

A needs-based pharmaceutical R&D agenda for neglected diseases

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Table of contents

Table of contents	2
Executive summary	4
Introduction	6
I. Characterising a disease as neglected: appraisal of criteria for priority-setting in an R&D agenda	8
1- What is a neglected disease?	8
2- How many people suffer and die from the disease? The traditional epidemiological indicators (incidence/prevalence, DALYs, etc.)	8
3- What are the health tools available (drugs, vaccines, diagnostic tests) for the disease? Are they safe, effective, affordable and appropriate for the conditions in the field? ----	10
Number of New Chemical Entities (NCEs).	10
Are they safe?	10
Are they effective?	10
Are they affordable?	11
Are they appropriate?	11
Do appropriate diagnostic tests exist?	11
4- What efforts are currently being made; what can be expected in the future? -----	11
Drugs under clinical development	11
Number of scientific publications	12
5- Conclusion : The priorities and opportunities must be identified in each unique situation-----	12
II. Needs-based assessment to guide priority-setting	15
1- Human African Trypanosomiasis	15
1-1- Size and nature of the disease burden	16
1-2- Control strategy/ why does disease burden persist?	17
1-3- What can be learned from current/past pharmaceutical interventions?	17
1-4- Current product pipeline	19
1-5- Gaps between current and potential research: a priority R&D agenda for HAT20	
1) Making better use of existing drugs:	21
2) Developing new drugs for HAT:	22
3) Other R&D opportunities with possible significant impact:	23
1-6 Conclusion for HAT	23
Summary of priority research agenda for HAT	24
2- Visceral leishmaniasis	25
2-1- Size and nature of the disease burden	26
2-2- Control strategy/ why does the disease burden persist?	27
2-3- What can be learned from current/past pharmaceutical interventions?	27

2-4- Current product pipeline-----	28
2-5- Gaps between current and potential research: a priority R&D agenda for VL	29
1) <i>Making better use of existing drugs:</i> -----	29
2) <i>Developing new drugs for VL</i> -----	30
3) <i>Other R&D opportunities with possible significant impact:</i> -----	31
2-6 Conclusion for Leishmaniasis-----	32
Summary of priority research agenda for VL -----	33
3- Buruli ulcer -----	34
3-1- Size and nature of the disease burden-----	35
3-2- Control strategy/ why does disease burden persist?-----	35
3-3- What can be learned from current/past pharmaceutical interventions?-----	36
3-4- Current product pipeline-----	37
3-5- Gaps between current and potential research -----	37
3-6- Conclusion for Buruli ulcer -----	38
Summary of priority research agenda for Buruli ulcer -----	39
III. Mobilizing needs-driven innovation to address priorities for neglected diseases -----	40
1- From a few diseases to a more comprehensive agenda-----	40
2- Adequate funding for neglected diseases-----	41
3- Involving the private and public sector : capacity building for R&D into neglected diseases-----	43
3-1- The limitations of the market-driven R&D framework-----	43
<i>The TRIPS model / Intellectual Property protection</i> -----	43
<i>A response to market failure in rich countries: The Orphan Drug model</i>	44
3-2- Towards a system ensuring commitment to R&D into neglected diseases ---	45
<i>A needs-driven priority R&D agenda</i> -----	45
<i>Public responsibility</i> -----	45
<i>A crucial role for public research</i> -----	46
<i>A role for the private sector</i> -----	47
<i>Bridging the gaps in the R&D pipeline: translational research is the key</i>	47
4- Upgrading the international effort to treat neglected diseases -----	48
<i>More than the “big three”</i> -----	48
<i>A moral challenge for Europe</i> -----	49
5- Conclusion -----	50
Specific Recommendations: -----	50
Acknowledgements-----	52
List of Annexes-----	52
References -----	55

Executive summary

Neglected diseases, such as sleeping sickness, Buruli ulcer or Chagas disease, cause enormous suffering and death, mostly in the poorest regions of the world. A huge medical need exists for appropriate treatments, vaccines and diagnostics for such diseases, a need that has been largely ignored by the pharmaceutical industry. Scientific advances into the nature of the diseases are not being translated into medical advances for patients. The Research and Development (R&D) pipeline remains virtually empty. Several reasons account for this neglect: market failure, because poor people cannot pay for expensive medicines in a system where R&D priorities are guided solely by market prospects, and failure of public policy to correct this perverse logic of “no money – no cure”. Today, less than 10% of global health research spending is devoted to the health needs of 90% of the world’s population.

Redressing this fatal imbalance requires public responsibility and commitment to:

1. Develop a global needs-driven essential health R&D agenda, and
2. Create appropriate mechanisms and incentives to allow the effective implementation of such an agenda

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 a different set of criteria to help identify and characterise neglect, which should guide priority setting in building an essential health R&D agenda. A detailed and patient-focused needs analysis must be done for each disease, and matched to scientific and technological opportunities, taking into account the specific circumstances of life of neglected patients.

Using the examples of sleeping sickness, visceral leishmaniasis and Buruli ulcer, a needs-based (as opposed to market-based) approach to drafting an essential health research agenda is proposed. For each disease, we provide a concrete list of high-priority research projects to be initiated, with tangible results for patients possible rapidly. The examples also illustrate that much can already be achieved by supporting innovative R&D to make better use of existing drugs and compounds, even though radically new solutions remain crucially 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.

The third and final section of the paper suggests opportunities to mobilise needs-driven innovation for neglected diseases. The EU, while supporting some excellent initiatives, lags behind in addressing the growing problem of neglected diseases. By a careful and needs-based allocation of limited 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 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 concerted and sustained response to the problem of neglected diseases is more than just a moral imperative- it also contributes to growing economic and social stability in traditionally neglected or exploited regions of the world, and will ultimately benefit Europe as well.

In addition to appropriate funding, governments must set up incentives and obligations to encourage neglected disease research in both the public and private sectors. Such a programme could include obligatory in-kind contribution from the pharmaceutical industry, preferential funding of translational research projects, and developing of alternative, needs-based models for the setting of research priorities.

Concrete 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 translational research** to transform the results of basic research into useful medical applications, adapted to the needs of neglected patients;
- **Expand the activities of the EDCTP** to include other neglected diseases as well as other phases of clinical development (phase I, phase IV);
- Create a **Centre for preclinical research** to bridge the continual gap of developing drug leads into clinical candidates for neglected diseases. This centre should complement the activities of the EDCTP;
- **Set up adequate incentives for public research**, including appropriate training, funding, and specific career incentives based on a reassessment of the way merit is evaluated in public research;
- **Mobilise the pharmaceutical industry by a mix of incentives and obligations** to contribute to the development of needed drugs;
- Investigate the possibility of an international R&D treaty for neglected diseases, to **establish an alternative model for drug development** based on a needs-driven priority R&D agenda and public responsibility, outside of the market- and profit-driven framework.

Introduction

Of the 1 393 new medicines marketed between 1975 and 1999, less than 1% are destined to treat tropical diseases, which are responsible for almost 10% of the global disease burden¹. Such diseases predominantly affect 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. Many millions of people, mostly in the poorer regions of the world, are suffering and dying from neglected disease.

New medicines are needed to replace the old and toxic treatments for sleeping sickness and leishmaniasis. No treatments exist to cure Dengue fever or Buruli ulcer. The few medicines that are safe and effective in treating neglected diseases are often not well adapted to conditions in the developing world – for example requiring complex storage or administration, or being very expensive – while drug resistance continues to reduce the arsenal. Substantial advances in molecular biology, pathophysiology and genetics have been made, including the genome sequencing of parasites causing leishmaniasis and sleeping sickness. But these results are not processed into new products directed at the needs of patients.

Most drug development is carried out by the pharmaceutical industry, who thus set drug R&D agendas. For these companies, developing a new dosage form of an expensive, already existing and high-selling drug prescribed in high-income countries is more rewarding than research into new drugs for Buruli ulcer or African sleeping sickness, diseases that lack a high-paying market. Public policies have largely contributed to this unethical discrepancy by focusing on the need for performance and competition in a knowledge-based market economy².

The diseases often referred to as “neglected” are diseases that are 1- common ; 2- are fatal or disabling ; and 3- for which no suitable treatments exist. They affect populations that are large but have little or no purchasing power.

The market incentives to treat neglected diseases may be low, but the terrible human suffering they cause is highly mobilising. Over 200 million people are estimated to be at risk for visceral leishmaniasis, over 100 million at risk for Chagas disease, and over 60 million people are at risk of developing sleeping sickness in Africa.

These people mostly have a very limited access to health care, and the illness is often made worse by chronic malnutrition or co-morbidity, such as 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 can be eliminated. Building on the impressive advances in science and technology, simple but innovative solutions should be developed that may have a dramatic impact on the lives of many people

Leaving areas of the world underdeveloped for financial reasons is not acceptable. To ignore the diseases of these regions would be to sanction an unacceptable double standard: where governments in rich countries fund expensive research into “orphan diseases”, which by definition affect only a small number of individuals, we cannot justify turning a blind eye to the suffering of the millions of patients who die of neglected diseases around the world. A

targeted international response to this unacceptable situation is urgently needed, and Europe, as a global leader, must respond to the crisis. Europe must provide a solid vision for the future of humanity, as acknowledged in the preamble to the new European Constitution³.

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. The recent SARS epidemic and the outbreaks in the West of multidrug resistant tuberculosis^{4,5} are warning signs of a growing threat.

The issue of neglected diseases has worsened in recent decades. During the first part of the twentieth century, tropical diseases were investigated by some European countries because of their impact on colonial expansion. Diseases such as onchocerciasis, trypanosomiasis or malaria were obstacles for the productivity of labour in mining camps and other areas of natural resource exploitation. This led to the study of tropical medicine (through public institutes) and later to drug development by the European drug industry (mostly UK, France, Belgium and Germany). As European involvement in tropical countries decreased, so too has the interest in these diseases.

A prerequisite for starting to address the research gap in neglected diseases is the need for an adequately funded, needs-driven priority R&D agenda for these diseases. Today, pharmaceutical R&D efforts are largely technology- and market-driven, pursued by a dominantly western scientific community and industry, focusing on the (market) needs in the North. There have been a number of very interesting attempts made to develop alternative priority setting models⁶ by considering, among other factors, the experience and needs of patients. However, this analysis needs to be developed much further, and, more importantly, appropriate mechanisms and incentives need to be set up to allow the actual implementation of the priority essential R&D agenda.

The current commitment of the EU into developing a response to this global imbalance is limited (see annex 1 for a detailed description of the current situation). The total budget for research into neglected diseases is limited to around ten million euros at most, woefully inadequate to address any aspect of the problem. Section III discussed the realities of the finances required, and some possible structures to be envisaged to ensure sustained support.

A needs-driven priority R&D agenda for neglected diseases requires a thorough knowledge of the relevant diseases and the treatment needs, but also of the populations affected, their living conditions and socio-economic environment, and their access to health care infrastructure and services. The research questions to be addressed should take into account the need for appropriate treatments, which are safe, effective and affordable and - equally important - that are practical to use.

1. Characterising a disease as neglected: appraisal of criteria for priority-setting in an R&D agenda

The ideas developed in this section come from a thorough analysis of priority-setting in the context of neglected diseases carried out by Depoortere et al.⁷, provided in annex 2.

1- What is a neglected disease?

The definition of neglect is not only economic, but is very often so: diseases that affect a large number of people who are unable to pay high prices for access to health care and thus represent an uninteresting market for pharmaceutical companies. This in practice is often poor populations in low income countries of the South, where even a cost of a few cents per treatment is beyond reach for patients¹. Neglected diseases disproportionately affect people living in developing countries. Over 17.7 million people died in 2000 from communicable diseases and nutritional deficiencies⁸, which represents one third of the total deaths in the world. The large majority of these people live in third world countries. Some of these diseases could be preventable and/or curable with existing drugs, but others have no treatment available.

Thus, neglected diseases are those diseases whose treatment -despite the disease's magnitude and severity- does not promise a profitable financial return. Compounding this market failure is a general lack of priority afforded by governments and the public research community into research for treatments specifically destined to improve health in low and middle income countries. The public and private sector together fail to address this public health need.

Identifying neglected diseases and finding appropriate criteria for priority setting in this area needs an appraisal of the various criteria available. Relevant criteria to describe neglect deal with the magnitude/severity of the disease on the one hand, and the quantity/quality of resources (available and foreseen) to prevent/diagnose/treat them on the other.

2- How many people suffer and die from the disease? The traditional epidemiological indicators (incidence/prevalence, DALYs, etc.)

It seems desirable, when trying to make objective decisions, to accumulate as much "objective" data on the extent, prevalence, severity of a disease, etc. However, by the very nature of the diseases under discussion, their neglect makes it very difficult to access accurate and reliable data. The existing statistics can be misleading in their underestimation of the problem and one may well make inappropriate decisions if relying only on this information.

For example, the exact prevalence or incidence of diseases such as sleeping sickness, visceral leishmaniasis or Buruli ulcer are unknown, because they affect neglected populations in remote and rural areas where health care services are rudimentary and are often disrupted by local conflicts and follow-up of patients is poor. Some 30,000 to 50,000 cases of Human African Trypanosomiasis (HAT) are reported each year, but only about 10% of the population

¹ The annual cost of life-long treatment with alglucerase for Gaucher's disease (an orphan disease, see section III), is about \$150,000 per patient, whereas the average annual per-head healthcare expenditure in sub-Saharan Africa is currently \$6, see ref 1

in endemic areas is thought to be under medical surveillance, which means that the true figure could be closer to 300,000 – 500,000 cases, but this is far from established⁹.

When trying to perform an assessment of disease burden, we see that different ways of looking at the problem can give different results (see tables 2.1, 2.2, 3.1, 3.2 in annex 2). For example, should we consider total number of deaths caused by a disease, percentage of deaths in low income countries, deaths relative to DALYs, etc.? These different points of view shift the focus in a subtle manner, and an objective assessment is made even more difficult by the uncertainty in the data and the difficulty of obtaining accurate information.

