World Health Organization

WHO GUIDELINE ON

Syphilis screening and treatment for pregnant women

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

Web annex D: Evidence tables and evidence-to-decision frameworks
Web annex E: Summary of the declarations of interest and management of conflicts of interest

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ABBREVIATIONS AND ACRONYMS

AIDS	acquired immune deficiency syndrome
AMR	antimicrobial resistance
CI	confidence interval
DOI	declaration of interests
FTA-ABS	fluorescent treponemal antibody absorbed
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GUD	genital ulcer disease
HIV	human immunodeficiency virus
HPV	human papillomavirus
HSV	herpes simplex virus
HSV-2	herpes simplex virus type 2
MSH	Management Sciences for Health
MSM	men who have sex with men
PICO	population, intervention, comparator, outcome
PMTCT	prevention of mother-to-child transmission
RPR	rapid plasma reagin
STI	sexually transmitted infection
TPHA	*Treponema pallidum* haemagglutination assay
TPPA	*Treponema pallidum* particle agglutination assay
VDRL	Venereal Diseases Research Laboratory

WHO GUIDELINE ON SYPHILIS SCREENING AND TREATMENT FOR PREGNANT WOMEN

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.

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. 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.

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.

Screening all pregnant women for syphilis at first antenatal care visit is recommended in many countries of the world and is being scaled up rapidly in countries committed to the elimination of mother-to-child transmission (EMTCT) of HIV and syphilis. In most settings, the screening and diagnosis of syphilis is based on serologic tests. Recent advances in the development of rapid treponemal syphilis tests means that there are additional testing options that could be added to the historical set of screening tools, which include laboratory-based non-treponemal tests (e.g. RPR and VDRL) and treponemal tests (e.g. TPPA, TPHA). Countries are in urgent need of guidance related to screening for syphilis in pregnancy.

This guideline provides updated recommendations for syphilis screening and treatment for pregnant women based on the most recent evidence and available serologic tests for syphilis. Recommendations relating to the treatment of syphilis for pregnant women have been directly copied from the 2016 *WHO guidelines for the treatment guidelines of Treponema pallidum (syphilis)* and reference is made (and links provided for ease of use) to the recommendations for treatment of congenital syphilis, which were also included in the 2016 publication.

This publication is one of several guideline modules for specific STIs. Other modules approved by the WHO Guidelines Review Committee (GRC) are for treatment of *Chlamydia trachomatis* (chlamydia), *Neisseria gonorrhoeae* (gonorrhoea), genital herpes simplex virus (genital HSV) and *Treponema pallidum* (syphilis). These modules were developed together and are linked. In addition, future work will provide guidance for STI syndromic approach, STI laboratory diagnosis and screening, clinical management, STI prevention, and treatments of other STIs. All these modules will also be consolidated to form comprehensive STI guidelines. 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 this guideline are:

- to provide evidence-based guidance on syphilis screening and treatment for pregnant women; and
- to support countries to update their national guidelines for syphilis screening and treatment for pregnant women.

METHODS

This guideline was 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 related to screening and treatment of syphilis in pregnant women. A methodologist and a team of systematic reviewers from McMaster University, the WHO Collaborating Centre for Evidence-Informed Policy, independently conducted systematic reviews or updated systematic reviews of the literature for the diagnostic accuracy and effectiveness of different syphilis screening and treatment strategies. Cost-effectiveness analyses were used to inform these recommendations. The evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach and presented to the GDG. Declarations of interests were obtained from the GDG and 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 recommendations summarized in Tables 1 and 2 apply to pregnant women for the screening and treatment of syphilis. These recommendations address syphilis screening strategies in different care settings, optimal sequence of tests for syphilis screening, and subsequent treatment. The recommendations for the treatment of syphilis in pregnant women and of congenital syphilis have been previously published and updated (2016) in the *WHO guidelines for the treatment of Treponema pallidum (syphilis)*. The same recommendations for the treatment of syphilis in pregnant women (see Table 2) are included in this guideline to provide a comprehensive approach to managing pregnant women, including recommendations for both screening and treatment.

Table 1. Summary of recommendations on syphilis screening and treatment strategies for pregnant women

Recommendations	Strength of recommendation and quality of evidence
Screening for maternal syphilis	
Recommendation 1 The WHO STI guideline recommends screening all pregnant women for syphilis during the first antenatal care visit. *Remarks:* This recommendation applies to all settings, including settings with high or low prevalence of syphilis.	*Strong recommendation, moderate-quality evidence*
Screening strategies[a]	
Recommendation 2 In settings with low coverage of syphilis screening and treatment for pregnant women, high loss to follow-up of pregnant women, or limited laboratory capacity, the WHO STI guideline suggests on-site tests (Strategies A, B and C) rather than the standard off-site laboratory-based screening and treatment strategy.	*Conditional recommendation, low-quality evidence*
Recommendation 3 In settings with a low prevalence of syphilis (below 5%), the WHO STI guideline suggests a single on-site rapid syphilis test (RST) be used to screen pregnant women (Strategy A) rather than a single on-site rapid plasma reagin (RPR) test (Strategy B).	*Conditional recommendation, low-quality evidence*
Recommendation 4 In settings with a high prevalence of syphilis (5% or greater), the WHO STI guideline suggests an on-site rapid syphilis test (RST) and, if positive, provision of a first dose of treatment and a rapid plasma reagin (RPR) test, and then, if the RPR test is positive, provision of treatment according to duration of syphilis (Strategy C). The WHO STI guideline suggests this sequence of tests and treatment rather than a single on-site RST (Strategy A) or a single on-site RPR test (Strategy B). *Remarks:* These recommendations do not apply to countries that can provide appropriate/high-quality laboratory-based screening and treatment strategies. However, in some settings there may be challenges providing such strategies and/or a sequence of tests. When resources do not permit the use of a sequence of tests, a single on-site rapid syphilis test (RST) (Strategy A) is suggested to ensure greater screening coverage despite the number of pregnant women who will be over-treated due to the high rate of false-positive results. Treatment is based on duration of syphilis, according to the WHO guideline for the treatment of *Treponema pallidum* (syphilis)[b].	*Conditional recommendation, low-quality evidence*

[a] Note: Refer to section 5.3 of the main guideline text for the explanations and flowcharts for the various screening and treatment strategies mentioned (Strategies A-D).

[b] WHO guidelines for the treatment of *Treponema pallidum* (syphilis). Geneva: World Health Organization; 2016 (http://www.who.int/reproductivehealth/publications/rtis/syphilis-treatment-guidelines/en/).

Table 2. Summary of existing recommendations on syphilis treatment for pregnant women

Recommendations	Strength of recommendation and quality of evidence
Early syphilis (primary, secondary and early latent syphilis of not more than two years' duration)	
Recommendation 5 In pregnant women with early syphilis, the WHO STI guideline recommends benzathine penicillin G 2.4 million units once intramuscularly over no treatment. **Recommendation 6** 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. 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. *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 in the WHO guidelines for the treatment of syphilis, which refer to 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.**	*Strong recommendation, very low-quality evidence* *Conditional recommendation, very low-quality evidence*

Late syphilis (infection of more than two years' duration without evidence of treponemal infection)	
Recommendation 7 In pregnant women with late syphilis (more than two years' duration) 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. *Remarks:* The interval between consecutive doses of benzathine penicillin should not exceed 14 days.	*Strong recommendation, very low-quality evidence*
Recommendation 8 In pregnant women with late syphilis (more than two years' duration) or unknown stage of syphilis, the WHO STI guideline suggests benzathine penicillin G 2.4 million units intramuscularly once weekly for three consecutive weeks over procaine penicillin 1.2 million units intramuscularly once a day for 20 days When benzathine or procaine penicillin cannot be used (e.g. due to penicillin allergy where penicillin desensitization is not possible) or are not available (e.g. due to stock-outs), the WHO STI guideline suggests using, with caution, erythromycin 500 mg orally four times daily for 30 days. *Remarks:* Although erythromycin treats the pregnant women, it does not cross the placental barrier completely and as a result the fetus is not treated. It is therefore necessary to treat the newborn infant soon after delivery (see recommendations 9 and 10 in the WHO guidelines for the treatment of syphilis, which refer to 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.**	*Conditional recommendation, very low-quality evidence*

Source: WHO guidelines for the treatment of Treponema pallidum (syphilis). Geneva: World Health Organization; 2016 (http://www.who.int/reproductivehealth/publications/rtis/syphilis-treatment-guidelines/en/).
Note: In the source guideline, these recommendations were numbered 3, 4, 7 and 8.

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)*. Resistance to azithromycin and treatment failure have been reported in strains of *Treponema pallidum*, *N. gonorrhoeae* and *Mycoplasma genitalium*. In addition, instances of treatment failure have been reported for tetracyclines and macrolides in the treatment of *Chlamydia trachomatis (14, 15)*. Low-level resistance to *Trichomonas vaginalis* has also been reported for nitroimidazoles, the only available treatment *(16)*.

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 azithromycin (2 g, single dose) as an alternative treatment for early syphilis *(17)*.

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 is now due to viral infections, as previously common bacterial infections (such as chancroid) approach elimination in many countries *(17, 18)*. 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 *(17)*. The chronic, lifelong nature of viral infections also requires that renewed attention be paid to developing effective prevention strategies, including expanding access 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 *(17)*.

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 *(17)*.

