

Research and Development for Neglected Diseases

Lessons Learned and
Remaining Challenges

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I ntroduction

In recent years, the global public healthcare community has increasingly turned its attention toward the problem of so-called “neglected” diseases – i.e., those disproportionately affecting primarily poor populations in low-income developing countries. International public health authorities have advocated that increased disease control programs, as well as new therapeutic tools are needed to adequately address this problem.

Most of diseases that disproportionately affect low-income countries can be treated or prevented with easily available existing agents, such as medicines from the WHO’s Essential Drugs List. Meanwhile, these diseases continue imposing important burden on health of millions of people affected, proving that the biggest challenge that remains is getting the interventions to the people who need them. Any considerations regarding the need for novel interventions should therefore be made within this specific context. Otherwise, they may lead to unnecessary resource waste and create expectations that cannot be met.

The objective of this paper is to identify and describe the challenges faced by the research community in the fight against diseases affecting primarily poor populations, as well as the vast array of on-going efforts to develop and deliver new medicines for these populations. In so doing our aim is to help identify critical gaps that would require tailored policies and initiatives from all public health stakeholders.

This paper addresses the following questions:

- Why is the health of some populations neglected?
- Which health needs are neglected?
- Why and what new medicines are needed?
- Are new drugs on their way?
- Is the level of financing sufficient to sustain the current R&D efforts?
- What are the critical gaps in the R&D process for neglected diseases?

SUCCESSFUL INITIATIVES HAVE INCREASED OUR EXPERIENCE AND UNDERSTANDING OF NEGLECTED DISEASES CONTROL...

LESSONS LEARNED

- ⇒ Important health needs of poor populations are neglected despite the availability of safe, effective and inexpensive medical tools that if applied properly, could rid these populations of their excessive health burden.
- ⇒ Successful disease control programs for several tropical diseases have been established thanks to the sustained commitment of various stakeholders, including pharmaceutical companies. These initiatives have largely improved health outcomes and the economic situation of millions of poor people, and have paved the road toward potential elimination of these diseases.
- ⇒ For a small number of diseases affecting poor populations, new medicines are needed to address shortcomings of existing treatments, such as safety, efficacy, appropriate dosing, length of treatment, as well as the on-going problem of growing drug resistance.
- ⇒ Important new initiatives have been established recently to address the existing therapeutic needs for neglected diseases through concerted multi-stakeholder efforts. Pharmaceutical companies have been actively participating in these endeavours, contributing significant resources and expertise and making significant new investments that focus exclusively on the health problems of poor populations.

...BUT CRITICAL GAPS REMAIN AND NEED TO BE ADDRESSED BY POLICY MAKERS TO ACCELERATE RESEARCH EFFORTS

REMAINING CHALLENGES

- ⇒ Despite certain progress achieved in funding research and development for new medicines for neglected diseases, with notable contributions from philanthropic foundations and pharmaceutical companies, more financial resources need to be mobilized in a sustainable way to create a strong and sustainable pipeline of drug candidates, a key condition for disease control and eradication.
- ⇒ With tremendous advances in science and technology, a joint effort of the global research community is needed to translate the accumulated basic scientific information into the applicable knowledge that could help identify new disease targets and novel compounds for neglected diseases.
- ⇒ Substantial additional research is needed to gather detailed epidemiological information for several neglected diseases, and to develop new methods and tools that would help evaluate potential new compounds as to their safety and efficacy at an early stage of development. Concerted efforts need to be made to streamline the development of new drugs in order to reduce the overall cost of R&D for neglected diseases.
- ⇒ Important efforts are required to accelerate capacity building in developing countries to facilitate late stage clinical trials, swift product registration and post-approval evaluation of medicines to identify best ways of applying new medicines to neglected diseases.
- ⇒ The global public health community needs to make sure that the new medicines that will be developed for neglected diseases will actually be delivered to patients in need, and the experience of successful disease control programs should be used as an example of how this can be achieved. This will require mobilisation of additional resources to support effective deployment of new agents.

Chapter I

The Challenging Healthcare Environment of Neglected Populations

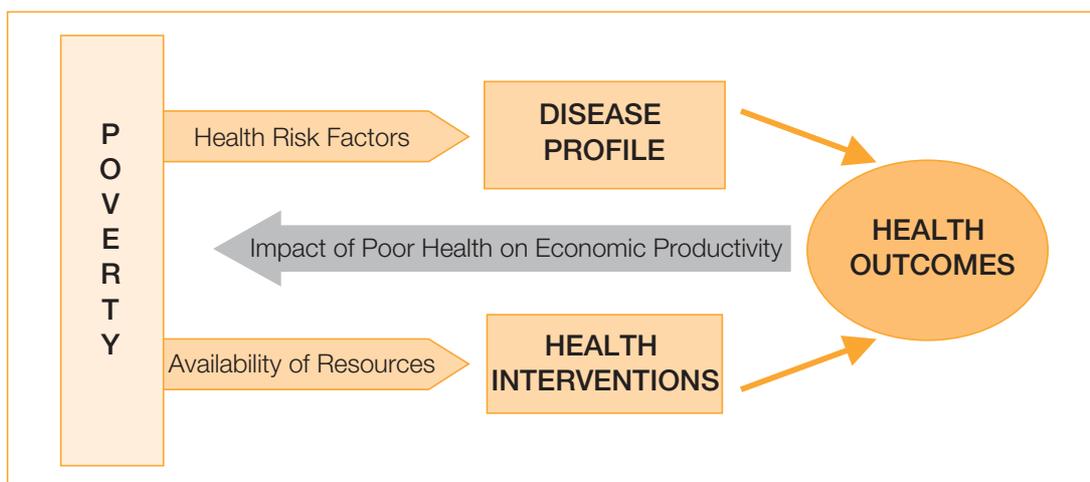
Poverty as a Major Health Determinant

In the world's poorest countries¹, the disease burden attributable to infectious diseases, maternal and perinatal conditions, and nutritional deficiencies represents roughly 60 percent of their entire disease burden. This is almost three times as much as in other developing countries, while in developed countries the combined burden of these diseases and conditions represents only a tiny fraction of their disease burden.²

The link between poverty and health has been extensively studied and analyzed^{3, 4, 5}, and the scope of this paper makes it impossible to describe the magnitude of interacting factors that determine this relation. In the most general terms, the impact of poverty on health outcomes can be presented through two broad channels of transmission: health risk factors influencing disease profile and availability of resources determining health interventions (Figure 1).

Poverty remains a key determinant of the health status of people living in developing countries.

FIGURE 1. POVERTY – HEALTH VICIOUS CIRCLE



A closer analysis of the excessive morbidity found in least developed countries shows that the bulk of the burden of disease is determined by the prevalence of poverty. Poverty is at the source of major health risks, such as insufficient and improper nutrition, poor sanitation and hygiene, toxic indoor smoke and extremely limited access to health education, all of which determine almost 45 percent of disease burden in least developed countries⁶. Such health risks are direct-

ly responsible for the majority of infectious diseases, maternal and perinatal conditions and nutritional deficiencies. Thus, poverty has a direct and powerful impact on the disease profile, which in turn highly influences health outcomes of the populations concerned.

Certainly, under 'normal' circumstances – i.e. with a functioning health system, the disease profile is radically different thanks to various health interventions, including health education and prevention, provision of necessary treatment and care, developed healthcare infrastructure, etc. However, the prevalence of poverty significantly decreases this possibility, as the availability of financial⁴, physical⁷ and human resources^{8,9,10} needed to establish such well-functioning healthcare systems is highly constrained. Also, the continuing political instability in many poor countries together with the lack of safety compounded by ongoing military conflicts,^{11, 12} and often questionable government prioritization¹³ - all these factors create conditions which are unfavorable for the establishment of healthcare systems that could adequately address the pressing health needs of the populations concerned.

