

WHO GUIDELINES FOR THE

Treatment of

Treponema pallidum (syphilis)



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CONTENTS

Acknowledgements	iii
Abbreviations and acronyms	iv
Executive summary	1
Overview of the guidelines for the prevention, treatment and management of STIs	6
STI epidemiology and burden	6
Why new guidelines for the prevention, treatment and management of STIs?	6
Approach to the revision of STI guidelines	8
References	9
WHO guidelines for the treatment of <i>Treponema pallidum</i> (syphilis)	10
1. Introduction	10
1.1 Epidemiology, burden and clinical considerations	10
Clinical presentation	10
Laboratory diagnosis	11
1.2 Rationale for new recommendations	13
1.3 Objectives	14
1.4 Target audience	14
1.5 Structure of the guidelines	14
2. Methods	15
2.1 Guideline Development Group (GDG)	15
2.2 Questions and outcomes	15
2.3 Reviews of the evidence	15
2.4 Making recommendations	16
2.5 Management of conflicts of interest	17
3. Dissemination, updating and implementation of the guidelines	18
3.1 Dissemination	18
3.2 Updating the STI guidelines and user feedback	18
3.3 Implementation of the WHO guidelines for the treatment of <i>T. pallidum</i> (syphilis)	18
Adaptation, implementation and monitoring	18
Identifying and procuring STI medicines	19
4. Recommendations for treatment of syphilis	20
4.1 Early syphilis	20
Recommendation 1	20
Recommendation 2	20
Recommendation 3	21
Recommendation 4	21
4.2 Late syphilis	22
Recommendation 5	22
Recommendation 6	22
Recommendation 7	22
Recommendation 8	22

CONTENTS (CONTINUED)

4.3 Congenital syphilis	23
Recommendation 9	23
Recommendation 10	23
5. Research implications	25
References	26
Annex A: STI guideline development teams	27
Annex B: Detailed methods for guidelines development	36
Questions and outcomes	36
Review of the evidence	42
Applying the GRADE approach to making the recommendations	44
Annex C: Lists of references for reviewed evidence	45
Recommendation 1 and 2	45
Recommendation 3 and 4	46
Recommendation 5 and 6	47
Recommendation 7 and 8	48
Recommendation 9	48
Recommendation 10	48

Web annexes available at:

www.who.int/reproductivehealth/publications/rtis/syphilis-treatment-guidelines/en/

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

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ABBREVIATIONS AND ACRONYMS

AIDS	acquired immune deficiency syndrome	NAAT	nucleic acid amplification test
AMR	antimicrobial resistance	PCR	polymerase chain reaction
CI	confidence interval	PICO	population, intervention, comparator, outcome
DFA	direct fluorescent antibody	PMTCT	prevention of mother-to-child transmission
DNA	deoxyribonucleic acid	RDT	rapid diagnostic tests
DOI	declaration of interests	RPR	rapid plasma reagin
FTA-ABS	fluorescent treponemal antibody absorbed	STI	sexually transmitted infection
GDG	Guideline Development Group	TPHA	<i>Treponema pallidum</i> haemagglutination assay
GRADE	Grading of Recommendations Assessment, Development and Evaluation	TPPA	<i>Treponema pallidum</i> particle agglutination assay
GUD	genital ulcer disease	TRUST	Toluidine Red Unheated Serum Test
HIV	human immunodeficiency virus	VDRL	Venereal Diseases Research Laboratory
HPV	human papillomavirus		
HSV	herpes simplex virus		
HSV-1	herpes simplex virus type 1		
HSV-2	herpes simplex virus type 2		
ICT	immunochromatographic		
IM	intramuscular		
IV	intravenous		
MSH	Management Sciences for Health		
MSM	men who have sex with men		
MU	million units		

WHO GUIDELINES FOR THE TREATMENT OF *TREPONEMA PALLIDUM* (SYPHILIS)

EXECUTIVE SUMMARY

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.

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.

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], Tolidine 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.

RATIONALE FOR THE GUIDELINES

Since the publication of the 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. These guidelines provide updated treatment recommendations for treatment of *Treponema pallidum* (syphilis) based on the most recent evidence. They form one of several modules of guidelines for specific STIs. Other modules will focus on treatments for *Chlamydia trachomatis* (chlamydia), *Neisseria gonorrhoeae* (gonorrhoea) and genital herpes simplex virus (genital HSV). In addition, future work will provide guidance for syphilis screening and treatment of pregnant women, STI syndromic approach, clinical management, STI prevention, and treatments of other STIs. It is strongly recommended that countries take updated global guidance into account as they establish standardized national protocols and adapt it to the local epidemiological situation and antimicrobial susceptibility data.

OBJECTIVES

The objectives of these guidelines are:

- to provide evidence-based guidance on treatment of *Treponema pallidum*; and
- to support countries to update their national guidelines for treatment of *Treponema pallidum*.

METHODS

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 syphilis and congenital syphilis 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 syphilis and congenital syphilis. 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.

RECOMMENDATIONS

The current guidelines provide treatment recommendations for *Treponema pallidum* and congenital syphilis. The recommendations summarized in Table 1 apply to all adults and adolescents (10–19 years of age), including pregnant women, people living with HIV, people who are immunocompromised and key populations, including sex workers, men who have sex with men (MSM) and transgender persons.

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

Recommendations	Strength of recommendation and quality of evidence
Early syphilis (primary, secondary and early latent syphilis of not more than two years' duration)	
Adults and adolescents	
<p>Recommendation 1</p> <p>In adults and adolescents with early syphilis, the WHO STI guideline recommends benzathine penicillin G 2.4 million units once intramuscularly over no treatment.</p> <p>Recommendation 2</p> <p>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.</p> <p>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.</p> <p><i>Remarks:</i> 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.</p>	<p><i>Strong recommendation, very low quality evidence</i></p> <p><i>Conditional recommendation, very low quality evidence</i></p>

Pregnant women	
<p>Recommendation 3</p> <p>In pregnant women with early syphilis, the WHO STI guideline recommends benzathine penicillin G 2.4 million units once intramuscularly over no treatment.</p> <p>Recommendation 4</p> <p>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.</p> <p>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.</p> <p><i>Remarks:</i> 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.</p>	<p><i>Strong recommendation, very low quality evidence</i></p> <p><i>Conditional recommendation, very low quality evidence</i></p>
Late syphilis (infection of more than two years' duration without evidence of treponemal infection)	
Adults and adolescents	
<p>Recommendation 5</p> <p>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.</p> <p><i>Remarks:</i> The interval between consecutive doses of benzathine penicillin should not exceed 14 days.</p> <p>Recommendation 6</p> <p>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.</p> <p>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.</p> <p><i>Remarks:</i> Doxycycline should not be used in pregnant women (see recommendations 7 and 8 for pregnant women).</p>	<p><i>Strong recommendation, very low quality evidence</i></p> <p><i>Conditional recommendation, very low quality evidence</i></p>

Pregnant women	
<p>Recommendation 7</p> <p>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.</p> <p><i>Remarks:</i> The interval between consecutive doses of benzathine penicillin should not exceed 14 days.</p> <p>Recommendation 8</p> <p>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</p> <p>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.</p> <p><i>Remarks:</i> 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 be avoided.</p>	<p><i>Strong recommendation, very low quality evidence</i></p> <p><i>Conditional recommendation, very low quality evidence</i></p>
Congenital syphilis	
Infants	
<p>Recommendation 9</p> <p>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.</p> <p>Dosages:</p> <ul style="list-style-type: none"> • 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 <p><i>Remarks:</i> If an experienced venipuncturist is available, aqueous benzyl penicillin may be preferred instead of intramuscular injections of procaine penicillin.</p> <p>Recommendation 10</p> <p>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.</p> <p><i>Remarks:</i> 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.</p>	<p><i>Conditional recommendation, very low quality evidence</i></p> <p><i>Conditional recommendation, very low quality evidence</i></p>

OVERVIEW OF THE GUIDELINES FOR THE PREVENTION, TREATMENT AND MANAGEMENT OF STIs

STI EPIDEMIOLOGY AND BURDEN

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. The prevention and control of STIs is an integral component of comprehensive sexual and reproductive health services that are needed to attain the related targets under Sustainable Development Goal (SDG) No. 3 (Ensure healthy lives and promote well-being for all at all ages), including: target 3.2 – to end preventable deaths of newborns and children under 5 years of age; target 3.3 – to end the epidemics of AIDS and other communicable diseases; target 3.4 – to reduce premature mortality from noncommunicable diseases and promote mental health and well-being; target 3.7 – to ensure universal access to sexual and reproductive health-care services; and target 3.8 – to achieve universal health coverage.

