World Health Organization

WHO GUIDELINES ON

Syphilis screening and treatment for pregnant women

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

August 2017

*The full guideline is available at:
www.who.int/reproductivehealth/publications/rtis/syphilis-ANC-screenandtreat-guidelines/en/

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WHO guideline on syphilis screening and treatment for pregnant women

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CONTENTS

RECOMMENDATION 1: SYPHILIS SCREENING FOR PREGNANT WOMEN

Population:	Pregnant women (all trimesters)
Intervention and comparator:	Universal screening for syphilis versus no universal screening or case finding
Main outcomes:	Treatment rate, side-effects of treatment (adverse events of medicines, including penicillin), infant outcomes, maternal outcomes Other: screening coverage, costs, accessibility, partner notification and treatment rates
Setting:	Clinics in high- to low-prevalence settings
Perspective:	Population level
Background:	Syphilis is a systemic disease from the outset and is caused by the spirochaete *Treponema pallidum*. The infection can be classified as congenital (transmitted from mother to child in utero) or acquired (through sex or blood transfusion). In 2007, the World Health Organization (WHO) launched a global initiative for the elimination of mother-to-child-transmission (EMTCT) of syphilis, to be achieved by ensuring that at least 95% of pregnant women are screened for syphilis, and 95% of those identified with syphilis are treated appropriately. Screening tests can include treponemal tests and non-treponemal tests that are reactive to current and past syphilis infection, while high titre reactive non-treponemal tests are indicative of active syphilis infection. Tests currently in use include laboratory-based tests, such as rapid plasma reagin (RPR), Venereal Diseases Research Laboratory (VDRL), *Treponema pallidum* particle agglutination assay (TPPA) and *Treponema pallidum* haemaggluinatiom assay (TPHA), and also rapid point-of-care tests (POCTs), such as the on-site rapid syphilis tests (RSTs) and on-site RPR tests. These tests can be provided either as a single test whereby treatment is based on the single result, or in a sequence of tests whereby a positive result on the first test leads to the second test for confirmation. In the case of a sequence of tests, treatment can be initiated based on the first result and then continued or discontinued when the second result is available, or treatment can be given only after getting positive results on both tests.

ASSESSMENT

	Judgement	Research evidence
Problem	**Is the problem a priority?** • No • Probably no • Probably yes • **Yes** • Varies • Don't know	**Research evidence** Global estimates for 2012 indicated that there were 217 678 live births with congenital syphilis per 1 360 485 pregnant women with untreated syphilis (approximately 16 live births per 100 untreated women) not including stillbirths (21 per 100), neonatal deaths (9 per 100) or premature births (6 per 100)[1]. The resource implications of hospitalization for infants with congenital syphilis is more than three times higher than for infants without the disease. When mothers are treated during pregnancy, the risk of congenital syphilis is 0.03 times the risk in infants born to untreated mothers (i.e. the rate of births with congenital syphilis falls to approximately 4.8 per 1000 treated mothers). **Additional considerations** None
Desirable Effects	**How substantial are the desirable anticipated effects?** • Trivial • Small • Moderate • **Large** • Varies • Don't know	**Research evidence** *Randomized controlled trials:* A systematic review (Shahrook, 2014) searched for randomized controlled studies comparing use of screening tests to no screening, including studies published up until September 2014. This search was updated to October 2016 for the purposes of this guideline. No randomized controlled studies were found. *Non-randomized studies:* Swartzendruber (2015) conducted a systematic review on the impact of rapid syphilis tests (RSTs) on syphilis screening among pregnant women in antenatal care (ANC) settings in low- and middle-income countries (LMICs). All six non-randomized studies reviewed reported substantial increases in antenatal syphilis testing at all sites following the introduction of RSTs. Results did not differ greatly by country (high/low-prevalence areas), rural/urban setting, whether rapid HIV testing was already offered or was simultaneously introduced with RSTs, or by levels of syphilis screening prior to introduction of RST. Even in settings where syphilis testing was not previously conducted or where only 1–2% of pregnant women were screened quickly (using rapid diagnostic tests), high levels of syphilis screening were achieved through the introduction of RSTs. It was noted that all studies reported on testing for a period of up to one year following the introduction of RSTs. *Outcomes based on modelling:* A cost-effectiveness model (Kahn, 2014) provides data on scaling up screening and treatment of syphilis to reach 1 000 000 pregnant women in low- and high-prevalence settings with high and low coverage. Laboratory-based RPR was used to model the outcomes (100% sensitivity).
Undesirable Effects	**How substantial are the undesirable anticipated effects?** • Large • Moderate • Small • **Trivial** • Varies • Don't know	

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

Certainty of evidence

What is the overall certainty of the evidence of effects?

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

	High prevalence, no screening	High prevalenwce, current coverage low	Low prevalence, no screening	Low prevalence, current coverage high
Prevalence	3%	3%	0.5%	0.5%
Current coverage	0	20%	0	70%
Target coverage	-	50%	-	90%
Over 4 years per 1 000 000 pregnant women				
Stillbirths/late fetal loss	6270	4521 averted	1045	278 averted
Neonatal deaths	2790	2012 averted	465	124 averted
Infected infants	4650	3353 averted	775	206 averted
Premature or low-birth-weight infants	1740	1255 averted	290	77 averted

Additional information from non-randomized studies comparing testing strategies:
Timing: There was an increased risk of adverse pregnancy outcomes and congenital syphilis if women were screened with RPR with confirmation or TPHA in the third trimester compared to the first and second trimester (Hawkes, 2013).

Additional considerations
While evidence was from non-randomized studies and from modelling, providing low certainty of evidence, the large effects that were found in the studies resulted in upgrading the certainty of the evidence to moderate.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

- Important uncertainty or variability
- Possibly important uncertainty or variability
- **Probably no important uncertainty or variability**
- No important uncertainty or variability
- No known undesirable outcomes

Research evidence
Main outcomes: Treatment rate, side-effects of treatment (adverse events of drug or penicillin), infant outcomes, maternal outcomes.

Additional considerations
The Guideline Development Group (GDG) agreed that a high value should be placed on preventing the serious adverse outcomes of congenital syphilis, neonatal death and stillbirth.

<table>
<tr>
<td>Balance of effects</td>
<td>Does the balance between desirable and undesirable effects favour the intervention or the comparison?
• Favours the comparison
• Probably favours the comparison
• Does not favour either the intervention or the comparison
• Probably favours the intervention
• Favours the intervention
• Varies
• Don't know</td>
<td>The GDG agreed that providing universal screening averted serious adverse outcomes of pregnancy, including congenital syphilis, and there were no harms reported.</td>
</tr>
<tr>
<td>Resources required</td>
<td>How large are the resource requirements (costs)?
• Large costs
• Moderate costs
• Negligible costs and savings
• Moderate savings
• Large savings
• Varies
• Don't know</td>
<td>Research evidence
Kahn, 2014: Assuming 1 000 000 pregnant women per year, the estimated four-year cost of the expanded RPR testing and treatment programme ranges from US$ 4 142 287 to US$ 8 235 796 (2010 US dollars).