Lastly, it has been widely documented^{14, 15, 16} that poor health outcomes, which are largely determined by poverty, actually contribute to further deterioration in the financial status of the populations concerned, thus creating a specific 'vicious circle'. It is believed that adequate investment in health of poorest populations is prerequisite to economic development of these least developed countries.^{3, 5, 17}

Neglected Populations and Neglected Successes

HIV/AIDS, malaria and tuberculosis have attracted substantial political and media attention over the last few years. The World Health Organization,¹⁸ the UN Millennium Development Goals,¹⁹ and a plethora of various initiatives²⁰ have focused on these three diseases that account for roughly 10 percent of global deaths, and almost 18 percent of the disease burden in least developed countries.² However, almost by default, a large group of diseases has been confined to the "other diseases" category by policy makers, receiving much less political attention and financial support.

These numerous "other diseases" include the viral, bacterial, parasitic and fungal infections of the tropics, together with acute respiratory infections and diarrhoeal diseases of children.²¹ Diseases most often referred to as "neglected" are those rife in tropics and affecting the most disadvantaged populations – i.e. Chagas disease, African trypanosomiasis, onchocerciasis, leishmaniasis, schistosomiasis, leprosy, lymphatic filariasis, Dengue fever, Guinea worm, or blinding trachoma. These diseases lead to severe disfigurement and long-standing disability and present a particular social and economic burden for the populations concerned.^{22, 23}

Medicines exist

Given that the policy debate around the issue of "neglected diseases" often focuses on the need for new products, it is important to highlight that many of these diseases can be treated with existing cost-effective therapies. For some diseases these therapies have led to successful control and elimination programs.²⁴ Nevertheless, a large number of the world's poorest people continue to bear a heavy but clearly avoidable health burden.

Table 1 lists diseases that predominantly affect developing countries and for which simple and inexpensive medicines exist. Childhood diseases, diarrheas and malaria represent roughly 15 percent of the burden of disease of high-mortality developing countries.² Most of these deaths are child deaths (under-five mortality) – around 3.4 million children die annually of these three diseases, which represent 35 percent of all under-five mortality occurring annually. It is estimated that 88 percent of child diarrheas, 91 percent of malaria and up to 100 percent of childhood

Millions of deaths could be avoided today if the existing, low-cost interventions were applied to the people in need.

diseases such as measles and tetanus can be prevented among children using existing treatments such as those listed in Table 1.²⁵ In absolute numbers, this represents 3 million child lives that could be prevented each year with existing tools.

Meanwhile, for many diseases that are often referred to as neglected (i.e., endemic in tropical zones), successful control and elimination programs have been established. Examples of such successful programs (“neglected successes”?) are briefly described in Table 2 on the next page.

TABLE 1. EXAMPLES OF DISEASES FOR WHICH EFFECTIVE MEDICINES EXIST

Disease Current	Disease Status	Existing Treatment
Childhood diseases	1.12 million children die each year ²	Effective, low cost vaccines exist for all major childhood diseases, including <i>pertussis</i> , <i>polio</i> , <i>diphtheria</i> , <i>measles</i> , and <i>tetanus</i>
Diarrhoeal diseases	1.8 million deaths result from diarrhoea each year ²	Oral rehydration therapy (ORT) , once considered <i>the most important medical advance in this century</i> ²⁶ , can prevent about 90% of child deaths from diarrhoeal dehydration at the cost of 10 cents per treatment. ²⁷
Malaria	1.3 million deaths result from malaria each year ²	Effective prevention and treatment tools exist , which if applied properly, could lead to elimination of malaria. ^{28, 29, 30}
Schistosomiasis	200 million people are affected globally, of which 85 percent in Africa ²²	Schistosomiasis can be treated with praziquantel at the cost of 30 cents per child, per year, including delivery costs. ²²
Vitamin A deficiency	140 million children at risk of blindness 500,000 children blinded each year and half of them die within a year ³¹	Vitamin A is low cost and can be easily administered as a food supplement. ³²

TABLE 2. SUCCESSFUL DISEASES CONTROL PROGRAMS

Disease/Program	Pharmaceutical Industry's Contributions ³³	Achievements
<p>Onchocerciasis <i>Mectizan Donation Program</i></p>	<p>Merck donates Mectizan® (ivermectin) to all who need it and as long as necessary. To date, the company has donated over one billion tablets, with more than 300 million cumulative treatments distributed.</p>	<p>Over 25 years, the Onchocerciasis Control Program has protected approximately 11 million children against onchocerciasis – and around 1 million people have been saved from blindness. Some 250,000 km² of previously infested areas has been resettled and is now being cultivated.³⁴</p>
<p>Leprosy <i>Global Alliance to Eliminate Leprosy</i></p>	<p>Novartis donates \$35 million in multi-drug treatment for leprosy, and works with WHO and other partners to improve delivery and care.</p>	<p>Over 13 million people have been cured of leprosy and the prevalence rate has dropped by over 90 percent since 1985, and the number of countries considered endemic has been reduced from 122 to 15.²²</p>
<p>Lymphatic Filariasis <i>Global Alliance to Eliminate Lymphatic Filariasis</i></p>	<p>GlaxoSmithKline donates albendazole, and Merck donates ivermectin (Mectizan®). To date 250 million treatments of albendazole and 20 million treatments of Mectizan® have been donated.</p>	<p>By the end of 2003 almost 80 million people in 37 countries had received treatment for lymphatic filariasis. This is a marked increase compared to the year 2000 when only 3 million people at risk were covered.³⁵</p>
<p>Guinea Worm <i>Guinea Worm Eradication Program</i></p>	<p>Johnson&Johnson has donated enough medical supplies such as Tylenol®, forceps and gauze, to treat more than 3,000 villages in the endemic countries.</p>	<p>The number of people suffering from guinea worm has dropped from 10-15 million at the start of the 1980s to 32,000 in 2003. Globally, over 150 countries and territories have been certified free of parasite transmission.²²</p>
<p>Blinding Trachoma <i>International Trachoma Initiative</i></p>	<p>Pfizer has donated more than \$130 million in product donations (Zithromax®) and health educational grants.</p>	<p>Over 5 million people have been rid of active trachoma infection through antibiotic treatment and more than 70,000 cases of blindness have been prevented through surgeries.³⁶</p>
<p>African trypanosomiasis <i>WHO Program to Eliminate Sleeping Sickness</i></p>	<p>Aventis has supplied some 1.2 million drug ampoules of three medicines used in treatment, as well as financially supported the work of mobile medical teams and research activities of WHO on a new formulation of a drug for African trypanosomiasis.</p>	<p>During the past three years, more than 60,000 people have benefited from this initiative, receiving medical counsel, screening and treatment.</p>

Key Success Factors of Control Programs

Focusing on creating surveillance and information systems, improved drug distribution management and logistics, local communities' participation in the provision of healthcare, and enhancing human resource capacities – all these programs represent a valuable contribution to the promotion of the principles of primary healthcare.³⁷ The success of these control programs result from various factors²¹:

- ⇒ Sustained national government and donor commitment,
- ⇒ Clear objectives (e.g. time frame),
- ⇒ Use of targeted effective interventions,
- ⇒ Sustained drug donation programs,
- ⇒ Monitoring and evaluation systems,
- ⇒ Embedded program-oriented and strategic research, and
- ⇒ Relative biological stability of targeted diseases.

Disease control initiatives would have not been possible without the contributions and the drive of individual pharmaceutical companies. Not only did these companies discover and develop the medicines used in treatment of these diseases, but their donations of these medicines, often for as long as it will be needed, has led to successful health interventions in the poorest settings.

