LANDSCAPE OF INNOVATIVE TOOLS AND DELIVERY STRATEGIES

FOR ELIMINATING VERTICAL TRANSMISSION OF HIV, SYPHILIS, HEPATITIS B, AND CHAGAS IN ENDEMIC AREAS

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ABBREVIATIONS AND ACRONYMS

AFRO	WHO Regional Office for Africa
AIDS	acquired immune deficiency syndrome
ANC	antenatal care
API	active pharmaceutical ingredient
ART	antiretroviral therapy
AVT	antiviral therapy
AZT	zidovudine
BPG	benzathine benzylpenicillin/benzathine penicillin G
CDC	U.S. Centers for Disease Control and Prevention
CE	Conformitè Europëenne
CHB	chronic hepatitis B
CI	confidence interval
CLIA	chemiluminescence immunoassay
CTC	controlled temperature chain
DBS	dried blood spot
DNA	deoxyribonucleic acid
EIA	enzyme immunoassay
ELISA	enzyme-linked immunosorbent assay
EMTCT	elimination of mother-to-child transmission
ERPD	Expert Review Panel for Diagnostic Products
FDA	U.S. Food and Drug Administration
FPP	finished pharmaceutical product
FTA-ABS	fluorescent treponemal antibody absorbed
HCC	hepatocellular carcinoma
HBeAg	hepatitis B e antigen
HBIG	hepatitis B immunoglobulin
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HepB-BD	hepatitis B birth dose vaccine
HIV	human immunodeficiency virus
IFN	interferon
IM	intramuscular
IV	intravenous
LMICs	low- and middle-income countries
MTCT	mother-to-child transmission
MU	million units
NAAT	nucleic acid amplification test
NAT	nucleic acid testing
NGO	nongovernmental organization
NRTI	nucleos(t)ide reverse transcriptase inhibitor
OOC	out of cold chain
PAHO	Pan American Health Organization (WHO)
PCR	polymerase chain reaction
PEPFAR	President's Emergency Plan for AIDS Relief

PMTCT	prevention of mother-to-child transmission
PQ	(WHO) prequalification program
RDT	rapid diagnostic test
RHD	rheumatic heart disease
RLS	resource-limited setting
RPR	rapid plasma regain
SRA	stringent regulatory authority
SSA	sub-Saharan Africa
STI	sexually transmitted infection
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TPHA	Treponema pallidum haemagglutination assay
TPP	Target product profile
TPPA	Treponema pallidum particle agglutination assay
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNICEF	United Nations Children's Fund
VDRL	Venereal Diseases Research Laboratory
WHO	World Health Organization
WPRO	WHO Regional Office for the Western Pacific

EXECUTIVE SUMMARY

Human immunodeficiency virus (HIV), syphilis, and hepatitis B virus (HBV) cause significant morbidity and mortality in low- and middle-income countries (LMICs), and vertical transmission, also referred to as mother-to-child transmission (MTCT), contributes substantially to incident infections for all three diseases. Because of this, the World Health Organization (WHO) first adopted three 5-year interlinked global strategies in 2016 to provide guidance towards their elimination as public health threats by 2030. Few of the interim goals were reached, so an updated and integrated strategy was released in 2022 with expanded milestones and targets. These efforts are part of the broader 'Triple Elimination' agenda, which seeks to encourage countries to pursue an integrated and coordinated approach to elimination of MTCT (EMTCT) of all three diseases. This has been expanded to include congenital Chagas disease ('EMTCT Plus') in endemic areas.

To better understand the current challenges for achievement of EMTCT Plus, Unitaid sought to assess availability, adaptability, accessibility, and affordability of key commodities and interventions related to EMTCT of HIV, syphilis, HBV, and Chagas disease. This landscape outlines key EMTCT tools and interventions in all four diseases with a focus on innovations in prevention, diagnosis, treatment, and service delivery that can contribute to EMTCT goals.

This report begins by providing an overview of the epidemiology, global targets, and current EMTCT guidelines for the four diseases, with a particular focus on syphilis and HBV to complement the recently published Chagas disease Unitaid landscape and Unitaid's extensive work in HIV. Given the large number of antenatal care (ANC) clinics, the relatively short window of time for initiation of interventions during pregnancy, and the constraints posed by centralized laboratory testing, this report focuses primarily on point-of-care (POC) and near-POC modalities.

Multiple tools and interventions are currently available for EMTCT, but there are key gaps in their use and implementation. For EMTCT of HIV, challenges remain in detection of incident infection during pregnancy and breastfeeding, viral suppression, and postpartum retention of mothers on antiretroviral therapy (ART). Access to and uptake of virological testing for HIV-exposed infants also remains a major challenge despite recent expansion of POC and near-POC assays.

Key barriers to congenital syphilis elimination include a lack of simple and easily interpreted tests, intermittent shortages of benzathine penicillin G (BPG), and limited funding and political will. Dual HIV/syphilis rapid diagnostic tests (RDTs) have shown great potential to improve antenatal screening coverage; however, their inability to distinguish between active and past syphilis infection has raised concerns. Recent shortages of BPG have largely resolved, but market and quality issues persist.

HBV EMTCT programs are nascent, and funding is severely limited. The cornerstone of HBV EMTCT efforts is provision of the monovalent vaccine within 24 hours of birth (timely 'birth dose' or HepB-BD). Coverage of HepB-BD ranges widely but is <10% in Africa and the high proportion of home-based deliveries is a major impediment to provision. Antiviral prophylaxis during the third trimester for eligible pregnant women with chronic HBV is also

recommended; recently released guidance outlines a multi-test algorithm that begins with hepatitis B surface antigen (HBsAg) during the first antenatal visit. Although affordable, quality-assured HBsAg RDTs are available, the price for the required HBV viral load follow-up testing is high and access is severely limited. Hepatitis B e antigen (HBeAg) RDTs, the alternative option recommended by WHO when HBV viral load is unavailable, have a wide range of performance, none have received regulatory approval, and more information is needed on expression of HBeAg and correlation with HBV viral load among the different HBV genotypes, especially those found in Africa.

Finally, although several diagnostic methods for Chagas disease detection are available, the multi-test screening algorithms, lack of global consensus on best practices for Chagas diagnostics, and limited funding for screening programs has hampered uptake. Low-cost Chagas treatment options are available, but the complicated dosing and prolonged course decrease treatment completion rates, and treatment is much less effective in cases of chronic Chagas disease.

This report also highlights key diagnostic technologies related to EMTCT that are recently available or in the pipeline with information on release dates, regulatory approval, and product specifications where available. The technology landscape demonstrates that the pipeline of emerging innovations for EMTCT is relatively sparse.

In addition, the report identifies a number of service delivery innovations with potential to facilitate more rapid, consistent, and equitable access to tools and interventions for EMTCT. These include integrated approaches such as bundling delivery of essential diagnostics in ANC, targeted behavioral interventions to improve provider knowledge and adherence to EMTCT guidelines, and new strategies to improve access to interventions like the HepB-BD through community delivery.

Lastly, the report outlines key opportunities for advancing new, emerging, or underutilized products and interventions, which can help expand access and overcome the public health and market challenges described. These specific areas are highly actionable and critical to accelerating progress towards global EMTCT goals. While there are some product development gaps, a key takeaway of this report is that much progress is possible with more widespread and strategic use of existing tools. For HIV, efforts to improve services in the postpartum period through retention of mother-infant pairs and repeat HIV testing in high-burden areas will be critical. Expanding access to early infant diagnosis, ideally with a device-free POC test, is also essential for decreasing pediatric HIV morbidity and mortality. Similarly for syphilis, effective tools for elimination of congenital syphilis are in place, especially with use of the dual HIV/syphilis test. However, stabilization of the BPG markets and ensuring widespread availability of quality-assured products are vital for treatment access; efforts to bolster and support markets for BPG could be beneficial for syphilis in addition to other major diseases such as rheumatic heart disease.

Although affordable HBsAg RDTs are available, the limited access and high cost of the follow-up tests required for determination of antiviral prophylaxis (i.e., HBV viral load or HBeAg) pose significant roadblocks to implementation. Support for development of low-cost POC HBV viral load tests could enhance EMTCT efforts while also benefitting broader HBV monitoring and treatment initiatives. Further research on how HBeAg expression and correlation with HBV viral load varies among different HBV genotypes is needed, especially in Africa. EMTCT of hepatitis B will also depend on improvement of HepB-BD coverage and promoting expansion of vaccine delivery systems for community-based administration could increase feasibility.

Determining the optimal mix of EMTCT technologies and integrated service delivery modalities will be context-specific, but availability of POC interventions will be essential for high coverage of services in resource-limited settings for all four diseases. There are several promising opportunities to promote a patient-centered holistic approach to EMTCT of HIV, syphilis, HBV, and Chagas. The opportunities are not specific to Unitaid's mandate, but rather represent a range of market-based interventions that are high priority and warrant dedicated attention from different global health actors and stakeholders.

1. INTRODUCTION

In 2016, due to the significant morbidity and mortality caused by HIV, syphilis, and hepatitis B virus (HBV) in low- and middle-income countries (LMICs), the World Health Organization (WHO) adopted three 5-year interlinked global strategies intended to provide guidance towards their elimination as public health threats by 2030. Because vertical transmission, often referred to as mother-to-child transmission (MTCT), contributes substantially to incident infections for all three diseases, the 2016 strategy outlined ambitious targets specifically related to elimination of MTCT (EMTCT). These included zero new HIV infections among children (0–14 years old) by 2020; a 30% reduction in new cases of chronic HBV infection by 2020; and <50 cases of congenital syphilis per 100,000 live births in 80% of countries.[1] None of these EMTCT targets were achieved, and most of the general HIV, syphilis, and hepatitis B global targets were also missed.[2] In 2022, an updated and unified Global Health Sector Strategy on HIV, viral hepatitis and sexually transmitted infections (STIs) was released that reflects new data and significant contextual shifts since the original document's inception.[3] The strategy calls for an integrated person-centered approach to program planning and service delivery and emphasizes the need for decentralized and community-based service delivery to promote universal health coverage. The strategies also include additional indicators and policy milestones related to EMTCT of the three diseases.

These efforts are part of the broader 'Triple Elimination' agenda, which seeks to encourage countries to pursue an integrated and coordinated approach to EMTCT of all three diseases. In endemic areas, primarily the Americas, this has been expanded to include congenital Chagas disease ('EMTCT Plus') with an impact target of ≥90% of children cured of Chagas infection with post-treatment negative serology.[4] The WHO Regional Office for the Western Pacific (WPRO) and the Pan American Health Organization (PAHO) have developed detailed regional implementation and monitoring plans to launch the initiatives.[5]

The Triple Elimination agenda includes a formal process for validation of elimination using pre-specified criteria for each disease. Global guidance for EMTCT of HIV and syphilis has been in place since 2014; since then, EMTCT of HIV and/or syphilis has been validated in 15 countries and territories.*[6] In addition, Botswana achieved silver tier status on the Path to Elimination, a set of criteria which recognizes progress in countries with a high burden of HIV and/or syphilis.[7] Interim guidance for validation of EMTCT for HBV was released in July 2021, [8,9] and consolidated guidance was released in November 2021 for all 3 diseases. [10]

It is becoming increasingly recognized that further coordination will be required to achieve the momentum needed to reach EMTCT targets and that efforts should leverage under-utilized, new, and emerging innovations in a holistic, integrated Triple Elimination approach. The EMTCT arena encompasses numerous technologies and interventions; some are new innovations that may require market interventions

* As of November 2021, the following 15 countries achieved validation: Cuba, Thailand, Belarus, Armenia (HIV only), Republic of Moldova (syphilis only), Anguilla, Montserrat, Cayman Islands, Bermuda, Antigua and Barbuda, St Christopher and Nevis, Malaysia, Maldives, Sri Lanka and Dominica.

to launch, while others have been available for many years, but uptake has been hampered by market bottlenecks, low demand, and other barriers. To better understand these challenges and help identify potential opportunities, Unitaid sought to assess availability, accessibility, and affordability of key commodities and interventions related to EMTCT of HIV, syphilis, HBV, and Chagas disease, with a particular focus on point-of- care (POC) and near-POC modalities. This report provides an overview of innovations in prevention, diagnosis, treatment, and service delivery that can contribute to EMTCT Plus goals.

2. METHODOLOGY AND SCOPE

This report was compiled between July and November 2021 using the following sources: previous work conducted by Unitaid, peer-reviewed published literature, conference abstracts, institutional and corporate websites, product instructions for use, and semi-structured telephone interviews with subject matter experts on maternal and child health (MCH), HIV, syphilis, HBV, and Chagas disease from public health organizations, academia, and industry. This report aims to provide a broad overview of key EMTCT interventions for all four diseases. However, given Unitaid's extensive work and published landscapes on HIV[11, 12, 13, 14] and the recently released Chagas Technology and Market Landscape[15], increased focus is placed on syphilis and HBV as well as coordinated approaches to achieving Triple Elimination. A limitation of this report is the risk that some products or developments have been omitted due to lack of publicly available information and manufacturer nondisclosure of key product specifications or pricing. This report also provides suggestions for products and interventions that may accelerate the Triple Elimination agenda; however, these are not exhaustive and are intended to inform further discourse.