Worldwide, more than a million curable STIs are acquired every day. In 2012, there were an estimated 357 million new cases of curable STIs among adults aged 15–49 years worldwide: 131 million cases of chlamydia, 78 million cases of gonorrhoea, 6 million cases of syphilis and 142 million cases of trichomoniasis (1). The prevalence of some viral STIs is similarly high, with an estimated 417 million people infected with herpes simplex virus type 2 (HSV-2) (2), and approximately 291 million women harbouring human papillomavirus (HPV) at any point in time (3). The burden of STIs varies by region and gender, and is greatest in resource-poor countries.

When left undiagnosed and untreated, curable STIs can result in serious complications and sequelae, such as pelvic inflammatory disease, infertility, ectopic pregnancy, miscarriage, fetal loss and congenital infections. In 2012, an estimated 930 000 maternal syphilis infections resulted in 350 000 adverse pregnancy outcomes, including stillbirths, neonatal deaths, preterm births and infected infants (4). Curable STIs accounted for the loss of nearly 11 million disability-adjusted life years (DALYs) in 2010 (5). The psychological consequences of STIs include stigma, shame and loss of self-worth. STIs have also been associated with relationship disruption and gender-based violence (6).

Both ulcerative and non-ulcerative STIs are associated with a several-fold increased risk of transmitting or acquiring HIV (7, 8). Infections causing genital ulcers are associated with the highest HIV transmission risk; in addition to curable ulcer-causing STIs (e.g. syphilis and chancroid), highly prevalent HSV-2 infections substantially increase that risk (9). Non-ulcerative STIs, such as gonorrhoea, chlamydia and trichomoniasis, have been shown to increase HIV transmission through genital shedding of HIV (10). Treating STIs with the right medicines at the right time is necessary to reduce HIV transmission and improve sexual and reproductive health (11). Efforts should therefore be taken to strengthen STI diagnosis and treatment.

WHY NEW GUIDELINES FOR THE PREVENTION, TREATMENT AND MANAGEMENT OF STIs?

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. Indeed, 88% of countries have updated their national STI guidelines or recommendations since 2006 (12). Updated global guidance reflecting the most recent evidence and expert opinion is therefore needed to assist countries to incorporate new developments into an effective national approach to the prevention and treatment of STIs.

There is an urgent need to update global treatment recommendations to effectively respond to the changing antimicrobial resistance (AMR) patterns of STIs, especially for *Neisseria gonorrhoeae*. Effective treatment protocols that take into account global and local resistance patterns are essential to reduce the risk of further development of AMR. High-level gonococcal resistance to quinolones, a previously recommended first-line treatment, is widespread and decreased susceptibility to the extended-spectrum (third-generation) cephalosporins, another first-line treatment for gonorrhoea, is on the rise (13). Low-level resistance to *Trichomonas vaginalis* has also been reported for nitroimidazoles, the only available treatment. Resistance to azithromycin has been reported in some strains of *Treponema pallidum* and treatment failures have been reported for tetracyclines and macrolides in the treatment of *Chlamydia trachomatis* (14, 15). A WHO STI expert consultation recommended updating the WHO 2003

guidelines for the first- and second-line treatments for *C. trachomatis*, increasing the dosage of ceftriaxone to 250 mg for treatment of *N. gonorrhoeae* with continued monitoring of antimicrobial susceptibility, and consideration of whether azithromycin (2 g, single dose) should be recommended in early syphilis (16).

The epidemiology of STIs is changing, with viral pathogens becoming more prevalent than bacterial etiologies for some conditions; this means that updated information is required to inform locally appropriate prevention and treatment strategies. An increasing proportion of genital ulcers are now due to viral infections as previously common bacterial infections, such as chancroid, approach elimination in many countries (16, 17). As recommended during the STI expert consultation, treatment guidelines for genital ulcer disease (GUD) should be updated to include HSV-2 treatment and a longer treatment duration for HSV-2 should be explored. In addition, suppressive therapy for HSV-2 should be considered in areas with high HIV prevalence (16). The chronic, lifelong nature of viral infections also requires that renewed attention be paid to developing effective prevention strategies, including expanding accessibility to available vaccines for HPV and development of new vaccines for HSV-2.

In the 2003 WHO guidelines, a syndromic approach was recommended for the management of STIs. The approach guides the diagnosis of STIs based on identification of consistent groups of symptoms and easily recognized signs and indicates treatment for the majority of organisms that may be responsible for producing the syndrome. The syndromic management algorithms need to be updated in response to the changing situation. In addition to changes to the GUD algorithm, other syndromes need to be re-evaluated, particularly vaginal discharge. The approach to syndromes for key populations also needs to be updated. For example, addition of a syndromic management algorithm for anorectal infections in men who have sex with men (MSM) and sex workers is urgently needed since a substantial number of these infections go unrecognized and untreated in the absence of guidelines (16).

New rapid, point-of-care diagnostic tests (POCTs) are changing STI management. Rapid syphilis diagnostic tests are now widely available, making syphilis screening more widely accessible and allowing for earlier initiation of treatment for those who test positive. Efforts are under way to develop POCTs for other STIs that will augment syndromic management of symptomatic cases and increase the ability to identify asymptomatic infections (12). Updated guidelines are needed that incorporate rapid tests into syndromic management of STIs and provide algorithms for testing and screening (16).

Although recent technological advances in diagnostics, therapeutics, vaccines and barrier methods offer better opportunities for the prevention and care of STIs, access to these technologies is still limited, particularly in areas where the burden of infection is highest. For optimal effectiveness, global guidelines for the management of STIs need to include approaches for settings with limited access to modern technologies, as well as for settings in which these technologies are available.

It is strongly recommended that countries take updated global guidance into account as they establish standardized national protocols, adapting this guidance to the local epidemiological situation and antimicrobial susceptibility data. Standardization ensures that all patients receive adequate treatment at every level of health-care services, optimizes the training and supervision of health-care providers and facilitates procurement of medicines. It is recommended that national guidelines for the effective management of STIs be developed in close consultation with local STI, public health and laboratory experts.

APPROACH TO THE REVISION OF STI GUIDELINES

To ensure effective treatment for all STIs, WHO plans a phased approach to updating the STI guidelines to address a range of infections and issues. Four phases have been proposed by the WHO STI Secretariat and agreed upon by the STI Guideline Development Group (GDG) members (see Annex A for members of these groups). Table 2 summarizes the proposed phases and timeline.

Table 2: Phases for development of the STI guidelines

Phases	Topics	Timeframe
Phase 1	Treatment of specific STIs: <i>Chlamydia trachomatis</i> (chlamydia), <i>Neisseria gonorrhoeae</i> (gonorrhoea), HSV-2 (genital herpes) and <i>Treponema pallidum</i> (syphilis) Syphilis screening and treatment of pregnant women	November 2013 – April 2016
	STI syndromic approach Clinical management package	May 2016 – December 2017
Phase 2	STI prevention: condoms, behaviour change communication, biomedical interventions and vaccines	2017–2018
Phase 3	Treatment of specific STIs and reproductive tract infections (RTIs) not addressed in Phase 1: <i>Trichomonas vaginalis</i> (trichomoniasis), bacterial vaginosis, <i>Candida albicans</i> (candidiasis), <i>Hemophilus ducreyi</i> (chancroid), <i>Klebsiella granulomatis</i> (donovanosis), human papillomavirus (HPV; genital warts/cervical cancer), <i>Sarcoptes scabiei</i> (scabies) and <i>Phthirus pubis</i> (pubic lice)	2017–2018
Phase 4	STI laboratory diagnosis and screening	2017–2018

Phase 1 will focus on treatment recommendations for specific STIs as well as other important and urgent STI issues. Recommendations for the treatment of specific infections will be developed and published as independent modules:

- *Chlamydia trachomatis* (chlamydia)
- *Neisseria gonorrhoeae* (gonorrhoea)
- HSV-2 (genital herpes)
- *Treponema pallidum* (syphilis)
- Syphilis screening and treatment of pregnant women.

In addition, guidelines for the STI syndromic approach and a clinical management package will be developed later in Phase 1. Phase 2 will focus on guidelines for STI prevention. The independent Phase 1 and 2 modules will later be consolidated into one document and published as comprehensive WHO guidelines on STI case management. Phase 3 will address treatment of additional infections, including *Trichomonas vaginalis* (trichomoniasis), bacterial vaginosis, *Candida albicans* (candidiasis), *Hemophilus ducreyi* (chancroid), *Klebsiella granulomatis* (donovanosis), HPV (genital warts/cervical cancer), *Sarcoptes scabiei* (scabies) and *Phthirus pubis* (pubic lice). Phase 4 will provide guidance on laboratory diagnosis and screening of STIs.

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01

INTRODUCTION

1.1 EPIDEMIOLOGY, BURDEN AND CLINICAL CONSIDERATIONS

Syphilis is a bacterial sexually transmitted infection (STI) caused by *Treponema pallidum*. It results in substantial morbidity and mortality. 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 and 1.5 per 1000 males. The estimated 18 million prevalent cases of syphilis in 2012 translates to a global prevalence of 0.5% among females and 0.5% among males aged 15–49 years, with the highest prevalence in the WHO African Region (1).

