ANTENATAL SYPHILIS MANAGEMENT IN SUB-SAHARAN AFRICA: PUBLIC HEALTH MANAGEMENT CHALLENGES AND THE IMPACT OF NEW HIV PROGRAMS IN ZAMBIA

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ABSTRACT

Maternal syphilis leads to adverse pregnancy outcomes and neonatal morbidity and mortality. Despite having had the means to treat the disease for decades, maternal syphilis remains prevalent in much of the developing world.

The objectives of this study were three-fold: (a) to identify through review of the published literature reported developing country barriers to achieving antenatal syphilis screening and therapy (when warranted); (b) to determine correlates of syphilis seroprevalence among HIV-infected and -uninfected antenatal attendees in an African multi-site clinical trial; and (c) to determine if seven years of staged implementation of human immunodeficiency virus (HIV) research and/or a prevention of mother-to-child transmission of HIV (PMTCT) service programs in Lusaka, Zambia were beneficial for the general antenatal care system in which they were nested.

The literature review revealed four main categories of barriers to developing country antenatal syphilis screening, namely: policy, health system, human resource, and patient-derived.

A cross sectional study was used to determine statistically significant correlates of syphilis seroreactivity: geographic site (Odds Ratio [OR]= 4.5, Blantyre; OR=3.2, Lilongwe; OR=9.0, Lusaka; vs. Dar es Salaam as the referent), HIV infection (OR=3.3), age 20 to 24 years (OR= 2.5), being divorced, widowed, or separated (OR= 2.9), genital ulcer treatment in the last year (OR= 2.9), history of stillbirth (OR= 2.8, one stillbirth;

OR=4.3, 2-5 stillbirths), history of preterm delivery (OR= 2.7, one preterm delivery). Many women without identified risk factors were syphilis seropositive.

Assessed through a quasi experimental design, PMTCT research and service programs in antenatal clinics was associated with less documented RPR screening as compared to before the programs were implemented, with prevalence odds ratios (OR) of 0.9 (0.7–1.1) for research and 0.7 (0.6-0.8) for service; both program implementations were associated with increased documented RPR screening frequency, with a prevalence OR of 2.5 (2.1–3.0).

Creative and strategic means to address barriers to full implementation of antenatal syphilis screening programs are warranted in resource-constrained regions of the world. Developing country and international HIV program implementers should plan explicitly for broad-based upgrading of primary care services outside the narrow scope of the program itself.

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LIST OF ABBREVIATIONS

AIDS	acquired immunodeficiency syndrome
ANC	antenatal care
CDC	Centers for Disease Control
ELISA	Enzyme-Linked Immunosorbent Assay
HIV	Human Immunodeficiency Syndrome
HIVNET	HIV Network
NIH	National Institutes of Health
NVP	Nevirapine
OR	Odds Ratio
PMTCT	Prevention of Mother to Child Transmission
RPR	Rapid Plasma Reagin
STD	sexually transmitted disease
STI	sexually transmitted infection
STS	serological testing for syphilis
TID	ter in die (three times a day)
TPPA	*T. pallidum* haemagglutination assay
UNICEF	United Nations Children's Fund
UNAIDS	United Nations AIDS
VCT	voluntary counseling and testing
WHO	World Health Organization

INTRODUCTION

The World Health Organization (WHO) estimates that 340 million new cases of sexually transmitted infections (STI) occurred worldwide in 1999, and approximately 12 million new cases of syphilis occurred among adults (2001). Sexually transmitted diseases (STD) not only cause complications and acute morbidity in the infected individual, but they also contribute to maternal and fetal mortality as well as adverse pregnancy outcomes (WHO). Syphilis in pregnancy has been associated with stillbirth, abortion, premature delivery, intrauterine growth retardation, and, in the newborn, heptosplenomegaly, failure to thrive, and high neonatal mortality (Brocklehurst, 1999; Gloyd, Chai, & Mercer, 2001; Walker & Walker, 2002; Centers for Disease Control [CDC], 2002). Congenital syphilis can lead to stillbirth and neonatal death, or to severe long-term morbidity in surviving infants, being a global health problem that should be largely preventable in developed as well as in developing countries (Brocklehurst, 1999; Watson-Jones et al., 2002).

Reported syphilis prevalence rates vary globally. Syphilis rates for the developed countries are better documented, whereas in developing countries, the data are fewer and the disease is more widespread (Walker, 2001). In Western Europe, syphilis prevalence has declined substantially since the 1940s (WHO, 2001). Incidence rates are generally below 5 per 100,000 persons in the majority of countries (WHO). In Asia and Eastern Europe, the figures may be as high as 8% and 14.5%, respectively (Gloyd et al., 2001). In contrast to declining rates observed in Western Europe and the industrialized world,

syphilis rates have increased markedly in many countries of the developing world since 1989 (Walker, 2002).

Syphilis prevalence rates vary on the African continent, ranging from published survey findings of 2.5% in Burkina Faso to 17.4% in Cameroon in sub-Saharan Africa (WHO). In much of Africa, venereal syphilis started to increase in prevalence following the highly successful yaws eradication campaigns of the 1950s and the 1960s (Richens, 1992). It is believed that the mass penicillin therapy used against yaws also suppressed syphilis; completion of the yaws campaigns then returned syphilis diagnosis and therapy to the health system (Wilcox, 1985; Meheus & Antal, 1992). A second plausible explanation for rising syphilis rates in Africa is that migration due to war, civil strife, employment, or drought/famine in the past three decades may have increased the number of men away from their families for long periods of time. Such a circumstance may be associated with higher STI infection rates (Idsoe & Guthe, 1967; Toure, 1985). A third possible explanation hinges on the fact that syphilis can be successfully controlled by public health measures due to the availability of highly sensitive diagnostic tests and affordable treatments (WHO). Hence, deterioration in sexually transmitted disease (STD) services may result in increasing syphilis rates. A fourth possible, not mutually exclusive reason for syphilis increases in Africa, involves the HIV epidemic; immunosuppressed persons may transmit and contract syphilis more readily, and syphilis may sometimes be more difficult to treat with conventional penicillin doses (Kaul et al., 1997; Augenbraun & McCormack, 1994; Pao, Goh, & Bingham, 2002; Walker, 2001).

In untreated or unsuccessfully treated maternal cases, syphilis can be transmitted transplacentally at all stages of disease (Walker, 2001). Vertical transmission of syphilis

may occur from an infected unsuccessfully treated or untreated pregnant woman via the placenta to her developing fetus (Walker, 2001) or during delivery by contact of the newborn with genital lesions or fluid (Ament & Whalen, 1996). Spirochetes readily cross the placenta and can cause chronic infection in the fetus. Congenital syphilis is a systemic infection in which a baby might have been delivered prematurely and the classic description of the congenital syphilitic baby is a severely infected premature infant with marasmus, a pot belly, 'old man face' and withered skin (Walker, 2001). Seventy to 100% of fetuses of mothers with early infectious syphilis will be infected, with stillbirths occurring in up to one third (Pao et al., 2002). It is documented that women with high-titer active syphilis are at greatest risk of having low birth-weight and/or preterm live births as compared to women with other serological stages of syphilis (Watson-Jones, et al. 2002). Likewise, among HIV + women with concurrent syphilis infection, there is a significant association with vertical perinatal HIV transmission (Lee, Hallmark, Frenkel, & Del Priore 1998).

The CDC in the United States recommend that all women be screened twice for syphilis during pregnancy (2002), even in the comparatively low incidence setting in the United States, and that positive cases be treated with penicillin (Mahoney, Arnold, & Harris, 1943). Penicillin G, administered parenterally, is the preferred drug for treatment of all stages of syphilis; the preparations used (in other words, benzathine, aqueous procaine, or aqueous crystalline), the dosage, and the length of treatment depend on the stage and clinical stage of disease (CDC, 2002). Syphilis that is documented as being of less than 1 year's duration is treated with 2.4 million international units of benzathine penicillin G intramuscularly in a single dose. In patients with infection of greater than 1-year

duration or with disease of unknown duration, 7.2 million U benzathine penicillin G should be administered as three doses of 2.4 million U intramuscularly each at 1-week intervals (CDC, 2002). Aqueous crystallilne penicillin (Xpen), aqueous procaine penicillin and benzathine penicillin (brand name, Retarpen) are all different preparations or salts of penicillin G. Aqueous procaine penicillin's half-life, although longer than aqueous crystalline penicillin, does not have as long of a half life as benzathine penicillin, making the latter the recommended therapy in areas such as the developed world where logistics or other factors may prevent multiple clinic visits for administration (Pao et al., 2002).

In developing countries financial and staffing constraints can hinder technological monitoring of therapeutic regimens of medications (Vermund & Powderly, 2003) or health care delivery in general. In most African countries, few syphilis screening programs achieve full implementation due to financial and logistical constraints (Fonck, Claeys, Bashir, Bwayo, Fransen, & Temmerman, 2000; Beksinska, Mullick, Kunene, Rees, & Deperthes, 2002). In addition to financial and logistical constraints to successful screening program, syphilis cases continue to be missed either because of late booking, treatment failures, re-infection, omission of testing or treatment, laboratory error, failure to retest patients at high risk in the third trimester penicillin shortage, poor clinic organization, and other means of faulty patient management (Clay, 1989; Rutgers, 1993; Gloyd et al., 2001. Since most therapeutic failures occur if syphilis treatment is offered late in pregnancy (Gilstrap & Faro, 1990), it is important to screen for syphilis at the first antenatal clinic visit using a clinic-based test so that results are available the same day as testing, and offer treatment for seroreactive cases before the woman leaves that day.

Study Significance

Sufficient information and effective treatment exist to control antenatal syphilis. Despite this, about a million babies are adversely affected by syphilis due to maternal infection each year (Walker & Walker, 2002). In southern Africa, where 10% or more of pregnant women are often syphilis seropositive, between 25% to 50% of all stillbirths are found in syphilis seropositive women, with 25% or more of all stillbirths being attributed to syphilis (Goldenberg, Stringer, Sinkala, & Vermund, 2002). Congenital syphilis is preventable and its occurrence is an indication of a systems failure or inadequate antenatal care service in a country or region (Pao et al., 2002).

Optimal provision of care in developing countries is different from administration of health services in industrialized countries because care is given in extremely resource-constrained circumstances. Providing orderly, high-quality, and efficient antenatal care while operating under severe financial and human resource constraints depends on creative strategic means to meet challenges to syphilis screening that may emerge in the developing country setting.

Research Objective

The objective of this study was three-fold: (a) to critically assess antenatal syphilis screening and care challenges in developing countries through a review of the published literature, (b) to determine correlates of antenatal syphilis seroprevalence among women enrolled in the HIVNET 024 trial in three sub-Saharan African countries, and, (c) to determine if the presence of either HIV-related research or PMTCT new standard of care service, or both programs, as 'systems inputs' in antenatal care clinics would improve existing 'systems process' or outputs of ancillary antenatal care as measured by

documented syphilis screening and treatment of seroreactive cases in a developing country health system.

Aims and Hypotheses

Three specific aims were composed to assess the situation of and address programmatic challenges to antenatal syphilis screening in developing countries.

Aim 1: To identify reported barriers to achieving universal antenatal serological testing and therapy for syphilis in developing countries, with a special emphasis on the experiences from sub-Saharan Africa.

Aim 2: To determine correlates of syphilis seroprevalence among HIV-infected and HIV-uninfected antenatal attendees in an African multi-site clinical trial.

Aim 2 Hypotheses:

Hypothesis 2a. Women enrolled in the HIVNET 024 trial who are unemployed or illiterate are more likely to be RPR syphilis seroreactive as compared to women who are employed or who are literate.

Hypothesis 2b. Women enrolled in the HIVNET 024 trial who have a higher number of lifetime sexual partners are more likely to be RPR syphilis seroreactive as compared to women with a lower number of lifetime sexual partners.

Aim 3. To assess the impact of the non-randomized introduction of research, PMTCT new standard of care service delivery, or both programs on documented antenatal syphilis screening and treatment rates in district clinics in Lusaka, Zambia from 1997 to 2004. Research was focused on prevention of mother to child human immunodeficiency virus (HIV); the new standard of care service was voluntary counseling and testing for HIV. Both program types were operated within the antenatal care clinics.

Aim 3 Hypotheses:

Hypothesis 3a. Prior to the introduction of research programs, we expect on average within the clinics that 60% of the antenatal records will not have documented screening for syphilis. After the introduction of research programs, we expect on average within the clinics that 40% of the antenatal records will not have documented screening for syphilis.

Hypothesis 3b. Prior to the introduction of a PMTCT new standard of care service program, we expect on average within the clinics that 60% of the antenatal records will not have documented screening for syphilis. After the introduction of the PMTCT new standard of care service program, we expect on average within the clinics that 40% of the antenatal records will not have documented screening for syphilis.

Hypothesis 3c. Prior to the introduction of research plus the PMTCT new standard of care service program, we expect on average within the clinics that 60% of the antenatal records will not have documented screening for syphilis. After the introduction

of research plus the PMTCT new standard of care service programs, we expect on average within the clinics that 40% of the antenatal records will not have documented screening for syphilis.

Hypothesis 3d. Prior to the introduction of research programs, we expect on average within the clinics that 60% of the antenatal records will not have documented treatment for RPR seroreactive cases. After the introduction of research programs, we expect on average within the clinics that 40% of the antenatal records will not have documented treatment for RPR seroreactive cases.

Hypothesis 3e. Prior to the introduction of PMTCT new standard of care service programs, we expect on average within the clinics that 60% of the antenatal records will not have documented treatment for RPR seroreactive cases. After the introduction of the PMTCT new standard of care service, we expect on average among the clinics that 40% of the antenatal records will not have documented treatment for RPR seroreactive cases.

Hypothesis 3f. Prior to the introduction of research plus the PMTCT new standard of care service program, we expect on average among the clinics that 60% of the antenatal records will not have documented treatment of RPR seroreactive cases. After the introduction of research plus the PMTCT new standard of care service programs, we expect on average among the clinics that 40% of the antenatal records will not have documented treatment for RPR seroreactive cases.

ANTENATAL SYPHILIS SCREENING IN DEVELOPING COUNTRIES: PROGRAMMATIC CHALLENGES AND ZAMBIA CASE STUDY

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ABSTRACT

Objective: Because maternal syphilis remains highly prevalent in developing countries with suboptimal antenatal care infrastructures and/or under-trained or under-supervised staff, we aimed to identify reported barriers in achieving universal antenatal serological testing and therapy for syphilis and suggest ways to scale-up programs.

Methods: We identified published studies from electronic database searches (National Library of Medicine, Medline, and Cochrane Database of Systematic Reviews).

Selection Criteria: Antenatal syphilis screening program studies in developing countries describing program barriers to screening and suitable treatment, with additional emphasis on syphilis program data from Zambia.

Data collection and analysis: We organized barriers identified from data based assessments by the type of service barrier and the potential for cost-effective intervention.

Results: We identified four main categories of barriers: policy, health system, human resource, and patient-derived. Identified barriers were often interrelated and had root causes that are not yet fully understood. Many, but not all barriers could be overcome with additional funds, though improvements via additional funding may not be sustainable.

Conclusions: Rigorous evaluation of barriers to syphilis testing and therapy is needed to identify solutions, including addressing barrier interdependencies. Expanding global programs in the prevention of mother-to-child transmission of HIV and maternal-child health are ideal venues to address syphilis within a broad-based upgrading of health systems.

INTRODUCTION

The World Health Organization (WHO) estimates that approximately 32% of pregnant women in the developing world do not receive any antenatal care (ANC) (2003). Although syphilis remains curable with penicillin (Mahoney, Arnold, & Harris, 1943), maternal and neonatal syphilis are still prevalent wherever there are severe constraints on the ANC infrastructure, including under-trained or under-supervised staff. Even for a subset of the approximately 68% of women who do receive ANC, serological testing for syphilis (STS) and penicillin treatment may be poorly implemented, representing a missed opportunity to reduce maternal, perinatal, and infant morbidity and mortality (Gloyd, Chai, & Mercer, 2001).

Syphilis re-screening is recommended both in areas of high and low syphilis prevalence in both developing countries and the US. Re-screening is the combination of testing at the first antenatal visit and, if seronegative, subsequent screening at a time prior to labor and delivery (Opai-Tetteh, Hoosen, & Moodley, 1993; Lumbiganon, Piaggio, & Villar, 2002; Qolohle, Hoosen, Moodley, Smith, & Mlisana, 1995; Centers for Disease Control [CDC], 2002). If untreated or inadequately treated, maternal syphilis can be transmitted transplacentally at all stages of disease (Walker, 2001). Evidence is overwhelming that successful antenatal screening and treatment of syphilis and other sexually transmitted infections (STIs) must be considered a global ANC standard (Mak, Murray, & Bulsara, 2003).

Congenital syphilis is an indicator of an ANC "systems failure", typically in the context of broadly inadequate ANC in a given facility or region (Pao, Goh, & Bingham, 2002). Despite having had the means to diagnose and treat the disease for decades, even

now early in the 21st century the global burden of neonatal morbidity and mortality due to maternal syphilis exceeds that of HIV or tetanus (Saloojee, Velaphi, Goga, Afadapa Steen, & Lincetto, 2004). The purpose of this review is to assess the barriers to successful antenatal syphilis screening programs that have been documented in developing countries, with a special emphasis on the experiences from sub-Saharan Africa.

Objectives

We seek to identify reported barriers in the process of achieving STS and therapy (when indicated) in developing country settings and suggest ways to scale-up effective programs.

Criteria for Considering Studies for this Review

Types of Studies

We reviewed studies that detailed syphilis screening programs, strategies, or approaches during pregnancy in a developing country, according to the World Bank Indicator of gross national income (World Bank, 2006). Studies in South Africa were also included in the review. We included those articles that published enough detail from a developing country syphilis screening program for us to be able to either judge the program successful or to identify gaps and challenges in the program. Excluded studies included reports from secondary sources, those that reported program activities without critical commentary, or those that were not from developing countries, e.g., Western Europe and North America. We also obtained Zambian government statistics and documents to pre-

sent a more in-depth case study of one of the world's poorest countries (United Nations Development Programme, 2002; World Health Organization, 2005).

Types of Intervention

We included studies regardless of the method of serological testing used. Non-treponemal tests (e.g., the Venereal Diseases Reference Laboratory test [VDRL] or the rapid plasma reagin test [RPR]) are used for screening. A confirmatory test is often not performed, though a repeat non-treponemal test or a treponemal test (preferred by WHO, e.g., *T. pallidum* particle agglutination test [TPPA] or the *T. pallidum* haemagglutination assay [TPHA]) is performed for confirmation in better funded and more highly functioning venues. We also included programs that rely only on syndromic recognition. Dark field microscopy for confirmation is not used commonly in most developing countries due to the cost of the microscope and reagents, though some settings like the University of West Indies Hospital in Kingston, Jamaica maintain this standard (SHV, personal observation, August, 2005).

Types of Outcome Measures

Even one occurrence of maternal or congenital syphilis should be considered a syphilis screening program failure. For our critical review, however, the principal outcomes assessed were the specifically reported barriers to successful antenatal syphilis prevention programs, rather than from surveillance data. Other outcomes considered were:

a) Compliance with syphilis screening and treatment;

b) Compliance with antenatal care; and

c) Cost to patient of syphilis screening or treatment.

Search Strategy for Identification of Studies

We searched the PubMed database of the National Library of Medicine on February 18, 2006 (February 1966-January 2006) using the following search strategy: syphilis AND (developing country OR Africa OR Asia OR Latin America OR South America OR Caribbean OR Central America OR Mexico OR Eastern Europe) AND (antenatal OR pregnancy OR prenatal OR labor OR labour OR obstetrics). A similar search strategy was used to search the MEDLINE (OVID) data base on February 18, 2006 (1996 to February Week 3 2006). An advanced search of the Cochrane Central Register of Controlled Trials (CENTRAL) was undertaken on February 18, 2006 using the term 'syphilis.'

