REPRODUCTIVE, MATERNAL, NEWBORN AND CHILD HEALTH THEMATIC NARRATIVE

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Unitaid
Innovation in Global Health

EXECUTIVE SUMMARY

This Thematic Narrative for Reproductive, Maternal, Newborn and Child Health (RMNCH) provides an update to the *Development of Strategy 2017 - 2021: Strategic Option – Reproductive, Maternal, Newborn and Child Health (RMNCH)*, which was presented to the Unitaid Executive Board in June 2016 to inform the inclusion of RMNCH in the *Unitaid Strategy 2017-2021*. The Unitaid Executive Board endorsed the inclusion of RMNCH, initially as a means of supporting more integrated approaches to health. To further advance Unitaid's commitment to RMNCH, the Executive Board recommended that the Secretariat undertake additional scoping to identify new opportunities.

This document provides an update on the global landscape of RMNCH to highlight commodity access challenges, and provides recommendations on potential areas where Unitaid's involvement could help respond to significant access gaps in the near- and longer-term.

RMNCH burden persists in many LMICs, particularly in sub-Saharan Africa

Over the last 30 years, the global RMNCH burden has decreased significantly, but many countries are far from achieving the national-level goals for maternal and child health – particularly in sub-Saharan Africa. Approximately 300,000 women die from pregnancy-related causes every year – 74% from complications during delivery. An estimated 2.5 million newborns died in the first month of life in 2017, which makes up nearly 50% of all under-5 deaths.

There are potential opportunities for innovative tools and approaches to impact RMNCH

Commodity barriers contribute to high maternal and newborn mortality rates. Unitaid has identified a number of potentially high impact interventions that could respond to key commodity access barriers.

New affordable versions of long acting hormonal contraceptives targeted at LMICs are in late-stage development and will soon be ready for regulatory review. Moreover, several multipurpose technologies are in clinical trial stages, and when available could provide a more suitable option for both contraceptive and HIV prevention options for women in LMICs.

New gonorrhoea and chlamydia point-of-care-tests that hold promise for improving accuracy and affordability are currently in late-stage development, and once available, opportunities could exist to catalyze introduction and scale up.

Innovative delivery mechanisms that integrate existing dual point-of-care HIV/syphilis, HBV and Chagas disease tests into existing RMNCH platforms could provide opportunities to identify and treat infections in pregnant women to prevent mother-to-child transmission of these diseases. New tools in development could also be evaluated and positioned for early introduction and scale up.

For newborns, oxygen concentrators to address respiratory distress that are more appropriate for LMIC settings are amongst the most promising new tools to address the key burdens of neonatal mortality.

New point-of-care diagnostic tests for pre-eclampsia are in late-stage development and are expected to be available in LMICs by next year. Fast, easy-to-use, and affordable, these tests

could improve diagnosis at the primary care level and inform referral decisions to avoid adverse outcomes. Moreover, portable dopplers are in the registration stage, and could be utilized in LMICs to identify risk of stillbirth in pregnant women.

Heat-stable carbetocin has recently been recommended by the WHO for prevention as an effective alternative to oxytocin that does not require cold-chain storage. Supporting activities that drive uptake would help respond to one of the key barriers to effective postpartum hemorrhage prevention. Emerging products for emergency treatment of PPH are also in the regulatory stage and could extend life-saving options to women in LMICs.

The RMNCH market landscape is challenging – but there are opportunities for sustainable scale-up

There has been a visible shift in the RMNCH funding landscape toward market shaping and coordination support. In recent years, the global RMNCH community has emphasized better use of funding to strengthen RMNCH markets. Funders are now emphasizing the need for strategic approaches that enhance markets, with new mechanisms evolving to support this approach.

This diverse and evolving funding landscape presents clear opportunities in terms of sustainability, but also requires more intensive and directed efforts to support transition, particularly through direct collaboration at the national level. The RMNCH funding landscape remains fragmented, with scale-up relying on domestic funding and just a few bilateral and multilateral funders. Interventions will need to include the development of national roadmaps for scale up, and demonstrate feasibility of national adoption. Market conditions for individual maternal health commodities are widely variable and as such, shortcomings require product-specific approaches.

While RMNCH does not have a global body that consolidates purchasing power at the same scale that the Global Fund does for HIV, tuberculosis and malaria, for example, there are mechanism that can be leveraged to facilitate effective procurement and scale-up. The Global Financing Facility (GFF) provides complementary financing to address RMNCH – working directly at the national level in LMICs. GFF funding enables countries to scale-up interventions that have demonstrated effectiveness, feasibility and value-for-money.

Unitaid could play a catalytic role to help drive uptake of high-potential innovations

Unitaid works in close cooperation with partners at different stages of the value chain to ensure that innovative tools are brought to market and scaled-up. Due to variable market conditions across the RMNCH landscape, support to individual commodities with product-specific approaches that address shortcomings and access barriers could effectively address key drivers of the RMNCH burden.

Given the current state of the RMNCH landscape, and opportunities that are emerging, Unitaid's role in catalyzing innovation for scale-up could be effectively applied to this space. Unitaid could support access to innovative tools and approaches for RMNCH by advancing R&D and innovation, supporting normative guidance and product quality, and catalyzing product introduction to address delivery challenges. In particular - Unitaid investment could potentially play a role in unlocking GFF funding for RMNCH innovations.

Expansion into the RMNCH space has already been actioned through new Areas for Intervention, Calls for Proposals, and investments. New interventions into RMNCH could complement these new investments, as well as the rich existing portfolio of HIV, TB and malaria grants that impact maternal and newborn health. As with these existing investments, bespoke country transition plans, coupled with scale-up activities that reflect a diverse set of actors should be applied to any RMNCH efforts.

CONTENTS

ABBREVIATIONS

ACS	Antenatal Corticosteroids
AfI	Area For Intervention
AMR	Antimicrobial Resistance
API	Active Product Ingredient
ART	Antiretroviral Therapy
bCPAP	Bubble Continuous Positive Airway Pressure
BMGF	Bill & Melinda Gates Foundation
BP	Blood Pressure
CHAI	Clinton Health Access Initiative
CHX	Chlorhexidine Digluconate
CPAP	Continuous Positive Airway Pressure
DPP	Dual Prevention Pill
EMTCT	Elimination Of Mother-To-Child Transmission
ESC	Extended-Spectrum Cephalosporins
EWEC	Every Woman Every Child
FCDO	Foreign, Commonwealth And Development Office
GARDP	Global Antibiotic Research And Development Partnership
GASP	Gonococcal Antimicrobial Surveillance Programme
GAVI	Global Alliance For Vaccines Initiative
GFF	Global Financing Facility
HBeAg	Hbv E Antigen
HBsAg	Hbv Surface Antigen
HBV	Hepatitis B Virus
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HSV	Herpes Simplex Virus
IFAz	Iron And Folic Acid Supplementation
IM	Intramuscular
IMCI	Integrated Management Of Childhood Illness
LARC	Long Acting Reversible Contraception
LMIC	Low- And Middle-Income Country
LNG-IUS	Levonorgestrel Intrauterine System
MA	Medical Abortion
mCPR	Modern Contraception Prevalence Rates
MDG	Millennium Development Goal
MPT	Multipurpose Technology
MTCT	Mother-To-Child Transmission
NAATs	Nucleic Acid Amplification Tests
NASG	Non-Pneumatic Anti-Shock Garment
NEST360°	Newborn Essential Solutions And Technologies
NNJ	Neonatal Jaundice
PDP	Product Development Partnership
PE/E	Pre-Eclampsia And Eclampsia
PPH	Postpartum Hemorrhage
PPIUD	Postpartum Intrauterine Device
PrCr	Protein-To-Creatinine
PrEP	Pre-Exposure Prophylaxis
R&D	Research And Development
RDS	Respiratory Distress Syndrome
RMNCH	Reproductive, Maternal, Newborn And Child Health
SDG	Sustainable Development Goal
SMO	Social Marketing Organization
SRA	Stringent Regulatory Authority
STI	Sexually Transmitted Infection
TPP	Target Product Profile
UBT	Uterine Balloon Tamponade
USAID	United States Agency For International Development
WHO	World Health Organization

CONTEXT AND INTRODUCTION

1.1 Thematic narrative background

As part of the development of the *Unitaid Strategy 2017-2021*, the Secretariat presented the *Development of Strategy 2017 - 2021: Strategic Option – Reproductive, Maternal, Newborn and Child Health (RMNCH)* at the 25th Session Unitaid Executive Board Meeting in June 2016. This document provided a snapshot of the global landscape of women's and children's health and assessed RMNCH as a potential area of expansion for the next strategic period. The Executive Board endorsed the inclusion of RMNCH in the *Unitaid Strategy 2017-2021* as a means of supporting more integrated approaches to health. This has since been actioned through new AfIs[1] covering integrated management of childhood fever, prevention and screening of cervical cancer in HIV-infected women, and elimination of congenital infection in Chagas disease. New opportunities in these areas complement a rich portfolio of HIV, TB and malaria grants that target pregnant women and/or children (e.g. TIPTOP project to prevent malaria in pregnancy, CaP TB project to incorporate tuberculosis screening into maternal and child health platforms). In total, grants that address RMNCH burden make up 50% of Unitaid's current portfolio.

In addition to the above efforts in RMNCH, the Executive Board requested the Secretariat to continue to monitor the RMNCH landscape for additional opportunities. Drawing on scoping work and research conducted by the Unitaid Secretariat, as well as input from external consultation, and extensive stakeholder and partner engagement, this RMNCH Thematic Narrative provides an update to the June 2016 document, with progress against the global RMNCH goals, challenges that impede the response, and developments that are responding to these barriers. This document also responds to recommendations made by the Executive Board, and identifies potential near- and longer-term opportunities that expand Unitaid's reach in RMNCH interventions (Section 5).

1.2 Scope

This Thematic Narrative responds to the need to monitor potential opportunities in RMNCH as per the *Unitaid Strategy 2017-2021*. RMNCH refers to a state of wellbeing throughout the continuum of care that follows from pre-conception family planning, through pregnancy, childbirth, and to the early years of childhood development.[2] Reproductive health includes sexual health throughout the life course for both men and women, including sexually transmitted infection prevention, diagnosis, and treatment services.

To define the scope of this Thematic Narrative, the Secretariat identified the main drivers of RMNCH morbidity and mortality. The Secretariat then undertook desk-based research and partner consultation to understand the main challenges that prevent progress against these key burdens. The Secretariat then investigated global efforts and opportunities to address these challenges with a focus on gaps in the global response, specifically for effective tools - both existing and underutilized, and those in the research and development (R&D) pipeline.

Given the strategic and targeted approach of this Thematic Narrative to analyze the largest contributors to RMNCH burden, and gaps to address them, this document does not provide an in-depth analysis of all challenges within RMNCH, or for all interventions that could potentially overcome them. Notably, given that nearly half of the under-5 health burden is in

infants in the first 28 days of life, and that Unitaid already has significant investments that respond to the main challenges of under-5 health (i.e. malaria case management, malaria prevention, pediatric HIV case management, and pediatric tuberculosis testing), this Thematic Narrative focuses specifically on opportunities for newborn health within the under-5 population. For more information on Unitaid's efforts in children under-5 years of age, please see relevant sections of the Disease Narratives for **HIV**, **Tuberculosis**, and **Malaria**.

2 RMNCH GLOBAL GOALS AND HEALTH BURDEN

Over the past thirty years, women's and children's health has gained momentum globally. On the back of robust advocacy and international leadership, this momentum is reflected in political commitment, relevant Millennium Development Goal (MDG) and Sustainable Development Goal (SDG) targets, and increased levels of funding. However, many countries are still falling short of the SDG targets set for RMNCH, and the situation has been made more challenging due to the COVID-19 pandemic and lockdown measures.

Women's and children's health are acknowledged as critically important to the health and wellbeing of a population – both as an indicator of general population health, and as a determinant for achieving broader development goals, including those outside of the health sphere. Investments in women's health, and particularly family planning, are considered "best buys" for global development in terms of value for money, generating savings through reduced maternal mortality, increased economic development, improved child health and education, and even decreased vulnerability to climate change.[3]

To align with the SDG indicators, the following narrative has been structured with sections on reproductive, maternal, and newborn health, introducing the key health burdens driving morbidity and mortality, the relevant global goals, and status towards their achievement. The burdens and causes of these conditions are often linked, and these crossovers have been highlighted where appropriate.

2.1 Reproductive health

WHO defines reproductive health as "a responsible, satisfying and safe sex life [with] capability to reproduce and the freedom to decide if, when and how often to do so".[4] SDG 3 highlights the essential role that reproductive health plays in promoting well-being for all. However, greater progress is needed to meet SDG 3.7 on ensuring universal access to sexual and reproductive health services, including family planning and sexually transmitted infection (STI) prevention, diagnosis, and treatment services by 2030.[5]

2.1.1 Family planning

Access to family planning is a determinant of maternal and child mortality, as well as many economic and social development indicators.[6] Family planning prevents adverse outcomes and maternal and newborn deaths by reducing women's exposure to high risk pregnancies, and helps to avoid unintended and closely spaced pregnancies.[7] Improvements in family planning access have been shown to increase educational attainment and employment for women and reduce health-care costs. Empowering women to choose if and when they get pregnant, and providing access to services that enable this choice, fundamentally advances human rights and supports vulnerable populations.[8]

Women who become pregnant in adolescence or over the age of 40 are at an increased risk of adverse delivery complications, and giving birth to premature or low-birthweight newborns. Complications during pregnancy and childbirth is the leading cause of death among adolescent women 15-19 years old,[9] and higher infant mortality rates in pregnant women younger than 20 years-old or older than 40 are found at every income level in LMICs.[10] Adolescent girls

and young women are also less likely to receive appropriate antenatal or intrapartum care.[11] When births to the under-20 and over-40 cohorts are combined, they account for up to 36% of births in LMICs, with proportion highest in sub-Saharan Africa. Births spaced less than 2 years apart also increase risk of adverse outcomes. Data from 34 LMICs shows that 20% of births are within two years from last delivery.[12]

As of 2019, 314 million women within the FP2020 countries (a group of LMICs committed to improving access to family planning services) used modern contraception methods. This is a significant increase from 53 million in 2012. However, estimates suggest that 230 million women and girls in LMICs still have unmet need for modern contraceptive methods.[13]

Many of the countries with the highest maternal mortality rates, and child mortality rates are also those with the lowest use of family planning methods, such as Chad, South Sudan, Somalia, and Nigeria. Sub-Saharan Africa has the lowest modern contraception prevalence rates (mCPR) globally. However, sub-Saharan Africa is also the region that has experienced the highest recent growth in mCPR. Between 2012 and 2019, mCPR growth in East and Southern Africa has been 1% per year on average, and 0.7% and 0.6% in West Africa and Central Africa, respectively. These rates are greater than all other regions, and at least double the growth of the next highest of Latin America and the Caribbean, and South Asia.[14]

2.1.2 Sexually Transmitted Infections

Sexually transmitted infections (STIs) contribute to significant morbidity and mortality globally and compromise quality of life for men and women.[15] STIs are mainly spread through sexual contact, including vaginal, anal, or oral sex, and some can be spread through blood or blood product, or through mother-to-child transmission (during delivery, or through postpartum breastfeeding). Of the eight pathogens that contribute to the highest STI incidence, four can be cured with available treatments: syphilis, gonorrhoea, chlamydia and trichomoniasis. The other four infections are viruses and are incurable but treatable, these include hepatitis B virus (HBV), herpes simplex virus (HSV or herpes), human immunodeficiency virus (HIV), and human papillomavirus (HPV).[16]

Incidence of STIs remains high, and are increasing in some settings. WHO estimates that in 2016 there were 376 million new infections of the curable STIs worldwide, including 127 million cases of chlamydia, 87 million cases of gonorrhoea, 6.3 million cases of syphilis, and 156 million cases of trichomoniasis[17]. Of the incurable STIs, an estimated 500 million people are living with genital herpes simplex virus[18] and more than 257 million are living with chronic HBV.[19] The global estimate for people living with HIV is 38 million as of 2019,[20] and more than 290 million women are estimated to have an HPV infection.[21] The disease burden varies significantly by WHO region. For example, the highest rates of HIV and syphilis are in the African region. Chlamydia is most prevalent in the Western Pacific region and the region of the Americas, and HBV is most prevalent in the African and Western Pacific regions.[22]

HIV, syphilis, HBV, gonorrhoea, and chlamydia can all be transmitted from mother-to-child during pregnancy and childbirth and lead to poor perinatal outcomes if untreated. Even though almost all LMICs are implementing lifelong antiretroviral therapy (ART) for prevention of mother-to-child transmission (MTCT) of HIV,[23] MTCT still contributes to an estimated 160,000 new HIV infections.[24] The other conditions receive far less attention. MTCT of HBV is responsible for more than one-third of the 257 million chronic infections globally, [25,26] and can lead to hepatocellular carcinoma.

