

Chapter 6

Prevention of Mother-to-Child Transmission of HIV and Syphilis

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INTRODUCTION

The past decade has yielded enormous progress in the prevention of mother-to-child transmission (PMTCT) of the human immunodeficiency virus (HIV) (UNAIDS 2015). Interventions that decrease mother-to-child transmission (MTCT) of HIV from more than 30 percent to 1 percent have been identified. Decentralized point-of-care (POC) approaches for detecting maternal HIV and immediate provision of comprehensive antiretroviral treatment (ART) have resulted in rapid decreases in the number of HIV-infected infants. Indeed, PMTCT has been credited with driving observed decreases in HIV incidence overall.

The guidelines for PMTCT of HIV have been dynamic: the World Health Organization (WHO) and Joint United Nations Programme on AIDS (UNAIDS) have revised their recommendations every two to five years, most recently to recommend combination lifelong ART for all pregnant HIV-infected women (WHO 2014a). The term *elimination of mother-to-child transmission* (EMTCT) was used to further spur global efforts to virtually eliminate pediatric HIV by 2015 (UNAIDS 2011; WHO 2014a).

PMTCT of syphilis (*Treponema pallidum*) has not received the same amount of attention as PMTCT of HIV, although syphilis is estimated to affect more children globally than HIV. PMTCT of syphilis requires less costly and less intensive interventions than HIV, making

its elimination potentially more feasible. The rollout of PMTCT of syphilis may be hampered by less political will to implement it than PMTCT of HIV, lack of accountability for monitoring PMTCT of syphilis, inconsistent availability of diagnostic tests, and use of tests that are not POC (WHO 2006). PMTCT of syphilis could readily leverage advances in PMTCT of HIV by using these programs to enhance the supply chain, lab testing, and accountability for prompt syphilis diagnosis and treatment.

The current momentum in PMTCT of HIV offers a unique opportunity to accelerate PMTCT of HIV and syphilis concurrently. Combining interventions for PMTCT of HIV and syphilis adds minimal cost while potentially benefiting twice as many mother-infant pairs as interventions focused solely on either HIV or syphilis. Health systems improvements for rapid diagnosis and treatment, partner engagement, and follow-up of mothers and infants can enhance both types of PMTCT programs. Combined PMTCT of HIV and syphilis will yield sustained and important benefits for women and children worldwide.

This chapter reviews the rates, burden, and consequences of mother-to-child transmission of HIV and syphilis; the effectiveness of interventions to decrease transmission; the estimated cost-effectiveness of these interventions; and several successful PMTCT programmatic approaches. The chapter also highlights

opportunities for integrated programming to efficiently decrease the number of infants infected with these chronically debilitating pathogens. Because syphilis testing is already currently recommended by WHO for all pregnant women (WHO 2006) and is at least partially implemented in most antenatal clinics, new costs for improving the program may be minimal: adapting programs to incorporate dual POC tests to diagnose syphilis, providing training to improve adherence to guidelines, and increasing accountability for tracking outcomes in PMTCT of syphilis within clinics can be added to existing programs with limited additional investment.

In 2015, Cuba became the first country to eliminate perinatal HIV and syphilis (WHO 2015). This experience demonstrates that the goal of dual elimination is attainable and feasible with effective integration of PMTCT of HIV and syphilis. Children do not need to suffer from the consequences of either of these devastating infections when these PMTCT programs function synergistically.

GLOBAL BURDEN AND CONSEQUENCES OF MTCT OF HIV AND SYPHILIS

MTCT Rates and Cofactors

Comparisons of MTCT of syphilis and MTCT of HIV are difficult because of differences in the precision of infant diagnosis (and thus in the precision of MTCT risk

estimates), and because of varied infant outcomes attributable to maternal infection, and differences in the timing and routes of transmission. Diagnosis of congenital syphilis is clinical and imprecise. In contrast, infant HIV diagnosis is based on a robust replicable measure—detection of HIV virus—that is highly sensitive and specific.

HIV Transmission

MTCT of HIV occurs either during pregnancy, at delivery, or through breastfeeding. Without intervention, HIV MTCT rates range from 20 percent to 35 percent in breastfed infants and from 15 percent to 20 percent in nonbreastfed infants (table 6.1) (De Cock and others 2000). Cofactors of MTCT of HIV include maternal viral burden (both systemically and in mucosal compartments to which the baby is exposed, such as genital secretions or breast milk), immunosuppression, and preterm birth (John and Kreiss 1996; John and others 2001).

Syphilis Transmission

MTCT of syphilis predominantly occurs during pregnancy, but few studies have been conducted on the estimated risk. The precision and accuracy of syphilis MTCT risk estimates are limited by the study design used (case control), varied diagnostic tests for maternal syphilis, and lack of a good diagnostic marker of infant infection. In a systematic review, Gomez and others (2013) screened 3,258 records and identified six studies

Table 6.1 Mother-to-Child Transmission of Syphilis and HIV, Selected Findings

Metric	Syphilis	HIV
Estimated annual number of pregnant women infected worldwide	1.36 million (summary from 2008 data [Newman and others 2013])	1.45 million (UNAIDS 2013)
Timing of transmission	In utero	In utero, intrapartum, postnatal (John and Kreiss 1996)
Method for detecting infant infection	Clinical manifestations, cerebrospinal fluid, and radiological	Detection of HIV virus by nucleic acid amplification tests
Transmission risk	15.5 percent of infants born to mothers with untreated syphilis have clinical signs of congenital syphilis (Gomez and others 2013)	20 to 35 percent infant HIV transmission depending on breastfeeding duration in the absence of maternal treatment or infant prophylaxis (De Cock and others 2000)
Adverse infant outcomes: fetal death, preterm birth, stillbirth, neonatal death, low birth weight	4.6-fold increased risk of combined adverse outcomes (66.5 percent among mothers with syphilis vs. 14.3 percent among mothers without syphilis) (Gomez and others 2013)	2-fold to 4-fold increased risk of combined adverse outcomes (Brocklehurst and French 1998)
Cofactors for MTCT	Maternal RPR level (Watson-Jones, Changalucha, and others 2002)	Maternal HIV viral load, other sexually transmitted infections, CD4 count, route of delivery, infant breastfeeding (John and others 2001)

Note: CD4 = cluster of differentiation 4 (blood count); HIV = human immunodeficiency virus; MTCT = mother-to-child transmission; RPR = rapid plasma reagin.

conducted between 1917 and 2000 (all case-control studies) to estimate the MTCT risk of syphilis. The estimated rates of congenital syphilis (diagnosed in infants showing signs of clinical infection) ranged from 2.2 percent to 40.9 percent, with a pooled MTCT rate of 15.5 percent (table 6.1). Cofactors of syphilis MTCT remain undefined (Gomez and others 2013); some evidence suggests that more recent maternal active syphilis (with high rapid plasma reagin [RPR] titer) is associated with increased adverse infant outcomes (Watson-Jones, Chagalucha, and others 2002).

In contrast to studies of MTCT of HIV, outcomes of maternal syphilis often emphasize estimated attributable adverse infant outcomes in addition to infant infections, because of difficulties in infant diagnosis and strong evidence of numerous additional adverse outcomes. Accordingly, combined adverse infant outcomes prevented by treatment of maternal syphilis are used to estimate cost-effectiveness. Gomez and others' (2013) systematic review attributed multiple adverse infant outcomes—including spontaneous abortion, stillbirth, fetal death, preterm birth, low birth weight, neonatal death, and congenital syphilis—to untreated syphilis. The pooled frequency of these adverse infant outcomes was 66.5 percent in mothers with syphilis, compared with 14.3 percent in mothers without syphilis (Gomez and others 2013). The authors noted marked heterogeneity and potential for bias in the estimates. Newer syphilis molecular diagnostics (polymerase chain reaction [PCR] assays) have greater than 70 percent sensitivity. To date, however, these newer diagnostic tests for syphilis have not been used to estimate MTCT syphilis rates (Grimprel and others 1991; Palmer and others 2003; Sanchez and others 1993; Shields and others 2012).

Other Infant Impacts from MTCT of HIV

Estimates of the impact of maternal HIV infection on infants have focused predominantly on HIV transmission risk itself, without including multiple adverse infant outcomes. However, untreated maternal HIV may contribute to adverse infant outcomes in addition to infant HIV infection, including fetal death, preterm birth, infant mortality, stillbirth, and low birth weight. In a systematic review of 31 studies, HIV-infected mothers had increased risk of spontaneous abortion, perinatal mortality, infant mortality, intrauterine growth retardation, low birth weight, and preterm birth (Brocklehurst and French 1998).¹

In addition, some of the new antiretroviral regimens for PMTCT may confer increased risk of adverse outcomes unrelated to HIV (Townsend and others 2007; Townsend and others 2010). The Promoting

Maternal-Infant Survival Everywhere (PROMISE) study, which enrolled more than 3,500 mother-infant pairs, compared two types of antiretroviral regimens for pregnant women who did not meet cluster of differentiation 4 (CD4) or clinical criteria for triple ART. One regimen type, Option A, was a short-course antiretroviral regimen that included different single or double drug regimens in pregnancy, delivery, and postpartum.² Option B was a combined three-drug ART regimen administered to all women during pregnancy and postpartum.³ Both regimens provided preventive antiretrovirals for breastfeeding MTCT; Option A relied on infant prophylaxis, while Option B relied on maternal ART with a six-week period of infant prophylaxis. Although Option A was inferior to Option B for PMTCT in this randomized controlled trial, Option B was associated with higher rates of prematurity, low birth weight, and neonatal death.⁴ Among the two Option B alternatives, lamivudine-ART was safer for infants than tenofovir-ART. Thus, the PROMISE study showed that the antiretroviral regimens a woman receives can affect both MTCT rates and rates of adverse infant outcomes. The WHO guidelines recommend Option B+, both for enhanced PMTCT effectiveness and for programmatic feasibility. Future guidelines and programs may adapt specific Option B+ antiretroviral regimens to concurrently decrease HIV and other adverse child outcomes.

Maternal HIV and Syphilis Coinfection

Some evidence suggests that women coinfecting with HIV and syphilis may have greater than twofold increased risk of HIV transmission than women with HIV infection alone; however, some studies have not found this association (Lee and others 1998; Mwapasa and others 2006; Schulte and others 2001; Yeganegh and others 2015). Children of coinfecting mothers may have HIV-syphilis coinfection and poorer outcomes than those with either infection alone (Mwapasa and others 2006).