Data from Kahn 2014 (based on WHO bulk procurement)
<table><tr><th>Syphilis test</th><th>Cost of test, labour, supplies and transport</th></tr><tr><td>Rapid syphilis test</td><td>$1.82 to $2.56</td></tr><tr><td>Rapid plasma reagin</td><td>$2.02 to $2.30</td></tr><tr><th>Treatment</th><th>Cost of treatment</th></tr><tr><td>3-dose course of penicillin</td><td>$3.72 to $3.79</td></tr></table>
Data from Management Sciences for Health 2015
<table><tr><th>Syphilis test</th><th>Median indicative unit cost</th></tr><tr><td>SD Bioline – rapid test</td><td>1.00*</td></tr><tr><td>Alere Determine™ – rapid test</td><td>1.75*</td></tr><tr><td>Trinity RPR</td><td>0.13*</td></tr><tr><th>Treatment</th><th>Median indicative unit cost</th></tr><tr><td>Benzathine penicillin 2.4 million units (vials)</td><td>0.28*</td></tr></table>
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).

Additional considerations
none</td>
</tr>
<tr>
<td>Certainty of evidence of required resources</td>
<td>What is the certainty of the evidence of resource requirements (costs)?
• Very low
• Low
• Moderate
• High
• No included studies</td>
<td></td>
</tr>
</table>

Cost–effectiveness	**Does the cost-effectiveness of the intervention favour the intervention or the comparison?** • Favours the comparison • Probably favours the comparison • Does not favour either the intervention or the comparison • Probably favours the intervention • **Favours the intervention** • Varies • No included studies	**Research evidence** Kahn, 2014: In countries with high prevalence of syphilis in pregnant women (defined as 3% or above) and with high or low cost of health services, increased screening would be save on costs. In countries with low prevalence (defined as 0.5% or below) and with high or low cost of health services, if screening were increased then the cost per DALY (burden of disease) would range from $24 to $111 USD (2014), which is highly cost-effective by WHO standards. Kuznik, 2013, and Kuznik, 2015: Syphilis screening would remain highly cost-effective at low syphilis prevalence rates of around 0.013% (or 13 cases per 100 000 pregnancies) in Asia, 0.005% (or 5 cases per 100 000) in Africa, and 0.006% (or 6 cases per 100 000) in Latin America. **Additional considerations** The GDG agreed that universal screening of pregnant women for syphilis would bring cost savings in settings with high prevalence of maternal syphilis, and that the costs per DALY were within WHO standards in low-prevalence settings (i.e. cost savings would be expected in these settings also).
Equity	**What would be the impact on health equity?** • Reduced • Probably reduced • Probably no impact • **Probably increased** • Increased • Varies • Don't know	**Research evidence** There is no direct evidence measuring the impact of the screening/testing strategies on equity. Bristow (2016) reported that willingness to test in Haiti was related to low-cost (or free) testing. **Additional considerations** The 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.

Acceptability	**Is the intervention acceptable to key stakeholders?** • No • Probably no • **Probably yes** • Yes • Varies • Don't know	**Research evidence** *Pregnant women:* Flores, 2014: In this pre/post-intervention study, RST was introduced in rural Peru where laboratory testing was mostly unavailable. Women were highly satisfied with the test process, appreciated the same-day service, trusted the results, and were not stressed. Smith, 2015: This was a study of the expansion of testing using RSTs in rural Guatemala. Women who did not accept testing feared positive results, long waiting times or partner disapproval. Nnko, 2016: In this study of the expansion of screening using rapid (on-site) or laboratory-based RPR testing (19% of women), some women refused the rapid testing because they mistook it for HIV testing. Mabey, 2012: Rapid testing was introduced in Brazil where testing was previously unavailable. Some women feared positive test results, pain from the finger prick, and/or had concerns about treatment. Mabey, 2012: Results from testing in rural China indicated that women were less likely to accept the testing due to their perception of being at low risk for syphilis, but this changed when the programme was established. Bristow, 2016: Willingness to test in Haiti was related to low cost (free) testing, fewer blood draws, availability of rapid tests and quick results; false-positive results were not a factor. Ansbro, 2015: Counselling was considered key to client and partner acceptance of testing and treatment. Bocoum, 2014: Stigma related to sexually transmitted infections (STIs) may be a barrier to screening, in particular in pharmacies, but clients preferred public health-care services. *Providers:* Bocoum, 2014: Health workers often do not have specific training for screening. Garcia, 2013: During the introduction of RSTs and HIV testing in Peru, it was found that health-care providers had poor knowledge of syphilis and little recognition that it is a problem, and did not trust or feared rapid tests. Nevertheless, defining clear roles of providers in the screening process, as well as ensuring availability of the tests and treatment led to good uptake of the services. De Jongh, 2016: Health workers may be reluctant to implement screening as they need to assume additional tasks, which may lead to an increased workload and longer waiting times for patients. *Health system level:* Smith, 2015: During the expansion of testing using RSTs in rural Guatamala, collaborative partnerships and early involvement of community health workers may have helped to remove barriers and improve uptake. **Additional considerations** None
Feasibility	**Is the intervention feasible to implement?** • No • Probably no • **Probably yes** • Yes • Varies • Don't know	**Research evidence** Swartzendruber, 2015: This systematic review of the literature found that introduction of on-site RST appears feasible and may increase screening. Badman, 2016: After one day of intensive training, clinic staff could conduct on-site RST with minimal supervision. De Jongh, 2016: A systematic review of the literature found that stock-out problems were often documented as a difficulty with implementation. **Additional considerations** The GDG agreed that provider training in screening, and raising awareness about the prevalence of syphilis and the risk of transmission from mother to fetus, are important factors to consider with implementation.

SUMMARY OF JUDGEMENTS

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

CONCLUSIONS

Syphilis screening for pregnant women					
Type of recommendation	Strong recommendation against the intervention •	Conditional recommendation against the intervention •	Conditional recommendation for either the intervention or the comparison •	Conditional recommendation for the intervention •	Strong recommendation for the intervention ●
Recommendation	**Recommendation 1** 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.				
Justification	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. **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.				
Subgroup considerations					
Implementation considerations	Health-care providers should receive training and information about the prevalence of syphilis in pregnant women and the risks of syphilis transmission from mother to fetus. Pregnant women and partners may need additional support when discussing partner treatment.				
Monitoring and evaluation					
Research priorities					

SUPPLEMENTARY TABLES

Changes to screening uptake: characteristics of studies (from Swartzendruber, 2015)

