Priority Medicines for Europe and the World
"A Public Health Approach to Innovation"

Update on 2004 Background Paper

Written by Els Torreele, Martine Usdin & Pierre Chirac

Background Paper 6.9
Neglected Tropical Diseases

By Jayasree K. Iyer, Emily R. Adams and Paul R. Klatser

Affiliations:
JKI: Foundation Top Institute Pharma, Leiden, The Netherlands;
ERA and PK: Royal Tropical Institute (KIT), KIT Biomedical Research, Amsterdam, The Netherlands

Table of Contents

Acknowledgements

The authors would like to thank the following for critical review of this manuscript: Richard Laing, Jutta Reinhard-Rupp, Peter Hortez, Julien Potet, Nines Lima, Eric Comte, Daniel O'Brien, Jeffrey Kipling, Mark Bradley and Audun Haga.

Executive Summary

Neglected tropical diseases cause immense suffering and death, mostly in the poorest regions of the world, resulting in a substantial socio-economic burden. A huge medical need exists for appropriate treatments, vaccines and diagnostics for such diseases. There is a significant lack of translation from early stage scientific research into real products for patients and impossible barriers for some products and technologies to become affordable for the poor people most affected by these diseases. Access to the solutions that exist is also limited. The Research and Development (R&D) pipeline has been more populated in the last few years, than ever before, although movement to real products and thereafter control, elimination, or eradication is limited. Two reasons account for this neglect: (a) market failure and (b) a failure of public policy to correct this perverse logic of "no money – no cure".

Redressing this imbalance requires public responsibility and commitment to the:

1. Development of a global needs-driven (as opposed to market-based) essential health R&D agenda for neglected tropical diseases, and;
2. Creation of appropriate mechanisms, incentives and monitors to allow the effective implementation of such an agenda towards sustainable, achievable solutions for these neglected tropical diseases.

Developing a needs-based R&D agenda for neglected diseases is an essential first step, but current practice in prioritising pharmaceutical research does not meet this goal. This paper explores various criteria to help identify and characterise neglect, which could guide priority setting in building an essential health R&D agenda for neglected tropical diseases. The first part of this paper addresses the needs of the agenda, the health tools available and what is currently being done in the area of neglected tropical disease R&D and programmatic interventions. A detailed and patient-focused needs analysis must be done for each disease, and matched to scientific, technological and programmatic opportunities, taking into account the specific circumstances of neglected poor patients.

The second section of this paper uses the examples of visceral leishmaniasis, Buruli ulcer and schistosomiasis with a needs-based approach to drafting an essential health research agenda. For each disease, we provide a concrete list of high-priority research projects to be initiated, with tangible results for patients. The examples also illustrate that much can already be achieved by supporting innovative and adaptive R&D to make better use of existing medicines (or compounds), diagnostics and technologies, even though radically new solutions remain critically needed if the situation is to improve in the longer term. In all cases, translational research to transform the results of basic research into useful applications is the key. We propose a "3T"approach to develop R&D projects, where a Therapeutic intervention (be it medicines, vaccines or diagnostics) is invented or adapted, there is appropriate Technology to make it useful and produce the intervention and that the intervention can be Transferred to the populations that need it, and complementary to existing programmatic interventions.

The third and final section of the paper suggests gaps that could make a difference to reducing the burden on the affected populations by accelerating the research and development of new solutions to these diseases. Opportunities to mobilise needs-driven

innovation for neglected diseases is also discussed. The EU, while supporting some excellent initiatives, can address the growing problem of neglected tropical diseases. By a careful and needs-based allocation of sustained funding, the EU can and must mobilise an appropriate response. There is a moral and ethical imperative to seriously address neglected diseases in developing countries. The EU-ACP (EU-African, Caribbean and Pacific Group of States) Joint Parliamentary Assembly resolution on poverty-related diseases and reproductive health in ACP states explicitly calls for European action for neglected diseases: *"[The Assembly] Calls on the European Commission to include the most neglected diseases, such as sleeping sickness, Chagas disease and leishmaniasis, among its priorities and to ensure that effective, appropriate, easy-to-use medicines are developed and placed on the market in the developing countries at an affordable price".*

A follow up UN Assembly resolution addresses this point and has led to some efforts in reallocating EU support towards neglected tropical disease R&D (through the EU Framework Program and government support for product development partnerships (PDPs)). Not all diseases or even needs are addressed by these supported grantees, and as such there needs to be more mechanisms. Pharmaceutical industry-driven agendas for the development of new therapeutics (such as the Innovative Medicines Initiative, IMI) have not yet addressed R&D efforts for these diseases. With this background paper, we hope that the support will be increased substantially and sustained (in the Horizon 2020 program and beyond), and R&D priorities will be based on societal and health values and not be solely market driven. The medical and public health needs and achievability of solutions to cater to these needs should drive priorities.

In addition to appropriate (sustainable) funding, governments must establish incentives and obligations to encourage neglected disease research and development in both the public and private sectors. Collaborative efforts are necessary, as the sharing of complementary resources and knowledge and the building of an integrated platform for neglected tropical disease R&D is necessary to keep costs low and impact high. Such a programme could include in-kind contributions from the (local and multinational) pharmaceutical industry, preferential funding of translational research projects (by public-private partnerships, public-driven R&D, integrated academic platforms and PDPs), risk mitigation from drivers of product development, reducing regulatory costs and developing of alternative, needs-based models for the setting of research priorities.

Organizations active in this area should be encouraged to pool their resources and work together to increase the opportunities for successful results. These include epidemiological tools and data (including drug resistance and monitoring), products developed, operational research outcomes and recommendations for implementation strategies.

Recommendations to help achieve this are:

- **Mobilise and sustain adequate funding** for neglected diseases. To ensure minimal impact, committed funding of **several hundreds of million euros** over a number of years must be freed to support the execution of a needs-based priority R&D agenda for neglected diseases;
- **Encourage translatable research** using the "3T" approach ("Therapeutics, Technology and Transfer") to transform the results of basic research into useful technologies for medical applications, adapted to the needs of neglected tropical disease patients and connected to existing programmes for neglected tropical diseases;

- **Establish adequate incentives for collaborative research**, **based on shared values** including appropriate training, funding, and specific career incentives based on a reassessment of the way merit is evaluated in public research;
- **Mobilise the pharmaceutical/diagnostics industry by a mix of incentives and obligations** to contribute to the development of needed medical interventions and commit to donate or provide sustained access to medical interventions, **based on shared value;**
- **Engage the innovators** from emerging economies, biotechnology, along with pharmaceutical/diagnostic companies, SMEs, PDPs and academic institutions through shared (societal and economic) values;
- **Monitor the performance** of PDPs, integrated academic platforms and pharmaceutical companies (including those in emerging economies) for public accountability for resources spent;
- **Expand the activities of PDPs and integrated academic platforms** to include product development for medicines, vaccines, diagnostics, drug resistance platforms and control strategies for these diseases along with strengthening health systems of affected countries. Support integrated academic platforms, where product development and operational research is directly done by academic innovators for neglected diseases;
- **Strongly encourage the expansion of the activities of the European and Developing Countries Clinical Trial Partnership (EDCTP)** to include several of the most neglected diseases as well as other phases of clinical development (phase I, phase IV), (and connect this to the efforts of the pharmaceutical industry-driven TransCelerate);
- **Create a centre for preclinical research** to bridge the continual gap of developing medicines and vaccines into clinical candidates for neglected diseases. This is a pool of resources available for preclinical research which should complement the activities of the EDCTP;
- Investigate the possibility for **centralized technology platforms for adaptive R&D** (adapting current and new medicines, vaccines and diagnostics to tropical countries, fixed dose combination, paediatric formulations, etc). This includes assessing medicines availability, stability, pricing dosing, using appropriate platforms and databases. (This should complement activities of existing organizations and should be a mandate for the recently established non-profit TransCelerate).

Introduction

Of 1 556 new drugs approved between 1975 and 2004, only 21 (1.3%) were specifically developed for tropical diseases and tuberculosis. [1] Of the 756 new drugs approved between 2000 and 2011, 29% (3.8%) were indicated for malaria, TB and neglected tropical diseases, of these there were no new chemical entities for neglected tropical diseases [2], even though these diseases account for 10.5% of the global disease burden. Such diseases predominantly affect poor patients in populations that do not represent a market of sufficient interest for the pharmaceutical industry. For this reason, no medicines, vaccines, or diagnostics are being developed to specifically address the health needs of these neglected populations, even if these needs are huge. Millions of people, mostly in the poorer regions of the world, are suffering and dying from neglected tropical diseases [3]. Over 200 million people are estimated to be at risk for visceral leishmaniasis, over 700 million at risk for schistosomiasis, and over 60 million people are at risk of developing sleeping sickness in Africa. [4] [5]

People at risk of contracting a neglected tropical disease mostly have a very limited access to health care, and the illness is often made worse by chronic malnutrition or co-morbidity, such as an accompanying HIV infection. These diseases have a profound negative impact on the economies of these countries and are responsible for enormous suffering. The most shocking aspect of this, however, is that with sufficient resources and coordination, a major part of this suffering could be eliminated. Building on the impressive advances in science and technology, simple but innovative solutions can be developed and delivered that will have a dramatic impact on the lives of many of these people

The diseases often referred to as "neglected" are diseases that are (a) common in defined areas; (b) fatal or disabling; and (c) for which no suitable treatments exist. They affect poor populations that are large but have little or no purchasing power.

New medicines are needed to replace the cumbersome or toxic existing treatments for sleeping sickness and leishmaniasis. No specific treatments exist for dengue fever or rabies. Simple diagnostics are unavailable for acute dengue, Buruli ulcer or yaws. Methods to monitor disease prevalence and accurate data to contain infectious epidemics are limited. Drug resistance also continuously threatens to reduce the existing arsenal of medicines. The few solutions that are safe and effective in treating neglected tropical diseases are often not well adapted to conditions in the developing world – for example medicines that requiring cold-chain storage or difficult administration, or that require costly production methods – or diagnostics that are inaccurate, difficult to use or taking too long to give a useful result. Substantial advances in molecular biology, pathophysiology and genetics have been made, including the recent genome sequencing of organisms causing leishmaniasis and Buruli ulcer. However, the rate at which these results are being processed into new products directed at the needs of patients is far from optimal.

Most medicines development (innovative and adaptive) is driven by the pharmaceutical industry, which sets the R&D agendas. For many other diseases this leads to new products, for neglected diseases this is lacking. Interestingly, in the last 10 years, there has been significant commitment from the pharmaceutical industry through their Corporate Social Responsibility (CSR) programs to improve access to medicines through R&D, philanthropy,

drug donation programs, patent pooling, pricing and participating in capacity strengthening through collaborative programs.[6] Dedicated centres for tropical disease R&D have been set up, and although largely catering to malaria, HIV/AIDS and tuberculosis (TB), these centres are aiming to be committed to the most neglected diseases.

Some 13 major pharmaceutical companies donate products at an estimated value of US$ 2 billion, which reach approx 800 million people each year.[7] More than 710 million preventive chemotherapy treatments were delivered in 2010, and the costs can be as little as US$ 0.4-0.5 per person per year. 4 Many of these neglected tropical diseases could have already been eliminated or eradicated with more global support. Public policies have largely contributed to this unethical discrepancy by focusing on the need for performance and competition in a knowledge-based market economy.[8]

In the last 15 years product development partnerships (PDPs) have been set up for some of the neglected tropical diseases, along with several integrated academic platforms (academia-driven R&D consortia sharing know-how and expertise for several neglected tropical diseases). PDPs develop medicines for sleeping sickness, Chagas, visceral leishmaniasis and vaccines for schistosomiasis and some soil transmitted helminths.[9, 10] PDPs also exist for technology applicable to several neglected diseases[11], or those that perform adaptive research to use innovative technologies that can be used for general global health.[12] Integrated academic platforms manage the control of diseases (like PCPs), and perform research on epidemiology and drug resistance, and product development for Buruli ulcer, schistosomiasis (among others.[13, 14, 15] Public-private partnerships also fill the R&D pipeline [16,17], although these efforts rely on sporadic, not sustained funding. Individual companies and organizations are also involved in product development, although this is more seen in diseases where there may be a paying market (like dengue and leishmaniasis).

While the global commitment exists to eliminate/reduce the neglect, a targeted international response to reduce the numbers affected is urgently needed. Europe, as a global leader, must respond to the crisis and provide a solid vision for the future of humanity, as acknowledged in the preamble to the European Constitution.[18] These are problems that seemingly may not directly impact EU citizens today, but globalisation, including global climate change, extensive international travel and population movement, and the changing political power equilibrium, may also globalise diseases that so far have remained in distant parts of the world.

A prerequisite for starting to address the research gap in neglected diseases is the need for an adequately funded, needs-driven and rational priority R&D agenda for these diseases towards achievable short and long-term goals. Appropriate mechanisms and incentives need to be established to allow the actual implementation of the priority-based essential R&D agenda. Encouraging commitments from both the private and public sectors were recently announced in the London Declaration for Neglected Disease[19], at which several organizations pledged their commitment to donate, perform essential neglected tropical disease R&D and fund projects.

The current commitment of the EU into developing a response to this global imbalance is better than when the first priority medicines report was published in 2004, but still limited. In recent years, with the financial crisis, the European investment and aid to global health seems to be decreasing. The total budget for research into neglected tropical diseases is

limited to around twenty million euros at most, woefully inadequate to address any aspect of the problem. Since the last Priority Medicines Report in 2004, the European Commission contributed 22% of government investments and 15% of total global investments. 76% of which went to malaria, HIV/AIDS and TB, with most of the money going towards PDPs and EDCTP (leaving several academic and SME innovators with minimal benefit). While this has led to 43 new diagnostics, vaccines and medicines registered to tackle neglected diseases and poverty related disease (including malaria, HIV/AIDS and TB) [20], there could have been more progress and products if investments and incentives were substantially higher. The Innovative Medicines Initiative (IMI) which supports precompetitive collaborations, is driven directly by research priorities of major pharmaceutical companies. The majority of the programme supports diseases relevant to European public health, and out of 30 projects, only two projects, accounting for 7.5% of the total IMI budget have poverty-related relevance, and not at all in neglected tropical diseases. Neglected tropical diseases deserve the attention of mechanisms like IMI. R&D in neglected tropical diseases could benefit the pharmaceutical industry (and other stakeholders) through shared values. Reputational benefits, opportunities for skilled personnel and knowledge sharing of emerging diseases and markets, access to data relevant to developed-country diseases are only some obvious benefits.

With the upcoming Horizon 2020 funding scheme, one hopes that there will be more commitment for innovative and adaptive R&D priorities for neglected tropical diseases, perhaps using the Framework Program for translatable research (including epidemilogy/resistance research), IMI for product development (through PDPs, SMEs, integrated academic platforms, public-private partnerships and EDCTP), and a new mechanism for operational research and capacity strengthening, with adequate monitoring and milestone reporting.

1. Characterising a Disease as Neglected

The ideas developed in this section come from a thorough analysis of priority-setting in the context of neglected diseases.

1.1 The neglected tropical diseases

The neglected tropical diseases are 17 diseases (19 if soil transmitted helminths are considered as three separate diseases) affecting global communities.[21] One hundred and fourty-nine countries are endemic for these diseases, and billions of people are at risk of contracting these diseases. They cause a huge health and socio-economic burden in the world, mostly in developing countries. Please refer to Appendix 1 for the list and analyses on the burden of these diseases.

The definition of neglect is due to economic reasons. Neglected tropical diseases affect a large number of people who are unable to pay for access to health care (even if it is less than a US dollar) and thus represent an uninteresting market for the development of new medicines. Medicines that are effective and available for some of these diseases are being donated by several pharmaceutical companies (see below) towards preventive

chemotherapy programs, but the amounts of medicines available and the capacity of programs to deliver these medicines is limited and has failed to eliminate or eradicate these diseases up to now. More resources is needed (including financial ones) to put these medicines to better use, along with resources to develop new medicines, diagnostics and vaccines for the rest of the diseases that are not currently treatable.

Relevant criteria to describe neglect deal with the magnitude or severity of the disease and the quantity and quality of resources (available and foreseen) to prevent, diagnose and treat these diseases in a sustainable manner.

1.2 The global health, societal and socioeconomic burden of neglected tropical diseases

Existing statistics on the size and nature of the burden of neglected diseases show that the magnitude and severity is large for these diseases, but they are sometimes misleading due to the unavailability of accurate and reliable data. Please refer to Appendix 1 for the burden of the neglected tropical diseases.

There are many aspects of neglect. These include the political, socio-economic and historical conditions in the different regions, leading to the existence of large neglected populations, and the specifics of the biology of the neglected disease itself. Other factors, such as malnutrition, lack of access to healthcare, sanitation and poorly developed infrastructure all contribute to the problem. However, the fundamental need that we address here is the lack of effective, safe, affordable and easy-to-use medicines to treat these terrible, often life-threatening diseases.

While the role that pharmaceutical companies play in developing and implementing new solutions to neglected tropical diseases has been disappointing, there have been pledges to increase that commitment in recent years through donations and R&D activities.[6,19] R&D in these diseases are mostly done by public institutions and partnerships. Since 1996, a few product development partnerships (PDPs) have arisen to integrate resources and mobilize them towards the neglected tropical diseases. All the efforts which employ a strong shared value attitude to collaboration have led to many successful breakthroughs, even if they subsist on non-sustainable funding. Several new products, tools and knowledge of the disease are all useful end-points for many of these efforts. There are still few integrated platforms to accurately assess where to place resources so as to use existing knowledge and to advance in the most efficient ways possible. One important aspect in doing so is to consult directly with the people involved (patients, health workers, clinical researchers) to target health research using a needs-based strategy.

1.3 The health tools available for managing these diseases and the persistence of the problem

A concerted effort must be made towards management, elimination and then eradication of these diseases. While many control strategies exist, there is a dire need for better, more affordable care for patients affected by these diseases.

1.3.1 Control strategies

Resolutions of the World Health Assembly lead the way as to how global intervention programmes can affect elimination and eradication of these diseases.[3] Efforts of the neglected tropical disease community when focused on realistic achievable milestones can lead to elimination of some of these diseases in many countries. The enhanced commitment of various members to eradicate guinea-worm was noted in a resolution passed in 2011. Guinea-worm eradication was a campaign started in the early 1980s. We have seen a 99% decline in annual incidence from almost 900 000 cases in 1989 to about 1000 cases in 2011.[3] A resolution related to yaws passed in 1978 saw 460 000 cases worldwide in 1999. It was due to effective campaigning and case management using treatment available that yaws was eliminated from India in 2006. Furthermore, the South-East Asia region in 2011 pledged the elimination of yaws in the last two countries in the region.[3]

There are essentially two main approaches taken in the last decade, both steered by the World Health Organization (WHO). The first approach is preventative chemotherapy (which began shortly after 2003) targeting the helminthiases (namely lymphatic filariasis, oncocercosis, schistosomiasis and soil-transmitted helminths) and trachoma. These rely on large donation programmes from various large pharmaceutical companies, with an annual value of US$ 2 billion and delivery costs of US$ 0.4-0.5 per person per year[4], and support from large donors to mobilize these medicines. The 2012 London Declaration saw more than US$ 785 million pledged to accelerate R&D for neglected diseases and expand drug distribution.[19] One would expect that a generic market could circumvent the main supply and procurement challenges and lower incidence; however this has not been the case, as in the example of praziquantel and ivermectin. Mass drug administration interventions now reach some 800 million people each year.[4]

The second approach was the start of intensified case management; this is done for 10 other neglected tropical diseases, and where caring for those affected and at risk, with existing tools and medicines, was prioritized.

The WHO estimates that these two approaches remain usable. For preventive chemotherapy, increased access to effective medicines, sustained donations, a continuous committed stream of funding, effective management and monitoring of control programs at country level and limiting the transmission is greatly needed.[3] For proper case management, early diagnosis and access to appropriate treatment to lower infection rates, disease severity and morbidity and the management of complications is needed. There is a wealth of opportunities for pharmaceutical interventions and new R&D programs for this approach.

Simple diagnostics that are less invasive and have a high diagnostic accuracy must be developed to ensure no delay in treatment initiation. Improved appropriate medicines that are safe and have short regimens are also needed for these interventions to be completely effective.

Vector control while underemphasized, is a key factor toward elimination of many of these diseases. Of significance is that 68 vector-borne disease endemic countries have established national policies for integrated vector management (IVM).[3] The need for better infrastucture, including better healthcare, education and access to sanitary conditions are some of the main problems facing control strategies.

1.3.2 New treatments

The treatment of the neglected diseases relies on relatively old medicines, some more than 50 years old. The number of NCE's marketed in the last 25 years can reflect the interest of the pharmaceutical industry in a specific disease or therapeutic area, and certainly reflects their investment in R&D. The assessment of NCE's reveals the staggering discrepancy between the allocation of resources for diseases affecting mainly high or low income countries. 1,556 new drugs approved between 1975 and 2004, only 21 (1.3%) were specifically developed for tropical diseases and tuberculosis [1], and of the 756 new drugs approved between 2000 and 2011, 29% (3.8%) were indicated for malaria, TB and neglected tropical diseases, of these there were no new chemical entities for neglected tropical diseases[2], even though these diseases account for 10.5% of the global disease burden. 1.4% of almost 150,000 registered clinical trials were for products for neglected tropical diseases, with only a few new chemical entities among them, thus showing that there needs to be more effort in designing new medicines.

