

MYCETOMA: NEW HOPE FOR NEGLECTED PATIENTS?



Developing effective treatments
for a truly neglected disease

DNDi
Drugs for Neglected Diseases *initiative*

Among the most neglected of neglected tropical diseases, the fungal form of mycetoma, eumycetoma, has no effective treatment. Currently, eumycetoma is managed with sub-optimal drugs and surgery, including amputation of affected limbs. An effective, affordable, and easy-to-administer treatment is urgently needed.

Mycetoma is a slow-growing bacterial or fungal infection, most often of the foot, that may spread to other parts of the body and can cause severe deformity. It is a debilitating disease that most often affects poor people in rural areas with limited access to health care.

Due to the lack of effectiveness of available treatment, most lesions do not heal and instead recur on other parts of the body, leading to amputation and sometimes repeated amputations.

In rare cases, when it affects the lungs or the brain, it can be fatal. In all instances patients are unable to work and often face severe social stigma.

Mycetoma is so neglected that until 2016, it was not even listed in the World Health Organization's list of neglected tropical diseases.

Despite the impact of mycetoma, there has been little or no funding or research attention to the disease until very recently.

Mycetoma is so neglected that until 2016, it was not even listed in the World Health Organization's list of neglected tropical diseases. The lack of awareness has led to a massive evidence gap that adversely affects patient care, and hampers action to prevent mycetoma.¹



“ I got mycetoma 19 years ago after I was pricked by a thorn. Even after numerous treatments, eight surgeries, and finally an amputation of my leg, I don't think I am healed. I dropped out of school after my first surgery and I had to stop working after the amputation. This disease has been difficult on me, my wife, and five children.”

Alsadik Mohamed Musa Omer, Sudan

¹ Fahal AH. Mycetoma: A global medical and socio-economic dilemma. *PLoS Negl Trop Dis.* 2017;11(4). e0005509. 2017;321:1-5.

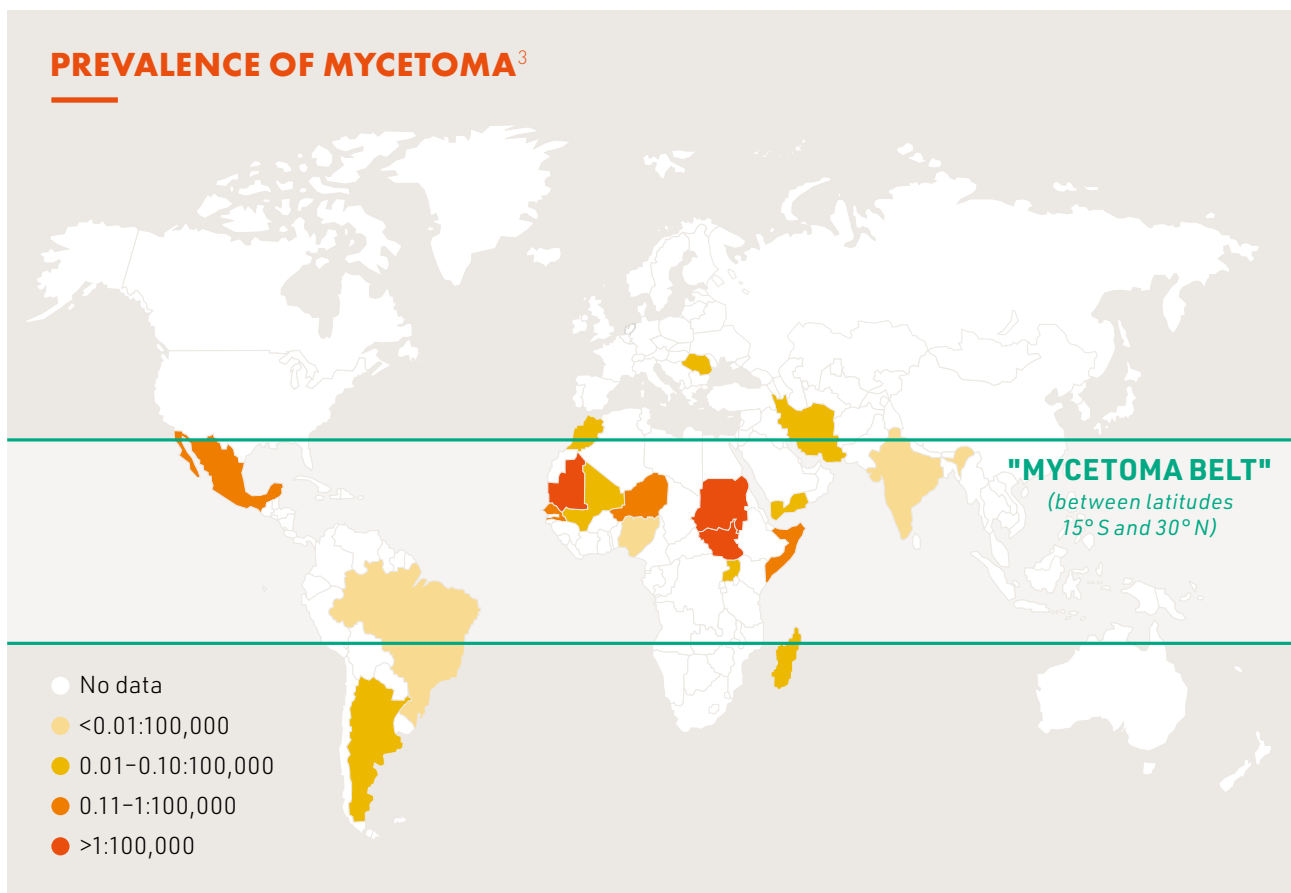
DNDi MYCETOMA: NEW HOPE FOR NEGLECTED PATIENTS?

