R&D SYSTEM IS FAILING TO MEET HEALTH NEEDS IN DEVELOPING COUNTRIES

MSF BRIEFING NOTE

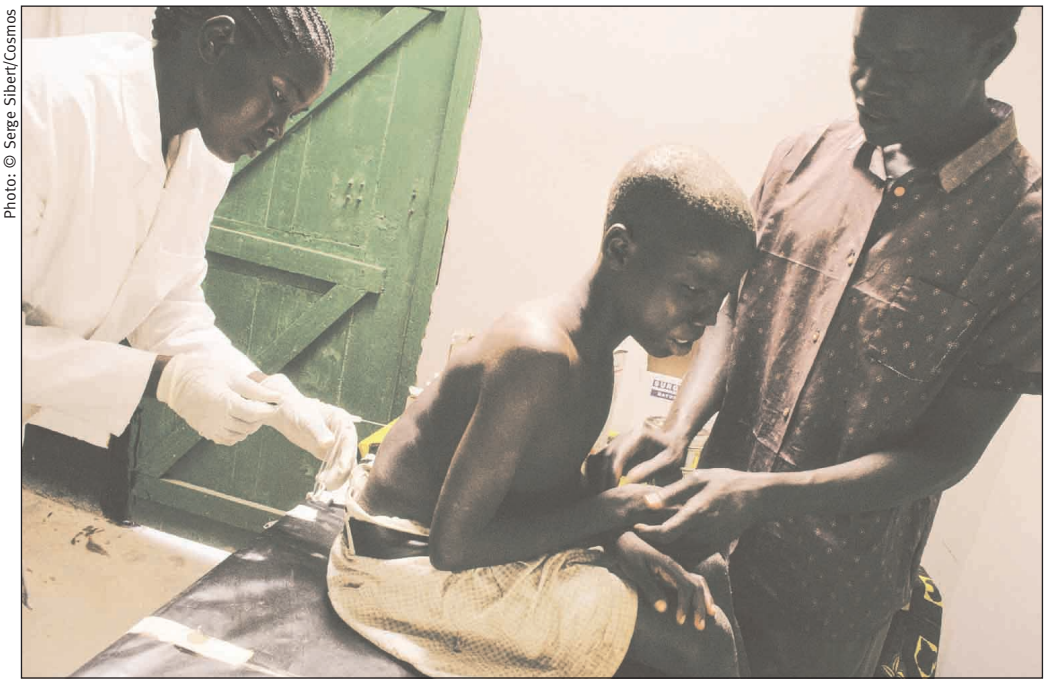


Photo: © Serge Sibert/Cosmos

Lumbar puncture in Uganda. A safer, more accurate test is urgently needed for diagnosis of sleeping sickness.

When there is enough concern and motivation, health research and development (R&D) can yield rapid results. The Severe Acute Respiratory Syndrome (SARS) outbreak in 2003, for instance, led to unprecedented international cooperation and a tremendous marshalling of resources to cope with this new threat. In a matter of weeks, scientists had sequenced the virus, and through successful public and private co-operation, a diagnostic kit was rapidly developed and deployed. Similarly, the anthrax scare in the United States in 2001 led biodefense research spending at the US National Institutes of Health (NIH) to increase from US$53 million in 2001 to US$1.6 billion in 2004.

Sadly, the sense of urgency that resulted in these swift and efficient responses is entirely lacking in R&D for diseases that exclusively or disproportionately affect the poor. Médecins Sans Frontières (MSF) medical teams have been increasingly frustrated in their efforts to treat people suffering from sleeping sickness, kala-azar, malaria, Chagas disease, tuberculosis and other "neglected diseases" for the simple reason that their therapeutic toolbox is virtually empty.

