Southern African HIV Clinicians Society

3rd Biennial Conference

13 - 16 April 2016
Sandton Convention Centre
Johannesburg

Our Issues, Our Drugs, Our Patients

www.sahivsoc.org
www.sahivsoc2016.co.za

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

Rapid Point-of-Care Tests for Syphilis

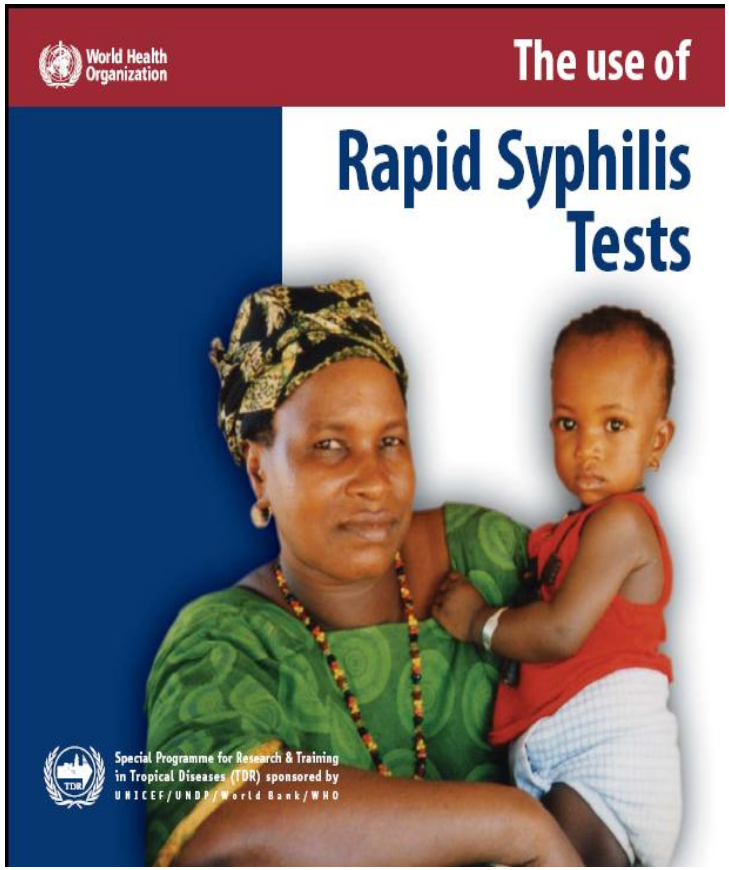
Ranmini Kularatne
MBChB, FCPath (SA)

Centre for HIV and STIs
National Institute for Communicable Diseases
National Health Laboratory Service
South Africa

WHO Criteria for POCT: ASSURED

- A - Affordable
- S - Sensitive
- S - Specific
- U - User-friendly
- R - Rapid & Robust
- E - Equipment-free
- D - Deliverable to end-users

