuscularly is an option.				

Type of recommendation	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	•	•	•	●	•
Justification	The overall quality of the evidence was very low. Nine non-randomized studies informed this recommendation, as well as historical use of the medicines to treat and prevent confirmed or suspected congenital syphilis. The sample size of most studies was low and rates of follow-up of babies after treatment was very low. When there was follow-up, it ranged from 6 months to 1 year. Treatments provided included aqueous benzyl penicillin and procaine penicillin and benzathine penicillin G; ceftriaxone was not assessed. In most studies of infants with confirmed congenital syphilis or infants with mothers who had inadequate or no treatment, treatment of infants resulted in 100% cures with no adverse effects. Aqueous benzyl penicillin or procaine penicillin was favoured over ceftriaxone due to little or no data and potential for side-effects and contraindications with ceftriaxone. There were very few data; some historical data indicate that benzathine penicillin G may have benefit and few adverse effects, but this is uncertain. There were no follow-up data for untreated infants who were clinically normal and born to mothers who had received adequate treatment. From global estimates, the risk of congenital syphilis for infants born alive to untreated mothers is approximately 16 per 100 mothers. A systematic review found that when mothers are treated, the risk of congenital syphilis is 0.03 times the risk in infants born to untreated mothers; from this it can be roughly estimated that there would be 4.8 births with congenital syphilis per 1000 treated mothers. Only half of these infants (2.4 per 1000) would be expected to show signs or symptoms of congenital syphilis. Therefore in 1000 treated mothers there would be a risk of 2–3 infants born with congenital syphilis who are clinically normal. There was little cost difference between aqueous benzyl penicillin or procaine penicillin, but ceftriaxone was more expensive. The GDG agreed that the medicines are available and this would probably not have an impact on equity. However, for people who need to travel for treatment, health equity may be reduced. The GDG agreed that intramuscular injections would be acceptable, given that finding a vein for intravenous administration is often very difficult for infants. However, if an experienced venipuncturist is present and willing, intravenous benzyl penicillin could be administered. Overall, historical data show benefits of treatment with aqueous benzyl penicillin and procaine penicillin with little to no adverse effects, and the costs are similar. There are few to no data for benzathine penicillin G, but there may be no adverse effects; and few to no data for ceftriaxone, but adverse effects may occur and it is more expensive than the other medicines. A preference for intramuscular injections or intravenous administration was not determined, but there is an option with either medicine. Overall, the risk for congenital syphilis for infants born to mothers who have received adequate treatment was very low and therefore monitoring was suggested over treatment of these infants.				
Subgroup considerations					
Implementation considerations	Injection is more painful to babies but is probably more practical as it is administered once per day. With intravenous administration it is often difficult for the clinician to insert the line, and it is administered multiple times per day. Same day diagnosis and treatment is ideal as high loss to follow-up after testing is likely.				

Monitoring and evaluation	
Research priorities	Trials investigating appropriate dosages and effectiveness of ceftriaxone use for early and late syphilis should be conducted. The trials should compare ceftriaxone with benzathine penicillin G and doxycycline. More research should be conducted into medicines taken orally for a few days, such as cephalosporins. Since benzathine penicillin G and other penicillins require injection by health workers, it was suggested that the safety of self-injection be investigated. The GDG discussed the need to develop new treatment. Ideally the new treatment should be a short course administered orally and that can treat pregnant women with syphilis and cross the blood–brain and placental barriers to prevent transmission to the fetus. Cephalosporins could be potential options. Trials investigating appropriate dosages and effectiveness of ceftriaxone use for early and late syphilis should be established. The trials should compare ceftriaxone with benzathine penicillin G. The extent to which the medicines cross the blood–brain and placental barriers should also be investigated. There were few data for ceftriaxone use in infants with confirmed congenital syphilis and therefore research is needed, in particular in comparison to procaine penicillin.

EVIDENCE PROFILE

Aqueous crystalline/procaine penicillin compared to ceftriaxone for infants with confirmed congenital syphilis

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aqueous crystalline/ procaine penicillin	Ceftriaxone	Relative (95% CI)	Absolute (95% CI)		
Infants with negative tests after treatment with aqueous crystalline penicillin (follow up: 3–6 months)[1]												
1	Observational studies	Serious[2]	Not serious	Not serious	Serious[3]	None	9/9 (100%)	-	-	-	⨁⨀⨀⨀ VERY LOW	
Aqueous crystalline penicillin adverse events[4]												
							Pharmaceutical label information described skin rashes ranging from maculopapular eruptions to exfoliative dermatitis; urticaria; and reactions resembling serum sickness, including chills, fever, edema, arthralgia and prostration and Jarisch–Herxheimer reaction; but without frequencies.				–	CRITICAL
Procaine adverse events[5]												
							Pharmaceutical label information described diarrhoea, candidiasis and skin rash; but without frequencies.				–	CRITICAL
Ceftriaxone adverse events (e.g. diarrhoea, vomiting, exanthema) in neonates (early unspecified follow-up)												
1[6]	Observational studies	Not serious	Not serious	Not serious	Not serious	None		14/161 (8.7%)	Not estimable		⨁⨁⨀⨀ LOW	CRITICAL
Ceftriaxone causing fatalities in neonates (calcium interaction)[5]												
							Caution for use in neonates because of "interaction with calcium". Most parenteral nutrition formulations and many IV solutions used contain calcium.				–	CRITICAL

1. Sangtawesin, 2005
2. Limited follow-up
3. Few neonates
4. Roerig, 2005
5. WHO, 2008
6. Fujii, 1988

EVIDENCE PROFILE

Benzathine penicillin compared to no treatment/ceftriaxone for infants who are clinically normal and whose mothers had syphilis that was adequately treated with no signs of reinfection

