Small Doses: Finding and making the medicines children need

EXECUTIVE SUMMARY

While there have been many significant improvements in maternal and child health over the last 20 years, medicines, vaccines and diagnostics still do not exist for many health conditions that are common in the poorer parts of the world but not in wealthier countries. Millions of people still die every year from preventable infectious diseases and other conditions and many more are left to suffer with the lifelong debilitating effects of untreated illnesses. This is truer for children in low- and middle-income countries (LMICs) than almost all others, as they are affected both by the lack of health technologies for conditions that primarily affect these parts of the world *and* the lack of those that are suitable specifically for children. Not only is there is a desperate need to both develop new health technologies and ensure that they are accessible to those that need them, human rights require it.

Developing new products, however, is a costly and time-intensive process – from identifying the problem, finding potential compounds, testing and trialling products, determining appropriate formulations, manufacturing a product and finally bringing it to market. Many different stakeholders are involved over the course of this process, including governments, the private sector, healthcare workers, academics, patients and others. Largely due to the way that research and development (R&D) for new health technologies is currently organised, they are rarely developed for conditions that primarily affect LMICs or for the children in those countries. Where the necessary health technologies do exist, they are often not developed in versions suitable for LMICs or for children, and they can be prohibitively expensive, due to a host of factors, including intellectual property barriers.

Most new health technologies are developed by the private sector, which makes decisions on what to produce based mostly on whether there is a large enough market to justify investment. Where there is no significant market – one that allows companies to generate enough profit for their shareholders – private companies are less likely to invest. This problem is often called 'market failure'. If we accept that the market and private companies will not alone be the solution, then additional public funding and support must be provided for R&D in these areas. Although governments already play a large part in R&D for neglected conditions, including funding much early research in academic institutions, along with the private sector, they must do more in order to meet their human rights obligations. Currently, there is a failure on the part of the whole global community to represent and protect the health needs and rights of the world's most vulnerable and marginalised people.

The international community has repeatedly attempted to address this problem over the last decade. However efforts have mostly been piecemeal and have left many structural factors unaddressed. Creative and concerted action must be taken by all stakeholders – governments, the private sector and donors – to systematically address the lack of health technologies for children.

This will require a combination of solutions, but some features are essential to meet both the demands of human rights and public health. First, there must be an increased and more stable source of public funding to make up for the current deficit in R&D funding for neglected conditions and for adaptation of products. Second, there must be greater and better coordination of this funding, so that areas of greatest need can be adequately and more effectively addressed. Third, all R&D must ultimately result in maximum access, so R&D mechanism must embrace three key principles: delinkage, open innovation and licensing for access.

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Introduction

Over the last 20 years, there have been hugely significant improvements in maternal and child health and survival in most parts of the world. Many of these gains are a result of increased access to existing health services and technologies. However health technologies simply do not exist for many health conditions that are common in the poorer parts of the world but not in wealthier countries. In situations where the necessary new medicines and vaccines do exist, often there are not versions available suitable to meet the needs of LMICs, or those that are available are too expensive. That an estimated 13 million people a year still die from preventable infectious diseases, maternal and child health issues and nutritional deficiencies makes the need to address this problem clear.[1] This figure does not include deaths related to many neglected conditions,[2] which affect 1 billion people globally, including an estimated 500 million children, or the rising burden of non-communicable diseases, nor does it take into account the debilitating effects of illnesses or conditions, which, if untreated, can result in lifelong disability and suffering.

It is unsurprising that treatments for diseases that predominantly affect the poor and are concentrated primarily in LMICs are underfunded and underdeveloped. This is, in part, because of the way that research and development for new medicines and vaccines is organised and funded.[3] Most new medicines are developed by the private sector, which makes decisions on what to make based mostly on whether there is a large enough market. Where there is no significant market to generate a return to investors, private companies are less likely to invest. While efforts have been made to address this problem in the last decade, as will be discussed in this paper, it is unsurprising that commercial considerations outweigh public health ones in the current R&D system. The lack of R&D into medicines and vaccines for diseases that affect poorer people in LMICs is generally designated as one of 'market failure', but in fact, it is a failure on the part of the global community to represent and protect the health needs and human rights of the world's most vulnerable and marginalised people.

Even in countries where there is a market, health technologies still target wealthier markets first, leaving poorer population segments neglected because medicines and vaccines are not adapted appropriately for them. This is particularly true for children, for whom there are often no suitable versions of existing medicines. Children in LMICs are therefore more deprived than any other group because they suffer both from a lack of medicines for conditions that primarily affect the parts of the world where they live *and* of medicines that are suitable for them.

Over the last decade there has been increasing recognition internationally that the global R&D system does not adequately serve the needs of people in LMICs, particularly the most excluded women and children. Ban Ki-Moon, UN Secretary-General, recently announced a high-level panel on access to medicines in order to further investigate this and related problems.[4]

As the World Health Organization's (WHO) Consultative Expert Working Group on Research and Development: Financing and Coordination (CEWG) said in its 2012 report, "The moral case for making life-saving products available applies equally to products that are needed but not yet developed. Men, women and children are suffering because there are no appropriate treatments for the diseases they face."[5] Instead of 'neglected diseases', we might discuss 'neglected people'; it always the poor and excluded whose rights are most at risk.

Save the Children has consistently advocated that improving and strengthening health systems, with the goal of achieving Universal Health Coverage, is the best route to improvements in health outcomes for women and children.[6] As one of the six building blocks of a health system,[7] access to health technologies – which includes medicines, vaccines and diagnostics – is a critical part of this. At the point of contact between the system and a patient, the intervention will frequently involve the administration of prescription of a medicine or vaccine. This is hard enough in many health systems but is impossible if the right drug does not exist, has not been developed or cannot be delivered in the setting it needs to be. This means we need both new medicines and vaccines and better adapted ones so that they are effective in resource-constrained and non-traditional settings.

Without adequate health systems in place, including well-trained healthcare professionals and functioning supply chains, these medicines and vaccines will not be able to be delivered and used in a timely and appropriate manner. Similarly, the underlying determinants of health, such as access to potable water, adequate sanitation and hygiene and nutrition, all need to be addressed in order to improve health outcomes.[8] All of these factors, along with persistent and various forms of discrimination, in particular gender discrimination, greatly affect access to health technologies. Governments must simultaneously address these other issues in order to meet their human rights obligations.

Save the Children's partnership with GSK

Save the Children has a five-year partnership with GSK and receives funding towards its activities. This partnership intends to find new ways through which the two organisations can make a contribution towards reducing deaths of children under five. Activities include joint advocacy to persuade political leaders to take action on health and exploring how pharmaceutical companies can ensure their activities consistently, equitably and sustainably promote access to medicines.

Save the Children also receives financial donations from other pharmaceutical companies. None of this funding has supported the production of this paper.

Why ending preventable child deaths will require new R&D

Changing conceptions of what is considered 'preventable'

Along with existing human rights obligations, world leaders have also made commitments to end 'preventable' child deaths – most notably goal 3.2 of the new Global Goals for Sustainable Development.[9] A death is preventable if knowledge and activities which can stop that death are or could be available. What can be treated, cured or prevented changes over time. A hundred years ago, before the advent of antibiotics, mortality from bacterial infections was not preventable. New medicines and vaccines – and the circumstances and services to make them available to those that need them – has expanded what can be considered preventable and thus the human rights obligations and responsibilities of different stakeholders.

The human rights to health and to enjoy the benefits of scientific progress and its applications

Nearly all of the major international human rights agreements and treaties recognise the right to health, including the Universal Declaration of Human Rights, the International Covenant on Economic, Social and Cultural Rights, the Convention on the Rights of the Child and the WHO Constitution. The right to health can also be found in many regional human rights agreements, such as the Additional Protocol to the American Convention on Human Rights in the Area of Economic, Social and Cultural Rights, and, either explicitly or implied, in many national constitutions, including those of South Africa, Guatemala and India.

Access to medicines is a core component of the right to health,[10] which also requires that special attention be paid to vulnerable and marginalised groups, communities, and individuals, including mothers and children.[11]

The right to enjoy the benefits of scientific progress and its applications is also widely recognised and found both in article 27 of the Universal Declaration of Human Rights and, in slightly different terms, in article 15 (1)(b) of the International Covenant on Economic, Social and Cultural Rights.[12]

Access to medicines, particularly in terms of affordability, and the development of appropriate new medicines, including for children, are central aspects of these rights.[13]

Taken together, these two rights point to a number of obligations relating to R&D of new drugs and access to these medicines:

- At a minimum, governments must ensure that health technologies are available, accessible, acceptable and of good quality without discrimination.
- Governments must do all that they can to ensure the development of new medicines and access to those medicines with a focus on those necessary to address conditions faced by vulnerable and marginalised groups.
- Where the private sector is not meeting the demands of the rights, governments must provide greater support for R&D into the necessary health conditions and must develop an enabling environment, fostering the development and diffusion of science and technology.
- Where government resources are limited, the international community has a responsibility to provide support to ensure that the requirements of the rights are met.
- Other countries and key stakeholders, including private companies, must refrain from actions that interfere with another government's ability to realise these rights, such as through expanding intellectual property protections in free trade or similar agreements.

The private sector, based on the UN Guiding Principles on Business and Human Rights, bears a responsibility to respect and remedy human rights.[14] This means that businesses should take active steps to avoid infringing rights and remedy violations where they occur. For children in particular, the Children's Rights and Business Principles, co-created by Save the Children, the UN Global Compact and Unicef, provide additional guidance on how businesses can ensure children's rights are respected and promoted.[15] In the case of R&D, this means that companies should endeavour to increase research into and development of medicines, vaccines and other health technologies that will be used by or are necessary to ensure realisation of the rights of vulnerable and marginalised populations; this will generally mean for neglected conditions.