3. BACKGROUND

HIV

There are an estimated 37.7 million people living with HIV (PLHIV) globally, most of whom live in sub-Saharan Africa. Significant and sustained investments of financial and human resources by the global community have resulted in substantial reductions in HIV-related morbidity and mortality and the number of new infections. However, HIV continues to be a major public health problem; despite widespread scale-up of antiretroviral therapy (ART), 680,000 people died from HIV-related causes in 2020. Prevention efforts have also fallen short of global goals; 1.5 million people acquired HIV in 2020 alone, far above the target of <500,000 for that year.[16]

Prevention of MTCT of HIV has been a noteworthy achievement; new HIV infections among children declined by more than half (54%) from 2010 to 2020 through routine HIV testing of pregnant women and provision of lifelong ART to HIV-infected mothers. However, progress has varied widely by region, and despite significant international and domestic funding support for PMTCT programs and a target of zero new HIV infections among children by 2020, 150,000 children worldwide acquired HIV in 2020; 74,000 of these infections occurred in East and Southern Africa. To address this gap, the 2021 Political Declaration on AIDS set the following targets for 2025: 95% of pregnant and breastfeeding women have access to combination HIV prevention, antenatal testing and re-testing; 95% of women living with HIV achieve and sustain viral suppression before delivery and during breastfeeding; and 95% of HIV-exposed children are tested within two months and, if HIV-positive, are provided with optimized treatment.[2]

SYPHILIS

According to WHO estimates, there were approximately 7.1 million new cases of Treponema pallidum infection (syphilis) in 2020, with the African Region and the Region of the Americas having the highest incidence in adults.[2] MTCT of syphilis (congenital syphilis) is a major cause of morbidity and mortality. In 2016, an estimated 1 million pregnant women worldwide had active syphilis infection, resulting in approximately 355,000 adverse pregnancy outcomes, including 143,000 early fetal deaths/stillbirths, 63,000 neonatal deaths, 44,000 preterm/low-birth-weight babies and 109,000 infants with clinical congenital syphilis. Almost 60% of syphilis-related adverse birth outcomes worldwide occur in Africa. Among the global adverse birth outcomes related to maternal syphilis infection, 57% occurred in pregnant women who attended antenatal care (ANC) but were not screened for syphilis and 16% occurred in mothers who were screened but not treated. The remainder occurred in women who did not attend ANC (21%) and in those who reported being screened and treated (6%).[17]

The majority of untreated syphilis infections in pregnancy result in severe adverse pregnancy outcomes. The most common manifestation of congenital syphilis is fetal loss in the second or third trimester or premature labor.[18] However, congenital syphilis can be averted with one dose of long acting benzathine penicillin G (BPG); the risk of adverse

birth outcomes related to maternal syphilis infection is minimal if the mother receives appropriate treatment, ideally before the second trimester.[19] For this reason, EMTCT of syphilis is feasible and achievable with detection and treatment of maternal infection during pregnancy. A key target for 2030 is elimination of congenital syphilis (defined as <50 cases of congenital syphilis per 100,000 live births in 80% of countries) with a goal that in 70% of countries ≥95% of pregnant women are screened for syphilis and ≥95% of syphilis-seropositive pregnant women receive effective treatment.[3] Although >90% of countries have policies for antenatal screening and treatment of syphilis, the high rate of congenital syphilis (estimated at 473 cases per 100,000 live births for 2016),[15] demonstrates that large gaps in screening and treatment remain.

There are also important synergies between HIV and syphilis infection. Children of women co-infected with both HIV and syphilis have a significantly higher risk of intrauterine HIV acquisition than those born to mothers who are infected only with HIV.[20] In addition, stillbirth and low birth weight are more common in babies born to mothers with HIV and syphilis co-infection.[21]

HEPATITIS B

The WHO estimates that approximately 296 million people worldwide have chronic hepatitis B virus (HBV) infection with 1.5 million new chronic HBV cases annually. The WHO regions with the most infected individuals are WPRO (116 million, prevalence estimate 5.9%) and AFRO (82 million, prevalence estimate 7.5%); together these regions account for 68% of the global burden.[2]

Although the risk is variable, individuals with chronic HBV infection have a 15–40% risk of developing cirrhosis, liver failure, or primary liver cancer (hepatocellular carcinoma (HCC)), and a 15–25% risk of dying from HBV-related liver diseases. Chronic HBV infections cause approximately 820,000 HBV-related deaths annually, comprising 49% of all hepatitis-related deaths worldwide; 40% of HBV-related deaths occur due to HCC.[22]

The WHO global hepatitis strategy aims to reduce new chronic HBV infections by 90% (as evidenced by a hepatitis B surface antigen (HBsAg) prevalence in children <5 years of <0.1% by 2030) and to achieve a 65% reduction in HBV-related deaths through improved diagnosis and treatment.[3] Although many countries achieved the 2020 HBsAg prevalence goals of <1%, the WHO AFRO and WPRO regions are notable outliers; 32% and 67% of countries have a <1% HBsAg prevalence in children <5 years of age in WHO AFRO and WPRO, respectively.[2]

In endemic areas, HBV is transmitted primarily through exposure to infected blood via vertical transmission (i.e., from mother to child) and horizontal transmission (e.g., household, intra-familial and child-to-child). The cornerstone of hepatitis B prevention is vaccination, with the WHO recommending that all infants receive the Hep-BD within 24 hours of birth, followed by 2 or 3 doses of the hepatitis B vaccine to complete the series. Vertical transmission of HBV during delivery is the most common timepoint for infection. In utero transmission accounts for <2% of perinatal infections. The risk of vertical transmission depends on maternal HBV viral load and the presence of hepatitis B e antigen (HBeAg). In women with a high HBV viral load (defined as >200,000 IU/ml), 70-90% of infants become infected in contrast to <30% in women with lower HBV viral loads. Breastfeeding does not pose any additional risks of HBV infection in infants of HBV carrier mothers.

In sub-Saharan Africa, horizontal transmission in children between the ages of 6 months and 5 years is common because of close interaction with infected household contacts and among children. The childhood HBV vaccine series (typically administered at 6, 10, and 14 weeks of age in sub-Saharan Africa) is highly effective at preventing acquisition of infection during childhood, and although gaps exist, immunization programs have had significant global success, with 85% global coverage of the 3-dose infant HBV immunization series (ranging from 73% in AFRO to 95% in WPRO).[2]

The synergy between HIV and HBV infection is also important, as an estimated 2.6 million HIV–HBV-co-infected individuals live in sub-Saharan Africa. Pregnant women with HIV–HBV co-infection are twice as likely to be HBeAg positive, three times more likely to have detectable HBV DNA, and have higher HBV viral loads, all of which greatly increase the risk of perinatal HBV transmission. In addition, HIV-HBV co-infection is associated with a more aggressive course of HBV infection.[23]

Because perinatal transmission occurs prior to the first childhood HBV vaccine at around 6 weeks of age, childhood vaccination alone cannot achieve elimination goals, and perinatal transmission is a growing proportion of all new chronic HBV infections. The proportion of new HBV infections caused by vertical transmission was 16% in 1990, 21% in 2010, and is expected to be 50% in 2030.[24] Perinatally acquired HBV infections contribute disproportionately to chronic infections because the risk of developing chronic HBV infection is inversely related to age at infection. Chronic HBV infection develops in 90% of young infants (up to 6 months of age), but the risk of chronicity decreases to approximately 20% by the age of 5 years. Less than 5% of adults newly infected with HBV develop chronic active infection. HBV-exposed newborns have increased risk of active HBV infection and HCC and a 25% risk of premature death from HBV-related liver disease by the second or third decade of life. Given these characteristics, stemming neonatal and early childhood infection is fundamental to preventing chronic HBV infections and subsequent complications of chronic liver disease and HCC.

CHAGAS DISEASE - PART OF EMTCT PLUS IN ENDEMIC AREAS

Chagas disease is a vector-borne illness that affects 6 to 7 million people, most of whom live in 21 Latin American countries where Chagas disease is endemic.

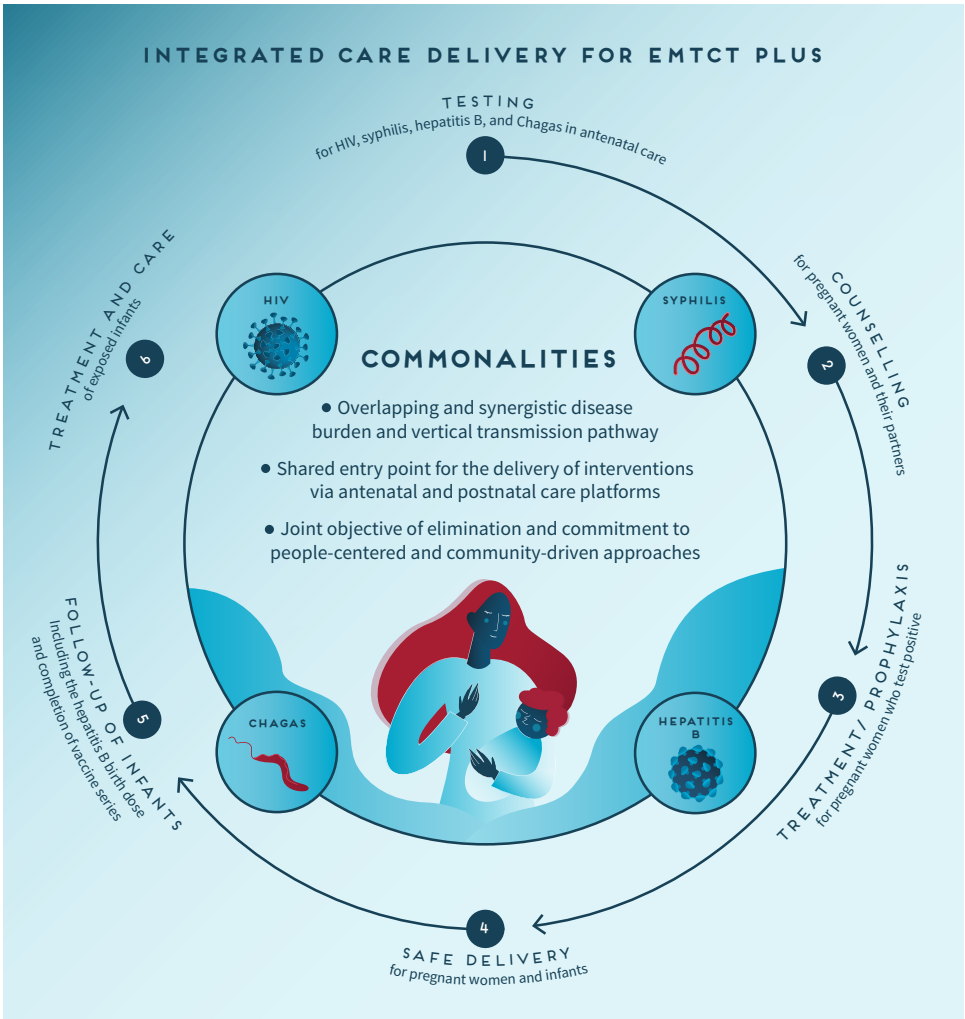
The main route of transmission to humans occurs through triatomine insects which carry *Trypanosoma cruzi (T. cruzi)*. Other routes of transmission include oral (food-borne) transmission, transfusion of blood/blood products, vertical transmission during pregnancy or childbirth, and organ transplantation and laboratory accidents. Housing conditions can also contribute to the spread of Chagas disease, where triatomine insects can be found living in dwellings. The geographic distribution of Chagas disease has recently shifted from primarily rural areas to also include peri-urban and urban centers.[25]

Vertical transmission of Chagas disease is estimated to cause about 9,000 new cases annually in newborns in Latin America.[26] The prevalence of Chagas disease in pregnant women varies widely across geographic areas of endemicity, ranging from 0.3% to 40%, and approximately 5-10% of pregnant women with *T. cruzi* infection will transmit the infection to their newborns without treatment. Because of successful efforts to curb other routes of transmission, the proportion of incident infections related to vertical

transmission has increased, accounting for approximately one-third of new infections in 2010.[27] This shift in epidemiology has led to a renewed focus on prevention of congenital Chagas disease as a key step towards elimination.

T. cruzi infection is curable if treatment is initiated soon after infection, but treatment efficacy declines as individuals progress to the chronic phase. For this reason, early detection is critical in pregnant women to maximize treatment efficacy for infected infants. However, since infected individuals may be asymptomatic or have non-specific symptoms, systematic screening, especially family screening, is required to ensure case-finding. The PAHO targets related to EMTCT of Chagas are: 1) Increase testing of pregnant women to ≥90%, 2) Increase testing of neonates with seropositive mothers to ≥90%, and 3) Increase treatment of seropositive mothers to ≥90%.[4] Because Chagas disease has historically been overlooked, it is hoped that incorporating it into the elimination framework for HIV, syphilis, and HBV can accelerate efforts and promote synergies towards a comprehensive package of services for pregnant women and their newborns in endemic areas.

FIGURE 1. Commonalities across diseases and interventions targeted under EMTCT Plus



HIV

PMTCT of HIV depends on prevention and early detection of HIV infection in women and girls, prompt initiation of ART, and adherence to ART throughout pregnancy and breastfeeding to ensure undetectable HIV viral load. Given the rapid progression of disease in neonates and infants with HIV infection, close follow-up and routine testing of HIV-exposed infants to allow prompt initiation of ART is also critical to decrease HIV-related mortality.

Key recommendations for HIV PMTCT are shown in Table 1.[28]

TABLE 1. WHO recommendations for prevention of perinatal transmission of HIV (2021)

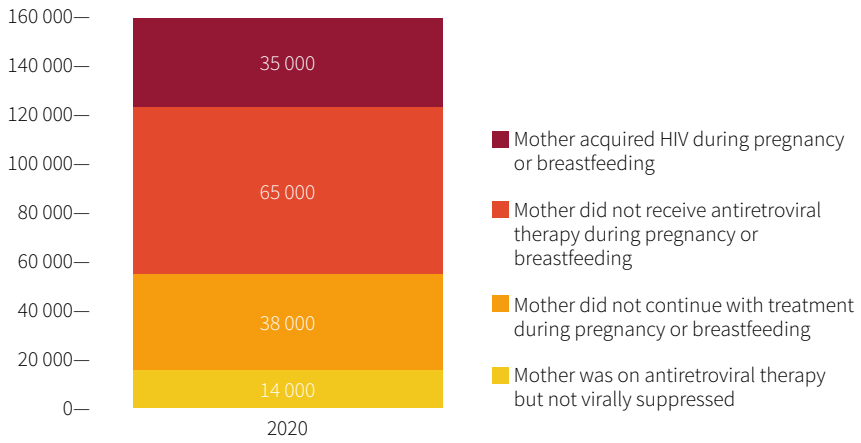
Screening for HIV in pregnancy
• All women with negative or unknown HIV status should be tested for HIV at least once during pregnancy and as early as possible. Dual HIV and syphilis rapid diagnostic tests (RDTs) can be the first test in HIV testing strategies and algorithms in antenatal care. • Couples and partners should be offered HIV testing with support for mutual disclosure. • Retesting during pregnancy and breastfeeding: » In high burden settings, all pregnant women with unknown or HIV-negative status should be retested in late pregnancy, ideally during the third trimester. An additional retest for women of unknown or HIV-negative status in the postpartum period can be considered. » In low burden settings, pregnant women at high risk should be retested during the third trimester.
Antiretroviral therapy (ART)
• ART (dolutegravir in combination with a nucleoside reverse transcriptase inhibitor (NRTI) backbone) should be initiated urgently for all pregnant and breastfeeding women living with HIV. • Whenever possible, use same-day point-of-care (POC) testing for viral load testing for monitoring ART response in pregnant women to decrease turnaround times and expedite patient management.
Testing of HIV-exposed infants
• POC nucleic acid testing (NAT) should be used to diagnose HIV among infants and children younger than 18 months. • NAT should be conducted at ages 6 weeks, 9 months, and at cessation of breastfeeding. Addition of NAT testing at birth can be considered.
Provision of antiretroviral prophylaxis to HIV-exposed infants
• Infants of mothers who are receiving ART and are breastfeeding should receive six weeks of infant prophylaxis with daily nevirapine (NVP). If infants are receiving replacement feeding, they should receive four to six weeks of infant prophylaxis with daily NVP (or twice-daily zidovudine (AZT)). • HIV-exposed infants at high risk of acquiring HIV should receive dual prophylaxis with daily AZT and NVP for the first six weeks of life, whether they are breastfed or formula fed. • Breastfed infants who are at high risk of acquiring HIV should continue infant prophylaxis for an additional six weeks using either AZT and NVP or NVP alone.
HIV prevention in HIV-negative pregnant and breastfeeding women
• Oral pre-exposure prophylaxis (PrEP) containing tenofovir disoproxil fumarate (TDF) should be considered for HIV-negative pregnant and breastfeeding women at high risk of HIV infection.