Mother-to-child transmission may occur if the expectant mother has syphilis. Mother-to-child transmission of syphilis (congenital syphilis) is usually devastating to the fetus in cases where 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. There is also an increase in mother-to-child transmission of HIV among pregnant women co-

infected with syphilis and HIV. Untreated primary and secondary syphilis infections in pregnancy typically result in severely adverse pregnancy outcomes, including fetal deaths in a substantial proportion of cases. Latent syphilis infections in pregnancy result in serious adverse pregnancy outcomes in more than half of cases. The burden of disease is highest in low- and middle-income countries, particularly in the WHO African Region (2).

Congenital syphilis is preventable, however, and elimination of mother-to-child transmission of syphilis can be achieved through implementation of effective early screening and treatment strategies for syphilis in pregnant women (3). The fetus can be easily cured with treatment, and the risk of adverse outcomes to the fetus is minimal if the mother receives adequate treatment during early pregnancy – ideally before the second trimester. There are indications that mother-to-child transmission of syphilis is beginning to decline globally due to increased efforts to screen and treat pregnant women for syphilis.

CLINICAL PRESENTATION

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.

Primary syphilis classically presents as a solitary, painless chancre at the site of inoculation, usually in the vagina, penis or anus (but it may be extra-genital), after a mean incubation period of 21 days (range: 9–90 days). The primary lesion begins as a raised papule and ulcerates before healing within 3 to 10 weeks, with or without treatment. The primary chancre may go unnoticed by patients. If untreated, the disease progresses to the secondary stage, four to eight weeks after the appearance of the primary lesion.

Secondary syphilis is characterized by generalized mucocutaneous lesions affecting both skin and mucous membranes. The rash of secondary syphilis can vary widely and mimic other infectious or non-infectious conditions, but characteristically affects the palms and soles. The rash is often symmetrical and non-itchy, but may have several manifestations and can be minimal enough to be overlooked. In warm and moist areas of the body, such as the anus and labia, large white or grey raised lesions develop as a result of the spread of the treponemes from the primary lesion.

These are known as condylomata lata. The lesions of the skin and mucous membranes may be associated with non-specific constitutional symptoms of malaise, fever and lymphadenopathy. 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 characterized by positive syphilis serology with no clinical symptoms or signs. Latent syphilis is often categorized in two phases: early latent syphilis is defined as infection for less than two years and late latent syphilis is the presence of the disease for two years or more. The treatment of latent syphilis is different for the early and late phases. Patients with unknown duration of infection should be treated for late latent syphilis. Sexual transmission typically occurs only during primary, secondary and early latent infection. Mother-to-child transmission, however, has been documented to occur up to several years after initial infection.

If left untreated, most patients will remain in the latent stage. Approximately 25% will develop the late clinical sequelae of tertiary syphilis (4), which can affect any organ system up to 30 years or more after infection. The main manifestations of tertiary syphilis are neurological disease (neurosyphilis), cardiovascular disease (cardiosyphilis) and gummatous lesions (gumma).

Neurosyphilis can occur at any stage of syphilis infection, even in the first few months. Early neurological manifestations include acute changes in mental status, meningitis, stroke, cranial nerve dysfunction and auditory or ophthalmic and ocular abnormalities. Late neurosyphilis occurs 10–30 years or more after infection and is characterized by tabes dorsalis and general paresis.

The most common manifestation of congenital syphilis is second or third trimester fetal loss or premature labour. Thus, serologic testing for syphilis should be performed for all mothers with stillborn infants, to document evidence of syphilis. In most countries, it is estimated that the majority of congenital syphilis cases result in syphilitic stillbirths, and these cases are often not recognized as having been caused by syphilis. Infants born to mothers with positive syphilis serology should be examined for signs and symptoms of early congenital syphilis, including bullous rash, rhinitis, laryngitis, lymphadenopathy, hepatosplenomegaly, osteochondritis, periostitis, meningitis and chorioretinitis. The signs of late congenital syphilis infection in children over the age of 2 years include inflammatory manifestations affecting the eyes, ears and joints, as well as skeletal malformations and

stigmata resulting from developmental damage during the early stages of syphilis. However, it is important to keep in mind that many infants with syphilis infection will not have obvious clinical signs or symptoms.

BOX 1. THE WHO GLOBAL SURVEILLANCE CASE DEFINITION FOR CONGENITAL SYPHILIS

- A stillbirth, live birth or fetal loss at greater than 20 weeks of gestation or more than 500 g to a syphilis seropositive mother without adequate syphilis treatment; or
- A stillbirth, live birth or child under 2 years of age with clinical (as above) or microbiological evidence of syphilis infection. The microbiological evidence of congenital syphilis includes any one of the following:
 - demonstration by dark-field microscopy or direct fluorescent antibody test of the presence of *T. pallidum* in the umbilical cord, the placenta, nasal discharge or skin lesion materials;
 - detection of *T. pallidum*-specific IgM;
 - infant with a positive non-treponemal serology titre at least four-fold higher than the mother's titre.

Source: Global guidance on criteria and processes for validation: elimination of mother-to-child transmission (EMTCT) of HIV and syphilis. Geneva: World Health Organization; 2014 (5).

LABORATORY DIAGNOSIS

Syphilis diagnosis is based on the patient's history, physical examination, laboratory testing and sometimes radiology. The available laboratory tests for diagnosis of syphilis include direct detection methods (i.e. dark-field microscopy, direct fluorescent antibody test and nucleic acid amplification test), serology (treponemal and non-treponemal tests), and examination of cerebrospinal fluids (6).

DIRECT DETECTION METHODS

Direct detection methods require exudates from lesions of primary, secondary or early congenital syphilis, and need careful collection of samples.

Dark-field microscopy demonstrating treponemes with characteristic morphology and motility in lesion exudate or tissue is the most specific method for diagnosis of the early stages of syphilis. The dark-field examination must be performed immediately after specimen collection from primary chancres, moist secondary lesions or lymph nodes or from mucocutaneous lesions in newborns. Dark-field microscopy requires specialized equipment and a trained, experienced microscopist, and is therefore usually limited to specialized laboratories. Dark-field microscopy is highly specific, therefore the presence of characteristic spirochetes is diagnostic of an active infection. Its sensitivity, however, is less than 50%, so a negative result does not exclude syphilis. Although dark-field microscopy is one of the simplest and most reliable methods for the direct detection of *T. pallidum*, its availability is increasingly limited.

The direct fluorescent antibody (DFA) test uses a fluorescence microscope to detect spirochetes that have been stained with fluorescein-labelled anti-*T. pallidum* globulin. Specimens are obtained in the same way as for dark-field microscopy, but the fluorescein-stained organisms are easier to detect and are not likely to be confused with other organisms, leading to a higher sensitivity and specificity for the DFA test. However, specialized equipment is required and the specific fluorescein conjugate is not commercially available in most countries.

Nucleic acid amplification tests (NAATs) directly detect *T. pallidum* DNA by polymerase chain reaction (PCR) from specimens of any lesion exudate, tissue or body fluid. The sensitivity varies according to the specific PCR assay; most assays can detect approximately 10 organism equivalents, although some can detect one organism per PCR reaction. Commercial PCR tests for *T. pallidum* are not yet commercially available and therefore are relatively costly compared with other tests used to diagnose syphilis. For studies with testing done in well-equipped laboratories, multiplex PCR assays have been developed for detection of the most common causes of genital ulcers, including syphilis, herpes simplex virus and *H. ducreyi* (chancroid).

SYPHILIS SEROLOGY

There are two types of serological tests for syphilis: non-treponemal and treponemal. A presumptive diagnosis of syphilis requires a positive result from at least one of these types of tests. A confirmed diagnosis requires positive results from both types of serologic tests.

Serum is the specimen of choice for serological testing, although plasma can be used in some non-treponemal serological tests. Cerebrospinal fluid is used to diagnose congenital and tertiary syphilis and when neurological symptoms are present.

The most widely available non-treponemal tests are the microscopic Venereal Diseases Research Laboratory (VDRL) and the macroscopic rapid plasma reagin (RPR) tests. These tests detect anti-lipid immunoglobulin M or G (IgM or IgG) antibodies. Since these antibodies can also be produced in other diseases, non-treponemal tests are not highly specific for syphilis and can give false-positive results in conditions such as acute febrile viral infections and some chronic autoimmune diseases. Most false-positive results have low titres of less than 1 : 4. Non-treponemal tests may be negative for up to four weeks after the lesion of primary syphilis first appears and can be negative in late latent syphilis; additionally in primary and secondary syphilis, these tests may be false negative due to a prozone reaction (i.e. interference by high concentrations of antibodies in a specimen, which can be uncovered with dilution and retesting). In primary syphilis, repeated testing at two and four weeks may be required to exclude syphilis when suspect lesions are present. A negative non-treponemal test at three months after onset of the primary chancre virtually excludes the diagnosis of syphilis.

