The need for innovation for RMNCH has been recognised by various international and national strategies, road maps and partnerships. Yet significant R&D gaps persist, due mostly to chronic underfunding.

While strengthening health systems in low- and middle- income countries is a key strategy to reduce reproductive, maternal, new-born and child mortality, R&D would complement this scaling up of existing approaches. It would help significantly by tackling the most important direct and indirect causes of maternal, perinatal and child deaths, reducing the global burden of disease.

Both public and private investments are needed to stimulate this area of R&D: indeed low political priority has been given to women’s and children’s health in the past; in addition, the nature of clinical research in pregnancy is a challenge, which is exacerbated by a vicious cycle of research capacity dearth due to chronic underinvestment.

This paper illustrates major risks to RMNCH, explains the need for innovation to tackle those risks and showcases some of the promising R&D work that has been done in recent years.

Promoting innovative technologies and the development of new diagnostic tools and adequate treatment are key to improve RMNCH.

There is a clear need for new and improved, safe and effective, technologies and products that are acceptable to end-users, adequate to address causes of maternal, new-born and child mortality, suitable to low- and middle- income countries (LMICs) settings and at a reasonable price through not-for-profit production for instance.

We therefore call on the Members of the European Parliament to ensure:

A sustainable EU investment in R&D for RMNCH, including funding for non-profit product developers partnerships which offer unique value in accelerating R&D through facilitating partnerships between the public, philanthropic and private sector, in mitigating R&D risks via a portfolio of product candidates, and in ensuring the affordability and adequacy of products in LMICs.

That the EU’s commitment to making global health science, research, and product development is a key component of the final post-2015 development framework, as without it good health for all cannot be reached.
I. R&D NEEDS

1. REPRODUCTIVE HEALTH

According to estimates, one in three deaths related to pregnancy and childbirth could be avoided if contraceptive services were accessible for all women.² Delaying and spacing births enables women to bear children in their healthiest years, reducing the risk of maternal mortality, and empowers them to have their desired number of children. Babies born less than two years after the next oldest sibling are more than twice as likely to die in the first year as those born after an interval of three years.³ By preventing closely spaced births, improved access to family planning choices could save the lives of over a million infants and children annually.³

In Sub-Saharan Africa, the reasons behind the low use of contraceptive methods are diverse and include previous bad experiences, fear of side-effects, and lack of access, often from logistical failures and products being out of stock.² Innovation is needed to improve the development and delivery of new and safe contraceptive methods in LMICs that are:

- Available and usable on demand,
- Appropriate, for example for lactating women,
- Acceptable to end users and health care workers in general.⁴

Achieving these types of products requires engaging end-users in the design and evaluation of innovative technologies from the start.

CASE STUDY SILCS diaphragm

Women are twice as likely to contract HIV as men, when exposed to it, but they are often less able to protect themselves. That is why PATH — a US-based non-profit product development organisation — is helping develop woman-initiated methods to guard against sexually transmitted infections, unintended pregnancy, or both. To better meet the need for a woman-initiated, non-hormonal, discreet contraceptive, PATH began to design and develop the SILCS diaphragm in 1994 with funding from the US Agency for International Development. PATH developed more than 200 prototypes, which were refined based on feedback from women, their partners, and health care providers. The resulting product — unlike typical diaphragms — is a single-size device that fits most women, and should be easy to supply and use.³

CASE STUDY Progesterone Vaginal Ring

For the first several months after childbirth, exclusive breastfeeding is an effective contraceptive option. Once a woman stops breastfeeding or begins supplementing her infant’s diet, or resumes menstruation, she is at risk of becoming pregnant. The three-month progesterone vaginal ring (PVR), developed by the Population Council - an international, non-profit, non-governmental organisation -, provides breastfeeding women with an effective, user-initiated contraceptive option. The PVR, developed by The Population Council researchers and its partners, is approved and being used in several Latin American countries. Furthermore, evidence is being generated (e.g. stakeholder interviews, focus group discussions and assessment of countries’ method mix) to determine whether and how the PVR could be introduced into Sub-Saharan African countries. It is anticipated that this new technology will have particular impact in this region, where the unmet need for contraception during this critical period in a mother’s and baby’s life is significant.⁵