In recent years, maternal prevalence of syphilis has remained stable.[27] In 2016, an estimated 988,000 pregnant women were infected with syphilis and this resulted in over 350,000 adverse birth outcomes, including 200,000 stillbirths and newborn deaths. This makes syphilis the second most common infectious cause of stillbirth worldwide.[28] Despite a decrease

in congenital syphilis since 2012, there were 661,000 congenital syphilis infections in 2016.[29] Among surviving infants with the congenital infection, there is increased risk of both physical and mental developmental disabilities. Most cases of congenital syphilis are preventable if women are screened for syphilis and treated early during prenatal care.

Gonorrhoea, chlamydia, and trichomoniasis contribute to significant morbidities for pregnant women with an untreated infection.[30, 31, 32] Women with untreated gonorrhoea and chlamydia infections can develop severe complications, including pelvic inflammatory disease, chronic pelvic pain, ectopic pregnancies, and infertility.[33] They are also at an increased risk of adverse outcomes such as spontaneous miscarriage, premature rupture of the amniotic sac, stillbirth, and preterm birth.

Infants born to women with cervical gonorrhoea can develop hyperacute conjunctivitis, which can lead to blindness if not quickly treated.[34] Chlamydia and gonorrhoea can be effectively prevented using antibiotics or silver nitrate ocular prophylaxis.[35] Vertical transmission of chlamydia and gonorrhoea can also cause pneumonia in infants.[36]

Syphilis, gonorrhoea, herpes, and trichomoniasis greatly increase the risk of acquiring or transmitting HIV infection. It has been estimated that approximately 50% of new HIV infections are attributable to STIs in women,[37] and STIs, including syphilis, gonorrhoea and HSV have been shown to increase the risk of HIV acquisition by three-fold or more.[38, 39]

For the incurable STIs, preventative interventions are especially critical. Both HBV and HPV have effective vaccinations that are the best means of prevention. HPV is responsible for nearly all cervical cancer as well as a large proportion of other anogenital cancers and oropharyngeal cancers,[40] and HBV is a well-recognized risk factor for chronic liver disease and primary liver cancer.[41]

Two strategies are key to driving the response to STIs as a global health priority. The first supports the global commitment of elimination of mother-to-child transmission (EMTCT) of HIV and syphilis. A framework to validate EMTCT of both diseases was released in 2014 and updated again in 2017 by WHO.[42] In 2021, this global strategy will be updated to address triple elimination of HIV, syphilis and HBV and will support the regional framework for the Americas that expands to quadruple elimination of HIV, syphilis, HBV and Chagas disease. The framework focuses on a harmonized approach to improving health outcomes for mothers and their children.[43] The second is the Global Health Sector Strategy on Sexually Transmitted Infections 2016–2021. The strategy has set the goal of ending STI epidemics as major public health concerns by 2030 and includes the following targets:

- A 90% reduction in syphilis incidence globally and 50 or fewer cases of congenital syphilis per 100,000 live births in 80% of countries
- A 90% reduction in gonorrhoea incidence globally
- 90% national coverage and at least 80% in every district in countries that include the HPV vaccine in their national immunization programme[44]

Based on the latest estimates, every day there are more than 1 million new cases of the curable STIs, and prevalence rates have not declined since the last published data in 2012.[45] Renewed investments in the introduction and scale-up of effective solutions are needed, as well as the development of new diagnostics and treatments in order to reach the targets.

2.2 Maternal health

Maternal mortality occurs due to complications during and following pregnancy and childbirth, which mostly develop during pregnancy. The WHO estimates that more than 211 women out of every 100,000 live births die from causes related to pregnancy or childbirth every year (300,000 women globally). Although the number of women who died as a result of preg-

nancy or childbirth related complications decreased by 38% between 2000 and 2017, maternal mortality rates remain high in many LMICs.[46]

The main causes of maternal mortality that account for nearly 75% of all maternal deaths are postpartum hemorrhage (PPH), hypertensive disorders (most prominently pre-eclampsia and eclampsia (PE/E)), sepsis and unsafe abortion. Forty percent of deaths are attributed to PPH and PE/E alone.[47] An additional, 11% are attributable to maternal sepsis.[48] Unintended pregnancies contribute to an estimated 69 million abortions each year, of which 35 million are unsafe, leading to 8% of maternal mortality.[49]

Anemia during pregnancy is another major contributor to maternal mortality that has been shown to double the odds of maternal death,[50] by increasing risk of premature labor,[51] PE, gestational diabetes,[52] and PPH, and antenatal and postnatal sepsis.[53] An estimated 40% of pregnant women have anaemia, with at least half due to iron deficiency. Severe anaemia affects 800,000 pregnant women worldwide,[54] with the largest burden in Africa and South-East Asia.[55]

Ninety-four percent of the maternal mortality occurs within LMICs.[56] Sub-Saharan Africa carries the greatest burden globally, where maternal mortality rate has only improved marginally over the last 30 years. Only two countries of the 40 countries with the highest maternal mortality rates lie outside of sub-Saharan Africa. Countries with lowest GDP per capita suffer from the highest maternal mortality rates, as well as countries that are considered at "high alert" or "very high alert" under the Fragile States Index.[57]

Given this persistent burden, many countries, including most countries in Africa, are not on-track to achieve the country-level SDGs to reduce maternal mortality rate by two-thirds and achieve a maternal mortality rate lower than 140 by 2030. At this rate, without a significant acceleration of efforts, the 2030 global SDG to reduce maternal mortality is unlikely to be achieved.

2.3 Newborn health

The neonatal period is defined as the first 28 days of life, and carries the highest risk of infant mortality, with an estimated 2.5 million deaths in 2018.[58] The global neonatal mortality rate fell approximately 50% between 1990 and 2018 – from 37 deaths per 1,000 live births to 18 deaths per 1,000 live births.[59] Nearly half of under-5 deaths occurred in the first month of life.[60] In the past 30 years, progress in reducing neonatal mortality has been slower than the broader under-5 bracket, and share of neonatal deaths relative to all under-5 deaths has increased.[61]

The main causes of neonatal mortality differ from the causes of death for older children in LMICs. The most prominent cause of newborn deaths in 2018 was preterm birth complications (35%). This constitutes nearly 1 million neonatal deaths every year, with respiratory distress syndrome (RDS) being the main complication leading to mortality.[62] In fact, neonates with respiratory distress are 2–4 times more likely to die than neonates without respiratory distress.[63]

Intrapartum-related complications (24%), sepsis (15%) and congenital abnormalities (11%) also contributed significantly to the neonatal burden,[64] with nearly all of these deaths occurring in LMICs. Sepsis is particularly deadly for neonates during the first five days of life and premature infants are at elevated risk.[65]

High rates of stillbirths are a persistent issue, particularly in LMICs, where 98% of the burden occurs. Each year, there are an estimated 2.6 million stillbirths worldwide.[66] Stillbirths are often associated with fetal growth restriction, preterm labor, post-term pregnancy, and sub-optimal care. Even with this high burden, stillbirth has not been prioritized in the MDGs and SDGs.[67] Progress in reducing this rate has been slow, particularly in Africa.[68]

It is also important to note that the high morbidity and mortality burden among newborns and infants in LMICs is directly associated with the leading causes of adverse maternal outcomes. For example, pre-term birth complications, intra-partum complications, and stillbirth occur more frequently among babies born to women with anaemia,[69] or PE/E.[70] Thus, many strategies to address the newborn and infant health burden will begin during the antenatal care period.

Other causes of newborn death include hypothermia and hyperbilirubinemia. As many as 85% of infants born in hospitals in low-resource settings develop a temperature less than 36.5°C, clinically known as hypothermia, and mortality rates increase with each degree Celsius of temperature lost.[71] Hyperbilirubinemia can occur in neonates born with neonatal jaundice (NNJ). NNJ is highly prevalent, affecting up to 60-80% of newborns.[72] In some cases, NNJ may become severe enough to put infants at risk for bilirubin-induced mortality or long-term neurodevelopmental impairments.[73] Although the contribution of NNJ to the global burden of disease remains largely unknown,[74] the Global Burden of Disease 2016 report suggests that NNJ prevention is important in the first week of life in sub-Saharan Africa and South Asia, especially in countries with the highest global burden of neonatal mortality.[75]

The largest declines in neonatal mortality rates were across South and East Asia, with little progress in sub-Saharan Africa. In fact, in sub-Saharan Africa, neonatal deaths increased between 1990 and 2000, and only decreased minimally by 2017, leading to a stagnated neonatal mortality rate in the region.

On current trends, most countries are progressing toward the child health SDG to reduce neonatal mortality to at least as low as 12 per 1,000 live births by 2030, but many will still not meet the target.[76] Accelerated progress will be needed in the highest burden countries (about a quarter of all countries) in order to reach this goal, which is essential for achieving the global SDG. More countries are at risk of missing the SDG target on neonatal mortality than on under-5 mortality.[77]

3 COLLECTIVE ACTION IN RMNCH

3.1 Partner landscape

The global RMNCH response is driven by the *Global Strategy for Women's, Children's, and Adolescents' Health, 2016-2030*. This Strategy, formally launched at the 70th session of the UN General Assembly in September 2015, is a roadmap for responding to preventable maternal, newborn and child deaths, including stillbirths, as part of an effort to improve overall health and well-being. It aligns with the SDGs for RMNCH – to reduce the global maternal mortality ratio to less than 70 per 100 000 live births, end preventable deaths of newborns and children under 5 years of age, and ensure universal access to sexual and reproductive health services, by 2030.

Several global initiatives have been developed to accelerate progress towards the SDGs set out for maternal and child health. *Every Woman Every Child* (EWEC) is a United Nations initiative, hosted by UNFPA, that mobilises action by governments, multi-laterals, the private sector and civil society to address global challenges facing women, children and adolescents. Efforts by EWEC include advocacy and fundraising for innovation, building on the work led by the UN Commission on Live Saving Commodities to identify and expand access to 13 life saving products. Another key alliance is the Partnership for Maternal, Newborn, and Child Health, which brings together over 1,000 partner organizations across 192 countries to agree on evidence for action to support attainment of the SDGs.

RMNCH has attracted significant support from across the health and development landscape to create a complex architecture of global partners including:

- Funders of upstream research and development (R&D) on new innovations such as the Bill & Melinda Gates Foundation (BMGF), Grand Challenges (a family of funding initiatives focused on global health and development innovations), Saving Lives at Birth (a collaboration between Grand Challenges Canada (GCC), United States Agency for International Development (USAID), BMGF, Foreign, Commonwealth and Development Office (FCDO), and Korea International Cooperation Agency (KOICA)), the US Government (USAID, National Institutes of Health), UK Government (FCDO), and other funders/bilaterals
- Product Development Partnerships (PDPs) that work to ensure there is a rich pipeline of RMNCH tools, such as PATH, FHI360, FIND, Newborn Essential Solutions and Technologies (NEST360°), and the Global Health Innovation Accelerator (a partnership between the South African Medical Research Council and PATH)
- Non-government, private industry and academic organizations that have a critical role to play in upstream innovation and R&D through diverse roles in product development, evaluation and commercialization
- Key players further downstream that work on normative guidance (WHO), regulation and quality assurance (WHO PQ/ERA/SRA, UNFPA), advocacy (Family Planning 2020, *Every Woman Every Child* global partnership), and goal alignment and accountability (Partnership for Maternal, Newborn and Child Health, Universal Health Coverage 2030)
- Funders of downstream introduction and delivery of new RMNCH innovations that include large foundations and bilateral donors such as USAID, FCDO, BMGF, Children's Investment Fund Foundation (CIFF), and MSD for Mothers, and funding partnerships like the Global Financing Facility (GFF) that works directly with LMIC governments to leverage innovation and prioritize RMNCH outcomes

- Implementers that focus on introduction, delivery and scale up, which includes national RMNCH programs at the heart of the response, supported by numerous local and international NGOs and coordinating bodies, procurement facilitation organizations (UNICEF, Reproductive Health Supplies Coalition), market shaping organizations (Clinton Health Access Initiative (CHAI), Results for Development (R4D), and Mann Global Health), and implementation research and service delivery strengthening organizations (PATH, Population Services International (PSI), Gynuity, Population Council, FHI360, Jhpiego, Save the Children, International Planned Parenthood Federation (IPPF), and DKT International).

The RMNCH landscape is complex and highly fragmented, including many health priorities, commodities, and key players. Gaps in access are driven by numerous factors including issues with product quality and appropriateness, weak forecasting and procurement systems, and inconsistent political will and financing for products. RMNCH markets are not supported by a strong, comprehensive global body that effectively coordinates different players and products in the same way, for example, as the Global Alliance for Vaccines Initiative (GAVI) has for immunizations or the Global Fund has for HIV, tuberculosis and malaria. That said, market conditions for individual commodities are widely variable and as such, addressing shortcomings will require product-specific approaches. Overall, there is a need for greater market shaping and coordination support. In the family planning space, efforts are underway to explore how a market coordination mechanism could address commodity access issues in LMICs, but broader support across the RMNCH landscape is needed as well.

Another complexity of the RMNCH sector is the limited opportunities for scaling new RMNCH tools and interventions. RMNCH lacks global bodies that provide scale-up at the volume of other disease areas. The GFF is active in this space, but does not intend to fill the financing gap for RMNCH. Rather, it is more catalytic in nature, by providing funding that can leverage funding from other partners, such as development assistance from bilateral and multilateral funders, private entities and other aligned external funders, and from domestic resources from target countries themselves. They also play an important role in ensuring alignment between these funding sources. Working in close collaboration with the GFF will be an important element of scale-up efforts. GFF investment decisions are country led but often require large pilot evidence to inform decisions on procurement and interventions. In this sense, Unitaid could be in a position to help unlock potential GFF funding for new efficacious RMNCH products and interventions.