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 3 summarizes the proposed phases and timeline.

Table 3: Phases for development of the STI guidelines

Phases	Topics	Timeframe
Phase 1	Treatment of specific STIs: *Chlamydia trachomatis* (chlamydia), *Neisseria gonorrhoeae* (gonorrhoea), HSV-2 (genital herpes) and *Treponema pallidum* (syphilis) Syphilis screening and treatment for pregnant women STI syndromic approach Clinical management package	November 2013 – April 2016 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: *Trichomonas vaginalis* (trichomoniasis), bacterial vaginosis, *Candida albicans* (candidiasis), *Haemophilus ducreyi* (chancroid), *Klebsiella granulomatis* (donovanosis), human papillomavirus (HPV; genital warts/cervical cancer), *Sarcoptes scabiei* (scabies) and *Phthirus pubis* (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 have been developed and published as independent modules:

- *Chlamydia trachomatis* (chlamydia) (published in 2016 *[19]*)
- *Neisseria gonorrhoeae* (gonorrhoea) (published in 2016 *[20]*)
- HSV-2 (genital herpes) (published in 2016 *[21]*)
- *Treponema pallidum* (syphilis) (published in 2016 *[22]*)
- Syphilis screening and treatment for pregnant women (this publication).

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 AND BURDEN OF DISEASE

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 *(3)*. 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.

1.2 LABORATORY DIAGNOSIS AND SCREENING

Syphilis diagnosis is based on the patient's history, physical examination, laboratory testing and sometimes radiology. However, many people with syphilis do not have any symptoms or have only minor symptoms and do not realize that anything is wrong. Identifying asymptomatic infection, especially among pregnant women, through screening using laboratory tests and treatment of positive cases will prevent further transmission and adverse pregnancy outcomes and congenital syphilis. The available laboratory tests for 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 *(4)*.

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. Interpretation of test results are detailed in section 5.

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. RPR tests can be performed within an hour depending on the laboratory set-up and can be done at the point of care or in an off-site laboratory. These tests detect anti-lipid immunoglobin 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 by 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 absorption (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.

RAPID SYPHILIS TESTS (RSTS)

In the past decade, a number of point-of-care rapid syphilis tests (RSTs) for treponemal antibodies in syphilis infection have been developed. RSTs provide treponemal antibody results in 10–15 minutes and can be performed on-site in any setting since they do not require refrigerated storage or laboratory equipment.

Most of the initial range of RSTs 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 RSTs, providing both a screening (RPR/VDRL equivalent) and confirmatory (TPHA/TPPA equivalent) component. However, these combined RSTs have not yet been sufficiently evaluated or field-tested to be recommended.

The different syphilis laboratory tests, laboratory procedures and interpretation are described in detail in the *WHO Laboratory diagnosis of sexually transmitted infections, including human immunodeficiency virus (4).*

1.3 RATIONALE FOR NEW RECOMMENDATIONS

The *WHO Guidelines for the management of sexually transmitted infections*, published in 2003 *(5)*, recommended early screening and treatment of pregnant women with syphilis, ideally prior to the second trimester of pregnancy, to prevent fetal complications. Screening all pregnant women for syphilis at first antenatal care visit is recommended in many countries of the world and is being scaled up rapidly in countries committed to the elimination of mother-to-child transmission (EMTCT) of HIV and syphilis.

Recent advances in the development of RSTs and dual treponemal–HIV rapid tests means that there are many testing options to add to the historical set of screening tools, which include laboratory-based non-treponemal tests (e.g. RPR and VDRL) and treponemal tests (e.g. TPPA, TPHA). Countries are in urgent need of guidance as to how to select and implement the most appropriate screening strategies for syphilis in pregnancy to ensure that coverage of syphilis screening is increased and that all pregnant women with syphilis receive adequate treatment. It is essential to provide recommendations on syphilis screening and treatment strategies for different health-care settings, including the optimal sequence of tests for syphilis screening and the optimal approach for subsequent treatment.

1.4 OBJECTIVES

The objectives of this guideline are:

- to provide evidence-based guidance on syphilis screening and treatment for pregnant women; and
- to support countries to update their national guidelines for syphilis screening and treatment for pregnant women.

1.5 TARGET AUDIENCE

This guideline is 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. It is 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.

This guideline is 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.

1.6 STRUCTURE OF THE GUIDELINE

This guideline provides evidence-based recommendations for syphilis screening and treatment for pregnant women to prevent mother-to-child transmission of syphilis. This guideline provides direction for countries as they develop national recommendations; however, national guidelines should also take into account the existing laboratory infrastructure, heath service capacity and resources.

This guideline includes recommendations related to syphilis screening and treatment strategies in different health-care settings, including the optimal sequence of tests for syphilis screening and the optimal approach for subsequent treatment based on the most recent evidence and on the available laboratory tests. This guideline incorporates recommendations for the treatment of syphilis for pregnant women from the *WHO guidelines for the treatment of Treponema pallidum (syphilis) (6).*

02 METHODS

This guideline was developed following the methods outlined in the 2014 edition of the *WHO handbook for guideline development* ***(7)*** (see Annex B for a detailed description).

The methods for the development of the recommendations for syphilis screening for pregnant women are described below and the methods specific to the treatment of syphilis in pregnant women are described in the *WHO guidelines for the treatment of Treponema pallidum (syphilis) (6)*.[1] These two guidelines have been developed together and are interlinked. They are two among several guideline modules that will be consolidated into a comprehensive STI guideline.

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. PICO questions were identified for syphilis screening for pregnant women including questions relating to the options of no screening, mass treatment and test strategies using different tests (see Annex B). Only outcomes that were ranked as critical or important to patients and decision-making were included: treatment rate (over- and under-treatment), cost per case detected, cost per women screened, screening coverage, side-effects, adverse events associated with medicines and penicillin, accessibility, partner notification and treatment, maternal completion of treatment before delivery, maternal complications and infant outcomes (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 October 2016. Additional searches were conducted to identify studies on patient values and preferences (e.g. qualitative research designs) and resources (e.g. cost-effectiveness studies).

Since there was little data directly comparing screening to no screening, or comparing different test strategies to each other and comparing their effects on important patient outcomes, cost-effectiveness modelling studies were used to provide evidence. For the question comparing screening to no screening, data from a previously published cost-effectiveness analysis were used *(8)*. Numbers of infant outcomes were presented.

1 Available at: http://www.who.int/reproductivehealth/publications/rtis/syphilis-treatment-guidelines/en/

For the question comparing different test strategies, the evidence was modelled from diagnostic test accuracy data and the calculated effects on important patient outcomes. A published cost-effectiveness analysis used field data for the rates of syphilis screening and treatment in countries with low and high prevalence of syphilis, as well as data on the sensitivity and specificity of single rapid syphilis tests (RSTs) in the field and from published research, and data on the effects of treatments *(9)*. The data used in the analysis were confirmed using another unpublished systematic review of test accuracy data of single RSTs *(10)*. The outputs of the cost-effectiveness analysis were presented by test strategy and by outcomes for screening rate, treatment rate, missed cases, over-treatment and cases treated (Web annex D). The reviews of evidence for the treatment of syphilis in pregnant women are detailed in the *WHO guidelines for the treatment of Treponema pallidum (syphilis) (6)*.

The quality/certainty of the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[2] Evidence came primarily from modelling of the patient-important outcomes which were based on appropriate inputs such as screening rates, diagnostic test accuracy and the effects of treatments. Therefore, the overall certainty of the evidence was based on the inputs and linking of these data in the model *(11)*.

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 the 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 (12)*. 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 annex D).

2.4 MAKING RECOMMENDATIONS

The evidence was presented and discussed 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. After discussion, it was decided that additional information should be obtained. Therefore, the screening recommendations were formulated during subsequent teleconference calls and electronic communications with the GDG working group for syphilis. To formulate the recommendations, the GDG working group for syphilis 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. The GDG working group for syphilis made judgements for each of the above criteria and an overall judgement about each recommendation and the strength of the recommendation was made. If there had been disagreements about the judgements, 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 judgements and recommendations. Following the discussions of the GDG working group for syphilis, the recommendations were finalized via teleconference and final approval was obtained from all GDG members electronically. This guideline was 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 guideline. The implications of the differing strengths of recommendations for patients, clinicians and policy-makers are explained in detail in Table 4.

2 For further information, see: http://www.gradeworkinggroup.org/

Table 4. 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 guideline 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 *(13)*. 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 E.

After analysing each DOI, the WHO STI Secretariat 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 not discussed.

03 DISSEMINATION AND UPDATING THE GUIDELINE

3.1 DISSEMINATION

The guideline 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)[3], and in the WHO Reproductive Health Library (RHL)[4]. The recommendations will also be available in a guideline application ("app") created with the GRADEpro GDT software. The guideline 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 this guideline using the WHO Department of Reproductive Health and Research guidance on *Introducing reproductive health guidelines and tools into national programmes (14)*. All levels of WHO (headquarters, regional offices and country offices) 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. These external partners will support the dissemination and implementation of this guideline. Reference to this document will be made within other relevant WHO guidelines. This guideline 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 this guideline will be conducted after it has been published. The results of the survey will be used to identify challenges and barriers to the uptake of the guideline, to evaluate its usefulness for improving service delivery, and to identify topics or gaps in treatment that need to be addressed in future editions.