The United Nations Millennium Development Goals has set ambitious targets for health, including reducing child mortality, improving maternal health, and combating HIV/AIDS, malaria and other neglected diseases. But these goals will not be met using the medical tools currently available to health professionals. Urgent action is needed to develop new drugs, tests and vaccines that are adapted to developing country needs, and to make them available at prices affordable to people in developing countries. The 2004 Mexico Ministerial Summit on Health Research, "Bridging the Know-Do Divide to Achieve the Millennium Development Goals", offers an important opportunity to explore ways to achieve this.

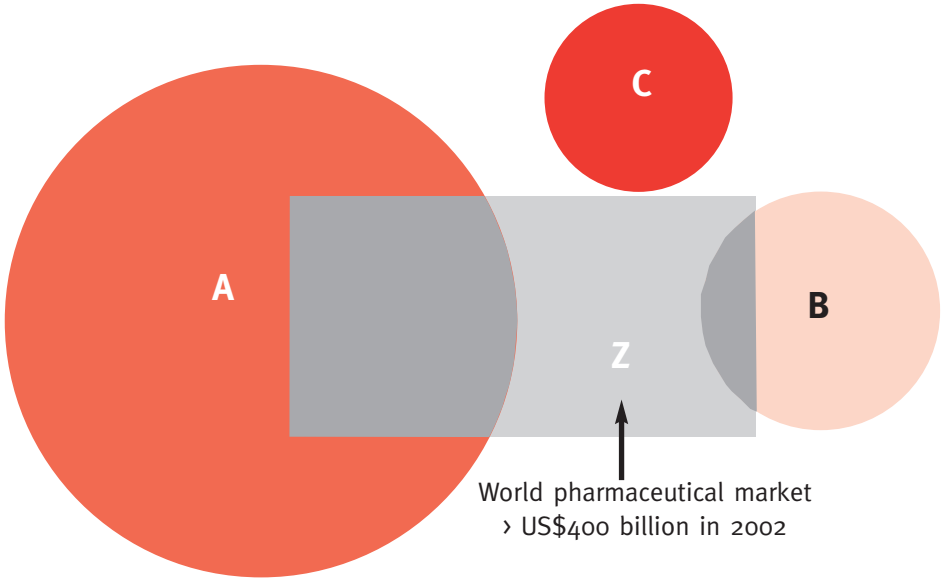
Crisis in access to essential medicines

Recent years have seen growing awareness of the barriers to access caused by intellectual property protection and resulting high prices. But still too little attention is being paid to the failure of the R&D system to develop new drugs for tropical diseases. While unprecedented medical advances in the last few decades have resulted in considerable improvements in health and quality of life in some countries, the vast majority of the world's population has been left behind.

"Neglected diseases" are so-called because few or no drugs exist – or are being developed – for their treatment. Some neglected diseases, such as malaria and tuberculosis (TB), remain of some limited interest to the pharmaceutical industry, while others – the "most neglected diseases" – fall completely outside the scope of industry[1] (see figure 1). They include kala-azar, lymphatic filariasis, Chagas disease, Buruli ulcer and schistosomiasis, tropical diseases which continue to cause significant illness and death across the developing world.

Since the mid-90s, successive "10/90" reports have tracked the imbalance in research spending. Global spending on health research has increased from $US 30 billion in 1990 to $US 105.9 billion in 2001[2]. Yet 90% of this money is still spent on the health problems of less than 10% of the world's population. As a result of this priority setting, only 16 (1%) of the 1,393 new drugs approved between 1975 and 1999 were specifically developed for tropical diseases and TB, diseases that account for over 10 % of the global disease burden[3].

Figure 1: Global pharmaceutical market and disease R&D targets



A – Global Diseases (e.g. cancer, cardiovascular diseases)
affect people everywhere and constitute the major focus of the R&D-based pharmaceutical industry.

B – Neglected Diseases (e.g. malaria, TB, HIV/AIDS)
mainly affect people in poor countries, but a small market in wealthy countries prompts R&D efforts.

