Satellite Symposium

Dual Elimination of Maternal-to-Child Transmission of HIV and Syphilis

The Time is Now

Welcome and Overview

Sanjana Bhardwaj
HIV and Nutrition
UNICEF

Global problem of maternal HIV and syphilis – why is that important?

Professor Helen Rees
Reproductive Health Research Unit
University of Witwatersrand

Dual Elimination: Efforts to eliminate maternal-to-child transmission of HIV and syphilis and the use of and performance of rapid dual HIV and syphilis tests

Professor Jeffrey D. Klausner
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Dual Elimination:
Efforts to eliminate maternal-to-child transmission of HIV and syphilis and the use of and performance of rapid dual HIV and syphilis tests

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Cape Town

UCLA FIELDING SCHOOL OF PUBLIC HEALTH

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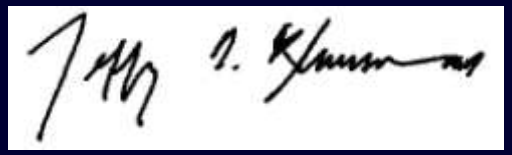
  - US CDC
  - Hologic Gen-Probe, Inc.
  - Cepheid, Inc.
  - Standard Diagnostics, Inc.
  - APLA Health and Wellness
  - Qpid.me



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Outline

1. WHO efforts to eliminate mother-to-child transmission of syphilis

2. UNAIDS efforts to eliminate mother-to-child transmission of HIV infection

3. Dual elimination

4. New dual rapid tests

What is elimination?

- Elimination of disease is the reduction in disease incidence below a threshold of public health importance in a geographic area
  - Perinatal HIV infection: < 90% reduction from 2011, < 50 per 100,000 live births
  - Congenital syphilis: < 50 per 100,000 live births

- Eradication of disease is the abrogation of disease from planet Earth, e.g., small pox

What is congenital syphilis?

- Miscarriage
- Prematurity
- Stillbirth
- Low birth weight
- Neonatal death
- Clinical syphilis in neonate

From Zhou, STD, 2007

Global Surveillance Case Definition for Congenital Syphilis

- A stillbirth, live birth, or fetal loss at >20 weeks gestation or >500g in a syphilis-seropositive mother without adequate* syphilis treatment

OR

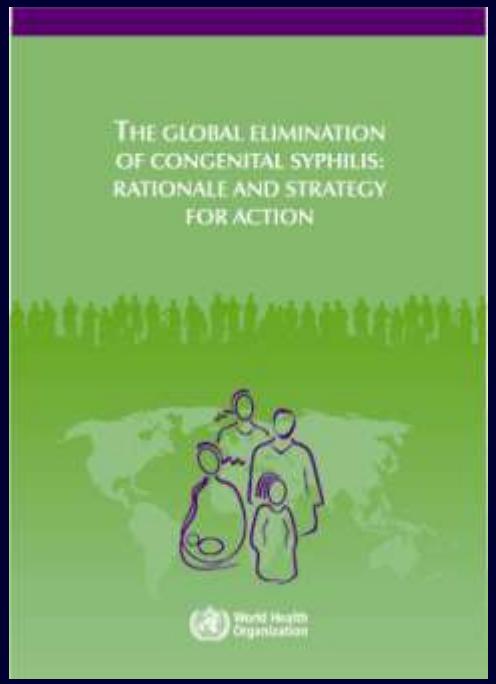
- A stillbirth, live birth, or child aged <2 years with microbiological evidence of syphilis infection

*Adequate treatment defined in syphilis-positive mothers receiving at least 1 dose of benzathine penicillin G before 24 weeks gestation

WHO. Global guidance on criteria and processes for validation: elimination of mother-to-child transmission (EMTCT) of HIV and syphilis. In press, 2013.

WHO Global Elimination of Congenital Syphilis Initiative, 2007

- **Objective**
  - To eliminate congenital syphilis as a public health problem
- **Aim**
  - Prevent transmission of syphilis from mother to child
- **Targets by 2015**
  - Screen > 95% of first antenatal care attendees for syphilis
  - Treat > 95% of syphilis-seropositive antenatal care attendees



Available at: http://whqlibdoc.who.int/publications/2007/9789241595858_eng.pdf

Rationale

- Almost all nations have national policies recommending universal syphilis screening for pregnant women
- Current technology allows testing even in settings that lack basic laboratory capacity
- Maternal syphilis testing/treatment is highly cost effective
  - <$1 per woman tested and treated
  - $200 per case averted
  - $15 per DALY saved

Broutet 2006, Hira1990, Jenniskens 1995, Fonck 2001, Terris-Prestholt 2003

Prevention of congenital syphilis is highly feasible and cost-effective

- Simple and accurate tests
  - Rapid point-of-care tests, no laboratory
  - Sensitivity > 95%
- Penicillin treatment
  - Widely available
  - One dose of penicillin early in pregnancy is highly-effective
  - Penicillin in pregnancy is safe
- Screening all pregnant women is cost-effective even in low prevalence settings

The Global Elimination of Congenital Syphilis: Rationale and Strategy. WHO, 2007.

Elimination of congenital syphilis helps reach global goals

Millennium Development Goals 4-6

- **4:** Prevention of congenital syphilis reduces neonatal mortality
- **5:** Early antenatal care and fewer spontaneous abortions and stillbirths improve maternal health
- **6:** Women with syphilis are at greater risk of acquiring and transmitting HIV

UN Secretary General's Global Strategy for Women's and Children's Health

Ensure universal access for women and children to a comprehensive, integrated package of essential interventions & services

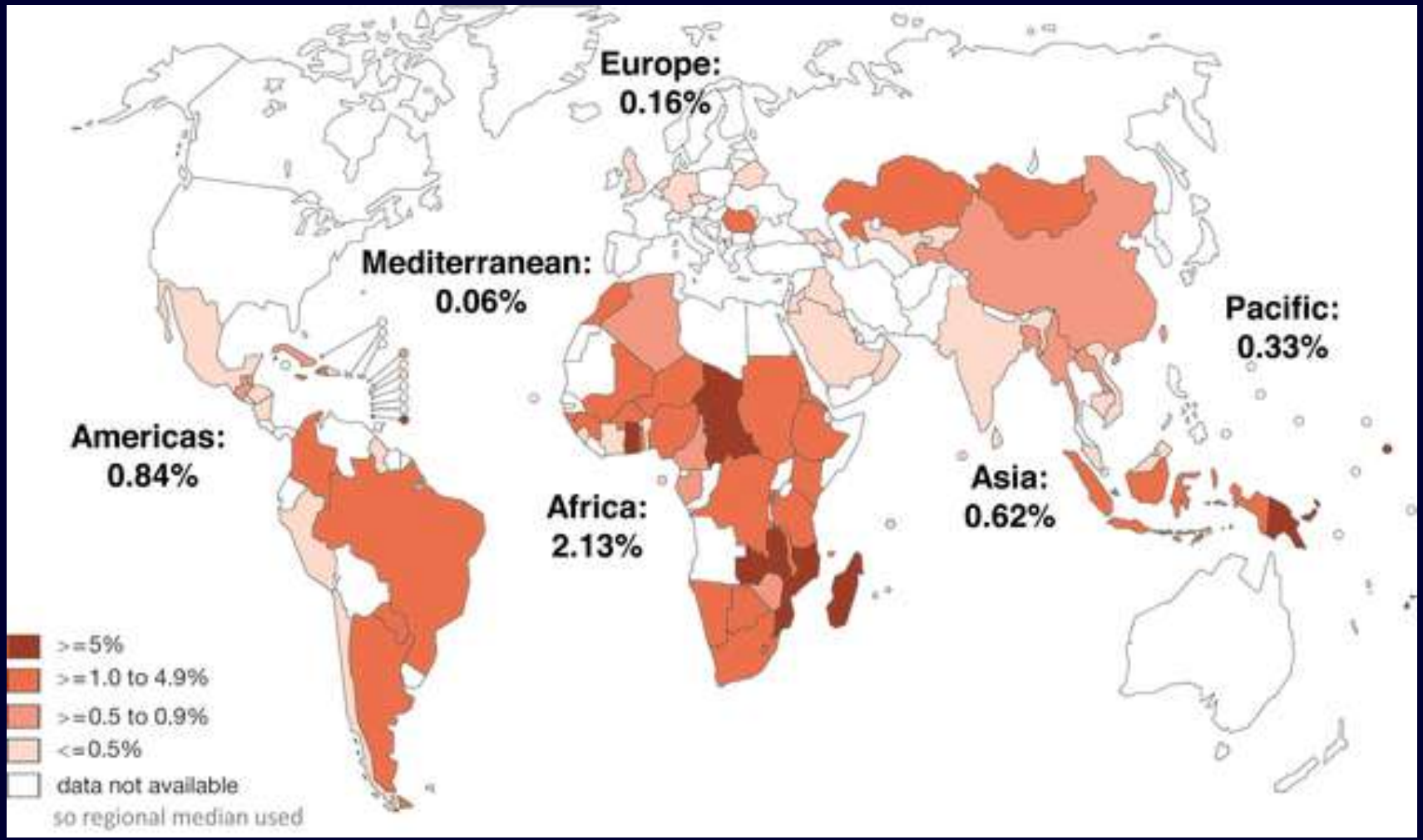
Congenital syphilis is common and severe
WHO estimates, 2008