With the efforts of product development partnerships, such as the Drugs for Neglected Diseases initiative (DNDi), some substantial steps have been taken towards combination treatments for these diseases. Notably, in 2009, DNDi (with partners) launched the first new therapy in 25 years, a Nifurtimox-Eflornithine Co-administration (NECT) for stage 2 Human African Trypanosomiasis (HAT). They have also launched co-administration of pentavalent antimonials and paromomycin for Visceral Leishmaniasis (Africa), a single-dose liposomal amphotericin B (AmBisome®) and new combination therapies (Asia) and (pediatric) benznidazole for Chagas disease (approved in Brazil 2011), though the availability of some of these medicines is uncertain.[22,23]

Safety and toxicity of available treatments

For some neglected diseases, such as visceral leishmaniasis and HAT, only a few treatments existed before 2009 (most dating from the colonial era) and these have many side effects. For example, melarsoprol, used since the 1940s to treat human African trypanosomiasis, causes a life-threatening encephalopathy in 5-10 % of cases with 50% mortality, for reasons that remain unknown. Other toxic medicines in widespread use are the antimonials used to treat leishmaniasis, medicines that would not pass regulatory approval for use in humans, were they to be developed now. While these medicines have saved many lives relative to having no treatment at all, considering the general progress in medicine, it is unacceptable that the same toxic medicines still remain the mainstay of treatment for these diseases today.

The effectiveness of available treatments

Many of the medicines in widespread use have limited efficacy data. For example, despite widespread use, there have been limited standardised assessments of the efficacy of benznidazole and nifurtimox in treating chronic Chagas disease. Some other medicines have limited efficacy, notably because of growing resistance. Chloroquine, which was developed in the 1940s, was still used until recently as a first-line treatment for malaria in many places, despite widespread resistance, and several of the other more recent antimalarials are being lost due to resistance as well.[24] Resistance levels of over 60% against antimonials have been documented in Indian visceral leishmaniasis, making this first line drug useless in the area with the highest incidence of this fatal disease.[25]

The affordability of available treatments

Many medicines are not affordable, purely because the affected people are too poor to pay for healthcare. As an example, the current most effective treatment for visceral leishmaniasis is AmBisome®, a lipid-encapsulated form of the antifungal agent amphotericin B. The product is expensive even at the preferential price offered by its producer (US$ 18 per vial, hence between US$ 126 and US$ 378 for an average 35 kg patient, depending on the necessary dosage) and it is seldom used to treat kala azar patients, and certainly not as a first line treatment.[25]

The appropriateness of available treatments

The medicines have to be appropriate for use in tropical countries and for specific situations of the patient. For example, many medicines need to be stored cold, or require reconstitution in clean water. Adapted dosage forms may not always exist (for example, oral rather than parenteral, short treatments rather than extended periods)? Some medicines are seen to be effective, but exist only in dosage forms that are highly impractical in the conditions encountered. Eflornithine, often termed a "miracle drug" because of its rapid action on even moribund sleeping sickness patients, needs to be administered as four daily infusions over 14 days, severely limiting its use in endemic areas such as rural South Sudan, Angola or the Democratic Republic of Congo.

1.3.3 Availability of appropriate diagnostic tests

A first step towards effectively treating patients (right drug, rational use, protect against resistance, etc.) is to make the right diagnosis and tests-for-cure. A huge gap has been identified in many neglected tropical diseases, including sleeping sickness, kala azar, Buruli ulcer and Chagas disease, for which no tests exist that are cheap, simple to use in the field, and of sufficient sensitivity and specificity. While technologies exist to detect these diseases, many of them are not suitable for "closed system" diagnostics (meaning requiring no complex sample handling steps. Simple lateral flow systems, dipsticks, and recently the LAMP technology appear to be the most suitable for field use.[11] This is due to their simple steps, single temperature requirements and easy readouts. Diagnostics for acute viral neglected tropical diseases such as dengue could dramatically improve care for severe disease and is lacking.

1.3.4 Vaccines against the neglected tropical diseases

With the continued success of mass drug administration programs, there could be indeed elimination of several of the neglected tropical diseases. To reduce the burden of high prevalence diseases (such as schistosomiasis, Chagas disease and leishmaniasis, apart form new drugs, vaccines are urgently needed. These diseases exhibit extensive geographical overlap [26,27], and there is widespread polyparasitic infections commonly in these developing countries. [28] It is thus important to integrate drugs with vaccines or vaccine-linked chemotherapy for global eradication.[29,30] At present there are no available vaccines for any of the neglected tropical diseases, although several are in early stages of development. With more appropriate resource allocation towards elimination tools, we could see some vaccines and packages of vaccines and drugs to be available within the next decade or so.

1.3.5 Areas of "hidden neglect" in a disease

For certain diseases that receive a lot of attention in general, it may still be that specific aspects remain neglected. For example, paediatric formulations are needed in HIV/AIDS treatment, especially in Africa, as are fixed dose combinations of the most frequently used antiretroviral medicines to simplify treatment and increase compliance.[31] Another example is that while praziquantel is available (even in the generic market) for schistosomiasis, elimination is still far from being achieved, and a paediatric formulation for children, especially pre-school level children is not available. Schistosomiasis is a disease that affects adults and also children. Such hidden aspects of neglect are too often not appreciated. Some patients being treated for Chagas disease are children, but no adapted dosage forms existed until recently. Health care workers had to cut up adult tablets to obtain a roughly correct dose.[32]

1.4 Efforts currently being made to address neglected tropical diseases and expectations in the future.

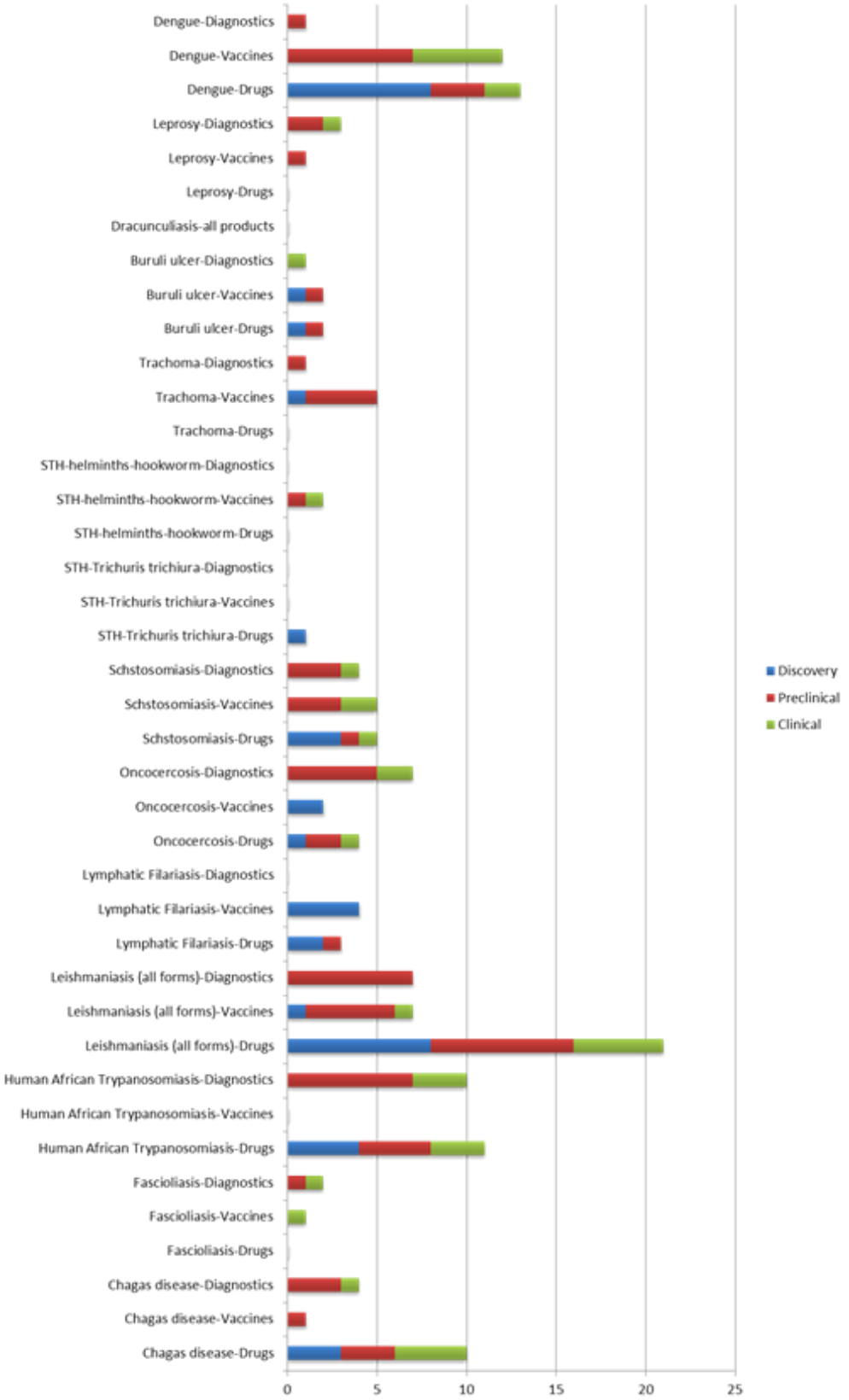
1.4.1 Medicines and diagnostics under development

In the past decade there has been a substantial commitment for development of new medicines and diagnostics for neglected diseases. While efforts in operational research are difficult to monitor, product development information is available through a recent source. A remarkable undertaking has been performed recently by the Bio Ventures for Global Health .[33] This organization tracks and analyzes progress in global health R&D, provides an evidence base to support decision making, policy change and performance and using the innovative WIPO Re: Search platform, brings innovators together to collaborate to address unmet medical needs in global health. Their analysis shows that the PDP model for neglected tropical diseases supports 40% of the overall neglected tropical disease pipeline. Academic participation is mixed in several stages of product development. More than 65% of pharmaceutical companies and less than 3% of biotechnology companies worldwide participate in neglected tropical disease product development. Only a third of the products in development are performed by a single organization alone, showing that for neglected tropical diseases, collaboration and a partnership case can be made for product development.[34]

The full involvement of innovators in the biotechnology sector and more depth of participation of pharmaceutical companies would be highly beneficial. Translational research initiatives targeting public and academic institutions should emphasize product and solution innovation, with increased engagement of emerging market innovators.

An analysis of the products in the pipeline shows a great promise for serious improvements (Figure 6.9.1 and Appendix 6.9.2). For some diseases such as trachoma and leprosy there are excellent medicines available when used correctly, with appropriate diagnostics. For guinea-worm, eradication campaigns to remove worms from people are proving to be very successful.[35] There is a dire need for appropriate diagnostics to match available medicines and initiate early treatment. For diseases such as Chagas disease, sleeping sickness, dengue and leishmaniasis there are still significant efforts being made to develop medicines to suit the global variations in patient needs. In areas where there are no PDPs, such as dengue, a lot

Fig 6.9.1: The neglected tropical disease product development pipeline



Source: (Adapted from www.BVGH.org Accessed August 2012).

The figure shows the number of active R&D projects for product development in each of these diseases. Similar figures for basic research (including epidemiology and resistance) and operational research is not available.

of knowledge is spread over many organizations, including private ones (as there is a dual market) while for Buruli ulcer, this comes together in more partnership-based product development.

The pipeline is more populated than ever before, due to the commitment of various stakeholders. Only 10 diseases have products being developed in clinical phases (albeit mostly in early clinical phases). Nevertheless, since their inception, 19 products have been developed by PDPs for poverty associated diseases[36], out of which only five are for the neglected tropical diseases. The rest are products for Malaria, HIV/AIDS and TB. It is important to note that with the engagement of appropriate technologies from innovators (for example in diagnostic platforms, enabling technologies and the like) one technology could lead to several new neglected tropical disease products that can be used in developing countries. What is missing is an analysis of the R&D activities and expected milestones for each of these projects, and any information on the landscape of all basic research activities (including mapping, epidemiology and drug resistance studies). Also missing is a landscape of efforts in operational research. Since there is a strong will to develop integrated neglected tropical disease programs in affected endemic countries, it is vital to monitor such activities and so that one can link R&D efforts with programmatic interventions (preventative chemotherapy or intensified case management), and plan for the future implementation of any developed products and solutions.

1.4.2 Number of scientific publications

Instead of screening publication databases such as PubMed, a thorough analysis was recently performed that showed some interesting trends.[4] This may provide a measure of the general scientific interest for a certain disease, and the current status of knowledge. However, published scientific papers reflect research at all stages, and tends to concentrate efforts in fundamental research, which does not give an idea as to whether the scientific knowledge may lead to any drug development, nor how far along the pipeline medicines are from use in actual therapy. It does illustrate the discrepancy between numbers of people affected and numbers of scientific publications (and thus amount of scientific activity).[37] Many of the conditions or diseases of global importance were underrepresented in clinical trials published in leading clinical journals.[38]

For the period from 1992 to 2011, there were 73 212 papers that were about at least one of the Neglected Tropical Diseases.[4] In the past 10 years most publications have been about dengue followed by soil-transmitted helminths, leishmaniasis and Chagas disease. The most notable increase in the last 10 years has been in the number of papers about Buruli ulcer, indicating more interest and thus activity in the development of solutions for this disease. Particularly since 2005, there has been more use for the term "Neglected Tropical Diseases", which represents the widespread use of the brand name rather than increased activity. The countries that publish these papers are also widespread.[4] What is interesting to note is the shift in geography of research, with Brazil and India leading the R&D publication output in regions affected by these diseases. The EU and North America globally are the top producers of publications about neglected tropical diseases.

1.4.3 The future trends of R&D efforts

There is fortune to be had, with estimates looking forward from the current pipeline showing an average of 4.7 new products each year (excluding vaccines) through 2018.[2] If this is realized, it is a striking improvement to the situation from previous decades. There are many valuable lessons that can be learnt from the past efforts and current pipeline of projects. For product development, to accelerate R&D efforts, it is useful to have integrated systems for comparing data of parallel efforts, preclinical and clinical data. The role of PDPs in integrating data and resources to single platforms (for those diseases where there is a PDP) and the role of EDCTP in expanding to integrated clinical trial centers beyond malaria, HIV/AIDS and TB to the neglected tropical diseases [39] will greatly enhance product development. The role of public institutes and alliances between public-public and public-private centers should remain important and supported for development of better tools useful in epidemiological assessment (including drug resistance mapping), product development and operational research. Section 3 of this paper outlines the gaps and opportunities for R&D efforts for pharmaceutical interventions and what should be mobilized by these players and the community in detail.

1.5 Conclusion: The priorities and opportunities must be identified in each unique situation

Using criteria of disease severity and prevalence alone, HIV, TB and malaria, as well as measles and hepatitis B repeatedly appear. However, including other more qualitative criteria to **characterise the extent of neglect** and need of actual control strategies and better interventions produces a different list. Opportunities lie in the creation of better medicines, vaccines and diagnostics and operational tools. A further complexity is added by the fact that different **aspects of a disease and treatment may be neglected** for these neglected tropical diseases, while others are not (for example, the lack of paediatric formulations for schistosomiasis or Chagas), and that even when a treatment is available, it may not be adapted (for example, while eflornithine is highly effective for sleeping sickness, a more adapted dosage form, such as an oral formulation, would be better).

Once the importance of commitment and performance in research into neglected diseases is acknowledged, we must then move towards deciding where to **allocate available resources** (money, time, research funding, advocacy, etc.). Should we use disease burden, disability-adjusted life years, geographical distribution, absence of research or interest, or combinations of these criteria? R&D agendas may focus on the global burden not diseases that are focal. There is no simple formula that can be applied. Rather, what is needed is a case by case assessment of the specific needs (of diseases, populations affected and concerted management of prevention, diagnosis and treatment), the constant evaluation of scientific and technical R&D opportunities linked to existing programs and the achievable solutions to the problems identified.

An important factor in the context of setting research priorities is the **expected impact** that providing a treatment, diagnostic test or vaccine might have. This is a crucial criterion that is less easily quantified but is often very obvious if the problem is approached appropriately (promising compounds, underexplored ideas, technical opportunities in formulations, finalising a clinical dossier for registration, etc.).

We live in an era of enormous advances in science and technology. An unprecedented knowledge base is available; billions are spent each year to fund public and private biomedical research. What is missing is a **coherent and needs-based strategy** to identify areas for intervention and to invest time, money and energy in an efficient and effective way. This requires an ongoing needs assessment complemented by an analysis of the "opportunities"- i.e. areas where R&D can provide solutions to these established needs. Also necessary is the ongoing **engagement of innovators and stakeholders** through creating **shared value** towards **collaborative projects and achievable solutions**. However, there is no simple equation, and each situation must be analysed separately and in consultation with a broad range of people who are deeply involved in the problem and the most likely solutions.

Thus:

1. **Priority-setting must be based on a needs analysis for each situation**
2. **The identified needs and an assessment of impact attainable through addressing the needs through achievable solutions must be used to guide the allocation of resources to maximise impact.**

In the following section, we will discuss some examples of how to identify specific areas for research and development, and what can be achieved by such a method to develop appropriate solutions by the allocation of resources to create impact. The examples shown here are for visceral leishmaniasis, Buruli ulcer and schistosomiasis. As an update from the 2004 background chapter, human African trypanosomiasis will be briefly mentioned.

2. Needs-Based Assessment to Guide Priority-Setting – Case studies

We outline priority research agendas for three of the 17 diseases, using a needs-based assessment. The examples were chosen to reflect the diversity in the needs of the 17 diseases. Visceral leishmaniasis (VL) was chosen as it has a wide distribution of endemic countries, and affects both patients who can and cannot pay for healthcare. There are medicines available for VL, with severe side effects. R&D for this disease is mainly driven by a PDP, DNDi, although there are several partnerships (including several consortia, and integrated academic platforms and one single innovator company) that are developing products.[33] Buruli ulcer, considered one of the most neglected of the neglected tropical diseases, was chosen as there has been historically little interest in this disease of the poor (Daiichi Sankyo is working in a Buruli ulcer drug discovery program in a partnership, and in vaccine development, there is one of the largest integrated academic platforms for Buruli vaccine development[33]). Schistosomiasis, was chosen as it is one of the most prevalent of the neglected tropical diseases, and while control strategies rely on an medicines donation program, and water and sanitation projects, there are many areas of "hidden neglect" for this disease. R&D involves various partnerships, and is led by all types of innovators (a PDP-the Sabin Vaccine Institute, academic institutions, an integrated academic platform (SCI), pharmaceutical companies (Dafra, Merck Astellas), biotechnology companies (several), and innovators in endemic areas (Brazil)).[33] An update of priority setting for human African trypanosomiasis (HAT) (from the 2004 Priority Medicines Report background chapter on Neglected Tropical Diseases) is given in Annex 1, this was kept as an update as while significant steps have been made for HAT (introduction of a new treatment-NECT- in

2009[40]), and while and the number of reported cases has been declining, the burden of disease is still high in some countries and it is likely to increase dramatically in case surveillance was to be relaxed.

2.1 Visceral Leishmaniasis

The leishmaniases

Today, the leishmaniases are endemic in 98 countries with an estimated 350 million people at risk. It has been estimated that 12 million people are affected by this group of diseases with around 0.9-1.6 million new cases occurring annually[41]; and this number is rising in some areas. Leishmaniasis threatens many poor countries and principally affects poor communities in isolated regions, often as devastating epidemics.

In the last decade progress has been made in disease control with the implementation of rapid diagnostic tests (RDTs), clinical trials with mono and combination therapies and a heightened awareness of the disease. In March 2010 the World Health Organization (WHO) convened the expert committee on Leishmaniasis which subsequently issued the first technical report on leishmaniasis after 20 years. In addition, an ambitious elimination program has been initiated in the Indian subcontinent with a target of less than one patient in 10,000 people, at district and sub-district level, by 2020.

There are four main types of leishmaniasis, all transmitted by the bite of an infected female infected sandfly:

> Visceral leishmaniasis (VL), is the most severe form of the disease; patients present with fever, wasting, anaemia and an enlarged spleen. If untreated symptomatic VL is considered fatal in less than two years. A large asymptomatic population exists, and only around 10% of patients become symptomatic.
> Post Kala azar Dermal Leishmaniasis (PKDL) is a late (usually post-treatment) complication of VL caused by *L. donovani*. Parasites migrate to the skin of patients in around 10% of cases in the Indian sub-continent (ISC) and in up to 50% of cases in Sudan. These patients are thought to be the reservoir of transmission for VL.
> Cutaneous Leishmaniasis (CL), the most common form, principally affects the skin, causing simple lesions which usually self-heal but leave scars.
> Mucocutanteous leishmaniasis (MCL) begins with skin lesions which then spread, causing massive tissue destruction around the mouth and nose.

