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Mycetoma in West Africa

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Background: Mycetoma is a neglected disease, which is socioeconomically important, and with the possibility of permanent disability in infected persons if not treated early. This is especially true in resource-limited settings such as West Africa, where there is a lack of facilities and skilled personnel to make a definitive laboratory diagnosis. Countries in West Africa have similar climatic conditions to Sudan. The majority of patients seek medical care very late, when there is already bone involvement, resulting in amputations. This results in poor capture of the true burden of the problem in the literature.

Methods: A review of the literature revealed about 2685 documented cases in West Africa from 1929 to 2020; from 15 out of 16 countries, Senegal accounted for 74.1% (1943) of cases in the subregion.

Results: The majority of lesions were found on the foot; however, other body parts were also reported. Rural dwellers accounted for most cases. Only 547 (20.4%) cases had identified isolates reported. Actinomycetoma accounted for 47.9% of cases, eumycetoma 39.7% and unidentified pathogens 12.4%. *Actinomadura pelletieri* was the predominant pathogen isolated (21.4%; 117 isolates).

Conclusion: There is a dire need for capacity building, provision of facility and health education to raise awareness of this debilitating disease in West Africa.

Keywords: actinomycetoma, capacity building, eumycetoma, mycetoma, West Africa

Introduction

In 2016, mycetoma was recognized as a neglected tropical disease (NTD) by the WHO in resolution WH69.21 in order to support member states where mycetoma is endemic, to strengthen their capacity to improve early detection and access to treatment and to assess the burden of disease.[1,2] Mycetoma is a subcutaneous granulomatous infectious disease[3,4] and as such is classified as a skin NTD. It is characterized by large subcutaneous lesions that are often stigmatizing.[4] To assess the burden of mycetoma, the WHO conducted a survey among five of the six WHO regions (Europe was excluded) from December 2016 to April 2017.[2] In Africa, based on the responses received, only half the countries had the capacity to diagnose and treat mycetoma. The majority of countries did not report on mycetoma. Therefore, the current knowledge on mycetoma is mainly based on the experiences with actinomycetoma in Mexico[5,6] and with eumycetoma in Sudan.[7] However, epidemiology and treatment might differ per region.[8] Therefore, in this review we focus on mycetoma in western Africa, discussing its epidemiology, etiology, diagnosis and treatment with reference to the practices currently used in other regions of the world.

Materials and Methods

Search strategy and selection criteria

The literature search for publications on mycetoma in West Africa preceding 30 March 2020 was performed using Pubmed, Web of Science, Google Scholar, Cochrane Library, African Journals Online

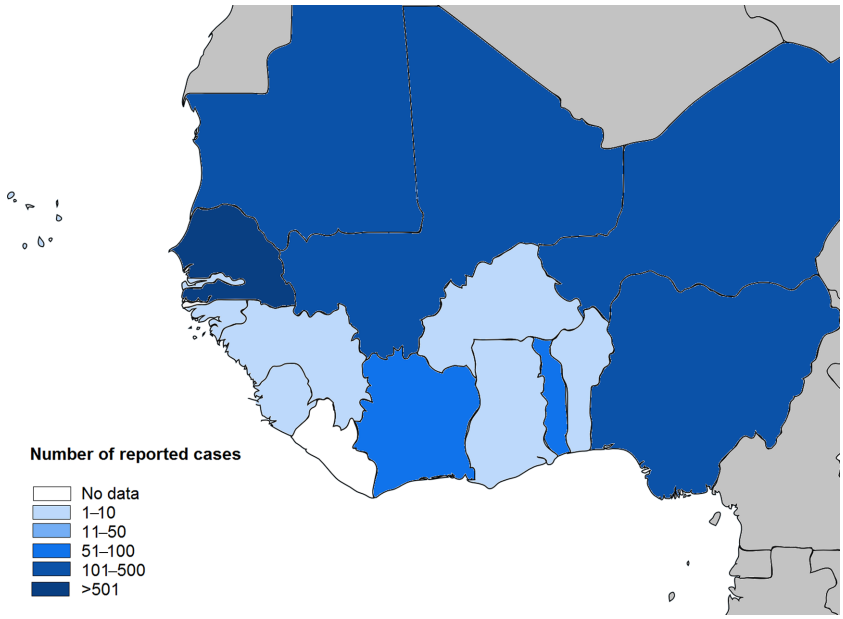

Figure 1. Frequency distribution of mycetoma across West Africa.

