

# Overcoming Neglect

Finding ways to manage and control Neglected Tropical Diseases

## **Acknowledgements**

We wish to acknowledge NTD patients, institutions and organisations involved in NTD control and patient care.

**Cover image:** ©Marizilda Cruppe. MSF mobile clinic staff run blood tests to diagnose sleeping sickness in the village of Emmaus, northeast Democratic Republic of Congo. 2015.

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Surgeon Christos Christou and anaesthetist Abdullahi Mohammed Ali operate on a patient at the MSF facility in Gogrial town, Warrap State. South Sudan, 11 June 2013.



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# Foreword

## No more neglected diseases, no more neglected patients

This report marks over 30 years of uninterrupted medical care for patients with neglected tropical diseases (NTDs). These illnesses almost exclusively affect people living in extreme poverty. For many of these deadly and debilitating diseases, there are no vaccines, diagnostic tools are limited, and treatments are often unavailable or unaffordable.

Despite affecting over 1.7 billion and killing hundreds of thousands of people each year, NTDs generally remain out of the field of interest for policy makers, and there are little resources to address them. If these diseases impacted high-income countries, there would be more research into them. There would be incentives for companies to develop new diagnostics and drugs. Effective prevention and control programmes would be implemented. But sadly that isn't the case because the people affected are too poor to constitute a market that can attract investment in drug research and development.

This means that MSF is often one of the only actors caring for NTD patients in remote places where resources are scarce and health systems fragile. Over the last three decades, we have treated hundreds of thousands of patients affected by some of the most overlooked NTDs. Many had life-threatening parasitic infections such as kala azar (*visceral leishmaniasis* or VL), Chagas disease (*American trypanosomiasis*) or sleeping sickness (*human African trypanosomiasis*). Some were affected by noma, a deadly bacterial disease so neglected that it is not yet recognised as an NTD. Others were the victims of snakebite envenoming, the medical condition resulting from a snakebite, which causes more death and disability than any other NTD.

When I was working as a surgeon in South Sudan, a family brought their terrified child to the MSF clinic. A venomous snake had bitten him on the arm. Despite daily surgical procedures to debride the dead tissue, we ended up having to amputate the affected limb. I will never forget how incredibly courageous that young boy was. Yet he was only one of the 6,000 snakebite patients MSF treats each year.

Compared to when MSF started treating NTD patients three decades ago, there has been much progress towards the control and elimination of these diseases. Looking

forward, a new road map for NTDs from the World Health Organization sets targets for 2030 that include eliminating at least one neglected tropical disease in 100 countries and reducing by 90 per cent the number of people requiring medical interventions for them. These ambitious targets present an opportunity to support the development of treatments, vaccines, and diagnostic tools for NTDs.

The new road map comes at a time when the COVID-19 pandemic threatens progress towards control and elimination of NTDs. NTD programmes have been disrupted, fragile health systems are under even further strain, and there are alarming indications that resources will be diverted and funding reduced. There is a real risk that NTDs could slide into further neglect, the significant achievements over the past years are reversed, and that even more lives are lost to NTDs.

The global response to the pandemic has shown is what is possible when there is political will and significant investment of resources. Although equitable access to these innovations is unsure, the world is mobilising to develop vaccines, treatments, and diagnostic tests for COVID-19. The same can be done for NTDs. We can overcome the neglect with commitments, funds and better tools to find, diagnose and treat patients. We can make NTDs diseases of the past.



**Dr. Christos Christou,**  
*International President, Médecins Sans Frontières/  
Doctors without Borders, Geneva, Switzerland*



# Introduction and Overview

Road in Paoua, northwestern Central African Republic, 27 December 2017. House-to-house surveys carried out by MSF in Central African Republic have shown that the incidence of snakebite can be very high. In Paoua results showed that snakebite envenoming was the fourth leading cause of death in the region. In settings where MSF offers treatment, always free of charge, people bitten by snakes are likely to promptly seek care and have a good chance of survival and recovery. In MSF's clinic in Paoua, a survey showed that 75 per cent of admitted patients reached the clinic less than 12 hours after being bitten, mostly due to a well-functioning motorbike taxi system. This reduced mortality significantly



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# Introduction

This year, the World Health Organization (WHO) launches a new Roadmap for Neglected Tropical Diseases (2021-2030). The aim of this roadmap, like the first, is to accelerate progress towards the prevention, control, elimination and eradication of NTDs. However, MSF witnesses remaining gaps and problems in endemic countries where we work. Our teams diagnose and treat less well-known tropical diseases that remain uncontrolled and for which there is little funding for research and development. We also care for patients with deadly tropical diseases that are so neglected that they are not yet classified as NTDs, which makes it even more difficult to harness resources and support for their control.

**There are currently 20 diseases that have been classified by WHO as priority-neglected tropical diseases (NTDs).<sup>1</sup>** Together, they affect more than 1.7 billion people, mostly the world's poorest, and can have devastating consequences, ranging from death to lifelong disabilities and permanent disfigurement. NTDs occur mostly in remote, rural settings where people do not have access to basic and specialized health care. Some of these diseases have become easy to prevent by mass drug administration and over the past few years, incredible progress has been made in reducing their burden and incidence. However, other diseases are still far from elimination or even control and remain truly neglected.

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## The first WHO roadmap for NTDs (2012-2020)

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The first WHO roadmap for NTDs, launched in 2012, inspired the London Declaration on Neglected Tropical Diseases, an agreement signed by a multitude of partners, including major donors and pharmaceutical companies to support control, and work towards elimination or eradication of at least 10 NTDs by 2020.

Since then, there has been an important increase in support for NTDs, both politically and financially, and much progress has been made. There have been some exceptional achievements in research and development

(R&D) for new diagnostics and treatments, such as fexinidazole a highly effective 10 day, once-a-day oral treatment for sleeping sickness developed by DNDi.

A number of multinational pharmaceutical companies have donated billions of drugs to enable the rollout of mass drug administration (MDA) campaigns for the prevention of several NTDs. In addition, selected drugs for the more complex case management of individual NTD patients were donated. For example, Gilead Sciences donated 380,000 vials of AmBisome (liposomal amphotericin B) for the treatment of deadly kala azar in south Asia and Africa, and Sanofi and Bayer donated drugs for the treatment of sleeping sickness.

Through increased donor funding, successful collaborations and drug donations, the incidence of many NTDs, such as sleeping sickness, kala azar (in South Asia only), trachoma, lymphatic filariasis and leprosy has substantially reduced. Several countries have eliminated at least one NTD as a public health problem.

However, despite these significant achievements, hundreds of thousands of people still die from NTDs and many of the targets for 2020 have not been met. There was a lack of political will and funding fell short of what was required. In 2015, WHO estimated that \$18 billion would be needed to achieve the 2020 Roadmap goals, but in the last decade funding for NTDs has not increased and the current finances available for NTDs are not remotely close to that number.

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## The second WHO roadmap for NTDs (2021-2030)

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The new WHO roadmap for NTDs<sup>1</sup> includes more diseases and disease groups than before: snakebite envenoming, scabies, mycetoma and other deep mycoses were added as priority NTDs. With its launch this year, the hope is that strong commitments from major donors, the pharmaceutical industry, endemic countries and other partners will follow. This is fundamental for achieving the newly formulated goals.

Working towards the 2030 roadmap goals will be very challenging. The new roadmap has not yet been costed, but a critical shortfall of funding is to be expected without an exceptional and united effort of all stakeholders. The continuation of most drug donations is uncertain too: pharmaceutical companies previously committed to these for a limited time range, and many such commitments are up for renewal.

### Progress towards control and elimination of NTDs under threat

Progress towards control and elimination of NTDs is under threat from humanitarian crises, natural disasters and population displacement from the impacts of climate change, and the Covid-19 pandemic. *There are already indications that NTD funding was affected for this year and last year.* The impact is still to be fully calculated, but it is recognised that some NTD resources were diverted towards control of the pandemic; and some funding rounds were cancelled. Indications are that funds will reduce further throughout 2021. In addition to the impact on funding, many NTD programmes were negatively impacted by COVID-19 in 2020, such as the interruption of mass drug administration, and previously attained gains may be lost.

A big limitation for NTDs is that there are no global initiatives to attract and distribute funds fairly, such as the Global Fund for malaria, TB and HIV/AIDS. Countries are left to fend for themselves, while donors pick and choose where, when, and for which diseases they want to provide financial support. This has resulted in a highly unequal attention allocation for NTDs. Donor support has mainly focused on NTDs that can be prevented via mass drug administration (with drugs donated by the pharmaceutical industry), as these programmes are relatively easy to implement.

Unfortunately, the NTDs that can only be controlled through resource-intensive efforts to detect and treat cases in remote areas are much less attractive to donors. For example, the three diseases caused by the family of trypanosome parasites, Chagas disease, sleeping sickness (HAT) and kala azar (visceral leishmaniasis) – all diseases that result in high fatality rates if not addressed – have received patchy support that has been far from adequate. While kala azar in south Asia and HAT are on track for elimination as a public health problem, there are no guarantees for sustained support. Kala azar in Africa is far from being controlled and remains a major public health problem. Africa now has the highest kala azar burden of the world.

These diseases have in common that their clinical management is complex and costly because they are ‘tool-deficient’: R&D of new, better and more affordable methods

for their rapid diagnosis and treatment is largely overlooked by the pharmaceutical industry, and only covered by private-public partnerships such as DNDi. Most treatments still need to be administered by injection, with long regimens and potentially serious side-effects.

For snakebite envenoming, the situation is deeply worrying. In 2019, WHO developed and launched a comprehensive Roadmap specifically to address snakebite envenoming, which required \$88 million from the international donor community, largely for the scale up of the production of affordable and quality-assured antivenoms. Unfortunately, the financial support it has received has remained extremely limited up to now, despite this being the most deadly NTD with more than 100,000 people killed each year.

### NTDs still neglected by the research community and pharmaceutical companies

Funding for research and development into NTDs has stagnated in the last decade. This is despite a dramatic increase in global funding for basic research and product development for diseases that affect low and middle-income countries.<sup>2</sup>

The private for-profit sector continues to have limited interest in developing new tools for NTDs as they overwhelmingly affect people with extremely limited financial resources. The global R&D system is skewed towards the development of highly priced drugs for diseases most prevalent in high-income countries. To be able to achieve the ambitions set out in the new roadmap, the system must reform so that NTDs can be prioritised by the research community as whole, and particularly by innovative pharmaceutical companies.

The majority of R&D for NTDs comes from public and philanthropic sources. A number of new drugs and diagnostic tests developed in recent years and now available in endemic countries are the result of collaborative efforts catalysed by not-for-profit product-development partnerships such as DNDi, FIND, and Medicines for Global Health with field actors such as MSF, research institutions and manufacturers. This encouraging progress shows that sustained investments in R&D for NTDs, combined with partnerships driven by the not-for-profit sector, are critical to discover, develop and distribute directly to patients the innovative tools needed to tackle NTDs.

### Poor access to diagnostics and treatments

Although there have been great advances in effective field-adapted diagnostic tools and treatments for some NTDs, national control programmes still struggle to access them. In addition, many drugs to treat NTDs are only produced by one or two manufacturers. For example, many low-income countries struggle to access miltefosine, an oral drug used to treat kala azar – which was fully developed through public funding. This is because Knight Therapeutics, the license holder and producer, will only sell a full production batch at a time, which often exceeds the need of a given country or organisation. MSF’s experience is that there are regular gaps in the supply of all existing diagnostics and drugs

for kala azar. Coordinated procurement is now planned between MSF, WHO and other stakeholders which will help in generating accurate forecasts, so that manufacturers can prepare to meet supply requirements, and will increase negotiating power with manufacturers to ensure guaranteed continued production and affordable prices.

Similarly, quality antivenoms to treat snakebite envenoming in Africa are hard to find. All the more so since a few major producers stopped making them as they did not find it profitable. This opened up a market for products of dubious quality. Antivenoms for Asia were inappropriately used to treat snakebite envenoming in Africa. This resulted in ineffectiveness, side-effects, catastrophic costs, and wastage. This is especially devastating because one vial of antivenom can cost several times an average monthly salary of a typical patient in Africa. It is imperative to establish financing mechanisms that drastically reduce direct costs for patients and improve access to quality-assured antivenoms.

### **The WHO list of priority NTDs does not include all of the most neglected tropical diseases**

WHO has not included all neglected tropical diseases on its list of priority NTDs, and it does not necessarily prioritise the diseases that are the most neglected. There are tropical infections which are not included that are life-threatening and deeply ignored by public health programmes, such as brucellosis and other neglected tropical fevers. One other clear example is noma, a neglected disease that mostly affects children under five years old. Up to 90 per cent of those infected will die within the first two weeks without treatment. The infection destroys the bone and tissue very quickly, affecting the jaw, lips, cheeks, nose or eyes. Survivors are left with severe facial disfigurements that make it hard to eat, speak, see or breathe.

Raising awareness and harnessing support for diseases not on the priority NTD list should be seen as equally important to ensure that no patient is left behind.

MSF laboratory manager Mercy Oluya performs a diagnostic test for visceral leishmaniasis (kala azar) in the MSF laboratory in Abdurafi, Ethiopia, 1 August 2018



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All people should have access to high quality, effective health services at affordable costs, no matter what their disease condition is or where they live. This ambition is at the heart of the Universal Health Coverage agenda and core to WHO's commitments to achieving health for all.

### Integration of care for NTDs

The new roadmap proposes a movement from vertical, disease-specific programming to the integration of screening, diagnosis and treatment into primary health care (although in some instances, a disease-specific focus will still be needed to achieve elimination). MSF is currently revising its strategies with the same goal. This is a novel approach and successful integration will need models that are context specific to make sure that integration does not inadvertently result in even more neglect.

Effectively integrating NTD care therefore requires implementation research to identify and pilot appropriate models of care. This is something for which MSF is often well placed to do. MSF has the privileged position to act as 'eyes on the ground' especially with very vulnerable populations, living in remote regions and for whom access to care is affected by displacement and insecurity. For example, in conflict zones in remote endemic areas, MSF is sometimes the only actor treating these diseases.

**For NTDs that are fatal when not treated, diagnosis and treatment should be made widely available within routine health care provision in endemic areas (although there will remain a role for a disease-specific approach). For example, care for kala azar and sleeping sickness can be integrated into medical emergency interventions and the management of fevers.**

### MSF's role in making the roadmap a success

The new Roadmap will need a level of support and continuity that will be highly challenging to achieve against the backdrop of the current Covid-19 pandemic. Overloaded health facilities and the suspension of active case finding and mass drug administration may have led to serious setbacks in the fight against NTDs. However now is not the time to lose sight of the 1.7 billion people whose lives are impacted by diseases of poverty. MSF strongly supports and endorses WHO's new NTD Roadmap, and will keep advocating for noma to be included in the list of priority NTDs.

To support the new roadmap and work towards its success, MSF commits to:

- Continue diagnosing and treating patients with visceral leishmaniasis (kala azar), cutaneous leishmaniasis, human African trypanosomiasis (HAT/sleeping sickness), snakebite envenoming and noma
- Continue to share expertise and experience with partners such as WHO and endemic countries at all levels, from participation in expert committees and advisory groups to field trainings.
- Join in advocating for increased funding for snakebite envenoming, CL, kala azar in Africa and noma.

#### Access to treatment

- Continue advocating to reduce financial barriers to access to care for NTDs, including for free diagnosis and treatment where needed

- Join pooled procurement of treatments for kala azar; continue to advocate for increased access to drugs by encouraging quality-assured suppliers to manufacture. This is especially important for miltefosine

#### Diagnostics

- Develop and pilot diagnostic algorithms for persistent fevers, which will include NTDs such as HAT, kala azar and brucellosis
- Launch an advocacy initiative to support continued access to rapid diagnostic tools for HAT

#### Research

- Continue advocating for increased funding of R&D for new diagnostics tools and treatments for NTDs,
- Continue to conduct operational research to help address knowledge gaps and evaluate new treatments for kala azar in Africa, cutaneous leishmaniasis by *L.tropica* and snakebite envenoming.
- Continue addressing knowledge gaps through operational research for NTDs treated by MSF which are not yet included in WHO's priority-NTD list, such as noma and brucellosis
- Participate in multi-country clinical trials to evaluate antivenoms for African countries

#### Post elimination

- Support and advocate for continued post-elimination activities for HAT and kala azar: to keep awareness among healthcare providers, maintain a pool of clinical and diagnostic experts, and keep up surveillance

# Overview

“Overcoming Neglect” details MSF’s involvement with neglected tropical diseases (NTDs) over the last three decades. Our work includes treating patients, carrying out operational research, supporting efforts to identify new treatments and diagnostics; and playing an active role in reducing their incidence. We call for an improved global response to NTDs, better access to diagnosis and safe, effective treatment and care for patients.

Each year, hundreds of thousands of people still die from NTDs. These diseases, and the people they impact, are overlooked by policy makers and there are little resources available to address them. For many of these diseases, there is no easy solution - diagnosis and treatment are difficult or simply not accessible. Chronic poverty in combination with NTDs often equals death or prolonged disability.

For some of the most life threatening NTDs, MSF is often one of the only actors providing direct patient care. Over the last thirty years, MSF teams have treated hundreds of thousands of patients suffering from **Chagas disease** (*American trypanosomiasis*), **sleeping sickness** (*human African trypanosomiasis*) and **visceral leishmaniasis** (*VL or kala azar*); deadly parasitic NTDs which affect impoverished populations living in very remote and underserved areas. MSF not only helped identify new treatments and ways to diagnose patients, but also played an active role in reducing the incidence of kala azar in Asia and sleeping sickness in Africa. To achieve this, MSF has increasingly engaged with other actors and donors, such as DNDi, DfID and ITM-Antwerp. These are all positive signals of lessening neglect, however, MSF’s focus is always on the most vulnerable and remote populations, where significant problems still exist.