Gaps and barriers in EMTCT of HIV

Although there are significant regional variations, HIV PMTCT programs have made remarkable achievements, especially with HIV testing at the first ANC visit (ANC1) and rapid provision of ART to pregnant women. Globally, the two most common reasons for the vast majority of new pediatric HIV infections are lack of maternal diagnosis and treatment due to 1) women living with HIV not being diagnosed during pregnancy and thus not starting ART or 2) women acquiring HIV infection during pregnancy or breastfeeding (i.e., undetected incident infection) (Figure 2).[15] This underscores the importance of systematic HIV testing and prompt ART initiation. However, coverage of the recommended repeat testing in the third trimester in high-burden settings remains suboptimal.[29,30] Identifying and testing HIV-negative breastfeeding women at risk of incident infection has been even more problematic, as follow-up of HIV-negative mothers throughout breastfeeding is not routine practice.[31]

Suppressing maternal HIV viral load in the prenatal, antenatal, and breastfeeding periods can nearly eliminate the risk of transmission and current ART is safe and very effective in rapidly decreasing HIV viral load. However, HIV can be transmitted in utero, during delivery, or through breastfeeding, so early and sustained virologic suppression is required for prolonged periods due to the risk of transmission with even transient and small levels of viremia.[32] In addition to late start of ART, another key factor in pediatric HIV infections is discontinuation of ART in women with known HIV infection, especially in the postpartum period. Approximately half of all perinatal HIV infections occur during breastfeeding, and postnatal retention and follow-up of mother-infant pairs remains a significant programmatic weakness. Despite long-standing recommendations for infant testing and scale-up of access to virological testing through both centralized testing platforms and point of care (POC) modalities, only 60% of HIV-exposed infants were tested in the first two months of life in 2019, with a range from 35% in West and Central Africa to 70% in East and Southern.[33] Rates of testing at the later time points is thought to be even lower (although data availability and quality is poor) which is concerning due to the prolonged duration of breastfeeding in many LMICs. For infants who are tested, delayed result return to facilities and caregivers and issues with linkage to ART leads to delayed ART initiation.

FIGURE 2. New vertical HIV infections by cause of transmission, global.
Source: UNAIDS report 2021



Source: UNAIDS epidemiological estimates, 2021 (https://aidsinfo.unaids.org/).

HIV RDTs

There are multiple quality-assured, low-cost commercially available HIV RDTs with excellent performance for HIV diagnosis; none are specifically targeted for use in pregnant or breastfeeding women, but they have served as the foundation for PMTCT programs in LMICs for many years. However, because of the multiple tests recommended during the antenatal period (e.g., HIV, syphilis, HBsAg, malaria, etc.), attention has turned to multiplex RDTs that allow pregnant women to be tested for multiple diseases with one fingerprick. This is particularly relevant to the Triple Elimination agenda and these combination RDTs will be discussed in later sections of the report.

HIV Self-tests (HIVSTs)

HIV self-testing (in which people collect their own specimen and then use a simple rapid HIV test to perform and interpret their results at the time and place of their choosing) has emerged as a safe and effective tool for expanding HIV testing services among people at risk of HIV, especially those who are reluctant to access traditional facility-based services. There is increasing interest in use of HIVSTs in the PMTCT arena for self-screening and partner testing because many incident infections during pregnancy and breastfeeding come from HIV-infected male partners who are unaware of their status. Studies have found that secondary distribution of oral HIVSTs by pregnant women attending ANC to their male partners is safe and highly acceptable. It is the only approach that has shown high uptake of HIV testing by male partners of pregnant women. These findings have prompted calls for prioritization of integration of secondary distribution of oral HIVSTs into routine PMTCT services.[34,35] However, more data is needed on the impact on case-finding and more research is needed to determine the best models for distribution, most effective counseling and information messages, and linkage modalities to confirmatory testing and ART for those with a reactive HIVST. Use of HIVSTs for breastfeeding women is also an area in need of further investigation; distribution points such as immunization clinics and MCH sites could potentially improve repeat HIV testing among breastfeeding women in high-burden areas who tested negative during pregnancy.

Another factor is the cost, as HIVSTs cost significantly more than conventional professional use RDTs. The Mylan blood based HIVST is now available for US$1.99 in 135 countries and OraSure announced in July 2021 that the price of the OraQuick intended for public health distribution will remain at US$2 for all customers. Abbott's CheckNOW HIVST is expected to enter the market at US$1.50.[36]

The HIVSTs that are commercially available and have WHO PQ or ERPD approval are listed in Table 2. Other HIVSTs are available that have approval outside of these pathways.

TABLE 2. Approved HIV self-tests

Test name	Manufacturer	Approval status (2022)
Oral fluid		
OraQuick HIV Self-Test	OraSure Technologies Inc, USA	PQ
Whole Blood		
Mylan HIV Self-Test (formerly Atomo HIV Self-Test)	Atomo Diagnostics Pty Ltd, Australia	PQ
INSTI® HIV Self Test	BioLytical Laboratories, Canada	PQ
SURE CHECK HIV SELF-TEST	Chembio Diagnostic Systems, USA	PQ
EXACTO© TEST HIV	Biosynex SA, France	ERPD
EXACTO© TEST HIV DUO	Biosynex SA, France	ERPD
CHECKNOW© HIV SELFTEST	Abbott Rapid Diagnostics Germany	PQ
WONDFO HIV SELF-TEST	Guangzhou Wondfo Bio-tech Co., Ltd China	PQ
PQ= WHO prequalification; ERPD= Expert Review Panel for Diagnostics		

Prevention of HIV during pregnancy and breastfeeding

In 2017, WHO released a technical brief on preventing HIV during pregnancy and breastfeeding that included use of tenofovir disoproxil fumarate (TDF)-containing pre-exposure prophylaxis (PrEP) for women at high risk of HIV acquisition during this period.[37] However, there are few studies of PrEP implementation during pregnancy and postpartum period in settings with high HIV burden so additional operational research and experience would help tailor programs to the needs of this population. Because compliance with oral PrEP has been highly variable among young women, other modalities that require less rigorous adherence would be highly advantageous. Event-driven dosing of oral PrEP (i.e., taking PrEP only when there is risk of HIV exposure through sexual activity, also known as 'on-demand' or 'intermittent' dosing) has shown promise in cisgender men who have sex with men but no data in women (pregnant or non-pregnant) is available.[38]

Long-acting cabotegravir is a novel HIV prevention option administered every eight weeks through intramuscular injection. It showed superiority compared to TDF/FTC for vulnerable cisgender women in Phase 3 trials and was approved by the United States FDA in December 2021.[39] Safety studies on use of long-acting cabotegravir during pregnancy are ongoing and based on the results, additional research may be needed to inform its use.

The dapivirine ring, an intravaginal silicone ring that slowly releases the antiretroviral drug dapivirine over 28 days, was recommended by WHO in 2021 as an additional prevention option for women at high risk of HIV infection,[40] but additional studies on safety during

pregnancy and breastfeeding are needed. Two studies (MTN-042 (DELIVER) and MTN-043 (B-PROTECTED)) are expected to provide data in 2022.[41,42]

Unitaid is currently funding a robust HIV prevention portfolio which includes efforts to accelerate new, near-to-market and available long-acting PrEP options that could remove barriers to EMTCT. Leveraging existing investments in oral PrEP, Unitaid has recently increased funding[43] to accelerate the uptake of effective PrEP by generating evidence through an implementation pilot targeting adolescent girls and young women in South Africa. This operational research will assess operational feasibility of integrating long -acting cabotegravir and the dapivirine ring into existing services models, with a focus on integration with sexual and reproductive health services. For more upstream opportunities, Unitaid undertakes work to enable access to emerging long-acting HIV PrEP technologies in LMICs, particularly through includes market shaping activities that address price, supply and regulatory barriers.

Virologic testing for HIV-exposed infants (POC and near-POC)

HIV infection among infants can only be definitively confirmed with virological testing using nucleic acid testing (NAT) technologies. Although there have been significant recent investments in improving the diagnostic networks for infant HIV diagnosis, it has become increasingly evident that the currently available centralized laboratory-based testing networks are unlikely to provide the widespread access and rapid turnaround time (TAT) required to reach all HIV-exposed infants. Because of this, programs have begun to use device-based POC technologies for infant virological testing, leading to reduced TAT and improved timely ART initiation compared to laboratory-based methods. As a result, there is now a strong WHO recommendation for the use of POC early infant diagnosis (EID) over laboratory-based methods.[44,45,46,47] The two POC EID devices currently available and with WHO PQ are the Xpert® HIV-1 Qual (Cepheid, USA) and the Abbott m-PIMA HIV-1/2 Detect (Abbott Diagnostics, Germany). These devices cost approximately US$15,000 with an additional cost of US$15-25 per test.[48] Although use of POC EID has been shown to be cost-effective, the absolute costs for national programs with a high number of HIV-exposed infants may hinder uptake in PMTCT programs facing a stable or shrinking budget. Currently available laboratory-based EID assay costs range from US$7.90 to US$17 per test.[49] Also, device-based EID POC is often a new skillset to the end user, requiring additional training and new knowledge, and devices come with expected issues such as breakdowns that require skilled troubleshooting and additional resources. The two current technologies are limited to district level facilities and cannot be used as true POCTs. In addition, most EID POCTs have limited daily throughput so may not be sufficient in busy MCH clinics.

Infant antiretroviral prophylaxis

Oral formulations of zidovudine (AZT) and nevirapine (NVP) remain the backbone for infant antiretroviral (ARV) prophylaxis. Many of the newer ARVs (e.g., dolutegravir) are not yet approved for use as prophylaxis. Unitaid, through the BENEFIT Kids PETITE sub-study is generating evidence for the use of alternative formulations for use in neonates including solid abacavir/lamivudine and lopinavir/r formulations and dolutegravir, with the anticipation that evidence generated from this study will close this knowledge and practice gap. Costs for the currently available drugs are low and do not pose a major barrier; the price per pack for NVP oral solution and AZT oral solution are US$1.45 and US$1.36, respectively. NVP procurement is decreasing because its use in infants as therapy is being phased out in favor of more effective ARVs, and in 2020 there were shortages and extended

lead times due to active pharmaceutical ingredient (API) issues.[42] Production and supply reliability of these niche formulations continues to be monitored by Unitaid and partners such as CHAI, PEPFAR, and The Global Fund through the ARV procurement working group (APWG) to ensure continued availability for infant prophylaxis.

Providing multiple daily drugs to newborns can be challenging for caregivers so there are persistent issues with ensuring adherence to infant prophylaxis. To address this, there is a need for product development efforts to advance fixed dose combinations of neonatal ARVs that align with the recommended prophylaxis dosing and are easy to administer. In addition, a recent survey conducted by WHO found that national guidelines for infant ARV prophylaxis vary widely in terms of medications and durations and are often not in compliance with global guidance, so efforts are ongoing to clarify and streamline approaches. In addition, further research is needed on the impact of ARV prophylaxis on infant diagnoses, and the clinical implications of HIV viremia in breastfeeding mothers and whether enhanced ARV prophylaxis (i.e., with additional or more potent ARVS and/or for longer duration) is beneficial, especially if newer drugs such as integrase inhibitors can be used.

SYPHILIS

Detection of maternal syphilis infection and treatment with one dose of BPG before 28 weeks gestation is a relatively simple and highly effective intervention for preventing vertical transmission of syphilis. For this reason, the foundation of congenital syphilis elimination is early screening in pregnant women and timely administration of appropriate treatment. Because syphilis re-infection is possible even after appropriate treatment, testing and treatment of the sexual partners of pregnant women with syphilis is also an important intervention. Close follow-up of infants born to mothers with syphilis (treated or not) is recommended and administration of penicillin is required for newborns of women who did not receive appropriate treatment (either due to late diagnosis, treatment less than 30 days before delivery, unavailability of BPG, or other reasons). Details on current recommendations related to preventing vertical transmission of syphilis are summarized in Table 3.[50, 51, 52]

TABLE 3. WHO-recommended clinical practices and strategies for EMTCT of syphilis

Screening in pregnancy
All pregnant women should be screened for syphilis at the first ANC visit. This applies to all settings regardless of syphilis prevalence.
The HIV/syphilis dual rapid test can be used as the first screening test (i.e., A1) in the algorithm in ANC settings.
Strategies for syphilis testing • In settings with low coverage of syphilis screening and treatment for pregnant women, high loss to follow-up of pregnant women, or limited laboratory capacity, on-site tests should be used instead of off-site laboratory-based tests. [These recommendations do not apply to countries that can provide appropriate/high-quality laboratory-based screening and treatment strategies.] • The most cost-effective screening and treatment approach in all prevalence settings is a single on-site RDT followed by same day treatment if positive.
For women diagnosed with syphilis, testing of all sexual partners should be conducted and treatment provided as indicated.
Treatment of maternal and infant infection
All pregnant women with early syphilis should receive benzathine penicillin G (BPG) 2.4 million units once intramuscularly (IM) as soon as possible to prevent congenital syphilis; this should ideally be given on the same day as diagnosis to prevent loss to follow-up and maximize efficacy. • Preferred alternative: Procaine penicillin (PCN) 1.2 million units IM once daily for 10 days. • When BPG or procaine PCN cannot be used (e.g., due to allergy and where penicillin desensitization is not possible) or is not available, potential alternatives for use, with caution, include erythromycin 500 mg orally four times daily for 14 days OR ceftriaxone 1 gram IM once daily for 10-14 days OR azithromycin 2 grams once orally, noting that these do not cross the placental barrier and therefore do not treat the unborn fetus.
Pregnant women with late syphilis or unknown stage of syphilis should receive BPG 2.4 million units IM once weekly for three consecutive weeks. • Alternative: Procaine PCN 1.2 million units IM once daily for 20 days.
Infant follow-up and treatment
All infants (live or stillborn) born to mothers with positive syphilis tests should be examined for evidence of congenital syphilis. Live infants should also be given a non-treponemal test at birth and at monthly intervals for three months until confirmed that serological tests in the infant remain negative.

• Infants with confirmed congenital syphilis or infants who are clinically normal, but whose mothers had untreated syphilis, inadequately treated syphilis, or syphilis that was treated with non-PCN regimens, should receive:
  • Aqueous benzyl PCN 100,000–150,000 U/kg/day intravenously (IV) for 10–15 days OR
  • Procaine PCN 50,000 U/kg/day single dose IM for 10–15 days.