- About 1.4 million pregnant women infected with syphilis per year
- Majority of infected women unidentified, untreated, or treated late in pregnancy
- **Over 500,000** infected pregnant women will have an adverse outcome of pregnancy attributable to syphilis (congenital syphilis)
  - 215,000 stillbirths / early fetal losses
  - 90,000 neonatal deaths
  - 65,000 preterm or low birth-weight infants
  - 150,000 infants with congenital disease

Congenital syphilis is an important cause of neonatal mortality and morbidity

Newman L, Kamb M, Hawkes S, Gomez G, Say L, et al. (2013) Global Estimates of Syphilis in Pregnancy and Associated Adverse Outcomes: Analysis of Multinational Antenatal Surveillance Data. PLoS Med 10(2): e1001396. doi:10.1371/journal.pmed.1001396

Percent pregnant women syphilis seropositive, 2008



Newman L, Kamb M, Hawkes S, Gomez G, Say L, et al. (2013) Global Estimates of Syphilis in Pregnancy and Associated Adverse Outcomes: Analysis of Multinational Antenatal Surveillance Data. PLoS Med 10(2): e1001396. doi:10.1371/journal.pmed.1001396

Reported syphilis prevalence for 2010 (2009 for Indonesia) in intensified support countries for the investment case for eliminating mother-to-child transmission of syphilis[a]

[a] Source: Data for Papua New Guinea are from the National Department of Health, STI, HIV and AIDS Surveillance Unit: The 2010 STI, HIV and AIDS Annual Surveillance Report. Data for Indonesia available at: http://www.who.int/hiv/pub/2010progressreport/en/index.html. Data for all other countries available at: http://www.who.int/hiv/pub/progress_report2011/en/.

The Four Pillars of Elimination of Congenital Syphilis

I. Ensure sustained political commitment and **advocacy**

II. Increase access to, and quality of, maternal and newborn health **services**

III. **Screen** all pregnant women and **treat** all positives

IV. Conduct surveillance, **monitoring** and **evaluation**

Available at: http://whqlibdoc.who.int/publications/2007/9789241595858_eng.pdf

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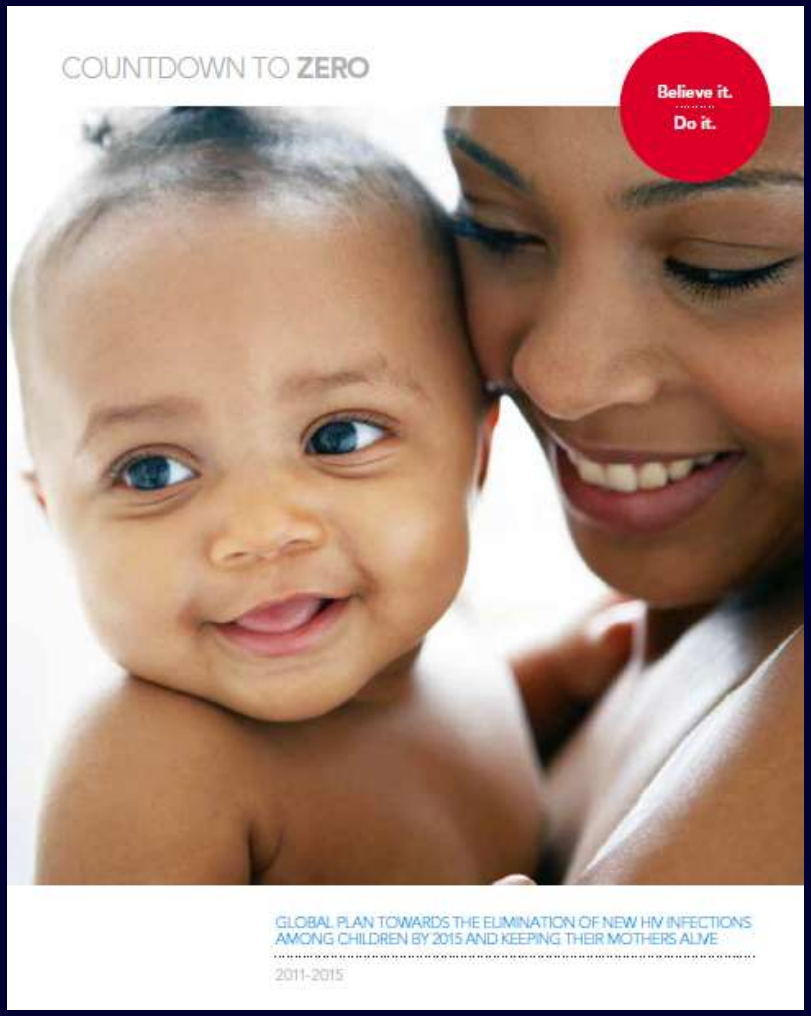
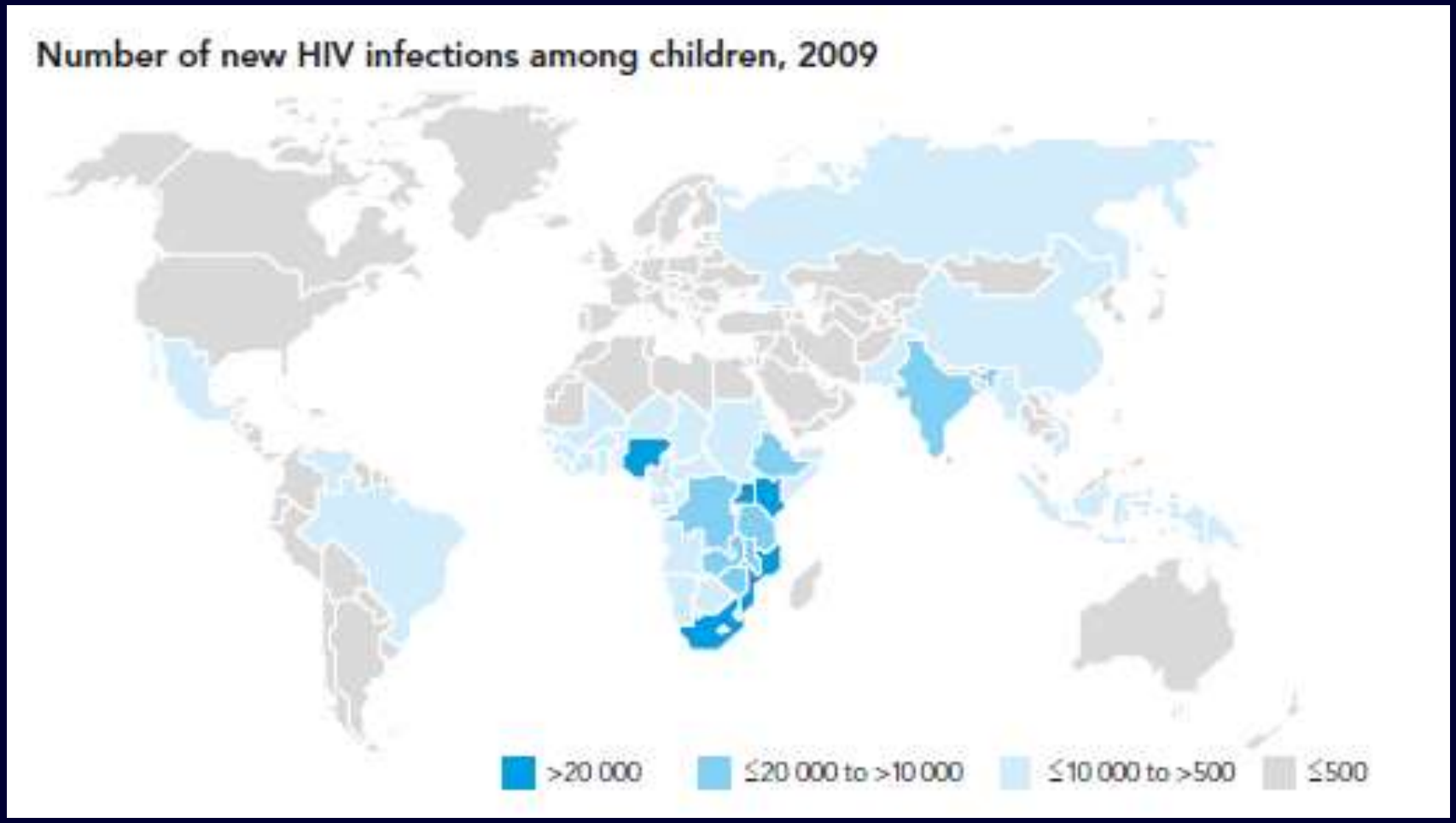
PMTCT HIV: The Global Plan