Maternal and Pediatric Burden of HIV and Syphilis

Maternal Burden of HIV and Syphilis

There are distinct regional and global patterns of maternal HIV and syphilis. In Sub-Saharan Africa, for example, both HIV and syphilis are highly prevalent; however, the distributions of HIV infection and syphilis vary distinctly by region. Consistently assessed national HIV and syphilis prevalence estimates are not produced; however, South Africa, which has a higher HIV prevalence, appears to have lower antenatal syphilis prevalence than do other southern and eastern African

countries. China has higher syphilis but lower HIV prevalence than the Russian Federation. Although syphilis and HIV are both sexually transmitted infections (STIs), their distinct regional distribution may stem from differences in transmission epidemiology, sexual networks, treatment program effectiveness and coverage, notification and tracing guidelines, and measurement methods (WHO 2013).

Map 6.1 shows the global distribution of HIV prevalence in women ages 15–24 years, and map 6.2 shows the distribution of maternal antenatal syphilis seroprevalence.

Pediatric Burden of HIV

Annually, an estimated 1.5 million pregnant women worldwide are HIV infected, which, during the peak of the HIV epidemic in the mid-1990s, resulted in more than 500,000 infant HIV infections per year (UNAIDS 2013). However, with active PMTCT programs, infant HIV infections have steadily declined to about half that peak level; in 2015, an estimated

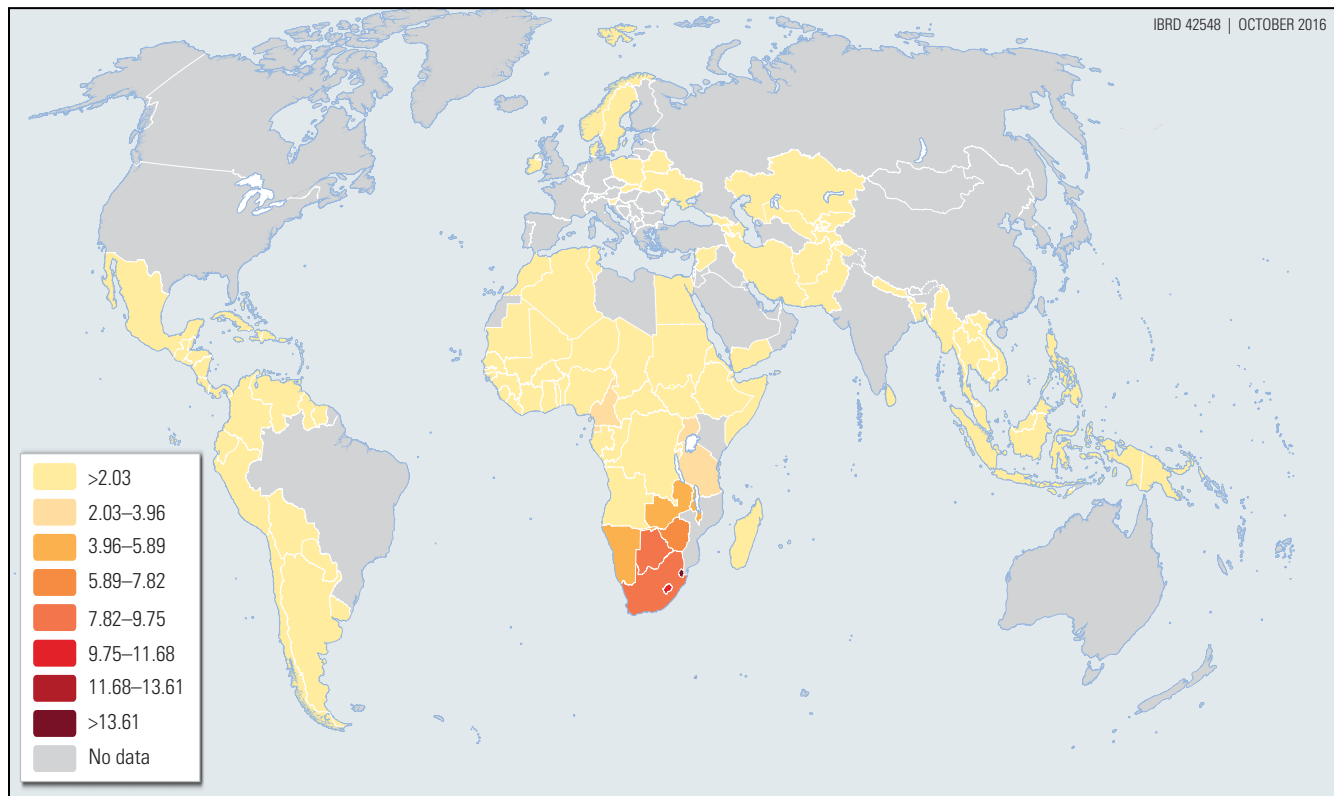
150,000 children younger than age 15 years were newly infected, as shown in map 6.3 (UNAIDS 2016a). This is a modeled estimate with confidence limits ranging from 110,000 to 190,000.

Although the annual number of HIV-infected infants has been decreasing, 1.8 million children younger than age 15 years are living with HIV, predominantly acquired through MTCT before the expansion of effective PMTCT programs, as shown in map 6.4 (UNAIDS 2016a). Many of these children remain undiagnosed and untreated until they become symptomatic. Although additional children older than age 15 years were infected with HIV in utero or at childbirth, it is difficult to estimate their numbers.

Pediatric Burden of Syphilis

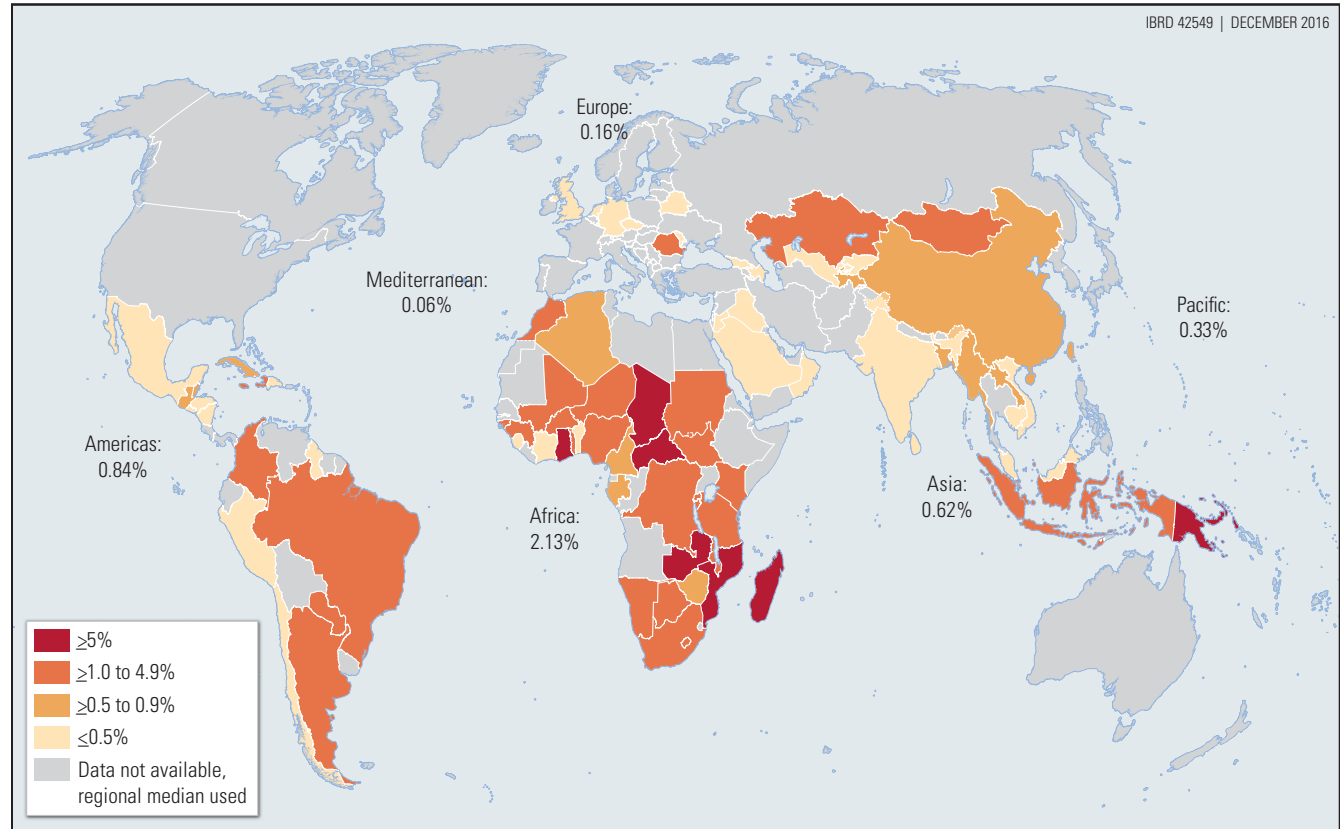
Similar maps for congenital syphilis are not available, although map 6.5 approximates relative burdens by country. Children with syphilis are harder to diagnose, map, and count than those with HIV. Worldwide between 1997 and 2003, an estimated 2 million women with

Map 6.1 Global HIV Prevalence among Women Ages 15–24 Years, 2014



Source: World Bank (<http://en.actualitix.com/country/wld/prevalence-of-hiv-women-15-24-years.php>).
Note: HIV = human immunodeficiency virus.

Map 6.2 Global Syphilis Seroprevalence among Pregnant Women, 2012



Source: Reprinted from "Global Health Estimates." 2013. Online Database. WHO, Geneva.

syphilis became pregnant, resulting in 728,000–1,527,000 new cases of congenital syphilis each year (Schmid and others 2007). This broad range in estimates of congenital syphilis is a result of poor ability to measure cases.

Other infant complications may also be partially extrapolated from maternal syphilis rates. The WHO estimated that, in 2008, 1.36 million pregnant women worldwide had active syphilis, of whom 80 percent had attended antenatal clinics (ANCs). Among those women, syphilis was responsible for more than 500,000 adverse pregnancy outcomes, including more than 200,000 stillbirths or early fetal deaths, 92,000 neonatal deaths, 65,000 preterm or low-birth-weight infants, and 152,000 infected newborns (Newman and others 2013). Two-thirds of these adverse outcomes occurred in women who had attended ANCs but were not screened or treated for syphilis (Newman and others 2013). The WHO estimates for 2012 illustrate a decline from 2008: 950,000 maternal syphilis infections

resulting in 360,000 adverse outcomes, including 150,000 early fetal deaths or stillbirths, 50,000 preterm or low-birth-weight infants, 60,000 neonatal deaths, and 110,000 infants with congenital infection (WHO 2013).

