RAPID DIAGNOSTICS

Rapid tests for sexually transmitted infections (STIs): the way forward

R W Peeling, K K Holmes, D Mabey, A Ronald

See end of article for authors' affiliations

Correspondence to: Dr Rosanna W Peeling, Sexually Transmitted Diseases Diagnostics Initiative (SDI), UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases, World Health Organization, 20 Avenue Appia, Geneva, Switzerland; peelingr@who.int

Sex Transm Infect 2006;**82**(Suppl V):v1–v6. doi: 10.1136/sti.2006.024265

Accepted 29 November 2006

In the developing world, laboratory services for sexually transmitted infections (STIs) are either not available, or where limited services are available, patients may not be able to pay for or physically access those services. Despite the existence of national policy for antenatal screening to prevent congenital syphilis and substantial evidence that antenatal screening is cost-effective, implementation of syphilis screening programmes remains unacceptably low because of lack of screening tools that can be used in primary health care settings. The World Health Organization Sexually Transmitted Diseases Diagnostics Initiative (SDI) has developed the ASSURED criteria as a benchmark to decide if tests address disease control needs: **A**ffordable, **S**ensitive, **S**pecific, **U**ser-friendly, **R**apid and robust, **E**quipment-free and **D**eliverable to end-users. Rapid syphilis tests that can be used with whole blood approach the ASSURED criteria and can now be deployed in areas where no previous screening has been possible. Although rapid tests for chlamydia and gonorrhoea lack sensitivity, more tests are in development. The way forward for STI diagnostics requires a continuing quest for ASSURED tests, the development of a road map for test introduction, sustainable programmes for quality assurance, and the creation of a robust infrastructure linked to HIV prevention that ensures sustainability of STI control efforts that includes viral STIs.

Recognising the tremendous burden of bacterial sexually transmitted infections (STIs) and the lack of access to laboratory diagnostic services in the developing world, in 1993 the Rockefeller Foundation posted a prize of US$1 million for the development of an inexpensive rapid simple test to detect genital chlamydial or gonococcal infection. The prize was never claimed and was withdrawn in 1998. In stark contrast, ultra sensitive and specific assays such as nucleic acid amplified tests were developed and became widely and effectively used in the developed world to screen for these infections and facilitate treatment. Not surprisingly, the prevalences of curable STIs remain very high in much of the developing world, where women and children continue to bear a disproportionate share of the disease burden. An estimated one million new cases of curable bacterial STIs occur each day worldwide[1] and in sub-Saharan Africa alone, half a million babies die each year from congenital syphilis.[2]

Diagnostic testing is particularly critical for STIs, including HIV, as most infected individuals are often asymptomatic but, nonetheless, infectious. Sensitive diagnostic tests are required for early detection to guide treatment, to prevent the development of reproductive sequelae, and to interrupt onward transmission.

Reasons for the failure to prevent and control STIs in the developing world are complex, but a major barrier to effective health care in Africa is the lack of access to reliable, affordable, accurate laboratory services.[3 4] The 2004 World Development Report cited lack of access and unaffordability as two major reasons why services fail.[5] Table 1 shows the mean distance to the nearest medical facility in selected countries.[6] Even if pregnant women manage to walk the long distance to the clinic, they are often unable to return for their test results and treatment.

The Sexually Transmitted Diseases Diagnostics Initiative (SDI) conducted an expert consultation in 2001 to determine the next steps for improving STI diagnostics for the developing world; priority was given to the evaluation of simple, affordable, commercially available point-of-care tests for the major curable bacterial STIs: syphilis, chlamydia and gonorrhoea. The tests should meet the ASSURED criteria[6] (table 2).

For syphilis, the evaluation of diagnostics that would increase access to prenatal screening was selected. For genital chlamydial and gonococcal infection, priority was given to the evaluation of diagnostics that can be used for screening of high risk populations as well as for increasing the specificity of syndromic management.

This review provides the background for the work on STI diagnostics featured in this supplement, and proposes 10 specific strategies or pathways for the way forward.