These obligations and responsibilities are discussed further elsewhere in this paper.

The causes of mortality and morbidity for pregnant women and children in LMICs

There is a clear disparity between the burden of disease on women and children in developing countries and the amount of money being spent on R&D for the conditions that affect them, as will be shown later, which is unacceptable from a human rights and public health standpoint. Before looking at this deficit, however, it will be helpful to quickly outline the conditions which most impact children and mothers, in order to determine where R&D investments should be made to alleviate these issues.

About half of maternal and childhood mortality is caused by conditions for which there are existing treatments or for which only a service is necessary. However, the UN Commission on Life-Saving Commodities for Women and Children (the Commission) identified that there is still a need for new treatments and re-formulations of many existing medicines for resource-constrained environments.

Alongside these conditions, nearly half of all under-five deaths – approaching 3 million in 2015 – are due to infectious diseases;[16] many of them could be prevented with appropriate medicines and the staff to diagnose and treat them. Among infectious diseases, pneumonia and diarrhoeal diseases cause approximately 25% of all under-five deaths – making these the leading causes of deaths in children under five.[17] Although, in recent years, vaccines for pneumococcal diseases and rotavirus have been developed, these diseases persist as leading causes of child mortality. Despite improvements in coverage, access to the vaccines is so far limited, and they may not be suitable for all parts of the world.[18]

Aside from pneumonia and diarrhoeal diseases, the global public health epidemics of HIV/AIDS, TB and malaria have had the largest impact on the lives of children and mothers around the world. AIDS is one of the leading causes of death among women of reproductive age. More than 200,000 children contract HIV every year and approximately 150,000 children a year die from AIDS.[19] Of the 3.4 million children living

with HIV, only 647,000 children receive the necessary treatments.[20] Nearly one-third of HIV+ children die by their first birthday and half die by their second without treatment.[21] Beginning antiretroviral therapy before the twelfth week of life reduces HIV-related mortality in children living with HIV by 75%.[22]

The number of adults on treatment is still low as a percentage of the total number of people with HIV (41%), but is still much greater than that for children (32%).[23] This continues to be true even as treatments for HIV/AIDS have received greatly increased attention over the last two decades. While there is now a relatively well-established market for HIV treatments, because of international donors, major gaps remain in terms of research into paediatric HIV treatments.[24] Although many factors limit children's access, a significant contributing factor is that in many cases the appropriate medicines are not available for most children. This gap led to the launch of the Paediatric HIV Treatment Initiative, meant to increase innovation for paediatric HIV treatments.[25]

At least 1 million children become ill with tuberculosis (TB) each year and approximately 140,000 HIV-uninfected children die of TB every year.[26] This is likely to be a significant underestimate.[27] Deeply troubling stories of parents having to split pills in order to treat children with the correct dose, and children dying from such inappropriate treatment. have been reported.[28]

In 2013, an estimated 437,000 African children died before their fifth birthday due to malaria.[29] Globally, the disease caused an estimated 453,000 under-five deaths in 2013.[30]

In terms of absolute numbers, other Type II and III diseases (discussed in the box below), such as leishmaniasis, Chagas and dengue, are not significant causes of mortality of children under five, they exclusively affect the poorest and the most excluded people in LMICs, represent a sizeable component of mortality of children over the age of five, and often result in lifelong disability or chronic illness. It is likely that millions of children are affected by these diseases in some way.[31] WHO has documented the massive impact of these diseases on children's lives. For example:

- Approximately 875 million children need annual treatment with preventive chemotherapy for soil-linked helminths (parasitic worms) but only 35% received treatment.[32]
- Rheumatic fever, which primarily affects children aged 5-14, caused about 240,000 deaths in 2013,[33] yet only $1.4m is spent on R&D for this illness. Although it can be treated using currently available drugs, the greatest need is for a vaccine for children.[34]
- Cases of buruli ulcer in Ghana are reported to have resulted in 19 days of school absenteeism per child and high rates of social isolation. 84% of children say they have been affected by this illness.[35]

These three diseases received less than 4% of the global funding for R&D in neglected conditions (itself small), and in absolute terms just about $100m in 2014.[36]

Disease types

The CEWG was tasked with framing its analysis around disease types that were first introduced by the Commission on Macroeconomics and Health and elaborated in the report of the Commission on Intellectual Property Rights, Innovation and Public Health. The classification of diseases into three types takes into account a number of factors including development level of countries, disease burdens and others factors.

The definitions themselves are combined such that:

> **Type I diseases:** occur in both rich and poor countries, with large numbers of vulnerable populations in each. Examples include appendicitis, liver cancer and inflammatory heart disease.
>
> **Type II diseases:** occur in both rich and poor countries, but with a substantial proportion of the cases in poor countries. Examples include dengue, HIV/AIDS and lower respiratory infections.

> **Type III diseases:** are those that are overwhelmingly or exclusively found in developing countries. Examples include Chagas disease, leprosy and malaria.

These definitions have been used by the international community very generally in trying to fashion solutions to problems related to R&D. As these are rough categories, the illnesses included within each category may change and be recalibrated based on available and changing evidence. This paper is primarily concerned with Type II and III diseases (which include all neglected tropical diseases) and those Type I diseases that have impacts on maternal and child health, such as Hepatitis C and some cancers, and which are under-resourced.

International recognition of the problem

Over the last decade increasing attention has been paid to the problem of the lack of R&D for health technologies for the developing world generally and specifically for mothers and children. Initially characterised as the '90/10 Gap' – as only 10% of global health research spending was spent on diseases or conditions accounting for 90% of the global disease burden[37] – understanding of the problem has become more sophisticated.

Early in this period, WHO (along with the World Trade Organization and the World Intellectual Property Organization) began to examine the problem in more detail and to fashion solutions. This began with the establishment of the WHO Commission on Intellectual Property Rights, Innovation and Public Health in 2006, and continued through to 2012, when the CEWG published its report on financing and coordination for R&D,[38] which stated that one of the ways to best ways to address deficits in R&D funding would be through a legally binding agreement on global biomedical R&D. Despite being supported by many Member States, this recommendation was put off until the World Health Assembly in 2016 due to resistance from the United States and the European Union.

The report also explored means through which public and private finance could be mobilised to fund more R&D. A key aspect of its analysis was a discussion of the effect of the patent system as the primary incentive model on innovation in this area and the difficulties of generating private sector investment where there is little to no financial return. One of the primary recommendations of the report was to make use of models that delink the cost of R&D from the eventual price of the produced good, a solution which will be discussed in greater detail later in the paper.[39]

The UN Commission on Life-Saving Commodities for Women and Children (the Commission) was established under the United Nations Secretary-General's Every Woman Every Child movement in order to support achievement of the health-related Millennium Development Goals (MDGs 4 and 5). It identified 13 essential commodities for reproductive, maternal, child and newborn care that were at the time insufficiently available and for which there was a need to produce products more suitable for mothers and children in the developing world.[40] The commodities included female condoms; implants; emergency contraception; oxytocin; misoprostol; magnesium sulfate; injectable antibiotics; antenatal corticosteroid; chlorhexidine; resuscitation equipment; amoxicillin; oral rehydration salts and zinc.

The Commission estimated:

> that an ambitious scaling up of these 13 commodities over five years would cost less than US$2.6 billion and would cumulatively save over 6 million lives including 230,000 maternal deaths averted through increased access to family planning.[41]

The commodities identified were based on those that are already known to be suitable for production in more appropriate ways on a larger scale. If R&D efforts for new and adapted products were better aligned with the need, mortality and morbidity rates could be reduced more quickly and human rights requirements better met.

Medicines for children

Problems resulting from a patent-based incentive structure are compounded when it comes to children, where R&D may be even more difficult and costly given children's increased biological sensitivity to medication and important regulatory and ethical concerns, such as conducting clinical trials with children. This is alongside the fact that there may not be a sufficiently profitable market for medicines for children in order for the private sector to produce these medicines on a systematic and ongoing basis.

WHO has acknowledged the problem of lack of development of paediatric medicines, specifically formulations, through its 'Make Medicines Child-Friendly' programme.[42] The purpose of this programme was to increase awareness of the problem of R&D for medicines for children. This programme has been reinforced and taken up by the work of the Commission and other global stakeholders. More recently, the report of the Commission on HIV and the Law has also identified this problem and the Secretary General's High-Level Panel on Access to Medicines and Innovation has set out try and tackle it.

Misaligned incentives

How new drugs come to market

Developing new products is a costly and time-intensive activity – from identifying the problem, finding potential compounds, testing and trialling products, determining appropriate formulations, manufacturing a product and finally bringing it to market. Over the course of this activity, many different stakeholders are involved, including governments, the private sector, healthcare workers, academics, patients and others.

Given the time, resource and risks involved, the public sector is often not well suited to the development of actual health technologies. The private sector therefore plays a pivotal role in the development of new health technologies.

Early research – such as determining how biological pathways work or looking at the nature of a particular pathogen – has no clear commercial application and tends to be publicly funded and conducted by public research entities and academic institutions.

As basic scientific research progresses towards commercial application, and specifically health technology development – bringing the products to market, including going through various regulatory processes such as conducting clinical trials – most of the financing is done by private companies. Companies bear a great deal of the risk in this process because while the costs of development are high, the likelihood of developing an approved product is very low.