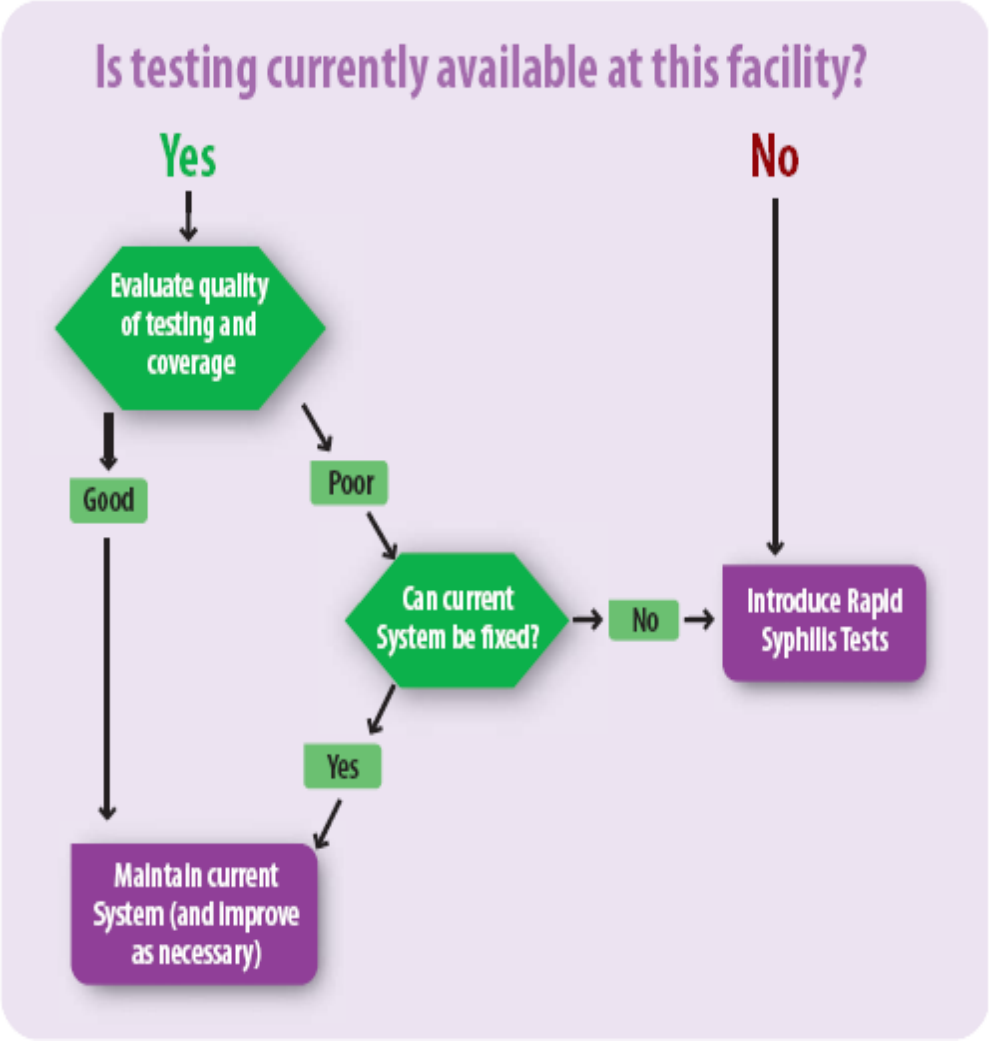
WHO guidance for introducing rapid syphilis POCTs



“ Countries that have already established effective syphilis control programmes, including screening for antenatal and high risk populations, may prefer to maintain their program rather than introduce rapid tests.