LACK OF ACCESS TO PRENATAL SYPHILIS SCREENING

In a survey conducted in 2000, Gloyd reported that in sub-Saharan Africa, antenatal screening was a national policy in 17 of 22 respondent countries.[7] Of the estimated 19.9 million pregnant women per year in these countries, 14.5 million (73%) received antenatal care but only 5.5 million (38%) had access to syphilis screening. If this survey is representative of sub-Saharan Africa, with an estimated mean syphilis seroprevalence of 8.3%, an estimated 2.3 million pregnant women each year in this region would harbour *Treponema pallidum* and potentially could transmit the infection to their babies, and 1.64 million of these would either not be diagnosed or not treated. As a result, in sub-Saharan Africa alone, half a million babies die of syphilis each year.[2 7]

The consequences of syphilis in pregnancy are so severe that universal screening of pregnant women for syphilis is national policy in most countries. Prenatal syphilis screening remains cost beneficial at prevalences as low as 5 per 100 000.[8–10] Antenatal screening and treatment for syphilis are among the most cost-effective health interventions available (table 3).

Abbreviations: DCP, disease control priorities in developing countries; EQA, external quality assurance; HPV, human papilloma virus; HSV, herpes simplex virus; MDGs, millennium development goals; RPR, rapid plasma reagin; SDI, Sexually Transmitted Diseases Diagnostics Initiative; STIs, sexually transmitted infections; VDRL, venereal disease research laboratory; WHO, World Health Organization

Table 1 Mean distance to nearest medical facility

Country	Distance (km)
Benin	7.5
Bolivia	11.8
Chad	22.9
Haiti	8.0
Madagascar	15.5
Niger	26.9
Tanzania	4.7
Uganda	4.7
Zimbabwe	8.6

Selected from the 2004 World Development Report,[5] page 22.

Simple rapid tests such as the rapid plasma reagin (RPR) or venereal diseases research laboratory (VDRL) tests are used for prenatal screening.[13] Unfortunately, these are often not available at primary health care settings in developing countries because they require a source of electricity to refrigerate the RPR or VDRL reagent, operate a centrifuge to separate sera from whole blood and power a rotator to mix the reaction. The requirement for cold storage also limits the volume of reagents and tests that can be procured by a central facility at any one time, leading to frequent stock-outs of the tests at district level hospitals and health care centres. Women must return to receive test results as the testing is batched to save time and reagents, or specimens may be sent to a central laboratory for processing. In a consultation conducted by the SDI on strategies to increase access to prenatal screening in Tanzania, a number of barriers to RPR testing were identified (table 4)

Despite recent successes in increasing coverage for antenatal services in developing countries, most pregnant women fail to get screened for syphilis.[14] In Bolivia in 1996, 76% of women had access to prenatal care but only 16% were screened for syphilis.[15] In the 1990s, demonstration projects showed that significant reductions in the prevalence of maternal and congenital syphilis can be achieved with decentralisation of antenatal screening.[16–19] In Haiti, the introduction of solar-powered generators to operate centrifuges and rotators, propane powered refrigerators to store the RPR reagent, and the training of field workers to perform RPR tests in rural health centres, resulted in a 75% decline in the incidence of congenital syphilis over two years.[20] However, these demonstration projects on decentralisation of screening services have not led to sustainable expanded coverage of antenatal screening for syphilis.

In this supplement, nine rapid syphilis tests that approach the ASSURED criteria in terms of operational characteristics were evaluated with well-characterised archived specimens from laboratories in diverse geographical settings.[21] Tests with reasonable performance characteristics which can be performed on whole blood were evaluated in field settings in Bolivia, Brazil, China, Haiti, Peru and Tanzania.[22–24] Mathematical models developed with data from the field site in Mwanza, Tanzania showed that the use of these rapid tests is cost-effective, and has the potential to make a substantial impact in averting congenital syphilis in primary health care settings.[25]

LACK OF DIAGNOSTIC TESTS FOR THE DETECTION OF GENITAL CHLAMYDIAL AND GONOCOCCAL INFECTIONS

The World Health Organization (WHO) has promoted syndromic management of STIs in settings where access to laboratory services or resources is limited.[26] Patients with syndromes such as urethral or vaginal discharge, genital ulcers or lower abdominal pain are treated for all the likely causes of that syndrome.