Co-infection with leishmaniasis and HIV is emerging as a growing threat. Because both diseases attack the immune system, it means the body has even less chance of resisting the infections and treatment becomes less effective. In Ethiopia, more than 20% of visceral leishmaniasis patients also suffer from HIV co-infection. Diagnosis and treatment of these patients remains difficult.

Pentavalent antimony, the most widely prescribed drug to treat *Leishmania* patients, has serious side effects, requires a prolonged course of treatment and is losing its efficacy in some regions, especially in India, due to increasing parasite resistance. New treatments have been implemented, including the liposomal amphotericin B; AmBisome® and miltefosine (the only orally available drug), although these they are not optimal due to problems of routes of administration (IV for AmBisome®), high price (AmBisome®), risk of resistance (miltefosine) and/or toxicity (teratogenicity for miltefosine). Combination therapies are also available including paromomycin and antimony combination, and other combination therapies have been studied in phase III trials in India to have excellent efficacy (over 96%) and safety outcomes (miltefosine and AmBisome® ; miltefosine and paromomycin, and paromomycin and AmBisome®). Single dose AmBisome® with 10 mg could play a pivotal role for elimination programs as well. All these new treatment modalities are currently being studied in a pilot project in India, looking at the feasibility, pharmacovigilance and effectiveness components under field conditions.

The elimination campaign for VL in the Indian subcontinent is underway with aims to reduce the burden to one in 10 000 people in endemic zones by 2015. New rapid diagnostic tests (RDTs) and freely available treatment are enabling the campaign although PKDL and asymptomatic patients in these areas may undermine these efforts. Diagnostic tests and novel therapies in East Africa and South America still remain priority areas for research as does further research into the impact of PKDL patients and asymptomatic patients over disease control efforts.
Treatments and diagnostics for CL patients seem a neglected area of disease control and should be prioritized.

2.1.1 Size and nature of the disease burden

Visceral leishmaniasis (VL), the deadly form of the disease, is endemic in 62 countries with a total of 200 million people at risk, and an estimated incidence of 202,200 to 389,100.[41] Mortality associated with VL is extremely difficult to evaluate and the WHO tentatively estimate between 20 000 and 40 000 deaths per year.[42] As is common for neglected diseases, the exact figures are not known due to limited data and surveillance means. More than 90% of global VL cases occur in six countries: India, Bangladesh, Ethiopia, Nepal, Sudan and Brazil. Population displacement as a result of war, famine, drought or rural-urban migration can underlie epidemics, for example in 2010-11 in South-Sudan. Leishmaniasis is a disease of poverty, with risk factors contributed by malnutrition and especially HIV co-infection, which is changing the face of the disease[43] especially in East Africa.[44] Communities once less at risk are becoming increasingly exposed to the disease where the urban HIV epidemic and the rural leishmaniasis epidemic are increasingly coming into contact. Co-infected patients may be difficult to diagnose, respond poorly to treatment and relapse repeatedly.[45,46]

A complication of VL, especially prevalent in Sudan and South Sudan and to a lesser extent Ethiopia, Kenya and ISC is post-kala-azar dermal leishmaniasis (PKDL)[47], occurring in

people who have recovered from VL following treatment. These patients may be a reservoir for ongoing transmission of disease.

Cutaneous Leishmaniasis (CL) is the most common form of the disease with between 0.7 and 1.2 million new cases per year.[41] CL is more widely distributed than VL, with about one-third of cases occurring in each of three regions, the Americas, the Mediterranean basin, and western Asia from the Middle East to Central Asia. The countries with the highest estimated case counts are, Afghanistan, Algeria, Colombia, Brazil, Iran, Syria, Ethiopia, North Sudan, Costa Rica and Peru.[41]

2.1.2 Progress in the last decade of VL research

In the last 10 years much progress has been made by a number of multilateral groups working on leishmaniasis. In March 2010, the World Health Organization (WHO) convened the expert committee on leishmaniasis which subsequently issued the first technical report on leishmaniasis after 20 years. Other groups including the WHO-TDR Visceral Leishmaniasis Laboratory Network, the Drugs for Neglected Diseases initiative (DND*i*) and the Leishmaniasis in East Africa Platform (LEAP), Institute for One World Health (iOWH) and other academic and non-academic groups are working towards the common goal of control of leishmaniasis.[29]

Although pentavalent antimonials do still remain the first-line therapy in most parts of the world, there has been a substantial improvement in the number of treatments available for VL, with both new products and new formulations of old medicines either recently approved or in clinical trials.[48] In Bihar State, India, where there is a high level of resistance to pentavalent antimonials alternative treatments have been sought. Here, single course AmBisome® therapy of 10 mg/kg has been shown to cure 95% of patients.[49,50] This success has not been repeated in East Africa as the single course is not efficacious enough (personal communication). However, implementation of the combination therapy paromomycin plus sodium stibogluconate (SSG) has been made possible in East Africa, and treatment duration has been reduced from 28 days to 17 days[51], an improvement.

The VL-Laboratory Network has performed an evaluation of the commercially available rapid diagnostic tests (RDTs) for rapid diagnosis of VL. The evaluation included separate analysis in the Indian subcontinent, East Africa and South America. Whilst all RDTs were found to work at an acceptable level in the Indian subcontinent[52], there was a significant decrease in sensitivity in East Africa and South America and progress in these areas should now be a priority. The rK39 tests are now being used for the elimination campaign in the Indian subcontinent as a non-invasive and accurate diagnostic test in clinical suspects[52], which are also used for diagnosis and management of suspected cases in East Africa. However, this still has limitations and cannot be used for relapse cases since it remains positive for a long period of time.

CL continues to be a neglected condition within the leishmaniasis presentations. Treatments, diagnostics and control strategies are limited and a push for research in this area would be of enormous benefit to the estimated 0.7-1.2 million new cases per year.[42]

2.1.3 Current Pharmaceutical interventions

Although improvements have been made, the current range of treatment options for VL is still limited.[53,54] Products have to be safe, effective and accurate as well as adapted to health systems in resource limited settings. Recently the combination therapy paromomycin plus SSG (antimony) a 17 day treatment was implemented in East Africa[51], and single dose treatment with AmBisome® showed very good outcomes in the Indian subcontinent.[49] Appendix 3 shows the situation of products available for VL in South Asia.

The new 17-day combination therapy of Paromomycin and SSG has reduced the length of treatment by 11 days, saving patients and their carers both time and money.[51] However, there still remains a need for an orally available, cheap medicine that is not prone to develop resistance. In addition, no new chemical space has been used by recent developments in treatments, and it is important that this option is also fully explored and developed.

AmBisome®, is a liposomal formulation of amphotericin B which was developed as a safer and more effective alternative to conventional amphotericin B to treat fungal infections. In particular in India, the effectiveness of this medicine in a single-course and even single-dose treatment of VL, has been clearly demonstrated.[49,55] WHO have negotiated a reduced price with the producers (Gilead, Foster City, CA) at $ 18/50 mg ampoule, however this still remains an expensive product as each patient may need several ampoules even in a single course treatment.[50] In addition, this product is administered by intravenous injection and temperature stability remains as issue, as the manufacturer guarantees stability only to 25°C. In December 2011, WHO signed a Memorandum of Understanding with Gilead for the donation of AmBisome® for five years to selected eligible countries. This is also a treatment for HIV and VL co-infections[44], although treatment programs should be scaled up to reduce the burden.

Miltefosine, was thought to be a breakthrough in VL (and HIV-VL) treatment as the only orally available drug for VL and is the drug of choice for the Indian subcontinent elimination programme.[44,50] However, the prolonged 28-day treatment regime (not requiring hospital stay) may be a threat for treatment compliance, and thus is a risk for rapid development of resistance. In addition, it has been noted that resistance to this drug can develop quickly and it would be a disaster if this drug becomes ineffective. Clinical trials of combination treatments in East Africa are ongoing and data will be available in the coming months (personal communication). The expense of miltefosine (US$ 200 per treatment in private pharmacies) means that a generic product would allow access for poor rural communities to this drug. There are concerns about the teratogenicity of the drug, and half-life of miltefosine in the body is longer than had been previously assumed.[56] This means that this drug cannot be administered to women of child-bearing age (except if a pregnancy test can be done, and with concomitant contraception to avoid pregnancy within the four months after miltefosine treatment).[56]

Paromomycin, an old and widely used broad-spectrum aminogycoside antibiotic, has also proved effective against leishmaniasis.[57,58] Paromomycin also appears to work well in combination with other medicines, such as antimonials.[59,60] The recent success with SSG combination has reduced treatment to 17 days in East Africa.[51] In addition, it is also a cheaper alternative to other new therapies at ~US$ 10 per course.[50]

Recently, a promising compound **sitamaquine**, was not taken forward to phase II trials due to less than 90% cure rates in well-conducted phase II trials.[50] This should guide future clinical trials in acceptable efficacy levels.

While interventions for VL are available, scaling up of programs, and (early) access to these medicines is still a problem.

There is as yet no effective vaccine as prevention against any leishmaniasis form. A limited efficacy was seen with whole killed parasites (promastigote forms) up to phase 1 clinical studies. A suboptimal vaccine for *Leishmania* could have a therapeutic effect. Combinations of administration of antimonials and such first generation *Leishmania* vaccines have shown some benefit in PKDL patients. Recombinant vaccines are being developed, along with genetically maniulted parasites as live vaccines are being tested.[61]

Cutaneous Leishmaniasis

The majority of CL infections are currently treatment by antimonial therapy. This includes a long course of injections (usually SSG) over 28 days. Miltefosine is also known to be an effective therapy for CL, but is currently only registered in Colombia as a second line treatment.[50]

2.1.4. Current diagnostics

The major toxicity associated with treatment, as well as the life-threatening nature of the disease makes the need for accurate diagnosis crucial before starting treatment for both VL and CL.

The current gold standard diagnostic for VL requires an invasive aspirate from the spleen which carries a severe risk of haemorrhage and is not recommended except under exceptional circumstances. Lymph node and bone marrow aspirates are also taken for microscopy but these samples are still invasive (and potentially harmful) tests. Reading of the microscope preparations to detect the parasites requires trained and experienced staff, usually present only in major health centres.

The Direct Agglutination Test (DAT) was developed in the 1990's to detect anti-leishmania antibodies in serum of patients. The test requires moderate technical expertise, laboratory equipment, reagents, micro-titre plates, and a toxic solution (chemical 2-mercaptoethanol). Despite this, it remains an important part of the diagnostic algorithm in some areas especially in East Africa.

The development of the lateral flow immuno-chromatographic tests (ICT), commonly referred to as rapid diagnostic tests (RDTs) has greatly improved the diagnostic landscape for VL. RDTs have now been adopted widely especially in the Indian subcontinent where they have been shown to have a high diagnostic accuracy (Cunningham 2012).[3] However, in a recent WHO-TDR evaluation, it was shown that these tests perform with decreased sensitivity in East Africa and in South America. Only one test performs with a sensitivity above 85%.[52]

For CL, the diagnostic landscape is poor. Serological diagnostics are not appropriate as there are few circulating antibodies in the blood, and therefore, only the parasitological tests are applicable (microscopy and culture) for case management. Since therapies for CL are

potentially toxic, they should only be administered to those with confirmed leishmaniasis infection. Therefore more efforts into diagnostics techniques (using antigen or molecular methods) is urgently needed.

2.1.5 Other control strategies

As leishmaniasis is maintained by a complex lifecycle between the human host, parasite and sandfly vector and on some occasions an animal reservoir it is unlikely that control will be achieved by a single strategy. Therefore, in addition to case management by diagnosis and treatment other strategies including integrated vector control and reservoir control (if present) are essential.
In Sudan and South Sudan, the on-going civil war makes such interventions difficult and the other regions most affected are poor, isolated or lack the necessary infrastructure.

Vector Control

Vector control strategies have been helpful in the past, including spraying of insecticide and use of bednets.[62] However, growing insecticide resistance and lack of infrastructure and government support has limited such programs. The situation is made even more complex by the many species of sandflies that transmit the disease and the large number of animal hosts, including humans.

Vaccines

Accumulated evidence from basic research on the immunology of *Leishmania* infection points to an important role for the immune system in controlling infection, suggesting that a preventive vaccine could, in theory, be an option. To date, work has been completed on first-generation vaccines, whole-killed parasites or extracts, with inconclusive or negative results for prophylaxis but encouraging for therapy. Second generation vaccines consisting of recombinant proteins and genetic vaccines have been investigated and one, Leish-111f+MPL-SE has entered clinical trials.[63] Trials indicate that this vaccine is safe and immunogenic in healthy subjects with and without history of previous infection with *Leishmania* as well as in patients with CL and ML.
Vaccination of the common reservoir of leishmaniasis, dogs is seen as an important control strategy. Recently, canine vaccines have been commercialised and studies analysing the ability of canine vaccines to interrupt transmission are encouraging.[64]

2.1.6 Current and potential research: a priority R&D agenda for VL

There are many organizations active in R&D for Leishmaniasis, including DNDi and alliances with pharmaceutical companies, a few SMEs and academic institutions. The following list shows some areas where there are opportunities for further R&D in VL. This list is non-exhaustive. The * indicates that some research activity is ongoing.

Combinations therapy to reduce treatment duration, prevent resistance, and obtain better cure rates*

A broad agreement exists within the scientific community that drug combinations are the best ways to protect effective anti-infective medicines against resistance, in particular when only a few medicines are available.[65] Clinical Trials of existing and new medicines combination therapies could be coordinated by EDCTP. Drug combinations also may reduce treatment duration (and possibly hospitalisation), and/or reduce toxicity. A phase III trial in East Africa is currently finishing with investigations into i) single dose AmBisome® and seven days oral miltefosine ii) single dose AmBisome® and 10 days IM paromomycin and iii) 10 days oral miltefosine and 10 days IM paromomycin and results will be available soon.

Fexinidazole* is a drug currently in phase I/II clinical trials for treating African trypanosomiasis. A bacteria-like nitroreductase has been implicated in both the mode of action and the mechanism of resistance to nitro-drugs in the related trypanosomatids, *Trypanosoma brucei* and *T. cruzi*. Given the closely related genomes of the *Kinetoplastida* investigations have begun to see whether fexinidazole could be an effective treatment for VL. Phase I trials are in the planning stage[48] as this drug shows promise in mice and has the potential to become a safe and effective oral drug therapy for treating VL.[66]

Identify new anti-leishmanial compounds*

New high throughput screening techniques of intracellular amastigote stages of the parasite lifecycle, which is relevant to disease in humans gives us the opportunity to identify new (classes of) anti-leishmanial compounds (references include personal communication with Erika Bogaart). Of particular interest is to screen libraries of already existing medicines and compounds currently under development for other indications, in particular antibiotics, medicines for cancer and veterinary medicines for parasitic diseases as this would offer an opportunity for extension of indication research, or parallel development (both scenarios significantly reduce the R&D efforts, time and resources needed to bring a new neglected disease drug to the patient). This would be suitable for the Innovative Medicines Initiative (IMI) programme if IMI were to extend their reach to include the neglected tropical diseases.

R&D for sensitive and easy-to-use diagnostics, including disease monitoring and test of cure*

A recently-developed simple serological test, the rk28 dipstick, has shown promising results (good diagnostic accuracy) for diagnosis of VL.[67] It is hoped that this test will perform well in East Africa where a specific problem exists with low sensitivity of existing rK39 tests[52] and is undergoing evaluation.

Serological tests cannot be used to monitor disease progression (antibodies remain detectable for months after parasite elimination), to diagnose relapses or to establish cure. Research for alternative markers (antigen-based or DNA/RNA-based or surrogate makers) and field-adapted detection of these still is a high priority, both for treatment programmes and as an important tool for future clinical research for improved treatments. The Foundation of Innovative New Diagnostics (FIND) have recently (2011) started working on diagnostics for leishmaniasis, in particular a molecular test called LAMP and an improved antigen detection system to be used as tests of cure.[48]

PKDL

Accurate epidemiological data about PKDL is sparse, and although there is an assumption that these patients are a reservoir of disease relatively little evidence is available. In view of the elimination campaign in the Indian subcontinent there is a priority to work on epidemiology, pathogenesis, diagnostics and treatment of this component of the leishmaniasis.

Vaccines*

Genetic vaccines have become an attainable target, due to the possibility of producing large volumes, standardisation and longevity of response. In addition, on-going analysis of canine vaccines shows that transmission of human disease can be interrupted by vaccination ultimately reducing incidence. Vaccine development, therefore, is a priority area in *Leishmania* research. Novel, second-generation vaccine antigens candidates must be identified and targeted for vaccine development and evaluation must be performed against a range of *Leishmania* species to ensure geographical utility. Prophylactic use of vaccines should be prioritised as well as for therapeutic use.

R&D on topical applications to treat cutaneous leishmaniasis*

While cutaneous leishmaniasis should have a complete chapter on its own, there is a wealth of knowledge from VL that can be applied to CL. Two formulations of topical treatments containing Amphotericin-B, a drug that is active against all species of *Leishmania* tested are in pre-clinical evaluation ready for clinical studies in the fourth quarter of 2012, if they meet all ICH/ European Pharmacopeia requirements.[48] It is possible that the efficacy of any topical formulation could be enhanced by an immunomodulator.

HIV co-infection: epidemiology, diagnosis and possible treatment*

Evidence suggests that prevalence of VL in HIV patients is between 100 and 2320 times greater than in immunocompetent or other non-HIV-positive, immunodeficient groups of people[68], while the current treatments prove only marginally effective (up to 50% relapse among HIV-positive VL cases). Because the incidence of VL-HIV co-infection is increasing sharply in certain regions, more than 20% of VL cases in Ethiopia, are HIV-positive), research is needed on different aspects of this problem, including epidemiology, diagnosis and possible treatment. New therapies are under investigation by DND*i.*

Study mechanisms of drug resistance

Because only very few medicines are available, with very little innovative and new classes of medicines in the pipeline, it is crucial to make all possible efforts to prevent drug resistance. Understanding the mode of action of the existing and new medicines, including the molecular biology of drug resistance mechanisms, is a prerequisite for this, and should include the development of field-adapted standardised methods to assess drug resistance (both for resistance surveillance purposes, and to guide the choice of treatment).[69]

Leishmaniasis in other regions.

The transfer of progress made in the Indian subcontinent and East Africa, to date, has been slow. The new SSG and Paromomycin therapy is undergoing assessment in South America, however, more effort must be directed towards clinical trials and transfer of technology also to Asia, South America, the rest of Africa and the Middle East.

2.1.7 Conclusion for Leishmaniasis

Leishmaniasis continues to affect millions in different parts of the world, with an alarming re-emergence linked to population movement (migration), urbanization, environment-related development activities and HIV co-infection. In the past decade progress has been made with new clinical trials of mono and combination therapies, diagnostic evaluations and screening of novel compounds for *Leishmania* treatment.

However, there are still research goals and objectives that should be urgently met. The diagnostic landscape for VL patients in East Africa and Brazil is inadequate and diagnostics for PKDL and CL patients are poor. Indeed, relatively little is known about PKDL patients are their potential effect on the elimination campaign in ISC, and we require research on epidemiology, pathogenesis, treatment and diagnostics.

New oral therapies which are not prone to resistance are essential as we await results of the combination trials in East Africa. We must also look for new anti-Leishmania treatment.

Summary of priority research agenda for visceral leishmaniasis

- **Basic research**
- Study on mechanisms of drug resistance
- HIV co-infection: epidemiology, diagnosis and possible treatments
- Impact of PKDL patients as reservoirs of disease. Full evaluation of the epidemiology, treatments, pathogenesis and diagnostic algorithm for these patients.
- Active disease markers for VL

- **Product development**
- Pharmaceutical research to develop long-acting and/or oral formulations
- Clinical trials for combination and novel therapies
- Identify new anti-leishmanial compounds
- R&D on topical applications to treat cutaneous leishmaniasis
- R&D on a preventive and therapeutic vaccine for human leishmaniasis
- R&D for sensitive and easy-to-use diagnostics, including treatment response monitoring and test of cure with increased sensitivity in East Africa and South America
- **Operational research**
- Delivery of interventions
- Resistance monitoring
- Role of asymptomatic leishmanial infection in transmission
- Health systems strengthening and pharmacovigilance

2.2 Buruli Ulcer

Buruli ulcer

Buruli ulcer is a progressively destructive skin disease caused by *Mycobacterium ulcerans*. The first descriptions of the disease were from Australia and Congo and appeared more than 60 years ago; on the basis of a report on a focus of cases in Buruli county, Uganda (north-east of Kampala, now Nkasongola district) the disease got its current name.[70] At least 33 countries have reported Buruli ulcer, most cases occur in rural communities in Africa and about half of them occur in children under 15.[71] Although the mode of transmission is unknown, hampering prevention, a combination of aquatic reservoirs and (biting) arthropods are probably involved. Yearly 5 000-6 000 cases are reported, but the disease is likely to be underreported and may increase due to man-made changes in the environment which result in an increase in wetlands.