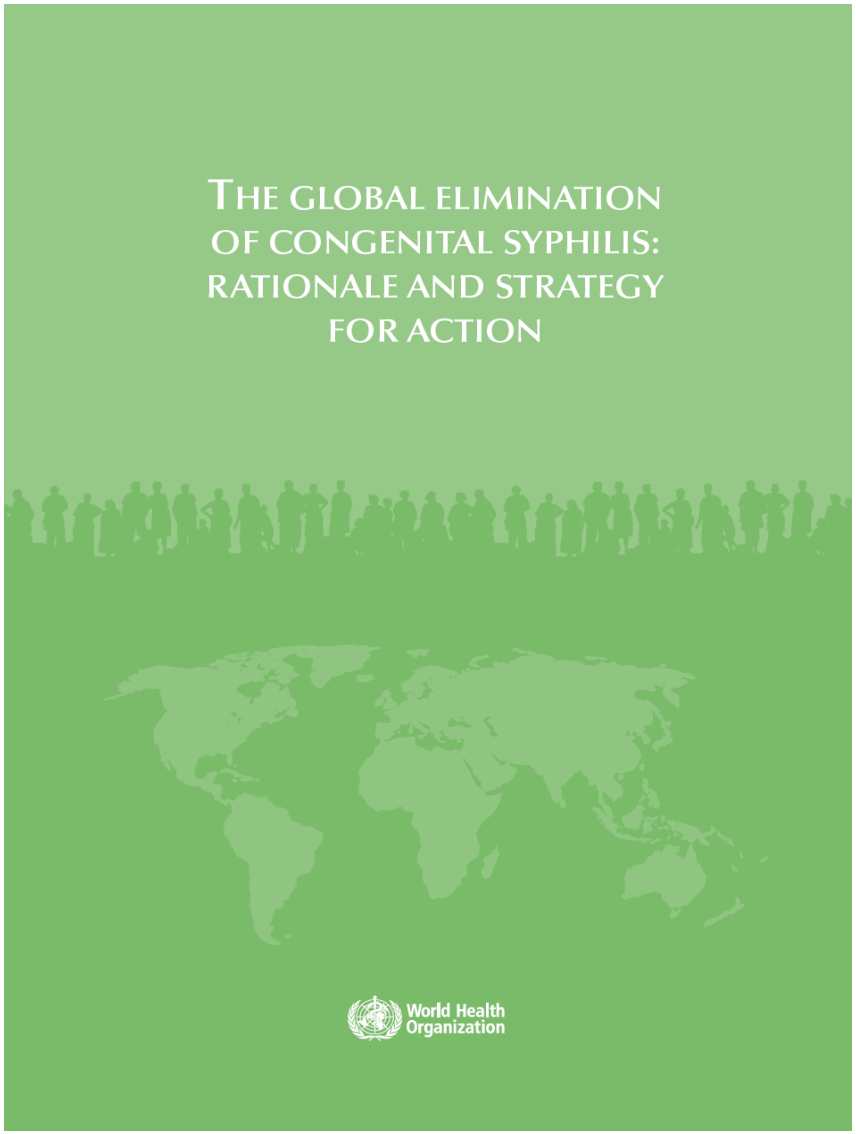
This decision to move to rapid test should be based on a careful assessment of the quality, coverage and efficacy of the current programme.”

WHO recommended process for implementing syphilis POCTs



Points to consider	Comments
Access	What is the % of pregnant or high risk individuals with access to testing?
Quality of testing	What is the quality of existing testing? Is there an on-going QA programme to monitor and ensure accurate results?
Treatment of sero-reactive cases	What % receive their test results and receive treatment in a timely manner?
Rapid tests	Will introducing rapid testing help improve coverage and programme efficacy?

Elimination of Congenital Syphilis



- Universal screening at ante-natal clinics.
  - Integration of syphilis testing into HIV PMTCT programs
- Rapid/ easily accessible diagnostic tests that reduce treatment delay.
- Effective surveillance and monitoring for congenital syphilis: standardised case definition + effective notification.

Overview of syphilis serological tests

	Specific Treponemal Tests	Non-specific Treponemal Tests
Types of Laboratory assays	TPHA, TPPA, EIA, CLIA, FTA	RPR, VDRL
Performance characteristics (Sensitivity)	70-90% in primary syphilis 90-100% in latent syphilis	70 – 80% in primary syphilis 70-100% in latent syphilis
Become negative after treatment?	No	Yes (upto 25% remain serofast)
Measure disease activity?	No	Yes (fourfold decline in titre in 6 months – 1 year)
False positivity in pregnancy?	Extremely rare	Can occur
Types of Rapid POCTs	Determine Syphilis TP Trinity Health Check VisiTect Syphilis SD Bioline Syphilis	Chembio DPP Syphilis Screen & Confirm

Types of rapid syphilis POCTs

Treponemal

Treponemal/ Non-Treponemal

Interpreting results of syphilis POCTs

- Reading of results

- Time to reading of results

  - **Chembio DPP**: read result 10-15 mins after addition of buffer; DO NOT read result after 20 mins from addition of buffer to well 1.

  - **VisiTect Syphilis**: negative results must be confirmed only at the end of 30 minutes.