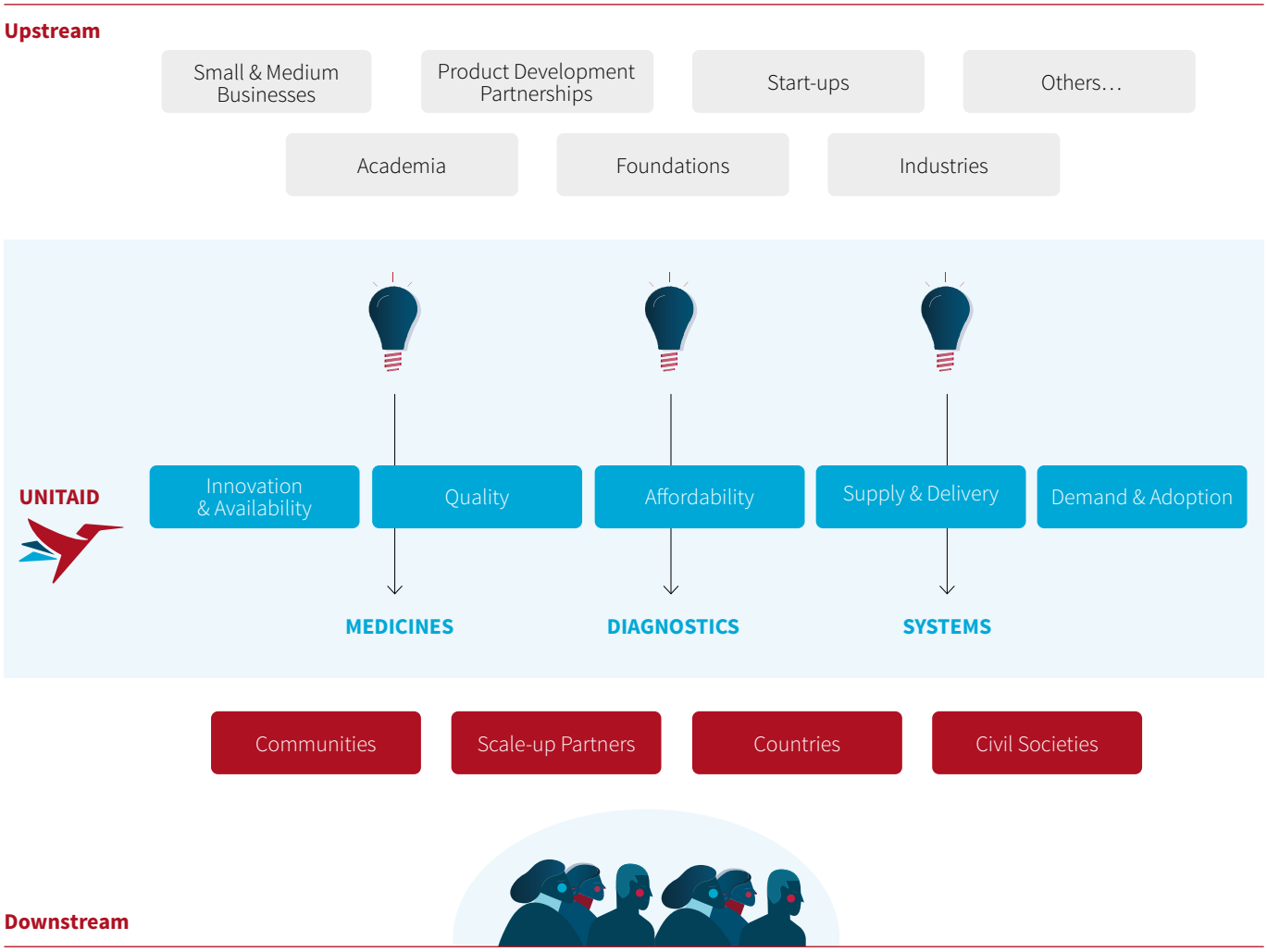
Bilateral donors such as USAID, FCDO also provide funding for scale-up – but effectively there is significant reliance on national programs to fund scale-up of new tools and innovations. As such, the conditions for scale up in the RMNCH space need to be considered differently to other disease areas. Interventions to catalyze innovations will need to be country focused, with transferrable scale-up models that can be applied at the national level.

The fragmentation of funding, and predominant reliance on domestic resources leads to significant gaps in the funding available to support RMNCH globally. The Guttmacher Institute estimates that annual costs for family planning, maternal and newborn health services, abortion services, and STI treatment in all LMICs is currently US$38 billion, but to meet the essential service needs of all women and children, an additional US$31 billion is needed. This translates to a total forecasted need of US$69 billion or an annual per capita cost of US$10.60.[78] Of this total need, the majority is required for maternal and newborn care (76%), with smaller amounts needed for contraception (18%), STI care (3%), and abortion and post-abortion care (2%). Data on overall demand for maternal health supplies is expected to increase as rates of facility-based births continue to grow in LMICs. Similarly, the greatest actual rise in forecasted demand for family planning products and services is expected to be in LMICs as well.[79]

Donor aid allocated for RMNCH peaked in 2017, when funding reached $15.9 billion. An evaluation of disbursements found that nearly half of this funding went to child health (46%, $7.4 billion), followed by reproductive health (34%, $5.4 billion), and maternal and newborn health (19%, $3.1 billion). The largest donors were the US government (36%, $5.8 billion), the UK government (10%, $1.6 billion), and BMGF (8%, $1.3 billion). While 2017 saw gains in RMNCH investments, there are still significant gaps, and maternal and newborn health remains the most neglected area.[80]

Unitaid works with partners at all stages of the value chain, connecting upstream partners such as academia and PDPs with downstream implementation partners such as countries and procurement agencies (Figure 1). Within a dynamic partner landscape, Unitaid has a clear role in supporting the use of innovative tools and approaches by advancing R&D and innovation, supporting normative guidance and product quality, and catalyzing product introduction and addressing delivery challenges.

FIGURE 1: Unitaid's role in global health – connecting the upstream with the downstream to unlock access



3.2 Current Unitaid investments

The *Unitaid Strategy 2017-2021* commitment to advance RMNCH through integrated approaches has been operationalized through new areas of focus in integrated management of childhood fever and innovations to increase access to oxygen therapy, prevention and screening of cervical cancer in HIV-infected women, and elimination of congenital infection in Chagas Disease. Grants within these new areas of focus that have recently been implemented, or are under development, are outlined below.

3.2.1 Integrated management of childhood fever

Malaria, pneumonia and diarrhoea together account for over 50% of mortality in children under-5. Malaria and pneumonia are febrile illnesses, and common causes of diarrhea in children can also include fever. Integrated approaches that aim to improve child health outcomes through holistic efforts to diagnose and treat childhood febrile illnesses (including malaria), are recommended by WHO.

Missed opportunities to effectively identify and treat sick children can result in severe disease (including severe malaria), which is often overlooked and contributes directly to increased child mortality. Hypoxaemia, or low oxygen saturation in the blood, is a key indicator of severe disease that requires onwards referral and treatment, including oxygen therapy. While screening for hypoxaemia with pulse oximetry is currently recommended at primary health care and is included in the Integrated Management of Childhood Illness (IMCI) guidelines, it is rarely implemented due in large part to a lack of tools adapted for use in these settings in LMICs.

In an effort to accelerate availability, adoption and scale-up of improved tools to identify severe disease, Unitaid is currently supporting grants with PATH and ALIMA to generate data on feasibility, cost and impact of pulse oximeters and dual/multimodal devices adapted for point-of-care use in LMICs. Through the TIMCI and AIRE projects, PATH and ALIMA are piloting the use of adapted pulse oximeters at primary health care, potentially alongside the use of a digital support algorithm. Additionally, through the TIMCI grant, PATH is catalyzing the development of point-of-care tools with broader functionality.

3.2.2 Tools for screening and prevention of cervical cancer in HIV-infected women

Cervical cancer is the leading cause of cancer deaths among women in LMICs. Over a quarter of a million women die of cervical cancer each year, with 90% of the deaths occurring in LMICs. Almost all cases of cervical cancer are caused by HPV. The disease distribution is notably overlapping with that of HIV infection and disproportionately affects women living with HIV.[81]

Following HIV diagnosis, cervical cancer screening is recommended annually for HIV-infected adolescent girls and women.[82] However, screening rates in LMICs are generally low, and women living with HIV are among the least likely to access these services.[83] Some of the more widely used tools for screening and treatment available in resource-limited settings, such as Visual Inspection with Acetic Acid, are severely constrained by low sensitivity and efficacy, and therefore result in poor linkage to care and loss to follow-up, logistics constraints, and lack of adequate financial resources to effectively deploy these tools at scale. More accurate screening tools exist, such as molecular testing, but are out of reach for the majority of women in LMICs. Fortunately, innovative tools are on the horizon that could address these challenges and make accurate and safe screening and treatment for secondary prevention of cervical cancer possible.

HPV screening and treatment services and emerging tools remain largely unaffordable, which restricts the ability of countries and funders to procure them. Limited demand and regulatory hurdles need to be addressed in order to create and sustain a market.

Unitaid has made two investments to address these barriers. A project with CHAI aims to expand access to appropriate diagnostics tools, and to develop an affordable screen-and-treat solution for secondary prevention of cervical cancer, utilizing an AI assisted cellphone application that can accurately detect signs of pre-cancerous lesions, in addition to scaling up access to molecular testing for HPV in order to identify women infected who may need screening for pre-cancerous lesions. The initiative also expands access to affordable and portable treatment devices for precancerous lesions, such as thermal ablation. A second project with Expertise France focuses on strengthening screening and secondary prevention to prevent the development of cancer in women infected with HPV who have precancerous lesions. Both projects address the supply side barriers by ensuring adequate supply and pricing of these products, and the demand-side barriers, through interventions to increase uptake and utilization to ensure better outcomes for women in LMICs.

3.2.3 Elimination of congenital infection in Chagas Disease

Worldwide, 75 million people are at risk of Chagas disease. This neglected tropical disease infects 6-7 million people a year and results in over 10,000 annual deaths.[84] Chagas is endemic in 21 Latin American countries where it causes more deaths than any other parasite-borne disease, including malaria.

Chagas is transmitted most commonly through vectoral, congenital or transfusional routes. A chronic Chagas infection can last for decades, during which 30-40% of people infected develop severe cardiac, gastrointestinal or neurological complications.

Despite high morbidity and mortality, and a high associated economic burden, only 7% of people with Chagas disease get diagnosed and only 1% receive appropriate treatment.[85] Mother-to-child transmission (MTCT) is a key infection route, but often undetected and untreated in both mothers and their newborns.[86] Given the success of therapy in newborns, early detection of infection in infants is critical. Evidence has further shown that active screening and optimal treatment of women of child-bearing age can effectively prevent congenital transmission.[87, 88]

Current challenges in the access to testing and treatment for Chagas disease include the lack of availability of diagnostic tools and drugs, lack of properly trained health care workers, poor awareness of Chagas disease, and limited options for effective and accessible diagnosis in newborns and infants. While the two available treatment options are highly effective in newborns and during the acute phase of Chagas infection, their efficacy decreases as the chronic phase progresses, making access to tools for early detection critical. Furthermore, both available drugs are contraindicated during pregnancy.

Following a Call for Proposal in 2019, Unitaid is pursuing work in Chagas disease through a pilot of the UnitaidExplore mechanism. Grant development is underway for an investment to address key challenges in MTCT of Chagas disease, with a primary focus on advancing access to diagnostic tools and medicines in the primary care setting. Working under the Framework for Quadruple elimination of MTCT of HIV, syphilis, HBV and Chagas disease, WHO/PAHO has laid out the pathway to measure, implement, and fulfil the criteria for validation of elimination.

4 OVERVIEW OF KEY CHALLENGES AND PROMISING NEW TOOLS AND INTERVENTIONS

The section below outlines the major challenges that prevent progress against the key causes of morbidity and mortality in RMNCH, and key responses that are emerging to address them.

4.1 Reproductive health

4.1.1 Unmet need for family planning products

In LMICs, 218 million women have unmet need for modern contraception, contributing to 111 million unwanted pregnancies every year. This need is greatest among adolescents 15-19 years-old, who face increased socio-cultural barriers to access.

Improving access to modern contraceptives fundamentally advances human rights by empowering women and girls with the ability to control if and when to become pregnant. Declines in fertility rates are associated with increases in women's health, financial earnings, and educational attainment.[89] It is for these reasons that investments in family planning are celebrated as catalytic to social development and equity, returning US$ 120 for every US$ 1 invested.[90]

While there are widely available methods of contraception on the market (e.g. pills, injectables, condoms, implants, diaphragms, fertility apps, IUDs), not all are accessible, acceptable, or suitable for all women, or at all stages of their reproductive lives. Improved contraceptive technologies that are more effective, affordable, and easier to access are required to address the unmet need for contraception, particularly in LMICs.[91] Evidence shows that when just one additional contraceptive method is available to women in a given location, contraceptive use increases by up to 8%.[92]

Long Acting Reversible Contraception (LARC)

There is a need for long-acting reversible options as an alternative to short-term methods of contraception, as well as short- to mid-term discrete products that are under the user's control and provide the level of protection comparable to pills and injectables. These options are at the top of the family planning agenda to expand reproductive choices.[93] LARC methods have high patient acceptability, limited contraindications for use, and overcome adherence barriers that are common with other contraceptive devices. As a result, they have been shown to be 20 times more effective than birth control pills, the patch, or the vaginal ring.[94]

In recent years, there has been significant success in scaling up LARCs through increased demand, supply, and use of contraceptive implants. This has contributed to significant increases in mCPR in some countries, especially in sub-Saharan Africa. While implant use has grown significantly over the last few years, there are still women who experience side effects such as change in bleeding patterns or cramping which forces them to discontinue the method.

Costs for these commodities are often high, and necessary resources often cannot be marshalled to bring products to scale. Without achieving scale, manufacturing at low volumes can result in high commodity costs. To overcome this barrier, a number of donors supported an implant access programme which included a volume guarantee to reduce the price of Jadelle (two rod, 5-year levongestrel implant) and Implanon/Nexplanon (one rod, 3 year, Etonogestrel implant). In parallel, support was provided to FHI360 to ensure that low cost

Sino-Implant (II)/Levoplant, a two-rod implant manufactured by Shanghai Dahua Pharmaceutical Co, Ltd prequalified by WHO, could also enter the market.

By the end of 2018, implants had secured a growing global footprint, and additional players such DKT International have helped to further reduce the price. Implants are now available at a reduced cost (between $6.90 - $8.50), and Merck and Bayer have extended their price commitments through to 2023 in FP2020 countries, based on production capacity and demand for a healthy marketplace. There is still a challenge with access to removal services in many LMICs, and a failure to provide reliable and ready access to removal services could easily undermine the device's potential.

The levonorgestrel intrauterine system (LNG-IUS) is a plastic T-shaped frame with a hormone (levonorgestrel) reservoir along the stem that releases minute amounts into the uterus every day. It is more than 99% effective at preventing pregnancy and lasts for five years. Until now, there has not been such a product that is affordable and suitable for LMIC settings. If taken to scale to provide a post-pregnancy FP tool, the LNG-IUS could provide a highly effective birth-spacing option, as well as reduce risk of anaemia in girls and women who are high-risk of having a low birth-weight baby. The LNG-IUS has also proven to be well tolerated among those with HIV.[95] For this method, as well as all available contraceptive options, WHO has determined that they are generally safe to use for women and girls living with HIV.[96]

However, the LNG-IUS is not currently utilized at scale as part of a broader method mix in any of the FP2020 focus countries. There are three LNG-IUS products that have been approved by a Stringent Regulatory Authority (SRA) that are currently available on a limited basis in FP2020 countries. The originator LNG-IUS (Mirena) has only been commercialized in high income countries and when sold in LMICs it is priced between $60 and $400, therefore, out of reach of most women. An unbranded LNG-IUD manufactured by Bayer can be accessed by donation through ICA Foundation (Bayer and Population Council), generally used to support small scale pilots. A lower cost LNG-IUS (Avibela) priced at around $15 recently became available, and has the potential to change the landscape dramatically and revitalize the underutilized IUD markets in a number of LMICs. There has been a recent global LNG-IUS product introduction coordinating platform convened by USAID and led by FHI 360 and CHAI, and UNFPA and USAID are working to add the LNG-IUS to their procurement catalogues, which will lead to donor procurement for the public sector in LMICs by the end of 2020.[97]

Multipurpose technologies (MPTs)

Male and Female condoms are currently the only methods that provide simultaneous protection against most STIs, HIV and unintended pregnancy. With multiple products in various stages of development, MPTs are biomedical interventions that protect women from a sexually transmitted infection (STI), such as HIV, and unintended pregnancy. For a product to be classified as an MPT, it must demonstrate, through preclinical or clinical studies, successful positive test results for two or more of the following indications: unintended pregnancy, HIV and/or other STIs.