Gaps and barriers in EMTCT of syphilis

At a national and global level, congenital syphilis elimination efforts have been impeded by issues with disjointed and inadequate funding streams, poor coordination between MCH and STI programs, inadequate prioritization, and poor uptake of interventions. According to the WHO, 93% of countries have policies in place to screen pregnant women for syphilis but actual global coverage of maternal syphilis screening is <50% globally.[53] Other barriers to uptake of global recommendations include:

- **Complicated diagnostic algorithms that relied on laboratory-based testing.** Historically, syphilis guidelines were not tailored to resource-limited settings and involved multiple laboratory-based tests that were inaccessible to many LMICs. Newer global guidance takes a more public health approach with simpler recommendations that are more feasible, especially for ANC sites in rural and remote areas. However, many countries have not adapted national guidelines and policies to reflect this more streamlined approach.

- **Lack of high-quality diagnostic tests that are easy to interpret.** Until recently, there were a limited number of reliable RDTs available for syphilis diagnosis, so countries were forced to rely on laboratory-based tests that require equipment, technical expertise, and electricity. In addition, the turnaround time for laboratory-based tests can impede the ability to provide immediate treatment and thus risks loss to follow-up (LTFU). Diagnosis of syphilis can be complex even with available laboratory-based tests; often, serial testing and extensive history-taking from the patient is required for interpretation.

- **Lack of healthcare provider knowledge about BPG administration and risks.** Due to misperceptions about BPG allergies, injection risks, and safety, many healthcare providers have been reluctant to adhere to guidelines for immediate therapy of women who screen positive for syphilis or to provide appropriate therapy to neonates in whom treatment or prophylaxis is indicated.[54]

- **Lack of political commitment to prioritize syphilis elimination.** Although many countries have policies for syphilis testing in ANC1, coverage of syphilis testing has traditionally lagged significantly behind that of HIV and malaria and there is often minimal political will to improve coverage.

- **Global stockouts and poor supply chain reliability of BPG.** Shortages of BPG have been a global issue affecting countries of all income levels. Between 2014-2017, over 40 countries reported BPG shortages.[55] These shortages have largely resolved, although the market remains fragile.

Screening/diagnostic tests

The most widely used tests for syphilis diagnosis are serologic tests. Historically, screening tools for syphilis are primarily laboratory-based non-treponemal tests (e.g., rapid plasma reagin (RPR) and Venereal Disease Research Laboratory (VDRL)) and treponemal tests (e.g., *Treponema pallidum* haemagglutination assay (TPHA), the *Treponema pallidum* particle agglutination assay (TPPA) and the fluorescent treponemal antibody absorption (FTA-ABS)). Because of difficulties in interpretation, expense, and human resources required to conduct these tests, uptake and access in LMICs has been patchy and they are generally not considered a viable long-term option in resource-limited areas. Although the RPR test can be performed as POC (i.e., 'on-site RPR'), the set-up requires significant infrastructure (e.g., rotator, blood centrifuge, refrigerator for reagents, and electricity) and can be difficult to perform and interpret.[45] For these reasons, in most LMICs the most feasible and cost-effective approach is a single on-site RDT followed by same-day treatment if positive, and this approach increases antenatal screening significantly.[56] In addition, the short TAT of RDTs allows immediate (same day) treatment. This is essential, since BPG treatment is most effective when given prior to 28 weeks gestation and many women in LMICs do not present to their first ANC visit before the second trimester.

RDTs for syphilis diagnosis

Current RDTs available for syphilis include syphilis RDTs and dual HIV/syphilis RDTs. RDTs are in the category of treponemal tests (i.e., they detect antibodies specific to *T. pallidum*). The sensitivity reported by the manufacturers for the syphilis component ranges from 87% to 99% and the specificity from 99% to 100%, compared to the TPHA or TPPA as reference standards. Currently available products with WHO PQ or ERPD approval are listed in Table 4.[57]

TABLE 4. Approved syphilis and dual HIV/syphilis RDTs

Test name	Manufacturer	Approval status (2022)
Syphilis only		
First Response® Syphilis Anti-TP Card Test	Premier Medical Corporation; India	PQ
BIOLINE Syphilis 3.0	Abbott Diagnostics Korea Inc.; Korea	ERPD until 5 May 2022
STANDARD™ Q Syphilis Ab test	SD Biosensor Inc; Korea	ERPD expired 25 August 2021
Dual HIV/syphilis		
Bioline HIV/Syphilis Duo (formerly SD Bioline HIV/Syphilis Duo)	Abbott Diagnostics Korea Inc.; Korea	PQ
First Response® HIV1+2/Syphilis Combo Card Test	Premier Medical Corporation; India	PQ
STANDARD™ Q HIV/Syphilis ComboTest	SD Biosensor Inc; Korea	PQ
PQ= WHO prequalification; ERPD= Expert Review Panel for Diagnostics		

Although RDTs have been available for several years and been shown to improve coverage over conventional lab-based modalities and, in the case of dual testing, screening using separate HIV and syphilis RDTs, uptake had been slow.[48] However, in the past several years there has been increasing interest in and uptake of syphilis testing, especially the dual HIV/syphilis test.[58] This was spurred by WHO release of guidance in December 2019 stating that the dual test can be used as the first screening test (i.e., A1) in the algorithm in ANC settings and by new evidence of its cost-effectiveness in ANC.

Despite this encouraging momentum, use of the syphilis RDTs has been hampered by several issues:

- **Operational and supply chain challenges.** The dual test is simpler from the patient and test operator perspective because two tests can be conducted from one fingerprick sample. However, use of the dual test creates additional complexity at the facility level from an operational and supply chain perspective. Because the dual test cannot be used for testing women with known HIV infection, separate single syphilis tests are still required and can make up a substantial proportion of the tests needed in areas of high HIV burden among pregnant women. The dual test is also not recommended for women diagnosed with syphilis during the current pregnancy (although this is much less common). Because of this, three RDTs are still required to meet all the guideline requirements: 1) syphilis-only RDTs for those with known HIV infection, 2) dual tests for women without either HIV or syphilis, and 3) single HIV tests for women with a recent syphilis diagnosis.

- **Cost considerations.** Until recently, the price of available dual RDTs was approximately US$1.50. However, in November 2021, SD Bioline decreased the price of its dual RDT to US$0.95 (minimum order of 100,000 tests) through a partnership with MedAccess and the Clinton Health Access Initiative.[59] However, although the dual test is less expensive than the separate HIV and syphilis RDTs, because few countries had achieved high coverage of syphilis testing, the absolute testing budgets associated with dual testing may translate to an increase in total costs. However, both PEPFAR and Global Fund have announced support for procurement of dual tests.

- **Limitations with available RDTs.** All the currently approved RDTs are treponemal tests that detect antibodies against treponemal-specific antigens.

Treponemal tests usually remain positive for the patient's lifetime, regardless of treatment. As a result, they cannot distinguish between active infection and infection that has been previously treated. In addition, the current RDTs cannot distinguish venereal from non-venereal treponematoses (e.g., yaws, pinta) so in regions where both are endemic, a positive RDT may result from infection with a non-venereal treponematoses during childhood. Both of these issues may result in unnecessary treatment with penicillin. This 'overtreatment' has been the source of concern for some providers and public health program managers despite the lack of evidence of harm with multiple BPG shots.

This issue has prompted interest in an RDT that can determine the presence of active versus treated infection for both case management and surveillance efforts. WHO released a target product profile (TPP) for such a test in 2014.[60] One test, the DPP® Syphilis Screen and Confirm (Chembio Diagnostic Systems, USA) is currently commercially available and is CE-marked. However, a recent study in an area of West Africa with endemic yaws found that use of the test did not reduce overtreatment for syphilis and underestimated women requiring treatment.[61]

- **Diagnosis of syphilis in newborns is particularly problematic.** Both RDTs and laboratory-based assays are hard to interpret in infants, as any positive serologic test may reflect passively acquired maternal antibodies from maternal current or previous infection. An IgM Ab test for diagnosis of syphilis in infants has been developed but it is not recommended due to poor performance.[62] Because no reliable complement of tests exists for infants, diagnosis of congenital syphilis in RLS often relies on symptoms and clinical exam.

Treatment

Benzathine penicillin G/ benzathine benzylpenicillin

The only treatment proven to prevent vertical transmission of syphilis is BPG (also known as benzathine benzylpenicillin). It is inexpensive (approximately $USD 0.20/dose), there is no documented drug resistance, and the one dose regimen necessary for prevention of congenital syphilis ensures completion of therapy.

However, several facility-level factors may limit uptake of syphilis treatment:

- **Route of administration.** Although injections are acceptable to most people, some women may refuse injections, especially if multiple injections are required for late latent syphilis. Also, intramuscular administration requires equipment (e.g., needles, syringes) and additional staff time and some healthcare providers are uncomfortable providing injections.

- **Provider reluctance.** Many providers continue to have misperceptions about the quality of BPG products and the risk of adverse outcomes, especially those related to penicillin allergies and the potential for anaphylaxis.

- **Difficult infant treatment regimens.** Treatment of infants requires multiple days of inpatient intravenous penicillin treatment, which is not feasible in many LMICs, prompting providers to use non-approved and non-standard regimens.

Market and quality assurance issues are also major impediments to uptake and access

to quality formulations of BPG. BPG is indicated for multiple diseases; the largest use worldwide is for rheumatic heart disease (RHD). Although the shortages have resolved, the market remains fragile because there is little incentive for manufacturers given the low unit margins and fragmented demand. In addition, there are currently only four suppliers of the API (three in China, one in Spain) so manufacturing delays or failures have global repercussions. Defining the market is challenging because both need and demand are difficult to quantify due to the limited and poor-quality data on diseases such as syphilis and RHD that require BPG.

Ensuring quality of both API and finished pharmaceutical product (FPP) is also a problem, prompting barring of imports in certain areas in the past due to major deficiencies. In response to ongoing concerns, the WHO added BPG to its PQ program in 2018 and at least 3 companies have expressed interest.[63]

Alternative treatments for syphilis elimination efforts

WHO guidelines list several alternatives to BPG, but all have significant concerns with efficacy, cost, and/or operational feasibility. Although procaine PCN is highly effective for PMTCT and is inexpensive, it is rarely available; in addition, the requirement for 10 days of daily injections is impractical and engenders a high risk for LTFU and non-compliance with therapy. Ceftriaxone has a similar unwieldy 10-day injection schedule, is expensive, does not have proven efficacy for PMTCT, and there are concerns with drug resistance. Lastly, azithromycin (a one dose alternative listed in the guidelines) only treats maternal infection and does not prevent vertical transmission. For this reason, it delays fetal treatment and infants whose mothers receive this regimen must receive postexposure prophylaxis and more intense postnatal follow-up. In addition, there are concerns with antibiotic resistance. An effective oral treatment for maternal syphilis infection would be ideal. Clinical trials evaluating twice daily cefixime for 10 days are ongoing. However, these trials exclude pregnant women, and the long treatment course poses the risk of non-adherence, so these results are not expected to have a near-term impact on guidance for congenital syphilis prevention.

HBV

The core interventions for perinatal HBV transmission prevention focus on 1) vaccination of all newborns with timely hepatitis B birth dose (HepB-BD) and completion of the full vaccine series 2) identifying pregnant women with high risk of vertical transmission of HBV and providing antiviral prophylaxis, and 3) provision of HBIG (if available) to HBV-exposed infants.

The cascade for PMTCT of HBV involves multiple steps:

- Antenatal HBsAg screening: HBV infection is largely asymptomatic, so diagnostic testing is essential. Identification of women who are HBsAg positive also provides opportunities to screen potentially infected partners, siblings, and children, thereby minimizing transmission within families.
- Follow-up testing in women who test positive for HBsAg: Follow-up testing with quantitative HBV VL (or HBeAg) is required to determine the level of viral replication.
- Third trimester antiviral therapy for women at high risk of MTCT
- Timely provision of the HepB-BD: If given within 24 hours of birth, HepB-BD is 72% protective against vertical transmission and is >90% protective if the mother is HBeAg negative.
- HBIG administration, if available, for infants born to women with chronic HBV infection
- Full HBV vaccine coverage: Due to continued risk for horizontal transmission, high coverage of the primary three dose series is essential to reach global elimination goals.

Further details of the current recommendations are shown in Table 5.[64]

TABLE 5. WHO recommendations for prevention of perinatal transmission of HBV (2021)

Screening for HBV in pregnancy
• All pregnant women should be screened for hepatitis B at the first ANC visit through testing for HBsAg.
• In women who test positive for HBsAg, conduct a quantitative HBV VL test. If HBV VL testing is unavailable, check for the presence of HBeAg. • The use of capillary whole blood dried blood spot (DBS) specimens for both serological and NAT technologies for HBV infection may be considered to facilitate access to testing. Assays for use with DBS should be validated for that specimen type by manufacturers.
Provision of antiviral prophylaxis and HBIG
• Pregnant women with a high risk of vertical transmission of HBV (as indicated by HBV VL>200,000 IU/ml and/or the presence of HBeAg) should receive antiviral prophylaxis with tenofovir from 28 weeks gestation until at least delivery. After delivery they should be referred for long-term monitoring to determine the need for continued treatment for their own health.
• If available, infants born to HBsAg-positive mothers should receive HBIG, especially in cases of high maternal HBV VL or HBeAg positivity. This should ideally occur within 12 hours of birth.
HBV vaccination of infants
• All infants should receive a dose of monovalent HBV vaccine within 24 hours of birth.
• All infants should receive 2 or 3 doses of HBV vaccine (monovalent or combination) after the birth dose to complete the primary immunization series.

Testing of HBV-exposed infants
• HBV-exposed infants should be tested for HBsAg at 12 months of age; If positive, then testing should be repeated in 6 months. CHB is diagnosed if there is persistence of HBsAg for six months or more. • Screening of asymptomatic infants or children for chronic HBV infection is not recommended.
Treatment of children with chronic HBV infection
• Antiviral therapy is not recommended for children without clinical evidence of cirrhosis (and with persistently normal ALT levels and low levels of HBV replication (HBV DNA <2000 IU/mL)), regardless of HBeAg status or age. If HBV DNA results not available, defer treatment in HBeAg-positive children with persistently normal ALT levels. • All children with chronic HBV infection and clinical evidence of compensated or decompensated cirrhosis should be treated, regardless of ALT levels, HBeAg status or HBV DNA levels. • For the small number of children who do meet criteria for treatment, WHO recommends TDF in children >12 years and entecavir for children >2 years.