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 February 2013 | Volume 8 | Issue 2 | e54695

- 33 studies: 19 (58%) evaluated POCT using whole blood
  - STI Clinic patients; female sex workers; antenatal clinic attendees; blood bank
  - *Treponema pallidum* specific reference standard used on serum

Sample	Determine TP (Abbott Diagnostics, UK)		SD Bioline (Standard Diagnostics, Korea)		SyphiCheck WB (QualPro Diagnostics, India)		VisiTect (Omega Diagnostics, UK)	
	Sensitivity (95% CrI)	Specificity (95% CrI)	**Sensitivity (95% CrI)**	Specificity (95% CrI)	**Sensitivity (95% CrI)**	Specificity (95% CrI)	**Sensitivity (95% CrI)**	Specificity (95% CrI
Serum	**90%** (80.4, 95.2)	94.1% (89.3, 97.7)	**87.1%** (75.7, 94.5)	95.8% (89.9. 99.5)	**74.5%** (56.8, 88.4)	99.1% (96.4, 100)	**85.1%** (72.8, 92.6)	96.5% (91.9, 99.3)
Whole blood	**86.3%** (77.3, 91.7)	95.8% (92.4, 97.7)	**84.5%** (78.8, 92.6)	97.9% (92.5, 99.3)	**74.5%** (63.9, 82.1)	99.6% (98.9. 99.9)	**74.3%** (53.6, 83.7)	99.4% (98.2, 99.9)

