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Cuba Validated as the First Country to Eliminate Mother-to-Child Transmission of Human Immunodeficiency Virus and Congenital Syphilis: Lessons Learned from the Implementation of the Global Validation Methodology

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MOTHER-TO-CHILD TRANSMISSION OF HUMAN IMMUNODEFICIENCY VIRUS AND SYPHILIS

The World Health Organization (WHO) estimates that each year 150,000 [110,000–190,000] infants are born with human immunodeficiency virus (HIV)[1] and 350,000 perinatal deaths are caused by untreated maternal syphilis at the global level.[2] Results from HIV clinical trials demonstrated effectiveness of antiretroviral therapy for prevention of HIV transmission from mother to child.[3,4] However, the goal of elimination of mother-to-child transmission (EMTCT) of HIV remained largely aspirational until the adoption of the HIV elimination target by the Americas region in 2010[5] and the launch of the Global Plan for EMTCT of HIV in 2011.[6]

An effective intervention against congenital syphilis—early serologic detection of infection in women before or during pregnancy, and treatment of syphilis-infected women with parenteral penicillin—has been available for 70 years.[7] However, until recently, syphilis testing in antenatal care (ANC) remained limited in countries with constrained laboratory capacity. In 2007, WHO launched a strategy for the elimination of congenital syphilis as a public health problem.[8] Congenital syphilis elimination had already been established as a priority in the Americas a decade before the launch of the global strategy.[9]

The Member States of the Pan American Health Organization (PAHO) formally adopted the dual EMTCT target in 2010.[5] The Regional framework combined the target for EMTCT of

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HIV with the existing regional commitment for elimination of congenital syphilis; and defined dual elimination as (1) reduction of the rate of MTCT of HIV to 2% or less per year, along with reduction of the incidence of MTCT of HIV to 0.3 cases or less per 1000 live births, and (2) reduction of the incidence of congenital syphilis to 0.5 cases or less (including stillbirths) per 1000 live births. These targets were developed based on evidence regarding effectiveness of treatment and modeled predictions of the transmission levels that can be reached with optimal coverage of detection and treatment services.[3,4,9] To monitor progress, PAHO developed a regional monitoring framework[10] and prepared periodic progress reports.[11–14]

VALIDATION OF EMTCT OF HIV AND SYPHILIS

With several PAHO countries close to achieving the EMTCT targets, PAHO and WHO coordinated development of a methodology for validation of achievement of dual EMTCT. The goal was to develop a globally agreed methodology that was adaptable to different regional contexts. The validation methodology was developed through a global consultative process with global partners, including the United Nations Population Fund, the Joint United Nations Programme on HIV/acquired immune deficiency syndrome, the United Nations Children's Fund and US Centers for Disease Control and Prevention. The process included 2 global consultations, review of validation and verification approaches used for other disease elimination processes (eg, neonatal tetanus, measles), and pilot applications in several countries. The process resulted in an agreed set of minimum requirements, a proposed validation structure, and assessment tools designed to respond to the following questions: (1) Does the country have an adequate structure of programs and services that provide essential and quality maternal and child health, HIV, and syphilis services?(2) Are the essential services available and accessible for all, including vulnerable and marginalized populations? (3) Does the country have an adequate laboratory network to provide appropriate services needed to achieve and maintain the goals set for EMTCT of HIV and syphilis? (4) Are the results generated by the laboratory network adequately reliable, sensitive, specific, and quality-assured? (5) Were the EMTCT targets achieved in a manner consistent with basic human rights considerations and gender equality and community engagement principles? (6) Are the data generated by the country reliable to assess achievement of the EMTCT targets? (7) Has the country achieved the EMTCT targets?

Minimum requirements for validation include reaching impact and coverage targets, and program-level requirements, including achievement of the EMTCT targets in at least one of the lowest-performing administrative units in the country (box 1). The validation structure consists of (a) a global secretariat at the WHO that coordinates the global validation process, provides official notification of validation, and monitors maintenance of targets; (b) a global validation advisory committee, a group of technical experts that review regional reports to ensure consistency and compliance with the minimum validation requirements, and advises the WHO regarding validation of candidate countries;(c) a regional validation mechanism for each of the 6 WHO regions, with responsibilities to coordinate country assessments, and recommend candidate countries for validation—for the Americas a regional validation committee was established, and(d) a national validation committee established by the

national health authority of the candidate country, that coordinates development of a country report, and serves as counterpart for the regional and global validation mechanisms.[15]

Countries applying for validation must submit a report making a case for achievement of the impact and coverage requirements (box 1). In addition, the report should describe the legal and policy framework, and the programs and services required to achieve and sustain the impact and coverage targets in a manner consistent with basic human rights considerations. A formal validation mission brings technical experts to the country to verify compliance with the validation requirements through field visits to service delivery sites and laboratories, review of data, and interviews with national and sub-national programs, civil society, and persons living with HIV.

