ISNTD Disease Brief

Mycetoma

The case for a new entrant to the WHO's list of Neglected Tropical Diseases

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Mycetoma: the case for a new entrant to the WHO's list of Neglected Tropical Diseases

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1 SUMMARY

Mycetoma is a devastating, chronic infectious disease of the skin and subcutaneous tissue that can be either bacterial in origin (actinomycetoma) or fungal (eumycetoma). Infection results from inoculation of the infectious pathogen via puncture wounds from thorns or other sharp objects, typically on the foot. Most of those affected by mycetoma live in remote rural locations and are very impoverished (and hence barefoot) and/or agricultural workers or herdsmen. The 'mycetoma belt', in which the disease is endemic, includes Mexico, Venezuela, India, Chad, Ethiopia, Mauritania, Senegal, Somalia, Sudan and Yemen. The incidence and prevalence of the disease is not known (mycetoma is not a notifiable disease and there are no surveillance mechanisms in place) but over 7,200 mycetoma patients have been registered since 1991 in Sudan at the national Mycetoma Research Center in Khartoum.

In terms of clinical manifestations, mycetoma progresses slowly and is characterised by the appearance of painless, subcutaneous lesions or masses which multiply and discharge fluid that contains bacterial- or fungal-infested grains. Persistent infection results in progressive inflammation and tissue destruction, leading to disability, disfigurement of the affected skin regions and limbs (which may be associated with social stigma and depression), impaired body function and secondary infections (which can be fatal). Treatment can be effective if the disease is caught at an early stage, especially for those with bacterial mycetoma (actinomycetoma) in whom antibiotics can yield 90%+ cure rates.

Unfortunately, a combination of the limited healthcare infrastructure in endemic regions (with no simple point-of-care diagnostic test available), limited health education and disease awareness, and the painless slow progression of mycetoma, leads many patients to present with advanced infection. For these patients, major destructive surgery (including amputation) may be the only viable treatment option. Fungal mycetoma (eumycetoma) presents an especially challenging prognosis with the requirement for lengthy and costly courses of anti-fungal drugs of limited efficacy and potentially serious side effects, together with surgery. Cure rates for fungal mycetoma are just 25-35% and disease relapse and further surgery and amputation is common.

New treatment options are desperately needed (the pipeline for mycetoma currently includes just one anti-fungal drug, fosravuconazule, under development by the Drugs for Neglected Diseases Initiative; DNDi), along with improved diagnosis, disease surveillance and disease awareness. What is clearly missing is a concerted international effort to support R&D into – and disease management of – this

terrible disease. There can be little doubt that mycetoma meets many of the criteria to be considered as an addition to the WHO's official list of neglected tropical diseases (NTDs), which currently numbers 17: it is a neglected, badly under-treated and under-diagnosed disease that affects developing countries, it impacts almost entirely on people and communities of low socio-economic status in remote rural locations, it has terrible long-term consequences (physical, psychological and economic), it is associated with very high morbidity and mortality, and up to 25% of those afflicted are children.

In this regard, we believe there are strong grounds for optimism as the World Health Assembly (WHA) will meet in May 2016 to consider a paper setting out the criteria for determining which diseases qualify as a "neglected tropical disease". If the WHA approves this, then mycetoma will be formally added to the WHO's list of NTDs and – in DNDi's words – "*mycetoma will have overcome a key barrier to R&D to tackle the disease to date: with official inclusion in the WHO NTD Department's activities, certain funding bodies will be able to consider taking up the disease within their funding scope and help to support the much needed research and development for diagnostics and effective treatment."*

2 MYCETOMA: OVERVIEW

Mycetoma is a chronic infectious disease of the skin and subcutaneous tissue, which most commonly affects the foot, but can also affect other parts of the body (eg, back, arms and legs). It was first reported in the scientific literature in 1694 and is also known colloquially as 'Madura foot' after a 19th century case in the Indian town of Madura. The causative agent of mycetoma can be either bacterial (in which case the disease is termed actinomycetoma; this is the most common form in Middle/South America) or fungal (in which case it is termed eumycetoma; this is the most common form in Africa). Infection is usually thought to result from accidental inoculation of the infectious pathogen via puncture wounds from thorns or other sharp objects, typically on the foot. Most of those affected by mycetoma (typically young men, aged 20-40 years, although up to 25% are children) live in remote rural locations and are either very impoverished (and hence walking barefoot) or they may be agricultural workers and/or herdsmen.