CrI = Credible Interval

SA Epidemiology: RPR Seropositivity among ante-natal care attendees

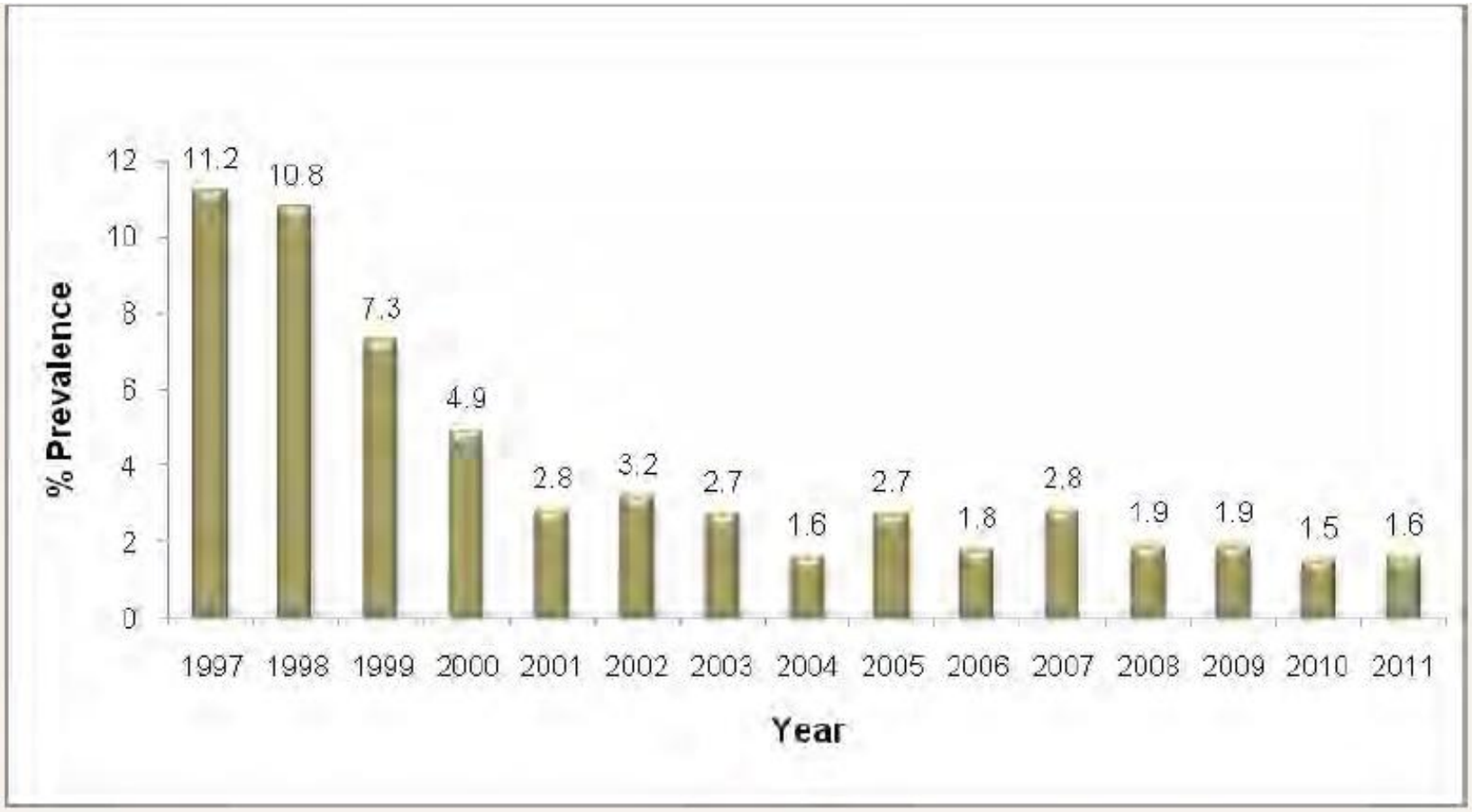
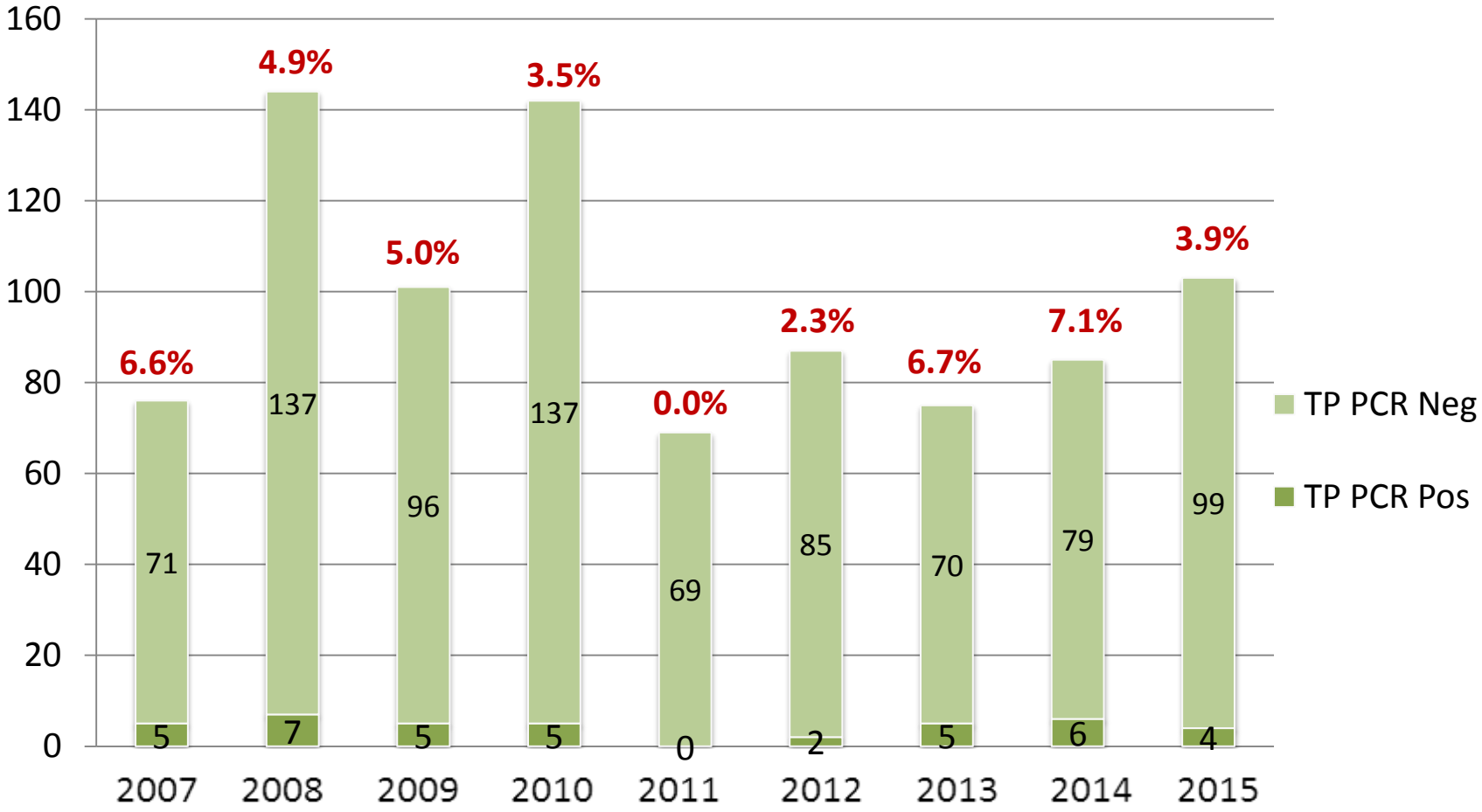


