



OPEN ACCESS

Improved rapid diagnostic tests to detect syphilis and yaws: a systematic review and meta-analysis

Ying Zhang ¹, Su Mei Goh,² Maeve B Mello,³ Rachel C Baggaley,³ Teodora Wi,³ Cheryl C Johnson,³ Kingsley B Asiedu,³ Michael Marks ^{4,5,6}, Minh D Pham ^{7,8}, Christopher K Fairley ^{2,9}, Eric P F Chow ^{2,9,10}, Oriol Mitjà,¹¹ Igor Toskin,¹² Ronald C Ballard,¹² Jason J Ong ^{2,4,9}

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/sextrans-2022-055546>).

For numbered affiliations see end of article.

Correspondence to

Dr Jason J Ong, Melbourne Sexual Health Centre, Carlton 3053, Victoria, Australia; jason.ong@monash.edu

YZ and SMG are joint first authors.

Received 9 June 2022
Accepted 16 August 2022

ABSTRACT

Background Current rapid tests for syphilis and yaws can detect treponemal and non-treponemal antibodies. We aimed to critically appraise the literature for rapid diagnostic tests (RDTs) which can better distinguish an active infection of syphilis or yaws.

Methods We conducted a systematic review and meta-analysis, searching five databases between January 2010 and October 2021 (with an update in July 2022). A generalised linear mixed model was used to conduct a bivariate meta-analysis for the pooled sensitivity and specificity. Heterogeneity was assessed using the I^2 statistic. We used the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) to assess the risk of bias and Grading of Recommendations, Assessment, Development and Evaluations (GRADE) to evaluate the certainty of evidence.

Results We included 17 studies for meta-analyses. For syphilis, the pooled sensitivity and specificity of the treponemal component were 0.93 (95% CI: 0.86 to 0.97) and 0.98 (95% CI: 0.96 to 0.99), respectively. For the non-treponemal component, the pooled sensitivity and specificity were 0.90 (95% CI: 0.82 to 0.95) and 0.97 (95% CI: 0.92 to 0.99), respectively. For yaws, the pooled sensitivity and specificity of the treponemal component were 0.86 (95% CI: 0.66 to 0.95) and 0.97 (95% CI: 0.94 to 0.99), respectively. For the non-treponemal component, the pooled sensitivity and specificity were 0.80 (95% CI: 0.55 to 0.93) and 0.96 (95% CI: 0.92 to 0.98), respectively.

Conclusions RDTs that can differentiate between active and previously treated infections could optimise management by providing same-day treatment and reducing unnecessary treatment.

PROSPERO registration number CRD42021279587.

KEY MESSAGE

We systematically reviewed the performance characteristics and clinical utility of rapid diagnostic tests (RDT) for syphilis and yaws. We report a slightly lower sensitivity, but very high specificity compared with laboratory reference tests. RDTs could reduce time-to-treatment, over-treatment and lost-to-follow-up.

BACKGROUND

Syphilis and yaws are human treponematoses that remain significant causes of morbidity and mortality globally. Syphilis is caused by *Treponema pallidum*

subspecies *pallidum* and is primarily transmitted through sex by skin-to-skin contact or through mother-to-child during pregnancy, causing congenital syphilis. Yaws is an endemic and neglected tropical disease caused by *Treponema pallidum* subspecies *pertenue* and is characterised by soft tissue and bone lesions.¹ Both infections are curable and preventable.

Globally, there are an estimated 6 million new cases of syphilis each year.² The burden of congenital syphilis is high, with an estimated 661 000 cases.³ Further, syphilis disproportionately affects key populations such as sex workers, transgender women (TGW) and men who have sex with men (MSM). Recently, a 2021 study estimated a pooled prevalence of 7.5% among MSM worldwide.⁴ Social and structural challenges often make it difficult for these populations to access healthcare services, resulting in delayed detection and lost to follow-up (LTFU) (from diagnosis to getting results or treatment).

For yaws, a systematic review in 2015 estimated the prevalence of active disease ranged from 0.3% to 14.5% in endemic areas, and of latent yaws from 2.5% to 31.1%.¹ Considering its severe morbidity, the WHO launched a strategy to eradicate yaws by 2020, later revised to 2030.⁵ The revised strategy included using rapid diagnostic tests (RDTs) for *T. pallidum* as a priority for yaws eradication.⁵

Diagnostic methods for active syphilis and yaws include direct detection of treponemes or treponemal DNA sequences (ie, darkfield microscopy, direct immunofluorescence test or nucleic acid amplification tests performed on material obtained from primary or secondary lesions). In the absence of primary or secondary lesions, such as in latent syphilis or tertiary syphilis, serological tests for treponemal and non-treponemal antibodies using whole blood, serum/plasma or cerebrospinal fluid are required.⁶ Over the past decade, several treponemal rapid screening tests have been developed with pooled sensitivity ranging from 85% to 98%, and specificity from 93% to 98%.⁷ In 2015, syphilis RDTs were adopted into the WHO prequalification system.⁸ However, these single-treponemal RDTs cannot differentiate between active and previously treated infections.

More recently, some novel RDTs have included both treponemal and non-treponemal test



© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Zhang Y, Goh SM, Mello MB, *et al.* *Sex Transm Infect* Epub ahead of print: [please include Day Month Year]. doi:10.1136/sextrans-2022-055546

components in the same device, such as the Dual Path Platform (DPP) Syphilis Screen and Confirm Assay (Chembio Diagnostic Systems, New York, USA), which will be referred to as the DPP-RDT.⁹ The Burnet Institute (Melbourne, Australia) also developed an RDT for syphilis using a treponemal IgA-specific assay.^{10 11} Furthermore, a new smartphone dongle triplex test targeting HIV, treponemal antibodies and anti-cardiolipin antibodies as the non-treponemal marker has been developed.¹² Of these novel RDTs, the only commercially available test currently is the DPP Screen and Confirm Assay which is accessible in Europe and the USA. The smartphone dongle and the Burnet tests are prototypes only at this stage and not yet commercially manufactured.¹³

In 2016, a meta-analysis on DPP-RDT to detect syphilis and yaws found an 85.2% concordance when comparing the DPP-RDT with reference serology.⁹ Since that publication, there have been further studies evaluating DPP-RDT in various settings, including the use of digital readers¹⁴ as well as newer RDTs.^{10 12} Thus, we conducted a systematic review on the performance characteristics and clinical utility of RDTs for syphilis and yaws to inform forthcoming WHO guidance on testing for these diseases.

METHODS

This review follows the recommendations in the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy¹⁵ and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) extension for Diagnostic Test Accuracy guidelines.¹⁶

Search strategy and selection criteria

Five databases (Medline, Embase, Global Health, CINAHL and Web of Science) were searched on 11 October 2021. The search strategy was adapted from a previous meta-analysis paper on DPP-RDT,⁹ built around overarching terms, including 'syphilis', 'yaws', 'rapid diagnostic test', 'treponemal', 'nontreponemal' and their Medical Subject Headings (MeSH) terms (eg, syphilis congenital, syphilis latent, neurosyphilis), and was modified for each database (see online supplemental appendix 1). The search was limited from 2010 to October 2021, the period since the DPP-RDT assay became available. No language restrictions were set. Reference lists were checked to locate any other relevant papers.