However, certain diseases have such an impact that they stand out: three diseases result in almost one third of deaths due to communicable diseases: HIV/AIDS, malaria and tuberculosis. But while HIV/AIDS, TB and malaria are together responsible for a substantial portion of the deaths, and obviously need new and better pharmaceutical tools, it is not acceptable to limit research efforts only to these three diseases. Measles, although mainly a problem of lack of access to vaccination, adds another 5% to this number¹⁰. The remaining diseases, which both individually and collectively are responsible for enormous death and suffering, then become even more neglected, and the needs continue to widen. This entrenching of neglect is the result of a too narrow application of a single criterion of assessment. This must be scrupulously avoided in priority setting.

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 and poorly developed infrastructures all contribute to the problem. However, the fundamental need that we address here is the lack of effective, safe, affordable and easy-to-use drugs to treat these terrible, often life-threatening diseases. Many of these diseases are responsible for an enormous socio-economic burden, but the treatment options remain limited. For example, 500,000 cases of meningococcal meningitis are reported each year, 50,000 of which are fatal, and shigellosis and typhoid each cause about 600,000 deaths per year. Despite this enormous disease burden, there are limited means to diagnose and treat patients. These three infectious diseases represent a huge need.

Although several new antibiotics have been developed over the past years (for instance the fluoroquinolones), some of which certainly could prove effective for these bacterial infections, no-one has looked specifically at their use in any of these indications or done the necessary clinical studies to document their value. Moreover, the typical high price of new antibiotics poses a further barrier to their use in developing countries, even though the needs are highest there. The same holds for the newly developed antifungals, which could have a huge impact if adapted formulations would be developed (for instance to treat opportunistic infections in HIV/AIDS), and if implementation research is performed, aimed at finding the best dose-regimes and uses of these drugs in the specific health context of developing countries. Of course, affordability remains a primary requirement.

Obviously, the possible solutions for measles, tuberculosis or sleeping sickness are not the same, because the type of treatment needed can be different, or the obstacles to get there are different. For measles, the issues revolve around access and availability of the effective vaccine, while for tuberculosis we lack adapted treatments, formulations and diagnostic tests. For sleeping sickness, as will be seen later, the main issue is to have new drugs that can cross the blood-brain barrier to cure advanced stage disease. Thus, an important aspect of the

problem is to 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.

If disease prevalence alone is used as a criterion, the six infectious diseases and nutritional deficiencies affecting the most people are (in decreasing order): tuberculosis, hepatitis B, malaria, schistosomiasis, trachoma and vitamin A deficiency⁷. However, there are also many other illnesses that are less commonly discussed and which represent a significant health burden and cause enormous suffering- such as Buruli ulcer. This is a disease that is so neglected that very few people know about it outside of affected areas and its exact prevalence is unclear.

3- What are the health tools available (drugs, vaccines, diagnostic tests) for the disease? Are they safe, effective, affordable and appropriate for the conditions in the field?

The treatment of most neglected diseases relies on relatively old drugs, some still dating from the colonial era. The number of such drugs is very limited, notably in comparison with the many drugs available to treat diseases prevalent in rich countries.

Number of New Chemical Entities (NCEs).

The number of NCE 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 reveals the staggering discrepancy between the allocation of resources for diseases affecting mainly high or low income countries. For example, from 1975-1999 there were 179 NCEs approved for cardiovascular disease, giving a ratio of NCE per DALY of 1.14, compared to development of 13 NCEs for tropical diseases, giving an NCE per DALY ratio of 0.21¹. Thus, R&D investments are not necessarily placed where the needs are largest (Table 1).

Are they safe?

For some neglected diseases, such as visceral leishmaniasis and trypanosomiasis, only a few treatments exist (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 a 50% mortality, for reasons that remain unknown. (See the text box describing HAT in section II for a description of treatment with melarsoprol). Other toxic drugs in widespread use are the antimonials used to treat leishmaniasis, drugs that would not pass regulatory approval for use in humans, were they to be developed now. However, while these drugs have saved many lives relative to having no treatment at all, considering the general progress in medicine, it is unacceptable that the same toxic drugs still remain the mainstay of treatment for these diseases today.

Are they effective?

Many of the drugs in widespread use have limited efficacy data. For example, despite widespread use, there have been limited standardised assessments of the use of benznidazole and nifurtimox in treating chronic Chagas disease. Some other drugs have limited efficacy, notably because of growing resistance. Until recently, chloroquine, developed in the 1940s, was still used 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 well¹¹. Resistance levels of over 60% against antimonials have been documented in Indian

visceral leishmaniasis, making this 1st line drug useless in the area with the highest incidence of this fatal disease.

Are they affordable?

The current most effective treatment for visceral leishmaniasis is AmBisome®, a lipid-encapsulated form of the antifungal agent amphotericin B. The product is so expensive (up to US\$ 3 000 per treatment) that it is very seldom used to treat kala-azar patients, and certainly not as a first line treatment¹².

Are they appropriate?

For example, does the drug need to be stored cold, a criterion difficult to assure in remote areas? Do adapted dosage forms exist (for example, oral rather than parenteral, short treatments rather than extended periods)? Some drugs 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 Sudan, Angola or the Democratic Republic of Congo. Most of the patients being treated for Chagas disease are children, but no adapted dosage forms exist. Health care workers must cut up adult tablets to obtain a roughly correct dose¹³.

Do appropriate diagnostic tests exist?

A first step towards effectively treating patients (right drug, rational use, protect against resistance, etc.) is to make the right diagnosis. A huge gap has been identified in many diseases, including malaria, TB, sleeping sickness, kala azar, Buruli ulcer, shigellosis and Chagas disease, for which no tests exist that are cheap, simple to use in the field, and of sufficient sensitivity and specificity.

Does a disease present areas of “hidden neglect”?

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 drugs to simplify treatment and increase compliance¹⁴. Such hidden aspects of neglect are too often not appreciated.

4- What efforts are currently being made; what can be expected in the future?

Drugs under clinical development

Are there any drugs currently being tested in clinical trials, or in preclinical development? It is not easy to obtain this information, especially from pharmaceutical companies, and several alternative sources may need to be consulted, such as WHO/TDR, specialised databases, regulatory authorities (such as the EMEA and the FDA) and private or government R&D organisations, such as the NIH, Institut Pasteur, Fiocruz, the Wellcome Trust or the Walter Reed Army Institute of Research.

A recent analysis of drugs under clinical development (annex 2) indicated that malaria leads, with 17 molecules in the pipeline. However, for onchocerciasis, lymphatic filariasis and schistosomiasis, the drugs under development are actually combinations of existing drugs. There are two development candidates for HAT, three for TB and four for visceral leishmaniasis (VL). However, this does not necessarily reflect a direct benefit to patients. For example, the development of paromomycin for treatment of VL had been stalled for many

years before it was revived recently and the development of meglizol for treatment of HAT has stopped because of toxicity concerns.

Number of scientific publications

This information can be obtained by screening publication databases such as PubMed. This may provide a measure of the general scientific interest for a certain disease, and the current status of knowledge. However, published scientific papers may reflect research at all stages, and tends to focus on fundamental research, which does not give an idea of whether it may lead to any drug development, nor how far away the drugs are from use in treating patients. A recent publication reported that many of the conditions or diseases of global importance were underrepresented in clinical trials published in leading clinical journals¹⁵.

Looking at the number of scientific articles published, dracunculosis, Lassa fever and pellagra are significantly underrepresented. If the same assessment is done for clinical trials published in the past five years, Buruli ulcer and Ebola fever are also identified as neglected. These results should be interpreted with caution, and should be considered in the context of other assessments, but reveal that many diseases are not receiving even minimal research attention.

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 produces a different list each time, depending on the criterion under consideration. The concept of neglect is not easily captured in a quantitative way.

A further complexity is added by the fact that different aspects of a disease may be neglected while others are not (for example, the lack of paediatric formulations for HIV/AIDS treatment, related to the fact that mother to child transmission is largely controlled in rich countries, where the paediatric AIDS market is consequently small), 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, is urgently needed).

Once the importance of research into neglected diseases is acknowledged, we must then move towards deciding where to place 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? There is no simple formula that can be applied. Rather, what is needed is a case by case assessment of the specific needs, the scientific and technical R&D opportunities and the possibility of providing 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. 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.

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 must be used to guide 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.

Therapeutic areas (Anatomical Therapeutic Classification, ATC)	Approved NCEs 1975-99 ⁱ		Disease burden (DALYs and distribution) ⁱⁱ				% of world- wide sales, 1999 ⁱⁱⁱ	NCEs by DALY	Drug sales (million \$) by DALY
	number	% of total	World number (x10 ⁶)	%	HIC %	LMIC %			
Central nervous system	211	15,1	159,46	11,5	23,5	10,5	15,1	1,32	193
Cardiovascular	179	12,8	143,02	10,3	18,0	9,7	19,8	1,25	283
Cytostatics (neoplasms)	111	8,0	84,87	6,1	15,8	5,2	3,7	1,31	90
Respiratory (non infectious)	89	6,4	61,60	4,5	7,4	4,2	9,3	1,44	307
Anti-infectives & antiparasitics ^{iv}	224	16,1	409,08	29,6	4,2	31,8	10,3	0,55	52
HIV/AIDS ^v	26	1,9	70,93	5,1	0,9	5,5	1,5	0,37	44
Tuberculosis ^{vi}	3	0,2	28,19	2,0	0,1	2,2	0,2	0,11	11
Tropical diseases (total) ^{vii}	13	0,9	130,35	9,4	0,3	10,2	0,2	0,10	3
Malaria	4	0,3	39,27	2,8	0,0	3,1	0,1	0,10	5
Other therapeutic categories	579	41,6	524,54	37,94	31,08	38,59	41,9	1,10	163
Total	1393	100	1382,56	100	100	100	100	1,01	148

Table 1: Ratio of NCEs per disease-adjusted life year for NCEs developed between 1975 and 1999ⁱ

ⁱ Source: IMS Health drug monitor 1999; EMEA and FDA data; Trouiller P, Olliaro P (1999)

ⁱⁱ Global disease burden per disease category expressed in DALYs (disability-adjusted-life years) and distribution, as well as relative distribution in high income countries versus low and middle income countries; data from WHO World Health Report, 1999.

ⁱⁱⁱ Total pharmaceutical sales for 1999 was US\$ 204,700 million (IMS health). This is for private pharmacy sales for all drug classes except anti-infectives and parasitics, which also include public pharmacy sales.

^{iv} Anti-infectives class includes the following sub-classes: antibiotics, antituberculosis, antivirals, vaccines and immunoglobulins.

^v AIDS antiviral drugs (20 approved antiretrovirals and antiproteases) and drugs for opportunistic infections (6 approved drugs) are included; atovaquone is quoted in two sub-classes (malaria and opportunistic infections indication)

^{vi} Approved anti-tuberculosis drugs are: pyrazinamide, rifabutin, rifapentine.

^{vii} Antiparasitics drugs approved for a tropical disease indication: benznidazole, nifurtimox (Chagas disease); albendazole (helminthic infection); eflornithine (human African trypanosomiasis); artemether, atovaquone+proguanil, halofantrine, mefloquine (malaria); ivermectin (onchocerciasis); oxamniquine, praziquantel (schistosomiasis) and 2 reformulations of already approved drugs: liposomal amphotericin B (leishmaniasis) and pentamidine (African trypanosomiasis). After 1999, two new drugs were registered for malaria: arteether and artemether/lumefantrine.

II. Needs-based assessment to guide priority-setting

There is no easy formula to guide priority setting for neglected diseases. Neglect deserves an in-depth assessment of the existing knowledge on various aspects of the specific disease in a specific geographical area, based on publications and unpublished reports, on field experience and in close consultation with a broad range of people involved, including patients. The next important step is to define the appropriate research questions to be addressed. From there, areas must be identified in which focused translational research (as opposed to additional basic research) can complete existing knowledge and provide (improved) drugs, vaccines and diagnostic tests in response to the identified needs. In some cases, fundamental research may still be required. We explain this in detail with the following case studies for three neglected diseases: African trypanosomiasis, leishmaniasis and Buruli ulcer.

1- Human African Trypanosomiasis

Human African Trypanosomiasis (HAT)

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 related parasite strains, *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense*, with different geographical distribution. *Gambiense* HAT is primarily a human disease while *rhodesiense* parasites infect both humans and animals and thus have a large animal reservoir.

HAT is a fatal disease endemic in 36 countries in Africa (see Figure 2). Patients with early stage disease present with non-specific symptoms such as fever and weakness. It is at this point that the disease is most easy to treat but most difficult to diagnose. If patients are not diagnosed and treated, 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. If left untreated, this disease is inevitably fatal, with enormous human suffering during this often long chronic phase.

Options: Death by drug or death by disease?

“Melarsoprol is a terrible drug. You don’t feel proud injecting it. It is caustic, it burns, and you don’t know if you are going to save your patient or kill him” MSF Doctor, Uganda.

Most infected people only seek treatment when the disease has already advanced to the second stage. The most common treatment at this stage is melarsoprol, an arsenic derivative. It is so toxic that it melts plastic syringes, is extremely painful when injected and ends up killing one in every twenty patients treated. Furthermore, melarsoprol is becoming less and less effective. In some areas of Africa, such as northern Uganda and southern Sudan, the drug fails to cure up to 30% of patients.

There is a safer, more recent alternative to melarsoprol, called eflornithine, originally developed to treat cancer. Its spectacular success at pulling people out of a coma led to it being called the “resurrection drug”. But even this “miracle drug” has its disadvantages: eflornithine must be administered by slow infusion every six hours over 14 days, a

complicated treatment schedule in the poor and remote setting where sleeping sickness is ravaging, which impairs wider use of this drug in most places.