Figure 54: National syphilis prevalence trends among antenatal women, South Africa, 1997 to 2011.

- **Source: Department of Health Annual HIV & Syphilis Antenatal Survey**

SA Epidemiology: *Treponema pallidum* PCR positivity in genital ulcer disease

Gauteng 2007 -2015



SA Epidemiology: over-treatment with use of specific treponemal serology as sole diagnostic test

STI aetiological surveillance data: 1,760 women presenting with VDS to Alexandra Health Centre (2007 – 2014)

Year	TPPA Pos RPR Pos	TPPA Pos RPR Neg	TPPA Neg RPR Pos	TPPA Neg RPR Neg	Total
2007	13 (6.6%)	25 (12.7%)	2 (1.0%)	157 (79.7%)	197
2008	2 (0.7%)	48 (15.8%)	1 (0.3%)	253 (83.2%)	304
2009	5 (2.4%)	30 (14.5%)	0 (0.0%)	172 (83.1%)	207
2010	1 (0.7%)	21 (14.9%)	3 (2.1%)	116 (82.3%)	141
2011	4 (1.3%)	33 (10.9%)	3 (1.0%)	263 (86.8%)	303
2012	11 (5.3%)	14 (6.7%)	1 (0.5%)	182 (87.5%)	208
2013	6 (3.0%)	17 (8.5%)	0 (0.0%)	176 (88.4%)	199
2014	7 (3.5%)	12 (6.0%)	1 (0.5%)	181 (90.0%)	201
Total	49 (2.8%)	200 (11.4%)	11 (0.6%)	1500 (85.2%)	1760

SA Epidemiology: over-treatment with use of specific treponemal serology as sole diagnostic test

Do Women With Persistently Negative Nontreponemal Test Results Transmit Syphilis During Pregnancy?

Sexually Transmitted Diseases • Volume 40, Number 4, April 2013

- Review of congenital syphilis cases reported to CDC between 1991-2009 (n= 23,843)

- Conclusion: " We found no convincing evidence of syphilis transmission from mothers with persistently negative nontreponemal results."

Probable active syphilis:

- Sero-reactivity in BOTH non-treponemal and treponemal tests.
- Used as reporting measure by WHO.

Clinic v laboratory performance of syphilis POCTs

Utility of the Determine Syphilis TP rapid test in commercial sex venues in Peru

Sex Transm Infect 2006;82(Suppl V):v22–v25.

	Gold standard					
	Serum RPR reactive and TPHA positive		Serum RPR ≥1:8 and TPHA positive		Serum RPR ≥1:16 and TPHA positive	
	Yes	No	Yes	No	Yes	No
Determine positive in whole blood	70	28	16	82	7	91
Determine negative in whole blood	108	3277	9	3376	3	3382
Total	178	3305	25	3458	10	3473
Sensitivity	39.3%		64.0%		70.0%	
Specificity	99.2%		97.6%		97.4%	
PPV	71.4%		16.3%		7.1%	

- Sensitivity of POCT with fingerprick blood was low, but increased with rising RPR titres.
- Sensitivity of POCT with TPHA positive sera was 97% (172/178).
- Utility of POCT relatively low in settings where large proportion of targeted population has been previously tested and treated.