Studies were included for meta-analysis if they contained primary quantitative data on the clinical performance of an RDT that detects treponemal and non-treponemal antibodies with no restrictions on populations, countries or study designs. Studies that evaluated secondary outcomes such as feasibility, usability and acceptability of the RDTs, testing uptake and cost-effectiveness were included for narrative synthesis.

Search results from each database were downloaded into the Covidence systematic review tool. After removing duplicates, two reviewers (YZ, SMG) independently screened the titles and abstracts of all articles potentially eligible for full-text retrieval, with a third reviewer (JJO) resolving any discrepancies. Non-English language articles were excluded at this stage. An updated literature search was undertaken in July 2022, and after screening, none of the articles met the inclusion criteria.

Data extraction

Two independent reviewers (YZ, SMG) extracted data from full-text articles that satisfied the inclusion criteria using a data extraction spreadsheet and checked by a third reviewer (JJO).

We extracted data on the specimen type, disease (syphilis or yaws), RDT reading method (visual vs digital reader), type of laboratory-based reference test, sensitivity and specificity, country (classified by country income level as per the World Bank Group), study design, study setting and secondary outcomes (if available).¹⁷

Data analysis

The Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 tool was chosen to assess the risk of bias in diagnostic test accuracy.¹⁸ Two reviewers (YZ, SMG) examined the risk of bias, and a third reviewer (JJO) resolved any discrepancies. Risk of bias was assessed using QUADAS¹⁸ and the certainty of the evidence was evaluated using Grading of Recommendations, Assessment, Development and Evaluations (GRADE).¹⁹

Statistical analyses were conducted in Stata V.17 (StataCorp, College Station, Texas, USA) using the *midas* and *metandi* Stata modules for meta-analysis of diagnostic test accuracy studies.^{20 21} We used a generalised linear mixed-model approach to conduct a bivariate meta-analysis of the sensitivity and specificity of the dual treponemal–non-treponemal RDTs. As the bivariate model assumes independent binomial distributions for the true positives and true negatives conditional on the sensitivity and specificity in each study,²¹ we calculated their associated 95% CI. Forest plots and hierarchical summary receiver operating characteristic (HSROC) plots were created separately for syphilis and yaws. Statistical heterogeneity was assessed using the I^2 statistic, and Deeks' funnel asymmetry test was used to evaluate publication bias.²² We calculated the positive and negative likelihood ratios. We used random-effects meta-regression to determine if any study-level covariates could explain the between-study heterogeneity. Meta-regression was not performed for yaws due to insufficient observations. We used narrative synthesis to describe the data for the secondary outcomes. This study is registered with PROSPERO (CRD42021279587).

RESULTS

The quality assessment results are summarised in online supplemental table 1 and online supplemental figure 1. There was potential for bias, particularly for client selection (33.3%, n=5). Most studies adequately described the index test (73.3%, n=11) and reference tests (73.3%, n=11). Results around the certainty of the evidence are shown in online supplemental table 2.

The PRISMA flow chart is presented in figure 1. In total, 750 records were retrieved and screened. We included 25 studies for data synthesis, 2 of which were unpublished data extracted from a previous publication following consultation with one of the coauthors (MM).⁹ Characteristics of the 25 studies are outlined in table 1. The majority of the studies were cross-sectional studies from high-income countries and conducted within clinical settings. In total, 13 articles on syphilis^{10 11 14 23–32} and 4 articles on yaws^{33 34} (including 2 unpublished studies) were included in the meta-analysis (see table 2). Fifteen articles contained enough information for the narrative synthesis of secondary outcomes.

Syphilis

For syphilis, the pooled sensitivity and specificity of the treponemal component were 0.93 (95% CI: 0.86 to 0.97) and 0.98 (95% CI: 0.96 to 0.99), respectively (figure 2). For the non-treponemal component, the pooled sensitivity and specificity for syphilis were 0.90 (95% CI: 0.82 to 0.95) and 0.97 (95% CI: 0.92 to 0.99), respectively (figure 3). High heterogeneity was observed for both the treponemal (sensitivity: $I^2=96.9\%$;

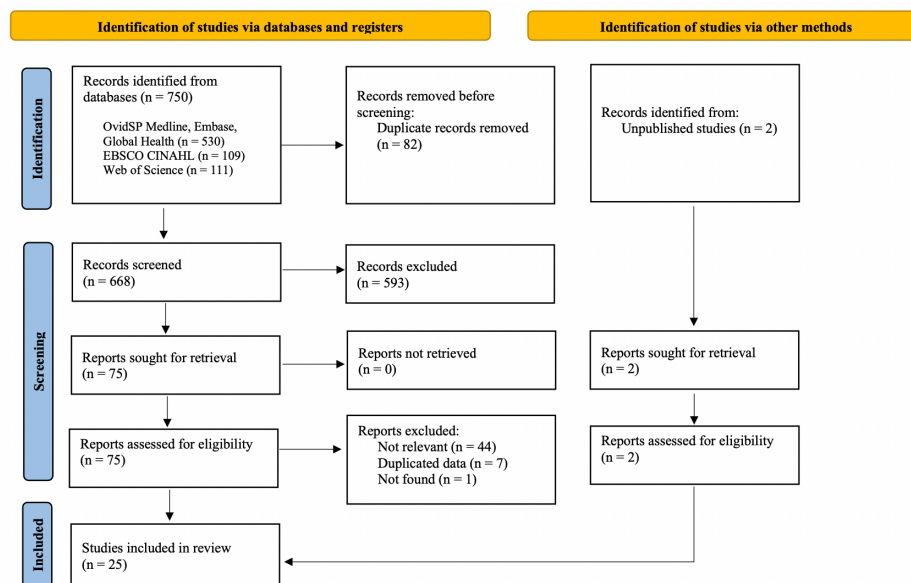


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

specificity: $I^2=94.7\%$) and non-treponemal (sensitivity: $I^2=98.3\%$; specificity: $I^2=99.3\%$) components. From the bivariate analysis, the positive and negative likelihood ratios were 55.1 (95% CI: 26.6 to 113.9) and 0.07 (95% CI: 0.04 to 0.14), respectively, for the treponemal component and 34.7 (95% CI: 11.4 to 106.1) and 0.10 (95% CI: 0.06 to 0.18) for the non-treponemal component. The diagnostic ORs were 777 (95% CI: 340 to 1776) and 339 (95% CI: 131 to 880), respectively.

