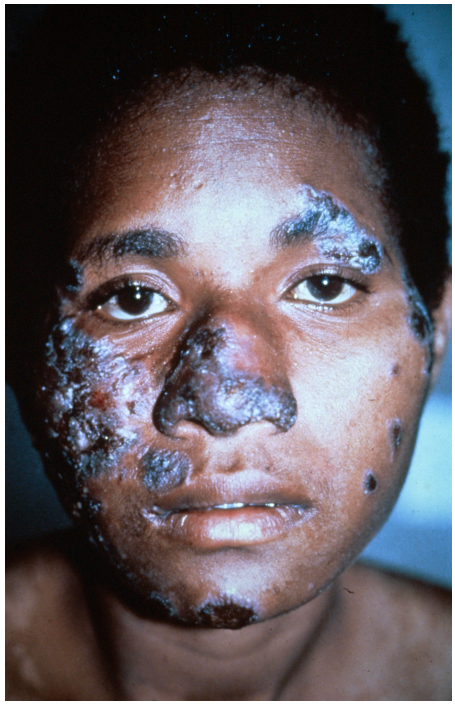
Proposal for WHO STAG adoption as an NTD

Chromoblastomycosis - a true tropical neglected tropical disease

Chromoblastomycosis should be designated a neglected tropical disease by WHO because its global distribution in tropical and sub-tropical areas, its impact on the impoverished rural population, its refractoriness to treatment when advanced and opportunities for prevention, early diagnosis and cure.



From the Global Action Fund for Fungal Infections, Geneva.

November 2016

Technical summary
Chromoblastomycosis is an uncommon or rare implantation mycosis found primarily among poor agricultural workers in tropical and sub-tropical regions. The true burden of disease is unknown, but in Madagascar is found in 14/100,000. Disease is limited to skin and subcutaneous tissue. It is curable with early resection, but tends to spread to other sites because of scratching and secondary implantation of severely pruritic lesions. While limited to skin and subcutaneous tissue, spread to other sites leads to huge and disabling lesions with major economic consequences for those affected. Diagnosis requires training personnel and laboratory availability. Current antifungal therapy is partially effective but takes months or years, and is too costly for most patients and often unavailable. Therefore, a point of care diagnostic method, global availability of affordable treatment and development of new antifungals more active against the pathogens are needed. The topical immunomodulator imiquimod may be valuable but needs further study. Prevention with improved protective clothing and washing has the potential to reduce new cases.

Lay summary
Chromo is a disfiguring disease usually occurring in farmers in poor and remote communities. It follows trivial skin injury with the several fungi involved being inoculated under the skin where they grow slowly over months and years. As they progress itching becomes severe, and scratching results in further inoculation to other body sites. As there are very few dermatologists, trained community workers or fungal labs, the diagnosis is usually delayed for years. When patients do ask for medical help, the lesions are usually extensive and disfiguring. Oral antifungal therapy is not very effective, and must be taken for months or years. More research is required to define the environmental sources, the disease burden, its impacts on patients, families and communities, and on better therapies. Awareness and prevention programs and additional training of health professionals is also required.

Introduction

Chromoblastomycosis, also known as chromomycosis or chromo for short, is a chronic and very difficult to treat cutaneous mycosis, affecting individuals living in low-income tropical and subtropical countries all over the world, but especially in Asia, Africa and Latin America. Chromoblastomycosis is caused by several species of melanized or "black" fungi which are found worldwide in soil and decaying plant debris, including wood. The etiologic agents are traumatically inoculated through the skin surface during several types of outdoor activities.