For example, even though kala azar case numbers are approaching elimination levels in Asia, MSF still treats thousands of patients every year in its clinics in Africa. And while thanks to successful international collaboration, the transmission of sleeping sickness in Africa has been brought back to very low levels, pockets of the disease still exist and will flare up again if surveillance and care are abandoned. MSF is concerned about post-elimination neglect for both these diseases.

MSF on Chagas disease, HAT and African kala azar:

- Ensure existing and future diagnostics and treatments are affordable, accessible, quality-assured and remain in production
- Development of better, simplified diagnostic tools and short-course, if possible oral, effective treatments
- Accelerate the implementation of newly developed diagnostics and treatments in endemic countries, and their swift uptake in World Health Organization and national guidelines
- Decentralisation and integration of screening, diagnosis and if possible, treatment in routine health care activities
- Algorithms to diagnose persistent fevers should include HAT and kala azar
- Reduce financial barriers to access to care for patients, and care at health centre/hospital level should be completely free
- Epidemiological studies to better understand burden and vector and host dynamics
- While governments of endemic countries should lessen dependency on external funds and increase domestic funding, donors must keep providing funds for an adequate response where national control programs lack capacity. Support to the countries with the highest endemic burden should be prioritized
- Sustainability after elimination: Keep awareness among health care providers, maintain a pool of clinical and diagnostic experts, keep up surveillance and not withdraw financial support once elimination milestones have been reached, in order to prevent future outbreaks of the disease

In recent years MSF has also expanded care for **snakebite envenoming** in its projects in Africa, and was surprised by the high numbers of patients who had nowhere else to go and seek care. MSF has been struggling to find suitable polyvalent antivenoms for sub-Saharan Africa, after a major producer, Sanofi, decided to stop production due to a non-profitable market. Much more support is needed to address the crisis of snakebite envenoming, thought to cause more death and disability in poor populations than any other NTD.

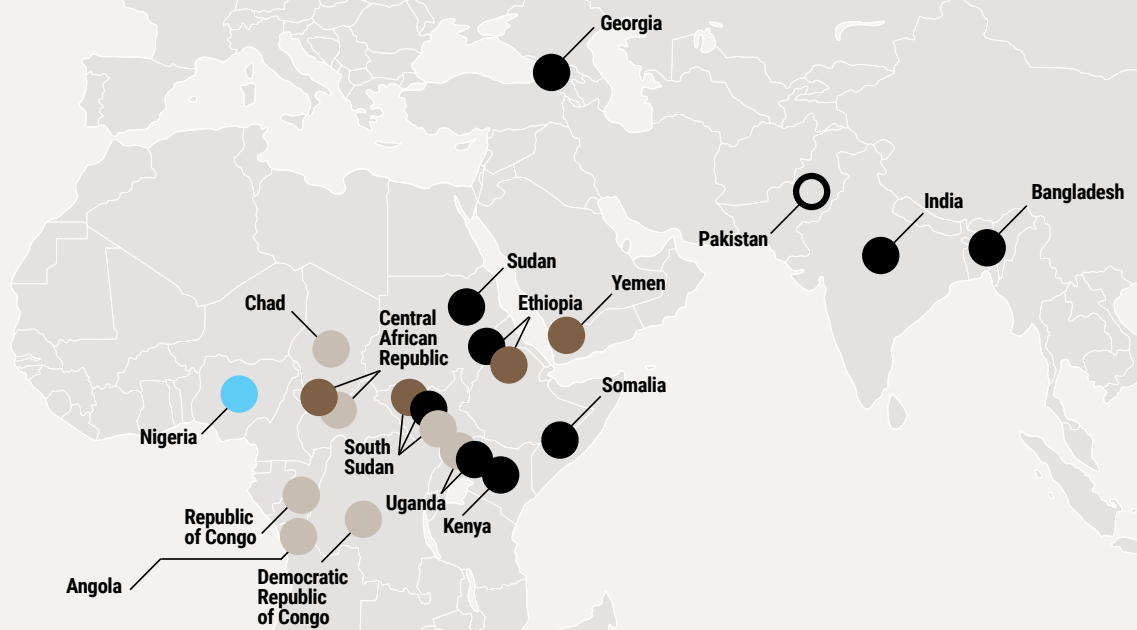
**Noma** is a little known neglected disease that mostly affects young children living in poverty. Up to 90 per cent of those affected by noma die in the first two weeks if they do not receive treatment with antibiotics in time. Those who survive are left with severe facial disfigurements that make it hard to eat, speak, see or breathe. MSF has provided surgical and other support to the Sokoto noma hospital in Nigeria since 2014. Noma remains a deeply neglected condition and is not yet recognized as a NTD by WHO.

Last, **cutaneous leishmaniasis** is a widespread and deeply neglected condition, and although it is not fatal, without treatment it can leave disfiguring or debilitating scars which lead to psychological distress and stigmatization. MSF treats many thousands of patients with this disease every year in Pakistan.

With this report, we aim to show the devastating impact NTDs have on millions of the world's poorest people. We hope that by highlighting the main issues facing their treatment and control, and sharing MSF's experience will result in more attention for NTDs, and an improvement in the lives of NTD patients.

**Fig. 1** Locations of current and former MSF NTD projects





- Kala azar
- Cutaneous Leishmaniasis
- Sleeping Sickness
- Chagas disease
- Snakebite
- Noma

Locations of current and former MSF NTD projects are indications only





# **Visceral and Cutaneous Leishmaniasis**



# Visceral and Cutaneous Leishmaniasis

Human leishmaniasis is a neglected parasitic infection prevalent in nearly 100 countries with more than 1 million new cases occurring every year. Most patients belong to very poor and disadvantaged populations, often living in conflict settings. Without treatment, leishmaniasis leads to death (in case of visceral leishmaniasis) or skin disease (in case of cutaneous leishmaniasis) which can cause stigmatizing facial scars, debilitating lesions and disfigurement.

The Leishmaniases are a group of diseases caused by *Leishmania* parasites, closely related to the *Trypanosoma* species that cause sleeping sickness in Africa and Chagas disease in the Americas. These parasites are transmitted to humans by the bite of an infected female sand fly.

The specific *Leishmania* species responsible for infecting humans differ around the world. Consequently, the epidemiology and dynamics of leishmaniasis varies greatly and infections can lead to a wide array of symptoms, ranging from self-healing or progressive skin lesions (*cutaneous leishmaniasis*) to fatal systemic disease (*visceral leishmaniasis*).

## Visceral leishmaniasis (kala azar)

Visceral leishmaniasis, also called kala azar, is endemic in 78 countries, mostly situated in tropical and sub-tropical regions.<sup>3</sup> Epidemiological hotspots are found in east Africa, south Asia and Brazil. In 2018, 83 per cent of reported cases occurred in five countries: India, Brazil, South Sudan, Ethiopia and Sudan, with each reporting more than 1000 cases.<sup>3</sup> Most cases occur in east Africa, which had

### Challenges

- In east Africa, national control programmes lack capacity and patients experience major financial and other barriers in accessing care
- In east Africa, both diagnosis and treatment are relatively complex and can only be given at hospital or advanced health centre level
- There are very few suppliers of drugs so that there are often problems with security of supply

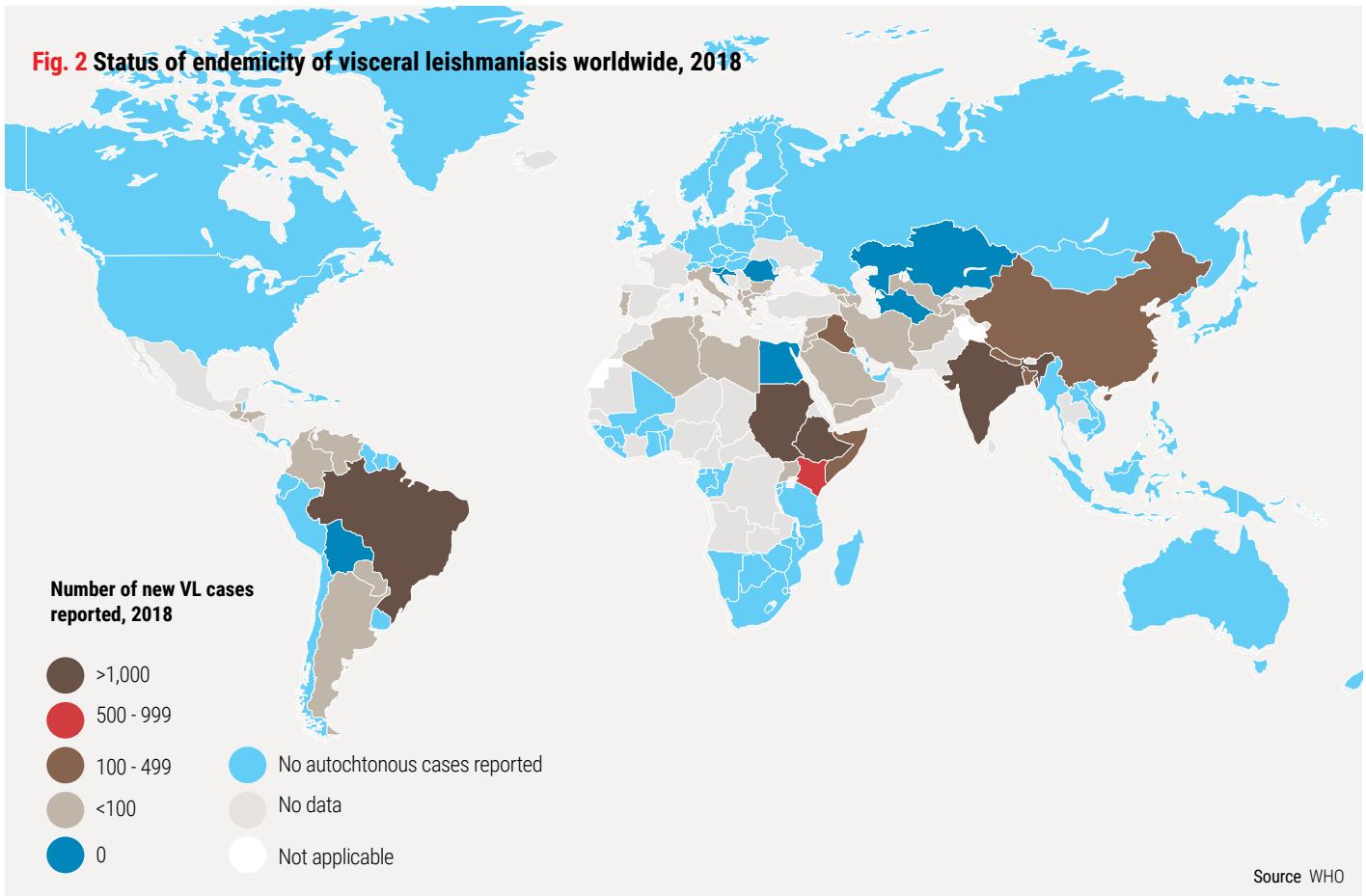
45 per cent of reported cases worldwide, in 2018.<sup>3</sup>

Kala azar manifests differently, responds differently to treatment, and has a different epidemiology in east Africa than in south Asia. In India, Bangladesh and Nepal, kala azar was historically highly endemic, with epidemic waves every 15 years and 77,000 reported cases in 1992. Following a regional kala azar elimination programme, initiated in 2005, case numbers steadily declined to 4,700 in 2018.

● *“We left everything behind and walked for an entire week. Even then I was not feeling well. My eighth child had already died of kala azar (...) during the day, I could still walk and carry my children but at night I had a high fever and needed to rest. We came to a place where there were many other displaced people. I knew I was sick with kala azar, as my child died of it before, and that MSF was in Lankien. We had to leave five children behind with some people we knew so as to be able to reach the hospital in Lankien. We walked for four more days to reach Lankien. I have been on treatment for 12 days now. As soon as I finish, and get stronger, we will go and collect the children and move to Akobo where my parents live. There I hope we will have peace, a tukul and food for the children.”*

—  
Musa, South Sudan – affected by kala azar

**Fig. 2 Status of endemicity of visceral leishmaniasis worldwide, 2018**



In east Africa the disease has a more severe presentation and is more difficult to treat. Kala azar epidemics leading to high mortality have been seen in conflict-affected areas, with large-scale population movements, malnutrition, and weak health infrastructures resulting in poor access to health care. All of these factors can accelerate the development and spread of the disease, and complicate control measures.

Kala azar usually occurs among the world's poorest people, who live in remote and rural areas with little access to health care. Studies in India, Ethiopia and Sudan show that awareness of kala azar is generally very low, and the disease is often misdiagnosed several times before patients finally reach a facility where it can be diagnosed and treated. The total costs of a disease episode have been found to be catastrophic to around 40-50 per cent of kala azar patients and their households (relative to their average annual household expenditure).<sup>4</sup>

### Clinical manifestation

Kala azar causes persistent fever, weight loss, weakness, anorexia, enlargement of the spleen and lymph nodes, anaemia and suppression of the immune system. Patients eventually become very weak and severely malnourished, and if not treated in time, they die, usually due to opportunistic infections causing pneumonia or sepsis. Many patients also

die of heart failure caused by severe anaemia. However, with timely diagnosis and treatment nearly all patients can be cured, although a small proportion may relapse within months or years. Relapse requires a more complex diagnostic and treatment approach than a primary episode.

Many patients (approximately 10-15 per cent in south Asia, and 40-60 per cent in Africa) develop isolated skin sequela after having been cured of kala azar, called post-kala azar dermal leishmaniasis (PKDL). PKDL causes depigmented skin lesions, papules and nodules and although symptoms are usually self-healing, they can last for several months to years. The affected skin can also infect biting sandflies and can therefore be a reservoir for onward transmission. Apart from skin lesions, PKDL does not cause serious problems for most patients who are otherwise healthy, but treatment is indicated for severe cases in east Africa and for all PKDL cases in the context of the kala azar elimination programme in south Asia.

A major challenge is the treatment of patients co-infected with kala azar and HIV. HIV patients are more susceptible to developing kala azar, and once infected, the two illnesses exacerbate each other and are much more difficult to treat. Patients relapse repeatedly, with a reduced chance of survival each time. Eventually they will become unresponsive to treatment. In addition, people living with HIV and kala azar may become 'super-spreaders' of kala azar in their communities as they have such a high parasite load.

## MSF and kala azar

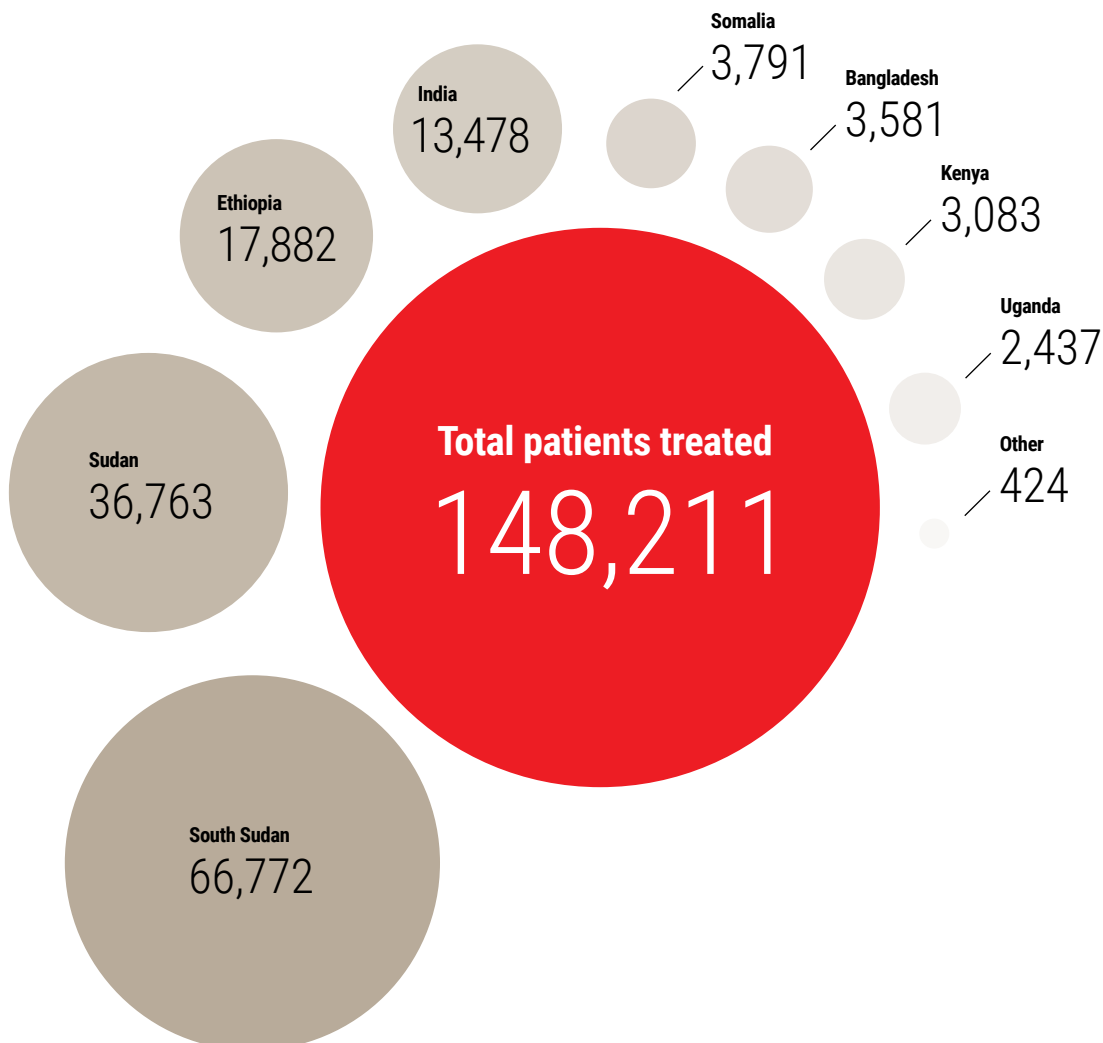
MSF first encountered kala azar in 1988 in Sudan. Internally displaced people living in camps near Khartoum reported an outbreak of an initially unknown 'killing disease' in the Western Upper Nile region. MSF located the epicentre of the outbreak in what is now Unity state in South Sudan, treating 20,000 kala azar patients in the area between 1989 and 1995. These activities took place in the height of the second Sudanese civil war in what was then southern Sudan. These difficult circumstances hampered MSF's ability to reach all patients in need. In later years, retrospective mortality surveys in the region found that an estimated 100,000 people had died because of kala-azar since the start of the epidemic in 1984.<sup>5</sup>

Since then, MSF has remained one of the very few actors actively involved in kala azar, treating about 60 per cent of

all cases in South Sudan. Globally, MSF has treated almost 150,000 patients, mainly in South Sudan, Sudan, Ethiopia, Kenya, Somalia, Uganda, India and Bangladesh.