UNAIDS, 2011



1.4 million HIV-infected pregnant women
~ 235,000 HIV-infected babies

UNAIDS, Global Plan. Available at: http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2011/20110609_JC2137_ Global-Plan-Elimination-HIV-Children_en.pdf

The Four Prongs of PMTCT HIV Infection

I. Prevent new HIV infections in women of reproductive age

II. Reduce unintended pregnancy in HIV-infected women

III. Prevent mother-to-child HIV transmission

IV. Provide care, treatment and support for HIV-infected women and children

Countdown to Zero: Global Plan towards elimination of new HIV infections among children by 2015 and keeping their mothers alive, 2011–2015

Congenital Syphilis is More Common than Perinatal HIV Infection

True or False?

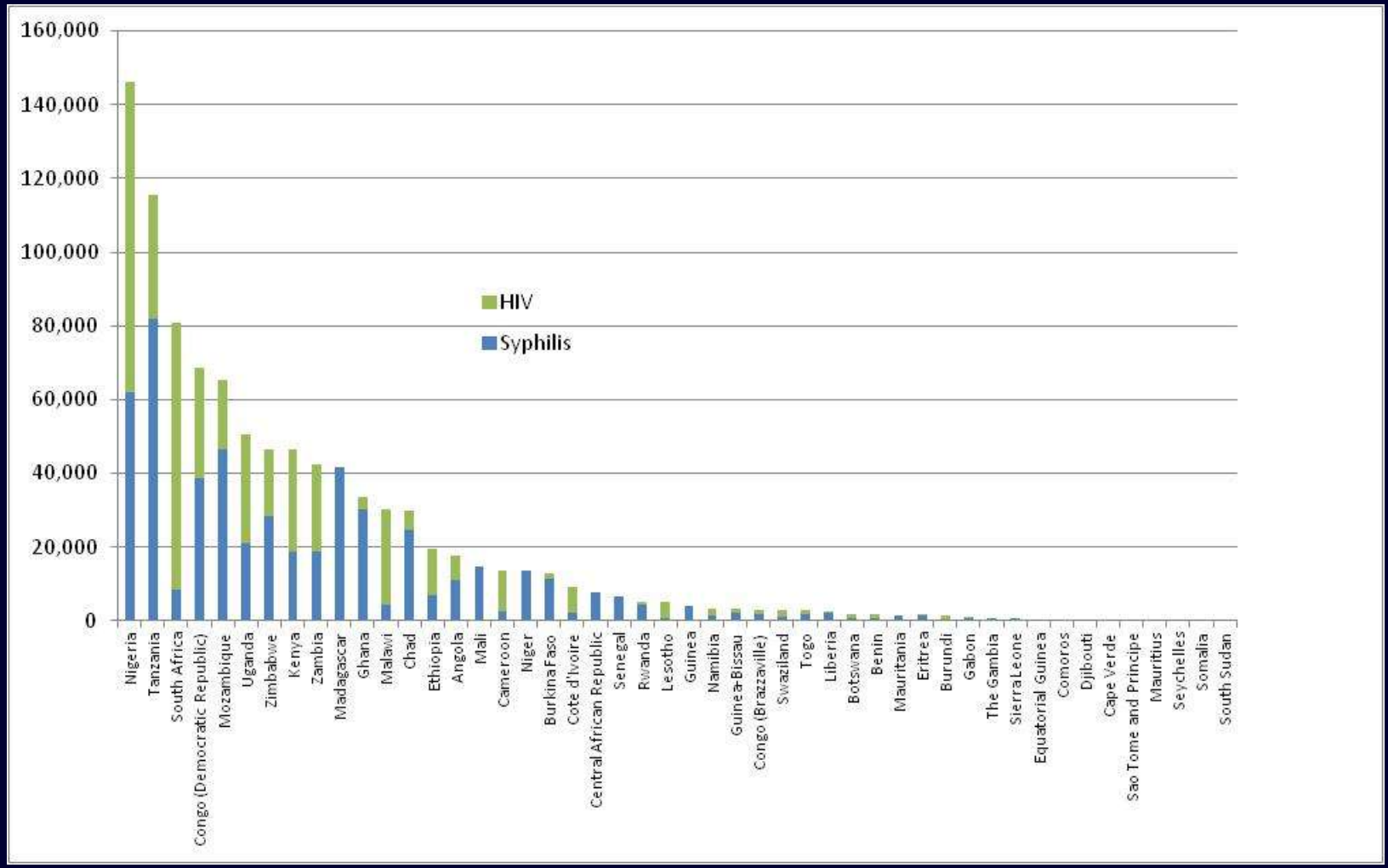
Congenital Syphilis is More Common than Perinatal HIV Infection Worldwide

- About same number pregnant women each year have HIV or syphilis
  - Most (80%) untreated maternal syphilis infections result in serious pregnancy complications—miscarriages, preterm deliveries and stillbirth
  - **500,000 adverse birth outcomes each year** each year are caused by inadequately treated maternal syphilis; many fetal losses (miscarriages) and stillbirths go unrecognized
  - Roughly 53% receive ART reducing transmission to < 5% (37,000 HIV+ infants)
  - Remaining 47% untreated transmit in 30% (197,400 HIV+ infants)
  - About **234,400 HIV-infected newborns** each year

Schmid, STD, 2007; UNICEF 2009; Childinfo.org/HIV_AIDS, 2012

World Health Organization

Number of estimated newborn HIV and congenital syphilis cases by country, 2008



Date from: http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001396

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Preventing MTCT of HIV and syphilis: Why do this together?

- Both are sexually transmitted infections that cause substantial global health burden to mothers and infants

- Both have evidence-based, scalable interventions using antenatal care platform
  - Early access to antenatal care, testing and treatment
  - Both require engaging partners

- Both have affordable, accurate point-of-care tests feasible for use in basic settings
  - Prompt test results & treatment
    - ideally **"STAT"** (Same-visit Testing and Treatment)
  - Testing at all antenatal care facilities - not just those clinics with lab capacity

- Comprehensive services may be more attractive to women
  - Preliminary evidence from Zambia & Uganda suggested positive impact on HIV testing, ARV, and referral when both tests provided

Globally important

- *"In Zambia, if we're going to be successful in eliminating pediatric AIDS, we also have to prevent congenital syphilis…It is simply unacceptable for this disease to continue to plague women and children."*
  Susan Strasser, Zambia Director, Elizabeth Glaser Pediatric AIDS Foundation

Maternal syphilis increases HIV transmission

- **Of 1147 HIV-infected pregnant women, 92 (8.0%) syphilis**
- Maternal syphilis was associated with increased in utero HIV transmission **aRR = 2.77; 1.40-5.46**,
- Maternal syphilis was associated with increased intra/post-partum HIV transmission **aRR = 2.74; 1.58-4.74**,

Characteristic	*In utero* HIV-1 MTCT [ARR (95% CI)]	*P*	Intrapartum/postnatal HIV-1 MTCT [ARR (95% CI)]	*P*
Syphilis infection				
No	Reference		Reference	
Yes	2.77 (1.40–5.46)	0.003	2.74 (1.58–4.74)	0.0003
Log_{10} HIV viral load				
< 3.993	Reference		Reference	
3.993 to < 4.547	1.98 (0.63–6.29)	0.24	1.54 (0.64–3.69)	0.34
4.557 to < 5.036	2.77 (0.91–8.40)	0.07	2.41 (1.07–5.43)	0.03
> 5.036	3.80 (1.31–11.02)	0.01	2.62 (1.16–5.90)	0.02
Low birth weight				
No	Reference		Reference	
Yes	1.52 (0.82–2.79)	0.18	1.88 (1.17–3.05)	0.01
Recent fever[a]				
No	NI		Reference	
Yes	NI		1.73 (1.09–2.74)	0.02
Breast infection				
No	NA	NA	Reference	
Yes	NA	NA	2.09 (1.06–4.12)	0.03

[a]Includes women with fever 1 week prior to enrolment and those with temperature > 37.5°C at enrolment. ARR, Adjusted relative risk; CI, confidence interval; NI, variable not included in the multivariate model.; NA, since breast infection was determined at least 6 weeks postnatally, this variable was not assessed as a predictor of *in utero* HIV-1 MTCT.

