

Starting from scratch—the unique neglect of mycetoma

Despite the often severe consequences of this disease its advocates have struggled for years for it to be internationally recognised. Talha Burki reports.

Few infections are as mysterious as mycetoma. One thing, however, is certain: it is a horrific disease. Patients endure swelling, sores, and pus-filled lesions. If it spreads, and without treatment it often does, the consequences are devastating. It can prove fatal—for example, if the pulmonary system is invaded, or if the patient develops sepsis (secondary bacterial infections are common). Flesh and bones are destroyed, and limbs are deformed. The affected area, usually the foot and arm, is colonised by tough black grains. By this point, the only feasible treatment is amputation, and even that might not halt the spread.

The disease comes in a bacterial form, prevalent in the Americas, and in a fungal form, mostly in Africa. Around two dozen countries are known to be endemic. Moving westward, these include India, Saudi Arabia, Ethiopia, Senegal, Brazil, Venezuela, and Mexico. The epicentre is Sudan. The country's capital, Khartoum, hosts the only WHO collaborating centre on mycetoma (and probably the only specialist institution in the world). Ahmed Fahal founded the Mycetoma Research Centre in 1991, and most of what has been learnt about the disease in the past couple of decades has some connection to his work there, including more than 120 research papers. Fahal has treated more than 7500 patients in the past 25 years. "We see around 300 new cases a year, but this is just the tip of the iceberg", he told *The Lancet Infectious Diseases*.

His patients are extremely poor. "They have to travel for days to get to the clinic, many sell their cattle or valuables", points out Fahal. When they finally arrive in Khartoum, they have to find somewhere to stay, and

pay for their diagnosis. The bacterial form of mycetoma is easily treated—a lengthy course of amikacin and cotrimoxazole—and has a cure rate of around 90%. But the fungal form is extremely tricky. Patients are treated with itraconazole, a drug with an

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observed efficacy that hovers around 30%, and has a high risk of recurrence.

"There is very little scientific data on the use of itraconazole on mycetoma", explains Nathalie Strub Wourgaft (Drugs for Neglected Disease Initiative, Geneva, Switzerland). "There are just a couple of publications with less than 20 patients—it is difficult to draw conclusions from this, but it is the best we can do for now." Last year, the Sudanese Government agreed to freely provide itraconazole. But this might not be sustainable. A single pill costs around US\$6. Patients need four pills a day, usually for 12 months or longer. A typical patient with mycetoma has an annual income of no more than a few hundred dollars. Small wonder that many drop out of treatment.

Experts do not even have a vague idea of the global incidence and prevalence of the disease. Nor is it certain how it is transmitted. The best guess is through some kind of abrasion or puncture wound. The strong and lengthy thorns of the acacia tree are a likely culprit—a barefoot African villager might step on a thorn, and the microorganism makes its way from the soil or dung into the subcutaneous tissue. In which case, should villagers in endemic areas be encouraged to wear shoes? In the

Americas, mycetoma is common on people's backs. Villagers in the region often carry piles of wood on their backs, perhaps the microorganism enters through a splinter wound.

"We cannot culture the microorganism from the surroundings, so we actually do not know where it is", points out Wendy Van de Sande (Erasmus University, Rotterdam, Netherlands). 70% of Sudanese infections are attributable to the fungus *Madurella mycetomatis*, but dozens of other causative agents have been identified. It is not known whether the agents prefer the same kind of environment, or whether the disease progression for each agent is similar. What makes one individual more likely to develop the disease than their neighbour is also unclear; unlike with some other fungal infections, patients with mycetoma do not seem to have any obvious immune impairment.

The initial infection results in a painless swelling, of a kind that residents of endemic areas are likely to ignore (health education is low in

For more on the **World Health Assembly's adoption of the mycetoma resolution** see http://www.who.int/neglected_diseases/news/WHA_69_adopts_mycetoma_resolution/en/

For more on **fosravuconazole** see <http://www.dndi.org/diseases-projects/portfolio/fosravuconazole/>

For more on **mycetoma** see *Review Lancet Infect Dis* 2016; **16**: 100–12



Mycetoma (here caused by *Nocardia brasiliensis*), although disfiguring and disabling, often goes untreated

such places). After months or even several years, this swelling can develop into a lesion. If caught early, surgical removal is possible, but further delay removes this possibility. "A lot of patients come with very advanced disease—in many cases amputation is the only solution", says Fahal. "This is a uniquely neglected disease."