Table 2 The ideal rapid test: ASSURED criteria

A = Affordable

S = Sensitive

S = Specific

U = User-friendly (simple to perform in a few steps with minimal training)

R = Robust and rapid (results available in less than 30 min)

E = Equipment-free

D = Deliverable to those who need them

(www.who.int/std_diagnostics)

The syndromic approach works particularly well for men with urethral discharge and genital ulcers, but evaluations showed that the algorithm for vaginal discharge lacks both sensitivity and specificity for the identification of women with *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infection.[27–29] Most women (usually over 90%) with this syndrome do not have these cervical infections, but many suffer from vaginal infections (especially bacterial vaginosis or trichomoniasis).[30]

Since facilities for culture, antigen detection or nucleic acid amplification tests are not available outside of major urban centres, it is not possible to diagnose gonorrhoea or *C trachomatis* infection in women at peripheral health services in most developing countries. Where microscopy is available, Gram stained smear of an endocervical swab can be used to diagnose gonorrhoea, but this technique is at best only about 50% sensitive in women and is also non-specific. Hence the syndromic approach is widely promoted and used. Although simple to use and inexpensive, the poor performance of the syndromic approach to the management of cervical infection is well documented and often can lead to problems in unnecessary treatment and difficulties with partner notification.[27–29] Unnecessary treatment results in increased drug costs, possible side effect of multiple drugs, changes in endogenous flora and the potential for increased drug resistance. Women may be at risk of stigma and violence from their sexual partners if they are asked to refer their partners for STI treatment when they do not have an STI.

There is a vast need for simple, affordable point-of-care tests for these infections in women. Articles in this supplement describe the results of evaluations of two rapid tests for gonorrhoea and one for chlamydia.[31–33] Although these tests have reasonable specificity, their sensitivity could be improved.

LACK OF REGULATORY CONTROL OF THE QUALITY OF STI DIAGNOSTICS

Clinical care for STIs in the developing world is compromised if regulatory control of diagnostics in both the public and private sector is not done effectively. Many countries do not have

Table 3 Cost-effectiveness of common health interventions[11 12]

Health interventions	Cost per DALY saved (US$)
Expansion of childhood immunisations	$ 2–20
Oral rehydration therapy	$ 7–28
Antenatal syphilis screening	$ 4–19
STI treatment to interrupt HIV transmission	$10–100
Prevention of mother to child transmission of HIV (15% prevalence)	$50–200

DALY, disability adjusted life-years lost; STI, sexually transmitted infection.

Table 4 Barriers to effective syphilis screening using rapid plasma reagin (RPR) tests

Health seeker	Health provider
Distance to clinic	Procurement—limited quantities because of need for refrigeration
Failure to return for test results and treatment	Limited facilities for cold chain transport and storage Clinic constraints: • Few trained personnel • Facilities inadequate, eg, – refrigerator, centrifuge and rotator may not be available – poor lighting Organisation of services—drugs and diagnostics stock-outs

sufficient infrastructure to determine the quality of diagnostic tests. A CE mark on a product only addresses manufacturing quality and does not imply acceptable test performance. WHO/TDR conducted a global survey of diagnostics regulatory practices in 2001. A questionnaire sent to 191 WHO member states inquired about regulation of in vitro diagnostics (other than those used for blood banking), and if clinical trials were required for regulatory approval.[34] Of the 85 countries that responded, 48% regulate in vitro diagnostics for infectious diseases. Of the 24 countries that provided data on which diagnostics were regulated, 83% regulate diagnostics for HIV, 92% for hepatitis, 42% for STIs and 13% each for tuberculosis and malaria.

Of the countries that regulate diagnostics, 68% require the submission of clinical trial data. However, no standard exists for diagnostic evaluation or approval in developing countries. An industry survey conducted by WHO/TDR in 2003 showed that company spending on evaluation of a product varied from US$2000 to more than $1 million. Diagnostic trials had been conducted in as few as 15 patients (unpublished TDR data). A recent dossier received at the WHO SDI on a syphilis rapid test contained a claim of 100% sensitivity and 100% specificity. The evaluation was conducted in just over 100 patients, of whom only three were positive for syphilis!

Physicians often select tests based on information provided in the product insert or from published data. Information on the performance of tests sold in developing countries is often biased because of flaws in the design and conduct of evaluations.[35] Hence diagnostics are often used without proof of their effectiveness. The consequences of low quality diagnostics for STIs include wasted precious resources and mismanagement of patients, potentially leading to serious sequelae in the infected individual and failure to interrupt the chain of transmission in the population.

THE WAY FORWARD

Rapid tests for HIV infection have shown the potential for such tests to be rapidly and widely introduced in both developed and developing countries. Having been evaluated by WHO and shown to be both sensitive and specific, they became available at affordable prices through the WHO bulk procurement programme, and were approved for use in the USA by the Food and Drug Administration. The demand for an immediate result, and the advantages in terms of patient management, are so great that rapid tests are now routinely used in voluntary counselling and testing centres and antenatal clinics worldwide. This will hopefully be similar for rapid STI tests that fulfill the ASSURED criteria. However, there are 10 areas where more work is needed before STI tests can be widely used.