(AJOL), Africa-Wide: NiPAD, CINAHL (accessed via EBSCO Host) databases and gray literature to identify all published papers concerning the topic. The references in all relevant papers were reviewed for additional publications that may not have been cited elsewhere ('snowballing'). Articles published in other languages (e.g. French) were considered if they were cited in any of the databases searched. The main search comprised individual searches using detailed medical subject heading terms for mycetoma and West Africa, as well as the names of the 16 West African countries, namely, Burkina Faso, cape Verde, Gambia, Ghana, Guinea, Guinea Bissau, Ivory Coast (Cote d'Ivoire), Liberia, Mali, Mauritania, Niger, Nigeria, Senegal, Sao Tome and Principe, Sierra Leone and Togo. The Boolean operators 'AND' and 'OR' were used to combine and narrow the searches. All publications found were included.

Results and Discussion

Distribution of mycetoma in West Africa

In order to determine the epidemiology and burden of mycetoma in West Africa, we identified 2685 reported cases in the literature from 1929 to 2020,[9–81] of which 63 were reported in two studies.[17,27] Of these identified cases, 1943 (74.1%) had occurred in Senegal, a hotspot in the subregion (Figure 1).[10–23,81] Decreased use of foot wear where the climate is warmer and the population is poorer has been attributed as a possible reason for mycetoma in these regions.[15] A few cases were exported, where diagnosis was made in Europe, the USA and South America.[12,14,15,22–25] Mycetoma usually involves the subcutaneous tissue after traumatic inoculation of the causative organism. Subcutaneous mycosis requires predisposing trauma, which serves as the entry point for the microorganisms. Several patients report

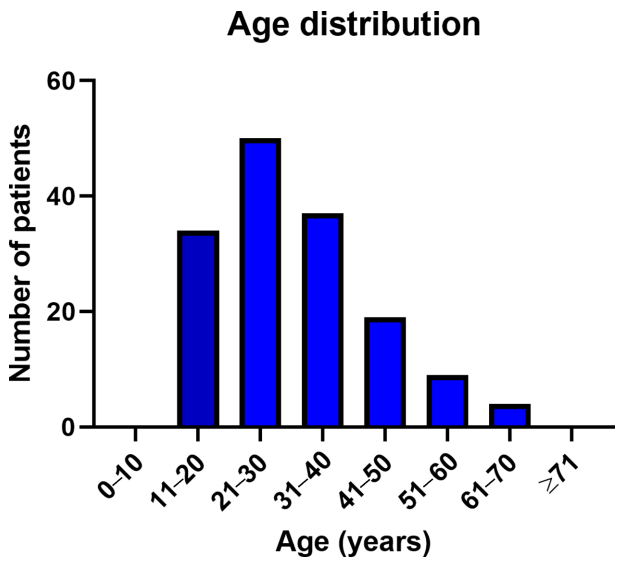

Figure 2. Age distribution of mycetoma in West Africa.

no history of trauma at the infection site. Case reports and series reveal that mycetoma is more frequent in males, comprising about 72–83% of cases.[8–80] In endemic countries, women participate in agricultural work and are exposed as much as men to inoculating trauma. The hypothesis of a hormonal virulence factor in women has been mentioned, based on a number of observations: first, the worsening of the disease in pregnant women, but also the observation of its different character before puberty, with as many boys as girls affected.[8] It affects all age groups, but most often occurs in individuals aged <45 y (Figure 2).[9–80] The incidence of mycetoma is highest in lower socioeconomic groups among men, farmers, animal

herders, field workers, nomads, those who walk barefoot and those in the third and fourth decades of life.[9] Although not confined to any occupational group, the majority of patients live in rural areas and are generally engaged in outdoor occupations that involve direct contact with soil or thorns, such as farmers, shepherds, fishermen and breeders.[9,20,81]