Because of the relative low optimal growth temperature of *M. ulcerans* of 30-33 ^{o}C, lesions develop in the cooler tissues, especially skin and subcutaneous tissue. Buruli ulcer presents as a spectrum of clinical forms from localized to disseminated and from an early painless lump to eventually invasive ulcerating lesions. Pathology is caused by the toxin mycolactone which is secreted by *M. ulcerans*. This polyketide-derived macrolide is diffused in the lesion and has necrotizing and immunosuppressive properties, the latter enabling the disease to progress without pain and fever. Available diagnostic tests either lack sensitivity or simplicity.

Currently most patients that are detected early can be effectively treated with antibiotics. Recent studies have confirmed the efficacy of antibiotics in treatment [72, 73.] However the 8-week regimen of daily oral rifampicin and injectable streptomycin is cumbersome, because of the need of repeated visits to health care centres. Issues of treatment failure and drug resistance could be a risk. Surgery is still needed in many cases for wound management and prevention of deformity. Osteomyelitis is a major complication of Buruli ulcer of which care and treatment are difficult. In many cases Buruli ulcer leads to deformity and permanent disability with psychosocial and socioeconomic implications in endemic regions.[74]

A WHO organized international conference on Buruli ulcer control and research in 1998 marked a significant first step in drawing the attention to the suffering caused by this disease.[75] In May 2004, the World Health Assembly (WHA) adopted a resolution to improve the surveillance and control of Buruli ulcer and accelerate research to develop better tools for its control and prevention.[76] In the last decade major progress has been made in both research and translation of this research into control policies. Still, many features of the disease are still unknown, such as the mode of transmission and the pathogenesis. Better tools to control the disease are badly required with simplified diagnostics and improved treatment regimens as the most prominent needs.

Buruli ulcer remains a neglected disease and much work, at all levels, needs to be done to improve prospects for rational control.

2.2.1 The size and nature of the disease burden

Buruli ulcer is endemic in humid, rural tropical climates around the world and has been reported from in 33 countries with a case detection rate of between 5000 and 6000 per year, but reliable DALY figures are not available. Buruli ulcer is the third most common mycobacteriosis of humans, after tuberculosis and leprosy. Cases from China, Australia and Japan have been reported, but most cases are from West Africa, notably Benin, Ghana and Côte d'Ivoire, the latter being the most affected country with over 2 500 cases/year. Cases are often localized in specific districts within regions. In many countries there is evidence of huge under-reporting of the disease. [71]

The exact mode of transmission is not known. Unlike the other mycobacterial disease tuberculosis and leprosy, Buruli ulcer does not likely involve human to human transmission, but is almost always found in association with an environmental source. Recently, a strong relationship between the presence of *M. ulcerans* in the environment and the presence of Buruli ulcer in humans was found in Benin.[77] Moreover the detection of *M. ulcerans* DNA in multiple sample types within a single village was a strong predictor of high Buruli ulcer case burden. It remains unclear though whether the association is a causal relationship, as Buruli patients may be as well the source of the environment contamination.

It has been reported that refugees from non-endemic Rwanda suffered from an epidemic in a refugee settlement in Uganda affecting 9% of that community; new cases disappeared when they moved to a new camp 150 miles away.[78] Riverine, swampy environments seem to be universally present in endemic areas in Western Africa. Biting arthropods as vectors have been implicated and zoonotic transmission by mosquitos from mammals has been suggested.[79,80] The negative influence of the use of insect repellent and wearing long trousers on the risk of disease, favor a role of insects in the transmission.[81]

Following infection, *M. ulcerans* proliferates and secretes the toxin mycolactone, a polyketide-derived macrolide, that causes necrosis and also spreads into neighbouring tissue, suppressing the local immune response and causing the severe and disfiguring ulceration.[82] The host target for mycolactone is as yet unknown. Most lesions occur on exposed parts of the body, particularly the limbs. Children under 15 are among the most incident cases. About half of Buruli patients have functional limitations after treatment.

Because Buruli ulcer presents in a spectrum of clinical forms and many other conditions resemble Buruli ulcer, only a few experienced medical practitioners can diagnose the disease on clinical features alone. Laboratory confirmation of diagnosis is required. The available diagnostic assays, direct smear microscopy, histopathology, culture and PCR lack either sensitivity or simplicity to be useful and operational in peripheral health centres where they would be most useful.[83] Because PCR targeting the IS2404 insertion element is the most sensitive technique (over 90%) and relatively fast (with 48 hours), WHO recommends that at least 50% of the cases reported should be confirmed by PCR.

2.2.2 Progress in Buruli Ulcer control and research

Multidrug therapy has been shown to be effective in the treatment of tuberculosis and leprosy, is now also the current accepted treatment for Buruli ulcer. The combination of oral rifampicin and injectable streptomycin both administrated daily for eight weeks is now the

standard treatment of which effectiveness has recently been proven in a randomized controlled trial.[84] Antibiotics kill the bacteria, stop further mycolactone production, which arrests the progression of disease and support healing. Complementary treatments such as wound care, surgery, physiotherapy and interventions to minimize disabilities may still be needed depending on the stage of the disease. Surgery can reduce sequelae but its main advantage is shortened treatment duration in some cases and more rapid wound healing.

2.2.3 Current pharmaceutical interventions

While Buruli ulcer is rarely fatal, the deformity and disfigurement it causes can result in serious loss of quality of life. This is why current control efforts focus on early detection followed by adequate treatment with multidrug therapy to minimize suffering, disabilities and socioeconomic burden.[71] However, both detection and treatment have still their shortcomings.

With the introduction of multidrug antibiotic treatment since 2004[85], new patients with Buruli ulcer have been offered hope for healing without extensive and destructive surgery, which was the standard treatment before. However, patients need to be encouraged to report early for the antibiotic treatment to be most effective and to prevent functional limitations resulting from extensive tissue damage caused by long patient delay. Due to wrong perceptions about treatment and social stigma of the disease, it is thought that a large number of patients never seek treatment, hiding their ulcers, disabilities and scars. A simple diagnostic tool which fulfills the ASSURED criteria (Affordable, Sensitive, Specific, User friendly, Rapid and robust, preferably Equipment-free and Deliverable) in conjunction with information, education and communication at community level are badly needed. Furthermore, health workers and village volunteers need to trained in early detection. More complicated diagnostics may have a useful role at district hospital level.

Development of a simple diagnostic for Buruli ulcer is not likely to be easy. Mycolactone seems to be an obvious target, but this compound is not water-soluble and lipid extractions suffer from a high background due to co-extracted human lipids. Serology, i.e. antibody detection to a number of well-defined protein antigens, has shown to be of little diagnostic value.[83] The search for alternative biomarkers and alternative detection systems seems warranted, including those employing blood and urine.

The current antibiotic treatment is cumbersome, mainly because of the need for daily injection with streptomycin (which is contraindicated in pregnancy) and thus repeated visits to health centres. Oral fluoroquinolones may be alternatives to be used in combination with rifampicin.[86] However, randomized controlled trials are needed to prove that these are as good as, if not superior, to the current treatment. A prerequisite is that the medicines can be procured and dispensed appropriately under field conditions and that patients and providers adhere to effective treatment protocols.

Prevention of the disease would be preferable over cure. However, there are few targets to focus on. If the mode and dynamics of transmission were better understood, control strategies could be focussed at cutting the transmission cycle, for example by vector control.
Because the incidence of Buruli ulcer is relatively low, vaccine development efforts specifically targeted at Buruli ulcer will not likely to be cost-effective. However, because the pathology of Buruli ulcer is mediated by an immunosuppressive toxin, passive

immunization may be a way forward. Current research is ongoing, and the BCG vaccine offers some short term protection.[87]

Since December 1997, when the World Health Organization (WHO), announced that they would take the lead in mobilizing an international response to Buruli ulcer as a serious public health problem, considerable progress has been made. In 1998, WHO launched the Global Buruli Ulcer Initiative (GBUI) to coordinate control and research efforts[75] and in May 2004, the World Health Assembly adopted a resolution on Buruli ulcer that called for increasing surveillance and control, and for intensified research to develop tools to diagnose, treat and prevent the disease.[76] The last 10 years have been very productive in terms of research and research outcomes which have led to better control. The total number of research publication has increased by a factor 3.9 from 98 in the 10-year period 1992-2001 to 379 in the period 2002-2011.[4] Nevertheless, compared with about 16 000 papers per year on HIV/AIDS and with a research budget of only $5.5 million in 2010 (0.2% of the global R&D funding), Buruli ulcer remains a truly neglected disease.[48]

2.2.4 Current and potential research: a priority R&D agenda for Buruli ulcer

There is a need for focused R&D, divided over basic research, product development and operational studies:

Basic research

Basic research to increase understanding of transmission dynamics will eventually lead to clues for better control. Biomarker research will be needed to feed the product development pipeline for diagnostics and high throughput screening. Immunological research will be needed to increase our understanding of fundamental mechanisms of protection (if any) and pathology (paradoxal reactions; interactions with HIV infection) and may lead to recommendation on interventions to prevent or decrease pathological features. Animal studies to determine bactericidal synergisms effects of drug combinations, like in the mouse footpad model, are useful to guide clinical trials in humans.

Product development

Appropriate clinical trials with all-oral therapeutic regimens are very much needed. Macrolides and fluoroquinolones could potentially replace injectable streptomycin. A close connection with the research community involved in developing and testing new medicines for treating TB would be useful.

There is a need for modern wound management and access to bandages. Topical applications could assist in facilitating or accelerating wound healing after surgery. In both phases, the protection against opportunistic infections would be an important secondary objective. Applied pharmaceutical research to design a formulation that helps the active compounds to effectively cross the skin and reach the bacteria is needed.

New biomarkers, or entire new concepts of diagnostic testing, are needed to feed POC test development. Simplifying molecular technology may be another way forward. Appropriate tests which could be used in assisting the mapping of the disease would be useful. Test systems employing urine or blood should be explored.

Operational research

Operational research is especially needed as to optimally deliver interventions. The current control of Buruli is dependent on early diagnosis followed by adequate treatment. How to ensure that patients report early with their lesions, how can medicines be procured and dispensed appropriately under field conditions and how to assure that both providers and patients adhere to treatment guidelines are important fields of investigation.

2.2.5 Conclusions for Buruli ulcer

Buruli ulcer is a neglected and re-emerging disease that predominantly affects children in Western Africa and other parts of the tropical world, causing terrible disabling and disfiguring ulcers, often leading to permanent lesions. Drug treatment is available provided the disease is detected at an early stage; extensive surgery followed by skin grafts, often out of reach for the poor in rural populations affected by the disease, is still warranted in many severe cases. The relatedness to other major mycobacterial infections (TB, leprosy), as well as progress in basic science provide a wealth of opportunities for focused adaptive R&D towards improved treatment options, in particular making use of existing topical treatments, oral medicines, and compounds in development for other indications. Coordinated efforts and serious financing is needed to move this essential R&D agenda forward, but major improvements are possible on the short to medium term.

Summary of priority research agenda for Buruli ulcer

- **Basic research**
- Dynamics of transmission
- Biomarker research
- Mechanism of protection and pathology
- Animal model studies

- **Product development :**
- All-oral antibiotic combination therapies
- Topical applications as curative treatment for small lesions and as supportive treatment
- POC diagnostics
- Detection assays for mapping the disease

- **Operational research:**
- Delivery of intervention (awareness on early diagnosis, drug delivery, adherence to treatment guidelines)
- Health systems strengthening and pharmacovigilance

2.3 Schistosomiasis

2.3.1 Size and nature of the disease burden

Schistosomiasis, or bilharzia, is a parasitic disease caused by trematode flatworms of the genus *Schistosoma*. Schistosomiasis affects at least 200 million people worldwide, is prevalent in tropical and sub-tropical areas, mainly in poor communities without potable water and adequate sanitation.[88] Over 80% of the schistosomiasis burden is concentrated in sub-Saharan Africa (SSA). The burden of disease due to schistosomiasis is underestimated, as chronic manifestations in the liver, bladder, and cancers are not recorded as schistosomiasis.

Urinary schistosomiasis is caused by *Schistosoma haematobium* and intestinal schistosomiasis by any of the organisms *S. intercalatum*, *S. mansoni*, *S. japonicum*, and *S. mekongi*. In urinary schistosomiasis, there is progressive damage to the bladder, ureters and kidneys. The disease is caused primarily by schistosome eggs, which are deposited by adult worms in the blood vessels surrounding the bladder or intestines and initiate immunopathology. In children schistosomiasis can cause anaemia, stunting and a reduced ability to learn. Infection with *S. haematobium* is the cause of a large number of cases of hydronephrosis, renal failure, and bladder cancer, although these may not be recorded as schistosomiasis. Women with urinary/genital schistosomiasis are at an increased risk of acquiring HIV infection. In intestinal schistosomiasis, there is progressive enlargement of the liver and spleen, intestinal damage, and portal hypertension.[89]

Few, if any, of the clinical manifestations are specific to schistosomiasis and overlap with other causes, including other helminth infections, malaria, and viral hepatitis, which often are co-endemic with schistosomiasis. The classical sign of urogenital schistosomiasis is haematuria (blood in urine). In women, urogenital schistosomiasis may present with a range of signs and symptoms including lesions of the cervix and vagina, vaginal bleeding, pain during sexual intercourse and nodules in the vulva. In areas endemic for urogenital schistosomiasis a large proportion of women may have female genital schistosomiasis (FGS). Genital schistosomiasis also affects men, inducing pathology of the seminal vesicles, prostate and other organs. This disease may also have other long-term irreversible consequences, including infertility.

Intestinal schistosomiasis has a nonspecific clinical picture of abdominal pain, diarrhea, and blood in the stool. Liver enlargement is common in advanced cases, frequently associated with ascites and other signs of increased portal pressure. In such cases there may also be splenomegaly.

Schistosomes require a molluscan intermediate host, freshwater snails, in which they undergo development[90]. Humans become infected when cercariae emitted by the snails burrow into human skin; the lifecycle is completed when miracidium in eggs in infected urine or faeces hatch in water and penetrates the snail host. Contact with freshwater is an everyday occurrence in endemic areas and collecting drinking water, washing, bathing and many rural occupations including fishing and agriculture are risk factors for infection. Co-infections with other helminth infections are common[90] and therefore control programmes should synergise efforts for control of multiple diseases.

Mass drug administration (MDA) of individuals is the main intervention for the control of schistosome infections.[91] Within control programmes it is essential that sanitation is also

improved and modifications are made to the environment to reduce exposure to the snail intermediate hosts and to cercaria that have been shed by snails, combined with education to reduce unsafe water contact.[92]

2.3.2 Progress in the last decade of Schistosomiasis control and research

Praziquantel has been used successfully over the past 20 years to control schistosomiasis in many countries, such as Brazil, Cambodia, China, Egypt, Morocco and Saudi Arabia [87]. In 2001 the World Health Assembly (WHA 54.19) recommended that 75% of children at-risk of schistosomiasis should be treated with regular chemotherapy by 2010.[93] In the year following, the Schistosomiasis Control Initiative (SCI) was set up by the Imperial College, UK (acting as an Integrated Academic Platform) with the aim of making progress towards this goal and the reduction of prevalence and intensity of infection and morbidity in sub-Saharan Africa.[92] SCI is an initiative that helps governments in African countries tackle neglected tropical diseases caused by worms. It was founded in 2002 and funded via grants from the Bill and Melinda Gates Foundation, USAID and Geneva Global.[94] SCI commenced treatment in 2003 and targeted half a million people, mainly in Uganda where the pilot programme took place. In 2005, close to 13 million doses of praziquantel (PZQ) were administered in the six SCI-supported countries and, by the end of 2008, a total of 45 million praziquantel treatments had been administered.[95]

SCI has demonstrated that treatment with praziquantel not only benefits those who are treated but also to those untreated members of the communities. In addition SCI showed it is possible to reach school age children and to treat them with PZQ for less than US$ 0.50 per capita and per year.[95] However, we are still far away from treating the targeted goal of 75% of school age children living in endemic areas.[96] SCI has been working with improving schistosomiasis in six countries in Africa, where there is good data that a single administration of praziquantel with effective community involvement works well.[97] Reports of treatment in the Philippines, emphasizes the need for more community involvement in MDA programs.[98]

More recently a meeting held in the UK (January 2012) produced a pledge, the 'London Declaration,' that public and private partners would unite and co-ordinate to combat 10 neglected tropical diseases by 2020. The aim for schistosomiasis is control by 2020.[48] An increased commitment for donated praziquantel (from Merck KgaA) was pledged.[19]

Until there is a vaccine developed for schistosomiasis, there needs to be effective chemotherapy along with proper public health initiatives to control this disease. Facilitating treatment programs using praziquantel at lower prices and health campaigns (for deworming) of school-going children could greatly help reduce the burden.

2.3.3 Current pharmaceutical interventions

The current goals of the WHO and the London Declaration are based on the use of a MDA strategy. Apart from praziquantel, two other drugs metrifonate and oxamniquine were also recommended by the WHO in the essential drug list, however the latter two were not made affordable or accessible. Praziquantel provides effective, safe, single-dose treatment with few side-effects, offering opportunities for improved schistosomiasis control. This is currently the only treatment used in schistosomiasis programmes.[96] The schistosomiasis community has

observed successful use of MDA in countries where political commitment has been strong, such as China, Brazil, Egypt, and Morocco, if additional measures including sanitation and environmental management are also implemented.[93,99]

However, the long-term impact of expanded MDA is uncertain and it is possible that this approach could result in emerging parasite resistance. This would alter the dynamics of control programmes and it is, therefore, essential that monitoring and evaluation of MDA, especially at the local community level, is applied.[96] The presence of schistosome populations that are refractory to praziquantel has already been reported and it has been estimated that around 10%–20% of infected patients will continue to excrete eggs after treatment.[100]

2.3.4 Other control strategies

Efforts to develop antihelminth vaccines have gone on for many years and continue with steady progress in identifying candidate antigens, recently aided with the generation of a number of helminth genomes. Where the transmission involves an animal reservoir it is possible that treatment or vaccination of the reservoir would contribute towards control [89]. It is now possible to create an effective vaccine against a multicellular parasite, as evidenced by the successful porcine cysticercosis vaccine, a massive step for helminth vaccine development.[101] Very promising leads in the development of schistosomiasis vaccines have been seen.[48] Vaccines developed could be used in combination with antihelminthics as adjunct prophylaxis, thus accessing the already existing control activities (by MDA) to reduce morbidity, reduce rates of infection and re-infection, and reduce the likelyhood of antihelminthic resistance. Recently, an anti-schistosome fecundity vaccine with an efficacy of 50%–90% is being evaluated for bovine vaccination.[102]

2.3.5 Current and potential research: a priority R&D agenda for Schistosomiasis

Basic research (and epidemiology):

As the prevalence of schistosomiasis decreases due to MDA programmes the need for improved diagnostics will increase. There are several important areas for diagnostic development.

1. Diagnostics capable of monitoring treatment response and therefore, ability to monitor and evaluate intervention programmes
2. Disease mapping to guide initiation of interventions including lot quality assurance (LQA) for identifying high risk communities.
3. Assays for individual diagnostics
4. Tools to determine and quantify infection prevalence and intensity
5. Detection of anthelmintic resistance
6. Treatment end-points.

It is likely that a single diagnostic tool will not provide the answer for these multiple problems. Investment in antigen and molecular detection tools may allow quantitative detection of active infection and monitoring of treatment response. It is important that these tools are simple and easy to implement and do not require large investment in laboratory infrastructure. Serological tools are appropriate for disease mapping and monitoring elimination programs.

Product development (and case management):

The London Declaration will see increased donations of praziquantel for MDA programmes. SCI have estimated 128 million school-aged children would need to be given praziquantel on a yearly basis. This is an estimated 192-384 million tablets every year in Africa alone. A persistent reduction in efficacy of praziquantel in schistosomes would represent a grave threat to control programmes, as there are very few alternative medicines. Therefore, research should be focused on the development of alternative treatments to praziquantel. This includes the use of combination anthelmintics; firstly, to increase the spectrum, effectiveness, and convenience of drug administration, and secondly, to slow the development of possible resistance.[91] Specific paediatric formulations of praziquantel should also be developed and evaluated to ensure effective population coverage.

Alternative compounds are also under investigation and recently artemisinin-based compounds have been shown to be active against immature stages of schistosomes, which are relatively refractory to praziquantel. The artemisinins could prove useful should praziquantel resistance become a problem. However, because the artemisinins are currently critically important for malaria chemotherapy artemisinins may not be used for schistosome MDA programmes.[91]

New chemical space should be explored for novel anti-schistosome compounds that can be used in combination or as second line therapies in case of an increased drug resistance or infections which are refractory to treatment.

Other Control Methods:

An essential aspect of control of schistosomiasis is improvement of sanitation in affected communities and access to clean water for washing, bathing etc. Any disease control programme must integrate clean water and hygiene activities into their efforts and promote education and awareness of this disease. Without these elements any control programme will not be sustainable and will fail as soon as MDA is removed. It is imperative that innovative methods to improve sanitation and implement interventions should be encouraged and invested in. As schistosomiasis is transmitted via direct penetration of cercaria through the skin people who work in or around water and who use infected water for washing are most at risk. Sustainable vector control is an important component of elimination programmes. Innovative methods to remove snails as well as prevention of circaria invasion would be beneficial.