Study	Methods	Intervention	Comparison	Setting	Impact on syphilis testing coverage
Delvaux, 2011; Cambodia	Pre/post-intervention study and comparison to non-interventional district	Rapid syphilis test (RST), as part of dual point-of-care test (POCT)	No screening	67 health-care facilities	**Intervention areas** Change in total: 0% to 77% Change in each district: 0% to 88%
Fleming, 2013; Kenya	Pre/post-intervention study	RST	No screening	8 rural health-care facilities	Change in total: 18% to 70% Change at each site: 0–33% to 47–94%
Flores, 2014; Peru	Pre/post-intervention study	On-site RCT	Laboratory-based test post-referral from the consultation room	One hospital in periurban area	Change (in receiving results within 45 minutes): 61% to 100%
Mabey, 2012; China, Peru, United Republic of Tanzania	Pre/post-intervention study	POCT	RPR confirmed with TPPA (China); RPR (Peru, United Republic of Tanzania)	One ANC clinic in a rural province (China); 15 clinics and one hospital in semi-urban areas (Peru); One hospital and 51 centres in a rural district (United Republic of Tanzania)	**China** Screening coverage: 96.0% **Peru** Change: 58% to 82% **United Republic of Tanzania** Change: 17.8% to 100%
Pai, 2012; India	Prospective cross-sectional study	RST (as part of triple POCT)	Non-treponemal serological assays, laboratory-based	One tertiary-care teaching hospital	change 9% to 96%
Strasser, 2012; Uganda, Zambia	Pre/post-intervention study	RST	RPR	One high-volume referral hospital and 8 health-care facilities in a rural district (Uganda); 9 health-care facilities in an urban district (Zambia)	**Uganda** Change in total: 1.7% to 90.3% Change in urban setting: 0.04% to 82.3% Change in rural setting: 3.8% to 99.7% **Zambia** Change in total: 79.9% to 95.6% Change in urban setting: 84.4% to 95.6% Change in rural setting: 46.2% to 96.0%

Acceptability and feasibility: Characteristics of studies

Study and methods	Population, intervention, comparison	Findings: Feasibility	Findings: Acceptability
Swartzendruber, 2015			
Systematic review on the impact of rapid syphilis tests (RSTs) on syphilis and HIV screening among pregnant women in antenatal care (ANC) settings in low- and middle-income countries (LMICs); description of factors influencing the effective implementation of RSTs and rapid HIV test in ANC settings	Pregnant women visiting ANC health-care centres 6 studies: Delvaux, 2011; Mabey, 2012; Pai, 2012; Strasser, 2012; Flores, 2014; Fleming, 2014	Simultaneous introduction of RST and rapid HIV test, as well as other rapid tests (e.g. hepatitis B), appears feasible and may increase screening for each infection. RST may contribute to the elimination of mother-to-child transmission (EMTCT) of both syphilis and HIV and serve as an opportunity to strengthen ANC and health systems in LMICs.	**Patient level** Pregnant women were highly satisfied with RST. Pregnant women preferred finger prick over venipuncture. Rapid testing reduced patient burdens (reduced waiting times and provided same-day results and treatment). **Facility level** Rapid testing required fewer staff resources. Rapid testing was well accepted by health workers. RST and immediate treatment increased health workers' job satisfaction. **Health system factors** Additional training for health workers supported the introduction of RST. There was an increase in the proportion of pregnant women screened for syphilis who received their results within 45 minutes.
Pai, 2012; India			
Prospective cross-sectional study of triple point-of-care test (POCT)	Pregnant women presenting to one tertiary care teaching hospital RST (Determine™) Non-treponemal serological assays	Feasibility was investigated by completion rates (96%), consent and recruitment rates (98%), uptake (86%) and time for conduct (testing: mean=25 minutes, range =21–27; strategy: mean = 45 minutes, range = 40–47; test results: 1–3 days; POC to action = 3–5 days).	99.3% (98.8–99.8%) preferred POCT to conventional strategy and would recommend to pregnant friend.

Study and methods	Population, intervention, comparison	Findings: Feasibility	Findings: Acceptability
Strasser, 2012; Uganda and Zambia			
Pre/post-intervention study design with retrospective data collection on RST integration in prevention of mother-to-child transmission (PMTCT)	First-time ANC attendees RST in PMTCT programme (post) Pre-RST: RPR (Zambia)	Pre-intervention rapid plasma reagin (RPR) test stock-outs occurred in Zambia. During the first 5 months of implementation, RST was provided in ANC in Zambia, there was a significant increase in percentage of women tested for HIV at first ANC visit (n = 11 151; 97.7%; *P* = 0.0001). Women who tested syphilis-negative but whose partner tested positive were treated, resulting in over 100% of positive cases in women treated (690 positive cases; 715 treated). During intervention, 11 460 of 11 985 (95.6%; *P* = 0.0001) first-time ANC attendees received RST, 1050 of 11 460 (9.2%) tested positive, and 1000 of 1050 (95.2%) positive cases were treated. Of those, 958 of 1000 (95.8%) received same-day testing and treatment (STAT).	Acceptability of RST was demonstrated by health workers satisfaction with RST and correct and consistent use of RST. Health workers incorporated RST into existing services in settings with high HIV disease burdens with no significant negative impacts on HIV service delivery.
Delvaux, 2011; Cambodia			
Pre/post-intervention study and comparison to non-interventional operational district	67 health-care facilities RST (post) Pre: no screening	The linked response (LR) approach was initiated and fully supported by the Ministry of Health. It included decentralization of PMTCT activities, set-up of a referral system between health-care facilities and between health-care facilities and community-based services.	The LR approach facilitated the introduction of syphilis screening and it was found that once blood samples were collected (for HIV), adding another test could be achieved quite easily.
Flores, 2014; Peru			
Pre/post-intervention time series study	Pregnant women attending one hospital On-site POCT (post) Laboratory post-referral from the consultation room (pre: standard of care)	Institutional feasibility	Women reported high satisfaction with POCTs, with the testing process, and understanding of test results.

Study and methods	Population, intervention, comparison	Findings: Feasibility	Findings: Acceptability
Fleming, 2013; Kenya			
Pre/post-intervention study	First-time ANC attendees at 8 rural health-care facilities; nurses RST (post) Post: no screening	Integrating RST into routine ANC services in low-level facilities in remote, rural settings where many women in sub-Saharan Africa receive MCH services was feasible, led to large increases in syphilis testing uptake, and uncovered higher syphilis prevalence than had been previously reported.	Although syphilis treatment practices varied among the nurses, none mentioned that patients are declining treatment because of partner violence. The overall programme had been successful but nurses identified three main challenges: (1) partner treatment was unaffordable for many (nurses recommended providing free partner treatment); (2) concern about sustaining the programme of free testing and treatment when the study ended; (3) some nurses did not receive the training because of staff shortages at their facilities and recommended making training available to all nurses. Interviews with 21 mothers revealed that they were not always fully informed about the tests and did not feel they could ask nurses for more information.
Smith, 2015; Guatemala			
Description of key lessons learnt following one year's implementation of triple POC screening for HIV, syphilis and hepatitis B	Pregnant women screened for syphilis Triple antenatal screening POCT; SD bioline Syphilis 2.0 test	Nurses and health promoters reported difficulties in partner notification as many women feared communicating positive results to their partners.	Women not tested either did not accept testing because of fear of a positive result, additional waiting time or partner disapproval, or were not offered testing due to staff turnover, absenteeism or stock-outs at the district health centre. In cases of indeterminate or ambiguous results, they were more likely to report these as negative.