Adjusted for recent fever, breast infection, low birth weight and maternal HIV-1 viral load.

Maternal syphilis infection is associated with increased risk of mother-to-child transmission of HIV in Malawi. Mwapasa, Victor; Rogerson, Stephen; Kwiek, Jesse; Wilson, Paul; Milner, Danny; Molyneux, Malcolm; Kamwendo, Deborah; Tadesse, Eyob; Chaluluka, Ebbie; Meshnick, Steven. AIDS. 2006. 20(14):1869-1877.

Mwapasa et al. AIDS 2006;20:1869-1877.

WHO Dual Elimination Strategy

Editorials

The sound of silence: missing the opportunity to save lives at birth

Jeffrey D Klausner[a]

The adverse impact of syphilis on child health has been known for over 500 years, yet the World Health Organization (WHO) only targeted congenital syphilis for elimination in 2007.[1] Syphilis in pregnancy is not rare. Far more pregnant women have syphilis than human immunodeficiency virus (HIV) infection: 1.9 million (2008) and 1.49 million (2010), respectively.[2] The fraction of pregnant women with syphilis that is detected and treated is unknown, but estimates suggest that it is less than 10%.[3] Whereas untreated maternal HIV infection is transmitted to infants in about one third of the cases, untreated maternal syphilis nearly always results in an adverse pregnancy outcome. For these reasons, syphilis is as important an infection during pregnancy as infection with the HIV. It therefore makes sense to build on global efforts to prevent and treat HIV infection during pregnancy to strengthen the fight against maternal syphilis.

The adverse pregnancy outcomes that can result from syphilis include fetal death, stillbirth or premature birth, low birth weight and congenital syphilis infection. The frequency of these outcomes has been poorly quantified. In a literature review published in the present issue of the *Bulletin*, Gomez et al. tried to generate summary estimates of syphilis-related adverse pregnancy outcomes by reviewing 3258 studies published through December 2011. They specifically looked for studies that compared pregnancy outcomes in untreated syphilitic women and non-syphilitic women belonging to the general population. Only 6 studies, representing 1715 pregnant women with untreated syphilis and 32 513 non-syphilitic women, satisfied these criteria and were included in the analysis. Adverse birth outcomes were observed in 66.5% (range: 13.4–81.8) of the women with untreated syphilis and in 14.3% (range: 10.25–20.8) of the women without syphilis. Hence, the frequency of adverse pregnancy outcomes was 4.5 times higher in the former than in the latter group.

The adverse pregnancy outcomes associated with maternal syphilis can be easily prevented, yet implementing proper measures within health systems has been difficult.[1] Laboratory-based and rapid point-of-care syphilis tests identify most maternal syphilis infections. A single dose of benzathine penicillin early in pregnancy is highly effective at preventing adverse pregnancy outcomes.[4] Testing and treatment combined cost less than one United States dollar. The problem, then, is not a lack of affordable tests or treatment, but the absence of political will. In many countries, most maternal syphilis infections remain unidentified and untreated. Currently 12 countries – the Central African Republic, China, Ghana, Honduras, Indonesia, Madagascar, Mozambique, Myanmar, Papua New Guinea, the United Republic of Tanzania, Uruguay and Zambia – are recognized by WHO as high priority countries for congenital syphilis elimination owing to their large burdens of maternal syphilis.[1] Additionally, countries such as Bangladesh, Brazil and Nigeria have large populations and high rates of maternal syphilis and should be considered priority countries as well.

No one knows why some global disease elimination programmes have traction while others, such as the one for congenital syphilis, do not. Shiffman & Smith articulated a four-category framework for the prioritization of global health initiatives: actor power (or leadership), ideas (or communication), political contexts and factors such as disease severity, availability of effective interventions and existence of credible indicators.[5] Since these are all well established in the case of congenital syphilis, the lack of traction must have to do with leadership, communication and politics. Aware that progress on congenital syphilis elimination has been slow, in June 2012 WHO updated its elimination strategy to twin the prevention of mother-to-child transmission (PMTCT) of HIV with that of syphilis. Thus, "PMTCT" should no longer be seen as applicable to HIV infection alone, but to both HIV and syphilis. Such integration is a major step towards the comprehensive prevention of congenital infections.

An exciting innovation that could accelerate the PMTCT of HIV infection and syphilis is the dual rapid test for syphilis and HIV infection.[6] In many countries supply chain management for syphilis tests is difficult. Dual rapid tests would greatly strengthen the PMTCT of syphilis because programmes for the PMTCT of HIV are better resourced and have stronger external and internal stakeholders than those for the prevention of syphilis. The community involved in the PMTCT of HIV infection is largely unaware that maternal syphilis greatly increases the risk of mother-to-child HIV transmission.[6] Identifying and treating maternal syphilis in mothers co-infected with the HIV should further reduce the mother-to-child transmission of HIV infection.

Gomez et al.'s study is an important contribution to the evidence base. Evidence, however, has not been lacking in the effort to eliminate congenital syphilis, a scourge for centuries. Neither have affordable, safe and effective diagnostic and therapeutic tools. The missing elements have been community advocacy, political will and private donor investment. What will it take? Is anyone listening to the sound of silence? ■

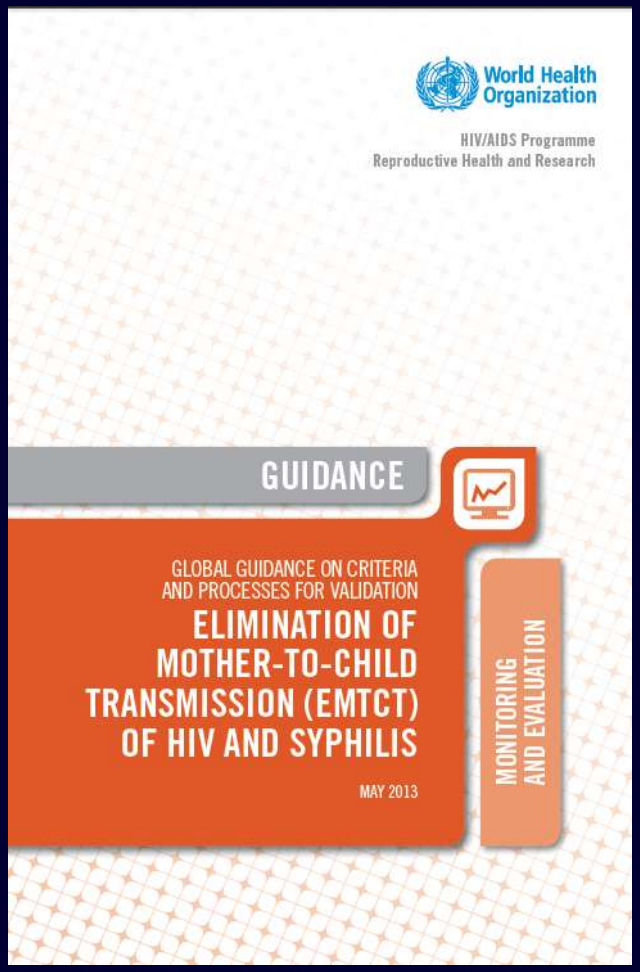
Acknowledgements

I warmly thank Kenneth Katz for his critical review of this manuscript.

