Appendix 1: Literature Search

A comprehensive literature search was carried out on October 11, 2021, and updated on July 19, 2022. Five databases were searched to look for information on dual treponemal and non-treponemal test in the diagnosis of syphilis and yaws.

1.1 Search methodology

The search strategy was initially developed in Ovid and adapted for the other databases. The search terms were built around overarching terms like "RDT", "point of care test", "treponemal", "non-treponemal", "syphilis" and "yaws"; relevant terms were included as well. The search limits were from 2010 to current. The search strategy was refined with the research team until the results retrieved reflected the scope of the project.

The following database were searched:

1. OvidSP Medline® All, 1946 to July 19, 2022
2. OvidSP Embase Classic + Embase, 1974 to July 19, 2022
3. OvidSP Global Health, 1973 to July 19, 2022
4. EBSCO CINAHL Complete, complete database
5. Web of Science, All Database,
   a) Web of Science Core Collections
   b) *Current Contents Connect*
   c) *BIOSIS Previews*
   d) *CAB Abstracts*
   e) *MEDLINE*
6. Preprints (MedRxiv, bioRxiv, SSRN)

1.2 Search results

Database name	Number of references before removal of duplicates
OvidSP Medline® + Embase + Global Health	530
CINAHL complete	109
Web of Science	111
Total	750

1.3.1 OvidSP Medline® + Embase + Global Health

Database name	Medline, Embase, Global Health
Database platform	OvidSP
Dates of database coverage	1946 to July 19, 2022 1974 to July 19, 2022 1973 to July 19, 2022
Date searched	July 19, 2022
Searched by	YZ
Number of hits	530

#	Query	Results from July 19, 2022
1	exp syphilis/	90772
2	syphilis.mp.	110496
3	exp yaws/	5120
4	yaws.mp.	5625
5	exp Treponema pallidum/	31646
6	treponema*.mp.	50740
7	(non-treponema* or nontreponema*).mp.	1519
8	1 or 2 or 3 or 4	116245
9	5 and 6 or 7	51534
10	8 and 9	36717
11	(RDT or RST).mp.	14403
12	(rapid adj2 diagnos* adj2 test*).mp.	17859
13	(rapid adj2 screening adj2 test*).mp	2717
14	(point-of-care adj3 test*).mp.	38901
15	(point adj1 of adj1 care adj3 test*).mp.	4571
16	11 or 12 or 13 or 14 or 15	66150
17	10 and 16	618
18	Limit 2010 to current	530

1.3.2 EBSCO CINAHL

Database name	CINAHL complete
Database platform	EBSCOhost
Dates of database coverage	2000 to July 19, 2022
Date searched	July 19, 2022
Searched by	YZ
Number of hits	109

#	Query	Results from July 19, 2022
1	TX syphilis OR TX yaws	16,231
2	TX treponema* OR (TX non-treponema* or nontreponema*)	2,348
3	1 AND 2	1,454
4	(TX rapid N2 diagnos* N2 test*) OR (TX rapid N2 screening N2 test*) OR (TX RDT OR TX RST) OR (TX point-of-care N3 test*)	47,143

	OR (TX point N1 of N1 care N3 test*)	
7	3 AND 4	141
8	Limit from 2010 to current	109

1.3.3 Web of Science

Database name	Web of Science All Database
Database platform	Clarivate Web of Science
Dates of database coverage	Complete to July 19, 2022
Date searched	July 19, 2022
Searched by	YZ
Number of hits	111

#	Query	Results from July 19, 2022
1	ALL=(syphilis OR yaws)	47,459
2	(ALL=(treponema*) OR ALL=(non-treponema* OR nontreponema*))	9,951
3	1 AND 2	3,748
4	AB=(rapid NEAR/2 diagnos* NEAR/2 test* OR rapid NEAR/2 screening NEAR/2 test* OR RDT OR RST OR point-of-care NEAR/3 test* OR point NEAR/1 of NEAR/1 care NEAR/3 test*) OR TI= (rapid NEAR/2 diagnos*NEAR/2 test* OR rapid NEAR/2 screening NEAR/2 test* OR RDT OR RST OR point-of-care NEAR/3 test* OR point NEAR/1 of NEAR/1 care NEAR/3 test*) OR TS=(rapid NEAR/2 diagnos* NEAR/2 test* OR rapid NEAR/2 screening NEAR/2 test* OR RDT OR RST OR point-of-care NEAR/3 test* OR point NEAR/1 of NEAR/1 care NEAR/3 test*)	25,687
5	4 AND 3	127
6	Limit from 2010 to current	111

1.3.4 MedRxiv

Database name	MedRvix

Database platform	Science, Nature, The BMJ, The Scientist
Dates of database coverage	Complete to July 19, 2022
Date searched	July 19, 2022
Searched by	YZ
Number of hits	32

#	Query	Results from July 19, 2022
1	Terms & Keywords =(syphilis OR yaws)	326
2	(Terms & Keywords =(treponema*) OR Terms & Keywords =(non-treponema* OR nontreponema*))	57
3	1 AND 2	32

1.3.5 bioRxiv

Database name	bioRvix
Database platform	bioRvix
Dates of database coverage	Complete to July 19, 2022
Date searched	July 19, 2022
Searched by	YZ
Number of hits	71

#	Query	Results from July 19, 2022
1	Terms & Keywords =(syphilis OR yaws)	854
2	(Terms & Keywords =(treponema*) OR Terms & Keywords =(non-treponema* OR nontreponema*))	370
3	1 AND 2	71

1.3.6 SSRN

Database name	SSRN
Database platform	SSRN All
Dates of database coverage	Complete to July 19, 2022
Date searched	July 19, 2022