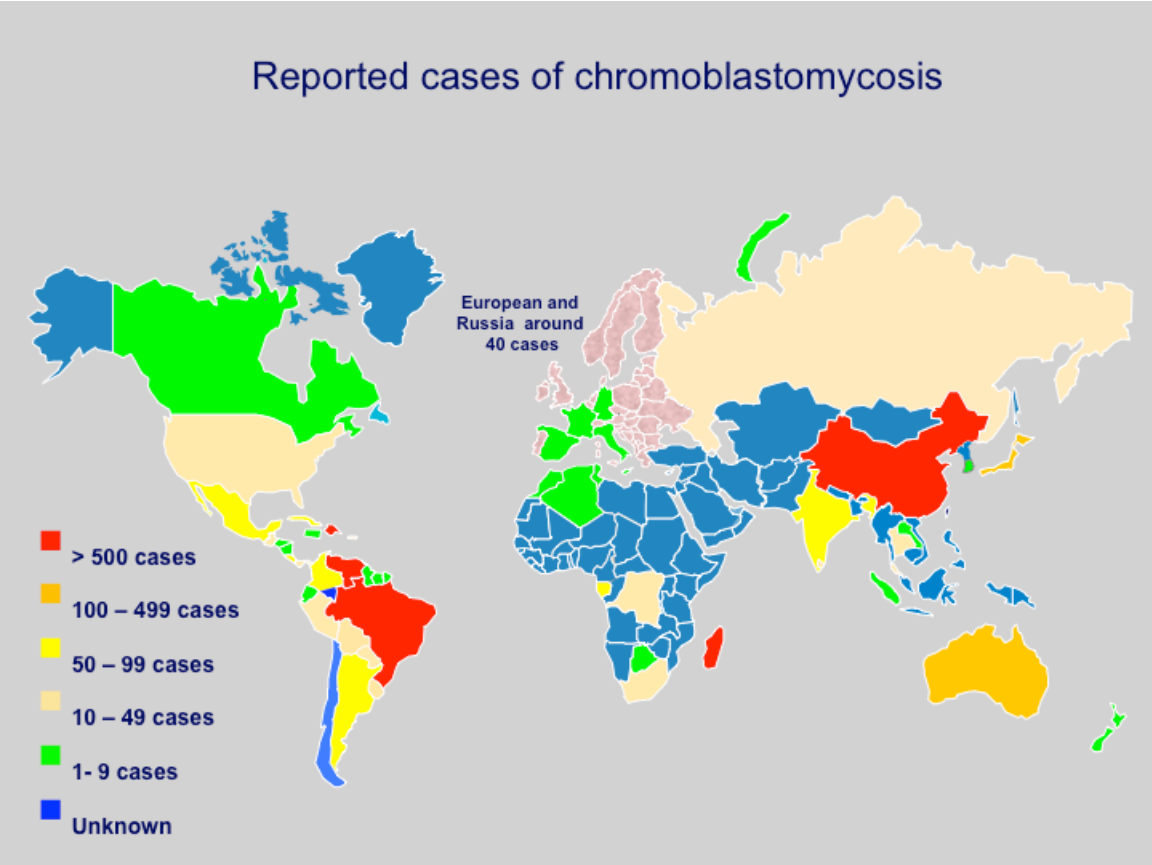
In many parts of the world, chromoblastomycosis is primarily an occupational disease, occurring in farm workers, lumberjacks, gardeners, or those handling farm produce. A potentially important source of infection was reported in an endemic area located in the state of Maranhão, on the fringes of the Amazon rainforest in Brazil, where thousands of families are involved in babassu (*Orbignya phalerata*), a wild palm tree, harvesting. The local population collects babassu nuts to extract the babassu oil, an important component for local and international beauty product manufacturers. Because melanized fungi have been isolated from babassu shield fragments, this may be a risk factor for hundreds of people developing chromoblastomycosis after trauma that occurred at work.

Unlike other implantation (and endemic) mycoses such as sporotrichosis and mycetoma, chromoblastomycosis is limited to subcutaneous tissues, and it does not affect fascia, tendons, muscles, and osteoarticular sites. Initial lesions and mild forms are oligosymptomatic, and usually do not lead to medical consultation and do not interfere with the patient's daily activities. With time, pruritus is the predominant complaint, which may be intense and accompanied by local pain, and scratching produces additional satellite lesions in other body sites. Disfigurement is the predominant issue, often leading to stigma.

