Fighting Neglect

Finding ways to manage and control visceral leishmaniasis, human African trypanosomiasis and Chagas disease

MEDECINS SANS FRONTIERES

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Children lining up for screening of sleeping sickness in remote villages, reached through the mobile clinic. Central African Republic, 2011.

Foreword

Despite affecting millions and killing tens of thousands each year, visceral leishmaniasis, sleeping sickness and Chagas disease garner little attention from drug developers, policy makers, or the mass media.

There are, at this very moment, hundreds of thousands of people who need a very specific kind of help. We know where they are likely to be found. We know what they need. The resources and the expertise to help them do exist. But in too many cases, they are neglected, and this neglect can be fatal.

There are 17 diseases that have been classified as neglected tropical diseases, or NTDs. They are, as the report that follows says, a collection of infections that tend to prey on the impoverished and nearly always take profound physical, medical, and economic tolls on their hosts and their families. It's been estimated that more than half a million people die from NTDs each year.

And yet most of these NTDs are neglected still. It has been far too long.

For the past 25 years, Doctors Without Borders/Médecins Sans Frontières (MSF) has been working with a special focus on three life-threatening NTDs: Kala azar (or visceral leishmaniasis), and sleeping sickness (or Human African trypanosomiasis), which are both always fatal if left untreated; and Chagas Disease, which can lead to fatal complications. Despite affecting millions and killing tens of thousands each year, these diseases garner little attention from drug developers, policy makers, or the mass media. MSF is publishing this report as part of its ongoing effort to show what these diseases are doing to people who live far from the public eye—and who, because of poverty and isolation, have no voice of their own. It is our hope that this report will illuminate the main issues facing the treatment and control of these diseases, that it will convey MSF's experience working with them, and that it will, ultimately, help spur the sort of research and development that can have a tremendous impact on the lives of those afflicted.

I have been part of MSF's sleeping sickness programs in Angola and the Republic of Congo, countries shaped by the conditions in which the disease thrives: conflict, poverty, mass movements of populations, and little in the way of an effective health care system. In many ways, the experience was indicative of the themes addressed in this report. A decade ago, the best drug available to treat sleeping sickness was so toxic that it killed 5% of the people who took it. Because of a dearth of available diagnostic options, performing a painful and invasive lumbar puncture was then, and still is today, the only way to ascertain the stage the disease was in. Though the number of patients was substantial, those patients were poor, meaning pharmaceutical companies felt there was no profitable market in designing new drugs and diagnostics for their care. And national governments and donor countries alike did little to push an agenda that could lead to greater research and development on their behalf.

There have, nonetheless, been advancements in sleeping sickness treatment, much of it spurred by research that has involved MSF working with other organisations, in particular the Drugs for Neglected Disease initiative (DNDi), which MSF helped found. But even the recent new drug combination has its drawbacks.

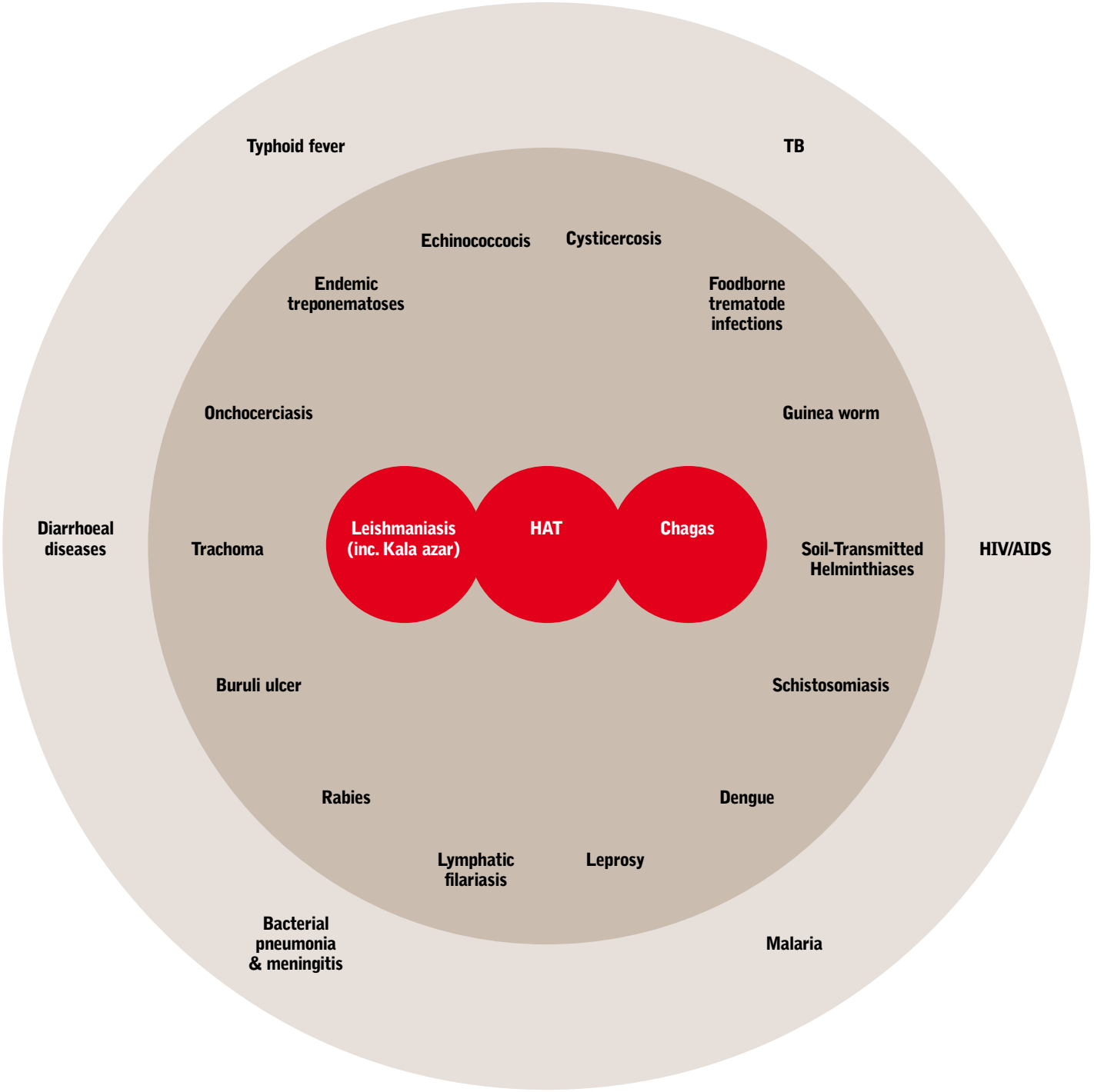
Organizations such as the Gates Foundation and some governments recently pledged more resources to NTD control, which is a very welcome development. But there remains an urgent need for additional, sustainable, and sustainably funded treatment programs that also cover life-threatening sleeping sickness, Chagas, and kala azar, in addition to the other NTDs. And there is room for national governments in disease endemic countries to take greater responsibility for their own efforts and a much greater role in setting the agenda going forward.

It is not an easy road ahead. The challenges are many. To cite just one: patients are hard to reach because many live in isolated or insecure environments, so screening is incomplete, surveillance is shoddy, and follow up care is limited. But having been so deeply involved with MSF's sleeping sickness program, and knowing what I do about MSF's commitment to the people who suffer from three of the deadliest NTDs, I also know what is possible. If the will is there, if the effort and resources are put forth, lives will be saved. People will be treated and cured and will go on to live healthy and productive lives. If these diseases are no longer neglected, they will not be nearly as fatal.

Dr. Unni Karunakara
International President
Médecins Sans Frontières/Doctors without Borders
Geneva, Switzerland

Overview

Tri-Tryps, NTDs and other poverty-related diseases



Poverty-related diseases

Neglected tropical diseases NTDs*

Tri-tryps / kinetoplastids

* Based on the WHO list of NTDS

Overview

New methods and medications have had positive results in the field, and there's now a clear sense of the new products that need be developed. But to make this translate into real progress towards the control of visceral leishmaniasis, sleeping sickness and Chagas disease, strong political will is required to increase programmatic funding and spur further innovation.

A total of one billion people—one of every seven individuals on Earth—are afflicted with what the World Health Organization (WHO) classifies as neglected tropical diseases, or NTDs. There are 17 in all, a collection of bacterial, parasitological, and viral infections that prey on the impoverished and take profound physical, medical, and economic tolls on their hosts[i]. The most common infections in people who live on less than $2 per day, NTDs kill an estimated 534,000 people each year[1] and force many others to expend inordinate amounts of time, money, and energy in order to maintain some semblance of a normal and active life.

And yet the fact that these diseases have been labeled "neglected" has not meant that they—and the people suffering from them—are getting the attention, the resources, or the research and development they require. For far too long now, contracting an NTD has meant entering into an even deeper state of marginalization and joining a population as neglected as the diseases themselves.

For more than 25 years, Doctors Without Borders/Médecins Sans Frontières (MSF) has been actively engaged in the case management and control of a subset of NTDs caused by the so-called Tri-Tryps, or kinetoplastids. These are sleeping sickness (Human African Trypanosomiasis, or HAT); visceral leishmaniasis (VL, also known as kala azar); and Chagas disease (or American trypanosomiasis).

These are life-threatening parasitological infections that are transmitted by insect vectors. They collectively affect hundreds of thousands of people on four continents. Visceral leishmaniasis (VL) alone causes more than 50,000 deaths

[i] Buruli Ulcer, Chagas disease(American trypanosomiasis), Cysticercosis, Dengue/dengue haemorrhagic fever, Dracunculiasis (guinea-worm disease), Echinococcosis Fascioliasis, Human African trypanosomiasis, Leishmaniasis, Leprosy, Lymphatic filariasis, Onchocerciasis, Rabies, Schistosomiasis, Soil transmitted helminthiasis, Trachoma and Yaws.

annually. It is difficult to estimate precisely the mortality associated with sleeping sickness. The 7,139 reported cases in 2010 are only a partial reflection of the burden of the disease[ii]. There are still thousands of cases that are left undiagnosed and untreated, therefore at high risk of death. Chagas disease affects between eight to ten million people worldwide and causes 12,500 deaths every year; it kills more people than any other parasitic disease in Latin America.

MSF has also developed specific programmes against Buruli Ulcer [see page 78], schistosomiasis, yaws and dengue, and treatment is provided to patients presenting with an NTD in any of the projects. But in the main, MSF's field work and advocacy has focused on the diseases linked to Tri-Tryps.

HAT, VL, and Chagas disease all tend to be focused in limited geographical areas and in specific groups. Within these endemic areas, the disease burden is relatively high and considered a major public health risk. MSF has programmes for each of the three diseases in the regions where they are most endemic.

Some of the poorest and most inaccessible regions in the world

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Most sleeping sickness "hot spots" are located in politically unstable countries, such as Democratic Republic of Congo, Central African Republic, and South Sudan. In India, VL is concentrated in Bihar, one of the poorest states of the country, while in East Africa, the incidence of VL is very high among migrant and displaced populations in places like Ethiopia and South Sudan. In Latin America, most communities with the highest burden of Chagas disease are located in remote rural areas in countries such as Bolivia and Paraguay. MSF programmes are usually housed in isolated primary health care facilities. If not for MSF's logistical support, these facilities would likely lack electricity, making it difficult to establish appropriate laboratory services or to store medicines at the low temperatures they require.

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Another shared characteristic of these diseases is that they all have limited diagnostic and treatment tools available for them. Investment in research and development (R&D) that might improve the situation is minimal, however, and political will is weak. In this context, MSF seeks both to meet the medical needs of patients and to speak out about the ongoing neglect at many levels in order to work towards bringing about a positive transformation.

Main MSF projects on neglected tropical diseases (NTD)
(in 1st trimester 2012)

[ii] This number refers to reported cases of both *t.b. gambiense* HAT and *t.b. rhodesiense* HAT. But in the following chapter, sleeping sickness or HAT will refer only to *t.b. gambiense* HAT, the most common form of sleeping sickness.

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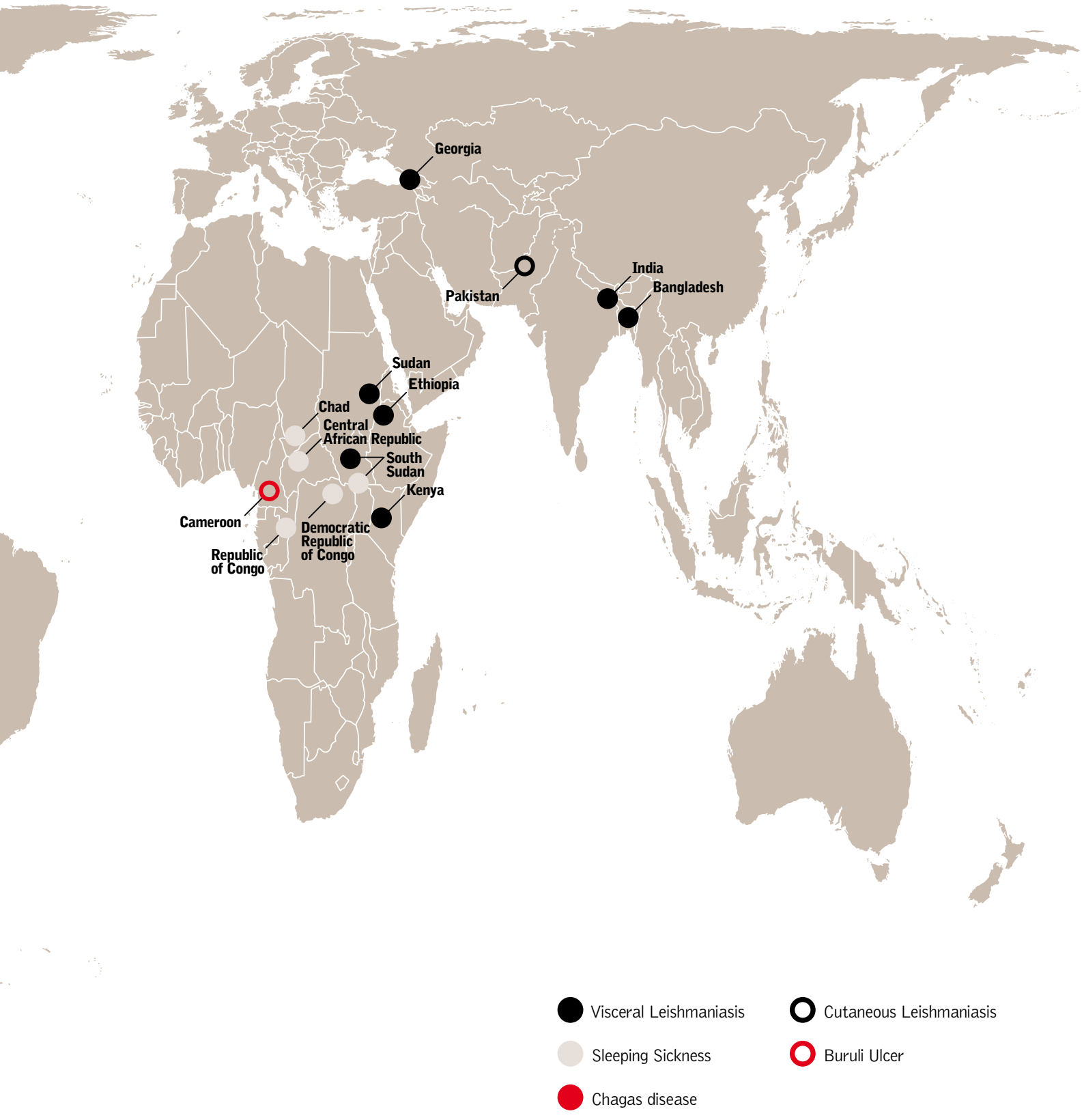
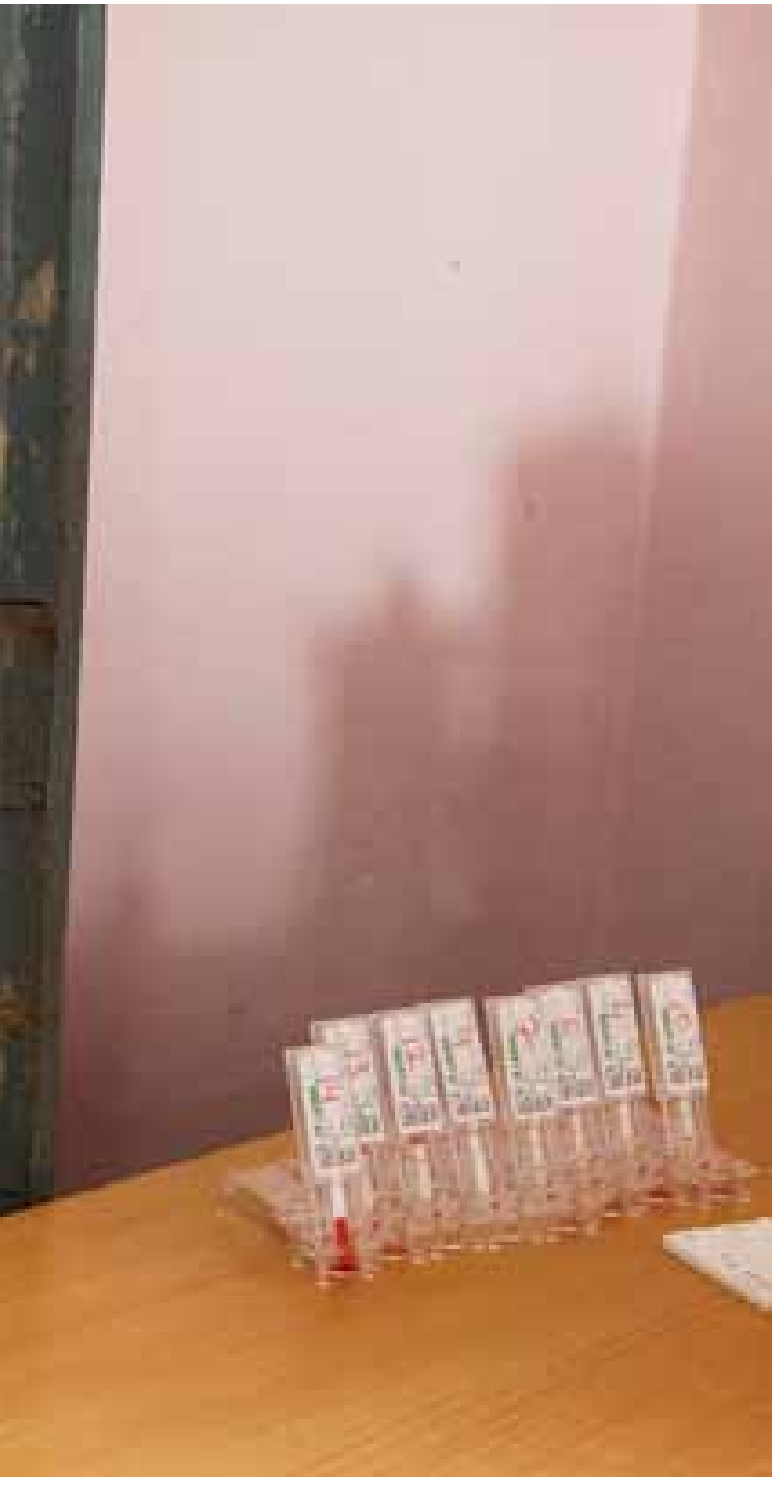

Georgia
Pakistan
India
Bangladesh
Sudan
Ethiopia
Chad
Central African Republic
South Sudan
Kenya
Cameroon
Democratic Republic of Congo
Republic of Congo
Visceral Leishmaniasis
Cutaneous Leishmaniasis
Sleeping Sickness
Buruli Ulcer
Chagas disease

So-called "tool-deficiency" is not an excuse for inaction

Sleeping sickness (HAT), visceral leishmaniasis (VL) and Chagas disease belong to a subcategory of neglected diseases that have been labelled "tool-deficient" because the majority of available diagnostics and treatments are antiquated due to lack of R&D and require specially trained staff and strong logistical support. While new tools are desperately needed for these diseases, this does not mean that nothing can or should be done today[2]. MSF's experience has shown that quality care can in fact be delivered to most of those affected—including in hard-to-reach communities—through innovative strategies and adapted, improved diagnostics and treatment protocols.