Non-treponemal tests may be qualitative or quantitative. Quantitative non-treponemal test titres can be used to monitor response to treatment. Titres are expected to decrease following effective treatment and increase in untreated active infection. A four-fold change or higher in titre, equivalent to a change of at least two dilutions (e.g. from 1 : 16 to 1 : 4 for effective positive response to treatment, or from 1 : 8 to 1 : 32 for continued active infection) is considered a significant difference between two sequential tests using the same method (e.g. VDRL or RPR) and preferably by the same laboratory. Titres that differ by only one dilution (e.g. 1 : 8 versus 1 : 4 or 1 : 2 versus 1 : 1) are not considered significant and may only represent differences in laboratory interpretation).

Treponemal tests include the *Treponema pallidum* haemagglutination assay (TPHA), the *Treponema pallidum* particle agglutination assay (TPPA) and the fluorescent treponemal antibody absorbed (FTA-ABS) tests. These tests are highly specific because they detect antibodies against treponemal-specific antigens; however, they do not differentiate venereal syphilis from endemic syphilis (the latter includes yaws and pinta). Classically, one of these tests is used as a confirmatory test following a positive non-treponemal test. Treponemal tests usually remain positive (85%) for the patient's lifetime, regardless of treatment. Thus, a positive treponemal test does not distinguish between active infection and infection that has been previously treated.

All live or stillborn infants of seropositive mothers should be examined for evidence of congenital syphilis. Live-born infants should be examined and tested at birth and at monthly intervals for three months until it is confirmed that serological tests in the infant are, and remain, negative. Antibodies can be passively transmitted from the mother, complicating the interpretation of laboratory results in neonates, but usually disappear within three to four months after birth. However, maternal antibodies can sometimes persist for up to 18 months. In such cases, repeat testing with titration should be carried out and if a four-fold or greater increase in titre of a non-treponemal or treponemal test is detected, the baby should be treated for congenital syphilis.

RAPID DIAGNOSTIC TESTS

In the past decade, a number of point-of-care rapid diagnostic tests (RDTs) for treponemal antibodies in syphilis infection have been developed. RDTs provide treponemal antibody results in 10–15 minutes and can be performed in any setting since they do not require refrigerated storage or laboratory equipment. The sensitivity of the RDTs ranges from 85% to 98% and the specificity from 93% to 98%, compared to the TPHA or TPPA as reference standards. In general, RDTs with higher sensitivities tend to have lower specificities and vice versa.

Most of the initial range of RDTs use *T. pallidum* antigens to detect treponema-specific antibodies. Many of the tests use immunochromatographic strips, which work by having a test strip impregnated with treponemal antigens that react with antibodies to syphilis in whole blood or serum. The tests work on the same principle as the specific treponemal tests described above, thus a positive result does not distinguish between active and previously treated infections.

More recently, tests that can detect antibodies against cardiolipin-like materials have been developed that work on the same principle as other non-treponemal tests. They are available in combination with the treponemal RDTs, providing both a screening (RPR/VDRL equivalent) and confirmatory (TPHA/TPPA equivalent) component. However, these dual RDTs have not yet been sufficiently evaluated or field-tested to be recommended.

1.2 RATIONALE FOR NEW RECOMMENDATIONS

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 (7), 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.

1.3 OBJECTIVES

The objectives of these guidelines are:

- to provide evidence-based guidance on treatment of infection with *Treponema pallidum*; and
- to support countries to update their national guidelines for treatment of *Treponema pallidum*.

1.4 TARGET AUDIENCE

These guidelines are primarily intended for health-care providers at all levels (primary, secondary and tertiary) of the health-care system involved in the treatment and management of people with STIs in low-, middle- and high-income countries. They are also intended for individuals working in sexual and reproductive health programmes, such as HIV/AIDS, family planning, maternal and child health and adolescent health, to ensure appropriate STI diagnosis and management.

The guidelines are also useful for policy-makers, managers, programme officers and other professionals in the health sector who are responsible for implementing STI management interventions at regional, national and subnational levels.

1.5 STRUCTURE OF THE GUIDELINES

These guidelines provide evidence-based recommendations for the treatment of specific clinical conditions caused by *T. pallidum*. These guidelines provide direction for countries as they develop national treatment recommendations; however, national guidelines should also take into account the local pattern of antimicrobial resistance (AMR), as well as health service capacity and resources.

Updated treatment recommendations based on the most recent evidence are included for the most important common conditions caused by *T. pallidum*. 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 guideline:

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

02

METHODS

These guidelines were developed following the methods outlined in the 2014 edition of the WHO handbook for guideline development (8) (see Annex B for a detailed description).

2.1 GUIDELINE DEVELOPMENT GROUP (GDG)

To update the WHO guidelines for the prevention, treatment and management of STIs, a GDG was established, comprising 33 international STI experts, including clinicians, researchers and programme managers (Annex A). A core subgroup to focus on the guidelines related to syphilis was created within the GDG, to provide more intensive feedback throughout the process (Annex A). The GDG participated in meetings and teleconferences to prioritize the questions to be addressed, discuss the evidence reviews and finalize the recommendations. Additional sub-working group teleconferences were organized to review the methodology and results of systematic reviews and to discuss and finalize the evidence reviews and recommendations. The GDG reviewed and approved the final version of the guidelines.

2.2 QUESTIONS AND OUTCOMES

In December 2013, the first GDG meeting was held to identify and agree on the key PICO (population, intervention, comparator, outcome) questions that formed the basis for the systematic reviews and the recommendations. Following this meeting, a survey of GDG members was conducted to prioritize the questions and outcomes according to clinical relevance and importance. Nine PICO questions were identified for the update on the treatment of early and late syphilis and congenital syphilis (see Annex B). These questions pertained to adults and other special populations, namely: adolescents; pregnant women; people living with HIV; populations at high risk of acquiring and transmitting STIs, such as men who have sex with men (MSM), transgender persons and sex workers; and infants and children below the age of 2 years (i.e. the questions on congenital syphilis). Only outcomes that were ranked as critical or important to patients and decision-making were included: serological response and clinical cure, transmission to partner, antimicrobial resistance (AMR), compliance, HIV transmission or acquisition, STI complications and adverse effects (including maternal and fetal effects in pregnant women) (see Annex B).

2.3 REVIEWS OF THE EVIDENCE

The systematic reviews for each priority question were conducted by McMaster University, the WHO Collaborating Centre for Evidence-Informed Policy. Evidence for desirable and undesirable outcomes, patient values and preferences, resources, acceptability, equity and feasibility were reviewed from published and unpublished literature. Comprehensive searches for previously conducted systematic reviews, randomized controlled trials and non-randomized studies were performed up to April 2015. Additional searches were conducted to identify studies on patient values and preferences (e.g. qualitative research designs) and resources (e.g. cost-effectiveness studies). Two members of the Systematic Review Team screened studies, extracted and analysed the data, and assessed the quality/certainty of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.¹

1 For more information, see: <http://www.gradeworkinggroup.org/>

The quality/certainty of the evidence was assessed at four levels:

- **High** – We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate** – We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low** – Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- **Very low** – We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

In addition, the direct costs of medicines were estimated using the 2014 edition of the Management Sciences for Health (MSH) International drug price indicator guide (9). References for all the reviewed evidence are listed in Annex C. All evidence was summarized in GRADE evidence profiles and in evidence-to-decision frameworks (see Web annexes D and E).

2.4 MAKING RECOMMENDATIONS

Recommendations were developed during a second meeting of the GDG in October 2015, which was facilitated by two co-chairs, one with expertise in GRADE and the other with clinical STI expertise. The methodologist presented the GRADE evidence profiles and evidence-to-decision frameworks at the meeting. When formulating the recommendations, the GDG considered and discussed the desirable and undesirable effects of the interventions, the value placed on the outcomes, the associated costs and use of resources, the acceptability of the interventions to all stakeholders (including people affected by STIs), the impact on health equity and the feasibility of implementation. Treatments were judged according to the above criteria and final decisions and guideline recommendations were agreed. The discussion was facilitated by the co-chairs with the goal of reaching consensus across the GDG. Disagreements among the GDG members were noted in the evidence-to-decision framework for each judgement. In the case of failure to reach consensus for a recommendation, the planned procedure was for the GDG to take a vote and record the results. However, no votes were taken because the GDG reached consensus during discussion for all of the recommendations. Following the meeting, the recommendations were finalized via teleconference and final approval was obtained from all GDG members electronically. These guidelines were subsequently written up in full and then peer reviewed. The External Review Group approved the methods and agreed with the recommendations made by the GDG (members are listed in Annex A).

According to the GRADE approach, the strength of each recommendation was rated as either strong or conditional. Strong recommendations are presented using the wording “The WHO STI guideline recommends...”, while conditional recommendations are worded as “The WHO STI guideline suggests...” throughout the guidelines. The implications of the differing strengths of recommendations for patients, clinicians and policy-makers are explained in detail in Table 3.