C – Most Neglected Diseases
almost exclusively affect people in developing countries who are too poor to pay for treatment. They do not represent a viable market, and therefore fall outside the scope of the drug industry's R&D efforts. Most neglected diseases include sleeping sickness, Chagas disease, Buruli ulcer, Dengue fever, leishmaniasis, leprosy, lymphatic filariasis and schistosomiasis.

Z – Pharmaceutical products that do not correspond to major public health problems (comfort and lifestyle).

Adapted from '*Fatal Imbalance: The Crisis in Research and Development for Drugs for Neglected Diseases*', Médecins Sans Frontières/DND working group, 2001

Photo: © Joanne Wong/MSF

Thailand: this ten-year old boy's daily treatment consists of twelve antiretroviral pills and one powder formulation. Because few children contract HIV/AIDS in wealthy countries, there is little R&D into paediatric antiretroviral treatment.

Neglected patients: People with HIV/AIDS in developing countries

The development of medicines to treat HIV/AIDS appears to be a remarkable success story, with more than 20 highly effective medicines developed in the past 17 years. How did this come about, when other diseases hitting poor countries have been entirely ignored by the pharmaceutical industry? First, AIDS activists in wealthy countries, particularly the US, successfully pushed for considerable public sector resources to tackle HIV/AIDS. Second, and most importantly, HIV/AIDS affects the whole world, so there is a market for antiretrovirals in wealthy countries. If HIV/AIDS had hit poor countries only, patients would probably still be waiting for the first antiretroviral to be developed. Instead, today's global market for HIV-related medicines is $US 5.3 billion. For pharmaceutical companies, AIDS is big business.

Even though this huge market stimulated pharmaceutical innovation, access to resulting health tools was by no means automatic. In poor countries, high prices seemed an impossible hurdle for a long time. But generic competition from manufacturers in developing countries such as Brazil, India and Thailand has brought the price of antiretroviral treatment down from US$15,000 per person per year to as little as US$140.

Yet there are still gaps in AIDS-related R&D, especially for patients in poor countries. For instance, some important medicines need to be refrigerated, which limits their usefulness in many settings. The dwindling number of paediatric cases in wealthy countries has also led to a dearth of paediatric formulations, and tools to diagnose infants and monitor their treatment are mal-adapted to use in many developing country settings.

People living with HIV/AIDS in developing countries can rightfully be called "neglected patients": just as for other neglected diseases, their specific needs in terms of diagnostic and treatment tools are not currently being addressed by the Western pharmaceutical industry.

The current system: Market madness and public policy failure

Universities and other publicly-financed research institutions have always been involved in the early phases of research and drug discovery, and produce a wealth of knowledge about tropical diseases. Basic research receives continuous support from both public research institutions and private foundations, with new information being rapidly generated as the genomes of many parasites are sequenced.

Yet little, if any, of this basic research is translated into the development of new drugs. The reason is that the expertise, infrastructure and management capacity for drug development are almost entirely concentrated in private industries in the West, and they direct their efforts towards developing highly profitable drugs for prosperous markets. To maximise profits, the pharmaceutical industry also increasingly targets lifestyle conditions (e.g. obsessive shopping) and normal lifecycle concerns (e.g. male pattern baldness), and medicalises these through marketing campaigns. On average, pharmaceutical companies spend twice as much on marketing as they do on R&D[4].

As a result of this approach, the pharmaceutical industry has been hugely profitable, occupying the top of the Fortune 500 list for most of the last two decades. Despite being lucrative, however, this system is inefficient, and not just from the perspective of developing countries. There is increasing recognition that relying solely on the profit motive to drive R&D is not only failing patients in the developing world, but is stifling true innovation across the board[5]. For instance, a study published in *The Lancet* in 2002 showed that 68% of all new chemical entities marketed worldwide in the last 25 years were "me-too" products, representing little or no therapeutic gain[6]. It is in any case a vastly wasteful mechanism for encouraging innovation, since only one tenth of drug sale profits is plugged back into R&D[7].