References

Available at: http://www.who.int/bulletin/volumes/91/5/13-118604

WHO Bulletin, March 2013



In press, 2013

WHO Integrated Strategy

- **Advocacy**
  - Pro-active support for dual elimination of MTCT of HIV & syphilis

- **Programmatic**
  - -- Pilot projects to assess impact of integrated services on pregnant women & their partners
  - Work with *priority countries*
    - Identify in-country partners, strengthen policy support , procurement processes and laboratory supply chain
  - Increase quality & coverage of antenatal care
  - Coordinated country support for dual screening to prevent infection
    - Encourage procurement of syphilis tests through PEPFAR, Global Fund
    - Integrate training & guidelines for health workers
    - Jointly strengthen pharmacy/laboratory supply chain & QA systems
    - Support field trials of dual rapid HIV/syphilis tests

World Health Organization

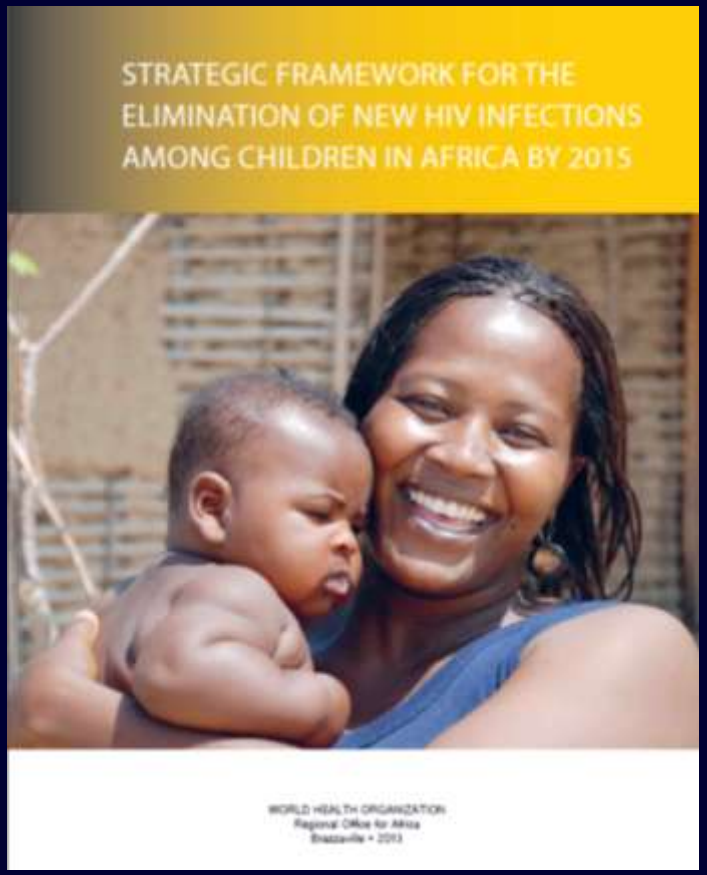
WHO Integrated Strategy

- **Surveillance & monitoring**
  - Lead global process to identify criteria and process for validation/certification of elimination of MTCT of HIV and syphilis
    - Motivate to improve quality of data
    - Motivate to reach even the hardest-to-reach populations
  - Include STI in agendas for HIV surveillance, M&E trainings
  - Include congenital syphilis in studies of how to assess impact of elimination

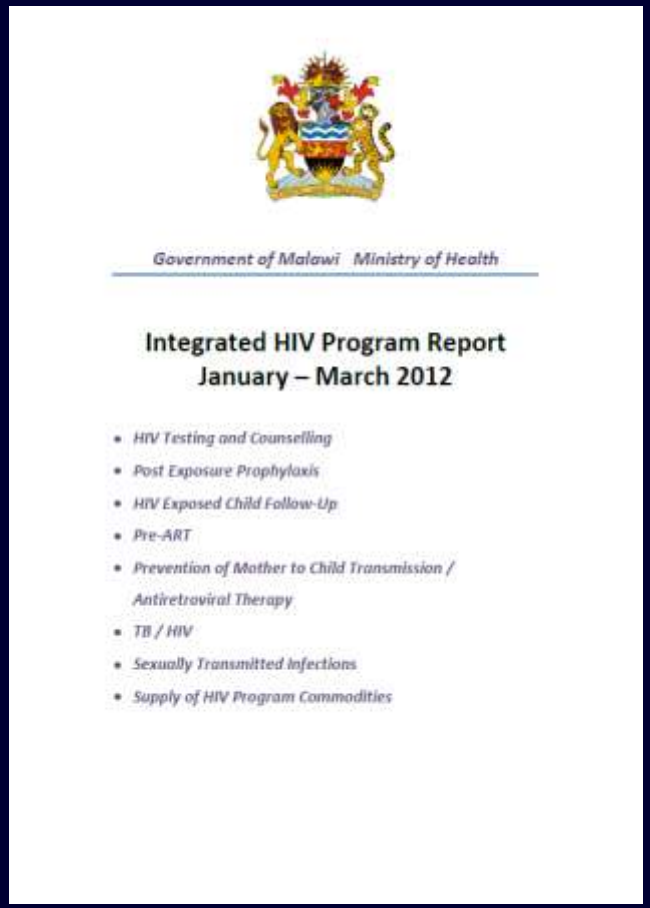
- **Implementation research**
  - Field testing of rapid dual HIV/syphilis tests
  - How to integrate syphilis and HIV interventions within ANC?
  - How to optimally measure impact of eMTCT syphilis interventions – similar methods as eMTCT HIV?

Dual Elimination Strategy: Africa, 2013

- Ensure leadership and country ownership
- Improve coverage, access and utilization of services
- Strengthen quality of MNCH services to deliver effective PMTCT interventions
- Enhance provision of linked services
- Strengthen human resource capacity, supply chain management and maintain information systems
- Improve measurement of performance and impact
- Develop and engage community systems.



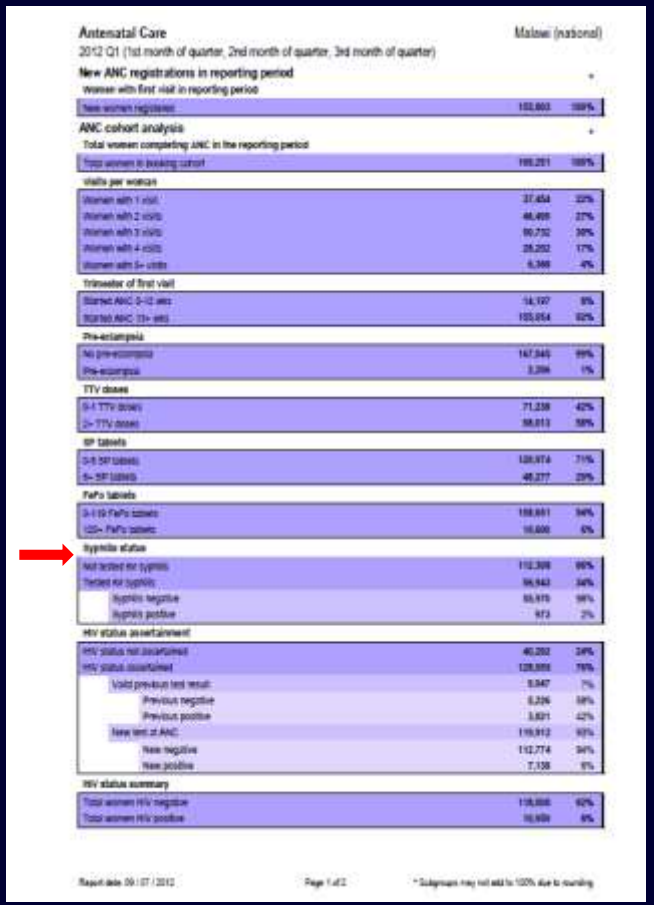
Malawi
Integrated monitoring and evaluation



Government of Malawi Ministry of Health

Integrated HIV Program Report
January – March 2012

- *HIV Testing and Counselling*
- *Post Exposure Prophylaxis*
- *HIV Exposed Child Follow-Up*
- *Pre-ART*
- *Prevention of Mother to Child Transmission / Antiretroviral Therapy*
- *TB / HIV*
- *Sexually Transmitted Infections*
- *Supply of HIV Program Commodities*



Antenatal Care — Malawi (national)
2012 Q1 (1st month of quarter, 2nd month of quarter, 3rd month of quarter)

New ANC registrations in reporting period
Women with first visit in reporting period

ANC cohort analysis
Total women completing ANC in the reporting period

Visits per woman
Trimester of first visit
Pre-eclampsia
TTV doses
SP tablets
FeFo tablets
Syphilis status
HIV status ascertainment
HIV status summary

Report date: 09 / 07 / 2012 Page 1 of 2 * Subgroups may not add to 100% due to rounding