Identification of the causative agents

Identification of the causative agents is based on microbiological techniques, histopathological examination and molecular methods. Swabs are used to collect grains and/or pus in open sinuses in most of African laboratories. However, these grains are not viable in general and are commonly contaminated. Deep surgical biopsy is recommended as the best technique with which to collect viable grains for culture purposes.[82] Grains have different sizes ranging from 2–5 μm to 2 mm in diameter.[82] The grains are washed several times with saline solution. Identification is performed using direct microscopic examinations after adding 30% potassium hydroxide and lactophenol cotton blue stain is used in laboratories in West Africa.

Actinomycetoma is caused by agents producing red, yellow or white grains while eumycetoma is due to organisms producing black and rarely white and yellow grains. Sabouraud's dextrose agar plus chloramphenicol medium (eumycetoma) and/or Lowenstein-Jensen agar (actinomycetoma) are used for culture, depending on the color of the grains. The cultures are incubated at room temperature (20–30°C) and observed for 5 wk before reporting a negative result.

The causative organisms are usually environmental saprophytes that are only incidental human pathogens. In some cases, the etiological agents remain unknown, as direct microscopy cannot discriminate between certain organisms and culture remains negative, particularly in yellow and white grains. Some authors have proposed the use of gram staining and the Ziehl–Neelsen (ZN) staining technique to discriminate the actinomycetoma and eumycetoma causative agents.[82,83] Actinomycetoma species are gram-positive while the agents responsible for eumycetoma are gram-negative.[82] ZN is positive for some species like *Nocardia* spp., while it remains negative for *Streptomyces somaliensis* and *Actinomadura madurae*.[82]

For cytological and histopathological aspects, biopsies and, in some cases, fine needle aspiration, are useful. Histopathological examinations are performed using different staining methods including Grocott's methenamine silver, the Periodic acid–Schiff and hematoxylin and eosin stains. Microscopic characteristics, including the fungal structure (type and size of hyphae) and the presence of grain cement, are captured in the result. These characteristics are mainly used in West Africa to identify the causative agent, particularly in mycetoma without visible grains. For example, in eumycetoma, *Madurella mycetomatis* grains appear brown-reddish and are firm to hard with a large size of 0.5 to 5 mm. The grain structure can be multi-lobed, with brown cement, dotted with regular filaments (filamentous type) or regular vesicular filaments and peripheral brown cement.[84]

In actinomycetoma, *Actinomadura pelletieri* grains (0.3 to 0.5 mm in diameter) are regular, soft, kidney-shaped and hematoxiphilic without clubs and cement.[84] Histopathology has been used in many west African reports to confirm the diagnosis of mycetoma.[21,52] Speciation is difficult with this method, thus PCR can be used to do this. However, few laboratories in West Africa routinely perform PCR on clinical samples.

Internal transcribed spacer (ITS) sequencing has been used, for example in Senegal, to confirm the dermatophyte etiology of pseudomycetoma cases.[42] Most of the reports describing the use of molecular biology are from Sudan, which hosts the WHO reference mycetoma laboratory.[84–87] Therefore, there is a need to improve the diagnostic capacity level by setting up molecular platforms in West Africa for accurate identification.