To date, the true incidence and prevalence of mycetoma are not well known. However, a prevalence of 14.5 cases per 1,000 inhabitants has been reported in some endemic areas of Sudan, including Gezira and White Nile states.² Likewise, the disease susceptibility, resistance, and risk factors have not been well studied. The route of transmission is also unconfirmed, and although it is thought that the infection comes from the soil or from animal dung entering the body after the skin has been pricked (by a thorn, for example), there have been no comprehensive studies to confirm this theory.

The lack of accurate data on mycetoma incidence and prevalence means that the governments of affected countries do not prioritize the improvement of diagnosis, treatment, and care. A notable exception is Sudan, with the result that the Mycetoma Research Centre (MRC) in Khartoum is visited by patients from other countries in the region and even outside Africa. Globally, there are only a very few organizations involved in treating the disease and leading community education, and even fewer are trying to find a cure.

Most cases of mycetoma are reported from the so-called "mycetoma belt", which includes Brazil, Mexico, and Venezuela in Latin America, Chad, Ethiopia, Mauritania, Senegal, Somalia, and Sudan in sub-Saharan Africa, Yemen in the Middle East, and India in Asia, among others.

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² Fahal A, Mahgoub ES, EL Hassan AM, *et al.* A New Model for Management of Mycetoma in the Sudan. *PLoS Negl Trop Dis.* 2014;8(10). doi:10.1371/journal.pntd.0003271.

³ Adapted from: Van de Sande WWJ. Global burden of human mycetoma: a systematic review and meta-analysis. *PLoS Negl Trop Dis.* 2013;7: e2550. doi: 10.1371/journal.pntd.0002550

ABOUT MYCETOMA⁴

Mycetoma is a slow-growing bacterial or fungal infection, most often of the foot, that may spread to other parts of the body and that causes severe deformity. Mycetoma slowly develops into a chronic infection of the skin tissues but can also affect the bone, deep tissues and, if left untreated, eventually results in amputation and sometimes death.

Mycetoma has two different forms:

- **Actinomycetoma** – caused by bacteria
- **Eumycetoma** – a fungal infection

Approximately 40% of mycetoma cases worldwide are eumycotic, the fungal form of the disease.



Photo: Neil Brandvold/DNDi.

“

I can't touch water, so I can't bathe – I can't do my daily activities. I've been late to school. I have no crutches and I don't own a wheelchair, which I need to borrow. It is very difficult to walk.”

Amasi, 18 year-old mycetoma patient living in the village of Shadida Agabna, Gezira State

Causes

Infection probably comes from the soil or animal dung, and it is suspected that most patients are infected by walking barefoot and sustaining minor cuts from thorns, which allows the pathogen to enter the body.



Photo: Neil Brandvold/DNDi.