Table 3. Implications of strong and conditional recommendations using the GRADE approach

Implications	Strong recommendation “The WHO STI guideline recommends...”	Conditional recommendation “The WHO STI guideline suggests...”
For patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guidelines could be used as a quality criterion or performance indicator.	Clinicians should recognize that different choices will be appropriate for each individual and that clinicians must help each individual arrive at a management decision consistent with the individual’s values and preferences. Decision aids may be useful to help individuals make decisions consistent with their values and preferences.
For policy-makers	The recommendation can be adopted as policy in most situations.	Policy-making will require substantial debate and involvement of various stakeholders.

2.5 MANAGEMENT OF CONFLICTS OF INTEREST

Management of conflicts of interest was a key priority throughout the process of guideline development. WHO guidelines for declaration of interests (DOI) for WHO experts were implemented (10). DOI statements were obtained from all GDG members prior to assuming their roles in the group. At the GDG meetings (December 2013 and October 2015), the members disclosed their interests, if any, at the beginning of the meetings. The DOI statements are summarized in Web annex F.

After analysing each DOI, the STI team concluded that no member had financial or commercial interests related to STI treatment. Other notified interests were minor; they were either not related to STI or were non-commercial grants or interests. The STI team concluded that there were no significant conflicts of interest that would exclude any member from participating fully in the guideline development process. Therefore, options for conditional participation, partial or total exclusion of any GDG member were no discussed.

03

DISSEMINATION,
UPDATING AND
IMPLEMENTATION OF
THE GUIDELINES**3.1 DISSEMINATION**

The guidelines will be made available as a printed publication, as a download on the website of the WHO Department of Reproductive Health and Research (where there will also be links to all supporting documentation)², and in the WHO Reproductive Health Library (RHL)³. The recommendations will also be available in a guideline application (“app”) created with the GRADEpro GDT software. The guidelines will be announced in the next edition of the RHL newsletter and in the Reproductive Health and Research departmental newsletter, and other relevant organizations will be requested to copy the announcement in their respective newsletters.

WHO headquarters will work with WHO’s regional offices and country offices to ensure that countries receive support in the adaptation, implementation and monitoring of these guidelines using the WHO Department of Reproductive Health and Research guidance on Introducing reproductive health guidelines and tools into national programmes (11). All levels of WHO (headquarters, regional offices and countries) will work with regional and national partners – including the United Nations Population Fund (UNFPA), the United Nations Children’s Fund (UNICEF), the Joint

United Nations Programme on HIV/AIDS (UNAIDS), nongovernmental organizations (NGOs) and other agencies implementing sexual and reproductive health and STI services – to ensure that the new recommendations are integrated and implemented in sexual and reproductive health, family planning, and maternal, neonatal, child and adolescent health services. Reference to this document will be made within other relevant WHO guidelines. These guidelines will also be disseminated at major conferences related to STIs and HIV and the aforementioned programme areas.

3.2 UPDATING THE STI GUIDELINES AND USER FEEDBACK

A system of monitoring relevant new evidence and updating the recommendations as new findings become available will be established within a year of implementing the guidelines. An electronic follow-up survey of key end-users of the STI guidelines will be conducted after the release of the guidelines. The results of the survey will be used to identify challenges and barriers to the uptake of the guidelines, to evaluate their usefulness for improving service delivery, and to identify topics or gaps in treatment that need to be addressed in future editions.

3.3 IMPLEMENTATION OF THE WHO GUIDELINES FOR THE TREATMENT OF *T. PALLIDUM* (SYPHILIS)**ADAPTATION, IMPLEMENTATION AND MONITORING**

These guidelines provide recommendations for treatment of syphilis based on the best global evidence available at the time of compilation. However, the epidemiology and AMR of STIs vary by geographical location and are constantly changing, sometimes rapidly. It is recommended that countries conduct good quality studies to gather the information needed to adapt these guidelines to the local STI situation as they update their national guidelines. In areas lacking local data as a basis for adaptation, the recommendations in these guidelines can be adopted as presented.

For further guidance on adaptation, implementation and monitoring of national guidelines please refer to Introducing WHO’s reproductive health guidelines and tools into national programmes: principles and processes of adaptation and implementation (11).

² These guidelines and all supporting documents will be available at: www.who.int/reproductivehealth/publications/rtis/syphilis-treatment-guidelines/en/

³ RHL is available at: <http://apps.who.int/rhl/en/>

In adapting the guidelines for national use, recommended treatments should have an efficacy of at least 95%. The criteria to be considered for the selection of medicines are listed in Box 2. Recommended medicines should meet as many of the criteria as possible, taking into account local availability, efficacy, route and frequency of administration.

BOX 2. CRITERIA FOR THE SELECTION OF MEDICINES FOR THE TREATMENT OF STIS

- High efficacy (at least 95% cure rate)
- High quality (potent active ingredient)
- Low cost
- Low toxicity levels
- Organism resistance unlikely to develop or likely to be delayed
- Single dose
- Oral administration
- Not contraindicated for pregnant or lactating women

Appropriate medicines should be included in the national essential medicines lists. When selecting medicines, consideration should be given to the competencies and experience of health-care providers.

Budgeting for medicines is critical. If the national ministry of health does not provide medicines for free and the patient cannot afford to buy the medicines, then there will essentially be no possibility of curtailing the spread of infection and the occurrence of complications. At the national level it is important that decision-makers, politicians and fiscal controllers understand the need to subsidize STI medicines. Low-cost STI medicines can be obtained through international vendors of generic products, non-profit organizations with procurement schemes such as UNICEF, UNFPA and UNHCR, and through joint medicine procurement schemes. By way of such schemes, national programmes can join other national programmes to jointly procure medicines, thus reducing the overall costs by sharing the overhead costs and taking advantage of discounts for purchasing in bulk. Placing STI medicines on national lists of essential medicines increases the likelihood of achieving a supply of these medicines at low cost.

IDENTIFYING AND PROCURING STI MEDICINES

It is important not only to identify medicines that will be recommended as first-line treatment for STIs but also the estimated quantities of medicines that will be required. Quantifying medication needs is important in order to estimate costs, to reconcile financial requirements with available budget, and to make orders in advance so that the unit and freight costs can be minimized.

In order to estimate the quantity of medicines needed, it will be necessary to review the medicines that are recommended for treatment, their unit prices, the quantity required per treatment and the epidemiological information on the prevalence of infection. One can estimate medicine needs by multiplying the estimated number of cases by the total quantity of medicine specified for treatment of one case. These figures can be derived from health centres providing care but they must be verified to avoid wasteful over-ordering.

04

RECOMMENDATIONS
FOR TREATMENT
OF SYPHILIS

The first eight recommendations (in sections 4.1 and 4.2) apply to adults and adolescents (10–19 years of age), including people living with HIV, key populations (including sex workers, men who have sex with men and transgender persons), and pregnant women. Specific recommendations have also been developed for congenital syphilis caused by *T. pallidum* – recommendations 9 and 10 apply to infants (see section 4.3).

4.1 EARLY SYPHILIS (PRIMARY, SECONDARY AND EARLY LATENT SYPHILIS OF NOT MORE THAN TWO YEARS' DURATION)

ADULTS AND ADOLESCENTS RECOMMENDATION 1

In adults and adolescents with early syphilis, the WHO STI guideline recommends benzathine penicillin G 2.4 million units 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 million units once intramuscularly over procaine penicillin G 1.2 million units 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 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.

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 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, recommendations for people with late syphilis should be followed.

SUMMARY OF THE EVIDENCE

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.

PREGNANT WOMEN RECOMMENDATION 3

In pregnant women with early syphilis, the WHO STI guideline recommends benzathine penicillin G 2.4 million units 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 million units once intramuscularly over procaine penicillin 1.2 million units intramuscularly once daily 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 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.

Conditional recommendation, very low quality evidence

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.**

SUMMARY OF THE EVIDENCE

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.

4.2 LATE SYPHILIS (INFECTION OF MORE THAN TWO YEARS' DURATION WITHOUT EVIDENCE OF TREPONEMAL INFECTION)

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 million units 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 million units intramuscularly once weekly for three consecutive weeks over procaine penicillin 1.2 million units once daily 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 (e.g. 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 recommendations 7 and 8 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 million units 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 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 daily 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 (e.g. due to stock-outs), the WHO STI guideline suggests using, with caution, 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 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 be avoided.**

SUMMARY OF THE EVIDENCE

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.

4.3 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.

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. 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.

SUMMARY OF THE EVIDENCE

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.

05

RESEARCH
IMPLICATIONS

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.