METHODS OF THE REVIEW

We searched the titles and abstracts obtained from the search for relevant studies and included articles expressing an informed judgment of any developing country ANC syphilis screening program. When uncertain from abstract reviews, full articles were assessed to determine whether the study met the inclusion criterion. For the Zambia case study, we searched Zambian government reports and published findings, as well as conducted a government official interview, to assess antenatal syphilis screening and treatment procedures for challenges to achieving universal antenatal syphilis screening and treatment.

We used the conceptual framework of Hanson, Ranson, Oliveeira-Cruz, & Mills (2003) to identify programmatic constraints by the degree to which a given constraint can be ameliorated through new funds in the short to medium term. We classified the identified barriers to STS and therapy by extent to which barriers are due to shortage of health systems inputs, such as equipment, drugs, or training (Hansone, et al., 2003). If a program reported more than one barrier, we recorded all barriers for an aggregate total.

RESULTS

There were 482 citations identified by the National Library of Medicine (Pub Med) search from which we selected 88 for review using the study inclusion criteria. No additional articles were identified by Medline (Ovid). One of two studies identified from the Cochrane Database of Systematic Reviews was selected for review. We based our findings on 60 of these 89 studies providing data according to the criteria for selection, all from the Pub Med search (Ali, 1990; Arya, 1995; Azeze, Fantahun, Kidan, & Haile, 1995; Bam, Cronje, Muir, Griessel, & Hoek 1994; Beksinska, Mullick, Kunene, Rees, & Deperthes, 2002; Bique Osman, Challis, Folgosa, Cotiro, & Bergstrom, 2000; Blankhart, Muller, Gresenguet, & Weis, 1999; Bogdanova & Bozhinova, 2004; Chang, Chao, & Huang,. 1992; Cossa, et al., 1994; Deperthes, Meheus , O'Reilly, & Broutet, 2004; Donders, Desmyter, Hooft, & Dewet, 1997; Duarte, Gir, de Almeida, Hayashida, & Zanetti, 1994; Duke, Michael, MgoneJ, Frank, Wal, & Sehuko, 2002; Fitzgerald, et al. 2000; Fonck, Claevs, Bashir, Bwayo, Fransen, & Temmerman, 2001; Fonn, 1996; Frank & Duke,2000; Frans, Brand, & Muskiet, 1994; Gloyd et al., 2001;Guinness, Sibandze, McGrath, & Cornelis, 1988; Hira, et al., 1985; Hira, et al., 1990; Jansone, Lindmark, &

Langhoff-Roos, 2001; Jenniskens, Obwaka, & Temmerman, 1995; Kamanga, 1995; Kambarami, Manyame, & Macq, 1998; Kambarami, Chirenje, & Rusakaniko ,2000; Le Roux, Pattinson, Tsaku, & Makin, 1998; Lech, 2003; Leoprapai, Pramualratana, Sirirassamee, Tangchonlatip, & Pattaravanich, 1992; Lim, Koh, & Sivanesaratnam, 1995; Majoko, Munjanja, Nystrom, Mason, & Lindmark, 2003; Mathai E, Mathai M, Prakash, & Bergstrom, 2001; Mati, Aggarwal, Sanghvi, Lucas, & Corkhill, 1983; McDermott, Steketee, Larsen, & Wirima, 1993; McDermott, Steketee, & Wirima, 1996; Meda, Sangare, Lankoande, Sanou, CompaoreI, Catraye, et al., 1997; Mefane & Toung-Mye, 1987; Mullick, Beksinksa, & Mso, 2005; Myer, Abdool Karim, Lombard, & Wilkinson, 2004; Myer, Wilkinson, Lombard, Zuma, Rotchford, & Karim, 2003; Obiesesan & Ahmed, 1999; Ortashi, El Khidir, & Herieka, 2004; Pattinson, Makin, Shaw, & Delport, 1995; Prual, Toure, Huguet, & Laurent, 2000; Qolohle, Hoosen, Moodley, Smith, & Mlisana, 1995; Rodrigues, Guimaraes, & Grupo Nacional de Estudo sobre Sifilis Congenita, 2004; Rotchford, Lombard, Zuma, & Wilkinson, 2000; Rutgers, 1993; Sikosana, 1994; Southwick, et al., 2001; Swingler & de Groot, 1993; Temmerman, Lopita, Sanghvi, Sinei, Plummer, & Piot, 1992; Temmerman, et al., 2000; Tikhonova, Salakhov, Southwick, Shakarishvili, Ryan, & Hillis, 2003; Watson-Jones, et al., 2005; Watson-Jones, et al., 2005; Wilkinson, 1993; Wilkinson, 1997; Wilkinson, et al., 1999). For our Zambian case study, we used 7 out of 28 key documents and statistical reports reviewed (Central Statistical Office, Zambia, 2003; Lake & Musumali, 1999; Jeppsson & Okuonzi, 2000; Gilson, Doherty, Lake, Mcintyre, Mwikisa, & Thomas, 2003; Policy Project, 2003; United Nations AIDS [UNAIDS] Zambia National Health Accounts, 2002; Zambian Ministry of Health, 2004).

The identified constraints could be grouped into four categories of barriers to successful screening program implementation: (1) policy framework gaps, (2) health system component failures, (3) human resource issues, and (4) patient-related constraints. Although not comprehensive, Tables 1-3 detail representative findings from the most apropos studies. Health system component failures and human resource issues were the most commonly reported barriers to antenatal syphilis screening and therapy (Table 4). Program evaluations commonly reported more than one of these four barriers to success. Of the 176 identifiable barriers from the 60 reports, we classified only seven (4%) as highly amenable to alleviation by additional funds; all seven were health systems related. We classified 129 (73%) of the barriers as moderately amenable to alleviation by additional funds, and 40 (23%) as poorly amenable to alleviation by additional funds (results not shown).

Table 1

Selected effectiveness studies (n=16) of maternal and neonatal syphilis screening and treatment from sub-Saharan Africa

Author, year (reference #)	Location	Population	Study type	Key Constraint(s) Noted
Azeze et al., 1995	Ethiopia: Gondar	n=270 antenatal attendees	Cross Sectional	Late booking of women into ANC resulted in delayed syphilis screening and lack of completing treatment
Bique Osman et al., 2000	Mozambique: Maputo	n=929 antenatal attendees	Case control study	Delayed results leading to incomplete treatment; Lack of treatment completion; Treatment costs; Lack of partner notification; Lack of equipment and/or supplies;
Cossa et al., 1994	Mozambique: Zambézia Province	n=1,728 antenatal attendees	Cross Sectional	Resource and logistical constraints
Fonck et al., 2001	Kenya: Nairobi	n=27,377 antenatal attendees	Intervention study	High false negative and false positive RPR results; High staff workload; lack of electricity; Lack of STS program oversight; Women unwilling to wait for test results; Policy women must be tested with partner; Fear of abuse by partner; Low partner treatment rate (53%)
Gloyd, et al., 2001	Sub-Saharan Africa: 22 ministries	n=1,640,000 records of antenatal attendees	Ministry of Health surveys	Costs of testing and treatment; Organization of services; Transport costs Inadequate health priority; Social or cultural resistance to testing; Health worker shortage; Low syphilis awareness; Lack of syphilis statistics within MCH
Hira et al., 1990	Zambia: Lusaka	n=150 antenatal attendees	Demonstra-tion intervention	Late booking of women into ANC resulted in delayed syphilis screening and lack of completing treatment; No retesting prior to delivery
Jenniskens et al., 1995	Kenya: Nairobi	n=13,131 antenatal attendees at 30 health centers	Demonstration intervention	Long turn around time for laboratory results; Low treatment rates Failure to screen women on first ANC visit

Table 1, continued

Author, year (reference #)	Location	Population	Study type	Key Constraint(s) Noted
Kamanga, 1995	Zambia: Lusaka	No subjects	Program Description	Lack of screening and treatment supplies; Late booking of women into ANC resulted in delayed syphilis screening and lack of completing treatment; Misconceptions of mothers regarding early ANC attendance Shortage of trained laboratory staff
Kambarami et al., 1998	Zimbabwe: Murewa District	n=1,556 booking antenatal attendees; n=1096 delivering women	Cross sectional	Low staff motivation to perform STS and therapy; Lack of transport for samples processing/results delivery; Loss to follow up of women commenced on treatment; Lack of contact tracing; Poor record keeping
Majoko, et al., 2003	Zimbabwe: Gutu District	N= antenatal attendees in 23 health centers	Cross sectional	Health worker shortage; Shortage of trained laboratory staff
Obisesan & Ahmed, 1999	Nigeria: Ibadan	n=110 records of syphilis seroreactive antenatal attendees	Case study (retrospective record review)	Missed cases due to non specificity of VDRL tests
Prual et al., 2000	Niger: Naimey, Zinder, Mirriah	n=330 antenatal attendees	Prospective case study	Lack of equipment and/or supplies; Lack of health worker time for STS/therapy; Lack of motivation of midwives
Rutgers, 1993	Zimbabwe: Umzingwane District	n=2,161 antenatal attendees	Retrospective medical record audit	Lack of equipment and/or supplies; Low health worker motivation for STS/therapy; Misconceptions of women regarding blood draws; Low rate of results communication

Table 1, continued

Author, year (reference #)	Location	Population	Study type	Key Constraint(s) Noted
Sikosana, 1994	Zimbabwe: Matebeleland North Province	n=171 antenatal attendees	Client interview, record audit, equipment assessment	Lack of equipment and/or supplies Poor record keeping
Temmerman, et al., 1993	Kenya: Nairobi	n=540 antenatal attendees	Cross sectional	Lack of equipment and/or supplies; Late booking of women into ANC resulted in delayed syphilis screening and lack of completing treatment; Centralized testing; Lack of laboratory transport
Watson-Jones, et al., 2005	Tanzania: Mwanza (Region and city), Dodoma, Morogoro	n=1,688 antenatal attendees	Retrospective cohort study	Lack of equipment and/or supplies; Need for health worker retraining Low health worker motivation; Health worker shortage; Low health worker understanding of antenatal STS and therapy; Policy that testing and treatment be on different days; Poor supervision of health worker staff Poor storage of treatment supplies

Table 2

Selected effectiveness (n=8) studies of maternal and neonatal syphilis screening and treatment from South Africa

Author, year (reference)	Location	Population	Study type	Key Constraint(s) Noted
Beksinska et al., 2002	South Africa: KwaZulu-Natal Province	n=51 antenatal attendees	Key informant interview	Late booking of women into ANC resulted in delayed syphilis screening and lack of completing treatment Lack of laboratory transport Minimal STS/therapy counseling
Fonn, 1996	South Africa: Gauteng Province	n=19 rural clinics	Laboratory results turn-around time study	Offsite laboratory testing Lack of transport for samples processing/results delivery
Guinness et al., 1988	South Africa: Kingdom of Swaziland	n=283 delivered women	Retrospective medical record audit	Missed cases due to low RPR sensitivity (36%) and 48% predictive accuracy Lack of partner notification
Lech, 2003	South Africa: Kingdom of Swaziland	n=2034 records of pregnant women	Prospective case study	Low rate of results communication (38%) Low treatment rates by midwives (42%) Lack of partner tracing and treatment (5%)
Myer et al., 2003	South Africa: KwaZulu-Natal Province	n=7134 pregnant women	Cluster-randomized controlled trial	Lack of STS and therapy Health worker staffing inadequate
Rotchford et al., 2000	South Africa: Hlabisa District	n=1783 rural antenatal attendees	Prospective case study	Late booking of women into ANC resulted in delayed syphilis screening and lack of completing treatment

Table 2, continued

Author, year (reference)	Location	Population	Study type	Key Constraint(s) Noted
Swingler et al., 1993	South Africa: Khayelitsha	n=607 delivered mothers	Retrospective medical record audit	Centralized testing system Lack of STS and therapy
Wilkinson, 1997	South Africa: Hlabisa	n=200 antenatal attendees	Case control	Lack of onsite testing Attrition from follow up visits

Table 3

Selected effectiveness studies (n=6) of maternal and neonatal syphilis screening and treatment assessing regions outside of sub-Saharan Africa

Author, year (reference)	Location	Population	Study type	Key Constraint(s) Noted
Ali, 1990	Trinidad: Mount Hope	n= 28 cases of congenital syphilis	Case Series	Cost of treatment
Deperthes et al., 2004	Bolivia:, La Paz, El Alto, Cochabama; Kenya: Nairobi; South Africa: Umlazi township	n=3 countries' screening programs	Program Evaluation	Late booking of women into ANC resulted in delayed syphilis screening and lack of completing treatment Lack of syphilis statistics within MCH Lack of health worker knowledge of desensitization protocol for women allergic to penicillin Poor implementation of notification system Partner tracing program poorly managed
Duke, et al., 2002	Papua New Guinea: Eastern Highlands Province	n=353 infant deaths	Prospective audit of deaths	Low ANC access
Fitzgerald, et al., 2000	Haiti: Artibonite Valley	n=811 pregnant women	Cross Sectional	Low ANC access

Table 3, continued

Author, year (reference)	Location	Population	Study type	Key Constraint(s) Noted
Frank & Duke, 2000	Papua New Guinea: Eastern Highlands Province	n=67 neonates	Prospective case study	Health system organization poor Low screening coverage (<30%)~ low coverage
Mathai et al., 2001	India: Tamil Nadu	n=50 ANC records of syphilis positive mothers	Retrospective case study of antenatal records	Lack of treatment (16 of 34 cases) Poor quality antenatal care system

Table 4

Barriers to effective syphilis screening programs in developing countries

Policy

Inadequate priority for Ministry of Health (Gloyd et al., 2001)

Lack of national syphilis screening coverage targets as health indicator (Gloyd, 2001)

Policy that patients pay for syphilis test and/or treatment (Fonck et al.,2001; Gloyd et al., 2001; Southwick et al., 1996)

Policy that woman be treated with her partner (Fonck et al., 2001; Jenniskens et al., 1995)

Health System

Health systems inefficiencies, lack of organization, quality issues (Azeze et al., 1995; Bogdonava & Bozhinova, 2004; Chang et al., 1992; Deperthes et al., 2004; Fonck et al., 2001; Gloyd et al., 2001; Guiunness et al., 1988; Mathai et al., 2001; Mati et al., 1983; Mefane & Toung-Mye, 1987; Ortashi et al., 2004; Pattinson et al. 1995; Sikosana, 1994; Southwick, et al., 1996, Watson-Jones et al., 2005, Wilkinson, 1993; Wilkinson et al, 1997)

Inadequate or inefficient partner tracing and/or treatment carried out by health center (Beksinkska et al., 2002; Bique Osman et al., 2000; Fonck et al., 2001; Guinness et al., 1988; Lech, 2003; Kambarami et all, 1998)

Ineffective supply procurement (test kits, needles, treatment) (Kamanga, 1995; Kambarami et al., 1998; Prual et al., 2000; Rutgers, 1993; Sikosana, 1994; Temmerman et al., 1992; Watson-Jones et al., 2005)

Laboratory issues (Cossa et al., 1994; Deperthes et al., 2004; Duarte et al., 1994; Fonn, 1996; Jenniskens et al., 1995; Kambarami et al., 1998; Mefane & Toung-Mye, 1987; Pattinson et al., 1995; Rutgers, 1993; Swingler et al., 1993; Wilkinson et al., 1997) and lack of electricity (Fonck et al., 2001)

Issues of staff training, supervision, staffing, workload (Bique Osman et al., 2000; Fonck et al., 2001; Kamanga, 1995; Kambarami et al., 2000; Leoprapai et al., 1992; Rutgers, 1993; Watson-Jones et al., 2005)

Table 4, continued

Human Resources

Poor staff attitudes about syphilis screening; failure to obtain screening results or follow treatment regimens (Ali, 1990; Bam et al., 1994; Bique Osman et al., 2000; Chang et al., 1992; Donders et al., 1997; Duke et al., 2002; Fonn, 1996; Frank & Duke 2000; Frans et al., 1994; Gloyd et al., 2001; Guinness et al., 1988; Hira et al., 1990; Jenniskens et al., 1995; Kamanga, 1995; Kambarami, 2000; Le Roux et al., 1998; Lech, 2003; Mathai et al., 2001; McDermott et al., 1993; McDermott et al., 1996; Meda et al., 1997; Mefane, 1987; Pattinson et al., 1995; Qolohle et al., 1995; Rotchford et al., 2000; Sikosana, 1994; Southwick et al., 1996; Temmerman et al., 2000; Tikhonova et al., 2003; Watson-Jones et al., 2005; Watson-Jones et al., 2002; Wilkinson et al., 1999; Wilkinson et al., 1997)

Lack of staff motivation or effort, poor rapport between nurses and patients (Beksinska et al., 2002; Kambarami et al., 1998; Lech, 2003; Mathai et al., 2001; Rodrigues et al., 2004; Saloojee et al., 2004; Van der Geest et al., 2000)

Patient

Late booking into antenatal care (Azeze et al., 1995; Beksinska et al., 2002; Blankhart et al., 1999; Chang et al., 1992; Cossa et al., 1994; Deperthes et al., 2004; Duke et al., 2002; Hira et al., 1985; Kamanga, 1995; Mefane, 1987; Temmerman et al., 1992)

Cultural beliefs or resistance regarding syphilis screening (Kamanga, 1995)

Partner notification hampered by fear of abuse (Fonck et al., 2001)

Attrition from treatment referrals or unwilling to await results (Duarte et al., 1994; Mullick et al., 2005; Myer et al., 2003; Rotchford et al., 2000; Temmerman et al., 2000; Wilkinson et al., 1997)

Zambia Case Study

Though Zambians have among the world's lowest per capita incomes, many favorable factors are in place for successful antenatal syphilis screening and therapy in Zambia. More than 90% of expectant mothers visit antenatal care clinics at least once

during pregnancy, according to a Zambia demographic health survey, affording an opportunity for syphilis screening and treatment (2002). One analysis suggests that a strengthening of antenatal services occurred in the country in the late 1980s through a syphilis intervention demonstration project, and then with assistance from the United Nations International Children's Fund (UNICEF), resulting in a decrease in the syphilis prevalence among pregnant women from 12.8% to 8.0% (Kamanga, 1995).

Zambia is one of several sub-Saharan African countries to have embarked on health reforms to strengthen health care delivery and processes (Lake & Musumali, 1999; Jeppsson & Okuonzi, 2000). Decentralization of essential health services was implemented in this context by 1992, and antenatal STS in Zambia became the responsibility of the local health authorities, rather than national as before reforms. Zambian health reforms sought to improve upon the benefits to STS and therapy that occurred in the late 1980s. While these health reforms were in their infancy, a 1993 survey conducted in all 19 public sector urban clinics operating at that time in Lusaka, the nation's capital and largest city, revealed shortages of screening reagents, needles, syringes, and penicillin to treat syphilis seroreactive pregnant mothers, as well as a critical shortage of trained workers (Kamanga, 1995). Despite improving the availability of drug and medical supplies after reforms were implemented (MS, personal communication), a 2001 Lusaka Urban Health District quarterly report documented severe ongoing antenatal syphilis screening challenges (Table 5). Though an initiative supporting 100% antenatal syphilis screening and therapy was in place, the Lusaka Urban Health District (relatively privileged as the nation's capital) experienced a disruption in

the provision of penicillin at this time, due to insufficient drug stocks at the National Medical Stores even while RPR kits were in good supply (MS, personal communication).

Table 5

Quotations from the 3rd quarter 2001 Report, Lusaka Urban District Health Management Team, Lusaka, Zambia

"Inadequate supply of syringes and needles, STI drugs, RPR reagents…"
"Inadequate supply of drugs, especially Benzathine penicillin and Retarpen,,," **
"Clients are not able to buy from the Chemists due to poor economic status."
"Shortage of staff which leads to poor tallying"
"Inadequate supply of syringes and needles for blood taking…."
"Inadequate or no RPR reagents in most Health Centers."