Today, access to treatment has increased dramatically in many affected countries, the result of continued advocacy, new tools to diagnose and treat the disease and increased involvement of donors and national programmes. The disease is now much better controlled in south Asia. The current low numbers of cases meant that MSF was able to hand over to the government its kala azar programmes in Bangladesh and India, but still provides technical advice and advocates for sufficient funds for the post-elimination phase surveillance. MSF remains actively involved in treating kala azar in several African countries, where it remains a significant public health problem and where the capacities of national control programmes are limited and largely donor dependant.

**Fig. 3** Total kala azar patients treated by MSF from 1989-2020



## Diagnosis and treatment

### South Asia

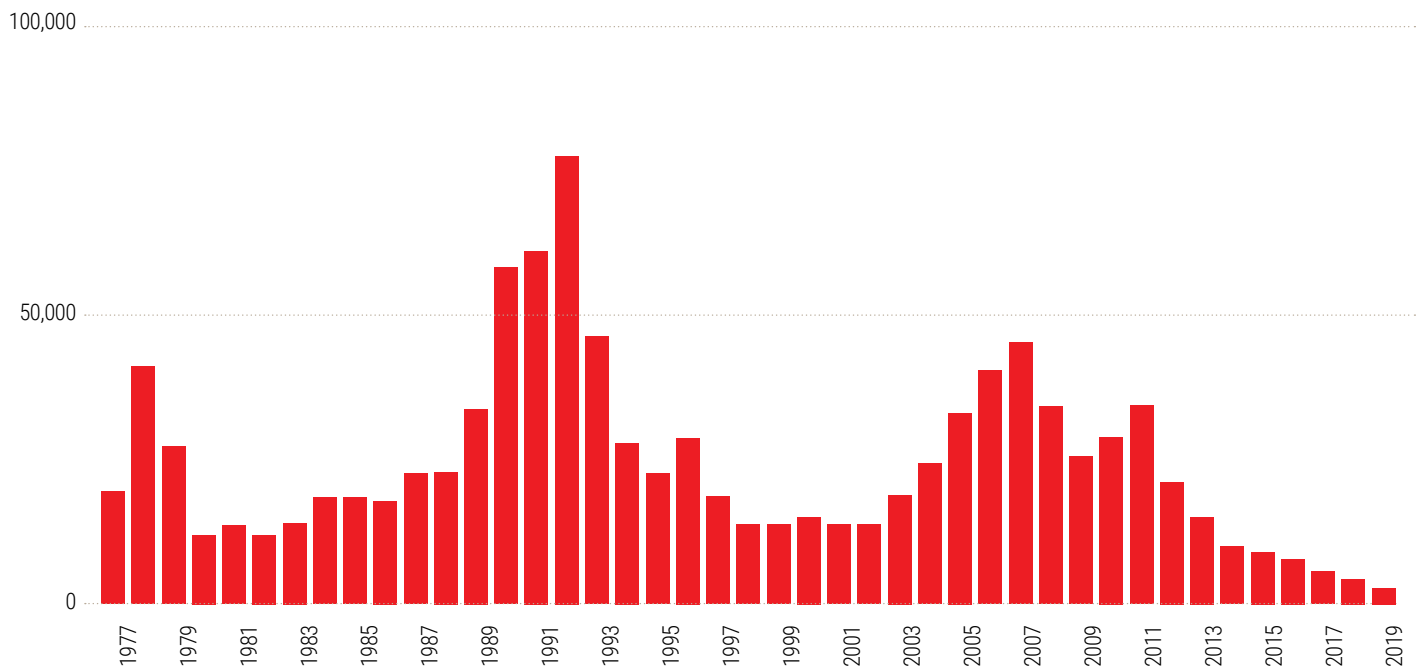
Kala azar has been targeted for elimination in India, Bangladesh and Nepal by 2020, with an aim for fewer than 1/10,000 cases per (sub) district level. Elimination is feasible, because the first line treatment is a single infusion of AmBisome (liposomal amphotericin B), which is easily tolerated, highly effective, and available for free as a donation for low and middle income countries from the manufacturer (Gilead Pharmaceuticals, USA). Moreover, almost all (more than 98 per cent) of primary kala azar patients can be diagnosed with rapid diagnostic (rK39) antibody detection tests. Additionally, the disease is anthroponotic (only transmitted from human to human) and the sand fly species transmitting kala azar in the Indian subcontinent is peridomestic, meaning that indoor residual insecticide spraying (IRS) can significantly reduce their numbers and therefore the risk of infection. With a winning combination of active case finding, early diagnosis and treatment and IRS, Bangladesh has already progressed from more than 9,000 cases in 2006 to reaching the elimination threshold in 2018. Nepal and India are also on track although hidden endemic hotspots remain.

There is, however, a risk that the disease could resurge after elimination. To avoid this, there needs to be continued active detection of all kala azar and PKDL patients in communities who should be treated immediately in order to limit transmission. This will require significant resources in the years to come, even after the elimination target has been reached, since PKDL can develop months to years after successful kala azar treatment.

### East Africa

Diagnosis and treatment of African kala azar is relatively complex. The current first line treatment is a 17-day combination of pentavalent antimonials (sodium stibogluconate, SSG) and an antibiotic (paromomycin, PM) which requires the hospitalisation of patients. It is unsuitable for some patient types because of the risk of potentially severe side effects. These patient types include pregnant women, the elderly and very young, the severely ill and HIV co-infected patients. These patients need treatment with AmBisome as it is much better tolerated, although not always as effective. Unlike in south Asia, the rK39 rapid diagnostic test can only confirm diagnosis in about 85-90 per cent of patient among those that are clinically suspect of having VL. For the rest, much more complex direct antiglobulin tests (DAT) or microscopy of tissue aspirates, requiring well-equipped laboratories, are needed. Such complexities make it difficult to roll out kala azar diagnosis and treatment at primary health care level, impacting on access for patients. Moreover, although transmission of kala azar in east Africa occurs mainly from human to human (anthroponotic), the disease also has a zoonotic reservoir. Opportunities to control the disease-transmitting sand fly populations are limited, as these are sylvatic and mostly live and bite outdoors. There is currently no evidence-based method for the prevention of sand fly bites in humans which are feasible for wider roll-out in Africa. Therefore, the focus in east Africa remains on early case detection and treatment, often complicated in endemic areas where there is poor access to functioning health care and where most patients live in extreme poverty.

**Fig. 4** Reported VL incidence India (1977-2018) <sup>6,7</sup>



Sources WHO Global Health Observatory data repository (2005-2018). National Institute of Communicable Diseases, Government of India (1977-2004).

## MSF's work on HIV/ kala azar

MSF has treated HIV/kala azar co-infected patients in Africa and India since the 1990s. Most of this work took place in MSF's clinic in Abdurafi, in northwest Ethiopia, where the rate of HIV/kala azar co-infection is very high (around one-fifth of kala azar patients in MSF's clinic are co-infected). Most patients are young male migrant workers, who are at risk of getting kala azar as they come from non-endemic areas and are exposed to sandfly bites while working and sleeping out in the fields. Migrant workers often face numerous barriers accessing health care.

## MSFs scientific studies in HIV/kala azar

MSF's in-depth and innovative research in HIV/kala azar started in the early 2000s with a clinical trial conducted in Ethiopia, which showed that miltefosine was safer than antimonials in this patient group. This was followed by several studies on the role of antiretroviral treatment in preventing relapses and the effectiveness and safety of AmBisome (liposomal amphotericin B). In the 2010s, MSF started working together with DNDi and ITM and initiated studies in the use of pentamidine as secondary prophylaxis to prevent kala azar relapses in Ethiopian co-infected patients. In this period, MSF also piloted a combination of AmBisome (liposomal amphotericin B) and miltefosine (AmB + MF) and found that this is a safe and effective treatment option in HIV/ kala azar, both in India and Ethiopia. This was followed by a joint MSF/DNDi clinical trial which demonstrated that AmB + MF is currently the most effective and safe treatment for HIV/ kala azar. MSF and partners' clinical studies have led to the validation of a standard diagnosis and treatment regimen for HIV/ kala azar that includes prompt initiation on antiretroviral therapy (ART), treatment with AmB + MF and secondary prophylaxis with pentamidine. In 2020, WHO convened an Expert Committee meeting where the use of AmB + MF for HIV/ kala azar co-infection in east Africa and south Asia was officially adopted.

MSF is conducting further studies with ITM to create a better understanding of HIV/kala azar co-infection and the progression of asymptomatic leishmaniasis infection to disease in HIV/kala azar co-infected patients in Ethiopia.

All studies were published in peer reviewed scientific journals (see <https://fieldresearch.msf.org/msf/>)

## Operational research

MSF has conducted numerous key operational research studies, since encountering kala azar in (what was then) southern Sudan in 1989. These have been driven by the need to improve survival rates and patient care, and to have diagnostic and treatment tools that can be used outside of hospital settings in remote areas. Most of the results have been adopted into national and international policies and guidelines. In total, MSF has published well over one hundred study papers on kala azar.

MSF's earliest research included clinical studies in what is now South Sudan, investigating the effectiveness of new treatments in its field operations (SSG+PM combination therapy; AmBisome for complicated kala azar), which are now standard first and second line treatment regimen in east Africa. MSF also field-tested the DAT test and antibody detection (rK39) rapid diagnostic tests in Africa, validated an affordable generic form of SSG as an alternative for the expensive branded drug (Pentostam, GSK), performed numerous outbreak investigations and validated diagnostic and treatment algorithms which enabled the safe treatment of all categories of patients in Africa.

## Persistent Fever Syndrome project

MSF frequently cares for patients with prolonged febrile illnesses (more than seven days) in its field projects. In addition to infections that are common worldwide, patients in the typical settings where MSF works may have a multitude of neglected and often deadly tropical infections such as kala azar, typhoid fever, Q-fever, brucellosis, and relapsing fever. For most of these diseases, diagnostic tools are either unavailable or too sophisticated for field settings. Often a diagnosis cannot be made with sufficient certainty, which leads to suboptimal treatment.

To help clinicians manage these prolonged fevers better, MSF, as part of a research consortium, participated in a multi-country study, the 'Neglected Infectious Diseases Diagnosis' study (NIDIAG). In MSF's kala azar project in Sudan, it was found that although kala azar, brucellosis and malaria were the most common cause of persistent fevers, 44 per cent of patients remained undiagnosed and were treated, often ineffectively, with antibiotics and antimalarial drugs. As a result, MSF is developing diagnostic and treatment algorithms for persistent fevers, which will include simplified diagnostic tests and updated epidemiological information on the prevalence of neglected diseases in different regions.

In Bangladesh and India, MSF performed clinical studies which showed that short course AmBisome is a safe and effective treatment for kala azar and PKDL, and together with the Drugs for Neglected Diseases *initiative* (DNDi) conducted studies looking at the field effectiveness and safety of new combination treatment regimens. In east Africa, MSF is participating in a DNDi-sponsored clinical trial to compare combination regimens with miltefosine and PM with the current first line SSG/PM kala azar treatment.

MSF's current research focuses on an integrated approach to diagnosis and treatment of persistent fevers, including those caused by kala azar and other febrile NTDs, and improved management of HIV/ kala azar co-infection in Asia and Africa. Most of MSF's recent studies in this field are conducted in close collaboration with partners, such as DNDi and the Institute of Tropical Medicine (ITM) in Antwerp, Belgium.

The hope is that future research can yield promising outcomes. DNDi has identified potential new candidate molecules for patient-friendly, simple, safe, affordable and highly effective oral therapies for both kala azar and PKDL, but it will still take several years of development before successful new oral drugs will be available for patients.

### **MSF collaboration for a donor-funded kala azar control programme**

In 2014, after strong advocacy by MSF and partners, what was then the UK Department for International Development (DfID) initiated and funded a four-year programme to support kala azar elimination and control in six highly endemic countries in south Asia and east Africa. A coalition including MSF, DNDi, the London School of Hygiene & Tropical Medicine (LSHTM) and Mott MacDonald (the 'KalaCORE' consortium) was chosen to administer the programme, which ended in March 2019. MSF, who remained financially independent, provided technical assistance to the implementing organisations and governments. Most key positions in the target countries were held by former and current locally-hired MSF employees with extensive experience in MSF's kala azar projects. The programme offered a unique and unprecedented opportunity for MSF to disseminate its experience and knowledge directly with national control programmes, and has led to significantly increased access to quality diagnosis and treatment for kala azar patients. A follow-up DfID (now part of the UK Foreign and Commonwealth Office) initiative, the ASCEND program, aims to build on this success and provide further funds to support national kala azar control programmes up to March 2022, with possible extension.

### **Miltefosine access**

Miltefosine (Impavido) is the only oral use drug licensed for the treatment of leishmaniasis. The product was originally developed in the mid 1990s by WHO/TDR (Special Programme for Research and Training in Tropical Diseases) and partners. Further clinical studies for its use in treating kala azar have been conducted by various groups including MSF and DNDi. Miltefosine is essential for the treatment of certain categories of patients, such as those co-infected with HIV and kala azar.

Currently, the ownership rights belong to Knight Therapeutics, a small pharmaceutical company in the United States. These rights have been exchanged on multiple occasions over the years through business mergers and acquisitions.

Despite the fact that the development of miltefosine was paid for by donors, access to this drug in low- and middle-income (LMIC) countries with the highest burden of kala azar has been very problematic. Although there is a negotiated preferential price for non-profit organisations and governments, even at this price, miltefosine is the most expensive anti-leishmanial drug by far, and is prohibitively expensive for low income countries. Additionally, there are large minimum purchase requirements by the manufacturer. In practice this means long lead times, wastage, lack of access to smaller quantities of the drug and regular shortages in endemic countries. In 2014, the US Food and Drug Administration (FDA) awarded Knight Therapeutics a Priority Review Voucher (PRV). This is an incentive aimed at rewarding research and development (R&D) for new treatments for neglected tropical diseases. This is despite Knight Therapeutics never having invested in R&D for miltefosine. The company sold the PRV to Gilead for \$125 million. None of this money was used to create better access to treatment for impoverished kala azar patients.



## MSF is calling for

- WHO to continue leading a coordinated effort to safeguard access to existing and future kala azar treatments. In order to improve supply security and keep prices low, it is important to encourage more quality-assured suppliers to manufacture leishmaniasis drugs. This is especially important for miltefosine.
- Decentralization of diagnosis to primary health care level; integrate VL in persistent fever diagnostic algorithms.
- An accelerated implementation of newly developed diagnostics and treatments in endemic countries, and their swift uptake in World Health Organization and national guidelines.
- Donors to continue providing funds for an adequate kala azar response in South Sudan and other east African countries where national control programmes lack capacity and the disease is far from elimination or even control. This call comes recognising that many governments of endemic countries need to increase domestic funding for kala azar control programmes.
- Patients to be able to access appropriate care, and diagnosis and treatment with no financial barriers in east Africa and south Asia.
- Donors and governments to commit to sustained elimination in south Asia, and to uphold support and funds once elimination milestones have been reached, in order to prevent future outbreaks of the disease.
- Continued investments in the development of oral short-course, safe, affordable and highly effective treatments for kala azar and PKDL.
- The development of a comprehensive and integrated disease management package for kala azar patients co-infected with HIV. This should include screening HIV patients in endemic areas for kala azar.
- The development of a rapid test for east Africa which is more sensitive than the currently employed rK39 antibody detection test, ideally a highly sensitive antigen-detection point of care test that can be used for primary diagnosis, test of cure and detection of relapse.
- Increased research into fuller understanding of the epidemiology of kala azar, in particular vector and host dynamics.
- Increased research into vector control and innovative approaches in east Africa to reduce transmission, taking into account the living conditions and habits of affected populations.

Kala azar patients gather in a tent to watch a movie at the Médecins Sans Frontières hospital in Lankien, South Sudan, 14 January 2015



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As CL is not fatal, policy makers often deprioritise it, despite the consequences being severe and lifelong

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## CUTANEOUS LEISHMANIASIS

Cutaneous leishmaniasis (CL) is one of the most widespread neglected tropical diseases in the world. The disease is endemic in most of the Americas, the Mediterranean, western Asia and northern Africa. More than one million cases were reported the five years from 2013 to 2018, but this represents only a fraction of the true number. WHO estimates that the real incidence is more than one million new cases each year. In 2018, only 251,533 cases worldwide were reported, 76 per cent of these came from seven countries, each with more than 10,000 cases: Syria, Afghanistan, Pakistan, Iraq, Iran, Brazil and Algeria.<sup>3</sup>

CL can cause a wide variety of skin afflictions ranging from self-healing single sores, which leave stigmatising scars, to muco-cutaneous lesions that destruct the cartilage and soft tissues of the face. This causes severe disfigurement and is very difficult to cure. As CL is not fatal, policy makers often deprioritise it, despite the consequences being severe and lifelong. It is estimated that 70 per cent of CL patients face psychological distress and stigmatisation because of scarring and disability. The clinical presentation depends on the causative parasite species, of which several are found around the world.