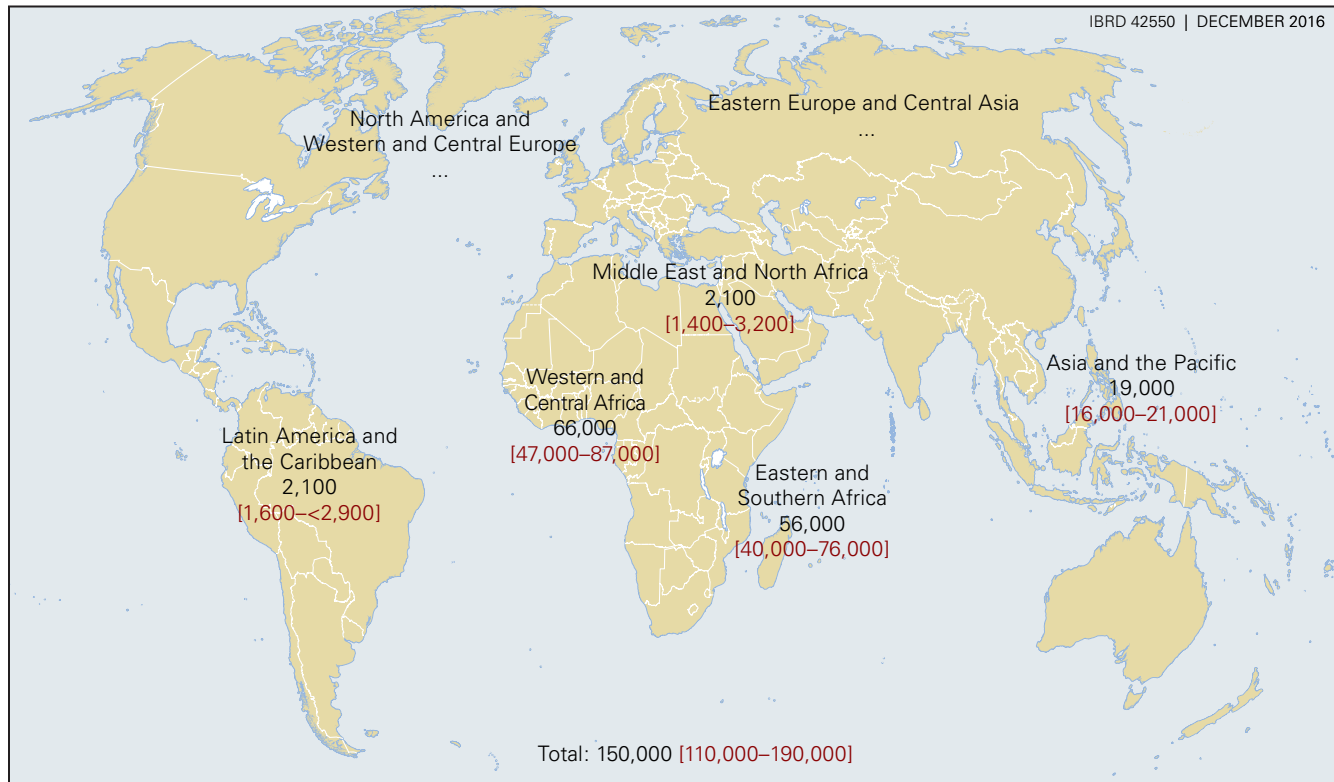
Consequences of Pediatric HIV and Syphilis

Consequences of Pediatric HIV

Infants who are infected with HIV through MTCT typically have a rapidly progressive course: about half die within two years (Newell and others 2004; Obimbo and others 2004). Infants with later MTCT of HIV through breastfeeding may have a more indolent course than infants with in utero or peripartum HIV acquisition (Becquet and others 2012; Obimbo and others 2009).

Children with untreated pediatric HIV infection have high risk of early mortality, severe malnutrition, and growth faltering, as well as recurrent infections,

Map 6.3 Estimated Number of Children Younger than Age 15 Years Newly Infected with HIV, by Region, 2015



Source: UNAIDS 2015. Reproduced, with permission, from UNAIDS; further permission required for reuse.

Note: HIV = human immunodeficiency virus. The estimated 150,000 new infections worldwide only include children younger than age 15 years.

including opportunistic infections such as tuberculosis (Obimbo and others 2004; Obimbo and others 2009), and neurocognitive delays. If given ART early, infants have significantly lower mortality but may have continued deficiencies in growth, persistent morbidity, and compromised neurocognitive ability (Wamalwa and others 2010).

Relative to uninfected mothers, HIV-infected mothers may have increases in other adverse outcomes of pregnancy, including stillbirth, prematurity, and low birth weight (Brocklehurst and French 1998). Their infants, if uninfected but HIV exposed, also have increased risk of morbidity and mortality compared with infants unexposed to HIV, perhaps because of increased immunologic susceptibility, sociodemographic factors, or increased exposure to other infectious diseases (Afran and others 2014; Mofenson and Watts 2014).

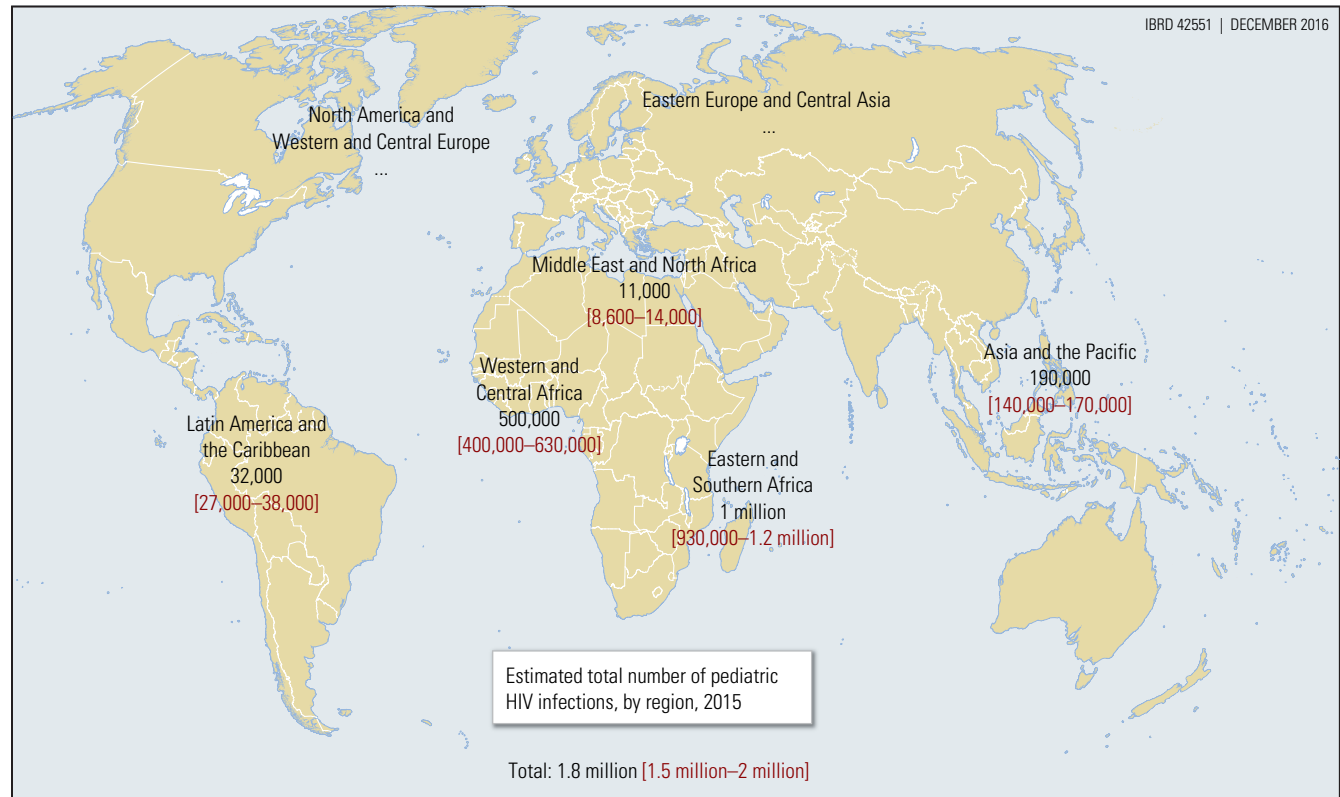
Consequences of Pediatric Syphilis

Children with congenital syphilis have a range of presentations, from asymptomatic to a variety of

symptoms including rash; skeletal changes; hepato-splenomegaly; and neurologic, renal, pulmonary, or ocular involvement. Moreover, congenital syphilis may result in lifelong disability, particularly when undetected or detected late in infancy (Arnold and Ford-Jones 2000).

A study of women who had not been screened for syphilis in ANC and delivered babies in a Tanzanian hospital found that, among those with serological evidence of active syphilis, 25 percent delivered a still-born baby, 20 percent a premature baby, and 33 percent a low-birth-weight baby. Overall, adverse events were noted in 49 percent of infants born to those women, compared with 11 percent of women without syphilis (Watson-Jones, Chagalucha, and others 2002). A systematic review of the impact of untreated syphilis on pregnancy outcomes found a consistently higher proportion of adverse pregnancy outcomes in women with untreated syphilis than in uninfected women (Gomez and others 2013). The pooled estimate of neonatal death was 12.3 percent in women with syphilis and 3 percent in women without syphilis.

Map 6.4 Children Younger than Age 15 Years Estimated to be Living with HIV, 2015



Source: UNAIDS 2015. Reproduced, with permission, from UNAIDS; further permission required for reuse.

Note: HIV = human immunodeficiency virus. The estimated 1.8 million infections worldwide only include children younger than age 15 years.

The pooled estimate for stillbirth or prematurity was 25.6 percent and for low birth weight was 12.1 percent among the infants of women with syphilis (Gomez and others 2013). Treatment of pregnant women is estimated to avert these outcomes as outlined in table 6.2.

