Essential Medicines List
Sexually Transmitted Infections

*Treponema pallidum* (syphilis)

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Background

WHO have just updated the treatment recommendations for specific Sexually Transmitted Infections (STI) in August 2016. Since the publication of the World Health Organization (WHO) Guidelines for the management of sexually transmitted infections in 2003, changes in the epidemiology of STIs and advancements in prevention, diagnosis and treatment necessitate changes in STI management.

Review and reassessment of the guidelines for treatment of syphilis is needed, taking into account recent evidence on the effectiveness and antimicrobial susceptibility patterns of azithromycin. Benzathine penicillin has been the recommended treatment for syphilis for more than 70 years. Doxycycline is recommended as an alternative treatment for penicillin-allergic, non-pregnant patients. Some studies suggest that azithromycin may be equivalent to benzathine penicillin for treatment of early syphilis. Azithromycin has the added advantage of single-dose oral administration and should be assessed as a possible alternative treatment for penicillin-allergic pregnant patients. However, those advantages need to be weighed against the increasing number of reports of T. pallidum azithromycin resistance. Other options for treating penicillin-allergic patients should also be explored, such as desensitization and injectable daily ceftriaxone.

The WHO Guidelines for the management of sexually transmitted infections, published in 2003, recommend early screening and treatment of pregnant women with syphilis, ideally prior to the second trimester of pregnancy, to avoid any fetal complications. In addition, the 2003 WHO STI guidelines recommended treatment for early and late congenital syphilis. Based on this recommendation, it is important for the health-care provider to make a diagnosis and to differentiate early and late congenital syphilis. Diagnosis of congenital syphilis remains a challenge because it requires clinical acumen and availability of laboratory tests. Given these challenges, countries have expressed the need for diagnostic guidelines and treatment recommendations based not only on clinical signs and laboratory tests for congenital syphilis, but also on maternal syphilis serostatus and treatment.

The WHO Essential Medicine Lists (EML) provide a list of the most efficacious and safe medicines for the treatment of illnesses that are considered high priority, including antibiotics. The new WHO guidelines for the treatment of Treponema pallidum are based on the latest evidence-based recommendations and antimicrobial resistance patterns and expert opinions, using the GRADE process. It would be essential that these new recommendations are reflected in the EML to ensure that appropriate treatment for syphilis is accessible.

Public Health Importance of Appropriate Treatment of Treponema pallidum

Epidemiology
Sexually transmitted infections (STIs) are a major public health problem worldwide, affecting quality of life and causing serious morbidity and mortality. STIs have a direct impact on reproductive and child health through infertility, cancers and pregnancy complications, and they have an indirect
impact through their role in facilitating sexual transmission of human immunodeficiency virus (HIV) and thus they also have an impact on national and individual economies. More than a million STIs are acquired every day. In 2012, an estimated 357 million new cases of curable STIs (gonorrhoea, chlamydia, syphilis and trichomoniasis) occurred among 15- to 49-year-olds worldwide, including 5.6 million cases of syphilis. There are an estimated 18 million prevalent cases of syphilis.

**Clinical presentation, complications and sequelae**

Syphilis is a bacterial STI caused by *Treponema pallidum* that results in substantial morbidity and mortality. Syphilis is transmitted through sexual contact with infectious lesions of the mucous membranes or abraded skin, via blood transfusion, or transplacentally from a pregnant woman to her fetus. Untreated, the disease lasts many years and is divided into stages. Early syphilis consists of primary syphilis, secondary syphilis and early latent syphilis, while late syphilis consists of late latent syphilis and tertiary syphilis (neurosyphilis, cardiosyphilis and gumma).

Primary syphilis classically presents as a solitary, painless chancre at the site of inoculation. However, the primary chancre may go unnoticed by patients. If untreated, the disease progresses to the secondary stage, characterized by generalized mucocutaneous lesions affecting both skin, mucous membranes and lymphnodes. The rash of secondary syphilis can vary widely and mimic other infectious and non-infectious conditions, but characteristically affects the palms and soles. The symptoms and signs of secondary syphilis spontaneously resolve, even without treatment, and if left untreated, the patient enters the latent stage.