Meta-regression was conducted using the study setting, sample type and RDT reading method (see online supplemental table 3). Serum samples performed better than whole blood samples in both treponemal (0.96 (95% CI: 0.93 to 1.00) vs 0.88 (95% CI: 0.79 to 0.97)) and non-treponemal sensitivity (0.95 (95% CI: 0.92 to 0.99) vs 0.83 (95% CI: 0.70 to 0.91)), but not for specificity. Studies conducted in laboratories had better sensitivity for both treponemal (0.95 (95% CI: 0.83 to 1.00)) and non-treponemal (0.93 (95% CI: 0.86 to 0.99)) test components compared with studies from clinical facilities (0.91 (95% CI: 0.82 to 1.00); 0.85 (95% CI: 0.72 to 0.98)). Although the use of digital readers to analyse RDT results resulted in greater specificity than the human eye (treponemal: 0.99 (95% CI: 0.99 to 1.00) vs 0.98 (95% CI: 0.96 to 0.99); non-treponemal: 0.99 (95% CI: 0.92 to 1.00) vs 0.97 (95% CI: 0.93 to 1.00), respectively), it only had slightly better sensitivity for the treponemal component (0.95 (95% CI: 0.86 to 1.00) vs 0.92 (95% CI: 0.87 to 0.98)) and added to the cost of the test.

Among all the studies, there were two outlier studies that were performed in clinical settings. A study in the USA reported the lowest sensitivity for both components due to participant selection as the sample included women who inject drugs and also reported higher-risk sexual behaviours.²⁸ In another outlier study exploring point-of-care tests for syphilis among MSM in Italy, Zorzi *et al* reported logistical problems with expired test assays that resulted in a subsample of recruited MSM's results being unavailable.³² These might have contributed to the heterogeneity in the pooled studies. Further sensitivity analysis by removing these two studies increased the pooled sensitivity from 0.93 (95% CI: 0.86 to 0.97) to 0.95 (95% CI: 0.93 to 0.97) in the treponemal component, and 0.90 (95% CI: 0.82 to 0.95) to 0.98 (95% CI: 0.96 to 0.99) for the non-treponemal part. The

I^2 statistic was reduced from 96.9% to 87.5%, and 98.3% to 98.2% for the sensitivity of the treponemal and non-treponemal components, respectively. The exclusion of these two studies increased the test performance of the non-treponemal component in clinical settings to 0.92 (95% CI: 0.85 to 1.00).

Yaws

For yaws, we found that for the treponemal component, the pooled sensitivity and specificity were 0.86 (95% CI: 0.66 to 0.95) and 0.97 (95% CI: 0.94 to 0.99), respectively, and for the non-treponemal component, 0.80 (95% CI: 0.55 to 0.93) and 0.96 (95% CI: 0.92 to 0.98), respectively (figures 4 and 5). The I^2 for sensitivity was 96.4% and 97.8%, and that for specificity was 84.2% and 88.5% for treponemal and non-treponemal components, respectively. The HSROCs for syphilis and yaws are depicted in online supplemental figure 2.

The positive and negative likelihood ratios were 27.8 (95% CI: 12.3 to 63.0) and 0.15 (95% CI: 0.06 to 0.39), respectively, for the treponemal component and 21.8 (95% CI: 8.9 to 53.5) and 0.21 (95% CI: 0.08 to 0.54) for the non-treponemal component. The diagnostic ORs were 187 (95% CI: 39 to 901) and 105 (95% CI: 20 to 553), respectively. Using Deeks' test, we did not detect any publication bias in the studies on syphilis (treponemal component: $p=0.08$; non-treponemal component: $p=0.53$) and yaws (treponemal component: $p=0.74$; non-treponemal component: $p=0.70$) (see online supplemental figure 3). The positive predictive values and negative predictive values for tests undertaken for syphilis and yaws are presented in online supplemental table 4.

Secondary outcomes

The narrative synthesis of the secondary outcomes is provided in online supplemental appendix 2. Briefly, RDTs were considered acceptable and feasible by healthcare workers and clients, and could reduce time to treatment, LTFU, overtreatment and improve cost-effectiveness. The usability of DPP-RDT was variable, with some studies advocating for digital readers to improve test accuracy.

Table 1 Characteristics of included studies

	Syphilis* (n=19) n (%)	Yaws* (n=7) n (%)
POCTs		
Chembio DPP-RDT	15 (78.9)	7 (100)
Smartphone dongle triplex test†	1 (5.3)	0
SpanDiagnostics‡	1 (5.3)	0
Burnet TP-IgA	2 (10.5)	0
Country income levels§		
High	9 (47.4)	0
Middle	6 (31.6)	6 (85.7)
Low	2 (10.5)	1 (14.3)
Mixed	2 (10.5)	0
Study setting		
General practice/clinic	11 (57.9)	1 (14.3)
Laboratory	8 (42.1)	0
Field/non-clinical facility	0	3 (42.9)
Unclear (includes unpublished data)	0	3 (42.9)
Population		
General population	11 (57.9)	3 (42.9)
Pregnant women	4 (21.1)	0
MSM	2 (10.5)	0
People living with HIV	1 (5.3)	0
Children	0	2 (28.6)
Other¶	1 (5.3)	0
Unclear (from unpublished data)	0	2 (28.6)
Study design		
Experimental/randomised controlled trial	0	1 (14.3)
Observational/cross-sectional	16 (84.2)	2 (28.6)
Modelling	2 (10.5)	1 (14.3)
Qualitative	1 (5.3)	1 (14.3)
Unclear (from unpublished data)	0	2 (28.9)
RDT reading method		
Visual	16 (84.2)	6 (85.7)
Digital reader	3 (15.8)	1 (14.3)
Secondary outcomes		
		Total (n=15)
Acceptability		2 (13)
Feasibility		2 (13)
Usability		5 (33)
Appropriate treatment following testing		4 (27)
Cost/resources		2 (13)

*The total of studies for each category does not add up to 25 as one paper contained data for both syphilis and yaws.

†HIV, treponemal and non-treponemal RDT, not commercially available.

‡Similar to DPP-RDT, manufactured by Span Diagnostics.

§Country income level is classified as per the World Bank Group.

¶(>15 years old+behavioural risk group): (1) injection drug users (IDUs) with verified track marks (eg, visible signs of injection); (2) women who reported at least two male partners in the last 2 years or engaging in anal intercourse, sex trading, or sex with an MSM, an IDU, or an HIV-positive man; (3) MSM and men who have sex with men and women; and (4) transgender individuals.

DPP, Dual Path Platform; MSM, men who have sex with men; POCTs, point-of-care tests; RDT, rapid diagnostic test; TP-IgA, treponemal IgA-specific assay.

DISCUSSION

This systematic review synthesised current evidence regarding RDTs for detecting both treponemal and non-treponemal antibodies for syphilis and yaws. Since the last review by Marks *et al*,⁹ new studies have evaluated DPP-RDT in various settings, and two new studies have data on the Burnet assay. We consolidated evidence regarding the acceptability, feasibility, usability,

cost-effectiveness and uptake of treatment post-diagnosis, providing helpful information for policy and planning (see online supplemental appendix 2).

Syphilis

While we observed high pooled sensitivity and specificity in our results, we acknowledge that it is challenging to define active syphilis using diagnostics without further medical history (including past syphilis results) and clinical examination (for signs of syphilis). In addition, no test will be 100% accurate and have limitations. According to Shields's study, routine PCR has a sensitivity of 84–89% and a specificity of 93–100% for primary syphilis, but sensitivity dropped to 50% for secondary syphilis, rendering it unsuitable as a screening tool for secondary syphilis.³⁵ Other studies report that although venereal disease research laboratory (VDRL) is specific for syphilis, it is more prone to human error and lacks the sensitivity to be used as a first-line screening test for primary syphilis.³⁶ Serum RPR and VDRL have 62–100% sensitivity, depending on the disease stage.³⁷ Although we could not stratify our results by different syphilis stages, our results demonstrated strong test performance even with a mix of disease stages.