The most prevalent types of CL are those caused by *Leishmania tropica* (*L.tropica*) and *L.major*, seen in northern Africa, the Middle East and western Asia. These types cause skin sores, often on the face, which generally self-heal without treatment but leave disfiguring scars. Lesions that occur on joints, hands and feet can become debilitating. CL by *L.major* is zoonotic, and usually spontaneously heals within three to six months. CL by *L.tropica* is anthroponotic, and often causes outbreaks.

The incidence of CL by *L.tropica* has soared, with hundreds of thousands of cases reported in recent years. Regions where there is conflict and poverty such as Syria and Afghanistan are particularly affected, as is Pakistan. Spontaneous healing can take one year or longer, and the facial scars are stigmatising and can lead to social isolation. Young women can be seen as non-eligible for marriage, raising children or household activities by their families and communities. Treatment will reduce scarring, but has many drawbacks. The mainstay treatment is a 3-4 weeks course of local (intra-lesional) or systemic injections with antimonials, which are cumbersome, painful, potentially toxic, and often not available.

### Challenges

- One of the most widespread and most neglected tropical diseases
- Little is known about the true burden of CL, but it is estimated to be much higher than the reported numbers and most people remain untreated
- Treatment is cumbersome, painful and potentially toxic and there is very little research into new treatment options



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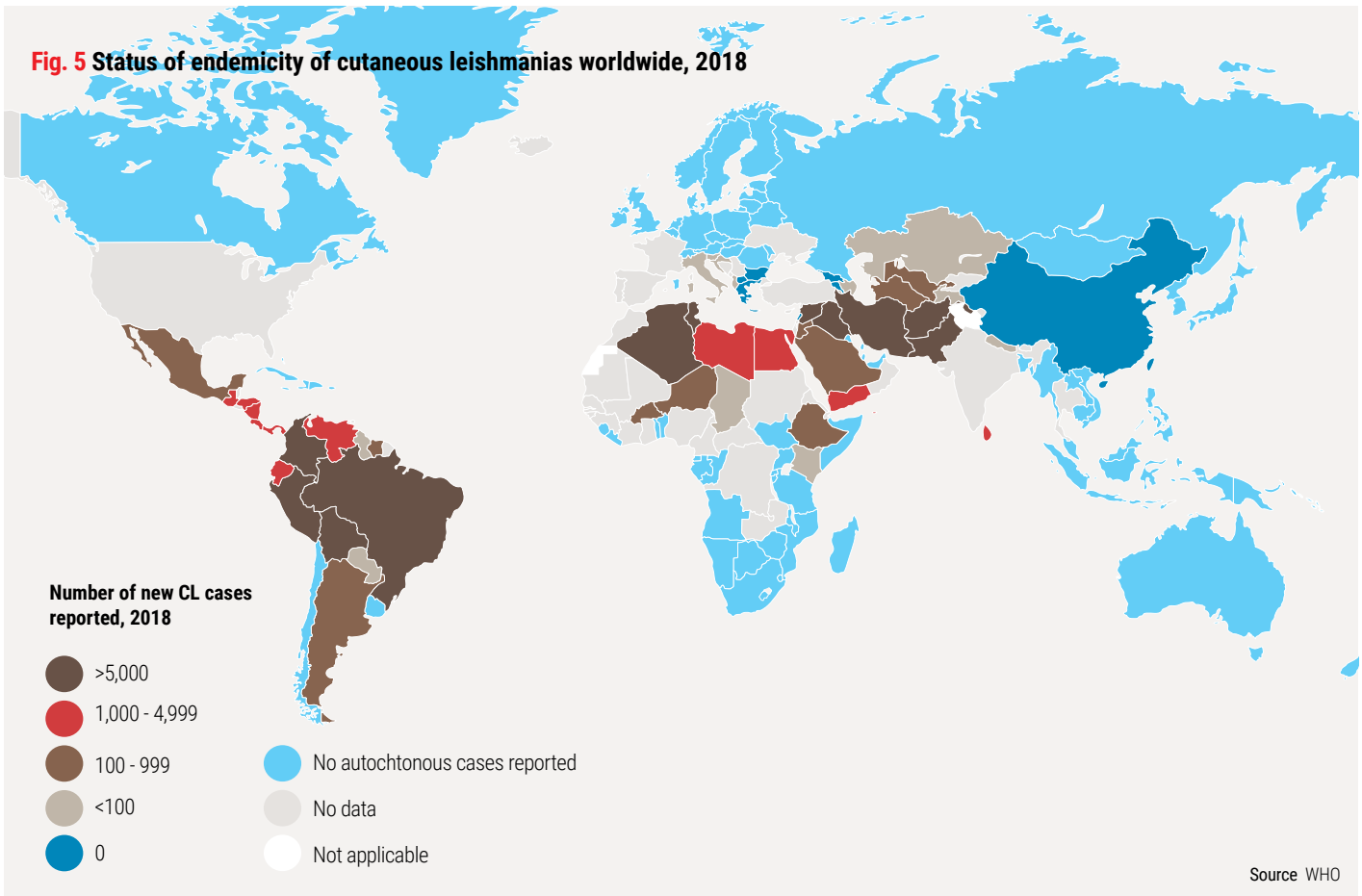
Subhan holds hand of his daughter Afia before she receives the injections for cutaneous leishmaniasis at the MSF treatment centre in Naseerullah Khan Babar memorial hospital, Peshawar. He also was treated for cutaneous leishmaniasis at the MSF facility a couple of months before his daughter contracted the same disease. The marks of the lesions are still fresh on the father's hands. 12 June 2019

A unique and potentially severe form of CL, caused by *L.aethiopica*, is found only in impoverished populations living in remote highland areas of Ethiopia. Although the burden is estimated at 20,000 to 40,000 new cases a year, only 882 cases were reported to WHO in 2018. This type of CL can result in mucosal involvement and diffuse chronic lesions, covering the whole body. It is probably the most neglected form of CL and because of a lack of research, no evidence-based treatment exists.

● “My savings are almost gone. I haven’t driven the taxi for many weeks now. I can’t. It is very painful to push the brake pedal with this wound on my foot. I thought it was a simple skin disease at first, but I now realise it’s a specific disease, which needs specialised treatment. I hope I can quickly go back to work and earn money again.”

—  
**Saeepur, Pakistan – affected by CL**

**Fig. 5 Status of endemicity of cutaneous leishmaniasis worldwide, 2018**

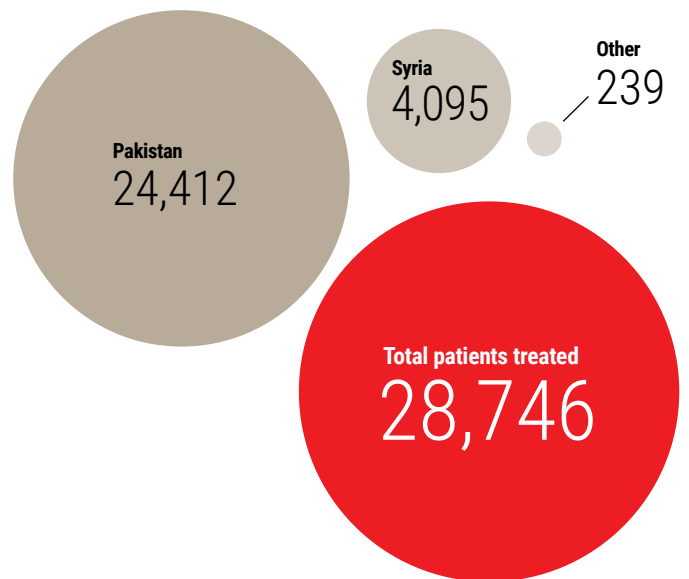


### MSF and cutaneous leishmaniasis

CL is a deeply neglected public health problem in Pakistan, with a largely underreported burden. The WHO estimates that the annual incidence of new cases may be over 100,000. Large outbreaks have occurred in the last few decades. There is hardly any treatment available in the country as the public sector is dependent on irregular and small donations by WHO. In the private sector, treatment comes at high cost and is often of poor quality, including counterfeit drugs. This situation is typical for most CL-endemic countries.

MSF has been present in Pakistan since 1986 and provides medical care to people in Baluchistan and Khyber Pakhtunkhwa. These regions in western and northern Pakistan are areas which are highly endemic for CL by *L. tropica*. MSF provides CL diagnosis and treatment in several hospitals and treated more than 6,500 CL patients treated in 2019 alone, one third of the total reported cases in the country. Patient numbers are increasing rapidly each year, reflecting poor access to treatment in other areas. Since 2017, MSF has been treating CL in Syria, another country with very high case numbers and little access to treatment.

**Fig. 6 Total CL patients treated by MSF from 2008-2020**



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## Operational research

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Most CL cases from around the cities of Quetta in Baluchistan and Peshawar in Khyber Pakhtunkhwa are caused by *L.tropica*, for which the only evidence-based treatment is a course of local or systemic antimonial injections. This is what MSF offers to patients. In case of treatment failures, and for patients who do not tolerate systemic antimonials, MSF uses oral miltefosine as a second line treatment. Although no clinical studies to evaluate its efficacy in CL by *L.tropica* have been conducted, an MSF retrospective study found that it was a safe and effective second line treatment.

A non-chemical treatment option, which has shown promise in several studies in CL caused by *L.tropica*, is radio-frequency generated thermotherapy. Lesions are heated to 50°C for 30 seconds with a portable, battery operated device, the ThermoMed machine. This is a promising treatment option, as studies report less scarring tissue, and just one treatment session is required. Despite these major benefits, the ThermoMed machine is hardly used anywhere in the world, most likely because of its high price, and on its own is probably not sufficient to achieve high cure rates.

To generate evidence for the efficacy of both miltefosine and thermotherapy, MSF will conduct a study, starting in 2021, comparing a combination of oral miltefosine and thermotherapy, against the current standard of care, intral-lesional injection with antimonials. It is hoped this study can provide evidence for much needed new treatment options, which are shorter, safer, more effective and more patient-friendly, for CL patients in other *L.tropica* endemic areas.

## MSF is calling for:

- Countries to be enabled to develop accurate estimates of the burden of CL, in terms of incidence, prevalence, geographical distribution and psychological stigma, so that these control programmes can be better budgeted and supported
- Increased efforts in research and development (R&D) to support the identification of effective, safe, topical or oral, well tolerated treatments for CL, which can be deployed as ambulatory treatment at primary health care level (with follow up to establish cure).
- Increased efforts in research and development for rapid diagnostic tests for the detection of cases.

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CL is a deeply neglected public health problem

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# **Human African trypanosomiasis (sleeping sickness)**



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# HUMAN AFRICAN TRYPANOSOMIASIS (sleeping sickness)

Sleeping sickness used to be one of the most neglected NTDs in the world. At the end of the 19<sup>th</sup> and beginning of 20<sup>th</sup> century, it was one of the main causes of death in (what was then) the Belgian Congo. Huge epidemics devastated large areas of the continent. In 1901 alone, half a million people in the Congo basin are estimated to have died from the disease. Today, after several highly successful interventions, sleeping sickness is on track for worldwide elimination, with fewer than 1,000 cases reported in 2019.

Human African Trypanosomiasis (HAT or sleeping sickness), is a parasitic, vector-borne disease transmitted by the tsetse fly. It is caused by *Trypanosoma brucei gambiense* in west and central Africa and a much less common form is caused by *T. b. rhodesiense* in east Africa.

Sleeping sickness invades its host progressively. The first stage of the disease is marked by fever, headache and joint pain, as the parasite spreads to the blood and lymph nodes.

Once the parasite crosses the blood-brain barrier, the second, late stage of the disease becomes apparent. Patients experience psychiatric symptoms such as confusion, agitation, aggressive behaviour and disinhibition. Sleeping sickness derives its name from one other striking symptom: a disruption of the sleep-wake cycle with bouts of insomnia at night but an overwhelming need to sleep during the day. If left untreated, the disease

## Challenges

- Elimination targets are close to being reached, but without continued support, re-emergence of the disease and new outbreaks could easily happen
- With few cases left, there may be little interest among manufacturers to continue producing existing and newly developed diagnostic tools and drugs
- It is important to offer screening and treatment in primary health care facilities in endemic areas, but confirmation of diagnosis is too complex to be done at this level

is eventually fatal. If treated too late, patients can experience permanent personality changes and psychiatric problems.

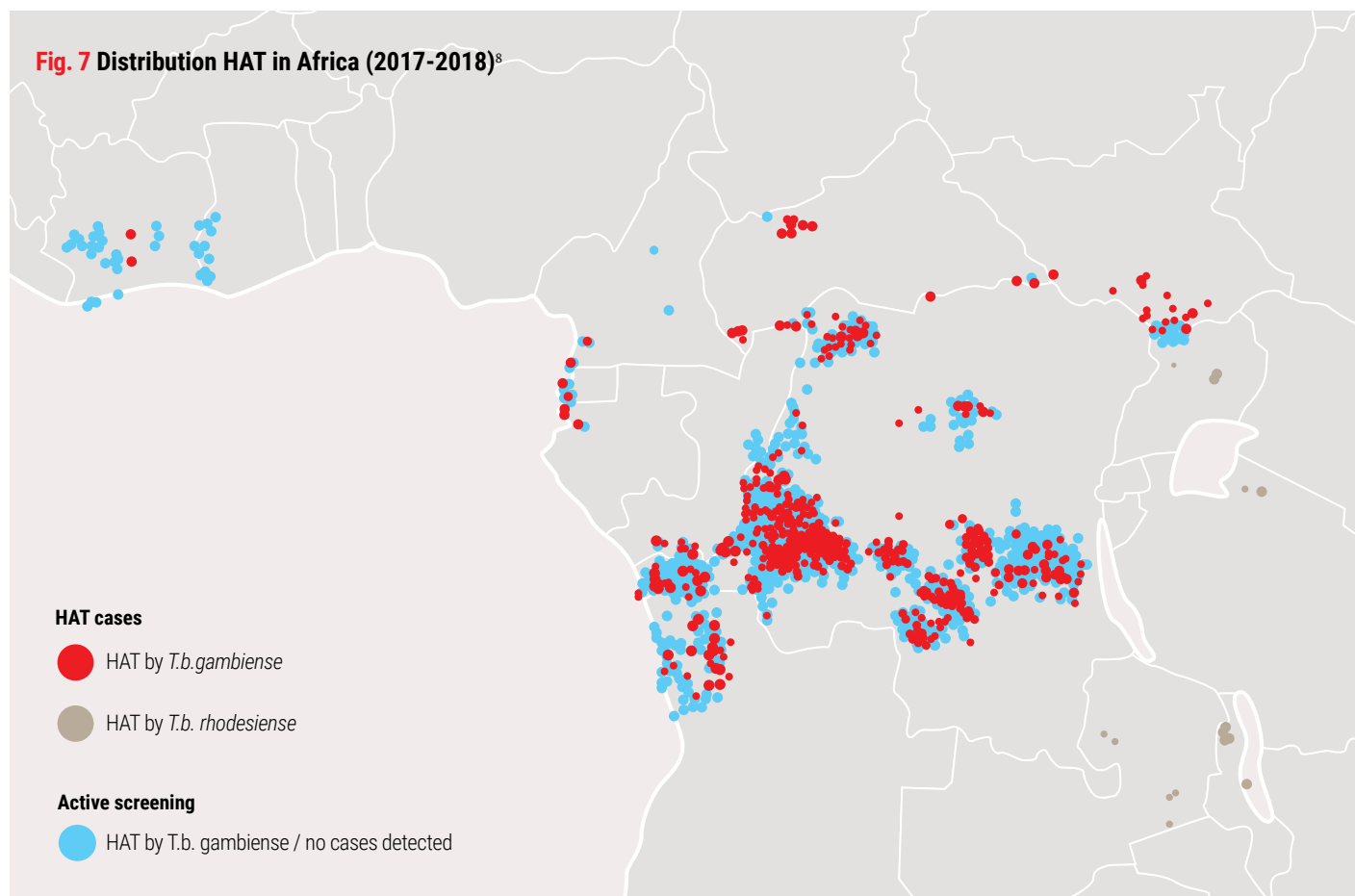
● *“I was so dizzy I would fall to the ground, I had no energy, I couldn’t eat, and I could only take sips of water. My family couldn’t understand what was wrong with me. They are so relieved that I’m getting treatment and am already starting to feel better.”*

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**Germaine, Democratic Republic of Congo – affected by sleeping sickness**

Sleeping sickness affects rural populations in Africa, living in remote areas and dependent on agriculture, fishing, animal husbandry or hunting. Case detection and treatment had some success in reducing the number of cases between the 1920s and 1960. During the colonial period there was also mass chemoprophylaxis with pentamidine (often without patient consent). But the prevalence of the disease quietly increased once again as low case numbers in many endemic countries and a lack of resources disrupted HAT control activities. Population displacement, caused by conflict and poverty, into endemic areas also led to increased transmission of the disease.

**Fig. 7 Distribution HAT in Africa (2017-2018)<sup>8</sup>**



The last re-emergence started in the 1980s, with a peak in 1998 when almost 38,000 new cases were reported to WHO. This was likely a severe underestimation of the true incidence due to the lack of diagnostic and treatment services. Some villages reported that as many as half of their inhabitants were infected. Since this outbreak, international collaboration and the commitment and investment of resources by national programmes has significantly improved. As a result, cases have been falling steadily. In addition, there are continued efforts to increase treatment centres, develop better performing diagnostics, find new drug regimens, perform active case detection, improve surveillance, roll out awareness raising campaigns, and train laboratory and medical staff.