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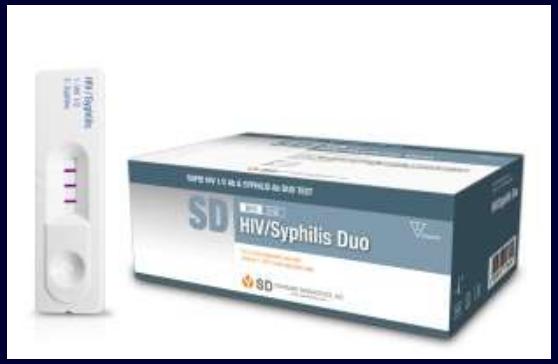
Dual rapid diagnostics

- Simplifies training
- Streamlines procurement
- Ensures testing for both HIV and syphilis
- Improves client experience

Currently available dual rapid tests

- SD BIOLINE Duo HIV/syphilis
  - Immunochromatographic IgA, IgM, IgG assay



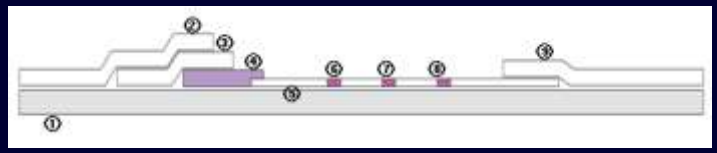
- Chembio DPP® HIV-Syphilis
  - Dual path platform

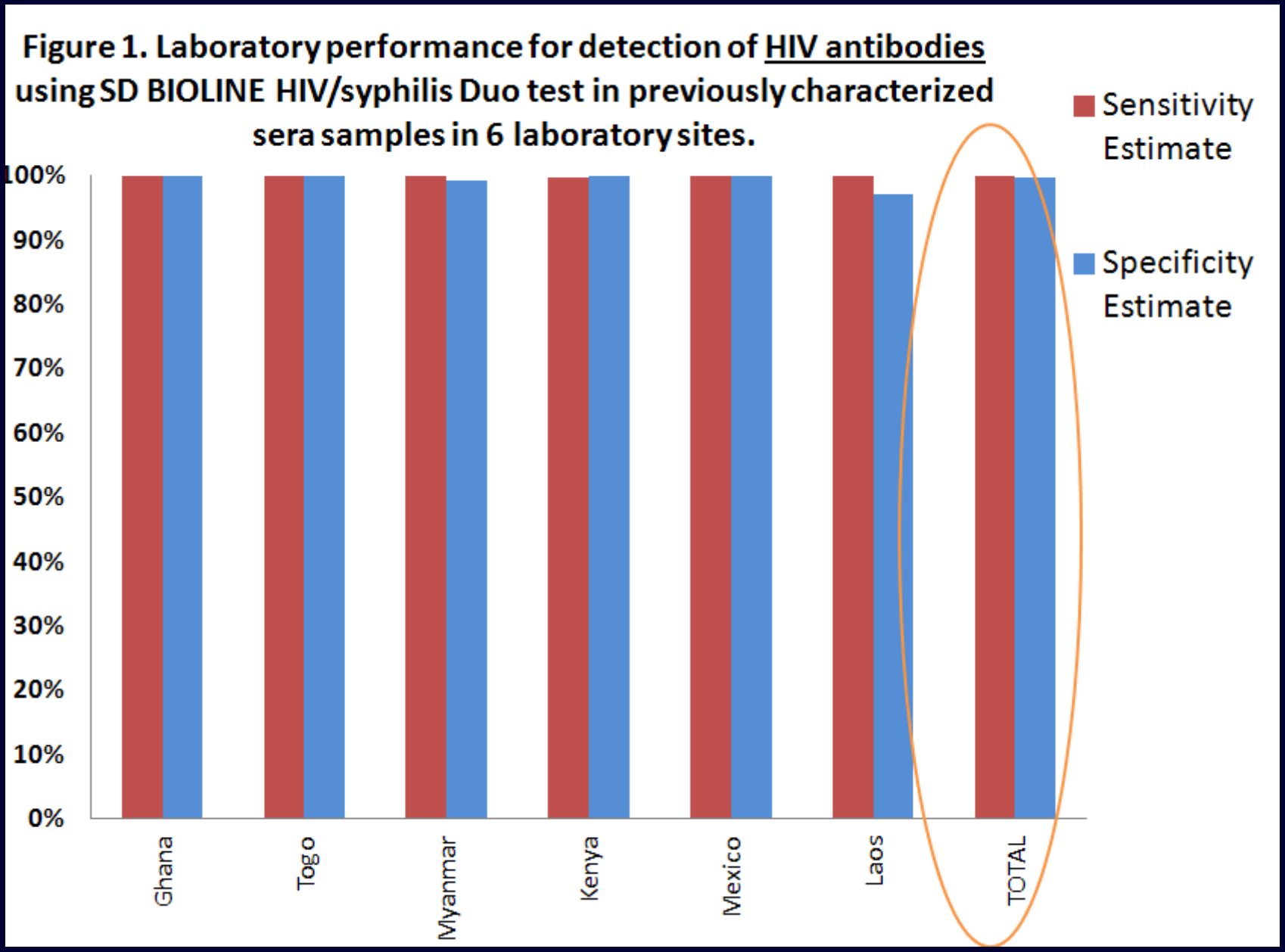
- MedMira Multiplo
  - Immunoreactive test membrane comprised of TP recombinant antigens (15 kDa, 17 kDa,47 kDa) and synthetic HIV peptides to gp36, gp41, gp120 and HIV-group O

DUO HIV/syphilis principle of action

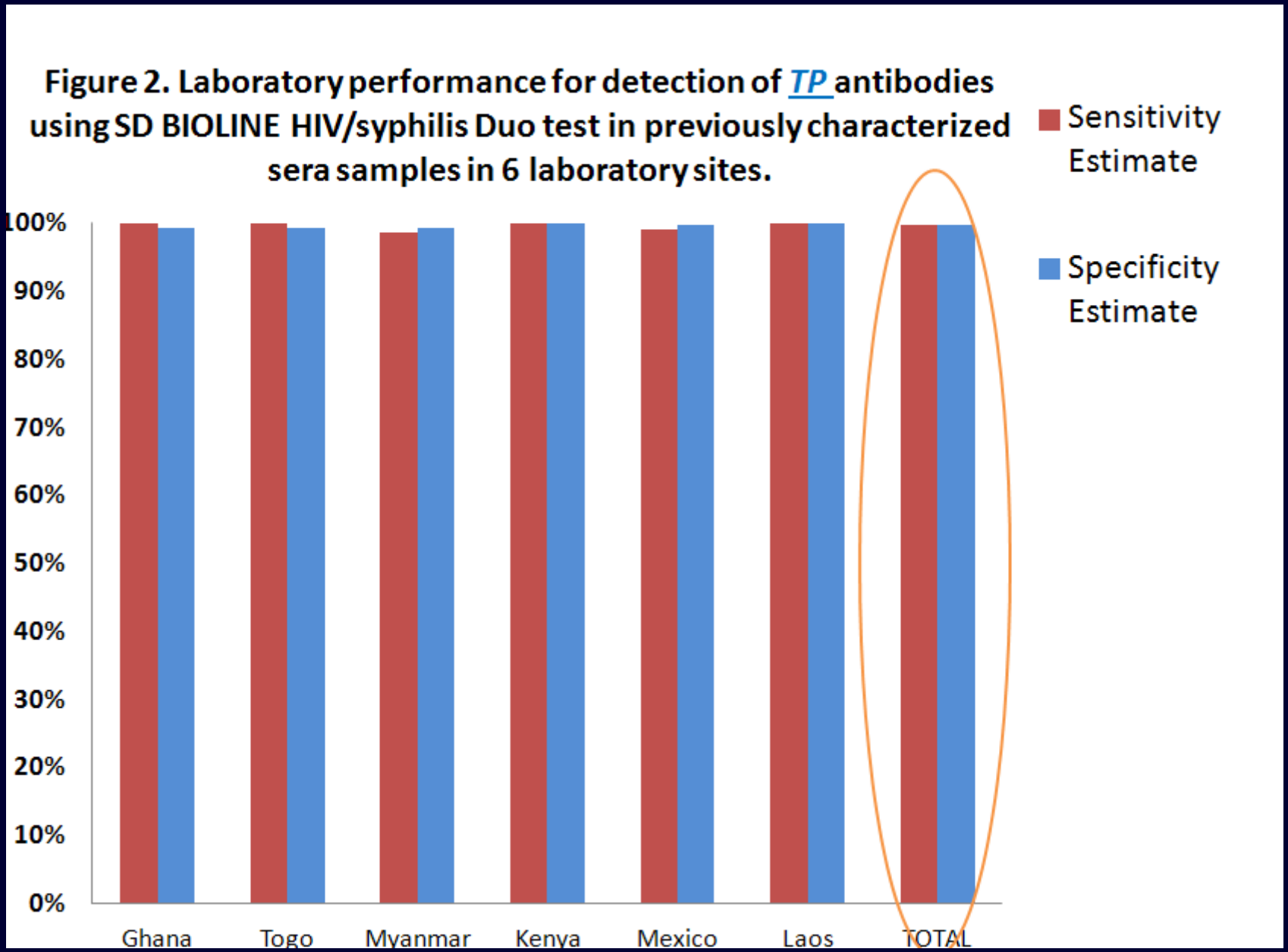
- Precoated strip with multiple antigens
  - gp41 (HIV-1)
  - gp36 (HIV-2)
  - HIV sub-O antigen
  - 17kDA TP antigen (syphilis)