Notably, we found that serum samples performed better than whole blood samples in test sensitivity but not for specificity. This finding is concordant with Jafari *et al*, where diagnostic performance for serum samples was higher than whole blood due to higher concentration of biomarkers and absence of interfering substances in whole blood.³⁸ In addition, we found higher test sensitivity in studies performed in laboratory settings than in clinic settings. This opens the possibility of using highly sensitive RDT for serum samples in laboratory settings, especially in antenatal syphilis screening, where no cases should be missed for treatment. On the other hand, the lower sensitivity of RDTs in the field may be an acceptable trade-off if RDTs can improve detection and reduce LTFU.

Early testing and treatment for syphilis are critical for pregnant women to prevent congenital disease and other negative pregnancy outcomes.³⁹ Scaling up the use of these newer dual treponemal–non-treponemal RDTs for syphilis could potentially benefit pregnant women and their babies. A modelling study comparing dual RDT with laboratory RPR+*T. pallidum* haemagglutination (TPHA) estimated that with every 1000 pregnancies, 34 and 26 adverse pregnancy outcomes would be averted, respectively with dual RDT versus RPR+TPHA.⁴⁰ Additionally, when RPR+TPHA was used to diagnose maternal syphilis, treatment rates declined from 100% to 67%, indicating that a significant number of clients were LTFU.⁴⁰ Hence, the WHO recommends immediate treatment initiation following any reactive syphilis test for pregnant women and their partner(s).³⁹ While this strategy may result in overtreatment due to false positives for previous syphilis infections, it is preferred to avoid missing syphilis treatment during pregnancy. The ability of the RDT to obtain results and initiate treatment at the same antenatal visit can reduce LTFU, prevent more cases of adverse birth outcomes and interrupt the chain of transmission, thus saving valuable client and provider time and resources.

Priority populations such as MSM and TGW are disproportionately affected by syphilis, and the presence of sociocultural stigma, violence, negative experiences with healthcare systems, prioritisation of hormone therapy by transgender people and frequent life instability place them at a higher risk of LTFU.⁴¹ In a study of MSM and TGW who tested positive with RPR or a single-treponemal rapid screening test, only 37% returned

Table 2 Summary of studies included in the meta-analysis (n=17)

Author	Study site	Population	T1 reference test	T1 reference prevalence (%)	T2 reference test	T2 reference prevalence (%)	Sample type	Sample size	T1 sensitivity (95% CI)	T1 specificity (95% CI)	T2 sensitivity (95% CI)	T2 specificity (95% CI)
Syphilis (DPP-RDT)												
Castro ²⁴	USA	General	TPPA	40.2	RPR	30.6	Serum	376	0.97 (0.93 to 0.99)*	0.99 (0.97 to 1.00)*	0.97 (0.91 to 0.99)*	0.98 (0.95 to 0.99)*
Castro ²³	USA	General	TPPA	62.9	RPR	52.1	Serum	1601	0.97 (0.95 to 0.98)*	0.95 (0.93 to 0.97)*	0.89 (0.86 to 0.91)*	0.99 (0.97 to 0.99)*
Castro ²⁵	Portugal	General	TPHA	74.6	RPR	69.8	Serum	248	0.99 (0.97 to 1.00)	0.89 (0.78 to 0.95)	0.99 (0.95 to 1.00)	0.95 (0.87 to 0.98)
Causser ²⁶	Australia	MSM (majority)	TPPA	73.2	RPR	55	Serum	1005	0.9 (0.87 to 0.92)	0.99 (0.97 to 1.00)	0.94 (0.92 to 0.96)	0.62 (0.58 to 0.67)
Constantine ¹⁴	USA	General	TPPA	31.5	RPR	31.2	Whole blood	1265	0.93 (0.90 to 0.95)	0.99 (0.99 to 1.00)	0.65 (0.60 to 0.70)	1 (0.99 to 1.00)
Guinard ²⁷	France	General	EIA	57.6	RPR	39.8	Serum, whole blood	T1=144 T2=108	0.9 (0.82 to 0.95)	0.98 (0.91 to 1.00)	0.95 (0.84 to 0.99)	0.92 (0.83 to 0.97)
Hess ²⁸	USA	Others	TPPA	12.2	RPR	3	Whole blood	T1=765 T2=763	0.53 (0.43 to 0.63)	0.99 (0.97 to 0.99)	0.48 (0.27 to 0.69)	0.99 (0.98 to 1.00)
Langendorf ²⁹	Burkina Faso	Pregnant women	TPPA	41.7	RPR	25.5	Finger prick, whole blood	T1=242 T2=188	0.95 (0.89 to 0.98)*	0.98 (0.94 to 1.00)*	0.85 (0.72 to 0.92)*	1 (0.97 to 1.00)*
Skinner ³⁰	Australia	Children	TPPA	75.9	RPR	50.6	Serum	449	0.94 (0.90 to 0.96)*	0.87 (0.79 to 0.93)*	0.96 (0.92 to 0.98)*	0.66 (0.60 to 0.72)*
Yin ³¹	China	General	TPPA	49.9	TRUST	35.6	Finger prick, plasma, whole blood	3135	0.96 (0.95 to 0.97)	0.99 (0.99 to 1.00)	0.89 (0.87 to 0.91)	0.91 (0.90 to 0.92)
Zorzi ³²	Italy	MSM	TPPA, CLIA	15.4	RPR	7.1	Finger prick, whole blood	227	0.69 (0.51 to 0.83)	0.99 (0.96 to 1.00)	0.62 (0.35 to 0.85)	1 (0.97 to 1.00)
Yaws (DPP-RDT)												
Ayove ³⁴	Papua New Guinea	Children	TPHA	55.3	RPR	43.4	Plasma, whole blood	704 500	0.88 (0.85 to 0.91)	0.95 (0.92 to 0.97)	0.88 (0.84 to 0.91)	0.92 (0.89 to 0.95)
					RPR ≤ 1:4†						0.76 (0.66 to 0.84)	
					RPR ≤ 1:8†						0.94 (0.90 to 0.97)	
Aziz†	Ghana	Unknown	TPPA	39.2	RPR	34.9	Finger prick	255	0.97 (0.91 to 0.99)	0.99 (0.96 to 1.00)	0.94 (0.87 to 0.98)	0.99 (0.96 to 1.00)
Marks ³³	Solomon Islands	Children	TPPA	29.6	RPR	28.9	Serum	415	0.59 (0.50 to 0.67)	0.98 (0.95 to 0.99)	0.42 (0.33 to 0.51)	0.95 (0.92 to 0.97)
					RPR ≤ 1:4†						0.62 (0.45 to 0.77)	0.89 (0.87 to 0.96)
					RPR ≤ 1:8†						0.72 (0.51 to 0.86)	0.91 (0.8 to 0.95)
					RPR ≤ 1:16†						0.92 (0.67 to 0.99)	0.89 (0.83 to 0.94)
Taleo†	Vanuatu	Unknown	TPPA	43.7	RPR	34.5	Finger prick	238	0.8 (0.71 to 0.87)	0.93 (0.88 to 0.96)	0.74 (0.64 to 0.83)	0.96 (0.92 to 0.99)

Syphilis (Burnet TP-IgA)

Author	Study site	Population	T1 reference test	T1 reference prevalence (%)	T2 reference test	T2 reference prevalence (%)	Sample type	Sample size	Sensitivity (95% CI)	Specificity (95% CI)
Pham ¹⁰	China	General	TPHA		RPR	33.7	Plasma	454	0.96 (0.92 to 0.99)	0.85 (0.80 to 0.89)
Pham ¹¹	South Africa	Pregnant women	TPAb		RPR	0.6	Whole blood	499	0.88 (0.29 to 1.00)*	0.99 (0.98 to 1.00)

Upper limit of 95% CI above 0.995 is rounded up to 1.00.