Source: MSF fact sheet¹⁶

1-1- Size and nature of the disease burden

Sleeping sickness was discovered at the beginning of the 20th century, as the colonial workforce was confronted with this fatal disorder, and started investigating its cause and transmission. HAT was almost brought under control during the early 1950s, with a significant decrease in the number of newly registered cases from 1949 to 1965, but a variety of factors has led to its recent re-emergence (Figure 1)¹⁷. These include socio-economic unrest -especially war - causing disruption of disease surveillance and control, inadequate financial allocation of critical resources to the disease during peacetime, increasing parasite drug resistance, changes in climate and vegetation, the emergence of new virulent parasite strains, unpredicted population movements of animal reservoirs and changes in host disease susceptibility. Many of these factors may operate simultaneously, and there have been several significant epidemics and focal resurgences of the disease in various regions of Africa in recent years.

Currently, HAT occurs in 36 countries in sub-Saharan Africa (Figure 2) ; about 60 million people worldwide are at risk of developing the disease, and the area of Africa that is infected by the tsetse fly covers approximately ten million square kilometers - a third of the land mass of Africa. HAT typically occurs in limited foci, where incidence peaks of 20-30% of the population in certain villages can occur. The exact number of cases is unknown. In 1998, 36,000 HAT cases were reported, yet with less than 10% of the population under medical surveillance, it is estimated that 300,000 people may be infected¹⁷.

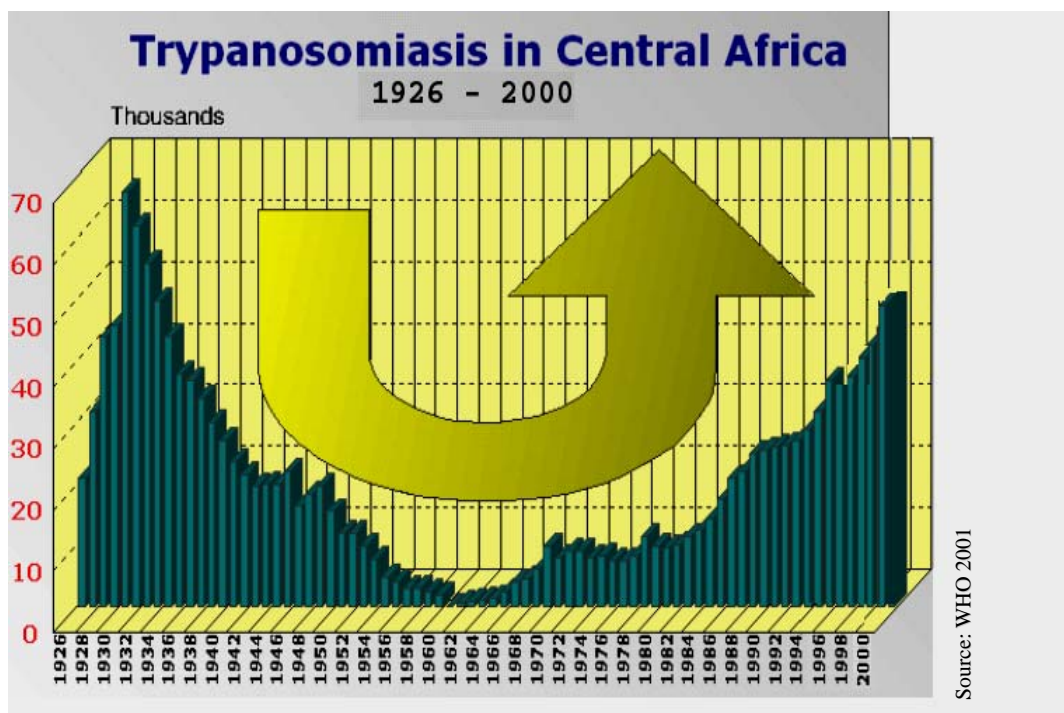


Figure 1: Re-emergence of HAT in central Africa

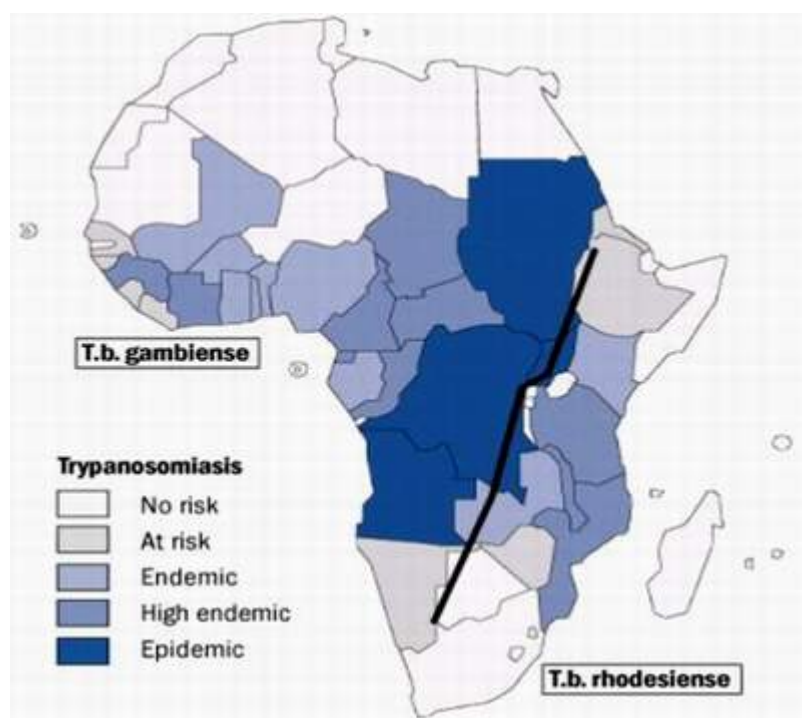


Figure 2 : Distribution of *T.b.gambiense* and *T.b.rhodesiense* sleeping sickness in sub-Saharan Africa, 1999 (Source: WHO, WHO/CDS/CSR/ISR/2000)

1-2- Control strategy/ why does disease burden persist?

Historically, the disease has been controlled by widespread insecticide and community-based fly-trap strategies (vector control strategies). In addition, during the colonial period, active case-finding and systematic treatment of early and late stage disease contributed to a relative control of the disease by the late 1950s. However, subsequent conflicts in the most affected countries (and the resulting disruption of health services), and lack of adequate tools and resources has resulted in a re-emergence of HAT¹⁸. Because of its complicated diagnosis and treatment, HAT control is usually organised into vertical programmes in endemic countries, resulting in very poor coverage and only fragmentary surveillance. With only one class of drugs to treat stage 2 HAT available for most of the past century (arsenicals), increasing drug resistance is inevitable¹⁹.

1-3- What can be learned from current/past pharmaceutical interventions?

Currently available treatments, in use since the colonial era, are scarce, toxic and encounter increasing parasite resistance^{20,21,22}. Treatment is stage-specific, with more toxic and more difficult to administer treatments for the treatment of stage 2 disease. Indeed, while a few stage 1 treatments exist (pentamidine and suramin), these are only useful when administered early in the disease, a phase that often goes unnoticed (no easy clinically recognisable signs and symptoms).

In certain areas, active screening is sometimes being done to detect HAT cases as early as possible, but available serological tests are not very specific and confirmation of the diagnosis, including stage determination, is complicated to perform in a rural setting²³. It requires a battery of increasingly complicated lab tests, with an obligatory lumbar puncture

for disease staging. Because of the high toxicity of the drugs, especially in stage 2, only confirmed HAT cases can be given the treatment.

Currently used drugs:

Pentamidine is an old injectable drug (marketed since 1940) that needs to be administered over a period of 1-2 weeks. Suramin is even older (1929), has severe side effects, and needs to be administered through 5-7 intravenous injections over a 30-day period. A safe, effective and short-course oral treatment for stage 1 HAT is crucially needed.

However, the main challenge for HAT lies in diagnosing and treating the fatal stage 2 disease²⁴. A crucial characteristic of an effective drug for second stage HAT is that it must pass the blood brain barrier²⁵.

Two drugs are available for second-stage HAT: melarsoprol and eflornithine; a third one, nifurtimox, is under consideration.

The standard first line treatment for stage 2 HAT has remained melarprosol, an organo-arsenical compound with very high toxicity. Between 5-10% of patients develop a reactive encephalopathy during treatment, which is fatal in half of the cases. Despite being used as first line treatment since the 40s, the reasons underlying this fatal toxicity remain unknown. In addition, resistance is emerging, with reports of up to 30% unresponsiveness in certain regions.

Eflornithine is the only new molecule registered for the treatment of HAT in the past 50 years. Initially developed as an anti-cancer drug, its activity against trypanosomes was discovered in the early 1980s, and a joint develop programme was initiated by Hoechst Marrion Roussel (HMR, later became Aventis) and the Word Health Organisation (WHO/TDR).²⁶ Eflornithine was registered in 1989 for use in sleeping sickness under the commercial name Ornidyl®. Soon after, however, production was stopped for lack of commercial interest and was only resumed in 2001 after intense lobbying by MSF and others,²⁷ when it became known that the same eflornithine was being commercialised as a cosmetic cream to remove unwanted facial hair (see box). Eflornithine is now available free of cost through a 5-year donation programme by Aventis²⁸ (also including pentamidine and melarsoprol). However, the availability of eflornithine for sleeping sickness has not brought much improvement for patients. The drug is extremely difficult to use in the field, requiring four daily intravenous infusions for 14 days, making its use almost impossible in most of the regions where HAT is endemic. WHO/TDR are investigating an oral form of eflornithine that would be of enormous practical benefit, but progress is painstakingly slow and chances are real that the oral form will not be active enough. The fact that the only new drug for this disease is inappropriate for the conditions of use clearly illustrates the lack of needs-driven pharmaceutical R&D.

A third possible drug for stage 2 HAT, nifurtimox, is an oral drug developed by Bayer to treat Chagas disease, a related trypanosomal illness endemic in large parts of South America²⁹. Both in *in vitro* and in *in vivo* animal models, nifurtimox is trypanocidal for *T.b.gambiense* and *T.b.rhodesiense*, which cause the 2 forms of HAT. Since the 1970s, clinical data have been obtained on the possible activity and utility of oral nifurtimox in the treatment of HAT, but the results are fragmentary and inconclusive. At the currently used dose-range (5-20 mg/kg/day for 14-60 days), experience with nifurtimox indicates a cure rate of no more than 60-75% in second stage HAT when used in monotherapy. Although a new oral treatment for

stage 2 HAT would be ideal, there have been no coordinated efforts to optimise the existing dosage regimen or otherwise demonstrate its usefulness in treating sleeping sickness.

Hairy business: Eflornithine's long road back to where it saves lives

Used to treat a neglected disease, eflornithine was never a profitable product. Hoechst Marion Roussel, the manufacturer at the time, ceased production in 1995, only five years after the drug had first reached the market. In early 2000 stock was running dangerously low, and WHO began searching for a long-term solution with the help of MSF. Twelve candidates were investigated to find a producer who would agree to continue manufacturing eflornithine. Meanwhile, in late 2000, Bristol-Myers Squibb was running six-page ads and TV commercials across the developed world to market Vaniqa, an eflornithine-based women's facial hair remover. There are now web sites, patient support groups and training software available designed to help women suffering from UFH (unwanted facial hair, in medical jargon). According to the official topical eflornithine (Vaniqa) website (www.vaniqua.com), "With VANIQ, you have an exciting way to help manage your UFH". The drug is sold by internet at around \$100 for a 30g tube.

There is little doubt that the media attention sparked by the Vaniqa launch accelerated eflornithine's subsequent return to the sleeping sickness medicine cabinet (for instance, Don McNeil, Jr. on 9 February 2001 in the New York Times: Profits on cosmetic save a cure for sleeping sickness). In May 2001, Aventis and WHO signed a deal ensuring the production of eflornithine and two other sleeping sickness medicines, melarsoprol and pentamidine. The donation covers global needs until 2006. The total value of the donation is US\$ 5 million per year and the agreement also included funding for WHO's programmes for sleeping sickness treatment and research over five years; in addition, Aventis agreed to transfer technology and provide technical assistance to potential long-term manufacturers of the drugs.

Bayer had announced that it would restart the production of two other sleeping sickness drugs, nifurtimox and suramin, in 2000. In addition to actively working to maintain a steady supply of these medicines, MSF shares the responsibility of distributing them to sleeping sickness programmes in central and southern Africa. Based on orders sent to WHO, WHO and MSF dispatch the drugs to programmes run by national governments or agencies like MSF, IMC, Malteser and CARE.

1-4- Current product pipeline

Only two molecules currently appear promising³⁰:

The DB-series of diamidine derivatives are currently being explored for several parasitic diseases³¹. Initially developed for use against *Pneumocystis carinii*, the most advanced compound, DB289, has shown good *in vitro* and *in vivo* activity against African trypanosomes and an acceptable safety profile in phase I clinical trials. It is currently in phase II clinical development for stage 1 HAT only, as it unfortunately does not seem to cross the blood-brain barrier. In parallel to the further development of D289, research is ongoing to find other derivatives that would be able to cure stage 2 HAT, but these candidates are still very early in the pipeline.

Megazol is another compound that has attracted considerable attention as a promising candidate HAT drug. Megazol is a nitro-imidazole that is orally available and does cross the

blood-brain barrier, making it a candidate for a new stage 2 treatment. It was discovered in 1968, and showed interesting *in vitro* and *in vivo* activity against trypanosomes, curing infection with a short course oral treatment in monkey models³². Despite this, it was never really pursued, mainly because of mutagenicity concerns. A thorough toxicological analysis finally has been done, which led to megazol being dropped as a promising candidate because it proved to be mutagenic in the standard Ames test³³. Still, lead-optimisation research to identify derivatives with an improved activity/toxicity ratio remains a promising avenue.

Thus, while there clearly is the need for a new and improved stage 1 HAT drug (DB-289: oral, shorter course, safer and more effective), there is currently no new drug in the pipeline for stage 2 HAT, where the needs are greatest. Although some improvement has been made towards more sensitive diagnostics, there is as yet no prospect of an alternative to the painful, cumbersome and risky lumbar punctures that are necessary for HAT diagnosis.