As a result in 2017, the WHO reported just 1446 cases of *T.b. gambiense* HAT from 16 countries and just 864 cases from 13 countries in 2019. The main endemic zone remains within the Democratic Republic of Congo (DRC) with 604 reported cases in 2019. Other hotspots of *T.b. gambiense* HAT are found in Guinea, Angola and Central African Republic (CAR). Several historically endemic countries have not reported new cases for over a decade. Transmission of the disease may have stopped in these countries, although there may also be insufficient surveillance and reporting.

## MSF and HAT

Between 1986 and 2019 MSF screened nearly 3.5 million people for sleeping sickness and treated more than 50,000 patients in seven countries (Angola, South Sudan, Democratic Republic of Congo, Central African Republic, Congo Brazzaville, Uganda and Chad). Gradually, there were fewer local outbreaks with high caseloads, and most cases appeared to be in relatively small foci.

In 2012, MSF shifted its approach, integrating HAT into its existing projects. At the same time a specialised mobile team was set up to actively detect and respond to new endemic foci and neglected areas. The idea was to identify and locate possible remaining HAT transmission hotspots.

The MSF mobile team consisted of nurses, laboratory technicians and health education staff. They visited remote villages, by motorbike, by canoe or on foot. Each village resident was tested and people who tested positive were referred for treatment. Health promotion was key to informing villagers about both the passive and active screening activities. The mobile team also worked to build up screening capacity by training laboratory technicians, nurses and physicians.

MSF introduced surveys and risk-ranking systems when performing exploratory activities and worked in collaboration with social science teams to help ensure the work was culturally appropriate in different contexts.

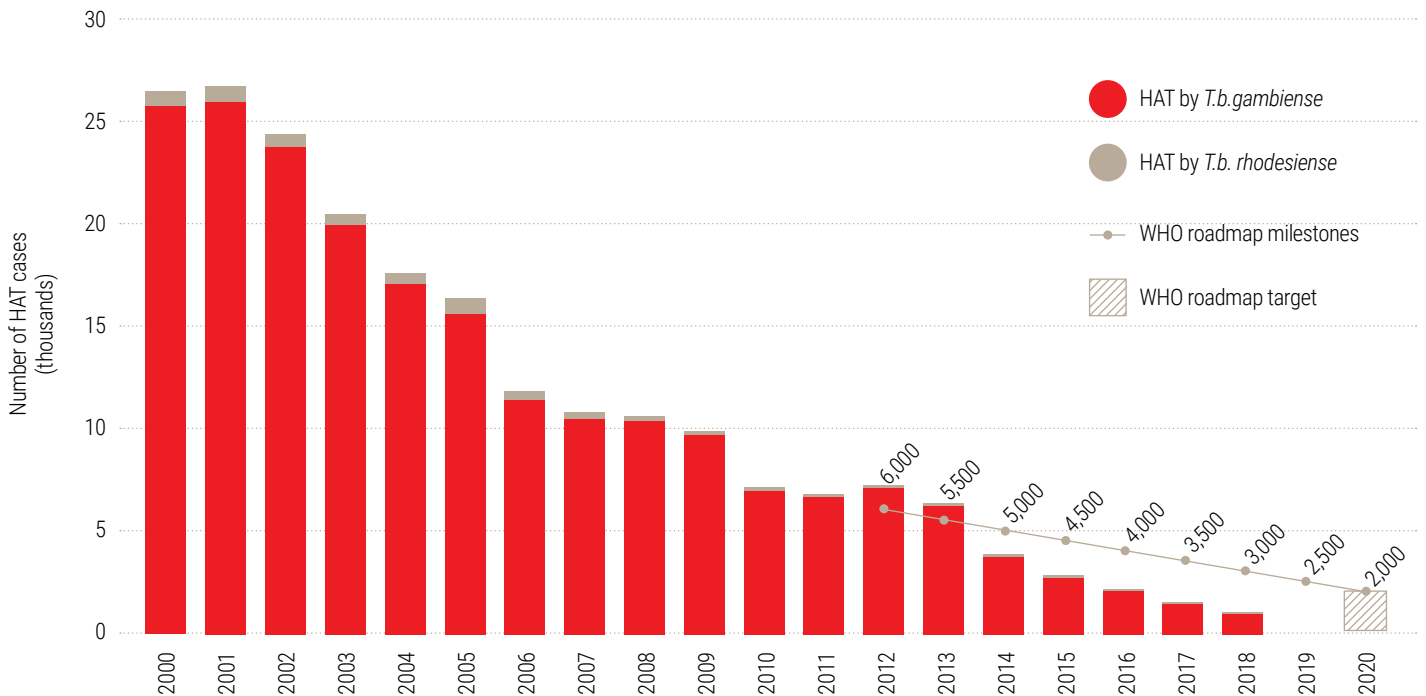
The risk-ranking system identified villages most at risk for HAT transmission, based on a risk index. This included the time of last screening, population size, environmental factors (such as closeness to rivers or streams, dense vegetation or other known tsetse fly habitats), HAT cases reported from national data, villagers' knowledge about sleeping sickness and whether there were residents with symptoms; and presence of people at high risk of infection such as hunters and fishermen.

This innovative approach initially proved highly successful in identifying new cases in remote and inaccessible areas that no other actor could reach.

Between 2015 and 2019, the mobile team visited hundreds of villages in the Democratic Republic of Congo and screened nearly 100,000 people for sleeping sickness and malaria. The team also actively screened people in South Sudan and Central African Republic.

After 2016, the number of detected cases remained consistently low, in parallel with the globally decreasing caseload, which led to the decision to end the team's activities in 2019. MSF now aims to integrate HAT passive screening, diagnosis and treatment into its existing projects in current and historical endemic areas, while remaining prepared to respond to a possible resurgence of cases.

**Fig. 8 Progress in HAT elimination over the years<sup>s</sup>**



## Diagnosis and treatment

Until very recently, before sleeping sickness patients could be treated, a 'staging' procedure (differentiation between stage 1 and stage 2 of the disease) was needed. This relied on the demonstration of trypanosome parasites in body fluids and a count of white blood cells in cerebrospinal fluid obtained via lumbar puncture, a risky and painful medical procedure. First stage sleeping sickness was treated from 1950 onwards with injectable pentamidine, a generally well tolerated medicine and administrable at village level. Second stage sleeping sickness could only be treated with injectable melarsoprol, a toxic and painful arsenic-based treatment, which killed one in 20 patients and had a high failure rate. Both these drugs were produced by companies eventually acquired by Sanofi.

There was a complete absence of funding for research into new and better diagnostic tools and drugs until the 1990s when an alternative to melarsoprol, eflornithine, was shown to be effective against *T. b. gambiense* and was soon licensed for use in the most highly endemic African countries. But some years later its production was discontinued by the original producer because it was not considered profitable. This prompted MSF via its newly launched Access Campaign (set up in 1999) to support the WHO to reach an agreement with Sanofi for the continued production and donation of its drugs for the treatment of sleeping sickness (pentamidine, melarsoprol and eflornithine), an agreement which still stands today. A further agreement was achieved between the WHO and Bayer, which provides the remaining drugs for HAT (suramine and nifurtimox). As the donations include

funds for logistical support, it has been possible to deploy eflornithine on a large scale in Africa since 2001.

Eflornithine's main draw-back was the need for 56 intravenous infusions (four daily for 14 days). The development of a shorter and simpler treatment, combining two existing drugs, was the only logical way forward. MSF initiated a clinical trial in 2001 in Congo-Brazzaville to study the combination of eflornithine with nifurtimox, a drug already used to treat Chagas disease. To complete the required sample size, this trial was continued between 2004 to 2008 in the Democratic Republic of Congo where MSF was supported by DNDi and the MSF affiliated epidemiological research association, Epicentre.

Once it was shown that nifurtimox-eflornithine combination therapy (NECT) was effective and safe, it was rolled out in African countries immediately. With NECT the number of eflornithine infusions was reduced from 56 to 14 (twice daily for seven days) and combined with nifurtimox tablets, three times a day for 10 days. By the end of 2010, only about one in 10 second stage patients were still treated

with melarsoprol. But diagnosis with lumbar puncture for the staging procedure, and treatment with seven days of infusions was still hard to implement at field level and difficult for patients.

In 2018, there was a major breakthrough in the treatment of sleeping sickness. DNDi, in partnership with Sanofi and the National Control Programmes of DRC and CAR, supported by MSF, completed the development and registration of fexinidazole, a highly effective 10-day, once-a-day oral treatment. Fexinidazole penetrates the blood-brain barrier and is now recommended by WHO as first line treatment for both stages of the disease, reducing the need for the staging procedure with lumbar puncture. In advanced stage-2 neurological disease, fexinidazole is less effective (87 per cent) and NECT remains the recommended treatment, but fexinidazole can be used in settings where NECT is not available. MSF is now working closely with DNDi on a simplified strategy for the implementation of fexinidazole at primary health care level in its operations in DRC and CAR.

MSF mobile clinic team travels by motorbike between the village of Doromo and the village of Bembese, in northeast Democratic Republic of Congo on 6 June 2014. Communities in this region are affected by sleeping sickness and MSF offers testing and treatment for this neglected tropical disease.



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## New diagnostic tools for HAT: where are we?

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### Screening

HAT is usually diagnosed in two sequential steps: serological screening by CATT (card agglutination test for trypanosomiasis), a test produced in the 1970s by ITM-Antwerp, followed by parasitological confirmation of the disease. CATT is highly sensitive, but lacks specificity, which makes it unsuitable for diagnosis in areas with low case numbers, as it is likely to result in false-positives. The method is dependent on skilled lab technicians and it is logistically challenging to implement in many areas as electricity is required, including for a cold chain. It is also expensive and labour-intensive. Since 2012, the Foundation for Innovative new Diagnostics (FIND), with ITM-Antwerp, have supported the development of rapid diagnostic tests which offer a more cost-effective screening strategy.

However, the validation process has shown limitations in their performance and efforts are still ongoing to improve these tools. There are also concerns about the necessary scale-up of their production and their long-term availability, as demand for these tests will decline as the number of cases reduces. It is vitally important that producers remain committed to the long-term quality production and availability of diagnostic tools for HAT. This is even more important in the future, as diagnostic tools will play a key role in validating and sustaining HAT elimination.

### Confirmation

Confirmation of infection requires microscopy to demonstrate the presence of trypanosomes in lymph node fluid or blood, and in cerebrospinal fluid for diagnosis of stage-2 disease. This continues to rely on relatively sophisticated techniques. MSF uses two laboratory-based procedures to concentrate trypanosomes in blood samples before microscopy, mAECT (mini anion exchange centrifugation technique) and WOO (microhematocrit centrifugation technique).

In parallel, the serological trypanolysis test (TL, developed by ITM-Antwerp), a highly specific test for identifying antibodies against *T.b gambiense*, has been used as the ultimate screening and confirmatory test, but its use is restricted to only two laboratories. Dried blood spots on filter paper can be taken in the field, stored and sent abroad for analysis, but this results in delayed diagnosis. For this reason, this test is not part of the routine algorithm. It is used for quality control and required by WHO for validation of HAT elimination.

### Challenges and future approach

Although HAT is on track for elimination, there is a real risk of re-emergence in the future. Recent research found that even if trypanosomes cannot be found in blood, they may still be present in the skin and therefore can form a reservoir of infection and sustain transmission. The primary challenge is how to detect any new outbreak in its early stage. This requires effective surveillance of HAT in low case incident populations, while maintaining diagnostic and treatment

skills in these settings, which is challenging in areas with security risks and poor health systems. Currently, insecurity continues to hamper HAT activities in endemic areas of Central African Republic, the Democratic Republic of Congo and South Sudan.

In the near future, diagnosis and treatment should become integrated into standard health care packages in HAT endemic regions and be free-of-charge to patients. To this end, health centres must be enabled to provide first-line diagnosis and treatment with fexinidazole and hospitals to test and treat advanced neurological disease.

The 2012 WHO Roadmap for NTDs aimed for the elimination of HAT by *T.gambiense* as a public health problem by 2020, with a main target of fewer than 2000 cases a year, globally. This was achieved in 2017, although surveillance remains incomplete. The 2020 WHO Roadmap proposes full and sustainable elimination (zero transmission) to be verified in 15 countries by 2030. There still is a considerable gap between the ambitions of the WHO and stakeholders, and available funds and the reality on the ground.

A potentially major breakthrough is a new single dose oral treatment identified by DNDi, acoziborole, for which a pivotal clinical trial was completed. This ongoing research could result in a safe, effective and ultra-short treatment in few years.

These are promising times for the goal of eliminating HAT. An ideal situation may soon be within reach, where a health worker in a remote primary healthcare centre in an endemic area is able to diagnose HAT with a rapid diagnostic test and treat a patient immediately with an effective single dose oral treatment. It is critical, however, that there is sustained investment of resources to avoid rolling back progress and to prevent re-emergence of the disease.

## MSF calls for

- Efforts to ensure that passive screening and treatment are integrated into standard health care packages in HAT endemic regions and are free of charge to patients.
- Guarantees that there will be continued surveillance activities post-elimination, keeping awareness of HAT among health care providers and maintaining a pool of clinical and diagnostic experts.
- Investment to ensure continued production of existing and new diagnostic tools and drugs.
- Development of simplified, more accurate and less invasive diagnostic tools that can be easily deployed in primary health care centres, and during mobile healthcare activities.



# Snakebite



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# Snakebite envenoming

Snakebite envenoming (the medical condition resulting from a snakebite) kills more people than any other disease on WHO's list of NTDs. According to WHO's figures, every year, more than five million people are bitten by snakes, and between 81,000 and 138,000 of them die. This is equal to around 11,000 deaths a month. In addition, hundreds of thousands of people bitten by snakes are left with life-changing disabilities, including blindness, walking difficulties and amputation. Snakebite may also lead to the development of significant psychological disorders, ranging from nightmares to post-traumatic stress disorder (PTSD).<sup>9</sup>

The true number of people affected may be much higher than official estimates by WHO that are mostly based on hospital data. As many people who are bitten do not receive treatment in formal healthcare settings, their envenoming remains unrecorded. Community based surveys can help us to understand the true burden of snakebites, but it is clear that it is a major neglected health crisis.<sup>10, 11</sup>

There are more than 3,000 kinds of snakes in the world, of which around 200 are responsible for most global deaths, injuries and disabilities. Snakebite envenoming affects the world's poorest, usually those living in remote rural areas, with a direct correlation between snakebite deaths and poverty. The people most exposed to snakebites are those who live in remote villages, work in fields without shoes, and sleep on the ground in huts with permeable walls, no electric lighting or mosquito nets. Snakebite often leads to financial ruin as, in their attempts to get treatment, survivors and their

## Challenges

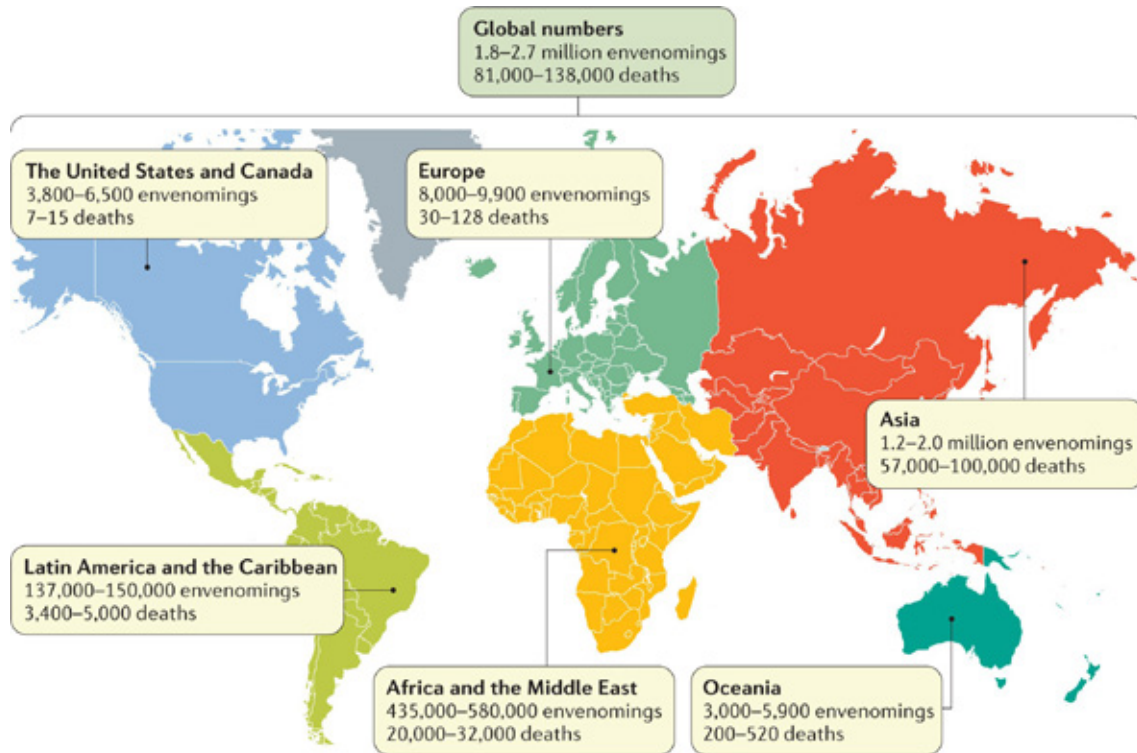
- Although good and timely clinical management can save lives, in remote rural locations many people do not manage to get to healthcare facilities in time due to a lack of ambulances or other transport
- In health facilities, antivenom is often not in stock, or might be substandard and ineffective against local snake species.
- Quality antivenoms are mostly not available, or far too expensive for people to afford

families are driven into catastrophic debt. In addition, patients often face social stigma and discrimination in particular as snakes are considered a bad omen in some areas.