The microorganisms underlying mycetoma are endemic in tropical and subtropical areas in the so-called 'Mycetoma belt'. This includes Mexico, Venezuela, India, Chad, Ethiopia, Mauritania, Senegal, Somalia, Sudan and Yemen. The main bacterial pathogens are *Nocardia brasiliensis, Actinomadura madurae*, and *Streptomyces somaliensis* while the primary fungal pathogen (and most common causative micro-organism of mycetoma worldwide) is *Madurella mycetomatis*. Although the incidence and prevalence of the disease is not known (mycetoma is not a notifiable disease and there are no surveillance mechanisms in place), a 2013 meta-analysis of 50 literature studies (by van de Sande; see key sources at the end of this document) showed that, of 8,763 cases of mycetoma reported since 1956, 75% were seen in three countries, namely Mexico (2,607 cases; 30%), Sudan (2,555; 29%) and India (1,392; 16%). Methodological issues with this study (eg, case numbers were based on archives from one hospital per city per country) strongly suggest that the real disease burden is probably much higher than indicated in this meta-analysis. In support of this assertion, we note that over 7,200 mycetoma patients have been registered since 1991 in Sudan at the national Mycetoma Research Center in Khartoum and that the prevalence in some Sudanese villages is estimated at up to 8.5 per 1,000 inhabitants.

In terms of clinical manifestations, mycetoma progresses slowly and is characterised by the appearance of painless, subcutaneous lesions or masses which multiply and discharge fluid that contains bacterial- or fungal-infested grains. Persistent infection and spread of lesions results in progressive inflammation and tissue destruction, leading to disability, disfigurement of the affected skin regions and limbs (which may be associated with social stigma and depression), impaired body function and secondary infections (which can be fatal, where septicaemia develops).

Treatment can be effective if the disease is caught at an early stage, especially for those with bacterial mycetoma (actinomycetoma) in whom antibiotics can yield 90%+ cure rates. Unfortunately, a combination of the limited healthcare infrastructure in endemic regions (with no simple point-of-care diagnostic test available for mycetoma, for example), limited health education and disease awareness, and the painless slow progression of mycetoma, leads many patients to present with advanced infection. For these patients, major destructive surgery (including amputation) may be the only viable treatment option. As we discuss later, fungal mycetoma (eumycetoma) presents an especially challenging prognosis with the requirement for lengthy and costly courses of anti-fungal drugs of limited efficacy and potentially serious side effects, together with surgery. Cure rates for eumycetoma are just 25-35% - dramatically below those achievable in the case of actinomycetoma - and disease relapse and further surgery and amputation is common. Eumycetoma therefore represents a major unmet medical need.