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ANNEX A: STI GUIDELINE DEVELOPMENT TEAMS

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AFR: WHO African Region; AMR: WHO Region of the Americas; EMR: WHO Eastern Mediterranean Region;
EUR: WHO European Region; SEAR: WHO South-East Asia Region; WPR: WHO Western Pacific Region

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AFR: WHO African Region; AMR: WHO Region of the Americas; EMR: WHO Eastern Mediterranean Region;
EUR: WHO European Region; SEAR: WHO South-East Asia Region; WPR: WHO Western Pacific Region

ANNEX B: DETAILED METHODS FOR GUIDELINES DEVELOPMENT

QUESTIONS AND OUTCOMES

To determine which recommendations to update, in December 2013 the World Health Organization (WHO) Department of Reproductive Health and Research reviewed current recommendations of key international guidelines:

- Sexually transmitted diseases treatment guidelines, 2010, Department of Health and Human Services, United States Centers for Disease Control and Prevention (CDC)⁴;
- United Kingdom national guidelines for the management of sexually transmitted infections, British Association for Sexual Health and HIV (BASHH), 2006–2011;⁵
- Canadian guidelines on sexually transmitted infections, Public Health Agency of Canada, 2013–2014;⁶
- European sexually transmitted infections guidelines, International Union of Sexually Transmitted Infections (IUSTI);⁷
- National management guidelines for sexually transmissible infections, Sexual Health Society of Victoria, Australia, 2008;⁸
- National guideline for the management and control of sexually transmitted infections (STIs), National Department of Health, South Africa, 2009;⁹ and
- National guidelines on prevention, management and control of reproductive tract infections including sexually transmitted infections, Ministry of Health and Family Welfare, Government of India, August 2007.¹⁰

Based on the review, four proposed categories of sexually transmitted infection (STI) conditions were prioritized:

- a. STI conditions included in the 2003 WHO STI guidelines¹¹ that were selected by the GDG to be reviewed and updated in the new WHO STI guidelines. These are important and common conditions.
- b. STI conditions not included in the 2003 WHO STI guidelines that were selected by the GDG to be reviewed and added in the new WHO STI guidelines. These are important and common conditions.
- c. STI conditions included in the 2003 WHO STI guidelines that were not updated but were selected by the GDG to be included in the new WHO STI guidelines. These STI conditions are rare and diagnosis is not often made in the majority of settings, or it is unlikely that there is new information available as a basis for making any changes to the 2003 WHO STI recommendations.
- d. STI conditions not included in the 2003 WHO STI guidelines that are part of other national guidelines, but were not selected by the GDG to be included in the new WHO STI guidelines. These conditions are rare and difficult to diagnose in the majority of settings, or it is unlikely that new research or information has become available; there are existing recommendations for these conditions that can be applied in other settings (e.g. reference hospitals that manage complicated conditions).

4 Available at: <http://www.cdc.gov/std/treatment/2010/std-treatment-2010-rr5912.pdf>

5 Available at: <http://www.bashh.org/BASHH/Guidelines/Guidelines/BASHH/Guidelines/Guidelines.aspx?hkey=072c83ed-0e9b-44b2-a989-7c84e4fbd9de>

6 Available at: <http://www.phac-aspc.gc.ca/std-mts/sti-its/cgsti-ldcits/index-eng.php>

7 Available at: <http://www.iusti.org/regions/europe/euroguidelines.htm>

8 Melbourne Sexual Health Centre Treatment Guidelines, available at: <http://mshc.org.au/HealthProfessional/MSHCTreatmentGuidelines/tabid/116/Default>

9 DA Lewis, E Maruma. Revision of the national guideline for first-line comprehensive management and control of sexually transmitted infections: what's new and why? *South Afr J Epidemiol Infect.* 2009;24(2):6–9 (<http://apps.who.int/medicinedocs/documents/s18369en/s18369en.pdf>).

10 Available at: http://www.ilo.org/wcmsp5/groups/public/---ed_protect/---protrav/---ilo_aids/documents/legaldocument/wcms_117313.pdf

11 Guidelines for the management of sexually transmitted infections. Geneva: World Health Organization; 2003 (<http://www.who.int/hiv/pub/sti/en/STIGuidelines2003.pdf>, accessed 30 May 2016).

A meeting was held in December 2013, at which the Guideline Development Group (GDG) discussed and decided on the initial list of population, intervention, comparator and outcome (PICO) questions identified by WHO. After the meeting, surveys pertaining to each of the four STI topic areas (i.e. gonorrhoea, chlamydia, syphilis and genital herpes simplex virus) were administered among subgroups of the GDG members with expertise relating to the relevant STIs. The goal of the surveys was to rank the population, interventions and outcomes for each specific STI condition by importance. The surveys required the members of the STI subgroups to rank the population, interventions and outcomes on a scale of 1 to 9, from lowest to highest priority.

Four different priority STI surveys were conducted, and each survey attained a 90–100% response rate from the STI subgroup members. The survey results for priority populations, interventions and outcomes were analysed. Populations, interventions and outcomes with an average rating of 7 to 9 were considered “critical”; those with an average rating of 4 to 6 were considered “important”; and those with an average rating of 1 to 3 were considered “not important” and were thus not covered in the guidelines. Some questions that scored less than 7 were kept for consistency.

The number of comparisons in each question was also reduced; only “critical” interventions were compared with each other and with important interventions. Thus, “important” interventions were not compared to each other.

A revised list of questions was then compiled and all members of the full STI GDG were requested to review the priority questions. The priority questions were then revised based on this feedback.

Nine questions were identified for the update of the syphilis guidelines and used to inform the recommendations. Each question is framed using the PICO format (population, intervention, comparison, and outcomes).

PRIORITY QUESTIONS AND OUTCOMES FOR *TREPONEMA PALLIDUM* (SYPHILIS)

EARLY SYPHILIS: ADULTS AND ADOLESCENTS (RECOMMENDATIONS 1 AND 2)

Question 1: Should benzathine penicillin G 2.4 million units (MU) x 1 compared with other treatments be used for treating adults and adolescents, including people living with HIV, with early syphilis?

Early syphilis (primary, secondary or latent < 2 years) in adults and adolescents and people living with HIV

Population	Intervention	Comparator	Outcome
Adults and adolescents and people living with HIV with early syphilis (primary, secondary or latent < 2 years)	Benzathine PCN 2.4 MU x 1	Ceftriaxone 1 g IM qd x 10–14 days Azithromycin 2 g x 1 Benzathine PCN 2.4 MU x 3 doses Benzathine PCN 2.4 MU x 2 doses Doxycycline 100 mg po bid x 14 days Erythromycin 500 mg po qid x 14 days	Critical: Serological response, clinical cure Important: Transmission to partner, antimicrobial resistance, compliance, side-effects (including allergy, toxicity), HIV transmission or acquisition, STI complications

bid: twice daily; IM: intramuscular; MU: million units; PCN: penicillin; po: by mouth (orally); qd: daily; qid: four times daily

Question 2: Should benzathine penicillin G 2.4 MU x 1 compared with other treatments be used for treating adults and adolescents, including people living with HIV, with early syphilis with penicillin allergy?

Early syphilis (primary, secondary or latent < 2 years) in patients with penicillin allergy

Population	Intervention	Comparator	Outcome
Patients with penicillin allergy with early syphilis (primary, secondary or latent < 2 years)	PCN desensitization and PCN	Ceftriaxone 1 g IM qd x 10–14 days Azithromycin 2 g x 1 Doxycycline 100 mg po bid x 14 days Erythromycin 500 mg po qid x 14 days	Critical: Serological response, clinical cure, allergic reaction/anaphylactic shock Important: Transmission to partner, antimicrobial resistance, compliance, side-effects (including allergy, toxicity), HIV transmission or acquisition, STI complications

bid: twice daily; IM: intramuscular; PCN: penicillin; po: by mouth (orally); qd: daily; qid: four times daily

EARLY SYPHILIS: PREGNANT WOMEN (RECOMMENDATIONS 3 AND 4)

Question 3: Should benzathine penicillin G 2.4 MU x 1 compared with other treatments be used for treating pregnant women with early syphilis?

Early syphilis (primary, secondary or latent < 2 years) in pregnant women

Population	Intervention	Comparator	Outcome
Pregnant women with early syphilis (primary, secondary or latent < 2 years)	Benzathine PCN 2.4 MU x 1	Ceftriaxone 1 g IM qd x 10–14 days Azithromycin 2 g x 1 dose Benzathine PCN 2.4 MU x 3 doses Benzathine PCN 2.4 MU x 2 doses Erythromycin 500 mg po qid x 14 days	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

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

Question 4: Should benzathine penicillin G 2.4 MU x 1 compared with other treatments be used for treating pregnant women with early syphilis with penicillin allergy?