3 The guideline and all supporting documents will be available at: www.who.int/reproductivehealth/publications/rtis/syphilis-screen-treat-pregnant-guidelines/en/

4 RHL is available at: http://apps.who.int/rhl/en/

04 RECOMMENDATIONS ON SYPHILIS SCREENING AND TREATMENT FOR PREGNANT WOMEN

The recommendations presented in this section apply to pregnant women for the screening and treatment of syphilis. These recommendations refer to strategies for syphilis screening and treatment in different health-care settings, including the optimal sequence of tests for syphilis screening and the optimal approach for subsequent treatment. The recommendations for the treatment of syphilis for pregnant women are detailed in the *WHO guidelines for the treatment of Treponema pallidum (syphilis)* ***(6)*** and are also found in Table 2 (see Executive summary) and in section 4.3 of this document. Figure 1 in section 5 of this guideline provides a decision-making flowchart for maintaining or introducing new syphilis screening and treatment strategies.

4.1 RECOMMENDATION ON SYPHILIS SCREENING FOR PREGNANT WOMEN

RECOMMENDATION 1

The WHO STI guideline recommends screening all pregnant women for syphilis during the first antenatal care visit.

Strong recommendation, moderate-quality evidence

Remarks: This recommendation applies to all settings, including settings with high or low prevalence of syphilis.

SUMMARY OF THE EVIDENCE

There is moderate-quality evidence for large desirable effects and trivial undesirable effects of universal screening versus no screening or case finding. This evidence is based on a study that modelled rates of screening, diagnostic test accuracy data (ranging from 71–100% test sensitivity) and effects of treatment, and based on a systematic review of non-randomized studies. As large effects were found, the evidence was assessed as moderate quality. The modelling studies found that large reductions are likely for important serious adverse outcomes of pregnancy (including congenital syphilis) in settings with low and high prevalence of syphilis (0.5% and 3% of women screened, respectively). If 1 million pregnant women are screened over four years, then 278–4521 stillbirths are averted, 124–2012 neonatal deaths are averted, 206–3353 infected infants are averted and 77–1255 premature or low-birth-weight infants are averted. Another systematic review found that there were greater risks of adverse outcomes if women were screened in the third trimester of pregnancy compared to the first and second trimester.

In cost-effectiveness studies conducted in 2013, 2014 and 2015, there were cost savings in high-prevalence settings, and the costs per disability-adjusted life year (DALY) were within WHO standards in low-prevalence settings. The Guideline Development Group (GDG) agreed that although there may be a cost to some women for screening tests, studies providing such testing have consistently shown increases in screening coverage in different countries and settings (e.g. rural and urban settings). Universal screening may increase equity by making screening available to all pregnant women. Most studies showed that women were satisfied with being tested for syphilis. However, some were concerned about the stigma of testing (particularly if it is perceived to be HIV testing), some feared a positive result and some had concerns about the treatment implications if results were positive. Health-care providers require specific training as well as information about syphilis prevalence and risks in order to implement screening. A review of studies found that increased screening is feasible, but that stock-outs of tests and medicines for treatment were often a difficulty with implementation. See Annex C for a list of references of reviewed evidence, and Web annex D for details of the evidence reviewed, including evidence tables and evidence-to-decision frameworks (pp. 2–20).

RATIONALE

Overall, the GDG agreed that universal screening is favoured over no screening because large reductions are likely for important serious adverse outcomes of pregnancy and congenital syphilis in settings with low or high prevalence of syphilis. Universal screening also probably increases equity and is cost-effective. It is likely to be acceptable to pregnant women and health-care providers, and also feasible with training and improved awareness of staff.

4.2 RECOMMENDATIONS ON SYPHILIS SCREENING AND TREATMENT STRATEGIES FOR PREGNANT WOMEN[5]

RECOMMENDATION 2

In settings with low coverage of syphilis screening and treatment for pregnant women, high loss to follow-up of pregnant women, or limited laboratory capacity, the WHO STI guideline suggests on-site tests (Strategies A, B and C) rather than the standard off-site laboratory-based screening and treatment strategy.

Conditional recommendation, low-quality evidence

RECOMMENDATION 3

In settings with a low prevalence of syphilis (below 5%), the WHO STI guideline suggests a single on-site rapid syphilis test (RST) be used to screen pregnant women (Strategy A) rather than a single on-site rapid plasma reagin (RPR) test (Strategy B).

Conditional recommendation, low-quality evidence

RECOMMENDATION 4

In settings with a high prevalence of syphilis (5% or greater), the WHO STI guideline suggests an on-site rapid syphilis test (RST) and, if positive, provision of a first dose of treatment and a rapid plasma reagin (RPR) test, and then, if the RPR test is positive, provision of treatment according to duration of syphilis (Strategy C). The WHO STI guideline suggests this sequence of tests and treatment rather than a single on-site RST (Strategy A) or a single on-site RPR test (Strategy B).

Conditional recommendation, low-quality evidence

Remarks: These recommendations do not apply to countries that can provide appropriate/high-quality laboratory-based screening and treatment strategies. However, in some settings there may be challenges providing such strategies and/or a sequence of tests. When resources do not permit the use of a sequence of tests, a single on-site rapid syphilis test (RST) (Strategy A) is suggested to ensure greater screening coverage despite the number of pregnant women who will be over-treated due to the high rate of false-positive results. Treatment is based on duration of syphilis, according to the *WHO guidelines for the treatment of Treponema pallidum (syphilis) (6).*

SUMMARY OF THE EVIDENCE

There were no randomized controlled trials comparing different screening and treatment strategies to each other. The absolute effects of the RST are derived primarily from a cost-effectiveness model which incorporated data for the screening rates, diagnostic test accuracy data, and effects of treatments.
The diagnostic test accuracy data were confirmed in a systematic review (for which the search was updated to October 2016) that pooled results from 10 studies assessing the test accuracy of on-site RST. It found that the RST had a sensitivity of 0.83 (95% CI: 0.58–0.98) and a specificity of 0.96 (95% CI: 0.89–1.00), and the rapid plasma reagin (RPR) test had a pooled sensitivity of 0.75 (95% CI: 0.54–0.88) and a pooled specificity of 0.97 (95% CI: 0.96–0.99). There is moderate certainty in these results. In the model, all tests were compared to a "gold standard" of laboratory-based tests of RPR-positive and TPPA- or TPHA-positive test results. Linking of the evidence from all sources resulted in low-certainty evidence.

Data from the model indicated the following:

- The use of either (i) a single on-site RST followed by treatment (Strategy A), or (ii) an on-site RST followed by the first dose of treatment if positive, and then an RPR test (either on- or off-site) followed by appropriate treatment if this test is also positive (Strategy C), may result in slightly to moderately greater numbers of people being treated as compared to the use of on-site RPR strategies (Strategies B and, if RPR is available on-site Strategy E) in all prevalence settings (approximately 4 more per 1000 pregnant women in low-prevalence settings, and 20–30 more per 1000 in higher-prevalence settings).

5 Refer to section 5.3 for the explanations and flowcharts for the various screening and treatment strategies mentioned (Strategies A-D).

- The difference in the occurrence of harms caused by over-treatment is trivial between the single on-site RST (Strategy A) and the single on-site RPR test (Strategy B) strategies in lower-prevalence settings (9 more per 1000 pregnant women with the on-site RPR strategy). However, in higher-prevalence settings, the difference in over-treatment between the single on-site RST and the single on-site RPR test strategies may be moderate and favour the single on-site RST strategy (approximately 30–50 more per 1000 pregnant women with the on-site RPR strategy). The difference in over-treatment between (i) the on-site RST followed by RPR (Strategy C) and (ii) the single on-site RPR test (Strategy B) strategies may be trivial.
- The difference in harms related to missed treatment is small between (i) a single on-site RST (Strategy A) and (ii) the single on-site RPR test (Strategy B) strategies in lower-prevalence settings (approximately 4 more per 1000 pregnant women with the on-site RPR strategy), but moderate in higher-prevalence settings (25–30 more per 1000 pregnant women with the on-site RPR strategy).
- The number of pregnant women screened appeared to be slightly greater or similar with the single on-site RST strategy (Strategy A) compared to other strategies, but similar among other strategies and among different prevalence settings.

The GDG agreed that more value should be placed on missed cases of syphilis because of the serious adverse effects of syphilis in pregnancy and the serious risks of congenital syphilis and fetal death. Although over-treatment resulted in minor side-effects such as gastrointestinal symptoms (and over-treatment is more likely to occur for women with higher titres due to the sensitivity of the tests), some over-treatment was acceptable, while over-treatment in large proportions of tested women was considered undesirable. Although there is no evidence for effects of the different screening and treatment strategies on partner notification, the GDG agreed that providing a sequence of tests (Strategy C) could ultimately increase partner treatment as additional tests may lead to increased belief in the positive results among the tested pregnant women and their partners.

The cost-effectiveness model showed that the total costs per 1000 women screened were lowest with RPR in the United Republic of Tanzania and Zambia, while in Peru use of RSTs was the cheapest due to labour costs related to the use of RPR. The model found that the most cost-effective screening and treatment approach in all prevalence settings is single on-site RST followed by treatment if positive (Strategy A; but it should be noted that the strategy may cost more in some settings).