In China, where targets for control of morbidity have been met, multi-factorial efforts for control of transmission are being tested and implemented. These include replacing buffalos (one of the reservoir hosts) with tractors, better livestock management e.g. fencing animals, improved access to clean water, sanitation and human faeces management.[103] Control programmes in sub-Saharan Africa should learn from the experiences in China in control of schistosomiasis including the recognizing the importance and power of political commitment to the campaigns.

2.3.6 Conclusions for Schistosomiasis

Schistosomiasis is a preventable and treatable disease, however even if medicines for this disease exist in the generic market, the disease is far from elimination, let alone eradication. The disease affects mostly children, a target group where existing medicines has to be adapted. A wealth of opportunities exist in enabling technologies to develop more specific forms of treatment (e.g. pediatric forms with appropriate dosing), diagnostic tools and vaccines and must be complemented with substantial infrastructure improvement to be effective in elimination. Coordinated efforts from both the public sector, the private sector (including the engagement of pharmaceutical industry, PDPs, sanitation and education organizations), along with substantial financing can lead to reducing the immense burden of disease and even complete elimination.

Summary of priority research agenda for schistosomiasis

- **Basic research**
- Study of resistance mechanisms

- **Product development**
- Improvements on existing medicines (including pediatric forms, adapted for tropical conditions)
- Use of new chemical space for novel therapies
- Diagnostic assays with increased sensitivity including those that can detect response to treatment and monitor drug efficacy. In addition, diagnostics that are directed towards individual case management are necessary
- Vaccine development

- **Operational Research**
- Better access of existing medicines including combination therapies
- Novel and innovative ways to improve sanitation and access to clean water for washing, including inventive ideas for implementation of these strategies
- Sustained and innovative vector control programmes in high risk areas
- Synergise efforts with other helminth control programmes due to poly-parasitism
- Acceptance of multi-factorial programmes for control and elimination of schistosomiasis
- Health systems strengthening and pharmacovigilance

See Annex 1 for a brief update on Human African Trypanosomiasis (HAT)

3. Mobilizing Needs-Driven Innovation to Address Priorities for Neglected Diseases

Research innovation and support is largely driven by market interest. For diseases where a paying market exists, this accommodates an R&D framework that develops new medicines steadily. For neglected tropical diseases, this is not the case. However, the commitment and performance for these diseases has improved significantly since the 2004 Priority Medicines Report was published.

There has been a steady increase in projects involved in neglected tropical disease R&D[33], and also some amounts of financial support from the EU, various governments and philanthropists towards neglected tropical disease R&D projects. This has led to more engagement of public academic institutions, PDPs and some industry in neglected tropical disease R&D. Support for neglected tropical diseases still lies far behind diseases with a paying market, despite the millions dying or being disabled. Perhaps to increase investments into neglected tropical disease R&D, one needs another approach. Investments into R&D should be based both on economic and societal progress, defined under the term shared value.[104] Companies such as the pharmaceutical, diagnostics and biotechnology industries that define markets through economic needs, need to avoid social harms (and thus take into account societal needs) and can bring down costs and increase opportunity into emerging economies. Many pharmaceutical and medical device companies are already embracing shared value, and are engaging in product development, advocating for affordability, ease of manufacturing and distribution[105], and are getting more involved in capacity strengthening programs. Neglected tropical disease product development needs more engagement of innovative biotechnologies, and pharmaceutical/diagnostic companies, (including those in emerging economies). PDPs and academic institutions (including integrated academic partnerships) are the source of many innovative inventions used for neglected tropical diseases, and rely currently on such companies to co-develop and market products for patients. If more companies embrace shared value, partnerships with PDPs and academic institutions towards neglected tropical diseases, with sustained financial support from the EU and other sources will greatly accelerate product development, operational research and alleviate disease burden. Ongoing negotiations on intellectual property, pricing of medicines and the incentives for innovation will all influence the setting of current and future R&D agendas. R&D effort should work closely with existing programmes and interventions, using the approach of preventative chemotherapy or intensified case management. Priority research agendas with clear milestones and roles for different stakeholders should be made for each of the 17 diseases, and for enabling technologies for adapting products and solutions to different circumstances of patients.

3.1 From a few diseases to a more comprehensive agenda. Identifying gaps in research issues that are priority to make a difference

The three examples described in Section 2 show how a needs-driven priority research agenda can be conceived and has identified the most pressing areas where resources and action is needed.

In leishmaniasis, having a PDP has elevated visceral leishmaniasis (VL) to one of the most "non-neglected"of the neglected tropical diseases. There is however still a dire need for medicines, diagnostics and organizational research. Here allocation of resources is driven by an R&D agenda for products that will be better than what is currently used. This could not have been done without the innovators that DNDi partners and co-develops solutions with (academia and private companies). In the second case, Buruli ulcer, there is no PDP active in this disease however, there has been more activity from academic institutions and integrated academic platform in the last few years (including one supported by the framework program). Accepting that no pharmaceutical company is going to make R&D for Buruli ulcer a priority (as the number of affected patients is very low and unable to pay), integrated academia-driven R&D projects should continue to be supported, and one can envision an academic-driven platform or PDP to emerge. Research agendas could use what is known from TB (caused by similar bacteria) and find solutions using repurposed products and technologies, and perhaps attract some investments from sources that support TB projects. In the last example, schistosomiasis, there is a PDP for developing a vaccine. An integrated academic platform (at the Imperial College, UK) that manages the Schistosomiasis Control Initiative (SCI) implements and monitors schistosomiasis control programs in various countries. There is a need for enabling technologies to adapt current products and solutions to these diseases (such as paediatric versions of effective medicines, better simpler closed-system diagnostics). In schistosomiasis, the engagement of local private sector involved in water and sanitation and the engagement of the local education system is vital for limiting transmission.

Visceral leishmaniasis, Buruli ulcer and schistosomiasis are only three examples of the many diseases that remain neglected within the current medical innovation framework. A continuous needs-identification process is needed, notably because some of these diseases only affect populations that have no access to decision makers or media attention, and thus do not benefit from organised patient advocacy groups or PDPs. For all of these diseases, the development of solutions and products start in innovators from academia, and are developed further by PDPs or delivered by Integrated Academic Platforms and include endemic countries. In Buruli ulcer, as in several neglected tropical diseases, having no PDP, no pharmaceutical company interest means that the challenge is placed on academic groups and partnerships to develop solutions, and priority setting and funding mechanisms may overlook these partners. Some involvement of pharmaceutical companies for R&D projects related to patent pools or for dual-market diseases exist (such as in dengue, where profit can be made). There are also innovations and technologies that never get translated to real products and solutions at all.

A needs assessment should involve both patients and health professionals in endemic countries and should include identifying the relevant therapeutic goal: primary or secondary prevention, alleviating a symptom, preventing relapse, diminishing mortality, etc. For example, in Chagas disease, there is still a debate as to what constitutes the appropriate therapeutic target. Chronic stage patients have chronic disorders such as cardiovascular complications, of which the link to parasite infections is not well understood. In Buruli ulcer, where available treatment is against the causative *Mycobacterium*, one cannot ignore treating the devastating ulcers and disfigurement itself. It is therefore not clear whether the one therapeutic strategy would be to develop a new drug that eliminates the causative organism, or whether in late stage disease, the presence of the organism is less important than treating

the other symptoms. Multiple interventions may have to be developed if each disease is to be eradicated.

The next step is to consider the currently available tools in the field and to identify their limits according to the therapeutic goal. For example, even if in the long term the target would be to have every HAT patient cured at stage 1, given the difficulty of identifying patients at this stage, a more relevant initial target is to have a safe and easy-to-use treatment for stage 2 infection. This field reality is glaringly obvious to health care workers treating patients in affected areas, not to innovators in R&D laboratories. The therapeutic target should take into account the field conditions and appropriate technologies that can solve this hurdle.

Development of treatment tools should include means of diagnosis and prevention as well as curative treatment. Indeed, diagnostic tools are key elements in a coherent treatment strategy. Just as there is little rationale in testing patients for a disease without a coherent treatment strategy to follow, there is equally little benefit in having a drug without a satisfactory diagnostic strategy and case management system.

Innovation in drug and diagnostic development is best defined by public health needs, which means that innovation should be assessed in relation to the relevant public health goal and the current treatment and prevention options.[106] An innovative treatment for neglected diseases, and arguably, for all diseases, should address the following criteria: it should be of pharmaceutical quality, efficacy and safety, and it should be available, affordable and easy to use, and with relevant diagnostic tools available (that are themselves sensitive, specific, easy to use and affordable).

Development of epidemiological tools, new medicines and diagnostics and operational tools are largely required in several of these diseases to reduce the burden. We outline some opportunities that could make a substantial difference to the burden of these diseases below.

3.2 Opportunities for a priority R&D agenda

In order to ensure solutions for neglected tropical diseases, priorities should be based on the public health need. Current performance of the development of solutions has been largely driven by the priorities of stakeholders and markets. Spending also depends on the short term achievability of each project. It is crucial to make the development of each solution (be it a therapeutic, diagnostic or vaccine) better than current pharmaceutical interventions, applicable to the situation of the patient living in affected countries and economically sustainable.

3.2.1 What needs to be mobilized

To ensure adequate opportunities for neglected disease R&D, several areas have to be fortified. There must be adequate incentives to make R&D projects attractive, so as to engage appropriate innovators from PDPs, academia, biotechnology, and multinational pharmaceutical and diagnostic companies, **including those in emerging economies and countries endemic for these diseases**. Projects should address products and solutions to be developed to be better than existing interventions or complement existing interventions and

actually reach the patient in a cost effective way. The setup and support of integrated platforms (such as PDPs, integrated academic platforms, etc) for research, development and the implementation of new medicines are needed. These platforms should be framed within a well-defined cooperation framework between developed countries and those endemic for these diseases if sustainability is to be achieved. These platforms should be able to create necessary therapeutics (products such as medicines, vaccines and diagnostics), technologies (to produce them in an affordable way) and transfer them to patients in countries.

Given that products developed for these diseases does not finish with regulatory approval as it requires validation in the actual countries affected, which is perhaps more variable than than for medicines for developed countries. Significant steps must be made to get health systems ready for some of these products. Of concern if the inability of most countries to conduct the pharmacovigilance activities required for new products.

Incentives for engaging innovators to perform R&D on neglected tropical diseases

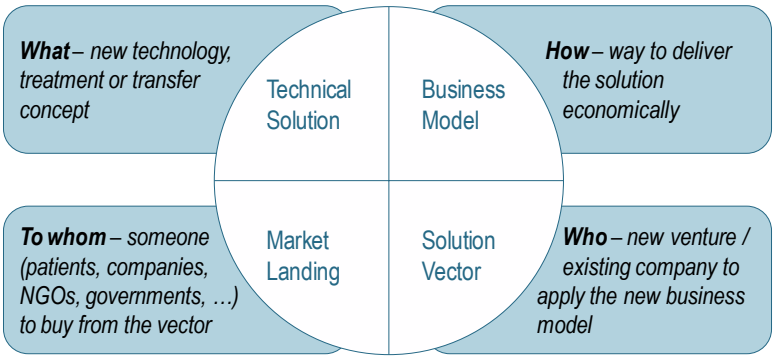
Financial, social and training incentives will stimulate more engagement from industry, both large and small companies. Currently the EC framework program includes support for small and medium enterprises (SMEs) involved in partnerships for translatable research and product development projects. Matching in-kind contributions from SMEs, and preferring collaborative R&D projects between public and private partners, supporting training of skilled personnel in these companies are all encouraging to engage more companies. Organizations not usually involved in neglected tropical disease R&D can (and do) contribute as part of their Corporate Social Responsibility (CSR) and enjoy reputational benefits, while increasing their profile to global consumer markets. The current EC Framework program also supports a number of academic institutions and integrated academic platforms which develop basic epidemiological and research tools and technologies and also recently translational product development. Taken together, academic groups and SMEs are some of the main source of R&D for neglected tropical diseases, and these are sources that PDPs rely on as well. These product development activities managed by academic-academic consortia should continue to be supported. The acceptance of any final product depends on the health systems and patients in endemic countries, thus they have to be engaged early in R&D agenda setting for the development of products. One could envision several integrated academic PDPs emerging, especially for the diseases where no PDP exists. After the London Declaration, several pharmaceutical companies and PDPs pledged more focused investments towards neglected tropical disease R&D. Advocacy for these diseases and setting proper R&D agendas for these diseases is vital for engaging innovators.

Necessary integrated platforms

Through shared value, various innovators such as PDPs, academic integrated platforms and public-private partnerships all attempt to address the needs of each disease and situation of patients. Every needs-driven priority R&D effort (or project) must follow a "3T approach"; (a) a better or new Therapeutic approach (diagnostics, treatments and/or prophylactic vaccines), have (b) the Technology to produce it (in the correct, affordable and sustainable form) and have (c) a way to – Transfer- to the users (the patients). Engagement of partners and innovators, financial support must follow this "3T" approach when committing to an R&D effort. Projects will have to address the technical solution with a business model (a cost-

effective way to deliver a solution), a solution vector (that will eventually deliver a solution using the business model) and an expected market landing (pre-arrangements, commercial and practical to ensure swift adoption and an early demand) (see Figure 6.9.2).

Figure 6.9.2: shows what is necessary for each needs-driven priority R&D project to become viable and successful



Source: Besteman, J.J.a.K., euSEND. 2009. [107]

Some examples of the 3T approach are shown in Appendix 6.9.4. While many projects within PDPs follow this principle, several partnerships and integrated academic platforms also have been employing this approach in their programs. Enabling technology projects (not specific to any one neglected tropical disease, but across several diseases) can also follow the 3T approach.

3.2.2 How can this be mobilized

To mobilize opportunities towards a priority R&D agenda for neglected tropical diseases, there must be a global call to action. There must be more commitment by innovators, product developers; there must be more steady monitoring of the global landscape of R&D efforts (research/epidemiology, product development and operational research) and monitoring of this commitment into performance. We also need to fortify the partnerships, Integrated academic platforms and PDPs that perform well through adequate funding.

A call to action. Enhanced commitment

There are many effective medicines for several of the neglected tropical diseases. Since the cost of these medicines is an issue, patients rely on drug donation programs to gain access to these medicines. Disease elimination programs also need large communities to be mass treated (as in the case of trachoma and schistosomiasis).[108] Donation programs in the past years have been largely led by industry, private foundations and funders that manage and mobilize these medicines, with the WHO guiding many programs (see Appendix 6.9.5). This is an area where industry plays a strongest role in the global fight against neglected tropical diseases, and should continue to do so. One such program is run by an integrated academic platform, SCI, while there are several product control partnership and the WHO who manage the rest of the donation programs. In early 2012, the London Declaration of Neglected Tropical Diseases showed 13 multinational pharmaceutical companies pledging their support to commit, coordinate and collaborate towards the control or elimination of at

least 10 of these neglected tropical diseases by 2020, affecting a total of 1.4 billion people).[48] The declaration also included non-governmental organizations, product development partnerships and public institutions pledging their support. Countries endemic for these diseases and the international community were also urged to provide necessary resources to remove the primary risk factors for these diseases, poverty and exposure. They were urged to contribute by ensuring "*access to clean water and basic sanitation, improving living conditions, vector control, health education, and strengthening health systems in endemic areas"*. Many neglected tropical diseases can be eliminated both in the short term and in the long run. For example, it is due to enhanced commitments of expertise and money that will shortly lead to the global eradication of guinea-worm. Appendix 4 gives a table of the medicines donation programs active (from pharmaceutical companies). A tool to measure and monitor the commitments and performance of industry (and others who pledged support) and hold those who pledged accountable is being developed. Those who pledged support must show within a reasonable timeframe the efforts they have made in contributing to these goals and this will develop into a benchmark towards real progress in the eradication of these diseases.

There have been an increased number of academia-driven consortia (integrated academic platforms) towards product development, especially in diseases where there is no PDP. Engagement of several biotechnology companies and companies in developing countries (as early co-inventors) is necessary. Existing partnerships and platforms are adding more diseases to their priority agendas (as evidenced by DNDi adding more neglected tropical diseases to their agenda and the recent proposal by EDCTP to start supporting neglected tropical disease clinical trials). Pharmaceutical companies and SMEs using the WIPO Re: Search tool for example have opened their libraries to share compounds, know-how and expertise for neglected tropical disease R&D.

Monitoring performance on neglected tropical disease priority agendas

There is an excellent tool for measuring the portfolio of projects and analyzing these available from the BIO Ventures Global Health Global Health Primer[33] Their work has been recognized and detailed in Section 1. To measuring the commitment of the pharmaceutical industry, a monitoring tool already exists. The Access to Medicines Index is a biennial report that measures multinational pharmaceutical companies' policies, practices and performance in contributing to access to medicine (including neglected tropical diseases) globally.[6] It compares performance of companies with each other and ranks them based on relevant metrics and provides a final chart of the top 20 pharmaceutical companies comparing how they contribute to access to medicine. This is a useful framework for transparent reporting about access to medicines performance, which will help companies inform their stakeholders and investors and also enables the comparison of companies among others. One could engage more companies if lessons learnt and best practices could be shared among these companies, and also engage stakeholders in emerging economies (e.g. generics companies) using this tool. A similar monitor for measuring the performance of PDPs and integrated academic platforms is needed. A monitor of projects supported by the European Commission Framework Program (and other supporters of neglected tropical disease R&D) would be useful to monitor R&D milestones and connect existing research priorities to programmatic interventions, while ensuring adequately prioritized agendas for the future.

Almost every multinational pharmaceutical company has dedicated part of its business strategy to improving access to medicine. While much of this sentiment is because of

philanthropy and corporate image setting, a large part is actually to reach a wider market share, as most products developed by pharmaceutical companies is needed also by patients in low and middle income countries, the challenge is in keeping these medicines affordable and accessible to all patients regardless of their geographical location. Commitment to spending is monitored by the G-FINDER index[109], where governments, philanthropists and other donors play an important position in supporting research priorities across the globe, and influence the rate at which products can be developed.

3.2.3 Existing mechanisms and tools

Following the '3T' approach, we outline opportunities for priority R&D using existing mechanisms.

Therapeutics:

For almost all of the neglected tropical diseases, one needs better cheaper medicines, vaccines and diagnostics. The different stages of a typical pharmaceutical R&D pipeline is shown in Appendix 6, where in neglected diseases, the **most important gap** is the transition from fundamental research or identified field need to a candidate drug or vaccine in the predevelopment stage. It is crucial to confirm the validity of the chosen development candidate, and if needed, to optimise it (i.e. assuring absence of toxicity, choosing a formulation, assuring ease of production, etc). Unless there is strong commercial interest, few candidates are taken through this phase

While some big pharmaceutical companies have set up specialized centers for tropical diseases (Novartis, GSK, Astra Zeneca), only some research applicable to neglected tropical diseases is performed at these centres. While this has the potential to change in the coming years due to the increased commitment and increased opportunities with neglected tropical diseases emerging in the (paying) developed world (such as leishmaniasis and dengue), most R&D is done through collaborative efforts with PDPs (usually in drug discovery programs with pharmaceutical compounds tested in neglected tropical disease assays managed by the PDPs), and in smaller capacity through lesser-known, direct R&D with academic groups and SMEs in bilateral or multilateral consortia in disease areas (where there are no PDPs or through integrated academic platfoms).[33] PDPs have the biggest ever portfolio of neglected tropical disease products ever, some of which are in late stage clinical trials. Apart from performing R&D, PDPs have extended their work into advocacy and capacity strengthening. There are many new PDPs established in the last decade and new ones are emerging. Some existing PDPs are taking on newer neglected tropical diseases. PDPs are clearly playing an increasing role in neglected tropical disease research[109, 110], claiming a bulk of the funding and spending, and playing a role where pharmaceutical industry had traditionally not been active in the past. In the Global Health primer, it is obvious that there are a vast number of other R&D projects that are involved in neglected tropical disease R&D, though these may not have one organized voice, and do not qualify for the typically PDP-oriented funds. EDCTP, when neglected tropical diseases are in the agenda, will play an important role in parts of the clinical trial process for some of these diseases. In September 2012, a non-profit organization called TransCelerate based on 10 pharmaceutical companies was set up to help speed up R&D of new and adapted medicines, by sharing appropriate resources, data and standardizing clinical trial processes. The focus will be on identifying and resolving common issues that delay R&D.[111] The disease focus has

not been outlined for this non-profit, and will hopefully include a mandate for neglected tropical diseases. TransCelerate also could offer a unique platform for enabling technologies to affect current and future neglected tropical disease R&D, using knowledge sharing in dosage, bioavailability and pharmacokinetics and pharmacodynamics, areas of hidden neglect within several of these diseases. It could also be a platform to connect complementary R&D activities with drug donation programs offered by these pharmaceutical companies. All of these initiatives will need to also partner with scientists and doctors in endemic countries to create and advance capability and capacity.