*Values are calculated by authors as they were not reported in the original studies.

†Sub-analysis with RPR titre.

‡Unpublished data.

CLIA, chemiluminescence immunoassay; DPP-RDT, Dual Path Platform-rapid diagnostic test; EIA, enzyme immunoassay; MSM, men who have sex with men; RPR, rapid plasma reagin; TPAb, *Treponema pallidum* antibody; TPHA, *Treponema pallidum* haemagglutination; TP-IgA, treponemal IgA-specific assay; TPPA, *Treponema pallidum* passive particle agglutination assay; TRUST, toluidine red unheated serum test.

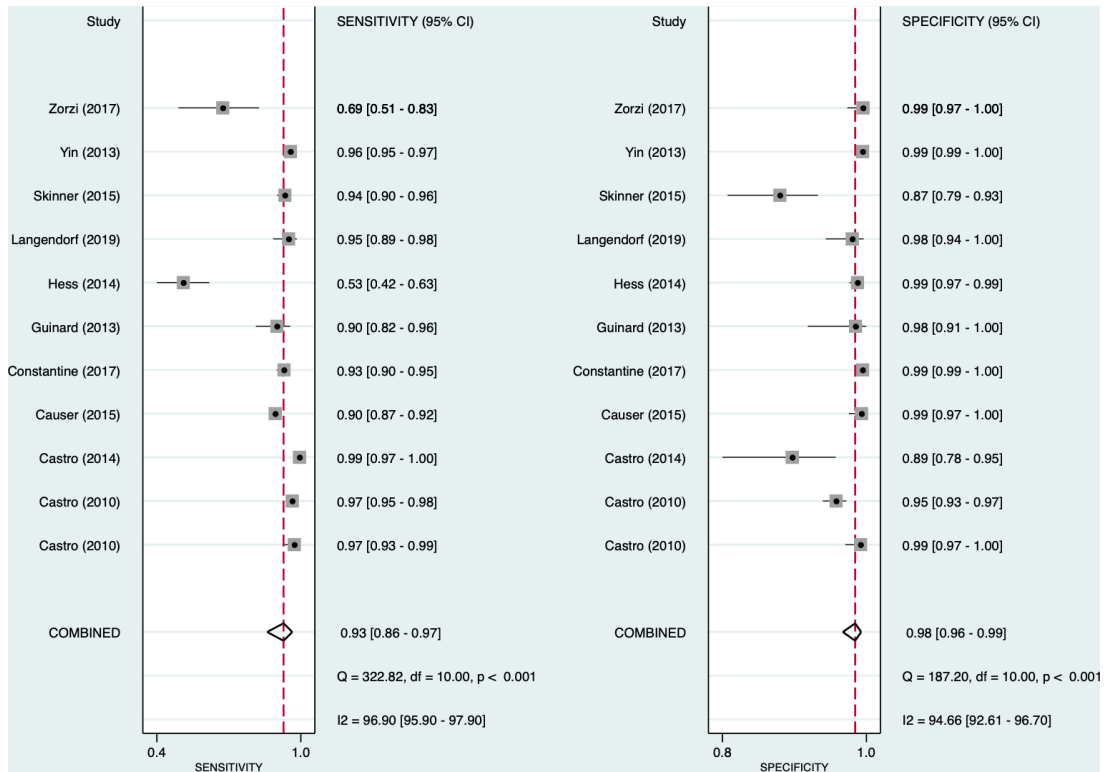


Figure 2 Forest plot of treponemal sensitivity and specificity for syphilis.

for a confirmatory test.⁴¹ Although test performance of RDT is slightly lower in clinical settings than in laboratories, given their high prevalence and LTFU, RDTs could be preferred over conventional laboratory testing. The added value of newer syphilis RDTs, compared with single-treponemal rapid screening

tests or conventional laboratory-based testing, lies in facilitating therapy on the same day and reducing overtreatment, particularly among users of HIV pre-exposure prophylaxis and in areas with a high background prevalence of syphilis. Given that they are recommended to undergo syphilis tests every 3–6 months,

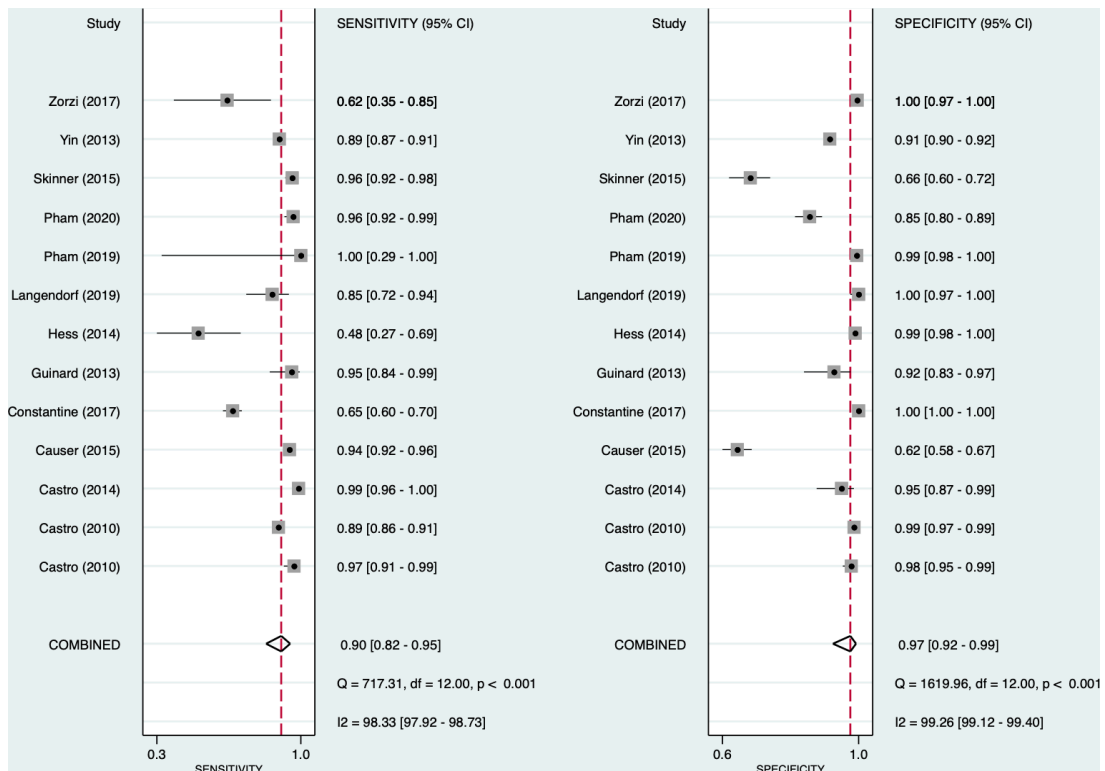


Figure 3 Forest plot of non-treponemal sensitivity and specificity for syphilis.