Study and methods	Population, intervention, comparison	Findings: Feasibility	Findings: Acceptability
Garcia, 2013; Peru			
Case study describing the experience of the introduction of POCT for syphilis in Peru for improving health delivery and health systems	One large maternity hospital, 15 semi-urban health centres, and one hospital in a resource-poor district of Lima Local and national authorities; key health workers, programme health centre coordinators, laboratory heads, heads of pharmacy programmes, logistics officers, midwives RPR test, STAT Baseline	During baseline surveys, providers demonstrated poor knowledge and little recognition of syphilis as a problem. Laboratory workers felt the test could compromise their "authority", while clinicians were concerned that a POCT for syphilis would increase their workload. ANC visits should include not only physical examination, but also a set of basic tests: blood typing, haemoglobin or haematocrit, glucose, syphilis test, HIV test, urine test. In the case of a positive syphilis test (which was commonly an RPR test) there was a delay of almost a month between screening and treatment if penicillin was available (and it was not always available). When implementing this POCT, it is important to include the visual evaluation of providers performing the test and to correct any visual problems to improve the accuracy of reading and interpreting the test results. The tests are bought locally and in small quantities, so stock-outs are common. Also, the "format" of the test varies, no quality control is available, and each time a new test is introduced there is no training for the health workers. Tests vary in the time required for incubation, and the number of drops of buffer added to the wells.	Several providers expressed fear and distrust of any diagnostic test called "rapid", saying "good things take time". These health workers were hesitant about the introduction of a POCT syphilis test as it was seen as similar to the "rapid HIV test". We were able to simplify processes, decrease the number of times a pregnant woman had to go to ANC, increase coverage of syphilis screening and treatment, improve information, and improve relations between providers by clarifying their roles within the system. Integration of syphilis and HIV screening with the use of POCTs is feasible and was very well accepted by health workers and pregnant women in our study.

Study and methods	Population, intervention, comparison	Findings: Feasibility	Findings: Acceptability
De Schacht, 2015; Mozambique			
Quasi-experimental operational research study with structured interviews to determine the effect of introduction of integrated POCT services	Women attending first ANC visit, nurses, laboratory technicians POCT (post-implementation) RPR at laboratory (pre-intervention)	Not reported	A survey of nurses and laboratory technicians showed that the POCT was well accepted. Results were similar in the pre- and post-evaluation for most questions. Although in the pre-evaluation participants thought that workload would be high when using POCT at during ANC, this was not reported as an ongoing concern after the introduction of the tests.
Nnko, 2016; United Republic of Tanzania			
Non-randomized study with in-depth interviews to understand the perceptions of health workers and pregnant women and acceptability of RST	Pregnant women visiting 50 health-care facilities for ANC services, health workers RST protocol RPR as standard but low rate of testing	Feasible based on the perceptions, attitudes and uptake of RST services in ANC clinics in the north-west of the United Republic of Tanzania. Quality of care improved, resulting from improved supply chain and improved supervision of health workers.	Only 50 (46.3%) women who had syphilis went back for treatment. Providing STAT worked in 94.8% of the positive women. Some study participants indicated that, there were community members who mistook RST for HIV testing. Male spouses refused to go to the health-care facilities for syphilis screening and treatment because they feared they would also be tested for HIV. Health workers shared the view that some men were reluctant to utilize RST services because of the widespread beliefs that HIV testing was synonymous with syphilis screening.

Study and methods	Population, intervention, comparison	Findings: Feasibility	Findings: Acceptability
Mabey, 2012; Brazil, China, Peru, Uganda, United Republic of Tanzania, Zambia			
Description of attempts to overcome challenges and introduce syphilis POCTs to prevent adverse outcomes of pregnancy in six LMICs	Pregnant women, health workers, sexually active population (Brazil) POCTs No screening (Brazil); RPR confirmed with TPPA (China); RPR (Peru, Uganda, United Republic of Tanzania, Zambia)	Introduction was effective in a range of settings. Increased testing and treatment was facilitated by working with the existing health-care system to integrate POCTs. Outcomes resulted in policy change in all countries to incorporate POCTs into national guidelines. Policy-makers and public health officials should be included from the beginning of POCT integration.	In Uganda, 82% of health workers described the POCTs as "very easy to perform". At sites where RPR had been previously performed, health workers reported that they could test more patients per day with the POCT. Both in Uganda and Zambia after introduction of POCTs, there was a significant increase in ANC attendance. Clients at all sites appreciated receiving results and treatment at their first visit, rather than being asked to return for their results as they had in the past. Most clients at all sites preferred a finger prick to venipuncture because of the smaller volume of blood required. The indigenous population in Brazil initially had reservations about the POCT because of the possibility of a positive test result, the pain caused by the finger prick, and concerns about the treatment. In rural areas of China, pregnant women of ethnic minorities were less likely to accept the test due to the perception of low risk of syphilis infection. In Peru, laboratory staff were initially opposed to the idea of nurses and midwives doing a task that should be done by laboratory technicians.
Kleutsch, 2009; United Republic of Tanzania			
Case study to explore what has occurred since the recommendation to use RST; examines why there is continued debate about RST use	Policy-makers 2003 recommendation for RST RPR, VDRL, no confirmatory test; syndromic management	The researchers recommend a programme of accelerated efficacy, effectiveness, feasibility and acceptability testing with consensus-building at both the national and international level, including attention to policy development and financing.	Policy-maker concerns with RSTs: cost/funding, quality/performance, past problems with RSTs

Study and methods	Population, intervention, comparison	Findings: Feasibility	Findings: Acceptability
Ansbro, 2015; Zambia			
Qualitative evaluation of experiences following RST pilot and national RST roll-out	Health workers RST; RST, RPR RST, RPR,TPHA Laboratory-based RPR, when available	RST is feasible to implement following a successful pilot, but must address issues around training (testing and counselling, quality assurance/quality control [QA/QC]) and supply (need consistent availability).	Most health workers were strongly motivated by the opportunity to deliver a better service and offer effective STAT to patients to ensure safer pregnancies. Health workers report patient satisfaction with the RST. Patients accepted it because of STAT, reduced clinic waiting time, reduced travel time and increased case detection and treatment.
Bocoum, 2014; Burkina Faso			
In-depth interviews and observations on barriers to ANC syphilis screening	Pharmacist, information systems specialist, reproductive health specialist, laboratory technicians, midwives, head of district, head of regional laboratory, community care workers, drug shop managers, NGO managers, pregnant women, traditional healers. RST for syphilis	A barrier to routine syphilis screening among pregnant women was related to providers' perception that syphilis in pregnancy was not an important issue relative to other diseases. Some health workers felt that syphilis was more prevalent in urban areas and, thus, screening was more systematic in urban-based facilities. Poor communication between health workers and pregnant women may be related to the lack of routine training; health workers stated that they had no specific training, except for a course on syphilis management during their professional training. **Community** Costs are a barrier to women Husbands and partners play a role in supporting the costs and/or approval for syphilis screening Poor knowledge on syphilis The stigma surrounding STIs was noted as a barrier to screening, particularly in certain settings like pharmacies. Quote: "It is difficult for them to go to the pharmacy and do an exam related to sex. They prefer to go to the laboratory of the hospital if they have money because it is a public service."	People don't accept follow-up testing that involves giving more blood samples.