Figure 1: Mycetoma overview

Cause	Mycetoma is a chronic infectious disease of the skin and subcutaneous tissue which can spread to connective tissue, muscle and bone. It results in progressive inflammation and tissue destruction due to persistent infection by bacteria (in which case the disease is termed actinomycetoma) or by fungi (in which case it is termed eumycetoma). Bacterial pathogens include *Nocardia brasiliensis, Actinomadura madurae*, and *Streptomyces somaliensis* while the primary fungal pathogen (and most common causative microorganism of mycetoma) is *Madurella mycetomatis*. Infection usually results from puncture wounds from thorns or other sharp objects, typically on the foot. Most of those affected by mycetoma (typically young men, aged 20-40 years) are either very impoverished (hence walking barefoot), agricultural workers and/or herdsmen.
Clinical manifestation	Mycetoma is typically a slowly progressing disease which is characterised by painless, subcutaneous lesions which multiply and discharge fluid that contains bacterial- or fungal-infested grains. Typically the foot is most affected but mycetoma can spread to other body extremities. If untreated, the disease can result in disability, deformity (and the resulting social stigma), secondary infections and ultimately it can be fatal (especially if septicaemia develops). Limited healthcare infrastructures and poor health education in endemic regions, together with the painless slow progression of the disease, means that many patients present with advanced infection where major surgery (including amputation) may be the only viable treatment option.
Affected regions	The bacterial and fungal organisms underlying mycetoma are endemic in tropical and subtropical areas in the so-called 'Mycetoma belt'. This includes Mexico, Venezuela, India, Chad, Ethiopia, Mauritania, Senegal, Somalia, Sudan and Yemen. A 2013 meta-analysis of 50 literature studies showed that, of 8,763 cases of mycetoma reported since 1956, 75% were seen in just three countries, namely Mexico (2,607 cases; 30%), Sudan (2,555; 29%) and India (1,392; 16%).
Treatment	Bacterial mycetoma (actinomycetoma) can be treated with a 90%+ cure rate by the antibiotics amikacin and co-trimoxazole. The fungal form, eumycetoma, on the other hand has low cure rates (c.25-35%) and high odds of recurrence. Treatment of eumycetoma involves lengthy (c.12 month) courses of anti-fungal drugs and surgery. The azole anti-fungal drugs are used although, following the banning of ketoconazole by the FDA and EMEA, itraconazole is effectively the only mainstay anti-fungal agent. This drug has drawbacks in terms of the treatment duration, limited efficacy, side effects, and cost (US$30/month). Over 50% of patients fail to complete treatment, often due to affordability. This exacerbates recurrence rates and the need for further surgery and amputation.

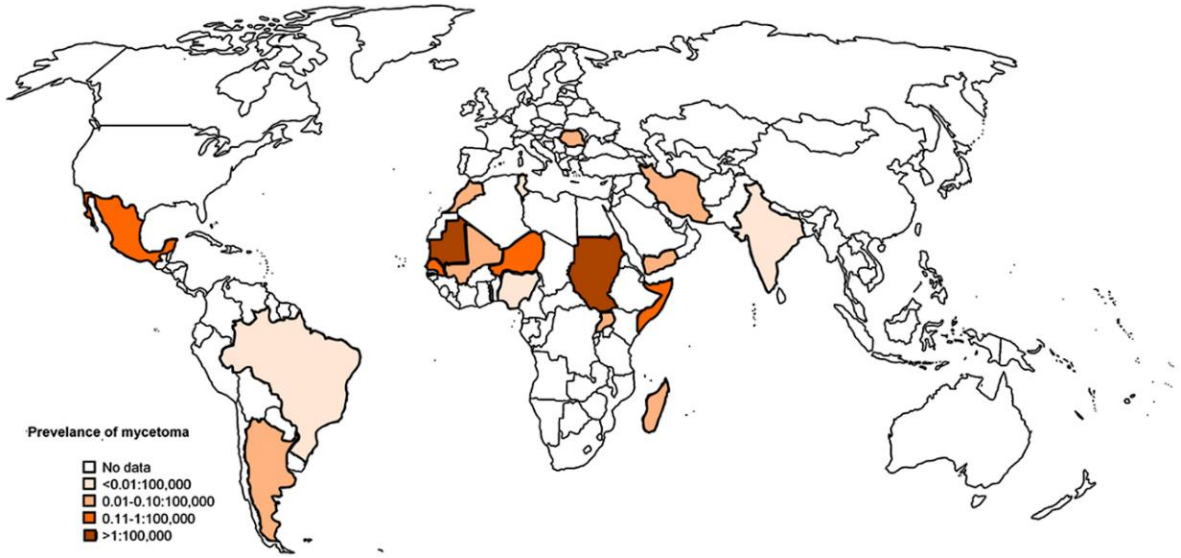
Source: WHO website, miscellaneous medical websites (eg, PLOS, DNDi)

Figure 2: Mycetoma prevalence and reported cases

A: Average prevalence of mycetoma cases as calculated by the number of cases reported in a year in a certain country divided through the total population of that country of that same year as reported by www.indexmundi.com/facts/indicators/SP.POP.TOTL/compare.