Clinic v laboratory performance of syphilis POCTs

Syphilis screening among female sex workers in Bangalore, India:

Sex Transm Infect 2010;86:193–198.

Test	RPR & TPHA positive		RPR (≥ 1:8) & TPHA positive	
	Sensitivity (95%CI)	Specificity (95% CI)	Sensitivity (95%CI)	Specificity (95% CI)
POCT Whole blood positive	**70.8%**	97.8%	**73.3%**	95.2%
POCT Serum positive	**97.5%**	93.6	**100%**	90.2

- Syphicheck-WB performed on fingerprick whole blood and compared to RPR, TPHA and repeat POCT using serum.
- Sensitivity of POCT with whole blood 70.8% compared with reference RPR & TPHA
- Due to low rate of return: 68.3% of women with active syphilis were treated using POCT protocol vs 44.8% with standard testing (p=0.003).

Clinic v laboratory performance of syphilis POCTs: Ante-natal Care

The Trade-Off between Accuracy and Accessibility of Syphilis Screening Assays PLOS ONE September 2013 | Volume 8 | Issue 9 | e75327

Test	TPPA Positive		RPR (≥ 1:8) & TPPA positive	
	Sensitivity	Specificity	Sensitivity	Specificity
POCT Whole blood positive	**59.6%**	99.4%	**82%**	100%
EIA Plasma	**95.2%**	97.7%	**100%**	100%

- Rural district in Northern Tanzania
- Prevalence of active syphilis is 2.3%
- 1 district hospital; rest were community health centres/ rural dispensaries.
- POCT (SD Bioline) would result in a higher proportion of pregnant women with active syphilis receiving treatment c/t standard testing (82% v 16%).

Clinic v laboratory performance of syphilis POCTs: Ante-natal Care

Onsite Rapid Antenatal Syphilis Screening With an Immunochromatographic Strip Improves Case Detection and Treatment in Rural South African Clinics

Sex Transm Dis, 2007; 34(7)

Test (number tested)	Sensitivity for high titre syphilis RPR ≥ 1: 8	Sensitivity for low titre syphilis RPR < 1:8	Specificity
Onsite POCT before retraining (n= 354)	100% (54-100)	**31.3%** (11-59)	94.8% (92-97)
Onsite POCT after retraining (n=341)	100% (63-100)	**85.7%** (57-98)	90.9% (92-97)
Onsite POCT for entire study period (n=695)	100% (77-100)	**56.7%** (37-75)	92.9% (91-95)
Onsite RPR (n=555)	71.4% (29-96)	39.3% (22-59)	96.6% (95-98)

- Utility of Determine Syphilis TP at 16 rural clinics in Eastern Cape (8 POCT, 8 standard testing)
- 6 week interim analysis: onsite POCT had poor sensitivity for detecting low titre syphilis (RPR < 1:8) due to insufficient blood withdrawn from fingerprick.
- Sensitivity improved after introduction of automatic lancets and calibrated, heparinized capillary tubes.

Clinic v laboratory performance of syphilis POCTs: Ante-natal Care

Onsite Rapid Antenatal Syphilis Screening With an Immunochromatographic Strip Improves Case Detection and Treatment in Rural South African Clinics

Sex Transm Dis, 2007; 34(7)

	Number of Weekly Doses of Penicillin Received by Antenatal Clients with Syphilis				
	One*	Two†	Three†	At Least One*	None*
Intervention clinics (n = 104)‡	52.9%	12.5%	24.0%	89.4%	10.6%
Standard practice clinics (n = 79)§	22.8%	2.5%	35.4%	60.8%	39.2%

- Women diagnosed and treated for active syphilis to prevent congenital infection:
  - 89.4% with onsite POCT
  - 63.9% with onsite RPR (low sensitivity)
  - 60.8% with offsite RPR/ TPHA (low return rate)

Integration of Preventing Mother-To-Child Transmission of HIV and Syphilis Testing and Treatment in Antenatal Care Services in the Northern Cape and Gauteng