Indeed, the neglect even extended to WHO. Despite tireless efforts from Fahal, for many years the organisation declined to add mycetoma to its roster of neglected tropical diseases. Large international donors use the list, which stood at 17 diseases, to inform their funding decisions. Diseases outside the roster fall into further neglect. "If you ask for funding for your research, you do not even make the short-list", explains Van de Sande. "People do not know what mycetoma is, they say it is not even on the WHO list, and they throw away your proposal."

The breakthrough came in May, 2016, when the 69th World Health

Assembly voted to classify mycetoma as a neglected tropical disease. All the machinery of WHO can now be put to work in tackling mycetoma, establishing a global strategy, convening expert committees, drafting guidelines, assigning targets for elimination and control, and arranging public awareness campaigns. "WHO can set up plans to detect the global burden of disease, help to do community work, and improve diagnostic measures", notes Strub. "We know very little about the epidemiology of the disease, but to address this we need to set up large-scale programmes." This demands the kind of centralised coordination in which WHO specialises. "The recognition means there is a much better chance of attracting researchers to the field, and of developing new drugs and diagnostic tools", adds Van de Sande. And, of course, the decision generated welcome publicity.

A randomised clinical trial, the first for mycetoma, will help

maintain some of this momentum. It is coordinated by the Drugs for Neglected Disease Initiative and the Mycetoma Research Centre. 138 Sudanese patients in early stage disease will be prescribed either itraconazole or the potential new drug fosravuconazole, the only new drug in the pipeline. "Whatever the results will be, this will be a kind of benchmark study", explains Strub. The trial is likely to launch later this year. In the meantime, Fahal will despatch a mobile clinic to an endemic rural village. 100 patients are expected to attend for treatment.

"WHO has sent a message to funders of research that this is a serious disease worth spending money on", concludes Strub. In which case, 2016 might well mark a turning point for mycetoma. For the first time in the history of this woefully neglected disease, its advocates have cause for optimism.

Talha Khan Burki

Infectious disease surveillance update

Yellow fever update

Since the first cases of the present yellow fever outbreak were reported in Angola, there have been 3748 suspected cases across all 18 provinces. 364 deaths have been reported, 119 of these deaths were among the confirmed cases. DR Congo has reported 1907 suspected cases as of July 20, and 95 deaths—cases have been reported in five of 26 provinces. Brazil, Chad, Colombia, Ghana, Guinea, Peru, and Uganda have reported yellow fever outbreaks or sporadic cases not linked to the Angolan outbreak. Transmission of yellow fever in Angola and DR Congo is mainly concentrated in cities and vaccination campaigns are ongoing in both affected countries. A recent review of the evidence has shown that using a fifth of a standard vaccine dose would provide protection against the disease for at least 12 months and possibly longer. It is a short-term measure to be

used in the context of potential or acute vaccine shortages seen in emergencies; this method is not proposed for routine immunisation. This fractional dosing approach will be implemented in a pre-emptive mass vaccination campaign in Kinshasa, DR Congo.

E coli O157 outbreak in the UK

Public Health England is continuing to investigate an outbreak of *Escherichia coli* in the UK. As of July 28, 161 cases had been reported: 154 in England, six in Wales, and one in Scotland. Two of the individuals infected with *E coli* O157 died. Investigations so far suggest that mixed salad leaves might be the cause; however, investigations are ongoing. Public Health England is advising people to maintain good hand and food hygiene practices at all times, especially anyone affected, to prevent the transmission of the

infection to others. Loose soil should be removed before storing vegetables and all vegetables (including salads) should be thoroughly washed if they are to be eaten raw unless they have been pre-prepared and specifically labelled as ready to eat.

H1N1 influenza in Panama

Since the first case of H1N1 influenza was reported in Panama in late April, 3500 people have needed admission to hospital, with 250 people currently hospitalised. The Ministry of Health is advising the public to get vaccinated—so far more than 2 million influenza vaccines have been administered. H1N1-related deaths have risen to 62 as of July 31; roughly 90% had underlying health issues and these deaths followed prolonged hospital admissions.

Ruth Zwizwai

For more on the **yellow fever outbreak** see <http://www.who.int/emergencies/yellow-fever/situation-reports/28-july-2016/en/>

For more on ***E coli* O157 in the UK** see <https://www.gov.uk/government/news/update-as-e-coli-o157-investigation-continues>

For more on **influenza in Panama** see <http://outbreaknewstoday.com/h1n1-influenza-deaths-in-panama-rise-to-62-81800/>