B: The average number of mycetoma cases reported per year per country. From van de Sande WWJ (2013) Global Burden of Human Mycetoma: A Systematic Review and Meta-analysis. PLoS Negl Trop Dis 7(11): e2550. doi:10.1371/journal.pntd.0002550

A



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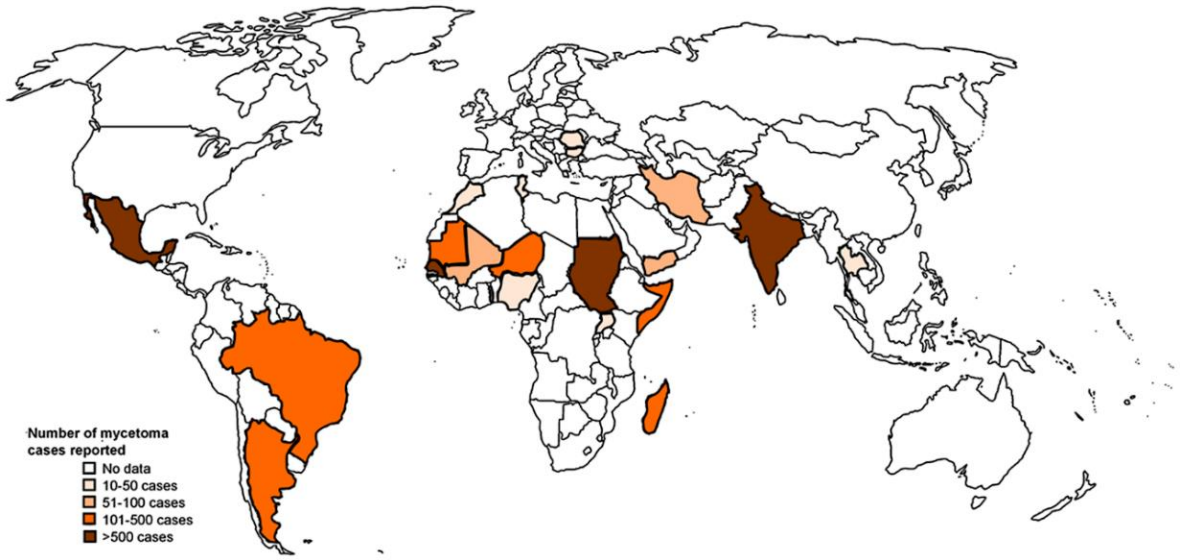

3 CURRENT TREATMENT OPTIONS

Bacterial mycetoma (actinomycetoma) can be treated very effectively (with a 90%+ cure rate) by repeat courses of the antibiotics amikacin and co-trimoxazole. The fungal form of the disease, eumycetoma, however, presents a much more intractable problem with low cure rates (c.25-35%) and high odds of recurrence. Treatment of eumycetoma typically involves lengthy courses of anti-fungal drugs and complex, destructive surgery. A particular issue is that many patients with eumycetoma present with advanced disease, by which stage amputation(s) is necessitated with the associated risk of surgical complications, secondary infections and resulting increased morbidity/mortality.