CUBA VALIDATED FOR EMTCT

Cuba initiated its validation process in 2013 through submission of a formal request and a country report to the PAHO Director. The country report described its primary care-based health system that provided a full range of reproductive and maternal and child health services with free access for all; a large number of well-trained health staff; an extensive network of laboratories providing HIVand syphilis diagnostic services; routine data monitoring at each level of the health system; high coverage of antenatal, HIV and syphilis testing, and HIV and syphilis treatment services for pregnant women consistently greater than 95% at national level and in all health regions (Table 1). Considering that the reported data indicated that all the fifteen provinces had achieved over 95% of the coverage indicators, a stepwise approach was applied to select the lowest-performing provinces for field visits, defined as the provinces with the lowest values in one or more coverage indicators. The first step resulted in selection of 9 provinces, which were clustered into urban, semiurban, and rural strata. From each stratum, the province with the highest registered number of pregnant women and/or infants born with HIV, pregnant women with syphilis, or cases of congenital syphilis over the past three years was selected, resulting in selection of 3 provinces: Santiago de Cuba, Villa Clara, and Havana. The 3 provinces represent approximately 14% of Cuba’s land surface, 35% of the population, and 34% of the number of live births. In each of the three provinces, priority municipalities were selected for site visits, based on HIV and syphilis prevalence in the general and ANC populations, relative poverty or other relevant sociodemographic characteristics, and cases of congenital syphilis or vertical HIV transmission in the previous 3 years. As there are no privately provided health care services in Cuba, all selected sites were public facilities.

The validation assessment, conducted during a 1-week onsite visit by a team of experts, concluded that Cuba had sufficient strategies in place to provide HIV and syphilis prevention, diagnosis and treatment services in a sustainable manner and with limited dependence on external funds. Reviews of antenatal logs and clinical records supported that essentially all pregnant women accessed ANC, usually early in pregnancy, received HIV and syphilis testing in the first trimester of pregnancy, and treatment for the pregnant woman and partner in case of positive test results. Maternity record reviews supported that close to 100% of women delivered in maternity hospitals, where HIV and syphilis testing were repeated.

The validation team found that Cuba had an adequate laboratory network for HIV and syphilis diagnostic services. Testing sites were located in policlinics, hospitals and municipal and provincial health units, easily accessible for pregnant women. The delegation observed that national norms and standards existed, that standard operational protocols for HIV and syphilis were part of the national algorithm, and that testing was conducted in compliance with the normative framework. HIV and syphilis reference laboratories provided quality control for the networks through proficiency panels and re-testing of samples.

The team members observed no criminalization of vertical transmission of HIVand syphilis, no mandatory or coerced testing and treatment, and no forced or coerced sterilization. They noted the observance of informed consent, confidentiality in conducting testing and maintaining records. Their review of laws and policies found equality and non-discrimination in legislation, policies and practices. Based on these findings, the validation team concluded that the Cuba dual EMTCT targets were achieved in a manner consistent with basic human rights considerations. Ample community engagement, including from women living with HIV, was also noted as well as the inclusion of strategies to address gender-based violence in the national program.

The delegation found Cuba had a surveillance system guided by a normative framework and standardized tools. Strong paper-based registration systems existed, ranging from records at the family health clinic to detailed policlinic and maternity hospital records, and these helped ensure that the population was systematically covered. Spot-checking of records, registers, and patient cards across the different levels of the health care system, indicated high levels of completeness, consistently over 90% and in most cases 100%. Audit systems were in place for documentation and review of all cases of vertical transmission. A challenge was noted with the calculation of HIV testing coverage at the national level, because the current system records the number of tests and not the number of women. However, this did not preclude validation, because the coverage data was available on the level of the policlinics, and confirmed in all regions visited that well over 95% of pregnant women were tested at least once and typically more than once during pregnancy.

Upon review and triangulation of the reported coverage and impact data, the team noted that some indicators were calculated with the number of live births as denominator, and some with the number of pregnant women as denominator. The validation team recalculated the indicators using pregnant women as the denominator, and concluded that the results still complied with the validation requirements. From 2012 to 2014, the congenital syphilis rate was 0.0, 0.02, and 0.05, respectively, the percentage of HIV seropositive women whose infants were HIV-positive was1.83%, 1.75%, and 1.60% respectively, and the HIV MTCT rate was 0.016, 0.016, and 0.008 per 1000, respectively.

Based on the outcome of the assessment, the validation team concluded that Cuba had complied with the global validation requirements and qualified to be recommended for validation. The results of the validation assessment were presented to the America’s regional validation committee, which carefully reviewed the data and agreed with the delegates’ findings. These results were submitted to WHO and assessed by the Global Validation Advisory Committee, which examined the data and ultimately endorsed the regional

findings. On this basis, on June 30, 2015, WHO formally declared Cuba as the first country in the world to have achieved EMTCT of HIV and syphilis.[16,17]

The Cuba validation assessment illustrated the feasibility of EMTCT of HIV and syphilis, even for countries with limited resources. Factors that can help countries advance toward EMTCT of HIV and syphilis include a high coverage of ANC services; routine, early HIV and syphilis screening in pregnancy; prompt follow-up of seropositive pregnant women and exposed infants, and a well-organized monitoring and surveillance system that captures national as well as subnational data.