Chromoblastomycosis progresses slowly inducing progressive fibrotic changes and lymphatic stasis, leading to lymphedema, which in some cases resembles elephantiasis. Secondary recurrent bacterial infection is a frequent complication. If not treated, the severity increases over time with progressive disfigurement, localized oedema and recurrent bacterial infection, leading to a limitation of or an inability to work. In advanced cases, chronic lymphedema, ankylosis, and malignant transformation to squamous cell carcinoma are observed.

Epidemiology

The global burden of chromoblastomycosis is comparable to or greater than that of mycetoma. This disease rarely occurs before adolescence with most of patients being 40 to 50-year-old men, with male- to-female ratios of 5:1 and 9:1[1]. The highest prevalence of the disease is within a zone between 30° latitude North and 30° latitude South, coinciding with most of the tropical and subtropical climates. Few epidemiology surveys have been done, so most data derives from published case series.

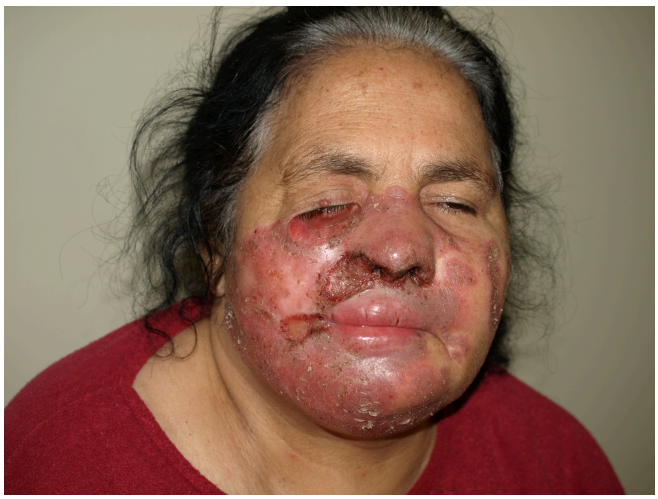


Its incidence rates range from 1:6,800 (14/100,000) (Madagascar) to 1/ 8,625,000 (0.012/100,000) (USA)[1]. In Brazil, the estimated incidence rate for this disease is 3/100,000. Most of the reported cases occur in Latin America, the Caribbean, Asia, Africa and Australia. Madagascar, Brazil, Mexico, Dominican Republic, Venezuela, India and south China report most cases. It has been has been reported in all South American countries except Chile. Cases are regularly identified in Sri Lanka, Pakistan, Thailand and Malaysia, as well as southern China, throughout India and in Japan, with a few cases reported from the Solomon Islands and Papua New Guinea (personal communication). In Africa, most cases have been reported from Madagascar, with substantial numbers also in Gabon, and eastern South Africa. These are shown in the map above. A major review summarizing the epidemiological situation is to be published in January 2017[1].

The disease is caused by a great number of fungi that inhabit the soil, plants, flowers, and wood, but they are difficult to isolate from the environment[1]. *Fonsecaea pedrosoi* is the most common pathogen associated with the disease in tropical areas with high rainfall. However in southern China all cases are associated with *Fonsecaea nubica. Phialophora verrucosa* is the second most prevalent fungus. *Cladophialophora carrionii* is the most important agent in dry countries and deserts of Australia, South Africa, and Cuba. *Rhinocladiella aquaspersa* is an infrequent cause as are *Wangiella dermatitidis*, *Exophiala spinifera* and *Cladophialophora boppii*.

Chromoblastomycosis is an occupational disease primarily affecting farm laborers, forestrly workers, gardeners, vendors of farm products, and other workers exposed to contaminated vegetal materials. As with mycetoma infection, the lack of protective shoes, gloves, or garments in association with poor hygienic habits and deficient nutrition probably favors acquisition by implantation and perpetuation of the disease. In Brazil, harvesting of the babassu coconut has been a major epicenter of disease and in India chromoblastomycosis is linked to black tea cultivation in Assam and rubber plantations in Kerala and Western Ghats.