Latent syphilis is asymptomatic, characterized by positive syphilis serology with no clinical manifestations. Latent syphilis is often divided into two phases: early latent syphilis is defined as infection for less than two years while late latent syphilis is the presence of the disease for two years or more. Sexual transmission typically occurs during primary, secondary or early latent stage infections; however, mother-to-child transmission has been documented to occur in untreated cases several years after initial maternal infection.

Mother-to-child transmission of syphilis (congenital syphilis) is usually devastating to the fetus if maternal infection is not detected and treated sufficiently early in pregnancy. The burden of morbidity and mortality due to congenital syphilis is high. In 2012, an estimated 350 000 adverse pregnancy outcomes worldwide were attributed to syphilis, including 143 000 early fetal deaths/stillbirths, 62 000 neonatal deaths, 44 000 preterm/low-birth-weight babies and 102 000 infected infants. Most untreated primary and secondary syphilis infections in pregnancy result in severe adverse pregnancy outcomes. Latent (asymptomatic) syphilis infections in pregnancy also cause serious adverse pregnancy outcomes in more than half of cases. Mother-to-child transmission of syphilis is declining globally due to increased efforts to screen and treat pregnant women for syphilis.

**Laboratory diagnosis**

Syphilis diagnosis is usually based on clinical history, physical examination, laboratory testing and sometimes radiology. In most laboratory settings, the diagnosis is based upon serologic tests. These include treponemal tests that measure antibodies to infection (including *Treponema pallidum* haemagglutination assay [TPHA], *Treponema pallidum* particle agglutination assay [TPPA], fluorescent treponemal antibody absorbed [FTA-ABS]) and non-treponemal tests that are indirect
markers measuring host immune response to infections (including rapid plasma reagin [RPR], Venereal Diseases Research Laboratory [VDRL], Toluidine Red Unheated Serum Test [TRUST]). Rapid treponemal tests for syphilis and dual HIV and syphilis tests are now available. These tests will increase coverage for diagnosing syphilis.

**WHO recommendations for the treatment of Treponema pallidum**

Table 1. Summary of recommendations for treatment of *Treponema pallidum* and congenital syphilis

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Strength of recommendation and quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early syphilis (primary, secondary and early latent syphilis of not more than two years’ duration)</td>
<td></td>
</tr>
<tr>
<td>Adults and adolescents</td>
<td></td>
</tr>
<tr>
<td><strong>Recommendation 1</strong></td>
<td><strong>Strong recommendation, very low quality evidence</strong></td>
</tr>
<tr>
<td>In adults and adolescents with early syphilis, the WHO STI guideline recommends benzathine penicillin G 2.4 million units once intramuscularly over no treatment.</td>
<td></td>
</tr>
<tr>
<td><strong>Recommendation 2</strong></td>
<td><strong>Conditional recommendation, very low quality evidence</strong></td>
</tr>
<tr>
<td>In adults and adolescents with early syphilis, the WHO STI guideline suggests using benzathine penicillin G 2.4 million units once intramuscularly over procaine penicillin G 1.2 million units 10–14 days intramuscularly.</td>
<td></td>
</tr>
<tr>
<td>When benzathine or procaine penicillin cannot be used (e.g. due to penicillin allergy) or are not available (e.g. due to stock-outs), 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.</td>
<td>Remarks: Doxycycline is preferred over ceftriaxone due to its lower cost and oral administration. Doxycycline should not be used in pregnant women (see recommendations 3 and 4 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.</td>
</tr>
<tr>
<td>Pregnant women</td>
<td></td>
</tr>
<tr>
<td><strong>Recommendation 3</strong></td>
<td><strong>Strong recommendation, very low quality evidence</strong></td>
</tr>
<tr>
<td>In pregnant women with early syphilis, the WHO STI guideline recommends benzathine penicillin G 2.4 million units once intramuscularly over no treatment.</td>
<td></td>
</tr>
<tr>
<td><strong>Recommendation 4</strong></td>
<td><strong>Conditional recommendation, very low quality evidence</strong></td>
</tr>
<tr>
<td>In pregnant women with early syphilis, the WHO STI guideline suggests using benzathine penicillin G 2.4 million units once intramuscularly over procaine penicillin 1.2 million units intramuscularly once daily for 10 days.</td>
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</tr>
<tr>
<td>When benzathine or procaine penicillin cannot be used (e.g. due to penicillin allergy where penicillin desensitization is not possible) or are 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.</td>
<td></td>
</tr>
</tbody>
</table>
**Remarks:** Although erythromycin and azithromycin treat the 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 9 and 10 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.**