1-5- Gaps between current and potential research: a priority R&D agenda for HAT

Following the framework set out in section I, an alternative process to identify R&D priorities was used as follows:

1. Accurately assess and characterise, describe the real needs of patients by talking with the people involved in the disease (including patients, local health care workers, international organisations in the field, etc). This needs-analysis takes into account all the elements elaborated above through 1-1 to 1-4, as well as the specific conditions and circumstances of the disease and the associated constraints (such as storage requirements and stability of the drug, mode of administration, health care facilities available, cultural perceptions, resistance patterns, etc.). It also identifies specific knowledge gaps and target research questions that need to be addressed;
2. Perform an R&D opportunity analysis that seeks to identify areas where existing knowledge can be applied to answer these specific questions, and to identify areas where additional research should be focused so as to arrive at solutions in the most effective way. This might involve, for example, funding a clinical trial in patients with HAT to determine the efficacy of combination treatments, or translational research to transform the progress of basic research into clinical applications. Thus, a judicious investment of limited funds could have a large impact.

Priority needs for HAT:

- 1) **A safe, effective, easy-to-use and affordable stage 2 HAT treatment**
Note that if a safe stage 2 drug would be available, there would no longer be the need to distinguish between stage 1 and 2 HAT. There could be a single treatment for all confirmed HAT cases, with a single diagnostic test to make an accurate diagnosis.
- 2) **A simple, sensitive and specific diagnostic test to identify HAT patients, including stage determination (without lumbar puncture)**
- 3) **Improved stage 1 HAT treatment: short course, preferably oral, safe, effective, easy to use and distribute in the field, affordable**

Before entering into specific research opportunities to address the above needs, it is important to realise the following general complications for **HAT clinical research**:

- There is no established clinical research capacity in most of the endemic areas

- HAT occurs in scattered small foci, the distribution of which is largely unknown
- When a new focus is identified, and a case-finding and treatment programme implemented, it is possible to significantly reduce disease incidence in that focus within a few years.
- While this is good news for the people affected, it means that the few clinical research centres that have been set up through specific capacity-building projects generally face the problem of too low patient numbers to continue clinical studies after a couple of years of operation.

There is thus a continuous need to identify new possible study sites, and develop the necessary capacity to do clinical studies in such sites.

A PRIORITY R&D AGENDA FOR HAT:

(non-exhaustive)

*(the * indicates that some research activity is ongoing, but generally with very limited resources and capacity – without significant support, impact will be minimal)*

1) Making better use of existing drugs:

- **Combination treatment for stage 2 HAT, in particular nifurtimox-eflornithine***

A consensus exists that the main use for nifurtimox in HAT treatment lies in a combination with eflornithine, with as the major objective to make eflornithine more easy to use, while protecting it from the development of drug resistance. Research is needed to clinically validate this combination as a safe, effective and practical treatment for second stage HAT. It should comprise a multicentre clinical phase III study of the efficacy and safety of an appropriate dose regimen of the two drugs, compared to the standard 14 days of eflornithine monotherapy, complemented by pharmacokinetic studies. To support the further optimisation of an appropriate dose regimen for the combination, *in vivo* efficacy studies need to be done in appropriate animal models (with CNS-involvement) to look at drug interactions and possible synergies.

- **Oral eflornithine***

Although clearly better tolerated than melarsoprol and very effective, eflornithine is not widely used as first line treatment because its treatment protocol is too complicated to implement in most HAT settings. The availability of an oral form of eflornithine could dramatically improve the accessibility of this newly available treatment. While some research has been ongoing on this issue over the past years (WHO/TDR, using the existing injectable formulation for oral use), progress is very slow, and results are not encouraging. An opportunity exists to use innovative pharmaceutical R&D approaches to develop an orally active eflornithine preparation (including new processes to efficiently produce the oral form). Another possibility would be to explore the use of oral eflornithine in a combination treatment. For this, drug interaction studies need to be performed *in vitro* and *in vivo* to assess possible positive interactions (synergism) and/or safety concerns before any clinical work can be initiated.

- **Shorter course pentamidine***

The current treatment for stage 1 HAT is 10 days of daily intramuscular injections with pentamidine. This dose-regime was established empirically. Preliminary data suggest that a shortened treatment could be equally effective. Research is needed to assess the efficacy of a shorter course (for instance 3 days) treatment in the field. Ideally, this should include pharmacokinetic studies to increase the evidence for the safe use of pentamidine.

- **Pharmaceutical research to make more appropriate formulations**

Progress in pharmaceutical sciences (formulation, carriers, etc.) may provide new ways to use existing drugs, by developing formulations with improved efficacy/toxicity ratios, or making an orally administered drug (for instance: liposomes or nanoparticles for a long-acting, less toxic formulation). Both stage 1 (pentamidine) and stage 2 (eflornithine, melarsoprol) drugs could be candidates for such investigations.

- **Decreasing melarsoprol toxicity**

Although in use since the 1940s, the reasons underlying the fatal reactive encephalopathy in about 5% of all treated cases remain largely speculative. More research is needed to understand the reasons for this severe toxicity, such that strategies can be designed to reduce or prevent reactive encephalopathy. Recent studies have indicated a neuro-inflammatory response, which could be prevented using for instance substance P antagonists (in development for other indications)³⁴. This and other approaches should be further explored, with the view of reducing or preventing melarsoprol-induced encephalopathy.

- **Shorter course melarsoprol regimen for *T.rhodesiense* HAT**

Over the past years, the evidence base has been developed (clinical research and pharmacokinetics) to reduce the duration of the standard melarsoprol treatment for *T. gambiense* HAT from a 30-day schedule to 10 consecutive days (which is far easier, and cheaper and has now become the new standard). Because of the more rapid progression of *T. rhodesiense* HAT, this shorter treatment schedule has not yet been assessed in this disease. As for *T. gambiense* HAT, clinical research and pharmacokinetics studies are needed to develop clinical evidence for this abbreviated protocol in *T. rhodesiense* HAT.

2) Developing new drugs for HAT:

From the very beginning of the drug discovery phases, the ultimate goal must be to obtain safe, effective, affordable, easy to use, preferably oral drugs which are stable at room temp (no need for cold chain) and have long shelf-life. These requirements must guide R&D strategies and choices all along the R&D process.

- **Long-acting, oral diamidines for stage 1 HAT: continue DB-289 development***

Work is in progress (in phase IIb clinical development, dose-finding ongoing) by a consortium coordinated by Richard Tidwell at the University of North Carolina at Chapel Hill, currently supported by the Bill & Melinda Gates Foundation.

Identified need: identify possible clinical sites with access to HAT patients to do the clinical studies (phase IIb, but especially future phase III), and build GCP clinical trial capacity at these sites.

- **Explore megazol derivatives for new stage 2 HAT treatments**

Although megazol was shown to be mutagenic, and thus is no longer a candidate for drug development, there is an as-yet underexplored opportunity to identify a more promising lead within that family of compounds, via focused medicinal and combinatorial chemistry.

- **Identify new trypanocidal compounds that cross the Blood Brain Barrier (BBB)**

This requires:

- Research on the role and dynamics of the BBB in HAT, including pharmaceutical research and medicinal chemistry to better understand how drugs can cross this barrier.
- Establishment of medium- to high-throughput screening assays to model crossing of the BBB, and allow screening and lead optimisation based on the capacity to cross the BBB
- Review known trypanocidal compounds and assess their capacity to cross the BBB, and adopt the latest technologies and strategies to enhance BBB crossing

- **Identify new trypanocidal compounds***

Building on the new knowledge accumulating through the progress in molecular biology, and more recently via genomics and proteomics, there certainly is an opportunity to identify new classes of trypanocidal compounds, including via high throughput screening of selected large compound libraries.

Of particular interest is to screen libraries of already existing drugs and compounds currently under development for other indications, in particular antibiotics, cancer drugs and veterinary drugs for parasitic diseases (half of the 11 drugs developed between 1975-1997 came from veterinary research¹), 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).

3) Other R&D opportunities with possible significant impact:

- **Develop a sensitive and easy-to-use diagnostic test***

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)

- **Monitoring disease progression and cure: identify and validate alternative markers**

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 not only the only method for stage determination, but also the only accepted efficacy measurement for treatment (assessed at the end of treatment, and then 6-12 and 24 months after treatment). This follow-up of 24 months is problematic as a significant proportion of the treated patients are lost to follow-up by that time. Both for control programmes and for clinical studies to assess efficacy, alternative and more practical markers should be identified and validated to monitor disease progression and cure / relapse.

- **Study mechanisms of drug resistance**

Because very few drugs are available, with very few new molecules in the development pipeline, it is crucial to prevent drug resistance. Understanding the mode of action of the existing and new drugs, including the molecular biology of drug resistance mechanisms, is a prerequisite in this regard. This should include the development of field-adapted standardised methods to assess drug resistance.

- **Develop cheap and sustainable manufacturing processes/sites**

To secure production and availability of these life-saving HAT drugs, efforts must be put into place to develop adequate (GMP, sustainable, cheap) production processes for otherwise possibly expensive drugs (for instance eflornithine).

1-6 Conclusion for HAT

Human African trypanosomiasis is re-emerging among poor people in poor countries. It is a progressively debilitating disease and is always fatal if left untreated. Nearly all the available drugs are very old and toxic, and the one newer drug is difficult to use. To improve the situation, new treatments as well as new diagnostics and surrogate markers are urgently needed. Possibilities exist to make better use of the existing drugs in the short term, and to develop much better tools in the longer term to help control this terrible disease. But without adequate funding to implement the needs-driven priority R&D agenda, significant progress is unlikely, leaving entire populations without treatment.

Summary of priority research agenda for HAT

Priority needs:

- A safe, effective, easy-to-use and affordable stage 2 HAT treatment
- A simple, sensitive and specific diagnostic test to identify HAT patients, including stage determination (without lumbar puncture)
- Improved stage 1 HAT treatment: short course, preferably oral, safe, effective, easy to use and distribute in the field, affordable

1. Making better use of existing drugs:

- Combination treatment for stage 2 HAT, in particular nifurtimox-eflornithine
- Oral eflornithine
- Shorter course pentamidine
- Pharmaceutical research to make more appropriate formulations
- Decreasing melarsoprol toxicity
- Shorter course melarsoprol regimen for *T.rhodesiense* HAT

2. Developing new drugs for HAT:

- Long-acting, oral diamidines for stage 1 HAT: continue DB-289 development
- Explore megazol derivatives for new stage 2 HAT treatments
- Identify new trypanocidal compounds that cross the Blood Brain Barrier (BBB)

3. Other R&D opportunities with possible significant impact:

- Develop a sensitive and easy-to-use diagnostic test
- Monitoring disease progression and cure: identify and validate alternative markers
- Study mechanisms of drug resistance

4. Develop cheap and sustainable manufacturing processes/sites

2- Visceral leishmaniasis

The leishmaniasis

Today, the leishmaniasis are endemic in 88 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 1.5 to 2 million new cases occurring annually; and this number is rising. Largely unknown in the developed world, leishmaniasis threatens many poor countries. The disease principally affects poor communities in isolated regions, often as devastating epidemics. In Sudan, where civil war had caused a flood of internal refugees, an epidemic of visceral leishmaniasis lasted from 1984 to 1994 and claimed more than 100,000 in the Western Upper Nile province, a third of the population of the affected area.

There are three main types of leishmaniasis, all transmitted by bites of infected sandflies:

- > Visceral leishmaniasis (VL), also known as kala azar (Hindi for “black fever”), is the most severe form of the disease, where the parasite infects the immune system. Patients present with fever, wasting, anaemia and an enlarged spleen. If untreated, visceral leishmaniasis is fatal in almost 100% of cases, within one to four months.
- > Mucocutaneous leishmaniasis begins with skin lesions which then spread, causing massive tissue destruction around the mouth and nose.
- > Cutaneous leishmaniasis, the most common form, affects principally the skin, causing simple lesions which usually self-heal but leave scars.

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, 20% of visceral leishmaniasis patients also suffer from HIV co-infection.

Treatment of leishmaniasis has been hampered by the inadequacies and high prices of existing medicines and slow progress in research and development into new cures. Pentavalent antimony, the most widely prescribed drug to treat *Leishmania* patients, was discovered a century ago, has serious side effects, requires a prolonged course of treatment and is losing its efficacy in some regions due to increasing parasite resistance. Although newer treatments exist, they are not optimal due to problems of toxicity, high price and difficulty of administration.

Source: MSF fact sheet³⁵

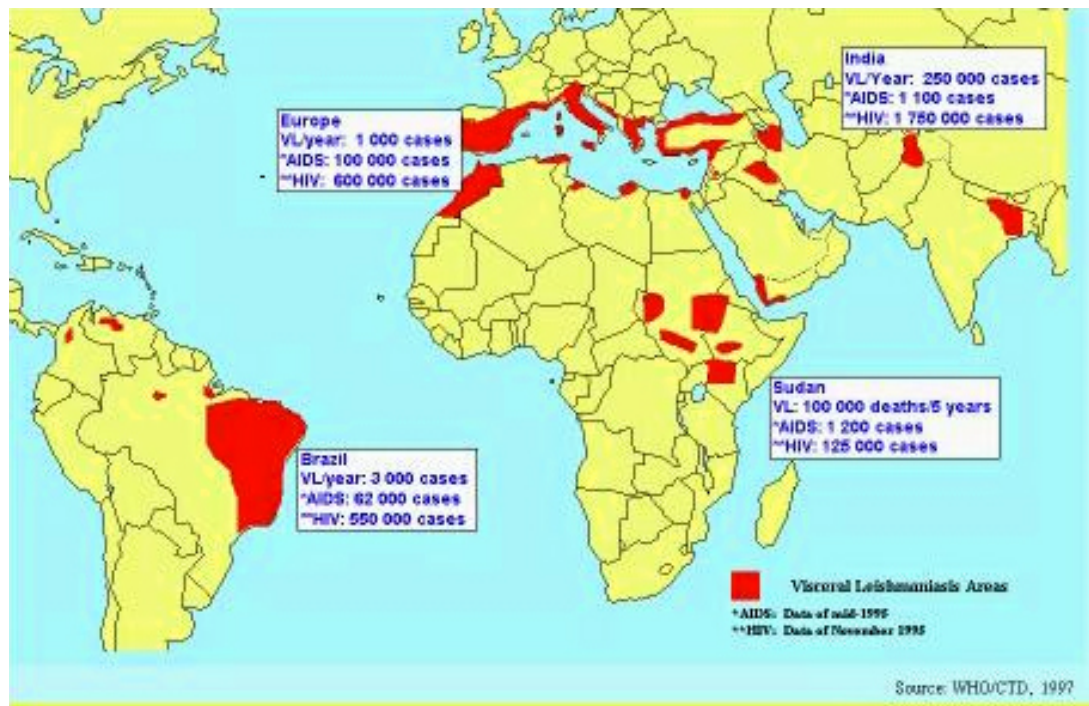


Figure 3: Distribution and incidence of visceral leishmaniasis (Source: WHO/CTD, 1997)

2-1- 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, 500,000 new cases per year and over 40,000 deaths recorded annually (Figure 3)^{36, 37}. As is common for neglected diseases, the exact figures are not known and these numbers are probably underestimates. Both the geographical area and the number of cases have been growing the past two decades. The lack of reliable data has been both the result of and the reason for the scarce resources allocated to this disease. In 2000, the disease burden was estimated to be a staggering 1,980,000 disability-adjusted life years¹².