Clinical manifestations



The disease starts as skin-colored papules that enlarge and can ulcerate (Figure 1)[2]. Usually lesions enlarge into nodules or plaques with a scaly, verrucous surface. Early lesions often resemble a dermatophyte infection, with a dull red or violet color. Sometimes the lesions heal as sclerotic plaques, scars, or keloid scars. In other cases, the primary site or the satellite lesions expands peripherally. Lesion growth is always very slow and insidious. After many years, some lesions evolve into the typical pattern of the disease: cauliflower-like masses, nodules, and sometimes, large vegetations. The lower limbs are the most common site, but upper limbs, buttocks, ear

pinna are often involved. During therapy, the lesions may present an intense fibrotic reaction resulting in scarring and, if they are in the face, eyelid retraction, ectropion, xerophthalmia and keratitis can happen.

Association of chromoblastomycosis with other infectious diseases have been reported, including osteomyelitis, paracoccidioidomycosis, leishmaniasis, and leprosy. These co-infections may increase the progression of both diseases, resulting in the need for prolonged antifungal therapy and potential for increased toxicity related to the respective therapies.

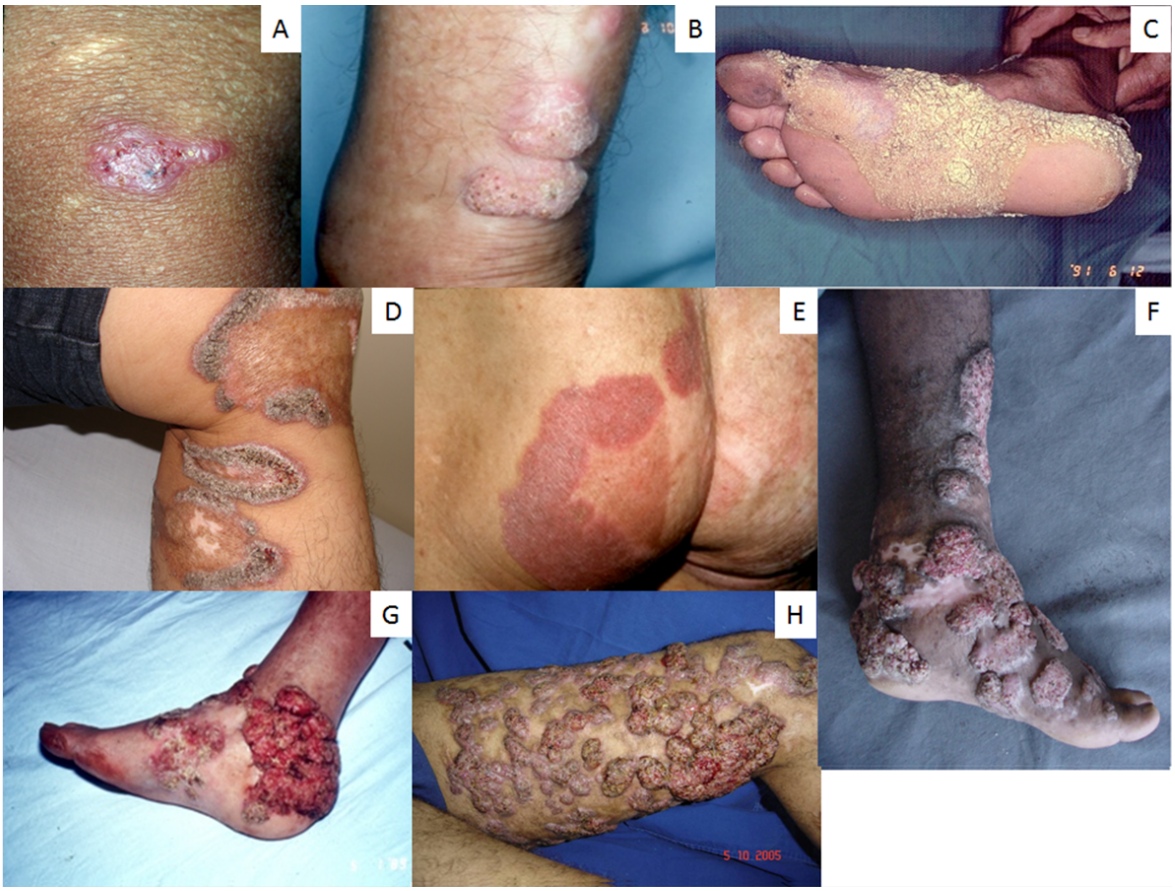


Figure 5. Lesions of chromoblastomycosis may depict clinical polymorphism end elicit several differential diagnosis. The Initial lesion of chromoblastomycosis (1 A), may evolve to five main clinical types: Nodular lesions on the lower leg (1 B), verrucous lesion of the foot (1 C), cicatritial lesions of the knee and lower leg (1 D), plaque lesion on the buttocks (1 E), tumoral (cauliflower) lesions on the foot (1G). and mixed lesions composed by plaque, nodular and verrucous lesions involving the lower limb (1 H).

Diagnosis