Only the azole anti-fungal drugs may be used in eumycetoma as other classes of drug have been shown to be ineffective *in vitro*. However, following the banning of ketoconazole by the FDA and EMEA on liver toxicity grounds (other than in restricted uses), this effectively leaves itraconazole as the mainstay anti-fungal agent. This drug has drawbacks in terms of the lengthy treatment duration needed (typically 12 months, after which the fungal lesion is usually removed via surgery), limited efficacy (in many cases the fungus persists in the lesion), side effect burden (serious side effects can include blurred vison, hearing disturbances, urinary dysfunction and potentially heart failure), and the cost of treatment (US$30 per month, according to DNDi). The latter is a particular problem in that over half of patients fail to complete treatment, many citing inability to afford the drug. This in turn exacerbates recurrence rates and the need for further surgery and amputation. As the DNDi clearly states, "*a more effective, affordable, shorter-term treatment appropriate for rural settings is urgently needed"* to address fungal mycetoma.

4 NEW DRUG PIPELINE FOR MYCETOMA

At present, the pipeline of potential new treatment options for fungal mycetoma comprises just one compound, the ergosterol biosynthesis inhibitor fosravuconazole (E1224, produced by Eisai) and no ongoing clinical trials in mycetoma are listed by www.clinicaltrials.gov (indeed only one study involving itraconazole, which completed several years ago, is listed on the website). Fosravuconazole is an oral triazole anti-fungal which has shown high potency *in vitro* against *Madurella mycetomatis* and is currently being developed by the Drugs for Neglected Diseases initiative (DNDi) in partnership with Eisai. We note that the drug is also under development by DNDi for the NTD, Chagas' disease, although clinical results in this particular setting have disappointed (explained by some observers as reflecting the lack of predictability of animal disease models in Chagas and by others on sub-optimal dosing or treatment duration).

DNDi intends to conduct a randomized, controlled proof-of-concept study of two different dosages of fosravuconazole versus itraconazole. This study – which will take place in Sudan - will examine the relative efficacy of these regimens in treating limited/moderate mycetoma lesions. While this brings considerable optimism for the potential introduction of an affordable, effective new treatment, PLOS cautions that "*more work is needed. If successful, fosravuconazole needs to be studied in more complex eumycetoma patients. Worryingly, after fosravuconazole there is no back-up: there is no pipeline for new compounds, and eumycetoma may become virtually untreatable, with amputation as the only option*."

Of course, new drugs alone will not lead to control of mycetoma and we highlight the need for improved diagnosis, disease surveillance/monitoring and public awareness. A point-of-care diagnostic test that would enable diagnosis in villages and rural communities, without the need for referral to a (potentially distant) hospital is especially badly needed. In the short term, improving disease awareness and highlighting the importance of protective measures (eg, footwear in the rainy season, when thorn bushes appear) is key. In the latter regard, the likelihood of contracting several NTDs (eg, Buruli ulcer; soil-transmitted helminths) has been shown to be lowered by appropriate footwear. Specific training of medical staff and provision of mobile surgical teams would also help in the management of this disease.

5 SUPPORT FOR MYCETOMA AS AN OFFICIAL WHO-LISTED NTD

There can be little doubt that mycetoma meets many of the criteria to be considered as an addition to the WHO's list of 17 NTDs. It is a neglected, badly under-treated and under-diagnosed disease that affects developing countries, that impacts almost entirely on people and communities of low socio-economic status in remote rural locations, that has devastating long-term consequences (physical, psychological and economic), that is associated with very high morbidity and mortality, and up to 25% of those afflicted by the disease are children.