Table 5 Score card for current rapid STI tests

Test characteristics	NG/CT	Syphilis
Affordable	US$6–15	US$0.19–3.0
Sensitive	43–65%	85–99%
Specific	98%	93–100%
User-friendly	7–14 steps	3–4 steps
Rapid/robust	30′/storage at 8–30°C	20′/storage at 8–30°C
Equipment-free	Yes	Yes
Deliverable	?	Negotiated pricing through the WHO Bulk Procurement Scheme

CT, *Chlamydia trachomatis*; NG, *Neisseria gonorrheoea*.

1. Continued search for ASSURED tests

The ASSURED score card based on select STI tests evaluated in this supplement is shown in table 5.[21–24 31–33]

Mathematical models developed at the Tanzania site for prenatal syphilis screening showed that screening with rapid tests is cost-effective if the price per test does not exceed US$0.63.[25] Currently eight rapid syphilis tests evaluated by the SDI are included in the WHO Bulk Procurement Scheme at negotiated pricing ranging from US$0.19–1.00. Improved tests for syphilis that can distinguish between active and past treated infection are still needed. The US Centers for Disease Control and Prevention has been assisting test developers and manufacturers to develop rapid tests that will combine non-treponemal and treponemal test on a solid phase, in either a flow-through or immunochromatographic strip format. These prototypes will soon be ready for evaluation.

Clearly there is a need for more sensitive, simpler and cheaper rapid tests for *C trachomatis* and *N gonorrhoeae*.[36 37] Gift *et al* have shown that a rapid test with a sensitivity of 65% can lead to a greater proportion of infected patients treated compared to a nucleic acid amplified test with a sensitivity of 90%, when the return rate for test results and treatment is low.[38] Mathematical models developed using data from the SDI site in Benin showed that rapid tests with sensitivity of 70% and specificity of 98% have the potential to reduce the prevalence of these infections in sex workers and the potential to avert HIV infections in their clients.[39] Encouraging data on an improved rapid test for ocular chlamydial infection have recently been published,[40] and a number of tests for gonorrhoea await evaluation by SDI.

2. Piloting a road map for test introduction

Too often, research findings are not effectively translated into control strategies, policies and programmes.[41] There is a gap between demonstrating the effectiveness of a novel intervention in a demonstration project and its adoption to scale in countries. In preparation for introduction of rapid tests into settings where no previous testing was possible, SDI conducted consultations in several regions of the world to define the key elements required for the successful and sustainable introduction of rapid syphilis tests (table 6). These activities form a basic road map for the introduction of new tools that can be used for diagnostics, vaccines and medicines.

As a result of the SDI regional consultations, 12 countries have initiated the development of a road map for the introduction of syphilis screening in their country. Such a road map can be broadly used for the introduction of other technologies for a variety of infectious diseases.

3. Developing sustainable diagnostic quality assurance programmes

Increasing access to testing in primary care settings means that tests will be stored at temperatures in excess of 30℃ and no

Table 6 Key elements of a road map for the introduction of rapid STI tests

Key elements	Enabling activities
Advocacy	Define disease burden, problems with status quo and what is needed to improve it, the attributable benefit of introducing new tool (such as a rapid test), eg, lives saved or morbidity prevented, cost-effectiveness of strategies for tool introduction
Policy	Accrue evidence needed for development or change of policy; determine fiscal and human resource implications of policy or policy change, feasibility of implementation
Testing algorithms and treatment	Convene expert group and stakeholders to review WHO guidelines for use of tests, and adapt as country or local guidelines and testing algorithms
Test selection and regulatory approval	Review data on test performance and operational characteristics available from the SDI website and peer-reviewed literature, compute costs based on volume of purchase, negotiated pricing available from the WHO Bulk Procurement Scheme; select tests and work with regulatory authorities on approval for sale in country
Procurement and logistics	UN member states can procure through the WHO or similar UN Bulk Procurement Schemes. Develop logistics for importation and distribution in country, in concert with the distribution of medicines to avoid stock-outs of either commodity at district level and remote settings
Training and supervision	Develop or adapt training modules and develop a system for training the trainers at different levels of health care system
Quality assurance	Develop a quality assurance scheme for ensuring validity of tests in remote settings, and proficiency of health workers at performing rapid tests
Monitoring and evaluation	Develop plans for monitoring and evaluating the effectiveness and impact of rapid test introduction
Surveillance	Monitor disease trends to assess benefit attributable to test introduction
Communications campaign	Develop and disseminate information on rapid tests to stakeholders and target populations
Partnerships	Develop partnerships (donors, public and private sector, NGOs, civil societies) for test introduction and coordinate effort to ensure synergy and minimise duplication
Academic sensitisation	Organise workshops for professional societies and introduce new diagnostics into continuing medical education and medical curriculum