Gaps and barriers to EMTCT of HBV

Programs that provide a comprehensive package of interventions for PMTCT of HBV in resource-limited settings (RLS) are scarce and uptake of interventions has been slow, especially in sub-Saharan Africa. A recent survey of countries found that only 33% have guidelines related to HBV EMTCT[65] and coverage of screening and other interventions is <20%.[66] Existing programs are largely run by non-governmental organizations (NGOs) in select areas and there are few national, large-scale programs directed by Ministries of Health.

Key issues affecting uptake of HBV EMTCT interventions include the following:

- **Lack of awareness.** Although hepatitis surpasses HIV, TB, and malaria in morbidity and mortality worldwide, HBV is largely overshadowed by those diseases and community awareness is low, especially in sub-Saharan Africa. Healthcare worker knowledge is also minimal, likely because chronic HBV infection is often asymptomatic and cirrhosis in pregnant women and young children is rare.

- **Lack of dedicated funding.** Although PEPFAR and Global Fund have indicated openness for funding for treatment of HBV-HIV co-infected patients, there is minimal dedicated funding for screening and prophylaxis in antenatal settings. Given the lack of major global funding initiatives for HBV, most HBV testing programs rely on financing from NGOs, patient fees, or, to a lesser extent, domestic financing.

- **Limited global guidance tailored to LMICs.** Until recently, guidance for HBV screening, prophylaxis, and treatment tailored for conditions in LMICs has not been available. However, in the past 4 years, the WHO has released recommendations for testing (2017), use of antiviral prophylaxis in pregnancy (2020), and validation of EMTCT of HBV (2021).[7,8] These documents represent a major step forward as they can serve as the basis for national guidelines for triple elimination.

- **Minimal focus on EMTCT within hepatitis programs.** Programs for hepatitis elimination in children have traditionally focused on immunization. In many LMICs, the small number of existing programs aimed at increasing knowledge of status and treatment coverage among those with chronic HBV have targeted groups with the highest prevalence and risk of HBV (e.g., PLHIV, people who inject drugs), although coverage remains low. Diagnostic and prophylactic interventions to prevent PMTCT have received less attention. [67,68]

- **Lack of data.** Hepatitis surveillance in LMICs is often weak or non-existent. National epidemiologic data is needed to raise awareness, generate political commitment to elimination, and aid strategic planning.

- **Limited evidence base.** Given the multiple interventions and complex cascade of care, there is limited evidence on efficacy and cost-effectiveness for combinations of HBV EMTCT interventions in real-world settings. In addition, there is less evidence on vertical transmission of HBV in Africa, and a perception that it is lower there than in other regions due to different HBV genotypes. There is also less data on use of HepB-BD in the African context.

- **Complex and costly algorithms for diagnosis and assessment.** The multi-step algorithms for assessment of HBsAg+ pregnant women require access to laboratory-based tests and are time-intensive for healthcare staff, making them difficult to implement at scale and in more isolated areas. In addition, because antiviral prophylaxis is not indicated for all pregnant women with HBV infection, the need for laboratory and clinical evaluation is a key bottleneck for prophylaxis initiation.

- **Lack of access to low-cost quality-assured diagnostic tests, especially for HBeAg and HBV VL.** Although affordable and quality HBsAg RDTs are available, the additional tests required for antiviral prophylaxis decisions are costly and limited. HBV NAT, the preferred test, is expensive and requires substantial infrastructure, even with POC assays. HBeAg testing, a potential alternative, is even less widely available. The limited availability of these two critical tests that appear later in the algorithm (and are the determining factor for administration of prophylaxis) severely blunts demand and uptake of HBsAg testing, since programs must be able to implement the full algorithm.

- **Lack of access to TDF for antiviral prophylaxis/treatment.** Although low-cost generic tenofovir is available, access to TDF for patients with HBV mono-infection is limited. Many treatment options are only for those with HIV-HBV co-infection through free TDF-based ART. In addition, many patients are required to pay for antiviral prophylaxis or treatment.

- **Delayed adoption of the HepB-BD.** In 2009, WHO recommended use of the HepB-BD in all countries[69], but uptake of the HepB-BD has been much slower, with only 42% global coverage as of 2019. However, there is considerable variation among regions, ranging from <10% coverage in the AFRO region and >80% in WPRO.[70]

- **Limited facilities and staff to coordinate and manage HBV EMTCT programs.** Management of chronic HBV and ensuring coverage of all necessary interventions for women and their infants requires long-term follow-up, continuous monitoring, retention, and linkage to care and limited human resources at the facility and program levels impede implementation.

- **Limited markets.** Lack of funding and low volumes restrict ability to take advantage of current access pricing for diagnostics tests for HBV EMTCT.

Screening/diagnostic tests

Due to the large number of antenatal clinics, widespread scale-up of HBV EMTCT interventions will require the availability of accurate, quality-assured tests that can be easily conducted at primary levels of health care.

HBsAg RDTs

Detection of HBsAg in blood, which indicates active viral infection, is the entry point for the cascade of care, so use of quality-assured diagnostics for HBsAg is critical. Multiple HBsAg POCs are commercially available, and most are qualitative lateral-flow immunoassays which can be used with multiple specimen types (whole blood, serum, and plasma) and provide rapid semi-quantitative results (usually in 15-20 minutes). Due to their diagnostic accuracy (especially in populations with a moderate-to-high prevalence of HBV), ease of use, and lower cost, these tests are considered desirable alternatives to laboratory-based testing. Although RDTs for HBsAg have reduced sensitivity and level of detection compared to EIAs, the clinical sensitivity is not greatly reduced because the vast majority of chronic HBV infections are associated with high HBsAg concentrations. [71]

There are currently 2 HBsAg RDTs that are WHO prequalified and appropriate for diagnosis in antenatal settings. Another WHO prequalified product, the VIKIA HBsAg (bioMérieux SA, France) was discontinued in January 2020.[72] An additional test, the First Response HBsAg Card Test, is CE-marked. (Table 6.)

Prices for the currently available HBsAg tests are similar to other RDTs and are shown in Figure 3 below.

FIGURE 3. Source: CHAI Hepatitis Market Report, 2021[73]

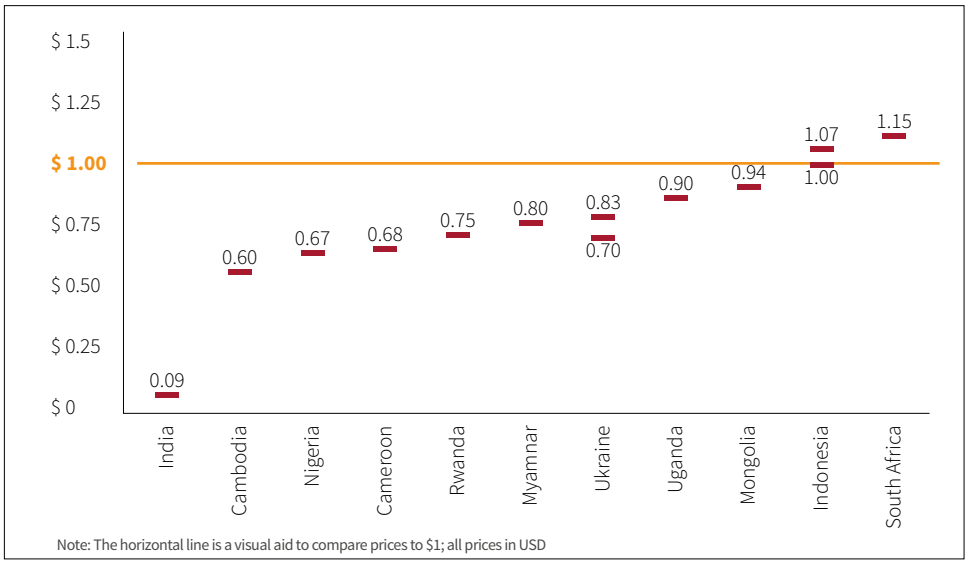


TABLE 6. HBsAg RDTs with approval

Test name	Manufacturer	Approval status (2022)
Bioline HBsAg WB Name changed from SD BIOLINE HBsAg WB in Aug 2020[74]	Abbott Diagnostics Korea	WHO PQ
Determine HBsAg 2	Abbott Diagnostics Medical Co., Japan	WHO PQ
First Response® HBsAg Card Test	Premier Medical Corporation, India	CE

Multiplex tests that include HBsAg

Several multiplex RDTs that include HBsAg are commercially available. Although none are WHO prequalified, a selection of CE-marked tests is listed in the table below. Most tests include an HCV antibody component. Because routine screening of pregnant women for HCV is not recommended in most settings, their utility in the antenatal arena is likely limited except in a small number of countries or contexts where HCV screening is also indicated.[59]

TABLE 7. Multiplex RDTs that include HBsAg[75]

Test name	Manufacturer	Approval status (2022)
HBsAg/HCV/HIV/Syphilis Combo Test	Euro Genomas	CE
HBsAg and HCV Combo Test	Euro Genomas	CE
Artron Detect 3 HIV/HCV/HBV Combo	Arton Laboratories	CE
HIV, HBsAg and HCV Rapid Test	Maternova Inc.	CE

HBV viral load quantification

HBV viral load quantification is the reference test to determine level of viral replication and subsequent risk for transmission. It has been rarely performed in RLS because of high costs and the need for sophisticated molecular testing platforms found in centralized laboratories. Test prices range from US$15–50 in the Americas to US$30–100 in the WPRO and AFRO regions. However, HBV viral load can be performed on many of the same platforms used for HIV viral load testing, so there is the potential to leverage the scale-up of HIV viral load testing. Many suppliers of these centralized testing platforms now have access pricing for select LMICs, so the cost of HBV viral load tests have decreased substantially, ranging from US$9-17.[69]

Although the decreased cost and use of existing platforms for multiple diseases is an encouraging development, the use of centralized platforms requires significant infrastructure and laboratory expertise. In addition, the need for phlebotomy and specimen transport makes use of these assays less feasible for widespread roll-out in ANC clinics. WHO guidelines provide a conditional recommendation for using DBS for HBV NATs if the assay has been validated for that sample type, which could simplify specimen transport and eliminate the need for phlebotomy. However, none of the manufacturers of current commercial technologies have validated their use with DBS samples.

Lastly, it is worth noting that although HIV viral load scale-up has been very successful in many countries, most HIV viral load testing is done at ART sites, not ANC clinics, so an existing mechanism for testing and specimen transport is less likely to be present. Another practical consideration is that rapid turnaround times for HBV viral load are important for ensuring that women receive results and, if eligible, are started on antiviral therapy by 28 weeks gestation. Given the late presentation of women to ANC in many RLS, this window is relatively short.

A more promising alternative approach is the use of POC cartridge-based systems which are amenable to integrated testing across diseases. There are currently two POC test

cartridges for HBV DNA detection in serum or plasma, the Moblio Diagnostics: Truenat test for HBV DNA (commercially available but not yet SRA-approved) and the HBV DNA VL GeneXpert (Cepheid Inc, Sunnydale, CA, USA).[76] Although the Xpert HBV viral load is CE-marked, it is not WHO pre-qualified. HBV programmes in sub-Saharan Africa could leverage the already existing networks of Xpert platforms for TB and HIV, although careful planning would be needed to ensure adequate capacity. In addition, the cost of approximately US$14.90 ex-works could be cost-prohibitive in countries with high numbers of pregnant women who are HBsAg positive and require follow-up evaluation.[69]

HBeAg RDTs

HBeAg is a key indicator to determine the phase of chronic hepatitis B infection and is used as a surrogate of HBV DNA measurement where HBV DNA is not available. In LMICs, barriers to use of traditional lab-based assays for HBeAg (enzyme immunoassay (EIA), chemiluminescence immunoassays (CLIA) or electrochemiluminescence assays (ECA)) include cost, lab infrastructure requirements, and need for reagent cold chain.

HBeAg RDTs are listed in the WHO EDL 2021 list, but no currently commercially available RDTs are WHO prequalified. Table 8 below shows a sample of commercially available HBeAg RDTs. Pricing data is limited but a recent report cited SD Bioline HBeAg procurement at $1.50 per test for the public program in Cambodia.[69]

TABLE 8. Select commercially available HBeAg RDTs

Test name	Manufacturer	Approval status (2022)	Sample type	Reported sensitivity and specificity (95% CI) by manufacturers
SD BIOLINE HBeAg	Abbott Diagnostics, Korea	-	Serum, plasma	95.5 (88.9-98.2); 98.6 (96.1-99.5)
HBeAg Serum Rapid Test (Cassette)	Creative Diagnostics, USA	-	Serum, plasma	96.3 (92.1-98.6); 97.9 (96.1-99.1)
HBeAg Rapid Test	Biopanda Reagents, United Kingdom	CE	Serum, plasma	99.9 (97.9-100); 98.8 (97-99.7)
Insight	Tulip Diagnostics, India	-	Serum	Not reported
OneStep	AMS		Serum, plasma	94.9; 99.4

Although manufacturer data reports a high accuracy of HBeAg RDTs, studies show a wide range with a sensitivity of 30–82% and specificity of 67–100%.[77] A recent study of HBsAg positive patients in Malawi that assessed three HBeAg tests found diagnostic sensitivity ranged from 28%-72% with specificity of 96–100%. Sensitivity for identifying patients at the threshold where antiviral treatment is recommended for PMTCT (i.e., HBV DNA >200,000 IU/ml) ranged from 22-54%.[78] A study in Senegal showed similarly low sensitivity among three tests (29%-43%) although specificity was high (98-100%).[72] These studies contrast with studies of these HBeAg RDTs in Asia, where they have shown improved performance.[79] These regional variations suggest a potential role for HBV genotype in the performance of HBeAg RDTs and highlight the need to ensure that diagnostic tests are validated within the relevant population.

The Senegal study also found that only half of highly viremic women of childbearing age were positive for HBeAg using the reference assay. This low prevalence of HBeAg in women with high

HBV DNA levels has been previously reported from other African studies and suggests that a high proportion of women at risk for transmission to their infants will be missed if only HBeAg-based screening is used.[80] More research is needed to fully characterize the regional differences among pregnant women in HBeAg positivity and how HBeAg presences correlates with HBV viral load.

HBIG

The dose of HBIG generally used in infants is between 100 and 200 IU, corresponding to 30-40 IU/kg. Although WHO guidance recommends administration of HBIG to infants (ideally within 12 hours of birth), it acknowledges that HBIG is expensive (US$80-$200/dose reported[81,82]) and access is limited. HBIG has a short shelf life, requires refrigeration, and must be screened for infectious diseases, making it impractical for widespread use in RLS.[83] For these reasons, WHO guidance clearly states that HepB-BD coverage should be the preferred intervention of focus and few LMICs are pursuing HBIG procurement and scale-up.

Vaccines

Timely HepB-BD for newborns followed by completion of the primary immunization series (two or three doses) decreases the risk of HBV transmission from mother to child by 90 percent and provides lifelong protection. In sub-Saharan Africa, vaccination was found to be the most cost-effective intervention to reduce perinatal HBV infection rates.[84] HepB-BD also prevents horizontal transmission from household contacts.

