HIV/AIDS & STI NEWS

From the DFID Knowledge Programme on HIV/AIDS & STI

MRC Medical Research Council

No. 6, July 2004

From the editorial board

This is the **newsletter** of the DFID* Knowledge Programme on HIV/AIDS and STIs. The Programme is funded by the Department for International Development, UK, and based at the London School of Hygiene and Tropical Medicine (LSHTM) and the Medical Research Council (MRC), Social and Public Health Sciences Unit (SPHSU), University of Glasgow. It has five Knowledge Areas: 1) Determinants of sexual behaviour; 2) Biological risk factors for HIV and STI transmission; 3) Factors affecting use and effectiveness of care and prevention services for HIV/AIDS and STIs; 4) Impact and cost-effectiveness of interventions against HIV and STIs; and 5) HIV/AIDS and STI prevention and care priorities and policies.

These newsletters provide a forum for the exchange of research within the Programme and introduce other relevant research from Programme members. They form a useful means to exchange information such as updates on projects underway, conferences, new grants, etc. Initially, the selected articles reflect the contents of our bi-annual scientific meetings in London (or Glasgow). Contributions from Programme members are invited. Please email comments and suggestions to: Tamsin.Kelk@lshtm.ac.uk. Also see the Programme's website at: http://www.lshtm.ac.uk/dfid/aids/

Philippe Mayaud, David Mabey, Graham Hart and Tamsin Kelk

In this issue

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Control of Congenital Syphilis

Introduction

Syphilis is an example of an STI that can be successfully controlled by public health measures due to the availability of a highly sensitive diagnostic test and a highly effective and affordable treatment. Yet it continues to be highly prevalent in many parts of the world, with rates in pregnant women ranging from 2.5% in Burkina Faso to 17.4% in Cameroon in 1999.

Maternal syphilis is associated with various adverse pregnancy outcomes such as spontaneous abortion, premature delivery, stillbirth, low birth weight and congenital syphilis – the latter occurring in about one-third of new-born babies of women with untreated syphilis. However, the screening and treatment of syphilis in pregnant women are inexpensive, simple and cost-effective interventions.

Strategies to control congenital syphilis will need to ensure that: 1) all pregnant women receive antenatal care early in their pregnancy; 2) syphilis screening is included in antenatal care services for all women; 3) care and treatment is provided to all infected pregnant women and their partners; and 4) all women remain uninfected during pregnancy.

Most countries have health policies for the control of congenital syphilis. However, very few countries implement these policies successfully. In contrast to the effort being expended on the control of vertical transmission of HIV, very few resources (financial, political, logistical) are expended on the control of congenital syphilis. This situation can and must change if congenital syphilis is to be brought under control.

WHO evaluation of rapid syphilis tests

The ideal STI diagnostic test should be affordable, sensitive, specific, user-friendly, rapid, robust (refrigeration not required) and equipment free (easily collected non-invasive specimens, e.g. urine). Over 20 rapid treponemal tests (*Treponema pallidum* is the causative agent of syphilis) for diagnosing syphilis are available, but reliable information on their performance is limited.

WHO's SDI* rapid test evaluations are being carried out in two phases: 1) laboratory-based evaluation of test performance and reliability, and to select the most promising tests to undergo field trials; 2) field trials of test performance, acceptability to patients and care providers, and utility for disease control and prevention.

Laboratory-based evaluation

Six tests have been evaluated: Determine Syphilis TP (Abbott Laboratories), Syphilis Fast (Diesse Diagnostica), Espline TP (Fujirebio Inc), Syphicheck-WB (Qualpro Diagnostics), SD Bioline Syphilis 3.0 (Standard Diagnostics Inc) and Visitect Syphilis (Omega Diagnostics). Evaluation sites were in South Africa, Tanzania, The Gambia, Haiti, USA, Sri Lanka, China (2 sites) and Russia. 789 archived serum samples were used.

Espline, Determine and Bioline showed the highest sensitivity, at 97.7, 97.2 and 95.0%, respectively (range 84.5–97.7%); scores significantly different from the other 3 tests. Highest for specificity were Visitect (98.0%) and Syphicheck (97.7%) (range 92.8.0–98.0%); again, these scores were significantly different from the other 4 tests. All six tests were very user friendly and were not significantly different in terms of reproducibility.