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Benzathine penicillin	No treatment/ ceftriaxone	Relative (95% CI)	Absolute (95% CI)		
Infants: sequelae (follow-up: at least 8 months)												
1 [1]	Observational studies	Serious[2]	Not serious	Not serious	Serious[2]	None	0/27 (0.0%)	-	-		⨁⊖⊖⊖ VERY LOW	CRITICAL
Infants: very low birth weight (not included in sequelae) (follow-up: at least 8 months)												
1 [1]	Observational studies	Serious[2]	Not serious	Not serious	Serious[2]	None	1/27 (3.7%)	-	-		⨁⊖⊖⊖ VERY LOW	CRITICAL
Infants: non infected (follow-up: 1 year)												
1 [3]	Observational studies	Serious[4]	Not serious	Not serious	Serious[4]	None	1/1 (100.0%)	-	-		⨁⨁⊖⊖ VERY LOW	CRITICAL
Benzathine adverse events5												
							Hypersensitivity reactions included the following: skin eruptions (maculopapular to exfoliative dermatitis), erythema, cellulitis, paresthesia, urticaria, laryngeal edema, fever, eosinophilia; other serum sickness-like reactions (including chills, fever, edema, arthralgia and prostration) and Jarisch–Herzheimer reaction; but without frequencies.				-	CRITICAL
Ceftriaxone adverse events (e.g. diarrhoea, vomiting, exanthema) in neonates (early unspecified follow-up)												
1 [6]	Observational studies	Not serious	Not serious	Not serious	Not serious	None		14/161 (8.7%)	Not estimable		⨁⨁⊖⊖ LOW	CRITICAL
Ceftriaxone: adverse event frequencies[7]												
							Caution for use in neonates because of "interaction with calcium". Most parenteral nutrition formulations and many IV solutions used contain calcium.				-	CRITICAL

1. Lago, 2013; 2. 27 followed up from 120 total population with mother who were adequately treated; 3. Valentini, 2004; 4. One treated out of 13 and 8 followed up; 5. Pfizer, 2011; 6. Fujii, 1988; 7. WHO, 2008.

EVIDENCE PROFILE

Aqueous crystalline/procaine penicillin compared to benzathine penicillin/ceftriaxone/no treatment for clinically normal infants whose mothers had untreated syphilis, inadequately treated syphilis or syphilis that was treated with non-penicillin regimens

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aqueous crystalline/ procaine penicillin	Benzathine penicillin/ ceftriaxone/ no treatment	Relative (95% CI)	Absolute (95% CI)		
Negative tests and normal growth aqueous crystalline (follow-up: 3–6 months)												
1 [1]	Observational studies	Serious[2]	Not serious	Not serious	Serious[3]	None	25/25 (100.0%)	-	-	-	⨁⨀⨀⨀ VERY LOW	CRITICAL
Infants: non infected (follow-up: 1 years) treated with crystalline penicillin												
1 [4]	Observational studies	Serious[2]	Not serious	Not serious	Serious[3]	None	5/5 (100.0%)	-	-	-	⨁⨀⨀⨀ VERY LOW	
Aqueous crystalline penicillin adverse events[5]												
							Pharmaceutical label information described skin rashes ranging from maculopapular eruptions to exfoliative dermatitis; urticaria; and reactions resembling serum sickness, including chills, fever, edema, arthralgia and prostration and Jarisch–Herxheimer reaction; but without frequencies.				-	CRITICAL
Procaine AND Benzathine Penicillin: non-reactive RPR titres (follow-up: 12 months)												
1 [6]	Observational studies	Not serious	Not serious	Not serious	Not serious	None	68/68 (100.0%)	84/84 (100.0%)	Not estimable		⨁⨁⨀⨀ LOW	CRITICAL
Procaine adverse events[7]												
							Pharmaceutical label information described diarrhoea, candidiasis and skin rash; but without frequencies.				-	CRITICAL
Benzathine: no immunoglobulin M (IgM) reactivity (follow-up: up to 6 months)												
1 [8]	Observational studies	Serious[9]	Not serious	Not serious	Serious [10]	None		10/10 (100.0%)	Not estimable		⨁⨀⨀⨀ VERY LOW	CRITICAL

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aqueous crystalline/ procaine penicillin	Benzathine penicillin/ ceftriaxone/ no treatment	Relative (95% CI)	Absolute (95% CI)		
Benzathine adverse events[11]												
							Hypersensitivity reactions included the following: skin eruptions (maculopapular to exfoliative dermatitis), erythema, cellulitis, paresthesia, urticaria, laryngeal edema, fever, eosinophilia; other serum sickness-like reactions (including chills, fever, edema, arthralgia and prostration) and Jarisch–Herzheimer reaction; but without frequencies.				-	CRITICAL
Ceftriaxone adverse events (e.g. diarrhoea, vomiting, exanthema) in neonates (early unspecified follow-up)												
1 [12]	Observational studies	Not serious	Not serious	Not serious	Not serious	None		14/161 (8.7%)	Not estimable		⨁⨁⊖⊖ LOW	CRITICAL
Ceftriaxone: adverse event frequencies[7]												
							Caution for use in neonates because of "interaction with calcium". Most parenteral nutrition formulations and many IV solutions used contain calcium.				-	CRITICAL

1. Sangtawesin, 2005
2. High loss to follow-up.
3. Few neonates.
4. Valentini, 2004
5. Roerig, 2005
6. Paryani, 1994
7. WHO, 2008
8. Radcliffe, 1997
9. No description of allocation process described.
10. 28% loss to follow up.
11. Pfizer, 2011
12. Fujii, 1988.

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