EFFECTIVENESS AND COVERAGE OF PMTCT INTERVENTIONS

Effectiveness of Interventions for PMTCT of HIV

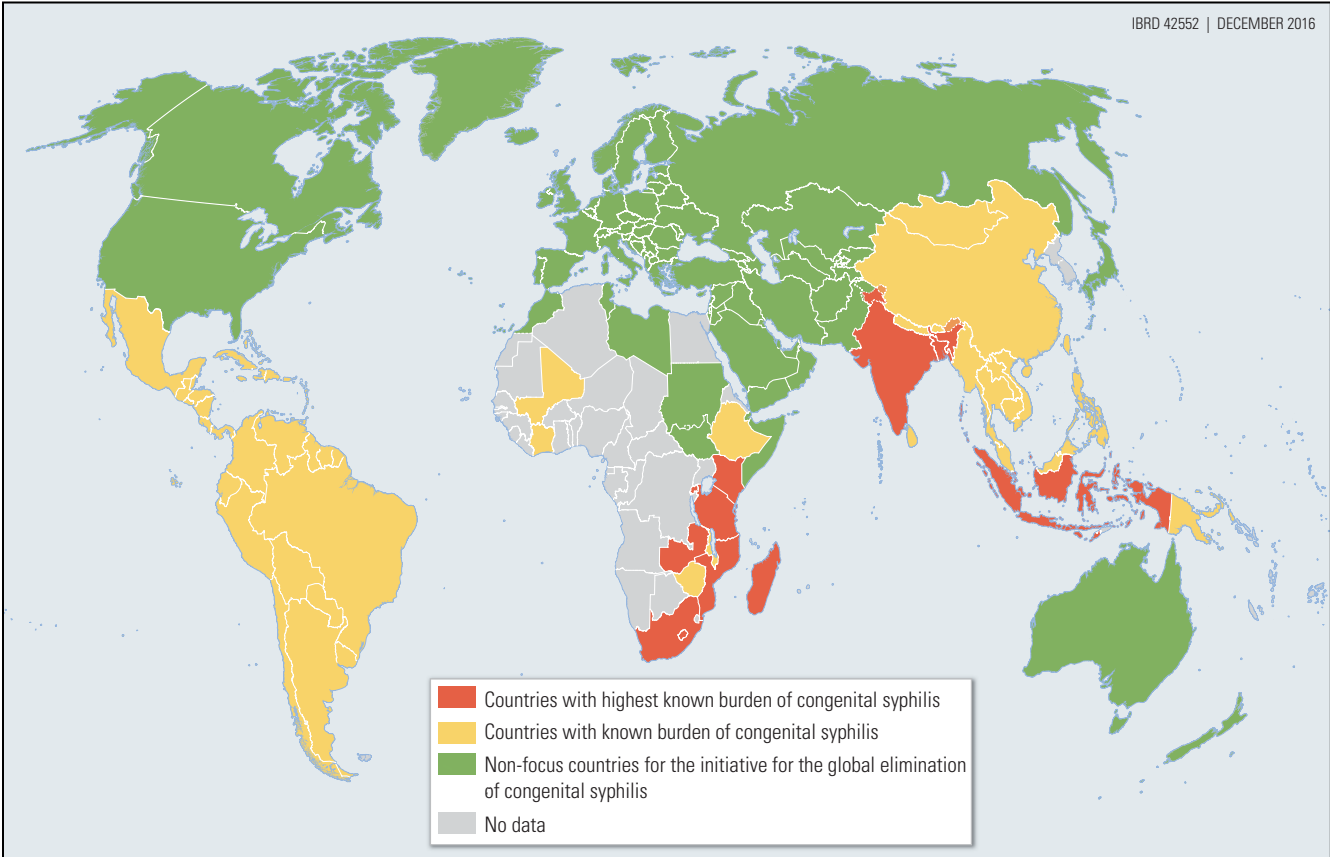
Identification of HIV during Pregnancy and in Infants
HIV testing during pregnancy initially used the enzyme-linked immunosorbent assay (ELISA) test with opt-in counseling, which resulted in attrition because women elected either not to have the test or not to return for results.⁵ The introduction of opt-out HIV testing—in which routine HIV testing is offered to all women unless a woman opts out—has substantially increased the number of women who are tested for HIV (Creek and others 2007; Day and others 2004). In addition, rapid

HIV testing, which can provide results during the same visit, significantly increases the proportion of women who receive their test results (Malonza and others 2003).⁶ Rapid HIV testing enables testing of women of unknown HIV status at any time they present to the health care system, including at delivery.

Testing for HIV needs to include not only diagnostic services but also careful counseling of women. Peer counselors and mother-to-mother models have been critically important for helping women cope with their diagnoses, make decisions about disclosure of their results to their partners, and adhere to their medication regimen (Futerman and others 2010; Shetty and others 2008; Shroufi and others 2013).

Women may become infected with HIV during pregnancy or postpartum, and repeat HIV testing is advised to detect and treat women with HIV seroconversion during this period. As PMTCT of HIV expands, women diagnosed with HIV at or before their first antenatal visit routinely receive HIV treatment. However, mothers who are initially seronegative but acquire HIV infection in pregnancy or postpartum are

Map 6.5 Relative Global Concentrations of Congenital Syphilis, by Country



Source: Reprinted from "Advancing MDGs 4, 5 and 6: Impact of Congenital Syphilis Elimination." Partner Brief, WHO, Geneva; http://apps.who.int/iris/bitstream/10665/70331/1/WHO_RHR_HRP_10.01_eng.pdf. 2010a.

Note: The Initiative for the Global Elimination of Congenital Syphilis was launched by the WHO in 2007 to support global efforts to achieve several of the Millennium Development Goals (MDGs): MDG 4 (reduce child mortality), MDG 5 (improve maternal health), and MDG 6 (combat HIV/AIDS, malaria, and other diseases) (WHO 2010a).

Table 6.2 Adverse Infant Outcomes Potentially Avertable by Treatment of Maternal Syphilis

Outcome	Outcomes averted by treatment (%)
Stillbirth	13.3
Miscarriage	8.1
Neonatal death (age 0–28 days)	9.3
Prematurity or low birth weight	5.8
Infant with clinical evidence of syphilis	19.4
Nonneonatal infant death (age 29–365 days)	3.4
Any adverse outcome	48.7*

Source: LSHTM 2011.

Note: "Treatment" refers to penicillin in pregnancy. * = "Any adverse outcome" is less than the sum of the individual outcomes because of differences in weighting and variance that occur when doing a meta-analysis, as well as the possibility of an infant's having more than one outcome.

often undiagnosed and contribute to an increasing proportion of infant HIV infections that may not be detected until the child presents with symptomatic disease (Drake and others 2014). Thus, repeat HIV testing during pregnancy and postpartum is recommended, although guidelines for frequency and timing of repeat HIV tests in follow-up vary by national setting.

Infants are born with maternal antibodies to HIV, making HIV serologic testing unhelpful for newborns. HIV DNA can be diagnosed from a dried blood spot (DBS) using PCR assays in a central laboratory. DBS HIV DNA virologic rather than serologic testing is recommended for infants (WHO 2010b). Early infant diagnosis (EID) is conducted using DBS HIV DNA tests at age six weeks, followed by testing at age nine months and again at six weeks following

cessation of breastfeeding (Luzuriaga and Mofenson 2016). New POC assays for HIV DNA are becoming available that may be useful for decreasing turnaround time for EID results and expediting treatment of infants with HIV.

Antiretroviral Treatment for PMTCT of HIV

ART to decrease MTCT of HIV has been assessed in numerous randomized clinical trials (Siegfried and others 2011). Initial simple short-course regimens, such as single-dose maternal and infant nevirapine administered to the mother during labor and to infants, decreased transmission by 50 percent. Triple-ART and infant prophylaxis regimens increase intervention efficacy.⁷ Evidence supporting the use of ART for PMTCT of HIV is Grading of Recommendations Assessment, Development and Evaluation (GRADE) A1 (with large decreases in HIV transmission risk—declining from more than 30 percent to less than 1 percent) (WHO 2012b and 2014b).

Effectiveness of Interventions for PMTCT of Syphilis

Identification of Syphilis during Pregnancy and in Infants

Because most pregnant women with syphilis do not have symptoms, a serological screening test is needed to identify those who are infected. A nontreponemal agglutination test such as the RPR test has traditionally been used. This test is cheap (less than US\$0.10) and rapid, but the reagents need to be refrigerated, serum needs to be separated from whole blood, and a plate shaker is needed, meaning that a reliable electricity supply is required. Simple, lateral-flow POC tests have become available in recent years; these tests are sensitive, specific, can be stored at ambient temperature, and can be performed with a sample obtained by finger prick (Jafari and others 2013; Mabey and others 2006). These tests detect treponemal antibodies and cannot distinguish between active and past or treated infection. However, given the disease complications and the simplicity and effectiveness of treatment (penicillin), these tests can provide a net public health benefit (Kuznik and others 2013). A dual POC test for HIV and syphilis has become available that detects both treponemal and nontreponemal antibodies and is both sensitive and specific, with good test performance for the diagnosis of active syphilis (Yin and others 2013). The dual POC test is a pragmatic and attractive approach to promoting integration of PMTCT of HIV-syphilis programs (Kiarie and others 2015).

Women should be tested antenatally at their first visit in pregnancy, preferably before 16 weeks' gestation, and retested in the third trimester. Women who have not been tested before delivery should be tested at delivery.

Infants are born with maternal antibodies, limiting diagnostic utility of routine treponemal or nontreponemal tests. Clinical diagnosis may be made in symptomatic infants, with signs including mucocutaneous lesions, bone changes evident on radiographs, syphilitic rhinitis ("snuffles"), lymphadenopathy, and hematologic changes.

Penicillin Treatment for PMTCT of Syphilis

Women with evidence of syphilis from either a treponemal or nontreponemal test should receive treatment with penicillin (WHO 2006). In Tanzania, women with syphilis who received a single dose of benzathine penicillin before 28 weeks' gestation had the same incidence of adverse pregnancy outcomes as women without syphilis (Watson-Jones, Gumodoka, and others 2002). A systematic review of the impact of penicillin treatment on pregnancy outcomes in women with syphilis showed that treatment with at least 2.4 million units of penicillin reduced the incidence of clinical congenital syphilis by 97 percent (relative risk 0.03) (Blencowe and others 2011). The pooled estimate for reduction of stillbirths was 82 percent, 64 percent for reduction in preterm delivery, and 80 percent for reduction in neonatal death (Blencowe and others 2011). The effect estimates were large and consistent across studies, leading to a strong recommendation for screening and treatment according to the GRADE criteria (Blencowe and others 2011). Seropositive women should receive benzathine penicillin (2.4 million units), and partners should also receive penicillin treatment. Infants of these women should receive 50,000 units/kilogram of benzathine penicillin if asymptomatic or 10 days of crystalline or procaine penicillin if symptomatic. The combined cost of diagnosis and penicillin treatment of maternal syphilis is less than US\$1.