The monovalent vaccine must be used for the birth dose, but the series can be continued with either the monovalent or combination vaccine. The monovalent vaccine is currently available in 1, 2, 6, 10 dose vials, and is very heat stable and freeze sensitive. Research has revealed that the HepB vaccine remains safe and effective after being stored out of cold chain (OCC) and vaccine potency is maintained after prolonged exposure to high temperatures, significantly increasing ability to use the vaccine in areas without vaccine storage equipment and/or in areas with high rates of home births.[85, 86] However, although WHO has encouraged the re-labeling of hepatitis B vaccines for use in a controlled temperature chain (CTC), no prequalified product is yet available.

Two generic suppliers, Serum Institute of India and LG Life Sciences Ltd., have received WHO PQ for HBV birth dose vaccine.[87] A 1-dose pre-filled auto disabled disposable syringe (Uniject) (HB-Uniject [BD Pharmaceutical Systems, Franklin Lakes, NJ, USA]) is also available. Uniject is a compact pre-filled auto-disable injection device that is simpler to use than standard needles and syringes; its use is supported by WHO and other international organization for administering hepatitis B vaccine in outreach settings.

Thus far, the HepB-BD vaccine has not been part of the vaccines supported by Gavi (the Vaccine Alliance) because the price (US$0.20) is below the minimum country co-financing level for low-income countries. However, in 2018 Gavi approved support for the introduction of HepB-BD vaccination for eligible countries in an attempt to help countries overcome introduction barriers; at that time there were 38 Gavi-supported countries that were not delivering HepB-BD. This change in support was scheduled to begin in 2021 but has been put on hold due to the COVID-19 pandemic and the timeline for initiation remains uncertain.[88] For other programs, the UNICEF supply division currently offers HepB-BD vaccines to LMICs at US$0.25 per child.[89]

In addition to funding, other key barriers to HepB-BD vaccine uptake include the following:[90,91]

- Lack of policy adoption for the HepB-BD within national programs
- High prevalence of home births (up to 50% of babies in the WHO AFRO region)

- Poor awareness and knowledge among the healthcare providers and the community
- Difficulty accessing newborn care services in rural areas and weakness in outreach vaccination services
- Limited buy-in from public health officials in Africa due to less evidence for birth dose vaccination in African newborns
- Unreliable vaccine supply in birth facilities

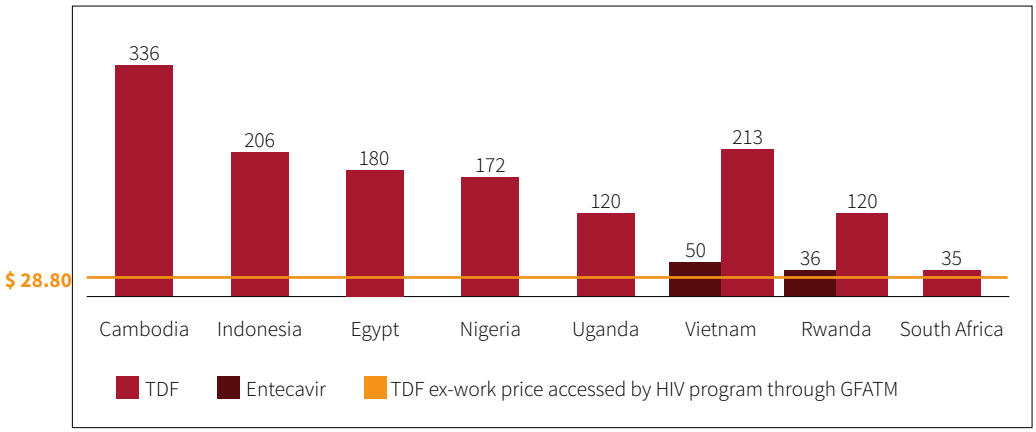
Treatments

Antivirals for use in prophylaxis in pregnancy and as treatment

Tenofovir disoproxil fumarate (TDF)

The recommended antiviral for maternal prophylaxis is TDF, an off-patent drug that has been part of the WHO Essential Medicines List for HIV since 2007 and was added for HBV in 2015. Because TDF is widely used for the treatment and prevention of HIV, there are six generic suppliers with WHO PQ. The median price of WHO PQ generic TDF fell from US$208 per year to US$32 per year in 2016. The current price of TDF negotiated by the Global Fund is US$28.80 per year. However, there is significant variability in prices for LMICs, and several countries (e.g., Cambodia, Indonesia) have reported that TDF for HBV mono-infection is significantly more expensive (>US$200 for a one year course of TDF).[69] Of note, antiviral prophylaxis is recommended only for approximately 12 weeks (28 weeks gestation until delivery) so the minimum course is shorter and thus costs would be less. Some women may require longer suppressive therapy after delivery based on clinical and laboratory assessment, but the expected proportion would be small (<5%).

FIGURE 4. Price of one year course of TDF and entecavir in 2020 in select countries. Source: CHAI Market Report



Entecavir

There is currently limited data on the use of entecavir for PMTCT, so it is not currently recommended as antiviral prophylaxis. Entecavir is a recommended treatment for HBV and can be used to treat children aged 2 years and older; it is available in oral solution as well as scored 0.5 mg and 1 mg tablets. Currently, only one generic (Hetero) has achieved WHO PQ, while an additional three have European Medicines Agency (EMA) approvals (Aurobindo, Mylan, and Accord). It is costlier than TDF; the current price negotiated by GFATM for a one-

year course of WHO prequalified entecavir is approximately US$96. TDF's wide use in HIV therapy has driven down the price, while the market for entecavir is much smaller than TDF and there has been less investment in the product.[69]

Tenofovir alafenamide (TAF)

TAF is a prodrug of TDF that is used due to its improved safety profile; it has been shown to be safe in combination ART in pregnant women.[92] However, it is not recommended in pregnancy for HIV treatment or as antiviral HBV prophylaxis due to limited data on its use in that context, but studies are ongoing for use in pregnant women with HIV and/or HBV infection.[93,94]

CHAGAS DISEASE

Screening of pregnant women, screening and treatment of Chagas-exposed newborns, and treatment of girls and women of childbearing age with *T. cruzi* infection are the foundations of EMTCT of Chagas. Table 9 summarizes the key recommendations.[95,96]

TABLE 9. Interventions for prevention of perinatal transmission of Chagas disease (PAHO, 2019)

Screening for infection prior to pregnancy
• All T. cruzi-infected girls and women of childbearing age who are not currently pregnant should receive trypanocidal treatment.
Screening for infection during pregnancy
• All pregnant women should be screened during pregnancy using two serological tests.
• Women who screen positive should be followed closely to ensure that treatment can be administered after delivery.
Screening and treatment of Chagas-exposed newborns
• All newborns of infected mothers should receive T. cruzi parasitological screening at birth. If negative, it should be repeated at 1 month of age. • For Chagas-exposed newborns in whom the initial newborn screen is negative or was not conducted, serological testing should be conducted at 10 months of age. • Treatment of infected infants should be given immediately after diagnosis with either benznidazole (5-7 mg/kg/day divided in 2 doses) OR nifurtimox (10-15 mg/kg/day divided in 3 doses) • The recommended duration of treatment is 60 days and should not be <30 days. • After treatment, serological monitoring should be conducted every 6 months until serology is negative.
Treatment of in Chagas disease
• All mothers with Chagas disease should receive treatment after delivery (or after the cessation of breastfeeding, if applicable) with either benznidazole or nifurtimox.

Unitaid published a comprehensive technology and market landscape for the screening and treatment for Chagas disease in 2020 that includes detailed information on available diagnostics and treatment.[14] A brief summary of key modalities related to EMTCT of Chagas is outlined below.

In April 2021, Unitaid started funding the Foundation for Scientific and Technological Development in Health (FIOTEC) Brazil and its CUIDA project that aims to improve the detection and treatment of mothers with Chagas disease and their newborns using innovative test, treat and care approaches.

Diagnostics

Diagnostics for Chagas disease fall into 3 areas – 1) parasitological methods, 2) serological detection of antibodies to parasite antigens, and 3) molecular detection of the parasite.

Parasitological methods, such as microscopy, are limited for use to identify acute or congenital infections, or reactivation, as this is when parasites are typically present in greater numbers in the bloodstream. These methods also include xenodiagnosis (exposing uninfected triatomine insects with blood from a patient and subsequently examining the insects under a microscope to look for parasites) and hemoculture (growing and isolating the parasite from a patient's blood sample in a laboratory culture medium). These methods require significant laboratory infrastructure, training, and time to perform, and consequently are not commonly used for the diagnosis of acute Chagas disease.

Serological tests to detect antibodies is the most common method to evaluate for chronic infection and is also recommended to evaluate infants. Currently only laboratory-based serology is recommended in the PAHO guidelines, though POC testing has been recognized for improving testing accessibility. Laboratory-based serology methods include enzyme-linked immunosorbent assay (ELISA), hemagglutination inhibition assay (HAI), indirect immunofluorescence (IIF), chemiluminescent microparticle immunoassay (CMIA), electro chemiluminescent (ECL) assay, and Western blot. POC testing is primarily immunochromatographic RDTs using lateral flow or blot-based membranes to create a visible chemical reaction in the presence of *T. cruzi* antibodies present in a blood sample to be read as a visible line or dot. Given the wide genetic diversity of *T. cruzi*, a serological test that performs well in one region may not perform well in another.

Molecular tests that look for the presence of *T. cruzi* DNA in a blood or tissue sample have become more common. Similar to parasitological methods, molecular detection is most useful during the acute phase of Chagas disease or during disease reactivation, when parasitemia is highest in the bloodstream. PCR provides higher sensitivity for the diagnosis of acute and congenital Chagas disease compared to microscopy, though it does require more complex laboratory infrastructure and staff trained in molecular techniques and thus is currently rare in LMICs. A positive PCR result after treatment can also be used to indicate treatment failure, though a negative result cannot necessarily confirm treatment success, particularly in chronic Chagas disease where there may not be detectable circulating parasite DNA in the blood.

Access and uptake of existing diagnostics for Chagas is low. Outside of blood transfusion screening programmes and local surveillance and pilot programmes, widespread screening programmes have not been taken to scale, even in the wealthiest countries in the Americas affected by Chagas disease.

There is no standardization and consensus amongst Chagas stakeholders on best practices for existing diagnostics. Despite the issuance of PAHO guidelines, different laboratories within countries may use different tests, develop their own tests, and follow different diagnostic algorithms.[97] The current PAHO recommendation for two, potentially three, laboratory-based serological tests may also be difficult to implement. To address this issue, a current Unitaid grant for Chagas includes an activity focused on validating simplified diagnostic algorithms using rapid tests at primary health centers.[98]

Treatment

Treatment is recommended for girls and women of childbearing age with acute or chronic *T. cruzi* infection and children with acute/congenital or chronic *T. cruzi* infection. Two antiparasitic drugs, benznidazole and nifurtimox, are the only medications currently available for treatment of Chagas disease, and neither are considered safe for use during pregnancy. Both benznidazole and nifurtimox have the highest efficacy during the acute phase, with cure rates of up to 100% in congenital Chagas disease and up to 80-90% in children and adults. Treatment of chronic Chagas disease is much more difficult, with cure rates of 10-20%, and no significant benefit is seen if a patient already has significant organ damage. A full treatment course typically takes 60-90 days, with 2-3 doses of tablets taken orally each day. Though the drugs are overall quite safe, the length of treatment increases the frequency of adverse drug reactions and may decrease patient compliance with finishing treatment. Studies of shorter courses of treatment are underway.[99] Benznidazole is available in child-friendly dispersal tablets of 12.5 mg and nifurtimox in tablets of 120 mg (dispersal tablets of 30 mg should be available proximately). Both drugs can be obtained free of charge through WHO/PAHO as a result of donations from NGOs and suppliers.[100,101, 102]

Less than 1% of the 6 to 8 million people currently living with Chagas disease were estimated to receive treatment in 2019.[103] Challenges included lack of sustained political will around Chagas disease in the face of many other competing health priorities, limited awareness among providers and patients to screen and treat for Chagas disease, and low treatment completion rates due to complicated dosing requirements and high loss-to-follow-up of infants and mothers postpartum.[25]

Chagas disease programs are also greatly underfunded; an analysis of Chagas funding from 2013 to 2018 showed that despite being an important public health problem, <1% of funding and financial support for research on neglected tropical diseases had been allocated to Chagas disease initiatives.[104] In recognition of this, WHO established a World Chagas Day on the 14th of April to raise awareness of this disease and launched an aggressive target of a 90% reduction in people needing intervention against neglected tropical diseases (including Chagas) by 2030.[105] Mobilization of awareness and financial support will be fundamental to the scale-up of routine prenatal screening, treatment of infected newborns and their mothers, and treatment of at-risk women before pregnancy.

5. EMERGING PRODUCT AND SERVICE DELIVERY INNOVATIONS

NEW AND NEAR-TO-MARKET PRODUCTS

The tables below provide an overview of new or promising diagnostic and treatment products that will support Triple Elimination and EMTCT of Chagas. Many of the products featured are already available but are underutilized. Considerations for products featured included suitability for use and access in LMIC settings, level of innovation, and potential for supporting an integrated approach. The tables include key product characteristics where available.

The tables demonstrate that there are a limited number of new HIV infant virological testing and viral load technologies in the pipeline, perhaps reflecting the surge of innovations in these areas (e.g., POC, use of DBS) over the last decade. Device-free virologic tests, such as paper-based assays, would be innovative and could provide further increased access to testing for a hard-to-reach population. There are multiple new HIV self-testing technologies with similar characteristics and format, although with different specimen types, including one that uses urine. Most report detecting HIV-1 and HIV-2 and have a range of 10–20 minutes for test TAT.

There is also a paucity of syphilis products, but new diagnostic modalities include the ability to detect recent from past infections. Two new dual HIV/syphilis tests allow for simultaneous detection of HIV and syphilis from the same fingerstick sample.

There were also a limited number of HBV diagnostic products (particularly for HBV viral load and HBeAg) but there are potential advancements in vaccine delivery. New vaccine delivery technologies allow for prefilled auto disposable devices to deliver accurate birth dosage and remove cold chain barriers. This technology promises to be more cost effective with minimum wastage. There is also the potential for HBV multiplex rapid testing, although no currently available product has the triple combination (HIV/syphilis/HBsAg) that would be most useful for ANC.

New Chagas products (non-exhaustive) listed below include an already available lateral flow assay and a potential new combination therapy (oral tablets) still undergoing trials. Another innovative technology for Chagas detection utilizes a disposable device and is based on LAMP technology. Not mentioned in the table were new techniques being researched for the use of clot samples to extract DNA for Chagas PCR testing and the ability to detect parasite antigen in urine. These techniques are referenced but not included in the table since they are laboratory techniques versus new products.