Over 200 million women of reproductive age in LMICs have an unmet need for contraception,[98] while, at the same time, in sub-Saharan Africa—where the epidemic's main driver is heterosexual transmission —women carry nearly 60% of the HIV burden. Young women in the region are more than twice as likely to acquire HIV as young men. Women in areas with high rates of HIV often have the greatest unmet need for modern effective contraception. Recent research also suggests that women's risk for HIV is up to three times higher during pregnancy.[99] In addition, STIs and HIV are syndemic, affecting many women with a double burden. Given the limitations of both HIV/STI prevention tools and effective contraception, access to long-acting multipurpose products would be a game-changer for RMNCH in LMICs.

In 2016 the WHO prioritized MPTs in their strategy, the US National Institutes of Health released several Requests for Applications in 2017 in alignment with The Initiative for MPTs, and there are now over a dozen promising MPT products in the development pipeline, mostly providing protection against HIV in addition to providing contraception. MPTs have the potential to overcome adherence and uptake challenges seen with oral pre-exposure prophylaxis (PrEP) and ensure access to women-controlled contraception options, as well as addressing stigma associated with HIV service delivery.

The Dual Prevention Pill (DPP) is an MPT comprising oral PrEP and an oral contraceptive and is relatively close to market. It will be able to prevent both HIV transmission and pregnancy when used daily. With delivery feasible in numerous setting, a DPP has potential to deliver public health impact by expanding choice and method mix. Adding an MPT to the available method mix could not only empower users with options that better fit their needs and lives,[100] but could also increase efficiencies for users and health systems by simultaneously addressing multiple sexual and reproductive health needs for more integrated approaches to care. In the near-term, a DPP could increase the uptake of PrEP — decreasing new HIV infections among women in high-burden settings and reducing the number of unintended pregnancies. Early estimates indicate a potential market of 251,000-1.25 million women in 15 countries in sub-Saharan Africa. A coalition of organizations led by the HIV PDP AVAC has developed a comprehensive go-to-market strategy and investment case, with the priority on making the DPP affordable in LMIC markets. Market entry in prioritized countries is expected in 2023.[101]

A DPP could also lay the groundwork for the development and rollout of other MPTs currently in the research pipeline, such as vaginal rings, injectables, implants and films. The International Partnership for Microbicides and Conrad are both developing vaginal rings containing an antiretroviral drug and the contraceptive hormone levonorgestrel in an effort to provide protection against HIV and unintended pregnancy.

Unitaid currently has an endorsed Area for Intervention (AfI) on accelerating impact of long-acting technologies in LMICs, which provides a mandate to explore investments in long acting opportunities, in which MPTs are identified as very promising tools that would warrant future attention. The AfI highlights MPTs that could deliver more than one drug, and hormonal contraception together, to prevent disease and unwanted pregnancy. In the short-term, Unitaid will monitor the space and focus on areas where the organization has a comparative advantage, such as advancing specific candidates in the long-acting technology pipeline, accelerating introduction of emerging long-acting multipurpose products and enabling sustained access to available products to meet the needs of LMICs.

Male contraception products

Contraception research and development (R&D) is a generally neglected sector, and male contraception receives among the least attention within the space. A reliable and reversible contraceptive method for men that is comparable to female methods of contraception is lacking. Due to side effects and other research complications, there are still only two non-hormonal contraceptives on the market for men today: condoms and vasectomy. According to a research study by the Male Contraceptive Initiative, two-thirds of men report that it is important for their contraceptive method to be reversible.[102]

There are male contraceptive hormonal and non-hormonal products in various stages of clinical development, from pre-clinical to Phase III. As hormonal methods seem to have challenges around side-effects, the greatest opportunity from a user and timeline perspective is non-hormonal methods that are reversible. Barriers to potential uptake include limited development by pharma in this space, perceived lack of profitability, cultural barriers, and behavior adoption and user adherence challenges.

Postpartum FP products

Women in LMICs still predominantly lack postpartum contraceptive options. Unintended and closely spaced births are associated with increased maternal, newborn, and child morbidity and mortality. More than 90% of postpartum women want to delay or avoid their next pregnancy, yet two-thirds do not use contraception.[103] The number of women giving birth in facilities is increasing, which creates opportunities for women to initiate a family planning method before they leave the clinic. This is supported by 2015 updates to the WHO's Medical Eligibility Criteria (MECs) for immediate postpartum IUDs and implants.

Improved IUDs and insertions make the process of getting an immediate postpartum IUD simpler and easier. New dedicated Postpartum Intrauterine Device (PPIUD) Inserters do not require providers to manipulate the IUD by hand, which creates potential for contamination and subsequent infection. A dedicated inserter could conceivably increase PPIUD acceptability among both providers and patients if it was convenient and efficient. Preliminary unpublished evidence suggests that the availability of PPIUDs could increase institutional deliveries in rural areas, where maternal mortality is highest and access to contraception is the lowest.[104]

4.1.2 Sexually transmitted infections

STIs are prevalent and often asymptomatic, and as a result, people with infections are often unaware and do not seek care, putting them at increased risk of complications and transmission to others. In LMIC settings, those who do seek screening and treatment face numerous barriers, including limited resources, stigmatization, and low-quality services due to a lack of trained personnel, laboratory capacity, and appropriate supplies and medicines. STI care is also often provided as a separate service that is not available within primary health care or family planning clinics.

A key challenge to controlling STIs is the lack of accessible low-cost, rapid diagnostic tools for use in LMIC settings. Available diagnostics are mostly expensive laboratory-based assays, which require skilled technicians, specialized equipment, and do not offer immediate results. Notable exceptions include rapid diagnostic tests for HIV and syphilis. With limited access to diagnostics, syndromic case management is common practice.[105] The inability to detect asymptomatic STIs leads to many missed infections, as well as overtreatment, contributing to antibiotic resistance. WHO and other key organizations have made the development of, and access to, reliable, rapid, low-cost, point-of-care tests for STIs a key priority, as well as their integration within existing reproductive health programs for linkage to care.

As many STIs pass from mother-to-infant during pregnancy or at delivery, and contribute to significant infant morbidity and mortality, it is important for pregnant woman to be screened and treated within antenatal care. STI screening for women seeking contraceptive services and adolescent health services is also critical. Early detection and treatment of STIs reduces transmission to infants and can prevent complications such as premature delivery, premature rupture of the amniotic sac, low birth-weight, and stillbirth.[106]

The WHO global health sector strategy for STIs highlights the importance of an integrated approach to detection and management.[107] As such, the following section addresses different infections and associated interventions as bundles to evaluate and scale. Appropriate prevention technologies, diagnostics, and treatments for STIs are critical to controlling and monitoring these infections. In addition to the development of biomedical tools, piloting innovative strategies and service delivery models to provide care to hard to reach populations will be essential.

4.1.2.1 Gonorrhoea and chlamydia

Chlamydia and gonorrhoea are the two most prevalent bacterial STIs globally, and frequently occur as co-infections. Often asymptomatic, if left untreated these infections can lead to infertility, adverse pregnancy outcomes and newborn infections. Dual detection and control efforts have been prioritized.

In high-income countries, accurate nucleic acid amplification tests (NAATs) are used to diagnose gonorrhoea and chlamydia, but their requirements in terms of robust laboratory infrastructure, highly skilled personnel, and cost limit widespread use in many LMIC settings and are frequently inaccessible. Use of NAATs in these settings requires a complex sample transport network in order to collect patient samples from rural, peri-urban, and urban settings and take them to the laboratory for processing. Often these networks are not well developed, causing long delays in receipt of test results and loss to follow-up.[108] While efforts to strengthen laboratory capacity and sample transport networks for HIV testing have grown in recent years and there are opportunities to leverage this infrastructure for additional STI testing, the highest-impact innovations will be new POCTs that can deliver results within a single patient visit and enable a test, treat and partner notification approach.[109]

For chlamydia, many antibody tests in the RDT format have been commercialized as well as rapid antigen detection POCTs. However meta-analyses have found that while these products have high specificity, they have widely varying sensitivities (often below 50%), which limit their value as screening tests.[110] A few POC immunoassays have been developed for gonorrhoea, but they similarly face limitations, with a recent review finding sensitivities as low as 12.5%.[111] While reduced sensitivity will lead to missed infections and continued transmission to partners and unborn children, it is important to understand the tradeoffs between accuracy, accessibility and health impact with these tools. In some settings, less sensitive but more accessible tests, with low-cost and rapid result turnaround, might be more easily deployed and impactful in settings where access to STI diagnostics is very limited.[112]

While POCTs for gonorrhoea and chlamydia remain a critical need, there are some products that provide near patient screening, including the GeneXpert® system (Cepheid), which has been found to have acceptable performance for screening and diagnosis for chlamydia and gonorrhoea[113] and operational feasibility in some setting, including in routine ANC in Papua New Guinea[114] and with HIV-negative women presenting for STI care in South Africa.[115] In resource-limited countries, GeneXpert® is more appropriate for use at the district hospital level or above. A benefit of the GeneXpert® system that makes it more cost effective is its ability to detect 20 pathogens on the same platform and its wider use for other infectious diseases, such as tuberculosis.[116] However these tests remain unaffordable in many resource-poor settings, and do not offer a sustainable option, even with price reduction.

WHO and FIND have spearheaded the development of target product profiles (TPPs) for several STI diagnostics including gonorrhoea and chlamydia, which new POCTs can be compared against.[117] Two emerging products that hold promise for meeting TPP criteria are in development and undergoing feasibility studies, supported by new grants from FIND.[118]

Another POCT in late-stage development is the GIFT Genital Inflammation Test, which is currently undergoing acceptability and feasibility trials. The GIFT detects genital inflammation in both symptomatic and asymptomatic patients, using three biomarkers of inflammation caused by STIs or bacterial vaginosis. Low-cost and rapid, the test could allow women to be tested in primary care and triaged for specific STI tests following a positive result, or excluded from the need for treatment.

Due to the emergence of antimicrobial resistance (AMR) in gonorrhoea, there is increased need for accurate and accessible molecular tests for antimicrobial suceptibility and resistance testing. This testing would inform patient management to prevent antibiotic overuse

and strengthen surveillance data for AMR monitoring, which is a key objective of the STI global strategy. Development of these products could also be pursued in collaboration of the WHO Global Gonococcal Antimicrobial Surveillance Programme (GASP), which was initiated to monitor gonococcal AMR worldwide.[119]

In addition to improved diagnostics, combatting antimicrobial resistance in gonorrhoea requires renewed efforts to catalyze the antibiotic drug development pipeline. Through development of a recent TPP, WHO is driving forward development efforts in partnership with the Global Antibiotic Research and Development Partnership (GARDP).[120] Treatment options for gonorrhoea are decreasing, with limited drug development in the pipeline. Drugs that were used to treat gonorrhoea, such as ciprofloxacin, azithromycin, and extended-spectrum cephalosporins (ESC), now have reported resistant cases in 97%, 81%, and 66% of countries, respectively.[121] The WHO currently recommends that gonorrhoea be treated with two antibiotics: ESC (either injectable ceftriaxone or oral cefixime) and oral azithromycin. In areas with strong surveillance data showing susceptibility, single therapy with injectable ceftriaxone is recommended.[122] The current cost per treatment of ceftriaxone plus azithromycin is $US1.66.[123] Three manufacturers have received WHO PQ approval for ceftriaxone, and azithromycin is widely manufactured, and PQ approved.

Given the threat of AMR, efforts to develop a vaccine for gonorrhoea have been prioritized and expanded, however, candidates are still in the early phase of development. There is some emerging evidence that the meningococcal group B vaccine induces some cross-protection against gonorrhoea,[124] which is being explored further in a safety and efficacy trial led by the US NIH.[125] Progress on a chlamydia vaccine has advanced to recent completion of a Phase I trial with promising results for further development.[126]

4.1.2.2 Mother-to-child transmission of HIV, syphilis and hepatitis B (and Chagas disease in endemic areas)

MTCT is a primary source of spread for key infectious diseases, notably HIV, syphilis, and HBV. WHO has set targets for triple elimination of MTCT of these infections as well as Chagas in endemic settings (the focus of a Unitaid Call for Proposals in 2019). Many vital product innovations already exist to prevent MTCT of these diseases. The main challenge to achieving the "triple elimination" agenda is developing innovative approaches to introduce and integrate these tools into RMNCH platforms in LMICs.

In the absence of any intervention, MTCT of HIV can vary at rates of 20%-35% for breastfed infants or 15%-20% for non-breastfed infants. Studies have shown that with MTCT interventions, infection rates can fall to less than 5%.[127] Evidence-based interventions to prevent perinatal HIV transmission include early detection RDTs as well as consistent lifelong maternal antiretroviral therapy (ART), throughout pregnancy and breastfeeding, with a short course of antiretroviral drugs for the infant upon delivery.[128] The global community has made significant progress in developing and deploying adequate tools for women living with HIV, which can be seen in the high rates of MTCT prevention coverage in LMICs. Adequate development and adoption of tools for infants is the gap which requires the most attention. Of note, the COVID-19 pandemic and the associated disruption in ART drug supply and MTCT programs may lead to an increase in infants born with HIV, threatening to reverse the decades-long progress made for pregnant women and children in the fight against HIV.[129]

For HIV-exposed infants, timely diagnosis and linkage to prophylaxis and treatment is essential. Due to the presence of maternal antibodies, antibody-based HIV rapid tests cannot be used to diagnose HIV infection in children under 18 months old, and therefore virological testing is needed. Virological testing is often laboratory-based, requiring robust infrastructure and personnel capacity, which is often lacking in resource-constrained settings. This can lead to missed cases, and slow results return with loss to follow-up.

WHO recently released a TPP for a new diagnostic test for infant HIV virological testing to guide product developers to develop a next generation diagnostic for this patient population.[130] The introduction of innovative infant testing for HIV is an area where Unitaid has ongoing investments, including supporting optimization of infant diagnosis and linkage to care. Through work with CHAI, UNICEF, and Elizabeth Glaser Pediatric AIDS Foundation, Unitaid has accelerated introduction and uptake of POC infant diagnosis technologies in sub-Saharan Africa. The grants have demonstrated the positive impact of these technologies in achieving earlier treatment initiation for infants testing positive, as well as the financial impact of efforts to improve pricing and service terms, and testing efficiency across both POC and laboratory-based systems.[131] Unitaid grants have also focused on child-friendly HIV treatment, including infant-treatment, and greatly contributed to accelerating development, access and early-adoption in collaboration with CHAI, DNDi, EGPAF, Stellenbosch, MPP, and WHO.

While HIV testing for pregnant women has relatively good coverage, syphilis cases often go undiagnosed and untreated in LMICs, despite normative guidance and cost-effective tools. There are many factors that affect uptake and implementation of programs for the treatment of maternal syphilis and the elimination MTCT of syphilis. Congenital syphilis has received less attention in high-level discussions on RMNCH and is not a major focus of most global health institutions or donors working on newborn health.[132] However, this is changing with the launch of the triple elimination agenda, creating urgency to advance prevention efforts.

Accurate, low-cost, easy to use rapid diagnostic tests for HIV and syphilis in pregnancy are available as single and dual-detection (SD Bioline) tests for use at the point-of-care, but have not been taken up by countries, and are often not part of national testing algorithms. WHO recommends that dual RDTs be used as the first test for pregnant women in ANC[133] and several have already been prequalified by the WHO. These tests enable more women to be diagnosed with HIV and syphilis so that they can access treatment and prevent transmission to infants.