Although there were no studies directly measuring the impact of different strategies on equity, there may be a direct cost for the screening and/or treatment services for some pregnant women in some countries. However, screening rates achieved still appear to be slightly higher with the single on-site RST strategy (Strategy A), regardless of cost, indicating that such costs may not reduce equity. There were no studies comparing the acceptability of RST to RPR. However, four studies of each of the rapid tests found that health workers and pregnant women were satisfied with the RSTs, which reduced clinic visits and were easy to use. One systematic review and six studies addressed feasibility of the on-site tests. A sequence of on-site tests may be unaffordable in some settings and require adequate provider training. However, on-site tests have been successfully implemented in many countries to date. See Annex C for list of references of reviewed evidence, and Web annex D for details of the evidence reviewed, including evidence tables and evidence-to-decision frameworks (pp. 21–36).

RATIONALE

Overall, the GDG agreed that a strategy of using a single on-site RST followed by treatment if positive (Strategy A) or a strategy of using an on-site RST followed by a first dose of treatment if positive and also followed by an RPR test and then second and third doses of treatment if that test is also positive (Strategy C) may lead to greater numbers of people treated, fewer missed cases and fewer incidents of over-treatment compared to other strategies (Strategies B and D). In lower-prevalence settings, the single on-site RST (Strategy A) or a sequence of screening tests and treatment (Strategy C) yielded similar results. However, in higher-prevalence settings, there were fewer pregnant women over-treated when using a sequence of tests and treatment (Strategy C). The single on-site RST strategy (Strategy A) is cost-effective, feasible to implement and acceptable to key stakeholders.

4.3 RECOMMENDATIONS ON SYPHILIS TREATMENT FOR PREGNANT WOMEN

For the treatment of pregnant women who have tested positive for syphilis based on the syphilis screening/testing strategies discussed, refer to the *WHO guidelines for the treatment of Treponema pallidum (syphilis) (6)*. Recommendations 5–8 have been directly copied from that guideline (where they were numbered Recommendations 3, 4, 7 and 8) in order to provide comprehensive information here on the appropriate approach to syphilis screening and treatment for pregnant women. Recommendations for how to prevent and treat congenital syphilis are not included here, however, but are available in that guideline.[6]

EARLY SYPHILIS (PRIMARY, SECONDARY AND EARLY LATENT SYPHILIS OF NOT MORE THAN TWO YEARS' DURATION)[7]

RECOMMENDATION 5

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 6

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.

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 in the WHO guidelines for the treatment of syphilis, which refer to congenital syphilis [6]). Ceftriaxone is an expensive option and is injectable. Doxycycline should not be used in pregnant women. Because syphilis during pregnancy can lead to severe adverse complications to the fetus or newborn, **stock-outs of benzathine penicillin for use in antenatal care should be avoided.**

LATE SYPHILIS (INFECTION OF MORE THAN TWO YEARS' DURATION WITHOUT EVIDENCE OF TREPONEMAL INFECTION)[8]

RECOMMENDATION 7

In pregnant women with late syphilis (more than two years' duration) 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 (more than two years' duration) 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.

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.

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 in the WHO guidelines for the treatment of syphilis, which refer to congenital syphilis [6]). 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.**

6 WHO guidelines for the treatment of *Treponema pallidum* (syphilis). Geneva: World Health Organization; 2016 (http://www.who.int/reproductivehealth/publications/rtis/syphilis-treatment-guidelines/en/).

7 This is defined as: positive syphilis test with history of primary syphilis manifested as genital ulcer (painless chancre) at the site of infection; or secondary syphilis manifested by skin rash often seen on the palms of the hands and soles, condylomata lata, mucocutaneous lesions and generalized lymphadenopathy; or early latent syphilis manifested by no symptoms and known duration of untreated infection of not more than two years.

8 This is defined as: positive syphilis test without presence of any symptoms of more than two years' duration (late latent syphilis) or of unknown duration of untreated infection.

05 IMPLEMENTATION CONSIDERATIONS

5.1 ADAPTATION, IMPLEMENTATION AND MONITORING

These guidelines provide recommendations for syphilis screening and treatment for pregnant women, based on the best global evidence available at the time of compilation. However, the epidemiology and antimicrobial resistance (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 this guideline can be adopted as presented here.

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 *(14)*.

5.2 CONSIDERATION ON THE IMPLEMENTATION OF ANTENATAL SYPHILIS SCREENING AND TREATMENT

A decision on whether to continue the current antenatal syphilis screening algorithm or to introduce a new syphilis screening strategy that includes treponemal-based rapid syphilis tests (RSTs) into the national system should be based on a careful assessment of the screening coverage, treatment rate, and quality of the existing system of testing. The following points should be taken into consideration.

- Coverage: An assessment should be made of the proportion of all persons at risk and pregnant women who have access to syphilis testing.
- Quality of testing: The quality of testing should be assessed to ensure accuracy of results.
- Treatment of seropositive individuals: The proportion of all persons tested who subsequently receive test results and obtain treatment in a timely manner.

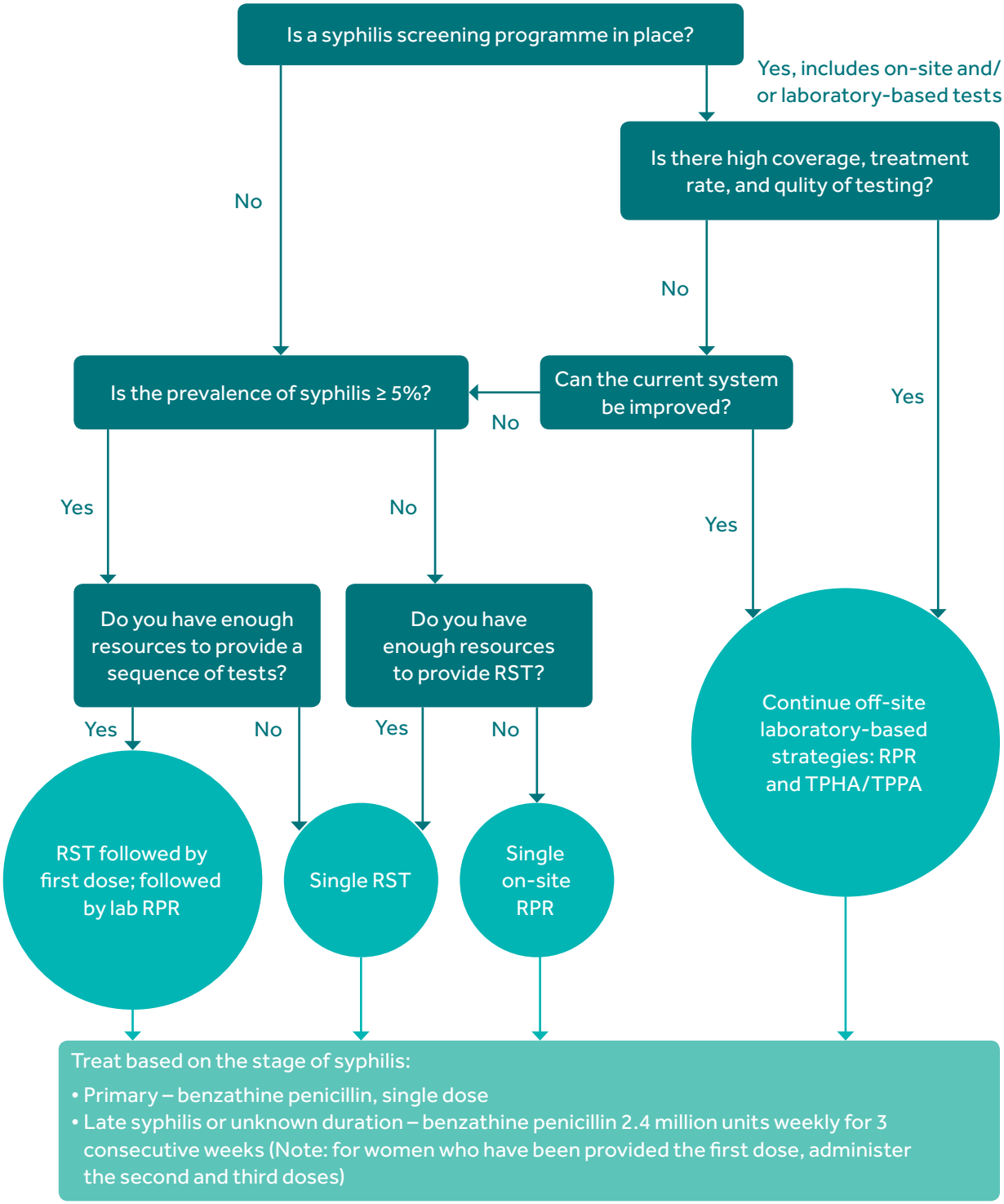
If the coverage of testing of pregnant women and the rate of treatment of seropositive individuals are not at least 95% each, consistent with the targets presented in the Global guidance on criteria and processes for validation: elimination of mother-to-child transmission of HIV and syphilis (15), then efforts should be made to rectify the inadequacies in the system. If the problems cannot be resolved, consideration should be given to introducing new screening and treatment strategies, following the decision-making flowchart presented in Figure 1.

A decision will also be based on the resources available. Country-level decision-makers should consider whether existing laboratory testing facilities meet the required standards, and the availability of other resources such as electricity for refrigeration of reagents, rotator and blood centrifuge, and if these resources are not available on-site at the point of care, then the costs of transporting laboratory samples will also need to be considered. In most settings, RSTs are less expensive than on-site and laboratory-based rapid plasma reagin (RPR) tests.