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Patient waiting for her results of the rapid test for visceral leishmaniasis. Vaishali district, Bihar State, India, 2011.

Reaching out to war-torn communities and the rural poor

Many of MSF's interventions with the Tri-Tryps diseases have been undertaken in places with ongoing conflicts. Most active HAT projects are located in regions where it is difficult to conduct comprehensive care and control programmes. Still, MSF has found that providing testing and care is not impossible if the interventions are well-planned, well-funded, and supported by strong logistics. In 2011, for example, MSF treated more than 1,200 HAT patients in the highly insecure Haut-Uélé and Bas-Uélé districts in eastern DRC [see page 68].

Another example: In East Africa, conflict-driven population movements contribute to the increased burden of VL. The outbreaks that have hit South Sudan between 2009 and 2011 are related to the large influx of returnees from the north, people who no longer have the natural immunity that many southerners developed over time. In spite of the pervasive violence, however, MSF was able to establish 11 treatment centres in South Sudan to improve access to health care for these communities [see page 32].

In more stable contexts, MSF has introduced strategies to diagnose and treat patients in remote areas through community outreach and decentralised services. The idea behind this is to reach patients before they become so sick that they need hospital care. And now the use of rapid diagnostic tests (RDTs) for VL and Chagas disease means there are far more effective ways to locate people actively suffering from these diseases.

We're really helped in our work by the rapid test now available for visceral leishmaniasis. It is so easy and simple to use that almost anyone on the medical team can now carry out the testing. This means that if there's an outbreak of the disease in some remote area of the region, we are able, through deployment of the rapid test, to identify and confirm the disease quickly in most patients and put them on treatment before their condition deteriorates.

Tito Gatkoi Kach, MSF Clinical Officer in Leer hospital, South Sudan

RDTs for VL and Chagas disease: An ongoing revolution

The rk39-antigen-based RDT is being used in suspected first-time episodes of VL in MSF's programmes in South Asia, East Africa and Georgia. This allows diagnosis to be carried out in a decentralized fashion and in peripheral health structures [see page 33]. In Fulbaria, in Bangladesh, rk39 is used to actively seek out cases by outreach teams that screen suspects in all households located within 200 metres of a reported index case.

Similarly, the Stat-Pak RDT, which has been shown to perform effectively when it comes to diagnosing Chagas disease, is being used as first-line diagnostic test in MSF programmes in South America. A comprehensive evaluation of RDTs is currently being coordinated by MSF. A combination of RDTs will hopefully soon replace the two complex serological tests that are still required for confirming Chagas disease, thus facilitating access to diagnosis of at-risk communities [see page 51].

MSF's Chagas programmes also decentralise treatment in rural settings in Latin America, and MSF's research data showed that it was feasible to manage the side-effects of treatment of adolescents and adults with chronic Chagas disease even in the most remote areas. Simultaneously, MSF coordinated both community-based and nation-wide campaigns to raise awareness about Chagas, and, wherever possible, primary health care workers were trained and supervised on case-management [see page 48].

Shorter and better treatments to ease burden on patients and health facilities

For many decades, there was little movement in the development of new drugs for VL, HAT and Chagas, simply because it was not considered a profitable market. In 2003, MSF, together with the Oswaldo Cruz Foundation (FIOCRUZ) of Brazil, the Indian Council of Medical Research (ICMR), the Kenya Medical Research Institute (KEMRI), the Ministry of Health of Malaysia, and the Institut Pasteur of France (with the Special Programme for Tropical Disease Research (WHO/TDR) as permanent observer) created the Drugs for Neglected Diseases initiative (DNDi) to develop new drugs and treatments for the most neglected communicable diseases. One of the first achievements has been the evaluation of new shorter-course combination therapies for HAT and VL that were soon after introduced in MSF programmes. Through its continued funding to DNDi—US$4.7 million in 2010—MSF is the fourth largest philanthropic funder of neglected disease R&D[3].

In 1999 MSF, having experienced the dire need for field-adapted treatments for neglected patients in remote settings, gave evidence to the unacceptable lack of R&D for neglected diseases. By committing the MSF Nobel Peace Prize money to the MSF Access Campaign for Essential Medicines and its "Drugs for Neglected Diseases Working Group", which led to the foundation of DNDi in 2003, MSF and other key actors – notably public institutions in neglected disease endemic countries – came together to show that medical innovation must also be applied to those who need it most. Ten years later, we can say that together we have made headway, but major gaps in R&D for neglected diseases still remain.

Bernard Pécoul, Executive Director, DNDi

DNDi had several objectives: to improve the safety of treatment, to lower its cost, to increase its effectiveness and to make it more patient friendly. Before the new combination treatment for HAT was introduced, for instance, many programmes used melarsoprol for stage 2 occurrences of the disease. Melarsoprol is a toxic arsenic derivative developed in 1949; it kills up to 5% of those who take it. NECT (Nifurtimox and Eflornithine Combination Therapy), which is the combination therapy MSF and DNDi developed, is a far safer combination. It has eliminated the need for dreaded melarsoprol treatment and contributes to the increased acceptance of HAT control programmes by communities [see page 66].

Similarly, DNDi's SSG-paromomycin (SSG-PM) combination therapy shortened the treatment duration for VL from 30 to 17 days (the previous treatment regimen involved SSG monotherapy). It improved outcomes and adherence rates, especially in unstable settings such as what is now South Sudan. It also reduced the congestion inside treatment centres and reduced the costs of both treatment and hospitalization [see page 33].

In South Asia, to cite another example, MSF was one of the first organisations to introduce liposomal amphotericin B (L-AmB) as first-line treatment for VL. L-AmB, unlike most other treatments, is well tolerated and shortens treatment time down from current treatment options to a mere two hours if used in single dose. L-AmB could soon become the primary first-line treatment in South Asia, either used alone or in a combination with another drug (as was recently recommended by a World Health Organization Expert Committee) [see page 36].

New challenges: Treating the most complicated cases

For a long time now, certain severe and complicated cases of neglected diseases were usually deemed too difficult to treat. But MSF is now exploring the treatment of patients with late-stage cardiac complications of Chagas disease. Tools to diagnose and to treat heart failure are key components of a new MSF programme scheduled to start in 2012 in Bolivia.

Likewise, HIV/ VL co-infection in Africa is an almost untreatable mix that results in repeated relapses, increased drug unresponsiveness, and eventually death. In northwest Ethiopia, MSF has been introducing a promising new combination therapy with high dose liposomal amphotericin B and Miltefosine [see page 34]. Randomized clinical trials are already planned in hopes of achieving further progress in the case-management of HIV/VL patients.

There has been some significant progress in efforts to control HAT, VL and Chagas disease. MSF has contributed to this effort through collaborations with the Ministries of Health of various countries and other partners. Since the late 1980s, MSF has screened more than 2.9 million people for HAT and treated more than 50,000 cases, while also treating more than 100,000 patients for VL. From 1999 through the present day, MSF screened over 80,000 people for Chagas disease and treated more than 4,100 patients.

These data are encouraging, but they also illustrate the need to extend access to quality case-management and control tools to all endemic areas. To reach all those who need to be treated for the three diseases, and to progress towards the ambitious objectives to eliminate VL in South Asia, and to eliminate HAT globally by 2020, as outlined by the WHO roadmap[4], greater national and global support for vector control and treatment programmes are needed, as is enhanced R&D to develop better and more affordable field-adapted diagnostics and treatments.

Combining vector control and treatment

HAT, VL and Chagas disease are all transmitted by insects—tsetse flies, sandflies and triatomine bugs respectively. In order to reduce the transmission of these diseases, it is crucial to combine vector control with the screening and treatment of patients. Before a patient starts treatment for Chagas disease, for example, their home should be cleared of bugs to prevent re-infection (or the infection of kin for the first time). The plan signed by the governments of India, Nepal and Bangladesh to eliminate VL in South Asia relies both on treating active cases and also spraying insecticide in people's houses. In Bangladesh, the Ministry of Health chose to start its indoor residual spraying programme within an area covered by the MSF treatment programme and used MSF's georeferencing of cases to identify priority targets. Regarding HAT, better tsetse fly traps are now available and should be deployed in affected villages to reduce the fly population and the incidence of the disease[5]. MSF is working on better integrating vector control within its NTD programmes at community level.

Preparing treatments for sleeping sickness patients. Tambura, South Sudan, 2006.

Better access, drugs and diagnostics

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One reason why these diseases remain neglected is that they do not constitute a lucrative market for pharmaceutical companies and R&D is therefore directed elsewhere. The result is that most available drugs and diagnostics for visceral leishmaniasis (VL), sleeping sickness (HAT) and Chagas disease are outdated, and the supply of what does exist is constantly in jeopardy because so few companies produce them.

A shaky supply of available drugs

Almost all drugs for these diseases currently rely on a sole supplier. This is a precarious situation that brings with it an increased risk that the supply will be interrupted and treatment targets will go unmet. Take benznidazole, the treatment for Chagas disease that was until March 2012 solely produced by LAFEPE, a state-owned Brazilian company. Delays in producing one ingredient in the compound (among other issues) caused a major shortage of the drug at the end of 2011 [see page 54].

Almost all the drugs used for the treatment of HAT, VL and Chagas disease also rely on a single supplier. Bayer, for example, is the only producer of nifurtimox, which is used for Chagas disease and HAT; Sanofi-Aventis is the sole producer of eflornithine, pendamidine and melarsoprol, which are used for HAT; and paromomycin, which is used for VL, is only manufactured by Gland Pharma. Private companies have shown little interest in taking over manufacturing of certain key products, such as the CATT-test for HAT screening. To date, the millions of CATT-tests supplied each year are produced because of the commitment of the publically-funded Institute of Tropical Medicine in Antwerp.

Access to liposomal amphotericin B (L-AmB), the WHO-recommended treatment for VL, is challenging for different reasons. L-AmB is a drug that can be used either for VL or for fungal infections. There are strong market opportunities in developed countries where L-AmB is widely prescribed for the treatment of opportunistic fungal infections in immunosuppressed cancer and transplant patients. To date, Gilead, an American pharmaceutical company, has the only product (AmBisome) that has been made available for purchase internationally by governments, the WHO, and non-governmental organizations. Gilead offers AmBisome for VL treatment at an "access" price of US$18 per vial for NGOs and the public sector in developing countries, a little less than one-tenth of its price in wealthier nations. In practice, a full treatment course for one average patient in developing countries now costs a total of between US$120 and US$450, depending upon what dosage of AmBisome needs to be used. This is still too high, however. A recent study suggested that L-AmB, although it's one of the treatments with the highest efficacy, would only become the most "cost-effective" option for VL in South Asia if its price was brought down to below US$10 per vial[6].

In December 2011, Gilead and the WHO signed a five-year agreement stipulating that Gilead would donate enough AmBisome to treat roughly 10,000 VL patients in low-income countries each year. This agreement will help address immediate needs. However, it only covers a small proportion of the

global annual case load of 250,000 to 300,000 patients. MSF is also concerned that others might see this donation as a reason to back off the search for the sustainable solution that the development of quality assured and affordable L-AmB would represent. Either way, with demand increasing over time, it will not be possible to rely on a donation as the sole source of the worldwide supply[7].

Quality assessment for NTD drugs faces multiple challenges

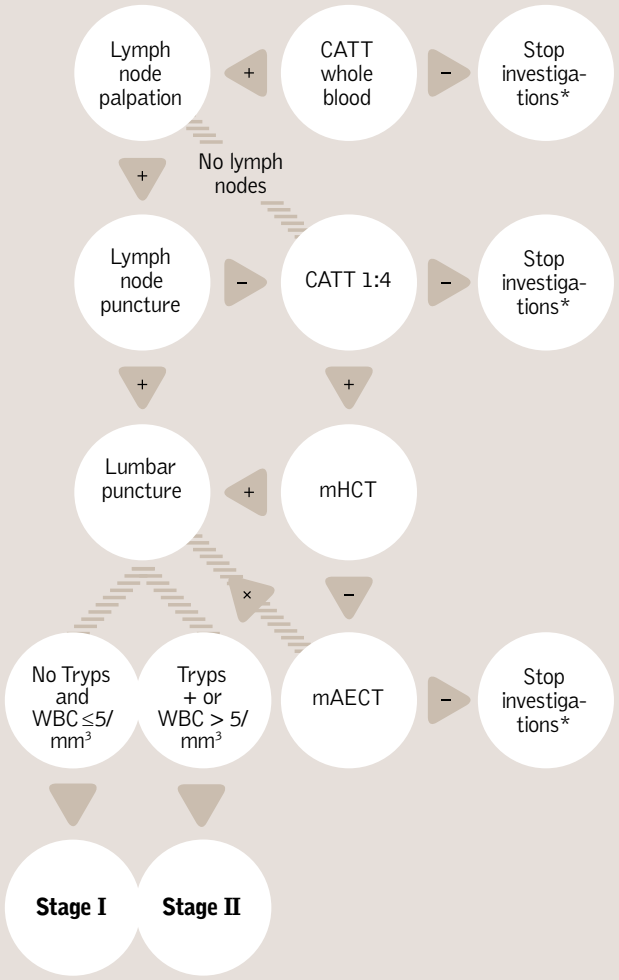
Access to quality assured drugs for NTDs is a challenge for several reasons. Because these diseases are essentially diseases of the developing world, several of the drugs required to treat them have not been licensed for use in industrialized countries (where they are not needed) and, thus, have not been evaluated by a stringent drug regulatory agency. The quality assurance of the product is evaluated at the point of registration in the country of use. The national drug regulatory agencies in many NTD-endemic countries have limited capacity to evaluate manufacturers for compliance with WHO guidelines on Good Manufacturing Practices (GMP) or to evaluate registration dossiers. The risk related to these products is further complicated because the majority of the drugs are very old and do not have monographs in international pharmacopoeias to guide product specifications.

Expanding the mandate of the WHO Prequalification of Medicines Programme (PQ) to NTDs would help to address this issue and give drug regulatory authorities in developing countries the option to "fast track" registration processes by recognising the WHO PQ assessment. However, companies will only apply and go through the process of the Prequalification Programme if all the main buyers in particular countries require such a quality standard.

Sleeping sickness: a complex diagnostic tree with multiple branches

Diagnosing HAT still relies on a three-step, resource-intensive process that ultimately requires a lumbar puncture to determine the stage of the disease the patient is in at that moment. There is profound need for both an RDT that can fully diagnose HAT and a staging marker that does not require lumbar puncture [see page 71].

Example of MSF diagnostic tree for sleeping sickness



*In case of suggestive symptoms or signs such as persistent fever and headaches, neuropsychiatric disorder, go to next step of the diagnostic algorithm

Seeking tests for cure desperately

While Rapid Diagnostic Tests (RDTs) now make it easier to diagnose VL, and with similar progress expected soon for Chagas disease, there have not yet been any breakthroughs in the quest to simplify the diagnosis of HAT.

In addition, for all three diseases, there is an evident need for newly-designed tools for the follow-up of patients after they complete treatment, especially in remote settings. In order to confirm cure, patients with HAT must now undergo several lumbar punctures up to two years after treatment. People treated for VL must undergo lymph node, bone marrow or spleen aspirates if it is suspected that they have not responded to treatment or that relapse may have occurred. These are invasive procedures that either lack sensitivity or carry significant risks.

At present, treatment for Chagas disease is considered successful if serological tests show that certain antibodies are no longer present. This is unreliable, though, because it can take more than ten years for the antibodies to disappear after successful treatment in adults. In practice, this means that there is no real-time means of assessing cure in treated Chagas disease patients [see page 51]. This can discourage people from seeking treatment and can undermine efforts to find new treatments.

New drugs needed for frontline health care facilities

In spite of recent improvements, all the available treatments for VL, HAT and Chagas disease have limitations in terms of safety, efficacy, duration and/or complexity of use. There is a need for new, safe and efficient short-course treatments, preferably oral ones.

DNDi has recently supported the development of a new paediatric dosage form of benznidazole. It was registered in Brazil in December 2011. A child-adapted treatment for Chagas disease had been long awaited since the production of the nifurtimox paediatric formulation was discontinued. Success rates of treatment of Chagas disease are higher—and side effects fewer—in infants and children. Clinicians had to cut and manually crush adult tablets of benznidazole to administer care to infants. This carried a risk that the children would not get the proper dosage.

Side-effects of benznidazole are more common in older patients, for whom precise treatment success rates are still not known. Better medicines are therefore needed, especially for the millions of adolescents and adults living with chronic Chagas disease. Ideally, the treatments of the future should be more effective and should have fewer side-effects and shorter treatment protocols.