** Trade name for benzathine penicillin

Antenatal syphilis screening coverage during health services reforms has improved, mostly due to continuing support by cooperating international partner organizations of RPR test kit purchases, but there is no indication that penicillin administration has reached optimal coverage levels in line with national targets (Van der Geest et al., 2000). Pregnant women have a very good chance to be screened for syphilis in Lusaka Urban District clinics. However, a diagnosis of RPR seropositivity may not guarantee treatment due to clinics frequently running out of benazathine penicillin at health centers. Even if women are given prescriptions to purchase benzathine penicillin from private pharmacies, many will not have funds to due so (World Health Organization, 2005). Health service-based reforms of 1992-2005 are considered not to have worked effectively

to address deficiencies in health service delivery, though data for this outcome were not available for this study.

Zambia is experiencing a severe shortage of trained clinical staff to perform ANC duties, including a shortage of workers nationwide and in Lusaka itself. In 2004, there was a 47.9% vacancy rate for nursing staff positions in the public sector nationally (Zambia Ministry of Health/Central Board of Health, unpublished data, 2004). In the Lusaka Urban Health District, generally approximately 35 nurses migrate each year, primarily to the United Kingdom, Botswana and South Africa. This represents about 1 in 18 nurses in the employ of the district (Dovlo, 2005). In May 2004, however, 30 nurses migrated in a single month from Lusaka Urban Health District employment (MS, unpublished data). The exact number of nurse migrations from Zambia as a whole is difficult to calculate. Many nurses go on paid- or unpaid-leave and then do not return to their posts. Thus, current vacancies are a minimum estimate of the true number. The émigré numbers nationally are at least double the Lusaka urban losses. Deaths among health care workers also contribute to the staffing shortages. In 1999, 41% of overall health care staffing losses were attributed to death; many or most were presumably HIV-related, given the younger-than-expected ages of the deceased (Policy Project, 2003). It is not known if health reforms might have been more successful in the absence of the HIV epidemic; an estimated 43% of Zambian health expenditures were HIV-related in 2002 (United Nations AIDS [UNAIDS] Zambia National Health Accounts, 2002).

In addition to health systems and human resources challenges, patient-related, or community issues serve to impede full implementation of ANC syphilis screening policies in Zambia. An insidious and persistent (greater than a decade) community myth

is that health care providers, both Zambian and foreign, take blood from patients to practice Satanism, both in Zambia and abroad. Pregnant women in ANC commonly report that fear of having their blood used for Satanism is their motive to refuse both RPR and HIV screening (Lusaka Urban Health District nurse midwife reports, unpublished). In 2004, we confirmed that at least one minister of a large church would preach that health workers in Lusaka sell or use collected blood for Satanic worship (Zachary et al., 2005).

A Ministry of Health policy signed in January 2005 dictated that all women should receive antenatal syphilis screening (Zambian Ministry of Health, 2004). It is not yet known how this directive, along with government health system re-centralization and restructuring of 2005-2006 will affect antenatal syphilis screening and appropriate syphilis therapy coverage.

Highlights of Programmatic Challenges

From our review we found that a need overall health systems improvement contributed to poor implementation of antenatal syphilis control programs (Azeze et al., 1995; Fonck et al., 2001; Frank & Duke, 2000; Gloyd et al., 2001; Guinness et al., 1988; Kambarami et al., 2000; Rutgers, 1993; Sikosana, 1994; Temmerman et al., 1992; Walker 2001). We noted from our Zambia Case Study that the barrier of running out of drug supplies was not specific to benzathine penicillin, leading us to believe that improvements in supply procurement systems at various levels, from policy, to health system, to human resource, could lead to greater antenatal syphilis screening and treatment coverage. In our review we found reports of offsite laboratory testing as a

programmatic challenge (Deperthes et al., 2004; Duarte et al., 1994). Among clinics with on-site laboratory facilities, reagents frequently ran short (Bique Osman et al., 2000), or transport hindered efficient offsite testing and results delivery (Beksinska *et* al., 2002; Kambarami et al., 1998).

We found human resource-related reports of poor staff motivation to screen for syphilis or treat seroreactive antenatal cases, as well as a lack of appreciation of the seriousness of syphilis in pregnancy (Kambarami et al., 1998). One study showed that a 'before and after' educational implementation directed at changing antenatal care practice resulted in increased knowledge of antenatal care practice, including syphilis testing, but midwives failed to alter their obstetric practice behaviors after the training (Le Roux et al., 1998).

Several studies we reviewed reported lack of patient demand for antenatal care services (Kambarami et al., 1998; Lim et al., 1995; Mati et al., 1983; Temmerman et al., 1992; Temmerman et al., 2000). Likewise, other patient-related barriers to antenatal syphilis screening served as programmatic challenges, such as the belief by women that it is culturally unsafe to have blood drawn for syphilis screening (Kamanga, 1995), or, from our Zambia Case Study, that blood is being used for Satanic purposes.

Most policy related barriers to antenatal syphilis screening and treatment programs we noted in our literature review were disease-specific (Fonck et al., 2001; Gloyd et al., 2001; Jenniskens et al., 1995; Southwick et al., 2001). Some disease-specific policy-related challenges, such as a requirement that the partner be present for treatment of the antenatal care patient (Jenniskens et al., 1995), may be readily changed by health leaders in the short term at little to no additional cost. However, broader policy related

barriers, such as those related to multi-tiers of government and health service funding (Omoleke, 2005), may require changes in governance which may only be realized in the long term.

The global impression from the literature is that, overall, developing country syphilis screening programs' challenges are complex and fresh new approaches to screening are called for as international health priority.

DISCUSSION

We identified four main categories of barriers (policy, health system, human resource, and patient-derived) to successful STS and treatment for syphilis seroreactive cases in ANC, with only 4% of the 176 barriers being considered as highly amenable to alleviation through additional funding. From our case study, health services reforms in Zambia based on decentralization and privatization promulgated from 1992-2005 are widely considered to have failed, though data-based confirmation and insights as to the causes of failure are beyond the scope of our study (Van der Geest et al., 2000; Dovlo, 2005).

We noted patient-related issues that were not primarily due to health systems financial constraints, notably the failure of women to notify a spouse or other sexual partner for fear of physical abuse and cultural or religious beliefs about blood being drawn for syphilis screening, HIV screening, or other purposes (Koenig et al., 2000; Zachary et al., 2005). A longer term community-level educational and economic development effort would be needed to address these issues, we believe, rather than a rapid infusion of short-term fiscal support. Thus, "lack of demand" is moderately

amenable to alleviation through funding in that funds can be directed to community outreach work and improved ANC services, working on attitudes and beliefs of both women and men.

Many human resource barriers are due, in part, to chronic financial constraints inherent in a globalized health care market, and these barriers could be reduced with an increase in financial resources. The emigration of health managers and nurses/nurse-midwives from the poorest nations is related to the higher wages offered in richer countries and the ease with which nurses can move to industrialized nations in western Europe, North America, Australia, and to more regionally prosperous nations (e.g., South Africa, Singapore, United Arab Emirates, Kuwait) through recruiting agencies that facilitate immigration formalities and job placements (Dovlo, 2005). Of course, South African nurses emigrate as well, creating a pattern of health care worker migration from lower income to middle income to higher income nations, with frequent direct migration from the lower to higher income nations directly (Nullis-Kapp, 2005). On the contrary, low motivation of staff to carry out syphilis screening and treatment when warranted, for example, is an example of a constraint which may require a change of work ethic norms; such constraints would be difficult to change with additional funding. Staffing shortages may reflect poor distribution of staff within the health system rather than a shortage per se (Dovlo, 2005). Policy-oriented barriers may require agreement across Ministries (Health and Education or Finance, for example) or overall changes in governance (Hansone et al., 2003).

Most barriers we identified had root causes that were interrelated (Travis et al., 2004). For example, a barrier such as 'health worker has low motivation to draw blood

for syphilis screening', may be due to the fact that the health worker knows that there are no stocks of benzathine penicillin to treat seroreactive cases. This barrier would have been categorized as a human resource constraint, but may actually be a health system or policy related constraint. Thus, there is room to debate the typology of the specific barriers as well as their 'root causes' in a given ANC setting.

Our Zambian case study suggested that many health system and human resource-related barriers could be ameliorated through additional funds and management support for antibiotics and test kits, health worker salaries and training, improved data collection procedures, and social marketing to sensitize communities to demand these services. Whether poor inventory management, resource diversion, ineffective procurement systems, or impoverishment of the Ministry of Health is responsible for penicillin shortages, we do not know at present. Systems-wide improvements in all four identified barrier classes are suggested for definitive programmatic improvement and setting higher local health care standards.

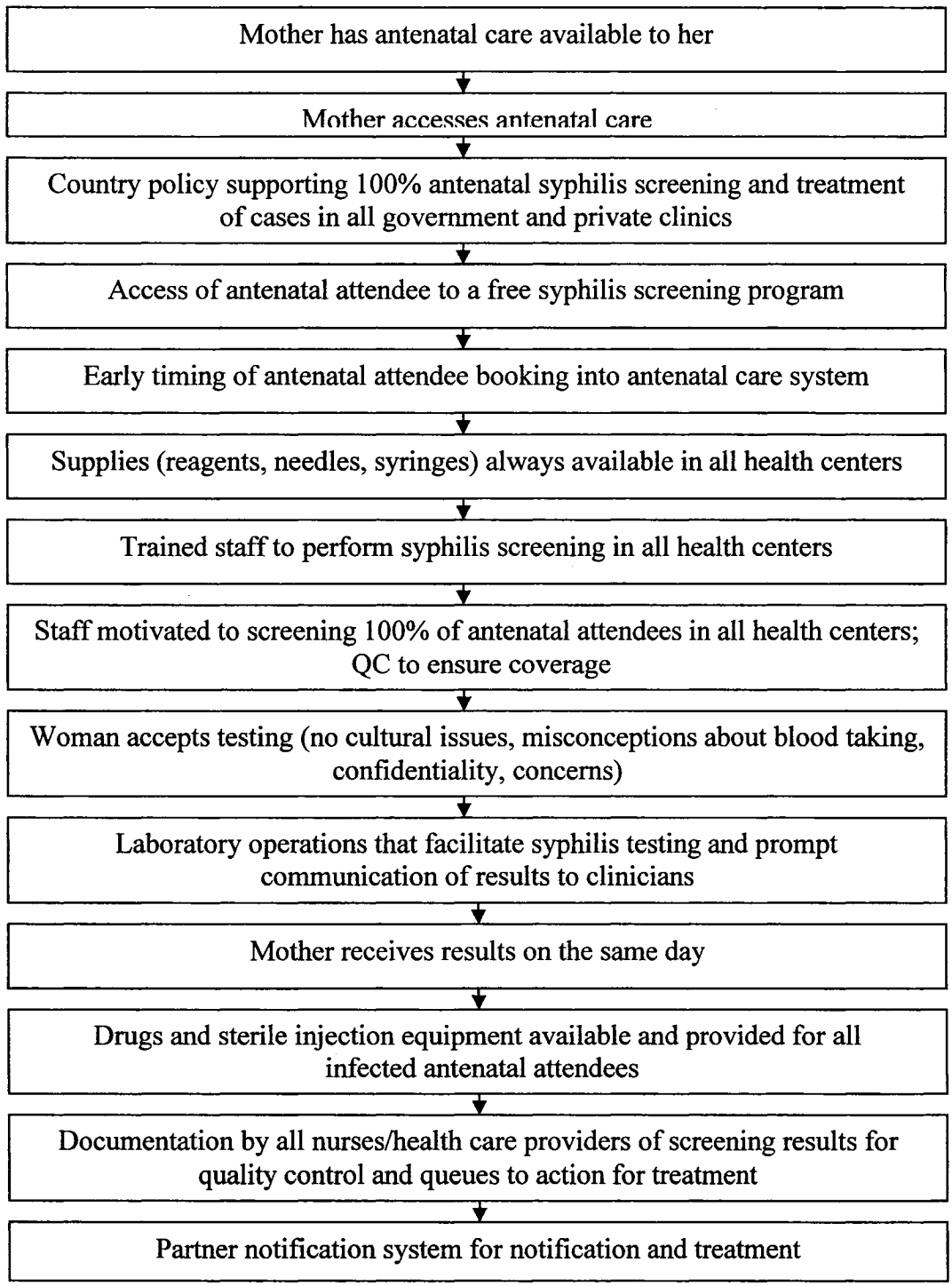
Our results reinforce the findings of others (Gloyd et al., 2001; Hawkes et al., 2004; Schmid, 2004; Watson-Jones et al., 2005). A strength of our study was the availability of a large number of published documents on antenatal syphilis screening programs in the sources that we queried. Our study limitations include those of the study designs of the publications included in our review, including possible recall bias, selection bias, or challenges of establishing a temporal relationship. Additionally, not all studies included in our review were specifically attempting to assess programmatic challenges to antennal syphilis screening and treatment programs; we extracted programmatic information as best we could. Since the 'root cause' of most identified

barriers to STS and therapy can only be postulated, superficial constraints were more often documented. Finally, studies that may have assessed programmatic challenges to ANC STS were not included in our review if they were not in the Index Medicus or our Zambian case study materials.

Syphilis diagnosis and therapy may seem relatively simple when compared to many other public health and medical interventions, yet there are many steps to achieving antenatal syphilis screening and therapy in the context of severe resource constraints (Figure 1). A barrier to full implementation at any one step can render a screening program unsuccessful, and each step may have several interrelated processes that must function effectively for the step to be achieved. For example, staff may not be motivated to screen all antenatal attendees if no treatment is available for syphilis seroreactive cases. Staffing shortages may deny nurse midwives enough time to offer proper antenatal care for all ANC attendees. Community rumors or cultural concerns may result in women refusing screening, or in health care worker ambivalence about its value. If screening and treatment are not monitored and linked to job performance, nurse-midwives may not receive feedback on suboptimal performance. Logistical dysfunction may result in depleted supplies of penicillin or test kits, particularly in rural areas, analogous to vaccine cold chain failures (Berhane & Demissie 2000). Another similar challenge is the prevention of mother to infant transmission of HIV (PMTCT) that depends on a cascade of events, each of which must succeed for program implementation to succeed (Stringer et al., 2005). This has proven to be a complex endeavor even for just a single-dose of nevirapine to be given to an infected mother in labor and her newborn, even when funding constraints are eased (Stringer et al., 2003).

Figure 1

Operational steps in antenatal syphilis screening and treatment



Partnering with local and international non-governmental organizations for technical assistance in program implementation and quality assurance can improve health care delivery and care, including collection of health information for monitoring or policy purposes (Peeling, Mabey, Fitzgerald, & Watson-Jones, 2004). A risk is that indigenous expertise remains underdeveloped when basic services depend on foreign assistance. The integration of syphilis screening programs into PMTCT has been suggested as a means to increase developing country syphilis screening program efficiency, in large part due to the added funding provided and logistical support by international sources for PMTCT (Duarte et al., 1994; Schmid, 2004; Watson-Jones et al., 2005; Peeling et al., 2004; Terris-Prestholt et al., 2003). Making PMTCT and other specific programs more "horizontal" could also "bundle" the response to constraints that are not disease-specific, e.g., those that depend on supply procurement, drug provision logistics, and lab testing and delivery of results (Travis et al., 2004).

Clinic-based efforts to eliminate maternal and congenital syphilis as a major public health problem are inadequate in the developing world (Hook & Peeling, 2004). The interdependent nature of many of the barriers to STS and therapy must be taken into account when addressing syphilis screening program failures. Local program-specific analysis that rigorously evaluates barriers to STS and therapy is suggested, as problems may vary by location. Proposed solutions that address overall barrier root causes with sustainable solutions are needed (Travis et al., 2004), with a special focus on global efforts to address the emigration of nurses (Dovlo, 2005). The new resources now available for PMTCT globally present an opportunity to ensure that, eventually, all

pregnant women will be screened and, when needed, treated for both syphilis and HIV in the context of broadly improved ANC (United Nations Millennium Declaration 2002).

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REFERENCES

Ali Z .(1990). Resurgence of congenital syphilis in Trinidad. *Journal of Tropical Pediatrics,* 36,104-8.

Arya OL. (1995). Screening for syphilis, HIV and HBV at delivery *African Health,* 17, 31.

Azeze B, Fantahun M, Kidan KG, Haile T. (1995). Seroprevalence of syphilis amongst pregnant women attending antenatal clinics in a rural hospital in north west Ethiopia. *Genitourinary Medicine,* 71, 347-50

Bam RH, Cronje HS, Muir A, Griessel DJ, Hoek BB. (1994). Syphilis in pregnant patients and their offspring *International Journal Gynaecology and Obstetrics,* 44,113-8.

Beksinska ME, Mullick S, Kunene B, Rees H, Deperthes B. (2002). A cases study of antenatal syphilis screening in South Africa: successes and challenges.*Sexually Transmitted Diseases,* 29, 32-7.

Berhane Y, Demissie M. (2000). Cold chain status at immunization centres in Ethiopia. *East African Medical Journal,* 77, 476-9.

Bique Osman N, Challis K, Folgosa E, Cotiro M, Bergstrom S. (2000). An intervention study to reduce adverse pregnancy outcomes as a result of syphilis in Mozambique. *Sexually Transmitted Infections,* 76, 203-7.

REFERENCES (Continued)

Blankhart D, Muller O, Gresenguet G, Weis P. (1999). Sexually transmitted infections in young pregnant women in Bangui, Central African Republic. *International Journal of STD AIDS,* 10, 609-14.

Bogdanova A, Bozhinova S. (2004). Clinical aspects of the issue "pregnancy complicated by syphilis". *Akush Ginekol,* 43, Suppl 3,13-7.

Centers for Disease Control. (2002). STD treatment guidelines. Retrieved February 24, 2006 from www.cdc.gov/std/treatment/default.htm.

Central Statistical Office (Zambia), Central Board of Health (Zambia), and ORC Marco. *Zambia Demographic and Health Survey 2001-2002.* (2003). Calverton, Maryland, USA

Chang YK, Chao SL, Huang LW. (1992). Gestational and congenital syphilis in Hualien. Journal *Formos Medical Association,* 91, 620-3.

Cossa HA, Gloyd S, Vaz RG, Folgosa E, Simbine E, Diniz M et al. (1994). Syphilis and HIV infection among displaced pregnant women in rural Mozambique *International Journal of STD AIDS,* 5, 117-23.

Deperthes BD, Meheus A, O'Reilly K, Broutet N (2004) Maternal and congenital syphilis programmes: case studies in Bolivia, Kenya and South Africa. *Bulletin of the World Health Organization,* 82, 410-6.

Donders GG, Desmyter J, Hooft P, Dewet GH. (1997). Apparent failure of one injection of benzathine penicillin G for syphilis during pregnancy in human immunodeficiency virus-seronegativeAfrican women. *Sexually Transmitted Diseases,* 24, 94-101.

Dovlo D. (2005). Wastage in the health workforce: some perspectives from African countries. *Human Resources Health,* 10, 6.

Duarte G, Gir E, de Almeida AM, Hayashida M, Zanetti ML. (1994). Fetal death from syphilis: an epidemiologic evaluation in Ribeirao Preto, Brazil. *Bulletin of the Pan American Health Organization,* 28, 42-9.

Duke T, Michael A, Mgone J, Frank D, Wal T, Sehuko R. (2002). Etiology of child mortality in Goroka, Papua New Guinea: a prospective two-year study. *Bulletin of the World Health Organization,* 80, 16-25.

Fitzgerald DW, Behets F, Caliendo A, Roberfroid D, Lucet C, Fitzgerald JW et al. (2000). Economic hardship and sexually transmitted diseases in Haiti's rural Artibonite Valley. *American Journal of Tropical Medicine and Hygiene,* 62, 496-501.

REFERENCES (Continued)

Fonck K, Claevs P, Bashir F, Bwayo J, Fransen L, Temmerman M. (2001). Syphilis control during pregnancy: effectiveness and sustainability of a decentralized program. *American Journal of Public Health,* 91, 705-7.