Searched by	YZ
Number of hits	4

#	Query	Results from July 19, 2022
1	Title, Abstract, Keywords, Authors = syphilis	73
2	1 AND treponema	3
3	1 AND non-treponema	1
4	1 AND non-treponemal	2
5	1 AND nontreponema	0
6	1 AND nontreponemal	1
7	Title, Abstract, Keywords, Authors = yaws	3

Appendix 2: Summary of secondary outcomes

Acceptability

Two studies assessed the stakeholder acceptability of the dual syphilis RDT in the diagnosis of syphilis – one of them was the DPP-RDT and the other was a smartphone dongle Triplex test. The DPP-RDT for the diagnosis of syphilis and yaws was perceived by most healthcare workers (16/20) in a study in the Solomon Islands to be reliable, and this perception was reinforced by concordance with reference laboratory results.[1] The healthcare workers found the DPP-RDT more favourable in comparison to standard testing which may take a week for results to come back.[1] Healthcare workers in Rwanda also reported satisfaction for the smartphone triplex test as they did not have to rely on user interpretation for results. In terms of client acceptability, overall high levels of satisfaction were reported. The vast majority of patients in the Rwandan study (97%) would recommend the Triplex Test to others, mainly due to the rapid turnaround time but also for the simplicity of the test and the ability to diagnose both HIV and syphilis in one test.[2] Almost all patients (98%) also preferred the RDT testing over conventional venepuncture, as generally only one fingerprick was needed and they cited various benefits including that it was less painful, faster than that compared to venepuncture, healthcare workers would have less difficulty in obtaining a blood sample.[2]

Feasibility

The smartphone dongle test was found to be viewed favourably by healthcare workers in terms of feasibility. As it does not require external power to operate, it would be useful in field settings or in the case of power outages in clinics.[2] In general, healthcare workers found the DPP-RDT also improved access to testing in settings where testing at the clinic level was advantageous as distance and cost of getting to hospital were deemed to be barriers to testing.[1]

Usability

Healthcare workers generally found the DPP-RDT to be easy to perform. All healthcare workers in one study in the Solomon Islands reported that familiarity with using the Malaria point-of-care test (POCT) helped them conduct the DPP POCT for syphilis and yaws, although some noted mistakes made with the timing of the test and volume of buffer had the potential to result in testing errors.[1] Only one healthcare worker out of 20, reported that the withdrawal of blood for fingerprick testing was difficult. Four studies assessed and compared digital and visual reading of the DPP-RDT for either syphilis or yaws.[3-6] Three studies suggested there was a high level of concordance with visual and digital results for both treponemal and non-treponemal tests.[3 4 6] However, one study in Botswana suggested that visual reading missed three out of five active syphilis infections, classifying them as past infections, and therefore suggested that the digital reader should be used to avoid missing cases with confirmed high titre non-treponemal test results.[5]

Appropriate treatment following testing

The rationale for using RDTs to better identify active infection is to eliminate lost to follow-up and reduce unnecessary treatment in clients with previously treated syphilis and yaws. In a modelling study using pilot data from three antenatal screening centres, it was discovered that the single treponemal-only test resulted in much more missed instances of syphilis infection and overtreatment in pregnant women than the dual RDT.[7] According to Owusu-Edusei Jr's study, when RPR+TPHA was used to diagnose maternal syphilis, treatment rates declined from 100% to 67%, indicating that a large proportion of clients were loss to follow-up due to delay with the provision of test results.[8] This lost to follow-up is concerning since these

untreated mothers are at an elevated risk of congenital syphilis and adverse birth outcomes. In another study conducted on pregnant women in Burkina Faso, of the women with RPR titres ≥ 1:8, 16% would not be treated if they were only screened with the DPP-RDT compared to the treponemal-only rapid test.[9] There was an unexpectedly high proportion of pregnant women who were found to be treponemal and non-treponemal positive based on reference tests (37.6%). A high proportion had high level RPR titres ≥ 1:8 (19%), suggesting they had either been incompletely treated for untreated bejel (an endemic treponematosis), or untreated active syphilis. The study highlighted the importance of establishing baseline treponemal/non-treponemal seroprevalence in any population when identifying the most effective strategy to screen and treat for treponemal diseases.

Thus, the utility of this test will depend on the proportion of people treated for syphilis and background prevalence of syphilis. As the first syphilis infection can be detected using the cheaper single treponemal-only test, the value of the DPP-RDT is to identify individuals with syphilis or yaws with confirmed high-titre non-treponemal tests. Moreover, Yin reported that the single-treponemal test will result in overtreatment and counselling, particularly in populations with high prevalence of syphilis such as MSM.[6]

In a study on diagnosis of yaws, Avoye advocated for the use of the DPP-RDT before mass treatment to identify clients with active yaws and during resurvey to support detecting new active cases.[3] Clients who were tested dually positive were given immediate treatment, and those who tested negative but had lesions were given syndromic treatment and followed up further.[3] The use of DPP-RDT would potentially reduce overtreatment in mass treatment compared to the standard single-treponemal rapid test, making it a suitable tool to support diagnosis in the renewed eradication effort for yaws-endemic countries.