It will be essential to have accurate baseline data on the prevalence of syphilis among pregnant women, based on RPR test results which have been subsequently confirmed by *Treponema pallidum* haemagglutination assay (TPHA) or *Treponema pallidum* particle agglutination assay (TPPA). This guideline defines low syphilis prevalence as a rate that is below 5%, and high syphilis prevalence as a rate of 5% or above.

The interpretation of results and decisions about subsequent treatment regimen, based on recommendations 5, 6, 7 and 8 for the treatment of early and late syphilis in pregnant women (see section 4.3) should be specified.

Figure 1. Decision-making flowchart for maintaining or introducing new syphilis screening and treatment strategies

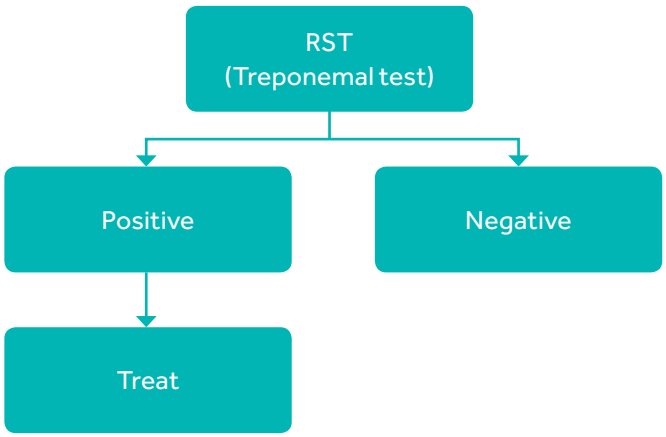


RPR: rapid plasma reagin test; RST: rapid syphilis (treponemal) test; TPHA: *Treponema pallidum* haemagglutination assay; TPPA: *Treponema pallidum* particle agglutination assay.

5.3 SCREENING AND TREATMENT STRATEGIES AND FLOWCHARTS

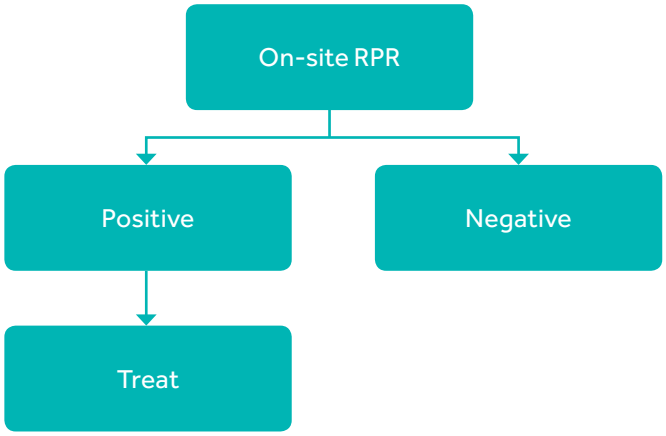
STRATEGY A: SINGLE ON-SITE RST FOLLOWED BY TREATMENT IF POSITIVE

The on-site RST can be provided as a single test and treatment provided during the same visit based on the results. The RST does not, however, distinguish between the presence of previously adequately treated syphilis and untreated syphilis. Therefore, pregnant women who test positive on the RST and are treated adequately for syphilis will likely still test positive on a subsequent RST (e.g. during a subsequent pregnancy). Pregnant women who tested positive on a previous RST (e.g. during a previous pregnancy) could therefore be treated again for syphilis without repeating the RST if the risk of re-infection is considered high. Alternatively, a quantitative RPR test could be performed in these women instead of an RST (i.e. to determine the titre).



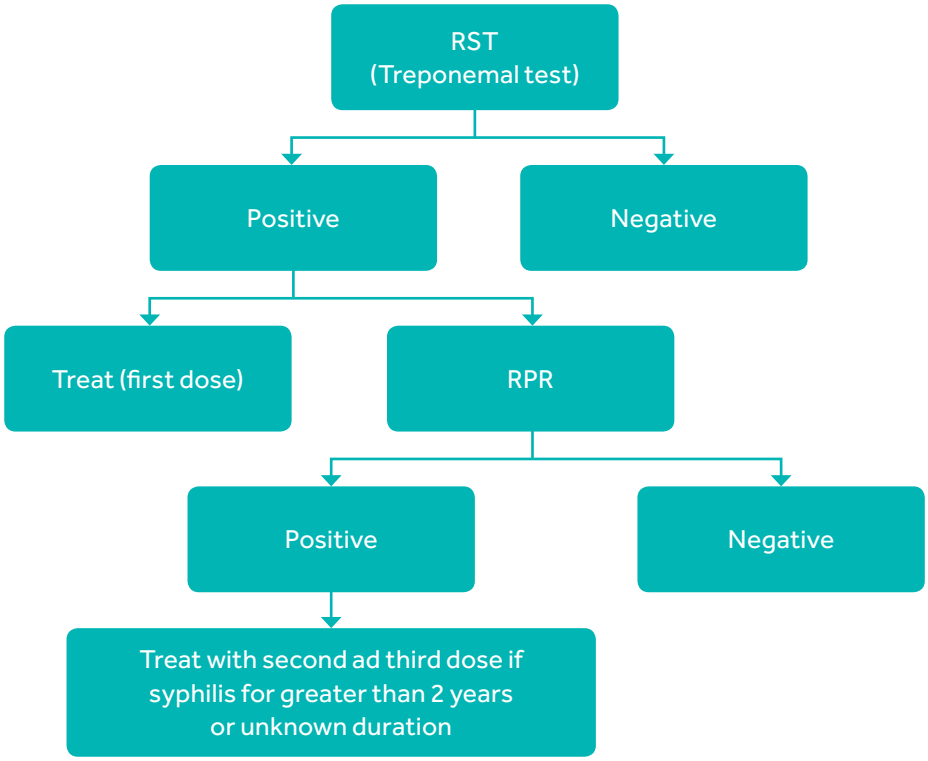
STRATEGY B: SINGLE ON-SITE RPR TEST FOLLOWED BY TREATMENT IF POSITIVE

The RPR test in this strategy is provided on-site as a single test and the results are available rapidly such that treatment can be provided the same day. This means that (as with the single on-site RST strategy), a pregnant woman can receive both testing and treatment during the same visit. If the RPR is negative, it can be repeated after approximately one month to obtain a correct (positive) diagnsosis for persons with early syphilis whose first RPR test was still negative. Women with early syphilis will be detectable by RPR test approximately a month after the onset of the primary chancre. Provision of on-site RPR will require a rotator, a blood centrifuge and a refrigerator for reagents, as well as electricity to operate this equipment.



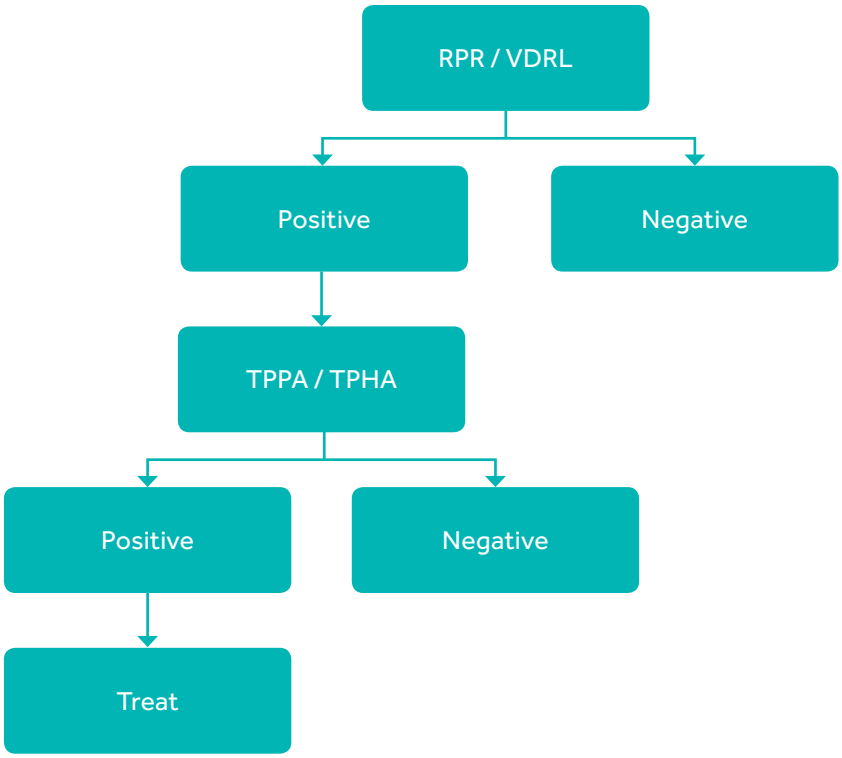
STRATEGY C: ON-SITE RST FOLLOWED (IF POSITIVE) BY FIRST DOSE AND RPR TEST

In this strategy, an on-site RST (treponemal test) is provided to the pregnant women first. If the result is seronegative, it can be interpreted as no syphilis infection and no treatment or further testing are given. If the on-site RST is positive, immediate treatment should be given to prevent adverse outcomes of pregnancy. A single dose of benzathine penicillin will be sufficient to prevent such adverse outcomes. The woman can then proceed to further testing with an RPR test (which may be conducted on- or off-site, depending on available resources), and if this test is also positive then she should be treated appropriately for syphilis according to the determined duration of her infection (see section 4.3). If the duration is less than two years then another dose is not needed, but if the duration is unknown or greater than two years then a second dose is needed a week after the first and a third dose a week later. If the RPR is negative, however, it can be repeated after approximately one month to obtain a correct (positive) diagnosis for persons with early syphilis whose first RPR test was still negative. Women with early syphilis will become detectable by RPR test approximately a month after the onset of the primary chancre. It should be noted that as with Strategy D, this strategy may also require the pregnant woman to make two visits to the clinic if her first test was positive (i.e. to receive the results of the second [RPR] test if it was not available on-site and for further treatment if indicated), but in this strategy she will have already received her first test results and first dose of treatment (if positive) on the first visit, whereas with Strategy D she will not receive any test results or treatment on the first visit.