Symptoms

The most common symptoms are painless masses under the skin that slowly grow to become large, badly oozing sores that expel "grains" and ultimately cause the affected limb to become deformed or unusable. These masses usually appear on a person's foot but can form anywhere on the body.

Impact

Mycetoma commonly affects young adults, mostly males aged between 15 and 30 years. People of low socioeconomic status and manual workers such as farmers, labourers, and herdsmen are the worst affected. The psychological impact of mycetoma is severe: many patients become depressed and need psychological support.

Diagnosis

There are no point-of-care diagnostic tests for use in mycetoma-endemic villages. Most available mycetoma diagnostic tests and techniques are invasive, expensive, lengthy, of low specificity and sensitivity, and not available in endemic regions. People must travel long distances to provincial hospitals to access them.

Treatment

The treatment depends on the cause. For the bacterial type (actinomycetoma), combination antibiotics are used, with up to 90% cure rates. For the fungal type (eumycetoma), a combination of antifungal drugs and surgery is used. Available eumycetoma treatment is frustratingly ineffective, even after 12 months of treatment, and very expensive, with many side effects.

⁴ WHO. Factsheet on Mycetoma, April 2018. Available at: <http://www.who.int/news-room/fact-sheets/detail/mycetoma>

New treatments for fungal mycetoma are urgently needed

Ineffective, lengthy, and unaffordable existing treatments

Treatment of eumycetoma is difficult and includes a combination of antifungal drugs and surgery. Most patients are from poor, rural areas, and as a result they may seek diagnosis very late, when the disease is more difficult to treat. In addition, patients tend to have high dropout rates from treatment. There are three fundamental limitations of existing medicines:

1. INEFFECTIVE

The fungal form of mycetoma requires prolonged use of limited antifungal drugs with low cure rates (around 25–35%) and a high chance of disease recurrence. Ketoconazole and itraconazole are the main antifungal drugs currently used for treating eumycetoma. Treatment courses last for a minimum of one year, and repeated courses may be necessary – often to no avail. Ketoconazole has side effects, and concern over its liver toxicity has caused the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to restrict its use.⁵ In practice, especially in low- and middle-income settings such as Sudan, itraconazole is therefore the only drug, but it also has many drawbacks.



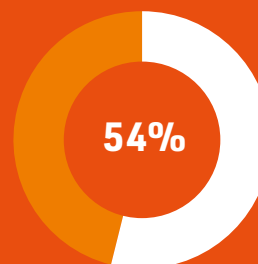
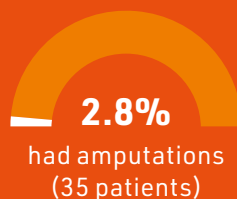
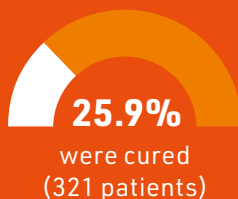
Photo: Abraham Ali/ Imageworks/DNDi.

“ Every time I give a patient the treatment, in my mind I know that there is a high risk it might not work. I know they will keep on coming for many years but might never fully recover. This is really sad.”

Dr Elsemani Widatla, Surgeon, MRC, Khartoum

EUMYCETOMA CURE RATES

One of the few studies on mycetoma, conducted at the MRC in Khartoum, Sudan, showed that of the 1,242 eumycetoma patients studied:



671 patients dropped out from the outpatient follow-up for various reasons, including treatment side effects and dissatisfaction with the therapy outcome.⁶

⁵ Zijlstra EE, van de Sande WWJ, Fahal AH. Mycetoma: A Long Journey from Neglect. *PLoS Negl Trop Dis*. 2016 Jan;10(1):e0004244.

⁶ van de Sande WWJ, Maghoub ES, Fahal AH, Goodfellow M, Welsh O, Zijlstra E. The Mycetoma Knowledge Gap: Identification of Research Priorities. *PLoS Negl Trop Dis*. 2014. 8(3): e2667. <https://doi.org/10.1371/journal.pntd.0002667>.

Photo: Abraham Ali/
Imageworks/DNDi.



“
Before I fell sick, I was active and I had many friends. My social life was very vibrant. Now, I am much slower at my activities since I cannot walk very far. I also avoid my friends because of this disease.”