No completely oral treatment for VL exists right now. Miltefosine, the only available oral medicine, needs to be used in combination with another drug to prevent development of resistance to the drug. Miltefosine cannot be used in women of reproductive age without contraception up to four months after treatment, because it may cause malformations of the foetus. And while liposomal amphotericin B is a very promising treatment, it is not practical for use in health posts with minimal infrastructure because it must be administered intravenously, it must be transported by cold chain, and it must stored at below 25°C. In East Africa, SSG & paromomycin offers a more adapted treatment for VL but it is not ideal. A new orally administered, safe, short-course treatment for VL is sorely needed.

Treatment of stage two HAT has improved since the introduction of NECT. The improved treatment still requires hospitalisation and multiple intravenous infusions. The goal of current R&D efforts is to develop an oral treatment that is effective for both stages of disease, eliminating the need to conduct an invasive lumbar puncture in order to determine whether the disease is at stage one or stage two [see page 71].

Diagnosing and treating VL, HAT and Chagas disease patients still requires trained medical staff and heavy logistics. MSF's vision is to further integrate diagnosis and treatment into primary health care facilities, which would increase coverage and sustainability. But this is very difficult to accomplish with the tools that exist today, and premature attempts to integrate treatment within the packages of care that polyvalent teams provide may even be counter-productive. Only the development of new tools that that respond better to patients' needs will fundamentally change the equation.

Negligible commercial markets, neglected patients

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New methods and medications have had positive results in the field, and there's now a clear sense of the new products that need be developed. But to make this translate into real progress towards the control of visceral leishmaniasis (VL), sleeping sickness (HAT) and Chagas disease, strong political will is required to increase programmatic funding and spur further innovation.

Prioritizing neglected diseases at international levels

To achieve sustained results on NTDs, sustained and intensive programmatic funding is needed. Knowing this will not make it so, however. The funding landscape for NTD programmes has been, and still is, limited and unstable.

Historically, donors have allocated very limited resources for the control of NTDs. On average, from 2003 to 2007, only 0.6% of total annual development assistance for health (health ODA) provided by OECD member states was allocated to NTDs[8].

Interestingly, the US government recently increased its funding for NTDs significantly, to US$89 million in 2012[9,10]. However, they have since announced that there will be a 25% decrease in this funding in 2013. In January 2012, the Gates Foundation pledged US$363 million commitment to support NTD over next five years[9]. Meanwhile, the British government committed to increase its support to NTDs from £50 million (US$79 million) to £245 million (US$386 million) between 2011 and 2015[11].

This is positive news, but all these initiatives almost exclusively target worm diseases and trachoma. The additional funding should be extended to other NTDs—especially the ones that are fatal if untreated. While the Obama administration has pledged to fund efforts to battle Chagas disease when it appears in the United States, it should also devote a portion of its overseas aid to the effort in countries where Chagas is endemic.

In essence, if there is going to be progress over the long term, donors needs to devote sustained and reliable funding to the effort. It does not bode well that by mid-2013, the Belgian Cooperation is expected to withdraw its critical support to the national HAT programme in the DRC, the country with more cases than any other nation in the world. If surveillance and treatment capacity are not maintained, the incidence of the disease will likely skyrocket again, reversing two decades of steady decline [see page 70]. In addition, this withdrawal would jeopardise the key contributions that the DRC HAT programme has made to international clinical trials.

I do believe that the establishment of the International Federation of Persons Affected by Chagas is the greatest sign of hope for the people who have this disease. It is important to know that there will now be a strong massive force to request governments from different countries to include, in their national health programmes, better resources and more structured actions.

Manuel Guttiérez, Chairman of the International Federation of Persons Affected by Chagas Disease (Findechagas). October 2010

Support at the national level

People affected by HAT, VL and Chagas disease often live in remote areas and have little political voice. The allocation of domestic public resources in treatment programmes are thus also usually minimal. Of late, there have been some positive political changes in countries where the diseases are endemic, but more money from the national budget has to be allocated to these efforts if they are going to yield sustained results. Among the recent developments:

- In 2011, Kenya became one of the first African countries to launch a comprehensive plan against several NTDs, including VL[12]. This is a good start, but an estimated US$70 million is needed to fully fund the five-year plan.

- Bolivia now recommends that everyone up to the age of 60 years that is diagnosed with Chagas disease be offered treatment. Other endemic countries should follow suit.

- In 2005, India, Nepal and Bangladesh launched an ambitious plan to eliminate VL in South Asia. The initial plan, which included the use of miltefosine monotherapy, needs to be revised to integrate the safe, effective and shorter treatments that were recently developed and recommended by the WHO.

Children receiving information and education about Chagas disease, its transmission and its prevention as part of the initial phase of the project. Chaco, Paraguay, 2012.

Recognising the limited scope of drug donations

In the absence of a global funding mechanism to supply diagnostics and drugs for NTDs, the WHO NTD strategy has been, for the most part, based on company donations of medicines[1]. All drugs for HAT are donated by companies. Nifurtimox is also donated for Chagas disease treatment. Donations of liposomal amphotericin B for VL will be obtained in 2012 for a relatively small number of patients.

These donations are important stop gap measures for diseases that affect a limited number of people. This is the case for HAT, as all needs assessed by the WHO are covered by the donations and MSF provides the global logistics for the HAT drug distribution. But not all donation agreements come with long-term commitments to supply a given treatment for all those who need it. In addition, donations can lead to using the most readily available treatments rather than the most appropriate treatments identified in evidence-based guidelines. This has been the case for Chagas disease treatment, as nifurtimox, the second-line drug, is donated, whereas benznidazole, the recommended first-line treatment is not[13].

Challenging the current R&D model

The market-driven and patent-based R&D framework has often failed to address public health needs in developing countries. According to an MSF study, only 18 of the 1,556 new drugs that were developed between 1975 and 2004 were for tropical diseases—and eight of those were for malaria only[14]. The main incentives in the current system for drug, diagnostic and vaccine development—the ability to sell products at high prices—do not encourage innovation for neglected diseases, for which the market is minimal. The best-case scenario for NTDs would be the introduction of new financing schemes that "de-link" or "separate" the funding of R&D from the sales revenues the end product generates and in this way pays for R&D upfront rather than through product prices—providing a pathway to orient R&D towards priority health needs rather than market priorities[15].

Overall, the dearth of resources for NTD drug development is striking. In 2010, for instance, the total reported funding for R&D for all neglected diseases, excluding HIV/AIDS, malaria, and TB, was US$903 million[3]. (To put this into perspective, Gillette reportedly spent upward of US$750 million developing its Mach 3 Razor, and that was more than a decade ago[16].)

Meanwhile, R&D funding for HAT, Chagas disease and leishmaniasis (including VL) decreased by almost 10% in 2010. More than 90% of the US$148 million earmarked for these diseases in 2010 came from philanthropic and public funders. In the same year, the pharmaceutical industry reported a total investment of less than US$12 million for the three diseases[3]. As a comparison, the reported overall R&D spending of Novartis, the Swiss giant pharmaceutical company, exceeds US$8 billion.

Market-driven R&D and public health needs: a mismatch

In a landmark 2006 report, the WHO's Commission on Intellectual Property Rights, Innovation and Public Health stated[17]: "Too few resources are likely to be devoted to developing drugs, vaccines and diagnostics that address the needs of people living in developing countries, because they are inherently unprofitable, or the relationship between investment and risk, in relation to potential profit, is unattractive to the private sector.(...) There is no evidence that the implementation of the TRIPS agreement (increasing patent restrictions) in developing countries will significantly boost R&D in pharmaceuticals on (neglected diseases)".

The bulk of R&D funding for NTDs comes through product development partnerships (PDPs). A PDP is a collaborative not-for-profit organization that steers and coordinates R&D of new diagnostics and treatments. Three major PDPs currently target HAT, VL and Chagas disease: the Drugs for the Neglected Diseases Initiative (DNDi: VL, HAT, Chagas), the Institute of One World Health (iOWH: VL), the Foundation for Innovative New Diagnostics (FIND: VL, HAT).

Currently, PDPs have promising compounds moving into clinical trials. But as these pipelines mature, they need more funding. Without sustained support, existing new drug candidates for neglected patients could wither and never reach those for whom they are intended. While PDPs have made significant progress, it should be said that they are part of the solution, not the solution itself. PDPs are elaborating new pathways for drug development, but their scope is limited compared to the vast R&D needs for neglected diseases. Furthermore, investments in R&D for neglected diseases are a far cry from those for more profitable areas such as cardiovascular diseases or even hepatitis C. More systematic changes are needed to ensure that innovation is driven in such a way that it meets health needs and that its fruits are affordable and available.

Drugs for Neglected Diseases initiative (DNDi), a PDP concerned with access

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The DNDi model was designed to reduce development costs and to ensure access for patients. Created in 2003 by a coalition of public institutes and not-for-profit organisations, including MSF, DNDi aims to address patient needs by combining a short-term strategy of improving existing treatments and drug formulations with longer-term goals of delivering innovative medicines by developing new chemical entities that correspond to a disease's ideal target drug profile. With a relatively small budget—approximately €120 million in total for the period running from 2003 to 2011—DNDi has facilitated the development and implementation of six new treatments, including NECT for HAT, SSG&PM for VL in Africa, combination therapies for VL in Asia, and a paediatric dosage form of benznidazole for Chagas disease. DNDi has built a robust pipeline as well, with more than 15 pre-clinical and clinical candidates, including 11 entirely new drugs. Continued investment is necessary to see the projects to fruition.

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More ways to "de-link" the costs of R&D from the prices of new medical tools

In addition to grants and subsidies through PDPs, other "de-linked" approaches are needed. Prize funds, for example, can incentivise innovation for the greatest medical needs by offering, once a product has been developed or a predefined milestone reached, cash prize rewards that cover the costs of research—rather than paying for research through high prices backed up by patent monopolies. At the same time, prizes can guarantee that end products will be affordable by including a price cap in the target product profile and/or by requiring open licensing to allow competition from other producers. MSF is exploring the feasibility of a prize for the discovery of new biomarkers to assess parasitological response to treatment of Chagas disease, a first step towards an early test for cure.

The Priority Review Voucher (PRV), which the US Food and Drug Administration (FDA) has offered since 2007, is another innovative approach to creating incentives for neglected disease research. A company obtaining FDA approval of a medicine for one of the listed neglected diseases receives a valuable voucher for fast-tracked review of any other (more profitable) medicine. The mechanism in its current format has several drawbacks, however. It does not cover all neglected diseases (Chagas is left out, for instance). It does not include provisions that guarantee access to the drug that is developed. And it does not exclude drugs that were developed long before the PRV was established but are not registered yet in the US. All these aspects must be revised for the PRV incentive to work effectively on behalf of patients.

Knowledge-sharing is another important concept that could speed up R&D. PDPs, including DNDi, have established several bilateral agreements that provide open access to compound libraries in which molecules can be screened for neglected disease applications. Additionally, WIPO Re:Search, a new consortium of private and public sector organisations and the World Intellectual Propriety Organisation (WIPO) to share intellectual property and other assets, was launched in October 2011. The objective is for different types of "contributors" to put their relevant intellectual property, including compounds and regulatory data, into a pool, allowing "users" the opportunity to use them to develop and produce new tools for a list of 21 neglected diseases. MSF supports the concept of open access to drive research, but the terms here are too limited. Re:Search restricts royalty-free licences to least-developed countries (LDC), with access for other developing countries subject to case-by-case negotiations. None of the 21 countries where Chagas is endemic is an LDC, and neither is India, the country with the highest number of cases of VL. At a minimum, WIPO needs to expand the scope of this initiative to cover all disease-endemic developing countries[18].

A need for radical changes

Addressing the challenges posed by neglected diseases requires radical changes in public health and R&D policies. MSF welcomes the recommendations of the WHO's Consultative Expert Working Group on R&D Financing and Coordination[19] which calls for the establishment of a binding instrument for R&D related to Type II and III diseases and the specific R&D needs of developing countries in relation to Type I diseases[iii]. Such an instrument can ensure that four fundamental questions for neglected disease R&D are addressed: how to ensure sufficient, sustainable funding; how to set R&D priorities; how to coordinate this research globally; and how to support incentives to spur innovation driven by health needs. Negotiations on the shape of this instrument should begin at the WHO in order that sufficient, predictable funding for R&D is secured, coordination is provided to direct this funding and incentives that delink the cost of R&D and price of the product are supported.

As these negotiations take place, comprehensive NTD plans still need to be implemented and backed in endemic countries, in the immediate term, by a greater commitment of domestic resources and international aid. Innovative ways to spur innovation on NTDs, such as Prize Funds that provide both R&D driven by health needs and equitable access, need to be designed and funded, and more public funding needs to be directed towards PDPs. In the medium term, as proposals at the WHO for a new global framework on R&D develop, UN member states should engage fully with the process in order to ensure that the instrument created is capable of overcoming the current deficiencies in financing and coordination for R&D.

[iii] According to the WHO's CIPIH report[17]: "Type I diseases (...) are incident in both rich and poor countries, with large numbers of vulnerable population in each. Type II diseases (...) are incident in both rich and poor countries, but with a majority of cases in poor countries. Type II diseases are often termed neglected diseases. Type III Diseases (...) are overwhelmingly or exclusively incident in the developing countries, such as sleeping sickness (...). Type III diseases are often termed very neglected diseases."

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Recommendations

After decades of neglect, the recent improvements in programmes and research on sleeping sickness (HAT), visceral leishmaniasis (VL) and Chagas disease offer some cause for optimism. Some of the recent advances are making it possible to find and treat more cases, which not only reduces mortality but also helps to reduce or even break disease transmission. MSF has spearheaded the implementation of new diagnostics and treatments that better address the needs of patients. And the results have been readily apparent. But coverage remains very low and millions of people still need to be screened and treated for HAT, VL and Chagas disease.

There's a long way to go before patients suffering from these diseases can expect to find universally accessible and medically adequate facilities and regimens. If greater programmatic support can be devoted, and if better tools can be developed, diagnosis and treatment capabilities in frontline health posts will be bolstered and coverage against these diseases will increase markedly.

In order to get better access to diagnosis and treatment for HAT, VL and Chagas disease, MSF calls upon:

Ministries of Health (MoH) in Endemic Countries to scale up outreach and active case-finding at the community level; to promote the use of the available rapid diagnostic tests; to prioritize these diseases (including financially); to train more treatment providers on case management.

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Donors to include VL, HAT and Chagas disease in the recent and future NTD financing initiatives; to fully support scale up of screening and treatment and to maintain surveillance when incidence of disease decreases.

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The World Health Organization (WHO) to provide enhanced guidance to endemic countries in order to implement the latest treatment guidelines; to extend the mandate of the Prequalification Programme to NTDs in order to assess quality assurance of drugs.

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Pharmaceutical companies to register relevant drugs in all endemic countries.

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WHO, MoH in endemic countries and **donors** to better shape the market of drugs through fully-financed pooled orders and support for generics suppliers; donation agreements with **pharmaceutical companies** should remain the first-line procurement strategy only for diseases with limited numbers of patients (HAT).

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In order to stimulate R&D on HAT, VL and Chagas disease in response to patients' needs, MSF calls upon:

WHO and its Member States to implement the recommendations of the Consultative Expert Working Group on R&D Financing and Coordination and to begin negotiation towards the establishment of a binding convention under the WHO constitution for R&D needs in developing countries.

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Donors to provide additional grants to product development partnerships as their pipelines of new diagnostics and drugs are maturing; to support new incentive mechanisms based on "delinkage" to spur innovation on neglected diseases, including prizes for early-stage discovery of biomarkers for follow-up of patients after treatment and other greatly needed tools.

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Pharmaceutical companies to invest more significantly into R&D for NTDs; to widen the geographic scope of open innovation platforms for neglected tropical diseases (e.g. WIPO Re:Search) to cover all disease-endemic developing countries, not only least developed countries.

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फैंटर

Visceral leishmaniasis (kala azar)

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Visceral leishmaniasis (kala azar)

The epidemiology and dynamics of visceral leishmaniasis are very different in East Africa compared to South Asia. Visceral leishmaniasis in East Africa comes in epidemic waves that flourish amid weak national health infrastructures, mass displacements, and the HIV pandemic. In South Asia, visceral leishmaniasis affects larger numbers, but there are more opportunities for effective disease control.

In its history, MSF has treated more than 100,000 patients for visceral leishmaniasis (VL), mainly in Sudan and South Sudan, but also in Ethiopia, Kenya, Somalia, Uganda, India, Bangladesh, Georgia and Yemen. The epidemiology and dynamics of visceral leishmaniasis are very different in East Africa compared to South Asia. Its control therefore requires different regional strategies.

Field-based innovation to improve case management and control

Over the years, important research and medical innovation has taken place in MSF programmes, driven by the evident need to improve survival rates and patient care. MSF continues to play a key role by performing operational research and using that research to advocate for changes in national and international policies and practices.

MSF publications in peer-reviewed medical journals[1] have included studies on rapid diagnostic tests, or RDTs, which expand access to early diagnosis and lifesaving treatment in remote areas; clinical trials that show the effectiveness of generic drugs, which makes treatment far more affordable; operational research on the implementation of new drugs and combination treatments, which can decrease mortality, reduce side effects and shorten treatment durations; papers putting forth our knowledge

MSF Nurse attends a patient with visceral leishmaniasis at the MSF Primary Health Care Center in Pibor, South Sudan, 2009.

Patient with visceral leishmaniasis being examined in Bihar, India 2011.

and treatment protocols for patients co-infected with HIV and VL; accounts of the clinical aspects and risk factors for death, which can contribute to improved patient management for severe VL; analyses of the existing obstacles to wider access to care; and evaluations of the impact of impregnated bednets on disease control.

As with other NTDs, MSF's work with VL goes beyond providing lifesaving treatment and improving diagnostic and treatment protocols. We also aim to address the neglect of people, go there where others do not and do what others do not.

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Visceral leishmaniasis in East Africa: fragile states, migration, HIV

© ASIA KAMBAL

Care being provided to visceral leishmaniasis patients, during the epidemic in Tabarak Allah, in Al-Gedaref state, Sudan, 2010.

Visceral leishmaniasis in East Africa comes in epidemic waves that flourish amid weak national health infrastructures, mass displacements of non-immune populations, and the HIV pandemic.