STRATEGY D: STANDARD LABORATORY-BASED SCREENING STRATEGY: OFF-SITE RPR OR VDRL FOLLOWED (IF POSITIVE) BY TPPA OR TPHA TEST AND FOLLOWED (IF POSITIVE) BY TREATMENT

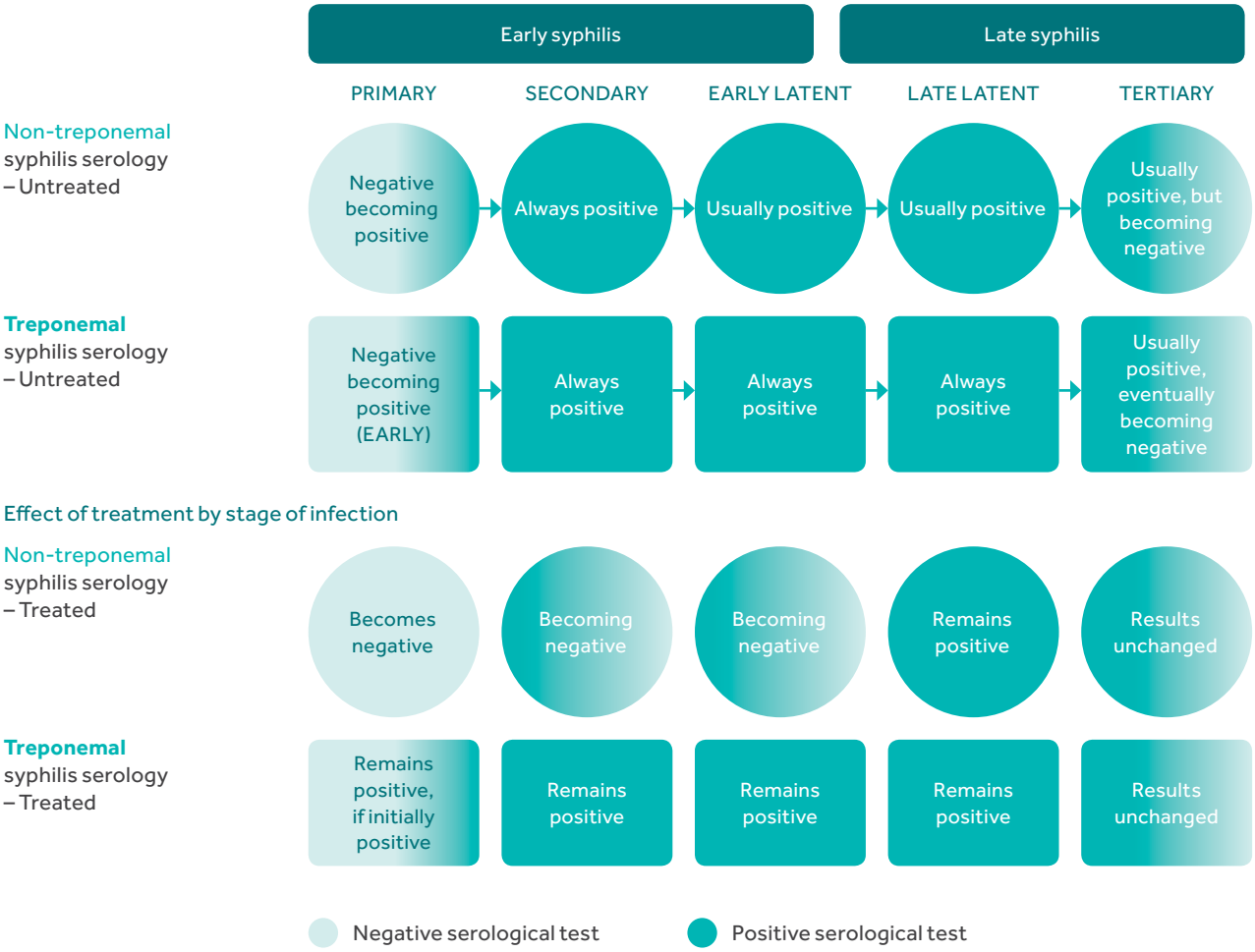
The standard screening strategy is an RPR or VDRL test, followed (if positive) by confirmation testing using TPHA or TPPA with the same blood sample; both tests are usually conducted at an off-site laboratory. Treatment is based on confirmed syphilis. Since confirmation takes 2–3 days, this strategy typically requires the pregnant woman to make two visits to the clinic: first to provide the blood sample for testing, and second to receive the final test results and appropriate treatment.



5.4 INTERPRETATION OF SYPHILIS TEST RESULTS

Figure 2 shows an overview of the reactivity of non-treponemal and treponemal serological tests for syphilis and the effect of successful treatment. Serological tests for syphilis give only a presumptive diagnosis of syphilis and their interpretation must be made together with a good sexual history of the individual, a physical examination, information about the stage of the disease and about any other underlying diseases or infections, and considering the possibility of false-positive or false-negative reactions. If possible, positive non-treponemal tests (i.e. RPR or VDRL) should be quantified (i.e. the titres should be determined). Above all, performance of RSTs require proficiency testing of providers and ongoing performance monitoring and quality assurance with negative and positive control specimens.

Figure 2. Reactivity of serological tests by stage of syphilis and effect of treatment



Source: Unemo et al., 2013 *(4)*.

The non-treponemal tests, such as RPR or VDRL, become positive within four to six weeks after infection, or some one to four weeks after the appearance of the chancre of primary syphilis. The tests are reactive almost without exception in secondary syphilis. As the duration of the early and late latent stages of syphilis increases, the antibody titre decreases and may eventually give a negative result in late syphilis (late latent and tertiary stages), even without treatment. With treatment, syphilis serology test may revert to negative depending on the stage of syphilis when treatment is instituted. This is more likely to happen if the individual is treated during the primary or secondary stage of syphilis. If the disease is diagnosed in late syphilis, non-treponemal tests remain positive for life.

The specific treponemal tests, including the TPHA, TPPA, FTA-ABS or RST, may become positive earlier than the non-treponemal tests. Once an individual tests positive on a treponemal test, most (85%) remain positive on subsequent treponemal tests even with successful treatment of the infection.

5.5 LABORATORY PROCEDURES AND QUALITY ASSURANCE

For details about the procedures for performing RSTs and RPR tests, refer to the WHO manual on *Laboratory diagnosis of sexually transmitted infections, including human immunodeficiency virus (4).*

It is essential that the quality of laboratory-based syphilis testing is maintained as part of the overall maintenance of laboratory operations. Staff performing the tests should be adequately trained and standard operating procedures should be developed. An internal quality assurance and external quality assessment system should be established, including periodic proficiency testing of staff syphilis testing skills. Consistent availability of test kits and treatment should be ensured.

06 RESEARCH IMPLICATIONS

The evidence used to develop the recommendations in this guideline came primarily from evidence that was modelled using diagnostic test accuracy data either from field research or published trials, or from studies evaluating the effects of treatments.

While there was evidence from single-test strategies (e.g. rapid syphilis tests [RSTs] and rapid plasma reagin [RPR] tests), there was no evidence for diagnostic test accuracy of a sequence of tests (e.g. RST followed by RPR [Strategy C in section 5]). Sequences of tests are of great interest and potential use but more research is needed to determine the real test accuracy of a sequence of tests, as opposed to using modelled test accuracy values.

The modelling also allowed for calculation of effects on infant and maternal outcomes, as there were few studies which followed the full path of pregnant women from testing to important outcomes. While follow-up data may be challenging to gather in the context of randomized controlled trials, when the recommendations are implemented in the coming months and years large-scale follow-up of cohorts of patients will provide important information about implementation and the level of success gained through the application of the screening and treatment strategies; in particular, for the strategy of on-site RST followed by first dose of treatment, if positive, and RPR testing followed by second and third doses of treatment, if positive (i.e. Strategy C in section 5). In addition, the acceptability of these strategies to pregnant women and health-care providers should be assessed, as well as the feasibility in different settings.

The focus of this guideline has been on the use of point-of-care (on-site) rapid tests for syphilis, including RSTs and RPR tests. Other tests which combine treponemal and non-treponemal tests in one test have also been developed and are being evaluated. Future guidelines will address these combined tests and provide recommendations for their use. There is also increasing evidence relating to the use of dual HIV and syphilis screening tests. This evidence will also be reviewed and recommendations on the use of these dual tests will be provided in future guidance.