**Late syphilis (infection of more than two years' duration without evidence of treponemal infection)**

<table>
<thead>
<tr>
<th>Adults and adolescents</th>
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</thead>
<tbody>
<tr>
<td><strong>Recommendation 5</strong></td>
</tr>
<tr>
<td>In adults and adolescents with late syphilis or unknown stage of syphilis, the WHO STI guideline recommends benzathine penicillin G 2.4 million units intramuscularly once weekly for three consecutive weeks over no treatment.</td>
</tr>
<tr>
<td><strong>Remarks:</strong> The interval between consecutive doses of benzathine penicillin should not exceed 14 days.</td>
</tr>
</tbody>
</table>

| **Recommendation 6** |
| In adults and adolescents with late syphilis or unknown stage of syphilis, the WHO STI guideline suggests benzathine penicillin G 2.4 million units intramuscularly once weekly for three consecutive weeks over procaine penicillin 1.2 million units once daily for 20 days. |
| When benzathine or procaine penicillin cannot be used (e.g. due to penicillin allergy where penicillin desensitization is not possible) or are not available (e.g. due to stock-outs), the WHO STI guideline suggests using doxycycline 100 mg twice daily orally for 30 days. |
| **Remarks:** Doxycycline should not be used in pregnant women (see recommendations 7 and 8 for pregnant women). |

<table>
<thead>
<tr>
<th>Pregnant women</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendation 7</strong></td>
</tr>
<tr>
<td>In pregnant women with late syphilis or unknown stage of syphilis, the WHO STI guideline recommends benzathine penicillin G 2.4 million units intramuscularly once weekly for three consecutive weeks over no treatment.</td>
</tr>
<tr>
<td><strong>Remarks:</strong> The interval between consecutive doses of benzathine penicillin should not exceed 14 days.</td>
</tr>
</tbody>
</table>

| **Recommendation 8** |
| In pregnant women with late syphilis or unknown stage of syphilis, the WHO STI guideline suggests benzathine penicillin G 2.4 million units intramuscularly once weekly for three consecutive weeks over procaine penicillin 1.2 million units intramuscularly once a day for 20 days |
| When benzathine or procaine penicillin cannot be used (e.g. due to penicillin allergy where penicillin desensitization is not possible) or are not available (e.g. due to stock-outs), the WHO STI guideline suggests using, with caution, erythromycin 500 mg orally four times daily for 30 days. |
| **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 9 and 10 for congenital syphilis). 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**
### Congenital syphilis

#### 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.

**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.

**Conditioned recommendation, very low quality evidence**

**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.

**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. 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.

**Conditioned recommendation, very low quality evidence**

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**Methodology in developing these guidelines**

These guidelines were developed following the methods outlined in the 2014 WHO handbook for guideline development. The Guideline Development Group (GDG) included international STI experts, clinicians, researchers and programme managers. The GDG prioritized questions and outcomes related to treatment of gonococcal infections to include in this update, and a methodologist and a team of systematic reviewers from McMaster University, the WHO Collaborating Centre for Evidence-Informed Policy, independently conducted systematic reviews of the effectiveness of different treatments for gonorrhoea. The evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach and presented to the GDG. Conflicts of interest were managed according to WHO guidelines and declared before the recommendations were discussed and finalized. Research implications were also developed by the GDG.