Causative agents

In West Africa, eumycetoma appears to be more common than actinomycetoma, excluding a case series in Niger[9–81] (Table 1). More than 20 species of fungi and aerobic actinomycetes have been identified as etiological agents in West Africa. In actinomycetoma cases, *A. pelletieri*, *A. madurae* and *S. somaliensis* are the most prevalent species (Table 1). *Actinomadura pelletieri* (red grain) is predominant in most series reported in West Africa, except in Niger, where *S. somaliensis* was identified as the most isolated species.[27] This distribution can be explained by the fact that *A. pelletieri* is mainly found in rainy regions (500–800 mm per year) while *S. somaliensis* is observed in desert areas like Agadez in Niger.[84] *Nocardia* spp. are rarely found in West Africa. From the 880 actinomycetoma cases in which the etiology was determined, only 99 were caused by *Nocardia* spp. (Table 1). From the 978 eumycetoma cases for which the etiology was determined, 669 (68.4%) were caused by the black grain causative agent *Madurella mycetomatis* (Table 1). The second most common fungal causative agent was *Falciformispora senegalensis*, which was found in 237 (35.4%) of cases. The number of *F. senegalensis* cases was much higher than that found in other regions in the world.[88] No known vector or animal reservoir has been established for mycetoma, however, a recent study reported the detection of *M. mycetomatis* in ticks[37] and *S. somaliensis* was retrieved in the gut of an earthworm.[89] A study in Mauritania isolated some of these causative agents from soil and trees.[37]

Mycetoma is most commonly found in the foot

The foot is the site most affected in reported case series[9–80] (Figures 3 and 4). This is not surprising, as infection is believed to be the result of a traumatic implantation of the pathogen into the skin or subcutaneous tissue via infected thorns or wood splinters or via subsequent contamination of a wound with soil organisms.[4] Podal localization is the most frequent, but the mycetoma can be localized anywhere on the body's surface. Most extrapodal mycetomas are actinomycotic.[22,31] The following sites have been described in the literature:

- Lower legs (involvement of the ankle is the most common and has the most difficult prognosis). The grain migration occurs early according to the vascular nervous sheaths.
- Legs and thighs: locations in the leg and thigh are superficial and extensive, the bone invasion is later.
- Knees: involvement is possible, and is often cystic and engages the functional prognosis of the joint. Extension to involve the patella has been recorded.

Table 1. Number of species identified by selected papers

Species	Color of the grain*	Number of isolates	%	Prevalence**
Actinomycetoma		880	47.36	
Actinomadura pelletieri	Red	478	26.03	C
Streptomyces somaliensis	Y	166	9.04	C
Actinomadura madurae	W/Y/P	137	7.46	C
Nocardia brasiliensis	W	30	1.63	O
Nocardia asteroides	W	3	0.16	R
Nocardia transvalensis	W/Y	1	0.05	R
Nocardia spp.	W/Y	65	2.34	
Eumycetoma		978	52.63	
Madurella mycetomatis	B	669	36.44	C
Falciformispora senegalensis	B	237	12.91	C
Medicopsis romeroi	B	25	1.36	O
Scedosporium boydii	W	13	0.71	R
Aspergillus nidulans	W	7	0.38	R
Neotestudina rosatii	W	6	0.33	R
Fusarium solani	W	3	0.16	R
Microsporum audouini		2	0.11	R
Exophiala jeanselmei		2	0.11	R
Trematosphaeria grisea	B	1	0.05	R
Aspergillus fumigatus		1	0.05	R
Cochliobolus lunatus		1	0.05	R
Acremonium spp.	W	4	0.22	R
Cladosporium spp.		3	0.16	R
Fusarium spp.	W	2	0.11	R
Penicillium spp.		2	0.11	R
Total		1858	100	

Abbreviations: *Y, yellow, W, white, P, pink, B, black; **C, common; O, occasional; R, rare.