Successful production of new medicines and vaccines under this model is predicated on the existence of a market that affords private companies a sufficient return on the financial investment made in the development of a product. Estimates of the costs of R&D of a medicine vary significantly, ranging from civil society estimates of $500m up to the $2.5bn indicated in a study by Tufts University.[43] $1.5bn is frequently cited by the industry as an approximate cost.[44] Exact figures are difficult to determine because there is extremely limited transparency related to costs and investments in medicines and vaccines. Regardless of the precise figure, which will vary greatly depending on the kind of health technology, R&D is clearly costly. These costs, along with projected returns, play a key part in decisions about whether to move forward with the development of a potential product.

In order to ensure companies can both recoup investment costs and generate profit, under the current global model countries grant them a period of market exclusivity in the form of intellectual property rights, specifically patents. This allows innovator companies to be the only producer of the medicine on the market and thereby theoretically able to set the highest price possible. In some countries, factors such as price controls or reimbursement schemes may have an impact on the price, but the point remains the same. The impact of this can be seen, for example, in the pricing of Gilead's new Hepatitis C treatment, *sofosbuvir*. It was priced at $84,000 for a 12-week course,[45]even though MSF and the Liverpool School of

Hygiene and Tropical Medicine reported that the medicine could actually be produced for $100 dollars per course.[46]

How the R&D system is failing the most excluded children

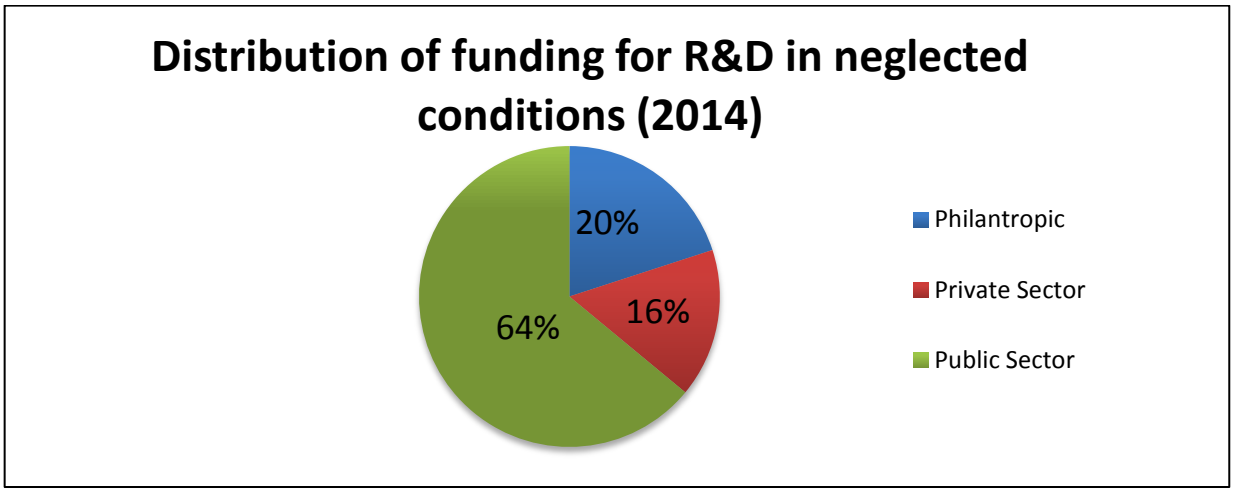
The low levels of investment by the public, private and philanthropic sectors into R&D for Type II and Type III conditions is apparent. Most information currently available on investments into these conditions, and into reproductive health commodities, is available through the GFinder database. The diseases covered in the database, identified in this paper as neglected conditions, all fall within WHO's Type II and III categories (with the exception of Hepatitis C). Type II and III diseases are otherwise broader than those looked at by GFinder, from which it can be inferred that there is likely an even greater shortfall than is suggested below. For the purposes of the following few sections, the paper will refer to neglected conditions, which are the 35 diseases for which Gfinder has collected information.[47] The WHO Global Observatory on Health R&D has recently come online and will soon be fully operational, which will allow for additional analysis to be conducted in this area.[48]

Private investment

Businesses have a responsibility under international human rights law to respect and remedy human rights violations. This means that pharmaceutical companies should commit to increasing research into and development of medicines, vaccines and other health technologies for Type II and III conditions, as these have the greatest impact on vulnerable and marginalised populations. Where industry practices result in human rights violations, it must commit to remedying these violations.

Private investment into R&D for neglected conditions, including those affecting children and mothers, is low compared both to Type I conditions and to need. Figures shown below are for investments as a whole and child-specific investments can be assumed to be only a small portion of these numbers. This further demonstrates the scale of the need for increased investment in this area.

Figure 1: Distribution of funding of R&D in neglected conditions (2014)



In 2014, the private sector spent $534m, 16% of total funding, on R&D on neglected conditions.[49] This is just about one-third of how much the industry indicates it costs to develop a single drug. Although this was a $98m increase over the previous year, almost $33m of that increase was funding toward Ebola.[50] Of total private sector funding, multinational companies contributed the lion's share, about 62%, or $279m, and small and medium pharmaceutical and vaccine businesses contributed $86m or 16% of the total.[51] The International Federation of Pharmaceutical Manufacturers Associations states, "The research-based pharmaceutical industry is estimated to have spent nearly $137 billion globally on pharmaceutical R&D in 2012."[52]

Unless pharmaceutical spending on R&D dramatically decreased between 2012 and 2014, this suggests that spending on neglected conditions makes up less than 0.004% of its total expenditure on R&D. It should be noted that some of the industry spending on R&D is on non-communicable diseases, which also affect LMICs.

Industry funding for neglected conditions research decreased between 2010 and 2013, with an annual drop of $74m (-19%). Last year saw a moderate increase from the previous year, largely to due increased funding for Ebola and HIV.[53] While the industry does fund nearly 40% of R&D for reproductive health commodities specific to the developing world in absolute terms (approximately $40 million), this makes up 10% of the total investment that industry is making into R&D for mothers and children in LMICs.[54] And although since 2012, 11 companies have been granted regulatory approval for 30 new products for diseases relevant to LMICs, there have been no new approvals for neglected tropical diseases and maternal and neonatal health conditions in that time, which means that no new medicines for any of these conditions have been brought to market for nearly four years.[55]

Most of the industry's contribution to R&D on neglected conditions in 2014, $279m or 62%, went to three diseases (TB, malaria and HIV/AIDS).[56] Diarrhoeal diseases, which constitute nearly 25% of under-five deaths, received was only about 7% of the total industry funding directed towards neglected conditions, amounting in absolute terms to only $32m in 2014.[57] This constitutes only 5% of total global R&D funding on neglected diseases.

It is impossible to know what proportion of any of this funding is directed specifically into R&D for paediatric conditions and formulations relevant to LMICs. Evidence suggests that, even with additional incentives in place in the US and Europe, R&D for paediatric medicines is still focused on wealthy high-income country (HIC) markets.[58]

Of course, many products badly needed in LMICs are also needed in HICs (categorised as Type I products by the CEWG). For example, treatments for HIV continue to be developed in part because people with HIV need new and better treatments and the health services of industrialised countries are able to pay for them. That medicines were available at high prices in HICs, and therefore unaffordable to the bulk of the populations of LMICs, led to the most sustained focus on access to medicines and actions, which addressed the intellectual property barriers that were keeping prices high. However, even for a condition with a lucrative market in the industrialised countries, the different epidemiology affected how it was researched and products that were ultimately produced. Paediatric treatments, which have no market in wealthy countries (due to successful interventions preventing mother-to-child transmission), have not been a priority for research.

There has been a very substantial market for pneumococcal vaccine in wealthy countries and through Gavi, so R&D costs incurred by companies are likely to have been paid for many times over. As will be discussed later, this did not mean that public money was not needed to get this product available in developing countries.

An additional concern regarding over-reliance on private sector investment is that it can be unpredictable and fluctuate from one year to another. The Treatment Action Group on Tuberculosis R&D Funding showed that private annual investment in drugs and vaccines drastically fell in 2012,[59] despite some promising drugs being at an advanced development stage.

Clearly, R&D by the private sector alone has not lead to sufficient spending on the products needed for LMICs. Therefore, the public and philanthropic sectors need to play a part to meet the public health needs and human rights of affected groups.

Ebola: an example of market failure

The recent Ebola outbreak had important consequences for the people living in affected areas, with nearly 28,400 cases and 11,300 deaths (as of 29 September 2015)[60]. Ebola is a disease for which a

vaccine or medicine could have been developed but, without additional financing and coordinated action by all sectors, was not.

When the recent outbreak started in 2013, the virus was already well known: Ebola had first been identified in 1976.[61] In 2005, a first vaccine had been reported to be effective after being tested on monkeys.[62,63] By 2009, no fewer than seven vaccines had shown encouraging results, but only one was tested in phase 1 trials and this was then abandoned.[64,65]

The reasons behind have less to do with scientific challenges than the absence of economic or political incentives. Dr Marie-Paul Kieny, WHO Assistant Director-General, recognised in August 2014:,"*…the fact that there is currently no registered drug for Ebola is a market failure. It's a market failure because this is typically a disease of poor people in poor countries where there is no market.*"[66]

Because of uncertainty about whether it would recur,, the nature of previous outbreaks which were not widespread, and because Ebola affected mainly poor populations who couldn't afford drugs,[67,68] the pharmaceutical industry had few incentives to invest in what represented a minor potential market.