All these programs, if sustained and expanded, have a real potential to eliminate the targeted diseases as major public health problems.^{23, 36, 38} These programs have not only saved millions of people from life-long suffering, but also have contributed to important socio-economic gains. Cost-benefit analysis of several existing programs provides significant evidence of their cost-effectiveness.^{16, 39, 40} Protecting vulnerable populations from diseases such as onchocerciasis, lymphatic filariasis, or malaria not only contributes to improved economic productivity but actually has a phenomenal effect on the way entire local communities operate and work.

Lastly, such disease control programs have shown capacity to radically improve healthcare interventions in resource-poor settings through the application of innovative methods and practical solutions.²³ Novel solutions that have brought success for one disease are being used for others. For example, the concept of community-directed distribution pioneered in the control of onchocerciasis has been adopted in other programs.⁴¹ Because neglected diseases often overlap geographically, there is a strong rationale for integrating various interventions by using the existing infrastructure, distribution systems and human resources. This is the case with integration of drug distribution for onchocerciasis, lymphatic filariasis and trachoma, and Vitamin A distribution.²¹ Integrated control programs encompassing several diseases and drawing upon the success of existing ones could benefit from important synergies and also facilitate advocacy for needed political and financial support to successfully address remaining neglected diseases.²³

Existing disease control initiatives offer successful solutions for tropical diseases.

Chapter II

Assessing the Need for New Drugs for Neglected Diseases

New Medicines Are Needed but What Should Our Research Priorities Be?

Diseases affecting poor populations are not strictly equal in need or similar in their profile. By way of illustration, good pharmaceutical products are available for schistosomiasis, lymphatic filariasis and onchocerciasis. As a result, the trends in these diseases appear to be stable or falling in response to successful control programs. In addition, as the threat of resistance requires constant research efforts, specific R&D efforts are underway through numerous collaborations between the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Disease (“TDR”) and pharmaceutical companies (see Table 5, page 20).

By contrast, existing products for African trypanosomiasis, Chagas disease and leishmaniasis (caused by kinetoplastid protozoa) are mostly parenteral in use, need multiple administrations, have serious side effects (including some that can be fatal) and are increasingly becoming compromised by acquired resistance.⁴²

Therefore, while the number of R&D projects for “neglected” diseases has been growing in recent years, new medicines to fight such diseases are needed.

Why new medicines are lacking has been widely debated and various reasons have been identified. Certainly, the key factor lies in the fact that these diseases are at the cross-section of major challenges: because of their specific localization and entrenchment in the world’s poorest regions, these diseases do not represent any direct threat for developed countries populations. This removes most incentives from both public and private sector research in developed countries which is the source of pharmaceutical innovation. This has resulted in a significant gap in the development of new drugs for these indications, as they have failed to attract sufficient attention from research facilities.^{43,44}

Another factor in creating a disincentive for R&D efforts is the fact that, for most of diseases often listed as “neglected”, treatments exist and have been available for many years. In some cases this has led to successful eradication campaigns. The theoretical quest for an “ideal” drug (very safe, very effective, very stable, and inexpensive) faces the realities of scientific and industrial research that lead to better products after decades of incrementally innovative steps, a luxury difficult to afford when addressing diseases affecting the poorest populations.

Although often cited as the main culprits, the relatively low number of R&D programs to address neglected diseases in pharmaceutical companies’ research facilities can also be explained by the similarly low interest of public sector and academic research in this field. Clearly, the lack of prospect of potential return on investment is a major impediment to attract the significant investments required for drug R&D. However, upstream research is also lacking. Important epidemiological data about prevalence and incidence of the neglected diseases is missing, as a result of

African trypanosomiasis, leishmaniasis and Chagas disease are in dire need of new therapeutic tools.

insufficient public health research into problems of least developed countries.⁴⁵ Leading medical journals also provide evidence of the relatively low academic interest in such diseases of poverty (the number of articles published is in the single percentage digits for most international peer-reviewed journals).⁴⁶ This composition of the editorial boards of major tropical medicine journals, only include 5% of members affiliated to countries with a low human development index. This may explain their lack of interest in the subject. Similarly, only 5 percent of the articles in these journals have been exclusively written by authors from least developed countries.⁴⁷

The Need to Prioritize R&D Efforts

Among neglected diseases that have not yet been adequately addressed, *African trypanosomiasis*, *Chagas disease*, *leishmaniasis* and *Dengue fever* have been repeatedly mentioned. Various studies, including a WHO/IFPMA working group, have identified these four diseases as priority for new drugs and vaccines R&D.^{42, 48} The fact that diseases such as African trypanosomiasis and Dengue fever have re-emerged as important health threats should be considered an alert for needed action.^{49, 50}

Table 3 summarizes the major features of diseases regarded as neglected in terms of needed R&D. As can be observed, for most of diseases the major problem lies in different shortcomings

TABLE 3. CURRENT STATUS OF DRUGS FOR NEGLECTED DISEASES

Disease	Existing Medicines	Limitations of Current Medicines	Need for Specific Uses
African trypanosomiasis	Yes	<ul style="list-style-type: none"> • Efficacy and safety • Dosage form (injectable) • Cost • Potential drug resistance 	No
Chagas disease	Yes	<ul style="list-style-type: none"> • Activity only in acute stage of disease • Safety 	No
Leishmaniasis	Yes	<ul style="list-style-type: none"> • Safety • Dosage form (injectable) • Cost • Potential drug resistance 	No
Dengue fever	No	N.A.	HIV co-infection
Malaria	Yes	<ul style="list-style-type: none"> • Compliance • Cost • Partially safe • Drug resistance 	Pregnant women Paediatric formulations
Tuberculosis	Yes	<ul style="list-style-type: none"> • 6-9 month course of treatment • Compliance • Drug resistance 	HIV co-infection

Source: UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Disease (TDR)

of existing treatments such as safety, (partial) efficacy, inappropriate dosage form, and only in one case (Dengue fever) is no effective drug available at all.

The Case of Malaria and TB

Important R&D efforts have recently been initiated to address both malaria and tuberculosis, resulting from increased mobilization of political will and interest which led to the establishment of two public-private partnerships to develop new needed medicines: Medicines for Malaria Venture (“MMV”)⁵¹ and Global Alliance for TB Drug Development (“TB Alliance”).⁵²

Malaria and tuberculosis primarily affect the poorest populations and as such require specific solutions to stimulate additional R&D. These diseases also represent specific challenges linked to the phenomenon of fast-developing resistance to existing treatments,^{53, 54} which requires constant R&D efforts to ensure sustained flow of new medicines. By contrast, the likelihood that drug resistance and insecticide resistance will develop in diseases caused by macroparasites or macrovectors (e.g., leishmaniasis, Chagas disease, African trypanosomiasis) is small in comparison with malaria or tuberculosis.²¹ Another important characteristic of drugs needed for malaria is the fact that the most vulnerable populations are small children and pregnant women⁵⁵ who require medicines with specific formulations (particularly, the need for paediatric formulations) and specific clinical studies.

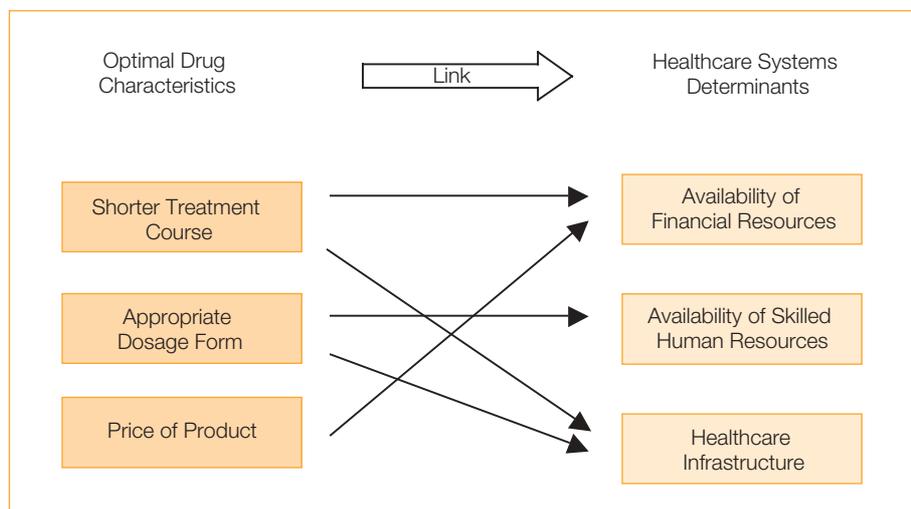
Despite existing R&D efforts, drug resistance fuels a continuous need for new drugs in the fight against TB and malaria.