Study and methods	Population, intervention, comparison	Findings: Feasibility	Findings: Acceptability
Badman, 2016; Papua New Guinea			
Descriptive feasibility study of ANC POCT and treatment for STI	Pregnant women attending government-run urban ANC clinic RST (SD Bioline Anti-TP), confirmatory test with RPR National STI syndromic management guidelines	Clinic staff were able to conduct POCT with minimal supervision after one day of intensive training. Increased resources required: Due to a clinic schedule that allocates one weekday to new ANC attendances (resulting in 20–25 new visits on a single day), the limited availability of testing facilities (just one four-module GeneXpert machine) and the requirement to provide same-day test results, they were unfortunately unable to enrol all those who asked to join.	High interest was shown in study participation and there was 100% completion of study procedures among those enrolled, which suggests the intervention has a high level of acceptability.
De Jongh, 2016; Mongolia, South Africa, Uganda, Zambia, United Republic of Tanzania			
Comprehensive review of drivers for integration of health programmes (including syphilis) with ANC	Syphilis services 5 reports: Dinh, 2013; Bronsan, 2007; Watson-Jones, 2005; Strasser, 2012; Munkhuu, 2009	Programmes aimed to extend PMTCT activities to lower-level health-care facilities, strengthen community outreach programmes and improve geographical access. Increases in workload from new tasks, additional training, existing staff shortages and high turnover of staff have been highlighted as hurdles to scale-up of integrated services. Unavailability of commodities and irregular supply of essential consumables and medicines were found to be major barriers to uptake.	Patients preferred receiving syphilis testing at the same place as ANC services, allowing for STAT as well as related counselling from ANC providers. Coverage was lower for services that were provided at different locations (not provided on site) and for those where results and treatment were not provided on the same day as testing.

Study and methods	Population, intervention, comparison	Findings: Feasibility	Findings: Acceptability
Manabe, 2015; Uganda			
Descriptive cohort study	Pregnant women enrolled in antenatal HIV clinic RPR No syphilis screening	Widespread screening of syphilis in pregnancy with no requirement for additional human resources. In resource-limited setting, possible barriers to testing included poor availability of validated methods of syphilis testing that are easy to perform and easy to interpret, and the long-standing debate about RPR as the screening test of choice (time-intensive, requires laboratory expertise and electricity for rotator, etc.). Intensive counseling did result in higher uptake than has previously been reported in the literature.	Not reported
Bristow, 2016; Haiti			
Conjoint analysis (preferences for hypothetical test scenarios)	298 men and women (including 237 women, of whom 49 [21%] were pregnant) at Haitian Study Group for Kaposi's Sarcoma and Opportunistic Infections (GHESKIO) clinic Willingness to test for syphilis	Not reported	**Testing preferences** Cost (free vs US$ 4), number of blood draws (1 vs 2), sample collection method (laboratory vs rapid) and time to result (20 minutes vs 1 week).

ANC: antenatal care; LMIC: low- and middle-income countries; LR: linked response; PMTCT: prevention of mother-to-child transmission; POCT: point-of-care test; RPR: rapid plasma reagin; RST: rapid syphilis test; STAT: same-day testing and treatment; TPHA: *Treponema pallidum* haemoglutinassay; VDRL: Venereal Diseases Research Laboratory

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RECOMMENDATIONS 2, 3 AND 4: SYPHILIS SCREENING AND TREATMENT STRATEGIES FOR PREGNANT WOMEN

Population:	Pregnant women being screened for syphilis
Tests:	Treatment following on-site rapid syphilis test (RST) used as a single test, or on-site RST followed by laboratory-based rapid plasma reagin (RPR) test, compared to on-site RPR as a single test or on-site RPR followed by on-site RST, mass treatment, or standard laboratory-based testing (off-site RPR or VDRL followed by treponemal assay TPPA or TPHA)
Main outcomes:	Treatment rate, over- and under-treatment, side-effects of treatment (adverse events of medicines, such as penicillin), infant outcomes, maternal outcomes Other: screening coverage, costs, accessibility, partner notification and treatment
Setting:	Clinics in high- to low-prevalence settings
Perspective:	Population level
Background:	Syphilis is a systemic disease from the outset and is caused by the spirochaete *Treponema pallidum*. The infection can be classified as congenital (transmitted from mother to child in utero) or acquired (through sex or blood transfusion). In 2007, the World Health Organization (WHO) began a global initiative for the elimination of mother-to-child-transmission (EMTCT) of syphilis, to be achieved by ensuring that at least 95% of pregnant women are screened for syphilis, and 95% of those identified with syphilis are treated appropriately. Studies have shown that syphilis screening and treatment for pregnant women is cost-effective. There are remaining questions about which syphilis serologic tests should be used for screening to ensure high coverage of antenatal syphilis screening and treatment. Rapid point-of-care tests (POCTs) include: • on-site RST – a treponemal test that is reactive to current and past syphilis infections; and • on-site RPR – a non-treponemal test that is reactive to current and past syphilis infection; moreover a high titre reactive test is indicative of active infection, and quantitative titre can be used to monitor response to treatment. These tests can be provided as a single test with treatment given based on the result, or they can be provided in a sequence whereby a positive result on the first test leads to the second test and treatment is based on the second positive result.

ASSESSMENT

	Judgement	Research evidence
Problem	**Is the problem a priority?** • No • Probably no • Probably yes • **Yes** • Varies • Don't know	**Research evidence** Global estimates for 2012 indicated that there were 217 678 live births with congenital syphilis per 1 360 485 pregnant women with untreated syphilis (approximately 16 live births per 100 untreated women), not including stillbirths (21 per 100), neonatal deaths (9 per 100) or premature births (6 per 100)[2]. The resource implications of hospitalization for infants with congenital syphilis is more than three times higher than for infants without the disease. When mothers are treated during pregnancy, the risk of congenital syphilis is 0.03 times the risk in infants born to untreated mothers (i.e. the rate of births with congenital syphilis falls to approximately 4.8 per 1000 treated mothers). **Additional considerations** None
Desirable Effects	**How substantial are the desirable anticipated effects?** • Trivial • Small • Moderate • Large • **Varies** • Don't know	**Research evidence** *Randomized controlled trials* A systematic review (Shahrook, 2014) found two cluster randomized controlled trials (no new trials were found when the search was updated to September 2016). The trials did not compare different rapid tests to each other. Munkhuu (2009) compared SD Bioline Syphilis 3.0 (RST) to RPR + TPHA (*Treponema pallidum* hemagglutination assay). Moderate-quality evidence showed that congenital syphilis is probably reduced with screening using the RST (45 fewer per 1000; range 50–14 fewer); screening coverage is probably greater (100% with RST versus 80% with RPR + TPHA); treatment rate is probably greater (99% versus 90%); and partner treatment rate is probably greater (95% versus 55%). Myer (2003) compared on-site RPR test to laboratory-based RPR but only followed women who tested positive. Low-quality evidence shows that perinatal deaths may be reduced with the on-site (rapid) test (18 fewer per 1000; range: 36 fewer to 22 more); treatment rate may be greater (69% with on-site RPR versus 64%); but screening coverage may be similar. *Test accuracy* A systematic review of 10 studies provides the sensitivity and specificity for VisiTect® Syphilis test, SD Bioline Syphilis test, and on-site RPR (all tests were compared to a "gold standard" of laboratory-based tests: RPR or VDRL followed by TPPA or TPHA if positive) (Rogozińska, 2016, no new trials were found when the search was updated to September 2016). The certainty of the evidence was assessed and found to be "moderate" due to some concern with risk of bias of the included studies, selective reporting and heterogeneity. In particular, the reference standard was not applied to all cases of positive laboratory RPR tests in the largest study, which provided the most weight to the analysis, and not all studies could be included in the meta-analysis. The results for the single on-site RPR test strategy appeared to be inconsistent across studies and dependent on the setting. The results are listed in the Evidence tables below (pp. 32 - 34). *Outcomes based on modelling:* A cost-effectiveness model (Terris-Prestholt, 2015) provides data for treatment, over-treatment, missed cases and screening coverage for each screening strategy based on field data in three different settings: low prevalence of 1.25%, and higher prevalence of 5.14% and 9.04%. The consequences of the treatment, over-treatment and missed treatment were adapted from the systematic review of treatments for syphilis reported in the 2016 WHO guidelines for the treatment of *Treponema pallidum* (syphilis). See Evidence tables below (pp. 32 - 34).
Undesirable Effects	**How substantial are the undesirable anticipated effects?** • Large • Moderate • Small • Trivial • **Varies** • Don't know	