PMTCT Implementation and Coverage

PMTCT of HIV

Concerns about stigma and loss of confidentiality motivated the initial intensive, opt-in voluntary counseling and HIV testing models. Routinizing HIV testing has led to much more efficient systems for PMTCT of HIV (Creek and others 2007). HIV stigma may continue to inhibit the likelihood of HIV testing or

ART adherence, but health-system bottlenecks appear to be a comparable or greater barrier to PMTCT implementation (Kinuthia and others 2011). On the positive side, male partner engagement may enhance maternal adherence to antenatal and postnatal care visits and ART, while also improving infant outcomes (Farquhar and others 2001; Taha and others 2007). Other implementation issues relevant to PMTCT effectiveness include the following:

ART Delays and Adherence Constraints. Previous PMTCT antiretroviral regimens, such as Option A, required waiting for CD4 count results to determine ART eligibility, which delayed ART initiation and compromised PMTCT programmatic effectiveness. Options B and B+ use an accelerated test-and-treat approach, with immediate ART following HIV diagnosis without waiting for a CD4 count (Taha and others 2007; WHO 2012b).⁸ Long-term adherence to ART may decline for PMTCT regimens postpartum. In an early Option B+ program model in Malawi, initiation of Option B+ led to a rapid increase in the number of women receiving ART, but only 77 percent of women remained on ART at one year following delivery (CDC 2013). Option B or B+ also may decrease sexual transmission of HIV to male HIV-uninfected partners relative to Option A (Cohen and others 2011). The health costs and benefits of Option B versus Option B+ are not well defined (Watts and others 2009). However, between pregnancies, Option B+ with continued ART will encounter fewer health-system bottlenecks than Option B, in which episodic ART is administered only during pregnancy and breastfeeding. Specifically, the maternal and child health (MCH) system will not need to restart ART; however, there may be supply chain challenges in consistent drug procurement. It is also not clear whether young asymptomatic women will maintain long-term adherence to Option B+ between pregnancies, or which strategies may optimize long-term adherence to ART.

Lack of Tailored Counseling Approaches. Other issues facing PMTCT programs require improvement or innovation. As PMTCT programs and HIV care programs expand, an increasing number of women will have been previously diagnosed with HIV and will have begun receiving treatment before they become pregnant. Stratified counseling approaches to previously diagnosed and treated women versus newly diagnosed women do not exist. With Option B+, newly diagnosed women initiate ART for life in the context of pregnancy and need counseling and other interventions to motivate long-term ART adherence.

Lack of Diagnostic System Tracking and Coordination. Medical records of mothers are often not

linked to infant medical records, which would facilitate tracking of maternal-to-infant outcomes (Chi, Bolton-Moore, and Holmes 2013). EID-of-HIV programs involve the collection of DBS from infants at age six weeks; the DBS are sent to a central laboratory for HIV PCR testing for detection of HIV DNA. Results from EID programs have unacceptably long turnaround times (Sutcliffe and others 2014; Woldesenbet and others 2014). Consequently, mothers often fail to receive infant results or remain unaware of infant HIV diagnosis, despite testing. Children may not get a diagnosis of HIV until they become ill, resulting in poor long-term outcomes. New POC EID assays may circumvent problems with existing infant HIV diagnostic systems (Jani and others 2014). EID detects perinatal infant HIV infections, but infants with negative early HIV tests remain at risk throughout the breastfeeding period, and repeat testing is important. In addition, in settings of high HIV prevalence, new maternal HIV infection acquired during the pregnancy and breastfeeding periods contributes appreciably to infant HIV infections despite good PMTCT programs (Drake and others 2014).

Late Postnatal Follow-Up during Breastfeeding. Following the six-week postnatal visit, retention decreases, and long-term follow-up to exclude or diagnose infant HIV is erratic. With the scale-up of Option B+, retention beyond the early infant period needs to be improved.

PMTCT of Syphilis

A 1996–97 survey of health ministries in 22 countries in Sub-Saharan Africa concluded that, although 73 percent of women attended ANC overall, and although syphilis screening of ANC attendees was national policy in nearly all countries, only 38 percent of women were estimated to actually have been screened for syphilis (Gloyd, Chai, and Mercer 2001). Reported reasons for not performing screening in this survey included costs of testing, treatment, and transport; inadequate prioritization; sociocultural resistance; and lack of compliance or awareness by health care workers. In Tanzania, where screening and treatment of ANC attendees for syphilis is national policy, a survey in nine districts found that only 43 percent of 2,256 ANC attendees had been screened, and only 61 percent of seropositive women and 37 percent of their partners had been treated. Watson-Jones and others (2005) found that adequate training, continuity of supplies, supervision, and quality control are critical elements for effective antenatal services but were frequently overlooked. The WHO noted that in 2012, 95 percent coverage of syphilis testing was achieved in only 29 percent of 51 low- and middle-income countries (LMICs) surveyed.⁹

A review of syphilis screening in 13 ANC in Nairobi, Kenya, where blood was sent to a central laboratory for syphilis serology, found that only 291 of 540 women (54 percent) had been tested. Of 11 who were seropositive, only 1 had been treated. However, after these clinics introduced same-day screening and treatment, 99.9 percent of ANC attendees were screened for syphilis, and 87.3 percent of seropositive women and 50 percent of their partners received treatment (Temmerman, Mohamedalf, and Fransen 1993). The new POC tests make it possible to offer same-day screening and treatment in any health facility, which increases the coverage of screening and treatment in many settings (Hawkes and others 2011; Jenniskens and others 1995).

Cross-Cutting Issues for PMTCT of HIV and Syphilis

MCH is addressed through public health systems and was prioritized in Millennium Development Goal (MDG) 4 (to reduce child mortality) and MDG 5 (to improve maternal health) (Chi, Bolton-Moore, and Holmes 2013); MCH is also part of Sustainable Development Goal 3 (health and well-being at all ages). PMTCT of HIV and PMTCT of syphilis are delivered through the same MCH system. Programs for PMTCT of HIV have used the cascade-of-care approach to identify bottlenecks in services.¹⁰ In many settings, most pregnant women visit an ANC at least once during their

pregnancy, at which time routine HIV and syphilis testing can occur. Downstream treatment of women with positive HIV results is measured systematically in countries targeted for PMTCT of HIV, specifically to assess whether mothers were started and maintained on ART, continued in follow-up care, and had their infants tested for HIV through EID programs (UNAIDS 2013). The MCH registers typically include information on syphilis testing. Registers could be enhanced to improve PMTCT of syphilis by leveraging current program evaluation of HIV PMTCT to include variables on syphilis indicators (table 6.3) (WHO 2014b). Enhancements should include monitoring infant receipt of antiretroviral prophylaxis and infant evaluation for clinical syphilis and treatment needs.

Other cross-cutting issue areas affecting PMTCT of both HIV and syphilis include the following:

Male Partner Involvement. Several studies have noted enhanced PMTCT and infant outcomes and treatment adherence among women whose male partners have participated in MCH programs, either through HIV testing or ANC attendance (Aluisio and others 2011; Kalembo and others 2013). A program offering home-based HIV testing to male partners noted high uptake of male HIV testing (Osoti and others 2014). It is difficult to discern whether these benefits are the result of male

Table 6.3 Cross-Cutting Health System Implementation Issues for PMTCT of HIV and Syphilis

Implementation need	PMTCT of syphilis	PMTCT of HIV
Community awareness	Community has not been mobilized	✓
Required ANC attendance	✓	✓
ANC attendance early in pregnancy (optimal for prevention)	✓	✓
MoH recommendation of maternal testing	✓	✓
Availability of POC diagnostic test	✓	✓
National use of POC diagnostic test	✓	✓
QA and QC of lab tests, good supply chain of lab tests	✓	✓
Use of opt-out approach	✓	✓
Availability of one-time treatment	✓	Needs lifelong treatment
Availability of low-cost treatment	✓	Not a one-time cost—ART currently provided by a combination of resources including from government, PEPFAR, or GAP
Usefulness of partner notification and engagement	✓	✓
Availability of standard infant diagnostic test	No laboratory test—clinical diagnosis	✓

Note: ANC = antenatal clinic; ART = antiretroviral treatment; HIV = human immunodeficiency virus; PMTCT = prevention of mother-to-child transmission; GAP = Global AIDS Program; MoH = Ministry of Health; PEPFAR = President's Emergency Plan for AIDS Relief; POC = point-of-care; QA = quality assurance; QC = quality control.

involvement or female self-efficacy, because few women involve male partners in ANC attendance. Efforts to increase this involvement include written invitations, weekend openings, initiatives to provide male partners with incentives to attend, male-friendly clinics, and home visits for male testing and education (Reece and others 2010). Rwanda made a concerted effort to mandate male attendance during antenatal care of women to improve maternal and infant outcomes (Irakoze and others 2012), and male HIV testing increased substantially in parallel with increased facility delivery. Conversely, this approach may stigmatize single mothers. In addition, since syphilis screening leads to male notification and treatment, such screening could be integrated into male partner programs for PMTCT of HIV.

Integration of Family Planning and Primary Maternal HIV and Syphilis Prevention. Postpartum visits are opportunities to increase uptake of contraception and to promote prevention of HIV and other STIs. However, family planning clinics and postpartum family planning clinics do not routinely incorporate HIV or STI prevention or testing.

Community Engagement to Reduce Stigma of Testing and Treatment. Both HIV and syphilis carry a community stigma as STIs. In the case of HIV infection, the combination of high community prevalence, mature epidemics, and increasing community knowledge and advocacy have led to vibrant activism and pragmatic peer mentoring and counseling (Namukwaya and others 2015). In contrast, syphilis awareness lacks community-level advocacy. Individuals are not familiar with the disease or its symptoms and typically do not know whether someone has been identified as having had syphilis. To our knowledge, peer mentoring is not used, and children and parents with syphilis do not have support groups comparable to HIV support groups.

Alignment of the Long-Term Health Benefits of Interventions with the MDGs and General MCH Goals. Comprehensive MCH requires detection and treatment of maternal HIV and syphilis to improve short-term and long-term outcomes for mothers and their children. Interventions may have impacts on multiple outcomes, including decreasing preterm birth, stillbirth, and other morbidity in addition to enhancement of growth, cognition, and survival.