The diagnosis is based on examination and culture of skin scrapings or biopsy. The pathognomonic muriform cells (dark-walled, polyhedral, chestnut-like structures, Figure 2B) are seen on tissue sections and may be referred to as sclerotic bodies[2]. They are easily seen in potassium hydroxide skin scrape preparations (sensitivity 90-100%) or with hematoxylin-eosin staining in tissue. The muriform cells are often seen in the deeper portions of the lesion, whereas hyphae and budding cells may be present at the lesion surface. To identify the etiological agent, a skin sample must be cultivated on routine fungal media. Growth of the fungi can take up to 6 weeks. Genus identification can be done by morphological examination of the fungi, but species identification requires sequencing of DNA informative genomic regions.

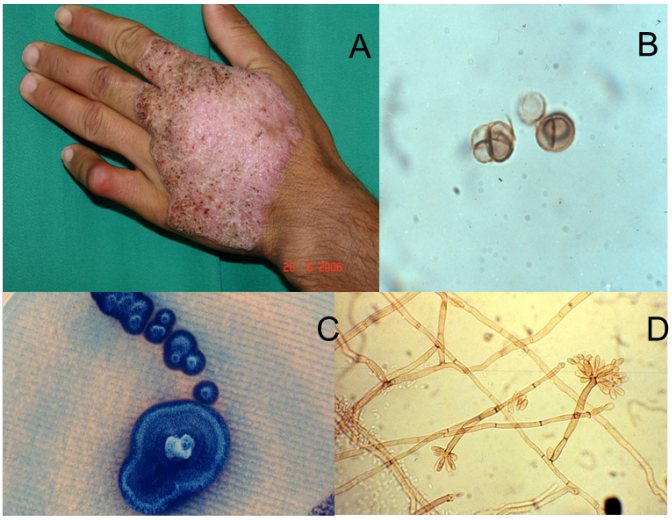


Figure 2. Clinical and microbiological aspects of chromoblastomycosis: The etiologic agent is easily found in the "black dot" lesion covered area (circled) A. Muriform cells are pathognomonic for this disease. They are observed either on wet mount (B) or in histologic sections. *Fonsecaea pedrosoi* is one of the prevalent agents in humid areas. Figures C and D depicts its macro and micromorphology aspects.

Opportunities for control

a. Diagnosis

i. Training of primary health care personnel in affected zones as well as dermatologists to recognize chromoblastomycosis and enabling them to undertake and process skin scrapings and biopsies is an important component of improving diagnosis.

ii. Laboratory training to facilitate recognition of characteristic muriform cells in direct microscopy and histopathology, cultivate the clinical samples and identify the isolates to species level. To this end, the Fungal Infection Trust has launched an online training course in fungal microscopy at www.microfungi.net, to allow remote training. The course is in English currently and being translated into Spanish, French and Portuguese over the coming months. Training workshops (which could be jointly organized with the Mycetoma community) would embed these direct skills more widely. GAFFI has called for a mycology reference laboratory in each country by 2025 (95-95 by 2025)[3], and such laboratories would be equipped to identify the causative fungi of chromoblastomycosis.