- The specimen sample and sample diluent move along the membrane chromatographically to the test region (T) and form a visible line as antigen-antibody-antigen gold particle complex forms with high degree of sensitivity and specificity





Bristow et al, Multi-site evaluation, submitted 2013



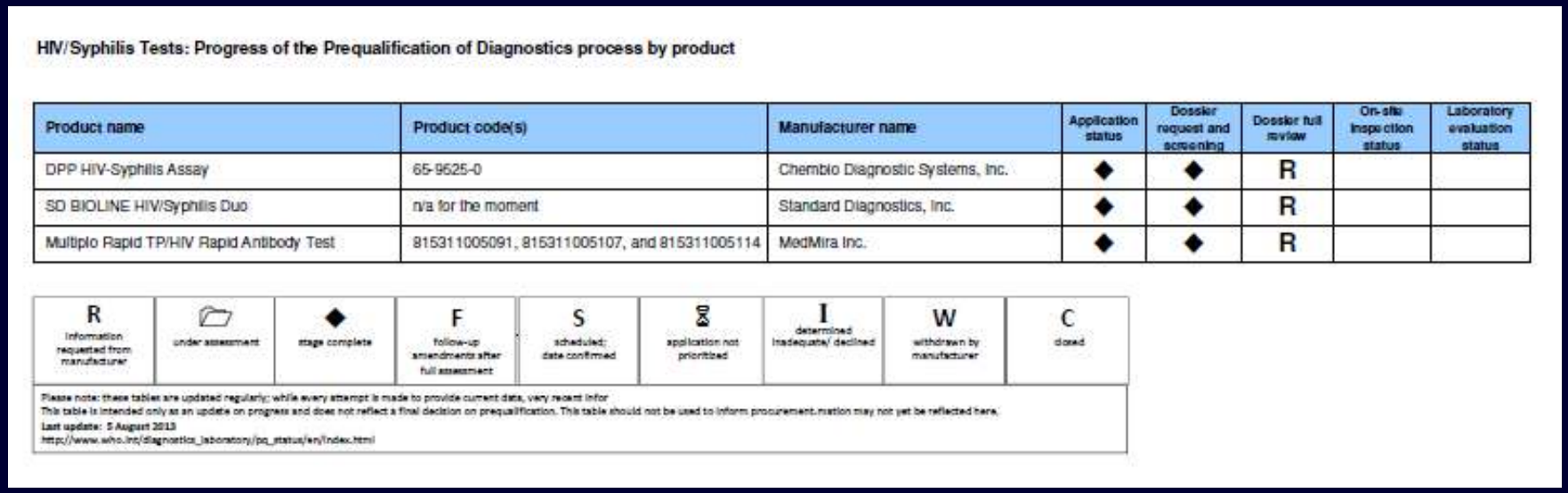
Bristow et al, Multi-site evaluation, submitted 2013

Summary laboratory test performance 3 rapid point-of-care dual tests

Test	Antibody	N	Sensitivity	Specificity
DPP	TP	939	95.7-100%	95.7-98.0%
DPP	HIV	939	99.1-100%	98.2-100%
Duo	TP	> 2000	98.7-100%	99.1-100%
Duo	HIV	> 2000	99.7-100%	99.2-100%
multiplo	TP	258	94.4-97.9%	100%
multiplo	HIV	Not reported	99.8%	99.7%

Studies from Standard Diagnostics, multiple country laboratory evaluations; Chembio Esfandiari et al., HIV Diagnostics Conference, Dec 2012, Atlanta, GA and MedMira multiplo product information http://www.medmira.com/products/multiple

WHO Prequalification Progress



HIV/Syphilis Tests: Progress of the Prequalification of Diagnostics process by product

Product name	Product code(s)	Manufacturer name	Application status	Dossier request and screening	Dossier full review	On-site inspection status	Laboratory evaluation status
DPP HIV-Syphilis Assay	65-9525-0	Chembio Diagnostic Systems, Inc.	◆	◆	R		
SD BIOLINE HIV/Syphilis Duo	n/a for the moment	Standard Diagnostics, Inc.	◆	◆	R		
Multiplo Rapid TP/HIV Rapid Antibody Test	815311005091, 815311005107, and 815311005114	MedMira Inc.	◆	◆	R		

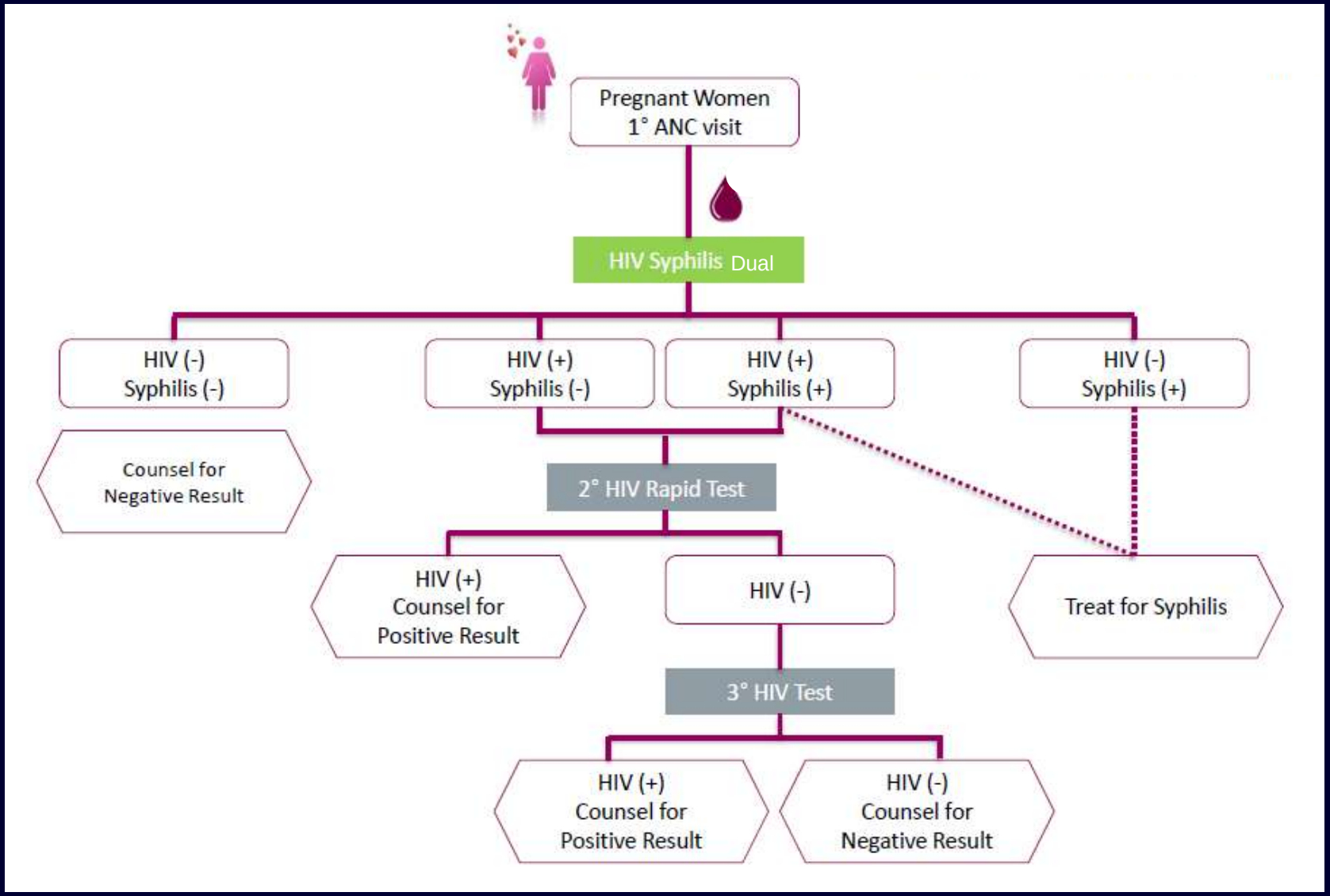
R	🗁	◆	F	S	⧖	I	W	C
information requested from manufacturer	under assessment	stage complete	follow-up amendments after full assessment	scheduled; date confirmed	application not prioritized	determined inadequate/ declined	withdrawn by manufacturer	closed