9. The World Health Organization defines perinatal mortality as the “number of stillbirths and deaths in the first week of life per 1,000 live births, the perinatal period commences at 22 completed weeks (154 days) of gestation and ends seven completed days after birth.”. http://www.who.int/maternal_child_adolescent/topics/maternal/maternal_perinatal/en/
2. MATERNAL AND NEW-BORN HEALTH
A. DIRECT CAUSES OF MORTALITY AND MORBIDITY

Maternal and perinatal disease accounts for nearly 10% of the global burden of disease. 99% of maternal deaths occur in LMICs, 75% due to preventable or treatable conditions such as blood loss, pregnancy-induced high blood pressure, sepsis, obstructed labour, and unsafe abortion. Excessive bleeding after childbirth or postpartum haemorrhage accounts for about 25% of all maternal deaths. Moreover, two major obstetric conditions (preterm labour and preeclampsia) can lead to low birth weight of new-borns, one of the leading causes of new-born death.

Other causes include prematurity, infections, asphyxia (lack of oxygen at birth) and birth trauma. The current standard for treating these conditions carries substantial risk of disability and death for both mother and baby. The treatment for preeclampsia and growth restriction remains expediting delivery, while preterm labour is managed by trying to stop labour with pharmaceutical interventions of questionable efficiency.

More than 80% of newborn deaths are in small babies (preterm or small for gestational age) in the highest burden settings.

Strengthening investment in R&D will prevent a great number of avoidable deaths by providing new treatment as well as technologies more suitable for LMICs (e.g. heat stable vaccines), which can be administered by local health staff or by patients, themselves. Unfortunately, despite the need, investment into R&D in maternal and new-born health remains inadequate and is not particularly strategic. The number of pipeline drugs to treat maternal and new-born mortality is only 1–5% of that for other major disease areas. Estimates suggest that equitable pharmaceutical R&D and public sector health research funding over the next 10–20 years could avert 1.1% and 1.9% of the global disease burden from maternal and new-born diseases, respectively.

CASE STUDY Non-Pneumatic Antishock Garment

Postpartum hemorrhage kills more mothers than any other cause — an estimated 71,800 annually. An anti-shock garment — originally conceived by NASA for use in space — can slow excessive bleeding after childbirth and stabilise the mother until she can be treated at an emergency care facility. The garment resembles a wetsuit that can be wrapped around the mother’s abdomen and lower body to direct blood to key organs. PATH has worked with collaborators from the public, private, and academic sectors to establish high-quality manufacturing for the garment, reduce its price, increase production, and expand access in low-resource settings.

CASE STUDY Oxytocin in Uniject

Instituto Biologico Argentino, an Argentine pharmaceutical manufacturer in collaboration with PATH, launched oxytocin in Uniject in 2009. Oxytocin is a hormone that induces or strengthens labour contractions during childbirth and is used to control bleeding after childbirth. The Uniject device is a prefilled, non-reusable syringe that offers delivery of the life-saving benefits of oxytocin to women in peripheral healthcare settings, and homes. These benefits can improve the ability of midwives and village health workers to administer oxytocin outside of health care facilities and in emergency situations or remote locations.

Source: WHO Global Health Observatory, 2014
B. INDIRECT CAUSES OF MORTALITY AND MORBIDITY

Indirect causes also significantly add to severe maternal and perinatal outcomes and are responsible for more than 25% of maternal deaths. Often pregnant women and children suffer from several of these conditions simultaneously. The leading indirect causes of maternal mortality and premature births are anaemia, also accompanied by many neglected tropical diseases (NTDs), and followed by HIV and AIDS, and malaria.

Almost every woman or girl living with less than $1.25 (USD) a day in Africa, Asia, and the Americas is infected by one or more of the WHO designated 17 NTDs. Hookworm is one of the most important parasitic maternal health issues. In total, almost 40 million African women of reproductive age are infected with hookworms, and seven million of these women are pregnant and are at risk of severe anaemia, leading to reduced birth weight for the baby, and even to the death of the mother or the baby. Additionally, more than 100 million women and girls in sub-Saharan Africa suffer from female genital schistosomiasis, a waterborne parasitic worm whose eggs affect the urinary and genital system. Urinary schistosomiasis is known to significantly increase the risk of being infected by HIV.

Despite the known negative health effects of NTDs, including on pregnant women, no vaccines for these diseases currently exist. There is a great need for additional R&D support to identify and develop new and improved preventative and therapeutic vaccines, diagnostics and treatments that can be delivered to girls and women to reduce parasitic infection before pregnancy and to improve sexual and reproductive health.