Fonn S. (1996). A blood-result turn-around time survey to improve congenital syphilis prevention in a rural area. *South African Medical Journal,* 86, 67-71.

Frank D, Duke T. (2000. Congenital syphilis at Goroka Base Hospital: incidence, clinical features and risk factors for mortality. *Papua New Guinea Medical Journal,* 43, 121-6.

Frans GJ, Brand PL, Muskiet FD. (1994). Inadequate screening for congenital syphilis on Curacao; 1987-1991. *Ned Tijdschr Geneeskd,* 138, 1712-5.

Gilson L, Doherty J, Lake S, Mcintyre D, Mwikisa C, Thomas S. (2003). The SAZA study: implementing health financing reform in South Africa and Zambia. *Health Policy Planning*, 18, 31-46.

Gloyd S, Chai S, Mercer MA. (2001). Antenatal syphilis in sub-Saharan Africa: missed opportunities for mortality reduction. *Health Policy Planning,* 16, 29-34.

Guinness LF, Sibandze S, McGrath E, Cornelis AL (1988) Influence of antenatal screening on perinatal mortality caused by syphilis in Swaziland. *Genitourinary Medicine,* 64, 294-7.

Hanson K, Ranson M, Oliveeira-Cruz V, Mills A. (2003). Expanding access to priority health interventions: a framework for understanding the constraints to scaling-up. *Journal of International Development,* 5, 1- 14.

Hawkes S, Miller S, Reichenbach L, Navyar A, Buses K. (2004). Antenatal syphilis control: people, programmes, policies and politics. *Bulletin of the World Health Organization,*. 82, 417-23

Hira SK, Bhat GJ, Chikamata DM, Nkowane B, Tembo G, Perine PL, Meheus A. (1990). Syphilis intervention in pregnancy: Zambian demonstration project. *Genitourinary Medicine,* 66, 159-64.

Hira SK, Bhat GJ, Patel JB, Din SN, Attili RV, Patel MI et al. (1985). Early congenital syphilis: clinico-radiologic features in 2002 patients. *Sexually Transmitted Diseases,* 12, 177-83.

Hook EW 3rd, Peeling R. (2004) Syphilis control-a continuing challenge. *New England Journal of Medicine,* 351, 122-4.

REFERENCES (Continued)

Jansone M, Lindmark G, Langhoff-Roos J. (2001). Perinatal deaths and insufficient antenatal care in Latvia. *Acta Obstetrical Gynecology Scandinavian,*. 80, 1091-5.

Jenniskens F, Obwaka E, Temmerman M. (1995). Integration of STD services. How to reach and involve men and women. *Action Contre SIDA,* 25, 6.

Jeppsson A, Okuonzi SA. (2000). Vertical or holistic decentralization of the health sector? Experiences from Zambia and Uganda. *International Journal of Health Planning and Management,* 15, 273-289.

Kamanga J. (1995). Maternal and congenital syphilis in Zambia. *African Health, 1*8, 15-7.

Kambarami RA,Chirenje M, Rusakaniko S. (2000). Situation analysis of obstetric care services in a rural district in Zimbabwe. *Central African Journal of Medicine,* 46, 154-7.

Kambarami RA, Manyame B, Macq J. (1998). Syphilis in Murewa District, Zimbabwe: an old problem that rages on. *Central African Journal of Medicine,* 44, 229-32.

Koenig MA, Lutalo T, Zhao F, Nalugoda F Wabwire-Mangen F, Kiwanuka N et al . (2000). Domestic violence in rural Uganda: evidence from a community–based study. *East African Medical Journal,* 77, 476-9.

Lake S, Musumali C. (1999). Zambia: the role of aid management in sustaining visionary reform. *Health Policy Planning,* 14, 254-263.

Le Roux E, Pattinson RC, Tsaku W, Makin JD. (1998). Does successful completion of the Perinatal Education Programme result in improved obstetric practice? *South African Medical Journal,* 88 (2 Suppl), 180-2, 184, 187.

Lech MM. (2003). Non-effective partner notification system: a missed opportunity for the reduction of sexually transmitted infections in sub-Saharan Africa. *Med Wieku Rozwo,* 7, 4 Pt 1, 503-9.

Leoprapai B, Pramualratana A, Sirirassamee B, Tangchonlatip K, Pattaravanich U. (1992). Health services providers and users' opinions on maternal health services in Bangkok metropolis. *Warasan Prachakon Lae Sangkhom,* 3, 85-122.

Lim CT, Koh MT, Sivanesaratnam V (1995) Early congenital syphilis—a continuing problem in Malaysia. *Medical Journal of Malaysia,* 50, 131-5.

REFERENCES (Continued)

Lumbiganon P, Piaggio G, Villar J, Pinol A, Bakketeig L, Bergsjo P et al. (2002). The epidemiology of syphilis in pregnancy. *International Journal of STD AIDS,* 13, 486-94.

Mahoney JF, Arnold, RC, Harris A. (1943). *Penicillin Treatment of Early Syphilis, A Preliminary Report.* Venereal Disease Information, United States Public Health Service. December, 355- 357.

Majoko F, Munjanja S, Nystrom L, Mason E, Lindmark G. (2003). Field efficiency of syphilis screening in antenatal care: lessons from Gutu District in Zimbabwe. *Central African Journal of Medicine,* 49, 90-3.

Mak DB, Murray JC, Bulsara MK. (2003). Antenatal screening for sexually transmitted infections in remote Australia. *Australia and New Zealand Journal of Obstetrics and Gynaecology,* 43, 457-62.

Mathai E, Mathai M, Prakash JA, Bergstrom S. (2001). Audit of management of pregnant women with positive VDRL tests. *National Medical Journal of India*, 14, 202-4.

Mati JK, Aggarwal VP,Sanghvi HC, Lucas S, Corkhill R (1983) The Nairobi birth survey. II. Antenatal care in Nairobi. *Journal of Obstetrics and Gynaecology of East Central Africa* 2, 1-11.

McDermott J, Steketee R, Larsen S, Wirima J. (1993). Syphilis-associated perinatal and infant mortality in rural Malawi. *Bulletin of the World Health Organization,* 71, 773-80.

McDermott J, Steketee R, Wirima J.(1996). Perinatal mortality in rural Malawi. *Bulletin of the World Health Organization,* 74, 165-71.

Meda N, Sangare L, Lankoande S, Sanou PT, Compaore PI, Catraye J et al. (1997). Pattern of sexually transmitted diseases among pregnant women in Burkina Faso, West Africa: potential for a clinical management based on simple approaches. *Genitourinary Medicine,* 73, 188-93.

Mefane C, Toung-Mye M (1987) Syphilis in pregnant women in Libreville (Gabon). *Bulletin of Social Patholgy Exot Filiales* 80,162-70.

Mullick S, Beksinksa M, Msomi S. (2005). Treatment for syphilis in antenatal care: compliance with the three dose standard treatment regimen. *Sexually Transmitted Infections,* 81, 220-2.

Myer L, Abdool Karim SS, Lombard C, Wilkinson D. (2004). Treatment of maternal syphilis in rural South Africa: effect of multiple dose of benzathine penicillin on pregnancy loss. *Tropical Medicine and International Health,* 9, 1216-21.

REFERENCES (Continued)

Myer L, Wilkinson D, Lombard C, Zuma K, Rotchford K, Karim SS.(2003). Impact of on-site testing for maternal syphilis on treatment delays, treatment rates, and perinatal mortality in rural South Africa: a randomized controlled trial. *Sexually Transmitted Infections,* 79, 208-13.

Nullis-Kapp C. (2005). Health worker shortage could derail development goals. *Bulletin of the World Health Organization,* 83, 5-6.

Obisesan KA, Ahmed Y (1999) Routine antenatal syphilis screening—a case against. *African Journal of Medical Science, 2*8, 185-7.

Omoleke II. (2005). The primary health care services in Nigeria: constraints to optimal performance. *Niger Journal of Medicine* 14, 206-12

Opai-Tetteh ET, Hoosen AA, Moodley J. (1993). Re-screening for syphilis at the time of delivery in areas of high prevalence. *South African Medical Journal,* 83, 725-6.

Ortashi OM, El Khidir I, Herieka E. (2004). Prevalence of HIV, syphilis, Chlamydia trachomatis, Neisseria gonorrhoea, Trichomonas vaginalis and candidiasis among pregnant women attending an antenatal clinic in Khartoum, Soudan. *Journal of Obstetrics and Gynacology,* 24, 513-5.

Pao D, Goh B, Bingham, J. (2002). Management issues in syphilis. *Drugs,* 62, 1447-61.

Pattinson RC, Makin JD, Shaw A, Delport SD. (1995). The value of incorporating avoidable factors into perinatal audits. *South African Medical Journal,* 85, 145-7.

Peeling RW, Mabey D, Fitzgerald DW, Watson-Jones D. (2004). Avoiding HIV and dying of syphilis. *Lancet,* 364, 1561-3.

Policy Project. (2003). *Country analysis of family planning and HIV/AIDS: Zambia* (p. 9). Retrieved February 25, 2006 from http://www.policyproject.com/pubs/countryreports/Zam_FPHIV.pdf.

Prual A, Toure A, Huguet D, Laurent Y. (2000). The quality of risk factor screening during antenatal consultations in Niger. *Health Policy Planning,* 15, 11-6.

Qolohle DC, Hoosen AA, Moodley J, Smith AN, Mlisana KP. (1995). Serological screening for sexually transmitted infections in pregnancy: is there any value in re-screening for HIV and syphilis at the time of delivery? *Genitourinary Medicine*, 71, 65-7.

Rodrigues CS, Guimaraes MD, Grupo Nacional de Estudo sobre Sifilis Congenita. (2004). Syphilis positivity in puerperal women: still a challenge in Brazil. *Rev Panam Salud Publica,* 16,168-75.

REFERENCES (Continued)

Rotchford K, Lombard C, Zuma K, Wilkinson D. (2000). 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,* 5, 800-4.

Rutgers S. (1993). Syphilis in pregnancy: a medical audit in a rural district. *Central African Journal of Medicine,* 39, 248-53.

Saloojee H, Velaphi S, Goga Y, Afadapa N, Steen R, Lincetto O. (2004). The prevention and management of congenital syphilis: an overview and recommendations. *Bulletin of the World Health Organization,* 82, 424.

Schmid, G.(2004). Economic and programmatic aspects of congenital syphilis prevention. *Bulletin of the World Health Organization,* 82, 402-409.

Sikosana PL. (1994). An evaluation of the quality of antenatal care at rural health centres in Matebeleland North Province. *Central African Journal of Medicine,* 40, 268-72.

Southwick KL, Blanco S, Santander A, Estenssoro M, Torrico F, Seoane G et al. (2001). Maternal and congenial syphilis in Bolivia, 1996: prevalence and risk factors. *Bulletin of the World Health Organization,* 79, 33-42.

Stringer EM, Sinkala M, Stringer JS, Myzece E Makuka I, Goldenberg RL et al. (2003). Prevention of mother-to-child transmission of HIV in Africa: Successes and challenges in scaling-up a nevirapine-based program in Lusaka, Zambia. *AIDS* ,17, 1377-82.

Stringer JS, Sinkala M, Maclean CC, Levy J, Kankasa C, Degroot A et al. (2005). Effectiveness of a city-wide program to prevent mother-to-child HIV transmission in Lusaka, Zambia. *AIDS*, 19, 1309-15.

Swingler GH, Van Coeverden de Groot HA. (1993). The antenatal prevention of congenital syphilis in a peri-urban settlement. *South African Medical Journal,* 83, 34-5.

Temmerman M, Gichangi P, Fonck K, Apers L, Claeys P, Van Renterghem L et al. (2000). Effect of a syphilis control programme on pregnancy outcome in Nairobi, Kenya. *Sexually Transmitted Infections,* 76, 117-21.

Temmerman M, Fonck K, Bashir F Inion I, Ndinya-Achola JO, Bwayo J et al. (1999). Declining syphilis prevalence in pregnant women in Nairobi since 1995: another success story in the STD field? *International Journal of STD AIDS,* 10, 405-8.

REFERENCES (Continued)

Temmerman M, Mohamedali F, Fransen L. (1993). Syphilis prevention in pregnancy: an opportunity to improve reproductive and child health in Kenya. *Health Policy Planning,* 8, 122-27.

Temmerman M, Lopita MI, Sanghvi HC, Sinei SK, Plummer FA, Piot P. (1992). The role of maternal syphilis, gonorrhoea and HIV-1 infections in spontaneous abortion. *International Journal of STD AIDS,* 3, 418-22.

Terris-Prestholt F, Watson-Jones D, Mugeye K, Mumaranayake L, Ndeki L, Weiss H, et al. (2003) Is antenatal syphilis screening still cost effective in sub-Saharan Africa. *Sexually Transmitted Infections,* 79, 375-81.

Tikhonova L, Salakhov E, Southwick K, Shakarishvili A, Ryan C, Hillis S. (2003). Congenital Syphilis Investigation Team. Congenital syphilis in the Russian Federation: magnitude, determinants, and consequences. *Sexually Transmitted Infections,* 79, 106-10.

Travis P, Bennett S, Haines A, Pang T, Bhutta Z, Hyder A et al. (2004). *Lancet,* 264, 900-06.

UNAIDS. (2004), *Zambia National Health Accounts 2002*: Main Findings, p.11. *United Nations Millennium Declaration*: resolution adopted by the General Assembly. Adopted 18 September, 2002. Retrieved February 25, 2006 from http://www.un.org/millennium/declaration/ares552e.pdf.

United Nations Development Programme, Human Development Report, 2002. Human development indices. Retrieved July 15, 2005 from http://www.undp.org/hdr2002/indicator/cty_f_BWA.html and http://www.undp.org/hdr2002/indicator/cty_f_ZMB.html.

Van der Geest S, Macwan'gi M, Kamwanga J, Mulikelela D, Mazimba A, Mwangelwa M. (2000). User fees and drugs: what did the health reforms in Zambia achieve? *Health Policy Planning,* 15, 59-65.

Walker GJ. (2001). Antibiotics for syphilis diagnosed during pregnancy. Cochrane Review. *Cochrane Database Systematic Reviews,* 3, CD001143, available through http://www.cochrane.org/reviews/en/ab001143.html

Watson-Jones D, Oliff M, Terris-Presholt F, Changalucha J, Gumodoka B, Mayaud P *et* al. (2005).Antenatal syphilis screening in sub-Saharan Africa: lessons learned from Tanzania. *Tropical Medicine and International Health,* 10, 934-43.

REFERENCES (Continued)

Watson-Jones D, Gumodoka B, Weiss H, Changalucha J, Todd J, Mugeye K et al. (2002). Syphilis in pregnancy in Tanzania. II. The effectiveness of antenatal syphilis screening and single-dose benzathine penicillin treatment for the prevention of adverse pregnancy outcomes. *Infectious Diseases,* 186, 948-57

Wilkinson D, Abdool Karim SS, Harrison A, Lurie M, Colin M, Connolly C et al. (1999). Unrecognized sexually transmitted infections in rural South African women: a hidden epidemic. *Bulletin of the World Health Organization,* 77, 22-8.

Wilkinson D, Sach M, Connolly C. (1997). Epidemiology of syphilis in pregnancy in rural South Africa: opportunities for control. *Tropical Medicine and International Health,* 2, 57-62.

Wilkinson D. (1993). Statistics of perinatal mortality due to error or omission: a suggestion of how to improve care. *Tropical Doctor,* 23,119-21.

World Bank. (2006). List of Economies. Retrieved on August 9, 2006, from http://siteresources.worldbank.org/DATASTATISTICS/Resources/CLASS.XLS.

World Health Organization World Health Report, Zambia and Botswana, Basic indicators for all WHO member states. Retrieved on July 15, 2005 from http://www.who.int/whr/2004/annex/country/zmb/en/, and http://www.who.int/whr/2004/annex/country/bwa/en/.

Zachary D, Mweemba A, Helova A, MaPhiri F, Sinkala M, Stallworth J. (2005). Beliefs regarding HIV/AIDS research participation in Lusaka, Zambia. *IAS Conference on HIV Pathological Treatment,* Jul 24-27; 3rd: Abstract No. TuPe11.9C07.

Zambian Ministry of Health. (2004). *Reproductive Health Policy,* Lusaka, Zambia.

World Health Organization. (2003). Antenatal care in developing countries: promises, achievements, and missed opportunities: an analysis of trends, levels, and differentials, 1990-2001. Geneva, Switzerland. Retrieved February 24, 2006 from www.who.int/reproductive-health/docs/antenatal_care.pdf.

CORRELATES OF SYPHILIS SEROREACTIVITY AMONG PREGNANT WOMEN: THE HIVNET 024 TRIAL IN MALAWI, TANZANIA, AND ZAMBIA

by

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ABSTRACT

Objectives: To determine correlates of syphilis seroprevalence among HIV-infected and -uninfected antenatal attendees in an African multi-site clinical trial.

Goal: To improve strategies for maternal syphilis prevention. *Study Design:* Cross sectional study, outcome of confirmed syphilis seroreactivity.

Results: 2270 (86%) women were HIV-infected, 366 (14%) were HIV-uninfected. 175 (6.6%) were syphilis seropositive (7.3% among HIV-infected, and 2.6% HIV-uninfected women). Statistically significant correlates included geographic site (Odds Ratio [OR]= 4.5, Blantyre; OR=3.2, Lilongwe; OR=9.0, Lusaka; vs. Dar es Salaam as the referent), HIV infection (OR=3.3), age 20 to 24 years (OR= 2.5), being divorced, widowed, or separated (OR= 2.9), genital ulcer treatment in last year (OR= 2.9), history of stillbirth (OR= 2.8, one stillbirth; OR=4.3, 2-5 stillbirths), history of preterm delivery (OR= 2.7, one preterm delivery).

Conclusion: Many women without identified risk factors were syphilis seropositive. Younger HIV-infected women were at highest risk. Universal integrated antenatal HIV and syphilis screening and treatment is essential in sub-Saharan African settings.

Summary: Syphilis seroprevalence was high in three of four sub-Saharan African sites, especially among HIV-infected women. Syphilis was associated with history of stillbirth, history of preterm delivery, marital status, and, unexpectedly, younger age.

INTRODUCTION

Syphilis is a serious cause of maternal and infant morbidity and mortality (Ament & Whalen, 1996; Pao, Goh, & Bingham, 2002; Watson-Jones , Gumodoka, Weiss, Changalucha, Todd, Mugeye, et al., 2002; Finelli, Berman, Koumans, & Levine, 1998; Brocklehurst, 1999). Syphilis during pregnancy is associated with stillbirth, spontaneous abortion, preterm birth, and intrauterine growth restriction (Genc & Ledger, 2000). A *Treponema pallidum*-infected newborn may exhibit hepatosplenomegaly, failure to thrive, and high neonatal mortality (Ament & Whalen, Watson-Jones, et al., 2002; Walker & Walker, 2002; Wendel, 1988). In addition to these serious reproductive outcomes, syphilis is a well-documented co-factor for horizontal (sexual), (Cossa, Gloyd, Vaz, Folgosa, Simbine, Diniz, et al., 1994; Quinn, Cannon, Glasser, Groseclose, Brathwaite, Fauci, et al., 1990; Cohen, 1998), as well as vertical (mother to child), transmission of HIV (Cossa, et al., 1994; Lee, Hallmark, Frenkel, & Del Priorie, 1998; Gray,, McIntyre, Newell, 2000). In sub-Saharan Africa and elsewhere, syphilis and HIV serve as synergistic infections, each exacerbating the transmission of the other (Wasserheit, 1992; Fleming & Wasserheit, 1999).

Women in resource-limited settings may not receive routine screening for syphilis in antenatal care, and even if they are screened, treatment for infected mothers may be unavailable (Gloyd et al., 2001). In a chart review of 622 women receiving public sector antenatal care in Lusaka, Zambia, the rapid plasma reagin [RPR] assay was recorded in 81% of records, while only two of 44 positive results had treatment documented in their records at a time of penicillin supply shortages (1999-2000) (R. MacDonald and SHV, unpublished data; M. Sinkala, personal communication, May 2005).