While public institutions funded the first research stages, the lack of private investment to further develop drugs and run trials contributed to the absence of an effective vaccine when most needed. As Dr Daniel Bausch, Associate Professor at Tulane University, noted in 2014, "…*if you look at the interest of pharmaceutical companies, there is not huge enthusiasm to take an Ebola drug through phase one, two, and three of a trial and make an Ebola vaccine that maybe a few tens of thousands or hundreds of thousands of people will use.*"[69]

It was only the 2014 outbreak and the fear of its spread to high-income countries that forced the international community to accelerate the development of a vaccine. At the end of July 2015, the WHO announced that a first vaccine, rVSV-ZEBOV, had been proven effective after a Phase 3 trial in Guinea.[70] This trial was permitted by the unusual sponsorship of WHO. This vaccine could have been ready many years before: it had first been developed by the Public Health Agency of Canada in 2010.[71]

The 2015 GFinder annual report states that $165m was invested in Ebola in 2014, which can be understood as a response to the epidemic.[72] This made it the fifth most funded neglected condition after HIV, malaria, TB and diarrhoeal diseases. This does not constitute a rational system of drug development.[73]

Ebola serves to demonstrate the urgent need for new and alternative incentive models to address market failures in R&D. The rapid acceleration of development of a vaccine that should have and could have reached the market many years earlier –only in response to an outbreak that took the lives of more than 10,000 people – suggests that the R&D system is not functioning as it should and does not support the right of people to essential medicines that can save lives.

Public investment

As discussed above, private funding alone is insufficient and unlikely to address the R&D needs of vulnerable and marginalised groups. Therefore, public funding has an essential role to play, particularly for Type II and III diseases. Public funding can do a number of things including supporting the formation of knowledge through basic research and potentially fostering the development of health technologies through the later stages (as has often happened through the military). Public financing is likely to be more predictable than private sector funding, which, along with absolute investments, is needed to ensure adequate financing throughout the life of a products' development. While the risk appetite of the public sector is also limited, there are compelling public health and human rights reasons for increased public investment in situations where the private sector is inadequately addressing the needs of the vulnerable and marginalised.

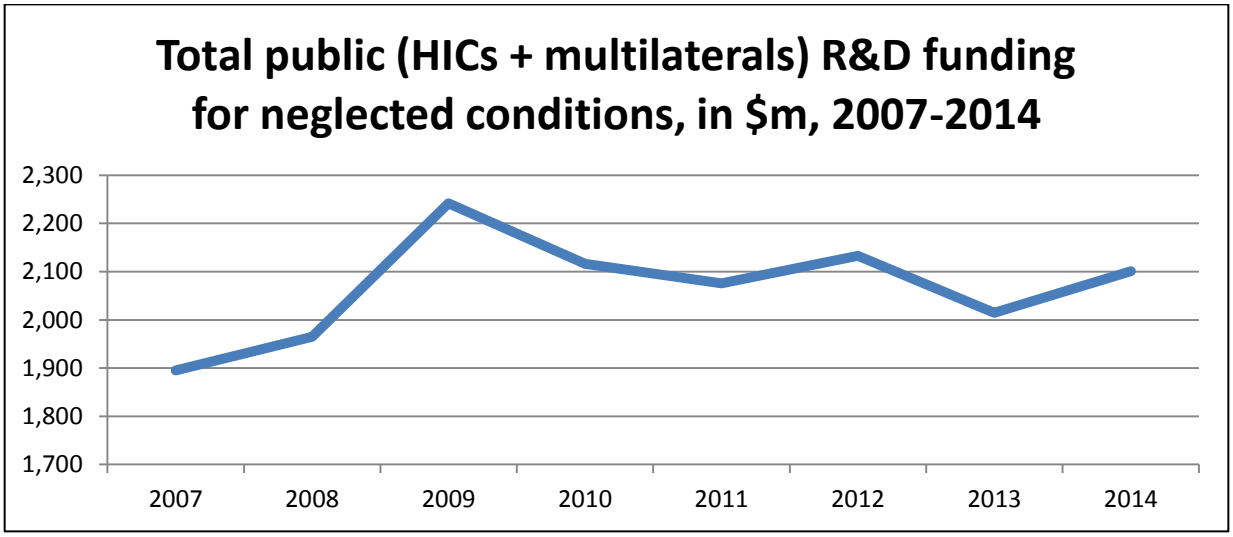
Governments are obligated by international human rights law to ensure that these rights are protected and fulfilled. Although international human rights law prescribes no specific system through which may be

accomplished, where the government has ceded its responsibility to the private sector and it is not meeting the needs of the vulnerable and marginalised groups in particular, governments are obligated to intervene.

Ensuring that rights are protected may entail, among other things, increased used of or modifications of existing laws and policies and creating new ones which facilitate meeting this obligation. For example, doing so may require governments to undertake modifications to IP law to ensure it does not present a barrier to access, mandatory use of TRIPs flexibilities and other such issues that address the implications of third party actions. Ensuring that rights are fulfilled will mean mobilising increased public support, financial or otherwise, and making changes in the overall policy environment, which meet the governments' obligation. For example, this may require governments to increase public spending on R&D for neglected conditions, committing to international support and cooperation for addressing neglected conditions, changes in regulatory regimes to lower development costs or the creation of new laws that give priority to human rights over existing IP where it may present an obstacle to R&D for neglected conditions.

Public funding currently constitutes the majority of all funding directed towards neglected conditions. In 2014, the public sector (both governments and multilaterals) provided two-thirds (64%) of all investments. The public sector provided significant funding for R&D into malaria and diarrhoeal diseases, respectively 50% and 51% of total funding. A significant amount of funding for bacterial pneumonia, however, which is the leading cause among children under-five worldwide, came from the pharmaceutical industry, with 65% of the global funding in 2014.

Figure 2: Total public expenditure on R&D funding for neglected conditions



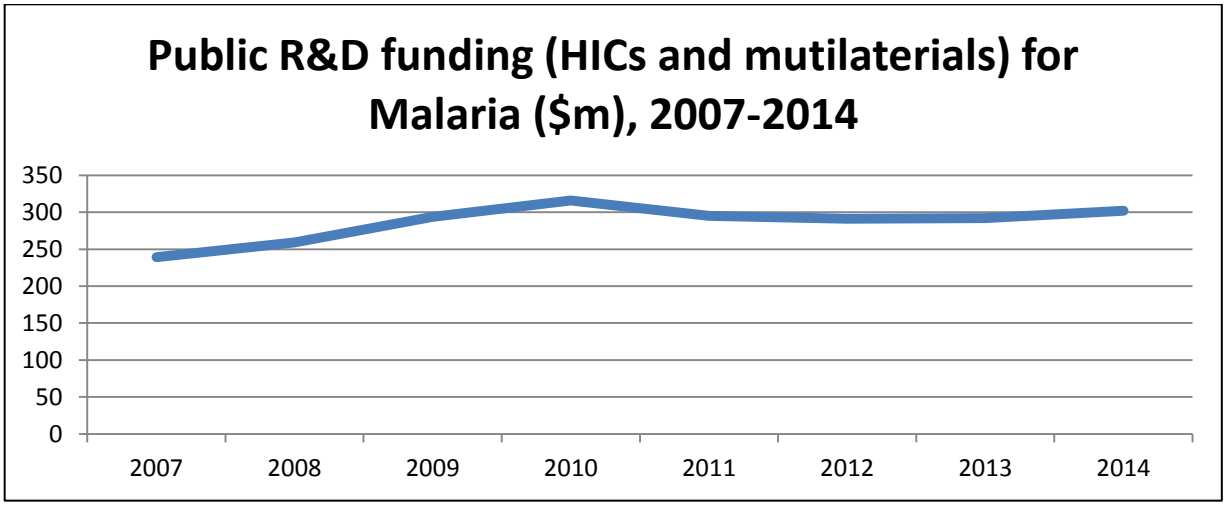
The bulk of public R&D funding is directed towards basic research. For example, from 2007 to 2014, nearly half (49%) of all public funding to malaria was allocated to basic research.[74] The US National Institute of Health is one of the biggest public funders of R&D. Between 2007 and 2012, it accounted for nearly two-thirds (61%) of global government funding to R&D.[75] There are many possible explanations for why most public funding is directed far upstream, but perhaps the most obvious is that in the early stages of research, potential commercial applications are unclear and the research is therefore unattractive to the private sector.

Funding for basic research is increasing but not across all conditions, in particular it is declining for those primarily affecting the poorest children. The total public basic research funding for diarrhoeal diseases decreased by 43% between 2009 and 2014.[76] This can only partly be associated with a drop in global public funding: between 2009 and 2014, public funding for basic research fell by 18% (from $755m in 2009 to $613m in 2014). This drop is in line with the recent fall in public R&D funding coming from high-income countries and multilaterals since 2009. Indeed public investment reduced by 6.3% between 2009 and 2014, from $2,242m to 2,101m. But it increased between 2013 and 2014 (from $2,015 to 2,101m); this was due to Ebola.

Public funding has also been directed towards downstream research and development through various innovative financing mechanisms, including product development partnerships (PDPs). PDPs, discussed in more detail later, are long-term collaborations between partners from academia, the public sector and pharmaceutical companies, aiming to develop new medicines.[77] PDPs have become increasingly popular uses of public funding for neglected condition research in recent years (in 2014, they received 16% of overall neglected condition R&D funding).[78]

However, although overall public investment in R&D for neglected conditions has remained stable over the past few years, figures show an important increase in upstream research while investments in product development have stagnated. Investments in basic research increased by 27.4% while those for product development decreased slight between 2007 and 2012.[79] Given that many promising products funded over the last 10-15 years, such as for malaria and TB, are currently reaching the development stage stagnation of funding in this area is concerning. As highlighted in a GFinder note, "Cutting funding for product development at a time when decades of effort is finally paying off is probably the most effective way of wiping out over a decade of public investment."[80] Simply shifting funding around between basic research and late-stage development while maintaining the same absolute amounts is, however, not the solution. Given that spending in this area is already extremely low compared to need, removing public funding from basic research presents the real danger of 'drying out' the development pipeline. If that happens, then there won't be any health technology development to undertake.