Details of the methods for developing these guidelines are described on page 36 to 44 of the WHO Guidelines for the Treatment of *Treponema pallidum*.¹

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Summary Evidence for the ten treatment recommendations for treatment of Treponema pallidum

The list of references of reviewed evidence are detailed below, and details of the evidence reviewed, including evidence profiles and evidence-to-decision frameworks used to make these recommendations are in Annex D.²

Early syphilis
(primary, secondary and early latent syphilis of not more than two years’ duration)

Recommendation 1 and 2
Overall, there was very low quality evidence for outcomes after treatment of early syphilis. Evidence was gathered from 7 randomized and 18 non-randomized studies, each of which included 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. The number of serological cures achieved with benzathine penicillin G 2.4 million units (MU) provided as a single dose intramuscularly (IM) was estimated on average as 840 per 1000 people with early syphilis. When compared to this single dose of benzathine penicillin G, the evidence suggests little to no difference in the numbers of serological cures achieved with a double dose of benzathine penicillin G; lower numbers cured with a triple dose of benzathine penicillin G; similar numbers cured when treated with ceftriaxone, azithromycin or doxycycline; and slightly lower numbers cured with doxycycline and tetracycline together. Evidence also 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 be less likely to cause 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 AMR in T. pallidum is not available in many settings. Resistance to azithromycin for other conditions is spreading, and therefore the Guideline Development Group (GDG) was concerned about the risk of azithromycin resistance in T. pallidum.

There was some research evidence relating to overall acceptability of injections versus medicines taken orally in people with syphilis: 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 IM 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 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. 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 to be 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 of benzathine and procaine penicillins by injection as being acceptable to most people.

**Recommendation 3 and 4**

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 included in the studies. In most studies, the stage of syphilis (early or late) was unknown. The evidence in adults and adolescents, and the evidence from successful historical use of benzathine and procaine penicillins and erythromycin, was used to inform the judgements about the benefits of different medicines. The benefits were large for the use of benzathine penicillin compared to no treatment. The differences in medicines in terms of benefits and harms were trivial. Prevention of mother-to-child transmission (PMTCT) was a critical outcome. Penicillins cross the placental barrier, while azithromycin and erythromycin do not, meaning there is an increased chance of mother-to-child transmission of syphilis with the use of the latter medicines.

There was no evidence for adverse effects, transmission to partner, antimicrobial resistance (AMR), 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.

**Late syphilis**  
*(infection of more than two years’ duration without evidence of treponemal infection)*

**Recommendation 5, 6, 7 and 8**

Overall, the quality of the evidence was very low. Most studies typically include people with early or late syphilis and don’t distinguish between the stage of syphilis when reporting the results. However, one study included over 300 people diagnosed with late syphilis. It evaluated benzathine penicillin G 2.4 MU given once IM and azithromycin 2 g given once orally. Serological cure was low (33–39%); these doses are typically provided for early syphilis. Another study included 135 pregnant women
treated for late syphilis. This study found that 99% of women with the double dose of benzathine penicillin G were cured. Historically, multiple doses of benzathine penicillin G (once a week for three weeks) or procaine penicillin 1.2 MU (once daily for 20 days) have been successful for serological and clinical cure of syphilis. For pregnant women, PMTCT is a critical outcome. Penicillins cross the placental barrier, while azithromycin and erythromycin do not, meaning that there is an increased chance of mother-to-child transmission of syphilis with the use of the latter medicines.

There has been some successful historical use of doxycycline 100 mg twice daily for 30 days, but not in pregnant women. There were no data for adverse events, transmission to partners, HIV transmission and acquisition, or STI complications. There are no reported data on resistance to azithromycin for treating syphilis in specific settings, and this will likely remain unknown in many places as the capacity to monitor AMR in *T. pallidum* is not available in many settings. Resistance to azithromycin for other conditions is spreading, and therefore the STI GDG was concerned about the risk of azithromycin resistance in *T. pallidum*.