Intersection of PMTCT Interventions with General Prevention and Treatment of HIV and Syphilis. Community-level HIV treatment and prevention

occur at voluntary counseling and testing centers, in comprehensive HIV care and treatment programs, and at PMTCT programs in MCH clinics. Women with HIV may shift between PMTCT and HIV care and treatment programs, and Options B and B+ approaches ensure comparable antiretroviral regimens during this process. Women's HIV care and treatment affect both sexual and mother-to-infant transmission and contribute to community HIV prevention. Because pregnancy is an identifiable trigger point for accessing HIV testing, it is often a sentinel event for family HIV diagnosis in young couples who do not perceive themselves at risk for HIV but who live in settings with high HIV prevalence.

Syphilis is similarly preferentially detected during pregnancy because of widespread access to care and testing. However, since no large syphilis care and treatment centers exist, prevention and detection of syphilis typically occur at primary health care visits or at sexually transmitted disease (STD) treatment programs. MCH clinics have limited experience with standard partner testing for STIs and often refer male partners to STD programs for syphilis testing. An alternative approach would be to include partner syphilis testing and follow-up in routine MCH care, analogous to HIV, without referral to STD services.

Methods for Assessing PMTCT Program Effectiveness

Program Evaluation Methodology for PMTCT of HIV

Standardized national surveys using routine infant DBS for HIV DNA testing at age six weeks can capture most mother-infant pairs, because uptake of routine six-week infant immunizations is high, regardless of HIV diagnosis or PMTCT intervention uptake (WHO 2012a). Thus, the evaluation of programs for PMTCT of HIV can be standardized because there is a hard outcome—infant HIV status. However, this outcome measure is not the final infant HIV outcome, because breastmilk transmission may occur until cessation of breastfeeding, particularly if women do not adhere to ART. Later time points—nine months and thereafter—for MCH visits are less well attended and do not include infants who become lost to follow-up or who die before assessment. Community household-based surveys may complement facility-based assessment, reach mother-infant pairs who do not attend facility services, and enable better estimation of HIV-free survival at later endpoints, but assessment of programmatic effectiveness may have shortcomings depending on participation and self-reporting (Conrad and others 2012; Kohler and others 2014; Larsson and others 2012).

UNAIDS has developed evaluation strategies for consistent assessment of national programs for PMTCT of HIV. In these surveys, several countries report higher than 90 percent PMTCT coverage, with a transmission risk of less than 5 percent (UNAIDS 2015). Remarkable progress has been made in Botswana, South Africa, and several eastern and southern African countries. Indeed, PMTCT interventions have been responsible for a substantial proportion of the declines in overall HIV incidence globally. However, although infant HIV infections have plummeted (figure 6.1), the world did not accomplish the UNAIDS PMTCT goal of no more than 15,000 infections by 2015 (UNAIDS 2016b).

Program Evaluation Methodology for PMTCT of Syphilis

The Rapid Syphilis Test Toolkit is a comprehensive guide for planning and management of syphilis prevention programs that includes guidelines on policy advocacy, supply chain, cost-effectiveness, clinical training, laboratory procedures, and monitoring and evaluation with clearly defined program indicators (LSHTM 2011). Specifically, it states that the number of women screened, who tested positive, and whose male partners were tested, as well as the number of syphilis-positive women who received same-day penicillin, should be summarized from clinic register data. In addition, the number of cases of congenital syphilis and other complications of syphilis should be summarized as a percentage of live

births. The guidelines also note the additional sequelae that are anticipated to decrease following implementation of an effective program for PMTCT of syphilis (figure 6.2 and table 6.4).

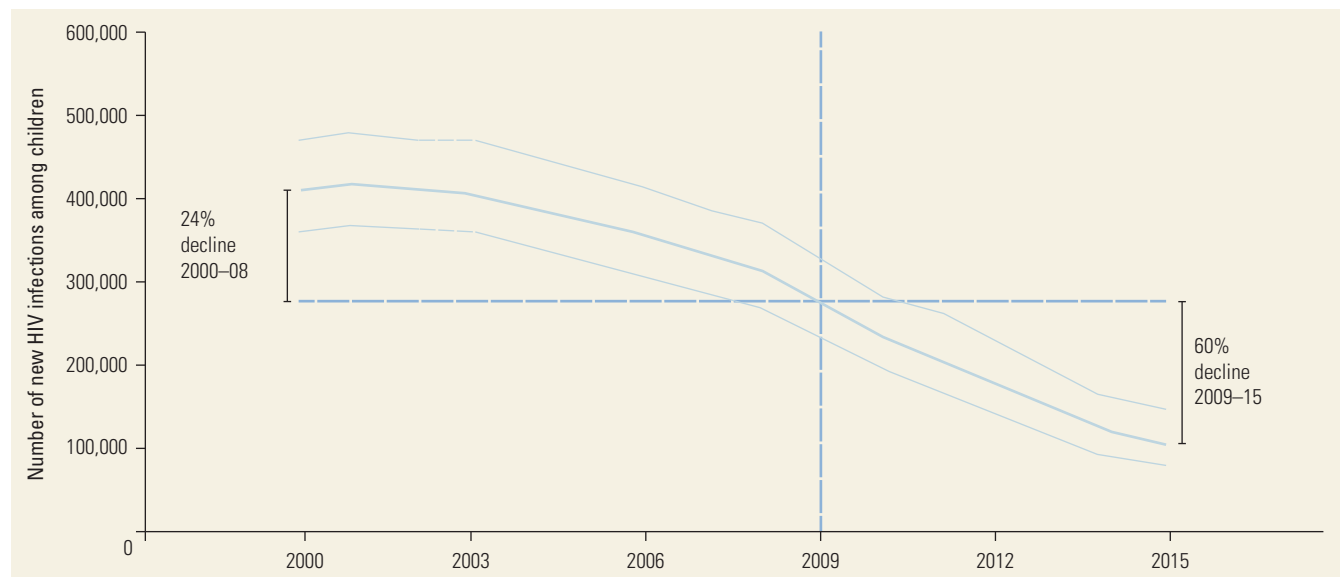
Combined Validation of PMTCT of HIV and Syphilis

In 2014, the WHO published a framework for validation of PMTCT of HIV and syphilis for program managers and policy makers (WHO 2014a). This framework was used to validate PMTCT of HIV and syphilis in Cuba in 2015. Measures assessed include MTCT of HIV and congenital syphilis rate, and coverage (greater than 95 percent) of antenatal syphilis and HIV testing and treatment (WHO 2015).

COST-EFFECTIVENESS OF PMTCT OF HIV AND SYPHILIS

Cost-effectiveness analyses allow policy makers to prioritize approaches for disease prevention. In this case, they help policy makers compare PMTCT of HIV with PMTCT of syphilis and potentially estimate the benefits of a dual approach to PMTCT. The cost-effectiveness studies presented are all from low- and middle-income settings. Tables 6.5 and 6.6 present cost-effectiveness estimates for PMTCT of HIV and PMTCT of syphilis, respectively, extracted from systematic reviews of the literature (Johri and Ako-Arrey 2011; Levin and Brouwer 2014) and using only those

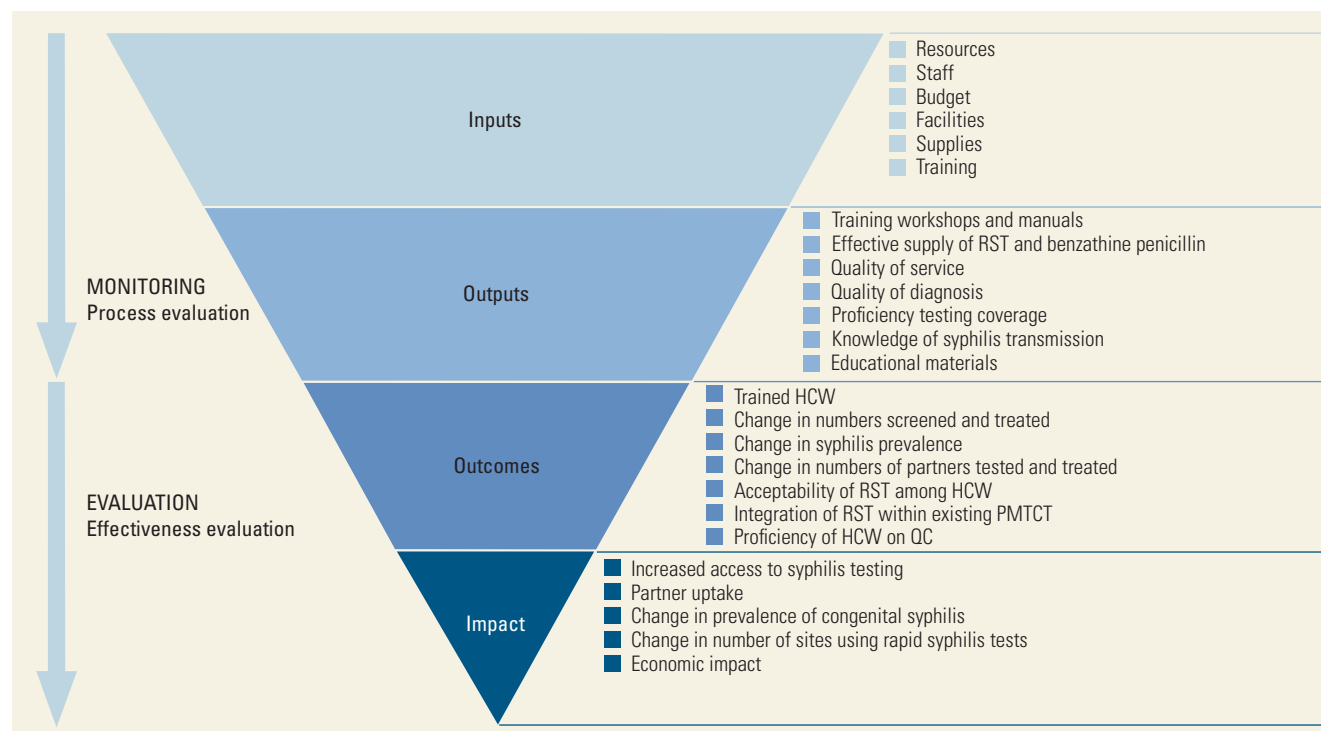
Figure 6.1 Number of New HIV Infections among Children in 21 Global Plan Priority Countries, 2000–15



Source: UNAIDS 2016b.

Note: HIV = human immunodeficiency virus.