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ANNEX A:
STI GUIDELINE DEVELOPMENT TEAMS

WHO STI STEERING COMMITTEE

WHO regional STI focal points		WHO Region
1.	**Massimo Ghidinelli (Unit Chief, HIV, Hepatitis, Tuberculosis and STIs)**	Division of Communicable Diseases Region of the Americas (AMR) Washington, DC – United States of America (USA)
2.	**Lali Khotenashvili (Medical Officer, HIV)**	European Region (EUR) Copenhagen – Denmark
3.	**Ying-Ru Lo (Coordinator, HIV, Hepatitis and STIs)**	Division of Communicable Diseases Western Pacific Region (WPR) Manila – Philippines
4.	**Frank Lule (Medical Officer, HIV)**	African Region (AFR) Brazzaville – Congo
5.	**Razia Pendse (Regional Advisor, HIV, STIs and Hepatitis)** **and** **Ornella Lincetto (WHO Country Representaive, Bhutan)**	Division of Communicable Disease South-East Asia Region (SEAR) New Delhi – India
6.	**Hamida Khattabi (Medical Officer, HIV and STIs)** **and** **Gabriela Reidner (Regional Advisor, HIV and STIs)**	Division of Communicable Disease Eastern Mediterranean Region (EMR) Cairo – Egypt
WHO headquarters		**WHO Department and Team**
7.	**Moazzam Ali**	Department of Reproductive Health and Research Human Reproduction Team
8.	**Avni Amin**	Department of Reproductive Health and Research Adolescents and at-Risk Populations
9.	**Rachel Baggaley**	Department of HIV/AIDS Key Populations and Innovative Prevention
10.	**Venkatraman Chandra-Mouli**	Department of Reproductive Health and Research Adolescents and at-Risk Populations
11.	**Jane Ferguson**	Department of Maternal, Newborn, Child and Adolescent Health; Research and Development
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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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ANNEX B:
DETAILED METHODS FOR GUIDELINE DEVELOPMENT

The methods for the development of the recommendations for syphilis screening for pregnant women are described below. The methods specific to syphilis treatment for pregnant women are described in the 2016 WHO guidelines for the treatment of *Treponema pallidum* (syphilis)[9].

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)[10];
- United Kingdom national guidelines for the management of sexually transmitted infections, British Association for Sexual Health and HIV (BASHH), 2006–2011[11];
- *Canadian guidelines on sexually transmitted infections*, Public Health Agency of Canada, 2013–2014;[12]
- European sexually transmitted infections guidelines, International Union of Sexually Transmitted Infections (IUSTI);[13]
- *National management guidelines for sexually transmissible infections*, Sexual Health Society of Victoria, Australia, 2008;[14]
- *National guideline for the management and control of sexually transmitted infections (STIs)*, National Department of Health, South Africa, 2009;[15] 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.[16]

A meeting was held in December 2013, at which the Guideline Development Group (GDG) discussed and decided on the questions to be addressed in the guidelines on syphilis treatment (2016 publication) and on syphilis screening and treatment (this publication), including the specific populations, tests and outcomes. Multiple questions were identified, including different screening/testing strategies, no screening and mass treatment. The questions are framed using the PICO format (population, intervention, comparator and outcomes).

9 Available at http://www.who.int/reproductivehealth/publications/rtis/syphilis-treatment-guidelines/en/

10 Available at: http://www.cdc.gov/std/treatment/2010/std-treatment-2010-rr5912.pdf

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

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

13 Available at: http://www.iusti.org/regions/europe/euroguidelines.htm

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

15 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).

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

Priority questions and outcomes on syphilis screening and treatment for pregnant women

Population	Intervention / Comparator	Outcome
Pregnant women – low prevalence and high prevalence syphilis settings	1. Single treponemal point-of-care test (POCT) 2. Single treponemal POCT *plus* dual treponemal/ non-treponemal POCT 3. Single treponemal POCT *plus* RPR/VDRL (lab) – give 1st dose if treponemal POCT is positive – treat only after RPR (if positive) 4. Dual trep/non-treponemal POCT 5. RPR/VDRL (lab) 6. RPR/VDRL (lab) *plus* single treponemal POCT 7. RPR/VDRL *plus* lab-based treponemal test OR 1. Mass treatment 2. No screening	• Treatment rate: over- and under-treatment • Cost per case detected • Cost per woman screened • Screening coverage • Side-effects, adverse events of drug or penicillin • Accessibility • Partner notification and treatment (over- and under-treatment) • Maternal completion of treatment before birth • Maternal complications • Infant outcomes • (HIV outcomes [not directly related to syphilis outcome])

RPR: rapid plasma reagin; VDRL: Veneral Diseases Research Laboratory.

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. We updated the searches of relevant systematic reviews to determine if more recent randomized controlled trials (RCTs) and non-randomized studies were available.

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 (with the exception of searches for systematic reviews).

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 October 2016.

Search strategy:

1. syphilis.mp.
2. pallidum.mp.
3. 1 or 2
4. rapid plasma reagin.tw.
5. rpr.tw.
6. rst.tw.
7. (rapid syphilis adj4 test*).tw.
8. (rapid test* adj4 syphilis).tw.
9. (treponemal adj3 test*).tw.
10. (non-treponemal adj3 test*).tw.
11. (immunochromographic adj3 (test* or strip*)).tw.
12. (immunochromatographic adj3 (test* or strip*)).tw.
13. or/4-12
14. 3 and 13
15. (antenatal or maternal or pregnan* or prenatal).tw.
16. (screen* or diagnos*).tw.
17. 15 and 16
18. 3 and 17
19. 14 or 18
20. remove duplicates from 19
21. (review or meta analysis).mp,pt. or search*.mp.
22. 20 and 21

Relevant systematic reviews (Hawkes et al., 2013;[17] Shahrook et al., 2014;[18] Rogozińska et al., 2016)[19] were updated by searching for additional primary studies (i.e. published since the latest publication date included in the previous search) in the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and Embase databases (up to October 2016).

The strategies included searching for subject headings and text words related to syphilis and specific interventions and tests. Additional strategies included checking reference lists and consulting with the GDG for any missed articles.

17 Hawkes SJ, Gomez GB, Broutet N. Early antenatal care: does it make a difference to outcomes of pregnancy associated with syphilis? A systematic review and meta-analysis. PLoS One. 2013;8:e56713.

18 Shahrook S, Mori R, Ochirbat T, Gomi H. Strategies of testing for syphilis during pregnancy. Cochrane Database Syst Rev. 2014;(10):CD010385.

19 Rogozińska E, Kara-Newton L, Zamora JR, Khan KS. On-site test to detect syphilis in pregnancy: a systematic review of test accuracy studies. BJOG. 2016;124(5):734–41. doi:10.1111/1471-0528.14455.

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 from the systematic reviews and studies. 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 or were narratively described by direction of the effect or by statistical significance as reported in the primary study.

Since there was little data directly comparing screening to no screening or comparing different test strategies to each other or comparing the effect on patient important outcomes, cost-effectiveness modelling studies were used to provide evidence. For the question comparing screening to no screening, data from a previously published cost-effectiveness analysis were used.[20] The number of infant outcomes was extracted from the model and then presented. For the question comparing different test strategies, the evidence was modelled from test accuracy data and from the calculated effects on patient important outcomes. A published cost-effectiveness analysis used: field data for the screening and treatment rates of syphilis in countries with low and high prevalence of syphilis; the sensitivity and specificity of single rapid syphilis tests (RSTs) in the field and from published research; and the effects of treatments.[21] The data used in the analysis were confirmed using another unpublished systematic review of test accuracy data of single RSTs.[22] The outputs of the cost-effectiveness analysis were extracted from the model and presented by test strategy and by outcomes for screening rate, treatment rate, missed cases, over-treatment, and cases treated (see Web annex D).

PATIENT VALUES AND PREFERENCES, ACCEPTABILITY, EQUITY AND FEASIBILITY

Systematic reviews and studies on patient values and preferences, acceptability, equity and feasibility were searched for and screened using two methods. First, while screening studies for the effectiveness of syphilis screening and costs, two investigators identified studies of potential relevance in these areas. Secondly, if a systematic review was not found on the subject, a separate search was conducted in MEDLINE and Embase from January 2012 to October 2016. Text words and keywords for syphilis were used in combination with words such as "preference", "adherence", "satisfaction", "attitudes", "health utilities" and "value", "equity" and "feasibility". The results included 42 unique references. 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.

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.

20 Kahn JG, Jiwani A, Gomez GB, Hawkes SJ, Chesson HW, Broutet N et al. The cost and cost-effectiveness of scaling up screening and treatment of syphilis in pregnancy: a model. PLoS One 2014;9:e87510.

21 Terris-Prestholt F, Vickerman P, Torres-Rueda S, Santesso N, Sweeney S, Mallma P et al. The cost-effectiveness of 10 antenatal syphilis screening and treatment approaches in Peru, Tanzania, and Zambia. Int J Gynaecol Obstet. 2015;130(Suppl 1):S73–80.

22 Rogozińska E, Kara-Newton L, Zamora JR, Khan KS. On-site test to detect syphilis in pregnancy: a systematic review of test accuracy studies. BJOG. 2016;124(5):734–41. doi:10.1111/1471-0528.14455.

d. Qualitative studies: These studies explore patients' views, attitudes, satisfaction or preferences related to different treatment options based on qualitative research methods including focus group discussions, interviews, etc.