Figure 3: Total public expenditure on R&D funding for malaria

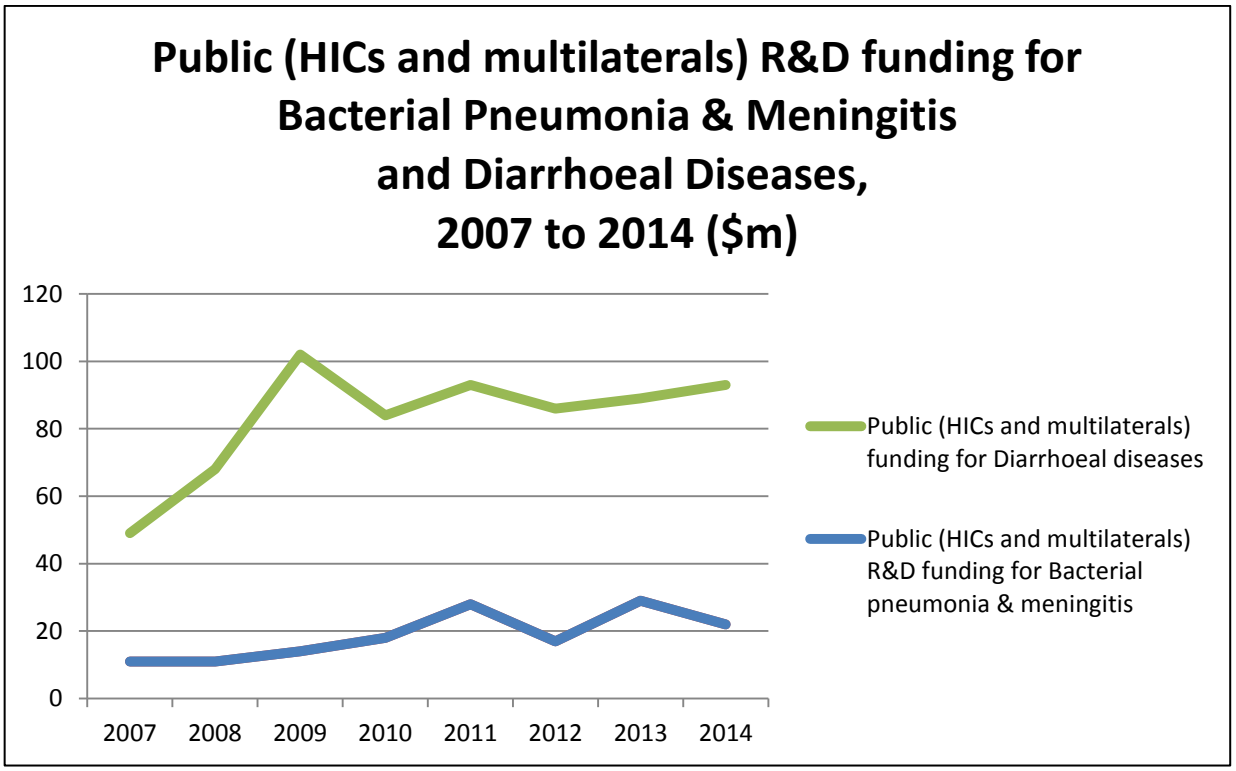


Reasons for these decreases in public expenditure on R&D have much to do with the general disengagement of governments in aid after the economic recession, including budgetary cuts and the reallocation of R&D investments in domestic areas. In particular, the disengagement of the US because of so-called 'sequestration-related funding cuts' (across-the-board spending reductions) from 2013 onward was an important milestone in the R&D public investment landscape.[81] All governments need to spend more in absolute amounts in order to meet need and human rights requirements in this area. Assessing spending relative to GDP, gives a more accurate reflection of ability to contribute to the global pool. If spending is viewed through this lens, some governments, such as Sweden, Denmark, Ireland and South Africa, move into the top 12 funders of R&D for neglected conditions, whereas others, such as Canada, Japan, the European Community and Brazil, all drop out of the top 12.[82]

There is tremendous need for more and continued public funding for R&D for neglected conditions. It is possible that, with a number of products ready for further development and clinical trials but not getting into development, that public money is overly skewed to the basic research stage. Creating basic knowledge can be efficient for diseases with a high occurrence and subsequent market in wealthy countries, because the development of pharmaceutical products will be ensured by the private sector. However investments in basic research alone do not guarantee the development of health technologies with the promise of little to no return – such as products for children in LMICs – through the later stages. In this context, investments in product development are absolutely essential. In these cases, it is especially

important to recognise the contribution of public funding to bringing a product to market. The use of public funding requires that the product that is ultimately brought to market is affordable. Governments' human rights obligations require that the use of public funds, whether through public or private drug development, should not allow access to these goods to be restricted for the people who need them whether due to intellectual property barriers or otherwise.

Figure 4: Total public expenditure on R&D funding for pneumonia and diarrhoeal diseases



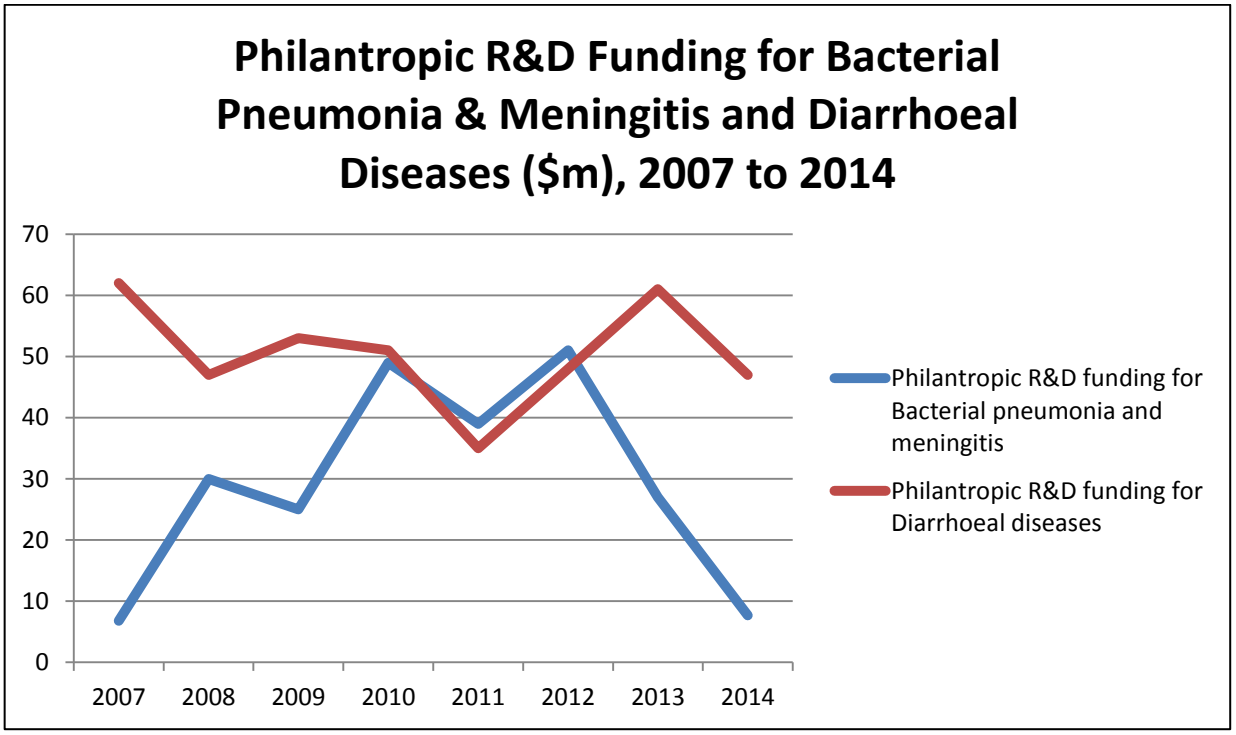
Philanthropic investment

In recent years, philanthropic support has been increasingly important for R&D into neglected conditions, reproductive health and other conditions that affect women and children in LMICs. In 2014, it constituted 20% ($688m) of total R&D for these conditions. Of this, the Bill and Melinda Gates Foundation made up 78% ($531m) and the Wellcome Trust 19% ($128m).[83] Furthermore, philanthropic investors constitute the major funders of PDPs, providing 59% ($308m) of PDP investments in 2014 (as a comparison, bilateral donors funded 35% of PDPs). They are an important source of funding and can provide *ad hoc* flexible support when needs are identified.

However philanthropic investments are also subject to annual fluctuations. Between 2012 and 2014, for example, funding on bacterial pneumonia R&D fell from $52m to $7.7m. In 2012, the philanthropic sector made up about half of all funding in this area, but by 2014, however, it made up only about 12% of all funding. In that time there was an overall absolute drop in funding for this area of about 40%.[84] This was essentially due to a drop in funding from the Bill & Melinda Gates Foundation for pneumococcal vaccine R&D after the product was starting to be widely used. What this means, however, is that reductions in funding from one philanthropic funder over this two-year period amounted to a very significant reduction in overall funding for bacterial pneumonia.