The overriding policy mechanism relied upon to stimulate innovation and finance R&D is the patent system. The rationale of patent protection is that by offering temporary market exclusivity, during which they can charge very high prices, companies can recoup their R&D investments. This system was instituted globally in 1994 through the World Trade Organization's Agreement on Trade-related Aspects of Intellectual Property Rights (TRIPS), which established obligatory standards in intellectual property protection. The TRIPS Agreement is currently the only major international policy instrument to stimulate and finance R&D.

Patents are part of a complex system that can motivate investment in R&D under certain circumstances, in particular when a profitable return on investment can be expected. However, people who suffer from neglected diseases are not a "profitable market". No matter how strong the level of intellectual property protection, R&D will not spontaneously happen for these diseases.

In fact, patents may actually hamper medical research activities because accessing research knowledge may require costly licensing agreements. Compounds which could show promise for the treatment of neglected diseases may therefore be hard to access for research purposes. This concern was clearly recognized by the WHO which, following a flurry of patents filed on the SARS virus, stated that such patents "could have a profound effect on the willingness of researchers and public health officials to collaborate regarding future outbreaks of new infectious diseases."[8]

Moreover, in 2003, the World Health Assembly established the Commission on Intellectual Property, Innovation and Public Health to "produce an analysis of intellectual property rights, innovation, and public health, including the question of appropriate funding and incentive mechanisms for the creation of new medicines and other products against diseases that disproportionately affect developing countries."[9] The creation of this Commission clearly reflects awareness that the current system for driving innovation requires serious examination and that new proposals for national and international action are urgently needed.

Photo: © Roger Job

Testing for TB in sputum samples only detects about 50% of people with the disease.

Efforts to address the problem

Awareness of the lack of effective treatments for neglected diseases has grown in recent years. However, despite considerable agreement on the nature of the challenge, governments have not developed meaningful and viable global policies to ensure needs-driven R&D. In 2000, the G8 committed to "increasing our support at the global level for the R&D of international public goods such as AIDS vaccines; treatment drugs for AIDS, TB and malaria; microbicides and other health commodities" and to "increasing incentives for the development of international public goods according to the priorities for vaccines, drugs and diagnostics set out in the Chairman's Summary." G8 Members also expressed strong commitment to the principle that new tools for diseases affecting developing countries should be considered international public goods (listing vaccines, drugs, methods of treatment and health commodities as examples)[10]. But since then, R&D has progressively fallen off the G8 agenda[11].

Some novel approaches have emerged to stimulate R&D for neglected diseases and produce health tools that are adapted to the needs of people in developing countries. Below is a summary of these initiatives.

■ **The UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR)** was established in 1975 in response to appeals from neglected disease-endemic countries. TDR develops new tools and methodologies to combat ten target tropical diseases, and develops research capacity in developing countries. TDR has contributed to the development of several new treatments for tropical diseases over the past 25 years, but suffers from chronic under-funding.

■ **Public/private partnerships (PPPs) and not-for-profit drug development initiatives** seek to foster R&D for neglected diseases by matching existing capacity, expertise and resources in both the public and private sector on specific projects or diseases. Typically, these initiatives play a coordinating role in setting a disease-specific R&D agenda, raising funds and managing R&D projects. The Bill & Melinda Gates Foundation has become a major source of financing for PPPs devoted to R&D for drugs, vaccines, and diagnostics for neglected diseases. Examples of PPPs include the Global Alliance for TB Drug Development (TB Alliance), the Medicines for Malaria Venture (MMV), the International AIDS Vaccine Initiative (IAVI), and the Institute for One World Health (IOWH). The recently established not-for-profit Drugs for Neglected Diseases Initiative (DNDi) aims to research and develop new drugs for neglected diseases, with an initial focus on sleeping sickness, Chagas disease and leishmaniasis[12]. The DNDi model places responsibility for public health on governments, and is based on leadership from the public sector with contributions and support for the R&D process from the private sector.