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

Certainty of evidence	**What is the overall certainty of the evidence of effects?** • Very low • **Low** • Moderate • High • No included studies	*Additional information from non-randomized studies comparing testing strategies:* • Uptake of syphilis testing and treatment at ANC clinics increased due to the availability of same-day testing and treatment (STAT); the number of women treated increased from 46.3% with the RPR to 94.8% with RST (Nnko, 2016). • Timing: There is an increased risk of adverse pregnancy outcomes and congenital syphilis if women are screened with RPR or TPHA with confirmation in the third trimester compared to the first or second trimester (Hawkes, 2013). **Additional considerations** The comparison of the effects of the rapid test is derived primarily from the cost-effectiveness model. The Guideline Development Group (GDG) agreed that although the diagnostic test accuracy data from the systematic review of the rapid tests were similar to the field data, the data from the systematic review may be more applicable. Based on this linked evidence the certainty of the evidence is low. There were also no data for the outcome of partner notification. The GDG agreed that providing a sequence of tests could increase partner treatment as additional confirmatory tests may lead to increased belief in positive results among the tested individuals and their partners. The GDG agreed on the following: • The use of either a single on-site RST followed by treatment (Strategy A), or an on-site RST followed by (if positive) a first dose of treatment and an RPR test followed by further appropriate treatment if positive (Strategy C), may result in small to moderately greater numbers of people being treated compared to the use of on-site RPR strategies (Strategies B and, if RPR is available on-site, Strategy C) 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). • The difference in harms related to 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 and (Strategy C) (ii) the single on-site RPR test strategies (Strategy B) 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 strategies (Strategy B) 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 with the single on-site RST strategy (Strategy A) but similar among the other strategies and among different prevalence settings.
Values	**Is there important uncertainty about or variability in how much people value the main outcomes?** • Important uncertainty or variability • Possibly important uncertainty or variability • **Probably no important uncertainty or variability** • No important uncertainty or variability • No known undesirable outcomes	**Research evidence** Main outcomes: Treatment rate, over- and under-treatment, side-effects of treatment (adverse events of medicines, including penicillin), infant outcomes, maternal outcomes **Additional considerations** 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.

Balance of effects

Does the balance between desirable and undesirable effects favour the intervention or the comparison?

- Favours the comparison
- Probably favours the comparison
- Does not favour either the intervention or the comparison
- **Probably favours the intervention**
- Favours the intervention
- Varies
- Don't know

Additional considerations

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 (Strategy B). 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, the higher-prevalence settings, there were fewer pregnant women over-treated when using a sequence of tests and treatment (Strategy C).

Resources required

How large are the resource requirements (costs)?

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

Research evidence

Estimated costs from field data:

Based on: 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.

For total costs per 1000 women screened, the RPR was cheapest in the United Republic of Tanzania and Zambia, but in Peru the RST was the cheapest due to labour related to RPR in Peru.

Clinic cost inputs and distributions (costs are presented in 2012 US dollars).*

Cost inputs	RPR			RST		
	1.35% (Peru)	5.14% (Tanzania)	9.64% (Zambia)	1.35% (Peru)	5.14% (Tanzania)	9.64% (Zambia)
Fixed systems costs				404.15 (380–619)	760.04 (684–893)	1,840.54 (1502–2046)
Fixed clinic costs	1563.13 (24.64–7130)	60.04 (45.61–76.89)	399.37 (183–645)	772.17 (320–2879)	135.48 (93.06–233)	311.66 (155–525)
RPR equipment	176.47 (10.61–724)	26.83 (26.83–26.83)	96.02 (23.14–136)			
Screening costs						
Personnel	1.66 (1.17–2.88)	0.36 (0.24–0.47)	1.74 (0.99–2.63)	0.21 (0.05–0.36)	0.17 (0.05–0.36)	0.45 (0.05–0.36)
Test kits	0.11	0.07	0.02	0.94	1.29	0.72
Supplies and others	0.99 (0.78–1.28)	0.79 (0.67–0.91)	0.2 (0.11–0.3)	0.38 (0.33–0.66)	0.18 (0.04–0.42)	0.09 (0.02–0.16)
Counselling costs	Counseling and treatment costs applied from RST observed costs					
Negative				0.19 (0.11–0.55)	0.03 (0.03–0.08)	0.13 (0.07–0.35)
Positive				1.13 (0.66–2.59)	0.14 (0.05–0.25)	0.33 (0.17–0.75)
Treatment costs						
Personnel first treatment				1.08 (0.783–1.94)	0.29 (0.15–0.51)	0.3 (0.23–0.36)
Supplies (incl. drugs)				0.63 (0.58–0.78)	0.74 (0.61–0.95)	0.69 (0.63–0.82)
Personnel second and third treatments				0.32 (0.23–0.77)	0.29 (0.15–0.51)	0.3 (0.23–0.36)

Abbreviations: RPR, rapid plasma reagin; RST, rapid syphilis test.

* Point estimates are averages across facilities in each country, and ranges are lowest and highest values observed across the clinics.

Data from Management Sciences for Health 2015

Syphilis test	Median Indicative Unit cost
SD Bioline – rapid test	1.00
Alere Determine™ – rapid test	1.75
Trinity RPR	0.13
Treatment	**Median Indicative Unit cost**
Benzathine penicillin 2.4 million units (vials)	0.28

Source: 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).

Additional considerations

There may be a direct cost for some pregnant women in different countries.

The GDG agreed that the costs may be higher for RST, but where labour costs are high then costs are lower for RST.