An emergency response to outbreaks

MSF first encountered VL in 1988, when the organization responded to an outbreak of an initially unknown disease in camps for displaced southern Sudanese in Khartoum. The disease, which was later identified as VL, was characterised by prolonged fever, extreme weight loss, anaemia, and an enlarged spleen[2]. These patients had fled from war-torn Western Upper Nile region, where VL had not been reported before, but where a devastating outbreak was at that moment decimating the population.

After those initial encounters with the disease, MSF treated 19,000 VL patients in what is now South Sudan from 1989 and 1995. The work took place under very difficult circumstances. Mortality rates had ranged from 38% to 57% of the total population since the start of the epidemic in 1984, according to an MSF mortality study[3]. Some 100,000 people from Western Upper Nile died of VL in those years[4]. And it became clear that MSF would need to engage with the disease in a significant way, particularly given its neglected nature, its links with conflict and extreme poverty, the geographical remoteness of the area, and the challenges posed by diagnostic shortcomings and expensive treatment protocols. In many ways, that has remained the case through the present day.

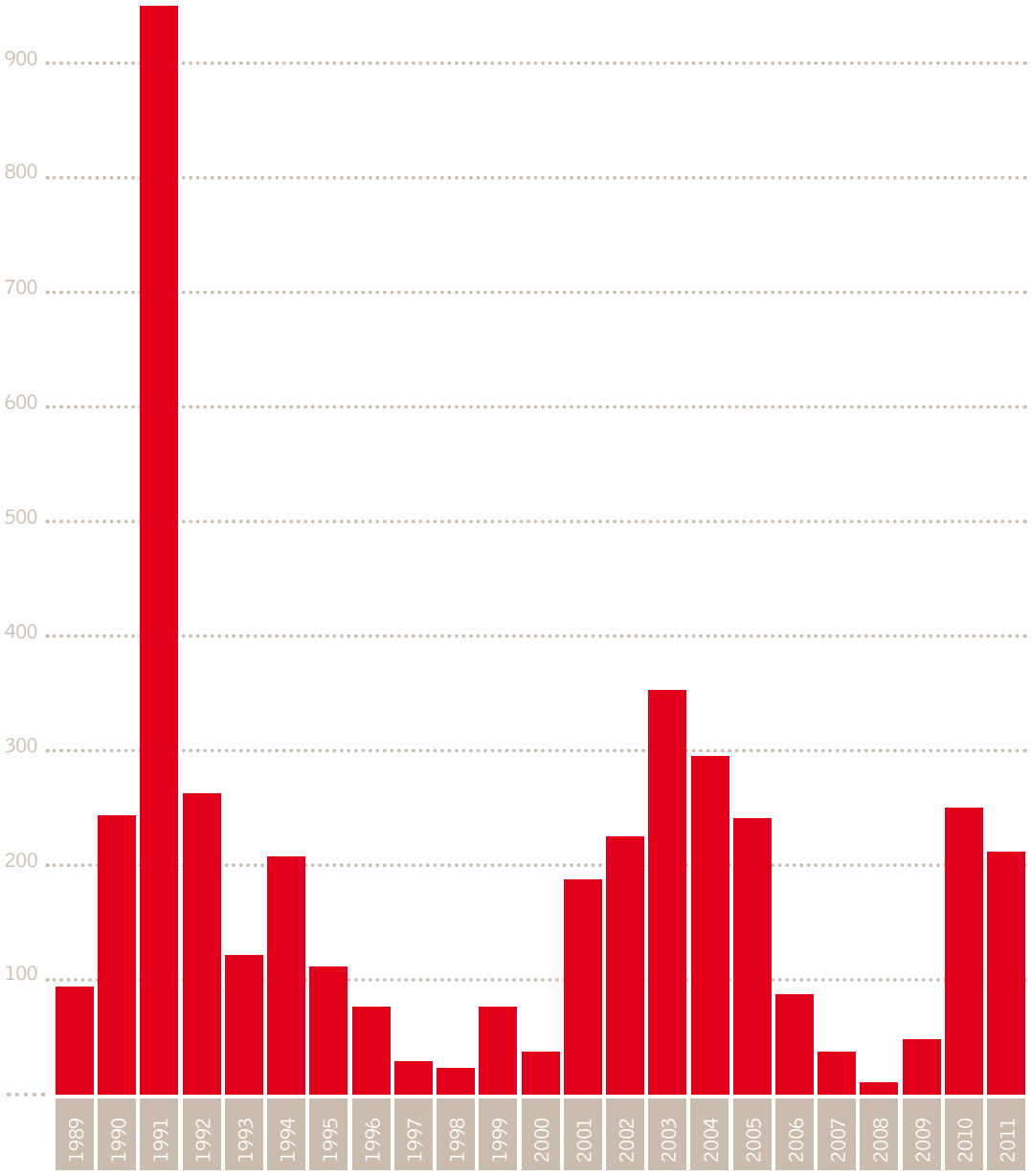
South Sudan: Decentralised treatment services in a fragile state

Over the past two decades, protracted epidemics in South Sudan have shown that VL can cause astonishingly high mortality and infection rates. The epidemiology of these outbreaks has been shaped—and enabled—by years of armed conflict and the complex humanitarian emergencies that ensued. These include the mass displacement of the population, widespread malnutrition, the absence of health services and infrastructure, and, more recently, an influx of non-immune returnees.

Currently, South Sudan is in another epidemic wave. It emerged in 2009 and 2010 in Jonglei and Upper Nile States, and through the middle of 2011 more than 10,000 cases were treated (4,500 of them by MSF). This latest outbreak is considered to be the beginning of a multiyear epidemic wave that tends to last three to five years and to occur every eight to ten years (See graph). In 2011 and into 2012, case numbers have remained high and the epidemic area has expanded geographically to other areas.

Primary VL cases treated by MSF in South Sudan, 1989-2011

Source: MSF program data



MSF currently has 11 VL treatment sites and provides support to the MoH and other NGOs in the form of technical support, the expansion of treatment sites, the training of health workers in the proper diagnosis and treatment, donations of drugs, and the facilitation and coordination of drug orders.

In 2002, MSF began implementing a combination treatment that involved 17 days of SSG (pentavalent antimony) and paromomycin. This combination regimen has recently been officially adopted by South Sudan as the first-line regimen, a decision that was influenced by DNDi-sponsored multi-country studies of its efficacy and the recommendations of WHO Expert Committee's. Previously, treatment with SSG monotherapy had taken 30 days. The shorter treatment duration reduces the burden on patients and staff and frees up space in the congested programs. The logistics are not as complex, the infrastructure needs are not as great, and, most importantly, the treatment results have been better[5]. The exception to this protocol are severely ill, pregnant and elderly (>45 years) VL patients, who receive liposomal amphotericin B at a dose of 30 mg/Kg total dose, because SSG and other antimonials have been shown to be associated with poor clinical outcome and high mortality in these patients[6]. Not all anti-leishmanial drugs are registered in VL endemic countries in East Africa, which limits the capacity to import them and to provide the needed treatment options.

MSF's strategic response to the epidemic has been to decentralise diagnostic and treatment services. This improves access, facilitates early diagnosis and treatment and thereby saves more lives. Even with decentralized services, however, many patients still have to walk for days to reach a treatment facility in a country that is largely without a functional health system, passable roads or basic services.

"My youngest boy, Deng, is 2 years old. He became very sick with a very high fever that lasted many weeks. He was vomiting, had diarrhoea and became very thin. I brought him to our closest health clinic from my village. There they told me he had malaria so he was given medicine for malaria, but it did not help him. Then they treated him for typhoid. That failed too. Because the health clinic did not know what was wrong with Deng, we were transferred to Malakal Hospital [where MSF works] 45 days ago. The MSF doctor told us he had kala azar and they began his treatment. He was so sick that we thought he wouldn't live.

Now he is cured of both kala azar and pneumonia and has been discharged today. Last month we would never have believed he would be standing healthy on his feet today! While we were in Malakal for Deng's treatment, two of my other boys, Makong, 7, and Garang, 5, also became sick. They were tested for kala azar at the MSF treatment centre in Malakal and they both were found to be positive for kala azar, too. Now they are receiving treatment. Garang cries and cries when he receives his injections because they hurt him. So I have to take them in each day and make sure they both get their injections and hold them when they cry."

South Sudanese mother of three sons, all of whom were treated for kala azar

In order to build better programs to respond to visceral leishmaniasis in South Sudan, MSF calls upon:

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Donors to provide emergency funding to NGOs and the MoH so that they can scale up their responses to VL epidemics for the 2012 and 2013 peak seasons, in part by building up an emergency stockpile of required diagnostic tests and drugs.

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Manufacturers to submit registration dossiers for VL medicines and drug regulatory authorities in endemic countries to facilitate fast-track registration.

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Stakeholders to increase R&D efforts for improved and simplified diagnostic tools. A test more sensitive than the currently employed rK39 RDTs is needed for primary diagnosis of VL in East Africa. The ideal product would be an RDT that can be used for primary diagnosis, test of cure and detection of relapse of VL in any context worldwide.

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The double burden: visceral leishmaniasis and HIV

In most MSF VL programmes, the percentage of patients who are co-infected with HIV is still low, less than 2%. In Ethiopia however, 20% to 41%[7] of VL patients (depending on the location) are co-infected with HIV. The vast majority of these VL patients are male migrant workers who come from other regions of Ethiopia to work for several months on the agro-industrial farms in the VL endemic lowlands in the northwest.

Both VL and HIV attack the cellular immune system; together, they propel each other into a destructive spiral. HIV/AIDS patients are much more susceptible to developing VL after being bitten by an infected sand fly, and because of the much higher parasite burden in their system, they are more infectious to sand flies. This also makes them an important reservoir for disease transmission.

VL is a stage 4 AIDS defining opportunistic infection and is more difficult to treat in HIV positive people. Pentavalent antimonials (SSG) have an unacceptably high mortality during treatment in HIV co-infected VL patients (16% to 33%) and should not be used[8, 9]. Although liposomal amphotericin B at 15-20 mg/kg total dose is safe and effective in treating HIV co-infected VL in India[10], it is not effective in many co-infected patients in East Africa, even in higher doses (30 mg/kg)[11]. The hope is that combining high-dose liposomal amphotericin B with another safe drug in HIV-positive VL patients can enhance its effectiveness, especially also in relapse patients. Combination treatment of liposomal amphotericin B/miltefosine has demonstrated hopeful results to date and will be studied further in the near future[12].

VL cannot be permanently cured in HIV infected patients, however. Co-infected VL patients are likely to relapse, and to become more drug-unresponsive with each subsequent relapse. Antiretroviral therapy (ART) may delay and reduce relapse, but does not effectively prevent it[13]. MSF, DNDi, ITM-Antwerp, and the University of Gondar will soon begin a collaborative research project on secondary prophylaxis of VL relapse after initial cure of VL in people co-infected with HIV.

"I know and I also feel that it is the kala azar that will lead me to death, not the HIV."

Ethiopian adult male patient with multiple relapse VL and HIV

Finally, in HIV-positive patients who are infected by *L. donovani* (the parasite causing VL) but who have not yet developed the disease, early ART use may be the best way of preventing the reactivation of latent VL as an opportunistic infection. This calls for the rapid implementation of the WHO guidelines in favour of early initiation of ART (CD4 < 350/mm^3) in countries where VL is endemic.

MSF calls upon:

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VL programmes to offer HIV testing to all VL patients, as it determines the treatment regimen (no SSG for people living with HIV).

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VL programmes to implement new recommendations that may result from ongoing research on high-dose combination treatments and on secondary prophylaxis of VL relapse in African HIV/VL co-infected patients.

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Donors and national HIV programs in VL endemic countries to include this severe opportunistic infection in HIV funding and allocation.

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Rapid tests: high accuracy in South Asia, limited sensitivity in Africa

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Diagnostics of first episodes of VL have drastically improved in South Asia, but there are still serious limitations for diagnostics that work in African contexts. The rK39 antigen-based rapid diagnostic test (RDT) can be used (alone) to confirm and exclude primary VL in clinically-suspected patients in South Asia and is used in active case finding at community level. But the test performs imperfectly in East Africa, with 80% to 90% sensitivity[14]. Therefore, clinically suspect primary VL patients with a negative RDT in East Africa need to be referred to a laboratory for further diagnosis by another serological test and/or microscopic examination of spleen, bone marrow or lymph node aspirates. However, due to physical barriers and insecurity, this referral is often not possible. Better, more sensitive RDTs are needed for the African context.

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A young boy being treated for visceral leishmaniasis by a nurse. Malakal, South Sudan, 2010.

This woman received a blood transfusion and medical care that saved her life, after reaching the late stage of visceral leishmaniasis infection. Malakal teaching hospital, South Sudan, 2010.

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Visceral leishmaniasis in South Asia: better treatments needed in the field

In South Asia, VL has a relatively milder presentation than in East Africa and is more sensitive to drugs other than antimonials. In 2005, the governments of Bangladesh, India and Nepal, supported by the WHO, joined forces and presented an ambitious plan to eliminate the disease from the region by 2015. To be feasible, this will require substantial and sustained action.

New treatment modalities in India and Bangladesh: the role of liposomal amphotericin B

MSF works in the areas with the highest VL prevalences in India (Bihar State) and Bangladesh (Mymensingh district). Prior to MSF's involvement, few people had access to VL care in these areas. Treatment was expensive and it required more than 30 days of hospitalization and painful daily injections of SSG or infusions of conventional amphotericin B, which is toxic.

In India, MSF established a workable operational model intended to drastically increase patients' access to high quality VL care. In the past four years, more than 8,000 VL patients were treated with a short-course regimen of liposomal amphotericin B (20 mg/kg total dose), many of them as outpatients, with an initial cure rate over 98%[15].

An Indian kala azar patient explains that it took six months before she was diagnosed with kala azar and received treatment free of charge. She had visited several private doctors and borrowed money to pay for her treatment. *"I couldn't pay it back so I had to mortgage my two pieces of land. I am a sick person, yet we do not have enough food to eat."*

In Bangladesh, MSF's strategy for effectively controlling the disease involves an innovative approach of active case finding using digital mapping and spatial risk factor analysis. A short-course regimen of three doses of liposomal amphotericin B (15 mg/kg total dose) is given as treatment on an outpatient basis. The initial cure rate is 99.6%, and the final cure rate at six months is 98.6%.

"The outreach work is not only important, but full of fun as we walk from village to village, home to home and house to house searching for suspected kala azar patients. I knew from before that so many people had died in the area because of kala azar; as there were no proper treatments for this disease."

MSF outreach worker in Fulbaria, Bangladesh

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Doctor checking the treatment of a patient receiving liposomal Amphotericin B for visceral leishmaniasis, Bihar, India, 2011.

Together with DNDi, MSF will soon start clinical studies that evaluate the effectiveness, pharmacovigilance, feasibility and cost-effectiveness of single dose liposomal amphotericin B (10 mg/kg); of the short-course combination regimen of liposomal amphotericin B (5 mg/kg single dose) with 10 days miltefosine; and of a combination regimen involving 10 days of miltefosine and paromomycin.

In 2012, WHO TDR will conduct an implementation trial together with the MoH on single dose L-AmB (10 mg/kg) as part of their effort to have this protocol introduced within the MoH. MSF is also planning to evaluate single dose liposomal amphotericin B treatment in Bangladesh. In an already completed independent clinical study (not conducted by MSF), this single dose regimen demonstrated cure rates over 98% at one month after treatment and 96% at six months follow up[16]. In 2010, the WHO's Expert Committee recommended liposomal amphotericin B in a single dose of 10 mg/kg, as well as the 15 mg/kg regimen over three to five doses as first-line treatments in primary VL for the Asian region (India, Bangladesh and Nepal). The recommendation cited its high efficacy, low toxicity and short treatment duration[17].

The national programs in India, Bangladesh and Nepal have not yet implemented these WHO recommendations. They instead still rely on miltefosine monotherapy as first-line treatment in their national elimination guidelines. Despite its convenience as an oral treatment, however, miltefosine is not the ideal drug. It requires 28 days of treatment, and it is teratogenic, and therefore contra-indicated in pregnancy and unusable in women of child bearing age without strict contraception up to four months after treatment. Because of its long half-life, the drug, when given as a monotherapy, can also lead to drug resistance, especially if adherence is poor.

Eliminating VL in South Asia is a feasible goal that was recently endorsed once more by WHO. The required tools are there—a very good RDT, a highly effective drug (even as single-dose), vector control and a political commitment expressed on paper. The next step is to tap this potential and make it reality.

To this end, MSF calls upon:

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National VL elimination programs in South Asia to implement better available treatment regimens:
· Single-dose or short-course liposomal amphotericin B, or
· Short-course combination treatments (liposomal amphotericin B/miltefosine or paromomycin/miltefosine).

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The **pharmaceutical company Gilead** to further reduce prices of liposomal amphotericin B, which it markets as AmBisome; other manufacturers to increase access through the production of more affordable versions of liposomal amphotericin B, meeting international quality standards.

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PKDL in South Asia: a more humane treatment to heal individuals and prevent disease transmission

Treating VL saves lives; treating Post-Kala azar Dermal Leishmaniasis (PKDL) helps prevent transmission of VL. PKDL is an immunological complication that occurs in a minority of VL patients. It is a macular, macula-papular or nodular skin rash in a patient who has recovered from VL and is otherwise well. There is very little research on PKDL. The PKDL skin lesions are not harmful for the patient, but sandflies can get infected by feeding on them as the parasites are present in the skin lesions. In South Asia, if PKDL occurs, it is usually three to four years after VL treatment and usually presents as hypopigmented macular lesions on the skin. Self-healing is rare.

In Bangladesh MSF is performing active case finding and treatment—not only for VL, but also for PKDL—as a disease control intervention. Nearly all PKDL patients in Bangladesh had previously been treated for VL with SSG, often in sub-optimal dose regimens. Studies have indicated, that VL patients treated with (liposomal) amphotericin B were much less likely to develop PKDL[18].

It is neither practical nor possible to adhere to Bangladesh's current PKDL treatment protocol of 120 toxic and painful SSG injections over six months, during which long periods of hospitalization are necessary. Access to PKDL treatment was therefore virtually non-existent. In an attempt to provide an ambulatory treatment that is safe and that causes minimal disruptions on a patient's life, MSF started an ambulatory short-course PKDL treatment regimen of AmBisome MSF and DNDi will continue efforts to identify better ways to treat PKDL, both in Bangladesh and also in Sudan.