Figure 6.2 Syphilis Monitoring and Evaluation Results Pyramid



Source: Adapted from LSHTM 2011, figure 1; originally published in UNAIDS/World Bank, panel 1.

Note: HCW = health care workers; PMTCT = prevention of mother-to-child transmission; QC = quality control; RST = rapid syphilis test.

Table 6.4 Required Indicators for Global Validation of PMTCT of HIV and Syphilis

HIV
Impact indicators
Case rate of new pediatric HIV infections resulting from MTCT of HIV of ≤ 50 cases per 100,000 live births; AND
MTCT rate of HIV of < 5 percent in breastfeeding populations OR MTCT rate of HIV of < 2 percent in nonbreastfeeding populations
Process indicators
ANC coverage (at least one visit) of ≥ 95 percent
Coverage of pregnant women who know their HIV status of ≥ 95 percent
ARV coverage of HIV-positive pregnant women of ≥ 90 percent
Congenital syphilis
Impact indicator
Case rate of congenital syphilis ≤ 50 cases per 100,000 live births
Process indicators
ANC coverage (at least one visit) of ≥ 95 percent
Coverage of syphilis testing of pregnant women of ≥ 95 percent
Treatment of syphilis-seropositive pregnant women ≥ 95 percent

Source: WHO 2014a.

Note: ANC = antenatal care; ARV = antiretroviral; PMTCT = elimination of mother-to-child transmission; HIV = human immunodeficiency virus; MTCT = mother-to-child transmission.

articles published after 2000. In addition, a supplementary search yielded more recent studies published between 2010 and 2015. We extracted 24 cost-effectiveness metrics or ranges from 18 articles for PMTCT of HIV and 23 from 8 articles for PMTCT of syphilis and integrated approaches. All estimates have been converted into 2012 US dollars.

Cost-Effectiveness of PMTCT of HIV

The cost-effectiveness of extended combination prophylaxis for PMTCT of HIV is well established, especially in high-risk areas, compared with no intervention or the use of single-dose nevirapine or short-course prophylaxis (Johri and Ako-Arrey 2011). In high-risk regions such as Sub-Saharan Africa, regional models estimate that Option A is cost-effective, ranging from US\$25 to US\$730 per disability-adjusted life year (DALY) averted. Since 2010, country-specific studies have focused on comparing the incremental costs and benefits of new guidelines related to treatment Options A, B, or B+. For the LMICs shown in table 6.5, these options benefit infants and mothers, save money over time, and are cost-effective (Ciaranello and others 2013; Fasawe 2013). For resource-constrained countries with high risk of HIV, there are

Table 6.5 Cost-Effectiveness Analyses since 2000 of Interventions for PMTCT of HIV

Region	Intervention	Comparator	Country or region	Cost in 2012 US\$	Unit of outcome	Study
<i>Sub-Saharan Africa</i>			Regional studies			
	Option A	No intervention	SSA	25.71–43.68	DALYs averted	Marseille and others 2000
	Option A	No intervention	SSA	184.48	Infection averted	Stringer and others 2000
	Option A	No intervention	SSA	136.67–730.49	DALYs averted	Sweat and others 2004
	Option A	No intervention	AFR-E	38.94	DALYs averted	Hogan and others 2005
	Country studies					
	Option A	No intervention	South Africa	47–99	DALYs averted	Wilkinson, Floyd, and Gilks 2000
	Option A and mass screening	No intervention	Chad	1,862	Infection averted	Hutton, Wyss, and N'Diekhor 2003
	Option B	Current practice	Malawi	40	DALYs averted	Orlando and others 2010
	Option B+	No intervention	Tanzania	251	DALYs averted	Robberstad and Evjen-Olsen 2010
	Option B	Option A	Nigeria	171	DALYs averted	Shah and others 2011
	Option B	Option A	Uganda	65–140	DALYs averted	Kuznik and others 2012
	Option B+	No intervention	Uganda	291–502	DALYs averted	Kuznik and others 2012
	Option B	Option A	South Africa	1,187	QALYs gained	Zulliger and others 2014
	Option B+	Option B	Zimbabwe	1370 ^a	YLS	Ciaranello and others 2013
	Option A	Current practice ^b	Malawi	30	DALYs averted	Fasawe and others 2013
	Option B	Current practice ^b	Malawi	54	DALYs averted	Fasawe and others 2013
	Option B+	Current practice ^b	Malawi	50	DALYs averted	Fasawe and others 2013
	Option B	Option A	Zambia	82	QALYs gained	Ishikawa and others 2014
	Option B+	Option A	Zambia	145	QALYs gained	Ishikawa and others 2014
<i>Latin America and the Caribbean</i>						
	Option A and mass screening	No intervention	Peru	3,092–7,924	DALYs averted	Aldridge and others 2009
<i>South Asia</i>						
	Universal screening	No intervention	India	32	YLS	Kumar and others 2006
	Targeted screening	No intervention	India	68	YLS	Kumar and others 2006
<i>East Asia and Pacific</i>						
	Option A	No intervention	SEAR-D	355	DALYs averted	Hogan and others 2005
	Option B	Option A	Thailand	2,299–3,225	DALYs averted	Teerawattananon and others 2005
	Option B	Option A	Thailand	Cost saving	QALYs gained	Werayingyong and others 2013

Note: AFR-E = WHO member states Botswana, Burundi, the Central African Republic, the Republic of Congo, Côte d'Ivoire, the Democratic Republic of Congo, Eritrea, Ethiopia, Kenya, Lesotho, Malawi, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Uganda, Tanzania, Zambia, and Zimbabwe; CEA = cost-effectiveness analysis; DALYs = disability-adjusted life years; PMTCT = prevention of mother-to-child transmission; HIV = human immunodeficiency virus; QALYs = quality-adjusted life years; SEAR-D = WHO member states Bangladesh, Bhutan, the Democratic People's Republic of Korea, India, Maldives, Myanmar, and Nepal; SSA = Sub-Saharan Africa; YLS = years of life saved.

a. This estimate is in 2013 US dollars, as in the publication, because a reliable consumer price index deflator was not available for Zimbabwe.

b. Mix of interventions including single-dose nevirapine, or dual-drug regimen containing zidovudine, or triple-drug antiretroviral prophylaxis until cessation of breastfeeding.

debates about the advantages and disadvantages of Option B+ (lifelong ART for all pregnant and HIV-infected women), in part because Option B+ is effective in saving lives but is associated with higher short-term costs compared with Options A and B (Saeed, Kim, and Abrams 2013). In low-prevalence settings, such as Thailand, PMTCT is cost-effective at US\$2,299–US\$3,225

per DALY averted; it may even be cost saving, depending on adherence to ART and relative costs of ARVs. HIV treatment guidelines and PMTCT intervention options are continuously evolving; country context (prevalence rates, drug costs, health utilization rates, health system capacity) will affect the relative cost-effectiveness of and the choice of best strategy from these and future options.

Table 6.6 Cost-Effectiveness Analyses since 2000 of Interventions for PMTCT of Syphilis

Region	Intervention	Comparator	Country or region	Cost in 2012 US\$	Unit of outcome	Study
<i>Sub-Saharan Africa</i>			Global or regional			
	Rapid point-of-care ICS ^a screen and treat with penicillin	No screening	Sub-Saharan Africa	11	DALYs averted	Kuznik and others 2013
	Laboratory RPR ^a screen and treat with penicillin	No screening	Global low prevalence	24–111	DALYs averted	Kahn and others 2014
	Laboratory RPR ^a screen and treat with penicillin	No screening	Global high prevalence	Cost-saving	DALYs averted	Kahn and others 2014
			Country studies			
	Laboratory RPR ^a screen and treat with penicillin	No screening	Tanzania	23	DALYs averted	Terris-Prestholt and others 2015
			Tanzania	16	DALYs averted	Terris-Prestholt and others 2003
			Zambia	26	DALYs averted	Terris-Prestholt and others 2015
	Rapid point-of-care ICS ^a screen and treat with penicillin	No screening	Tanzania	17	DALYs averted	Terris-Prestholt and others 2015
			Zambia	16	DALYs averted	Terris-Prestholt and others 2015
	Dual screening with ICS ^a and RPR and treat with penicillin	No screening	Tanzania	18	DALYs averted	Terris-Prestholt and others 2015
			Zambia	70	DALYs averted	Terris-Prestholt and others 2015
	ICS screen and treat with penicillin	RPR screen and treat	Tanzania	16	DALYs averted	Terris-Prestholt and others 2015
			Zambia	11	DALYs averted	Terris-Prestholt and others 2015
	ICS screen and treat with penicillin	Current practice: 62 percent tested, 2.8 percent positive, 10.4 percent of positives treated	Zambia	453	DALYs averted	Larson and others 2014
		Improved treatment: 100 percent of positives treated	Zambia	48	DALYs averted	Larson and others 2014
		Improved screening and treatment: 100 percent tested and treated	Zambia	45	DALYs averted	Larson and others 2014
<i>Latin America and the Caribbean</i>						
	Laboratory RPR ^a screen and treat with penicillin	No screening	Peru	139	DALYs averted	Terris-Prestholt and others 2015
	Rapid point-of-care ICS ^a screen and treat with penicillin	No screening	Peru	54	DALYs averted	Terris-Prestholt and others 2015
	Dual screening with ICS and RPR and treat with penicillin	No screening	Peru	76	DALYs averted	Terris-Prestholt and others 2015
	ICS screen and treat with penicillin	RPR screen and treat	Peru	Cost-saving	DALYs averted	Terris-Prestholt and others 2015
	Rapid point-of-care ICS screen added to rapid HIV screen and treat	National HIV screening program with no syphilis screening	Haiti	21	DALYs averted	Schackman and others 2007

table continues next page

Table 6.6 Cost-Effectiveness Analyses since 2000 of Interventions for PMTCT of Syphilis (continued)

Region	Intervention	Comparator	Country or region	Cost in 2012 US\$	Unit of outcome	Study
<i>East Asia and Pacific</i>						
	Laboratory TRUST ^a and TTPA ^b test and treat with penicillin	No screening	China	369	DALYs averted	Hong and others 2010
	Laboratory RPR screen and treat with penicillin	No screening	China	200	DALYs averted	Owusu-Edusei and others 2014
	Rapid ICS screen added to rapid HIV screen and treat		China	160	DALYs averted	Owusu-Edusei and others 2014

Note: DALYs = disability-adjusted life years; PMTCT = prevention of mother-to-child transmission; HIV = human immunodeficiency virus; ICS = point-of-care immunochromatographic strip; RPR = lab-based rapid plasma reagin test; TTPA = *T. pallidum* particle agglutination lab-based treponemal test; TRUST = lab-based Toluidine Red Unheated Serum Test.

a. Nontreponemal tests that cannot distinguish between recent and previous infection.

b. Treponemal test.