Reported syphilis rates vary markedly between and within sub-Saharan African populations. Antenatal syphilis prevalence rates in Malawi, Tanzania, and Zambia are reported as 2.7% (year 2003; Venereal Diseases Reference Laboratory tests [VDRL], no confirmatory testing) (HIV Sentinal Surveillance Report, Malawi, 2003) , 7.2% (year 2000; RPR confirmed with *T. pallidum* hemagglutination assay [TPHA]) (Ministry of Health Tanzania/National AIDS Control Program, 2005), and 8.2% (2001; RPR confirmed with TPHA) (Zambia Demographic and Health Survey 2001-2002), respectively. Regional seroprevalence differences may reflect a variety of socio-cultural and economic factors, varying surveillance methods, and differential access to syphilis diagnosis and treatment (World Health Organization, 2001). We examined demographic, sexual risk, and obstetric characteristics to predict syphilis seroprevalence among HIV-infected and -uninfected antenatal attendees enrolled in a multi-site clinical trial in Africa.

METHODS

Study Setting and Population

The HIVNET 024 trial was a randomized, double-blinded, placebo-controlled Phase 3 clinical trial of antibiotics to prevent perinatal HIV transmission and preterm birth by reducing chorioamnionitis (Kafulafula, Martinson, Msamanga, Sinkala, & HIVNET 024 Team, 2004; Goldenberg, Vermund, Goepfert, & Andrews, 1998). The intervention studied in the trial was a relatively inexpensive (<US$5.00), two-course antibiotic prophylactic regimen. Trial participants were recruited in four sub-Saharan African cities: Blantyre and Lilongwe, Malawi; Lusaka, Zambia; and Dar es Salaam,

Tanzania. Enrollment started in July 2001 and was completed in February 2003. Consenting pregnant women were screened for HIV infection between 16-23 weeks gestation during an antenatal clinic visit prior to enrollment into the trial. Laboratory evaluations included HIV-1 serology screening by dual rapid test algorithm and Western blot confirmation of all positive or indeterminate results at three sites, while the Dar es Salaam site performed two ELISAs - Dade Behring Enzygnost anti-HIV-1/2 Plus™ (1st ELISA) followed by Abbott Murex Wellcozyme anti-HIV-1™ recombinant, with discrepant results between the two ELISAs being confirmed by Western blot. Additional study laboratory evaluations included comprehensive screening for sexually transmitted infections (STIs), and complete blood counts (Kafulafula, Martinson, Msamanga, Sinkala, and the HIVNET 024 Team, 2004). At 20 to 24 weeks gestational age, women were randomized to receive either metronidazole 250 mg three times a day (TID) and erythromycin 250 mg orally TID for 7 days or placebo for the control group. Participants were also given metronidazole 250 mg and ampicillin 500 mg (or placebo) at the 26-30 week visit to be taken at the onset of labor, continuing after delivery TID until the one week course was completed. Five HIV-infected women were recruited for every one HIV-uninfected woman at the two Malawi and Zambian sites, while the Dar es Salaam site recruited only HIV-infected women, as per the design of the parent trial. The primary study outcome was mother-to-child transmission of HIV, while secondary outcomes included other causes of morbidity and mortality such as preterm birth. Sociodemographic, living environment, obstetric, and sexual history data were collected at the study enrollment visit using a standardized structured questionnaire enabling the present nested study. Research nurses interviewed enrolled participants confidentially in

private rooms. The study was approved by US and in-country institutional ethical review boards or committees in each country. Written informed consent was obtained from all enrolled participants.

Laboratory Procedures

HIV testing was performed at a screening visit according to site-specific procedures using either conventional HIV ELISA tests or dual HIV rapid tests. These tests were validated by a central reference laboratory in the U.S. HIV-infected women were offered mother-to-child transmission prophylaxis with nevirapine (Guay, Musoke, Fleming, Bagenda, Allen, Nakabiito, et al., 1999; Stringer, Sinkala, Stringer, Mzyece, Makuka, Goldenberg, et al., 2003). Women were tested for syphilis using RPR tests (Blantyre, Lilongwe, and Lusaka) or VDRL tests (Dar es Salaam) as part of pre-entry evaluations at the enrollment visit. Confirmation of the syphilis screening test was performed with the microhemagglutination *T. pallidum* test (MHA-TP) (Lilongwe), *T. pallidum* particle agglutination test (TPPA) (Dar es Salaam), or TPHA (Blantyre). Both TPPA and TPHA tests were used to confirm positive RPR samples from Lusaka. Women with a reactive syphilis test were treated with intramuscular benzathine penicillin at no cost.

Statistical Analysis

For purposes of this study, a confirmed test was used as the basis for syphilis diagnosis. Data obtained at the enrollment visit (20 to 24 weeks gestation) were used for this study. A woman was considered to have maternal syphilis if at the time of HIVNET

024 enrollment her serum was reactive according to one of the screening and one of the confirmatory tests. Higher socioeconomic status was estimated from data on availability of electricity or running water in the home.

Associations between syphilis serostatus and demographic, sexual history, or obstetric variables were assessed using odds ratios (ORs), and chi-square, Student's t, or Fisher's exact tests, as appropriate, to determine statistical significance. Multivariable logistic regression analysis was used to further investigate those associations that were significant at a $p<0.05$ (two-tailed) level with syphilis seroprevalence in the bivariate analyses. Findings are presented as adjusted odds ratios (OR_{adj}) with corresponding 95% confidence intervals (95% CI.) and/or p-values. The logistic models were performed for the overall population of HIV-infected and -uninfected women, and separately stratified by HIV infection status. All statistical analyses were performed with SAS™ version 9.1 (SAS, Inc., Cary, NC).

RESULTS

Study Population, Syphilis Seroprevalence

Of 2661 women who gave informed consent for enrollment into HIVNET 024, 2636 (99%) had a syphilis screening test, and, if screening test positive, a confirmatory test. All 2636 of these women were included in this syphilis sub-study. As per the study design, 2270 (86%) were HIV-infected and 366 (14%) were HIV-uninfected. At enrollment, 175 (6.6%) women were confirmed syphilis positive, 7.3% among HIV-infected and 2.5% among HIV-uninfected (OR=3.1, 95% CI= 1.6 – 6.2). Overall site-specific seroprevalence rates ranged from 1.4% in Dar es Salaam, Tanzania to 11.7% in

Lusaka, Zambia. The rates were intermediate in Lilongwe (5.1%) and Blantrye (6.3%), Malawi (Table 1). Among the HIV-infected women, the site-specific syphilis seroprevalences were: 1.4% in Dar es Salaam, 5.9% in Lilongwe, 7.3% in Blantrye, and 13.0% in Lusaka. Among the HIV-uninfected women, the site specific confirmed syphilis rates were: 1.1% in Blantyre, 1.4% in Lilongwe, and 4.9% in Lusaka.

Sociodemographic Characteristics, Sexual and Obstetric History

In bivariate analyses, women were more likely to be syphilis seropositive if they came from the Malawi or Zambia sites, were HIV-infected, were 20 to 24 years old, had completed less than 6 years of formal education, were illiterate, were divorced/separated/widowed, were of lower socioeconomic status, had a greater number of lifetime sexual partners, had been treated for genital ulcers in the last year, had a greater number of past pregnancies, had a history of prior stillbirth, and a history of prior preterm delivery (Table 1).

Table 1

Confirmed Syphilis Seropositive and Baseline Socio-Demographic and Sexual/Obstetric History Characteristics Among 2636 Enrolled Antenatal Attendees in the HIVNET 024 Clinical Trial in Sub-Saharan Africa

Characteristic	Women n (%)	% confirmed syphilis seropositive and *p* value
Site	n=2636	
Blantyre, Malawi	559 (21.2)	6.3
Lilongwe Malawi	896 (34.0)	5.1
Dar es Salaam Tanzania	428 (16.2)	1.4
Lusaka, Zambia	753 (28.6)	11.7
		p<0.0001
HIV serostatus	n=2636	
Positive	2270 (86.1)	7.3
Negative	366 (13.9)	2.5
		p=0.0005
Age in years	n=2636	
16 – 19	322 (12.2)	3.7
20 – 24	1013 (38.4)	9.1
25 – 29	845 (32.1)	5.3
30 – 45	456 (17.3)	5.7
		p=0.0007
Years of formal education (completed years)	n=2635	
None	233 (8.8)	10.3
1 – 5	614 (23.3)	8.5
6 - 18	1788 (67.9)	5.5
		p=0.002
Literate (self-reported)	n=2636	
Yes	2051 (77.8)	5.3
No	585 (22.2)	11.3
		p≤0.0001
Marital status	n=2636	
Married and/or living with partner (ref)	2431 (92.2)	6.3
Never married or living with partner	141 (5.4)	4.3
Divorced, separated, or widowed	64 (2.4)	23.4
		p≤0.0001

Table 1, continued

Characteristic	Women n (%)	% confirmed syphilis seropositive and *p* value
Electricity on premises	n=2636	
Yes	1048 (39.8)	5.1
No	1588 (60.2)	7.7
		p=0.008
Running water on premises	n=2636	
Yes	1084 (41.1)	5.3
No	1552 (58.9)	7.6
		p=0.02
Cook with paraffin stove	n=2636	
Yes	470 (17.8)	2.3
No	2166 (82.2)	7.6
		p≤0.0001
Number of lifetime sexual partners including spouse or partner	n=2617	
1	628 (24.0)	4.6
2	848 (32.4)	5.7
3 – 25	1141 (43.6)	8.5
		p=0.003
In the last year, treated for genital ulcers	n=2633	
Yes	93 (3.5)	21.5
No	2540 (96.5)	6.1
		p≤0.0001
Number of pregnancies, including current	n=2636	
1	501 (19.0)	4
2 – 4	1712 (65.0)	7.3
5 – 12	423 (16.1)	7.1
		p=0.03
Number of stillbirths	n=2636	
0	2425 (92)	5.7
1	180 (6.8)	15.6
2 - 5	31 (1.2)	25.8
		p≤0.0001

Table 1, continued

Characteristic	Women n (%)	% confirmed syphilis seropositive and *p* value
Number of children born >3 weeks early	n=2636	
0	2509 (95.2)	6.2
1	95 (3.6)	16.8
2 - 8	32 (1.2)	9.4
		p=0.002

In bivariate analyses, the following variables were not significant: years of formal education of spouse/partner, occupation, spouse/partner's occupation, housing type, use of gas/electric or charcoal stove or firewood for cooking, number of lifetime sexual partners in current pregnancy, condom use during current pregnancy, having been treated for abnormal vaginal discharge in the last year, and number of abortions or miscarriages.

Women at each of the four sites were of similar age, education, literacy, marital status, and occupation, except that women in Dar es Salaam were of higher socioeconomic status as measured by electricity and running water on their premises and use of a paraffin stove or firewood for cooking. Results of site-specific analyses were very similar to the findings of the overall analysis (data not shown).

Correlates of Syphilis Seroprevalence

In the multivariable logistic regression analysis for the four sites combined, seven factors were found to be independent and statistically significant correlates of syphilis seroprevalence among the antenatal attendees (Table 2): geographic site (OR= 4.5, Blantyre; OR=3.2, Lilongwe; OR=9.0, Lusaka, vs. Dar es Salaam referent population), HIV infection (OR=3.3), maternal age 20 to 24 years (OR= 2.5 vs. age 16 to 19 years), being divorced/widowed/separated (OR= 2.9 vs. married or living with partner), having had treatment for genital ulcers in the last year (OR= 2.9), history of stillbirth (OR= 2.8 for one stillbirth; OR=4.3 for two to five stillbirths) or having had a preterm delivery (OR= 2.7 for one preterm delivery).

Table 2

*Results of multivariable analysis: risk factors for syphilis (RPR or VDRL [+] with confirmation by TPHA, MHA-TP, or TPPA)**

Characteristic	Crude OR*	Adjusted OR* (95% CI)	p value
Site			
Dar es Salaam, Tanzania (referent)	1.0	1.0	
Blantyre, Malawi	4.7	4.5 (1.4 -14.4)	0.01
Lilongwe, Malawi	3.8	3.2 (1.0-10.0)	0.04
Lusaka, Zambia	9.3	9.0 (2.9- 28.2)	0.0002
HIV infection status			
Seronegative (referent)	1.0	1.0	
Seropositive	3.1	3.3 (1.6- 6.9)	0.002
Age (years)			
16-19 (referent)	1.0	1.0	
20-24	2.6	2.5 (1.3 - 5.0)	0.01
25-29	1.5	1.2 (0.6 - 2.6)	0.6
30-45	1.6	1.4 (0.6 - 3.2)	0.4

Table 2, continued

Characteristic	Crude OR*	Adjusted OR* (95% CI)	p value
0 (referent)	1.0	1.0	
1 – 5	0.8	0.9 (0.5 - 1.5)	0.6
6 - 18	0.5	0.7 (0.4 - 1.5)	0.4
Literacy (self-reported)			
Not able to read (referent)	1.0	1.0	
Able to read	0.4	0.7 (0.4 - 1.2)	0.2
Marital status			
Married/living with partner (referent)	1.0	1.0	
Never married/not living with partner	0.7	0.8 (0.3 - 2.0)	0.7
Divorced/separated/widowed	4.5	2.9 (1.5 - 5.7)	0.001
Presence of utilities on premises:			
No electricity (referent)	1.0	1.0	
Electricity on premises	0.6	0.9 (0.6 - 1.3)	0.5
No running water on premises (referent)	1.0	1.0	
Running water on premises	0.7	0.9 (0.6 - 1.3)	0.6
Method used for daily cooking			
No paraffin stove (referent)	1.0	1.0	
Paraffin stove	0.3	1.1 (0.5 - 2.6)	0.8
Number of lifetime sexual partners including spouse			
1 (referent)	1.0	1.0	
2	1.2	1.1 (0.7 - 1.9)	0.6
3 – 25	1.9	1.5 (1.0 – 2.4)	0.1
In the last year:			
Not treated for genital ulcers (referent)	1.0	1.0	
Treated for genital ulcers	4.2	2.9 (1.6 - 5.3)	0.0003
Number of pregnancies, including this pregnancy			
1 (referent)	1.0	1.0	
2 – 4	1.9	1.5 (0.8 - 2.5)	0.2
5 - 12	1.8	1.2 (0.6 - 2.7)	0.6

Table 2, continued

Characteristic	Crude OR*	Adjusted OR* (95% CI)	p value
0 (referent)	1.0	1.0	
1	3.0	2.8 (1.7 - 4.5)	<0.0001
2 – 5	5.7	4.3 (1.7 - 11.2)	0.002
Number of children born >3 weeks early			
0 (referent)	1.0	1.0	
1	3.1	2.7 (1.5 - 5.0)	0.002
2 - 8	1.6	1.5 (0.4 - 5.4)	0.5

* Rapid Plasma Reagin assay (RPR); Venereal Diseases Reference Laboratory tests (VDRL); *T. pallidum* hemagglutination assay (TPHA); microhemagglutination *T. pallidum* test (MHA-TP); *T. pallidum* particle agglutination test (TPPA)

The same variables were found significant in bivariate analyses for the HIV-infected women as for the combined cohort and were used in a multivariable analysis assessment. The multivariable logistic regression analysis results were similar for the combined HIV-infected and -uninfected cohort (n=2636) as for the HIV-infected cohort alone (n=2270) (results not shown for HIV-infected cohort). There were 9 syphilis seropositive women among the HIV-uninfected cohort of women (n= 366). No variables were found to be independent and statistically significant correlates of syphilis seroreactivity among the HIV-uninfected women in multivariable analysis.

DISCUSSION

There were variations in syphilis seroprevalence among sites, with the Lusaka, Zambia site having an especially high seroprevalence (11.7%). Women with HIV infection were more likely to be syphilis seropositive, as were women who were

divorced, separated, or widowed. Women with a history of stillbirth or preterm delivery were significantly more likely to be syphilis seropositive, confirming the well-known reproductive health consequences of maternal and congenital syphilis. A surprising result was the significant association of syphilis among women in the 20 to 24 years age group, as compared to older women. Typically, syphilis rates are highest in older women, but given 86% of women enrolled in the study were HIV-infected and the extremely limited access to antiretroviral therapy in the time period of the study, older women with syphilis and HIV may well have died prior to study commencement, distorting the age-risk associations (Hoover, Munoz, Carey, Odaka, Taylor, Chmiel, et al., 1991).

Though the number of sexual partners during the current pregnancy was not significantly associated with syphilis, the number of lifetime sexual partners was found to be statistically significant on bivariate and multivariable analyses, suggesting that syphilis risk is not specific to the time of pregnancy per se (Cossa et al., 1994; Grosskurth, Mosha, Todd, Mwijarubi, Klokke, Senkoro, et al., 1995).

Higher syphilis risk is documented in divorced and widowed women in Senegal (Lagarde, Guyavarch, Piau, Gueye-Ndiaye, Seck, Enel, et al., 2003), though single marital status was the risk factor noted in a previous Tanzania study (Gertig, Kapiga, Shao & Hunter, 1997). Previous studies related to pregnant women in developing countries reported the following risk factors for maternal syphilis, similar to our findings: HIV infection (Sombie, Meda, Cartoux, Tiendrebeogo, Ouangre, Yaro, et al., 2000), history of stillbirth (Lumbiganon, Piaggio, Villar, Pinol, Bakketeig, Bergsjo, et al., 2002), history of preterm delivery (How & Bowditch, 1994) previous perinatal death (Wilkinson, Sach, & Connolly, 1997), high risk sexual behaviors (Lago, Rodrigues, Fiori,

& Stein, 2004) history of abortion (Kebede & Chamiso, 2000), genital ulcer disease (Ortashi, El Khidir, & Herieka, 2004) and lower socioeconomic status (Behets, Desormeaux, Joseph, Adrien, Coicou, Dallabetta, et al., 1995). The economic indicators in this study (presence of water or electricity in the home) suggest that antenatal attendees in Dar es Salaam had a higher socioeconomic status, perhaps associated with lower sexual and syphilis risks. Higher socioeconomic status is associated with decreased syphilis seroreactivity (Lago et al., 2004; Bruisten, 2003; Fitzgerald, Behets, Caliendo, Roberfroid, Lucet, Fitzgerald, et al., 2000). A history of stillbirth was significantly associated with syphilis seroreactivity in our study; in southern Africa, up to half of all stillbirths are found in syphilis seroreactive women, with ≥25% of all stillbirths being attributed to syphilis (Goldenberg & Thompson, 2003).

In a study of 1058 HIV-infected women in Dar es Salaam, Tanzania (2001), antenatal attendees, independent risk factors for syphilis seroreactivity (positive on both VDRL and TPHA) were: age 20 to 24 years and 30 to 34 years (compared to women 15 to 19 years old); abnormal vaginal discharge in the past year; a genital ulcer on examination; or current *Trichomonas vaginalis* infection (Urassa, Kapiga, Msamanga, Antelman, Coley, Fawzi, 2001). Women who were fully supported by their male partners were at a reduced risk of active syphilis compared to those with their own personal income source (Urassa, 2001).

Inefficient and ineffective antenatal syphilis screening programs in developing countries are well documented (Gloyd et al., 2001; Beksinska, Mullick, Kunene, Rees, & Deperthes, 2002; Fonck, Kidula, Kirui, Ndinya-Achola, Bwayo, Claeys, et al., 2000 ; Kambarami, Manyame, & Macq, 1998; Hook & Peeling, 2004). While each of the

women enrolled in this study was screened for syphilis and, if reactive, treated, we do not know the coverage rates of the antenatal syphilis screening programs in these four sites for non-research patients. In Zambia and Malawi, in particular, high seroprevalence rates suggest the need to improve syphilis screening and treatment in concert with other essential antenatal services (Goldenberg, Stringer, Sinkala, & Vermund, 2002). Advocacy by developing country governments and international economic and/or technical assistance are needed to support strapped health workers and systems to achieve a long term goal of sustainability.