Technologies

This is an area widely underestimated in priority R&D agendas. Scanning for technologies not usually used for neglected tropical diseases and engaging innovators, manufacturers of the final products is vital. Biotechnology companies and academic researchers have been developing new technologies at a rapid rate. Although these have been predominantly used in applications for 1st world diseases, they can be "rediscovered" to look for adaptability and affordability in neglected tropical disease product development. New ways of culture, analytical systems, platform technologies and types of delivery methods and innovative therapeutics are emerging. With genome sequences available for more causative organisms (such as *M. ulcerans*, the causative agent of Buruli ulcer) there is a wealth of resources available for creating the next new neglected tropical disease medicine or diagnostic, and producing this in an affordable, sustainable way. Technologies can be used to adapt medicines, vaccines and diagnostics to tropical conditions, while retaining sensitivity, specificity, affordability, and ease of use is important. Adaptive R&D projects in heat stabilizing both medicines and diagnostic reagents[112], developing closed systems diagnostics, studying (fixed dose) combinatorial drug chemistries for polypills are available and should be tied into neglected tropical disease R&D efforts.

In technology platforms for diagnostics, the most adaptable to developing countries is lateral flow or dipstick type diagnostic technologies (closed system diagnostics requiring simple handling of infected samples), and these can be produced cheaply and correctly. Recently with the commitment of a biotechnology company, Eiken, the proprietary LAMP technology reputed to be highly sensitive and specific, yet requiring simple (albeit multiple) handling is being tested for a range of neglected tropical diseases.[113] Nonetheless a closed extraction and amplification systems should be explored.

Transfer

Health improvement programs and capacity strengthening are vital for the success of any developed solution. Early engagement of manufacturers and distributors, procurers and users, and adapted pricing may be necessary. GeneXpert for TB is an example that uses concessional pricing to roll out quickly into the developing world. The Global Health monitor[34] shows some projects with early engagement of local manufacturers. Adapted packaging, training and education, ensuring multiple suppliers (of reagents or components of each solution) helps to reduce cost and increase emerging opportunities.

3.2.4 Adequate Funding for Neglected Tropical Diseases

Neglected tropical diseases have for too for many years been ignored by the private and public R&D sectors. The G-FINDER index was set up to monitor annual funding of several tropical diseases, including Malaria, HIV/AIDS and TB.[109] The global spending on tropical diseases is about US$ 3 billion in R&D of new products in 2011 (which is US$ 443 million increased investment since 2007). Of these, nearly 80% is for malaria, HIV/AIDS and TB. While product R&D was heavily focussed on innovative medicines, vaccines and diagnostics and enabling technologies (for adaptive R&D) received only 0.4% of R&D investments.[109]

Continuous R&D for neglected diseases will mean committing substantial amounts of money. It is a widely contested and controversial topic to deduce the true cost of developing a new pharmaceutical product. Apart from the actual cost of out-of-pocket expenses to develop a drug, capital costs due to the long time it takes to develop, register and market a drug also plays a role. It is approximated that it could be anywhere between 55 million and 1.2 billion, as evidenced by several studies.[114]

It has widely been perceived that the revenues generated from drug sales are to be spent on R&D. Recent reports estimate up to 26% of gross profits for some pharmaceutical companies spent back in R&D, though there are certainly a majority of companies that spend lesser amounts.

It is difficult to determine the exact cost of developing a drug when including the contribution from public-funded research, tax credits, inter-company licensing agreements, etc.[115] Moreover, it is well known that there is significant attrition, meaning that the risk of failure is high, especially in earlier stages of the development process. Moreover, the cost of developing a medicine is not the same for all indications. While industry's figure may be inflated and may not be relevant at all for the development of a drug for neglected tropical diseases (due to the more needs-based decision-making process and the pooling of resources to cut costs), it remains clear that pharmaceutical R&D is a lengthy and costly process. Not-for-profit drug development initiatives such as the Global Alliance for Tuberculosis Drug Development (GATB)[116] or Medicus Mundi Switzerland and the DNDi project a cost of 35-40 million US dollars to develop a new drug (not including the enormous cost of failure).[10,117]

A minimum response to the 10/90 gap (where currently less than 10% of global R&D spending is relevant to the health of 90% of the worlds' population) will require new funding of the order of several hundreds of millions of euros over a number of years.[118] This is itself only a part of the solution, The Commission on Macroeconomics and Health determined that an additional global yearly investment of US$ 3 billion per year is needed to reach an appropriate level of health R&D to meet the needs of the poor.[119]

In the London Declaration, more than US$ 785 million was pledged to accelerate R&D of new and adapted medicines and expand existing drug distribution was pledged. This amount will at least see significant steps in the elimination of trachoma and some of the helminthiasis.

In the European Union, the European Commisson contributed 22% of government investments and 15% of total global investments. 76% of which went to malaria, HIV/AIDS and TB, and most of the money going towards PDPs and EDCTP. This has led to 43 new

medicines, vaccines and diagnostics registered to tackle neglected diseases and poverty related disease (including malaria, HIV/AIDS and TB).[20] It is important to note that the main source for products developed by PDPs and EDCTP include academic institutions, Pharmaceutical companies and some private SMEs, who may not have received much of this support themselves. Looking at the landscape developing, one could consider that funding will be also reserved for integrated academic platforms and public-private partnerships (as well as PDPs), knowing especially that for several of the neglected tropical diseases, there are no PDPs and no advocates.

Given the current EU budget for neglected diseases it is clear that a serious effort needs to be sustained if one hopes to have an impact. Furthermore, the current EC-research funding for neglected diseases is structured mainly through the Framework Programmes, where neglected infectious diseases (which are mostly the neglected tropical diseases, with diarrhoeal diseases additionally in the list). In the FP6 program, research projects were mostly supported two or three years with budgets of around 1-2 million euros, and the FP7 program awarded larger amounts of around 3 up to 10 million euros of support.[120] In the past years the FP6 and 7 programs have focused more and more on translational research, and such a mechanism will hopefully continue. It is important for any such mechanism to keep track of the achieved milestones of each of these projects, and plan for the implementation of any appropriate results, products and solutions.

Moreover, the EU focuses on basic research, and through the European Developing countries Clinical Trials Platform (EDCTP) on phase II and III clinical trials (so far only for HIV/AIDS, malaria and tuberculosis). There is more to be done in EU support for **translational neglected tropical disease research**, to take the results of basic research through the tedious, costly and time-consuming steps of preclinical research and the initial clinical safety studies (phase I) and link successful product development into existing programmatic interventions.

The Innovative Medicines Initiative (IMI) supports precompetitive collaborations, with scope related directly to the research priorities of pharmaceutical companies.[121] The majority of the program supports diseases relevant European public health, and out of 30 of such projects, only two projects, accounting for 7.5% of the total IMI budget have poverty-related relevance, and not at all in neglected tropical diseases. This worrying trend of having a market-driven agenda will hamper the already starved for funding pipeline of neglected tropical disease product development. If we take into account the pharmaceutical commitments in the London Declaration and the global need to embrace shared value, an neglected tropical disease mandate must become available in the IMI scheme. It is of great concern to advocates of neglected tropical diseases that IMI have and may in the future overlook these devastating diseases.

With the upcoming Horizon 2020 funding scheme, one trusts that there will be continued stream of support for R&D priorities for neglected tropical diseases.

There are currently some substantial sources of investment, the National Institutes of Health (NIH) through the TRIND program and the private charity, the Bill and Melinda Gates Foundation, and the Wellcome trust that are starting to respond to this problem. Governments such as the UK DFID are also responding to this issue. Recently governments have been investing in neglected tropical disease R&D, mostly through PDPs, leaving product development from public collaborations, integrated academic platforms and public-

private collaborations in diseases where no PDP exists with limited support. With the current EU budget deficit, one expects member state government support for neglected tropical disease R&D and innovation to also be slashed.

It is clear that money per se is not the limiting factor- rather it is the priority allocation of money that needs to be reassessed. Clearly, when the political will to respond is present, research can be accelerated- for example, a diagnostic test for SARS, deemed a serious threat to the world economy, was developed in an unprecedented three months.[122]

3.2.5 Involving the private and public sector: capacity building for R&D into neglected diseases

The current pharmaceutical R&D framework has been left by governments in the hands of the private sector, which is not enough to meet the medical need of neglected tropical diseases. The balance of shared value across public and private people and organizations where economic interests and social needs need to drive the priority setting.

The limitations of the market-driven R&D framework

During the few last years, the global community has become more aware of the dramatic health needs in developing countries. The debate about the implication of WTO/TRIPS agreements and patents on drug affordability for the poorest has drawn attention to several key issues regarding access to essential care on the one hand, and stimulation of drug innovation on the other.[123] At the global level, these two aims should be complementary: we need new solutions (medicines, diagnostics, vaccines), and we want these solutions to reach the patients who need them. In practice, these two aims are potentially contradictory. For instance, when drug innovation is dependent on private investment and is patent-protected – giving a temporary market monopoly to the patent holder – medicines may be marketed at such a high price that only a fraction of patients in need can have access. But, in such a market-driven framework, mandatory very low prices for new medicines would be a strong disincentive for private investment and thus for drug innovation. For prices to be lowered, shared value must be generated. Innovative strategies engaging multinational, local, public and private stakeholders must be encouraged. Means such as reconceiving (emerging) markets, refining productivity, supply chains and manufacturing and adaptive sales and distribution and enabling local cluster development all make opportunity increase and costs decrease in the long term.[105]

Most public decision makers in industrialised countries still expect new medicines to come from the pharmaceutical industry, an expectation too often arrived at without sufficient analysis of the efficacy and cost of this choice. This expectation implicitly shifts the responsibility for public interest missions to the private sector, which lacks the (financial) incentives to fulfil this role, and seems to be unwilling to accept this responsibility.

A crucial role for public research

While a clear commitment exists within the public research community to work on neglected diseases, as can be seen from the large number of related publications, for instance in the area of trypanosomiasis and leishmaniasis[124], this research mainly focuses on basic research and epidemiology. Because of the way public sector research is organised, financed and

assessed, there are not enough monitors to determine how much translational projects come from the public sector that directly cause an impact to the burden of neglected tropical diseases. There is clearly a continued focus on "upstream" research has resulted in less than expected research capacity and expertise for pre-clinical R&D phases in the public sector. The exceptions are the few integrated academic platforms (for example the SCI or BuruliVax consortium) who with limited support, engage in disease control strategies and product development. Whether this is because of the lack of interest in even PDPs for these diseases of increased social responsibility, this has led to a stronger role for public organizations in neglected tropical disease priority R&D. A concerted effort to build more centralised pre-clinical research capacities in pharmaceutical sciences in the public sector should be considered, using some of these integrated academic platforms already present.

Furthermore:

- Incentives for public sector researchers need to be adjusted to ensure that their work provides health benefits. Focus needs to shift from publishing or patenting as the end goal of research, to designing and implementation of new effective technologies for patients. Incentives should include for example valuing pharmaceutical development projects, or applied research.
- In parallel, established scientists should be encouraged to publish in open-access websites and in specialist journals, when appropriate, and in this way set an example to show that sharing knowledge freely, especially in the field of neglected diseases, is more important than being caught up in the current evaluation system.[125]
- Career advancement in the public sector should not be dependent on the classical system of number of citations and impact factors of journals, where researchers in the less fashionable and less populated area of neglected diseases are at a disadvantage. Rather, funding agencies should be sensitized about the importance of applied research into neglected diseases and access to funding facilitated.
- Public sector commitment to priority setting and funding within public and private partnerships is crucial. The public sector should be encouraged to provide technical support and external expertise for protocol assistance, legal issues in drug development, and information access.
- Projects emerging from any public sector or public collaborations should ensure that the core principles of the business model, market landing and solution vector are thought of, to ensure achievable solutions.

A role for the private sector

Finally, the role of the private sector needs to be redefined. The pharmaceutical, biotechnology and diagnostic industry (including those in emerging markets) has a responsibility to contribute to the search for essential health tools, even though it may be less profitable economically. Specific incentives (and obligations) could be designed to more actively involve industry, but care should be taken that these remain cost-effective in terms of public investment. Possible measures to be explored include:

- Tax-deductible, in-kind contributions to publicly-driven R&D, for example by doing toxicology studies, pharmaco-kinetic studies, bioequivalence studies (as suggested by the Global Alliance for TB Drug Development);
- Higher tax breaks for in-kind contribution to publicly-driven research rather than industry-driven research to encourage business sector support for essential public health R&D;

- A tax-deductible requirement for industry to open their compound libraries and knowhow and include data and content.
- A non-working clause on compounds: if a promising compound has not been developed by a drug company after a given period, then it should be put on the market for licensing to a group willing to pursue it, with appropriate remuneration for the originator company in case of profit. Open access to information on all clinical trials remains a priority (as announced by in GSK)[126]

3.3 Towards a system ensuring commitment and performance to solutions to neglected diseases

3.3.1 A needs-driven priority R&D agenda

As detailed in sections I-II, such an agenda should encompass the following elements:

- For each disease, a definition of the optimal preventative and therapeutic objectives, based on patient needs, the expectations and skill of health professionals and on achievability of the solution; the ultimate goal of obtaining safe, effective, easy-to-use and affordable solutions must guide decision-making;
- An analysis of creative R&D opportunities based on the current state of the art in medical research (engaging multinational and emerging Pharmaceutical and Diagnostic companies, biotechnology innovators, PDPs (where there is one for a disease) and the public sector, and a definition of the innovation expected (medicine, vaccines and diagnostics or enabling technologies) to respond to the identified needs;
- The setting up of incentives/obligations for both the public and private sectors in terms of responding to the priority R&D agenda.

3.3.2 Public responsibility

Addressing the unmet health needs of the world's population, including those of people suffering from neglected diseases, is a public responsibility. Governments from the North and the South must be more proactive, i.e.

- Allocate sufficient funds
- Design specific policies to strengthen R&D into medicines for neglected diseases. These policies should balance incentives and obligations for the public and the private sector.

It is essential that governments equip themselves with the means to ensure that theoretical advances into priority health needs are translated into practical applications, with the goal being real therapeutic advances for patients. This requires a substantial shift in the current power balance in the setting of priorities, and a change in the current mind-set. Policy-makers must accept the challenge of setting up a paradigm shift, and develop a new and more justifiable health care policy. A **not-for-profit model** of essential drug development should be explored, at least to address those needs falling outside of market interests. Health and medicine must be treated as strategic sectors requiring large and sustainable investments, as occurs today for weapons and defence, space exploration, the telecommunications industry, etc.

In setting the public research agenda, scientists can be encouraged through specific programmes, sustainable financing and appropriate career incentives to focus on neglected

diseases and particularly on translational research to move basic research results into medical applications. Governments can also target the private sector by a mixture of incentives and obligations. One possibility is a tax analogous to the eco tax, where industries are required to develop their own system of waste elimination or pay a tax subsidising the public waste management system. Initiating these changes requires strong political will and commitment, but is a crucial aspect of the collective responsibility to address neglected diseases.

The pursuit of needs-driven health R&D to generate global public good, in particular in areas such as neglected diseases where the market fails, is an example of "enlightened" self interest for all members of the international community.[127] Examples are the recent emergence of West Nile virus in North America and the growing incidence of primary malaria, tuberculosis and multidrug resistant-TB in the West. Changing global populations, local conflicts and the ongoing economic imbalance mean that diseases that today affect countries far from Europe may soon be found closer to home. Pursuing health R&D as a global public good is not charity, but an endeavour from which all nations stand to benefit through shared value.

3.3.3 Upgrading the international effort to treat neglected diseases

A number of international initiatives have been set up to address the issue of neglected diseases but this can only been seen as a start. The oldest one, the WHO/UNDP/ WorldBank/UNESCO programme on Tropical Disease Research (TDR), was created in 1975, in response to a plea from developing countries for an international commitment to their health problems.[128] Although TDR has been instrumental in bringing to the market several new tools for tropical diseases, the increasingly huge needs of neglected patients demonstrate that a much stronger response is needed.

Over the past few years, international awareness has grown around the unacceptable inequities in access to essential medicines, including the lack of adequate treatments for certain diseases. Several types of initiatives have been set up to start addressing some aspects of this vast problem. For instance the Global Fund against AIDS, Tuberculosis and Malaria (GATM)[129] exclusively focuses on access to existing medicines for these three diseases (there is only a limited "end fund" for Neglected Tropical Diseases-[130] who are garnering private support in developing countries for operational neglected tropical disease programs); others are donation programmes for a specific medicine (for instance for the helminthiasis and trachoma). A few are public private partnerships (PPP) focused on neglected tropical diseases (See chapter 8.3 of this report), especially those focusing on pharmaceutical or vaccine or diagnostics development, such as the Drugs for Neglected Disease Initiative (DNDi), the Sabin Vaccine Institute (SVI), the Foundation for Innovative New Diagnostics (FIND) and the Institute for One World Health (IOWH) but they are generally engaging pharmaceutical companies and academics and their sustainability is not secured.

Among the major challenges for all these initiatives is access to (proprietary) compound libraries and technologies (from biotechnology, pharmaceutical companies and public innovators), to medicinal chemistry expertise, and to sustainable long term financing that is compatible with the lengthy, complex and costly drug development process.

3.3.4 More than Malaria, HIV/AIDS and TB

Today, malaria, HIV/AIDS and TB receive much media attention, and increasingly also more research attention. However, these diseases present only a part of the global disease burden contributed by neglected diseases. While the ongoing mobilization for these diseases is more than justified, and should be strengthened, it should not create a false sense of having dealt with the problem. The lack of knowledge about other neglected diseases is both a cause and a consequence of their neglect, and serves to entrench a hierarchy of "neglected" and "more neglected" diseases. Unfortunately, the recent attention of wealthy countries of the north, including Europe, to "poverty-related" global disease has been limited to the "big three", in an exclusive rather than inclusive way. Several of the activities developed to increase R&D efforts into malaria, HIV/AIDS, and TB may also benefit the most neglected diseases. For instance, access to compound libraries or high throughput screening capacity might benefit discovery projects for all neglected diseases, and setting up a joint preclinical research facility would bridge a gap encountered for all non-commercial drug development projects- if clinical trials capacity is built in Eastern Africa for a malaria study (eg by EDCTP or a pharmaceutical company), a subsequent leishmaniasis trial may be run by the same clinical research group, provided disease pattern overlap geographically.

3.3.5 A moral challenge for Europe

Currently, neglected diseases are not a major focus of interest for the EU. Apart from the Framework Program, most of the available funding is for the EDCTP which so far focuses on phase II-III clinical trials for malaria, HIV/AIDS and TB. Recently there is interest for EDCTP to expand into more neglected infectious diseases, although the choice of the disease(s) is pending. This is a very important and laudable commitment, but presupposes that a mechanism exists to develop the medicines to be tested. Such a mechanism is glaringly lacking. To obtain one clinical candidate starting from a characterised lead compound may easily take two to four years and require several millions of euros. Without specific public funding to finance this type of research, and more importantly, a broadly accessible technology platform or facility equipped to do the necessary chemistry, toxicology and lead optimisation research for non-profit drug candidates, there is little hope that new candidate medicines for neglected diseases will reach clinical phases. If the intermediate steps in the development pipeline are not being filled, to go from discovery to clinical studies (gaps 1-2 in Appendix 5), there will be no medicines to test in the clinical trials platform.

There is a moral and ethical imperative to seriously address neglected diseases in developing countries, especially as the EU has existing relations with many of these countries through the ACP agreements.[131] The EU-ACP Joint Parliamentary Assembly Resolution on poverty-related diseases and reproductive health in ACP states acknowledges Europe's responsibility for and commitment to addressing these diseases.[132] The Resolution states that "*poverty diseases and reproductive health must continue to be tackled through joint efforts from the international community*", while pointing out that "*there is an uneven political commitment among donor countries*". The resolution explicitly calls for European action for neglected diseases: *"[The Assembly] Calls on the European Commission to include the most neglected diseases, such as sleeping sickness, Chagas' disease and leishmaniasis, among its priorities and to ensure that effective, appropriate, easy-to-use medicines are developed and placed on the market in the developing countries at an affordable price*".

Politicians will need the courage to strongly promote a paradigm shift in the way that medicines are developed, in order to address the needs of both the European and the global community. It is not enough to focus only on the needs of Europe, wealthy countries can no longer escape the need to stabilize and develop the global economy, and need to redress the imbalance of resources and access to wealth. Furthermore, diseases and health needs are globalizing, and ignoring these problems is more than just shortsightedness - it may also prove to be a gross strategic error.

4. Conclusion

Developing countries carry an enormous burden of (neglected) disease, yet lack the infrastructure and the human and financial resources to develop new medicines for these neglected diseases. This capacity does exist in Europe and other developed countries. Through public sector support for basic and in particular appropriate translational research, product development and operational research through innovative mechanisms such as public-private-partnerships (that act to bridge the gap between industry and the public sector) or public-responsibility oriented initiatives, relatively small investments could have a dramatic impact. Innovative R&D aimed at radically new products and solutions for neglected tropical diseases, or adaptive R&D designed to make better use of existing medicines, vaccines, diagnostics, and technology platforms, should be supported.