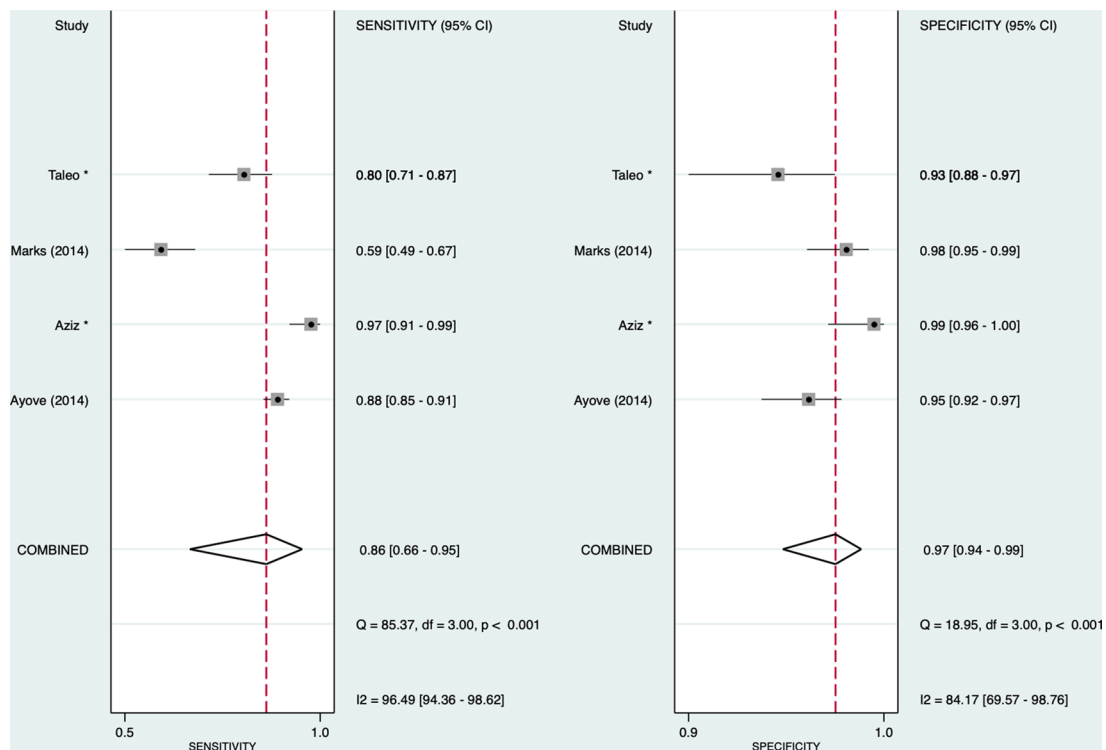


Figure 4 Forest plot of treponemal sensitivity and specificity for yaws. *Unpublished studies.

treatment based solely on a positive single-treponemal rapid test will result in significant overtreatment.

Yaws

Access to quality diagnostics has been identified as a priority in controlling, eliminating and eradicating neglected tropical diseases, and the expanded use of RDTs for yaws is central to

WHO's eradication effort. Currently, most countries rely solely on clinical diagnosis, which is not sufficiently accurate and leads to unreliable surveillance data. RDTs allow easier identification of cases of latent yaws in the community who potentially represent an important disease reservoir.⁴² As most yaws-endemic countries lack sufficient laboratory capacity for traditional serological assays, these novel RDTs play a pivotal role in supporting

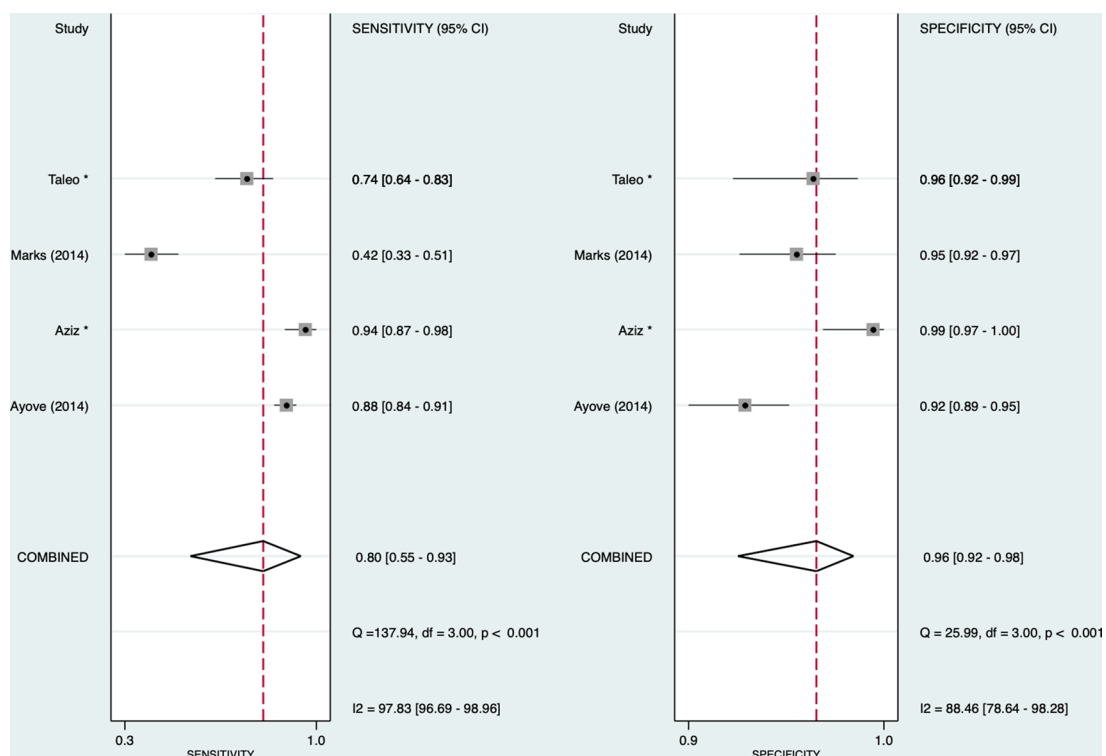


Figure 5 Forest plot of non-treponemal sensitivity and specificity for yaws. *Unpublished studies.

yaws eradication efforts. The use of additional automatic readers can potentially monitor changes in the quantity of the non-treponemal antibodies, thereby assisting in the diagnosis of new infections or monitoring treatment response. In Papua New Guinea, children with yaws were followed up using a DPP-RDT automatic reader to measure optical density after treatment.³⁴ At 6 months, 95% had attained a fourfold reduction in optical density (serological cure) or seroconversion.³⁴ This demonstrates that post-treatment serological follow-up might be done in the same way that reference RPR testing is used without relying on laboratory facilities. In a community surveillance study, Marks *et al* reported the sensitivity of the DPP-RDT against *T. pallidum* passive particle agglutination assay and RPR was 47.1%, with the sensitivity of the DPP-RDT being strongly related to the RPR titre. This reduced sensitivity compared with other studies reflects a greater population of asymptomatic latent yaws cases where lower antibody titres contribute to lower sensitivity compared with those with active clinical disease and higher titres.³³ This is important, particularly in antenatal settings, as pregnant women with yaws and lower RPR titres may be less likely to transmit the infection to their infants.