■ **Some pharmaceutical industry initiatives** specific to neglected diseases have been announced in the last few years in response to criticism of the lack of R&D for neglected diseases. AstraZeneca has

invested US$35 million over 5 years on R&D for TB in India; GlaxoSmithKline has established an R&D facility in Spain, focusing research on TB and malaria, as well as other neglected diseases such as visceral leishmaniasis; and the Novartis Institute for Tropical Diseases, a partnership between Novartis and the Singapore government, is investing US$122 million over ten years on dengue fever and TB.

Correcting the fatal imbalance: Greater public responsibility

Although the initiatives outlined above may provide valuable lessons for policy-makers in developing innovative mechanisms to stimulate R&D for neglected diseases, they remain patchy and suffer from under-funding. They will require increased support from governments and industry if they are to contribute significantly to R&D for neglected diseases in a sustainable and needs-driven manner.

They also need to be situated within a larger framework that guarantees sustainable health R&D according to global needs and priorities. The current global system for encouraging innovation has failed to ensure access to new medicines and failed to encourage R&D into diseases of the poor. The 2001 Doha Declaration on TRIPS and Public Health acknowledged the need to address intellectual property barriers to accessing drugs, but there has been no similar movement in international policy to address the crisis in pharmaceutical innovation. Redirecting today's knowledge and scientific expertise to address global health needs, and in particular the needs of neglected patients, will require a paradigm shift in the way life-saving or other essential health tools are developed, and how their widespread availability is ensured.

Governments should design and implement policies to stimulate health R&D. These could build on the Essential Medicines concept, acknowledging that some research is more important than other research, just as some medicines are more essential than others. The WHO should lead the process of drawing up an "essential R&D agenda" to define needs and priorities for the developing world. In parallel, an alternative mechanism for stimulating R&D should be developed to overcome the current dependency on the patent system.

It has been suggested that governments could contribute to R&D according to a set "norm", based on the level of drug sale profits that are currently re-invested into R&D[13]. These countries could then choose to achieve this through implementation of the conventional patent system, or try out some other model – for instance, providing increased direct funding for specific R&D through existing not-for-profit structures or other mechanisms, or setting up a competitive system that rewards organisations providing specific R&D output with a one-off or long-term payment. This idea shows definite potential and should be seriously considered as an innovative way to redirect R&D towards developing country needs.

Stimulating R&D for neglected diseases will not be possible without genuine involvement of developing countries themselves. They are best placed to evaluate needs and priorities, and often also to implement R&D. Sharing knowledge and transferring technology will enable developing countries to build on their existing expertise and capacity in R&D and lead the process of redressing the imbalance in today's status quo. Communicating research outcomes in an open and collaborative way disrupts the standard profit-based research process, but can substantially speed up the rate of innovation and could rapidly help boost R&D into neglected diseases.

[1] Pécoul B., Orbinski J, Torreele E (eds). Fatal Imbalance: the Crisis in Research and Development for Drugs for Neglected Diseases. Médecins Sans Frontières/Drugs for Neglected Diseases Working Group, Geneva, Switzerland, 2001.
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The Mexico summit offers an ideal platform to address the failure of the current system to stimulate R&D for neglected diseases. Countries should come to an agreement to achieve the following:

- ***Define an international needs-driven R&D priority agenda***

  A well-defined and needs-driven R&D agenda is required to assist policy makers, funding agencies and the research community in setting priorities for developing safe, effective and affordable medicines. As the only legally mandated international government agency responsible for global health, the WHO should work toward establishing an essential R&D agenda for neglected diseases.

- ***Adequate international financing of health R&D***

  There is an urgent need for a new funding mechanism to support R&D on an ongoing basis. All governments will need to participate according to their means. Among other measures, not-for-profit initiatives working to develop new drugs, vaccines and diagnostic tools for neglected diseases should be funded at levels which enable them to reach their objectives.