Cost-effectiveness

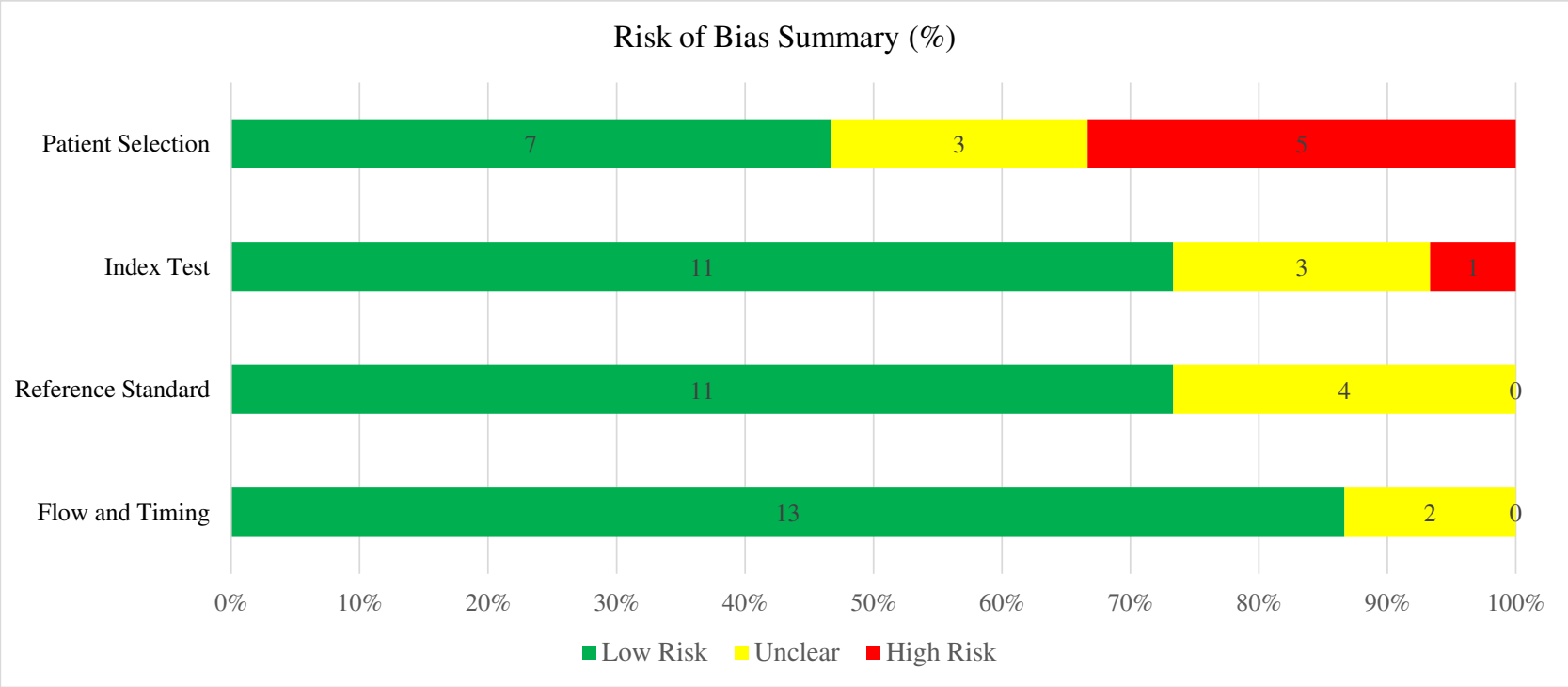
In a modelling study where several antenatal syphilis screening and treatment strategies were compared, the incremental cost-effectiveness ratio (ICER) of the clinical RPR approach (ICER: US$23–138 per DALY averted) was dominated by the single treponemal-only rapid test (ICER: US$16–53 per DALY averted), the dual treponemal–nontreponemal RDT (ICER: US$18–76 per DALY averted) and the sequential approach (single rapid test followed by dual RDT) (ICER: US$19–62 per DALY averted).[7] Although the dual RDT detected more true cases of syphilis and reduced overtreatment compared to the other three strategies, the cost of per woman screened with the dual RDT was highest, with the exception of Peru where labour cost for RPR testing was high. Further univariate sensitivity analysis showed that the cost of the dual test kit had to be reduced by approximately 38% from the assumed baseline unit price of US$2.50 to achieve the same cost per DALY averted as the treponemal-only rapid test [7]. Even though the single treponemal-only rapid test was most cost-effective among the four strategies, it may lead to overtreatment.[7]

Yet, in another cost-effectiveness study on yaws, the sequential screening strategy (single rapid test followed by dual RDT) versus was concluded to be more cost-effective than the dual RDT for both individual diagnosis and community surveillance of yaws.[10]

Despite the fact that the dual RDT is more expensive than the single rapid test and RPR (excluding labor costs), Owusu-Edusei Jr discovered that test performance had a significant impact on the cost-effectiveness of antenatal syphilis screening.[8] The greatest cost savings occurred when the sensitivity of the dual RDT was increased to 0.97 and this conclusion held

true when the unit price was varied from US$0.50 to $5.00, indicating that test performance has a bigger impact on cost-effectiveness than the RDT's price.[8]

Supplementary Figure 1. Risk of bias summary as percentage



Supplementary Table 1. Risk of bias of studies included for meta-analysis

	RISK OF BIAS				APPLICABILITY CONCERNS		
STUDY	**PATIENT SELECTION**	**INDEX TEST**	**REFERENCE STANDARD**	**FLOW AND TIMING**	**PATIENT SELECTION**	**INDEX TEST**	**REFERENCE STANDARD**
Ayove (2014)[3]	−	+	+	+	−	+	+
Castro (2010)[11]	−	?	+	+	−	+	+
Castro (2010)[12]	+	+	+	+	+	+	+
Castro (2014)[13]	−	?	?	?	−	+	+
Causer (2015)[14]	+	+	+	+	+	+	+
Constantine (2017)[4]	+	+	+	+	+	+	+
Guinard (2013)[15]	?	+	+	+	?	+	+
Hess (2014)[16]	+	+	+	+	+	+	+
Langendorf (2019)[9]	+	+	+	+	+	+	+
Marks (2014)[17]	+	+	+	+	+	+	+
Pham (2020)[18]	−	−	+	+	−	+	+
Pham (2019)[19]	?	?	?	?	?	?	+
Skinner (2015)[20]	?	+	+	+	?	+	+
Yin (2013)[6]	−	+	?	+	−	+	+
Zorzi (2017)[21]	+	+	?	+	+	+	+

+ Low risk − High Risk ? Unclear Risk

N.B. Quality assessment was not conducted for the two unpublished papers (Aziz et al. and Taleo et al.).