Over 90% of VL cases occur in five countries: India, Bangladesh, Nepal, Sudan and north-eastern Brazil. Population displacement as a result of war, famine, drought or rural-urban migration underlies the recent epidemic in the Sudan and is contributing to the resurgence of the disease in India and its urban spread in Brazil. Leishmaniasis is a disease of poverty, with risk factors contributed by malnutrition and especially HIV co-infection, which is changing the face of the disease³⁸. Communities once less at risk are becoming increasingly exposed to the disease, especially in India and Brazil, where the urban HIV epidemic and the rural leishmaniasis epidemic are increasingly coming into contact. VL is also being seen in areas previously escaping infection, imported by patients with HIV co-infection. Co-infected patients may be difficult to diagnose, respond poorly to treatment and relapse repeatedly^{39,40}. A complication of visceral leishmaniasis, especially prevalent in Sudan (and to a lesser extent Ethiopia, Kenya and India) is post-kala-azar dermal leishmaniasis (PKDL)⁴¹, occurring in people who have recovered from VL following treatment.

2-2- Control strategy/ why does the disease burden persist?

Vector control strategies have been helpful in the past, including spraying of insecticide and use of bednets¹². However, growing insecticide resistance and lack of infrastructure and government support has limited such programs. In Sudan, the ongoing civil war makes such interventions difficult and the other regions most affected are poor, isolated or lack the necessary infrastructure. 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.

Systematic case-finding and effective treatment of patients should help reduce this reservoir of disease, but the lack of safe, effective and affordable drugs has contributed to disease persistence and further spread. Another major source of transmission is domestic or semi-domestic dogs, which are difficult to treat or control.

Clearly, vector and host control strategies are important, but a major factor in this needs to be an intervention allowing early diagnosis and effective treatment. Thus, an efficient diagnostic test, a vaccine and appropriate treatments are urgently and critically needed.

2-3- What can be learned from current/past pharmaceutical interventions?

The current treatment options are severely limited^{42,43}. Antimony treatment has remained the mainstay of VL therapy, despite considerable toxicity and the need for hospitalization during the 4-week treatment. In northern Bihar (India), the area of the highest kala azar incidence, resistance levels of up to 65% have rendered antimony treatment largely ineffective⁴⁴. The main alternative currently available is amphotericin B, another relatively toxic drug needing a hospital setting to cope with the frequent side-effects.

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. However, current diagnostic procedures require invasive interventions such as spleen, lymph node or bone marrow punctures in rural settings often not equipped to perform such invasive (and potentially harmful) tests. Moreover, reading of the microscope preparations to detect the parasites requires trained and experienced staff, usually present only in major health centres. More appropriate and field-adapted diagnostics are crucially needed, and much of the technology needed for their development exists. For example, the DAT test has been validated for use in the field, but no commercial source exists. A simple serological test in dipstick format has recently been developed, and while an initial assessment in the field gave promising results⁴⁵, it still needs to be further assessed in control programmes. A comparative field testing of different tests including dipstick, DAT and a urine Ag-based test is ongoing but progress is painstakingly slow³⁶.

Most currently available drugs are injectable, require hospitalisation for several weeks and are associated with serious adverse effects. In most cases, the lack of affordability is also an issue.

As mentioned above, a four week treatment course of daily injections with **antimonials** still remains the first-line VL treatment in most areas. In addition to the toxicity problems, the available brand-name antimonial drugs are expensive, while the availability of quality generic preparations has proven erratic.

Second-line treatment **amphotericin B**, another old drug, is even more toxic and difficult to administer when health care staff and infrastructure is limited. Again, lengthy treatment and the need for prolonged hospitalisation compound to the problem.

Recently a new drug, **miltefosine**, has been developed and registered for use in VL in India^{46,47}. Miltefosine is the first oral drug for VL, but it still requires a 28-day treatment. While the oral drug was hailed as a breakthrough⁴⁸, the prolonged treatment duration (not requiring hospital stay) is seen as a serious threat for treatment compliance, and thus is a risk for rapid development of resistance. It would be a tragedy if this drug, the only new treatment available in the last 60 years, becomes ineffective. Clinical trials of combination treatments are urgently needed to limit the emergence of resistance. Moreover, in addition to being relatively expensive (US\$ 200 / treatment in private pharmacies), the drug is being sold over the counter in Indian pharmacies, where it can even be bought per tablet. In other endemic regions (Eastern Africa, Brazil), miltefosine has not yet been registered. Because of the known differences in disease severity and response to treatments between regions, specific clinical studies will be needed to demonstrate safety and efficacy, and to optimise dose regimens. Finally, there are concerns about the possible teratogenicity of the drug, raising issues about administering the drug to women of child-bearing age (except if a pregnancy test can be done, and with concomitant contraception to avoid pregnancy within the 3 months after miltefosine treatment).

Paromomycin, an old and widely used broad-spectrum aminoglycoside antibiotic, has also proved effective against leishmaniasis^{49,50}, although the final studies to register the drug for VL have not yet been completed. Paromomycin also appears to work well in combination with other drugs, such as antimonials^{51,52}, but again, the evidence-base to support a clear clinical recommendation is still missing. Concerns have been raised about the possible eye toxicity of paromomycin, a known adverse effect of aminoglycosides.

Without doubt the best option available today is **Ambisome®**, a liposomal formulation of amphotericin B which was developed as a safer and more effective alternative to conventional amphotericin B to treat opportunistic infections in HIV patients. During the 1990s, the great promise of relatively short course treatment with liposomal amphotericin B to treat severe and complicated drug-resistant visceral leishmaniasis in field conditions was documented⁵³, and confirmed in different VL endemic countries⁵⁴. In particular in India, the effectiveness of this drug in a short course treatment of VL, even as a single dose, has been clearly demonstrated^{55,56}. However, this patented drug has remained prohibitively expensive (as much as 3000 US\$ for a treatment course), posing an insurmountable barrier to its use in kala-azar (even if price negotiations with Gilead have recently resulted in a differential price for MSF, treatment still remains unaffordable for most kala azar patients). This high price is also a barrier for further studies to optimize the dose-regimen, or investigate possible combination therapy strategies using Ambisome®.

2-4- Current product pipeline

The injectable antibiotic paromomycin has shown promising activity against visceral leishmaniasis, both in monotherapy as a 3-week treatment and in combination treatment with antimony. Such a combination may allow further reducing treatment duration (and thus hospitalisation) to 14-17 days, although the safety and effectiveness of this shorter course combination still needs definite demonstration.

Clinical trials are underway in India⁵⁷ and Africa (DNDi, personal communication) to complete the registration dossier of paromomycin, and finally make the drug available to the patients. The clinical trials in Africa (a multicenter study in Sudan, Kenya and Ethiopia) will be the first of its kind in this VL-endemic region, requiring a significant capacity-building effort before being able to start.

Another promising compound is sitamaquine, a possible new oral drug in development by GSK. The development of this compound, initially tested by the US army to protect its soldiers in endemic countries, has been slow (in phase II development for several years now) but may soon move to phase III clinical trials.

2-5- Gaps between current and potential research: a priority R&D agenda for VL

The above analysis resulted in the following areas being identified as particularly important:

A PRIORITY R&D AGENDA FOR VISCERAL LEISHMANIASIS:

(non-exhaustive)

*(the * indicates that some research activity is ongoing, but generally with very limited resources and capacity – without significant support impact will be minimal)*

1) Making better use of existing drugs:

• Paromomycin*

While phase II clinical studies have demonstrated the efficacy and safety of paromomycin in a small number of visceral leishmaniasis patients, the phase III clinical studies on a larger group of patients for both paromomycin in monotherapy and in combination with antimonials have not been completed. A consolidated effort is needed to finalise the registration dossier of paromomycin for submission in the different endemic countries, taking into consideration the regional differences in the disease patterns and in the drug sensitivities of the *Leishmania* strains (Indian subcontinent, Eastern Africa and Brazil). Furthermore, the clinical evidence-base in support of a treatment recommendation for the shorter course paromomycin-antimony combination needs to be strengthened.

• Miltefosine*

Based on clinical studies performed in India, miltefosine was registered there in 2002, and phase IV studies are currently ongoing, while the drug is already being commercialised freely through the private health system. In other endemic regions, the studies to confirm efficacy and safety still need to be done. Moreover, additional research is needed to investigate the possible teratogenicity of miltefosine, and devise strategies to deal with this issue in implementation (rational, controlled drug use).

In order to protect this new drug from a rapid development of resistance (predicted based on lab data⁵⁸), an urgent need exists to study the possible mechanisms of miltefosine drug resistance and develop strategies to counter it, in particular through combination treatment⁵⁹. To this end, possible drug interactions between miltefosine and other anti-leishmaniasis drugs need to be assessed *in vitro* and in animal models, to identify the most promising combinations for clinical testing. Subsequently, clinical testing (dose-finding and safety-efficacy studies) of the most promising combinations needs to be done.

- **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 possibly the best ways to protect effective anti-infective drugs against resistance, in particular when only a few drugs are available⁶⁰. Drug combinations also may reduce treatment duration (and possibly hospitalisation), and/or reduce toxicity. Thus, drug combinations are a priority in a general strategy for leishmaniasis treatment.

To build an evidence base for the implementation of this strategy, possible drug interactions between different anti-leishmaniasis drugs need to be studied *in vitro* and in animal models, to identify most promising combinations for clinical testing. In addition to the already mentioned combinations, a highly promising combination would be a short course (single dose?) treatment with AmBisome, followed by a 1-2 week oral treatment (miltefosine, sitamaquine?).

- **Pharmaceutical research to develop alternative (cheap) formulations of AmBisome®**

By far the best drug available today to cure visceral leishmaniasis is AmBisome®, a well defined liposomal formulation of the old and relatively toxic amphotericin B, which has a dramatically improved activity/toxicity ratio. State of the art pharmaceutical research is needed to explore other formulation strategies for amphotericin B, to obtain a similar or better activity/toxicity ratio in a more affordable way. This can include developing alternative liposome-based strategies, or other drug targeting and delivery systems such as micro- and nano-particles, polymer-based preparations, emulsions, etc.

- **Pharmaceutical research to develop long-acting and/or oral formulations**

Along the same lines, state of the art pharmaceutical research could explore formulation strategies of existing anti-leishmanial drugs to make them easier to use, for instance by reducing treatment duration and/or frequency of injections/intakes or to develop oral formulations of other drugs that are not normally administered orally.

2) Developing new drugs for VL

From the very beginning of the drug discovery phases and all along the R&D process, the ultimate goal of obtaining safe, effective, affordable, easy to use, preferably oral drugs which are stable at room temp (no need for cold chain) and have long shelf-life must guide R&D strategies and choices. A specific challenge is posed by the increasingly frequent HIV co-infection, requiring drugs that can cure leishmaniasis infection in immunocompromised patients.

- **Miltefosine derivatives and alternative formulations**

Because of the urgent need for new treatment options, development of miltefosine was pursued despite its poor therapeutic index (which is an issue of concern for this new drug). However, it is likely that better candidates exist within the same family of alkyl phosphocholines⁶¹. Moreover, preliminary results suggest that alternative formulations of such alkyl phosphocholines (for instance liposomal formulations) can contribute to a better therapeutic index. This line of research is currently being explored for veterinary purposes (leishmaniasis in dogs), but could also show promise for humans. This is an opportunity for parallel development and translational research.

- **Accelerate, finalise development of sitamaquine**

Sitamaquine is another oral drug candidate, currently in phase II clinical development by GSK, but progress has been slow. Ways could be explored to boost this development

programme (if indeed promising), or to assess whether any back-up drug candidates of this chemical family need to be brought forward.

- **Immunotherapy**

In animal models, the immunology of leishmania infection has been relatively well studied, showing that protection against disease or even cure can be achieved by strengthening particular functions of the immune system (Th1 versus Th2 responses). This suggests that a combination of chemotherapy with an appropriate immunostimulator may result in effective treatment. As much of the basic research has been done, efforts must be directed towards translational research. Immunotherapy may be particularly promising for PKDL and cutaneous leishmaniasis.

- **Identify new anti-leishmanial compounds***

Building on the new knowledge accumulating through the progress in molecular biology, and more recently via genomics and proteomics, there certainly is opportunity to identify new (classes of) anti-leishmanial compounds, including via high throughput screening of selected large compound libraries. Of particular interest is to screen libraries of already existing drugs and compounds currently under development for other indications, in particular antibiotics, cancer drugs and veterinary drugs for parasitic diseases (half of the 11 drugs developed between 1975-97 came from veterinary research¹) 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). Specific attention should be given to compounds that are capable of curing leishmaniasis in immuno-compromised animal models.