Key Features of Needed Drugs

Based on the above analysis, it is possible to describe a generic optimal profile of the drugs that are needed to treat the poor in developing countries: the shortest treatment courses at the appropriate dosage form at the lowest price possible (Figure 2). Clearly, any new optimal drug first needs also to be safe, efficient, stable and bioavailable – an obvious set of features not mentioned in Figure 2.

The specificity of the healthcare environment in least developed countries, as described in Chapter I of this paper, imposes important constraints on new drug R&D for neglected diseases. Based on experience with other tropical diseases that are successfully being addressed such as

FIGURE 2. OPTIMAL CHARACTERISTICS OF NEW DRUGS FOR NEGLECTED DISEASES



onchocerciasis, the simplest and least expensive drug that can shorten a treatment course to the minimum is likely to have the biggest (or the only real) impact on health outcomes of patients suffering from any of these diseases. Some drugs, while safe and effective, may require complex and costly manufacturing (e.g., eflornithine), or are derived from costly natural resources (e.g., artemisinin-based antimalarials). Other drugs may be safe, effective and inexpensive but the disease profile requires a long treatment course with close patient monitoring to ensure compliance (e.g., Tuberculosis) – both increase costs and require the presence of scarce skilled medical personnel. Also, dosage form plays a key role in disease control programs – injectable drugs are far less practical than oral ones in resource poor settings, as they require involvement of medical per-

TABLE 4. EXAMPLES OF COST-RELATED LIMITATIONS OF EXISTING DRUGS

Disease	Product Limitations
<p style="text-align: center;">African Trypanosomiasis</p>	<p>For eflornithine – the most potent medicine for African trypanosomiasis -manufacturing process is so costly that no generic company in the world has yet decided to manufacture this drug, despite its originator’s decision (Aventis) to donate the required technology. Also, because the drug is only available in injectable form, it is difficult to apply in the resource-scarce settings where it is needed.</p> <p><i>The provision of the drug is possible thanks to the decision by Aventis to donate the needed quantities of the drug. The company is also collaborating with TDR to develop an oral formulation of eflornithine.</i></p>
<p style="text-align: center;">Malaria</p>	<p>Coartem®, which is currently the only fixed-dose artemisinin-based combination available, despite its excellent properties in terms of efficacy and safety, is also relatively expensive (as compared to very old and very inexpensive products). The latter results from the fact that the drug is derived from a Chinese plant ‘qinghao’ (<i>Artemisia annua</i>), making it much more costly to manufacture than other synthetic antimalarials. Also, Coartem® dosage needs careful explanation to avoid poor compliance and treatment failure.</p> <p><i>The provision of the drug has been secured thanks to the decision of Novartis to offer Coartem® at not-for-profit prices. The company is also investing in training of health workers, to ensure that the drug is used rationally.</i></p>
<p style="text-align: center;">Tuberculosis</p>	<p>Four different antibiotics are needed for treatment of tuberculosis, and the treatment course lasts 6 months. Because it is extremely important to follow the full 6-months course of treatment (otherwise treatment is ineffective and results in relapse of disease and emergence of drug resistance) the Directly Observed Treatment – Short course strategy (“DOTS”) was developed. DOTS requires important involvement of health personnel and healthcare infrastructure, and more than 90 percent of treatment costs are non-drug costs.</p> <p><i>The provision of antibiotics needed in treatment of TB in poorest countries is facilitated through partnerships involving Eli Lilly and Novartis. Both companies offer these medicines at highly discounted prices, and Eli Lilly’s initiative also involves technology transfer agreements to manufacture needed drugs locally in several developing countries</i></p>

sonnel and better healthcare infrastructure. Ensuring that the drug formulation is stable in the demanding climatic conditions of most endemic countries is another important consideration in new drug development. Table 4 below offers a more thorough analysis of these different limitations.

Other features could be added to this generic profile of drugs for neglected diseases in order to make it more disease-specific. For example, for malaria the WHO recommends only drug combinations (artemisinin-based) as first line treatments, because monotherapies tend to be much more susceptible to the development of drug resistance.⁵⁷ Also, safety aspects are of particular concern in development of new antimalarials, given the fact that small children and pregnant women represent the most important risk groups.

It seems that the optimal characteristics of new drugs for neglected diseases, as described above, represent yet another level of complexity for R&D. This is in addition to the existing and very specific R&D environment for these health problems. This covers scarcity of funding, insufficient epidemiological information, lack of healthcare infrastructure and services - as well as the more general challenges of pharmaceutical R&D such as substantial investment required, high risk, and significant time-scale. All these factors will have important implications for the design of R&D processes for neglected diseases and for the distribution of different roles among a very diverse group of stakeholders. To better understand this, it is worth analyzing the current R&D pipeline for the diseases concerned.

The Growing R&D Pipeline for Neglected Diseases

Thanks to the growing awareness and understanding of the necessity to address the health needs of the most neglected populations, the R&D landscape for neglected diseases has seen some major changes over the last few years, resulting in the proliferation of research projects and players. Two of the most striking features of the acceleration of R&D efforts are the growing number of public-private partnerships and the creation of dedicated research centers as part of the pharmaceutical companies' research strategy. Another emerging factor is the greater involvement of developing countries' pharmaceutical private sector in global research efforts to address the specific health needs of their populations.⁵⁸

Important R&D efforts for neglected diseases are underway through a wide array of collaborative initiatives.

The Acceleration of R&D Efforts Through Partnership

Recent years have seen the emergence of a new organizational form of conducting R&D, known as the virtual R&D organization. Virtual R&D originally started in the private sector, as small biotech companies sought to move promising compounds beyond pre-clinical development, but were lacking the expertise and financial means. To address the specific pharmaceutical needs of developing countries, the virtual R&D model is now being used in the context of public-private partnerships (PPPs) for product development.^{59, 60}

Public-private partnerships are based on R&D collaborations of different organizations such as pharmaceutical companies, public research and academic institutes, international organizations, and small-sized specialized companies. PPPs enable the utilization of both the private sector expertise in product R&D and product specification, and the public sector expertise in the diseases and populations of interest and an understanding of the environments in which the products will be tested and used. PPPs also lead to the sharing of resources and existing infrastructure, thus limiting the risk to both private and public sector partners, and limiting the need for unjustifiable capital outlay from the public sector (given the magnitude of related investments and low success rate common to all pharmaceutical R&D endeavors).⁶¹ Product development PPPs aim to ensure that viable projects involving neglected diseases are adequately funded and their progress accelerated.⁶²

TABLE 5. LIST OF INDUSTRY PARTNERS OF TDR (PAST AND PRESENT)⁶³

ACF Beheer	Merck and Co., Inc
Bayer AG	E. Merck Pharma
Biobras-Bioquimica	Novo Nordisk
Ciba Geigy (currently Novartis)	Pasteur-Merieux-Connaught.
Daiichi Pharm	Pharmacia Farmitalia
Eli Lilly	Rhône-Poulenc Rorer Doma (currently Aventis)
Genetic Institutes	Shin Poong
GlaxoSmithKline	Vestar
Hoffmann – La Roche	Wyeth
Iharabras	Wanxing Pharmaceuticals
Janssen Pharmaceutica	Zeneca Pharmaceuticals
Jomaa Pharmaka	Zentaris
Laboratorios Gador	