CASE STUDY HOOKVAC - Clinical Testing of the Human Hookworm Vaccine

The Sabin Vaccine Institute Product Development Partnership (Sabin PDP) is expanding work to develop and test a vaccine for human hookworm. The HOOKVAC consortium, led by the Academic Medical Center (AMC) at the University of Amsterdam with partners from the EU, United States and Africa, is conducting first-ever Phase I clinical studies that test the Sabin PDP’s two lead candidate antigens, Na-GST-1 and Na-APR-1, in African adults and children. Through the EC FP7 programme funded project, European small-and-medium-sized enterprises (SMEs) are also enhancing global understanding of vaccines for NTDs through development of an optimised manufacturing process and vaccine formulation. A vaccine could provide a sustainable and effective means for controlling hookworm infection, reducing the anaemia, delayed physical growth and impaired cognitive development caused by hookworm infection.

CASE STUDY Dapivirine Ring

The HIV epidemic continues to disproportionately affect women in LMICs, yet they lack practical tools they can use on their own, without the involvement of a male partner. Innovative technologies in development could help empower women with discreet, safe, effective and long-acting tools they can use to protect their own health. The International Partnership for Microbicides (IPM) - a non-profit product development partnership (PDP) – is working to develop the first long-acting, female-initiated HIV prevention technology brought to market, pending study results. The so-called dapivirine ring is now in two parallel Phase III studies, the first efficacy studies of a microbicide ring for HIV prevention. These studies are expected to provide the evidence needed to secure regulatory approvals and licensure for this new tool when all study results become available by 2016.

In Sub-Saharan Africa, malaria during pregnancy is responsible for 400,000 cases of severe maternal anaemia and 200,000 new-born deaths each year. At the same time, pregnant women are twice as likely to die from malaria as other adults. In addition to malaria, children and pregnant women in Sub-Saharan Africa are often simultaneously infected with one or more neglected tropical diseases (NTDs), which further enhances the risk of anaemia.

The current treatment (the artemisinin combination therapy) is not yet available for the first trimester of pregnancy and there is a general need for R&D for new malaria treatment in pregnancy.

Tuberculosis (TB) also places pregnant women and their babies at heightened risk. Women with TB are twice as likely to give birth to a premature or low-weight baby and four times more likely to die in childbirth. TB also impacts fertility and increases the risk of maternal and infant mortality by almost 300% in pregnant women who are HIV positive. Additionally, mother to child transmission of TB is estimated to be 15% within three weeks of birth. Women living with HIV and TB also stand an increased risk of transmitting HIV in utero.

In addition, TB is a leading killer of women of reproductive age. Each year nearly 3 million women contract TB and more than half a million women die from the disease. In addition, one in four HIV deaths is caused by TB.

A new, improved TB vaccine is an essential part of the global strategy to curb the epidemic of TB/HIV co-infection and disease.
In 2020, it was estimated that 11 million cholera cases occur globally every year among children under 5 years of age. The International Vaccine Institute - an international non-profit organisation - advanced a new low-cost two-dose vaccine in response to the need for a cost-effective cholera vaccine for LMICs. It was developed in collaboration with partners in Sweden, Vietnam, and India, and was licensed in 2009 as Shanchol. It was prequalified by the WHO in 2011, meaning that it meets international recognised quality standards and can be purchased by UN agencies and other organisations for use in countries around the world to fight cholera. So far the vaccine has been introduced in India and Bangladesh, with plans for deployment in Ethiopia and Haiti.

**CASE STUDY**

**New TB vaccine for maternal & child health**

Drug-drug interactions between the current first-line TB regimen and certain commonly used Antiretroviral drugs (ARV) complicate treatment for co-infected patients. People with HIV/AIDS who contract TB must often change their ARV regimens to avoid dangerous interactions, or delay needed ARV treatment until their TB is under control.

ARIES a non-profit product development partnership and its partners are testing vaccines in its portfolio in HIV positive individuals to see if they are safe and effective in preventing TB in HIV positive adults and in infants whose HIV status is unknown.

**3. CHIL HEALTH**

Evidence shows that infants whose mothers die within the first six weeks of their lives are more likely to die before reaching age two than infants whose mothers survive. The leading causes of death of children under five are pneumonia, diarrhoea and malaria.