Please note: these tables are updated regularly; while every attempt is made to provide current data, very recent infor
This table is intended only as an update on progress and does not reflect a final decision on prequalification. This table should not be used to inform procurement.mation may not yet be reflected here.
Last update: 5 August 2013
http://www.who.int/diagnostics_laboratory/pq_status/en/index.html

As of 5 August 2013

http://www.who.int/diagnostics_laboratory/evaluations/en/

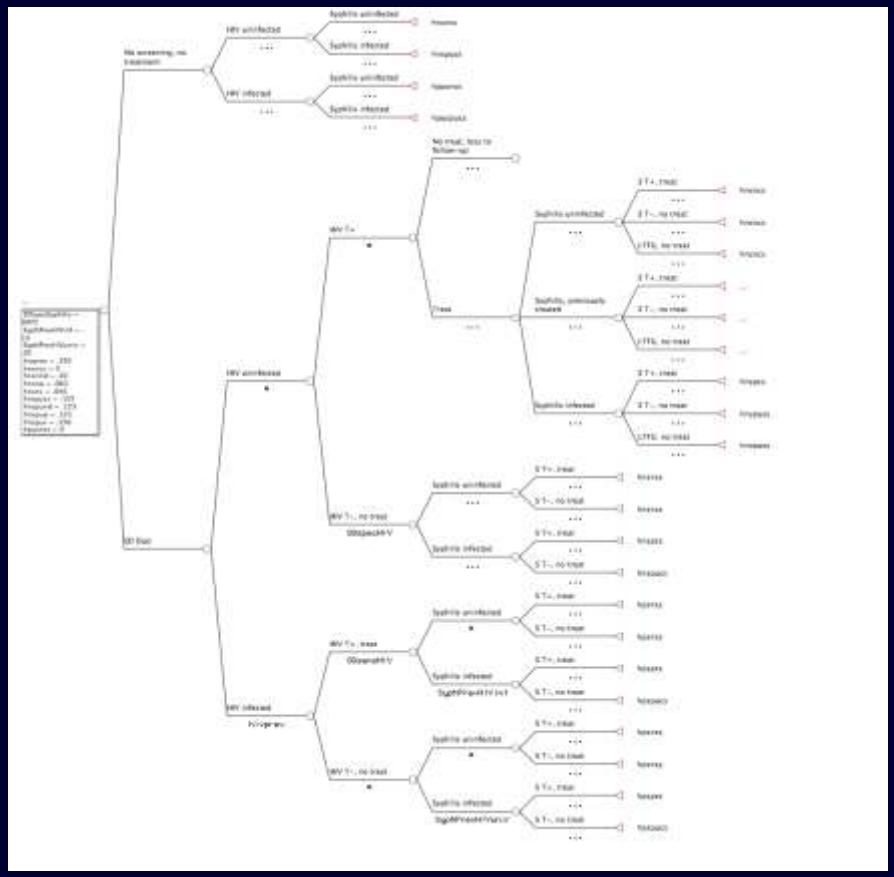
Sample Dual Testing Schema



Cost-Effectiveness Analysis for HIV and Syphilis Screening

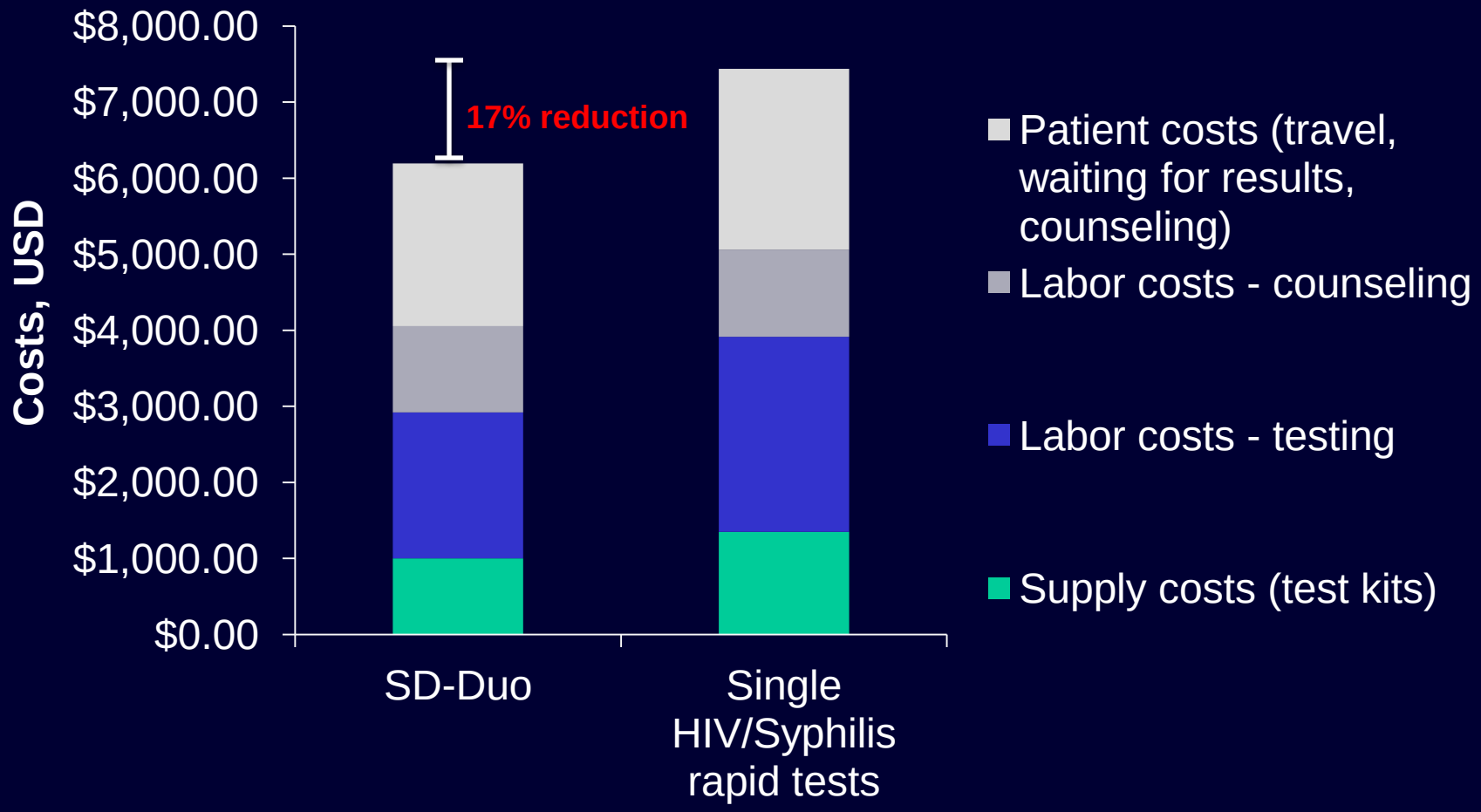
Full Cost-Effectiveness Analysis

- Four alternative testing algorithms
- Health outcomes averted
- Cost per DALY



Cost of Dual Rapid tests vs. Single Rapid tests for HIV and Syphilis

Hypothetical cohort of 1,000 ANC patients in South Africa



*Preliminary results; not for reproduction

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Summary

- Maternal syphilis and HIV infection are common and serious infections in pregnancy causing substantial newborn morbidity and mortality

- New dual elimination strategy capitalizes on existing policy, health systems, and infrastructure to improve birth outcomes
  - Dual rapid HIV/syphilis tests are highly accurate and increasingly available

- We have the potential to transform maternal health to improve infant outcomes with new strategy of dual elimination and new tools such as dual rapid tests

Thank you

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A generation free of HIV and syphilis

Special thanks to:
Claire Bristow, Emily Huang, Lori Newman, Nathalie Broutet, Sarah Hawkes, Rosanna Peeling, Mary Kamb, David Mabey, Nicola Low, George Schmid, Brad Stoner, Patty Garcia and many others

Happy Holidays