In 2013, following advocacy efforts by the Mycetoma Consortium, the WHO recognized mycetoma as an 'other neglected condition' alongside its official list of 17 NTDs and started to provide information about the disease on its website. It has also recently recognized the Mycetoma Research Center in Sudan as a WHO Collaborative Center. While this has to a degree raised the profile of mycetoma, as DNDi highlights "*this particular status … can limit the possibilities of major funding and R&D opportunities. This is a chronic, very slowly progressing disease that does not gain media attention because of outbreaks, which contributes to its neglect. There are no control or prevention programmes and the extent of the disease worldwide is not known*." The Public Library of Science (PLOS), which describes itself as "*a nonprofit publisher and advocacy organization founded to accelerate progress in science and medicine by leading a transformation in research communication*" notes that the WHO's efforts so far have not been "*sufficient to raise donors' interest"* and has effectively also called into question the lack of full recognition of mycetoma. It believes there are multiple NTDs beyond the WHO's list of 17 which deserve greater attention and notes the "*need to highlight the importance of mycetoma as a major poverty-related NTD".* From our literature review, the PLOS NTD Collections web pages on mycetoma appear to be the most comprehensive resource for research into this disease.

Further advocacy efforts led to a WHO Secretariat report in October 2015 which set out the WHO's response to mycetoma. As part of this, the WHO noted that "*elaborating a public health strategy for the prevention and control of mycetoma will undoubtedly require significant investment in research and product development, so that cost-effective prevention, diagnosis, early treatment and case management can be practised in low-resource settings. Some product development partnerships have begun to provide support to research and development; the Drugs for Neglected Diseases initiative, for example, will test a promising new treatment for eumycetoma as part of a 2015–2023 business plan. It will be essential to mobilize additional resources in order to facilitate the inclusion of public health interventions against mycetoma among those advocated by WHO against neglected tropical diseases. At*

present, early diagnosis and treatment with currently available tools is the most appropriate approach for lessening the disease burden imposed by mycetoma." Additionally it committed, amongst other things, to intensify its efforts to advocate for improved surveillance and control, to seek "*focused support"* from international donors and partners and to provide technical assistance to the Mycetoma Center in Khartoum, noting that *"in this respect, mycetoma will serve as a model for advancing the agenda of other tropical, poverty-related diseases that currently remain neglected*."

On 28 January 2016, the WHO Executive Board met to consider a resolution by Sudan, Nigeria and Egypt to add the mycetoma to the WHO's official list of NTDs. After much debate a resolution was adopted for the May 2016 agenda of the World Health Assembly in Geneva regarding the systematic selection of NTDs (specifically, the WHO's Strategic and Technical Advisory Group for Neglected Tropical Diseases must present a paper by May 2016 outlining criteria for determining what constitutes a "neglected tropical disease"). If the World Health Assembly approves this, then mycetoma will be added to WHO's list of NTDs and – in DNDi's words – "*mycetoma will have overcome a key barrier to R&D to tackle the disease to date: with official inclusion in the WHO NTD Department's activities, certain funding bodies will be able to consider taking up the disease within their funding scope and help to support the much needed research and development for diagnostics and effective treatment*."

In closing, this author sincerely hopes that mycetoma will indeed be formally adopted as an official NTD by the WHO. The PLOS asserts that "*the most important impact [for transforming the outlook for mycetoma] would … come from increased international recognition by governments, WHO, nongovernmental organizations (NGOs), and donors*" and official WHO recognition would be the single biggest step on this crucial and deserved path.

KEY SOURCES:

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www.clinicaltrials.gov

ISNTD Disease Brief, 'Benchtop to Barrios: the challenge of developing new drugs for Chagas disease'; Clark et al (January 2016)

ABOUT THE AUTHOR:

Mark Clark is a 30-year veteran analyst of the pharmaceutical industry and set up the consultancy firm BIApharma LLP in late-2015. Prior to this, he jointly headed the Deutsche Bank European pharmaceutical research team (from 2009-15). His interest in the field of tropical diseases led to his authoring the well-received report 'Tropical diseases; social responsibility, neglected market' in September 2014. Copies of this report, which was referenced by all of the leading news services (eg, WSJ, FT, Reuters), can be requested from Deutsche Bank and a link is available on the Access to Medicine Index website (www.accesstomedicineindex.org). Mark has also volunteered for Malaria No More UK and authored the ISNTD Disease Brief, 'Benchtop to Barrios: the challenge of developing new drugs for Chagas disease'.