Zeinab Ibrahim, who has been living with mycetoma for the past 20 years

2. DIFFICULT

Treatment of eumycetoma requires the prolonged use of antifungal drugs (mainly itraconazole) which are unsatisfactory, have many side effects, are expensive, and are often not available in endemic areas. This is usually followed by stigmatizing surgery ranging from a wide local surgical excision to repetitive excisions and finally amputation of the affected part. The lack of treatment effectiveness often leads to multiple amputations and ultimately the loss of entire limbs, with the associated risk of complications and death. Since duration is long, more than half of the patients do not complete their treatment.

3. UNAFFORDABLE

In Sudan, most patients pay for their treatments out of pocket. Equivalent to an average monthly salary, the cost of itraconazole treatment is a severe financial burden on households and is out of reach for most patients in rural communities. The debilitating nature of the disease means that patients are unable to work. This leads to loss of income for families, and many patients therefore stop treatment prematurely, resulting in a vicious cycle of recurring lesions.

Photo: Neil Brandvold/DNDi.



THE UNBEARABLE PRICE OF TREATMENTS

Judah Mohammed Bellah is 10 years old and travelled with his father to the MRC from the Sennar region, about six hours away by bus. They stayed with relatives for two weeks while Judah was being treated. A few years ago, Judah was running along the river Nile and stepped on a thorn. He became infected. When his lesion became swollen, he could no longer go to school with his seven siblings. Judah's father stopped working to take care of him and eventually hired a rickshaw driver to take him to school. Judah had surgery in the city of Wad Medani and was given a lengthy course of treatment with ketoconazole. His father had to take an extra job to pay for the costs.

First-ever clinical study for potential new mycetoma drug

Interim results in 2019

Faced with the appalling neglect of patients with eumycetoma, DNDi added mycetoma to its Research & Development portfolio in 2015.⁷ In 2017, together with the MRC in Sudan and the Japanese pharmaceutical company Eisai, DNDi launched a clinical trial for a promising new antifungal treatment, fosravuconazole, in the first-ever double-blind randomised clinical study for mycetoma.⁸

The trial, which will ultimately enroll 138 patients, is testing the efficacy and safety of fosravuconazole,⁹ a potent drug candidate that was previously under development for Chagas disease. Fosravuconazole has shown strong antifungal activity against mycetoma in the laboratory and has the potential to be an affordable, oral drug. The efficacy

of fosravuconazole is being compared to the current treatment (itraconazole) in the randomised, controlled clinical trial, which is examining its effect on moderate mycetoma lesions. The goal is to develop an effective, safe, affordable, and curative treatment that is appropriate for rural settings.

Eisai provides the supply of the drug for the clinical study and, if the study is successful, has also the option to become DNDi's industrial partner to manufacture, register, and make available fosravuconazole at an affordable price to the public sector in endemic areas.

In January 2019, enrolment into the clinical trial reached 84 patients, allowing for an interim analysis to be conducted as stipulated in the protocol. Once this analysis

The goal is to develop an effective, safe, affordable, and curative treatment that is appropriate for rural settings.

is completed, one of the two fosravuconazole study arms – either 300mg or 200mg weekly – will be dropped. The most viable arm will continue together with comparative arm of itraconazole 400mg daily, which is standard of care treatment. It is expected that enrolment in the study will be completed by the end of 2019 and follow-up will end in early 2021. If shown to be effective, fosravuconazole would allow for weekly treatment rather than twice daily.

“

With patients now being enrolled in the study, what we have been working towards for the last 28 years is at last becoming a reality. An effective, safe, affordable, and shorter-term curative treatment which is appropriate for rural settings is desperately needed for neglected patients suffering from mycetoma.”

Dr Ahmed Fahal, Professor of Surgery, University of Khartoum and Director, MRC



Photo: Abraham Ali/Imageworks, DNDi.

7 DNDi. Business Plan 2015-2023. Available at: https://www.dndi.org/wp-content/uploads/2009/03/DNDi_Business_Plan_2015-2023.pdf

8 DNDi. Clinical trial for a better treatment for mycetoma starts in Sudan, June 2017. Available at: <https://www.dndi.org/2017/media-centre/press-releases/clinical-trial-for-mycetoma-treatment-starts-in-sudan/>

9 Eisai. Sato Pharmaceutical and Eisai to Co-promote New Oral Antifungal Agent Containing Active Ingredient Fosravuconazole in Japan. Available at: <https://www.eisai.com/news/news201756.html>

Sudan

The Mycetoma Research Centre leads the way in mycetoma research

Every Monday morning at a clinic on the outskirts of the Sudanese capital, Khartoum, people affected by one of the world's most neglected diseases flock to the only place in the world that can offer them specialized care and treatment. Patients stream through the gates limping, on crutches, pushed by worried relatives on rusty wheelchairs or carried. Most have bandaged legs, many are amputees. Most were probably infected through a simple thorn prick to the foot.