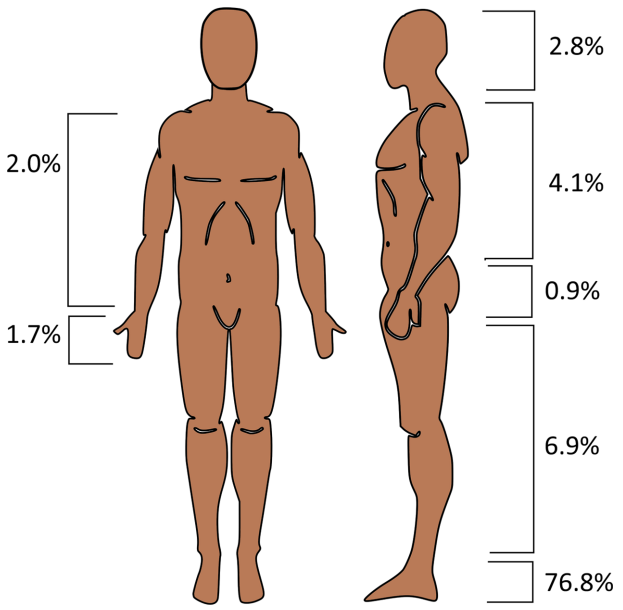

Figure 3. Distribution of the parts of the body affected by mycetoma.

- Upper limbs: mycetomas of the upper limb are dominated by those of the hand; however, they are relatively rare. Isolated involvement of the fingers may occur. These injuries to the hand are serious because of the risk of rapid invasion of the bone and soft tissue. The other topographies at the level of the upper limb are the forearm, the arm, the elbow and the shoulder; the latter is very rare.
- Trunk and abdomen: mycetomas are mainly confined to the surface, but they can have a fatal evolution, through pulmonary, hepatic, splenic and pancreatic extension.
- Dorsolumbar involvement can result in bone involvement with the risk of neurological complications due to spinal medullary extension.
- Buttock locations are rare and are sometimes complicated by pelvic invasion. They tend to encyst, as in the elbow or the knee. Damage to the groin is possible with, sometimes, invasion of the perineum, making the prognosis grim. However, primary involvement of the groin is exceptional. Mycetoma of the groin is most commonly metastatic but evolves independently.
- Axillary area involvement is similar to that of the groin and there are lymph node metastases.

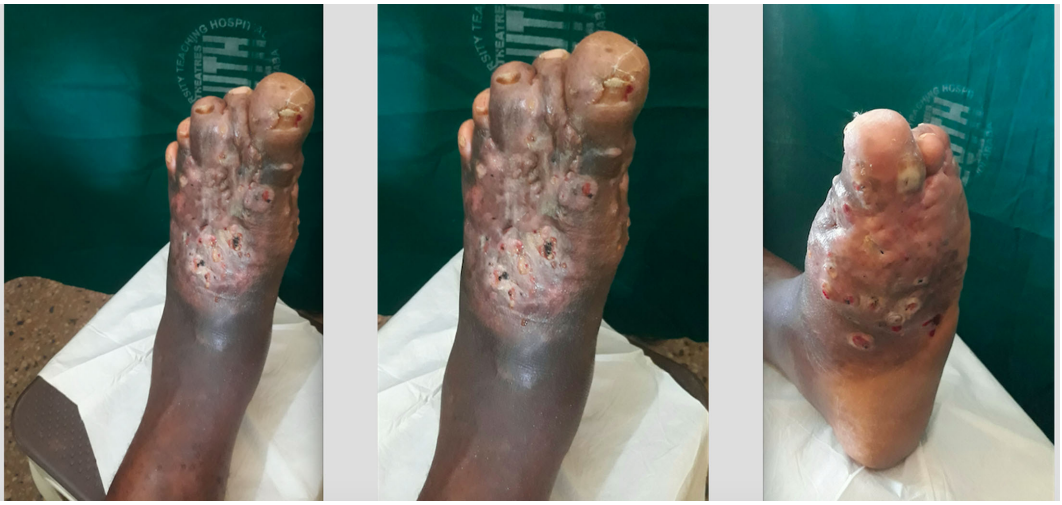

Figure 4. Mycetoma of the foot.

- Head and neck: mycetomas of the neck and head also have a poor prognosis, due to the risk of local invasion and early bone damage. The locations, craneo-encephalic and vertebro-medullary, are respectively secondary to infection originating on the scalp, with extension to the dura mater or to a dorsal or cervical attack with deep extension, responsible for spinal compression.