Specific recommendations:

- **Mobilise and sustain adequate funding** for neglected diseases. To ensure minimal impact, committed funding of **several hundreds of million euros** over a number of years must be freed to support the execution of a needs-based priority R&D agenda for neglected diseases;
- **Encourage translatable research** using the "3T" approach "Therapeutics, Technology and Transfer" to transform the results of basic research into useful technologies for medical applications, adapted to the needs of neglected patients and connected to programmatic interventions;
- **Set up adequate incentives for collaborative research**, **based on shared value** including appropriate training, funding, and specific career incentives based on a reassessment of the way merit is evaluated in public research;
- **Mobilise the pharmaceutical/diagnostics industry by a mix of incentives and obligations** to contribute to the development of needed medical interventions and commit to donate or provide sustained access to medical interventions, **based on shared value;**
- **Engage the innovators** from emerging economies, biotechnology, along with pharmaceutical/diagnostic companies, SMEs, PDPs and academic institutions through shared (societal and economic) value;
- **Monitor the performance** of PDPs, integrated academic platforms and pharmaceutical companies (including those in emerging economies) for public accountability for resources spent;

- **Expand the activities of PDPs and integrated academic platforms** to include product development for medicines, vaccines, diagnostics, drug resistance platforms and control strategies for these diseases along with strengthening health systems of affected countries. Support integrated academic platforms, where product development and operational research is directly done by academic innovators for neglected diseases;
- **Strongly encourage the expansion of the activities of the European and Developing Countries Clinical Trial Partnership (EDCTP)** to include several of the most neglected diseases as well as other phases of clinical development (phase I, phase IV), (and connect this to the efforts of the pharmaceutical industry-driven TransCelerate)[133];
- Create a **centre for preclinical research** to bridge the continual gap of developing medicines and vaccines into clinical candidates for neglected diseases. This is a pool of resources available for preclinical research which should complement the activities of the EDCTP;
- Investigate the possibility for **centralized technology platforms for adaptive R&D** (adapting current and new medicines, vaccines and diagnostics to tropical countries, fixed dose combination, pediatric formulations, etc). This includes assessing medicines availability, stability, pricing dosing, using appropriate platforms and databases. (This should complement activities of existing organizations and should be a mandate for the newly formed non-profit TransCelerate).

Given the enormity of the needs of patients, with literally millions of people dying due to the lack of safe, effective and easy-to-use drugs, real innovation lies in utilizing current knowledge and ongoing technological progress to design, promote and implement treatment options for those in need. Innovative medical research should refer not to the means but to the ends, and the primary criterion should be the impact of R&D efforts on the life and health of neglected patients. The role of the European Community is crucial in this respect, and policy makers are encouraged to follow this global view of their mandate and responsibility.

References

[1] Chirac, P. and E. Torreele, Global framework on essential health R&D. Lancet, 2006. 367(9522): p. 1560-1.

[2] MSF, D.a., Medical Innovations for Neglected Patients. 2013.

[3] WHO, Accelerating work to overcome the global impact of neglected tropical diseases. A roadmap for implementation. 2012.

[4] Adams, J., K. Gurney, and D. Pendlebury, Neglected Tropical Diseases. Thomson Reuters Global Research Report, 2012.

[5] WHO TDR Diseases and Topics. 2012 [cited 2012 1 Oct 2012]; Available from: http://www.who.int/tdr/diseases-topics/en/.

[6] Access to Medicines Index. [cited; Available from: www.accesstomedicineindex.org.

[7] Policy, C.f.S.i.P. A Review of Pharmaceutical Company Contributions. 2004 [cited 2012 1 Nov 2012]; Available from: http://www.hudson.org/files/publications/AdelmanNorrisPharmCoReview.pdf.

[8] MSF, A.t.E.M.C. and W.G. Drugs for Neglected Diseases, Fatal Imbalance: the crisis in research and development in drugs for neglected diseases. 2001.

[9] Sabin Vaccine Institute. [cited; Available from: www.sabin.org.

[10] Drugs for Neglected Diseases initiative. [cited; Available from: www.dndi.org.

[11] Foundation for Innovative New Diagnostics. [cited; Available from: www.find.org.

[12] Program for Appropriate Technology in Health. [cited; Available from: www.path.org.

[13] Consortium, B. BuruliVac Consortium. [cited 2012 1 Oct 2012]; Available from: http://www.burulivac.eu/.

[14] SCORE. Schistosomiasis Consortium for Operational Research and Evaluation. 2012 [cited 2012 1 Nov 2012]; Available from: http://score.uga.edu/.

[15] Program, E.C.F. EC Research in Neglected Infectious Diseases. 2012 [cited 2012 1 Oct 2012]; Available from: http://ec.europa.eu/research/health/infectious-diseases/neglected-diseases/index_en.html.

[16] Louet, S., Public-private partnerships boost research on neglected diseases. Nat Biotechnol, 2003. 21(11): p. 1254-5.

[17] Schachter, B., Partnering with the professor. Nat Biotechnol. 30(10): p. 944-52.

[18] EU. European convention. [cited 2012 1 Oct 2012]; Available from: european-convention.eu.int/docs/Treaty/cv00797.en03.pdf.

[19] London Declaration for NTDs. [cited 2012 7 Oct 2012]; Available from: http://www.unitingtocombatntds.org/endorsements.

[20] DSW and P. Cures, Saving Lives and Creating Impact: EU investment in poverty-related neglected diseases. 2012.

[21] WHO. Neglected Tropical Diseases. 2012 [cited 2012 1 Aug 2012]; Available from: http://www.who.int/neglected_diseases/diseases/en/.

[22] DNDi. DNDi Treatments. 2012 [cited 2012 1 Sept 2012]; Available from: http://www.dndi.org/index.php/overview-treatments.html?ids=3.

[23] DNDi, Businss plan. 2003.

[24] Guerin, P.J., et al., Malaria: current status of control, diagnosis, treatment, and a proposed agenda for research and development. Lancet Infect Dis, 2002. 2(9): p. 564-73.

[25] Guerin, P.J., et al., Visceral leishmaniasis: current status of control, diagnosis, and treatment, and a proposed research and development agenda. Lancet Infect Dis, 2002. 2(8): p. 494-501.

[26] Hotez, P.J., et al., Rescuing the bottom billion through control of neglected tropical diseases. Lancet, 2009. 373(9674): p. 1570-5.

[27] Hotez, P.J., Mass drug administration and integrated control for the world's high-prevalence neglected tropical diseases. Clin Pharmacol Ther, 2009. 85(6): p. 659-64.

[28] Pullan, R. and S. Brooker, The health impact of polyparasitism in humans: are we under-estimating the burden of parasitic diseases? Parasitology, 2008. 135(7): p. 783-94.

[29] Hotez, P.J. and B. Pecoul, "Manifesto" for advancing the control and elimination of neglected tropical diseases. PLoS Negl Trop Dis. 4(5): p. e718.

[30] Hotez, P., Enlarging the "Audacious Goal": elimination of the world's high prevalence neglected tropical diseases. Vaccine. 29 Suppl 4: p. D104-10.

[31] MSF treatment experience: Rapid Expansion, Emerging Challenges. [cited; Available from: www.accessmed-msf.org/documents/BKKconferencebriefingdocument.pdf.

[32] Umezawa, E.S., et al., Chagas' disease. Lancet, 2002. 359(9306): p. 627.

[33] BIO Ventures Global Health. [cited 2012 1 Nov 212]; Available from: www.bvgh.org.

[34] BVGH, Developing new drugs and vaccines for neglected diseases of the poor: The product developer landscape. 2012.

[35] Dracunculiasis. [cited 2012 23 Nov 2012]; Available from: http://www.who.int/dracunculiasis/en/.

[36] DNDi, et al., Research and Innovation for Neglected Diseases. Key Recommendations from product development partnerships (for inclusion in Horizon 2020). 2012.

[37] What does it mean to be neglected. 2012 [cited; Available from: http://hugin.info/143316/R/1620469/517714.pdf.

[38] Rochon, P.A., et al., Relation between randomized controlled trials published in leading general medical journals and the global burden of disease. CMAJ, 2004. 170(11): p. 1673-7.

[39] Charting research: opportunities for collaborative research on poverty-related and neglected infectious diseases. 2012 [cited; Available from: http://www.edctp.org/Announcement.403+M5688d77058d.0.html.

[40] WHO List of Essential Medicines. [cited 2012; Available from: http://www.who.int/medicines/publications/essentialmedicines/en/.

[41] Alvar, J., et al., Leishmaniasis worldwide and global estimates of its incidence. PLoS One. 7(5): p. e35671.

[42] WHO. World Health Organization. [cited 2012 1 Aug 2012]; Available from: www.who.int.

[43] Desjeux, P., The increase in risk factors for leishmaniasis worldwide. Trans R Soc Trop Med Hyg, 2001. 95(3): p. 239-43.

[44] MSF, HIV/ visceral leishmaniasis co-infection in east africa. 2011.

[45] Deniau, M., et al., The biological diagnosis of leishmaniasis in HIV-infected patients. Ann Trop Med Parasitol, 2003. 97 Suppl 1: p. 115-33.

[46] Russo, R., et al., Visceral leishmaniasis in those infected with HIV: clinical aspects and other opportunistic infections. Ann Trop Med Parasitol, 2003. 97 Suppl 1: p. 99-105.

[47] Zijlstra, E.E., et al., Post-kala-azar dermal leishmaniasis. Lancet Infect Dis, 2003. 3(2): p. 87-98.

[48] [cited; Available from: www.dndi.org.

[49] Sundar, S., et al., Comparison of short-course multidrug treatment with standard therapy for visceral leishmaniasis in India: an open-label, non-inferiority, randomised controlled trial. Lancet. 377(9764): p. 477-86.

[50] Croft, S.L. and P. Olliaro, Leishmaniasis chemotherapy--challenges and opportunities. Clin Microbiol Infect. 17(10): p. 1478-83.

[51] Musa, A., et al., Sodium stibogluconate (SSG) & paromomycin combination compared to SSG for visceral leishmaniasis in East Africa: a randomised controlled trial. PLoS Negl Trop Dis. 6(6): p. e1674.

[52] Cunningham, J., et al., A Global Comparative Evaluation of Commercial Immunochromatographic Rapid Diagnostic Tests for Visceral Leishmaniasis. Clin Infect Dis. 55(10): p. 1312-1319.

[53] Sundar, S. and M. Rai, Advances in the treatment of leishmaniasis. Curr Opin Infect Dis, 2002. 15(6): p. 593-8.

[54] Croft, S.L. and G.H. Coombs, Leishmaniasis--current chemotherapy and recent advances in the search for novel drugs. Trends Parasitol, 2003. 19(11): p. 502-8.

[55] Thakur, C.P., et al., Comparison of three treatment regimens with liposomal amphotericin B (AmBisome®) for visceral leishmaniasis in India: a randomized dose-finding study. Trans R Soc Trop Med Hyg, 1996. 90(3): p. 319-22.

[56] Dorlo, T.P., et al., Miltefosine: a review of its pharmacology and therapeutic efficacy in the treatment of leishmaniasis. J Antimicrob Chemother. 67(11): p. 2576-97.

[57] Jha, T.K., et al., Randomised controlled trial of aminosidine (paromomycin) v sodium stibogluconate for treating visceral leishmaniasis in North Bihar, India. BMJ, 1998. 316(7139): p. 1200-5.

[58] Thakur, C.P., et al., Treatment of visceral leishmaniasis with injectable paromomycin (aminosidine). An open-label randomized phase-II clinical study. Trans R Soc Trop Med Hyg, 2000. 94(4): p. 432-3.

[59] Thakur, C.P., et al., A prospective randomized, comparative, open-label trial of the safety and efficacy of paromomycin (aminosidine) plus sodium stibogluconate versus sodium stibogluconate alone for the treatment of visceral leishmaniasis. Trans R Soc Trop Med Hyg, 2000. 94(4): p. 429-31.

[60] Seaman, J., et al., Epidemic visceral leishmaniasis in Sudan: a randomized trial of aminosidine plus sodium stibogluconate versus sodium stibogluconate alone. J Infect Dis, 1993. 168(3): p. 715-20.

[61] IDRI. Leishmaniasis vaccine R&D programs. 2013 [cited 2012 25 Dec 2012]; Available from: www.idri.org/leishmaniasis.php.

[62] Vanlerberghe, V., et al., Determinants of bednet ownership and use in visceral leishmaniasis-endemic areas of the Indian subcontinent. Trop Med Int Health. 15(1): p. 60-7

[63] Coler, R.N., et al., Leish-111f, a recombinant polyprotein vaccine that protects against visceral Leishmaniasis by elicitation of CD4+ T cells. Infect Immun, 2007. 75(9): p. 4648-54.

[64] Duthie, M.S., et al., The development and clinical evaluation of second-generation leishmaniasis vaccines. Vaccine. 30(2): p. 134-41.

[65] White, N.J. and P.L. Olliaro, Strategies for the prevention of antimalarial drug resistance: rationale for combination chemotherapy for malaria. Parasitol Today, 1996. 12(10): p. 399-401.

[66] Wyllie, S., et al., The anti-trypanosome drug fexinidazole shows potential for treating visceral leishmaniasis. Sci Transl Med. 4(119): p. 119re1.

[67] Vaish, M., et al., Evaluation of rK28 antigen for serodiagnosis of visceral Leishmaniasis in India. Clin Microbiol Infect. 18(1): p. 81-5.

[68] Cruz, I., et al., Leishmania/HIV co-infections in the second decade. Indian J Med Res, 2006. 123(3): p. 357-88.

[69] Kaladrug-R drug consortium. [cited 2013 8 January 2013]; Available from: http://www.leishrisk.net/leishrisk/Default.aspx?Menu=MenuMain&MIID=35&WPID=41&L=E.

[70] Clancey, J.K., et al., Mycobacterial skin ulcers in Uganda. Lancet, 1961. 2(7209): p. 951-4.

[71] WHO, Buruli ulcer, Fact Sheet Fact sheet N°199, Aug 2012. 2012 [cited; Available from: http://www.who.int/mediacentre/factsheets/fs199/en/index.html.

[72] Etuaful S et al. Efficacy of the combination rifampin-streptomycin in preventing growth of *Mycobacterium ulcerans* in early lesions of Buruli ulcer in humans. *Antimicrob Agents Chemother*, 2005, 49: 3182–3186.

[73] Nienhuis WA et al. Antimicrobial treatment for early, limited *Mycobacterium ulcerans* infection - a randomised controlled trial. *Lancet*, 2010, 375: 664–672.

[74] Walsh, D.S., F. Portaels, and W.M. Meyers, Buruli ulcer: Advances in understanding Mycobacterium ulcerans infection. Dermatol Clin. 29(1): p. 1-8.

[75]Yamoussoukro Declaration.[cited 2012; Available from: http://www.who.int/buruli/yamoussoukro_declaration/en/index.html.

[76] WHO, Resolution WHA 57.1 Surveillance and control of Mycobacterium ulcerans disease (Buruli ulcer), in Fifty-seventh World Health Assembly, Geneva. Resolutions and decisions. 2004.

[77] Williamson, H.R., et al., Detection of Mycobacterium ulcerans in the environment predicts prevalence of Buruli ulcer in Benin. PLoS Negl Trop Dis. 6(1): p. e1506.

[78] Epidemiology of Mycobacterium ulcerans infection (Buruli ulcer) at Kinyara, Uganda. Trans R Soc Trop Med Hyg, 1971. 65(6): p. 763-75.

[79] Marion, E., et al., Seasonal and regional dynamics of M. ulcerans transmission in environmental context: deciphering the role of water bugs as hosts and vectors. PLoS Negl Trop Dis. 4(7): p. e731.

[80] Fyfe, J.A., et al., A major role for mammals in the ecology of Mycobacterium ulcerans. PLoS Negl Trop Dis. 4(8): p. e791.

[81] Quek, T.Y., et al., Risk factors for Mycobacterium ulcerans infection, southeastern Australia. Emerg Infect Dis, 2007. 13(11): p. 1661-6.

[82] George, K.M., et al., Partial purification and characterization of biological effects of a lipid toxin produced by Mycobacterium ulcerans. Infect Immun, 1998. 66(2): p. 587-93.

[83] Herbinger, K.H., et al., Comparative study of the sensitivity of different diagnostic methods for the laboratory diagnosis of Buruli ulcer disease. Clin Infect Dis, 2009. 48(8): p. 1055-64.

[84] Nienhuis, W.A., et al., Antimicrobial treatment for early, limited Mycobacterium ulcerans infection: a randomised controlled trial. Lancet. 375(9715): p. 664-72.

[85] WHO, Provisional guidance on the role of specific antibiotics in the management of Mycobacterium ulcerans disease (Buruli ulcer). 2004: Geneva, Switzerland.

[86] O'Brien, D.P., et al., Successful outcomes with oral fluoroquinolones combined with rifampicin in the treatment of Mycobacterium ulcerans: an observational cohort study. PLoS Negl Trop Dis. 6(1): p. e1473.

[87] WHO. Buruli Ulcer fact sheet. 2013 [cited 2013 1 Jan 2013]; Available from: www.who.int/buruli/en.

[88] Lustigman, S., et al., A research agenda for helminth diseases of humans: the problem of helminthiases. PLoS Negl Trop Dis. 6(4): p. e1582.

[89] WHO. WHO Factsheet Schistosomiasis. 2012 [cited 2012 Aug 2012]; Available from: http://www.who.int/topics/schistosomiasis/en/.

[90] Fenwick, A., D. Rollinson, and V. Southgate, Implementation of human schistosomiasis control: Challenges and prospects. Adv Parasitol, 2006. 61: p. 567-622.

[91] Prichard, R.K., et al., A research agenda for helminth diseases of humans: intervention for control and elimination. PLoS Negl Trop Dis. 6(4): p. e1549.

[92] McCarthy, J.S., et al., A research agenda for helminth diseases of humans: diagnostics for control and elimination programmes. PLoS Negl Trop Dis. 6(4): p. e1601.

[93] Taylor, M., Global trends in schistosomiasis control. Bull World Health Organ, 2008. 86(10): p. 738.

[94] The Schitosomiasis Control Initiative. 2012 [cited; Available from: http://www3.imperial.ac.uk/schisto.

[95] Stothard, J.R., et al., Control of schistosomiasis in sub-Saharan Africa: progress made, new opportunities and remaining challenges. Parasitology, 2009. 136(13): p. 1665-75.

[96] Humphries, D., et al., The promise and pitfalls of mass drug administration to control intestinal helminth infections. Curr Opin Infect Dis. 25(5): p. 584-9.

[97] Toure, S., et al., Two-year impact of single praziquantel treatment on infection in the national control programme on schistosomiasis in Burkina Faso. Bull World Health Organ, 2008. 86(10): p. 780-7, A.

[98] Tallo, V.L., et al., Is mass treatment the appropriate schistosomiasis elimination strategy? Bull World Health Organ, 2008. 86(10): p. 765-71.

[99] Fenwick, A. and L. Savioli, Schistosomiasis elimination. Lancet Infect Dis. 11(5): p. 346; author reply 346-7.

[100] Doenhoff, M.J., et al., Praziquantel: its use in control of schistosomiasis in sub-Saharan Africa and current research needs. Parasitology, 2009. 136(13): p. 1825-35.

[101] Garcia, H.H., et al., Strategies for the elimination of taeniasis/cysticercosis. J Neurol Sci, 2007. 262(1-2): p. 153-7.

[102] Da'dara, A.A., et al., DNA-based vaccines protect against zoonotic schistosomiasis in water buffalo. Vaccine, 2008. 26(29-30): p. 3617-25.

[103] Utzinger, J., et al., From innovation to application: social-ecological context, diagnostics, drugs and integrated control of schistosomiasis. Acta Trop. 120 Suppl 1: p. S121-37.

[104] Porter, M. and M. Kramer, Creating Shared Value. Harvard Business Review, 2011: p. 62-77.

[105] FSG, Competing by Saving Lives: How Pharmaceutical and Medical Device Companies Create Shared Value in Global Health. 2012.

[106] ISDB Declaration on therapeutic advance in the use of medicine. [cited 2012 1 Nov 2012]; Available from: http://www.icf.uab.es/informacion/boletines/ISDB/ISDB.pdf.

[107] Besteman, J.J.a.K., euSEND. 2009.

[108] International Trachoma Initiative. [cited; Available from: trachoma.org.

[109] Cures, P. G Finder. [cited 2012 1 Sept 2012]; Available from: http://g-finder.policycures.org/gfinder_report/.

[110] Financial Times-Remedies for drug development. 2011 [cited 2012; Available from: http://www.ft.com/cms/s/0/36e4f5a4-b2fb-11e0-86b8-00144feabdc0.html#axzz2BwsGnG2s.

[111] TranscelerateTransCelerate. 2012 [cited; Available from: www.centerwatch.com/news-online/article/3925/10-pharmas-unite-to-accelerate-development-of-new-medicines%22.

[112] Hot medicines project. 2012 [cited; Available from: www.tpharma.com.

[113] Loop-mediated isothermal amplification technology towards point of care diagnostics. 2012 [cited 2012 1 Oct 2012]; Available from: http://www.finddiagnostics.org/resource-centre/scientific-articles/12_njiru.html.

[114] Costs of developing a drug. [cited; Available from: http://en.wikipedia.org/wiki/Drug_development.

[115] Riggs, T.L., Research and development costs for drugs. The Lancet, 2004.