Public-private R&D collaborations already have a long history. For example, the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (“TDR”), a public international organization, has obtained its most impressive accomplishments in drug R&D for neglected diseases through close collaboration with more than 20 pharmaceutical companies over the last 25 years (Table 5). As a result, 67 disease control tools have been developed (including diagnostics and medicines), of which 38 are in use in international disease control initiatives. 1

The past few years have seen the acceleration of public-private collaboration, with the creation of several disease-focused product development PPPs (Table 6). Because these initiatives are still at an early stage of their development, their achievements can be solely based on the outcomes of intermediate success indicators.⁶⁰ The Medicines for Malaria Venture (MMV) and the Global Alliance for TB Drug Development (TB Alliance) are often referred to as examples of the most promising R&D organizations, which have managed to significantly raise the public profile of partnerships and develop important drug development pipelines for two major diseases previously lacking significant and sustained R&D efforts – malaria and tuberculosis.^{60, 64, 65, 66}

Several new non-profit R&D ventures have been established in recent years to deal exclusively with neglected diseases. Drugs for Neglected Diseases Initiative (DNDi) is following the path of PPPs such as MMV and TB Alliance, focusing on African trypanosomiasis, leishmaniasis and Chagas disease.⁶⁸ Institute for OneWorld Health (IOWH) is another initiative that aims to reformulate existing drugs and develop promising compounds against leishmaniasis, malaria, Chagas disease and diarrhoea.⁶⁹ Finally, Bio Ventures for Global Health (BVGH) is a new non-profit venture that aims to facilitate new R&D programs that would leverage the promise of biotechnologies to meet the health needs of poor populations.⁷⁰

All these PPPs have successfully applied the virtual R&D organization concept, in particular at the drug discovery stage. In particular, MMV and TB Alliance have initiated a new drug discovery approach that seems to be showing strong promise for diseases other than malaria and TB.⁶⁰

TABLE 6. EXAMPLES OF PRODUCT DEVELOPMENT PPPs FOR NEGLECTED DISEASES⁶⁷

Malaria	Medicines for Malaria Venture (MMV) Malaria Vaccine Initiative (MVI) European Malaria Vaccine Initiative (EMVI) Japanese Pharmaceutical, Ministry of Health, WHO Malaria Drug Partnership (JPMW) Lapdap™ Antimalarial Product Development (Lapdap)
Tuberculosis	Global Alliance for TB Drug Development (TB Alliance) Global TB Vaccine Foundation (Aeras) Foundation for Innovative New Diagnostics (FIND)
African trypanosomiasis Leishmaniasis Chagas disease	Drugs for Neglected Diseases Initiative (DNDi) Gates Foundation/University of Carolina Partnership (GFUNC) Infectious Disease Research Institute (IDRI) Institute for One World Health (IOWH)

One recent and notable example of such multi-partner approach comes from MMV where a virtual team consisting of chemists in Nebraska, USA, pharmacokineticists in Melbourne, Australia, and parasitologists in Basel, Switzerland, who were linked to Swiss pharmaceutical company Roche for overall guidance and toxicology expertise, has been working on a synthetic peroxide – a potential revolutionary compound that could replace artemisinin in the treatment of malaria.⁷¹ The drug candidate moved swiftly to pre-clinical development in 2003, and it has been recently announced that it is now entering clinical development that will be conducted in partnership between MMV and Ranbaxy, a pharmaceutical company based in India.⁷²

Table 7 below presents the current distribution of compounds targeting neglected diseases in the global R&D pipeline. As one might expect, in absolute numbers, malaria and tuberculosis have the largest number of compounds in the pipeline. Two thirds and almost half of these compounds are being developed through the MMV and the TB Alliance respectively.^{65, 66} As noted by MMV, *perhaps more important than the total number of projects is the level of breakthrough innovation – MMV now has eight new therapeutic targets filling its research pipeline.*⁶⁵

Another important fact that can be derived from Table 7 is that only a small proportion of compounds in development have reached late stage clinical development (Phase II or III). Among the most promising therapeutic areas is visceral leishmaniasis, with three new products in late-stage development:

- *miltefosine* - developed jointly by TDR and Zentaris AG, and currently undergoing pharmacovigilance tests in India
- *sitamaquine* – developed by GlaxoSmithKline, and currently completing Phase II trials; and
- *pararomycin* – developed jointly by the Institute for One World Health and TDR, and currently at Phase III trials.

Product development public-private partnerships have generated a number of new therapeutic targets.

TABLE 7. CURRENT DRUG R&D PIPELINE FOR NEGLECTED DISEASES

	Discovery & Preclinical Development	Phase I	Phase II	Phase III
African trypanosomiasis	3	1	1	
Chagas disease	5			
Leishmaniasis	3		1	2
Dengue fever*	5	2	1	
Malaria	21	1	3	5
Tuberculosis	18	2	2	

* For Dengue fever, the majority of projects under development are vaccines. For other diseases, vaccines under development are not included in Table 7.

Source: Bio Ventures for Global Health; Pharmaprojects: MMV; GATB; DNDi.

Pharmaceutical companies remain the critical element of successful R&D efforts for neglected diseases and have increased their involvement in this field.

A striking feature of all late stage R&D projects is that they are, in great majority, conducted in close collaboration with major pharmaceutical companies. Four out of five new products to be launched for malaria are developed by global pharmaceutical companies, and two of these projects are sponsored by MMV. This confirms speculations of various observers that this most demanding part of drug R&D cannot be completed without the involvement of these companies. They retain a set of critical capacities, know-how and cross-disciplinary expertise in product development, regulatory processes and manufacturing that cannot be found elsewhere.^{59, 73} By contrast, pharmaceutical companies themselves also seek public partners to finalize late stage clinical trials of products specifically targeting developing countries to ensure completion of the development program.⁷⁴ These observations further illustrate both the actual impact and the need for a strong public-private partnership to undertake R&D efforts in the field of neglected diseases.

The Emergence of Dedicated R&D Centers

Analysis of the R&D pipeline for neglected diseases also draws attention to another important development: in the last five years, several global pharmaceutical companies have established dedicated R&D centers targeting neglected diseases (Table 8).

Created as integral parts of their global R&D organizations, these research facilities have access to the critical resources of their company, including compound libraries, databases, scientists and sophisticated technologies. Certainly, these drug discovery centers enable a focused approach towards some of the neglected diseases, disposing of needed resources and capacities that are uniquely deployed for that purpose. However, they represent only the most visible part of R&D efforts for the diseases concerned. Many more resources and individuals from within companies participate in these efforts, and this is particularly important, as drug candidates identified in these centers reach the development stage.