Supplementary Table 2. A) Summary of findings for treponemal test component for syphilis; B) Summary of findings for nontreponemal test component for syphilis, C) Summary of findings for treponemal test component for yaws; D) Summary of findings for nontreponemal test component for yaws

A)

T1 Sensitivity	0.93 (95% CI: 0.86 to 0.97)
T1 Specificity	0.98 (95% CI: 0.96 to 0.99)

Prevalence	0%	10%	20%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 0%	pre-test probability of 10%	pre-test probability of 20%	
True positives (patients with syphilis)	11 studies 4695 patients	cross-sectional	not serious [a,b,c,d]	not serious	serious [e]	not serious	none	0 (0 to 0)	93 (86 to 97)	186 (172 to 194)	⊕⊕⊕◯ MODERATE
False negatives (patients incorrectly classified as not having syphilis)								0 (0 to 0)	7 (4 to 13)	14 (8 to 26)	
True negatives (patients without syphilis)	11 studies 4762 patients	cross-sectional	not serious [a,b,c,d]	not serious	serious [e]	not serious	none	983 (964 to 992)	884 (868 to 893)	786 (771 to 794)	⊕⊕⊕◯ MODERATE
False positives (patients incorrectly classified as having syphilis)								17 (8 to 36)	15 (7 to 32)	14 (6 to 29)	

Explanations

a. Most studies had low risk of patient selection bias[4 9 12 14 16 21] and was scored "low" for risk of bias using the QUADAS checklist in the patient selection criterion. Two studies [15 20] were unclear in their description of random sampling of patients. Three studies[6 11 13] were at

high risk of bias in patient selection, as samples were not selected at random[11 13], or subjects deemed at higher risk for syphilis were oversampled.[6]

b. All the studies had low potential of index test bias except two unclear studies.[11 13] In one study, all the patient identifiers were removed before receipt at the CDC but it did not specify if the assay was performed blinded to the results.[11]
c. All the studies had low potential of reference test bias except three studies which were unclear.[6 13 21]
d. All the studies had low potential for flow and timing bias,[4 6 9 11 12 14-16 20 21] except one. Castro[13] did not present a clear description of the patient flow.
e. There is considerable heterogeneity (p< 0.001), I^2= 96.9% and 94.7% for sensitivity and specificity, respectively, with some overlap in confidence intervals

B)

T2 Sensitivity	0.90 (95% CI: 0.82 to 0.95)
T2 Specificity	0.97 (95% CI: 0.92 to 0.99)

Prevalence	0%	10%	20%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 0%	pre-test probability of 10%	pre-test probability of 20%	
True positives (patients with syphilis)	13 studies [a] 3699 patients	cross-sectional	not serious [b,c,d,e]	not serious	serious [f]	not serious	none	0 (0 to 0)	90 (82 to 95)	180 (164 to 190)	⊕⊕⊕◯ MODERATE
False negatives (patients incorrectly classified as not having syphilis)								0 (0 to 0)	10 (5 to 18)	20 (10 to 36)	
True negatives (patients without syphilis)	13 studies [a] 6619 patients	cross-sectional	not serious	not serious	serious [f]	not serious	none	974 (920 to 992)	876 (828 to 893)	779 (735 to 794)	⊕⊕⊕◯

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 0%	pre-test probability of 10%	pre-test probability of 20%	
False positives (patients incorrectly classified as having syphilis)			b,c,d,e					26 (8 to 80)	23 (7 to 72)	21 (6 to 64)	MODERATE

Explanations

a. There were 2 additional studies for the nontreponemal component.[18 19]
b. Most studies had low risk of patient selection bias[4 9 12 16 21] and was scored "low" for risk of bias using the QUADAS checklist in the patient selection criterion. Four studies[13 15 19 20] were unclear in their description of random sampling of patients. Four studies[6 11 13 18] were at high risk of bias in patient selection, as samples were not selected at random[11 13 18], or subjects deemed at higher risk for syphilis were oversampled.[6]
c. Most of the studies had low potential of index test bias except three unclear studies.[11 13 19] In one study, all the patient identifiers were removed before receipt at the CDC but it did not specify if the assay was performed blinded to the results.[11] Pham[18] had high risk of bias.
d. Four studies had unclear risk of bias for reference standard.[6 13 19 21]
e. All the studies had low potential for flow and timing bias,[4 6 9 11 12 14-16 20 21] except two. Two studies[13 19] did not present a clear description of the patient flow.
f. There is heterogeneity observed in the studies, I^2= 98.3% and 99.3% for sensitivity and specificity, respectively, with some overlap in confidence intervals.