Our seroprevalence findings are a legitimate comparison between four African cities, but they might not reflect background syphilis seroprevalence because: 1) 86% of the women were HIV-infected due to the design of the parent clinical trial; 2) antenatal attendees who consented to join the research study may have been more likely to have had STIs or history of obstetrical complication than other women; and, 3) recruitment for the study occurred among women already in the antenatal care system; thus, women who joined the study were those who "booked early" since enrollment only occurred from 20 to 24 weeks gestation. These selection factors indicate that our study seroprevalence is not generalizable; higher syphilis seroprevalence might be expected from HIV-infected women; lower rates might be seen in women booking relatively early (20-24 weeks gestation) for antenatal care; higher rates might be seen in women booking early due to reproductive tract symptoms; lower rates might be seen in women seeking care through research-related programs because they potentially perceived it of higher quality than the government care system. We did not find the higher syphilis rates among HIV-infected women in the lower HIV prevalence nation; the lowest syphilis rates were noted in

Tanzania where HIV prevalence is lower than in Malawi or Zambia (Grosskurth, Gray, Hayes, Maybe, & Wamer, 2000; UNAIDS, 2003).

Antenatal syphilis screening programs must be evaluated for effectiveness and reformed accordingly. Infants receiving antiretroviral prophylaxis as part of a prevention of mother to child HIV transmission (PMTCT) program have been documented to die of congenital syphilis in a program where syphilis screening had not been a part of HIV prevention activities (Peeling, Mabey, Fitzgerald, & Watson-Jones, 2004). Vertical integration of syphilis screening in antenatal HIV-prevention programs is a way to strengthen existing health systems and to improve upon health outcomes, particularly in resource-limited settings where obstacles to universal antenatal screening may abound (Peeling, 2004), analogous to joint HIV and tuberculosis screening that is advocated in high prevalence regions (Reid, Reid, & Vermund, 2004). A routine, universal, "opt-out" approach to joint syphilis and HIV screening would improve coverage and care for both (Institute of Medicine, 1998). In Lilongwe, Malawi for example, where a mature PMTCT program has resulted in almost universal acceptance of voluntary counseling and testing (VCT) based on finger stick, whole blood HIV rapid testing, a pilot program is being conducted to routinely perform syphilis rapid tests (and treatment) during the VCT session (Taha, Dallabetta, Hoover, Chiphangwi, Mtimavalye, Liomba, et al., 1998). Given the high rates of HIV and syphilis co-infection, antenatal care providers may consider an antenatal attendee's marital status and age; if resources are scarce and must be prioritized, those attendees who are younger, divorced, widowed or separated are likely to be at higher risk for both infectious diseases. While recognition of syphilis risk

factors is useful, many women without the risk factor characteristics were syphilis seroreactive; universal testing is clearly the superior approach.

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REFERENCES

Ament LA, Whalen E. (1996). Sexually transmitted diseases in pregnancy: diagnosis, impact, and intervention. *Journal of Obstetrics & Gynecology Neonatal Nursing*, 25, 657-66.

Behets FM, Desormeaux J, Joseph D, Adrien M, Coicou G, Dallabetta G, et al. (1995). Control of sexually transmitted diseases in Haiti: results and implications of a baseline study among pregnant women living in Cite Soleil Shantytowns. *Journal of Infectious Diseases*, 172, 764-71.

Beksinska ME, Mullick S, Kunene B, Rees H, Deperthes B. (2002). A case study of antenatal syphilis screening in South Africa: successes and challenges. *Sexually Transmitted Diseases,* 29, 32-7.

Brocklehurst, P. (1999). Update on the treatment of sexually transmitted infections in pregnancy – 1. *International Journal of STD AIDS*, 10, 571-80.

Bruisten SM. (2003). Genital ulcers in women. *Current Women's Health Reproductivity*, 3, 288-98.

Central Statistical Office (Zambia), Central Board of Health (Zambia), and ORC Marco. (2002). *Zambia demographic and health survey 2001-2002 (p. 231).* Calverton, Maryland, USA.

Cohen MS. (1998). Sexually transmitted diseases enhance HIV transmission: no longer a hypothesis. *Lancet,* 351 Suppl 3, 5-7.

Cossa HA, Gloyd S, Vaz RG, Folgosa E, Simbine E, Diniz M, Kreiss JK. (1994). Syphilis and HIV infection among displaced pregnant women in rural Mozambique. *International Journal of STD AIDS*, 5, 117-23.

Finelli L, Berman SM, Koumans EH, Levine WC. (1998). Congenital syphilis. *Bulletin of the World Health Organization,* 76 Suppl 2, 126-8.

Fitzgerald DW, Behets F, Caliendo A, Roberfroid D, Lucet C, Fitzgerald JW, et al. (2000). Economic hardship and sexually transmitted diseases in Haiti's rural Artibonite Valley. *American Journal of Tropical Medicine & Hygiene*, 62, 496-501.

Fleming DT, Wasserheit JN. (1999). From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. *Sexually Transmitted Infections*, 75, 3-17.

REFERENCES (Continued)

Fonck K, Kidula N, Kirui P, Ndinya-Achola J, Bwayo J, Claeys P, et al. (2000). Pattern of sexually transmitted diseases and risk factors among women attending an STD referral clinic in Nairobi, Kenya. *Sexually Transmitted Diseases,* 27, 417-23.

Genc M, Ledger WJ. (2000). Syphilis in pregnancy. *Sexually Transmitted Infections*, 76, 73-9.

Gertig DM, Kapiga SH, Shao JF, Hunter DJ. (1997). Risk factors for sexually transmitted diseases among women attending family planning clinics in Dar-es-Salaam, Tanzania, *Genitourinary Medicine*, 73, 39-43.

Gloyd, S, Chai S, Mercer MA. (2001). Antenatal syphilis in sub-Saharan Africa: missed opportunities for mortality reduction. *Health Policy Planning*, 16, 29-34.

Goldenberg RL, Vermund SH, Goepfert AR, Andrews WW. (1998). Choriodecidual inflammation: a potentially preventable cause of perinatal HIV-1 transmission. *Lancet,* 352, 1927-30.

Goldenberg RL, Stringer JS, Sinkala M, Vermund SH. (2002). Perinatal HIV transmission: developing country considerations. *Journal of Maternal Fetal Neonatology Medicine,* 12,149-58.

Goldenberg RL, Thompson C. (2003). The infectious origins of still birth. American Journal of Obstetrics & Gynecology, 189, 861-73.

Gray G, McIntyre J, Newell ML. (2000). Congenital and perinatal infections: prevention, diagnosis and treatment. Edited by Newell, ML and McIntyre J. *HIV-1 Infection* (pp. 232-257). Cambridge, MA: Cambridge University Press.

Grosskurth H, Mosha F, Todd J, Mwijarubi E, Klokke A, Senkoro K, et al. (1995). Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomised controlled trial. *Lancet,* 346, 530-6.

Grosskurth H, Gray R, Hayes R, Maybe D, Wamer M. (2000). Control of sexually transmitted diseases for HIV-1 prevention: understanding the implications of the Mwanza and Rakai trials. *Lancet,* 355, 1981-7.

Guay LA, Musoke P, Fleming T, Bagenda D, Allen M, Nakabiito C,et al. (1999). Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. *Lancet,* 354, 795-802.

REFERENCES (Continued)

National AIDS Commission and Ministry of Health of the Republic of Malawi. (2003). *HIV Sentinel Surveillance Report.*

Hook EW III, Peeling RW. (2004). Syphilis control - a continuing challenge. *New England Journal of Medicine,* 351,122-4.

Hoover DR, Munoz A, Carey V, Odaka N, Taylor JM, Chmiel JS, et al. (1991). The unseen sample in cohort studies: estimation of its size and effect. Multicenter AIDS Cohort Study. *Statistics Medicine*, 10, 1993-2003.

How JH, Bowditch, JD. (1994). Syphilis in pregnancy: experience from a rural aboriginal community. *Australia & New Zealand Journal of Obstetrics and Gynaecology*, 34,383-9.

Institute of Medicine (1998). Committee on Perinatal Transmission of HIV. Edited by Soto, MA, Almario DA, McCormick MC. *Reducing the odds preventing perinatal transmission of HIV in the United States.* Washington, D.C.: National Academy Press.

Kambarami RA, Manyame B, Macq J. (1998). Syphilis in Murewa District, Zimbabwe: an old problem that rages on. *Central African Journal of Medicine*, 44, 229-32.

Kebede E, Chamiso B. (2000). Prevalence of syphilis in pregnancy in Addis Ababa. *East African Medical Journal,* 77, 212-6.

Kafulafula G, Martinson F, Msamanga G, Sinkala M, and the HIVNET 024 Team. (2004). Phase III Trial of Antibiotics to Reduce Chorioamnionitis-Associated MTCT of HIV. *XV International AIDS Conference (Bangkok, Thailand; July 11-16, 2004) Program and Abstracts* (abstract ThOrC1418).

Lagarde E, Guyavarch E, Piau JP, Gueye-Ndiaye A, Seck K, Enel C, et al. (2003). Treponemal infection rates, risk factors and pregnancy outcome in a rural area of Senegal. *International Journal of STD AIDS*, 14, 208-15.

Lago EG, Rodrigues LC, Fiori RM, Stein AT. (2004). Congenital syphilis: identification of two distinct profiles of maternal characteristics associated with risk. *Sexually Transmitted Diseases*, 2004, 31:33-7.

Lee MJ, Hallmark RJ, Frenkel LM, Del Priorie G. (1998). Maternal syphilis and vertical perinatal transmission of human immunodeficiency virus type-1 infection. *International Journal of Gynaecology & Obstetrics,* 63, 247-52.

REFERENCES (Continued)

Lumbiganon P, Piaggio G, Villar J, Pinol A, Bakketeig L, Bergsjo P,et al.(2002). The epidemiology of syphilis in pregnancy. *International Journal of STD AIDS*, 13, 486-94.

Ministry of Health Tanzania/National AIDS Control Program (NACP) surveillance of HIV and syphilis infection among antenatal clinic attendees 2003/2004 (2005). April 2005 report. Dar es Salaam, Tanzania.

Ortashi OM, El Khidir I, Herieka E. (2004). Prevalence of HIV, syphilis, *Chlamydia trachomatis, Neisseria gonorrhoea, Trichomonas vaginalis* and candidiasis among pregnant women attending an antenatal clinic in Khartoum, Sudan. *Journal of Obstetrics & Gynaecology,* 24, 513-5

Pao D, Goh BT, Bingham, JS. (2002). Management issues in syphilis. *Drugs,* 62,1447-61.

Peeling RW, Mabey D, Fitzgerald DW, Watson-Jones D. (2004). Avoiding HIV and dying of syphilis. *Lancet,* 364, 1561-3.

Quinn TC, Cannon RO, Glasser D, Groseclose SL, Brathwaite WS, Fauci AS, et al. (1990). The association of syphilis with risk of human immunodeficiency virus infection in patients attending sexually transmitted disease clinics. *Archives of Internal Medicine*, 150, 1297-302.

Reid SE, Reid CA, Vermund SH. (2004). Antiretroviral therapy in sub-Saharan Africa: adherence lessons from tuberculosis and leprosy. *International Journal of STD AIDS*, 15, 713-6.

Sombie I, Meda N, Cartoux M, Tiendrebeogo S, Ouangre A, Yaro S, et al. (2000). Seroprevalence of syphilis among women attending urban antenatal clinics in Burkina Faso, 1995-8. The DITRAME Study Group. DIminuation de la TRAnsmission Mere-Enfant. *Sexually Transmitted Infections,* 76, 314-6.

Stringer EM, Sinkala M, Stringer JS, Mzyece E, Makuka I, Goldenberg RL, et al. (2003). Prevention of mother-to-child transmission of HIV in Africa: successes and challenges in scaling-up a nevirapine-based program in Lusaka, Zambia. *AIDS,* 17, 1377-82.

Taha TE, Dallabetta GA, Hoover DR, Chiphangwi JD, Mtimavalye LA, Liomba GN, et al. (1998). Trends of HIV-1 and sexually transmitted diseases among pregnant and postpartum women in urban Malawi. *AIDS,* 12, 197-203.

REFERENCES (Continued)

UNAIDS. Country HIV and AIDS estimates, end 2003. Retrieved June 3, 2005, from http://www.unaids.org/en/geographical+area/by+country/malawi.asp; http://www.unaids.org/en/geographical+area/by+country/united+republic+of+tanzania.asp; http://www.unaids.org/en/geographical+area/by+country/zambia.asp;

Urassa WK, Kapiga SH, Msamanga GI, Antelman G, Coley J, Fawzi WW. (2001). Risk factors for syphilis among HIV-1 infected pregnant women in Dar es Salaam, Tanzania. *African Journal of Reproductive Health,* 5, 54-62.

Walker DG, Walker GJ. (2002). Forgotten but not gone: the continuing scourge of congenital syphilis. *Lancet Infectious Diseases*, 2, 432-6.

Wasserheit JN. (1992). Epidemiological synergy: interrelationships between human immunodeficiency virus infection and other sexually transmitted diseases. *Sexually Transmitted Diseases,* 19, 61-77.

Watson-Jones D, Changulacha J, Gumodoka B, Weiss H, Rusizoka M, Ndeki L, et al. (2002). Syphilis in pregnancy in Tanzania. I. Impact of maternal syphilis on outcome of pregnancy. *Journal of Infectious Diseases,* 186, 940-7

Wendel GD. (1988). Gestational and congenital syphilis. *Clinical Perinatology*, 15, 287-303.

World Health Organization. Global Prevalence and Incidence of Selected Curable Sexually Transmitted Infections. Geneva. 2001. Retrieved April 13, 2005, from http://www.who.int/docstore/hiv/GRSTI/.

Wilkinson D, Sach M, Connolly C. (1997). Epidemiology of syphilis in pregnancy in rural South Africa: opportunities for control. *Tropical Medicine & International Health*, 2, 57-62.

DO TARGETED HIV/AIDS PMTCT RESEARCH AND NEW STANDARD OF CARE SERVICE PROGRAMS HAVE OTHER HEALTH SERVICE IMPACTS? MEASURING ANTENTAL SYPHILIS MANAGEMENT IN ZAMBIA BEFORE AND AFTER NEW PROGRAMS WERE IMPLEMENTED

by

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ABSTRACT

Background. Research or service investments may have benefits or harms beyond their targeted program goals.

Methods. We assessed the impact of staged-implementation of human immunodeficiency virus/acquired immunodeficiency virus (HIV/AIDS) mother to child transmission (PMTCT) research and/or "vertical" PMTCT service programs on two untargeted outcomes, (1) antenatal rapid plasma reagin (RPR) screening, and (2) syphilis treatment rates, by reviewing 5,801 antenatal record books from women seen from 1997 to 2004 in Lusaka, Zambia clinics that experienced a diversity of PMTCT research and/or service interventions.

Findings. PMTCT research and service implementations were associated with less documented RPR screening as compared to before the programs were implemented, with prevalence odds ratios (OR) of 0.9 (0.7–1.1) for research and 0.7 (0.6-0.8) for service; both program implementations were associated with increased documented RPR screening frequency, with a prevalence OR of 2.5 (2.1–3.0). Our study suggests that combined PMTCT research and service within an existing antenatal care system was associated with improved ancillary antenatal care as measured by syphilis screening, but neither research nor service alone improved RPR screening rates. HIV program implementers should plan explicitly for broad-based upgrading of primary care services outside the narrow scope of the program itself, even as they tackle the daunting challenges of PMTCT.

INTRODUCTION

Externally-funded, disease-specific research and service delivery programs are a popular choice for international health investments, with program investments made for the specific purpose of reducing the impact of the disease in question. Monitoring and evaluation of such "vertical programs" are of interest to developing country policy makers, public health leaders, clinicians working on disease management and treatment guidelines, and international donors (Stringer JS, Sinkala M, Goldenberg RL, Vermund SH, and Acosta E, 2003). Such data are often provided without contextual data on other conditions that may or may not be impacted. Single focus service programs may be assumed to be narrowly beneficial within the health system, while research programs may be perceived as irrelevant to health care improvements per se, but evidence for either view is scarce. Because research in developing countries is often externally initiated, funded, and/or managed (Finau SA, Finau E, Ofanoa M, 2000; Hyder AA, Walk SA, Khan AN, Teoh NB, Kass NE, Dawson L, 2004; Gonzolez-Block, M, 2004) developing country officials and global advocates may express concerns that donor country researchers act as 'parachute researchers' or 'research imperialists'(Finau SA et al., 2000; Wilmshurst P, 1997; Macklin R, 1999; de Zulueta P, 2001; Kopelman LM, van Niekerk AA, 2002). In contrast, some clinical trials research in the developed world has been shown to result in health care gains (Johnston SC, Rootenberg JD, Katrak S, Smith WS, Elkins JS, 2006).

The extent to which research or service delivery in one arena might bring ancillary, measurable benefits (presumably due to enhancements in training and resources) or harms (presumably due to resource reallocation towards the research or

the single target condition) within the developing world clinical care environment has not been studied extensively. We assessed whether seven years of staged implementation of antenatal human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) research and/or a prevention of mother-to-child transmission of HIV (PMTCT) new standard of care program in Lusaka, Zambia were beneficial for the general antenatal care system in which they were nested, specifically assessing documented antenatal syphilis screening and treatment of syphilis seroreactive cases before and after programs were implemented. Our goal was to determine if the presence of either or both of these single topic programs as 'systems inputs' in antenatal care clinics would improve existing 'systems process' (i.e. documented syphilis screening and treatment) or outputs of ancillary antenatal care in a developing country health system.

METHODS

Population

Our study was conducted in Zambia's capital, Lusaka, whose population is estimated at 1.5-2.0 million persons. In Lusaka District, allopathic health care for an estimated >90% Lusaka residents is provided by a network of satellite clinics and a referral teaching hospital. While all 26 Lusaka District clinics provide antenatal care, 24 are principal antenatal providers, 8 have small inpatient units, and 12 have labor wards. Twenty-two of the 26 clinics were under the management of the Lusaka District system in the time period of the study. The 22 included clinics varied in size. The four excluded clinics were two that were brought under the administration of the Lusaka Urban District in or after year 2003, one that did not provide antenatal care services, and, one that

serviced highly transient female prisoners. At the time of this study, 9 of these 22 clinics had labor wards.

Antenatal Clinic and RPR Screening Procedures

A nurse midwife interviewed a pregnant woman at her first clinic visit as to her demographic and past obstetric history, recording assessments and test results in the antenatal record book given to each woman upon booking. A physical examination was performed, including: blood pressure; height; weight; gestational age determination; hemoglobin, and rapid plasma reagin (RPR) screening. Thanks to foreign aid, RPR shortages were minimal in Lusaka during the time period of our study, though intramuscular (IM) benzathine penicillin availability from the Zambian government was irregular (MS, personal observations). When interviewed, district staff indicated that it would be exceedingly uncommon for a woman to be RPR screened or treated with IM benzathine penicillin without her test results or treatment being recorded in the antenatal record (MS, personal observations). If RPR screening does not occur, the designated space in the antenatal record book is left blank or the staff writes that it was not done. Oral antibiotics are not offered as an alternative during times of penicillin shortages; instead, a prescription is given to RPR seroreactive women with instructions to buy the drug and return to the clinic for its IM administration with recording in the antenatal record. In the experience of District management, these prescriptions are rarely filled by the women, who have little to no discretionary family income (MS, unpublished data).