**CASE STUDY**

**Cholera Vaccine Shanchol**

Pneumonia

Pneumonia is the single largest killer of children under five as well as the leading infectious cause of childhood mortality. It accounts for 17% of all under-five deaths, claiming the lives of 1.1 million children under 5 in 2012.

Current pneumococcal conjugate vaccines are effective, but do not protect against the more than 90 types of the virus that exist. They are also complicated and relatively expensive to produce, limiting the number of suppliers thereby adding to this vicious cycle and maintaining their high cost. This leads to difficulties for poorer countries in most urgent need in affording them without assistance.

There is a need for new and more affordable vaccines that can provide either focused or broad protection against pneumonia.

**DIARRHOEAL DISEASE**

Diarrhoea accounts for 9% of all under-five deaths — a loss of more than 580,000 child lives in 2012.

Effective vaccines against the rotavirus, the leading cause of severe childhood diarrhoea, exist but they are not yet widely available in or affordable for low-resource countries, where 95% of rotavirus-related deaths occur. Moreover, current vaccines against diarrhoeal diseases such as cholera are not always suitable for infants under the age of one, and some are relatively ineffective.

New vaccines that are suitable for infants, and which have longer durations of protection, are needed for most of the diarrhoeal diseases.

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MALARIA

Malaria accounts for 7% of child deaths worldwide —roughly 0.5 million deaths in 2011. Moreover, malaria infection may increase one’s susceptibility to, or severity of, pneumonia or diarrhoea.

Proper diagnosis helps ensure that patients are given the right treatment for their condition, and avoids unnecessary use of antimalarial drugs that leads to drug resistance in malaria-causing parasites.

Despite WHO guidelines encouraging diagnosis, access to diagnosis is still low, especially among the poorest households. In some sub-Saharan African countries fewer than 10% of children with fever receive a confirmatory malaria diagnosis.

In some cases, cheap, sensitive and specific Rapid Diagnostic Tests are available, but their quality and heat stability can be problematic.

New diagnostics are needed to distinguish between uncomplicated and severe malaria, and between malaria and other febrile illnesses. Finally, the emergence of resistance to artemisinin-based combination therapies (ACTs) and insecticides means new therapies are needed and only a vaccine for malaria could eventually eradicate the disease.

CASE STUDY Diagnostics for malaria/ LAMP

A new, highly sensitive blood test developed by The Foundation for Innovative New Diagnostics (FIND), with the Hospital for Tropical Diseases (HTD), London, UK, the London School of Hygiene and Tropical Medicine, and Eiken Chemical Company, Ltd., Japan quickly detects even the lowest levels of malaria parasites in the body.

This first commercially available malaria assay called LAMP (“loop-mediated isothermal amplification”) is a simple test, which can be performed by a non-specialist health worker and does not need refrigerating like other tests. It requires a sample of blood to be processed and placed in a test tube with a reactive powder then heated. If the malaria-causing Plasmodium parasites are present, the tube glows green. The whole process takes less than an hour.

CASE STUDY Protecting children against malaria when they are most vulnerable

In some parts of Africa, more than 60% of malaria cases occur in just 4 months of the year, during the rainy season. Around 39 million African children under the age of 5 years live in these regions and an estimated 152,000 die from malaria each year.

To support the protection of children in areas of seasonal malaria, the Medicines for Malaria Venture (MMV) - a non-profit foundation – is working as part of the West Africa Roll Back Malaria (RBM) Seasonal Malaria Chemoprevention (SMC) working group to support the implementation of SMC in the Sahel sub-region. SMC is the intermittent administration of full treatment courses of an effective antimalarial medicine during the malaria season: it has been shown to prevent 75% of malaria episodes. MMV is also working with Guilin to develop child-friendly formulations of the medicine used for SMC.

HIV/AIDS

HIV places a child at high risk of pneumonia or diarrhoea and more severe and chronic forms of these conditions. Pneumonia is commonly due to an opportunistic infection among HIV-positive children.39

Without antiretroviral treatment (ART), most children with HIV die of common childhood diseases before the age of 5. HIV-attributable mortality in 2012 among children under 5 ranged from 4% to 19% of total under-five mortality in some countries with high HIV prevalence in sub-Saharan Africa.40

This is particularly concerning as about 1.5 million girls and women (ages 15 and above) were pregnant and living with HIV in 2011 — more than 90% of them in sub-Saharan Africa. Without any intervention to prevent mother-to-child transmission of HIV (PMTCT), about half of these girls and women will pass infection on to their children during pregnancy, delivery or breastfeeding.