Sexually Transm Dis 2013; 40 (11): 846-851

- Systematic review of 2,379 maternity clinic records at 6 public clinics in Northern Cape and Gauteng
- Only 41% tested for HIV and 71% tested for syphilis at first pregnancy visit
- **Women tested for syphilis were almost 4 times more likely to have had no HIV test** (OR 3.9, 95% CI = 2.7-5.5)
- 243 had reactive HIV tests: only 104 (43%) had documented sdNVP treatment before delivery
- 98 with reactive syphilis: 73% received one penicillin injection, only 36% received all 3 injections
  - Only 47% began treatment within 2 weeks of test
- **Lack of functional integration of care at facility level**

Impact of rapid syphilis tests on screening and treatment at ante-natal care facilities

International Journal of Gynecology and Obstetrics 130 (2015) S58–S62

Proportion of pregnant women tested and treated.[a]

	Baseline (n = 1365)	Midline (n = 1446)	Endline (n = 1337)	Total (n = 4148)	P value
Received RPR as first test	140 (10.3)	0	0	140 (33.8)	
Received RST as first test	0	976 (67.5)	752 (56.3)	1728 (41.7)	<0.001
Positive first test	2 (1.4)	23 (2.4)	25 (3.3)	50 (2.7)	0.015
Received 1 penicillin dose	1 (50)	3 (13)	2 (8)	6 (12)	0.1992

- Rural district in Zambia: 18 healthcare facilities
  - Improved syphilis testing uptake in first 6 months
  - Endline test period: frequent stock-outs of RST kits; lack of sustained on-site supervision
  - Lack of impact of increased screening on treatment

Lessons learned from integrating simultaneous triple point-of-care screening for syphilis, hepatitis B, and HIV in prenatal services through rural outreach teams in Guatemala

International Journal of Gynecology and Obstetrics 130 (2015) S58–S62

- Ante-natal HIV prevalence 0.71%; syphilis prevalence 0.1%
- One municipality: low literacy, poor maternal/ child health
- 1 year after rapid test introduction
  - Testing uptake increased significantly
  - Limited by: poor supply change management and shortage of HCWs
  - Partner notification limited: gender inequity, economic vulnerability
  - Fear of disclosure by HCWs: indeterminate and ambiguous results read as negative

Quality Assurance

The development and validation of dried blood spots for external quality assurance of syphilis serology

Smit *et al. BMC Infectious Diseases* 2013, **13**:102

Table 2 Correlation between detection of *Treponema pallidum* antibodies by plasma TPPA and DBS TPPA

(n=1147)		TPPA plasma		
		Positive	Negative	Total
DBS TPPA	Positive	169	10	179
	Negative	8	960	968
	Total	177	970	1147*

sensitivity of DBS against plasma 95.5% (95% CI: 91.3–98,0%).
specificity of DBS against plasma 99.0% (95% CI: 98.1–99.5%).
* excluding 34 indeterminate results.

Cost-effectiveness of Syphilis POCTs

Antenatal Syphilis Screening Using Point-of-Care Testing in Sub-Saharan African Countries: A Cost-Effectiveness Analysis PLOS Medicine November 2013 | Volume 10 | Issue 11 | e1001545

- Decision-analytic model for 43 SSA countries

- Use of rapid POCTs for antenatal syphilis screening is highly cost-effective in SSA: reduction in DALYs per health care dollar spent higher in countries with high prevalence rates.

	Stillbirths averted	Neonatal deaths averted	Cases of congenital syphilis averted	DALYs averted	Increase in direct medical cost	Cost/ DALY averted 95% CI	Probability screening is cost-effective	Prevalence Target rate
SA	739	284	372	30,028	$ 920,106	$ 31 (12-170)	99.8%	0.008%

WHO Criteria for POCT: ASSURED

- **A** • Cost-effective, integration into HIV PMTCT
- **S** • Field evaluation studies at PHCs using whole blood
- **S** • Dual TP/ NTP rapid tests can reduce over-treatment
- **U** • Training: technical aspects, results interpretation, ongoing
- **R** • EQA/ PTS, timeous results delivery
- **E** • Adequate sample collection, stock management
- **D** • Treatment availability, patient education, HCT