3) Other R&D opportunities with possible significant impact:

- **R&D on a preventive vaccine for leishmaniasis**

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. In academic and veterinary research, important efforts have already been made to identify possible protective antigens and to optimise vaccination strategies (via appropriate carriers or adjuvants, or more recently through DNA-vaccination)⁶². Translational research is needed to move this research towards human vaccine development.

- **R&D on topical applications to treat cutaneous leishmaniasis**

Cutaneous leishmaniasis is a highly disfiguring disease belonging to the same family as VL, but caused by other *Leishmania* strains. Over the past 15 years, several topical formulations of existing drugs such as paromomycin, amphotericin B or ketokonazole have been tested, not always in the most optimal circumstances and with variable success⁶³. Today, there is the opportunity to apply state-of-the art pharmaceutical research to develop an effective topical treatment for this disease using already known active anti-leishmanial compounds, possibly enhanced by an immunomodulator.

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

So far, little is known on the impact of HIV co-infection on leishmaniasis, but preliminary evidence suggests that HIV-positive individuals are more susceptible to develop full-blown VL, 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 regions³⁹ (up to 30% of VL cases in the Humera region, Ethiopia, are HIV-positive), research is needed on different aspects of this problem, including epidemiology, diagnosis and possible treatment.

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

A recently-developed simple serological test, the rk39 dipstick, has shown promising results (good sensitivity and specificity, very easy to use) for diagnosis of primary kala-azar. Still, a thorough comparative field analysis to assess its performance compared to the currently used diagnostic methods (parasitology on spleen, lymph node or bone marrow aspirates) is needed, and the production of cheap, high-quality tests needs to be secured. While the rk39 dipstick is a great advance to detect primary kala azar, this serological test cannot be used to monitor disease progression (antibodies remain detectable for months after parasite elimination), 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.

- **Study mechanisms of drug resistance**

Because only very few drugs are available, with very little new 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 drugs, 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).

2-6 Conclusion for Leishmaniasis

The leishmaniasis, in particular the devastating visceral leishmaniasis, continue to affect millions in different parts of the world, with an alarming re-emergence linked to HIV co-infection. Patients still mainly rely on two old and toxic drugs for treatment. Yet, with relatively little effort, several much better alternatives could be made available within a few years, provided adequate funding to implement the priority R&D agenda for leishmaniasis can be mobilised. Furthermore, there is sufficient basic research to support the development of much better tools in the longer term. This will require moving pre-clinical drug and vaccines candidates into clinical development.

Summary of priority research agenda for VL

1. Making better use of existing drugs:

- Paromomycin: phase III clinical studies in monotherapy and combinations, finish clinical registration
- Miltefosine: combination studies to counter resistance, characterise teratogenicity, test use in other regions
- Combinations therapy to reduce treatment duration, prevent resistance, and obtain better cure rates
- Pharmaceutical research to develop alternative (cheap) formulations of AmBisome®
- Pharmaceutical research to develop long-acting and/or oral formulations

2. Developing new drugs for VL

- Miltefosine derivatives and alternative formulations to improve therapeutic index
- Accelerate, finalise development of sitamaquine
- Investigate immunotherapy strategies
- Identify new anti-leishmanial compounds

3. Other R&D opportunities with possible significant impact

- R&D on a preventive vaccine for leishmaniasis
- R&D on topical applications to treat cutaneous leishmaniasis
- HIV co-infection: epidemiology, diagnosis and possible treatment
- R&D for sensitive and easy-to-use diagnostics, including disease monitoring and test of cure
- Study mechanisms of drug resistance

3- Buruli ulcer

Buruli ulcer

In 1950, one of the first reports of Buruli Ulcer was published in the Annals of the Belgian Society of Tropical Medicine with the staggering title: “Should we take into consideration a new acid-fast bacterial infection in Africa?”⁶⁴. It has taken more than 50 years for the international community to respond positively to this question. Buruli Ulcer is caused by *Mycobacterium ulcerans*, a pathogen belonging to the same family of organisms that causes tuberculosis and leprosy⁶⁵.

Buruli ulcer is a cruel disease that destroys skin, muscle and bone and, in its worst form, leaves victims with disfiguring and disabling ulcers⁶⁶. About 70% of the cases occur in children. The disease starts with the appearance of a painless nodule. At this stage, simple excision is often curative, but for a complex combination of reasons, treatment is usually not sought until later stages, when the disease has evolved and treatment is more radical and disfiguring.

If left untreated, the initial nodule progresses to a massive ulceration that may cover 15% of the body, especially the limbs, and can also affect bone, eyes, and genitalia. At this stage, major surgical interventions are required, including major excision, skin grafts and extended and costly hospital stays. Healing is long and often leads to deformity and permanent disability⁶⁷. Often, amputation of affected limbs is required to stop spread of the disease, especially in the most severe form of Buruli ulcer which involves osteomyelitis.

There are no medications available to treat this disease. Extensive surgery is the only option, if available at all.



Figure 4: Disfiguring lesions caused by Buruli ulcer^{68,69}

3-1- Size and nature of the disease burden

Buruli ulcer is most common in West Africa. All countries along the Gulf of Guinea are now affected. In Côte d'Ivoire, approximately 15,000 cases have been recorded since 1978 where up to 16 percent of the population in some villages are affected. In Benin, 4,000 cases have been recorded since 1989; in Ghana (6,000 recorded cases in a national survey in 1999) up to 22 per cent of villagers are affected in some areas. There is evidence of huge under-reporting of the disease.

But the disease has a worldwide spread: cases have been reported in over 30 countries in Africa, Asia, Latin America, the Western Pacific and Australia (Figure 5)⁷⁰. Even more neglected than most diseases, there are no estimates available on the total number of people affected by this disease.

Buruli ulcer is the third most common mycobacteriosis of humans, after tuberculosis and leprosy. Following infection, *M. ulcerans* proliferates and secretes a toxin, mycolactone, that causes necrosis and also spreads into neighbouring tissue, suppressing the local immune response and causing the severe and disfiguring ulceration⁷¹.

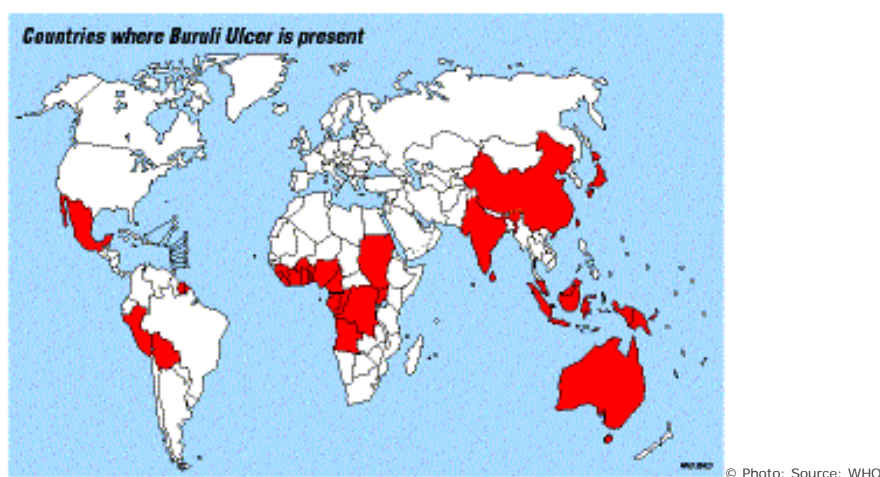


Figure 5: Countries where Buruli ulcer cases have been reported (Source: WHO)

3-2- Control strategy/ why does disease burden persist?

Largely ignored by the world, Buruli ulcer victims and a global control strategy for Buruli ulcer has received little attention. Because of the etiological link to leprosy and tuberculosis, some organisations traditionally focusing on these diseases have extended their activities to include Buruli ulcer. Most cases are found in remote areas in poor countries, often with little access to health care infrastructure, and case management of Buruli has largely relied on charity and vertical programs within the health structures.⁷²

The majority of infected patients are children, and it has been speculated that transmission occurs through exposure to infected water or to plants carrying the mycobacterium⁷³. One report suggest that infection can also be spread by water insects, but it remains to be conclusively demonstrated⁷⁴. This implies that environmental control of disease spread is

difficult, although protection, such as wearing long trousers when working in plantations, seems helpful.

Experienced observers can often make accurate clinical diagnoses of Buruli ulcer, but laboratory diagnosis to confirm *M. ulcerans* infection is more cumbersome and requires lengthy culture techniques or sophisticated molecular methods, not usually available in rural areas. As treatment of confirmed cases relies on surgery, Buruli ulcer control activities are usually limited to regions with hospital infrastructure and specifically trained staff, limiting treatment access for most patients. Moreover, due to the lengthy hospitalisation period, treatment costs are significant, and certainly beyond the reach of most patients. In Ghana, the average cost to treat Buruli ulcer is over US\$ 780 per person⁷⁵, while in Australia this may be as much as US\$ 20,000⁷⁶. Taken together with the social stigma of the disease, it is thought that a large number of patients never seek treatment, hiding their ulcers, disabilities and scars.

For those who do seek treatment, surgery is the only option. Depending on the skill of the doctor and the stage of the disease, up to 50 % of the patients may relapse, probably due to insufficient resection of tissue during surgery. No medicines exist to treat this severely disfiguring and disabling disease.

In December 1997, 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. In 1998, WHO launched the Global Buruli Ulcer Initiative (GBUI) to coordinate control and research efforts⁷⁷. Since then, a yearly International Conference on Buruli ulcer Control and Research has been organized, bringing together representatives of the national health programs of affected countries, NGOs, scientists and donors. Although laudable, the chronic lack of funding for Buruli-related activities has limited the impact of this effort. 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. However, without serious financial commitment to support this, the resolution remains theoretical and will not be implemented.

3-3- What can be learned from current/past pharmaceutical interventions?

The limitations of surgery are obvious, and unless care is taken to excise large areas of skin and tissue around the lesions (with its problems for the subsequent healing process), relapses are common. A huge need exist to explore other options for therapeutic intervention.

A recent review of the literature and other reports carried out by Epicentre (given in annex 6) lists the different treatments in use or under study⁷⁸. A series of topical treatments has been explored, mainly to slow disease progression and limit the size of the lesions before surgery, or to facilitate or accelerate wound healing after surgery. These include classic antiseptic products, heat treatment, nitric oxide preparations, and clay. Although certain of these may have a place in Buruli ulcer case management, no controlled studies have been done to assess their real value. Their current use is empirical. No evidence exists for the effectiveness of topical treatments, but topical antibiotics have not been tested.

In view of the generally advanced stage of the disease when treatment is sought, including disseminated disease, systemic treatments likely offer more promise. Also here, several strategies have been explored to a certain extent, but usually either only in animal models or if clinically, mainly empirically, on a compassionate use basis, without randomised controlled

clinical study to make definite conclusions. Even if it seems obvious to assess the potential value of existing antibiotics, in particular anti-mycobacterials, only few studies have been performed, with disappointing results. The poor response to antibiotics has been attributed to reduced penetration of antimycobacterials into the necrotic tissue that characterizes Buruli ulcers. The only antibiotic treatment tested which showed relatively good activity in humans is the combination of streptomycin and rifampicin⁷⁹, evaluated on a small group of patients in Ghana under the auspices of WHO/TDR. Although a clear reduction of the lesion can be achieved, current experience suggests that even after a lengthy treatment of 4-8 weeks, additional surgery may still be required to eliminate the lesion. It has recently been demonstrated that BCG vaccination (*Mycobacterium bovis*, the tuberculin vaccine) show some protection against Buruli ulcer infection, in particular against the severe disseminating form of the disease.⁸⁰

3-4- Current product pipeline

No specific treatment for Buruli ulcer is currently being developed. The only ongoing activity is the clinical assessment of existing antibiotics in late-stage disease (streptomycin and rifampicin, see above), with limited promise for a breakthrough.

3-5- Gaps between current and potential research

There is a huge need for focused R&D for effective new treatments, which are safe and easy to use, as well as simple diagnostic tools. Given the difficulty of environmental control, a vaccine could have enormous benefits, especially if cross-protection against other mycobacterial infections could be achieved. More generally, a close connection with the research community involved in developing new tuberculosis drugs, diagnostics and vaccines would be extremely valuable.

The nearly total lack of any research activities so far leaves a wealth of opportunities to be explored. As for other neglected diseases, care should be taken to ensure that safe, effective, easy to use and affordable treatment options are being pursued. Without being exhaustive, it is clear that the following lines of research deserve priority attention:

- **Specific treatments aimed at neutralising mycolactone**

The *M. ulcerans*-specific toxin mycolactone, the causative agent of the main pathological features of the disease, has been identified and characterised⁸¹. This provides an excellent opportunity for rational drug or vaccine design, to develop curative or preventive treatments which interfere with this toxin.

- **Systemic treatments with combinations of existing antibiotics**

Although the initial results have not been encouraging, it is clear that only a handful of all possibilities in this field have so far been explored, certainly not including the most recently developed antibiotics (or those currently in development for tuberculosis). Moreover, only few of the *in vitro* tested (and active) compounds have gone through animal testing, let alone clinical assessment. Specific drug combination studies need to be performed to screen for possible synergisms on *M. ulcerans*.

- **Topical applications containing antibiotics as curative treatment for small lesions**

Several topical applications exist, or can be made, of known antibiotics. A topical application with one or a combination of antibiotics known to be active against *M. ulcerans in vitro* may

show promise to cure the initial small nodules of Buruli ulcer, or even small lesions. Applied pharmaceutical research to design a formulation that helps the active compounds to effectively cross the skin and reach the bacteria is needed. Again, controlled clinical studies will be needed on early stage patients to establish the efficacy of such a treatment.

- **Topical applications as supportive treatment**

Two objectives can be pursued: slowing disease progression and limiting the size of the lesions before surgery, or facilitating or accelerating wound healing after surgery. In both phases, the protection against opportunistic infections would be an important secondary objective. Looking at existing products, for instance in the field of wound healing, topical treatments exist that may well be of benefit to Buruli ulcer patients. An example is a cream of cerium nitrate and silver sulfadiazine, which is being used for burns and various types of ulcers⁸². The therapeutic benefit of such products in Buruli ulcer case management would need to be established through a controlled clinical study.