NGOs, non-governmental organisations; SDI, Sexually Transmitted Diseases Diagnostics Initiative; UN, United Nations; WHO, World Health Organization.

longer be performed by trained laboratory technicians. It is therefore critical that countries set up external quality assurance (EQA) schemes to ensure that the quality of the tests has not been compromised during storage and that health workers are proficient at performing the tests. These national schemes can be developed in conjunction with quality assurance schemes for other diagnostic testing and should be supported technically by a network of expert laboratories, inside and outside of the country. This requires the development of a business plan for obtaining sufficient funds to cover set up costs and identify means of sustaining the programme.

4. Taking advantage of available programme infrastructure and resources

Capacity for introduction of new tools varies significantly between countries, and between rural and urban areas within countries. The success of increasing access to syphilis screening depends on the level of political commitment, the existence of a robust health infrastructure to facilitate the implementation, and the availability of screening tools. In resource limited settings, health service providers have to prioritise their scarce monetary and human resources to accommodate many competing demands. There are also operational and administrative difficulties such as frequent stock-outs of tests or drugs for treatment, leading to poor motivation in implementing and scaling-up screening services. Instead of setting up a new infrastructure for decentralised STI diagnostic services, every effort should be made to take advantage of new or existing initiatives, such as antenatal care programmes, Prevention of Mother to Child Transmission programmes for HIV, and HIV Voluntary Counselling and Testing programmes.

5. Using the internet more creatively

In recent years, the internet has emerged as a risk environment for STIs and many STI testing services are available from the internet.[42–45] The sensitivity of nucleic acid amplification tests has made it possible to use non-invasive specimens, such as urine or vaginal swabs, for the diagnosis of bacterial STIs. As these specimens can be stored and transported at ambient temperatures, there has been a proliferation of internet-based STI testing services. The type of tests and the quality of testing used on these internet services are unknown. Simple rapid STI tests are sold on the internet or ''over the counter''. Few countries regulate STI tests sold through these venues. STI control programmes need to exploit the popularity of the internet to provide scientific information to health care professionals and the lay public on how STIs should be diagnosed and treated, and make the public aware of the consequences of misdiagnosis.

6. Ensuring a sustained effort at disease control programmes

The availability of new tools that can be used to increase coverage for prenatal screening has sparked interest in planning for the global elimination of congenital syphilis. While ''eradication'' or ''elimination'' are laudable goals, eradication has been achieved for smallpox, and is being pursued for river blindness and polio, with local success in some regions. Another treponematosis, yaws, has been eliminated from some regions, but not globally. Elimination of syphilis is being pursued in the USA, and has been achieved transiently in some areas of the world, such as China and King County, Washington, USA. However, it returned with a vengeance as sexual behaviours and patterns of sexual mixing changed.[46 47] Syphilis outbreaks elsewhere in the USA, eastern Europe and the Russian Federation are also testament to the resilience of the pathogen.[48 49] In general, the concept of elimination of syphilis, given available tools, is unrealistic and diverts attention for the need for continuous and sustained control programmes. The addition of ASSURED rapid diagnostics for syphilis, as one component of a sustained effort, can improve the potential for better control of adverse consequences of syphilis globally regardless of ongoing endemic disease.

7. Defining the role of rapid diagnostics for viral STIs

Recent studies have identified herpes simplex virus 2 (HSV-2) as a major risk factor for the acquisition and transmission of HIV.[50] A vaccine for human papilloma virus (HPV) has been shown to be effective in preventing the infection by the major oncogenic types.[51] Although the role of diagnostics in the control of many viral STIs remains unclear, more strategic planning needs to be given to the role of diagnostics in the control and prevention of HSV.

8. Assessing the need for rapid tests for vaginal discharge

The syndromic management of vaginal discharge remains problematic. Rapid tests could improve the specificity of syndromic management. The performance, operational characteristics and costs of rapid tests for *C trachomatis, N gonorrhoeae, Trichomonas vaginalis* and bacterial vaginosis are

now available. In the absence of a multiplex test, the cost of using multiple rapid tests to detect all the major causes of this syndrome may be prohibitive, and certainly not cost-effective compared to presumptive treatment. A consensus meeting to review and recommend how these tests should be used in the management of vaginal discharge is warranted.