While maternal treatment for early syphilis is inexpensive and includes only a single intramuscular injection of benzathine penicillin, there are known challenges with drug stockouts in many LMICs.[134] Sole sourcing, a highly consolidated market for benzathine penicillin, and issues linked to the quality of the active product ingredient (API) are common challenges for country supply chains. Given that benzathine penicillin is an off-patent medication with a low price, manufacturers have stopped production or put in place stringent ordering protocols and inflexible production cycles that make procurement more difficult. Inaccurate forecasting, weak procurement systems, and knowledge gaps on syphilis treatment also hinder demand in LMICs.[135] To address these issues, improvements in drug forecasting, procurement, and quality manufacturing standards are needed, as well as improved global supply.

The cornerstone of preventing mother-to-child transmission of HBV is vaccination, which offers over 95% protection. In the last twenty years, coverage of the three-dose vaccine among children has risen from 30% to 85% worldwide. This scale-up was spearheaded by GAVI, in partnership with country governments and civil society.

WHO furthermore recommends that all infants receive a first dose of HBV vaccine within 24 hours of birth. This 'birth dose' is a key element of preventing MTCT of HBV. The coverage of the 'birth-dose' remains uneven; it stands at 43% globally, and only at 6% in the WHO African region.[136] Early administration of the birth dose is essential as studies have shown that the risk of HBV infection among infants whose mothers were HBV surface antigen positive is 8 times higher when the birth dose is administered after 7 days, rather than within the first 3-days.[137]

Infant HBV exposure is a major contributor to chronic HBV and subsequent mortality rates. The likelihood of developing chronic HBV infection is much higher following exposure as an infant rather than as an adult. An estimated 90% of HBV-exposed neonates will go on to develop chronic infection, whereas this is found to be 5-10% in exposed adults.[138]

In the absence of widespread availability and uptake of the birth dose, early maternal screening for HBV surface antigen and prompt treatment are critical prevention measures. WHO recommends that all pregnant women be screened during ANC for HBV surface antigen (HBsAg). Currently there are three WHO pre-qualified rapid tests for HBsAg that are available for screening.[139] If this test returns a positive result, further HBV DNA testing is needed to understand viral load. Women with a viral load above the recommended threshold should receive prophylaxis as a preventive therapy until they deliver their baby. Tenofovir is a widely used antiviral drug for the prevention of MTCT of HIV, which costs less than US$3 per month in many countries, and can also be used for HBV prophylaxis. When HBV DNA testing is not available, WHO recommends that HBV e antigen (HBeAg) testing be conducted to determine eligibility for prophylaxis.[140, 141] There are only a few HBeAg rapid diagnostic tests on the market and none have been WHO PQ approved. Efforts to develop and evaluate new and emerging RDTs to strengthen the pipeline and support introduction would help to expand testing access and advance triple elimination efforts.

4.2 Maternal health

4.2.1 Anaemia during pregnancy

Anaemia is defined by low levels of hemoglobin in the blood, leading to fatigue, weakness and shortness of breath, among other symptoms. It is often caused by nutritional deficiencies, such as iron, folate and vitamin B12 deficiency. Infectious diseases like malaria, HIV, and parasitic infections also cause anaemia.[142] WHO recommends daily oral iron and folic acid supplementation (IFA) to prevent maternal anaemia, with hemoglobin concentration measurement at 12, 26, and 36 weeks of pregnancy. Following a positive diagnosis, increased daily iron supplementation is recommended.

The lack of low-cost tools to quantify hemoglobin levels in antenatal care leads to under detection and treatment of maternal anaemia. The recommended method is full blood count testing but due to lacking availability in many low-resource settings, hemoglobinometers are suggested.[143] Hemoglobinometers are portable, point of care hemoglobin measurement devices that use a finger-prick blood as the sample type. The POC reference method, and the most widely used hemoglobinometers are the HemoCue® devices. However, the cost of the HemoCue® limits its use in some routine ANC settings in LMICs. In these settings, the WHO color scale or clinical examinations are standard care, however, both are considered subjective and less accurate.[144]

Product development efforts have focused on developing new, accurate, and low-cost hemoglobinometers. A TPP was developed by PATH to guide product development[145] in addition to a product landscape of available technologies.[146] One promising, newly launched, low-cost device is the TrueHb by Wrig Nanosystems, which was found to have good performance in studies conducted in India[147] and Uganda,[148] as well as usability in ANC clinics in Ghana.[149] Many noninvasive approaches to hemoglobin measurement for anaemia screening are also in development. Most are still in the pilot and validation phases, and there is currently a lack of evidence on their accuracy,[150, 151] with some studies showing reduced performance among non-invasive devices as compared to HemoCue®.[152]

As malaria in pregnancy is associated with severe anaemia, a key approach towards reducing maternal anaemia and associated complications is to prevent malaria infections. Through investments advancing access to malaria chemoprevention in pregnant women, Unitaid has worked to address the maternal malarial anaemia burden. A Unitaid-funded project led by Jhpiego is demonstrating the effectiveness of intermittent preventive treatment in pregnancy delivered at the community-level in several countries with high levels of malaria burden.

In malaria endemic settings, concerns have been raised about the potential for iron supplementation to fuel the growth of the malaria parasite, however, most literature has shown no adverse impacts on maternal risk of malaria, when systems for prevention, detection and treatment of malaria are in place.[153] Consequently, the WHO recommendation on daily iron and folic acid (IFA) supplementation during pregnancy were updated in 2016, recommending that iron supplements be provided for all women as part of routine ANC. Integrated efforts to strengthen malaria prevention, diagnosis, and treatment, alongside effective use of IFA supplementation would be synergistic is reducing the dual burdens of anaemia and malaria. In addition to strengthening IFA supplementation, there are opportunities to trial integrated delivery of multiple micronutrient supplements, as recommended by WHO in 2019 to address maternal anaemia and other nutritional deficiencies that contribute to poor perinatal outcomes.[154] Strategies to improve adherence and availability of IFA supplementation are in development,[155] and may be relevant for multiple micronutrient supplementation as well.

4.2.2 Pre-eclampsia and eclampsia

PE occurs during the second half of pregnancy, and if not managed appropriately can lead to seizures, kidney and liver damage, and increased risk of maternal complications, preterm births, low birthweight, neonatal anaemia, and infant growth restriction. Nearly all PE related deaths are preventable with early diagnosis and appropriate interventions such as treatment with hypertensives, magnesium sulphate, and timed delivery. The only definitive treatment for PE is delivery of the fetus and placenta. All other management serves to stabilize the mother to improve birth outcomes.[156]

The primary clinical indicators of PE are protein in urine (proteinuria) and elevated blood pressure (BP). WHO recommends that women are screened for proteinuria and have their BP checked at every ANC visit, however, studies have shown that PE screening during ANC is inconsistent in many LMICs.[157] In low-resource settings, PE is typically diagnosed using a sphygmomanometer to detect elevated BP and urine dipsticks measuring protein to detect proteinuria. The accuracy of urine dipsticks measuring protein is low[158] and blood pressure devices are often unavailable or not well maintained or calibrated. This can lead to inaccurate measurements. Access to laboratory-based tests for improved proteinuria detection, such as the gold standard method of 24-hour urine collection, is often very limited due to technical complexity and cost, and leads to significant time delays for providing appropriate treatments. More appropriate point-of-care tests could improve early identification and treatment of women at risk, as well as lead to health system efficiencies, such as reducing wait times in obstetrical triage areas, informing referral practices and avoiding unnecessary admissions.[159] Several improved diagnostic tools are now becoming available with potential to significantly improve PE detection in LMICs.

Magnesium sulphate is the anticonvulsant drug recommended by the WHO as the most effective, safe, and low-cost treatment available for severe PE/E. It is administered via intravenous infusion, or intramuscular (IM) injection in low-resource settings. Magnesium sulphate is associated with a reduction in the risk of seizures and the risk of maternal death and may have some benefit to the baby.[160] It has been on the WHO's Model List of Essential Medicines since 1996 and there are six prequalified products available. Magnesium sulfate is relatively easy to manufacture and is temperature stable. For the drug to be effective, it must be quality assured, properly transported and stored, and administered by trained providers, who understand the proper dosing calculations and patient monitoring guidelines. These requirements raise challenges in low-resource settings.

Stockout rates are known to be common due to inefficiencies in budgeting and procurement practices. This leads to increased demand for drugs through unofficial markets, where qual-

ity is uncontrolled and falsified and expired products are pervasive.[161] One study found that approximately 25% of facilities globally fail to stock magnesium sulphate.[162]

Other challenges with magnesium sulphate relate to how it is administered, including gaps in knowledge around proper use of the drug and low uptake in many settings, due to concerns related to potential toxicity.[163] In order to address challenges related to proper administration, the WHO has collaborated with MSD for Mothers to identify alternate dosing regimens that simplify administration and will be the focus of planned non-inferiority studies.

As the capacity to provide magnesium sulphate is more often available at higher levels of health service provision, some studies have found that magnesium sulphate access at lower levels of health care would have a smaller impact on PE/E associated maternal mortality in low-resource setting, than would more effective diagnostics to triage patients to appropriate care.[164]

4.2.3 Unsafe abortion

WHO defines unsafe abortion as a procedure for terminating an unintended pregnancy that is undertaken by individuals lacking the necessary skills and/or in an environment that does not conform to minimal medical standards.[165] Morbidity and mortality caused by unsafe abortion can be prevented with improved access to contraception, sexual education, and efforts to strengthen safe abortion practices and policies.

WHO and other global and local partners have spearheaded efforts to improve access to medical abortion. The two medications recommended to induce abortion are mifepristone and misoprostol in combination or misoprostol-only, where mifepristone is unavailable. These drugs are non-invasive, safe, and effective alternatives to surgical abortion that have the potential to greatly improve access to safe abortion at the primary care level in LMICs and for self-management. They are sold as medical abortion (MA) combi-packs. In 2019, WHO pre-qualified the first combi-pack for medical abortion.[166]

To date, few countries in sub-Saharan Africa have made medical abortion combi-packs available to women. A recent review found that only two countries—Zambia and Sierra Leone—were distributing combi-packs through commercial distributors, rather than solely through social marketing organizations (SMOs) or NGOs.[167] NGOs and SMOs have worked to register products locally in order to improve access. A quality-assured combi-pack called Medabon® currently has the widest availability in LMICs and is registered in 15 countries.[168]

WHO released revised clinical guidelines for the MA management in 2019, clarifying the components of comprehensive abortion care and improved service delivery.[169] Access to post-abortion care is critical as well. Every year, an estimated 6.9 million women seek treatment due to abortion complications. The risk of complications is highest in settings where abortion is illegal and among women of lower socioeconomic status. Complications from unsafe abortion can include hemorrhaging, sepsis, and death.[170]

4.2.4 Postpartum hemorrhage

PPH is defined as blood loss of 500 ml or more within 24 hours after birth,[171] and is the leading cause of maternal mortality in LMICs. Most this burden could be avoided through appropriate management of the third stage of labor, including use of preventive uterotonics.[172]

The most commonly recommended drug for PPH prevention, oxytocin, is often of poor quality or unavailable in low-resource settings. It requires cold-chain storage to remain effective, and given limitations in many LMICs, particularly in remote locations, it is often unavailable to those who are most in need. Product degradation due to improper storage adds to quality concerns for oxytocin, and distrust amongst providers. A review found that 36% of oxytocin samples collected in 15 LMICs had insufficient amount of active ingredient.[173]

Poor quality oxytocin has also been documented, due to factors including manufacturing deficiencies, poor regulatory oversight and procurement practices, and challenges maintaining cold chain infrastructure. Oxytocin is widely available in LMICs at low costs, with more than 100 manufacturers producing nearly 300 different products. High levels of competition drive down the price and can create incentives to reduce quality to lower costs. Most oxytocin available in LMICs is produced in China, India, and Indonesia. Challenges with sub-standard products can be mitigated through procurement practices that require registered products adhering to WHO product specifications or preferably having SRA or WHO PQ approval. Currently there are only two oxytocin products with WHO PQ approval.[174] Market shaping activities, such as working with national procurement and regulatory agencies to ensure high-quality of products that enter the country have been proposed to improve the quality of oxytocin available in LMICs.[175]

Misoprostol is an alternative to oxytocin, which is in tablet form and is heat-stable and low-cost. However, misoprostol comes with its own set of challenges as it can also be used for medical abortion and post abortion care. As a result, access is restricted in many countries.

Heat-stable carbetocin, an oxytocin alternative to prevent PPH, was recently launched by Ferring Pharmaceuticals. It does not require cold chain storage and is sold at a comparable price. In 2018, WHO's randomized controlled Carbetocin Haemorrhage Prevention (CHAMPION) trial showed that carbetocin is non-inferior to oxytocin. It requires administration by a skilled health professional, but does not require refrigeration.

Oxytocin is also recommended for PPH treatment when prevention is not effective. The same access barriers that restrict access to oxytocin as a prevention option also apply to oxytocin as a treatment option. Tranexamic acid, a drug used in routine care to stop bleeding during surgery, is also recommended as treatment to reduce excessive bleeding. Tranexamic acid is, heat-stable, easy to store and to produce. It has long been available for use to prevent blood loss during surgery and to treat trauma, but its recommendation for PPH is recent.[176] As a result, awareness and knowledge for this indication is limited, and its cost is restrictive in some cases, preventing uptake.

Several products are also emerging for the emergency treatment of PPH in LMICs. Uterine balloon tamponades (UBTs) are used to manually prevent excess bleeding where preventive drugs and treatment fail. However, existing products are prohibitively expensive for low-resource settings. New UBTs developed for LMICs would respond to the high cost of existing products and provide an effective alternative to condom-catheters that are assembled from available resources at the point of care. The Jada System is another new technology that can prevent bleeding when PPH prevention and treatment fail. The device received US FDA clearance this year and uses a low-level vacuum to induce uterine contractions to prevent bleeding. This device could hold promise for LMICs in the future.[177] Other products, such as the non-pneumatic anti-shock garment (NASG) are available to manage and stabilize a patient who has suffered excessive blood loss while they are transferred to higher levels of care for transfusion. Although the NASG has been shown to be efficacious, it is expensive, and uptake of the product remains low.[178]

4.2.5 Maternal sepsis

Maternal sepsis occurs when the body's response to an infection causes harm to its own tissues and organs. Sepsis during pregnancy, during or after giving birth, or after abortion is avoidable, but remains a major cause of mortality.

Research conducted by the WHO found vital signs for maternal sepsis are often under reported for women who are diagnosed with an infection, delays in antimicrobial therapy were

frequent, and health workers were often unaware of the signs and symptoms of sepsis, so are unable to recognize the condition and treat it in time.[179, 180]

Sepsis management depends on good implementation of established technologies, and program-based approaches to improve uptake of care.[181] Infection-control protocols and evidence-based procedures—including prophylactic antibiotics for cesarean section or preterm rupture of membranes, and updated antibiotic regimens should be widely adopted to address the maternal sepsis burden. Devices such as hand rubs, needle-disposal systems, and rapid microbiological diagnostic tests can improve adherence and efficiency. Operational research on developments like vaginal cleansing with antiseptics, and vitamin A supplementation hold promise for expanding tools to address maternal sepsis. Antibiotics administered during labor or after birth can prevent or treat sepsis for pregnant women and newborns. However, low-quality medicines are often used to manage sepsis. One study found that 1 in 7 injectable antibiotic samples in LMIC settings (13%) were of low quality.[182] A further issue is the growing threat of antibiotic resistance, which reduces the ability of care providers to effectively treat sepsis infections. In addition to the need for new antibiotics, it is critical to strengthen systems to track antibiotic use and monitor AMR in LMICs.[183]

4.3 Newborn health

Basic care provided by trained health workers can save lives of newborns.[184] The increasing percentage of institutional deliveries globally offers an opportunity to provide essential newborn care, and identify and manage high-risk newborns.[185] Tools for facility-based care of newborns have mainly sought to address basic care needs, such as hand hygiene, clean delivery practices, clean cord care, breastfeeding, basic resuscitation, Kangaroo Mother Care and early postnatal care, whilst more comprehensive facility-based care of small and sick babies receives less attention. Addressing the persistent barriers to tools that could improve the quality and accessibility of effective care for small and sick newborns could save many lives.[186]

Fragmentation in the newborn landscape limits efficient coordination of procurement, and poses a key challenge for the development and scale-up of effective interventions. Even where rugged technologies exist for newborns, prohibitive distribution costs and uncertain market size impede the introduction of medical technologies in SSA where they are most needed. Newborn care units in Africa often rely on an opportunistic selection of donated medical equipment not designed for heat, humidity, and electrical surges, which often end up being used sub-optimally, or not at all.