Our review has several limitations. First, many studies were performed in a laboratory setting and included samples with different patterns of serological reactivity but unknown clinical stages of infection. Further comparative studies are needed in syphilis and yaws, where the clinical stages of infection are documented together with direct detection of treponemes (in primary and secondary disease), clinical and treatment histories (including information about serofast status) so that active disease can be ascertained with greater certainty. Second, we did not have information on coinfection status, re-infection status or other diseases in subjects providing samples that might have affected the results. Third, we did not search grey literature, so we may have missed other relevant data. Lastly, we tried to use meta-regression to explain the heterogeneity in our results but was limited by the small number of studies and not enough information to account for other important factors such as the clinical stages of syphilis and yaws, and treatment histories of patients.

CONCLUSIONS

RDTs that can differentiate between active and previously treated infections could optimise management by providing same-day treatment and reducing unnecessary treatment. This systematic review and meta-analysis found that current RDTs for syphilis and yaws had slightly lower sensitivity but a very high specificity than laboratory-based testing. If distributed widely with appropriate training, these tests can potentially decrease the incidence of both adult and congenital syphilis and contribute to the global eradication of yaws.

Author affiliations

¹School of Public Health, The University of Sydney, Campertown, New South Wales, Australia

²Melbourne Sexual Health Centre, Melbourne, Victoria, Australia

³Global HIV, Hepatitis and STI Programmes, WHO, Geneva, Switzerland

⁴Clinical Research Department, London School of Hygiene and Tropical Medicine, London, UK

⁵Hospital for Tropical Diseases, University College London Hospital, London, UK

⁶Division of Infection and Immunity, University College London, London, UK

⁷Burnet Institute, Melbourne, Victoria, Australia

⁸School of Public Health and Preventive Medicine, Monash University Faculty of Medicine, Nursing and Health Sciences, Melbourne, Victoria, Australia

⁹Central Clinical School, Faculty of Medicine, Nursing and Health Sciences, Monash University, Melbourne, Victoria, Australia

¹⁰Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Victoria, Australia

¹¹Fight AIDS and Infectious Diseases Foundation, Catalonia, Spain

¹²Department of Sexual and Reproductive Health and Research, WHO, Geneva, Switzerland

Correction notice This article has been corrected since it was first published online. The disclaimer section has been updated.

Handling editor Laith J Abu-Raddad

Twitter Ying Zhang @lovie_sally, Eric P F Chow @EricPFChow and Jason J Ong @DrJasonJong

Contributors MM, TW, RB, CJ and JJO conceived the idea. YZ and SMG did the screening and data extraction. YZ and JJO conducted the statistical analysis. All authors contributed to the interpretation of the results and subsequent edits of the manuscript and had final responsibility for the decision to submit for publication.

Funding The WHO supported this work through a grant from the Ministry for Development Cooperation and Humanitarian Affairs, Luxembourg. JJO and EPFC are each supported by the Australian National Health and Medical Research Council (NHMRC) Emerging Leadership Investigator Grant (grant number GNT1193955 for JJO; GNT1172873 for EPFC). CKF is supported by an Australian NHMRC Leadership Investigator Grant (grant number GNT1172900).

Disclaimer Some of the authors are present or former staff members of the World Health Organization. The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the views, decisions, or policies of the institutions with which they are affiliated.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval No ethical clearance was required.

Provenance and peer review Not commissioned; externally peer reviewed.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Ying Zhang <http://orcid.org/0000-0001-7717-5691>

Michael Marks <http://orcid.org/0000-0002-7585-4743>

Minh D Pham <http://orcid.org/0000-0002-5932-3491>

Christopher K Fairley <http://orcid.org/0000-0001-9081-1664>

Eric P F Chow <http://orcid.org/0000-0003-1766-0657>

Jason J Ong <http://orcid.org/0000-0001-5784-7403>

REFERENCES

- World Health Organization. Yaws Geneva; 2021. <https://www.who.int/news-room/fact-sheets/detail/yaws> [Accessed 30 Oct 2021].
- World Health Organization. Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021, 2021. Available: <https://www.who.int/publications/i/item/9789240027077> [Accessed 30 Dec 2021].
- Gomez GB, Kamb ML, Newman LM, *et al*. Untreated maternal syphilis and adverse outcomes of pregnancy: a systematic review and meta-analysis. *Bull World Health Organ* 2013;91:217–26.
- Tsuboi M, Evans J, Davies EP, *et al*. Prevalence of syphilis among men who have sex with men: a global systematic review and meta-analysis from 2000–20. *Lancet Glob Health* 2021;9:e1110–8.
- World Health Organization. Ending the neglect to attain the sustainable development goals: a road map for neglected tropical diseases 2021–2030; 2021. <https://www.who.int/publications/i/item/9789240010352> [Accessed 10 Nov 2021].
- Unemo M, Ballard R, Ison C. Laboratory diagnosis of sexually transmitted infections, including human immunodeficiency virus. Geneva World Health Organization; 2013: xi, 228 p.
- World Health Organization. Who guidelines for the treatment of *Treponema pallidum* (syphilis). Geneva World Health Organization; 2016. <https://www.who.int/>