Details of these results can be found at http://www.who.int/std_diagnostics

Field evaluation

Rapid syphilis tests are currently being evaluated in 6 field sites: Durban (South Africa), Mwanza (Tanzania), Manaus (Brazil), Port au Prince (Haiti), China (2 sites) and Moscow. Preliminary results suggest that sensitivity is reduced when whole blood is used, compared to serum.

Conclusion

In general, tests with higher sensitivities tend to have lower specificities and vice versa. In the laboratory evaluation, all tests showed reasonable reliability and were considered by site staff as easy to use.

Most of these tests utilize treponemal antigens. Since treponemal antibodies tend to be retained for years, treponemal tests may be less useful in areas of high disease prevalence as they cannot be used to distinguish between new and prior (successfully treated) infection. Thus the challenge ahead is to develop a test to distinguish between past treated infection and current infection.

Rosanna W Peeling, SDI, WHO, Geneva*

*The Sexually Transmitted Diseases Diagnostics Initiative (SDI) is a programme within the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR).

Maternal syphilis in Mwanza, Tanzania

Study objectives were to measure the proportion of adverse pregnancy outcomes attributable to syphilis in pregnant women, and to measure the impact of ANC syphilis screening and treatment with single dose benzathine penicillin to prevent adverse pregnancy outcomes. Two cohort studies were undertaken in Mwanza, Tanzania.

1) Untreated maternal syphilis – impact on pregnancy outcome

Outcomes (stillbirth, low birth weight, premature delivery and intra-uterine growth retardation, or IUGR) were compared retrospectively in 380 women, with and without serological evidence of syphilis at delivery, who had not been screened antenatally.

Maternal syphilis was found to be associated with adverse pregnancy outcomes, especially high titre active syphilis. Untreated women have very high risk of stillbirth and prematurity.

Birth outcomes and high titre active syphilis

	Preterm	IUGR	Stillbirth	Normal
High titre active syphilis	15%	9%	25%	51%
No syphilis	3%	7%	1%	89%

Most women (83%) attended ANC at some point in pregnancy, thus how effective is screening and single dose treatment with benzathine penicillin during ANC visits to prevent adverse pregnancy outcomes?

2) Effectiveness of screening and treatment with single dose benzathine penicillin

This prospective study recruited pregnant women who were attending ANC and had no prior RPR test. A routine RPR test was administered. For those testing positive, benzathine penicillin G, 2.4 million units IM, was given.

19,878 women (RPR+ 8%) were screened. 1688 (RPR+ 561; RPR- 1127) were recruited and interviewed. 1538 (91%) were tested and followed at delivery, and 1437 followed-up at 3 months post-delivery.

Delivery outcomes by syphilis serostatus

	RPR-TPHA-	Treated TPHA +/- FTA+		Treated BFP	P
		RPR ≥1:8	RPR <1:8		
Stillbirth	2.5%	2.3%	4.8%	0.9%	0.12
Live births					
Low birth weight	9.2%	6.3%	5.2%	7.1%	0.25
Premature	11.8%	8.5%	9.3%	11.4%	0.54
IUGR	4.1%	3.1%	1.6%	3.0%	0.38
Any adverse outcome	17.3%	15.2%	15.2%	16.0%	0.86

Risk of adverse birth outcomes

	No syphilis OR	Treated high titre active, RPR ≥1:8 OR (95% CI)	Treated low titre active, RPR <1:8 OR (95% CI)	Treated BFP OR (95% CI)
Stillbirth	1	0.68 (0.2-2.4)	1.81 (0.9-3.9)	0.31 (0.04-2.4)
Live births				
Low birth weight	1	0.53 (0.2-1.3)	0.67 (0.3-1.4)	0.60 (0.3-1.4)
Prematurity	1	0.58 (0.3-1.1)	0.76 (0.5-1.2)	0.86 (0.5-1.6)
IUGR	1	0.62 (0.2-2.1)	0.52 (0.2-1.8)	0.60 (0.2-2.1)
Stillbirths / live births All outcomes	1	0.76 (0.4-1.4)	0.95 (0.6-1.5)	0.86 (0.5-1.5)

Conclusion

Women who received treatment at ANC for active syphilis with single dose benzathine penicillin had the *same* or *lower* risks of adverse pregnancy outcomes compared to seronegative women. Single dose treatment was found to be effective in preventing adverse outcomes attributable to maternal syphilis. Therefore, early attendance at ANC for screening (and other benefits) should be encouraged, and ANC syphilis screening programmes scaled up.