● *“My niece was bitten by a snake in her arm at night while she was sleeping (...) she didn't improve and the swelling continued so we decided to go to the hospital. She was dizzy and couldn't walk, so I ran, carrying her on my back. When I got tired, I had to put her down on the side of the road to rest, she is heavy because she is not a young child. It took five hours to get to the hospital (...) they gave her antivenom and marked her body with a pen where the swelling was. It continued swelling up to the chest. The doctor proposed to operate her and I signed a paper to give my consent. Thanks to this operation, she is now still alive.”*

**Athian Akol Madut, South Sudan – his 10 year old niece Awien was bitten by a snake**

**Fig. 9 Geographical distribution of snakebite envenomings and deaths<sup>12</sup>**



Source Gutiérrez, J. M. et al. (2017) Snakebite envenoming *Nat. Rev. Dis. Primers* doi:10.1038/nrdp.2017.63

## Treatment

Death by snakebite is avoidable, but time is of the essence. For a person bitten by a black mamba, paralysis and suffocation can occur within one to four hours, with the venom causing rapid respiratory paralysis. Good clinical management can save lives, requiring stabilisation with fluids, the administration of antivenoms, and sometimes assisted ventilation. There must be daily wound care, and in some cases, surgery and the amputation of an affected limb is necessary.

But for most snakebite victims, the reality is that access to care is very poor. A 2010 study estimated that only two per cent of people bitten by venomous snakes in sub-Saharan Africa had access to quality antivenoms,<sup>13,14</sup> and not much has changed since then. There is often no available transport to a health facility. Most health centres have no or only low quality antivenoms in stock, lack essential equipment such as ventilators, and have no health workers trained to deal with snakebite envenoming.

When quality antivenoms are available, they are often unaffordable. The two antivenoms most frequently used in MSF projects are expensive. A full course of three vials of EchitabPlus (from ICP, Costa Rica) costs about €100, while a treatment with SAIMR (from SAVP, South Africa) can cause up to nine times as much (almost €900).

Although MSF provides antivenom treatment to patients free of charge, elsewhere snakebite victims are faced with staggering costs. Only in a few notable countries, such as Burkina Faso and Nigeria, were antivenoms sold at subsidised prices for a while but it has been extremely challenging to maintain that policy over time.<sup>15</sup> With limited options available, victims may buy fewer doses of antivenom than they need or they may have to rely on cheap and less effective alternatives. Some turn to traditional healers. As a proportion of snakebites are non-poisonous or 'dry' (no poison is injected), it can appear as if people have been cured this way. Working hand-in-hand with traditional healers and community health workers is crucial to ensure snakebite victims are rapidly transferred to facilities where antivenom and advanced life-support is available.

## MSF and snakebite

MSF treats around 6,000 snakebite victims each year in projects spanning 10 countries. Four thousand of those patients are found in just five projects. These are Paoua in Central African Republic (CAR), Agok in South Sudan, Abdurafi in Ethiopia, and Abs and Ibb in Yemen. Around one third of all patients need treatment with an antivenom. MSF focuses not only on case management (antivenom treatment, resuscitation and surgery) but also on epidemiological and

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# Timely treatment of snakebite is crucial

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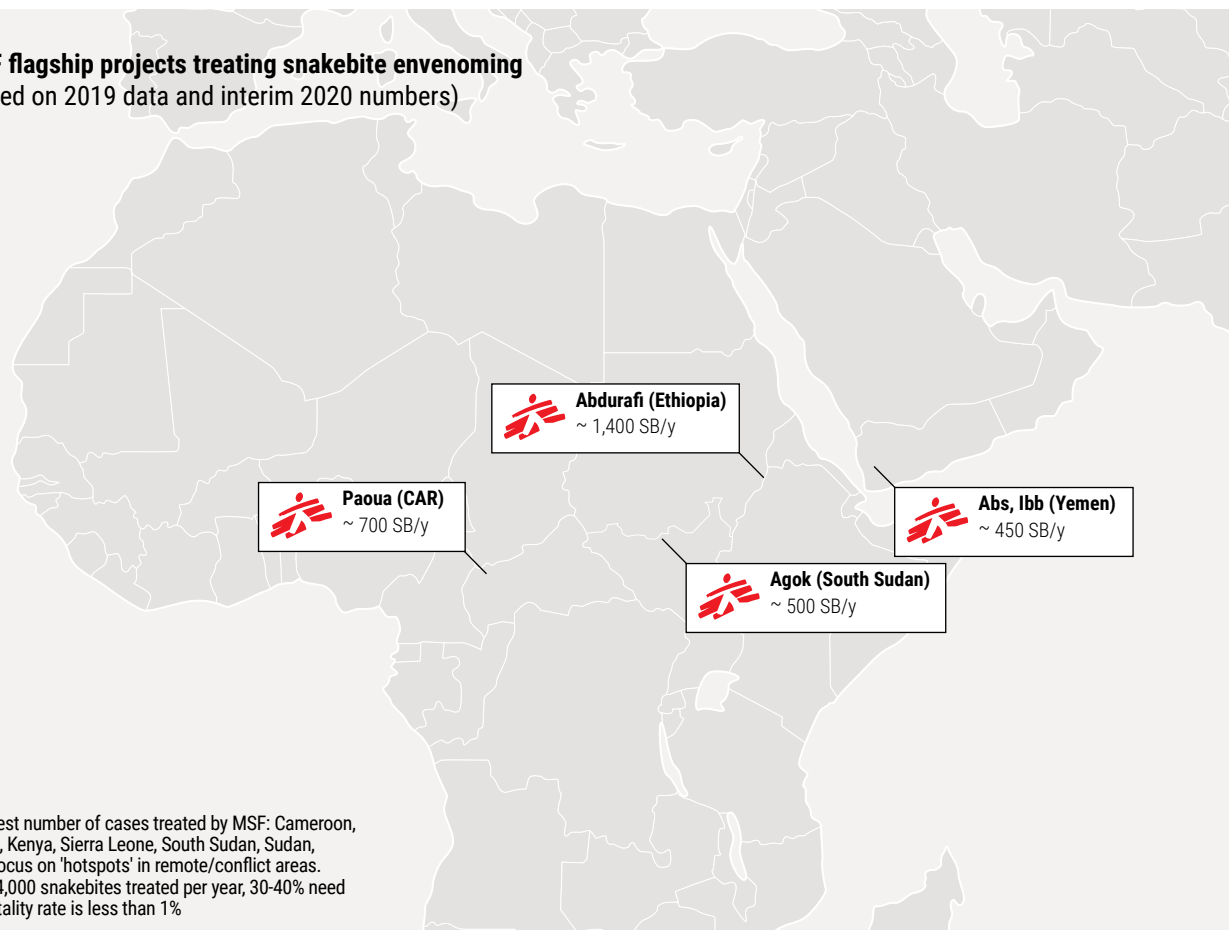
herpetological surveys, to determine which species of snakes are the most prevalent so that treatment can be adapted accordingly. MSF is also actively advocates with ministries of health and the WHO to improve access to affordable quality antivenoms, and increase training of health workers.

In settings where MSF offers treatment, always free of charge, people bitten by snakes are likely to promptly seek care and have a good chance of survival and recovery. In MSF's clinic in Paoua, a survey showed that 75 per cent of admitted patients reached the clinic less than 12 hours after being bitten, mostly due to a well-functioning motorbike taxi system. This reduced mortality significantly.

In South Sudan, around MSF's hospital in Agok, mortality has been reduced by more than half, with currently less than 1 death per 500 snakebite victims. People bitten by snakes were eight times more likely to die if they did not access MSF's hospital in time.

House-to-house surveys carried out by MSF in South Sudan and Central African Republic have shown that the incidence of snakebite can be very high in its project areas. In Agok MSF estimated that there were 3,596 snakebites bites per 100,000 people per year, many of whom did not reach a hospital. In Paoua (CAR) results showed that snakebites represented 6.7 per cent of community deaths, with snakebite envenoming the fourth leading cause of death in the region.

**Fig. 10 MSF flagship projects treating snakebite envenoming**  
(Update based on 2019 data and interim 2020 numbers)



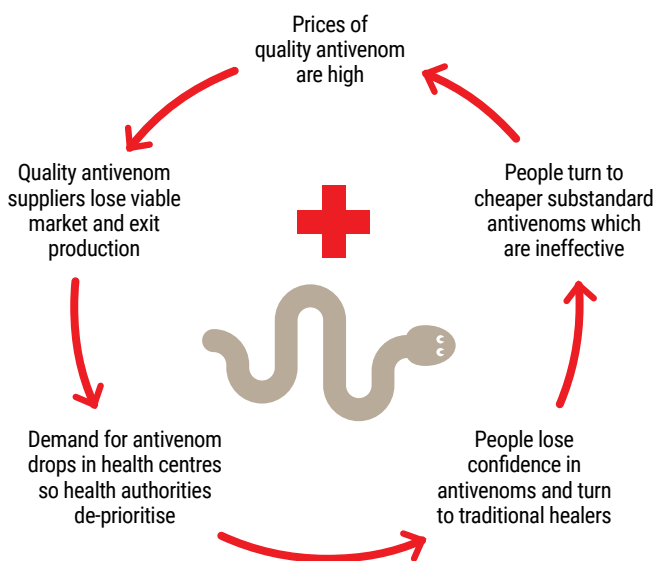
Countries with highest number of cases treated by MSF: Cameroon, CAR, Chad, Ethiopia, Kenya, Sierra Leone, South Sudan, Sudan, Tanzania, Yemen. Focus on 'hotspots' in remote/conflict areas.  
**Total MSF:** Around 4,000 snakebites treated per year, 30-40% need antivenom. Case fatality rate is less than 1%



© MICHAEL TSEGAYE

At night, migrant workers cook dinner in a field in Abdurafi, Ethiopia, November 2010. They work, cook, eat and sleep in the fields, either under trees or out in the open. They are at risk of snakebites and of kala azar, a common but neglected disease and face an impossible choice: either they can sleep under a tree and risk being bitten by sandflies, or they can sleep in the open fields and risk being bitten by snakes

**Fig. 11 The vicious circle of antivenom shortages**



In MSF’s hospitals, almost all snakebite patients survive. This demonstrates the crucial importance of well-trained staff, immediate access to quality care and the availability of quality antivenoms.

**Lack of access to antivenoms**

MSF has faced many difficulties in importing quality antivenoms as these are often not registered in the countries that need them. This has led to stock ruptures with serious consequences: the mortality of admitted patients increased and admissions went down as patients tried to seek care elsewhere.

Cheap substandard or inappropriate (e.g. targeting a different snake species) antivenoms were a problem on the African market a few years ago. Although the situation has improved somewhat, it is not uncommon, for example, to find hospitals in African countries supplied with antivenoms that are only active against Asian snake species. As these substandard and inappropriate products are ineffective and unsafe, people may lose confidence in antivenoms and start to avoid them. With reduced demand for antivenoms,

health authorities do not prioritise their supply to local health facilities and in turn, local health workers cannot gain experience in administering antivenom treatment. Of even greater concern is that some antivenom manufacturers have ceased production, as they did not see a profitable market.

An example is Sanofi's discontinuation of the production of the polyvalent antivenom 'Fav-Afrique', the last vial of which expired in June 2016. Experts considered it as one of the most effective antivenoms for the treatment of envenoming by a variety of sub-Saharan snakes. It was safe and could neutralise the venom of 10 deadly African snakes, ideal for settings where different types of small and large vipers, spitting and neurotoxic cobras, and black mambas all have venomous bites. Meanwhile in 2020 MSF is using Echitab-Plus (Costa-Rica) for haemotoxic and cytotoxic viper bites and SAIMR (South Africa) for the few neurotoxic cobra or mamba bites.

After a concerted advocacy effort, Sanofi eventually handed over the production technology to another producer. Fav-Afrique is expected to be on the market again, but not before 2023. The temporary absence of this safe and effective

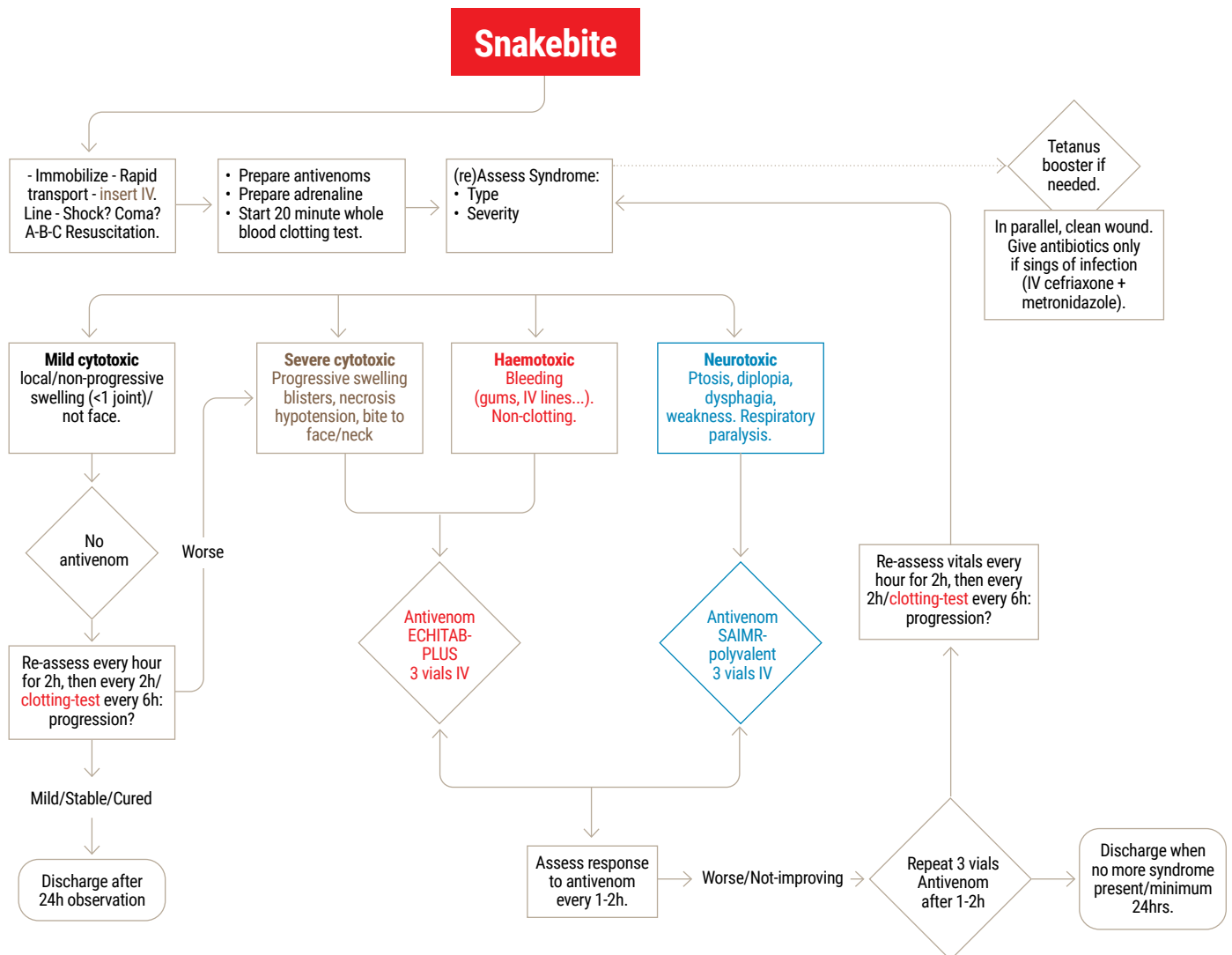
polyvalent antivenom causes considerable problems. In Ethiopia, MSF was forced for some time to use the only other antivenom approved in the country, one manufactured in Egypt, that is not active against the most common snake species in Ethiopia.

MSF gathered expert opinions and studied clinical data on alternative antivenoms marketed in Africa, but found very limited scientific evidence on their efficacy, safety and quality. Of 16 antivenom products currently available, only three products were found to be highly effective, based on data of acceptable quality.<sup>16</sup>

Poor quality products are not only ineffective in neutralising venom toxins, but can also cause life-threatening allergic reactions. Antivenoms are still produced according to a method, initially developed in the late 19<sup>th</sup> century, which involves inoculating horses with snakebite venom and then isolating and purifying the antibodies produced in their plasma. This equine serum can cause severe allergic-anaphylactic reactions, especially when not well purified.

To help address these problems, MSF contributed funds to

**Fig. 12 MSF diagnostic and treatment algorithm for snakebite envenoming**



the WHO Prequalification Programme for an evaluation of antivenoms currently marketed in sub-Saharan Africa. But as of November 2020, the WHO had listed only one antivenom product, a “monospecific” antivenom that is effective against just one snake species. The WHO evaluation, although necessary, has so far not been able to provide guidance on antivenom quality to MSF and other treatment providers.

Much more evidence is needed on existing African antivenoms. In particular, further clinical studies in humans are of paramount importance to provide evidence that antivenoms are safe and effective. MSF is helping to fill this gap by participating in a multicentric clinical trial of several African antivenoms.

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## New antivenoms

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A more standardised manufacturing process for antivenoms, for example using monoclonal antibodies, could greatly improve their safety and effectiveness as well as potentially reduce costs. However, this technology involving multiple antibodies against multiple toxins is still experimental. Researchers say it cannot be expected to become the standard within the next five years or more. Oral treatment that can either complement or replace conventional antivenom therapy may be another future possibility, for a few types of venom.