9. Developing a consensus on how rapid tests for *C trachomatis* and *N gonorrhoeae* should be used

The performance and operational characteristics of rapid tests for the screening and case management of individuals with genital chlamydial and gonococcal infections need to be better defined. Given the psychosocial consequences of a misdiagnosis for STIs, tests should be highly specific. From the perspective of STI control programmes, rapid tests can improve control of STIs in high risk populations. In the general population, where the prevalence may be low, even a test with a specificity of 98% may yield more false than true positives. Once rapid tests become commercially available, it would be difficult to prevent their widespread use. Guidelines are needed on how rapid tests should be used and updated as test performance improves.

10. Inclusion of STI diagnostics as part of an essential diagnostics package for improving health in developing countries

The control of infectious diseases of public health importance in the developing world is often hampered by lack of resources. WHO has developed an Essential Medicines package with the aims of ensuring that public health programmes in developing countries have access to medicines that are deemed essential for a sound public health programme. As it is increasingly clear that the lack of affordable appropriate diagnostics is a major barrier to health in the developing world, an essential diagnostics package that includes rapid tests for HIV, tuberculosis, malaria and STIs should be developed.

CONCLUSIONS

At the Millennium Summit in 2000, representatives from 189 countries committed to the attainment of a set of millennium development goals (MDGs). Goal number 4 calls for the reduction of mortality under 5 years of age (U5MR) by 75%; goal number 5 calls for improvements in maternal health; and goal number 6 calls for halting and reversing the spread of AIDS by 2015. Now nearly half way towards the deadline, most countries are still struggling to sustain a course of action that will achieve the desired results.

In the second global project on disease control priorities in developing countries (DCP2), released in 2006 after consultations with over 600 experts worldwide, two concerns are:

- Half of all deaths (including stillbirths) of children under age 5 years occur at ages under 28 days, but little attention has been paid to this age group. Cost-effective interventions exist.
- Treatment of HIV positive mothers, treatment of STIs, free distribution of condoms, and other interventions can cost-effectively interrupt HIV transmission. These preventive interventions continue to receive inadequate attention.

Almost certainly if we are to achieve the MDGs of reducing mortality under the age of 5 years by 75% by 2015, comprehensive clinic based screening and treatment programmes using rapid tests will need to be made routine in prenatal care. It is hoped that increased access to quality-assured rapid STI tests will go a long way towards addressing DCP2 recommendations, and help countries to achieve their MDGs.

Authors' affiliations

R W Peeling, Sexually Transmitted Diseases Diagnostics Initiative (SDI), World Health Organization, Geneva, Switzerland
K K Holmes, University of Washington, Seattle, Washington, USA
David Mabey, London School of Hygiene and Tropical Medicine, London, UK
Allan Ronald, National Collaborating Center for Infectious Diseases, Winnipeg, Manitoba, Canada