Recent revised recommendations for maternal and newborn care at the global level have begun to consider these additional components of newborn care as essential to substantially impact neonatal health.[187] Newborn Essential Solutions and Technologies 360 (NEST360°), in a series of TPP and Landscape publications promotes the use of an essential package of tools in 6 categories of care (hydration, nutrition, and drug delivery; infection prevention and control; jaundice management; point-of-care diagnostics; respiratory support; and thermal management). Delivered as a comprehensive package of services, access to 16 specific tools within these categories could address the leading causes of newborn death.[188]

4.3.1 Stillbirth

Stillbirth remains a neglected issue globally. Stillbirths are often associated with fetal growth restriction, preterm labor, post-term pregnancy, and suboptimal care. Common causes are reported to be asphyxia, placental disorders, maternal hypertensive disorders, infections, cord problems and ruptured uterus due to obstructed labor. However, a recent study investigating stillbirths across sub-Saharan Africa found that in 18%-26% of cases, the cause of death was reported as unknown.[189]

Common risk factors for stillbirth across LMICs include extremes in maternal age, poor socio-economic conditions, a history of prior pregnancy loss and complicated or multiple pregnancies. Alongside these, the lack of quality health care is a significant risk factor, particularly the lack of access to antenatal care services, quality of care during childbirth and delayed caesarean sections.[190]

In many LMICs, fetal growth rate is determined manually with a tape measure. This technique can effectively determine growth trend, but cannot distinguish between a small and healthy fetus and a pathologically small fetus at risk. The consequence is that all fetuses measuring small for their gestational age are referred to a higher level of care for confirmation, using expensive, pulsed-wave dopplers that requires a sonographer with specialist training.

A number of handheld dopplers that can be used for ultrasound are available, or will soon be available. Specifically for fetus health to prevent stillbirth, the South African Medical Research Council (SAMRC) and the Council for Scientific Industrial Research (CSIR) have developed a simple handheld device that uses ultrasound waves to assess blood flow in the umbilical cord of unborn babies. This allows health care practitioners to assess placental function, and risk signs for stillbirth without the need for a trained sonographer. Future versions will have the capacity to process signals and calculate the clinical referral recommendation in real time. This technology could be used at lower levels of health service provision, or where a trained sonographer is not available to triage pregnancies that are identified as high risk. Portable ultrasound technology such as this will be most effective when implemented in the context of clear referral pathways, and management options.

4.3.2 Neonatal sepsis

Infections like sepsis are a leading cause of newborn death. In low-resource settings, neonates born outside of healthcare facilities can be prone to community acquired pathogens even after 72 hours of life. Newborn sepsis needs to be identified and treated quickly to ensure survival, and minimize morbidity. Serious infections often result in death regardless of level of treatment facility. Premature infants are at increased risk.

Optimal umbilical cord care practices for newborns and during the first week of life, especially in settings with poor hygiene, has the potential to avoid sepsis. Chlorhexidine digluconate (CHX) in low concentrations has long been a low-cost antiseptic widely used for hand sanitizers, mouth wash, and preoperative skin preparation. A novel formulation for umbilical cord care has a higher concentration of active ingredient than other currently marketed products and can prevent cord infection that leads to neonatal sepsis.[191] Multiple trials in Asia and Africa have demonstrated CHX to be effective in reducing neonatal infections and mortality.[192] Despite successful clinical trials that demonstrate CHX as part of a package of priority interventions, expanded dosage forms, local manufacturing, and country introductions, CHX is still underutilized in many LMICS. Working with PATH, a Nigerian manufacturer of Chlorxy-G, a CHX gel manufactured for umbilical cord care recently received approval for introduction in 15 countries.[193,194] Other interventions to prevent infection and sepsis include frequent hand-washing, exclusive breastfeeding and cleanliness of birthing facilities, however widespread implementation of these interventions is challenging in low-resource settings.

Because sick newborns present with non-specific signs and symptoms, diagnosing neonatal sepsis is difficult in even the most sophisticated healthcare settings, but especially in LMICs. In fact, many neonatal deaths occur in the community before the child has contact with appropriate health services.[195] In addition to the under-recognition of sepsis, delay in care seeking, lack of appropriate training for health workers, and limited resources to manage illness are also key barriers to addressing the burden. Even where quality services are available, the cost of treatment is beyond the reach of many.

Due to the immaturity of neonatal immune systems, natural history of late deterioration, and high morbidity in the presence of a serious bacterial infection, the standard of care in neonates is to treat while simultaneously screening for sepsis with blood, urine, and spinal fluid cultures and microscopy. Currently available diagnostic tests have significant barriers for effective use, and new tools that can diagnose sepsis and are suitable for LMIC settings are urgently needed. However, there are no new tools identified in the pipeline to address these access barriers.

WHO recommends injectable gentamicin and procaine benzylpenicillin for ten days as first-line treatment for neonatal sepsis, and ceftriaxone treatment for ten days as second line.[196] These antibiotics are on the WHO Model List of Essential Medicines for Children and have been targeted by the United Nations Commission for Life-Saving Commodities for Women and Children as key commodities to reduce neonatal mortality.[197] Guidelines to help identify neonates and young infants at risk of sepsis are available to help guide clinical management, but even when these guidelines are used, antibiotics are often administered to those who do not need them.[198]

The emergence of drug-resistant neonatal sepsis poses an additional challenge that is estimated to result in 214,000 neonatal deaths each year globally. However, there have been developments in the pipeline to address this issue. GARDP has identified an antibiotic called polymyxin B as a priority area and is developing a pediatric investigation plan to facilitate initial registration of polymyxin B targeted countries in Europe, Africa and Asia. Furthermore, GARDP has started a collaboration with Sandoz to accelerate the development and availability of antibiotic treatments for children in LMIC settings (including heat-stable child-appropriate formulations such as dispersible tablets to treat bacterial infections, including neonatal sepsis and pneumonia).[199]

4.3.3 Prematurity

Among pre-term birth complications, respiratory disorders are the leading cause of early neonatal mortality (up to 7 days of age),[200] and of morbidity in newborns.[201] Antenatal corticosteroids (ACS) can be provided to a pregnant woman before birth if a baby is anticipated to be born preterm to help prevent respiratory distress syndrome (RDS).[202] These are not widely used in low-resource settings. Both dexa- and betamethasone are listed on the WHO Priority Medicines list as a key commodity to reduce mortality in preterm babies. However, WHO guidelines only recommend the use of ACS when a number of pre-conditions are met, including gestational age assessment, preterm birth assessment, absence of clinical evidence of maternal infection, adequate childbirth care availability, and access to resuscitation, thermal care, feeding support, infection treatment and safe oxygen if needed.[203] In LMIC's these pre-conditions may be met in well-equipped referral hospitals, but are less likely to be met in lower- level facilities where many deliveries occur.

If ACS is not available, or RDS occurs even after ACS administration, assisted breathing with continuous positive airway pressure (CPAP) is required. If CPAP is not sufficient, intubation, surfactant and/or ventilation may be needed.[204] Commercialized CPAP devices are often too expensive for LMIC settings (a stand-alone device can cost $6,000), and while lower cost devices exist, they still cost in excess of $800. Thus, in low-resource settings resuscitation equipment needed to help babies breathe is often lacking.

Bubble Continuous Positive Airway Pressure (bCPAP) therapy is a common mode of treatment for RDS in premature newborns and for respiratory illness in young children that provides a continuous flow of pressurized air into the patient's nostrils via nasal prongs or a mask.[205] Health care workers often devise improvised solutions such as nasal bCPAP kits—assembled using tubing, nasal prongs, and a water bottle as a bubbler in low-resource settings. While improvised kits can provide low-cost lifesaving respiratory support where requirements for

power or dedicated equipment are not met, little is known about their construction, quality, and safety. They also rely on a 100% source of oxygen and lack the ability to blend air into the gas for the newborn. Excessive oxygen is extremely dangerous to preterm newborns, frequently resulting in complications including chronic lung disease and brain damage.

In the 2012 Global Action Report on Preterm Birth, the WHO highlighted low-cost, robust CPAP equipment with standardized settings as a required technical innovation for reducing child deaths.[206] There are number of affordable, portable, robust bCPAP machines in various stages of development in the technology pipeline. To support developments in this area, Unitaid has made a recent investment through the UnitaidExplore platform to further develop, seek FDA approval for, and undertake feasibility studies of Vayu's bCPAP and oxygen blender devices. These devices do not require an electricity supply or a compressed air tank, and once available could increase opportunities for newborns in low-resource settings to access essential oxygen therapy.[207]

4.3.4 Neonatal Jaundice (NNJ)

NNJ is a condition that affects most newborns in the first week of life, with predominantly benign consequences. It typically resolves within 3 to 5 days without significant complications (if in the absence of comorbid prematurity, sepsis, or hemolytic disorders). However, in some cases, NNJ may become severe enough to put infants at risk for bilirubin-induced mortality or long-term neurodevelopmental impairments.[208]

The most common treatment for NNJ is phototherapy, but technologies to effectively monitor bilirubin levels and diagnose jaundice and not always available in LMICs, delaying treatment. Treatment with blue light phototherapy is necessary for severe cases of NNJ, of which there are a few already commercially available that may be suitable for low-resource settings.

Severe jaundice may not be readily evident to the naked eye until already at dangerously high levels, and may not present until several days after birth when an infant has already left the hospital. Thus, early monitoring of bilirubin in at-risk infants is critical in order to prevent severe jaundice, particularly in premature babies, who are already at greater risk of death and disability. Infants require a laboratory evaluation of serum bilirubin (with result turn around within six hours) to diagnose jaundice and to guide treatment. In low-resource settings, many facilities do not have the ability to run a blood test, and those that do face many challenges both to run the test and obtain results within an appropriate timeframe.

The BiliDx System, a handheld, POC device designed to measure bilirubin quickly and accurately is being developed by the NEST360° consortium to respond to the need for an appropriate diagnostic. The device is currently undergoing clinical trials in NEST360° target countries, with market entry planned for 2021. This device, and others like it (such as the Bilistick) are in different regulatory and development stages, with target use settings in hospitals, clinics, physician's offices, or family counselling in LMICs. Effective diagnosis of NNJ with appropriate tools, particularly in preterm infants, will enable immediate referral for phototherapy treatment.

4.3.5 Hypothermia

Hypothermia in newborns requires rapid diagnosis and increases the chances of acidosis, sepsis and RDS, and can also indicate the presence of system illness such as infection or hypoglycaemia.

Hypothermia can be treated using Kangaroo Mother Care (KMC), blankets/hats, warming cribs, warming mattresses, and radiant warmers. Attempts to warm a cold baby without careful monitoring of temperatures can lead to hyperthermia, and these rapid swings in temperature (thermal shock) can lead to morbidity and mortality.[209] While the risks of hypothermia are well known, it remains largely undiagnosed in low-resource settings. Temperature monitors for infants have recently become available for use with newborns and will alert

caregivers to changes in temperature. These products provide an advantage over traditional thermometers as they provide constant surveillance, removing the need to check the temperature at regular intervals. The BEMPU wearable TempWatch has recently become available and has been identified as a promising global health tool by USAID.[210]

Hypothermia can be managed using radiant warmers that carefully control heat based on manual settings or the infant's own temperature. Radiant warmers provide heat using an overhead heating source and are preferred for infants who may require greater access or closer short-term monitoring. Radiant warmers are preferred, in the short term, to warming cribs or incubators for infants who are unstable and may require significant intervention (such as resuscitation or invasive procedures). Radiant and conductive warmers that are suitable for LMICs that are commercially available, with others in various stages of product development.[211] NEST360° is currently working on a temperature monitor and a conductive warming system that can provide an alternative to currently available radiant warmers. Better suited to low-resource settings where they are needed most, the conductive warming system is being developed to provide an affordable option that can adapt to existing space and structures of LMIC facilities, while providing essential controlled warmth for at-risk newborns.

4.4 RMNCH Innovation pipeline

Against a broader backdrop of increasing national income, stronger health systems, and aligned political and advocacy agendas, the increased availability and uptake of RMNCH products have contributed to improved outcomes in LMICs.[212] Further and accelerated improvements will require conditions that support the continued development, introduction and scale-up of new products alongside efforts to improve access to existing, proven interventions.

RMNCH research and development efforts are predominantly focused on innovations that reduce the burden on already weak and understaffed health systems in LMICs. Products that are quicker and easier to administer, for example, are gaining attention, as are 'self-care' products that have the potential to be administered without a health provider.

There are promising innovations in the later stages of the maternal health pipeline that could offer life-saving options to women in LMICs (Figure 2).

New affordable versions of long acting hormonal contraceptives targeted at LMICs are in late stage development and will soon enter regulatory stage. Postpartum IUDs are newly available and supported by easy to use inserters and removal devices.

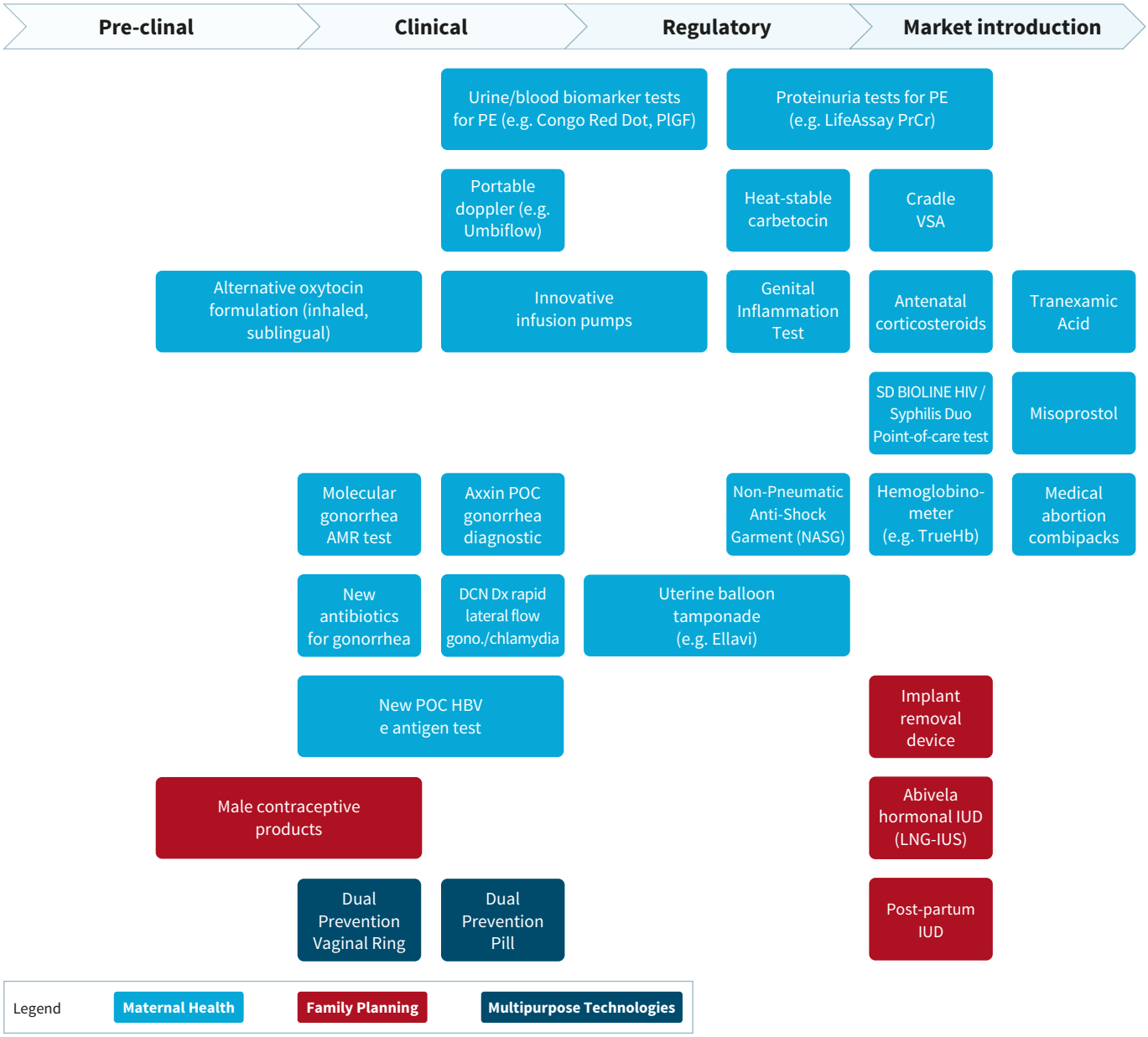
Several multipurpose technologies are in clinical trial stages, and when available could provide both contraceptive and HIV prevention options for women in LMICs. The dual prevention pill presents the nearest-term potential opportunity, while other delivery methods, such as the dual acting vaginal ring and transdermal patch are further back in the pipeline. It is important to note that beyond these specific MPTs, the pipeline for these products is dynamic, and continually evolving. A full review of the landscape and pipeline would be beneficial, and Unitaid will continue to monitor the space though ongoing exploration under the *Enabling scale-up of PrEP and linkage to test* AfI.