Early syphilis (primary, secondary or latent < 2 years) in pregnant women with penicillin allergy

Population	Intervention	Comparator	Outcome
Pregnant women with penicillin allergy with early syphilis (primary, secondary or latent < 2 years)	PCN desensitization and PCN	Ceftriaxone 1 g IM qd x 10–14 days Azithromycin 2 g x 1 Erythromycin 500 mg po qid x 14 days	Critical: Mother-to-child transmission, serological response, low birth weight/preterm, stillbirth/neonatal death, clinical cure, congenital deformities, side-effects (Including allergy, toxicity), anaphylaxis Important: Compliance, antimicrobial resistance, STI complications, transmission to partner, HIV transmission or acquisition

IM: intramuscular; PCN: penicillin; po: by mouth (orally); qd: daily; qid: four times daily

LATE SYPHILIS: ADULTS AND ADOLESCENTS (RECOMMENDATIONS 5 AND 6)

Question 5: Should benzathine penicillin G 2.4 MU x 1 dose weekly x 3 weeks compared with other treatments be used in adults and adolescents, including people living with HIV, with late syphilis?

Late syphilis (latent syphilis or syphilis of unknown duration) in adults and adolescents and people living with HIV

Population	Intervention	Comparator	Outcome
Adults and adolescents and people living with HIV with latent syphilis > 2 years or syphilis of unknown duration	Benzathine PCN 2.4 MU IM 3 doses (1 dose per week x 3 weeks)	Azithromycin Ceftriaxone 1 g IM or IV qd x 10 days Benzathine PCN 2.4 MU x 1, 2 doses over 2 weeks Doxycycline 100 mg po bid x 30 days Erythromycin 500 mg po qid x 30 days	Critical: Serological response, compliance Important: Transmission to partner, antimicrobial resistance, side-effects (including allergy, toxicity), HIV transmission or acquisition, STI complications

bid: twice daily; IM: intramuscular; IV: intravenous; MU: million units; PCN: penicillin; po: by mouth (orally); qd: daily; qid: four times daily

LATE SYPHILIS: PREGNANT WOMEN (RECOMMENDATIONS 7 AND 8)

Question 6: Should benzathine penicillin G 2.4 MU x 1 dose weekly x 3 weeks compared with other treatments be used for treating pregnant women with late syphilis?

Late syphilis (latent syphilis or syphilis of unknown duration) in pregnant women

Population	Intervention	Comparator	Outcome
Pregnant women with latent syphilis > 2 years or syphilis of unknown duration	Benzathine PCN 2.4 MU IM 3 doses (1 dose per week x 3 weeks)	Azithromycin Ceftriaxone 1 g IM or IV qd x 10 days Benzathine PCN 2.4 MU x 1, 2 doses over 2 weeks Erythromycin 500 mg po qid x 30 days	Critical: Mother-to-child transmission, serological response, low birth weight/preterm, stillbirth/neonatal death, congenital deformities, compliance Important: Antimicrobial resistance, STI complications, transmission to partner, HIV transmission or acquisition, side-effects (including allergy, toxicity)

IM: intramuscular; IV: intravenous; MU: million units; PCN: penicillin; po: by mouth (orally); qd: daily; qid: four times daily

CONGENITAL SYPHILIS: INFANTS (RECOMMENDATIONS 9 AND 10)

Question 7: In infants with congenital syphilis, or in infants whose mothers had untreated syphilis, inadequately treated syphilis or adequately treated syphilis, what are the treatment options?

Multiple scenarios of proven or possible infection:**Scenario 1: Infants with congenital syphilis**

Population	Intervention	Comparator	Outcome
Infants with congenital syphilis	Benzyl penicillin 100 000–150 000 U/kg/day x 10–15 days Procaine penicillin 50 000 U/kg/day x 10–15 days	Ceftriaxone: <ul style="list-style-type: none"> • Infants < 30 days: Ceftriaxone 75 mg/kg BW IM/IV single dose x 10–14 days • Infants ≥ 30 days: Ceftriaxone 100 mg/kg BW IM/IV single dose x 10–14 days 	Critical: Clinical cure, serologic response, congenital syphilis manifestation

BW: body weight; IM: intramuscular; IV: intravenous

Question 8: In infants who are clinically normal but whose mothers had untreated syphilis, inadequately treated syphilis or syphilis that was treated with non-penicillin regimens, what are the treatment options?

Scenario 2: Infants who are clinically normal but whose mothers had untreated syphilis, inadequately treated syphilis or syphilis that was treated with non-penicillin regimens

Population	Intervention	Comparator	Outcome
Infants clinically normal, but mother with syphilis not treated, inadequately treated or treated with non-penicillin	Benzyl penicillin 100 000–150 000 U/kg/day x 10 days to 15 days Procaine penicillin 50 000 U/kg/day x 10–15 days	Benzathine penicillin 50 000 U/kg IM single dose Ceftriaxone: <ul style="list-style-type: none"> Infants < 30 days: Ceftriaxone 75 mg/kg BW IM/IV single dose x 10–14 days Infants ≥ 30 days: Ceftriaxone 100 mg/kg BW IM/IV single dose x 10–14 days No treatment	Critical: Clinical cure, serologic response, congenital syphilis manifestation

BW: body weight; IM: intramuscular; IV: intravenous

Question 9: In infants who are clinically normal and whose mothers had syphilis that was adequately treated with no signs of reinfection, what is the recommended course of action?

Scenario 3: Infants who are clinically normal and whose mothers had syphilis that was adequately treated with no signs of reinfection

Population	Intervention	Comparator	Outcome
Infants clinically normal, but mother treated, no signs of reinfection	Benzathine penicillin 50 000 U/kg IM single dose	No treatment Ceftriaxone: <ul style="list-style-type: none"> Infants < 30 days: Ceftriaxone 75 mg/kg BW IM/IV single dose x 1 day Infants ≥ 30 days: Ceftriaxone 100 mg/kg BW IM/IV single dose x 1 day 	Critical: Clinical cure, serologic response, congenital syphilis manifestation

BW: body weight; IM: intramuscular; IV: intravenous

REVIEW OF THE EVIDENCE

SEARCH FOR EVIDENCE FOR EFFECTS OF INTERVENTIONS

To avoid duplication of reviews that have been previously published, evidence was searched using a hierarchical approach. The team first searched for synthesized evidence then searched the primary studies for all the factors needed to complete the evidence-to-decision framework for each question (i.e. benefits and harms, patient values, acceptability, feasibility, equity and costs).

The hierarchical approach consisted of identifying pre-existing synthesized evidence, including from previously published guidelines that included systematic reviews of the literature. When synthesized evidence about benefits and harms for an intervention was not available or the synthesized evidence was not up to date, a new systematic review of randomized controlled trials (RCTs) and non-randomized studies was conducted.

The search strategies were developed by an information specialist trained in systematic reviews. The strategies included the use of keywords from the controlled vocabulary of the database and text words based on the PICO questions. There were no restrictions based on language, publication status or study design. RCTs were included for critical and important outcomes, and non-randomized studies for critical outcomes when no evidence was available from RCTs. Additional strategies included contacting Cochrane review groups and authors of study protocols.

The Cochrane Library suite of databases (Cochrane Database of Systematic Reviews [CDSR], Database of Abstracts of Reviews of Effects [DARE], Health Technology Assessment [HTA] database and the American College of Physicians [ACP] Journal Club) was searched for published systematic reviews and protocols up to January 2014.

Search strategy:

1. treponema.mp.
2. pallidum.mp.
3. syphilis.mp.
4. chancre*.mp.
5. or/1-4

Primary studies were searched for in the Cochrane Central Register of Controlled Trials (CENTRAL) (up to March 2015), MEDLINE and Embase databases (up to 26 February 2015) and LILACS (up to 19 April 2015).

The strategies included searching for subject headings and text words related to syphilis and specific interventions (e.g. medication names and classes). Additional strategies included checking reference lists and consulting with the GDG for any missed articles.

SCREENING STUDIES, DATA EXTRACTION AND ANALYSIS

Two researchers independently screened titles and abstracts of systematic reviews identified through database searching to determine studies eligible for inclusion in the analysis. Disagreements were resolved by discussing study inclusion with a third member of the research team. Data were extracted using a pilot-tested form for patient characteristics (including the subgroups identified by the GDG), diagnosis, treatment (dose, schedule, etc.), setting, follow-up and outcomes. Two investigators independently abstracted data. Risk of bias of each study was also assessed using risk of bias tools appropriate for RCTs (http://handbook.cochrane.org/chapter_8/8_assessing_risk_of_bias_in_included_studies.htm) and using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I; previously called ACROBAT) tool to assess non-randomized studies (www.riskofbias.info).

To measure the treatment effect, the data were analysed using RevMan 5.2.¹²

For dichotomous outcomes, we calculated relative risks with 95% confidence intervals (e.g. risk ratios and odds ratios) by pooling results from RCTs and pooling results from non-randomized studies using the random effects model. Moderate to high heterogeneity ($I^2 > 50\%$) was explored. Effects were converted to absolute effects using the calculated relative effect and a representative baseline risk (agreed upon by the GDG). When non-randomized studies with one group were included, a pooled proportion of an event (and confidence intervals) were calculated across the studies using the generic inverse variance. For continuous outcomes, a mean difference or a standardized mean difference (when studies used different scales to measure an outcome) was calculated. When possible, the forest plots of the meta-analyses were made available to the GDG.