While philanthropic financing may be helpful as a supplementary source of funding, it cannot be relied upon to ensure that the appropriate health technologies are made for the necessary conditions. The fluctuations discussed above demonstrate the importance of stability of funding streams and accountability regarding financing commitments. This potential volatility is even more concerning considering that two funders make up 99% of all philanthropic funding.

Figure 5: Total philanthropic expenditure on R&D funding for bacterial pneumonia and meningitis and diarrhoeal diseases



Why the R&D system is not working for the most excluded children

As the figures above demonstrate, investment from all sources for R&D into health technologies that primarily affect the developing world is far too low, both compared to need and as a proportion of all R&D spending. There's some evidence that, even in industrialised markets, the current R&D system is not necessarily delivering the innovative products needed. Numerous publications have catalogued the decreasing number of patent filings for new chemical entities over the last few decades. For example, the number of new drug approvals by the Federal Drug Agency of the United States declined from an average of 33 new approvals a year between 1995-2001 to 19 between 2005-2011.[85] This is alongside the already-stated fact that no new products have been approved for neglected tropical diseases or maternal and neonatal conditions since 2012. This is while at the same time, the industry reports that it is spending increasing amounts on R&D, much of it due to the increasing expense of clinical trials.[86]

There are some indications that returns on existing incentive models may be diminishing. In the United States there have been numerous recent attempts to reform the intellectual property system.[87] The data presented earlier suggests that not only has the currently incentive model created a situation where R&D on certain conditions are underfunded; it has also ensured that much R&D is tailored towards intellectual property production and protection, resulting in largely non-innovative modifications to patented products rather than the development of new treatments.

In HICs, where populations are relatively wealthy (or there are functioning medicine reimbursement schemes through insurance or otherwise) and there is a greater degree of income equality, companies can charge more for their medicines because either the household or some other entity can generally afford higher prices. This ability to pay means both that people will be able to access medicines and, more importantly for the purposes of this paper, that R&D investment shifts to health technologies for conditions that affect these people.

LMICs are poorer, with greater income inequality and less reimbursement or public support for the purchase of medicines. In these markets, companies have been more focused on selling medicines to the

small percentage of people who are able to pay higher prices.[88] This was the model that was being followed with antiretrovirals for HIV until campaigns by human rights activists challenged this.

So for LMICs, the existing system has two interrelated and simultaneous consequences:

- New medicines and vaccines are often too expensive for most people, including the most excluded children, to afford. There has also been limited uptake of new medicines and vaccines in middle-income countries, where 75% of the world's poor now live.
- The medicines and vaccines that are needed to improve public health are not the ones that are researched and developed.

In order to ensure that R&D is driven by health priorities and access considerations and thereby is human rights compliant – especially for drugs needed by the poorest and most excluded people, who will never be able to afford high prices – new incentive models need to be used.

New models for new medicines: Addressing lack of public and private investment

Over the last decade, many new models of drug development have been established to try to spur R&D for Type II and III conditions. These mechanisms have, very broadly, attempted to generate and make use of public, private and philanthropic investment to fill funding gaps where there is an insufficient commercial incentive. The mechanisms can be grouped into three categories: push, pull and pooling mechanisms. Each of these, discussed below, is suited to different purposes, and aims to enable particular kinds of R&D or reduce specific barriers.

Alternative incentive mechanisms

Push mechanisms

Push funding is that which is provided to researchers and developers before the research takes place, so it 'pushes' researchers into investigating particular areas. It may take the form of grants to universities or government laboratories, for example, which build up a source of basic scientific knowledge that is easily accessible for further drug development. This often means giving money directly to these institutions or, in the case of PDPs, to companies or partnership entities which use it to support research. In some cases, push funding is stimulated through calls for research proposals for areas determined by the donor and funds are made available through a competitive process. Push mechanisms allow cost savings for the private sector which will hopefully be passed along to the consumer or redirected towards other necessary R&D and encourage investments in applied research.[89] Through coherent and need-based grant-making it can also influence priorities, as can be seen with PDPs.

Product development partnerships

PDPs have arisen in the last decade as non-profit entities that work with public and philanthropic funds, in partnership with private sector health technology corporations, academic institutions and others to design and implement programmes for specific health technologies.[90] As discussed, PDPs have proved to be a very popular method of creating alternative incentives for innovation, as demonstrated by the amount of public and philanthropic funding that is currently directed towards them. There are numerous efforts ongoing, including the Drugs for Neglected Diseases Initiative, the Global Alliance for TB Drug Development, and the Malaria Vaccine Initiative.

The design and scope of a PDP will determine whether it is successful and on what grounds. One model is the Meningitis Vaccine Project. This was established by WHO and PATH in 2001 in order to develop a vaccine to combat bacterial meningitis in certain parts of Africa where the illness was widespread.[91]

Although there were other vaccines on the market, these were too expensive for most countries in which they were needed and not epidemiologically appropriate for all regions. Numerous stakeholders were instrumental in the development of the vaccines: relevant technology was licensed from the US Food and Drug Administration and an Indian partner, the Serum Institute, developed the vaccine.[92] Unlike some other PDPs, the Meningitis Vaccine Project was deliberately limited in scope, focusing on a very specific product for a very specific part of the world. It engaged developers from LMICs with the clear intention of ensuring a lower-cost product that would be appropriate for resource-constrained environments.

PDPs may also have a role to play in reviving research in particular areas. For example, GSK had terminated work on its malaria vaccine, known as RTS,S, until the Malaria Vaccine Initiative began to share its costs for development.[93] This vaccine has now just been approved by the European Medical Authority and set for piloting through the WHO.

While PDPs have shown some success in spurring research into areas that would otherwise not have moved forward, questions remain over whether the innovations they have generated have been sufficiently accessible. Information on this is relatively sparse.[94] As with any situation where there is a significant amount of public funding, products developed by a PDP must consider, right from the start, how to reduce the financial barriers and ensure equitable coverage. Given that the whole rationale for developing a PDP is to address the problem of market failure, price and other access considerations are particularly important. Perhaps more importantly, PDPs provide piecemeal and *ad hoc* solutions to a problem that requires a more systematic one. Fragmentation of funding amongst innumerable PDPs to address every neglected condition is not a viable or cost-effective solution in the long term. While the current PDPs have made very valuable contributions, they do not address the structural problem because they are not designed to do so. Even prominent PDPs, such as the Drugs for Neglected Disease Initiative, have acknowledged the need to coordinate and address the problem in a systematic way.[95]

Grants and other mechanisms

Grants or other direct awards to universities or research institutions are often made available, primarily by governments, to conduct pre-clinical research. The large majority of basic biomedical research is funded through public grants to research institutions, such as those provided by the US's National Institute of Health.

Chlorhexidine sachets

In 2012, GSK and Save the Children entered into a five-year global partnership to help save the lives of a million children. A key component of this partnership is research and development of new medicines for children in LMICs. The first focus of this programme has been the development of a reformulation of chlorhexidine (CHX) to adapt it for use in resource-constrained environments.

CHX is on the WHO Model List of Essential Medicines and the compound was identified by the Commission on Life-Saving Commodities for Women and Children as one for which additional and adaptive R&D would be welcome. In 2013, WHO published a new recommendation for the use of 4% chlorhexidine (7.1% chlorhexidine digluconate) in all home births in countries with high neonatal mortality rates. There was, as far as possible, international consensus and recognition of the importance of CHX in reducing child mortality and the need for new products to address the gap.

Having identified the new formulation of this existing product as a necessary one, GSK solicited input from child and newborn health experts at Save the Children and more broadly to determine the kind of product that might best serve the populations that would use it. After consultation and other investigations, GSK decided to produce CHX in individual use sachets, differing from other formulations on the market which were available in dropper liquids or in aluminium tubes.

The company committed from the outset to invest a substantial amount of money into the development of this product with no expectation of return on investment. It also decided that the

R&D costs, some millions of pounds sterling, would not be factored into the final price of the medicine. They made a commitment both to sell the product at a not-for-profit price and to share the development and production information with other manufacturers to see if they can develop sustainable businesses.

This model suggests a particular role for such innovative partnerships, one which might prove a model for future R&D in situations where companies are willing to commit time and money without aiming for a profit. Pairing with civil society organisations and those with first-hand experience of working in resource-constrained environments and allowing them to contribute very early on to the development process can provide knowledge that is critical to making a product or reformulation successful. If more companies recognised the public health need and addressed their responsibility to help solve global health problems with their product development portfolios, and committed to ensuring maximum availability and access, many more missing medicines could be developed.

Of course, a company being willing to operate at a loss for a given product is neither predictable nor sustainable and is unlikely to happen on a large enough scale to generate a supply of new and adapted medicines for mothers and children. It may be better suited to generating new formulations which do not have to go through the full development and trialling process, which increase costs dramatically. While other companies should be encouraged to follow GSK's example, all partners need to help change the R&D structure to address the global gaps in R&D.

Pull mechanisms

Pull funding is essentially a financial reward provided to researchers and developers for meeting specific criteria detailed by the donor. Such mechanisms serve to draw the attention of investors and producers by creating a future market for a particular product that 'pulls' them into R&D. Ideally, pull funding will ensure that commercial reward for production of any particular product is contingent upon assurances of low prices and accessibility. Perhaps the best current example of a pull mechanism is Gavi, the vaccine alliance. Part of the purpose of Gavi is to pool resources from donor countries in order to generate increased demand for vaccines, as low-income governments could not otherwise afford to purchase these vaccines. This newly created market attracts producers who might not otherwise see a justification for investment. It also serves to drive down the price of vaccines by procuring in bulk and allowing companies security and lower costs through economies of scale.