TABLE 8. NEW RESEARCH AND DISCOVERY FOR NEGLECTED DISEASES

<p>AstraZeneca</p> <p>Bangalore Research Institute</p>	<p>This dedicated research facility, located in Bangalore, India aims to discover novel compounds efficacious in treatment of TB which would shorten the treatment course to less than 4 months. The company has already invested \$40 million and currently 100 scientists work in Bangalore. The institute has completed screening of 5 targets, a novel target has been identified and several compounds are currently being evaluated as potential leads. First drug candidates can be expected in three years.⁷⁵</p>
<p>Novartis</p> <p>Novartis Institute for Tropical Diseases (NITD)</p>	<p>A collaborating project between Novartis and the Government of Singapore, NITD is a \$122 million research institute located in Singapore and employing about 100 scientists. It focuses on research and discovery of novel drugs for Dengue fever and TB – two neglected diseases that have been found complementary to Novartis’ activities. NITD has secured funds for 10 years of operations, and it will collaborate both internally within Novartis (e.g., with Novartis Institute of Genomics) and externally with various organizations and academic institutions (e.g., Singapore Dengue Consortium, or TB Alliance).⁷⁶</p>
<p>GlaxoSmithKline</p> <p>Tres Cantos Centre for Diseases of the Developing World Drug Discovery</p>	<p>This drug discovery Centre located in Madrid, Spain, is a part of GSK’s Diseases of the Developing World (DDW) Initiative. The plant’s facilities, expertise and human resources cover all elements needed in the drug discovery process, from medicinal, computational and structural chemistries to biochemical, whole cell and animal models evaluation. The mission of this research centre is to assess disease targets and identify candidate compounds for further development for malaria and TB. Projects are prioritized primarily on their socio-economic and public health benefit rather than on commercial considerations. As part of its activities the Tres Cantos facility is a principal location for discovery projects within the joint GSK/MMV portfolio of four malaria discovery programs.⁷⁷</p>

While other companies have also specific research activities in the field of neglected diseases within their organization, these dedicated research and discovery facilities will have a significant impact on the future of neglected diseases research in the medium to longer term, as they deal with research and discovery of new potential drug compounds, thus prospectively providing new drug candidates for further development. The latter is particularly important to ensure the strengthening of the overall R&D pipeline for neglected diseases and allow for an on-going flow of novel therapeutics. As the success rate characterizing the drug R&D process is extremely low, particularly in early drug discovery,⁶⁰ only strong and balanced pipelines with an important number of compounds under preclinical development can lead to new drug approvals for neglected diseases.

Lastly, among organizations involved in R&D for neglected diseases that have been under-explored or under-utilized as partners that can contribute to the effort, are small specialized biopharmaceutical companies, which may be an interesting source of new compounds as well as platform technologies.^{78, 79} Recent initiatives such as BIO Ventures for Global Health (www.bvgh.org) illustrate the growing interest of the biotech community in neglected diseases.

The Importance of Intellectual Property Rights to support R&D Initiatives

Intellectual property protection transforms the intangible capital generated in the process of innovation into financial flows indispensable to maintain the innovation continuum. Thus, intellectual property rights promote innovative activity (both in the private and public sectors) for the overall public good and as such are regarded as the heart of the whole system of innovation, with particular, well-documented relevance to pharmaceuticals.^{80, 81, 82}

Although by definition, intellectual property protection plays a primary role in discovery and development of new products targeting established markets (i.e. offering prospects for revenue), IP considerations have also proven relevant in the case of the generally not-for-profit R&D efforts for neglected diseases.

A new, hybrid conception of IP management has emerged with the proliferation of players active in this field, and especially resulting from the increased drive towards a private-public collaboration, as described above. In general, the public sector representatives use IP to define and structure the technology development and distribution relationships to guarantee public health outcomes. For the private sector partner, agreement over access, exploitation and ownership of IP provides the needed clarity, predictability and freedom to operate, all necessary to make investment decisions.⁸³

Thus, IP negotiations have a strategic importance in product development PPPs and major considerations involve the following aspects^{59, 83}:

- ⇒ Ownership of IP generated by the funded research,
- ⇒ Access to background IP needed in the process of R&D and/or manufacturing,
- ⇒ Provisions governing licensing of new technologies
- ⇒ Considerations related to availability of new drugs (in particular with reference to the use of the protected test data)
- ⇒ Provisions for exit strategies of any of the partners.

In terms of access to new products, both individual companies conducting R&D into neglected diseases, and product development PPPs adopt policies that facilitate access and benefit populations affected. Some partnerships that develop drugs for which a more lucrative market exists (e.g. antimalarials for tourists) develop licensable or marketable IP with applications outside of their target field of use, as a source of potential revenue to finance future R&D.⁸³

Intellectual property rights not only stimulate innovation but also have an important role in establishing collaborative R&D ventures for neglected diseases.

Chapter III

R emaining Challenges in the Fight against Neglected Diseases

Financial Challenges

The need for sustained financing mechanisms

The challenging scientific profile of neglected diseases added to the lack of sufficient prospects of return on investment into R&D for neglected diseases are undoubtedly among the key reasons behind the stagnation of private R&D activities in this area. This is compounded by ever escalating R&D costs, currently calculated to be in the range of \$0.5-1 billion per a new 'marketable' drug^{84, 85}. In the special case of neglected diseases, where the opportunity cost of capital can be excluded from cost estimates, as any potential R&D efforts are not-for-profit, the cost of R&D has been estimated at \$200-300 million.^{86, 87} This fact has been widely recognized and has resulted in various recommendations for both extra funding by public sector (including a proposal to create a Global Health Research Fund with disbursements of around \$1.5 billion a year⁴), and additional 'push' and 'pull' incentives for increasing R&D spending by the private sector.^{45, 88}

As described in the preceding chapter, the acceleration of R&D efforts came about primarily thanks to the establishment of several collaborative initiatives between public and private sector players.

This proliferation of R&D players has been made possible thanks to increased funding opportunities through philanthropic institutions, development agencies, multilateral agencies and some governments. For example, the Bill and Melinda Gates Foundation, which was the US largest health-related giver in 2002 spending,⁸⁹ is also the most important financial contributor to product development PPPs, providing strategic resources to both MMV and TB Alliance.

This increase in funding has been paralleled by the growing interest among pharmaceutical companies to actively contribute to addressing health problems of the world's poorest populations. As described in Chapters I and II, pharmaceutical companies have become key partners, and often leaders, of various health initiatives related to neglected diseases.³³ By contributing critical resources, expertise and technology, the pharmaceutical companies are a major pillar of successful drug R&D partnerships.⁶² These contributions represent a very substantial part of the resources available to PPPs, leveraging at least an equivalent amount of the institutional funding of those partnerships. *In some cases, the ratio of company to public sector investment has been greater than 10 to 1.*⁶¹

Overall, the pharmaceutical industry's contributions on R&D efforts for diseases affecting the poorest populations match that of the public sector altogether. This gives a total increase in resources available for neglected diseases of around \$200 million per year since the late 1990s, with the amount possibly rising to around \$400 in the coming five years.⁶¹

Public and private contributions have increased financial resources for neglected diseases...

... but the long-term sustainability of the R&D PPP model urgently requires additional financing.

Future Financing Gap

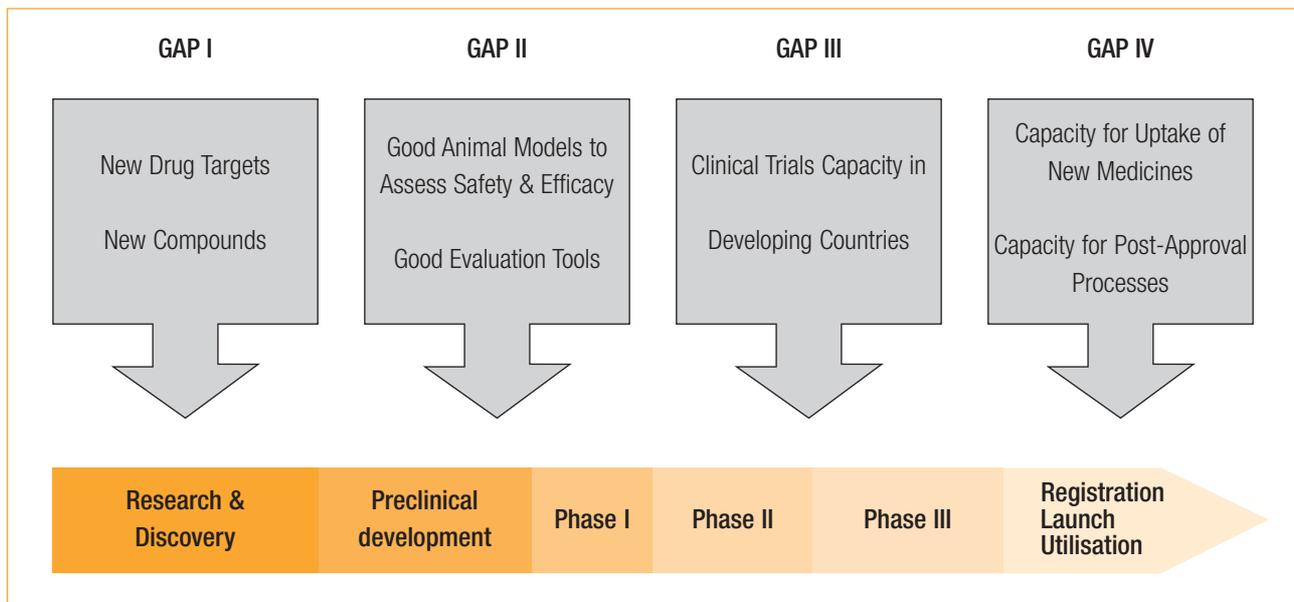
However, when one looks at the financial needs of major PPPs, it becomes apparent that such organizations are faced with a major financing gap. For both MMV and the GATB, cumulative funding pledged to 2007 is \$97 million and 35.75 million respectively. Compared to cumulative required resources for the same period, an important funding shortfall is apparent, amounting to \$83 million and \$255 million for MMV and the TB Alliance respectively.⁹⁰ When it comes to other neglected diseases, the situation is even worse, with DNDi so far unable to mobilize any of the needed funds estimated at \$255 million until 2007.