As well as the classical appearance of mycetoma, there are several cases in which the signs are different from the typical signs. There are three main variations:

- Inflammatory mycetoma: there are inflammatory pockets covered with innumerable fistulae and often visible grains, without real tumors.[41]
- Tumoral mycetoma forms: characterized by real tumor masses with very few fistulas and without visible grains.[42]
- Encapsulated forms characterized by a long evolution and little inflammation, often localized on the calf, thigh or buttocks without fistulae or grains and are either nodular or cystic. They are the most benign and benefit from permanent healing after surgical excision. They can only be diagnosed by pathological examination of a biopsy-excision sample.[43] There are two types: the cystic type with intact skin and necrotic, purulent or exudative content; or the non-fluctuating type, which is limited by a fibrous shell that makes it possible to dissect the lesions.

Rural dwellers constitute the majority of cases; the geographical and financial inaccessibility of healthcare services is the origin of the delay in consultation and the delay in diagnosis, with most patients presenting with advanced disease. This also results in patients using inappropriate and ineffective traditional treatments such as traditional plants, animal dung and amulets. During the late stage, the exacerbated pain at night with relative functional disability is a feature suggestive of bone involvement. Information, education and communication programs during decentralized consultations in rural areas would make it possible to reduce the diagnostic delay and thus improve care.

Risk factors

There are no large-scale studies available; however, case series and reports in addition to smaller observational studies have documented certain factors predisposing individuals to the development of mycetoma. These include geographic variation (humid climate, rainfall, ecological factors), low socioeconomic status (particularly in rural areas), trauma (usually in the lower legs, but also in other exposed parts of the body), certain occupations (e.g. farmer, agriculturist), poor health education and poor accessibility to healthcare facilities.[3,9,14,16–18]

An impaired immune system has not been implicated as a risk factor. Affected individuals usually have a normal functioning immune system. Nevertheless, two cases of mycetoma have been identified in transplant patients: one Ghanaian (kidney) and one Gambian (heart) immigrant in the UK and USA, respectively.[13,21] In eastern Sudan, mycetoma was associated with the presence of certain single nucleotide polymorphisms in resistance genes.[90–93] However, their presence and association in populations of different genetic backgrounds have never been determined.

Treatment

Currently, there are no standardized or WHO-recommended treatment guidelines for mycetoma. Several factors contribute to this and include, but are not limited to, access to treatment, cost, side effects and a lack of compliance, follow-up or standard treatment guidelines. The different causative organisms of mycetoma have resulted in different treatment recommendations and this may be partly responsible for the lack of a set of guidelines. Treatment options also differ based on the type of mycetoma. Response to medical treatment is usually better in actinomycetoma than in eumycetoma, which is difficult to treat with current therapies.[90]

The therapeutic outcome of mycetoma depends on several factors. These include early diagnosis (identifying the bacterial or fungal etiology of the infection), the patient's social and economic status, cultural background, nutrition, therapeutic compliance and resistance to previous therapies, as well as the extent and location of the disease.[16] Medical treatment for both types of mycetoma must be continued until the patient is clinically, radiologically, ultrasonically and cytologically cured.[21] Complete cure is a challenge and treatment options vary with each patient, the setting and the pre- and co-existing conditions. The time taken for remission in actinomycetoma can vary from 3 mo to 1 y, whereas eumycetoma requires prolonged treatment ranging from 1 to 3 y.[31,94]