Advanced market commitments

The Advanced Market Commitments (AMC) is a contractual pre-agreement to buy a product, a medicine or vaccine in this case, on predetermined criteria if it should become available. The objective of AMCs is to reduce the risk to manufacturers by demonstrating the level of financial return guaranteed for a particular product. The parties making the financial commitment are not bound to purchase anything beyond the agreed commodity, which means that if it is not developed, no payment is made. The most notable of AMCs has been the Gavi-initiated AMC for pneumococcal vaccine, which is discussed below.

AMC for pneumococcal vaccines

The pilot AMC for pneumococcal vaccine was a mechanism designed by a number of partners and coordinated by Gavi with the goal of both generating new products for pneumococcal diseases and bringing them to market in a sustainable manner.[96] In June 2009, the governments of Italy, the United Kingdom, Canada, the Russian Federation and Norway and the Bill & Melinda Gates Foundation launched the pilot AMC with a collective $1.5 billion commitment.[97]

According to early documents, the pneumococcal AMC was designed to:

- accelerate the development of vaccines that meet developing country needs.
- bring forward the availability of effective pneumococcal vaccines through scaling up of

production capacity to meet developing country demand.
- accelerate vaccine uptake through predictable vaccine pricing for countries and manufacturers.
- test the AMC concept for potential future applications.[98]

The results are generally accepted to have been mixed. New vaccines were produced by Pfizer and GSK, did come to market and were made available to Gavi countries for a price lower than that at which the vaccine would have otherwise been available. However, these products were actually very far into the development process and well on their way to market before the AMC and have found a lucrative market in high-income countries.[99] Ideally, an AMC would encourage development at an earlier stage to ensure the development of products that would not have come about without their support and designed specifically for use in LMICs. It should also encourage support to emerging manufacturers from the developing world, both because they likely have lower operating costs and to support R&D capacity in the developing world.

That being said, it is likely that the AMC was able to secure pneumococcal vaccine for a price lower than would have been available without Gavi or the AMC, thereby ensuring increased access to the vaccine. This, however, does not answer the challenge of whether an even lower price could have been obtained from manufacturers. Given that pneumococcal vaccine has been on the market for nearly five years and the manufacturers have made significant money outside the Gavi market, many civil society organisations have argued that there should be scope to lower the price further as many countries still cannot afford to bring pneumococcal vaccine into their national immunisation programmes. A further question is whether AMC funding recipients might now be able to replenish the AMC for future pull investments.

Prize funds

Prize funds have recently been promoted as an alternative to the intellectual property-based innovation regime by various advocates, particularly James Love of Knowledge Ecology International.[100] As discussed, the current incentive model is based on granting exclusive rights to intellectual property holders as a means through which they may recoup their investments and to reward them for discovery and production of a new product.

What prize funds allow, compared to the other funding mechanisms discussed, is the explicit decoupling of the costs of investment from the ultimate price of the goods. This has the added benefit of ensuring greater alignment of incentives with social benefit, in this case public health benefit, and with areas of need. Prize funds have yet to be implemented on a broad scale, but there has been some thought recently about making use of this model in the area of anti-microbials.[101] The US government has listed more than 600 different prize incentives through its Challenge.gov programme, which lists federal government prizes for innovations across a wide range of fields.[102]

Determining when to use push and pull mechanisms

The primary difference between push and pull funding is that risk is allocated to different parties at different rates depending on which method of funding is used. Push funding relies on funding streams largely generated by public donors upfront, without any assurance that there will be a positive return in terms bringing a product to market. As such, this method places the burden of risk on the donors. In the case of pull funding, risk sits primarily with the developers, who undertake R&D without assurance that they will be able to develop a product that meets the donor's requirements. Donors generally withhold money until certain conditions, such as the development of a usable product, are met.

Ultimately the choice of which mechanism to use will depend on where the research and development gaps lie and what kinds of incentives are necessary to start or accelerate R&D.

Pooling mechanisms

The purpose of pooling mechanisms is to allow producers and other interested parties who do not own the patents on certain compounds to make use of those compounds to generate new products, combinations or reformulations that are specifically suited to particular needs. Pools of this variety are important for a number of reasons but especially if the R&D deficit is in the area of new formulations or fixed dose combinations of medicines, both of which are particularly important for paediatric medicines.

There are a number of reasons why companies may choose this course of action. First, they may do so altruistically in order to improve access to medicines. Second, they can accrue reputational benefits by taking part in pooling and licensing schemes that improve or are seen to improve access. Third, pooling and licensing allows companies to generate profit from markets that they may not otherwise enter through royalties from licensees operating in those markets. As discussed earlier however, where there are difficulties in access or necessary new products are not being developed due to intellectual property barriers, companies have a human rights responsibility to license their products to remove these barriers.

Medicines Patent Pool

The Medicines Patent Pool (MPP) was started in response to the global HIV crisis and the tremendous treatment gap across the world.

It works by acquiring licenses for patented medicines from originator companies and providing them to generic manufacturers. This accomplishes two things. First it allows for generic production of licensed products at much lower costs than the medicine would otherwise be available for, generally for a limited geographic scope. Second, the licenses allow for combinations of therapies into fixed dose combinations – even if they belong to different originator companies – thereby overcoming patent barriers, further lowering costs and making treatment regimes much simpler, thereby increasing adherence. Treatment simplicity is a critical aspect of ensuring paediatric adherence to medicines that must be taken over a period of time.

So far the MPP has granted 12 licences with originator companies and is working with nearly 50 sub-licences.[103] While there remain questions about the scope of the licences granted, strides have been made in expanding the scope over time.

A relatively new venture between WHO, UNITAID, the MPP and the Drugs for Neglected Diseases Initiative, known as the Paediatric HIV Treatment Initiative, addresses the lack of paediatric formulations of HIV medicines.[104] Estimates indicate that nearly three million children eligible for ARVs are not currently receiving treatment; only about 20% of those that need ARVs are being treated.[105] Although there are many contributing causes, one factor is that very few ARVs are specifically formulated for children. The treatment gap is still much greater for children than for adults.[106] It is too soon to judge the impact of the Paediatric HIV Treatment Initiative.

While this collaboration is particular to paediatric HIV, something similar could conceivably work for therapeutic areas which lack child-specific formulations, such as TB and vaccines. Inventive solutions like these will be necessary to ensure the development of appropriate paediatric medicines, formulations and combinations. The MPP has recently announced that it will expand its mandate to include TB and Hepatitis C.[107] This is a welcome development which it is hoped will enable increased licensing of these medicines and the development of new, less expensive combination therapies.

WIPO Re:Search

WIPO Re:Search is an effort of the World Intellectual Property Organisation to create a forum in which its partners may pool patents relevant to under-served diseases. Its mandate is therefore broader than the MPP (which has expanded to include Hepatitis C and TB), which has both benefits in terms of scope of coverage and potential impact and drawbacks in terms of diffusion of resources.

No products have yet been developed through WIPO Re:Search. While the sharing of information and know-how is critical, the need for new medicines is urgent. There needs to be positive effects on financing or production in order for the venture to be a success. Civil society has also been critical of WIPO Re:Search primarily because of the limited scope of its licences, currently limited to 49 countries. Given that neglected conditions are endemic in 149 countries and that 75% of the world's poor now live in middle-income countries, it is hard to see how this limitation in scope is justified.

Open innovation models

The need for information sharing goes beyond just intellectual property sharing (though that is essential). It is critical that technical expertise, know-how and even platforms are shared to ensure the best kinds of research happen. Open innovations models, such as open laboratories, may fulfil such a purpose so long as they are designed with the right principles in mind and equal participation between all relevant stakeholders. It is critical that any products generated through this kind of arrangement have conditions covering access terms and are developed without any sort of proprietary right. An example of one such laboratory is GSK's Tres Cantos Open Lab which deals with research into tuberculosis, malaria and kinetoplastid infections.

Addressing shortfalls in public and private investment

In absolute terms, investment in R&D for the conditions discussed throughout this paper, whether public or private, is far below what is needed. It is critical that governments, the private sector and philanthropic organisations expand investment into R&D for Type II and Type III diseases but also for Type I diseases, such as non-communicable diseases which are an increasing burden for LMICs.

Most models for increasing the scope and effectiveness of R&D for these conditions depend on increasing public investment to make up for the lack of market incentives. In order for countries to meet their human rights obligations, they must commit both to increasing public funding for R&D in relevant areas and should ensure that all products developed from publicly-funded research have strong conditions to ensure access to health technologies.

Save the Children believes this may mean that countries agree to the CEWG's recommendation that there be a global framework convention on global health R&D housed at WHO,[108] which would both demonstrate commitment to R&D for diseases of LMICs and also provide sustainable sources of financing to back up this commitment. The CEWG has suggested a suite of potential tools to generate additional financing for R&D in Type II and III diseases, including financing through various direct and indirect taxes, different international commitments and increased and innovative forms of voluntary contributions from business and consumers and others.[109] In order to implement all of their various recommendations, including on financing for R&D, the CEWG suggested beginning negotiations towards a binding global convention, known as the Global Framework on Heath and Innovation.[110] To meet their human rights obligations, countries must also hold private sector partners to account, particularly with respect to affordability of medicines, and especially when they make use of research funded by the public sector, or public sector funding, to develop products.