Competing interests: none declared

REFERENCES

1 **World Health Organization**. *Global prevalence and incidence of selected curable sexually transmitted infections: overview and estimates*. Geneva: WHO, WHO/HIV_AIDS/2001, 02.
2 **Schmid G**. Economic and programmatic aspects of congenital syphilis prevention. *Bull World Health Organ* 2004;**82**:402–9.
3 **Petti CA**, Polage CR, Quinn TC, *et al*. Laboratory medicine in Africa: a barrier to effective health care. *Clin Infect Dis* 2006;**42**:377–82.
4 **Oliff M**, Mayaud P, Brugha R, *et al*. Integrating reproductive health services in a reforming health sector: the case of Tanzania. *Repro Health Matters* 2003;**11**:37–48.
5 **World Bank**. *World development report 2004: making services work for poor people*. New York: Oxford University Press for the World Bank, 2004.
6 **UNICEF/UNDP/World Bank/WHO Special Program for Research and Training in Tropical Diseases, World Health Organization**. Sexually Transmitted Diseases Diagnostics Initiative (SDI). www.who.int/std_diagnostics.
7 **Gloyd S**, Chai S, Mercer MA. Antenatal syphilis in sub-Saharan Africa: missed opportunities for mortality reduction. *Health Policy Plan* 2001;**16**:29–34.
8 **Stray-Pedersen B**. Economic analaysis of maternal screening to prevent congenital syphilis. *Sex Transm Dis* 1983;**10**:167–72.
9 **Phaosavasdi S**, Thasanapradit P. Cost-benefit analysis of diagnosis and treatment of syphilis in pregnant women. *J Med Assoc Thail* 1997;**12**:90–4.
10 **Connor N**, Roberts J, Nicoll A. Strategic option for antenatal screening for syphilis in the United Kingdom: a cost effectiveness analysis. *Journal of Medical Screening* 2000;**7**:7–13.
11 **World Bank**. *Priorities in health*. Oxford University Press for the World Bank, 2006.
12 **Terris Prestholt F**, Watson Jones D, Mugeye K, *et al*. Is antenatal syphilis screening still cost effective in sub-Saharan Africa. *Sex Transm Infect* 2003;**79**:375–81.
13 **Peeling RW**, Ye H. Diagnostic tools for preventing and managing maternal and congenital syphilis: an overview. *Bull World Health Organ* 2004;**82**:439–46.
14 WHO/UNICEF joint press release 2004: Far more pregnant women getting antenatal care.
15 **Southwick KL**, Blanco S, Santander A, *et al*. Maternal and congenital syphilis in Bolivia, 1996: prevalence and risk factors. *Bull World Health Organ* 2001;**79**:33–42.
16 **Hira SK**, Bhat GJ, Chikamata DM, *et al*. Syphilis intervention in pregnancy: Zambian demonstration project. *Genitourin Med* 1990;**66**:159–64.
17 **Jenniskens F**, Obwaka E, Kirisuah S, *et al*. Syphilis control in pregnancy: decentralization of screening facilities to primary care level, a demonstration project in Nairobi, Kenya. *Int J Gynaecol Obstet* 1995;**48**(Suppl):S121–8.
18 **Rotchford K**, Lombard C, Zuma K, *et al*. Impact on perinatal mortality of missed opportunities to treat maternal syphilis in rural South Africa: baseline results from a clinic randomized controlled trial. *Tropical Medicine and International Health* 2000;**5**:800–4.
19 **Fonck K**, Claeys P, Bashir F, *et al*. Syphilis control during pregnancy: effectiveness and sustainability of a decentralized program. *Am J Public Health* 2001;**91**:705–7.
20 **Fitzgerald DW**, Behets F, Preval J, *et al*. Decreased congenital syphilis incidence in Haiti's rural Artibonite Region following decentralized prenatal screening. *Am J Public Health* 2003;**93**:444–6.
21 **Herring AJ**, Ballard RC, Pope V, *et al*. A multi-centre evaluation of nine rapid, point-of-care syphilis tests using archived sera. *Sex Transm Infect* 2006;**82**(suppl v):v7–12.
22 **Mabey D**, Peeling RW, Ballard R, *et al*. Prospective, multi-centre clinic-based evaluation of four rapid diagnostic tests for syphilis. *Sex Transm Infect* 2006;**82**(suppl v):v13–16.
23 **Campos PE**, Buffardi AL, Chiappe M, *et al*. Utility of the Determine Syphilis TP rapid test in commercial sex venues in Peru. *Sex Transm Infect* 2006;**82**(suppl v):v22–5.
24 **Tinajeros F**, Grossman D, Richmond K, *et al*. Diagnostic accuracy of a point-of-care syphilis test when used among pregnant women in Bolivia. *Sex Transm Infect* 2006;**82**(suppl v):v17–21.
25 **Vickerman P**, Peeling RW, Terris-Prestholt F, *et al*. Modelling the cost-effectiveness of introducing rapid syphilis tests into an antenatal syphilis screening programme in Mwanza, Tanzania. *Sex Transm Infect* 2006;**82**(suppl v):v38–43.
26 **World Health Organization**. *Guidelines for the management of sexually transmitted infections*, WHO/HIV_AIDS/2001.01. Geneva: WHO, 2001.
27 **Alary M**, *et al*. Decline in the prevalence of HIV and sexually transmitted diseases among female sex workers in Cotonou, Benin, 1993–1999. *AIDS* 2002;**16**:463.