C)

T1 Sensitivity	0.86 (95% CI: 0.66 to 0.95)
T1 Specificity	0.97 (95% CI: 0.94 to 0.99)

Prevalence	0%	10%	20%

Outcome	№ of studies (№	Study design	Factors that may decrease certainty of evidence	Effect per 1,000 patients tested	Test accuracy

	of patients)		Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 0%	pre-test probability of 10%	pre-test probability of 20%	CoE
True positives (patients with yaws)	4 studies [a] 716 patients	cross-sectional	not serious [b,c]	not serious	serious [d]	not serious	none	0 (0 to 0)	86 (66 to 95)	171 (132 to 190)	⊕⊕⊕◯ MODERATE
False negatives (patients incorrectly classified as not having yaws)								0 (0 to 0)	14 (5 to 34)	29 (10 to 68)	
True negatives (patients without yaws)	4 studies [a] 895 patients	cross-sectional	not serious [b,c]	not serious	serious [d]	not serious	none	969 (935 to 985)	872 (841 to 886)	775 (748 to 788)	⊕⊕⊕◯ MODERATE
False positives (patients incorrectly classified as having yaws)								31 (15 to 65)	28 (14 to 59)	25 (12 to 52)	

Explanations

a. Of the 4 studies, there were 2 unpublished studies where assessment of certainty of evidence was not possible.
b. One study[17] was at low risk of bias for patient selection, while another study[3] presented high risk of bias as it was a community-based survey and no comment on randomisation or further detail on recruitment was reported.
c. Both studies[3 17] reported low risk of bias for index test, reference standard and patient flow and timing.
d. There is some heterogeneity observed in the studies for sensitivity (I^2= 96.4%, p<0.001) and specificity (I^2= 84.2%, p< 0.001).

D)

T2 Sensitivity	0.80 (95% CI: 0.55 to 0.93)
T2 Specificity	0.96 (95% CI: 0.92 to 0.98)

Prevalence	0%	10%	20%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 0%	pre-test probability of 10%	pre-test probability of 20%	
True positives (patients with yaws)	4 studies [a] 597 patients	cross-sectional	not serious [b,c]	not serious	serious [d]	not serious	none	0 (0 to 0)	80 (55 to 93)	160 (110 to 186)	⊕⊕⊕◯ MODERATE
False negatives (patients incorrectly classified as not having yaws)								0 (0 to 0)	20 (7 to 45)	40 (14 to 90)	
True negatives (patients without yaws)	4 studies [a] 1015 patients	cross-sectional	not serious [b,c]	not serious	serious [d]	not serious	none	963 (920 to 983)	867 (828 to 885)	770 (736 to 786)	⊕⊕⊕◯ MODERATE
False positives (patients incorrectly classified as having yaws)								37 (17 to 80)	33 (15 to 72)	30 (14 to 64)	

Explanations

a. Of the 4 studies, there were 2 unpublished studies where assessment of certainty of evidence was not possible.
b. One study[17] was at low risk of bias for patient selection, while another study[3] presented high risk of bias as it was a community-based survey and no comment on randomisation or further detail on recruitment was reported.
c. Both studies[3 17] reported low risk of bias for index test, reference standard and patient flow and timing.
d. There is some heterogeneity observed in the studies for sensitivity (I^2= 97.8%, p<0.001) and little heterogeneity for specificity (I^2= 88.5%, p<0.001).

Supplementary Table 3. A) Meta-regression of treponemal test component for syphilis; B) Meta-regression of nontreponemal test component for syphilis

A)

Variable	Number of studies	Univariate				Multivariable		Joint model	
		Sensitivity	p-value	Specificity	p-value	Sensitivity	Specificity	I^2 (95% CI)	p-value
Study setting								87 (74 - 100)	< 0.001
General Practice/Clinic	5	0.91 (0.82 - 1.00)	0.22	0.98 (0.95 - 1.00)	0.59	0.91 (0.82 - 1.00)	0.98 (0.97 - 1.00)		
Laboratory	5	0.95 (0.89 - 1.00)	1.00	0.98 (0.97 - 1.00)	0.14	0.95 (0.89 - 1.00)	0.98 (0.95 - 1.00)		
Field/Non-clinical facility	0	NA		NA		NA	NA		
Sample type								70 (34 - 100)	0.03
Serum	5	0.96 (0.93 - 1.00)	0.83	0.96 (0.93 - 0.99)	<0.001	0.96 (0.93 - 1.00)	0.96 (0.93 - 0.99)		
Finger-prick	1	NA*		NA*		NA*	NA*		
Whole blood	5	0.88 (0.79 - 0.97)	<0.001	0.99 (0.98 - 1.00)	0.47	0.88 (0.79 - 0.97)	0.99 (0.98 - 1.00)		
Plasma	0	NA		NA		NA	NA		
RDT reading method								60 (9 - 100)	0.08
Human eye	9	0.92 (0.87 - 0.98)	0.56	0.98 (0.96 - 0.99)	<0.001	0.92 (0.87 - 0.98)	0.98 (0.96 - 0.99)		
Digital reader	2	0.95 (0.86 - 1.00)	0.83	0.99 (0.99 - 1.00)	0.56	0.95 (0.86 - 1.00)	0.99 (0.99 - 1.00)		