[116] TBAlliance, The economics of TB drug development. 2001.

[117] Mundi, M., Bulletin of Medicus Mundi Switzerland No. 92, April 2004. 2004.

[118] Ziemba, E., Public-private partnerships for neglected diseases: oportunities to address pharmaceutical gaps for neglected diseases. Background paper for Priority Medicines for Europe and the World. 2004.

[119] Final report of the Commission on Macroeconomics and Health. [cited; Available from: www.cmhealth.org.

[120] EC Framework Program 2012 [cited; Available from: http://ec.europa.eu/research/health/infectious-diseases/neglected-diseases/index_en.html.

[121] Innovative Medicines Initiative. [cited 2012; Available from: http://www.imi.europa.eu/.

[122] US Department of Health and Human Services. [cited; Available from: www.hhs.gov/.

[123] Pecoul, B., et al., Access to essential drugs in poor countries: a lost battle? JAMA, 1999. 281(4): p. 361-7.

[124] Wirth, D., A harvest not yet reaped. DNDi working paper 2001.

[125] See Public Library of Science PLOS. [cited; Available from: www.plos.org.

[126] GSK Clinical Trial Register. [cited 2012; Available from: http://www.gsk-clinicalstudyregister.com/.

[127] Ford, N. and E. Torreele, Neglected diseases of global importance. JAMA, 2001. 286(23): p. 2943-4.

[128] Morel, C.M., Reaching maturity - 25 years of the TDR. Parasitol Today, 2000. 16(12): p. 522-8.

[129] The Global Fund to fight AIDS, Tuberculosis and Malaria. [cited; Available from: www.theglobalfund.org.

[130] The END Fund. [cited; Available from: endfund.org.

[131] Resolution ACP-EU 3640/04/fin of the ACP-EU Joint Parliamentary Assembly.

[132] EU ACP Joint Parliamentary Assembly Resolution on poverty related diseases and reproductive health. 2004 [cited 2012 5 Aug 2012]; Available from: http://www.europarl.europa.eu/intcoop/acp/60_07/pdf/resolution02_en.pdf.

[133] TransCelerate Biopharma Inc. http://transceleratebiopharmainc.com

Annexes

Annex 6.9.1: An update on the priority agenda for Human African Trypanosomiasis (HAT)

HAT was covered extensively in the background chapter for neglected tropical diseases in the Priority Medicines Report of the WHO published in 2004. We give a short update on the status of HAT priority setting. There have been significant steps taken recently in medicine development, which has strengthened both clinical case management, however the mortality remains immense.

Human African trypanosomiasis (HAT, also known as sleeping sickness) is a life-threatening disease caused by parasites transmitted by infected tsetse flies. There are two forms of HAT-caused by *Trypanosoma brucei gambiense* and *T. b. rhodesiense*, with different geographical distribution. *Gambiense* HAT is primarily a human disease in West and Central Africa while *rhodesiense* parasites infect both humans and animals and thus have a large animal reservoir in East Africa.

Patients presenting with early stage disease have non-specific symptoms such as fever and weakness. Without diagnosis and treatment, they go on to develop stage 2 HAT, when the parasite crosses the blood brain barrier. This occurs weeks to years after initial infection. At this point the patient develops neurological and psychiatric symptoms such as confusion, lethargy and convulsions.

The priority for HAT research for the past 10 years was to find a safe and effective therapy for stage II disease to replace the toxic drug melarsoprol. Simplified stage 2 treatment combining seven days eflornithine (two infusions/day) and 10 days oral nifurtimox proved successful for *gambiense* HAT and this combination therapy was added to the WHO list of essential medicines in 2009 [10, 40]. The WHO secured a donation of nifurtimox through an agreement with Bayer to match the donation of eflornithine by Sanofi-Aventis and created a kit to facilitate the distribution and administration of this cumbersome therapy. [134] Unfortunately to treat the second stage of *rhodesiense* HAT, melarsoprol remains the only drug available. Figure A shows the current status of available tools for HAT (Source: Julien Potet, MSF).

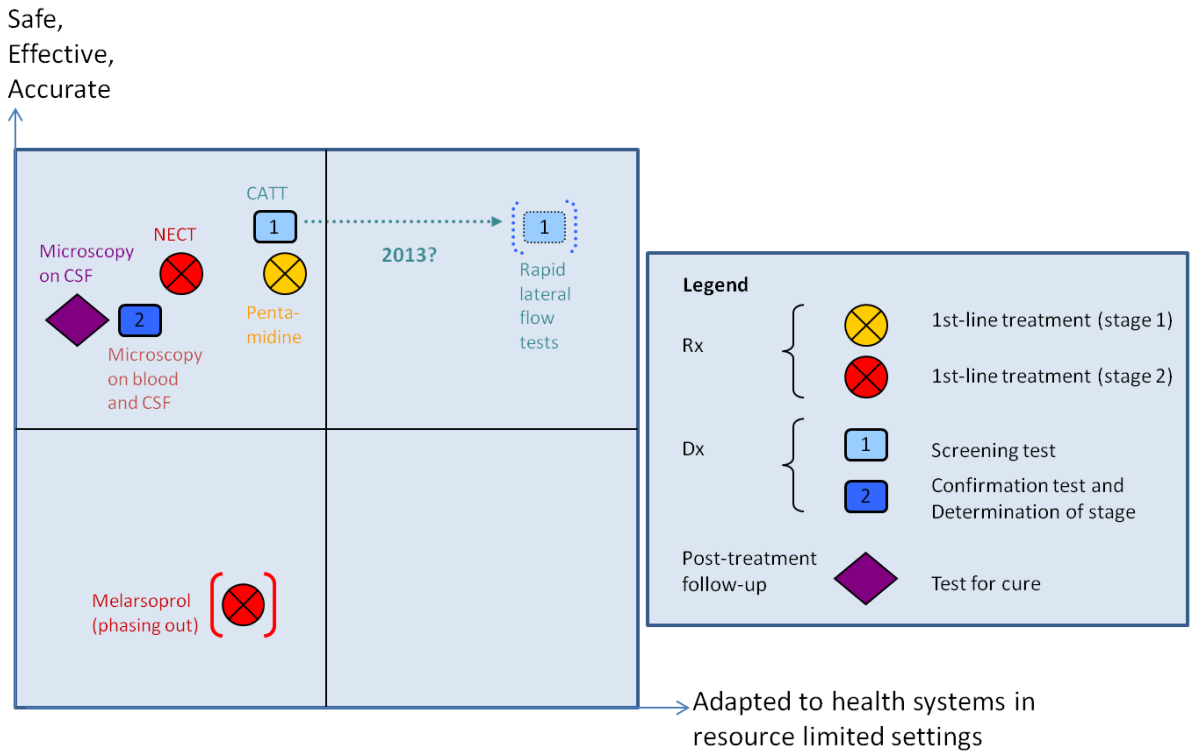
Current priorities:

- Today there is clearly a need for the development of an easy to administer, safe and oral drug for stage II HAT. Recently one oral compound, a nitroimidazole called **fexinidazole**, started phase II/III clinical trials with the HAT platform for clinical trials run by DND*i*. This compound was dropped from drug development by Hoechst in the 1980's and recently rediscovered as a potential new treatment for HAT[135] and is also interesting for the leishmaniasis (see section 2.1).
- New drugs are in development including the **oxaboroles** which have progressed through HAT lead optimization to pre-clinical phase I trials which are currently in recruitment.[10]
- To identify new drugs the use of **medium- to high-throughput screening assays** to model crossing of the blood-brain-barrier, and allow screening and lead optimisation based on the capacity to cross the blood-brain-barrier are currently being used.
- In addition to new treatments, sensitive and **easy-to-use diagnostic tests** are also essential for the control of HAT.[136] New markers need to be identified to accurately detect HAT in blood, or preferably even in saliva or urine, including stage determination (but without invasive lumbar puncture). Two prototype rapid

screening tests are currently under evaluation, and fluorescent microscopy is being investigated.[33]

- Today, there are no surrogate markers to assess disease progression or cure in HAT. Analysis of the cerebrospinal fluid (CSF) collected via lumbar puncture to detect the presence of parasites and/or measure the white blood cell count is the only method for stage determination and treatment efficacy. An accurate and preferably non-invasive tool to **measure treatment efficacy** is essential.

Figure A:
Products available for HAT. A model is shown here to show the tools available and their efficacy and adaptedness to health systems in resource-limited settings.



(Source : Julien Potet, Access Campaign, Médecins Sans Frontières).
Diagnostics must be affordable, user friendly, rapid, robust, Equipment free and deliverable to those who need them, and medicines must be affordable, short course, oral, with no cold chain, with minimal monitoring and for outpatient use.

[134] Simarro, P.P., et al., Update on field use of the available drugs for the chemotherapy of human African trypanosomiasis. Parasitology. 139(7): p. 842-6.
[135] Tweats, D., B. Bourdin Trunz, and E. Torreele, Genotoxicity profile of fexinidazole--a drug candidate in clinical development for human African trypanomiasis (sleeping sickness). Mutagenesis. 27(5): p. 523-32.
[136] Matovu, E., et al., Towards Point-of-Care Diagnostic and Staging Tools for Human African Trypanosomiaisis. J Trop Med. 2012: p. 340538.

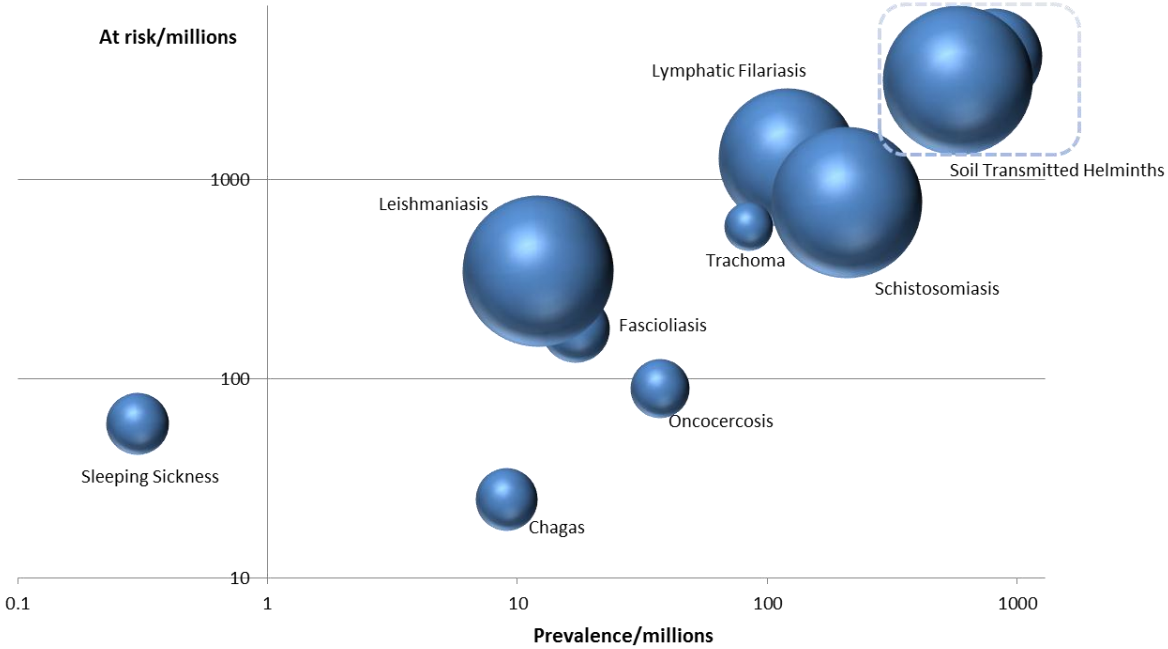
Appendices

Appendix 6.9.1:

(a) The 17 Neglected Tropical Diseases (Neglected Tropical Diseases) are as follows:

Chagas disease (American trypanosomiasis)
Fascioliasis (Distomatosis)
Sleeping sickness (Human African Trypanosomiasis)
Leishmaniasis (all forms)
Lymphatic filariasis (elephantiasis)
Oncocercosis (River blindness , Robles' disease)
Schistosomiasis (Bilharzia, Snail fever)
Soil-transmitted helminths - *Ascaris lumbricoides*
Soil-transmitted helminths - *Trichuris trichiura*
Soil-transmitted helminths - hookworm
Trachoma (Granular conjunctivitis, Egyptian opthalmia)
Buruli ulcer
Cysticercosis / Taeniasis
Dracunculiasis (guinea- worm disease)
Leprosy (Hansen disease)
Dengue / severe dengue
Echinococcosis (Hyatid disease)
Rabies
Yaws

(b) **Prevalence of neglected tropical diseases (logarithmic scale). Bubble size represents DALYs of the different diseases.[4,42,137] For Dracunculiasis, Buruli ulcer, leprosy and cysticercosis, reliable data on population at risk are unavailable.**



Disease	Prevalence/millions	DALYs/'000
Buruli ulcer	0.05	616
Cysticercosis / Taeniasis	50	503
Dracunculiasis (Guinea- worm disease)	0.01	
Leprosy (Hansen's disease)	0.4	6

[137] Murray, C.J., et al., Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 380(9859): p. 2197-223.

Appendix 6.9.2.

Table on the current product development landscape (from BIO Ventures Global health Accessed Oct 2012). Number of active R&D projects in different stages of product development for each disease is shown below. R&D activities for basic research and operational research is unavailable.

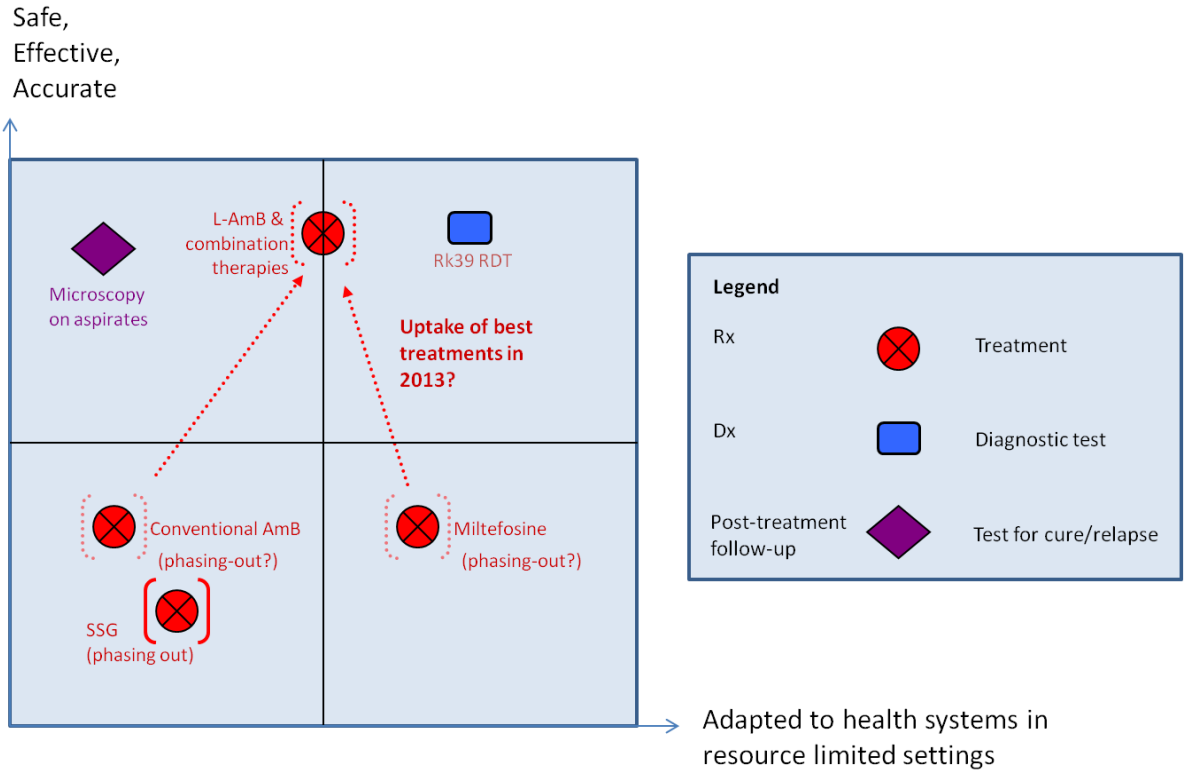
	Drugs			Vaccines			Diagnostics	
Disease	**Discovery**	**Preclinical**	**Clinical**	**Discovery**	**Preclinical**	**Clinical**	**Preclinical**	**Clinical**
Chagas disease	3	3	4	0	1	0	3	1
Fascioliasis	0	0	0	0	0	1	1	1
Human African Trypanosomiasis	4	4	3	0	0	0	7	3
Leishmaniasis (all forms)	8	8	5	1	5	1	7	0
Lymphatic Filariasis	2	1	0	4	0	0	0	0
Oncocercosis	1	2	1	2	0	0	5	2
Schstosomiasis	3	1	1	0	3	2	3	1
STH-Trichuris trichiura	1	0	0	0	0	0	0	0
STH-helminths-hookworm	0	0	0	0	1	1	0	0
Trachoma	0	0	0	1	4	0	1	0
Buruli ulcer	1	1	0	1	1	0	0	1
Dracunculiasis	0	0	0	0	0	0	0	0
Leprosy	0	0	0	0	1	0	2	1
Dengue	8	3	2	0	7	5	1	0

Appendix 6.9.3:

Products available for VL in South Asia. A model is shown here to show the tools available and their efficacy and adaptedness to health systems in resource-limited settings.

(Source : Julien Potet, Access Campaign, Médecins Sans Frontières).

Diagnostics must be affordable, user friendly, rapid, robust, equipment free and deliverable to those who need them, and medicines must be affordable, short course, oral, with no cold chain, with minimal monitoring and for outpatient use. The graph below shows the situation of tools available in South Asia only. The situation in other settings, including East Africa is very different, as tools have different levels of efficacy depending upon geographical regions.



Appendix 6.9.4:

Table showing the 3T approach, which all needs-driven priority R&D in neglected tropical diseases should follow.

Platform	Therapeutics	Technologies	Transfer
Priorities (based on)	Unmet medical needs	Resolving main hurdles to delivery	Improving local access and ability to access health
Examples	Diagnostics for detection Drugs for treatment, Vaccines for prevention	Heat stability for drugs and vaccines, Combination diagnostics, drugs and vaccines, closed system diagnostics	Local infrastructure, Economic and financial stimuli (health improvement programs)
Basic criteria	Safe, effective, cost effective, affordable.	Effective, Cost effective, affecting a wide range of products	Ansuring self sufficiency and sustainable access to health

Appendix 6.9.5 : Donation programs of medicines for neglected tropical diseases by pharmaceutical companies (adapted from the Gates Foundation[138] and WHO)

Donated by	Product	Indication	Donated through
GSK	Albendazole	Lymphatic filariasis and Soil-transmitted helminths	WHO
Gilead	AmBisome	Visceral Leishmaniasis	WHO
Pfizer	Azithromycin	Trachoma	International Trachoma Initiative
Eisai	Diethylcarbamazine (DEC)	Lymphatic Filariasis	WHO
Sanofi-Aventis	Eflornithine	Human African Trypanosomiasis	WHO
Merck and Co	Ivermectin	Lymphatic Filariasis and Oncocercosis	Mectizan Donation Program
Novartis	Multidrug therapy (rifampicin, clofazamine and dapsone) and single-dapsone	Leprosy	WHO
Johnson and Johnson	Mebendazole	Soil-transmitted helminths	several programs
Sanofi Aventis	Melarsoprol	Human African Trypanosomiasis	WHO
Bayer	Nifurtimox	Human African Trypanosomiasis and Chagas disease	WHO
Sanofi Aventis	Pentamidine	Human African Trypanosomiasis	WHO
Merck KGaA	Praziquantel	Schistosomiasis	WHO
Bayer	Suramin	Human African Trypanosomiasis	WHO
Novartis	Triclabendazole	Fascioliasis	WHO

[138] The Bill and Melinda Gates Foundation. 2012 [cited 2012 1 Sept 2012]; Available from: www.gatesfoundation.org.

Appendix 6.9.6 : Bridging the gaps in the R&D pipeline: translational research.

The different stages of a typical pharmaceutical R&D pipeline. A schematic view of a typical development pathway, from identification of need in the field or fundamental research, to the development of a drug. This long and costly process is typically quoted as taking 10-12 years. However, a large part of the process can be made more efficient (in terms of cost and time) by identifying the existing gaps and targeting efforts to the necessary area ("making better use of existing knowledge and tools"). In neglected tropical diseases, the **most important gap that** could make a big difference to innovation and the global burden is the transition from fundamental research or identified field need to a candidate drug or vaccine in the predevelopment stage (gap 1). The pre-development phase is scientifically less exciting for some, but is crucial to confirm the validity of the chosen development candidate, and if needed, to optimise it (i.e. assuring absence of toxicity, choosing a formulation, assuring ease of production, etc). Unless there is strong commercial interest, few candidates are taken through this phase (gap 2). Even clinically developed drugs sometimes do not reach their target population (gap 3), because they are too expensive, or too difficult to use in the field, or because production is not secured.