b. Treatment

i. Surgical resection of all small and well-demarcated lesions is curative. This is often accompanied by a short course of itraconazole or terbinafine. It is not clear how useful wide surgical excision of larger lesions is, but if 'cauliflower-like' may be appropriate for cosmetic or comfort reasons, but are not usually curative.

ii. Cryotherapy with liquid nitrogen is useful for small lesions. More than one treatment may be required, especially for larger lesions. Antifungal therapy is given in

addition.

iii. Heat treatment (1 month of disposable pocket warmers with an occlusive dressing) applied continuously has been shown to be useful. Shorter duration heat treatments (2 hours daily) with antifungal therapy may accelerate healing.

iv. Laser therapy with a 10,600nm wavelength CO2 laser has been used successfully, again with antifungal therapy in most cases.

v. Antifungal therapy is given to most patients who can afford it, if it is available. No prospective studies of therapy have ever been done. Itraconazole, 200-400mg daily, is the most common treatment and patients benefited of the therapy in 72% (63-90%) of cases. Treatment courses are long with some improvement usually apparent by 8 months. Terbinafine 250-500mg daily is also frequently used, especially in those taking medication that interacts with itraconazole, notably anti-tuberculous therapy. A few data suggest that posaconazole may be more effective than itraconazole, and some recalcitrant cases have been treated with voriconazole. The newly licensed isavuconazole is highly active against *Fonsecaea* and *Cladophialophora* spp.

GAFFI has recently applied for itraconazole and voriconazole to be listed on the WHO EML.

vi. Recently the topical immunomodulator imiquimod was found to induce responses in chromoblastomycosis, with and without antifungal therapy[4]. Imiquimod cream is licensed for the treatment of sun-damage in the form of some superficial pre-cancerous (actinic keratoses), cancerous skin conditions (superficial basal cell carcinoma) and external genital viral warts. Imiquimod may cause minor redness, swelling, flaking, scabbing, or burning at or around the application site. Back pain and changes in skin color may occur and be permanent.

c. Prevention

The majority of lesions are observed on the extremities of outdoor rural workers. The main risk factors associated with chromoblastomycosis are: lack of protective shoes, gloves or garments, combined with poor nutrition and hygienic habits. Training and provision of preventative clothing for workers at risk could reduce cases.

d. Awareness

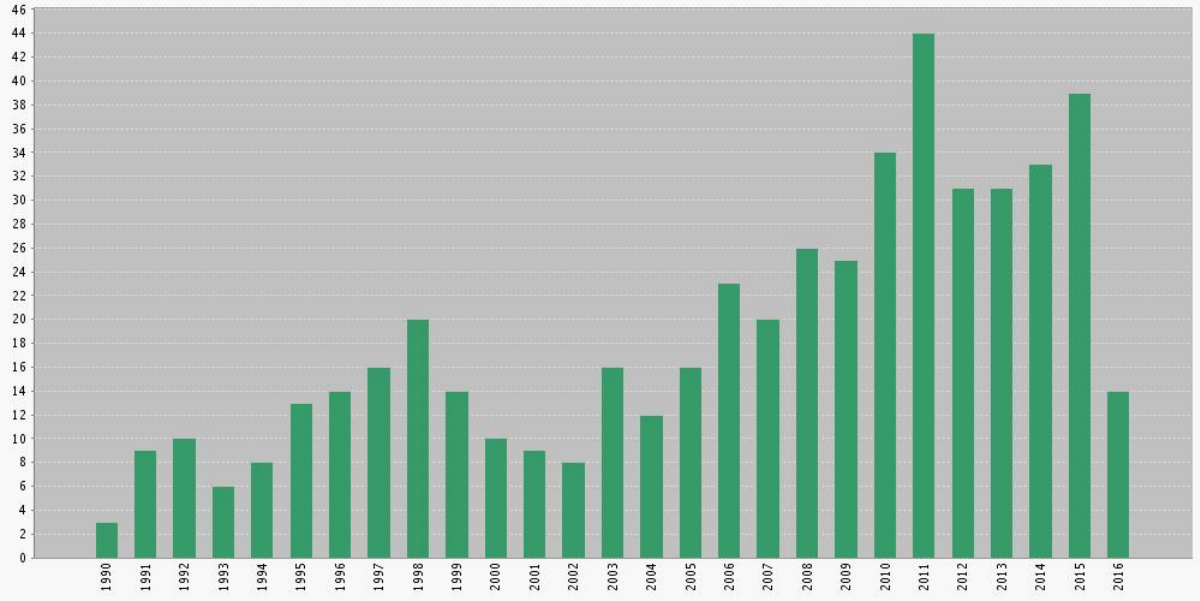
i. Awareness among local rural and farming communities could be enhanced and possibly facilitated with engagement with food and other agricultural product companies and exporters.