Given the variety of toxins that constitute venoms, final products will inevitably be cocktails of different compounds coming from different research groups. There is a need for optimal coordination between end-users (clinicians), stakeholders such as donors, toxinologists, biotech and pharmaceutical companies. As new products will need to be field-tested, support to clinical trial sites for snakebite poisoning in Africa is crucial.

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## Outlook and prospects

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Although global health agencies, donors, governments and pharmaceutical companies have failed to take action in the past, recently there are signs of positive change.

In 2017, MSF and many other groups successfully campaigned for snakebite to be re-introduced into WHO's list of priority neglected tropical diseases after it was removed in 2013. Then, in 2018, 194 countries adopted a ground breaking World Health Assembly resolution which mandated WHO to develop an ambitious roadmap to tackle snakebite envenoming. This roadmap was launched during the World Health Assembly in May 2019 (see box).<sup>17</sup>

MSF was part of WHO's snakebite roadmap working group. Its newly released strategy will help to mobilise governments and donors to respond to the snakebite crisis. But in order for it to be successful, substantial financial support (\$88 million) from the international donor community is needed, especially for the large-scale production of affordable and quality assured antivenoms, and so far, pledges remain insufficient.

## WHO's 2019 Roadmap for Snakebite Envenoming

By 2030, WHO aims to increase the number of competent manufacturers by 25 per cent, reduce snakebite deaths and disability by 50 per cent and supply 3 million treatment courses annually worldwide, including 500,000 treatment courses to Sub-Saharan Africa. The roadmap addresses several other important aspects: community and prevention, training of health workers, health system strengthening, epidemiological surveillance and mapping, accessibility to antivenoms and innovation.

## Syndromic Approach

There are three types of envenoming, causing the following symptoms:

**NEUROTOXIC** (cobras, mambas): paralysis, rapid suffocation leading to death

**HAEMOTOXIC** (vipers): haemorrhage, tissue damage, shock, death

**CYTOTOXIC** (spitting cobras, vipers, adders): severe tissue damage, often leading to necrosis and amputation if not treated, blindness (spitting cobra)

For appropriate treatment and care to be given, it is helpful to identify the snake species so that the type of envenoming is known. This, however, often proves impossible, and treatment and choice of antivenom is based on symptoms instead. These are complex and difficult clinical decisions. Therefore, polyvalent antivenoms (effective in multiple types of snakebites) are of paramount importance in settings such as in some African countries, where many different kinds of venomous snakes are found.

## MSF is calling for:

- Increased resources for prevention and management of snakebites, especially through pledging funds for the WHO roadmap.
- The swift development of an international financing mechanism for procurement and supply of affordable, quality-assured antivenoms, including national and regional stockpiles so that they are both accessible and affordable for snakebite victims.
- The allocation of sufficient resources for the assessment of antivenoms by the WHO Prequalification Programme, so that a list of safe and effective antivenoms is established for different regions and countries and regularly updated.
- Governments of countries with high burdens of snakebite to incorporate specific courses on snakebite management and prevention in medical and paramedical curricula at all levels.
- Improved access to treatment through facilitation of transport to equipped hospitals where life-saving treatment can be given. Reduced out-of-pocket expenses for antivenom treatment.
- Investment in community education and prevention activities, including first aid, improved housing, use of torches, protective shoes, mosquito nets and other appropriate measures.
- Implementation of epidemiological studies to explore the true incidence and distribution of snakebite, map hotspots and register their specific antivenom needs.
- Prioritisation of the development of new and better tools against snakebite poisoning, and ensure they are affordable and accessible to those who need them.
- Support for the development of rapid diagnostic tools that will allow for the identification of snake species and quick lifesaving interventions.
- Standardisation of methodologies for the evaluation of therapeutics and diagnostics.

A boy on the banks of the Pibor river in what is now South Sudan, 24 July 2010. His leg had to be amputated after he was bitten by a snake



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# Noma



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# Noma

Noma is a little known neglected disease that mostly affects children living in poverty. It is a rapidly progressing infection of the oral cavity that destroys bone and tissue. Up to 90 per cent of children affected by noma die in the first two weeks if they do not receive treatment with antibiotics in time. Those who survive are left with severe facial disfigurements that make it hard to eat, speak, see or breathe. They often face stigma, social exclusion and discrimination in their communities.

Noma, or cancrum oris, is found in low-income countries in Africa and Asia. It mostly affects young children who live in vulnerable and isolated communities with limited access to healthcare and vaccination. Noma patients and the disease itself are often invisible within communities, the health systems that are supposed to serve them and the global health community. The disease is not included on the WHO priority list of NTDs. This limits the amount of global attention noma receives and hampers efforts to raise funds for further research, prevention and treatment initiatives.

Little is known about noma. There is a lack of robust epidemiological and surveillance data. The pathogenesis is not fully understood and the microbiology is debated. Knowledge about the disease is also limited amongst health care workers. In 1998, WHO estimated that 140,000 new cases of noma occur each year globally and that 770,000 patients were living with noma sequelae. These estimates, based on expert opinion, are more than 20 years old, and more robust epidemiological studies on the burden of noma are urgently needed.

## Challenges

- To restore the severe facial disfigurement and impairment noma can cause, extensive and complex reconstructive surgery is needed. Only very few patients have access to this.
- Noma is entirely preventable and treatable if caught in time, but this requires routine oral screening of children which is mostly lacking
- Noma is a deeply neglected disease, but it is difficult to harness support and resources as it is not included in WHO's priority list of Neglected Tropical Diseases

Depending on where the infection has started, noma rapidly destroys the jaw, lips, cheeks, nose or eyes. While the clinical manifestation and sequelae of noma in each case is unique, the WHO has classified noma into stages. The first acute stages last only a couple of weeks: simple gingivitis; acute necrotising gingivitis; oedema; gangrene and scarring. The final stage is known as the chronic stage and refers to the condition of patients who survive the acute stages of infection with varying degrees of physical and/or functional deformities. There are no reports of noma reoccurring once reaching the chronic stage and noma is not reported to be contagious. Deaths from noma are primarily due to starvation (as patients are unable to eat), aspiration pneumonia, respiratory insufficiency or sepsis.

● *“I got noma when I was just one year old. Some people would run away when they saw my face. They didn't think I was human (...) I thought I was the only person with this disease, but then I came to the hospital and saw others in my situation. It was a relief.”*

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**Bilya, Nigeria – affected by noma**

## Prevention and screening

Noma is preventable, and treatable if caught in the early stages. Treatment with antibiotics, wound debridement and nutritional support can reduce the duration and severity of the acute phase and the extent of tissue damage, in turn reducing mortality and morbidity. Patients who survive can live into adulthood, but many have severe facial disfigurements meaning they face stigma and isolation. Furthermore, the multiple physical impairments such as difficulties with speech, sight and food intake are often so severe that only extensive and complex surgical reconstruction can restore form and function.

Food security, malaria and HIV prevention, and measles vaccination can all help to prevent noma. Early detection and good general health care, including oral health and treatment of gingivitis and stomatitis, are also important. Noma progresses alarmingly fast, and it is therefore essential to screen young, malnourished children for early signs of noma in order to prevent disfigurement and death. The integration of oral screening for noma should be considered in all tropical regions among young,

malnourished infants and children. Raising awareness of the disease among health care workers and traditional healers, as well as in communities, is crucial.

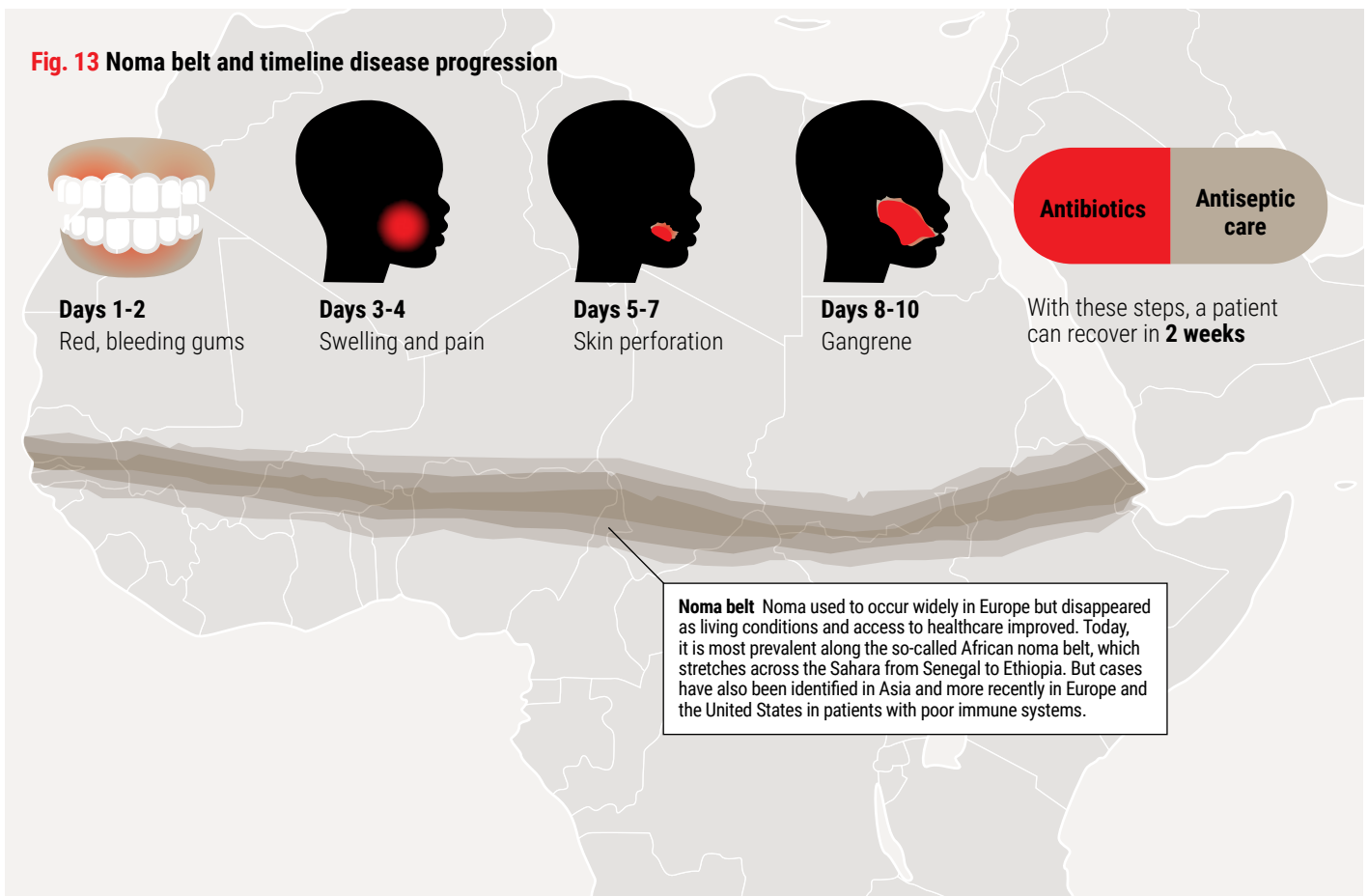
## MSF and noma

The Nigerian Ministry of Health has been offering care for noma patients for many years at the Sokoto Noma Hospital in north west Nigeria. MSF has supported these initiatives since 2014. The model of care consists of four main components: acute care; chronic care (surgery); integrated hospital based services (including the provision of mental health care) and community-based services (outreach). Along with these healthcare services is a strong focus on adding to the literature on noma through operational research studies.

## Surgical intervention

Given the highly specialised skills required for reconstructive surgery for noma, MSF sends specialised maxillofacial and plastic surgical teams to Nigeria four times a year, who work with Nigerian specialists to perform 30-40 operations

Noma starts with gingivitis, an inflammation and bleeding of the gums. In three or four days, an ulcer appears and the gums and cheek begin to swell. Before a week has passed the disease has destroyed cheek tissue and a hole appears. In the following days, the infection spreads and gangrene covers the affected area. Depending on where the infection has started, it quickly destroys the jaw, lips, cheeks, nose or eyes.





© CLAIRE JEANTET – FABRICE CATERINI

Amina, an 18-year-old noma patient at the Sokoto Noma Hospital, Nigeria, 18 October, 2017. She has undergone multiple operations since early childhood when a hole suddenly formed in her cheek. Amina's story is featured in the documentary *Restoring Dignity*, by the filmmakers Claire Jeantet and Fabrice Catérini, produced by Inediz in collaboration with MSF

over a two-week period. In total, there were 766 surgeries performed on 473 patients by MSF between August 2015 and July 2020. Patients frequently require more than one operation in order to improve function and aesthetics. Unfortunately, although surgery can ameliorate the effects of noma, it rarely fully restores anatomy. Post-surgery rehabilitation for many patients includes physiotherapy for trismus (difficulty in opening the jaw/mouth) and speech therapy. However, it is difficult to find speech therapists that speak local languages (such as Hausa).

### **Mental Health**

Many noma patients have lived with disfigured faces for years, which has affected their ability to speak and interact with others. They are often stigmatised and ostracised from their communities. In 2014, MSF initiated a noma-specific mental health intervention at the hospital in collaboration with the Ministry of Health. Mental health activities include preparing patients and caretakers for surgery and the recovery process. Patient and caretakers are also taught about noma and group and individual mental health support is provided.

### **Outreach work**

In 2017, MSF started a community outreach programme in three states (Sokoto, Zamfara and Kebbi), targeting villages with known cases of noma. These activities include active case detection, follow-up of patients treated at the hospital and awareness raising initiatives, including the use of radio spots, distributing posters, and training for health workers and traditional healers on early recognition of noma and referral options. In 2019, active case finding in 343 villages resulted the detection of 157 noma cases.

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### **Operational research**

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Due to the limited evidence base around noma, MSF developed a comprehensive operational research initiative, aimed at helping to fill the main gaps in knowledge around the disease. By employing both qualitative and quantitative methods, MSF sought to examine the biopsychosocial features of noma, its epidemiology and treatment in northwest Nigeria to inform advocacy and prevention efforts. As of September 2020, five studies have been completed. More research is needed and is being planned on various aspects of noma (epidemiological, clinical, health care capacity and knowledge gaps).

### Completed studies (see <https://fieldresearch.msf.org/msf/>)

**Risk factors for diagnosed noma:** MSF found that poor social conditions and childhood feeding practices are associated with noma in northwest Nigeria.

**Language and beliefs in relation to noma:** Naming of the disease differed between caretakers and healthcare workers. Beliefs about the causes of noma were varied (spirits, animals, insects, previous infections). A lack of trust in the health system was mentioned as a barrier to care.

**Traditional healing and noma:** Traditional healers could play a crucial role in the early detection of noma and the health-seeking decision-making process of patients. Intervention programmes should include traditional healers through training and referral partnerships.

**Prevalence survey:** MSF found many, widely distributed, early-stage noma cases in northwest Nigeria indicating a large population at risk of progressing to the later stages of disease.

**Case series:** Following their last surgical intervention, noma patients do experience some improvements in their quality of life, but continue to face functional challenges that inhibit their daily life.

### Restoring Dignity, a documentary about noma

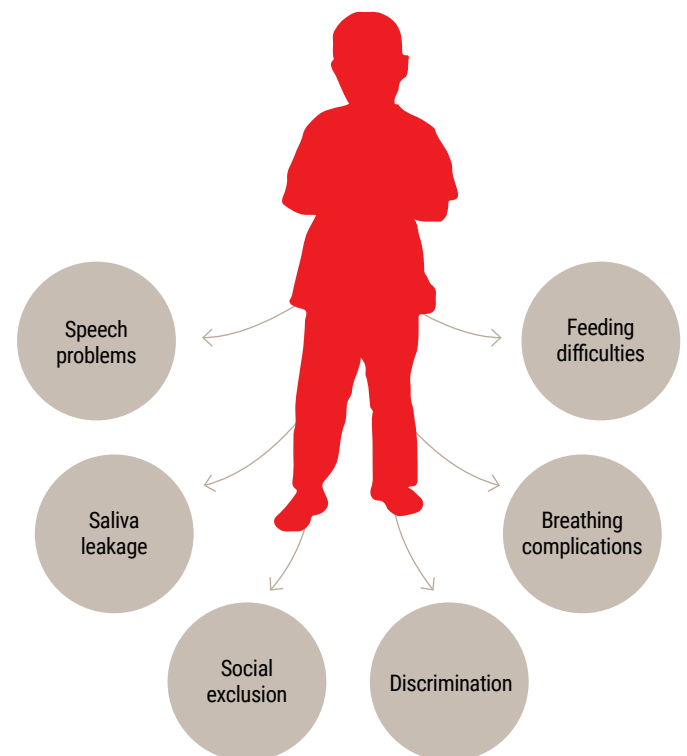
The production company Inediz produced, in collaboration with MSF, an award-winning documentary about noma survivors in northwest Nigeria titled 'Restoring Dignity'. This documentary has been screened widely in Nigeria, and internationally. Its short-form version 'Surviving noma' was shortlisted at the inaugural Health for All film festival organized by the WHO in 2020. More information can be found here: <https://noma.msf.org/>

### Noma elimination in Nigeria

The Ministry of Health of Nigeria included noma in the national disease surveillance system in 2018 and set the ambitious target of eliminating noma by 2020. Momentum has stalled and COVID-19 has had a detrimental effect on these ambitions. MSF aims to refocus these ambitions and raise awareness about noma as a neglected tropical disease both nationally in Nigeria and at an international level. This will be achieved through MSF's continued operational research portfolio, collaboration with ministries of health and other noma NGOs.

### Fig. 14 Consequences of Noma

Many people with noma are at great risk of dying from secondary complications. Survivors experience physical and mental consequences which isolate them from their communities and can cause mental health problems. Many people also have difficulty speaking and eating and face stigma and discrimination in their communities because of their facial disfigurement. Children can experience developmental delays because of their social isolation, or due to childhood diseases linked to noma like measles and malaria.