Most come from regions of Sudan far from Khartoum – often from areas in the country consumed by conflict and poverty. Some sleep at the mosque across the street. For these patients, the MRC's founder Dr Ahmed Fahal and his staff are their only hope.

Sudan hosts one of the world's leading centres on research and management for mycetoma: the Mycetoma Research Centre (MRC). For the past 28 years, it has provided quality medical care for mycetoma patients mainly from rural Sudan but also from a number of other countries, including Chad and Yemen. The MRC was established in 1991 and in 2015, the World Health Organization (WHO) designated it as a WHO Collaborating Centre, the first and only one dedicated to mycetoma.¹⁰ To date, the MRC has treated over 8,200 patients. On any given day, as many as 150 patients wait outside of the MRC for appointments.

The first-ever clinical trial to find a better treatment for mycetoma is underway at the MRC. To enable the effective conduct of the study, DNDi strengthened the capacity of the MRC by improving laboratory functions, renovating the pharmacy and wards, and training staff on the research protocol. A Research Unit was also set up with additional wards for men and women, a research laboratory, and a pharmacy. The Unit was developed with support from DNDi as part of the capacity-building initiative and will support current and future research as well as setting a standard for mycetoma care in the region and globally.



Photo: Abraham Ali/Imageworks/DNDi

The patients have come from surrounding villages and far-away regions – often from areas in the country consumed by conflict and poverty.

Although Sudan currently has the highest number of reported mycetoma cases in the world, the disease remains an international problem with cases reported in other countries across the "mycetoma belt". Working closely with WHO, the Federal Ministry of Health, Sudan, has led the way in fighting mycetoma internationally. Other affected countries also need to intensify the battle against the disease.

¹⁰ WHO. Fighting NTDs in Sudan. Available at: http://www.who.int/neglected_diseases/global-partners-meeting/sudan/en/index1.html

Advocating for the most neglected of neglected diseases

Global efforts lead to the inclusion of mycetoma on WHO's Neglected Tropical Diseases list

For many years, mycetoma faced abject neglect, with little or no attention from national or global health partners. In the absence of an effective drug, the Mycetoma Research Centre (MRC) in Khartoum, Sudan pioneered the best available care using existing drugs and surgery, while advocating for greater engagement and investment in research and development for more effective and affordable medicines with fewer side effects.

Following advocacy efforts by the MRC and other groups, mycetoma was recognized by the World Organization (WHO) as an 'other neglected condition' in 2013. This did little to increase funding for research, and DNDi began to partner with others to boost advocacy efforts to have the disease considered for inclusion in WHO's list of neglected tropical diseases.

Awareness-raising efforts continued, led by DNDi, the MRC, the Mycetoma Consortium,¹¹ some notably active student advocates, including Simran Dhunna and Annie Liang from the University of Toronto, and others, including researchers from the 'mycetoma belt'

and beyond. In May 2016, with a proposal championed by the governments of Sudan, Egypt, Jordan, Canada, and others, the 69th World Health Assembly approved a resolution¹² recognizing mycetoma as a neglected tropical disease, the 18th disease to be included on the WHO Neglected Tropical Disease list.

The inclusion of mycetoma in the main WHO NTD list has led to an increase in funding for researchers engaged in R&D for new tests and treatments, health education, and advocacy programmes. However, the disease remains highly neglected, and it continues to lack adequate political attention and funding, particularly in affected countries outside Sudan, which is notable for its strong health ministry support.

At the 6th International Conference on Mycetoma in Khartoum in February 2019, WHO and MRC will launch a call to action to be signed by governments of endemic countries and by organizations engaged in mycetoma research and advocacy, committing to greater support for mycetoma research, diagnosis, treatment, and care.

“

Including mycetoma on the WHO list gives the disease the political prominence it so desperately needs. It will also encourage funding of global programmes to better define the epidemiology, risk factors, and strategies for treatment and early diagnosis. Sudan has been a model of commitment, and we now hope to see similar levels of engagement from other countries from the 'mycetoma belt'.”