- **A protective anti-mycobacterial vaccine**

Current experience with the BCG vaccine indicates a cross protective capacity against Buruli ulcer, suggesting that protective immunity could be achieved. Immunological research to characterise this immunity, and develop vaccines with improved efficacy, is a priority. Ideally, a cross protection against other anti-mycobacterial diseases should be pursued.

- **R&D for sensitive and easy-to-use diagnostics**

A simple and sensitive diagnostic test would be instrumental to facilitate early case detection, before the disease has progressed into its destructive late phase. The possible utility of mycolactone as a marker could be explored, as well as other specific (serological, salivary, urinary) markers.

- **New drug targets and novel drugs**

The genome of *M. ulcerans* is currently being sequenced at the Pasteur Institute⁸³; those of other *Mycobacterium* species are already more advanced. This basic knowledge may bring important new findings towards identifying new drug targets (or diagnostics or vaccine targets), but will need to be translated into useful clinical applications (“translational research”).

3-6- Conclusion for Buruli ulcer

Buruli ulcer is a totally neglected but re-emerging disease that affects predominantly children in Western Africa and other parts of the tropical world, causing terrible disabling and disfiguring ulcers, often leading to permanent lesions. No effective medicinal treatment is available; the only option is extensive surgery followed by skin grafts, often out of reach for the poor in rural populations affected by the disease. The relatedness to other major *Mycobacterium* infections (TB, leprosy), as well as progress in basic science provide a wealth of opportunities for focused R&D towards improved treatment options, in particular making use of existing topical treatments, drugs, 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

1. Making better use of existing drugs:

- Systemic treatments with combinations of existing antibiotics
- Topical applications containing antibiotics as curative treatment for small lesions
- Topical applications as supportive treatment

2. Developing new drugs for VL

- Specific treatments aimed at neutralising mycolactone
- New drug targets and novel drugs

3. Other R&D opportunities with possible significant impact

- A protective anti-mycobacterial vaccine
- R&D for sensitive and easy-to-use diagnostics

III. Mobilizing needs-driven innovation to address priorities for neglected diseases

The current pharmaceutical research innovation framework is based on the business interest of private companies in making a profit - or at least in recovering their R&D investments - by selling the products of this research in a high-paying market. To maintain a competitive advantage and because patent protection is limited in time, drug companies seek to renew their product portfolio and develop molecules that can be presented as unique, if not better than the competitors' drugs. Priority setting in drug R&D therefore follows market needs, rather than health needs.

A significant part of this search for new drugs is directed towards "me-too" drugs (drugs similar to existing ones) so as to acquire part of larger and more profitable markets (e.g. cholesterol-lowering drugs from the "statin" family). In the United States, less than 5% of the drugs introduced by the top 25 pharmaceutical companies between 1981 and 1991 resulted in therapeutic advances⁸⁴. Of 2257 new products brought to market in France between 1981 and 2000, 63 % were "me-too" medicines. Of these, only 7 products (0.13%) represented a real breakthrough⁸⁵. The American National Institute for Health Care Management performed a comprehensive analysis of the 1,035 new drug products approved by the FDA from 1989 to 2000, only 35% of which were based on new molecular entities, the remaining 65% being based on existing active substances, without any distinct identifiable advantage other than that of broadening the physician's choice⁸⁶.

The more innovative activities of the pharmaceutical industry focus on the search for new breakthrough drugs, new classes of active compounds or new disease targets, often based on knowledge arising from (and funded by) public sector research (e.g. protease inhibitors against HIV in the mid-90s). According to the National Institute of Health (NIH), taxpayer-funded scientists conducted 55% of the research projects that led to the discovery and development of the five top-selling drugs in 1995⁸⁷. These breakthrough drugs may in turn give rise to new families of "me too" drugs, if there is a large enough market to be exploited.

This framework, based on private business interests that exploit fundamental knowledge often accumulated and funded by the public sector, has provided significant advances for human health, but it fails to prioritise real patient needs, notably for diseases that are not frequent in rich countries and thus lack sufficient market incentive.

The fact that this private-interest framework poorly addresses the needs of the millions of people suffering from neglected diseases means that we need to adopt a different, more appropriate framework. Such a framework should mobilise the international research community (public and private) to implement a needs-driven priority agenda, supported by adequate funding and other incentives, and an appropriate capacity-building process.

1- From a few diseases to a more comprehensive agenda

The three examples described in section II clearly show how a needs-driven priority research agenda can be conceived and has identified the most pressing areas where action is needed now. The most benefit can be obtained by targeting these specific areas, while continuing to develop a global structure and policy to ensure a sustained response to these needs and to continue identifying other existing and emerging neglected needs.

Human African trypanosomiasis, visceral leishmaniasis and Buruli ulcer are only three examples of the many diseases that remain neglected within the current medical innovation framework. Obviously, it would be unfair to focus only on those diseases that have been able to attract attention. Neglected diseases are often also forgotten diseases. A continued needs identification process is needed, notably because some diseases only affect neglected populations that have no access to decision makers or media attention, and thus do not benefit from organised patient advocacy groups.

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 (American trypanosomiasis), 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. It is therefore not clear whether the best therapeutic strategy would be to develop a new drug that eliminates the parasite load, or whether in late stage disease, the presence of the parasite is less important than treating the other symptoms.

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 not necessarily known to a researcher in Paris or London, but is glaringly obvious to health care workers treating patients in Sudan or Congo. This example shows that the therapeutic target should take into account the field conditions.

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 prevention or treatment strategy to follow, there is equally little interest in having a drug without a satisfactory diagnostic strategy.

Innovation in drug development is best defined by a therapeutic progress for patients, which means that innovation should be assessed in relation to the relevant therapeutic goal and the current treatment options⁸⁸. An innovative treatment for neglected diseases, and arguably, for all diseases, should address the following criteria: it should be of sufficient pharmaceutical quality, efficacy and safety, and it should be affordable and easy to use, and with relevant diagnostic tools available (that are themselves sensitive, specific, easy to use and affordable).

In the remainder of this paper, we present a strategy to mobilise needs-driven innovation for neglected diseases.

2- Adequate funding for neglected diseases

Neglected diseases have too long been ignored by the private and public R&D sectors. This situation is not acceptable. The impetus for change must come from the public sector in Northern and Southern countries, and with significant implication of the private sector.

How much is needed?

Restarting R&D for neglected diseases will mean committing significant amounts of money. It has always been in the interests of the pharmaceutical industry to inflate estimates of their R&D costs so as to justify the high price of the final product. According to some sources close to the pharmaceutical industry, the cost of developing a new drug can approach 1 billion dollars⁸⁹, but this figure is highly contested. However, it is a telling statistic that in 2001 the pharmaceutical giant Merck spent 13% of its revenues on marketing and only 5% on R&D, Pfizer spent 35% on marketing and only 15% on R&D, and the industry overall spent 27% on marketing and only 11% on R&D⁹⁰.

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, etc⁹¹. 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. Also, the costs of developing a drug is not the same for all indications. While industry's figure certainly is inflated and may not be relevant at all for the development of a drug for neglected diseases (due to the more needs-based decision-making process), it remains clear that pharmaceutical R&D is a lengthy and costly process. Recent not-for-profit drug development initiatives such as the Global Alliance for Tuberculosis drug development (GATB) or the Drugs for Neglected Diseases initiative (DNDi) project a cost of 35-40 million dollars to develop a new drug (not including the cost of failure)⁹².

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 world's population) will require new funding of the order of several hundreds of million euros over a number of years⁹³. 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 poor⁹⁴.

Public responsibility

Given the current EU budget for neglected diseases (no more than 20-25 million for the whole 6th framework programme, except for HIV/AIDS, malaria and tuberculosis, see also annex I), it is clear that a serious effort is needed if one hopes to have an impact. Furthermore, the current EC-research funding for neglected diseases is structured through the Framework programmes, which mostly support research projects for 2-3 years with budgets of around 1 to 2 million euros. Funding application procedures are long and cumbersome, with a typical lag phase between submission and start of the project of 8-12 months. Clearly, this is totally inappropriate for drug R&D, where a project needs to be taken through a costly and complex pipeline over 5-10 years, involving changes in focus and strategy to respond to research results and project needs, and where speed, flexibility and efficient decision-making are crucial.

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 a striking gap in EU support for **translational 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).

There are currently some significant sources of investment from the US, in particular the National Institutes of Health (NIH) and the private charity, the Bill and Melinda Gates

Foundation, that are starting to respond to this problem. Neither the EU nor individual European countries currently have a concerted response to this lack, and the public sector remains noticeably absent.

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 months⁹⁵.

3- 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, with limited success.

3-1- 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 other⁹⁶. At the global level, these two aims should be complementary: we need new medicines, and we want these medicines 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 – drugs 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 drugs would be a strong disincentive for private investment and thus for drug innovation.

Most public decision makers in industrialised countries still expect new drugs 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.

The TRIPS model / Intellectual Property protection

The TRIPS agreement (Trade-Related Aspects of Intellectual Property Rights⁹⁷) is a landmark decision by politicians to globalise and entrench this private interest R&D framework. It is based on the assumption that patents are necessary to stimulate private investment in innovation, the basis of our current knowledge economy.

Some argue that TRIPS will also facilitate private investment in developing countries in general, and in tropical and other neglected disease research in particular⁹⁸. However, the expert analysis of the UK Commission on Intellectual Property Rights (CIPR) concluded in its influential report that “All the evidence we have examined suggests IP hardly plays any role at all in stimulating R&D on diseases prevalent in developing countries, except for those diseases where there is a large market in the developed world (for example diabetes or heart disease)”⁹⁹, a viewpoint that confirmed the earlier statement of the WHO commission on Macroeconomics and Health¹⁰⁰. A striking example of this is that the biggest Indian drug

companies, with a significant R&D capacity, often target their portfolio to the needs and markets of rich countries rather than to the local needs of Indians, a large but low-income market. Ranbaxy and Dr Reddy, two of the leading Indian pharmaceutical companies, are investing heavily in strategies to conquer markets in rich countries¹⁰¹.

Serious concerns have been raised about the possible barrier that patents can represent for R&D. Today, 97% of the patents held world-wide are in the hands of individuals and companies of industrialised countries¹⁰², and obtaining access to these patented compounds and technologies may be a serious hurdle. Moreover, it has been argued that too many patents can stifle innovation rather than encourage it, notably in the areas where its practise is strongest— software, biotechnology and business methods.¹⁰³ Patents limit access to basic technologies and research tools, and increase the cost of public research and make access much more difficult. As the public sector has also started to patent the results of its publicly-funded research, it may be worthwhile to consider specific policies to ensure access to these patents for neglected diseases research.

Thus, the current intellectual property model is unsuitable for needs that do not represent a profitable market. There can be a limited incentive for private companies to invest in drugs for malaria or tuberculosis, because there is a limited high-paying market, especially among international travelers. But there is no rationale at all for private companies to invest in diseases such as Human African Trypanosomiasis, visceral leishmaniasis or Buruli ulcer, where the needs are exclusively those of poor people in poor countries. Not only is there no R&D into new treatments, but the production of the very few drugs available was or is still not secured (pentamidine and eflornitine for HAT, antimony treatment for leishmaniasis, etc.). The failure of the current system is that it aims to fund R&D exclusively through sales.

A response to market failure in rich countries: The Orphan Drug model

In one specific case, governments of rich countries have responded to the limits of a purely market-driven pharmaceutical R&D system: the case of rare diseases. After strong advocacy from patient interest groups, policy makers have addressed this market failure via specific Orphan Drug policies.

It is tempting to draw a parallel between neglected and rare diseases. Rare diseases are responsible for suffering or premature death for a relatively small number of people in the West (and elsewhere), thus representing another small market; “neglected” diseases concern many people in poor countries, who thereby also represent a small market. The needs of patients suffering from these two groups of diseases are not properly addressed by the current market-driven R&D framework, where private companies choose to invest in the most profitable drug markets, such as cardiovascular diseases, central nervous system disorders, stomach ulcer, and more and more lifestyle disease (smoking cessation, weight loss, cures for compulsive shopping, etc.). One major difference however is that in the case of orphan diseases, an artificial market is created (via health insurance systems) by allowing these drugs to be marketed at very high prices. For example, Carbaglu (carglumic acid), used to treat certain rare urea cycle disorders, costs up to 250,000 €/per year¹⁰⁴.

To respond to the lack of R&D for orphan diseases, the EU, USA, Japan and Australia have set up a specific “orphan drug legislation” to create incentives for the industry to develop drugs for these diseases⁹³. These include temporary monopolies even when the drug cannot be patented, tax deductions, grants for clinical trials and very importantly, free drug price-setting

(see example above). This guarantees similar returns on investments for pharmaceutical companies as they would have for drugs developed for standard profitable markets.

The current market-based framework of pharmaceutical R&D is supported by governments, who are also responsible for the ongoing globalisation of this framework. The current pharmaceutical R&D framework does not work for specific needs that fall outside of a high-paying market, but the orphan drug example shows that governments are able to design ad hoc policies to address such particular needs. While the example of orphan diseases cannot be simply extrapolated to neglected diseases, because the key element (purchasing power to reimburse private investment in research) is absent, it demonstrates that if political will exists, specific policies can be designed to correct failures of the system. Neglected patients deserve a similar kind of initiative. **Thus, the EU must consider a strong response to the problem of neglected diseases, as has been done before for orphan diseases.**

3-2- Towards a system ensuring commitment to R&D into neglected diseases

A system must be set up that ensures a sustained commitment into R&D for neglected diseases. Such a framework should integrate:

A needs-driven priority R&D agenda

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

- A comprehensive identification of neglected therapeutic needs throughout the world;
- For each disease, a definition of the optimal therapeutic objectives, based on patient needs and the expectations of health professionals; the ultimate goal of obtaining safe, effective, easy-to-use and affordable therapeutic tools must guide decision-making;
- An analysis of creative R&D opportunities based on the current state of the art in medical research, and a definition of the innovation expected (diagnostics, vaccines, drugs) 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.