Certainty of evidence of required resources	**What is the certainty of the evidence of resource requirements (costs)?** • Very low • Low • **Moderate** • High • No included studies	Costs obtained from field data were reported in non-randomized studies (Terris-Prestholt, 2015).
Cost-effectiveness	**Does the cost-effectiveness of the intervention favour the intervention or the comparison?** • Favours the comparison • Probably favours the comparison • Does not favour either the intervention or the comparison • **Probably favours the intervention** • Favours the intervention • Varies • No included studies	**Research evidence** Cost-effectiveness modelling (Terris-Prestholt, 2015) used field data from three countries with different levels of syphilis prevalence (1.25%, 5.14% and 9.04%). Outcomes included in the model were congenital syphilis, stillbirths, and low birth weight (not included were outcomes of live births to mothers with untreated syphilis or maternal outcomes in women with or without treatment). The model found that the most cost-effective screening and treatment approach across all prevalence settings is Strategy A: the single on-site RST followed by treatment (note that the strategy may cost more in certain settings). Mass treatment, however, was the most cost-effective (and cheapest) in the higher prevalence setting (but resulted in more over-treatment). **Additional considerations** The GDG agreed that cost-effectiveness favoured on-site RST strategies.
Equity	**What would be the impact on health equity?** • Reduced • Probably reduced • **Probably no impact** • Probably increased • Increased • Varies • Don't know	**Research evidence** There is no direct evidence measuring the impact of the test strategies on equity. **Additional considerations** The GDG agreed that although the cost of RST to pregnant women may be greater than RPR, 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. RPR is currently available in many countries but screening coverage is still not optimal. If screening coverage is greater with RST, then equity may be increased with RST. Additional research on the effect of greater costs to pregnant women on equity and accessibility is warranted.

Acceptability	**Is the intervention acceptable to key stakeholders?** • No • Probably no • **Probably yes** • Yes • Varies • Don't know	**Research evidence** There are no trials comparing antenatal syphilis screening and treatment strategies. **A review of the literature from 2010 to 2016 included non-randomized studies providing data for the acceptability of RST testing in patients and health-care providers:** • Nnko (2016) conducted in-depth interviews with 16 health workers and 31 pregnant women attending ANC clinics six months after the introduction of RST services in the United Republic of Tanzania in 2009. Participants shared folk perceptions on syphilis, including that it was associated with promiscuity, but less fatal than other STIs such as HIV. Many community members mistook RST services for HIV testing and therefore some men were reluctant to be screened with RST. Pregnant women were more enthusiastic about the RST than the RPR because same-day testing and treatment (STAT) saved time and the cost of travel for an additional visit. They were also less fearful of the RST because it does not require large amounts of blood. Health workers perceived the RST algorithm to be familiar and easier to perform, and felt that it simplified testing and produced more reliable results than the RPR test. • Ansbro (2015) administered questionnaires through structured interviews with 16 health workers and 4 senior administrative and management staff in Zambia in 2010–2011. Health workers accepted RST as a suitable addition to existing services and were satisfied with its reliability and accuracy. Participants were happy with RST usability, specifically RST technology and its integration within existing services; patient benefits included STAT, reduced clinic waiting time, reduced travel time and increased case detection and treatment. • Mabey (2012) measured several health systems indicators to evaluate the introduction of RSTs compared to laboratory-based RPR in Brazil, China, Peru, Uganda, the United Republic of Tanzania and Zambia. Coverage exceeded 90% in all countries. RSTs were well accepted and considered easy to perform by health workers and there was synergy with existing programmes. The inclusion of policy-makers from the beginning and keeping them informed during implementation led to policy change to incorporate RSTs into national guidelines. • Stasser (2012) conducted a pre/post-intervention study in Uganda and Zambia in 2010. Acceptability of RST was demonstrated by health worker satisfaction with RST and correct and consistent use. Health workers incorporated RST into existing services in settings with high HIV prevalence with no significant negative impacts on HIV service delivery. **Additional considerations** The GDG agreed that partners may accept treatment more readily if a sequence of tests were provided.

Feasibility	**Is the intervention feasible to implement?** • No • Probably no • **Probably yes** • Yes • Varies • Don't know	**Research evidence** *Professional factors:* • Health-care providers need high-quality training on testing procedures, including specific training on counselling patients and partners, the testing algorithm and quality assurance/quality control systems, as well as regular supervision and monitoring, and there must be consistent availability of (reliable supply chain for) test kits and treatment (Ansbro, 2015). • Quality of care improved due to improved supply chain and improved supervision of health workers (Nnko, 2015). • There was improved identification and treatment of syphilis without compromising HIV services and it was feasible to conduct multiple rapid tests concurrently (Strasser, 2012). • Support by laboratory staff is needed for nurses and midwives to administer point-of-care tests (Mabey, 2015). *System factors:* • Increased testing and treatment was facilitated by working with the existing health-care system to integrate point-of-care tests (POCTs) (Mabey, 2012). • Policy-makers and public health officials should be included from the beginning of POCT integration (Mabey, 2012). • Per unit costs of tests made RSTs unaffordable for some programmes (Kleutsch, 2009). • Sufficient donor contribution to overall national health spending is needed (Kleutsch, 2009). *Patient factors:* • Screening interventions to improve the coverage and effects of screening programmes including decentralized screening using RPR (on- and off-site) and treatment increased uptake of testing, increased treatment rates and decreased adverse pregnancy outcomes (especially perinatal death and stillbirth attributable to syphilis) in low- and middle-income countries (Hawkes, 2011). • Syphilis screening using RST has been effectively introduced in a range of settings, from cities in China and Peru, to remote villages in East Africa, and even more remote indigenous populations in the Amazon rainforest (Mabey, 2012). • Compared to RPR, introduction of POCTs increased coverage to over 90% in Brazil, China, Peru, Uganda, the United Republic of Tanzania and Zambia (Mabey, 2012). • Transport costs for a return trip to collect laboratory results, geographical distance between homes and health-care facilities and long waiting times at health-care facilities all act as barriers, such that availability of rapid tests and STAT increases accessibility (Ansbro, 2015). • There was a small increase in the rate of partner testing following a general invitation letter to partners of ANC attendees and a targeted invitation letter for partners of syphilis-positive women (Strasser, 2012). **Additional considerations** The GDG agreed that training and quality assurance are important when implementing rapid tests.

SUMMARY OF JUDGEMENTS

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

CONCLUSIONS

Syphilis screening and treatment strategies for pregnant women					
Type of recommendation	Strong recommendation against the intervention •	Conditional recommendation against the intervention •	Conditional recommendation for either the intervention or the comparison •	Conditional recommendation for the intervention ●	Strong recommendation for the intervention •
Recommendation	**Recommendation 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)[3].				

3 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/, accessed 11 July 2017)

Justification	**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 C) 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). • 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 the 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 2; but it should be noted that the strategy may cost more in some settings).

Justification continuation	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. **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 (Strategy B). 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.
Subgroup considerations	See above for differences in settings with low and high prevalence of syphilis and resource-constrained settings.
Implementation considerations	See above for recommendations in different resource-constrained settings. Health-care providers should receive training and information about the prevalence of syphilis in pregnant women and the risks of syphilis transmission from mother to fetus. Pregnant women and partners may need additional support when discussing partner treatment.
Monitoring and evaluation	
Research priorities	Trials comparing sensitivity and specificity of the sequence of tests are needed, as well as trials assessing important outcomes. Studies should compare the different test strategies in similar populations and measure outcomes such as partner notification and treatment, and long-term consequences of screening and treatment in mothers and infants.