Rapid specific treponemal tests need to be evaluated as confirmatory screening tests in regions with high BFP reactions on RPR. Research is needed on strategies, effectiveness and consequences of partner notification.

Deborah Watson-Jones, LSHTM

Collaborators

NIMR: J Changalucha. Municipal Office of Health: K Mugeye, L Ndeki, Z Kanga, J Marealle, J Lucas. Sengerema DDH: D Ngeleja. Bugando Medical Centre: B Gumodoka. Sekou Toure Regional Hospital: M Rusizoka, K Magese. AMREF: A Gavyole. LSHTM: D Mabey, R Hayes, H Weiss, J Todd, T Hurst, A Hunt-Cooke, J Tucker. Institute of Tropical Medicine, Belgium: A Buve, E Van Dyck. Universities of Montreal & Quebec, Canada: R Peeling, M Alary. University of Newcastle: J Bulmer. Royal Free Hospital: S Blackmore. *Funded* by The Wellcome Trust, London.

Cost-effectiveness of antenatal syphilis screening in Tanzania

Study objectives were 1) to estimate the cost-effectiveness of on-site antenatal syphilis screening and treatment in Mwanza, Tanzania, and 2) to compare this intervention with other antenatal and child health interventions, specifically the prevention of mother-to-child transmission of HIV (PMTCT).

Methods

The economic costs of adding the intervention to routine antenatal care were assessed. Cost-effectiveness (CE) ratios of the intervention were obtained for low birth weight (LBW) live births and stillbirths averted and cost per disability-adjusted life year (DALY) saved. Cost per DALY saved was also estimated for previous CE studies of syphilis

screening. The CE of the intervention at different syphilis prevalence rates was modelled.

Results
The economic cost of the intervention is $1.44 per woman screened, $20 per woman treated, and $187 per adverse birth outcome averted. The cost per DALY saved is $110, with LBW as the only adverse outcome. When including stillbirth, this estimate improves 10-fold to $10.56 per DALY saved. The cost per DALY saved from all syphilis screening studies ranged from $3.97 to $18.73.

Conclusions
Syphilis screening is shown to be at least as cost-effective as PMTCT and more cost-effective than many widely implemented interventions. There is urgent need for scaling up syphilis screening and treatment in high prevalence areas. The cost-effectiveness of screening interventions is highly dependent on disease prevalence. In combination, PMTCT and syphilis screening and treatment interventions may achieve economies of scope and thus improved efficiency.

Fern Terris-Prestholt, LSHTM

From: Terris-Prestholt F et al. 'Is antenatal syphilis screening still cost-effective in sub-Saharan Africa?' *STI* 2003; 79(5): 375-81.

Collaborators
NIMR, Tanzania; AMREF, Tanzania; Municipal Office of Health, Mwanza; Makongoro Clinic, Bugando Medical Centre, Sekou Toure Regional Hospital and Sengerema Designated District Hospital, Mwanza; LSHTM, London. *Funding* from The Wellcome Trust, London.

Integrating syphilis screening in Tanzania

The provision of integrated syphilis screening services in antenatal care was a focus of this study, which reviewed overall: 1) Arguments for and against the 'integration approach' and the 'vertical approach' for delivery of reproductive health (RH) services; 2) Definitions and roles of each component of the health system within the context of health sector reform; 3) Key barriers to comprehensive reproductive health care at each level of the Tanzanian health care system; and 4) Key neglected opportunities for providing comprehensive reproductive health care. A multi-disciplinary approach was used.