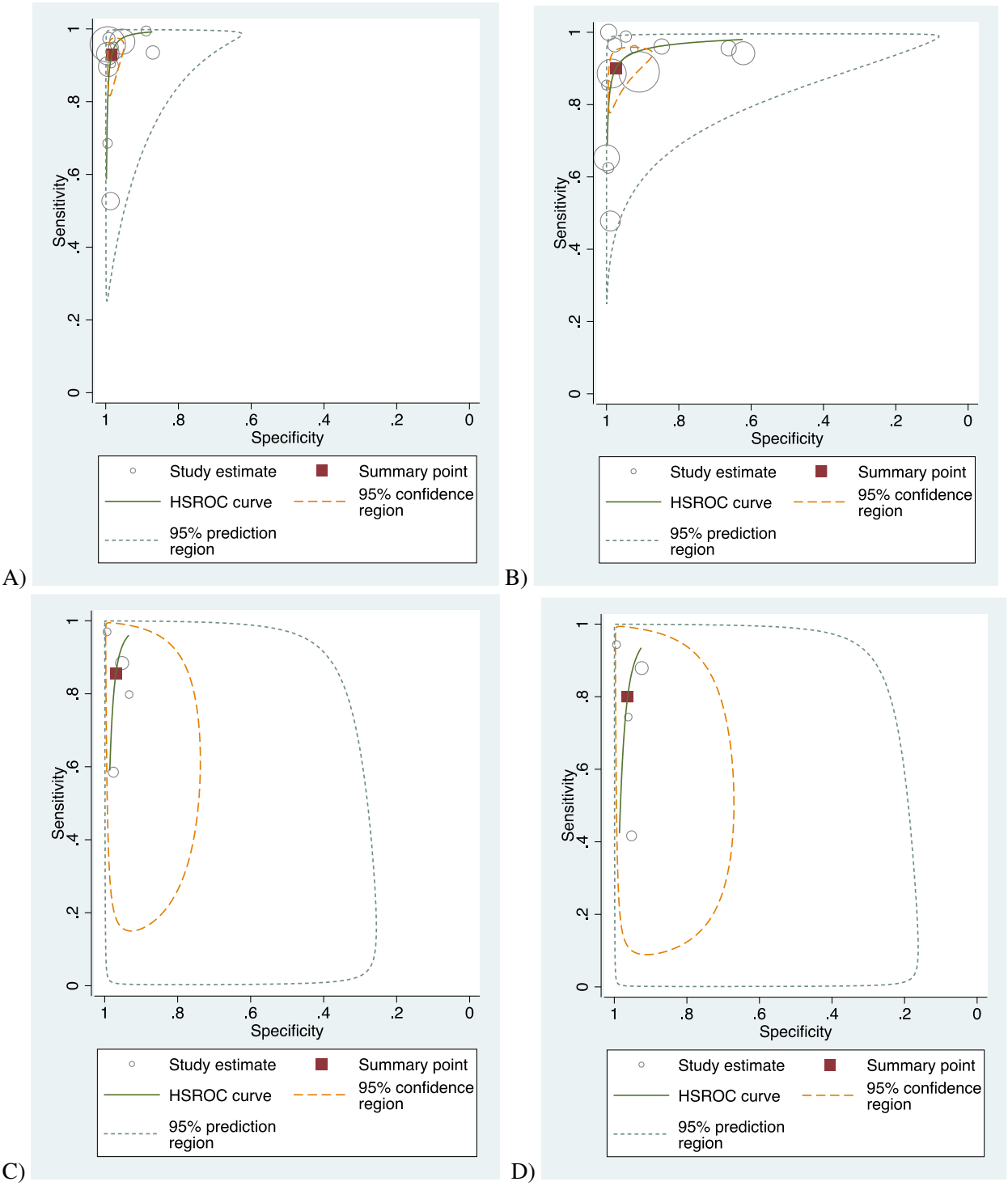
Abbreviations: EIA= enzyme immunoassay, TPHA= *Treponema pallidum* hemagglutination, TPPA= *Treponema pallidum* passive particle agglutination assay
* fingerprick combined with whole blood, TPHA combined with TPPA

B)

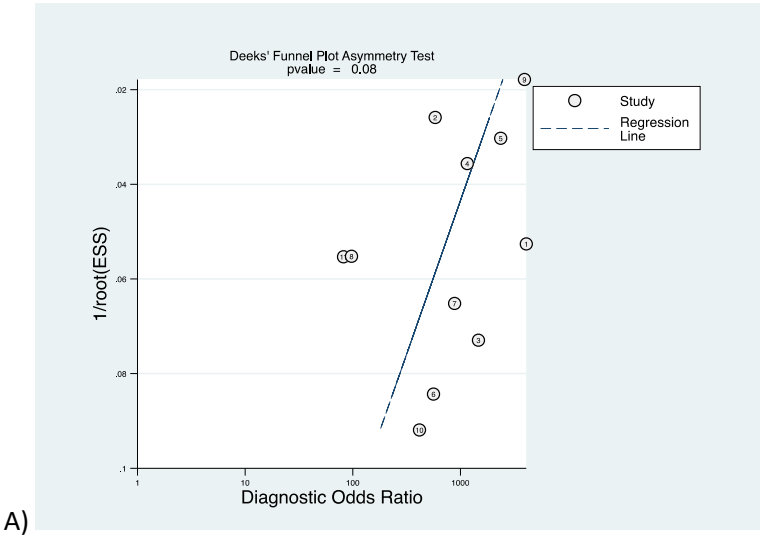
Variable	Number of studies	Univariate				Multivariable		Joint model	
		Sensitivity	p-value	Specificity	p-value	Sensitivity	Specificity	I^2 (95% CI)	p-value
Brand of RDT								0 (0 - 100)	0.74
DPP	11	0.89 (0.83 - 0.96)	0.55	0.98 (0.94 - 1.00)	0.12	0.89 (0.83 - 0.96)	0.98 (0.94 - 1.00)		
Burnet's	2	0.95 (0.85 - 1.00)	0.37	0.97 (0.88 - 1.00)	0.25	0.95 (0.85 - 1.00)	0.97 (0.88 - 1.00)		
Study setting								92 (85 - 99)	< 0.001
General Practice/Clinic	6	0.85 (0.72 - 0.98)	0.05	0.99 (0.97 - 1.00)	0.18	0.85 (0.72 - 0.98)	0.99 (0.97 - 1.00)		
Laboratory	6	0.93 (0.86 - 0.99)	0.94	0.97 (0.92 - 1.00)	0.56	0.93 (0.86 - 0.99)	0.97 (0.92 - 1.00)		
Field/ non-clinical facility	0					NA	NA		
Sample type								64 (20 - 100)	0.05
Serum	5	0.95 (0.92 - 0.99)	0.94	0.92 (0.79 - 1.00)	0.09	0.95 (0.92 - 0.99)	0.92 (0.79 - 1.00)		
Finger-prick	1	NA*		NA*		NA*	NA*		
Whole blood	7	0.83 (0.74 - 0.93)	<0.001	0.99 (0.97 - 1.00)	0.03	0.83 (0.74 - 0.93)	0.99 (0.97 - 1.00)		
Plasma	0	NA		NA		NA	NA		
RDT reading method								0 (0 - 100)	0.48
Human eye	11	0.92 (0.86 - 0.97)	0.48	0.97 (0.93 - 1.00)	0.64	0.92 (0.86 - 0.97)	0.97 (0.93 - 1.00)		
Digital reader	2	0.80 (0.56 - 1.00)	0.13	0.99 (0.97 - 1.00)	<0.001	0.80 (0.56 - 1.00)	0.99 (0.97 - 1.00)		