Antiretroviral drugs are available, but most are not adapted for children: for instance, paediatric formulations and fixed-dose combinations are needed.41 An improved first-line therapy for children would ideally be safe, easy to administer, well-tolerated and palatable, heat-stable, readily dispersible, and dosed once daily or less. It must also carry minimal risk for developing resistance, be compatible with drugs against tuberculosis, and affordable.42

Current methods for early diagnosis and support of HIV treatment are also often unsuitable for LMICs. Ultimately, an HIV vaccine is needed if we are to fully control and eradicate HIV. Since women and girls bear a disproportionate burden of HIV/AIDS, the ability to prevent disease and eliminate HIV/AIDS through an effective vaccine is of urgent R&D priority in RMNCH.

To this end, there are several promising candidates in preclinical and clinical development.43

TUBERCULOSIS

Conservative estimates show that 490,000 children suffer from tuberculosis (TB) every year and up to 64,000 die as a result. In HIV-infected children the risk of developing TB meningitis is also high and often results in deafness, blindness, paralysis, mental retardation and death. No point-of-care TB test currently exists and current diagnostics require sputum samples which are difficult for children to produce. Similarly to HIV, no paediatric formulation and child-friendly TB treatment currently meet WHO’s specified guidelines. Drug companies perceive paediatric TB to be a small market with little profit.

It is therefore essential to invest in research to develop a TB test that is simple, accurate, uses a non-sputum sample such as blood or urine, and produces results on the spot.

II. ROLL OUT OF NEW PRODUCTS

R&D is also an important component to securing access to life saving commodities addressing issues such as effectiveness, problems of resistance, acceptability and supply. Furthermore, investing in implementation research is key to put the end-users at the heart of the development cycle.45

At the same time, innovative and existing medical interventions (such as oral rehydration solution (ORS), breastfeeding, the provision of bed nets, sanitation, wash and nutrition programs) need to be rolled out together as an overall package of care in order to leverage their respective efficacy. The GAVI Alliance and the Global Fund to Fight AIDS, Tuberculosis and Malaria ensure the availability of currently existing medical interventions by redressing global inequities in access to new and underused vaccines (e.g. for rotavirus, pneumonia, cholera), prevention and treatment.

However, not all conditions critical to RMNCH are covered by similar global procurement mechanisms. Creation of incentives for private sector investment and public sector procurement is needed to ensure that all innovative technologies are being rolled out.

Lastly, weak capacity of national regulatory authorities in overseeing the evaluation and manufacture of new tools creates bottlenecks which increase costs and delays. According to a WHO survey only 65% of the 145 responding countries reported having a national authority that was mandated to implement and enforce medical device regulations. In addition, few countries that have drafted regulations have actually implemented them.46 Investment into strengthening regulatory capacity and infrastructure as well as clarifying the regulatory pathways for innovative medical devices is crucial.

44. Eurek Alert. (2012). DNDi and Cipla to develop 4-in-1 pediatric antiretroviral drug combination - announced a new collaboration with Indian drug manufacturer Cipla to develop and produce an improved first-line antiretroviral (ARV) combination therapy specifically adapted to meet the treatment needs of infants and toddlers living with HIV and AIDS.

Once delivered, this new paediatric ARV combination could help accelerate the provision of care to the world’s youngest children living with HIV and AIDS, who are at very high risk of dying without treatment.44

R&D NEEDS TO IMPROVE RMNCH

Supportive reference documents:

A. International Conference on Population and Development (ICPD) 1994: “Governments, assisted by the international community and donor agencies, the private sector, non-governmental organisations and the academic community, should increase support for basic and applied biomedical, technological, clinical, epidemiological and social science research.”

B. UN Global Strategy for Women’s and Children’s Health 2010: “Partners must find innovative ways to provide high-quality care and to expand research programs that develop new interventions, such as vaccines, medicines and diagnostic devices. They must develop, fund and implement a prioritised and coordinated global research agenda for women’s and children’s health, and strengthen research institutions and systems in low- and middle-income countries.”

C. A Promise Renewed 2012: “Invest in innovation (including operations research) to accelerate results” to create high impact solutions that would accelerate ending preventable child deaths

D. UN Commission on Life-Saving Commodities for Women and Children 2012: one objective is to “promoting innovative technologies and new product development” to increase the availability, affordability, accessibility and rational use of selected commodities for women’s and child health