Study setting
The study, in 2000-01, included 3 regions (Mwanza, Dodoma and Morogoro) and 9 districts at different stages of STI services integration. Nine facilities were visited: 2 district hospitals, 4 health centres and 3 dispensaries. Currently ANC, family planning and MCH care are delivered entirely separately.

Key barriers to comprehensive RH care were identified as: 1) ineffective supplies of drugs and other items; 2) training; 3) time management; 4) incomplete care; and 5) inadequate syphilis screening and supervision, on which we focus here.

Syphilis screening and supervision
According to Tanzanian standards of care for pregnant women, RPR status for syphilis is supposed to be checked once during pregnancy. Based on our direct observation of 342 antenatal consultations and review of antenatal cards, only 39% of the women were or had been screened at some point during their pregnancy. However, those who were screened were not necessarily treated.

An audit of the RPR registers (n=2256 over 4 months) revealed that 43% (970) of women were screened, 15% of those tested were positive, 61% of those who were positive were treated with one dose of benzathine penicillin, and 36% of those who were positive brought at least one partner to be treated.

Screening for RPR was assigned a day and women were given a card with a date to return for testing. Similarly, once they were tested they were given a card with a date to return for the results and treatment if necessary.

Problems encountered
The review of monthly screening activities in the 9 sites revealed that 2 sites were unable to perform testing due to lack of reagents, and for the others we noted extreme fluctuations in reported RPR positivity rates, which question the quality of testing and the adequate supervision to detect these problems.

We also found there was a misunderstanding among the health service providers (HSPs) that the testing cards should be dealt with like vaccine vials – used in their entirety once opened. We cannot underestimate the extent to which this compartmentalizing of health has become ingrained. This example illustrates the absence of adequate supervision and the way in which activities that are convenient for HSPs can become barriers to care for clients. Skills around managing clients and activities more effectively are lacking, as are skills in managing time both for HSPs and district teams.

Conclusion
The main operational limitations for syphilis screening in Tanzania are:

1) Failure to screen and treat eligible clients
- ***Supplies*** – Lack of RPR testing kits, drugs and consumables due to complex ordering and supply systems, and inadequate STI drug supply, compensated by borrowing from other units' stocks.
- ***Health care workers*** – low priority given to syphilis prevention; few trained staff (due to transfers, illness, no refresher training); screening unpopular and time consuming; belief that kits must be used in entirety (leads to postponement of screening); lack of training or prescribing authority for nurses to give injections, preventing same day treatment.

2) Quality of RPR screening
- Little effective supervision (lack of qualified staff)
- No quality control procedures
- No refresher training of health care workers
- Storage of RPR kits inadequate
- Rate of biological false positive results probably high.

Monique Oliff & Philippe Mayaud, LSHTM

Collaborating institutions:
LSHTM, London, UK; AMREF, Tanzania; MUCHS, Dar es Salaam, Tanzania. *Funding* from DFID-Innovations Grants Scheme.

Syphilis treatment with single dose azithromycin in Mbeya, Tanzania

The study was undertaken to determine whether the treatment of syphilis with a single oral dose of 2gr of Azithromycin is as effective as the standard treatment with 2.4 MU benzathine penicillin IM. Azithromycin is a macrolide antibiotic with high tissue concentration and long tissue half-life. It has few side-effects and at the 1gr single dose is effective against *Haemophilus ducreyi* (causing chancroid) and *C trachomatis*, whilst the 2gr single dose is effective against *N gonorrhoeae* and *T pallidum*. Oral administration of 2gr (4 tabs) on the spot is easy in any PHC facility.

Randomized controlled clinical trial

A sample size of 110 participants per treatment arm was required to detect a maximum difference in cure rates of 7.5% if overall cure rate is 95%, or 10% if overall cure rate is 90%, at the 95% significance level with 80% power.

328 participants were recruited, with 31 lost to follow up. Loss to follow up was higher in clinic patients, males and young (18–24 years) participants, but did *not* differ between treatment groups: 8.6% in the Azithromycin group and 10.3% in the Penicillin group.

Study participants were recruited from a barworker cohort (n=65), clinic patients (149) and traditional brew sellers (114). 71% were female. 45% were aged between 18–24; 27% were 25–29 and 28% were 30 or over. 29% were single, 53% married and 19% widowed or divorced.