To move in this direction, MSF calls upon:

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National VL elimination programs in South Asia to update protocols to:
· Prevent PKDL by providing VL treatment based on liposomal amphotericin B.
· Change current PKDL treatment of 120 painful and toxic SSG injections and prolonged hospitalization.

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Stakeholders to increase R&D efforts for a short-course, safe, cheap, oral and effective treatment for PKDL.

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Patient with PKDL, Bihar State, India, 2011.

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Fact Sheet
What is Visceral Leishmaniasis?

Visceral leishmaniasis (VL), also known as kala azar, is a worldwide protozoal vector-borne disease, endemic in 76 countries. The annual incidence is estimated to be 250,000 to 300,000 cases, with over 90% of those cases occurring in India, Bangladesh, Sudan, South Sudan, Ethiopia and Brazil, where it often affects the poorest populations in those countries.

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VL is the second largest cause of parasitic death (after malaria). It is characterized by prolonged fever, weight loss, enlarged spleen, anaemia and suppression of the immune system. Without treatment, almost all patients will ultimately die, but timely diagnosis and treatment will cure nearly all patients, even in resource-limited and remote circumstances.

VL epidemics associated with high mortality are frequent in contexts marked by conflict, population movements, malnutrition, and a lack of access to health care—all factors that can accelerate the development and spread of the disease. In the current outbreak in South Sudan, more than 10,000 patients (5,000 by MSF) were treated between the end of 2009 and October 2011.

A major challenge is management of patients co-infected with VL and HIV. Both diseases influence each other in a vicious spiral: HIV/AIDS patients are much more susceptible to develop VL, and once infected, VL accelerates AIDS, is much more difficult to treat and usually relapses.

Transmission and diagnosis

Different species of the *Leishmania* parasite cause the disease and are transmitted through bites of phlebotomine sand flies. In East Africa and South Asia, humans are the main reservoir of the parasites. In these regions, post kala azar dermal leishmaniasis (PKDL), a rash that sometimes appears following VL treatment, further contributes to disease transmission.

Patients who are clinically suspected to have VL can be tested using the rK39 antigen-based rapid diagnostic test (RDT). In the Indian subcontinent, even if used alone, this test has sufficient sensitivity and specificity to exclude or confirm VL. In East Africa, a positive rk39 RDT confirms the diagnosis, but suspected cases with a negative result still need further investigation by another serological test, the diagnostic agglutination test (DAT), or by microscopic examination of spleen, bone marrow or lymph node aspirates. These techniques require technical expertise and laboratories that are seldom available in areas where VL thrives.

Treatment

Current treatment options include pentavalent antimonials (i.e. sodium stibogluconate (SSG) and meglumine antimoniate), paromomycin, miltefosine, amphotericin B deoxycholate and liposomal amphotericin B (L-AmB) (currently registered as AmBisome). Treatment guidelines are continent-specific because of different levels of efficacy according to regions. Although the list of treatment options seems extensive, each has significant limitations. Combination treatments with existing drugs have also been developed to optimize the efficacy and safety of treatment and reduce costs and hospitalization time.

Pentavalent antimonials (SSG), when used alone, require 30 days of painful daily intramuscular injections. This drug also has serious (cumulative) toxic side effects and is dangerous in HIV co-infected patients, with mortality being five to ten times higher than in non HIV-infected. Paromomycin (PM) is a cheap anti-leishmanial drug but needs to be administered in combination with another drug in order to optimize its use. African countries are in the process of switching from 30 days SSG to the WHO-recommended combination regimen of 17 days SSG&PM (in those without HIV), developed by DNDi and the Leishmaniasis East African Platform (LEAP) partners, including MSF. Both drugs are administered by intramuscular injections.

Miltefosine, an oral drug, is contra-indicated during pregnancy, and should ideally be taken in combination in order to avoid the development of drug resistance. The treatment in monotherapy lasts 28 days and requires strict adherence.

L-AmB is administered intravenously and must be stored and transported in a manner that ensures the vial is not exposed to temperatures over 25° Celsius [77° Fahrenheit]. Its current cost remains an important barrier to treatment. Nevertheless, there are many reasons to believe that L-AmB could soon become the mainstay of first-line treatment for all patients, either used alone or in combination with an oral drug.

In India and Bangladesh, MSF has used short-course regimens of L-AmB (15-20 mg/kg total dose) with an initial cure rate over 98% and a very good safety profile. In 2010, a WHO Expert Committee recommended L-AmB in a *single dose* or in short-course regimen as first-line therapy in South Asia. MSF is now working together with DNDi and other partners in a clinical study evaluating effectiveness and feasibility in the field of single dose L-AmB (10 mg/kg) and combination regimens (L-AmB with miltefosine and miltefosine with paromomycin). The results of this study will help countries in South Asia to update their treatment recommendations. The current VL elimination plan launched in 2005 by India, Nepal and Bangladesh still relies on miltefosine only. L-AmB in Africa is less effective and requires higher doses compared to

the Indian subcontinent. However, it should be used in treatment failures, severely ill patients, those co-infected with HIV, pregnant women and those over 45 years of age.

Amphotericin-B deoxycholate is a cumbersome treatment that needs to be given in slow intravenous (IV) infusions daily or every other day for 15 doses. Careful hydration and potassium intake of patients are needed to avoid renal toxicity and hypokalemia. With the advent of L-Amb, its use should be discouraged.

MSF and visceral leishmaniasis

Since 1988, MSF has treated more than 100,000 VL patients, mainly in Sudan, South Sudan, Ethiopia, Kenya, Somalia, Uganda, India and Bangladesh.

MSF and others have validated and introduced a rapid diagnostic test (rK39 antigen-based dipsticks) that can be used in remote settings. The ease and convenience of this test has allowed for the decentralization of diagnostic and some treatment services to remote areas, where laboratories cannot be established, and thus has improved access to care in endemic areas.

In East Africa, Georgia and Asia, MSF's findings and operational research have actively influenced national and international treatment policy changes. For African VL, a WHO Expert Committee has now recommended the combination therapy of SSG&PM, which was studied and implemented by MSF in South Sudan since 2002 and recently thoroughly evaluated in DNDi-sponsored studies.

In Ethiopia, where 20% to 40% of the VL patients are HIV infected, VL and HIV care are closely integrated. A major challenge in the management of HIV/VL co-infected patients is the high toxicity of antimonials and the poor effectiveness of liposomal amphotericin B (even in high doses) in these patients. VL in HIV infected patients needs to be better managed in order to reduce the very high relapse and mortality rates seen in many centres. Based on initial promising data, MSF is now working to validate a standard package of management that includes an optimized primary treatment (L-AmB combined with miltefosine), prompt ART initiation and secondary prophylaxis (monthly pentamidine injections).

MSF is calling for:

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- **National VL elimination programmes in South Asia to implement the available better treatment regimens:** single dose or short course L-AmB or short course combination regimens.
- **Endemic countries to register VL drugs:** not all treatment options are registered in all endemic countries, limiting access to these drugs in those countries.
- **Reduced price for liposomal amphotericin B** to accelerate its roll-out wherever it is needed.
- **Donors and endemic countries** to increase funding for VL control programs.

MSF is calling for increased funding of more needs-driven R&D:

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- **Improved and simplified diagnostic tools:** For primary diagnosis of VL in East Africa, a more sensitive test than the current rK39 RDTs is needed. Overall a single, practical rapid diagnostic test that can be used for primary diagnosis, test of cure and detection of relapse worldwide is also required.
- **New drugs** that are oral, safe (including during pregnancy), short course, cheap and effective in all endemic regions are needed. Improved treatments for patients co-infected with HIV and the development of an oral drug for PKDL are both required

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Timeline
Visceral Leishmaniasis (VL)

1988: MSF responds to an outbreak of an unknown disease in a camp for displaced southern Sudanese outside Khartoum, discovering it is VL. Start of the first MSF VL treatment programme in Khartoum.

1989: Discovery of the devastating VL epidemic in Western Upper Nile in southern Sudan. Start of a response programme in Leer in the middle of an acute conflict.

1990: Access established to the heart of the epidemic in Duar (Western Upper Nile); more than 10,000 VL patients treated in the first year of this project.

1992-1994: First clinical studies conducted by MSF in South Sudan investigating the effectiveness of new treatments under field conditions (SSG&PM combination; AmBisome for complicated VL).

1996: Publication of a retrospective mortality study indicating that around 100,000 people have died during the epidemic in Western Upper Nile between 1984 and 1994.

1995-1997: MSF expands VL care and treatment to war-ravaged northern Jonglei in southern Sudan, Gedaref State in Sudan and Humera in Ethiopia.

1997-1999: Three MSF clinical studies in Sudan, Kenya and Ethiopia demonstrate the non-inferiority of generic SSG compared to the branded drug. These studies result in the acceptance of the much cheaper generic SSG in Sudan and Ethiopia.

2000-2002: MSF starts VL programs in the Pokot community in eastern Uganda, in Somali refugee camps in Kenya, in Bakool region in Somalia and in the Upper Nile region in Sudan.

2002: The combination of SSG-paromomycin for 17 days is introduced as first-line treatment of VL in South Sudan during a major outbreak.

2003-2004: A clinical trial conducted by MSF in Ethiopia shows that miltefosine was safer than antimonials in HIV/VL co-infected patients.

2003-2004: Diagnostic evaluation studies conducted in MSF field sites in Sudan and Uganda leads to introduction of rK39 RDT in MSF diagnostic algorithms in East African programs, including in Ethiopia, resulting in dramatically improved access to diagnosis and treatment for the migrant workers in the region.

2005: After a long preparation, MSF hands over the VL activities in Sudan's Gedaref state to the Ministry of Health.

2005/2006: MSF provides an emergency VL intervention in Ethiopia's Amhara region.

2007-2008: MSF hands over the VL activities in Uganda, and starts two new VL projects across the border in the Kenyan Pokot region.

2006: MSF studies on HIV/VL co-infection focus on the role of ART in preventing relapses and on the accuracy of rK39 rapid diagnostic test in HIV/VL co-infected patients.

2007: MSF begins an intervention in India's Bihar State, the most highly endemic VL foci in the world. Within three years, 6,000 patients are treated with liposomal amphotericin B with excellent outcomes (98% cure rate).

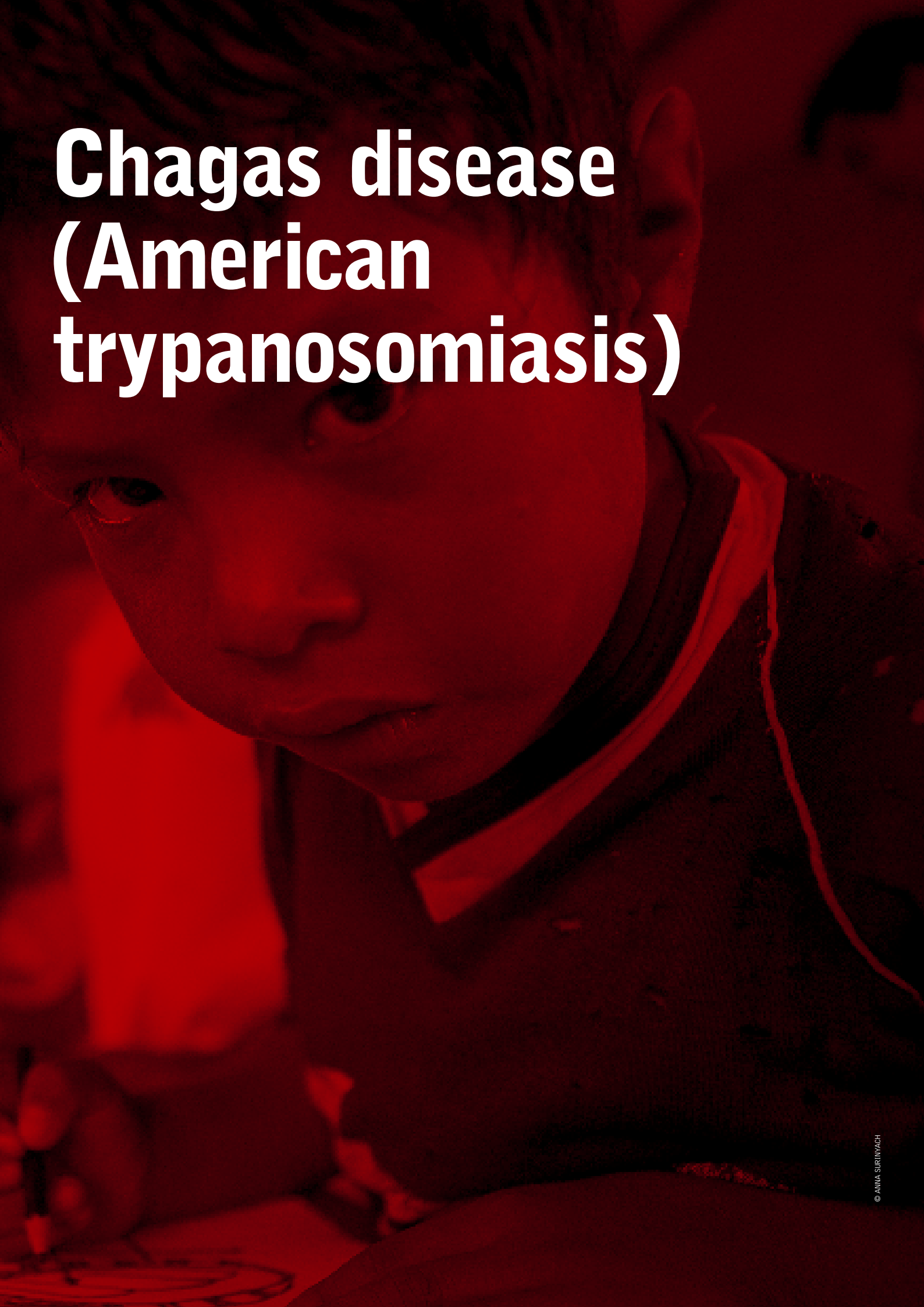
2009: Due to a serious security incident, MSF has to evacuate the project in Bakool region in Somalia.

2009-2011: MSF responds to a new major outbreak of VL in South Sudan; 11 treatment centres are established, and support given to MoH and other NGOs, to improve access for to the affected communities in a context which is subject to continuing conflict and violence.

2010: MSF re-starts VL activities in Gedaref, northern Sudan and starts VL activities in Bangladesh.

2011: The threshold of 100,000 VL patients treated by MSF is passed.

Chagas disease (American trypanosomiasis)



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Chagas disease (American trypanosomiasis)

More than a decade ago, MSF decided to break the silence surrounding this disease and attend to the neglected populations. Providing treatment is possible, even in the most isolated areas.

"I would request the Ministers of Health to pay more attention to the people who are vulnerable, those who are living in the countryside where it is more difficult to access health care services. Those living in rural areas are forgotten."

55-year-old patient, Cochabamba, Bolivia

Doctor meeting farmers in rural areas to talk about Chagas disease. Honduras, 2001.

[i] Adobe is a natural building material made from sand, clay, water, mixed with organic material (sticks, straw, and/or manure)

The majority of the estimated 8 to 10 million people afflicted with Chagas disease are poor and live in rural Latin America. The triatomine bug that transmits the parasite *Trypanosoma cruzi* that causes the disease thrives in the adobe[i] housing in which the majority of patients live. Chagas disease is often known as an "invisible disease", as most patients do not present symptoms. It often becomes known only when people die suddenly of the consequences of the disease, the conditions to which Chagas has left them vulnerable. In recent years, as migration and travel to other parts of the world have increased, people in Europe, North America and Asia have also been diagnosed. But they are a very small minority of all cases, and the primary profile of a Chagas patient remains the same.

Patient access to health care for diagnosis and treatment is extremely limited in rural areas of disease-endemic countries. There are several factors that exacerbate this situation: many doctors and nurses are not aware of what Chagas disease is, or that it can be treated; health posts in rural settings lack the necessary diagnostic tools and treatments; and the disease is often asymptomatic for many years.

More than a decade ago, MSF decided to break the silence surrounding this disease and attend to the neglected populations. Since 1999, MSF has screened more than 80,000 people and treated more than 4,160 patients. By adapting models of intervention to the context, raising awareness of the disease and building capacity within MoH health systems, MSF has shown that providing treatment is possible, even in the most isolated areas.

Operational models of intervention: Increasing patient access to treatment

"In 2000 and 2001, an NGO came to San Agustin to test the community for Chagas, Hepatitis B, syphilis and Hanta virus. That is when many of the community found out that they had Chagas. The NGO left, and I had no treatments to give to all those diagnosed. The community made requests to the regional health care services for treatments. They would ask me to tell them where they could buy the drugs. I had persons coming with chest pains. Then one of the women in our community died. Everyone knew it was because of Chagas. It was frustrating to have no help from the ministry of Health. In 2011, MSF arrived, and we are so happy that we have finally been able to treat many of our community members."

Health Promoter for 23 years in the community of Pedro P. Peña, Chaco, Paraguay.

MSF has used three different operational models to approach Chagas disease, each one adapted to the context and needs of the affected populations. The intervention models evolved over time to expand prevention and control activities through a more comprehensive program that included vector control, diagnosis and treatment. The models, which are not mutually exclusive and have at times been used in concert, are the integrated model, the community model, and the vertical model.

The Integrated Model

The essence of the integrated approach is that all diagnosis and treatment mechanisms are placed into existing health structures. Staff, mainly at the primary care level, must follow appropriate referral guidelines. This model is highly sustainable if there is, from the outset, adequate planning and long-term commitment from the MoH. This ensures the effective execution of the project and sets the stage for a smooth handover process when the time comes.

The integrated approach requires fewer resources, most of which should come from the government, or from community or regional actors. For the time being, due to absence of funding, NGOs and others will likely be the driving force. That said, a program that proves relevant and effective will have a better chance of securing additional resources from national programs as time passes, as was the case in Urban Cochabamba, in Bolivia, between 2007 and 2010.

The Community Model

The community model seeks to respond to a community as a whole, rather than the individuals within it, and to establish a program that the community itself can one day take control of. With this approach, diagnosis and treatment protocols are simplified and adapted to the limitations faced working in rural areas. Coverage rates of diagnosis and treatment are higher, but significant additional resources are required.

In practice, MSF initially guarantees the quality and continuity of care by delivering a "Chagas package" to the community and supplying most of the human resources and equipment needed. The focal point should be the primary care clinic where local staff is based and rapid diagnostic tests (RDTs) and drugs are stored.