Multiple products that could improve access to quality ANC are also in clinical and regulatory stages. These tools include portable dopplers, such as the Umbiflow to identify pregnancies at risk of prematurity, and several point-of-care PE tests to enable better referral to high levels of care for appropriate management. New STI diagnostics that are better suited to low-resource settings are currently in late development and regularly stages.

For PPH, heat-stable carbetocin was recently added to WHO's suite of recommended uterotonics for PPH prevention, specifically when oxytocin is unavailable or its quality cannot be guaranteed, and its cost is comparable. It is current undergoing regulatory approval in early

implementer countries. Emergency tools in regulatory stage, such as the Ellavi pre-assembled UBT, and the NASG add to the new tools to address PPH in LMICs. Further back in the pipeline, alternative oxytocin formulations, and tools to help deliver treatment for PPH could help overcome some of the major barriers to care in high burden settings.

FIGURE 2: Maternal, family planning and MPT pipeline (non-exhaustive)



The newborn product landscape published by NEST360°, provides an overview of the package of technologies needed to deliver appropriate care to newborns, particularly sick and small infants in LMICs. The pipeline for technologies in the NEST360° Landscape is reproduced below (Figure 3). Target Product Profiles, for the technologies were developed in collaboration with UNICEF and published in March 2020, and most of the product categories already have products commercially available. NEST360° systematically evaluated and attributed qualified status to many of these technologies that are on the market and align with TPP characteristics, and meet technical, environmental and usability standards.[213]

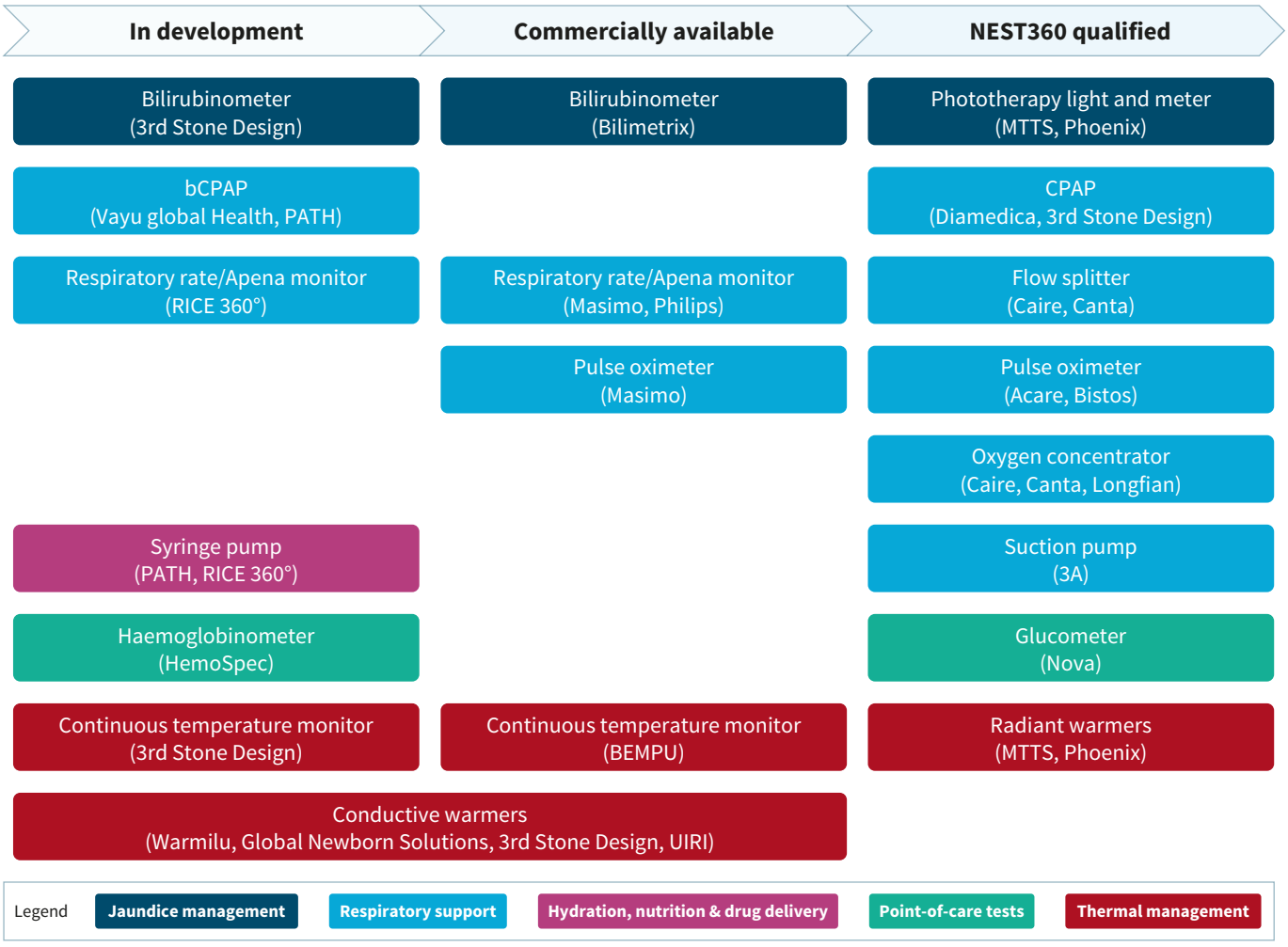
For jaundice management, handheld bilirubinometers targeted at low-resource settings are in late stage development and undergoing clinical trials. Several phototherapy and light-meter devices to treat jaundice in newborns are also commercially available and qualified by NEST360°.

Commercial CPAP products are available and have been qualified by NEST360°. In addition, new innovative bCPAP devices that do not require electricity or compressed air are in late stages of development, and may be reviewed for qualification by NEST360°. Additional products for respiratory support, including flow splitters, oxygen concentrators, handheld pulse oximeters and a suction pump developed for use in low-resource settings are also commercially available and NEST360° qualified. Several handheld devices that can be used to measure respiratory rate of newborns are commercially available, and a new version suited to low-resource settings that also monitor risk of apnea is in development.

For thermal management, a number of conductive warmers for small and sick newborns, such as insulating blankets, warming packs, and warming cribs are in various stages of development. Several devices to monitor temperature of newborns at high risk of hypothermia, including wearable bracelet devices, are already on the market, and radiant warmers have been qualified by NEST360° as well.

In addition, advances in hemoglobin measurement are taking place. A multimodal device that can measure hemoglobin among other vital signs in newborns is commercially available. Rice University is also developing a portable point-of-care hemoglobin test that can diagnose infant anaemia in minutes and two glucose measurement devices are commercially available and have been qualified by NEST360°.

FIGURE 3: Newborn package pipeline (non-exhaustive)



5 HIGH POTENTIAL OPPORTUNITIES

The Secretariat has been actively exploring areas where Unitaid's specific role in the global health architecture could be applied to RMNCH. Through desk-based research, pipeline analysis and partner consultation, over 50 innovative tools and solutions were identified that respond to key challenges in the RMNCH response. Unitaid's criteria were then applied to assess potential fit with Unitaid's principles for AfI identification:

- Unitaid's expertise: focus on challenges that are inherently commodity access issues
- Potential public health impact: focus on challenges for which there is strong evidence of high potential public health impact
- Feasibility: focus on challenges for which the necessary technology can be available in the relevant timeframe
- Optimized use of resources: focus on challenges for which critical gaps exist in the global response and where scale up is possible

These criteria were used to identify potentially high-impact opportunities that address key RMNCH challenges, and fit with Unitaid's mandate. These opportunities were validated with key partners. Of these opportunities, a number are already covered under existing AfIs, and/or existing or planned grants (Table 1). Further analysis of these opportunities remains a priority but will be undertaken through existing channels.

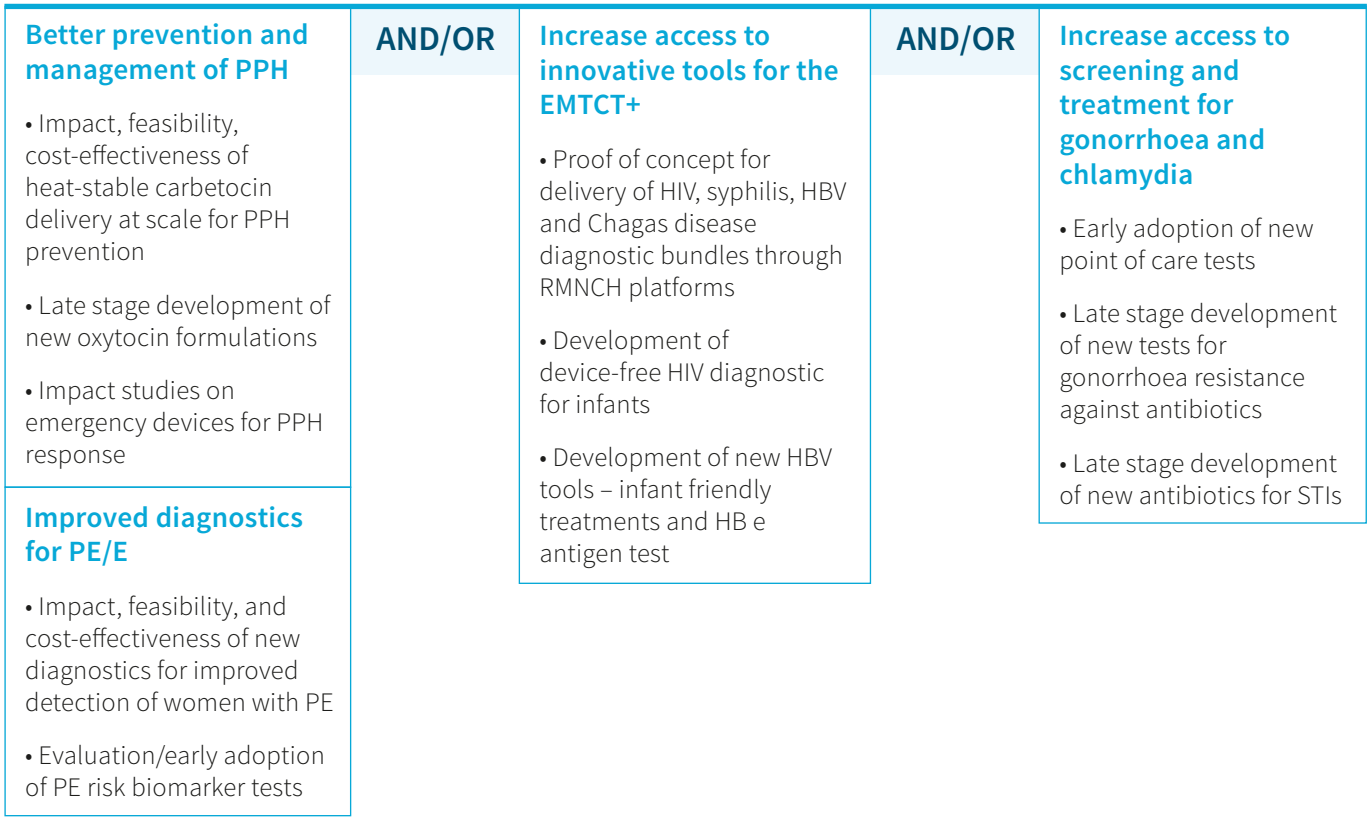
TABLE 1: Near-term RMNCH opportunities covered in existing Unitaid AfIs or grants

Innovation	Public health gap	Opportunity	Unitaid AfI/portfolio best-fit
Bubble continuous positive airway pressure (bCPAP)	Low-resource settings often lack the infrastructure required to support bCPAP, the recommended treatment for RDS in premature newborns.	Affordable, portable, robust bCPAP machines are in various stages of development that do not require electricity or compressed air.	Currently supporting innovations in bCPAP through **UnitaidExplore**.
Portable doppler to identify high risk pregnancies	Current dopplers to identify high risk pregnancies are expensive, and require skilled sonographers and sophisticated infrastructure. Manual methods to identify fetal risk in low-resource settings lack accuracy.	Simple, hand-held doppler devices that use ultrasound waves to identify high risk pregnancy, suitable to ANC in low resource settings are now available.	Ecosystem of handheld dopplers for LMIC use actively scoped under UnitaidExplore.
Dual prevention pill (DPP) for HIV/contraception	HIV incidence rates are high among women who are accessing modern contraception in LMICs.	A DPP comprising oral PrEP and an oral contraceptive will likely be available over the next few years, and could offer significant advantages to the current standard of care by expanding choice and method mix.	DPP, as well as other MPTs are actively scoped within the HIV and comorbities portfolio, and could be actioned under the *Enabling scale-up of PrEP and linkage to test* AfI.
Hormonal IUD	The cost of available levonorgestrel IUD is prohibitively expensive for use in LMIC, where unmet need for modern contraception is highest.	A new generic levonorgestrel IUD is now available at a fraction of the cost and is undergoing registration phase in a number of LMICs.	Levonorgestrel IUD, as well as other methods of long-acting contraception are actively scoped, and could be actioned under the *Accelerating impact of long-acting technologies* AfI.

The remaining opportunities are considered high priorities for further investigation as part of Unitaid's specific response to RMNCH. These opportunities are described further below, and summarized for the near-term in Figure 4.

It should be noted that these opportunities are subject to change considering the dynamic nature of commodity markets, changes in partner activities, or other factors.

FIGURE 4: Summary of potential near-term opportunities



Better prevention and management of postpartum hemorrhage

Findings from a WHO systematic review found that resource constraints, such as low-quality, heat instability and the need for a skilled health provider, can prevent effective use of oxytocin for PPH prevention in LMICs.[214] There are near-term opportunities to support interventions that respond to the high burden of PPH in LMICs.

Manufacturer Ferring has developed a heat-stable formulation of carbetocin that can add a heat stable option to the suite of recommended uterotonics for PPH prevention. The new carbetocin formulation does not require refrigeration, and can retain efficacy for at least 3 years when stored at 30 degrees Celsius and 75% relative humidity. Heat-stable carbetocin also has a longer duration of action than oxytocin.