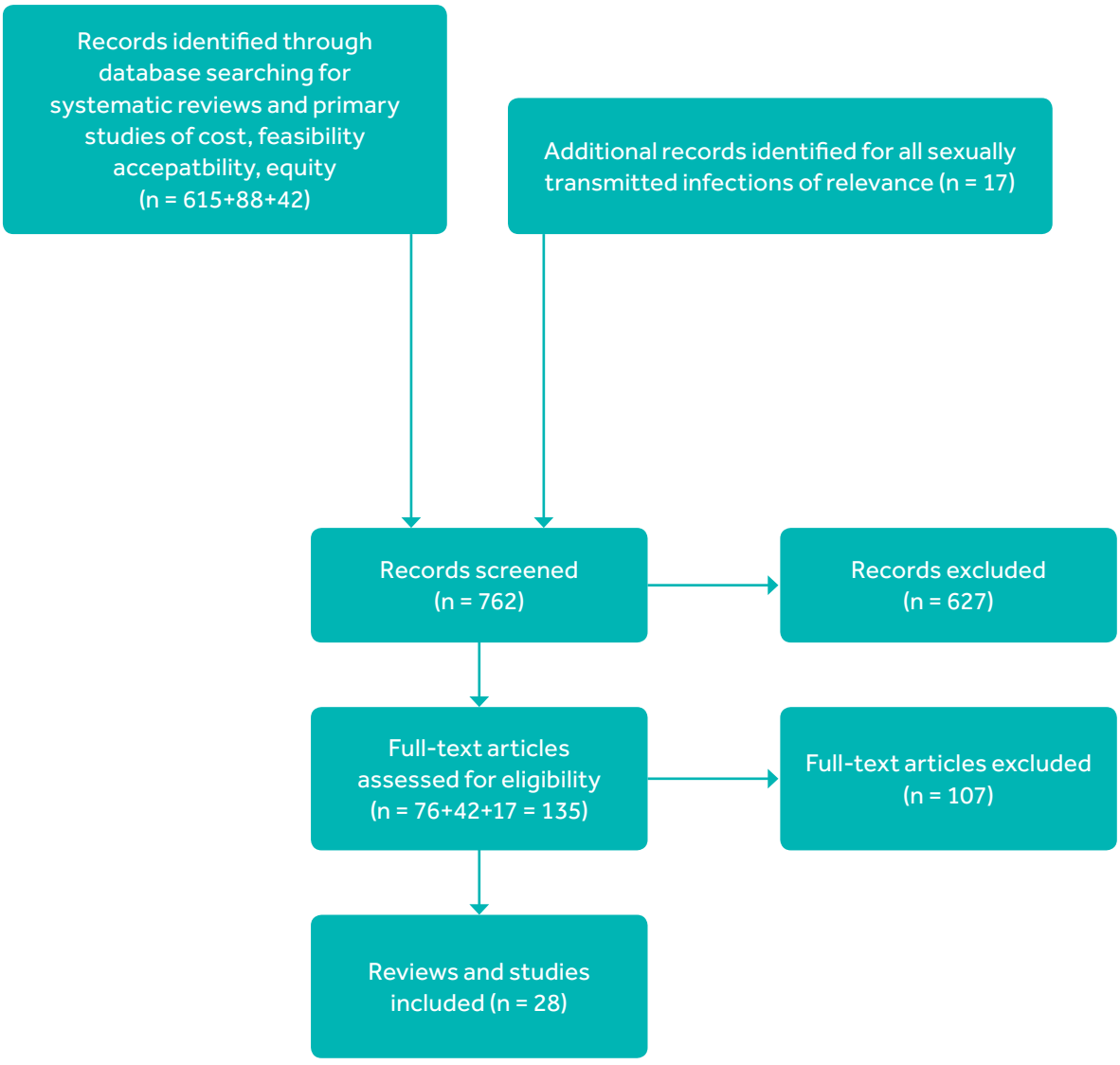
From the search, we included 19 studies reporting information on issues of acceptability, feasibility or equity related to screening, no screening or different syphilis screening tests and strategies.

RESOURCES

We searched the published literature for evidence on use of resources and obtained data on direct costs of syphilis tests. A separate table was presented on the indicative cost of syphilis tests (RPR and RSTs) as defined in the 2014 Management Sciences for Health (MSH) *International drug price indicator guide*)[23]. Costs and cost-effectiveness of different screening strategies, as well as mass treatment and no screening, were also presented from the data gathered from the cost-effectiveness modelling studies.

RESULTS OF SEARCH

PRISMA flow chart



23 International drug price indicator guide, 2014 edition (updated annually). Medford (MA): Management Sciences for Health; 2015 (http://apps.who.int/medicinedocs/documents/s21982en/s21982en.pdf, accessed 10 July 2017).

APPLYING THE GRADE[24] APPROACH TO MAKING THE RECOMMENDATIONS

EVIDENCE-TO-DECISION FRAMEWORKS

Evidence-to-decision frameworks were developed using GRADEpro software (www.gradepro.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. The evidence-to-decision frameworks for each recommendation are available in Web annex D.

MAKING THE RECOMMENDATIONS

The evidence was presented and discussed 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. After discussion, it was decided that additional information should be obtained. Therefore, the recommendations were formulated during subsequent teleconference calls and electronic communications with the GDG working group for syphilis. To formulate the recommendations, the GDG working group for syphilis 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.

The GDG working group for syphilis made judgements for each of the above criteria and an overall judgement about each recommendation and the strength of each recommendation was made. If there had been disagreements about the judgements, 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 judgements and recommendations. Following the discussions of the GDG working group for syphilis, the recommendations were finalized via teleconference and final approval was obtained from all GDG members electronically. This guideline was 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).

24 For further information, see: http://www.gradeworkinggroup.org/

ANNEX C:
LISTS OF REFERENCES FOR REVIEWED EVIDENCE

REFERENCES FOR SCREENING VERSUS NO SCREENING

Systematic review of randomized studies

1. Shahrook S, Mori R, Ochirbat T, Gomi H. Strategies of testing for syphilis during pregnancy. Cochrane Database Syst Rev. 2014;(10):CD010385.

Systematic review of non-randomized studies

1. Swartzendruber A, Steiner RJ, Adler MR, Kamb ML, Newman LM. Introduction of rapid syphilis testing in antenatal care: A systematic review of the impact on HIV and syphilis testing uptake and coverage. Int J Gynaecol Obstet. 2015;130(Suppl 1):S15–21.

Additional information from non-randomized studies

1. Hawkes SJ, Gomez GB, Broutet N. Early antenatal care: does it make a difference to outcomes of pregnancy associated with syphilis? A systematic review and meta-analysis. PLoS One. 2013;8:e56713.

Costs

1. International drug price indicator guide, 2014 edition (updated annually). Medford (MA): Management Sciences for Health; 2015 (http://apps.who.int/medicinedocs/documents/s21982en/s21982en.pdf, accessed 10 July 2017).
2. Kahn JG, Jiwani A, Gomez GB, Hawkes SJ, Chesson HW, Broutet N et al. The cost and cost-effectiveness of scaling up screening and treatment of syphilis in pregnancy: a model. PLoS One. 2014;9:e87510.
3. Kuznik A, Lamorde M, Nyabigambo A, Manabe YC. Antenatal syphilis screening using point-of-care testing in sub-Saharan African countries: a cost-effectiveness analysis. PLoS Med. 2013;10:e1001545.
4. Kuznik A, Muhumuza C, Komakech H, Marques EMR, Lamorde M, Antenatal syphilis screening using point-of-care testing in low- and-middle-income countries in Asia and Latin America: a cost-effectiveness analysis. PLoS One. 2015;10(5):e0127379.

Acceptability, equity, feasibility

1. Ansbro E´ M, Gill MM, Reynolds J, Shelley KD, Strasser S, Sripipatana T et al. Introduction of syphilis point of-care tests, from pilot study to national programme implementation in Zambia: a qualitative study of healthcare workers' perspectives on testing, training and quality assurance. PLoS One. 2015;10:e0127728.
2. Badman SG, Vallely LM, Toliman P, Kariwiga G, Lote B, Pomat W et al. A novel point-of-care testing strategy for sexually transmitted infections among pregnant women in high-burden settings: results of a feasibility study in Papua New Guinea. BMC Infect Dis. 2016;16:250.
3. Bocoum FY, Kouanda S, Zarowsky C. Barriers to antenatal syphilis screening in Burkina Faso. The Pan African Med J. 2014;17(Suppl 1):12.
4. Bristow CC, Lee SJ, Severe L, Pape JW, Javanbakht M, Comulada WS, Klausner JD. Attributes of diagnostic tests to increase uptake of dual testing for syphilis and HIV in Port-au-Prince, Haiti. Int J STD AIDS. 2016;28(3):259–64.
5. de Jongh TE, Gurol-Urganci I, Allen E, Jiayue Zhu N, Atun R. Barriers and enablers to integrating maternal and child health services to antenatal care in low and middle income countries. BJOG. 2016;123:549–57.
6. De Schacht C, Lucas C, Sitoe N, Machekano R, Chongo P, Temmerman M et al. Implementation of point-of-care diagnostics leads to variable uptake of syphilis, anemia and CD4+ T-Cell count testing in rural maternal and child health clinics. PLoS One. 2015;10(8):e0135744.
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