Education and empowerment are crucial elements of this approach. Teams from the clinic conduct extensive information, education and communication (IEC) activities in the communities. Diagnosis and treatment take place in the town or village's own facilities, facilitating the eventual handover of the program to the local actors who can then sustain it, which was the case in Rural Cochabamba, Bolivia, from 2008 to the present day.

The Vertical Model

With this approach, programs are established in parallel to the state systems and act almost independently from them. The idea is to streamline processes so that more targeted, faster, more reactive, and less bureaucratic prevention, screening and treatment initiatives can be implemented. A separate team executes the IEC, conducts mass screening campaigns, confirms diagnostics and delivers treatment. There is little interaction with the primary or secondary health system, with the exception of hospital referrals for complex cases and the treatment of side effects from antiparasitic treatment.

The target population is selected based on criteria that can include how much or how little access to health care they have, how high the seroprevalence for Chagas disease is or how pervasively the areas where they live are infested by bugs. This approach has high coverage rates of screening and treatment because it makes a point of accessing all targeted groups within the defined geographic areas. The cost is higher and the emphasis on quick and thorough action—on screening, diagnosing and treating the maximum number of persons within a specific target population—limits efforts to build up the long-term sustainability of the program which is the major disadvantage of this approach. An example of this model was the Tarija project in Bolivia, which lasted from 2003 to 2006.

´Standing up to Chagas disease´. Awareness-raising amongst the population. Chaco, Paraguay, 2012.

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RDTs and a Test of Cure: What´s on offer for Chagas diagnostics?

"Fifteen years ago I got tested for Chagas as I had some problems with my heart. The health workers used triatomine bugs attached to my arm to feed on my blood (xenodiagnosis) to test me for Chagas. After 90 days they found the parasites in the bugs, so then I knew I had Chagas. This was a long time to wait for a diagnosis, and then I had no treatment options. In 2010, when I joined MSF I wanted to participate in the Chagas Platform PCR study (which I knew about through working in MSF), and then got treated. I was happy to be part of a study looking to improve understanding of this disease affecting so many people in my community."

55-year-old patient, and MSF staff member, Cochabamba, Bolivia

According to the World Health Organization (WHO), diagnosing Chagas disease during the chronic phase involves performing two serological conventional tests that detect circulating IgG antibodies (immunoglobulin). These include Enzyme Linked Immunosorbent Assay (ELISA), Indirect Immunofluorescence Assay (IFA) or indirect hemagglutination (IHA) methods. Such laboratory tests require qualified staff, as well as specific equipment and infrastructure. These are either unaffordable or unavailable in many settings impacted by Chagas disease, meaning that there is not enough diagnostic capacity at present to enable timely treatment.

Currently, there are several rapid diagnosis tests (RDTs) available for detecting *T. cruzi* antibodies in whole blood, serum or plasma. The tests are qualitative or semi-quantitative and rely on different principles—immunochromatography, particle agglutination, immunofiltration or immunodot—and all deliver results in 15 to 30 minutes without the need for electrical equipment.

In 2008, MSF performed a cross-sectional study in Bolivia to assess the performance of a test called Chagas Stat Pak, using whole blood in field conditions and comparing results to those of conventional diagnostic tests. This test showed high specificity (99.0%). It shows suboptimal sensitivity (93.4%) but this is compensated by the increased access to diagnosis. The RDT positive results must go through the process of confirmation with ELISA alone or combination ELISA/HAI following international recommendations.

Simplified diagnostic trees expected soon

This is all promising, but the current need for laboratory confirmation is a significant impediment to the goal of diagnosing Chagas disease within primary health care facilities in remote areas. The best option would be a diagnostic tree based on a single RDT, or a combination of more than one RDT in which sensitivity and specificity are not inferior to the conventional serology done through laboratory testing. In addition, an ideal RDT would be inexpensive and easy to use. It would not require external equipment, reagents or refrigeration. It would also, preferably, be individually packaged.

At present, there are 11 commercially available RDTs for diagnosing Chagas disease and two others available only for research purposes. Aside from Chagas Stat Pak, though, all of them have been evaluated for sensitivity and specificity only by their manufacturers.

In 2010, the WHO passed a resolution that called for the "availability of diagnostic and treatment for Chagas disease patients in primary health care settings in all endemic countries." MSF thought that a thorough evaluation of existing RDTs was necessary. The study began with WHO's support in late 2011. It is divided in two phases. The first will be conducted in ten national reference laboratories located both in disease endemic and non-endemic countries and will evaluate the 11 commercialized RDTs in the Americas, Europe, and the Western Pacific. The second phase will be conducted at the field level and will assess the effectiveness and ease of use of RDTs using whole blood. Both phases are designed to add to our knowledge and understanding of existing RDTs, and MSF does expect to propose changes in the Chagas disease diagnostic tree based on its findings

Testing for Cure; PCR?

When is Chagas disease cured? Determining that someone is "cured" is an extremely complex matter that has inspired highly divergent opinions and no shortage of controversy. The notion of a "parasitological cure" is interpreted in many ways, given the need to completely eliminate the parasites from both the blood and the tissue. The WHO's definition of "cured" is currently "negativization" of the conventional serological tests ELISA/IHA/IFA, meaning they are cleared of antibodies.

Getting to this point could take years, though, which has dissuaded many people infected with Chagas disease from even beginning treatment—a dynamic that makes research and development into new medicines very difficult, to say the least.

There are, at present, very few ongoing initiatives designed to find a test that could confirm a cure sooner. Not more than a handful of labs are trying to identify new biomarkers, but nothing has reached consensus yet at the international level. The long-term investments and deep commitment necessary to find such a test are simply not being made. New incentives to spur the development of a test of cure such as prizes should be explored.

The absence of more effective tests of cure also holds up the validation of new treatment molecules, thereby slowing down R&D, as the efficacy of new drugs is difficult to measure. In the short-term, the international community sees some promise in the Polymerase Chain Reaction test (PCR), which some hope could identify treatment failures and allow evaluation of new treatment tools. Thus far, however, only one PCR protocol has been validated[1] —but without any clear design for follow-up strategies—and many others that are being developed fall into the category of "homemade" PCRs.

DNDi and MSF have been collaborating on a study that would assess how well PCR could measure the parasitological response of patients to benznidazole treatment in one Bolivian community. The main objective would be "to estimate the gain in sensitivity of several multiple-sample strategies of PCR toward the current standard (single sample of 10 ml) to detect Chagas chronic stage at baseline and post-treatment." Results are expected by the end of 2012. The information collected will be used to identify the optimal sampling strategy based on a number of factors, including the sensitivity, the cost, the scope of sampling, and the clinical response from patients. Ideally, the study will also help MSF and others develop strategies and schedules for following up after treatment, while also helping generate a better understanding of how effective certain drugs are in the treatment process.

Antiparasitic treatment for Chagas patients: It is possible!

Young patient with her antiparasitic medication. Sucre, Bolivia, 2006.

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"I was diagnosed with Chagas disease in 2001, and have only now been able to get treatment. I had a really bad skin reaction to the benznidazole, and was told to stop treatment for a week. Then I started on nifurtimox, and was able to complete my treatment without any problems. I was desperate to get treated, and even stopped breast-feeding at eight months so that I could be treated. All these years I have feared my diagnosis; I was too young to die, and I have a family. My mum, brother, husband and sister-in-law have all completed treatment, too."

32-year-old patient, San Agustín, Pedro P. Peña, Chaco, Paraguay

MSF has been providing patients with Chagas disease in Honduras, Nicaragua, Guatemala, Colombia, Bolivia and Paraguay free diagnosis and antiparasitic treatment, which is treatment that negates the causal parasite rather than symptomatic treatment, or treatment of heart or digestive complications that tend to occur. MSF is currently running projects in Bolivia—the country with the world's highest Chagas prevalence rate—just across the border in Paraguay, and in Colombia.

The earliest programs focused on treating children and adolescents, because they have a greater chance for cure (if they are infected for a shorter period of time) and better tolerance to the drugs than chronic adult patients with a longer term of infection[2]. Over time, new evidence supporting treatment in adults was accumulated and MSF began first treating older children up to 18 years and then adults up to the age of 60. Ideally, people, especially those in rural areas, should have increased access to treatment through the primary health care system. However, there is a lot more scaling up of activities to go.

In its 12 years of experience in various programs of prevention, diagnosis and treatment of Chagas disease in resource limited settings (including within existing primary health care systems), MSF has collected a sizable store of information that highlights the safety for the antiparasitic treatment of Chagas disease using benznidazole. It is important to consider that of the more than 4,000 patients treated with benznidazole as first-line therapy in our projects, there were no deaths, and only 1% of patients had serious adverse effects. This is clear evidence that doctors and nurses should not hesitate to treat patients for fear of the side effects caused by these medications if they do a proper follow up of the course of treatment. These findings were supported by several scientific publications[3, 4, 5] that showed that the antiparasitic treatment of adults presenting with no clinical signs of disease is indeed viable. The second drug available is nifurtimox which remains a second-line treatment option since safety, specifically in adult patients remains a big concern.

MSF data have driven change at an international level. The Pan-American Health Organisation (PAHO) passed a resolution entitled "Elimination of Neglected Diseases and Other Poverty-Related Infections" in 2009[6]. The resolution's key recommendations address the provision of antiparasitic treatment to all children, the integration of Chagas disease diagnosis in the primary health care system, and the extension of treatment to adults where possible. This is an important step forward, but governments must now ensure that the resolution is implemented at the national level and that financial and human resources are properly allocated by donors, by PAHO itself, and by Ministries of Health in endemic countries.

Two subsequent resolutions that passed[7, 8] recommended that the diagnosis and treatment of Chagas in both its acute and chronic phases be integrated at the primary health care level and that the provision of existing treatments in disease-endemic countries be reinforced in the present with the aim of making access universal in the future. Both resolutions will help enable the inclusion of diagnosis and treatment through national Chagas disease control programmes.

The sizable gap between the number of people living with Chagas disease and the number being treated needs to be closed.

MSF calls upon governments in Chagas disease endemic countries to:

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Implement PAHO's recommendation to integrate diagnosis of those infected at the primary care level and to treat children and, wherever possible, adults, in the primary care system, free of charge, with monitoring of possible side effects.

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Establish a data collection system to determine the prevalence of Chagas disease.

-

Reinforce and refine supply chains so medicines and diagnostic tests reach primary care centres in the most remote areas.

-

Implement vector control activities after assessing the houses and surrounding environs of a given patient for the presence of the vector, and fumigating, if necessary, to avoid re-infection.

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Critical shortage of first-line therapy: The story of benznidazole:

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In 2011, there were delays in rolling out screening and diagnosis activities in communities at risk in MSF projects in rural Bolivia and Paraguay due to the shortage of benznidazole. This was not just MSF's problem; shortages in this first-line treatment were experienced in most endemic countries also. The production of benznidazole has been undermined by discontinued production, delays, and mismanagement of distribution mechanisms.

In some ways, this cuts to the heart of the issue when it comes to neglected tropical diseases, and the Tri-Tryps in particular. Since 2006, when more people began to understand and recognise Chagas disease, the demand for benznidazole increased, not only in endemic countries but also in Europe and North America, where the number of patients diagnosed with Chagas disease is increasing.

In 2003, Roche Pharmaceuticals, which was, until then, the primary manufacturer of benznidazole, transferred the technology necessary for its production to LAFEPE, a public laboratory in Brazil that worked under the mandate of that country's Ministry of Health. LAFEPE thus became the world's sole manufacturer of this medicine.

Although LAFEPE had the industrial capacity to produce benznidazole, it did not meet deadlines or properly manage orders of the drug. It also performed poorly when it came to distributing the final product to different countries and it did not have the support of the Brazilian Ministry of Health to do so. There were delays in procuring a new source of active pharmaceutical ingredient (API) and a lack of coordination between the API supplier Nortec, LAFEPE and the Brazilian Ministry of Health. The global shortage ensued.

Mechanisms to coordinate the orders and distribution of the benznidazole stocks through international organizations—PAHO for the Americas (Rotation Fund), and WHO for the European and Asia-Pacific demand— have so far failed to prevent the disruption of the benznidazole supply chain.

In November 2011, the Brazilian Ministry of Health committed to take measures to resolve the shortage by the end of the year. By mid-January 2012, the MoH confirmed that 1.7 million tablets were produced and approved by the regulatory body, with an additional 1 million tablets produced to be held as stock. It is not clear whether this will really cover current demand, as PAHO has never shared a plan to ensure the proper distribution of existing stocks to the countries and patients who need it most.

At the end of 2011, ELEA, a private pharmaceutical company based in Argentina, announced that it had produced and registered generic benznidazole. The first batch produced is being donated to treatment programmes in Argentina. Future production could be launched to respond to the needs of other Chagas endemic countries. Other initiatives in Europe are looking into new formulations of the drug.

However, these are not the only issues. At present, there is not enough of the active pharmaceutical ingredient (API) to produce future benznidazole batches in LAFEPE. The price of the API for new batches of benznidazole may increase by 40%, resulting in a 30% increase in the final product. (ELEA has not had issues in production of benznidazole as they also produce the API.)

MSF will be following all these initiatives very closely. Access to benznidazole needs to be facilitated through registration of the product in countries and its inclusion on the essential medicines list (EML) needs to be considered. The price of benznidazole needs to remain as low as possible, so that price does not become a barrier to treatment.

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Patient receiving antiparasitic treatment for Chagas disease. Arauca, Colombia, 2010.

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Fact Sheet
What is
Chagas disease?

Chagas disease, or American trypanosomiasis, is a parasitic disease caused by *Trypanosoma cruzi* and transmitted mainly by the insect called triatomine, also known as the "assassin bug" or "kissing bug". The disease is endemic in 21 countries in Latin America and associated with socio-economic exclusion. Cases have also been reported in Europe, the US and Japan. The WHO estimates that there are eight to ten million cases worldwide and that the disease kills 12,500 people each year, making it the largest parasitic killer in the Americas.

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In its natural clinical course, Chagas disease (without treatment) has two phases: acute and chronic. The acute phase may be symptomatic, but it is usually asymptomatic and characterized by the presence of T. cruzi in the direct parasitological examination of the blood. The chronic phase is characterized by low parasitemia and high levels of antibodies (IgG). It presents itself in one of the following clinical forms: indeterminate, cardiac or digestive. Without diagnosis and antiparasitic treatment in the early stage, approximately 30% will develop cardiac problems, and 10% might develop irreversible digestive tract damage in the chronic phase of the disease. There are currently no tools to determine which infected person will develop the chronic complications. The majority of people infected with *T. cruzi* will not develop symptoms of disease for years. Many patients die suddenly in early adulthood without ever knowing they had Chagas disease.

Transmission and Diagnosis

The transmission of Chagas disease can be categorized in three cycles: domestic, peridomestic and sylvatic, each with particular characteristics determined by the vector species and its biological behaviour, the presence of wild or domestic mammals that act as reservoirs, as well as socioeconomic and environmental factors. The most common transmission mechanisms are: vectorial, transfusional, congenital and oral transmission (through contaminated food).

Specific diagnosis classically relies on two laboratory tests that detect antibodies against the parasite. Unfortunately, these tests are too complex to be widely used at the primary health care level. It is essential that communities living in endemic zones have access to diagnosis through simpler tools and can find out if they have been infected with *T. cruzi*.

Vector control strategies, which are fundamental to limit the spread of the disease, depend on detecting the vector (the assassin bugs) and spraying houses and peri-domestic areas with insecticides. In some areas, the assassin bugs have been found to be resistant to certain products. To eliminate the insects from houses, spraying must be completed thoroughly and housing conditions must be improved. It is important to conduct vector control activities in parallel to treating patients to avoid re-infection.

Greater effort must be made to ensure the quality of blood banks to avoid contamination from transfusions, in screening mothers for early detection of congenital transmission and in early diagnosis and treatment of all patients infected.

MSF and Chagas disease

MSF has provided free diagnosis and treatment for children and adults infected with Chagas disease since 1999 in countries including Honduras, Nicaragua, Guatemala, Colombia, Bolivia and most recently Paraguay, using different operational models of intervention. Currently MSF runs projects in Bolivia, the country with the world's highest disease prevalence, just across the border in Paraguay, and Colombia. Through 2011, MSF had tested more than 80,000 people for Chagas and treated more than 4,200 patients.

This shows that although current resources are not ideal, the diagnosis and treatment of Chagas disease is viable in environments with limited resources and in remote areas.

Treatment

There are currently only two medicines to treat Chagas disease: benznidazole and nifurtimox. Both drugs were developed more than 40 years ago in investigations not specifically aimed to treat Chagas disease. Benznidazole is the recommended first-line treatment. Nifurtimox remains a second-line treatment option since safety, specifically in adult patients, is a big concern.

The treatment success rate reaches almost 100% in acute cases. However, for chronic cases this treatment is much less effective and can have multiple side effects, and therefore has to be taken under medical supervision. Of the 4,200 patients treated by MSF, no deaths have been reported.

As the side effects of the treatment are more common in older patients and as there is no practical test of cure, doctors have been reluctant to administer the medicine until recently. The experience of MSF and other programmes have shown that the adverse effects are manageable with regular medical follow-ups. It is feasible and beneficial to treat patients in the chronic phase, even after the heart is mildly affected (initial clinical forms of the chronic phase).

Challenges

With the limited resources currently available to treat patients with Chagas disease, medical teams have to deal with many shortfalls and at times don't have any treatment options. Secured production of benznidazole, new diagnostic tests, better medicines and a test for cure are all urgently needed to provide wider access to quality diagnosis and treatment for the millions of infected people.

MSF is calling for increased support to control programmes:

- **Inclusion of diagnosis and treatment of both acute and chronic Chagas disease** as part of any disease control strategy in addition to the current focus on vector control by governments of endemic countries, funders and WHO/PAHO.
- **Systematic testing and diagnosis of Chagas disease at the primary care level in endemic areas and parts of the world with population movements from endemic areas:** The lack of resources and awareness at the primary health care level limits proactive and integrated approaches.
- **Rolling out of currently available RDT and validation of other RDTs:** Simple and affordable diagnostic tools are required to make diagnosis of patients in the field possible and accessible.
- **Increased access to treatment for children and adults in the primary health care system:** Millions of people, especially in rural areas, have neither the opportunity to find out that they are infected nor the possibility of being treated.
- **Integration of vector control with patient care:** Ineffective prevention efforts will result in continued infestation and risk of (re-)infection.
- **Improved estimates of the burden of disease:** The burden of Chagas disease is significantly underestimated in official statistics. Inadequate systems for surveillance and reporting of this disease translate into severe underreporting of Chagas cases worldwide. This leads to a lack in demand forecasting data for the medicines.