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 drugs 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 community¹⁰⁵. 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.

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 leishmaniasis¹⁰⁶, this research mainly focuses on basic research. Because of the way public sector research is organised, financed and assessed, it is far more rewarding for a researcher to continue working on the fundamental biology of a pathogen than to use this knowledge to design and develop new ways to diagnose or treat the diseases caused by them. This continued focus on “upstream” research has resulted in the almost complete absence of research capacity and expertise for pre-clinical R&D phases in the public sector.

Any serious public response to the needs in neglected disease R&D will need to bridge this capacity gap. To avoid further fragmentation of the already-scarce research into neglected diseases, a concerted effort to build centralised pre-clinical research capacity in pharmaceutical sciences in the public sector should be considered. 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 the furthering of 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 system¹⁰⁷.
- 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 sensitised 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.

A role for the private sector

Finally, the role of the private sector needs to be redefined. The pharmaceutical industry 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 to such R&D groups as GATB, MMV, DNDi;
- 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.

Bridging the gaps in the R&D pipeline: translational research is the key

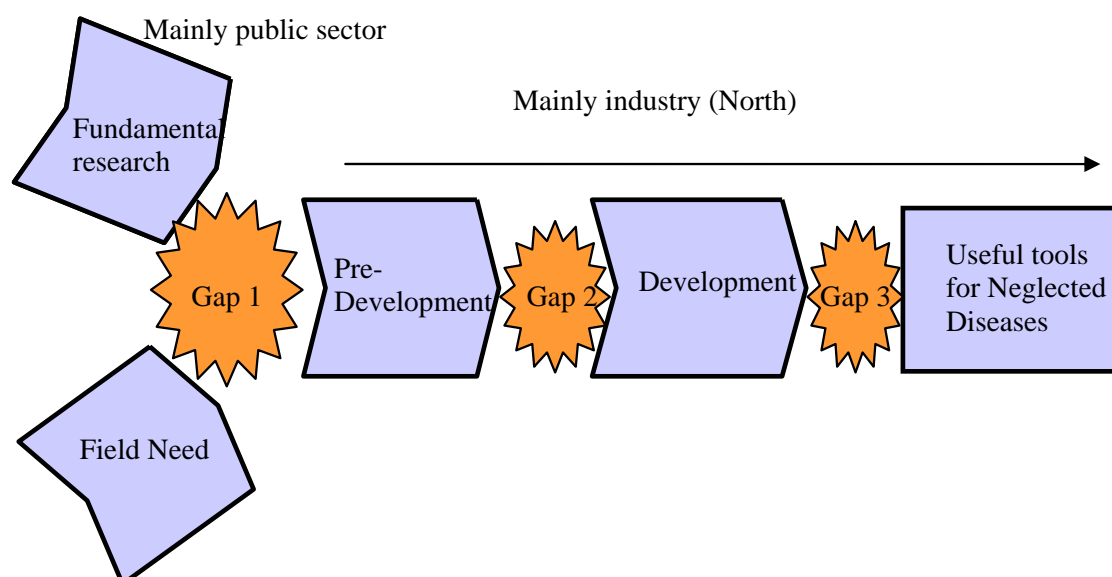


Figure 6: The different stages of a typical pharmaceutical R&D pipeline.

Figure 6 represents 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 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 (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.

4- 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 be 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 problems¹⁰⁸. 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, and especially since the G8 summit in Okinawa in July 2000, 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)¹⁰⁹ exclusively focuses on access to existing drugs for these three diseases; others are donation programmes for a specific medicine (for instance the ivermectin donation programme¹¹⁰). Many are Public Private Partnerships, especially those focusing on pharmaceutical development, such as Medicines for Malaria Venture (MMV), the Global Alliance for TB drug development (GATB) and the International AIDS Vaccine Initiative (IAVI),¹¹¹ but they are generally small and their sustainability is not secured⁹³. Only a few specifically focus on the most neglected diseases, in particular the Institute for One World Health (IOWH) and the Drugs for Neglected Diseases initiative (DNDi) (see box).

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

More than the “big three”

Today, HIV/AIDS, malaria and tuberculosis (TB) receive much media attention, and increasingly also more research attention. However, the “big three” represent 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 HIV/AIDS, malaria and tuberculosis 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, a subsequent leishmaniasis trial may be run by the same clinical research group, provided disease pattern overlap geographically.

Recent responses to the lack of non-profit pharmaceutical development:

The Institute for One World Health and the Drugs for Neglected Diseases Initiative

In recent years, two new initiatives have been created to develop new and improved drugs for some of the most neglected diseases. The US-based Institute for One World Health (IOWH)¹¹² describes itself as a non-profit pharmaceutical company, using existing knowledge and drug research and development capacity in developed countries, using donated intellectual property of candidate drugs to produce new drugs for the poor. IOWH is mainly financed through charitable donations, with a significant part of the funding from the Bill and Melinda Gates Foundation. IOWH has drug development projects ongoing in malaria, diarrhoeal diseases, visceral leishmaniasis and malaria.

The Drugs for Neglected Diseases initiative (DNDi)¹¹³ is a not-for-profit drug development organisation set up by Médecins Sans Frontières (MSF), bringing together a group of founder partners including the Indian Council for Medical Research, Fiocruz, The Kenya Medical Research Institute, the Ministry of Health of Malaysia, Institut Pasteur and MSF, with WHO/TDR as a permanent observer. Mobilising public responsibility for neglected diseases, DNDi will develop collaborative R&D projects with research partners in the North and South, in the public and private sectors. Funding will be sought from governments as well as private donors. The initial priority diseases are sleeping sickness, leishmaniasis, Chagas disease and chloroquine-resistant malaria, and R&D projects cover the whole range of pharmaceutical development, from drug discovery to clinical development. DNDi is based in Geneva, with regional networks in Latin America, Africa and Asia.

A moral challenge for Europe

Currently, neglected diseases are not a major focus of interest for the EU (see annex 1 for a detailed analysis). Most of the available funding is for the European Developing Countries Clinical Trials Platform (EDCTP) which so far focuses on phase II-III clinical trials for AIDS, malaria and tuberculosis. This is a very important and laudable commitment, but presupposes that a mechanism exists to develop the drugs to be tested. Such a mechanism is glaringly lacking. To obtain one clinical candidate starting from a characterised lead compound may easily take 2-4 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 drugs 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 Figure 6 above), there will be no drugs 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 agreements¹¹⁴. The EU-ACP Joint Parliamentary Assembly Resolution on poverty-related diseases and reproductive health in ACP states, provided in annex 7, acknowledges Europe's responsibility for and commitment to addressing these diseases. 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.

5- 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, 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 such as DNDi, relatively small investments could have a dramatic impact.

Specific Recommendations:

- **Mobilise and sustain adequate funding** for neglected diseases. To ensure minimal impact, committed funding of **several hundreds of million euros** must be freed to support the execution of a needs-based priority R&D agenda for neglected diseases;
- **Encourage translational research** to transform the results of basic research into useful medical applications, adapted to the needs of neglected patients
- **Expand the activities of the EDCTP** to include other neglected diseases as well as other phases of clinical development (phase I, phase IV).
- Create a **Centre for preclinical research** to bridge the continual gap of developing drug leads into clinical candidates for neglected diseases (translational research). This centre should complement the activities of the EDCTP.
- **Set up adequate incentives for public research**, including appropriate training, funding, and specific career incentives based on a reassessment of the way merit is evaluated in public research
- **Mobilise the pharmaceutical industry by a mix of incentives and obligations** to contribute to the development of needed drugs.
- Investigate the possibility of an international R&D treaty for neglected diseases, to **establish an alternative model for drug development** based on a needs-driven

priority R&D agenda and public responsibility, outside of the market- and profit-driven framework.

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.

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List of Annexes

- Annex 1: The current commitment of Europe to neglected diseases research
- Annex 2: Depoortere, E, Legros, D, Torreele, E. **Developing a needs-based and rational approach to identify neglected diseases and select R&D projects that could maximally impact treatment options.** *Drugs for Neglected Diseases Working group, MSF, 2001*: A thorough analysis of neglected diseases and the problems in priority setting. Includes analyses of different ways of presenting available data and proposes a “policy strategy” for priority setting for neglected diseases
- Annex 3: Trouiller P, Olliaro P, Torreele E, Orbinski J, Laing R, Ford N. **Drug development for neglected diseases: a deficient market and a public-health policy failure.** *Lancet. 2002 Jun 22;359(9324):2188-94.* An in-depth analysis of the current pharmaceutical discovery process and the failure of the system to address the needs of neglected diseases.
- Annex 4: Legros D, Ollivier G, Gastellu-Etcheberry M, Paquet C, Burri C, Jannin J, Buscher P. **Treatment of human African trypanosomiasis--present situation and needs for research and development.** *Lancet Infect Dis. 2002 Jul;2(7):437-40.* A needs-based analysis of the problems identified in treating HAT
- Annex 5: Guerin PJ, Olliaro P, Sundar S, Boelaert M, Croft SL, Desjeux P, Wasunna MK, Bryceson AD. (2002a) **Visceral leishmaniasis: current status of control, diagnosis, and treatment, and a proposed research and development agenda.** *Lancet Infect Dis. 2002 Aug;2(8):494-501.* An analysis, carried out in a similar way to annex 4, of the needs-based priority agenda for a response to VL.
- Annex 6: Ahoua L. & Torreele E. **Prise en Charge de l'ulcère de Buruli: médicament disponibles et perspectives.** *Epicentre working paper, 2004.* An analysis of the current treatment options for Buruli Ulcer including available treatments and future possibilities.
- Annex 7: **ACP-EU Joint Parliamentary Assembly Resolution on poverty-related diseases and reproductive health in ACP States, ACP-EU 3640/04/fin.** A clear commitment on the part of the EU to addressing health needs in developing countries, and affirms the EU responsibility to act.

Annex 1 - The current commitment of Europe for neglected diseases research

In response to the G8 summit in Okinawa in July 2000 where a global plea was made to “implement an ambitious plan on infectious diseases, notably HIV/AIDS, malaria and tuberculosis”, the European Commission adopted a new policy framework presented in the Communication on “Accelerated Action targeted at major communicable diseases within the context of poverty reduction”¹¹⁵.

The framework aimed to establish a broad and coherent Community response in this area over the period 2001-2006, and identified three objectives for targeted action: impact of existing interventions, affordability of key pharmaceuticals, and research into and development of specific global public goods. This approach has received a high level of political support from developing countries, EU Member States and international development agency partners, civil society and industry. It combines a mix of development, trade and research policy.

Taking into account the outcome of the international ‘High-Level Round Table’ on the new European Community policy, and following the conclusions by the Council, the Commission has then developed a “Programme for Action: Accelerated action on HIV/AIDS, malaria and tuberculosis in the context of poverty reduction”¹¹⁶, limiting its action radius to the three diseases that today have the highest impact (HIV/AIDS, malaria and tuberculosis).

The programme for action (PfA) covers three objectives and corresponding areas of action:

1. Reaching optimal impact of existing intervention, services and commodities targeted at the major communicable diseases affecting the poorest populations;
2. Increasing affordability of key pharmaceuticals through a comprehensive and synergistic global approach;
3. Increasing investment in research and development of global goods targeted at the major communicable diseases.

The 6th Framework Programme (6FP) of the European Commission (2002-2006) is the main instrument of the EC for investing in R&D, with an overall budget of 17.5 billion euro. Under this programme, and following the implementation of the PfA, 400 million Euro was allocated to research related to poverty-related diseases, specifically HIV/AIDS, malaria and TB for 2002-2006. Half of this budget or 200 million Euro goes directly to the European Developing Countries Clinical Trials Platform (EDCTP, www.edctp.org), a new organization set up under article 196 of the EC Treaty to support and implement clinical trials of both drugs and vaccines for the three target diseases in Africa. The other half is available through the Life Sciences and Health section within the main 6FP for basic molecular research, taking advantage of microbial genomics, through to pre-clinical testing and proof-of-principle studies on promising new candidate interventions (vaccines, therapies, and microbicides) against the three target diseases.

While this certainly represents a significant EC support for pharmaceutical research on the three major poverty-related communicable diseases, the other diseases mainly affecting developing countries are left in the cold. Diseases such as “dengue, Chagas disease, sleeping sickness, haemorrhagic fevers, schistosomiasis, river blindness, filariasis and leishmaniasis” as well as other “neglected specific parasitic, bacterial and viral infections, which are an important problem on the regional scale” are mentioned in under the header “A.1.3. Knowledge and technologies to improve control of neglected communicable diseases” in the work program of the INCO-DEV activity of the 6FP, but budget allocations are minimal.

According to the currently open call for projects (call identifier FP6-2003-INCO-DEV-2), some 36.2 million Euros will be allocated to research projects related health and health systems in developing countries by the end of 2004, covering projects ranging from R&D for new interventions for above-listed neglected diseases, research into health care systems and policy management, to research into bio-diverse, bio-safe and value-added crops. The total budget allocated for all other neglected diseases therefore will unlikely be more than 10-15 million euros, possibly even less. In the previous INCO-DEV call for projects within the 6FP, the neglected diseases area was not open for funding. It is expected that the next (2005) round of calls for projects within this FP will allocate another 10 million euro to these diseases, but this still needs to be confirmed.

On April 27th 2004, the Committee on Development and Cooperation of the European Parliament held a public hearing on neglected diseases, to discuss the urgent need for more tools to fight a variety of communicable diseases that mainly affect poor countries. It was concluded that while Europe has taken responsibility towards HIV/AIDS, malaria and TB, and is having impact there, it has increasingly overlooked the other important diseases, which have since become even more neglected. A commitment was made to address this subject during the next legislature of the EP, and to identify appropriate ways to stimulate relevant R&D. It was however emphasized that the reality of the most neglected diseases is very different from the three major ones, also in terms of socio-economic interests and possible R&D incentives, and that solutions can unlikely be extrapolated in a simple way. Public responsibility, both at the national and international level, will need to be the driving force for the most neglected diseases.

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