- ***Equitable pricing and access principles for government-funded research***

  Countries investing in health research should adopt equitable pricing policies to ensure that the poor also have access to innovations resulting from government-funded or university research. Governments should also require access to the compounds and tools that result from research in order to stimulate follow-on innovation elsewhere.

- ***Establish and strengthen international mechanisms for exchanging and transferring research results, knowledge and technology***

  Open information is a cornerstone of scientific development. Strengthening openness and transfer of technologies on a global basis will greatly help developing countries, by improving access to information and ideas, and by accelerating the development of science and technology. Financial commitments should be supplemented by commitments to help deal with possible intellectual property difficulties, such as obtaining access to patented platform technologies to enable the development of needed products.

A global approach to health research will only be possible with true international cooperation and public sector leadership firmly committed to ensuring that advances in science and medicine contribute to alleviating suffering and meeting the critical medical needs of the developing world.

NEGLECTED DISEASES: FACTS AND FIGURES

■ **Sleeping sickness:** 60 million people in 36 African countries at risk, over 60,000 deaths per year.

"*The first-line protocol for second-stage sleeping sickness here is melarsoprol, a horrible, Frankenstein drug. It burns the vein when you inject it and you can never predict the patient's reaction: whether they'll tolerate it or convulse or even go into a coma.*"

Virginia Morrison, nurse, MSF Angola.

Virtually eliminated in the 1960s, sleeping sickness is making a vengeful comeback in Africa. But there is currently no means of accurately detecting whether the disease has advanced to its second phase, in which the parasite invades the victim's brain. Without treatment, patients in this second phase will inevitably die. Existing treatments are old, toxic, and poorly adapted to resource-poor settings.

MSF treats patients with sleeping sickness in Angola, the Central African Republic, the Democratic Republic of Congo, Congo Brazzaville, Uganda and Sudan. From MSF's perspective, the greatest obstacle to fighting the disease is the lack of new, better diagnostic tools and drugs.

■ **Chagas disease:** 100 million people at risk across Latin America, 50,000 deaths per year.

"*Chagas patients are of no interest to pharmaceutical companies and have no-one to advocate for their cause; many of them die without ever being diagnosed. We desperately need new drugs to treat people with Chagas.*"

Silvia Moriana, coordinator, MSF Bolivia

Chagas is a parasitic disease endemic in Latin America. It causes irreversible damage to inner organs and Chagas sufferers usually die of heart failure. Existing Chagas treatments are toxic and take one to two months to complete. They are only effective in the acute and undetermined stage of the disease in children – there is currently no treatment for the chronic form of the disease.

MSF cares for patients with Chagas disease in Bolivia and Nicaragua. MSF advocates for R&D to improve early diagnostic tools effective at all stages of the disease, and to develop new drugs for both the acute and the chronic form of the disease.

■ **Tuberculosis:** 2 million deaths and 8 to 9 million new infections per year.

"*It is now 2004 and we still struggle to accurately diagnose TB. Sometimes when we are treating patients for TB based on clinical symptoms, they don't respond, and we don't know whether the person has multi-resistant drug TB or hasn't got TB at all.*"

Dr Olga Ascurra, MSF Malawi

Fuelled by the HIV/AIDS pandemic, TB is spiralling out of control. The diagnostic test still in use today in most developing countries was developed in 1882 and only detects about half of the people with TB – in children or people with HIV/AIDS, this figure is even lower. Treatment takes six to eight months to complete and relies on drugs that were developed 40-60 years ago.

MSF treats TB patients in Angola, Abkhasia/Georgia, Burma, Burundi, Caucasus/Chechnya, Chad, China, Congo, DRC, Ethiopia, Guinea, Ivory Coast, Kenya, Malawi, Sudan, Somalia, Thailand, Uganda and Uzbekistan. MSF believes the development of new diagnostic tests and R&D into new TB medicines is critical if we are to have any hope of tackling the enormous global burden of tuberculosis.

CAMPAIGN FOR ACCESS TO ESSENTIAL MEDICINES

MEDECINS SANS FRONTIERES

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