At this point, Option B+ is the recommended strategy and is aligned with the WHO 2015 recommendations to treat all individuals with lifelong ART.

Cost-Effectiveness of PMTCT of Syphilis

Several models have demonstrated the cost-effectiveness of PMTCT in Sub-Saharan Africa, demonstrating that antenatal syphilis screening is cost-effective, even at low prevalence rates; it may even be cost saving in high-prevalence settings (Blandford and others 2007; Kahn and others 2014; Kuznik and others 2013; Rydzak and Goldie 2008). In high-risk areas, PMTCT of syphilis is among one of the most cost-effective interventions available. For example, a study of the cost-effectiveness of prenatal syphilis screening in Tanzania found that the cost was US\$1.44 per woman screened, US\$20 per woman treated, US\$16 per DALY averted, or US\$10.56 per DALY averted if stillbirths averted were included in the calculation (Terris-Prestholt and others 2003). Operational costs of testing may influence cost-effectiveness (Levin 2007). Cost-effectiveness analysis using country-level evaluation data has been critical for informing the choice of screening strategy and for highlighting the importance of achieving higher screening rates and full adherence to guidelines (Larson and others 2014; Terris-Prestholt and others 2015). Of 10 screening and treatment approaches, Terris-Prestholt and others (2015) found that treponemal-based rapid POC syphilis test-and-treat strategies were the most cost-effective, at US\$16–US\$17 per DALY averted in Zambia and Tanzania and US\$54 per DALY averted in Peru. In Peru, the incremental cost-effectiveness of switching from a lab-based test to a rapid POC test was cost saving.

Larson and others (2014) showed that the cost per DALY averted falls from US\$628 to US\$60 with full adherence to screening and treatment guidelines.

Cost-Effectiveness of Integrated PMTCT of Syphilis and HIV

Although information on the integration of PMTCT of syphilis and HIV is limited, two studies provide information on the potential benefit of adding syphilis diagnosis and treatment to existing PMTCT of HIV services. In Haiti, a high-prevalence country for both HIV and syphilis, adding an RPR test-and-treat model in rural areas cost US\$6.83 per DALY averted, while the estimate for an urban program was US\$9.95 per DALY averted (Schackman and others 2007). In a recent study in China—a low-prevalence country for both HIV and syphilis—syphilis screening or integrated HIV and syphilis screening were both more cost-effective than HIV screening alone (Owusu-Edusei and others 2014). This is a conservative finding, given the low prevalence of both HIV and syphilis. Based on the results from the Haiti and China studies, it is likely that in settings with higher prevalence rates for both HIV and syphilis, integrating HIV and syphilis services would be the most cost-effective option.

LESSONS FROM CASE STUDIES

PMTCT of HIV: Success in South Africa

As an upper-middle-income country, South Africa has been able to make enormous progress in implementing PMTCT. MTCT rates decreased from more than 30 percent to approximately 4 percent in a national programmatic evaluation of all six-week-old infants tested at 572 clinics throughout the country (Goga, Dinh, and

Jackson 2010). Maternal HIV seroprevalence had been 32 percent at the time of the study.¹¹ An astonishing 98 percent of pregnant women received testing, and almost 92 percent of HIV-positive women received ART. Gaps remained in CD4 testing and EID.

The study also illustrates that high maternal HIV seroprevalence contributes to the effectiveness of PMTCT programs. When large numbers of mothers in a given health center or community are HIV infected, large networks of peer counselors can lead to more effective peer counseling, dissemination of education and programs, and acceptability of HIV testing and ART.

PMTCT of Syphilis: Successful Rapid POC Models

A study conducted in six countries showed that the introduction of POC testing for syphilis in ANC was well accepted in a wide variety of settings and delivery platforms, from the Amazon rain forest in Brazil to the cities of China, and from primary health posts to teaching hospitals. After the introduction of POC testing, more than 90 percent of those who attended ANCs were screened for syphilis in all six countries, and more than 90 percent of women testing positive received treatment on the same day (Mabey and others 2012).

Table 6.7 Estimated Costs and Benefits of Screening for HIV and Syphilis in Theoretical Sub-Saharan African Population of 20,000 Pregnant Women Yearly

	Syphilis	HIV*
Seroprevalence	8%	15%
Test positive	1,600	3,000
Result		
Stillbirth averted ^a	200 cases	—
LBW averted ^a	184 cases	—
HIV averted*	—	246 cases
Cost of counselling and testing per woman	\$1.44	\$18.50
Cost of treatment	\$0.5–1.00	\$4.00 for single-dose nevirapine
Cost per case averted	Stillbirth, \$318; all adverse pregnancy outcomes, \$44–187 ^b	\$506
Cost per DALY saved	\$4.0–18.7 ^b	\$19.2

Source: Peeling and others 2004.

Note: DALY = disability-adjusted life year; HIV = human immunodeficiency virus; LBW = low birth weight; — = not available.

*Data from Sweat and others 2004; Marseille and others 2000.

a. Assuming 4 percent of women have rapid plasma reagin titer of 1:8 or more, of whom 25 percent will have stillbirth, and 33 percent will deliver live baby weighing below 2.5 kilograms, compared with 10 percent of seronegative women (Brocklehurst and French 1998; Grimpel and others 1991).

b. Range taken from studies summarized in UNAIDS 2013.

In Peru, 604 trained health providers implemented POC testing for syphilis using the two-for-one strategy: offering both syphilis and HIV testing with one finger prick. This approach resulted in testing and treatment on the first visit; before POC testing was introduced, a woman would typically not receive her syphilis result until her fifth clinic visit, 27 days later (Garcia and others 2013). In Uganda and Zambia, the integration of HIV and syphilis screening in ANCs, using two POC tests, was well accepted and led to increased coverage of syphilis screening (Strasser and others 2012).

PMTCT of HIV and Syphilis: An Integrated Model

Peeling and others (2004) described cases of infants born to HIV-infected mothers in Haiti who successfully escaped HIV transmission following ART and formula feeding but who acquired congenital syphilis. These cases highlight the lost opportunity to prevent syphilis among women attending ANCs; despite receiving interventions for PMTCT of HIV (testing and treatment), the women failed to access simple measures to detect and prevent congenital syphilis.

In the authors' assessment of a Sub-Saharan African population of pregnant women (table 6.7), the costs of testing and treatment per DALY averted were estimated to be lower for syphilis (US\$4–US\$18.70) than for HIV (US\$19.20). They noted that more efficient POC diagnostic testing for syphilis and development of oral regimens could further enhance congenital syphilis prevention efforts.

CONCLUSIONS

During the next few years, the concerted efforts to prevent infant HIV infection will continue and perhaps accelerate (IATT 2014). This intensive focus on HIV provides an opportune time to leverage program improvements to similarly target elimination of congenital syphilis and other adverse outcomes of maternal syphilis. Programs that monitor HIV outcomes can also track syphilis testing, treatment, and transmission and motivate prompt, efficient management of newly diagnosed cases in pregnancy, as shown in China, Haiti, Peru, Uganda, and Zambia. In short, improving PMTCT of syphilis within PMTCT of HIV is a feasible, low-cost strategy that would yield enormous benefits to mothers and infants. The incremental cost is small and the gains—prevention of stillbirth, preterm birth, and long-term disability of children delivered by women with maternal syphilis—are substantial.

NOTES

World Bank Income Classifications as of July 2014 are as follows, based on estimates of gross national income (GNI) per capita for 2013:

- Low-income countries (LICs) = US\$1,045 or less
 - Middle-income countries (MICs) are subdivided:
 - (a) lower-middle-income = US\$1,046–US\$4,125
 - (b) upper-middle-income (UMICs) = US\$4,126–US\$12,745
 - High-income countries (HICs) = US\$12,746 or more.
1. Increased risk of spontaneous abortion: odds ratio (OR) 4.05, 95 percent confidence interval (CI) 2.75–5.96; perinatal mortality: OR 1.79, 95 percent CI 1.1–2.81; infant mortality: OR 3.69, 95 percent CI 3.03–4.49; intrauterine growth retardation: OR 1.7, 95 percent CI 1.43–2.02; low birth weight: OR 2.09, 95 percent CI 1.86–2.35; preterm birth: OR 1.83, 95 percent CI 1.63–2.06.
 2. In Option A, women received zidovudine as early as 14 weeks into the pregnancy, a single dose of nevirapine during labor, and two weeks of tenofovir and emtricitabine after delivery.
 3. In Option B, women received one of two triple anti-HIV drug regimens as early as 14 weeks into the pregnancy—either (1) lamivudine, zidovudine, and ritonavir-boosted lopinavir (called the “lamivudine combination”); or (2) tenofovir, emtricitabine, and ritonavir-boosted lopinavir (called the “tenofovir combination”). Option B+ is lifelong ART.
 4. This study has not yet been published, but the press release noted increased adverse outcomes (NIH 2014).
 5. The ELISA test detects antibodies to HIV, usually from either a blood sample (drawn from a vein) or saliva. A positive result is often confirmed with a follow-up test such as the Western blot, which is less likely than the ELISA test to yield a false positive result. Results from most ELISA tests and confirmatory Western blot tests are usually available within 2 to 14 days.
 6. A rapid HIV test uses technology similar to the ELISA test (except blood is drawn from a finger prick instead of from a vein) but produces results in approximately 20 minutes. As with the ELISA test, however, a “preliminary positive” result must be confirmed with a second test, either a Western blot test or a second rapid test from another manufacturer.
 7. The studied triple-ART in PROMISE was either lamivudine, zidovudine, and ritonavir-boosted lopinavir, or tenofovir, emtricitabine, and ritonavir-boosted lopinavir. All infants received six weeks of nevirapine prophylaxis.
 8. Option B+ refers to lifelong ART initiated in pregnancy
 9. WHO, Global Health Observatory Data Repository, Antenatal care (ANC) attendees tested for syphilis at first ANC visit, Data by country (<http://apps.who.int/gho/data/node.main.A1358STI>).
 10. The cascade of care model refers to following interventions from diagnosis to receipt of interventions to continued retention in care.
 11. Maternal HIV seroprevalence was 32.0 percent (95 percent CI 30.7–33.3).

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