Health Systems Implementations

Our study intervention was defined as the implementation of either PMTCT-related research or the PMTCT new standard of care services, or both research and service programs introduced together, within the antenatal clinic setting. In the Lusaka District clinics, PMTCT-related research studies of varying magnitude have been introduced in some, but not all clinics at different time-points beginning in year 2000. For the timeframe of our study, nine of 22 clinics had research programs. PMTCT service was first introduced in the Lusaka District in year 2000 through a single-clinic, United Nations International Children's Fund (UNICEF)-supported program. Beginning in year 2001, all 22 clinics in our study population had staged introduction of PMTCT as a new standard of care in service (i.e., several clinics at a time from 2001 until all were covered); nine of these 22 clinics had PMTCT research activities, but seven of the nine clinics had research implemented prior to the PMTCT service expansion. The PMTCT new standard of care services consisted of universal counseling and voluntary HIV testing with single dose nevirapine (NVP) offered to HIV-infected pregnant women and their infants (Stringer EM, Sinkala M, Stringer JS, Myzece E, Makuka I, Goldenberg RL, et al., 2003). For research, clinics were often selected due to logistical concerns including the number of patients available for recruitment. These research and service programs had multiple partners and financing sources (Table 1).

Table 1

Research studies in Lusaka, Zambia, 1988- 2003. Only those implemented from 2000-2003 were related directly to the prevention of mother to child transmission of HIV

Research Study Title	Year of Implementation
Zambia AIDS Related Tuberculosis (ZAMBART) program*	1988
Japanese International Corp. Agents (JICA) supported programs†	1997
Elizabeth Glaser Pediatric AIDS Foundation (PAF) study	2000
Prevention of Mother to Child HIV Transmission (PMTCT) programs	2000
UNICEF zidovudine-based PMTCT Study	2000
HIV Prevention Trials Network (HPTN) 024 Clinical Trial (study)	2001
Zambia Exclusive Breastfeeding (ZEBS) Study	2001
World AIDS Foundation (WAF) Study	2001
Mastitis Study	2001
Intrauterine Device (IUD) Study	2002
Mother to Child HIV Transmission Plus (MTCT+) Study	2003

Note: ZAMBART* operated in four antenatal clinics, but not as a part of maternal child health (MCH) services, only as part of outpatient services and not on a global scale throughout outpatient. Patients found to be TB+ were counseled and HIV tested. TB related programs began in 1988, and an HIV counseling and testing program was commenced in the four outpatient services departments in 1996.

JICA†Community based programs encompassed: nutrition awareness, environmental health constructions and activities, referral system planning and training, school health activities, and district level strategic planning activities and were not considered to have impacted maternal and child health clinic level operations.

PMTCT research and service programs included these components in varying degrees depending upon the specifics of the program: clinical care and/or research training; record-keeping training; supply procurement systems/resources for NVP distribution; counseling training, as previously detailed; quality control training and systems; and, community sensitization endeavors. Clinics participating in research and/or service delivery may have been supplied with RPR test kits, needles reagents, and/or penicillin when government supplies could not be procured. The study period extends from July 1997 through July 2004.

Study Design and Data Collection

A quasi-experimental design was feasible because PMTCT research and/or service were introduced in a fashion in which we discern no bias in that all clinics had either research or service or both implementations during the timeframe of the study. Clinics were included in research from diverse zones of the city to ensure minimal cross-contamination of interventions that were implemented by clinic. Similarly, PMTCT service upgrades were introduced in different geographic zones to ensure that no part of the city was favored over another. To determine if the staged implementation of programs impacted general antenatal care, we used two well-accepted markers of effective antenatal service delivery, the use of syphilis screening, and penicillin treatment for women with seroreactive results. As is typical in resource-limited settings of sub-Saharan Africa, women with seroreactive screening results did not receive a confirmatory syphilis test before treatment.

Systematic chart sampling of documented antenatal syphilis screening and/or treatment at booking in the 22 district clinics was conducted to assess RPR and penicillin coverage (when indicated with positive screening results) before and after initiation of a PMTCT research study, new standard of care services program, or research/service combined. In order to have a seasonal comparison and a more precise point prevalence estimate, 50 randomly selected records from antenatal booking months of January and June were sampled for each distinct timepoint 'before' and similarly January and June records 'after' research and/or service delivery program implementation for each participating clinic. In cases where the number of clinic records was inadequate for the targeted January or June months, as occurred with a smaller clinics, records were sampled from months prior to the targeted month (for example, December or May). Likewise, if records were unavailable for the months prior to target months, we sampled months after the target month (for example, February or July). For clinics where more than one implementation had occurred in a short timeframe such that only one of our targeted sampling months occurred between program implementations, records were sampled for whichever targeted month fell between the programs implemented (in other words, either January or June but not both). As per these inclusion criteria, we used 5801 records for review among 13054 records available in the months of interest.

The study outcome measures were two-fold: (1) the proportion of antenatal records with documented RPR screening within clinics before and after research, before and after PMTCT new standard of care services, or before and after both research and service program implementations; and (2) the proportion of antenatal records from RPR

seroreactive mothers with documented IM benzathine penicillin treatment before and after research, service, or both implementations. All data were entered into an MS Access® 2002 (Microsoft Corporation, Redmond, WA) database. The study was approved by both the University of Alabama at Birmingham Institutional Review Board and the University of Zambian Research Ethics Committee.

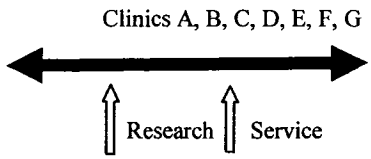
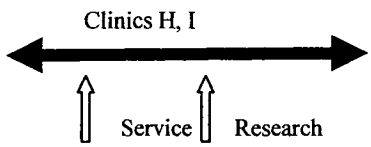
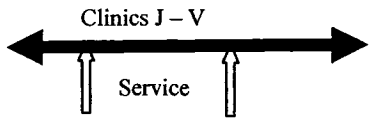
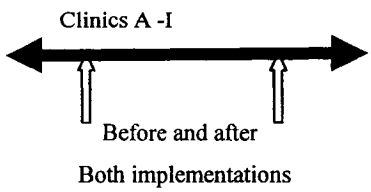
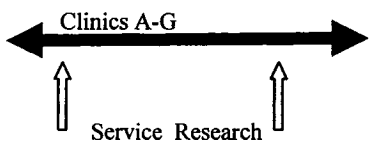
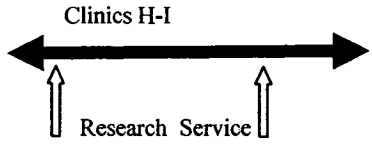
Statistical Analyses

Within-clinic comparisons were performed using logistic regression analyses to determine the proportion of documented RPR screening and treatment coverage (pre- and post-implementation type) within all clinics with research, within all clinics with PMTCT services, and within all clinics with both research and service delivery implemented, as well as Odds Ratios (OR) and 95% confidence intervals (95% CI). To disaggregate the association of PMTCT research, service, or both programs on documented RPR screening and treatment of seroreactive cases we used five discrete comparisons. First, we assessed the association of research in the 7 clinics where research was implemented prior to service (comparison #1) (Figure 1). Next, we assessed the association of service alone in clinics where the service was implemented prior to research (15 clinics) (comparison #2). In order to assess the association of research plus service delivery, we assessed our outcomes before and after both program implementations in all 9 clinics with both implementations irrespective of the order of either program introduction (comparison #3). To further assess these dual program implementations, we assessed the 7 clinics where research was implemented prior to PMTCT service (comparison #4), and in the 2 clinics where research was implemented after service (comparison #5).

We performed these comparisons in order to improve our ability to make inferences, given the non-random assignment of clinic status. Using a two-tailed confidence level of 0·05, with the number of records available, we had 82·5% power for comparison #1, and more than 99% power for comparisons 2 - 5 to detect a 20% difference in the proportion of documented screening before as compared to after program implementation. Student's paired t-test was used to assess any change in documented screening or treatment prior to the implementation of either program in 20 of the 22 clinics where baseline data were available, with two clinics excluded due to unavailability of records prior to the implementation of research in each. Findings are presented as screening and treatment frequencies, rates, prevalence odds ratios (OR) and 95% confidence intervals (CI). All data were analyzed in SAS™ version 9·1 (SAS, Inc., Cary, NC). No corrections for multiple comparisons were employed.

Figure 1

Timeline depicting before and after assessments of research, PMTCT new standard of care service, or both implementations

Assessment	Before and After Timeline
Comparison #1 (n=7 clinics) Research only, no PMTCT service influence	
Comparison #2 (n=15 clinics) PMTCT new standard service only, no research influence	
	
Comparison #3 (n=9 clinics) Research plus PMTCT new standard of care	
Comparison #4 (n=7 clinics) Research plus PMTCT new standard of care	
Comparison #5 (n=2 clinics) Research plus PMTCT new standard of care	

RESULTS

In assessing all pre-intervention data, a non-significant downward change in documented RPR screening was evident over two time periods sampled (pre-intervention baseline was the average of a January and June assessment, whenever possible, as per the Methods), prior to any implementation of research or service delivery programs (t-value- 0.6, pr |t|= 0.5).

Clinic characteristics, count of records assessed

Clinics differed by the number of monthly antenatal bookings and the number of monthly deliveries (among the nine clinics with labor wards) (Table 2). Average monthly antenatal bookings ranged from 24 (clinic V) to 471 (clinic A), while monthly deliveries ranged from 92 (clinic E) to 620 (clinic A). The number of records used in subsequent assessments varied by clinic, with some clinics contributing records to either research or PMTCT service or both assessments.

Table 2

Clinic Characteristics, total records abstracted (n=5801) by clinic, and clinic-specific record counts for subsequent assessments of documented RPR screening immediately before and immediately after implemented research, PMTCT new standard of care service, or both programs, among 22 Lusaka Urban District clinics, where all 22 clinics had implemented PMTCT new standard of care service, and nine of 22 clinics had research studies in addition to the PMTCT service programs, 1997- 2004

	Clinic Characteristics		Records
Clinic	Average monthly antenatal bookings (%)*	Monthly deliveries (%) †	Records assessed (%)
Total	5333	2905	5801

Table 2, continued

Clinic	Clinic Characteristics		Records
	Average monthly antenatal bookings (%)*	Monthly deliveries (%) †	Records assessed (%)
[redacted]			
A	471 (17%)	620 (24%)	367 (100%)
B	236 (8%)	190 (7%)	489 (66%)
C	450 (16%)	395 (15%)	365 (76%)
D	437 (16%)	363 (14%)	326 (76%)
E	176 (6%)	91 (3%)	255 (78%)
F	638 (23%)	654 (25%)	327 (56%)
G	410 (15%)	294 (11%)	295 (63%)
Total	2818 (53%)	2607 (90%)	2424 (42%)
[redacted]			
H	248 (10%)	‡	327 (10%)
I	316 (13%)	198 (66%)	354 (10%)
[redacted]			
J	185 (7%)	‡	222 (7%)
K	127 (5%)	‡	248 (7%)
L	108 (4%)	‡	168 (5%)
M	179 (7%)	‡	213 (6%)
N	289 (11%)	‡	267 (8%)
O	108 (4%)	‡	273 (8%)
P	53 (2%)	‡	180 (5%)
Q	210 (8%)	‡	189 (6%)
R	203 (8%)	‡	219 (6%)
S	175 (7%)	‡	219 (6%)
T	143 (6%)	100 (34%)	260 (8%)
U	147 (6%)	‡	166 (5%)
V	24 (1%)	‡	72 (2%)
Total	2515 (47%)	298 (10%)	3377 (58%)

*Average July 01 and January 02 antenatal clinic booking attendees

† January 04 deliveries

‡ Antenatal clinic without delivery facility

Documented RPR Screening Coverage Before and After Research, PMTCT New Standard of Care Services, and/or Both Program Implementations

Records were approximately equally likely to have documented RPR screening prior to as after research programs had been implemented (comparison # 1; n= 7 clinics), with a prevalence OR of 0.9 (0.7-1.1) for research (Table 3). The prevalence OR of documented RPR screening for women attending clinics after the implementation of the new PMTCT services program as compared to those attending before (comparison #2; n=15 clinics) was 0.7 (0.5-0.8). For the dual program assessments, the prevalence ORs were as follows: 1.9 (1.5-2.3) for the 7 clinics where research was implemented prior to service (comparison #3). The OR was 7.3 (4.6-11.6) for the two clinics where research was implemented after PMTCT service (comparison #4), and 2.5 (2.1-3.0), for the 9 clinics with both implementations irrespective of the order of program introduction (comparison #5).

Table 3

Documented RPR screening coverage, among records sampled before and after research studies, PMTCT new standard of care service, or both programs were implemented, n=22 clinics, Lusaka, Zambia, 1997-2004

Assessment	Documented RPR coverage before program implementation			Documented RPR coverage after program implementation			Prevalence Odds Ratio for documented RPR screening
	Total Records	Documented Screening (%)	No Documented Screening (%)	Total Records	Documented Screening (%)	No Documented Screening (%)	Odds Ratio (95% CI)
Research only: July 1997 - July 2002							
Clinics A-G, n=7 clinics	807	524 (65%)	283 (35%)	693	433 (62%)	260 (28%)	0.9 (0.7-1.1)
PMTCT new standard of care service only: July 2000 - July 2002							
Clinics H-V, n=15 clinics	1689	1364 (81%)	325 (19%)	1406	1045 (74%)	361 (26%)	0.7 (0.6-0.8)
Research plus PMTCT new standard of care: July 1997 - February 2004							
Clinics A-I, n=9	1099	692 (63%)	407 (37%)	1206	975 (81%)	231 (19%)	2.5 (2.1-3.0)
Research plus PMTCT new standard of care: July 1997 - February 2004							
Clinics A-G, n=7 clinics	807	524 (65%)	283 (35%)	924	719 (78%)	205 (22%)	1.9 (1.5-2.3)
Research plus PMTCT new standard of care: January 2001 - February 2004							
Clinics H-I, n=2 clinics	292	168 (58%)	124 (42%)	282	256 (91%)	26 (9%)	7.3 (4.6-11.6)

Documented Treatment Coverage of RPR Seroreactive Cases Before and After Research, PMTCT Services, and/or Both Programs were Implemented

Records of women with documented RPR seroreactivity were more likely to have documented treatment if they attended clinics after the implementation of research (comparison #1, n=7 clinics), with a prevalence OR of 2.8 (0.89–9.7) (Table 4). The prevalence OR of documented treatment for women attending clinics after the PMTCT new standard of care service (n=15 clinics, comparison #2) was 0.7 (0.4–1.3). In assessing the association of research combined with the PMTCT new standard of care service on documented treatment, the prevalence ORs were: 1.7 (0.8–3.6) in the 9 clinics with both programs regardless of the order of implementations (comparison #3); 1.2 (0.5–2.8) for the 7 clinics where research was implemented prior to PMTCT service(comparison #3); and, 3.8 exact OR (1.0–14.8) in the 2 clinics where PMTCT service was implemented prior to research (comparison #4).

Table 4

Documented treatment coverage among documented RPR+ screened women, among records sampled before and after research studies, PMTCT new standard of care service, or both programs were implemented, n=22 clinics, Lusaka, Zambia, 1997-2004

Assessment	Documented treatment coverage before program implementation			Documented treatment coverage after program implementation			Prevalence Odds Ratio (OR) of documented treatment of RPR seroreactive cases
	Total Records	Documented Treatment (%)	No Documented Treatment (%)	Total Records	Documented Treatment (%)	No Documented Treatment (%)	Odds Ratio (95% CI)
Research only, July 1997- February 2002							
Clinics A-G, n=7 clinics	42	26 (62%)	16 (38%)	22	18 (82%)	4 (18%)	2.8 (0.8-9.7)
PMTCT new standard of care service only, July 2001- February 2004							
Clinics H-V, n=15 clinics	117	92 (79%)	25 (21%)	105	75 (71%)	30 (29%)	0.7 (0.4-1.3)
Research plus PMTCT new standard of care, July 1997- February 2004							
Clinics A-I, n=9	50	29 (58%)	21 (42%)	59	41 (69%)	18 (31%)	1.7 (0.8-3.6)
Research plus PMTCT new standard of care, July 1997- February 2004							
Clinics A-G, n=7 clinics	42	26 (62%)	16 (38%)	47	31 (66%)	16 (34%)	1.2 (0.5-2.8)
Research plus PMTCT new standard of care, January 2001- February 2004							
Clinics H-I, n=2 clinics	8	3 (38%)	5 (62%)	12	10 (83%)	2 (17%)	3.8* (1.0-14.8)

*Exact OR

DISCUSSION

Our study suggests that research combined with PMTCT standard of care services programs, when embedded within the existing antenatal care system, was associated with improved ancillary antenatal care as measured by documented RPR screening coverage. However, neither research nor the PMTCT new service implementations alone improved RPR screening rates consistently across clinics. Research and the combined programs were associated with improved documented treatment, though the findings were not statistically significant.

Zambia is among the world's poorest nations with per capita income of about US$1-2 per person per day (World Health Organization [WHO], 2004; United Nations Development Program [UNDP], 2002). Compared to neighboring Botswana, the year 2000 Zambian gross domestic product (GDP) was approximately nine times less and the per capita spending on health as a percent of GDP was approximately 17 times less (table 5). At the end of 2001, ≈21·5% of the adult Zambian population was HIV-infected, and >30% of antenatal attendees were HIV seropositive in the higher prevalence urban antenatal clinics (United Nations AIDS, Zambia Epidemiologic Fact Sheet, 2002). In women aged 25 to 29 years, the 2001 syphilis prevalence rate was 11·8% as estimated by RPR testing and 9·4% in those specimens confirmed by the Treponemal Haemaglutination Assay (TPHA) (Zambia Central Statistics Office, 2002).

In the face of declining health expenditures and a health system reeling from under-capacitation (Zambia MOH/CBOH internal data, 2004), it was not surprising that our pre-intervention assessments were non-salutary ones, with syphilis coverage declining even as the HIV programs were being implemented. We found that overall

health systems improvements were realized only after the introduction of PMTCT research plus PMTCT new standard of care services interventions. We believe that as both PMTCT-related research and services are further promulgated, health staff should instill as many antenatal care improvements as a part of the PMTCT program as possible. While our Zambia-based programs sought to do this, we have faced the daunting challenge of providing voluntary counseling and testing services to the approximately 50,000 women who deliver yearly in public-sector clinics and the University Teaching Hospital in Lusaka, along with efforts to offer nevirapine to the 25% of HIV-infected mothers and exposed infants (Stringer EM, et al., 2003; WHO, 2004; UNDP, 2002; UNAIDS, 2002; Zambia Central Statistics Office, 2002; Stringer JS, et al., 2003). Integrating PMTCT and other HIV services into broad-based, upgraded antenatal care services were expected to have provided more substantial benefits to antenatal care in general, as measured by our syphilis screening and treatment indices, than proved to be the case.

Table 5

Measured levels of expenditures on health, Zambia vs. neighboring Botswana, 1997-2002

	1997	1998	1999	2000	2001	2002
ZAMBIAN GDP in year 2000 purchasing power parity US$ (UNDP)				$780		$865
Zambian total expenditure on health as % of GDP (WHO)	6.0%	6.0%	5.7%	5.5%	5.7%	5.8%
Zambian per capita total expenditures on health at average exchange rate in each year, in US$ (WHO)	$24	$20	$19	$18	$19	$20
Botswana GDP in year 2000 purchasing power parity US$ (UNDP)				$7,184		
Botswana total expenditure on health as % of GDP (WHO)	5.7%	5.5%	6.0%	6.0%	6.6%	6.0%
Botswana per capita total expenditures on health at average exchange rate, in US$ (WHO)	$260	$260	$294	$309	$381	$387

Qualitative assessments through key informant interviews (data not presented) indicated that Lusaka District clinicians and administrators perceived a number of antenatal care patient benefits beyond those funded for PMTCT. Staff indicated that the financial infusions (Hansone K, Ranson M, Oliveeira-Cruz V, Mills A, 2003) by the PMTCT programs within the individual clinics helped decompress the often desperate financial circumstances under which Zambian nurse-midwives work. Staff reports of the favorable impact of PMTCT programs include: staff salary "top-ups" to perform HIV screening, counseling, and PMTCT-related treatment; staff PMTCT training that includes broad antenatal care retraining; and the purchase of reagents, syringes and needles, and

often pharmaceuticals for clinic subjects even if they are not included in the PMTCT programs per se (Chi BH, Sinkala M, Stringer EM, McFarlane Y, Ng'uni C, Myzece E, et al., 2003).