It seems that despite the generosity of a narrow group of donors, and the growing involvement and goodwill of the pharmaceutical industry, more funds need to be made available within the global public health community, to secure, accelerate and sustain important R&D efforts that are taking place and are showing promises. The long-term cycle and statistical realities of drug R&D are such that if these efforts are to succeed, many more R&D projects will have to be initiated and complex and costly scientific, technological and regulatory challenges will have to be overcome before new therapies actually reach poor populations.

Systemic Challenges in the Quest for New Drugs

As observed in Chapter II, despite the upsurge of R&D activities in the area of neglected diseases, we are still at a very preliminary stage of a concerted R&D effort that could yield needed therapeutic results in the future. Future success in the form of new medicines requires that different elements of the innovation system need to be synchronized, and some apparent 'critical gaps' in the R&D process have to be addressed (Figure 3).

FIGURE 3. CRITICAL GAPS IN DRUG R&D FOR NEGLECTED DISEASES



Such 'critical gaps' primarily result from the specific profile of neglected diseases. Lack of funds to purchase needed medicines and even more importantly lack of interest within the public health sector to develop new agents⁹¹ has led to gradual withdrawal of the private sector from this field of research, leaving some diseases without any new compounds in development, thus **creating**

important knowledge gaps at the level of discovery (Gap I) and preclinical development (Gap II) for these diseases.

Similarly, insufficient or inexistent healthcare infrastructure in developing countries, compounded by little interest of public health researchers in these countries led to a lack of **needed epidemiological data (Gap III)**, thus making it difficult to design and conduct clinical trials among concerned populations **(Gap III)**.

Finally and crucially, the lack of interest among public health policy makers to invest in neglected diseases control has created a disincentive barring the undertaking of costly and lengthy R&D efforts, with a **real threat of developed products being underutilized, if at all (Gap IV)**.

Gap I – Need for new targets and compounds

Because of little interest of the global research community in neglected diseases over the last two decades, research into these diseases has missed out on the substantial advances in drug discovery technology in such areas as molecular and structural biology, medicinal chemistry and robotics.⁹² Despite the accumulation of basic scientific literature on selected neglected diseases,⁹³ including extensive information from various parasite and human bacterial genomes,^{94, 95, 96} little 'practical' knowledge has been generated that could contribute to new drugs development.

On one hand, the publicly funded research in the area of neglected diseases is no substitute for targeted and focused product R&D of the type found in the pharmaceutical industry.⁹⁷ On the other hand, the technology of parasite genome science has outpaced the capacity of the scientific community to assimilate the information, as new scientific domains such as bioinformatics remain underdeveloped in the area of neglected diseases research.⁹⁸

What is missing is 'translational research' – i.e. research that moves an interesting scientific observation to a stage where it justifies significant investment to identify a promising compound, optimize it and develop it into a product for testing and clinical evaluation. In practical terms, this means translating genomic information into robust biochemical assays and the availability of modern drug discovery technologies to generate lead molecules worthy of optimization.⁶¹ It is argued that if latest advances in science (such as pharmacogenomics, proteomics and combinatorial chemistry) and technology (such as high throughput screening) were utilized in drug discovery for neglected diseases, an important number of new biological targets could be identified leading to the generation of interesting new compounds addressing these diseases through novel approaches.⁹⁹ The potential of new science and technologies in drug discovery has already contributed to progress in certain areas, such as malaria (Table 9).

TABLE 9. NEW SCIENCE AND TECHNOLOGY FOR NEGLECTED DISEASES

Several important new leads have been identified for antimalarial drugs resulting from *Plasmodium falciparum* genomic sequence data. In one noted example, researchers determined that the parasite used an enzymatic pathway that is critical for its viability. The pathway is present in bacteria and plants, but absent in humans. A drug targeting this pathway – fosmidomycin - had been developed for an entirely different purpose by a Japanese company in the 1970s, but had never been marketed, as it was ineffective against its original purpose and its potential use against *Plasmodium falciparum* was unknown at that time. Fosmidomycin is now in initial clinical trials for treatment of malaria in Africa and South-East Asia with positive results¹⁰⁰, which significantly improve through combination therapy¹⁰¹.

Some progress has already been achieved, as noted in Chapter II, with the increasing involvement of major pharmaceutical companies, specialized biopharmaceutical companies, establishment of organizations such as the TB Structural Genomics Consortium¹⁰² and efforts in parasite genomics and proteomics funded by the National Institutes of Health (NIH) or the Wellcome Trust¹⁰³. Some of the remaining challenges include the following:

- ⇒ Sophisticated techniques, which would enable to utilize the information available within genomes, such as transfection, microarrays, proteomics, and bioinformatic analysis need to be developed and perfected to benefit from the genomic revolution.
- ⇒ Focused collaboration between specialized organizations that generate drug targets for neglected diseases (e.g., TDR, NIH) and organizations that have sufficient technological capacities and know-how, including chemical compound libraries, to identify innovative lead structures.
- ⇒ Strengthening capacity, understanding of bioinformatics and improving access to sequence data among scientists working on tropical medicine.

Gap II – Better Evaluation of Safety and Efficacy

It has been widely recognized that one of the biggest challenges in modern drug R&D process are the escalating costs of clinical development.^{104, 105} It is believed that such escalating costs are partly due to the use of largely outdated clinical tools to evaluate safety and efficacy of drugs during the clinical development phase.¹⁰⁴

A strategy that could lead to important reduction in development costs should focus on developing new drug evaluation tools and techniques, which would allow assessing safety and efficacy aspects of a drug before hugely expensive and problematic Phase II and III clinical trials are started. Several options for improvement of clinical evaluation process have been suggested, including the following¹⁰⁴:

- ⇒ The employment of proteomic and toxicogenomic approaches to create sensitive and predictive safety assessment techniques
- ⇒ Greater predictive power could be obtained from *in silico* (computer modeling) analyses such as predictive toxicology thanks to advances in bioinformatics
- ⇒ Identification of additional biomarkers (quantitative measures providing informative links between mechanisms of action and clinical effectiveness) and surrogate markers (quantitative measures that can predict effectiveness), for example through emerging techniques of pharmacogenomics
- ⇒ Use the concept of model-based drug development, in which models of drug efficacy are developed from preclinical and available clinical data.