As stated, the private sector has a human rights responsibility to demonstrate a greater commitment in this area. It can meet this responsibility in part, by investing significantly more money, participating in innovative models of R&D for medicines which are needed in LMICs, sharing patented compounds where necessary to further drug development for children, and ensuring that price is not a barrier to access. Voluntary action by the private sector may be a first step, but mechanisms could be introduced to ensure that increased tax on profits was earmarked towards R&D for Type II and III diseases, something Brazil proposed and which the CEWG found "particularly attractive", though it has yet to be explored further.[111]

While the philanthropic sector has taken up a fair share of financial responsibility, there remain issues and areas in which it could improve. Most importantly, it could ensure that its investments are made in a rational and coherent manner and that there is accountability and the participation of affected groups in their decision-making.

If designed in a human rights compliant manner, a coordinated global financing and coordination mechanism for health R&D would allow for a number of existing problems to be addressed. First, it would ensure an increased and more stable source of public funding to make up for the current absolute deficit in R&D funding for Type II and III diseases. Second, it would allow for greater and better coordination of such funding, potentially allowing funding to be driven more efficiently towards areas of public health need. However, it would only be effective in addressing the problem of access to health technologies if it also made use of the three key principles: delinkage, open innovation and licensing for access. [112]

This is simply to say, of course, that how additional funding is used will determine whether it is effective in meeting human rights obligations and achieving access. It is clear that in order to adequately address the problem of lack of development of health technologies for conditions affecting LMICs, and in particular children, it will be necessary to make use of all of the different mechanisms discussed above, potentially in tandem. In some sense the key will be complementarity. Most of the methods of funding discussed above fill certain sorts of gaps or address particular problems. It may be that all solutions are *sui generis*, but what is more likely is that different varieties of funding and pooling mechanisms will have to be combined in innovative ways to achieve results generating sustainable pipelines for new health technologies in different areas. As long as the three principles articulated by the CEWG are embedded in the design of various mechanisms, access will remain at the core of the R&D process.

Save the Children believes that at a minimum, a new R&D mechanism should be developed for the sustainable development of medicines and vaccines needed for the reproductive, maternal, newborn and child health continuum of care and for illnesses that affect significant numbers of children. It should be based on the principles of delinkage, open innovation and licensing for access. It should make use of alternative incentive models that delink R&D investments from the ultimate cost of the medicine, endeavour to allow for the sharing of information across the world, and enable pooling of patents where they exist for the production of new formulations and fixed dose combinations for paediatric use.

Delinkage and its benefits

As discussed earlier in the paper, the price of health technologies is largely based on the relationship between R&D investments and the eventual cost of the product. If one of the two main reasons health technology's prices are so high is because they are expensive to research and develop, then finding a way to disconnect the costs of investment from the prices charged is an obvious solution. It is also a solution that would meet the various human rights responsibilities of governments and the private sector by aligning health technology development better with the public health needs of the vulnerable and marginalised while at the same time reducing financial barriers to access to these technologies.

We can see the effects of a delinked model in the operation of generic companies. These companies do not engage in full drug development. They only do so to demonstrate that the medicine has the same biological effect as the original. Their costs are therefore substantially lower and they can sell their medicines at substantially lower prices. They also operate in a more competitive environment, where the lack of market exclusivity means they must compete on price (along with other factors such as quality).

Other arguments for moving towards delinked models, particularly for the kinds of diseases and populations that are discussed in this paper, include the potential to target R&D towards areas where there is public health need – so the right medicines get made – instead of being skewed by sales considerations.

MSF 3Ps Project

Over the last 50 years only two new medicines have been developed to treat tuberculosis.[113] Most existing TB medicines, while inexpensive, are very toxic and many people experience significant adverse effects. Second and third line treatments used against drug-resistant TB can often require two years of continuous daily treatment, are even more toxic than first line treatments, and many times

more expensive. Given that TB affects nearly 9 million people and kills almost 1.5 million a year, there is an urgent need to develop new medicines that are less toxic, work faster and better, and are affordable.

MSF has recently proposed a new model through which to develop new TB medicines and combinations of existing medicines, which it calls the 3Ps Project.[114] This aims to operate in a delinked way and takes into account both the development of new drugs and the production of combination therapies.[115]

The 3P Project addresses the lack of TB R&D by simultaneously making use of push, pull and pooling mechanisms (thus the 3 Ps). In short, the 3P Project will:

- offer prizes, through funds generated by donors, to encourage the development of early phase TB compounds.
- couple the granting of prizes with negotiating licenses for these new compounds, which will allow developers to immediately recoup and make de-linkage possible.
- pool the intellectual property through licences, which will allow other developers to make use of these compounds in novel ways and, critically, enable the development of combination regimens.
- use push funding mechanisms to encourage clinical trials on novel combination regimens as compared to individual ones.
- license the intellectual property amongst various producers to develop a competitive market for the final products.[116]

In this way, all of the specific barriers to the production of new and adapted TB medicines are taken into account and, it is to be hoped, addressed. At the moment, there is a huge gap in treatment for children with TB. Combination and adapted therapies would pave the way for a treatment revolution for populations for whom often effectively no treatments are available.

There are of course some risks with the 3P model, stemming primarily from the fact that, although the three component Ps have been well tested, their combination in this mechanism has not. There is a danger that the financial incentives are either too high or too low. The consequence of incentives being too high will mean wasting substantial amounts of resource. The danger of incentives being too low will be lack of participation or impact. Another risk is that funding may replace, rather than complement, existing donor commitments. [117]

While these are legitimate concerns, thoughtful design of the project should be able to overcome most of these issues. And ultimately the 3P model presents a comprehensive rethinking of how to encourage innovation in a therapeutic area where there is market failure but public health need is readily apparent, without market exclusivity being the way to reward innovators.

Conclusions and recommendations

There is clear evidence that the current R&D system is not developing the medicines and vaccines that the world needs, and the poorest people in the poorest countries are being neglected. We need to have a more rational, coherent system for R&D that better serves the human rights and health needs of vulnerable and marginalised people in the poorer countries and especially children. Piecemeal efforts can help but can only go so far towards ensuring health technologies continue to develop. International human rights and public health goals require that steps be taken to more systematically address deficits.

A mix of mechanisms is needed to generate new medicines and vaccines and these require much greater investment from both the public and private sectors. Governments' obligation to protect human rights require that where public and philanthropic funding is used to develop products, it is tied to ensuring that the products are always affordable to governments and free to the public. The private sector

simultaneously has a responsibility to ensure that it finds ways to support R&D for neglected diseases, conditions affecting maternal and child health, and other conditions where drugs are not available to the poor. And it should ensure that the prices it charges for such medicines and vaccines remain affordable to those who most need them.

Recommendations

We call on governments to:

- Commit to a binding global framework convention on global health R&D which is based on the CEWG's recommendations, ideally financed through mandatory public contributions, and which supports R&D for new health technologies based on the principles of delinkage, open innovation and licensing for access.
- Explore a pooled financing mechanism for R&D into health technologies needed for conditions related to the reproductive, maternal, newborn and child health continuum of care and paediatric formulations and fixed dose combinations of medicines, also based on the principles of delinkage, open innovation and licensing for access.
- Increase financing for R&D across the full spectrum of disease areas where there is public health need (Type II and III diseases and Type I affecting LMICs) and specifically for paediatric health technologies.
- Establish alternative incentive models, such as prize funds, to further encourage R&D in these areas.
- Establish or make use of existing laws and policies that create incentives for companies to participate in these mechanisms and, in particular, to create versions of health technologies suitable for children.
- Ensure that the development of any new health technology within existing development systems requires that companies commit to developing all necessary paediatric formulations and combinations where there is demonstrable need or where paediatric products are currently unavailable on the market.
- Ensure that where public and philanthropic funding is used to develop products it should be tied to making sure that the products are always affordable to governments and free to the public.
- Increase transparency and accountability for products made with public investments. Where public investments have contributed to private health technology development, these should be made publicly available. Public investments made into products that ultimately result in private development of health technologies must also have access conditions. This may take various forms, including conditions on government grants, on the grant of marketing approval, or at other points.

We call on the private sector to:

- Substantially increase investment into R&D for Type II and III conditions and those Type I conditions affecting LMICs.
- Focus on the development of paediatric formulations and fixed dose combinations of all health technologies.
- Participate in delinked models of health technology development for conditions where there is public health need.
- Create structures, such as open laboratories, that operate on the basis of open innovation and knowledge sharing.
- Participate in voluntary licensing mechanisms that allow for the production of new health technologies, formulations and combinations suitable for children.
- Establish an open library or pool of compounds which links up to new, innovative maternal and child health R&D mechanisms.

- Make use of models, like that for chlorhexidine, which involve information sharing, experiential learning and not-for-profit pricing, in order to develop paediatric medicines, formulations and combinations.

We call on international organisations to:

- Commit to the goal of a comprehensive global framework on global health R&D for Type II and III conditions and those Type I conditions that affect vulnerable and marginalised groups around the world.
- Work to better coordinate global health R&D based on the recommendations of the CEWG.
- Support the core principles of delinkage, open innovation and licensing for access in new health technology development models.
- Collect and make available information regarding resource flows for R&D in the areas of concern.

We call on private and institutional donors to:

- Demonstrate ongoing financial support for alternative financing and innovative R&D models for Type II and III diseases and Type I diseases that have a substantial impact on LMICs.
- Support efforts for a binding framework convention on global health R&D as recommended by the CEWG.

We call on civil society to:

- Monitor resource flows around R&D and hold governments, the private sector and donors accountable to commitments made and press them to make new commitments towards the development of health technologies for Type II and III conditions and those Type I conditions affecting LMICs.
- Participate in unique and innovative partnerships with government and the private sector to contribute on-the-ground knowledge to R&D efforts for neglected conditions.

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