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Lady Bello, a nurse, takes care of a noma patient after his first surgery at the Sokoto Noma Hospital, Nigeria, 1 November, 2016

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Poverty and poor health are the main factors behind the infection that leads to noma

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### **MSF is calling for:**

- WHO to recognise the neglected nature of noma, include it on its list of NTDs and produce a roadmap for its elimination.
- Epidemiological surveys and improved reporting so that the burden of noma can be better understood.
- The creation of regional and national plans for the elimination of noma, including prevention and early detection, immediate treatment, awareness raising, social mobilisation and increased access to reconstructive surgery.
- Routine oral screening in health care assessments, malnutrition surveys, vaccination campaigns and mass drug administration programmes.
- Research into the microbiology, physiology, nutritional deficiency and other underlying factors of noma to guide the development of more specific prevention and management strategies.





# **American trypanosomiasis (Chagas disease)**



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# Chagas disease

According to WHO estimates, six to seven million people are infected with Chagas disease and more than 70 million people are at risk of infection. Chagas disease is the most common parasitic disease in Central and South America, and the leading cause of cardiac failure and death in countries where it is endemic. Yet, an estimated 99 per cent of people infected with Chagas disease remain undiagnosed, with only around 38,500 new cases reported each year. For every 1,000 people infected with Chagas, just two receive the treatment they need.

Chagas disease, also known as American trypanosomiasis, is an infection caused by the *Trypanosoma cruzi* parasite. The disease is transmitted via an insect known as the Triatomine bug (or ‘assassin bug’), which colonises poorly built houses in dense urban settings and rural areas, predominantly in Central and South America. Transmission can also occur through blood transfusions, organ transplants or by eating contaminated food. Mother-to-child transmission is also very common, with an estimated 1.1 million women of childbearing age infected, and between 8,000 to 15,000 children born with Chagas disease, each year.

Chagas used to affect predominantly poor people living in rural areas with extremely limited access to diagnosis and treatment. However, increased population mobility, urbanisation and emigration means the disease is increasingly seen in urban areas and cases have been recorded in North America, Asia and Europe (although these represent only a minority of global infections).

## Challenges

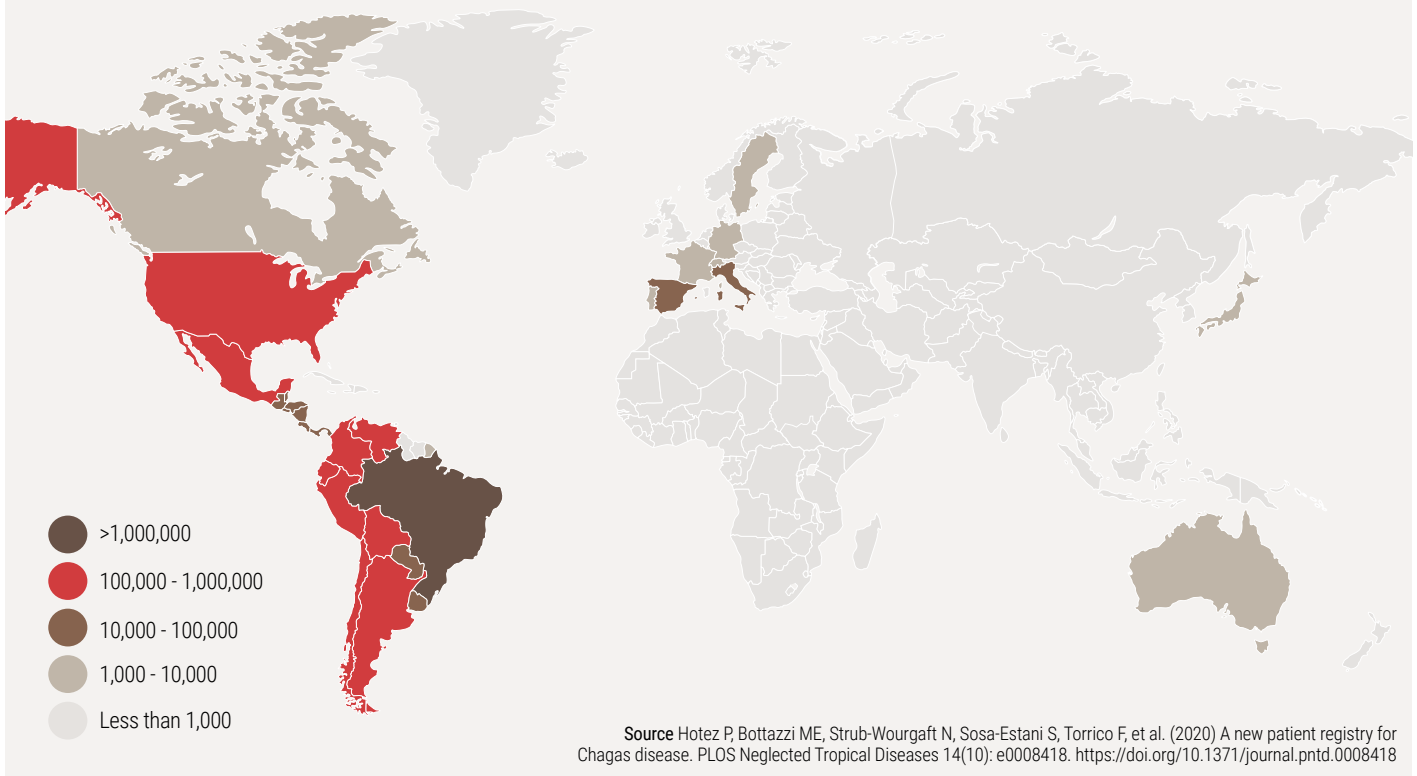
- Chagas mostly affects people who have very limited access to health care who experience financial and other barriers in accessing diagnosis and treatment
- Chagas can be cured with diagnosis and treatment soon after infection. But most people who are infected do not display symptoms for many years, even decades, and are diagnosed only at a late stage of the disease, when it has become incurable.
- Chagas can be transmitted from mother to child, but Chagas in the mother is often not detected and it is complex to diagnose Chagas in new-borns

● *“We lived in a mud house and slept on a wooden bed. That was where I got the kissing bug. It does not hit right away. It takes 25 years for the symptoms to come. Mine came when I was 30 years old.”*

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**José Pedro, Brazil – affected by Chagas**

**Fig. 15 Global prevalence of Chagas disease, 2017<sup>18</sup>**



Chagas disease is known as the ‘invisible disease’. Most people who are infected do not have any symptoms, and it can take decades before these appear. Chagas disease can be cured, but only with diagnosis and treatment at an early stage. If not, approximately 30 per cent of infected people develop serious cardiac problems, which puts them at risk of sudden death within 5 to 20 years. Around 10 per cent develop irreversible damage to their digestive tracts. As there is currently no way of determining which people will end up developing these symptoms, it is necessary to treat everyone who is infected.

Diagnosis relies on serological tests. Many of these are complex diagnostic procedures which cannot be performed outside of relatively sophisticated laboratories. This is why the majority of people with Chagas disease, particularly those in remote areas, are never diagnosed. However, this situation is improving, with rapid diagnostic tests now being available and introduced in many countries.

Treatment options are based on two drugs developed more than 45 years ago: benznidazole and nifurtimox. Benznidazole is the first line treatment and effectively cures early infections. Nifurtimox is used as a second line treatment, but it is difficult to tolerate as it causes serious side effects in up to 40 per cent of people. Both treatments last 60-90 days and are not effective against long-standing infections, which very often become incurable. There is an urgent need

### Evaluation of rapid diagnostic tests for Chagas

Conclusive diagnosis of Chagas relies on two laboratory tests that detect antibodies against the parasite. Unfortunately, these tests are too complex to be widely used at primary health care level. MSF supported a study to evaluate the performance of 11 commercially available serological rapid diagnostic tests (RDTs), and found eight to be viable for use. The results of this evaluation opened the possibility of using RDTs to screen patients at primary health care level, reducing the time it takes for patients to receive treatment. It also enabled further research into using a combination of RDTs in order to reach a conclusive diagnosis.

### **How MSF's Chagas care model was successfully integrated into primary health care in Oaxaca State, Mexico**

In 2013, an agreement between MSF, the Oaxaca Health Secretariat and the Mexican Social Security Institute (IMSS in Spanish) to implement a Chagas care model at primary health care level in San Pedro, Pochutla and Mazunte, which ensured diagnosis and treatment for everyone with Chagas disease. In this region, Chagas prevalence was estimated at between 4 and 12 per cent of the population.

Developed as an integrated intervention, the project included technical support by MSF to the health staff working in the medical facilities in the area, the supply of rapid diagnostic tests to primary health care units and the donation of electrocardiography equipment and medicine (benznidazole) to treat patients. MSF also carried out community information, education and communication (IEC) activities, and capacity building for health staff in preventing mother-to-child transmission and in making blood transfusions safe. As cured people can easily become re-infected, MSF offered technical support to the National Vector Control Programme to eradicate the Triatomine bug from houses.

Between 2013 and 2016, when the project ended, 6,864 patients were screened, of which 149 tested positive using a rapid diagnostic test. Of these patients, 38 were confirmed positive using laboratory diagnosis.

to develop oral, short-course treatments that are safe and effective for both the acute and chronic phase of infection. To this end, DNDi initiated the Chagas Clinical Research Platform in 2009, with 150 institutions working together to test promising new compounds, such as fexinidazole, as well as combinations of existing drugs.

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### **MSF and Chagas disease**

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Between 1999 and 2016 MSF screened more than 90,000 people for Chagas disease and more than 4,000 patients were diagnosed and treated. MSF has demonstrated that increasing access to care for patients living in remote endemic areas is feasible and improves early case-finding. MSF has strongly advocated for early diagnosis and treatment of Chagas disease.

From 1999 until 2010, MSF implemented specific Chagas programmes for the diagnosis and treatment of the disease in Guatemala, Honduras, Bolivia and Paraguay. From 2010, MSF focussed on integrating these programmes into national health systems in collaboration with the respective ministries of health. Between 2014 and 2016, MSF developed and evaluated comprehensive care models for Chagas

disease for use at primary health care level, in Monteagudo, Bolivia and Oaxaca, Mexico. MSF has also trained healthcare professionals and provided technical support to national Chagas control programmes in several countries.

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### **Working together for improved control of Chagas disease**

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Since MSF's first involvement with Chagas disease in the 1990s, there has been a huge increase in institutions, patient associations, NGOs and other groups that have worked at local and international levels to raise awareness, diagnose and treat patients, and increase prevention activities.

Since 2009, MSF has been working with other organisations to advocate for Chagas in global health fora. This led in 2010 to a resolution at the 63<sup>rd</sup> World Health Assembly for the integration of Chagas diagnosis and treatment into primary and secondary health facilities in all endemic areas. In 2012, the WHO set ambitious milestones for Chagas disease in the London Declaration on Neglected Tropical Diseases. The Chagas Coalition, founded in the same year, is a communication, advocacy and coordinating body that provides a platform for key Chagas actors. The formation of this coalition, the ongoing leadership of DNDi in developing new drugs and diagnostic tools, the collaboration with DNDi for drug delivery and implementation, and the increased roles of other organisations led to MSF being able to hand over its Chagas projects and activities in 2016.

The burden of Chagas disease continues to be reduced as a result of increased country-level activities, successful collaboration between governments and numerous dedicated organisations. The WHO has now set a goal to interrupt the transmission of Chagas in its new NTD Roadmap (2021-2030) and aims for 75 per cent treatment coverage. Achieving these targets, will however, require a considerable boost in resources and activities in the coming years.

### **MSF is calling for:**

- Accelerate the implementation of rapid diagnostic tests at primary health care level in endemic countries, and their swift uptake in national guidelines and policies.
- Reduce financial barriers to access to care, including free diagnosis and treatment for all patients.
- Integrate Chagas screening in mother and child care services in endemic areas.
- Continue research efforts into improved diagnostic tools and oral, short-course treatments that are safe and effective for both the acute and the chronic phase of infection.
- A diagnostic test for new-borns.

## End notes

All MSF's peer reviewed scientific studies are available for free in full text on this website: <https://fieldresearch.msf.org/msf/>

<sup>1</sup> Buruli ulcer, Chagas disease, dengue and chikungunya, dracunculiasis, echinococcosis, foodborne trematodiasis, human African trypanosomiasis, visceral and cutaneous leishmaniasis, leprosy, lymphatic filariasis, mycetoma, chromoblastomycosis and other deep mycoses, onchocerciasis, rabies, scabies and other ectoparasitoses, schistosomiasis, soil-transmitted helminthiasis, snakebite envenoming, taeniasis and cysticercosis, trachoma and yaws. See 'Ending the neglect to attain the Sustainable Development Goals: a road map for neglected tropical diseases 2021–2030', WHO, 2020.

<sup>2</sup> G-Finder 2019: *Neglected Disease Research and Development: Uneven Progress*. Policy Cures Research.

<sup>3</sup> Global leishmaniasis surveillance, 2017–2018, and first report on 5 additional indicators. WHO Weekly Epidemiological Record, 19 June 2020.

<sup>4</sup> *The Catastrophic Economic Burden of Visceral Leishmaniasis in Bangladesh, India, Ethiopia & Sudan*. Lucy Paintain, Lydia Boudarène, Jayne Webster (LSHTM) on behalf of the KalaCORE M&E Task Team & partners, as presented at the 11th European Congress on Tropical Medicine and International Health, 16-20 September 2019, Liverpool, UK.

<sup>5</sup> Seaman J, Mercer AJ, Sondorp E. *The epidemic of visceral leishmaniasis in West Upper Nile, southern Sudan: course and impact from 1984 to 1994*. Int J Epidem 1996;25(4):862-871.

<sup>6</sup> WHO Global Health Observatory data repository (2005-2018).

<sup>7</sup> National Institute of Communicable Diseases, Government of India (1977-2004).

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<sup>9</sup> Williams, S.S., et al. *Delayed psychological morbidity associated with snakebite envenoming*. PLoS Negl Trop Dis 2011, 5(8): e1255.

<sup>10</sup> Ediriweera DS, Kasturiratne A, Pathmeswaran A, Gunawardena NK, Wijayawickrama BA, Jayamanne SF, et al. *Mapping the Risk of Snakebite in Sri Lanka - A National Survey with Geospatial Analysis*. PLoS Negl Trop Dis 2016, 10(7): e0004813.

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<sup>12</sup> Gutiérrez, J. M. et al. (2017) *Snakebite envenoming*. Nat. Rev. Dis. Primers 2017, 3, 17063.

<sup>13</sup> Brown, N.I. *Consequences of neglect: analysis of the sub-Saharan African snake antivenom market and the global context*. PLoS Negl Trop Dis 2012, 6(6): e1670.

<sup>14</sup> Longbottom, Joshua, Shearer, Freya M, Devine, Maria, Alcoba, Gabriel, Chappuis, Francois, Weiss, Daniel J, Ray, Sarah E, Ray, Nicolas, Warrell, David A, Ruiz de Castañeda, Rafael, Williams, David J, Hay, Simon I and Pigott, David M. *Vulnerability to snakebite envenoming: a global mapping of hotspots*. Lancet 2018, 392, 10148, 673-684.

<sup>15</sup> Habib AG, Musa BM, Iliyasu G, Hamza M, Kuznik A, Chippaux J-P. *Challenges and prospects of snake antivenom supply in sub-Saharan Africa*. PLoS Negl Trop Dis 2020, 14(8): e0008374

<sup>16</sup> Potet, J., J. Smith, and L. McIver. *Reviewing evidence of the clinical effectiveness of commercially available antivenoms in sub-Saharan Africa identifies the need for a multi-centre, multi-antivenom clinical trial*. PLoS Negl Trop Dis 2019, 13(6): e0007551.

<sup>17</sup> *Snakebite envenoming - A strategy for prevention and control*, WHO, May 2019

<sup>18</sup> Hotez P, Bottazzi ME, Strub-Wourgaft N, Sosa-Estani S, Torrico F, et al. *A new patient registry for Chagas disease*. PLoS Negl Trop Dis 2020, 14(10): e0008418.

## Glossary

<b>CAR</b>	Central African Republic
<b>CATT</b>	Card Agglutination Test for Trypanosomiasis
<b>CL</b>	Cutaneous Leishmaniasis
<b>DAT</b>	Direct Agglutination Test
<b>DFID</b>	Department for International Development (UK)
<b>DNDi</b>	Drugs for Neglected Diseases initiative
<b>DRC</b>	Democratic Republic of Congo
<b>FDA</b>	US Food and Drug Administration
<b>FIND</b>	Foundation for Innovative New Diagnostics
<b>gHAT</b>	Human African Trypanosomiasis caused by <i>T. gambiense</i>
<b>GSK</b>	Glaxo Smith Kline
<b>HAT</b>	Human African Trypanosomiasis
<b>HIV</b>	Human Immunodeficiency Virus
<b>ITM Antwerp</b>	Institute of Tropical Medicine, Antwerp
<b>LSHTM</b>	London School of Tropical Hygiene and Medicine
<b>mAECT</b>	Mini anAion exchange centrifugation technique
<b>MSF</b>	Médecins Sans Frontières
<b>NECT</b>	Nifurtimox Eflornithine Combination Therapy
<b>NTD</b>	Neglected Tropical Disease
<b>PKDL</b>	Post Kala azar Dermal Leishmaniasis
<b>PM</b>	Paromomycin
<b>PRV</b>	Priority Review Voucher
<b>R&amp;D</b>	Research and Development
<b>SSG</b>	Spidium stibogluconate
<b>TB</b>	Tuberculosis
<b>TL</b>	Trypanolysis test
<b>VL</b>	Visceral Leishmaniasis
<b>WHO</b>	World Health Organisation