Abbreviations: RPR= rapid plasma reagin, TRUST= toluidine red unheated serum test
* fingerprick combined with whole blood

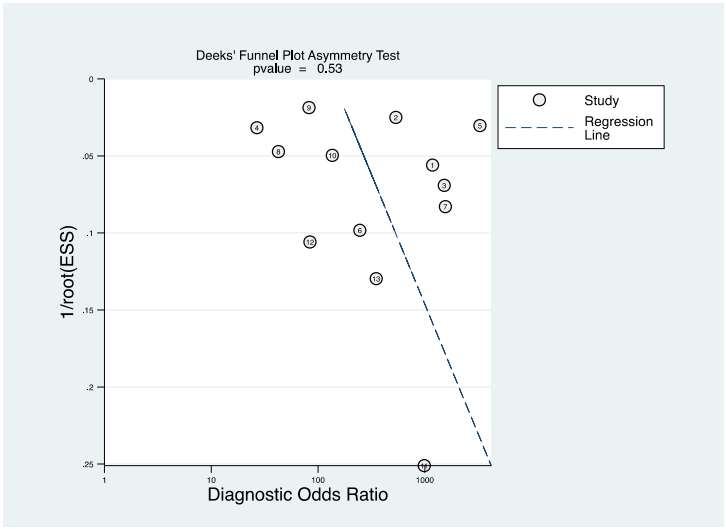
Supplementary Figure 2. A) Hierarchical summary receiver operating characteristic (HSROC) plot for treponemal test component for syphilis; B) HSROC plot for nontreponemal test component for syphilis; C) HSROC plot for treponemal test component for yaws; D) HSROC plot for nontreponemal test component for yaws



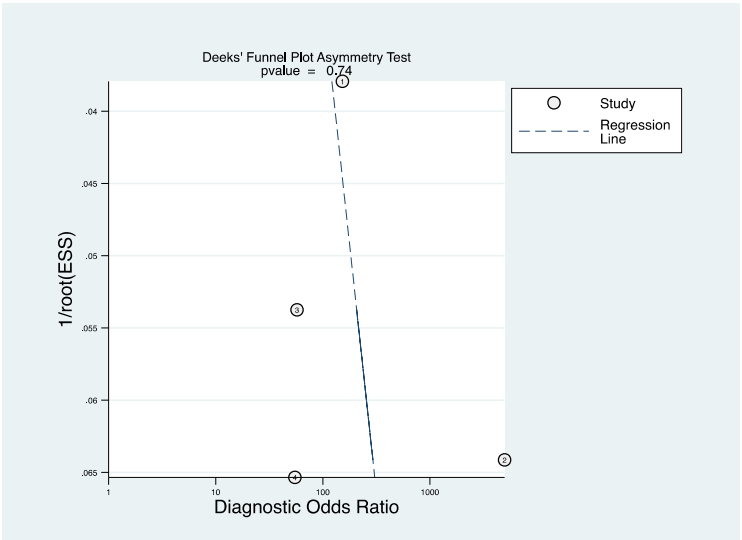
Supplementary Figure 3. A) Deeks' plot for treponemal test component for syphilis; B) Deeks' plot for nontreponemal test component for syphilis; C) Deeks' plot for treponemal test component for yaws; D) Deeks' plot for nontreponemal test component for yaws



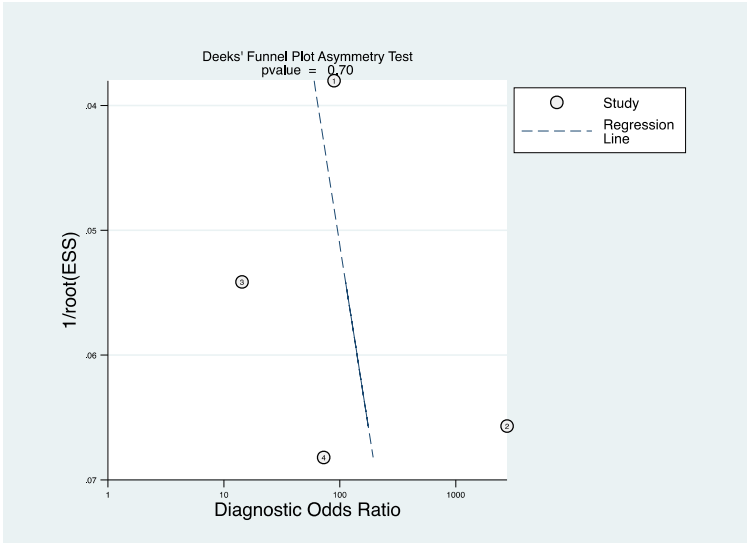
A)



B)



C)



D)

Supplementary Table 4. A) The positive predictive value (PPV) and negative predictive value (NPV) for treponemal component of syphilis, over a range of background prevalence of syphilis; B) PPV and NPV for nontreponemal component of syphilis, over a range of background prevalence of syphilis; C) PPV and NPV for treponemal component of yaws, over a range of background prevalence of yaws; D) PPV and NPV for nontreponemal component of yaws, over a range of background prevalence of yaws