ii. Although not proven, improved cleanliness is likely to reduce infection, and allow earlier diagnosis.

Current research activities

There is a small community of scientists focused on chromoblastomycosis. The graphs below show the publications mentioning it and citations from 1990-2016 (Web of Science). In total, there were 504 publications and 6,175 citations, many of which were ‘passing references’ to the disease. This compares to 820 publications and 7,970 citations to mycetoma (excluding pulmonary and paranasal sinus ‘mycetomas’). There is an International Society for Human and Animal Mycology working group on diseases caused by black fungi, that has held a couple of meetings attracting about 100 people (www.isham.org/WorkingGroups/index.html and www.blackyeast.org/).

Publications



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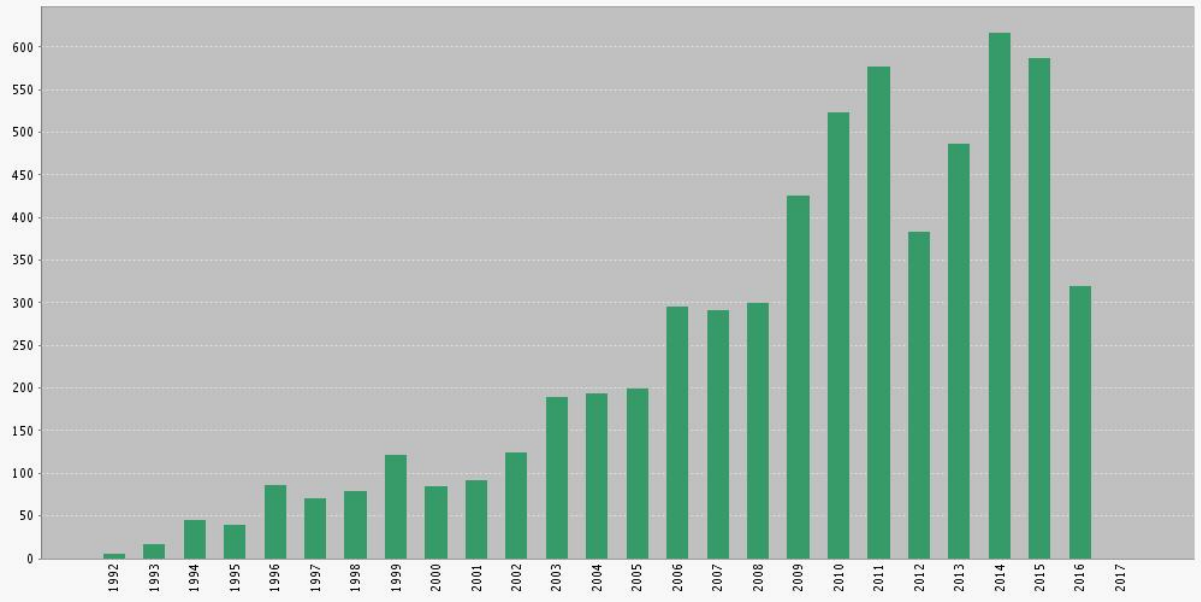

Research activities required include:

- Environmental studies to define the sources of the fungi in outdoor settings
- Case finding and burden assessments in many tropical and sub-tropical countries;
- Rapid diagnostic tests including a point of care and species specific testing will accelerate diagnosis and may allow more tailored therapy;
- Impact of chromoblastomycosis on quality of life and DALS etc., need to be determined;
- Topical immunotherapy with imiquimod needs to be properly studied;
- Prospective treatment studies are required, and novel agents (possibly including posaconazole and/or isavuconazole) should be evaluated for this as an orphan disease indication;

- It is likely that there are genetic or other susceptibility factors allowing chromoblastomycosis to develop and cause progressive disabling lesions. These factors need to be investigated.

Criteria for NTD adoption

Disease conditions that:

1. *Disproportionately affect populations living in poverty; and cause important morbidity and mortality – including stigma and discrimination - in such populations, justifying a global response* – Chromoblastomycosis is a multi-country problem of remote, rural populations, typically subsistence farmers. It is a major stigmatising disease, with many patients unable to work and others partially ostracized by their communities.

2. *Primarily affect populations living in tropical and sub-tropical areas* – Chromoblastomycosis is predominantly seen seen in tropical and sub-tropical areas, and probably imported with food produce into colder locations.

3. *Are immediately amenable to broad control, elimination or eradication by applying one or more of the five public health strategies adopted by the Department for Control of NTDs,*

a) *Preventive chemotherapy* (not applicable)

b) *Intensified Case Management* – Improved diagnostic capability, awareness campaigns for early diagnosis, surgical excision, early institution of antifungal chemotherapy

c) *Vector control*, (not applicable)

d) *Veterinary public health,* (not applicable)

5) *Safe water, sanitation and hygiene* – emphasis on improved cleanliness in at risk populations, requiring adequate water supply

4. *Are relatively neglected by research – i.e., resource allocation is not commensurate with the magnitude of the problem - when it comes to developing new diagnostics, medicines and other control tools* – Chromoblastomycosis is grossly under-researched in public health (basic epidemiology), environmental sources, pathogenesis, especially or remote and satellite lesions, remedies for symptom control, efficacy of all drugs, including the new agents, and immunotherapy.

Alignment with current interventions of the NTD Department

As per the WHO resolution A69/35 for Mycetoma (11/03/16), with which chromoblastomycosis has many similarities, the focus of WHO efforts to minimize the burden of chromoblastomycosis could be:

- Part of WHO general response to overcome the global impact of neglected tropical diseases, focused on interventions;
- facilitate advocacy in support of awareness of both conditions;
- stimulate the generation of further knowledge, especially epidemiological and risk factors information;
- encourage the development of appropriate control tools and strategies, notably the efficacy of existing and future antifungal agents and topical immunotherapy;
- Encourage postgraduate training in the topic to identify evidence-based research priorities
- Support product development partnerships, possibly in association with DNDi;

- Improve access to early diagnosis with microscopy, histopathology and culture
- Improve access to early surgical resection, and therapy with itraconazole (application for inclusion on the WHO EML pending).
- In parallel with Mycetoma, support improved surveillance and therefore control, through WHO Regional offices.

Conclusion

Chromoblastomycosis is a disabling chronic disorder, amenable to early diagnosis and cure, and improvement with current therapies. NTD designation will spur direct engagement of countries most affected with prevention and early diagnosis programs, recognition of the disease in countries where no cases have been reported and development of better approaches to therapy in those with more advanced disease, driven by research.

Key sources and references

1. Queiroz-Telles F, de Hoog S, Santos DW, Salgado CG, Vicente VA, Bonifaz A, Roilides E, Xi L, Azevedo CM, da Silva MB, Pana ZD, Colombo AL, Walsh TJ. Chromoblastomycosis. Clin Microbiol Rev 2017;30:233-276.
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4. de Sousa Mda G, Belda W Jr, Spina R, Lota PR, Valente NS, Brown GD, Criado PR, Benard G. Topical application of imiquimod as a treatment for chromoblastomycosis. Clin Infect Dis 2014;58:1734-7.