The validation team found that the validation methodology was suitable to characterize Cuba's national programs and verify compliance with global EMTCT targets. Cuba's validation for EMTCT of HIV and syphilis generated an enormous interest and response from within and outside of the region of the Americas, illustrating the benefits of validation as a public health measure beyond the scope of the candidate country to mobilize political will and intensify efforts for achievement of EMTCT of HIV and syphilis in other countries.

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Box 1:

Minimum Validation Requirements[1] for Elimination of Mother-to-Child Transmission of HIV and Syphilis

- National-level evidence of achievement of the following EMTCT Impact targets for at least one year:
  - ≤0.3 new paediatric infections per 1000 live births and a transmission rate of <2% in nonbreastfeeding populations
  - ≤0.5 cases of congenital syphilis[2] (including stillbirths) per 1000 live births
- National-level evidence of achievement of EMTCT coverage targets for at least 2 years:
  - At least 95% of pregnant women attend at least one antenatal care visit
  - At least 95% of pregnant women are tested for HIV
  - At least 95% of pregnant women are tested for syphilis
  - At least 95% of syphilis seropositive pregnant women receive adequate treatment[3]
  - At least 95% of HIV-infected women receive appropriate antiretroviral treatment coverage[4]
- Evidence that the impact and coverage targets have been achieved in at least one of the lowest-performing sub-national administrative units
- Existence of an adequate "validation standard"[5] national monitoring and surveillance system that can capture service delivery and outcome data and detect the majority of cases of MTCT of HIV and/or syphilis, from both the public and private health sectors;
- Validation criteria must have been met in a manner consistent with basic human rights considerations[6]

[1] PAHO requirements for EMTCT in the Americas Region differ from the WHO global EMTCT requirements in the following areas: i) PAHO requires countries to apply for elimination of both EMTCT of HIV AND syphilis, reflecting dual elimination of both perinatal conditions; whereas WHO allows countries to apply for elimination of only one perinatal infection; ii) PAHO requires at least two years of impact data while WHO requires at least one year of data; iii) the Americas regional target for perinatal HIV transmission is 2% without stipulating a higher target for breast feeding women, while WHO requirements include the target of <5% in breastfeeding populations; and iv) the regional target for perinatal HIV is 0.3 cases per 1000 live births; whereas the WHO global target is 0.5 cases per 1000 live births; V) The regional coverage target for antiretroviral treatment coverage is 95%, and the WHO global target is 90%.

[2] Clinical congenital syphilis definitions vary; however, for global elimination countries are encouraged to use a surveillance case definition that captures all adverse outcomes associated with untreated maternal syphilis. An example of a surveillance case definition for congenital syphilis is: “live born or still born infant born to a syphilis-seropositive mother who did not receive adequate treatment at least 30 days prior to delivery OR an infant with signs or symptoms suggestive of syphilis without documentation of negative maternal syphilis testing.”

[3] At least 2.4 *mu* intramuscular benzathine penicillin G (BPG) given at least 30 days prior to delivery

[4] A single dose of nevirapine (NVP) is not considered to be adequate treatment

[5] A high-quality and sensitive system that captures delivery and outcome data from the public and private health sector, enables accurate assessment of intervention coverage and timely detection and reporting of the vast majority of cases of MTCT of HIV and syphilis, and has minimized sources of systematic bias.

[6] Absence of criminalization of vertical transmission, mandatory or coerced testing and treatment, or forced or coerced sterilization, and compliance with the principles of informed consent, confidentiality, and privacy.

TABLE 1.

EMTCT Indicators Reported by Cuba 2012–2014 and Validated in 2015

Impact Indicators	2012	2013	2014
Annual rate of reported cases of congenital syphilis (including stillbirths) per 1000 live births	0	0.02 (2 per 100,000)	0.05 (5 per 100,000)
Percentage of HIV seropositive women whose infants were HIV positive	1.83%	1.75%	1.60%
Annual rate of reported cases of mother-to-child transmission of HIV per 1,000 live births	0.016 (1.6 per 100,000)	0.016 (1.6 per 100,000)	0.008 (0.8 per 100,000)
Coverage indicators	2012	2013	2014
Percentage of pregnant women attended by skilled health personnel during the prenatal period	97.0% (denominator: 125674)	97.0% (denominator: 125880)	97.0% (denominator: 87484)
Percentage of pregnant women who were tested for HIV and received their results during pregnancy	Unable to calculate national coverage, but the coverage rates reported at each ofthe validation sites was consistently above 95%		
Percentage of pregnant women who were tested for syphilis during pregnancy	99.5% (denominator: 125674)	99.9% (denominator: 125880)	99.3% (denominator: 125880)
Percentage of HIV-positive pregnant women who received antiretroviral drugs to reduce the risk of MTCT	95.4% (denominator: 144)	98.2% (denominator: 146)	98.9% (denominator: 161)
Percentage of syphilis-seropositive pregnant women who are appropriately treated *	100% (denominator: 129)	97.8% (denominator: 135)	97.6% (denominator: 144)

* Received at least 2.4 μ intramuscular penicillin in a single dose more than 30 days before delivery.