MSF is calling for increased funding of more needs-driven R&D:

- **An early test of cure** is essential to both confirm success of treatment for the patient, and measure efficacy for new drugs. This requires long-term investment and commitment to be made by laboratories, investigators and funders.
- **New treatments with improved efficacy and safety profiles** are urgently needed to replace the two current medicines developed more than 40 years ago.
- **Increased and sustainable investment in R&D:** Overall R&D funding on Chagas amounted to only $20 million in 2010.

Timeline
Chagas disease

1999: MSF starts the first program of diagnostic and treatment for Chagas disease in Yoro, Honduras, after Hurricane Mitch devastates the infrastructure of the country. MSF, in collaboration with the Ministry of Health and National Laboratory of Tegucigalpa, and with the population demanding it, starts an integrated and comprehensive program with vector control, diagnostic and treatment for children < 12 years old.

2002: MSF opens its first Chagas Disease Program in the world's most affected country, Bolivia, in a highly endemic area of Tarija Department, treating the largest cohort of patients < 15 years old with benznidazole (massive screening, diagnostic and treatment with vector control support in rural communities).

2003: MSF project opens in Guatemala, Olopa, offering diagnosis and treatment of Chagas patients in a primary health care setting with an important IEC component in the communities.

2005: MSF starts the first inclusion of patients < 18 years in a periurban setting in Sucre, Bolivia.

2007: MSF project opens in Urban Cochabamba, Bolivia (Integrated approach within the MoH structures and health staff) / Adult antiparasitic treatment included until 60 yrs old.

2007: MSF is invited to be part of the WHO Chagas Diagnostic and Treatment Working Group.

2008: MSF project opens in Rural Cochabamba, Bolivia, implementing the community approach.

2008: MSF does a crossover study to assess the performance of a RDT called Chagas StatPak in Sucre, Bolivia, using whole blood in field conditions.

2009: Based on the regionalization concept, MSF opens a new project in Paraguay's Chaco area.

2009: MSF participates along with WHO and DNDi in the technical and advisory group for the Posaconazol Phase II Study in Vall d´hebron.

2009: On the 100th anniversary of the discovery of Chagas, MSF launches "Break the Silence", a Chagas awareness campaign that calls for development of new diagnostic and treatment tools.

2010: MSF opens a project in Norte de Santander, Colombia.

2011: A PCR study that starts with MSF, DNDi, and the Chagas Platform in Cochabamba, Bolivia, launches with the intent to estimate the gain in sensitivity of multi-sample PCR to detect Chagas chronic stage. Outcomes are expected at the end of 2012.

2010: MSF leads a study on the validation of RDTs for a simplified diagnostic tree for Chagas disease.

2011: MSF introduces non-etiological treatment for Chagas chronic patients.

2011: MSF carries Exploratory Missions to open projects in Chagas non-endemic countries (USA and Italy) focused on migrants with lack of access to Chagas Diagnosis and Treatment.

1999- 2011: MSF has screened over 80,000 people and treated more than 4,100 patients in the last 11 years. MSF's operational models have been adopted elsewhere and MSF has published numerous articles about its operational experience with the disease. MSF has also participated in all PAHO initiatives that promote the treatment and management of benznidazole side effects.

Human African trypanosomiasis (sleeping sickness)

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Human African trypanosomiasis (sleeping sickness)

Simplified diagnosis-treatment tools and algorithms are a pre-condition to the successful integration of sleeping sickness activities in primary health care and would facilitate control activities, especially in remote and unstable contexts.

Human African trypanosomiasis (HAT or sleeping sickness) is a parasitic disease transmitted to humans by the tsetse fly in sub-Saharan Africa[1]. There are two types of sleeping sickness. They are caused by two sub-species of parasites: *Trypanosoma brucei (T.b.) gambiense*, found in western and central Africa), and *T.b.rhodesiense*, found in eastern and southern Africa (the line of separation goes through the Rift valley). The most widespread form is due to *T.b. gambiense*.

The sickness occurs in two stages. Fever, headache, and joint pain predominate during the first stage. Stage 2, the neurologic phase, occurs after the parasite crosses the blood-brain barrier and invades the central nervous system. The patient can suffer from confusion and reduced coordination, which leads to bouts of fatigue punctuated with periods of heightened agitation. The sickness progresses to daytime slumber, night-time insomnia, mental deterioration, and, finally, coma. Without treatment, the disease is fatal.

Humans are the reservoir of the *T. b. gambiense* parasite. HAT can thus be controlled by mass population screening and treatment of all infected patients. Mass population screening relies on mobile teams that visit all villages of the affected area and screen the highest possible proportion of the population for infection. Vector control is another approach to control the disease.

Calling patients to be screened for sleeping sickness, in a remote village. Central African Republic, 2011.

In 1986, MSF teams provided care to people affected by a HAT epidemic in Uganda. Since then, MSF has become a primary actor in the field of *T. b. gambiense* HAT control in sub-saharan Africa. By June 2011, 23 MSF programmes in seven countries had screened nearly 3 million people and treated approximately 50,000 patients. Considering the paucity of actors committed to combating HAT, MSF also considers it a responsibility to advocate and lobby for safe, effective and accessible diagnostics and treatment, and to participate in—or lead—clinical research projects.

Numbers of patients with sleeping sickness treated within MSF programs from 1986 to 2010

Location	Period	Number of persons screened	Number of patients treated*
Angola**			
N'dalatando	1995 - 2001	216,309	7,584
Caxito	2002 - 2006	93,961	1,104
Camabatela	2004 - 2005	8,300	167
Mbanza Congo***	2001 - 2003	unknown	248
Chad			
Moïssala	2009 - 2010	34,744	33
Central African Republic			
Haut Mbomou	2001 - 2006	60,621	2,197
Batangafo	2006 - ongoing	147,265	1,555
Maitikoulou-Markounda	2007 - ongoing	14,498	1,183
Democratic Rep. Congo			
Equateur Sud	1998 - 2002	300,017	655
Equateur Nord	2004 - 2005	4,624	154
Isangi	2004 - 2007	139,594	1,378
Haut - Bas Uélé	2007 - ongoing	81,642	2,318
Republic of Congo			
Plateaux	2001 - 2003	58,417	913
Bouenza - Cuvette Est	2002 - 2005	254,842	1,854
Mobile team - Ignie	2005 - 2007	48,507	416
South Sudan			
Ibba - Maridi - Mundri	1999 - 2006	171,584	5,653
Kajo - Keji	2000 - 2006	161,577	2,845
Tambura - Ezo	2005 - 2006	52,076	764
Yambio	2006 - 2009	45,500	348
Uganda			
Moyo	1986 - 1993	399,311	8,798
Adjumani	1991 - 1996	286,120	5,697
Omugo - Yumbe	1997 - 2002	300,718	3,668
West Nile (other)	2010 - ongoing	36,928	16
Total	**1986 - 2010**	**2,917,155**	**49,548**

* Only patients treated with parasitologically proven HAT are shown

** Patients with intermediate stage (6-20 white cells in CSF) have been included in stage 1 patients

*** Data from the Mbanza Congo program could not be retrieved, apart from the number of patients treated by stage in 2001

Source: MSF program data

Drop of blood being colected for the screening of sleeping sickness. Central African Republic, 2011.

Community activities to raise awareness about sleeping sickness. Central African Republic, 2011.

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From melarsoprol to NECT, a revolution in the treatment of second stage HAT

Patient receiving painful arsenic derivative, melarsoprol for the treatment of stage 2 sleeping sickness prior to the NECT availability. Ibba, Sudan, 1999.

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Treatment of first stage *T. b. gambiense* HAT with seven to ten daily intramuscular injections of pentamidine has not changed for decades. Apart from the pain of the injections and occasional bouts of hypotension and hypoglycemia, pentamidine is generally well-tolerated and can even be administered at village level during or following active screening sessions.

Treatment of second stage HAT is a different story. Melarsoprol, an arsenic derivative, has been used since 1949. Administered in three to four series of three to four intravenous injections—and more recently in ten consecutive injections—melarsoprol is associated with frequent and severe adverse events such as bloody diarrhoea, mucocutaneous allergies, peripheral neuropathies and vein sclerosis. But the most dangerous adverse event is an encephalopathic syndrome that occurs in 5% to 10% of treated patients, resulting in 3% to 5% overall case-fatality rate. This is not only a tragedy for patients and their families, but also very traumatic for care-givers, including MSF medical teams working in Uganda and later in other countries. In addition, up to 30% treatment failure rates with melarsoprol were reported in some MSF programmes—in Omugo, northwestern Uganda, for instance[2].

The frustration of care-givers was magnified by the fact that eflornithine, a presumably safer treatment, existed but was not available. Initially developed as an anti-cancer drug, eflornithine was shown to be active *in vitro* against *T. b. gambiense* in the late 1970s. Shortly after, it was shown to be effective in patients in Sudan who were relapsing after treatment with melarsoprol. Intravenous eflornithine in dosages of 400mg/kg/d for 14 days was approved by the US Federal Drug Administration for the treatment of *T. b. gambiense* HAT in 1990. Despite the registration of eflornithine in Uganda in 1993 and in other African countries in subsequent years, production was discontinued by the original producer (Marion Merrel Dow, which became Hoechst Marion Roussel) for lack of profitability, and a search by the WHO and MSF for a third party producer failed.

This was a wholly unacceptable situation—which was pushed into the realm of the absurd when a cosmetic product containing eflornithine and designed to prevent facial hair was put on the market. MSF's Campaign for Access to Essential Medicines, which had itself been founded not long before, launched an advocacy effort that helped bring about a five-year agreement, lasting from 2001 to 2006, between the WHO and Aventis Pharma. This agreement included adequate production of eflornithine for HAT, a donation of the key anti-trypanosomal drugs (pentamidine, melarsoprol and eflornithine) and significant funding to support HAT control activities.

The donation agreement allowed eflornithine to be deployed on a large scale for the first time since it was found to be effective against *T. b. gambiense* more than 20 years earlier. MSF introduced eflornithine as first-line treatment in its programmes and confirmed its efficacy and safety profile.[3-5]

Eflornithine monotherapy was doubtlessly an improvement over melarsoprol, but it did demand a good deal of resources to transport and administer. It requires 56 two-hour intravenous infusions over a period of 14 days, which necessitates constant hospitalization of patients, the presence of trained health staff and good nursing care. This contributed to the slow roll-out of eflornithine in endemic countries, where, as of 2008, roughly

half of all patients were still being treated with melarsoprol. The potential for resistance, when used in monotherapy, was an additional concern. The development of a shorter and simpler treatment combining two drugs was the logical way ahead.

The only existing potent drug to be combined with melarsoprol or eflornithine was nifurtimox, an oral drug commonly used for Chagas disease in Latin America, which had shown a moderate level of efficacy when used in prolonged monotherapy in sleeping sickness patients. Preliminary findings from an aborted randomized trial and a subsequent case series in Uganda showed that the eflornithine-nifurtimox combination was safe and effective.[6-7] This encouraged MSF and Epicentre, MSF's epidemiological arm, to initiate a clinical trial in the Republic of Congo (RoC) that compared standard eflornithine monotherapy with a shorter and simpler regimen of eflornithine (twice a day for 7 days) combined with oral nifurtimox for 10 days. The trial was extended to three additional study sites in the DRC thanks to a partnership with DNDi and others (Ministries of Health of RoC and DRC, Swiss Tropical and Public Health institute). NECT (nifurtimox-eflornithine combination therapy) proved to be at least as efficacious (96.5% versus 91.6% cure rate) and safe as standard eflornithine monotherapy,[8] and was added to the WHO Essential Medicines List in May 2009. The NECT rollout in endemic countries has been very fast and comprehensive. By the end of 2010, only one in ten patients was receiving melarsoprol. NECT was introduced in MSF programmes since January 2010 and has since proved to be very safe (in-hospital mortality rate below 0.5%) and effective.

The challenge of HAT control in conflict areas

MSF sleeping sickness mobile team transporting a mobile laboratory for large-scale screening in several particularly remote areas of the northern Bandundu Province,Democratic Republic of Congo, 2011.

The epidemiology of *T.b. gambiense* HAT is closely intermingled with conflict. Political instability and military action often disrupts HAT control activities. Mobile teams in charge of active screening are dismantled or rendered inoperable. Vector control activities are impeded, supplies of drugs and diagnostics wane, trained medical workers flee insecurity, and community networks are ruptured. In addition, internal displacement or cross-border migration of affected communities may trigger new foci or reactivate old ones—as infected persons carrying the parasite may trigger transmission if tsetse flies are present—or expose the displaced population to tsetse bites and HAT[9]. During the last 25 years, MSF implemented HAT control programmes in numerous conflict areas such as Angola, Republic of Congo, South Sudan, Central African Republic and, as illustrated below, Uganda and DRC.

At the beginning of the 1980s, political upheaval in northern Uganda led to the breakdown of health structures and disease control programmes. The civil war forced most of the population of West Nile state, in the country's northwest, to seek refuge in neighbouring Sudan (now South Sudan), an area where HAT was still highly endemic. Beginning in 1985, these refugees, some of them newly infected, started returning to Uganda and resettling on long untilled lands where tsetse flies had proliferated. This led to a major HAT outbreak in the West Nile region. MSF responded by screening almost one million individuals and treating more than 18,000 patients from 1987 to 2002.

In July 2007, MSF initiated a HAT control project in Doruma, in the district of Haut-Uélé in northeastern DRC, near the borders of what is now South Sudan and the Central African Republic. Screening activities and treatment of infected patients were initiated in the health districts of Doruma and Ango, and started in Bili in January 2009 by a second MSF team.

The prevalence of HAT averaged 3.6% in the villages that could be screened and 1,570 patients were treated until March 2009, when all activities had to be stopped and the teams evacuated following attack on the MSF base in Banda by the Lord's Resistance Army militia. The capacities of local public health facilities were too weak for MSF to hand over responsibility for the diagnosis and treatment of the disease, however.

MSF resumed its HAT activities in Doruma in December 2009 and began them in and around Dingila in September 2010, treating more than 1,800 additional patients in 2010 and 2011. The complex security environment has severely restricted the movements of mobile teams and thus affected all aspects of HAT control throughout the region. Moreover, massive displacements of people fleeing the conflict probably contributed to the reemergence of HAT in Bas-Uélé, and forced MSF (jointly with other partners) to screen refugees from DRC who were seeking sanctuary in South Sudan[9].

Widespread insecurity also interrupted MSF's active screening activities in Batangafo, Central African Republic, in 2011.

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Global and sustained elimination of HAT: still a long road

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HAT was a historical scourge in Africa, but major control efforts by the colonial powers last century meant that by the 1960s it was thought to be a plague of the past. However, from the 1970s onwards there have been several serious epidemics. Since the 1990s, renewed efforts to actively detect and treat HAT within specific control programmes resulted in a decrease in numbers of reported cases – from more than 26,000 cases in 2000 to below 7,200 cases in 2010[10, 11]. This undeniable success triggered some hope that the disease was on its way to elimination. The disease has indeed been *de facto* eliminated in several countries[12], but some "hot spots" still occur in remote areas and conflict zones, as evidenced by MSF's experience in CAR and DRC in the recent years[13]. In addition, "blind spots," or large areas in endemic countries where at-risk populations are not covered by active surveillance, remain. Therefore, the true number of patients currently affected by HAT in Africa is unknown. MSF's current focus is thus cooling off "hot spots" and surveying "blind spots", activities that should be prerequisites to any talk of global HAT elimination.

Once HAT is controlled or eliminated in a given area, continuous surveillance and response are needed to prevent subsequent flare-ups. As the numbers of HAT patients reported by the countries keep decreasing, it is crucial that the funding of both national control programmes and research activities for new diagnostic and treatments hold steady. MSF is concerned by a move among donors to push for integration of HAT activities into existing health structures. This approach could be counterproductive as integration of HAT activities within public health systems is currently possible only in a few settings due to the weakness of public health services in most HAT endemic areas and the complexity of diagnostic and treatment approaches. Research and development for (i) simplified diagnostic tools and (ii) safe, practical and efficacious drugs applicable to both disease stages remain crucial. Simplified diagnosis-treatment tools and algorithms are a pre-condition to the successful integration of HAT activities in primary health care and would facilitate control activities, especially in remote and/or unstable contexts.

The diagnostic approach needs rethinking

Classical diagnostic algorithms for HAT follow a three-step approach: screening, parasitic confirmation and staging (determining at which stage of disease the patient is). Screening relies on the Card Agglutination Test for Trypanosomiasis (CATT), a serological test produced by the Institute of Tropical Medicine in Antwerp, Belgium. The currently available format (50 tests/vial) is only suitable for set up with "high" workload scenarios, since a vial is only stable for 7 days after it is reconstituted. A more adapted format (10 tests per vial, thermostable) was recently developed but has yet to be purchased and deployed by national control programs in areas of low HAT prevalence[14]. Parasitic confirmation relies on the microscopic observation of trypanosomes in lymph node fluid (after puncture) or blood after concentration with fairly complicated techniques, such as microhematocrit centrifugation or mini-anion-exchange centrifugation. The latter is the most sensitive technique, but its production as a standardized kit has been erratic during the last 20 years. Staging still relies on the microscopic examination of cerebro-spinal fluid obtained by lumbar puncture in which white cells can be counted and parasites searched for.

This diagnostic approach requires a sizable amount of equipment and materials, as well as the specialized training and sustained supervision of laboratory workers. Current diagnostic algorithms are primarily designed for mass population screening by specialized mobile teams. Moreover, they do not take into account clinical features and ignore other diseases responsible for persistent fever and neurological disorders. The diagnostic approach therefore needs to be drastically simplified to allow integration of HAT activities within public health structures.

Therefore, MSF calls for:

- **Increased R&D** for simplified, more accurate and less invasive tools,
- **A rapid diagnostic test** (RDT) for use in both screening and diagnosis, and
- **Staging and follow-up test** that does not require lumbar puncture and examination of Cerebro-Spinal Fluid (CSF)

Patient having a lumbar puncture to confirm the staging of sleeping sickness. Maitikoulou, Silambi, Central African Republic, 2012.