In general, actinomycetoma is treated by a combination of antibacterial agents. Most commonly, the so-called Welsh regimen is used, consisting of 5-wk cycles, during which, in the first 3 wk a combination of 7 mg/kg/day trimethoprim with 35 mg/kg/day amikacin is given, then in the last 2 wk only 7 mg/kg/day trimethoprim.[94,95] This cycle is repeated till cured. Another often used treatment regimen consists of 2 g amoxicillin/clavulanate and 1600/280 mg sulfamethoxazole/trimethoprim three times a day.[96] The choice of antibacterial agent(s) generally depends on preference of hospital, not on the species causing the actinomycetoma. In Senegal, patients are treated with either trimethoprim-sulfamethoxazole or trimethoprim-sulfamethoxazole combined with amoxicillin/clavulanate and streptomycin. From the 33 patients with red-grain (*A. pelletieri*) mycetoma and treated with trimethoprim-sulfamethoxazole alone, 20 recovered, 4 were lost to follow-up and 9 were still on treatment. When only those patients who were followed till the end of treatment were considered, a 100% cure rate was obtained. From the five white-or-yellow-grain mycetoma patients treated with trimethoprim-sulfamethoxazole, four patients were cured and one patient had a recurrence, resulting in a cure rate of 80%. When red-grain mycetoma was treated with trimethoprim-sulfamethoxazole combined with amoxicillin/clavulanate and streptomycin, the cure rates were less favourable. From the 38 red-grain mycetoma patients treated with this regimen, only 12 had finished their treatment by the time of this report. Of these 12, 10 (83.3%) were cured and 2 (16.7%) had a recurrence.

Eumycetoma is treated with a combination of antifungal agents and surgery.[43] The surgical mode of treatment (excision or debulking) is combined with antifungal therapy to achieve a better outcome.[18] Certain factors determine the outcome: the extent of tissue and bone involvement and the site of the disease. Postoperatively, medical treatment is required to ensure complete treatment and follow-up is mandatory to ensure early detection of recurrence.

Evidence-based guidelines published by the Mycetoma Research Centre in Sudan outline the medical and surgical treatment options.[97] For medical management, a combination of therapeutic drugs is preferred to monotherapy to avoid drug resistance and eradication of residual infection. Therapeutic management involves the long-term use of antifungal therapy, which in some situations results in a poor response. However, antifungal therapy does help in localizing the disease into a well-encapsulated lesion that can then be excised surgically. Most commonly, the regimen from the Mycetoma Research Centre is used. In this regimen, the patient is treated with 200–400 mg itraconazole daily for 6 mo to create a good fibrous capsule around the lesion, followed by wide local excision. After surgery, the patient continues on 200–400 mg itraconazole daily until cure is achieved.[94] In regions where itraconazole is not widely available, terbinafine is used as an alternative. In this case, eumycetoma is treated with 500 mg terbinafine twice daily and surgery.[43] In Senegal, both itraconazole and terbinafine have been used. In a recent study, 23 patients were treated with trimethoprim-sulfamethoxazole combined with amoxicillin/clavulanate, itraconazole and surgery and 68 were treated with terbinafine and surgery. Of the 23 black-grain mycetoma cases treated with trimethoprim-sulfamethoxazole combined with amoxicillin/clavulanate, itraconazole and surgery, all were cured (a 100% cure rate). Of the 68 black-grain eumycetoma cases treated with terbinafine and surgery, data for only 22 cases were available until the end of treatment.[17] Of these 22 patients, 20 were cured and 2 had a recurrence, resulting in a cure rate of 90.9%.[17] Treatment for mycetoma usually continues for several years and is stopped when clinical, serological, radiological and ultrasonic cure is achieved.[97]

In conclusion, mycetoma is a neglected disease in Africa. The majority of reported cases were diagnosed by histology due to a lack of skilled personnel or facilities to isolate and identify the pathogen in routine hospital laboratories. In the whole of West Africa there is no reference mycology laboratory; few tertiary hospitals have functional mycology benches and thus there is lack of skilled personnel to make the diagnosis, especially in those regions most at risk. There is an urgent need to address this gap.

Authors' contributions: Conceived and designed the study: ROO, FL, DS, AOA, BKO, AHF and WWS. Conducted the data collection: ROO, FL, DS, AOA, BKO, AHF and WWS. Analyzed the data: ROO, FL, DS, AOA, BKO, AHF and WWS. Contributed materials/analysis tools: ROO, FL, DS, AOA, BKO, AHF and WWS. Wrote the paper: ROO, FL, DS, AOA, BKO, AHF and WWS.

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