Last, bundling of tests targeting EMTCT is included; this has the potential to simplify procurement and optimize workspace flow and efficiency for healthcare providers in antenatal clinics who must conduct multiple tests, especially at ANC1.

Connectivity

Many new instrument-based technologies now have connectivity capability to allow for automated data capture and transfer. Data can be reported directly to laboratory management information systems and dashboards to allow review and use by multiple stakeholders (e.g., laboratory staff, program managers, supply chain specialists, etc.) This

type of technology improves the content and quality of the data and allows for more timely and strategic use for program management and patient care. There are also innovative digital solutions in development that are compatible with non-instrument-based technologies (e.g., lateral flow assays).[106] While a detailed assessment of these options is beyond the scope of this report, these connectivity solutions, especially for RDTs, offer promising options for data on HIV, syphilis, HBV, and Chagas in pregnant women and their infants that is greatly needed.

TABLE 10. New and near-to-market products (non-exhaustive)

HIV ST (Assay/Company)	Target/ Sample Type	Process/Training	Turn around time	Actual or proposed cost (USD)	Approval Status (2022)	Date of market entry
Asante HIV-1/2 ORAL SELF-TEST (Sedia Biosciences Corporation)[107]	Detects HIV-1 and HIV-2, combined Oral fluid (swab)	Swab gums, mix in buffer. Add strip to buffer. Color reference guide provided.	20 mins	1.50	Planned WHO PQ submission	In development; Expected 2022
CheckNOW HIV SELF TEST (Abbott Rapid Diagnostics)[108]	Detects HIV-1 and HIV-2, combined Whole Blood	Lancet, alcohol pads, buffer, specimen dropper	15-20 mins	$1.50	WHO PQ	Entered market second half of 2021
Exacto Test HIV ST (Biosynex)[109,110]	Detects HIV-1 and HIV-2, combined Blood (whole blood, serum, or plasma)	Lancet, pipette, add buffer	10 mins	$2-$3	WHO PQ Submitted	Expected 2022
First Response (Premier)	Serum/Plasma/ Whole Blood	Unknown	In development	$1 - $1.50	Planned WHO PQ submission	Expected 2022
HIV SELF TEST BY URINE (Beijing Wantai Biological Pharmacy Enterprise)[111]	Urine	Cassette with capability of sample metering, discharging reagents; and handheld visual reader provided	In development	Unavailable	WHO PQ Submitted	Expected 2023
Manufacturer SD Biosensor HIV blood based self-testing[112]	Whole blood	Lancet, dropper, cassette	In development	$1	WHO PQ submission 2023	In testing phase, Expected 2023
Wondfo One Step HIV 1/2 Whole Blood Home Test[113]	Oral fluid or blood (whole blood, serum, or plasma)	Lancet, dropper, cassette	15 mins	Unavailable	WHO PQ	Expected 2022

HIV Viral Load (Assay/ Company)	Target/ Sample Type	Process/Training	Turn around time	Actual or proposed cost (USD)	Approval Status (2022)	Date of market entry
Lumira Viral Load POC	Whole blood	Lumira device, cartridge, reagents	Unavail-able	Unavailable	Validation of device for EID and VL	Expected 2022

EID RDT (Assay/ Company)	Target/ Sample Type	Process/Training	Turn around time	Actual or proposed cost (USD)	Approval Status (2022)	Date of market entry
The CARD HIV p24 RDT (Mologic)	Whole blood	Lateral flow assay	Unavailable	Unavailable	Ongoing evalua-tion in Uganda	TBD

Syphilis (Assay/ Company)	Target/ Sample Type	Process/Training	Turn around time	Actual or proposed cost (USD)	Approval Status (2022)	Date of market entry
Treponomal and non-treponomal						
Chembio DPP Syphilis Screen & Confirm[114]	Detects both treponomal and non-treponomal so can distinguish active vs. past infections Serum, plasma, whole blood (ve-nous, finger stick)	Blood + buffer, lateral flow cartridge	15 - 20 minutes	Unavailable	ERPD status expired; listed as no longer available for procurement (GF)	Available
TP-IgA						
In-house TP-IgA POCT prototype (Australia)[115]	Lateral flow, in-house manufac-tured immunochro-matographic test designed to detect TP-specific IgA class anti- bodies Whole blood	Blood + buffer lateral flow	30 min	Unavailable	In-house assay	In-house assay
Treponemal						
Determine Syphilis TP (Abbott Diagnos-tics Medical)	Detects TP (Trepo-nema pallidum) antibodies blood	Sample, buffer, cartridge Qualitative results, visually read	About 15 min	Unavailable	Under PQ Review	Available

Multiplexing or Bundling (Assay(s)/ Company)	Target/ Sample Type	Process/Training	Turn around time	Actual or proposed cost (USD)	Approval Status (2022)	Date of market entry
Molbio Diagnostics: Truenat test for HBV DNA[116]	Whole blood, serum, plasma	Chip, dropper, buffer	35 mins	Unavailable	Not yet SRA-ap-proved	Available
HBsAg/HBeAg/ HBsAb/HBeAb and HBcAb Combo Test (Euro Genomas)[117]	Serum, plasma	Cassette, dropper	Unavail-able	$4.27	CE approval no WHO PQ yet	Available
New Hep B immunoglobulin formulation with prefilled syringes	Intramuscular administration	Prefilled neona-tal syringes	Unavail-able	$50 - $75	Status unknown	Available

HIV/HBV (Assay/ Company)	Target/ Sample Type	Process/Training	Turn around time	Actual or proposed cost (USD)	Approval Status (2022)	Date of market entry
Medmira Multiplo HBsAg/HIV/HCV	HIV 1 and 2 and hepatitis B core antigen and hepatitis C virus (anti-HCV) whole blood (venipuncture and fingerstick), serum, and plasma	Mix blood and buffer in tube, add contents to cartridge, cap and add more buffer	Read immediately	Unknown	Not listed by PQ	Available

Multiplexing or Bundling (Assay(s)/ Company)	Target/ Sample Type	Process/Training	Turn around time	Actual or proposed cost (USD)	Approval Status (2022)	Date of market entry
ANC panel (Abbott)[118]	Whole blood	Individual tests for HIV, syphilis, HBV, malaria bundled	< 30 min	Combined cost of all tests	Approval dependent on each individual test	Available

Chagas (Assay/ Company)	Target/ Sample Type	Process/Training	Turn around time	Actual or proposed cost (USD)	Approval Status (2022)	Date of market entry
New combination therapies in development - benznidazole and fosravuconazole[119]	Oral tablets	Frequency to be determined	2 weeks treatment	Unavailable	Still in trials	Post 2023
Chagas Detect™ Plus Rapid Test (In Bios)[120]	Lateral flow rapid test; utilizes a recombinant antigen Venous and capillary whole blood or serum	ICT cassette, buffer	20 minutes	Unavailable	CE, FDA	Available
Loop-mediated isothermal amplification method (LAMP)[121]	Disposable device, simple detection principle based on paper discs coupled to contactless conductivity (C4D) sensors	Unavailable	Unavailable	Unavailable	Unavailable	Available

Vaccine Delivery (Technology/Company)	Target/ Sample Type	Process/Training	Actual or proposed cost (USD)	Approval Status	Date of market entry	Comments
ApiJect[122,123]	Intramuscular administration	Compact Prefilled Autodisposable Device (CPAD)	$0.12	Unavailable	Available	Minimum vaccine wastage.
Bio Farma - Uniject (BD)[122]	Intramuscular administration	Compact Prefilled Autodisposable Device (CPAD)	$0.66	WHO PQ	Available	Minimum vaccine wastage. Combination of differentiated care with vaccines in facility and in community Uniject HBV vaccine for community settings proven to be cost effective in LMICs.

The table below highlights the timelines for market entry for the products above.

TABLE 11. Product pipeline for market entry

	AVAILABLE OR NEAR LAUNCH	END OF 2022	2023
HIV	CHECKNOW HIV SELF TEST (ABBOTT RAPID DIAGNOSTICS) ONE STEP HIV 1/2 WHOLE BLOOD HOME TEST (WONDFO)	ASANTE HIV-1/2 ORAL SELF-TEST (SEDIA BIOSCIENCES CORPORATION) FIRST RESPONSE (PREMIER) VL POC (LUMIRA) EXACTO TEST HIV ST (BIOSYNEX)	HIV BLOOD BASED SELF-TESTING (SD BIOSENSOR) THE CARD HIV EID P24 RDT (MOLOGIC) HIV SELF TEST BY URINE (BEIJING WANTAI BIOLOGICAL)
SYPHILIS	DPP SYPHILIS SCREEN & CONFIRM (CHEMBIO) IN-HOUSE TP-IGA POCT PROTOTYPE (AUSTRALIA) DETERMINE SYPHILIS TP (ABBOTT DIAGNOSTICS MEDICAL)		
HBV	TRUENAT TEST FOR HBV DNA (MOLBIO DIAGNOSTICS) HBSAG/HBEAG/HBSAB/HBEAB AND HBCAB COMBO TEST (EURO GENOMAS)		
CHAGAS	CHAGAS DETECT™ PLUS RAPID TEST (IN BIOS) LOOP-MEDIATED ISOTHERMAL AMPLIFICATION METHOD (LAMP)		
BUNDING OR MULTIPLEXING	ANC PANEL (ABBOTT)		

SERVICE DELIVERY APPROACHES

Bundling of diagnostics

Abbott recently released an ANC 'panel' that bundles their HIV, syphilis, HBsAg and malaria RDTs in one package. The package also includes a plastic tray to optimize workspace efficiency. All tests can be performed with a single fingerstick, and results are provided the same day. The Rwanda Ministry of Health has piloted the panel and conducted feasibility studies and plans to expand its use beyond the pilot sites (personal communication). The panel is also compatible with the Abbott Sympheos data capture platform, which attempts to improve collection and reporting of EMTCT data. This bundling of commodities aims to increase coverage of required ANC1 tests while also simplifying procurement, test storage, and test administration. Previous efforts to bundle supplies (e.g., for EID DBS preparation) have been well-received by healthcare providers for streamlining sample collection.

Targeted interventions to improve provider knowledge and adherence to guidelines

Access to RDTs for syphilis is the cornerstone of increasing screening in antenatal care settings.[52] Guideline-adherent provision of antenatal HIV and syphilis screening is not strongly associated with patient-level factors[124] but depends heavily on buy-in and uptake of facility-level providers. An example of this is illustrated in a study conducted in Democratic Republic of the Congo (DRC) and Zambia that assessed whether use of a multifaceted behavioural intervention for providers improved syphilis screening and treatment in seropositive pregnant women attending antenatal care clinics in Kinshasa (DRC) and Lusaka (Zambia). The behavioral intervention was aimed at healthcare staff and included specific training by respected site clinicians on syphilis RDT use and administration of BPG, reminders, audits and feedback, and supportive supervision. In both arms (intervention and control) all necessary supplies for POC syphilis screening and treatment were provided. In the intervention group, rates of syphilis screening and treatment were higher compared to sites without the behavioral intervention. Of note, the largest difference was in syphilis treatment, with 100% of women at intervention sites receiving treatment and only 43% of women at control sites. The intervention clinics did not show differences in other antenatal care practices not covered, including screening for anemia, HIV, and proteinuria.[125] This suggests that targeted and explicit interventions for HCWs are necessary for impact on different components of antenatal care. Several other studies have found that provision of a reliable supply of RDTs is sufficient to achieve high rates of syphilis screening coverage[126], especially with use of the dual test[127] but that given entrenched issues related to administration of BPG and concerns about adverse effects, additional training and intervention for HCWs is necessary for improving same day treatment rates. These same types of interventions could be utilized for a cohesive Triple Elimination intervention for ANC providers.

Integrated health messaging to parents and community leaders

Using the critical first ANC1 visit to provide high-quality, culturally sensitive counseling and education to mothers and families on prevention of transmission of HIV, syphilis, and HBV could lay the groundwork for improved retention in the PMTCT cascade and adherence to therapy. An integrated counseling approach can also support planning for interventions needed during delivery and the postnatal period (e.g., HepB-BD, provision of ARV prophylaxis to HIV-exposed infants); this planning is especially important in rural and remote areas where facility birth rates are low and neonatal services are harder to access. Specific health promotion efforts aimed at parents about the importance of HepB-BD has been shown to improve uptake of the birth dose, especially in home-based deliveries.[128] These messages should be crafted with input from community leaders and civil society organizations to ensure alignment with ongoing community-based awareness and demand generation efforts to advance Triple Elimination initiatives and dispel misinformation. Other approaches such as Group ANC, might be particularly well-suited for EMTCT service delivery that is women-centered and locally tailored. Group ANC provides an integrated approach incorporating physical assessment, peer support, and health education delivered by a provider to a cohort of women of the same gestational age, and has been shown to improve delivery of gestational-age dependent interventions, and increase facility birth rates.

Improving standardization of postnatal care for exposed newborns

A postnatal care package for HIV-exposed newborns is under development to provide a framework for ensuring retention of mother-infant pairs in the vulnerable breastfeeding period. This could ensure adherence to ART in the mother, timely infant virological testing

at all recommended timepoints, and provision of other key well-baby checks. Incorporating the necessary testing and treatment for syphilis-, HBV- and Chagas-exposed newborns into this package of services could also be a potent and resource-efficient way to fill the significant gaps in this part of the EMTCT cascade.

Birth dose service delivery innovations

Due to the high number of home births, innovative approaches for community-based administration of HepB-BD will be critical to expanding coverage. Several key service delivery innovations for HBV EMTCT deserve mention; they are not 'new' but could be revisited in this era of increased interest and momentum given evidence of efficacy and cost-effectiveness.[129]

- **Provision of HepB-BD by community health workers for home deliveries.** An innovative approach that has shown promise in Asia in improving timely HepB-BD coverage among infants born at home is administration of heat stable HepB-BD vaccine by community-based midwives/health workers, especially with the use of Uniject. Studies have found Uniject to be safe, feasible, reliable, and well-accepted by mothers and providers. In addition, its use increased safety, reduced the vaccine wastage associated with multi-dose vials, and decreased syringe diversion to other uses.Although the data is limited, studies have shown increased HepB-BD coverage in rural home-based birth settings in West Africa and Asia.[130,131,132] This approach could also be used to integrate HepB-BD vaccination into the early postnatal care package (home visits within 1 day of a home birth) recommended by WHO-UNICEF.

- **Promotion of the OCC strategy for vaccine transport and storage.** OCC vaccine strategies are also a useful tool for improving HepB-BD access in rural settings.[133] Acceleration of efforts to license HepB-BD products for OCC use should be a priority, as the CTC approach has been shown to increase coverage and be cost-effective.[133,134]

6. CROSS-CUTTING BARRIERS TO ACCESS

Based on in-depth reviews of the currently available diagnostic technologies and market for key products, as well as key stakeholder input, several cross-cutting access barriers have been identified and are summarized below. These barriers fall across five dimensions of market health: 1) innovation and availability, 2) quality, 3) affordability, 4) demand and adoption, and 5) supply and delivery.