A vision for the clinical management of HAT

"Having experienced first-hand what it means for physicians to subject their patients suffering from sleeping sickness to treatment with melarsoprol, I knew—as did many of us at MSF—that things had to change. And they have. Today we have two promising oral drug candidates in the pipeline for sleeping sickness: oxaborole and fexinidazole. If they deliver on their promise, we could be looking at a new paradigm for treatment of sleeping sickness. MSF and DNDi worked together to bring the first major change in treatment of sleeping sickness in 25 years—with NECT—and MSF will be a key partner for testing and introducing the new treatments we have coming out of the pipeline."

Bernard Pécoul, Executive Director, DNDi

In the future—and hopefully not that far off—first-line physicians, clinical officers and nurses in busy outpatient clinics in rural Africa will consider HAT as a possible diagnosis for patients presenting with symptoms such as persistent fever or neuropsychiatric disorders. They will use highly sensitive and specific point-of-care rapid diagnostic tests to validate their hypotheses. If the HAT RDT result is positive, the diagnosis of *T.b. gambiense* HAT will be highly probable and an oral treatment will be administered under close supervision. The treatment will be safe, cheap and efficacious in both disease stages. Then, it would no longer be necessary to visualize the parasite for absolute confirmation or to subject the patient to an excruciating lumbar puncture to know the disease's stage.

Patient receiving treatment for sleeping sickness, Sudan, 2000.

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Fact Sheet
What is Human African Trypanosomiasis?

Human African Trypanosomiasis (HAT or sleeping sickness) is a parasitic, neglected tropical disease transmitted to humans by the tsetse fly. Historically, HAT has occurred in the poorest rural areas of Africa, where weak health systems and political instability make disease surveillance and management difficult. Seventeen sub-Saharan Africa countries reported cases of HAT to the WHO in 2009. The Democratic Republic of Congo alone, recorded 74% of all cases, and 97% of cases occurred in a total of seven countries.

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HAT was long a scourge in Africa, but major efforts by the colonial powers last century meant that by the 1960s it was thought to be a plague of the past. However, from the 1970s onwards there have been several serious epidemics. Since the 1990s, renewed efforts to actively detect and treat HAT within specific control programs resulted in a decrease in numbers of reported cases—from over 26,000 cases in 2000 to below 7,200 cases in 2010. However, "hot spots" still occur in areas of conflict or instability and large areas in endemic countries ("blind spots") are not covered by active surveillance.

Transmission and Diagnosis

HAT is caused by two sub-species of parasites--*Trypanosoma brucei (T.b.) gambiense*, which is found in western and central Africa, and *T.b.rhodesiense*, which is present in eastern and southern Africa. A demarcation line of sorts runs through the Rift Valley.

The most common form of HAT, on which this fact sheet is focused, stems from *T.b. gambiense*. The sickness occurs in two stages. The first stage is marked by fever, headache and joint pain. The second stage, the neurologic phase, occurs when the parasite crosses the blood-brain barrier and infects the central nervous system. The patient can suffer from confusion and reduced coordination, along with bouts of fatigue punctuated with periods of agitation. The sickness makes it so people cannot stay awake during the day but cannot sleep at night. Their mental faculties deteriorate and they eventually fall into a coma. Without treatment, the disease is always fatal. Even after successful treatment, the neurological phase can lead to chronic sequelae.

Currently the diagnosis and staging of the disease requires a complicated series of tests, including painful and invasive procedures such as lumbar punctures. It requires trained staff and can be difficult to perform in remote areas where the disease occurs. There is a pressing need for simpler, better diagnostic tools and algorithms.

Treatment

The treatments currently available are few in number, dated and stage-specific. Stage 1 treatments, Pentamidine (dating from 1941) and Suramin (dating from 1921) are fairly well-tolerated but require injections. They do not, however, pass the blood-brain barrier and are thus ineffective for the treatment of advanced (stage 2) HAT.

The current first-line therapy for stage 2 HAT is NECT (nifurtimox-eflornithine combination therapy), which replaced eflornithine monotherapy and melarsoprol.

Melarsoprol (dating from 1949) is an arsenic derivative that is highly toxic. The treatment consists of 10 days of painful intravenous injections. It is increasingly ineffective with up to 30% treatment failure in some areas, and the drug itself kills up to 5% of those who receive it. In 2008, half of stage 2 HAT patients were still receiving it as first-line treatment; in 2010 this figure was reduced to 10%. Melarsoprol use should be restricted to second-line therapy in *T. b. gambiense* HAT, but is still the only choice for stage 2 *T.b. rhodesiense*.

Eflornithine monotherapy (used from 1980 on compassionate basis, and WHO recommended in 1985) is far safer than melarsoprol and is effective, but it is also resource-intensive and difficult to administer because it requires complex logistics, trained health staff, 56 intravenous (IV) infusions over a period of 14 days and constant follow up. The potential for resistance when used in monotherapy is an additional concern.

NECT (nifurtimox-eflornithine combination therapy): In May 2009, the WHO added NECT to the Essential Medicines List (EML) for the treatment of stage 2 HAT. NECT was developed by MSF, Epicentre, the Drugs for Neglected Diseases initiative (DNDi), the Swiss Tropical and Public Health Institute (Swiss-TPH) and control programs from most affected countries. NECT is a simplified combination treatment of eflornithine with nifurtimox. This improved treatment is a step in the right direction; it combines oral nifurtimox for 10 days and reduces the number of infusions necessitated by eflornithine treatment from 56 over 2 weeks to 14 over 7 days. The NECT rollout has been very successful in endemic countries since 2010, with an estimated 60% of patients receiving the new combination.

MSF and sleeping sickness

Since 1986, MSF has been a leading organization working in the diagnosis and treatment of HAT patients, particularly in war-torn areas. Between 1986 and 2010, MSF screened more than 2.8 million people and treated more than 51,000 cases of HAT in seven countries (Uganda, Southern Sudan, Central African Republic, Republic of Congo, Democratic Republic of Congo, Chad and Angola). Current projects are being implemented in the Central African Republic (and cross-border in Chad), Democratic Republic of Congo, Uganda and South Sudan, where MSF teams screened around 123,000 patients and treated 1,197 cases in 2010. A regional mobile HAT team was made available by MSF in 2011 to provide additional screening and treatment activities in central African countries.

Challenges

Global control of HAT is currently constrained by (i) a lack of simple-to-use diagnostic and treatment tools, (ii) high disease prevalence in some remote and often insecure contexts, (iii) wide areas where HAT is potentially endemic with little or no active surveillance, (iv) a lack of skilled human resources in remote endemic areas and (v) shrinking international financing of HAT programmes. MSF is concerned by the current optimism that global elimination of HAT is feasible. Sustainable elimination will not be possible without improved diagnostic and treatment tools and stronger surveillance systems. Moreover, the current donor policy to integrate HAT diagnosis and treatment into existing health structures is somehow premature and poses a serious risk of leaving out people who live in places with little or no access to health care. These policies could give rise to a neglect of the most at-risk areas and lead to new outbreaks—as has been the case in the past.

MSF is calling for increased support to control programmes:

- **Sustained funding for surveillance and control activities:** Lack of disease surveillance leads to an underestimation of disease burden and a risk of upsurge in areas where HAT was previously controlled. Mobile teams remain needed to control HAT in the remaining areas of high prevalence and to respond early to local or regional outbreaks.

MSF is calling for increased funding of more needs-driven R&D:

- **Improved and more practical treatments:** While the development of NECT is a real breakthrough, it is still far from an ideal treatment. A treatment that is oral, safe, effective in both stages of the disease and easy to use in remote primary health care centers is urgently needed.
- **New and simplified diagnostic tools:** Current diagnostic tests and algorithms need to be simplified (e.g. rapid diagnostic tests) to allow their integration in primary health care.
- **Less-invasive staging tools:** Lumbar puncture is still needed for staging of the disease and for post-treatment follow-up. A new biomarker that allows staging of HAT and assessment of cure using whole blood or serum would remove the need for lumbar puncture.

Timeline Sleeping Sickness (HAT)

1986: MSF begins its first HAT intervention in responding to a huge outbreak in Uganda following a devastating civil war. Over the next 25 years, MSF opens HAT projects in Democratic Republic of Congo, Angola, Republic of Congo, Central African Republic, South Sudan and Chad.

1999: MSF publishes high failure rates (on top of high mortality) to the established first-line treatment melarsoprol in Uganda. Similarly high failure rates are subsequently documented in DRC and Southern Sudan.

1999: MSF sets up the Access to Essential Medicines Campaign: the campaign fights for access to eflornithine because its production is under threat and it remains inaccessible for most patients.

2001: Following the first WHO/Aventis agreement to provide free HAT drugs, MSF switches to using eflornithine as a first-line agent to treat HAT: high cure rates and low mortality rates are quickly demonstrated in MSF projects in what is now South Sudan and Republic of Congo, Angola and Uganda.

2001: MSF initiates first clinical trial on combination treatment for HAT in Uganda.

2003: NECT trial is initiated by MSF in the Republic of Congo. DNDi and others joined as partners and the trial became multicentric. The study results were published in 2009, showing that NECT was at least as efficacious and safe as standard eflornithine therapy.

2005: Completion of the first MSF Manual for the treatment and control of HAT.

2007: Despite a general decreasing prevalence of reported cases in Africa, MSF starts HAT projects in high HAT prevalence areas ("hot spots") and insecure contexts in CAR and DRC.

2010: NECT is approved for use in most HAT endemic countries and is implemented as first-line treatment in all MSF projects.

2011: MSF launches mobile projects within DRC and in other endemic countries to screen populations in areas of unknown HAT prevalence ("blind spots").

2011: MSF screened over 2,900,000 persons and treated approximately 50,000 patients within 23 projects in 7 countries since 1986.

Fact Sheet
What is Buruli Ulcer?

Buruli ulcer, a disease caused by infection with *Mycobacterium ulcerans*, is one of the most neglected but treatable tropical diseases. It is the third most common mycobacterial disease after tuberculosis and leprosy, but Buruli ulcer has received less attention and is the least understood.

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Buruli ulcer is mainly endemic in western Africa, although it has been reported elsewhere in Africa, the Americas, Asia and the Western Pacific. It is typically a focal disease, affecting communities living along slow-flowing water bodies such as ponds, swamps and lakes. The overall burden of Buruli can be seen as low, but the prevalence can be high in some areas, reaching 0.25% of the population, and countries such as Benin, Ivory Coast or Ghana report a few thousands of cases each every year. It is believed that many cases go unreported, however, due to limited knowledge of the disease, its focal distribution and the fact that it affects mainly poor, rural communities. All ages and sexes are affected, but most patients are under 15 years of age. The disease can affect any part of the body, but most lesions are found on the limbs, mainly the lower limbs.

A chronic infection of the skin, Buruli ulcer usually starts with a nodule that progressively develops into ulcer. Over time, it can lead to massive tissue destruction and debilitating deformities. The initial clinical manifestations are nonspecific and the disease has a slow course; many of those affected do not seek care until there is large skin necrosis requiring extensive surgery and prolonged hospitalization. In some areas, a significant segment of adult Buruli patients is coinfected with HIV, although the exact relationship between HIV and Buruli is still unclear and needs further studies.

Transmission and Diagnosis

The exact mode of transmission is unknown and still under investigation; some patients state that lesions develop at the site of antecedent trauma, while some research suggests that in Africa aquatic insects can harbor *M. ulcerans* in their salivary glands. More recent studies from Australia and Cameroon suggest that a type of mosquito may be a vector; if this were confirmed, Buruli ulcer would be the only known mycobacterial disease to be transmitted by insects.

Although the recommendation is to make a confirmed diagnosis before starting treatment, Buruli ulcer is often diagnosed and treated based on clinical findings by experienced health workers in endemic areas. Laboratory diagnosis can be made using direct microscopy of swabs or fine needle aspirates from the lesions, using Ziehl-Neelson staining (as with tuberculosis). Sensitivity can be enhanced with polymerase-chain-reaction (PCR) techniques or culture, but this requires a sophisticated laboratory. Many health workers who deal with Buruli do not have access to laboratory services, however, and would be well served by the development of a simpler, more efficient diagnostic tool they could use in the field, particularly in remote settings.

Treatment

The current recommendations for treatment is a combination of rifampicin and streptomycin/amikacin for 8 weeks as a first-line treatment for all forms of the active disease. A combination of rifampicin and clariythromycine can be used if there are contraindications. Nodules or uncomplicated cases can be treated without hospitalization. Proper wound care and physiotherapy areis essential to guarantee good recovery.

Surgery is often needed to remove necrotic tissue, cover skin defects, treat osteomyelitis, and correct deformities. If the patient show signs of complications or is referred at the very late stage of the disease, they may require amputation. Early diagnosis can simplify the surgical management and reduce the likelihood of deformities or the need for amputations. It can also help alleviate the economic burden borne by Buruli patients and their families, and limit the stigmatisation and ostracism they can face in their communities.

MSF and Buruli ulcer

MSF has been diagnosing and treating Buruli ulcer in Cameroon since 2002, offering antibiotic treatment, wound care, physiotherapy, surgery and general medical care. So far 800 patients have been treated in the project to date.

Challenges

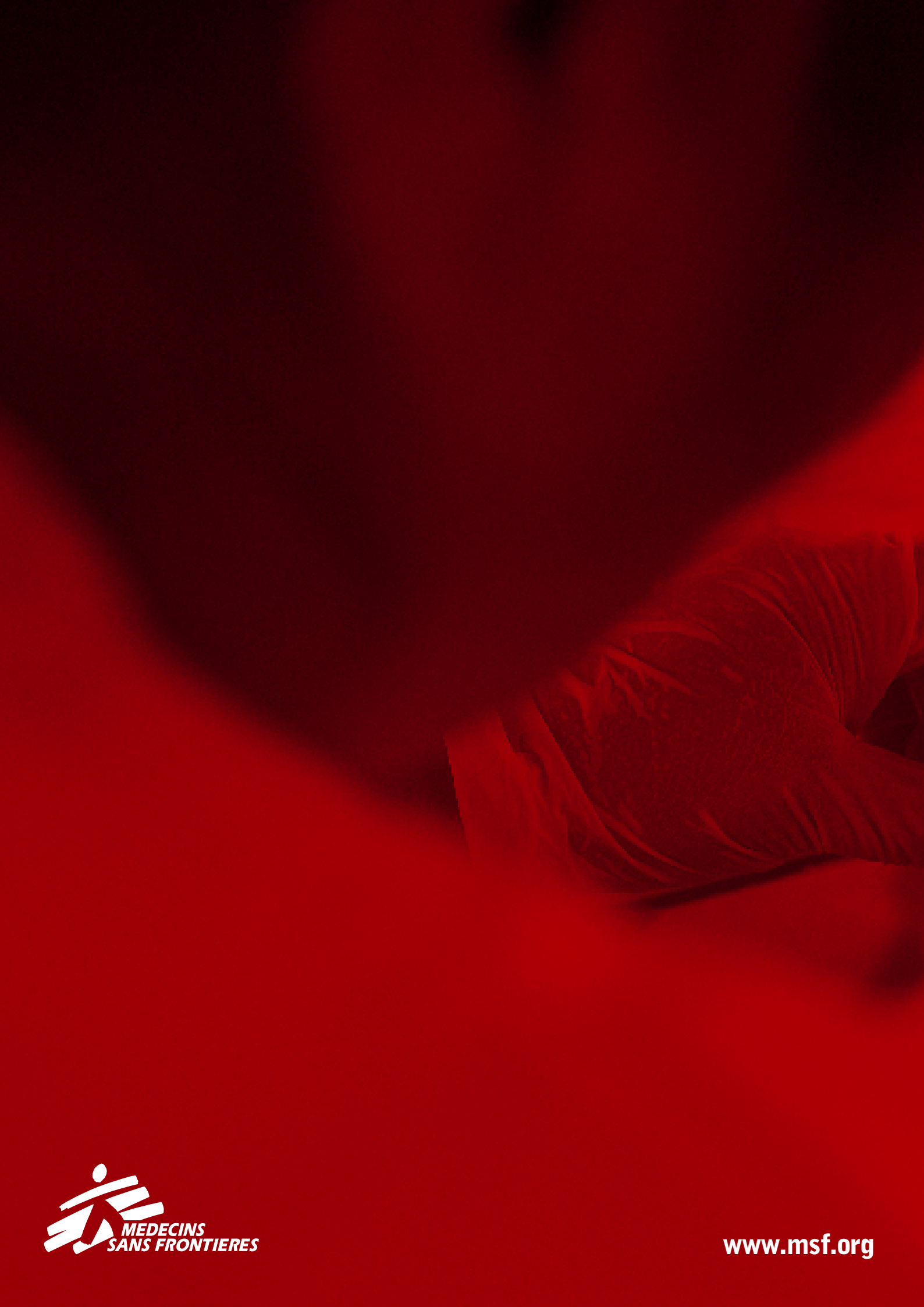
The disease typically affects poor communities, primarily children, where medical services are unavailable or too expensive. And yet there is almost no research and development funding dedicated—either privately or publicly—to the study of the disease, its diagnosis, or its treatment.

MSF is calling for increased support to and improvement of treatment programmes:

- **Increased access to existing treatments**: Existing treatments are not always readily available both for medication and wound dressings.
- **Raising awareness:** Patients, healthcare professionals and governments need to be made aware of the disease, its prevalence and its negative social impact.
- **Better data collection:** Epidemiological studies must be done to map the disease and determine its real public health burden.

MSF is calling for increased funding and needs-driven R&D efforts:

- **New diagnostic tests:** A simple and rapid diagnostic field test for Buruli ulcer is urgently needed because the early disease (a nodule) can be treated locally and inexpensively at the community level.
- **Research into disease pathology:** Basic research to understand the pathology of Buruli ulcer and the mode of transmission is required to develop tools for prevention and treatment.
- **More practical treatments:** New treatments are needed that can be implemented outside secondary health care facilities, therefore reducing the cost and burden on health systems.
- **Increased and sustainable investment in R&D:** MSF is concerned about the complete neglect of Buruli ulcer for any significant funding for R&D. Currently Buruli ulcer receives the least amount of funding of all neglected tropical diseases.
- **Innovative R&D incentives:** The traditional incentive mechanisms have failed to spur innovation. New incentive and funding mechanisms that de-link the cost of R&D from the price of products are needed.



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