EVIDENCE TABLES

TEST ACCURACY DATA

We found a review of test accuracy data of the different syphilis tests (Rogozińska 2016) and a published model using test accuracy data from the field (Terris-Prestholt 2015). The test accuracy data from the review confirmed the data used in the model.

EFFECTS OF SCREENING BY DIFFERENT STRATEGIES

We used the modelled outcome data from a published model to determine the effects of screening using different test strategies (Terris-Prestholt 2015). The downstream consequences of that data were then used to make recommendations.

Outcome tables based on modelling effects of screening 1000 pregnant women

Prevalence 1.25% (12.5/1000)

Based on field data	RST	Sensitivity	77 (70 to 83)	Specificity	100	**Based on review**	Sensitivity	83 (58 to 98)	Specificity	96 (89 to 100)[a]
	RPR	Sensitivity	56 (42 to 69)	Specificity	99 (97 to 99)		Sensitivity	75 (54 to 88)[b]	Specificity	97 (96 to 99)

[a] Using field data for RST, the number of women over-treated is underestimated compared to results from the systematic review of the literature.
[b] Using field data for RPR, the number of missed cases is overestimated and the number of cases treated is underestimated compared to results from the systematic review of the literature.

	Mass treatment (Strategy F)	On-site RPR then RST then treat (Strategy E)	On-site RPR then treat (Strategy B)	On-site RST then treat (Strategy A)	Onsite RST then treat then RPR then treat (Strategy C)	Consequences
Screened	-	91%	91%	96%	96%	-
Treated	85%	77%	77%	89%	89%	-
No. true cases treated	11.1 (8.0 to 22.9)	3.8 over (1.6 to 7.3)	4.9 (2.0 to 9.4)	8.2 (5.8 to 16.5)	8.2 (5.8 to 16.5)	Per 1000 women treated: 5 births with congenital syphilis; 250 gastrointestinal side-effects; 70 central nervous system side-effects
Missed cases (12.5)	1.4 (0.4 to 4.2)	8.7 over (6.9 to 20.4)	7.6 (6.1 to 18.9)	4.3 (3.1 to 10.0)	4.3 (3.1 to 10.0)	Per 1000 women missed: 160 births with congenital syphilis; 210 stillbirths; 90 neonatal deaths; 60 premature births; syphilis transmission
Over-treated	841.7 (705 to 900)	0	9.8 (2.0 to 15.6)	0.8 under (0.7 to 0.9)	0	Per 1000 women over-treated: 250 gastrointestinal side-effects; 70 central nervous system side-effects; 2/1 000 000 risk of penicillin allergy; unnecessary use of medication, facility, personnel; unnecessary stigma

Prevalence 5.14% (51.4/1000)

Based on field data	RST	Sensitivity	71 (55 to 83)	Specificity	93 (91 to 95)	**Based on review**	Sensitivity	83 (58 to 98)	Specificity	96 (89 to 100)[a]
	RPR	Sensitivity	46 (29 to 63)	Specificity	97 (95 to 98)		Sensitivity	75 (54 to 88)[b]	Specificity	97 (96 to 99)

[a] Using field data for RST, the number of women over-treated is underestimated compared to results from the systematic review of the literature.
[b] Using field data for RPR, the number of missed cases is overestimated and the number of cases treated is underestimated compared to results from the systematic review of the literature.

	Mass treatment (Strategy F)	On-site RPR then RST then treat (Strategy E)	On-site RPR then treat (Strategy B)	On-site RST then treat (Strategy A)	On-site RST then treat then RPR then treat (Strategy C)	Consequences
Screened	-	18%	18%	86%	86%	-
Treated	83%	74%	74%	94%	94%	-
No. treated	48.2 (8.9 to 130)	2.0 (0.3 to 15.3)	2.9 (0.4 to 23.0)	29.3 (5.5 to 74.9)	29.3 (5.5 to 74.9)	Per 1000 women treated: 5 births with congenital syphilis; 250 gastrointestinal side-effects; 70 central nervous system side-effects
Missed cases	3.1 (0.4 to 13.4)	49.3 (8.5 to 13)	48.5 (8.2 to 129)	22.1 (3.8 to 74.1)	22.1 (3.8 to 74.1)	Per 1000 women missed: 160 births with congenital syphilis; 210 stillbirths; 90 neonatal deaths; 60 premature births; syphilis transmission
Over-treated	760.5 (579 to 857)	0.3 (0.1 to 1.3)	3.9 (1.0 to 18.7)	50.7 (31.6 to 67.0)	1.2 (0.7 to 1.6)	Per 1000 women over-treated: 250 gastrointestinal side-effects; 70 central nervous system side-effects; 2/1 000 000 risk of penicillin allergy; unnecessary use of medication, facility, personnel; unnecessary stigma

Prevalence 9.04% (90.4/1000)

Note: same sensitivity and specificity as above

Based on field data	RST	Sensitivity	71 (55 to 83)	Specificity	93 (91 to 95)	**Based on review**	Sensitivity	83 (58 to 98)	Specificity	96 (89 to 100)[a]
	RPR	Sensitivity	46 (29 to 63)	Specificity	97 (95 to 98)		Sensitivity	75 (54 to 88)[b]	Specificity	97 (96 to 99)

[a] Using field data for RST, the number of women over-treated is underestimated compared to results from the systematic review of the literature.
[b] Using field data for RPR, the number of missed cases is overestimated and the number of cases treated is underestimated compared to results from the systematic review of the literature.

	Mass treatment (Strategy F)	**On-site RPR then RST then treat (Strategy E)**	**On-site RPR then treat (Strategy B)**	**On-site RST then treat (Strategy A)**	**On-site RST then treat then RPR then treat (Strategy C)**	**Consequences**
Screened	-	80%	80%	97%	97%	-
Treated	75%	57%	57%	77%	77%	-
No. treated	70.0 (19.8 to 193)	12.4 (0.7 to 29.9)	17.6 (1.0 to 44.1)	48.0 (13.5 to 126)	48.0 (13.5 to 126)	Per 1000 women treated: 5 births with congenital syphilis; 250 gastrointestinal side-effects; 70 central nervous system side-effects
Missed cases	20.5 (4.6 to 66.3)	78.1 (24.5 to 228)	72.9 (22.7 to 218.8)	42.5 (11.6 to 134)	42.5 (11.6 to 134)	Per 1000 women missed: 160 births with congenital syphilis; 210 stillbirths; 90 neonatal deaths; 60 premature births; syphilis transmission
Over-treated	683.0 (499 to 768)	0.8 (0.1 to 1.4)	12.7 (1.2 to 19.7)	45.2 (28.1 to 59.2)	1.1 (0.6 to 1.4)	Per 1000 women over-treated: 250 gastrointestinal side-effects; 70 central nervous system side-effects; 2/1 000 000 risk of penicillin allergy; unnecessary use of medication, facility, personnel; unnecessary stigma

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