- reproductivehealth/publications/rtis/syphilis-treatment-guidelines/en/ [Accessed 30 Dec 2021].
- 8 World Health Organization. Who list of prequalified in vitro diagnostic products, 2021. Available: https://extranet.who.int/pqweb/sites/default/files/documents/210827_prequalified_product_list.pdf [Accessed 01 Mar 2022].
 - 9 Marks M, Yin Y-P, Chen X-S, *et al.* Metaanalysis of the performance of a combined treponemal and nontreponemal rapid diagnostic test for syphilis and yaws. *Clin Infect Dis* 2016;63:627–33.
 - 10 Pham MD, Wise A, Garcia ML, *et al.* Improving the coverage and accuracy of syphilis testing: the development of a novel rapid, point-of-care test for confirmatory testing of active syphilis infection and its early evaluation in China and South Africa. *EClinicalMedicine* 2020;24:100440.
 - 11 Pham MD, Wise A, Garcia ML. Novel rapid test for improved diagnosis of active syphilis at the point of care. *Sex Transm Infect* 2019;95:A319.
 - 12 Laksanasopin T, Guo TW, Nayak S, *et al.* A smartphone dongle for diagnosis of infectious diseases at the point of care. *Sci Transl Med* 2015;7:273re1.
 - 13 Pham MD, Ong JJ, Anderson DA, *et al.* Point-of-care diagnostics for diagnosis of active syphilis infection: needs, challenges and the way forward. *Int J Environ Res Public Health* 2022;19. doi:10.3390/ijerph19138172. [Epub ahead of print: 04 07 2022].
 - 14 Constantine NT, Sill AM, Gudesblat E, *et al.* Assessment of two rapid assays for diagnostic capability to accurately identify infection by *treponema pallidum*. *J Appl Lab Med* 2017;1:346–56.
 - 15 Deeks J, Bossuyt P, Leeflang M. *Cochrane Handbook for systematic reviews of diagnostic test accuracy (version 2)*. Cochrane, 2022. <https://training.cochrane.org/handbook-diagnostic-test-accuracy>
 - 16 McInnes MDF, Moher D, Thoms BD, *et al.* Preferred reporting items for a systematic review and meta-analysis of diagnostic test accuracy studies: the PRISMA-DTA statement. *JAMA* 2018;319:388–96.
 - 17 The World Bank Groups. World bank country and lending groups. Available: <https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups> [Accessed 19 July 2022].
 - 18 Whiting PF, Rutjes AWS, Westwood ME, *et al.* QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011;155:529–36.
 - 19 Schünemann HJ, Mustafa RA, Brozek J, *et al.* Grade guidelines: 21 part 1. study design, risk of bias, and indirectness in rating the certainty across a body of evidence for test accuracy. *J Clin Epidemiol* 2020;122:129–41.
 - 20 Harbord RM, Whiting P. Metandi: meta-analysis of diagnostic accuracy using hierarchical logistic regression. *Stata J* 2009;9:211–29.
 - 21 Dwamena B. Midas: stata module for meta-analytical integration of diagnostic test accuracy studies. *Statistical Software Components* 2007 <https://ideas.repec.org/c/boc/bocode/s456880.html>
 - 22 van Enst WA, Ochodo E, Scholten RJPM, *et al.* Investigation of publication bias in meta-analyses of diagnostic test accuracy: a meta-epidemiological study. *BMC Med Res Methodol* 2014;14:70.
 - 23 Castro AR, Esfandiari J, Kumar S, *et al.* Novel point-of-care test for simultaneous detection of nontreponemal and treponemal antibodies in patients with syphilis. *J Clin Microbiol* 2010;48:4615–9.
 - 24 Castro AR, Mody HC, Parab SY, *et al.* An immunofiltration device for the simultaneous detection of non-treponemal and treponemal antibodies in patients with syphilis. *Sex Transm Infect* 2010;86:532–6.
 - 25 Castro R, Lopes Ângela, da Luz Martins Pereira F. Evaluation of an immunochromatographic point-of-care test for the simultaneous detection of nontreponemal and treponemal antibodies in patients with syphilis. *Sex Transm Dis* 2014;41:467–9.
 - 26 Causer LM, Kaldor JM, Conway DP, *et al.* An evaluation of a novel dual treponemal/nontreponemal point-of-care test for syphilis as a tool to distinguish active from past treated infection. *Clin Infect Dis* 2015;61:184–91.
 - 27 Guinard J, Prazuck T, Pérè H, *et al.* Usefulness in clinical practice of a point-of-care rapid test for simultaneous detection of nontreponemal and treponema pallidum-specific antibodies in patients suffering from documented syphilis. *Int J STD AIDS* 2013;24:944–50.
 - 28 Hess KL, Fisher DG, Reynolds GL. Sensitivity and specificity of point-of-care rapid combination syphilis-HIV-HCV tests. *PLoS One* 2014;9:e112190.
 - 29 Langendorf C, Lastrucci C, Sanou-Bicaba I, *et al.* Dual screen and confirm rapid test does not reduce overtreatment of syphilis in pregnant women living in a non-veneral treponematoses endemic region: a field evaluation among antenatal care attendees in burkina faso. *Sex Transm Infect* 2019;95:402–4.
 - 30 Skinner L, Robertson G, Norton R. Evaluation of the dual path platform syphilis point of care test in North Queensland. *Pathology* 2015;47:718–20.
 - 31 Yin Y-P, Chen X-S, Wei W-H, *et al.* A dual point-of-care test shows good performance in simultaneously detecting nontreponemal and treponemal antibodies in patients with syphilis: a multisite evaluation study in China. *Clin Infect Dis* 2013;56:659–65.
 - 32 Zorzi A, Cordioli M, Gios L, *et al.* Field evaluation of two point-of-care tests for syphilis among men who have sex with men, Verona, Italy. *Sex Transm Infect* 2017;93:S51–8.
 - 33 Marks M, Goncalves A, Vahi V, *et al.* Evaluation of a rapid diagnostic test for yaws infection in a community surveillance setting. *PLoS Negl Trop Dis* 2014;8:e3156.
 - 34 Ayove T, Hounie W, Wangnapi R, *et al.* Sensitivity and specificity of a rapid point-of-care test for active yaws: a comparative study. *Lancet Glob Health* 2014;2:e415–21.
 - 35 Shields M, Guy RJ, Jeoffrey NJ, *et al.* A longitudinal evaluation of treponema pallidum PCR testing in early syphilis. *BMC Infect Dis* 2012;12:353.
 - 36 Knaute DF, Graf N, Lautenschlager S, *et al.* Serological response to treatment of syphilis according to disease stage and HIV status. *Clin Infect Dis* 2012;55:1615–22.
 - 37 Tuddenham S, Katz SS, Ghanem KG. Syphilis laboratory guidelines: performance characteristics of nontreponemal antibody tests. *Clin Infect Dis* 2020;71:S21–42.
 - 38 Jafari Y, Peeling RW, Shivkumar S, *et al.* Are treponema pallidum specific rapid and point-of-care tests for syphilis accurate enough for screening in resource limited settings? evidence from a meta-analysis. *PLoS One* 2013;8:e54695.
 - 39 World Health Organization. Who guideline on syphilis screening and treatment for pregnant women. Geneva; 2017. <https://www.who.int/reproductivehealth/publications/rtis/syphilis-ANC-screenandtreat-guidelines/en/> [Accessed 30 Dec 2021].
 - 40 Owusu-Edusei K, Gift TL, Ballard RC. Cost-effectiveness of a dual non-treponemal/treponemal syphilis point-of-care test to prevent adverse pregnancy outcomes in sub-Saharan Africa. *Sex Transm Dis* 2011;38:997–1003.
 - 41 Tang EC, Segura ER, Clark JL, *et al.* The syphilis care cascade: tracking the course of care after screening positive among men and transgender women who have sex with men in Lima, Peru. *BMJ Open* 2015;5:e008552.
 - 42 World Health Organization. Report of a global meeting on yaws eradication surveillance, monitoring and evaluation Geneva, 29–30 January 2018; 2018. <https://www.who.int/publications/i/item/WHO-CDS-NTD-IDM-2018.08> [Accessed 01 Feb 2022].