Evidence used for making recommendations for treatment in early syphilis was used to inform this recommendation for late syphilis. There was some research evidence relating to overall acceptability of injections versus medicines taken orally in people with syphilis: 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 IM 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 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 the administration of benzathine and procaine penicillins by injection as being acceptable to most people.

**Congenital syphilis**

**Recommendation 9 and 10**

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 sizes of most studies was small, and rates of follow-up of babies achieved after treatment were very low. When there was follow-up, it ranged from six months to one year. Treatments provided included aqueous benzyl penicillin, procaine penicillin and benzathine penicillin G; ceftriaxone was not assessed. In most studies of infants with confirmed congenital syphilis or infants whose mothers received inadequate or no treatment, treatment of infants resulted in 100% cures with no adverse effects. Aqueous benzyl penicillin or procaine
penicillin were favoured over ceftriaxone due to little or no data, and known potential for side-effects and contraindications with the use of ceftriaxone to treat other conditions. There were some historical data (but no other data) indicating 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 mothers with untreated syphilis 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 two to three 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 thus availability would likely not have an impact on equity. However, for people who need to travel for treatment, health equity may be reduced. The GDG agreed that IM injections would be acceptable, given that finding a vein for intravenous (IV) administration is often very difficult for infants. However, if an experienced venupuncturist is present and willing, benzyl penicillin could be administered IV.

Overall, historical data show benefits of treatment with aqueous benzyl penicillin and procaine penicillin with few to no adverse effects, and similar costs. There are little to no data for benzathine penicillin G, but there may be no adverse effects; there are also little to no data for ceftriaxone but adverse effects may occur and it is more expensive than the other medicines. A preference for IM injections or IV administration was not determined, but these options are available with either medication. Overall, the risk of congenital syphilis in infants born to mothers who have received adequate treatment was judged to be very low and therefore, monitoring of these infants is suggested over treatment.

Research

The Guideline Development Group (GDG) discussed the need to develop a new treatment. Ideally the new treatment should be a short course administered orally which 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 conducted. The trials should compare ceftriaxone with benzathine penicillin G and doxycycline. To what extent the medicines cross the blood–brain and placental barriers should also be investigated. 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.

There was little data for ceftriaxone use in infants with confirmed congenital syphilis and therefore research is needed, in particular comparing ceftriaxone to procaine penicillin.
Conclusions

The updated recommendations for the treatment of syphilis were developed based on the WHO guidelines using the GRADE process. Updated treatment recommendations based on the most recent evidence are included for the most important common conditions caused by *T. pallidum*. These are evidenced-based recommendations taking into consideration antimicrobial susceptibility patterns, quality of evidence, balance between benefits and harms, patient values and preferences, acceptability, feasibility, cost, and cost effectiveness. Recommendations were not updated for rare conditions including neurosyphilis and tertiary syphilis (gumma and cardiovascular syphilis) for which no new information became available since the 2003 WHO STI guidelines were issued.

Treatment recommendations for the following conditions caused by *T. pallidum* are included in these guidelines:

- early latent syphilis
- late latent syphilis
- congenital syphilis.

Lists of references for reviewed evidence

Recommendation 1 and 2

*Systematic reviews*


*Included studies*

5. González-López JJ, Fernández Guerrero ML, Luján R, Fernandez Tostado S, de Górgolas M,


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


Penicillin allergy

Systematic review


Included studies

Recommendation 3 and 4

Systematic review


Included studies


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


**Recommendation 5 and 6**

*Systematic review*


*Included studies*


**Patient values and preferences, acceptability and cost: specific to syphilis infections**


**Recommendation 7 and 8**

*Systematic review*


Included studies


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


Additional references


**Recommendation 9 and 10**

Systematic review

Included studies


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