While new technology innovations are needed to address gaps and support achievement of the Triple Elimination agenda, it is critical that they are fit-for-purpose and meet the needs of the intended target audience and use setting. Efficacy, performance, cost-effectiveness and appropriateness are important considerations to evaluate in LMICs to assess the potential value-add and support uptake. As new products are introduced, support to address supply-side barriers related to the regulatory system and quality assurance is essential. Better forecasting is also needed to improve market transparency, support coordination across the EMTCT disease areas and avoid stockouts. Table 12 summarizes the cross-cutting barriers that limit access to products for Triple Elimination and EMTCT of Chagas.

TABLE 12. Cross-cutting access barriers facing products for Triple Elimination, including Chagas in endemic areas.

INNOVATION AND AVAILABILITY		QUALITY ASSURANCE	
Limited new technology	Unsuitable new tech	Lack of QA programs	Weak regulatory systems
• Insufficient engagement of manufacturers. • Rapidly changing guidelines that create uncertainty about demand. • Lack of market transparency • Perceived low returns on investments due to lack of shared program data and impact evidence. • Limited evidence on adoption of new tests. • Regulatory barriers that are perceived as overly burdensome, including costly evaluations and trials. • Technical performance requirements to meet target product profiles. • Resistance to change – due to perceived lack of added value compared to additional resources requirements.	• Overemphasis on the technical characteristics with less consideration to the operational and health system challenges. • Minimal solicitation of community perspectives and input from end-users (e.g., laboratory professionals, MCH nurses pregnant women) during development. • TPPs that do not consider or highlight fit-for-purpose characteristics and the intended settings. • Limited understanding of the balance between accuracy, accessibility, and affordability.	• Lack of robust national QA programs and standardized quality assurance processes (e.g., data reporting) across the multiple diseases and programs. • Lack of quality assurance across the entire value chain (e.g., distributors).	• Absent regulatory controls allow poor quality products to enter the market, which undermines program and facility-level confidence and belief in the utility of testing. • Lack of post-market surveillance data. • Lack of harmonized approaches and information sharing. • Duplication of clinical performance studies.

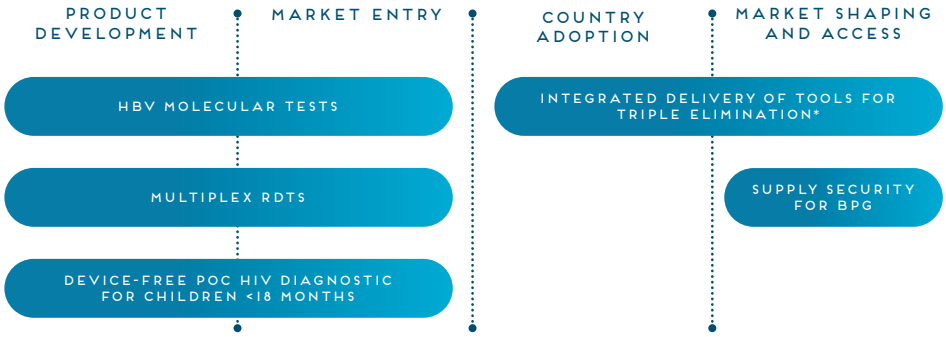
AFFORDABILITY	DEMAND AND ADOPTION		SUPPLY AND DELIVERY
High costs and funding disparities	Poor adoption of global guidance	Limited uptake of new technologies	Inefficient forecasting and weak supply chains
• Pressure to decrease costs can reduce product quality as well as drive promising technologies out of the market. • HIV and other better funded programs can create funding disparities across syphilis, HBV, and Chagas. • Lack of advocacy around the value of new diagnostics and treatments. • Limited cost transparency (e.g., hidden costs/fees, large volume requirements that are impractical for smaller programs), and wastage due to inaccurate forecasting and/or budgeting.	• Lack of support and political will among key stakeholders to pursue EMTCT (especially for syphilis, HBV, and Chagas). • Lack of coordination and collaboration between HIV, STI, MCH, and hepatitis programs and ill-defined roles within the national EMTCT agenda. • Competing priorities within the HIV, STI, or hepatitis programs that draw attention from EMTCT. • Inadequate resources for key programs that make policy adoption seem impractical.	• Lack of 'buy-in' from program managers and/or facility-level providers due to limited awareness of the importance and/or utility of new products. • Programmatic siloes lead to different implementation and scale-up approaches, creating facility-level fragmentation of services. • Lack of community engagement to inform product introduction. • Lacking alignment and coordination across programs and stakeholders. • Concerns about the accuracy and utility of certain RDTs, especially HBeAg. • Concerns about the feasibility of implementing new HBV PMTCT recommendations in primary health services due to perceived complexity.	• Limited attention to demand forecasting for commodities outside of HIV, and lacking efforts to develop comprehensive forecasts across the diseases. • Supply disruptions and stock outs. • Lacking alignment of availability and access to both diagnostics and treatments for EMTCT. • Short expiration dates and delays in product transport that result in product wastage.

7. POTENTIAL OPPORTUNITIES

The Triple Elimination initiative itself is an opportunity for a paradigm shift in how we have approached innovations. This landscape of current and emerging technologies and systems for each disease presents a chance to assess successes and challenges and work to address the gaps in EMTCT through a holistic MCH lens. Disruption of 'business as usual' in EMTCT can strengthen the value chain and allow the application of a more sustainable and patient-centered approach.

The section below highlights several opportunities that exist to accelerate Triple Elimination efforts, summarized in Figure 5 below. The opportunities are not specific to Unitaid's mandate and business model, but instead represent a range of market-based interventions that could be undertaken by different global health actors and stakeholders.

FIGURE 5. Opportunities to accelerate development and introduction of new products for Triple Elimination (illustrative and non-exhaustive).



*Introduction support for integrated delivery includes several opportunities

NEW PRODUCT DEVELOPMENT

Where existing products fail to support countries' efforts to reach global targets, the development of new technologies that meet the needs of specific populations are needed. Diagnostic innovations that provide faster and affordable quality testing could include new targets and biomarkers, delivery systems, digital solutions and specimen types. These innovations could be complemented by tools like readers and data capture connectivity solutions that increase result reporting and add to much-needed prevalence and program data for syphilis, HBV, and Chagas. Innovations in other areas that could accelerate Triple Elimination include easier methods of vaccine delivery (e.g., pre-filled syringes, new administration methods) and less restrictive cold chain requirements for vaccine storage and delivery.

TPPs have been useful for developers but often come out too late for the timelines required for research and development. Development of preliminary TPPs for key testing gaps (particularly HBV POC viral load) and review of existing TPPs (e.g., RDTs to detect active syphilis infection) may be useful in addition to landscapes and other scoping exercises.

This would also increase communications and collaborations with developers; including input from industry as early as possible for TPPs could provide an opportunity to leverage innovations and expedite market entry.

Smart market research can help to better understand the needs of the target audience and provide new solutions for how to potentially meet those needs, with a focus on the right test and right place. In addition to industry, other stakeholders should also be included in market research and TPP discussions, particularly for research on values and preferences for end-users (e.g., patients and HCWs).

The following three product development opportunities represent critical gaps that warrant prioritization.

Accelerate development of HBV molecular tests

Access to HBV viral load and HBeAg testing are major bottlenecks in initiation of antiviral prophylaxis in pregnant women who are HBsAg positive.

For HBeAg testing, the lack of clear data on the role of genotypic differences in HBeAg expression and concerns about its ability to serve as a reliable proxy for level of HBV viremia, especially in Africa, poses a significant challenge to development and uptake of an HBeAg RDT. Further data is needed on the presence and correlation of HBeAg in Africa before pursuing use of HBeAg testing as a definitive and acceptable proxy for HBV viremia. In contrast, HBV viral load is the gold standard for determination of viral replication level and access to reliable HBV viral load assays at the primary health level could provide evidence-based and accepted results that would guide patient management. Furthermore, even if future WHO guidance eliminates the HBV viral load threshold for PMTCT TDF prophylaxis decisions, HBV viral load testing will still be required for children and non-pregnant adults with chronic HBV infection, all of whom require routine HBV viral load monitoring to determine treatment eligibility and response. Validation of DBS for currently available platforms would be a significant advancement, although the time required for specimen transport and result return makes this less appealing in the ANC setting, where the window of time is short and there is risk of LTFU. For this reason, an inexpensive HBV DNA POC assay (ideally device-free) could have significant public health value in the PMTCT arena and beyond.

Development of multiplex RDTs for HIV, syphilis, and HBsAg

Interventions to promote development of a quality-assured multiplex RDT for HIV, syphilis, and HBsAg has the potential to make a significant impact for advancement of Triple Elimination efforts, especially for HBV. Use of the dual test has demonstrated how the addition of a multiplex test to an existing ANC screening platform can rapidly increase coverage of the added test. In regions without existing strong ANC testing platforms (e.g., West and Central Africa), a low-cost multiplex test could potentially serve as the impetus for re-invigorating languishing PMTCT programs. However, attention to cost will be crucial for uptake of a multiplex test, especially considering the limited financing for hepatitis elimination programs. Experiences with the dual test have shown that finite budget envelopes make price a major issue (even given the programmatic value and advantages of operational efficiency), so a cost-neutral test would be ideal.

Development of device-free POC HIV diagnostics for children <18 months

Current products aimed at identifying HIV-infected children use virological methods that require device-based technologies. A simple, accurate, device-free rapid POC test that provides reliable results and can be used in primary MCH clinics could further expand access to testing for HIV-exposed infants; in addition, a device-free POC EID test could also be used in other non-PMTCT settings (e.g., malnutrition clinics, tuberculosis clinics, inpatient pediatric wards) that are high-yield for case finding.A TPP for such a test was released by WHO in 2020 but none are currently available.[135] While most HIV RDTs require results be read no more than 15-20 minutes later, this TPP suggests a minimum of 1 hour result stability. It also notes the need for connectivity and readers to ensure data is captured.

It is important to emphasize to developers and program managers that lower standards of performance in a device-free test may be an acceptable trade-off for the improved access to EID that a device-free test could provide.[136] WHO has suggested that even with lower sensitivities, a device-free EID POC test could provide added value to programs and substantially affect the morbidity and mortality of HIV-exposed infants. Further research and/or modeling is needed to generate evidence to support this approach to diagnostic test development for EID and potentially other EMTCT modalities.

PRODUCT INTRODUCTION

Accelerating adoption and integrated delivery of tools for Triple Elimination

There are opportunities to accelerate adoption and secure the supply of tests and treatments for HIV, syphilis, HBV and Chagas by leveraging existing technologies and building on new market interventions, such as the new volume guarantee for SD Biosensor's STANDARD Q HIV/Syphilis Combo test that was negotiated by CHAI, MedAccess, and SD Biosensor.

Implementation pilots that focus on developing pragmatic integrated approaches to screening and treatment of HIV, syphilis, HBV, and Chagas (where applicable) in ANC sites could provide valuable insights for achieving a more holistic antenatal package of care. Evidence on the feasibility, cost-effectiveness and impact of delivering an optimal mix of tools and delivery strategies for Triple Elimination in different contexts would catalyze adoption and could provide a roadmap to programming that overcomes traditional disease silos and maximizes the overlap between tools and platforms. Pilots could also address supply side gaps, leveraging procurement volumes to support access to generic TDF for HBV patients as well as quality BPG for syphilis treatment.

Given the access, performance, and cost limitations of the current assays for HBeAg and HBV viral load, some experts have suggested that pregnant women with chronic HBV infection be provided antiviral prophylaxis based only on HBsAg positivity and referred for further assessment after delivery.[137] This is based on the proven safety, short duration, and low cost of TDF prophylaxis during pregnancy and the major operational advantages associated with substantial simplification of the patient algorithm. This public health approach represents a compelling option for rapidly expanding HBV EMTCT programs given the current availability of affordable and quality assured HBsAg RDTs. Further research on this strategy that includes cost-effectiveness data and anticipated impact of TDF prophylaxis could accelerate consideration of this approach. Further market assessments to investigate the higher prices of TDF in some settings may also be warranted as part of this research.

Other promising service delivery strategies, such as postnatal care packages and innovative approaches for community-based administration of HepB-BD, could also be considered within implementation pilots and were detailed in section 5.

Improvement in supply security for BPG for congenital syphilis elimination

With a rise in screening due to normative guidance and scale-up of dual testing, BPG demand is expected to increase up to 160%, further underscoring the need to improve supply reliability.[138] Prioritization of universal access to BPG can produce significant impact in both congenital syphilis prevention and prevention of RHD. The WHO PQ process for BPG is an opportunity to ensure a reliable supply of an affordable, high-quality product, but the WHO PQ process is complex and resource-intensive, and manufacturers currently have limited incentives to pursue PQ due to low BPG prices and uncertain demand. Investing in suppliers to achieve PQ would ultimately improve the overall quality of products and support a more long-term stable market supply of BPG. To address this issue, WHO has put forth a proposal in which they would support selected manufacturers to achieve PQ status for benzathine penicillin API and FPP.

Once WHO pre-qualified, a catalytic procurement mechanism could be mobilized as an effective market-accelerating intervention to rapidly introduce commodities and mobilize investment from major procurers, stimulate enhanced monitoring, and accelerate development of the market for a quality-assured product (i.e., rapid product access and uptake).

WHO plans to develop a collaboration framework with major donors/procurers to ensure rapid and coordinated uptake of prequalified BPG, and work with national counterparts to ensure early recognition of the value addition of the new prequalified product and its inclusion in the WHO Model List of Essential Medicines. This would smooth the pathway to registration and introduction. This approach could also be viewed as compelling business opportunities for manufacturers to achieve and maintain WHO PQ and/or other international good manufacturing practice (GMP) standards.

8. CONCLUSION

There has been increasing global momentum for Triple Elimination efforts and the milestones and targets outlined in the new Global Health Sector Strategies on HIV, viral hepatitis and STIs should be viewed as a call to action to re-energize the EMTCT movement and accelerate progress. In many cases, the evidence for interventions is strong and the tools are currently available, so countries should focus on leveraging and optimizing current systems towards an integrated approach. However, significant data and evidence gaps remain for key areas, particularly within the HBV space, that may hinder buy-in and implementation. In addition, awareness of EMTCT of syphilis, HBV, and Chagas remains sub-optimal so early and sustained input and planning with communities will be vital. By building a more integrated approach, we can leverage synergies to develop a coordinated and multidisciplinary package of care that addresses the needs of pregnant women and their families in a holistic, patient-centered way and ensures EMTCT of HIV, syphilis, HBV, and Chagas disease.

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