Dr Nathalie Strub Wourgaft, NTD Director, DNDi



Photo: Neil Brandvold/DNDi.

11 The Mycetoma Consortium was founded in 2013 and supported by DNDi. Members included: the Mycetoma Research Centre; World Health Organization, Sudan Country Office; the MSF Access to Medicines Programme; and researchers from: UANL University Hospital, Monterrey, Mexico; ErasmusMC, Rotterdam, Netherlands; Newcastle University, UK; and the Swiss Tropical Public Health Institute.

12 WHO. Addressing the burden of mycetoma. WHA69.21. Sixty-ninth World Health Assembly. 28 May 2016. Available at: https://www.who.int/neglected_diseases/mediacentre/WHA_69.21_Eng.pdf?ua=1

Using innovative science to find new drug candidates for mycetoma


Collaborative approaches in drug discovery





SEARCH FOR NEW CHEMICAL ENTITIES THROUGH AN OPEN SOURCE PROJECT

In 2018, the University of Sydney, Erasmus MC, and DNDi launched the Mycetoma Open Source project (MycetOS), which uses an Open Pharma¹³ approach to discover new drug candidates (new chemical entities, or NCEs) for eumycetoma using open-access data and collaborative methods.

With this radically open approach, it is hoped that MycetOS will drive the advancement of promising new chemical compounds targeting *Madurella mycetomatis*, the main cause of eumycetoma.

The project, which is not owned or led by any individual or research institute, will progress drug discovery efforts through community-driven, in-kind scientific contributions, and a robust, fully transparent online presence. Anyone interested can participate by following the community's interactions on Twitter at @MycetOS. All ideas and results will be published immediately in real time to an open-access database.

MycetOS  @MycetOS #OpenScience

PURPOSE	<p>Fungal mycetoma: Neglected disease that leads to disability and stigma and has no effective treatment </p> <p>Develop new medicine to treat fungal mycetoma (eumycetoma) using an Open Pharma approach </p>
CONCEPT	<p>Virtual community: Invite the scientific and global health community to contribute </p> <p>Open access database: Drive lead optimization of compounds targeting <i>Madurella mycetomatis</i> </p>

Free of intellectual property constraints

“

While MycetOS merely starts a process of discovering potential new chemical entities for eumycetoma, we invite anyone interested to identify how they might contribute and participate as an equal partner in this search for a new treatment for this most neglected of tropical diseases.”

Dr. Wendy van de Sande, Associate Professor, Erasmus MC



¹³ Balasegaram M, Kolb P, McKew J, Menon J, Olliaro P, Sablinski T, et al. An open source pharma roadmap. *PLoS Med.* 2017. 14(4): e1002276. <https://doi.org/10.1371/journal.pmed.1002276>

Thank you to our mycetoma programme partners and donors

Photo: Neil Brandvold/DNDi



Two women from Shadida Agabna village, a dusty and deeply poor settlement of farmers south of Khartoum. Village elders estimate that up to 4% of the village of 700 is infected with mycetoma. In one year alone, 12 people from the village received amputations due to mycetoma.

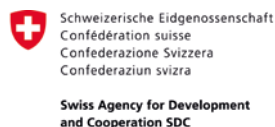
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A not-for-profit research and development organization, DNDi works to deliver new treatments for neglected diseases, notably leishmaniasis, human African trypanosomiasis, Chagas disease, specific filarial infections, and mycetoma, and for neglected patients, particularly those living with paediatric HIV and hepatitis C.

Since its inception in 2003, DNDi has delivered eight treatments: two fixed-dose antimalarials (ASAQ and ASMQ), nifurtimox-eflornithine combination therapy (NECT) for late-stage sleeping sickness, sodium stibogluconate and paromomycin (SSG&PM) combination therapy for visceral leishmaniasis in Africa, a set of combination therapies for visceral leishmaniasis in Asia, paediatric dosage forms of benznidazole for Chagas disease, and a 'super-booster' therapy for children co-infected with HIV and TB, and the first all-oral drug for sleeping sickness (fexinidazole).

Cover image: A patient at the Mycetoma Research Centre in Khartoum – the only treatment centre specialized in the disease worldwide. Photo: Neil Brandvold/DNDi.

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