HIV prevalence was 77% in the barworker cohort, 48% for the clinic patients, and 44% for the brew sellers.

Results

The overall cure rate was 98.6% (95% CI: 93.5–99.9), slightly higher in HIV-negative than in HIV-positive participants [92.1%; (85.4–96.5)].

Cure rates at 3, 6 and 9 months

	3 months		6 months		9 months	
	%	95% CI	%	95% CI	%	95% CI
Azithromycin (n=159)	59.4	51.8–67.1	85.5	79.4–90.6	97.7	94.0–99.4
Penicillin (n=153)	59.5	51.8–67.3	81.5	74.8–87.4	95.0	90.6–97.8

Cure rates by syphilis stage

Syphilis stage	3 months		6 months		9 months	
	Azi	Pen	Azi	Pen	Azi	Pen
Primary syphilis (n=25)	90.9% (66.7–99.5)	92.9% (72.5–99.6)	100%	100%	100%	100%
Non-primary syphilis (n=283)	56.9% (49.0–65.1)	56.1% (48.0–64.4)	84.4% (77.8–89.9)	79.6% (72.3–86.0)	97.5% (93.5–99.3)	94.5% (89.6–97.6)

Summary

Azithromycin appears to work as well as benzathine penicillin, but there was insufficient power to exclude difference for primary syphilis. RPR titre at treatment and syphilis stage affects treatment response; HIV status does not.

Gabriele Riedner, LSHTM

Collaborating institutions:

LSHTM, London, UK; Regional Medical Office, Mbeya, Tanzania; MUCHS, Dar es Salaam, Tanzania; Institute of Tropical Medicine, Antwerp, Belgium; University of Manitoba, Canada; Dept of Infectious & Tropical Diseases, LMU, Munich, Germany.

Funding from Wellcome Trust and DFID, UK.

Selected New Publications

Charalambous S, Grant AD, Day JH, Rothwell E, Chaisson RE, Hayes RJ, Churchyard GJ (2004) Feasibility and acceptability of a specialist clinical service for HIV-infected mineworkers in South Africa. *AIDS Care* 16: 47-56.

Glynn JR, Caraël M, Buvé A, Anagonou S, Zekeng L, Kahindo M, Musonda RM, and the Study Group on Heterogeneity of HIV Epidemics in African Cities (2004) Does increased general schooling protect against HIV infection? A study in four African cities. *Tropical Medicine and International Health* 9: 4-14.

Hawkes S, Mayaud P, Mabey D (2003) Partner notification for the control of sexually transmitted infections. *British Medical Journal* 327: 633-4.

Jaye A, Sarge-Njie R, Schim van der Loeff M, Todd J, Alabi A, Sabally S, Corrah T, Whittle H (2004) No differences in cellular immune responses between asymptomatic human immunodeficiency Type 1 and Type 2- infected Gambian patients. *Journal of Infectious Diseases* 189: 498-505.

Mabey D, Peeling R, Ustianowski A, Perkins M (2004) Diagnostics for the developing world. *Nature Reviews in Microbiology* 2: 231-40.

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Oliff M, Mayaud P, Brugha R, Semakafu A-M (2003) Integrating reproductive health services in a reforming health sector: the case of Tanzania. *Reproductive Health Matters* 11: 37-48.

Pepin J, Mabey D (2003) Sexually transmitted infections in Africa: treatment options revisited following reductions in drug prices. *Sexually Transmitted Infections* 79: 432-4.

Riedner G, Rusizoka M, Hoffmann O, Nichombe F, Lyamuya E, Mmbando D, Maboko L, Hay P, Todd J, Hayes R, Hoelscher M, Grosskurth H (2003) Baseline survey of sexually transmitted infections in a cohort of female bar workers in Mbeya Region, Tanzania. *Sexually Transmitted Infections* 79: 382-7.

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Todd J, Changalucha J, Ross DA, Mosha F, Obasi AIN, Balira R, Grosskurth H, Mabey DCW, Hayes R (2004) The sexual health of pupils in years 4 to 6 of primary schools in rural Tanzania. *Sexually Transmitted Infections* 80: 35-42.

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