When data could not be pooled across studies, narrative synthesis methods were used (see <http://methods.cochrane.org/sites/methods.cochrane.org/files/Mckenzie.pdf>). Results were presented in tables (e.g. median effects with interquartile ranges), or were narratively described by direction of the effect or by statistical significance as reported in the primary study.

PATIENT VALUES AND PREFERENCES, ACCEPTABILITY, EQUITY AND FEASIBILITY

Studies on patient values and preferences, acceptability, equity and feasibility were searched for and screened using two methods. First, while screening studies for the effects of treatments and costs, two investigators identified studies of potential relevance in these areas. Secondly, a separate search was conducted in MEDLINE, Embase and PsycINFO from January 2000 to July 2015. Text words and keywords for the different STIs were used in combination with words such as "preference", "adherence", "satisfaction", "attitudes", "health utilities" and "value", "equity" and "feasibility". The results included 2563 unique references. Two investigators screened the studies, and 162 studies were identified for full text retrieval. Any study design was included that addressed equity or feasibility. In addition, when adherence was measured in RCTs or non-randomized studies, the data were collected, synthesized and presented in the evidence profiles for each PICO question.

The following study designs were included:

- a. Patient utilities and health status values studies: These studies examine how patients value alternative health states and their experiences with treatment. The measurement techniques used can include: standard gamble, time trade-off, visual analogue scale, or mapping results based on generic surveys (EuroQol five dimensions health questionnaire [EQ-5D] or the 36-Item Short Form Health Survey [SF-36]) or specific measurement (e.g. St George Respiratory Questionnaire) of health-related quality of life.
- b. Studies of patients' direct choices when presented with decision aids: These studies examine the choices patients make when presented with decision aids for management options (i.e. probabilistic trade-off techniques).
- c. Studies on non-utility measurement of health states: These studies quantitatively examine patients' views, attitudes, satisfaction or preferences through questionnaires or scales; these are neither utility studies nor studies of patients' responses to decision aids. Patients are asked about how desirable or aversive a particular outcome is for them. This category includes some studies that use questionnaires or scales.
- d. Qualitative studies: These studies explore patients' views, attitudes, satisfactions or preferences related to different treatment options based on qualitative research methods including focus group discussions, interviews, etc.

From the search, we included 17 studies reporting information relating to different STIs. In many instances, data for all infections informed the evidence for syphilis specifically.

RESOURCES

We searched the published literature for evidence on use of resources and obtained data on direct costs of medicines.

Based on the list of possible treatments identified by the GDG, an estimate of the cost associated with each alternative was calculated. This costing estimate refers only to the actual market price of the medication and does not include the costs of other resources that could be involved, such as syringes, injection time or needle disposal.

Data were presented in a table and included: treatment, dose per day, treatment duration, days, medicine cost per dose, medicine cost per full course of treatment, and 25% of procurement costs (as defined in the 2014 Management Sciences for Health (MSH) International drug price indicator guide)¹³. A final price for a full course of treatment for each medicine by dosage was calculated as the number of doses per day, multiplied by the number of days of the treatment, plus 25% of the procurement costs for the medicines used. The unit price of the medicine was obtained from the median prices provided in the 2014 MSH International drug price indicator guide and information available on the Internet. In order to determine a precise and reliable estimate, the price per unit (all expressed in US dollars) was provided only when the information available matched the dosage of interest (grams per pill or 1000 units per vial). No calculations were made based on assumptions about the cost per unit of hypothetical packaging not listed in the directory.

The major medical databases were also searched (MEDLINE, Embase and the Cochrane Library for Economic Evaluation and Technology Assessment reports) from January 2005 to July 2015. In addition, while screening studies for the effects of treatments, two investigators also identified studies of potential relevance for costs. No studies were identified for resource use relating to treatment of syphilis.

13 International drug price indicator guide, 2014 edition (updated annually). Medford (MA): Management Sciences for Health; 2015 (http://erc.msh.org/dmpguide/pdf/DrugPriceGuide_2014.pdf, accessed 6 June 2016).

APPLYING THE GRADE APPROACH TO MAKING THE RECOMMENDATIONS

EVIDENCE PROFILES

An evidence profile was made for each PICO question using the GRADEpro software (www.grade.pro.org). Each profile included the critical and important outcomes, the relative and absolute effects, and the quality of evidence according to the GRADE domains (see the GRADE handbook)¹⁴. Briefly, the GRADE approach assesses the quality of evidence for treatment interventions using well-established criteria for the design, risk of bias, inconsistency, indirectness, imprecision, effect size, dose–response curve and other considerations that may affect the quality of the evidence. Two investigators used the GRADE approach to assess the quality and level of certainty of the evidence. The evidence profiles for each recommendation are available in Web annex D.

EVIDENCE-TO-DECISION FRAMEWORKS

Evidence-to-decision frameworks were also developed using GRADEpro software (www.grade.pro.org). Evidence-to-decision frameworks present the desirable and undesirable effects of the interventions, the value of the outcomes, the costs and resource use, the acceptability of the interventions to all stakeholders, the impact on health equity, and the feasibility of implementation (i.e. the GRADE criteria for making decisions). The evidence-to-decision frameworks are based on a population perspective for these recommendations. All GRADE criteria were considered from this perspective.

MAKING THE RECOMMENDATIONS

In October 2015, the GDG met to make the recommendations. This meeting was facilitated by two co-chairs – one with expertise in GRADE and the other with clinical expertise of syphilis. During the meeting, the evidence profiles and evidence-to-decision frameworks were presented by the methodologists. The GDG discussed each GRADE criterion and judged which intervention was favoured. Then a final decision and guideline recommendation was developed. The goal was to arrive at agreement across all members of the GDG and this was facilitated by the chairpersons through discussion. When there was disagreement for a criterion, it was noted in the evidence-to-decision framework for the relevant judgement. If there was disagreement for any of the final recommendations, the plan was for the GDG to vote and the numbers to be recorded. Because there was no disagreement for any of the final recommendations, however, votes were not taken or reported in these guidelines.

The GDG made a strong or conditional recommendation for or against each intervention and described special circumstances in the remarks. Research implications were also developed and presented, based on the gaps identified in the evidence. Following the meeting, the recommendations were finalized via teleconference, and final approval was obtained from the GDG members electronically. All decisions and discussions from the GDG for each recommendation are available in the evidence-to-decision frameworks in Web annex D.

14 Schünemann H, Brożek J, Guyatt G, Oxman A, editors. GRADE handbook. Hamilton, Ontario: McMaster University and Evidence Prime Inc.; 2013 (http://gdt.guidelinedevelopment.org/central_prod/_design/client/handbook/handbook.html, accessed 31 May 2016).

ANNEX C: LISTS OF REFERENCES FOR REVIEWED EVIDENCE

RECOMMENDATION 1 AND 2

Question 1: Should benzathine penicillin G 2.4 million units (MU) x 1 compared with other treatments be used for treating adults and adolescents including people living with HIV with early syphilis?

Question 2: Should benzathine penicillin G 2.4 MU x 1 compared with other treatments be used for treating adults and adolescents, including people living with HIV, with early syphilis with penicillin allergy?

Systematic reviews

- Bai ZG, Wang B, Yang K, Tian JH, Ma B, Liu Y, Jiang L, Gai QY, He X, Li Y. Azithromycin versus penicillin G benzathine for early syphilis. *Cochrane Database Syst Rev.* 2012;(6):CD007270.
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RECOMMENDATION 3 AND 4

Question 3: Should benzathine penicillin G 2.4 MU x 1 compared with other treatments be used for treating pregnant women with early syphilis?

Question 4: Should benzathine penicillin G 2.4 MU x 1 compared with other treatments be used for treating pregnant women with early syphilis with penicillin allergy?

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RECOMMENDATION 5 AND 6

Question 5: Should benzathine penicillin G 2.4 MU x 1 dose weekly x 3 weeks compared with other treatments be used in adults and adolescents including people living with HIV with late syphilis?

Systematic review

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RECOMMENDATION 7 AND 8

Question 6: Should benzathine penicillin G 2.4 MU x 1 dose weekly x 3 weeks compared with other treatments be used for treating pregnant women with late syphilis?

Systematic review

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RECOMMENDATION 9

Question 7: In infants with congenital syphilis or in infants whose mothers had untreated syphilis, inadequately treated syphilis or adequately treated syphilis, what are the treatment options?

Question 8: In infants who are clinically normal but whose mothers had untreated syphilis, inadequately treated syphilis or syphilis that was treated with non-penicillin regimens, what are the treatment options?

RECOMMENDATION 10

Question 9: In infants who are clinically normal and whose mothers had syphilis that was adequately treated with no signs of reinfection, what is the recommended course of action?

Systematic review

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