We noted that successful integration of vertical programs has risks. In clinic T, 87% of records assessed before implementation of the PMTCT service program had documented RPR screening, whereas only 52% of the records had documented RPR screening after program implementation (RR= 0·27 (0·16- 0·44)). We observed that the PMTCT "stamp" used to guide midwives in documenting HIV testing and Nevirapine uptake (Stringer EM, et al.) for seroreactive cases occasionally had been placed over the printed antenatal care book space where RPR results would otherwise have been indicated. A reasonable hypothesis is, therefore, that poor implementation of the PMTCT service protocol, by incorrectly placing the "stamp" for HIV-specific information, may have lead some midwives to forget to offer RPR screening or omit its documentation. Other clinics that fared worse after PMTCT research or service program implementation may have had other forces at play that outweighed the PMTCT program-related infusions of resources, i.e., individual clinic personnel or policy issues (Stringer SA, Sinkala M, Stout JP, Goldenberg RL, Acosta EP, Chapman V, 2003). That RPR screening rates were declining prior to implementation of research or service programs may suggest a change unrelated to new PMTCT programs that would minimize any detection of salutary syphilis-related outcomes; that we saw benefits nonetheless might be considered a minimum estimate of what might have been found if Zambian health services had not been so beleaguered in the time frame of our study.

We do not yet know why RPR seroreactive women at some clinics were more successfully treated than those at others. Some clinics may have staff with greater procurement skills, better drug security precautions, or may be more likely to receive penicillin when supplies from the District Board were limited. In our PMTCT program reviews (data not presented), we noted that at least five district clinics (clinics A, D, E, F, and G) received a relative oversupply of benzathine penicillin from research supplies, beyond that needed for the research participants themselves, a deliberate subsidy of the researchers for the overall clinic efforts. Besides the clinic differences detailed in Table 1, clinic differences other than those studied could have led to the results we found.

A strength of our study was the large number of historic antenatal records available for examination through systematic sampling. Another strength was lack of evident bias in that all clinics had a research and/or service program within the timeframe of the study. Study limitations are also evident. We did not test our hypothesis of ancillary benefit from PMTCT in a randomized clinical trial. All data obtained were from clinic records and are an imperfect representation of what might have actually occurred at an antenatal booking visit. It is possible that in some cases, RPR testing was provided but not documented. However, we believe that the data provide a realistic account of RPR screening and treatment of seroreactive cases at this visit, as judged from our key informant interviews, suggesting that recording of screening or treatment was near universal with the possible exception of Clinic T discussed above, where the PMTCT stamp had been placed over the RPR screening space in the antenatal records. We recognize that there may have been non-independence among nurses both within and

possibly across clinics if they transfer work sites. Likewise, there could have been non-independence among women which deliver multiple times within the district clinics during the study timeframe. Missing records, particularly for Clinic E, was a study limitation. Missing data were noted on several records. Sustainability of the combined programs after the research studies end was not assessed since several of these studies were still in progress at the end of our study time frame. Finally, all clinic characteristics were not known, such as staffing to patient ratios by clinic.

Several factors could have led to the changes in documented RPR screening and syphilis treatment rates over time. While our quasi-experimental design implicates research plus PMTCT service programs as salutary overall, we do not know which PMTCT component(s) contributed to the improvement, e.g., training, additional human resource support, improved job motivation, supply procurement support, laboratory upgrading, and/or money savings from various program subsidies of the antenatal clinics. Besides the clinic differences detailed in Table 1, clinic differences other than those studied could have led to the results we found. For example, the nine clinics which had both research and service delivery were not necessarily representative of all 22 clinics in that they were the only included clinics with delivery centers.

We believe that the present study has broad implications for clinical prevention and care, as well as public health policy in developing countries. In sub-Saharan Africa, shortages of human resources, social capital, and health care expenditures may undermine implementation of health policy reforms and provision of health care (Dovlo

D, 2005; Van der Geest S, Macwan'gi, M, Kamwanga J, Mulikelela D, Mazimba A, Mwangelwa M, 2000; Nullis-Kapp C, 2005; Chen L, 2004; Kajula PW, Kintu F, Barugahare J, Neema S, 2004; Buor D, Bream K, 2004). The results of inadequate health care spending can simultaneously compound the burden on an existing healthcare system, as well as impact the population's health. The ability of developing country healthcare leaders to provide quality and efficient care when operating under severe financial and human resource constraints may depend on creative or strategic means to meet unmet health system challenges that may emerge (Prata N, Greig F, Walsh J, West A, 2004). Global health investments that result in effective systems which contribute to broad health gain are warranted, as are ways to maximize the modest proportion of biomedical research investment that targets research for the health problems of resource-limited countries (Flanagin A, Winker M, 2003; Matlin S, 2004). Developing country public health officials may partner with development organizations and donor country researchers for the proposed programs themselves, but also in the expectation that ancillary benefits will accrue to the participating health system.

Our study demonstrated, in spite of evidence of an economic crisis in the Lusaka, Zambia health system, some improvements in antenatal care quality were evident, coincident with introduction of outside resources for targeted PMTCT programs. However, research or PMTCT new standard of care service programs alone did not show evidence of this "spin-off" benefit on documented RPR screening or a statistically significant improvement for treatment coverage, suggesting that service delivery leaders and researchers should not overstate, without evidence, the putative benefits of their programs in developing countries. Since clinics did best when both research and service

activities were implemented, developing country health authorities and local and international researchers should plan explicitly for how the targeted programs, service and/or research, can have a broader programmatic impact. Sustainability of spin-off benefits which can accrue to an existing health system after targeted research studies or service programs end is unknown. We urge research and service delivery program implementers in the HIV/AIDS field to consider including quality of care measures outside the narrow scope of the program itself, to better assess the broader impact that such programs may or may not have on the health service systems in which they are nested. Evolution of vertical programs to a more horizontal agenda may be desirable.

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REFERENCES

Buor D, Bream K. (2004). An analysis of the determinants of maternal mortality in sub-Saharan *Africa. J Women's Health* (Larchmt), 13, 926-38.

Chen L. (2004). Human resources for health: overcoming the crisis. *Lancet*, 364, 1984-90.

REFERENCES (Continued)

Chi BH, Sinkala M, Stringer EM, McFarlane Y, Ng'uni C, Myzece E, *et al.*(2003). Employment of off-duty staff: a strategy to meet the human resource needs for a large PMTCT program in Zambia. *J Acquired Immune Deficiency Syndrome,* 40,381-2.

de Zulueta P. (2001). Randomised placebo-controlled trials and HIV-infected pregnant women in developing countries. Ethical imperialism or unethical exploitation? *Bioethics*, 15, 289-311.

Dovlo D. (2005). Wastage in the health workforce: some perspectives from African countries. *Human Resources Health,* 10, 6.

Finau SA, Finau E, Ofanoa M. (2000). Research imperialism in Pacific health: the case of Tonga (1966-1997). *Pac Health Dialog,* 7,109-14.

Flanagin A, Winker M. (2003). Global Health- Targeting problems and achieving Solutions. A call for papers. *JAMA*, 290,1382-84.

Gonzolez-Block, M. (2004). Health policy and systems research agendas in developing countries. *Health Res Policy Sys,* 2, 6.

Hansone K, Ranson M, Oliveeira-Cruz V, Mills A. (2003). Expanding access to priority health interventions: a framework for understanding the constraints to scaling-up. *J Int Dev*, 15, 1-14.

Hyder AA, Walk SA, Khan AN, Teoh NB, Kass NE, Dawson L. (2004). Ethical review of health research: a perspective from developing country researchers. *J Med Ethics,* 30, 68-72.

Johnston SC, Rootenberg JD, Katrak S, Smith WS, Elkins JS. (2006). Effect of a US National Institutes of Health programme of clinical trials on public health and costs. *Lancet* 367, 1319-27.

Kajula PW, Kintu F, Barugahare J, Neema S. (2004). Political analysis of rapid change in Uganda's health financing policy and consequences on service delivery for malaria control. *Int J Health Plann Manage*, 19, Suppl. 1, S133-53.

Kopelman LM, van Niekerk AA. (2002). AIDS and Africa. Introduction. *J Med Philos* 27, 139-42.

REFERENCES (Continued)

Macklin R. (1999). International research: ethical imperialism or ethical pluralism? *Account Res*, 7, 59-83.

Matlin, S. (2004). Disease control priorities program, September 7-8. Merck Headquarters, Whitehouse Station, NJ, USA. Global Health Forum for Health Research, Helping correct the 10/90 gap. http://www.fic.nih.gov/dcpp/ppts/matlin.pdf, accessed 24 Sept, 2005.

Nullis-Kapp C. (2005). Health worker shortage could derail development goals. *Bull World Health Organ,* 83, 5-6.

Prata N, Greig F, Walsh J, West A. A. (2004). Ability to pay for maternal health services. What will it take to meet WHO standards? *Health Policy,* 70, 163-74.

Stringer EM, Sinkala M, Stringer JS, Myzece E, Makuka I, Goldenberg RL, et al. (2003). Prevention of mother-to-child transmission of HIV in Africa: successes and challenges in scaling-up a nevirapine-based program in Lusaka, Zambia. *AIDS*, 17,1377-82.

Stringer JS, Sinkala M, Chapman V, Acosta EP, Aldrovandi GM, Mudenda V, et al., (2003). Timing of the maternal drug dose and risk of perinatal HIV transmission in the setting of intrapartum and neonatal single-dose Nevirapine. *AIDS,* 17, 1659-65.

Stringer JS, Sinkala M, Goldenberg RL, Vermund SH, Acosta E. (2003). Monitoring nevirapine-based programmes for prevention of mother-to-child transmission of HIV-1. *Lancet*, 362, 667.

Stringer JSA, Sinkala M, Stout JP, Goldenberg RL, Acosta EP, Chapman V, et al., (2003). Comparison of two strategies for administering nevirapine to prevent perinatal HIV transmission in high-prevalence, resource-poor settings. *JAIDS,* 32, 506-513.

United Nations AIDS. Zambia Epidemiologic Fact Sheet on HIV/AIDS and Sexually Transmitted Infections, 2002 update.

United Nations Development Programme, Human Development Report, 2002. Human development indices. Retrieved July 15, 2005 from http://www.undp.org/hdr2002/indicator/cty_f_BWA.html and http://www.undp.org/hdr2002/indicator/cty_f_ZMB.html.

Van der Geest S, Macwan'gi, M, Kamwanga J, Mulikelela D, Mazimba A, Mwangelwa M. (2000). User fees and drugs: what did the health reforms in Zambia achieve? *Health Policy Planning*, 15, 59-65.

Wilmshurst P. (1997). Scientific imperialism. *British Medical Journal*, 314, 840-1.

World Health Organization World Health Report, Zambia and Botswana, Basic indicators for all WHO member states. Retrieved on July 15, 2005 from http://www.who.int/whr/2004/annex/country/zmb/en/, and http://www.who.int/whr/2004/annex/country/bwa/en/.

Zambia Central Statistical Office, Central Board of Health (Zambia), and ORC Marco. Zambia Demographic and Health Survey 2001-2002. Calverton, Maryland, USA: Central Statistical Office, Central Board of Health, and ORC Marco. 2003.

CONCLUSION

Uncontrolled antenatal syphilis management is a reality in the developing world, with high prevalence rates looming and inadequate or inefficient resources to address the problem. We have seen that the mere existence of a 100% antenatal syphilis screening policy does not necessarily translate into its policy-intended outcome. Likewise, we noted that an inefficient antenatal syphilis screening program may be due to one or more root causes, each possibly having interrelated components (Travis et al, 2004), contributing to the complexity of resolving barriers to serological testing for syphilis (STS) and therapy. Merely addressing a noted barrier or challenge to antenatal syphilis screening, such as an insufficient supply of treatment medication, may not actually solve the problem of low treatment rates, for example.

Per capita health care expenditures in developing countries may not meet even basic health care needs. Donor funding for antenatal syphilis screening is minimal (Gloyd, Chai, & Mercer, 2001). In turn, task force approaches have been implemented in some areas to step-up antenatal screening and treatment programs via flexible approaches to the tragic situation of ineffective antenatal screening and treatment programs (Walker, 2002). However, the global impression from the literature is that, overall, developing country syphilis screening programs' successes are chaotic and continue to operate inefficiently. Furthermore, resources needed to address the concern on a county-by-country basis may not be insubstantial.

In year 2000, the United Nations Millennium Declaration was signed and developed into eight goals for development and poverty eradication (UN, 2002). Two of these goals (4 and 5, respectively) are specifically designed to reduce child mortality by two thirds and maternal mortality by three quarters by year 2015. With sub-Saharan Africa having among the world's highest disease burden, but with the lowest distribution of health workers by level of health expenditure (WHO, 2006), in-country ways to maximize health systems efficiency must be sought. Identifying if resources for maternal and neonatal conditions are being used effectively and efficiently has been suggested, as well as scaling down less cost-effective health interventions (Adam et al., 2005).

The idea covered here of expanding targeted programs to improve upon non-targeted diseases could prove fruitful in achieving the Millennium Development Goals for reducing child and maternal mortality. The National Institutes of Health, the Centers for Disease Control and Prevention, the United States Agency for International Development, and other key funding agencies for research and service such as the Bill and Melinda Gates Foundation are explicitly increasing their investments for international infectious disease control and prevention, notably in the prevention of maternal to child transmission of HIV arena. Programs implemented by these and other organizations most generally include components which could improve upon an existing health systems, but for a single disease. Piggy-backing delivery of care for other target diseases, whether through improved drug and supply procurement processes, shared transportation to laboratory or other clinical sites, health worker record-keeping or care delivery training, or other process improvements could serve to expand care delivery in the developed country health system in which the funded program is nested. Explicit

planning by partnering country health leaders at program start-up, or even mid-program implementation, to expand single-topic disease prevention services, along with careful monitoring and evaluation of the expanded program, is suggested. Future research should address the effectiveness of such programs, as well as the sustainability of any benefits which might accrue within the health system.

A willful, coordinated response among partnering country health leaders to address the challenge of successful developing country STS and therapy is called for as international health priority. Programs that enable developing country ministries to take the lead role in managing an inherently unstable environment with a changing group of actors and partners in the complex environment could facilitate implementation of their health sector-wide, as well as the, Millennium Development Goals.

REFERENCES

Adam T, Lim SS, Mehta S, Bhutta ZA, Fogstad H, Mathai, M, et al. (2005). Cost effectiveness Cost effectiveness analysis of strategies for maternal and neonatal health in developing countries. *BMJ,* 12, 1107.

Ament, LA Whalen, E. (1996). Sexually transmitted diseases in pregnancy: diagnosis, impact, and intervention. *Journal of Obstetric Gynecology and Neonatal Nursing,* 25, 657-66.

Augenbraun MH, McCormack WM. (1994), Sexually transmitted diseases in HIV-infected persons. *Infectious Disease Clinical North America*, 8, 439-48.

Beksinska ME, Mullick S, Kunene B, Rees H, Deperthes B. (2002). A case study of antenatal syphilis screening in South Africa: successes and challenges. *Sexually Transmitted Diseases*, 29, 32-7.

Brocklehurst, P. (1999). Update on the treatment of sexually transmitted infections in pregnancy–1. *International Journal of STD & AIDS,* 10, 571-580.

REFERENCES (Continued)

Centers for Disease Control. (2002). Sexually Transmitted Diseases Treatment Guidelines. *Morbidity and Mortality Weelky,* 51, 18- 29.

Clay, JC. (1989). Antenatal Screening for Syphilis. *British Medical Journal,* 12, 409-10.

Fonck K, Claeys P, Bashir F, Bwayo J, Fransen L, Temmerman M. (2001). Syphilis Control During Pregnancy: Effectiveness and Sustainability of a Decentralized Program. *American Journal of Public Health,* 91, 705 – 707.

Gilstrap L, Faro, S. (1990), *Infections in pregnancy*. 2nd Edition. Sebastian Fargo, Editor. John Wiley & Sons Incorporated. p. 144.

Gloyd, S, Chai S, Mercer MA. (2001). Antenatal syphilis in sub-Saharan Africa: missed opportunities for mortality reduction. *Health Policy & Planning,* 16, 29-34.

Goldenberg, RL, Stringer JS, Sinkala M, Vermund SH. (2002). Perinatal HIV transmission: developing country considerations. *Journal Maternal Fetal Neonatal Medicine*, 12, 149-58.

Idsoe O, Guthe T. (1967). The rise and fall of the treponematoses. I. Ecological aspects and international trends in veneral syphilis. *British Journal Venereal Diseases,* 43, 227-43.

Kaul R, Kimani J, Nagelkerke NJ, Plummer FA, Bwayo JJ, Brunham RC, et al. (1997). Risk factors for genital ulcerations in Kenyan sex workers. The role of human immunodeficiency virus type 1 infection. *Sexually Transmitted Diseases,* 24, 387-92.

Lee MJ, Hallmark RJ, Frenkel LM, Del Priore G. (1998). Maternal syphilis and vertical perinatal transmission of human immunodeficiency virus type-1 infection. *International Journal of Gynaecology & Obstetrics,* 63, 247-52.

Mahoney JF, Arnold, RC, Harris A. (1943). *Penicillin Treatment of Early Syphilis, A preliminary Report.* Venereal Disease Information, United States Public Health Service, December 355 – 357.

Meheus A, Antal GM. (1992). The endemic treponematoses: not yet eradicated. *World Health Statistics Quarterly,* 45, 228-37.

Pao D, Goh B, Bingham, J. (2002). Management issues in syphilis. *Drugs,* 62, 1447-1461.

REFERENCES (Continued)

Richens J. (1992). Syphilis control: new challenges. *African Health,* 14, 12-3.

Rutgers S. (1993), Syphilis in pregnancy: a medical audit in a rural district. *Central African Journal of Medicine,* 39, 248-53.

Toure IM. (1985). Endemic treponatoses in Togo and other west African states. *Review of Infectious Diseases,* 7 Suppl 2: S242-4.

Travis P, Bennett S, Haines A, Pang T, Bhutta Z, Hyder A et al. (2004). *Lancet,* 264, 900-06.

United Nations. *United Nations Millennium Declaration*: resolution adopted by the General Assembly. Adopted 18 September, 2002. Retrieved on February 25, 2006 from http://www.un.org/millennium/declaration/ares552e.pdf,.

Vermund SH, Powderly WG. (2003). On behalf of the Infectious Diseases Society of America (IDSA) and the HIV Medicine Association of IDSA. Developing a human immunodeficiency virus/acquired immunodeficiency syndrome therapeutic research agenda for resource-limited countries: a consensus statement. *Clinical Infectious Diseases,* 37 (Suppl 1), S4-S12.

Walker DG, Walker GJA. (2002). Forgotten but not gone: the continuing scourge of congenital syphilis. *The Lancet Infectious Diseases,* 2, 432-36.

Walker GJA. (2001). Antibiotics for syphilis diagnosed during pregnancy. *Cochrane Review*, In The Cochrane Database of Systematic Reviews, Issue 3, Art. No. CD001143. DOI: 10.1002/14651858.CD001143.

Watson-Jones D, Gumodoka B, Weiss H, Changalucha J, Todd J, Mugeye K, et al. (2002). Syphilis in pregnancy in Tanzania. II. The effectiveness of antenatal syphilis screening and single-dose benzathine penicillin treatment for the prevention of adverse pregnancy outcomes. *Journal of Infectious Disease,* 186, 948-57.

Wilcox RR. (1985). Mass treatment campaigns against the endemic treponematoses. *Review of Infectious Diseases,* 7 Suppl. 2, 278-83.

World Health Organization, Department of HIV/AIDS. (2001). Global prevalence and incidence of the selected curable sexually transmitted infections: overview and overview and estimates. Retrieved March, 2003 from http//www.who.org.