A)

Prevalence	Sensitivity	Specificity	PPV	NPV	Number of cases	Missed cases	False Positive (Overtreated)
0.05	0.930	0.983	0.742	0.996	50	4	16
0.1	0.930	0.983	0.859	0.992	100	7	15
0.15	0.930	0.983	0.906	0.988	150	11	14
0.2	0.930	0.983	0.932	0.983	200	14	14
0.25	0.930	0.983	0.948	0.977	250	18	13
0.3	0.930	0.983	0.959	0.970	300	21	12
0.35	0.930	0.983	0.967	0.963	350	25	11
0.4	0.930	0.983	0.973	0.955	400	28	10
0.45	0.930	0.983	0.978	0.945	450	32	9
0.5	0.930	0.983	0.982	0.934	500	35	9
0.55	0.930	0.983	0.985	0.920	550	39	8
0.6	0.930	0.983	0.988	0.903	600	42	7
0.65	0.930	0.983	0.990	0.883	650	46	6
0.7	0.930	0.983	0.992	0.858	700	49	5
0.75	0.930	0.983	0.994	0.824	750	53	4
0.8	0.930	0.983	0.995	0.778	800	56	3
0.85	0.930	0.983	0.997	0.712	850	60	3
0.9	0.930	0.983	0.998	0.609	900	63	2
0.95	0.930	0.983	0.999	0.425	950	67	1
1	0.930	0.983	1.000	0.000	1000	70	0

B)

Prevalence	Sensitivity	Specificity	PPV	NPV	Number of cases	Missed cases	False Positive (Overtreated)
0.05	0.900	0.974	0.646	0.995	50	5	25
0.1	0.900	0.974	0.794	0.989	100	10	23
0.15	0.900	0.974	0.859	0.982	150	15	22

0.2	0.900	0.974	0.896	0.975	200	20	21
0.25	0.900	0.974	0.920	0.967	250	25	20
0.3	0.900	0.974	0.937	0.958	300	30	18
0.35	0.900	0.974	0.949	0.948	350	35	17
0.4	0.900	0.974	0.958	0.936	400	40	16
0.45	0.900	0.974	0.966	0.923	450	45	14
0.5	0.900	0.974	0.972	0.907	500	50	13
0.55	0.900	0.974	0.977	0.889	550	55	12
0.6	0.900	0.974	0.981	0.867	600	60	10
0.65	0.900	0.974	0.985	0.840	650	65	9
0.7	0.900	0.974	0.988	0.807	700	70	8
0.75	0.900	0.974	0.990	0.765	750	75	7
0.8	0.900	0.974	0.993	0.709	800	80	5
0.85	0.900	0.974	0.995	0.632	850	85	4
0.9	0.900	0.974	0.997	0.520	900	90	3
0.95	0.900	0.974	0.998	0.339	950	95	1
1	0.900	0.974	1.000	0.000	1000	100	0

C)

Prevalence	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Number of cases**	**Missed cases**	**False Positive (Overtreated)**
0.05	0.856	0.969	0.592	0.992	50	7	29
0.1	0.856	0.969	0.754	0.984	100	14	28
0.15	0.856	0.969	0.830	0.974	150	22	26
0.2	0.856	0.969	0.873	0.964	200	29	25
0.25	0.856	0.969	0.902	0.953	250	36	23
0.3	0.856	0.969	0.922	0.940	300	43	22
0.35	0.856	0.969	0.937	0.926	350	50	20
0.4	0.856	0.969	0.948	0.910	400	58	19
0.45	0.856	0.969	0.958	0.892	450	65	17
0.5	0.856	0.969	0.965	0.871	500	72	16
0.55	0.856	0.969	0.971	0.846	550	79	14
0.6	0.856	0.969	0.976	0.818	600	86	12
0.65	0.856	0.969	0.981	0.784	650	94	11
0.7	0.856	0.969	0.985	0.743	700	101	9
0.75	0.856	0.969	0.988	0.692	750	108	8

0.8	0.856	0.969	0.991	0.627	800	115	6
0.85	0.856	0.969	0.994	0.543	850	122	5
0.9	0.856	0.969	0.996	0.428	900	130	3
0.95	0.856	0.969	0.998	0.262	950	137	2
1	0.856	0.969	1.000	0.000	1000	144	0

D)

Prevalence	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Number of cases**	**Missed cases**	**False Positive (Overtreated)**
0.05	0.800	0.963	0.532	0.989	50	10	35
0.1	0.800	0.963	0.706	0.977	100	20	33
0.15	0.800	0.963	0.792	0.965	150	30	31
0.2	0.800	0.963	0.844	0.951	200	40	30
0.25	0.800	0.963	0.878	0.935	250	50	28
0.3	0.800	0.963	0.903	0.918	300	60	26
0.35	0.800	0.963	0.921	0.899	350	70	24
0.4	0.800	0.963	0.935	0.878	400	80	22
0.45	0.800	0.963	0.946	0.855	450	90	20
0.5	0.800	0.963	0.956	0.828	500	100	19
0.55	0.800	0.963	0.964	0.798	550	110	17
0.6	0.800	0.963	0.970	0.762	600	120	15
0.65	0.800	0.963	0.976	0.722	650	130	13
0.7	0.800	0.963	0.981	0.674	700	140	11
0.75	0.800	0.963	0.985	0.616	750	150	9
0.8	0.800	0.963	0.989	0.546	800	160	7
0.85	0.800	0.963	0.992	0.459	850	170	6
0.9	0.800	0.963	0.995	0.349	900	180	4
0.95	0.800	0.963	0.998	0.202	950	190	2
1	0.800	0.963	1.000	0.000	1000	200	0

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