All these proposals refer to the general drug evaluation process and yet need to be successfully employed in “mainstream” research projects. Certainly, these considerations are also applicable to neglected diseases, more specifically as the drug development barriers are even greater in this field. With very few clinical evaluations undertaken on drugs for these diseases over last decades on one hand, and the promises of recent advances in science and technology for new drugs on the other, it seems that there might be important knowledge gaps that need to be filled.

For example, one of the major problems facing research into TB is the uncertainty as to which biomarkers and surrogate markers should be used to assess new drug effectiveness.¹⁰⁶ This is particularly relevant in designing drugs that would pursue a novel mechanism of action, and for many neglected diseases this is critical to overcome current treatment problems.

Also, the role of interaction between drug and clinical researchers on one hand, and patients and physicians on the other is crucial for proper design of new medicines and their clinical development process.⁷⁶ As the neglected diseases in question affect populations in remote areas, with very constrained access to any healthcare facilities, innovative solutions are needed to overcome this problem.

It seems that close collaboration between R&D organizations, academia and regulatory agencies is absolutely necessary to both accelerate development of new drugs for neglected diseases and reduce the cost of development. There is a potential role for regulatory agencies to provide specific incentives targeting neglected diseases which could parallel the existing US FDA's Orphan Products grant program, including tax breaks, development grants, fast-track approval and registration fee waiving.¹⁰⁷ Further options for collaboration should be investigated, as well as the critical research areas to facilitate drug development for neglected diseases should be identified.

Gap III – Clinical Trials Capacity in Developing Countries

Phase II and III clinical trials are probably the most critical elements of the R&D process, as they “make or break” promising compounds. To be conducted, they require reliable clinical trials sites, skilled clinicians, opinion leaders, access to patient pools, etc. Given the resource constraints in developing countries, it is not a surprise that the majority of all trials are conducted in developed countries, and only recently a few major developing countries such as India, Thailand, or China are emerging as potential clinical trial sites.

Neglected diseases may represent a particular challenge in terms of clinical trials, as they affect the most marginalized populations, without access to any (even most basic) healthcare facilities. These populations often have poor literacy, which creates additional difficulties for overcoming important culture barriers and to ensure actual informed consent.¹⁰⁸ A number of regions where neglected diseases are endemic are also ravaged by ongoing military conflicts, which may have a negative impact on the discipline required to conduct valid trials.

In short, clinical trials infrastructure in developing countries where neglected diseases endemic seems very limited and may become an important bottleneck, as the number of compounds in development for these diseases will increase. For example, different R&D projects within the MMV may soon compete with each other not for financial resources, but for clinical trials sites in Africa.¹⁰⁹

Such a situation calls for capacity building initiatives targeting clinical trials. Different stakeholders need to collaborate to develop necessary infrastructure, including appropriate training of clinicians. This is the mandate of the newly established European & Developing Countries Clinical Trials Partnership (EDCTP)¹¹⁰ with a focus on capacity building for HIV/AIDS, malaria and tuberculosis trials. EDCTP needs to establish effective working relationships with existing R&D organizations and also needs to be sufficiently funded to succeed. Without any doubt, an expanded initiative is needed for neglected diseases, so that they do not fall, again, in the “other diseases” category.

Lastly, there is an important issue of regulatory capacities in developing countries that are needed to fully evaluate regulatory submissions. In most countries, local regulatory authorities rely on at least one developed country approval. However developed countries authorities such as the US Food and Drug Administration (FDA) or the European Medicines Evaluation Agency (EMA) will have to apply Northern risk-benefit calculations to their evaluations, which may be inappropriate in the endemic countries. Best example is the rotavirus vaccine withdrawal from the US market in 1999, due to the observed risk of developing intussusception during the post-marketing surveillance.¹¹¹ This risk, while significant according to the US standards (where very few deaths

Concerted action between regulatory authorities and drug companies is needed to develop innovative models for drug assessment and thus increase R&D productivity.

result from diarrhoea), could probably be accepted in high-burden developing countries where 1.8 million children die of diarrhoea every year.

Gap IV – Uptake of New Medicines into Developing Countries Healthcare Systems

Ensuring that adequate efforts are made into developing new medicines for neglected diseases is critical. Equally important is the way in which new drugs are actually going to be used, if at all. As described in Chapter I, there are many examples of existing effective medical tools that have not been adequately utilized, resulting in continued and excessive mortality and morbidity. Malaria is the most recent example, where despite clearly declared policies of global public health authorities, established specialized organizations, such as the Roll Back Malaria initiative, and funds being made available, the most recent and most potent and efficient antimalarials are not being sufficiently utilized.¹¹²

With regard to other neglected diseases, such as African trypanosomiasis or leishmaniasis, the situation is even more complex, as currently there are no global funding and institutional mechanisms in place that could facilitate the uptake of new medicines. In particular, what is also needed is the ability to forecast the future need for treatments, which is essential for designing manufacturing process. Without estimates of demand for new drugs, no company will be willing to invest in a new manufacturing plant or manufacturing process. Such calculations need to be relatively precise and prospective, in order to create necessary capacities for production scale-up. The most recent example of inconsistency in this field is the WHO forecast of demand for artemisinin-based combination treatment (ACT) for malaria which soared 10-fold from one year to another.¹¹³ Given the limited existing manufacturing capacities of ACT, it will be very difficult to meet the forecast need immediately.

Also, because the populations concerned are very difficult to access, there is a great need for concerted action of various stakeholders to trigger needed public health research and capacity building to create appropriate delivery systems and establish well-functioning disease control programs. Important and valuable lessons can be learned from the experience of existing programs, as described in Chapter I, in which pharmaceutical companies have played pivotal roles.

Equally important in introducing new medicines for neglected diseases is the post-approval process of assessing these medicines in real-life conditions, and adapting their usage, formulation and dosing to specific needs and patients' profiles. Recent experience with novel antimalarials illustrates the critical importance of proper infrastructure to monitor drug use in real-life conditions and carry out effectiveness and safety studies after the regulatory approval (Phase IV clinical trials). Capacity building in this key area would be very valuable, so to ensure that, once new drugs are available, the R&D efforts described in this paper have a real impact for patients.

New therapeutic tools from the "bench" will not help if they do not reach patients in the field.

C onclusion

Addressing the health needs of poor populations requires a well-planned systematic and holistic approach of the global public health community. As shown in this paper, **an excessive disease burden continues to ravage the populations in least developed countries, despite the availability of effective medical tools.**

Examples of successful interventions exist for several tropical diseases, where pharmaceutical companies, working with different partners, have managed to implement effective disease control programs using existing medicines. Many of these programs, if sustained, may actually lead to the elimination of diseases previously regarded as neglected.

A small number of diseases prevalent among the poor require increased R&D activities to develop new medicines that would be safer, easier to administer and more effective. Not only should these medicines overcome the shortcomings of existing therapies (better safety profile and appropriate formulations), but they should also be inexpensive – as financial capacities of populations in need are largely limited. Such a high threshold imposes important limitations on the R&D process itself, which has become extremely sophisticated and costly by virtue of advances in science and technology, as well as regulatory requirements it needs to meet.

Under these specific circumstances, **a new wave of initiatives and activities is emerging that focus on new drug discovery and development for neglected diseases.** Pharmaceutical companies play a major role in these endeavors, devoting important resources, invaluable expertise and know-how, and collaborating with different partners to best address remaining challenges. The establishment of several product development public private partnerships is an important step forward that enables collective multi-stakeholder effort to find needed solutions. However, global funding mechanisms will need to be in place to sustain these endeavors.

Nevertheless, **critical gaps remain in the R&D process that impede development of new medicines for neglected diseases.** Involvement of all stakeholders is essential to make sure that financial, scientific and regulatory barriers will not prevail, and that new medicines will be discovered, developed and successfully used by patients in need.

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