Following findings from a randomized controlled trial comparing effectiveness and safety of heat-stable carbetocin to oxytocin in the prevention of PPH after vaginal births, WHO updated its global guidance to recommend heat-stable carbetocin where oxytocin is unavailable or its quality cannot be guaranteed, and its price is comparable. Heat-stable carbetocin has also been added to the WHO Essential Medicines List, and approved by SwissMedic, allowing for fast track WHO prequalification and national registrations. Registrations have started in Kenya, India and Nigeria – all countries with significant maternal mortality burdens, and a regulatory strategy is being put into place to register heat-stable carbetocin in more countries.

Broad uptake of heat-stable carbetocin as an addition to the existing tools for PPH could potentially expand access to uterotonics in LMICs. Country level pilot introductions of heat-stable carbetocin that could generate impact, cost-effectiveness and feasibility evidence could help position the recently recommended PPH preventive for scale-up. Operational guidance that demonstrates effective country level scale-up of heat-stable carbetocin in diverse settings could provide the evidence that would enable countries to integrate it into maternal care guidelines and procurement plans for use as per WHO recommendations. If scaled-up, heat-stable carbetocin could add an option that responds to one of the key gaps that prevent uptake of quality uterotonics at the clinical and primary level, and potentially improve efficiencies for better delivery of care at the hospital level.

There are also potential opportunities to undertake clinical studies to expand the indication of heat-stable carbetocin for treatment of PPH. Opportunities could also include working with manufacturers to ensure affordability of health-stable carbetocin where it is needed most.

Moreover, investment into new formulations of oxytocin that are heat-stable and do not require injection for administration could further extend prevention options to the large portion of women in LMICs that cannot access PPH prevention through low-resource clinics, and potentially those that do not require a skilled birth attendant to provide necessary injections. PATH is undertaking early stage development on sublingual heat-stable oxytocin in a fast-dissolving tablet format, and Monash University is working with industry partners on inhalable oxytocin, which is approaching Phase III trials. Once available, these products will provide heat-stable and needle-free oxytocin that can be utilized in areas without reliable cold chain equipment, and/or with capacity to administer intramuscular injections. Catalytic funding for late-stage development and market entry of new oxytocin formulations could accelerate access to these life-saving drugs. Delivery of these products at scale as part of a suite of tools would respond to some of the key access barriers for PPH prevention, and could increase uptake of preventive uterotonics at various levels of health care. This could contribute to efforts to decrease incidence of PPH, a key driver of maternal mortality.

The addition of tools that respond to haemorrhage, where uterotonics and treatment are unavailable or ineffective, will help strengthen the PPH management toolbox. UBT is a device that is used to put pressure on the uterus to manually prevent bleeding when preventive drugs and treatment fail. Despite data that demonstrates efficacy of the UBT for refractory bleeding, it is still underutilized in LMICs due to high prices, and questions around impact when utilized in a low-resource health system. Effectiveness studies that demonstrate potential impact of newly available, fully assembled UBTs for PPH in low-resource settings could complement the heat-stable carbetocin work and strengthen access to emergency care for pregnant women in areas of high PPH burden. The Ellavi UBT developed by PATH and Sinapi Biomedical recently received CE marking and regulatory approval for use in Ghana and Kenya, positioning it as the first commercially available, low-cost, and fully assembled UBT. Similarly, evidence that demonstrates effectiveness of the NASG in stabilizing women who require higher levels of care could further inform operational guidance to help follow WHO recommendations. Additional price reductions through supply side interventions could also expand access to the tool. These interventions together could help scale-up the tools that strengthen PPH care across various levels of the health system to fill gaps that result in maternal mortality.

Improved diagnostics for pre-eclampsia and eclampsia

Access barriers prevent identification of PE in primary and community-based care facilities in LMICs. Currently available urine dipsticks to detect proteinuria are cheap, but inaccurate, and blood pressure measurement devices are often poorly maintained, inaccurate and unavailable. Near-term opportunities exist to address the high burden of PE in LMICs, particularly through better diagnosis.

PATH, South African Medical Research Council and LifeAssay Diagnostics (LAD) have developed a urine strip test to support accurate point-of-care PE/E diagnosis. The LAD Test-it™ Protein-to-Creatinine (PrCr) urinalysis dipstick test is easy to use and gives a result in 60 seconds.[215] It provides a more accurate measurement of proteinuria than protein-only dipstick measurements and is significantly more affordable than other dipsticks measuring PrCr.[216]

Urine and blood-based biomarker tests to identify PE/E in LMICs are in various stages of development.[217] Two POCTs for PE that detect misfolded urinary proteins using the Congo Red biomarker are being developed and validated by Gyunity and GestVision in the US, and Shuwen Biotech in China, with market entry planned for 2020. These simple paper-based urine tests for diagnosis and triage of PE provide easy to interpret results and do not require complicated instruments or reagents.[219] Pilot studies could help establish the clinical utility of these tools in ANC settings in LMICs.

Handheld blood pressure measurement devices to detect gestational hypertension and help diagnose PE are also available and in the pipeline. Validation studies of the low-cost CRADLE Vital Signs Alert device have demonstrated its accuracy in detecting increased risk of severe PE complications,[219] and feasibility for use in rural clinics.[220] Future product development in this space will be shaped by WHO's new technical specifications for automated non-invasive BP measuring devices, released in 2020.[221]

An investment that can generate evidence on the impact, feasibility and cost-effectiveness of new diagnostic tools for PE could position these innovations for scale-up. The addition of recently validated prognostic models and clinical decision support tools for PE could potentially be incorporated into diagnostic tool pilots. The most advanced model developed for use in LMIC settings is the MiniPIERS, which considers demographics, symptoms and signs to identify pregnant women at increased risk of death or hypertension-related complications to support rapid clinical decision-making.[222] The model has been externally validated in multiple countries,[223] and integrated into a mobile phone application for health workers.[224] Other promising digital clinical support tools, like the WHO antenatal care module,[225] incorporate recommended care algorithms with diagnostic inputs measured by mobile phone, including the OptiBP software for cuffless non-invasive BP measurement.[226] Scale-up of clinical decision support tools in parallel to new and effective diagnostics could improve opportunities for low-level health care workers to provide quality care and accurate referral, increasing opportunity to avoid life-threatening complications from PE/E.

Increase access to screening and treatment for gonorrhoea and chlamydia

Current diagnostic tests available to detect gonorrhoea and chlamydia are ill-suited to use in low-resource settings. Lab based tests are often unavailable due to high cost, technical complexity and infrastructure requirements, and current POCTs are inaccurate. New diagnostic tools are in the pipeline, which are suited to LMICs settings. These new diagnostics are potentially high impact tools that can improve STI case management, reduce missed treatment and overtreatment, and increase STI surveillence. These improvements will be impactful in STI control, which currently depends on syndromic case management.

A new POC nucleic acid molecular diagnostic for gonorrhoea developed by Axxin Pty Ltd and a rapid lateral flow assay for gonorrhoea and chlamydia by DCN Dx can provide diagnosis within 30 minutes in primary health care settings.[227] These products were recently awarded grants by FIND following a competitive process based on alignment with TPP criteria.[228, 229, 230] An investment from Unitaid could help these technologies through late stage development, and with market entry as they become available. Early introduction with implementation pilots that demonstrate impact, feasibility and cost-effectiveness could support adoption through RMNCH platforms. Support could also be provided to establish regulatory approval pathways for these diagnostics to catalyze accessibility and scale-up. The addition of innovative deliv-

ery approaches, effective surveillance platforms, and demand generation interventions could also help drive uptake. These investments could help catalyze new tools for scale up. Increased diagnosis through antenatal care platforms will increase access to accurate and efficient testing, enabling same-day results and reducing loss to follow-up. This could effectively increase uptake of treatment, thus reduce MTCT and avoid complications during pregnancy as a result.

Additionally, as new tools are developed, self-collection strategies could be considered to improve uptake and access to STI testing and screening, due to the high reported accuracy, acceptability and uptake of this approach.[231] Building on past learnings introducing new innovations, identification of early adopter countries will be critical to understand and overcome barriers to greater scale-up when norms, standards and regulatory processes have been approved.

Antimicrobial resistance is also a significant and increasing issue in the treatment of gonorrhoea and chlamydia. Most countries have now proven drug resistance to the recommended first line drugs for these infections. An emerging product being developed by SpeeDx and QuantuMDx aims to identify resistance of gonorrhoea. In addition to improved diagnostics, Unitaid will continue to monitor the antibiotic drug development pipeline for new antibiotic options for gonorrhoea. WHO has developed a new TPP to guide new antibiotic development of a first-line treatment of diagnosed urogenital gonorrhoea and extra-genital gonorrhoea (ano-rectal and oropharyngeal) in areas with high resistance to the current recommended first-line treatment for adults and adolescents.[232] A new option that may be suited to LMIC needs is zoliflodacin, which is currently in a Phase III study. Support to address access and market conditions would be needed to rapidly introduce this promising new therapy. Zoliflodacin is the first drug in a new class of antibacterial agents called spiropyrimidinetriones, which offer a potential new mode of action against AMR.[233] Another experimental treatment in the pipeline is gepotidacin, which began a Phase III trial in 2019.[234] The Global Antibiotic Research and Development Partnership (GARDP) is supporting efforts to establish clinical efficacy of these treatments and suitable partner drugs.[235] An investment to accelerate these drugs through the late stages of development and market entry would catalyze introduction, and improve treatment options that can address the increasing burden of STIs, and resistance to existing treatments.

Increase access to innovative tools for the elimination of mother-to-child transmission of HIV, syphilis and hepatitis B (and Chagas disease in endemic areas)

Although testing and diagnosis of HIV in pregnant women during antenatal care is increasing in LMICs, syphilis and HBV testing is not performed as consistently. Without accurate identification of these STIs, health providers are unable to provide appropriate care that can avoid adverse complications during delivery, and prevent transmission of the infections to the fetus. Appropriate tools are available to provide diagnosis and are recommended by the WHO, yet uptake is poor. The synergies and overlap between tools to prevent MTCT of HIV, syphilis and HBV create opportunities for efficient coordinated interventions that could be evaluated as locally-tailored screening and care bundles in ANC. This could include innovative approaches to introduce integrated bundles of point-of-care diagnostic tools for the elimination of mother-to-child transmission of HIV, syphilis, and HBV (and Chagas in endemic areas) into existing maternal and child health services, considering operational feasibility, cost-effectiveness and clinical impact. These include underutilized diagnostics, such as single- or dual-detection HIV and syphilis tests, as well as HBV surface antigen tests. Integrated implementation also has potential for cost and time savings for the health system and patients, such as through streamlined procurement, simplified training for health care workers, reduced unit costs, and rapid result turnaround and treatment. Improved diagnosis of HIV, syphilis, HBV will help provide treatment to reduce adverse events during pregnancy, and prevent MTCT of the diseases.

There are also opportunities to support late stage development and early adoption of new tools to reduce the burden of HBV. These opportunities including product development and evaluation of new and near-to-market POC HBeAg tests as well as pediatric formulations of HBV treatment. Following the WHO 2020 recommendation that HBeAg testing be conducted to determine eligibility for prophylaxis when HBV DNA testing is not available,[236, 237] there is new attention to the diagnostic gap in available rapid HBeAg test products. Efforts to develop and evaluate new and emerging HBeAg RDTs are needed to strengthen the pipeline. Similarly, studies are needed to support WHO prequalification decisions on new products, as currently no available tests have been pre-qualified.[238] Once appropriate and accurate products are identified, there are opportunities to support the introduction of HBeAg RDTs within integrated implementation packages for triple elimination.

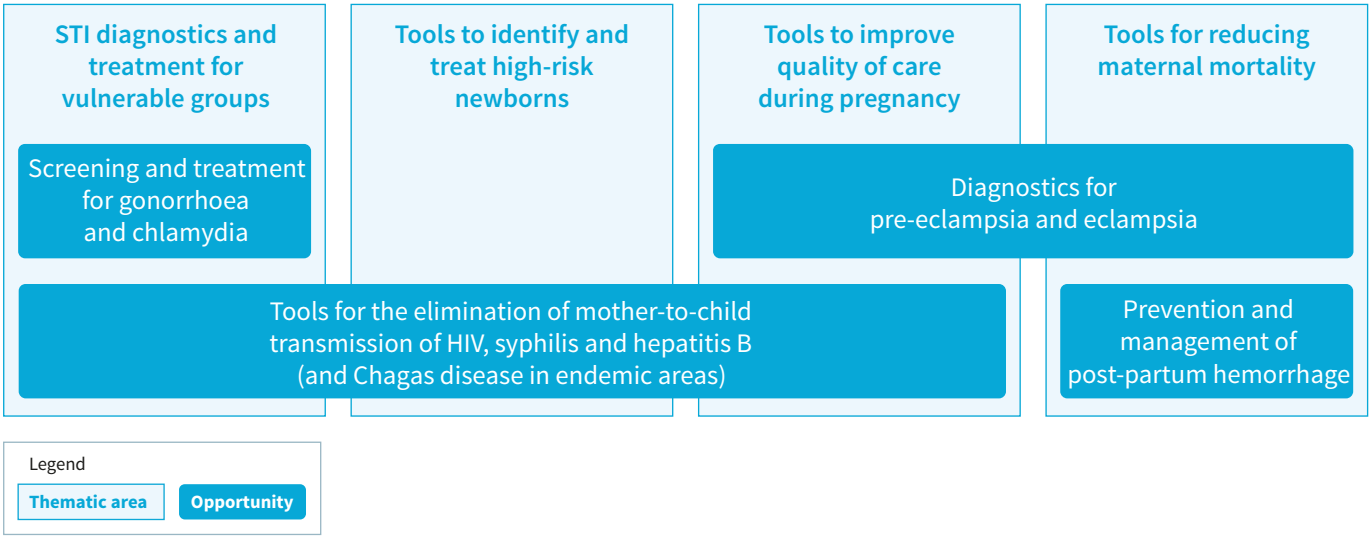
In the longer term, a new device-free, POC test would help meet the need for multiple rounds of virological testing for HIV-exposed infants up to 18 months old. Unitaid has great expertise in the introduction of innovative EID testing for HIV, and will monitor opportunities to support the validation of emerging products against the WHO's TPP criteria[239] as well as advance the introduction of validated products.

6 CONCLUSIONS AND NEXT STEPS

This Thematic Narrative has identified the key challenges that prevent progress in RMNCH, and emerging innovations that could potentially address them. Many of these new innovations with high potential to impact RMNCH are currently in the late development and regulatory stages. By providing support that can help catalyze these high potential innovations for scale-up, Unitaid has the potential to play an important role in delivering RMNCH impact.

Given the broad scope of RMNCH, the high potential opportunities described above can be considered in the context of unmet needs for priority populations (Figure 5). These areas are as follows: Sexually transmitted infections (STIs) diagnostics and treatment for vulnerable groups; tools to identify and treat high-risk newborns; tools to improve quality of care during pregnancy; and tools for reducing maternal mortality. Recommended opportunities can be considered within one or more of the areas of unmet need for priority populations, and provide a logical framing to consider these opportunities within potential AfIs going forward.

FIGURE 5: Key opportunities and priority populations



The opportunities outlined in this section will be monitored and further scoped, with a vision to consider potential investments in these areas under the current and future Unitaid Strategy. The Secretariat will also continue to explore opportunities to operationalize other high potential innovations that can impact RMNCH under other Unitaid portfolio areas outlined in Table 1. The Secretariat will continue to engage relevant stakeholders to ensure complementarity of efforts for highest impact, as the organization continues to expand its activity in this area.

ENDNOTES

[1] Note: Areas for Intervention (AfIs) pinpoint where Unitaid's investments can most effectively help advance global health goals.

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