28 **Hawkes S**, Morison L, Foster S, *et al*. Reproductive-tract infections in women in low-income, low-prevalence situations: assessment of syndromic management in Matlab, Bangladesh. *Lancet* 1999;**354**:1776–81.
29 **Pepin J**, Deslandes S, Khonde N, *et al*. Low prevalence of cervical infections in women with vaginal discharge in west Africa: implications for syndromic management. *Sex Transm Infect* 2004;**80**:230–5.
30 **Patel V**, Pednekar S, Weiss H, *et al*. Why do women complain of vaginal discharge? A population survey of infectious and psychosocial risk factors in a South Asian community. *Int J Epidemiol* 2005;**34**:853.
31 **Alary M**, Gbénafa-Agossa C, Aïna G, *et al*. Evaluation of a rapid point-of-care test for the detection of gonococcal infection among female sex workers in Benin. *Sex Transm Infect* 2006;**82**(suppl v):v29–32.
32 **Benzaken AS**, Galban EG, Antunes W, *et al*. Diagnosis of gonococcal infection in high risk women using a rapid test. *Sex Transm Infect* 2006;**82**(suppl v):v26–8.
33 **Yin Y-P**, Peeling RW, Chen X-S, *et al*. Clinic-based evaluation of Clearview Chlamydia MF for detection of *Chlamydia trachomatis* in vaginal and cervical specimens from women at high-risk in China. *Sex Transm Infect* 2006;**82**(suppl v):v33–7.
34 **World Health Organization**. *Diagnostics for tuberculosis: global demand and market potential. Annex regulation of in vitro diagnostics: a global perspective*. Geneva: WHO, 2006, 194–203.
35 **Peeling RW**, Smith PJ, Bossuyt PMM. A guide for diagnostic evaluations. *Nature Microbiology Reviews*. September 2006: S2–6, www.nature.com/nrmicro/supplements, (Suppl).
36 **Vickerman P**, Watts C, Alary M, *et al*. Sensitivity requirements for the point of care diagnosis of *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. *Sex Transm Infect* 2003;**79**:363–7.
37 **Vickerman P**, Peeling RW, Watts C, *et al*. Detection of gonococcal infection: pros and cons of a rapid test. *Mol Diagn* 2005;**9**:175–9.
38 **Gift TL**, Pate MS, Hook EW, *et al*. The rapid test paradox: when fewer cases detected lead to more cases treated: a decision analysis of tests for *Chlamydia trachomatis*. *Sex Transm Dis* 1999;**26**:241–2.
39 **Vickerman P**, Watts C, Peeling RW, *et al*. Modeling the costeffectiveness of rapid point-of-care diagnostic tests for the control of HIV and other sexually transmitted infections among female sex workers. *Sex Transm Infect* 2006;**82**:403–12.
40 **Michel CEC**, Solomon AW, Magbanua JPV, *et al*. A rapid point-of-care assay to target antibiotic treatment for trachoma elimination. *Lancet* 2006;**367**:1585.
41 **Berwick D**. Disseminating innovations in health care. *JAMA* 2003;**289**:1969–74.
42 **Peeling RW**. Testing for sexually transmitted infections: a brave new world? *Sex Transm Infect* 2006;**82**:425–30.
43 **McFarlane M**, Bull S, Rietmeijer CA. The internet as a newly emerging risk environment for sexually transmitted diseases. *JAMA* 2000;**284**:443–6.
44 **McFarlane M**, Kachur R, Bull S, *et al*. Women, the internet, and sexually transmitted infections. *Women's Health (Larchmt)* 2004;**13**:689–94.
45 **McFarlane M**, Kachur R, Klausner JD, *et al*. Internet-based health promotion and disease central in the 8 cities: Successes, barriers, and future plans. *Sex Transm Dis* 2005;**32**:S60–4.
46 **Lin C**, Gao X, Chen XS, *et al*. China's syphilis epidemic: a systematic review of seroprevalence studies. *Sex Transm Dis* August 10 2006 (E-Pub).
47 **Williams LA**, Klausner JD, Whittington WL, *et al*. Elimination and retroduction of primary and secondary syphilis. *Am J Public Health* 1999;**89**:1093–7.
48 **Marra CM**, Holmes KK. Update on syphilis: resurgence of an old problem. *JAMA* 2003;**290**:1510–4.
49 **Tichonova L**, Borisenko K, Ward H, *et al*. Epidemics of syphilis in the Russian Federation: trends, origins, and priorities for control. *Lancet* 1997;**350**:210–13.
50 **Celum C**, Levine R, Weaver M, *et al*. Genital herpes and human immunodeficiency virus: double trouble. *Bull World Health Organ* 2004;**82**:447–53.
51 **Schiller JT**, Lowry DR. Prospects for cervical cancer prevention by human papillomavirus vaccination. *Cancer Res* 2006;**66**:10229–32.