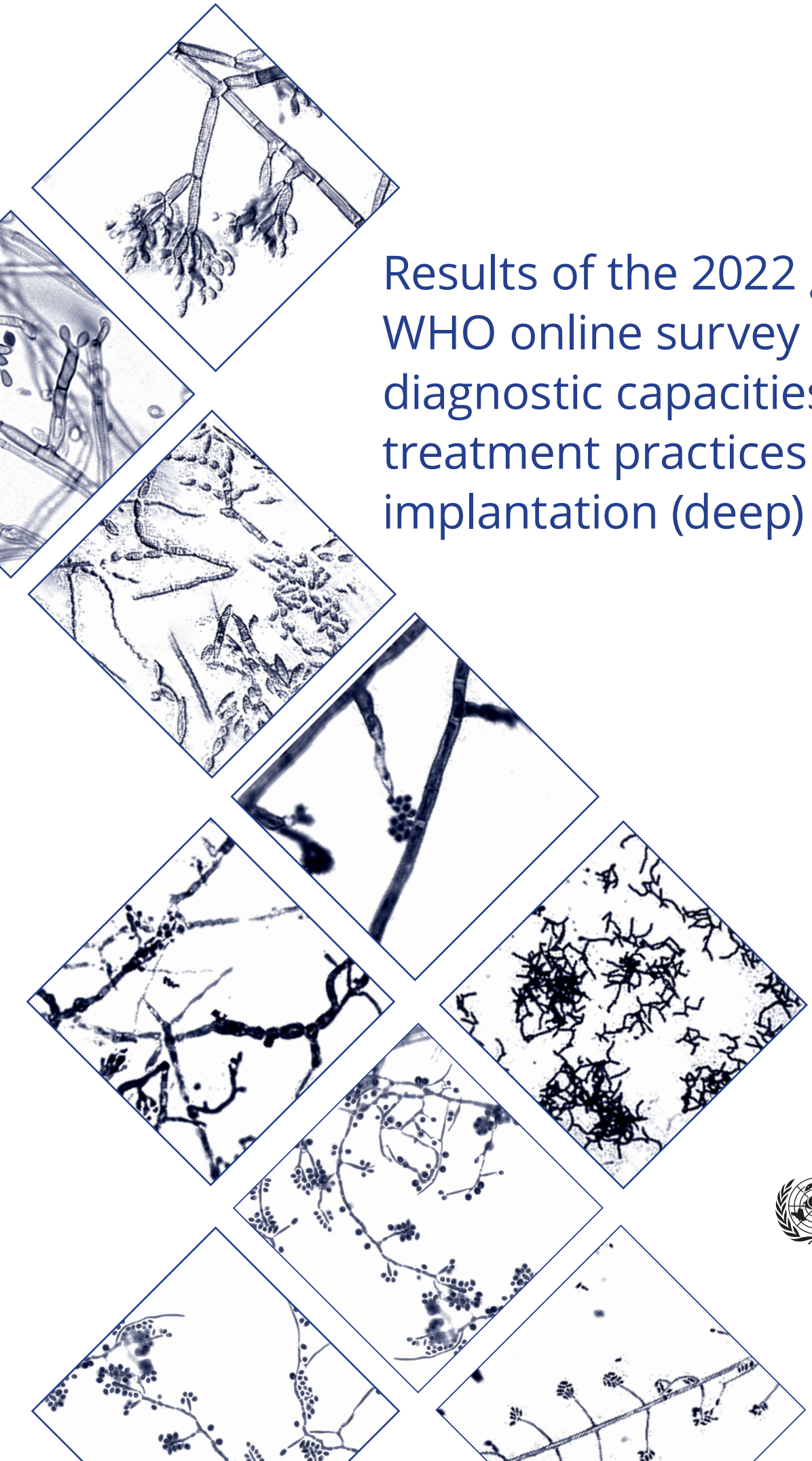

Results of the 2022 global WHO online survey on diagnostic capacities and treatment practices for implantation (deep) mycoses

World Health Organization

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Contents

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1. Introduction

In June 2022, the World Health Organization (WHO) launched a framework for integrated control and management of skin-related neglected tropical diseases ("skin NTDs") that describes how mycetoma, chromoblastomycosis and other deep (implantation) mycoses including sporotrichosis should be addressed and integrated in interventions against skin NTDs and in broader primary health care *(1)*.

Between January and March 2022, WHO conducted a global online survey to collect information on the medicines used to treat subcutaneous or implantation mycoses worldwide. The survey was designed as part of a WHO collaborative project with the United States Food and Drug Administration (USFDA) to identify priority disease areas for pilot testing in CURE ID, a web-based application to help clinicians share their experiences in managing difficult-to-treat infectious diseases and thereby inform clinical research needs to support drug repurposing (**Box 1**).

The survey aimed to collect information on diagnostic capacities and treatment practices in different settings for four implantation mycoses: eumycetoma, actinomycetoma, cutaneous sporotrichosis and chromoblastomycosis (**Box 2**). The survey also enquired about the level of drug repurposing for the four implantation mycoses to provide grounds for the added value and use of CURE ID as a repository of clinical information to inform drug repurposing for treatment of these difficult-to-treat infectious diseases.

In 2021, WHO collected information through an initial enquiry with key informants in middle income countries. The results suggested that there could be added value to collecting information on diagnostic capacity and treatment not only for actinomycetoma and eumycetoma but also for sporotrichosis and chromoblastomycosis. To obtain meaningful information on whether drug repurposing is an important area of scientific advancement for improving treatment options, it was decided to tailor and translate the survey into French and Spanish to reach the widest possible audience and consolidate findings from scientific publications and the initial WHO enquiry.

The 2022 global WHO online survey investigated the use, and value in the use, of the CURE ID platform to inform drug repurposing for implantation mycoses in their non-respondent forms. The outcome of the survey will help WHO to better understand

the epidemiological situation as well as current practice and limitations in the management of these diseases in different regions.

The survey investigated the type of diagnostic methods available in countries within different health care settings (tertiary, secondary, primary level) and the medicines used to treat implantation mycoses, to obtain a better understanding of the level of drug repurposing for treatment of these diseases. The survey also assessed (i) the availability and affordability of the medicines used to treat implantation (deep) mycoses, (ii) the use of non-pharmacological interventions, (iii) the presence of refractory cases and (iv) the rate of loss to follow up.

Mycetoma and chromoblastomycosis were recognized and officially classified as neglected tropical diseases in 2016 *(2)* and 2017 *(3)* respectively. Sporotrichosis, although not officially listed as a neglected tropical disease, was included in the road map for neglected tropical diseases 2021–2030 published by WHO in 2020 ("the road map") as part of the other deep mycoses *(4).*

In 2016, the Sixty-ninth World Health Assembly adopted resolution WHA69.21 on addressing the burden of mycetoma, requesting WHO, inter alia: (i) to include mycetoma among the diseases termed "neglected tropical diseases"; (ii) to support Member States in which mycetoma is endemic to strengthen their capacity to improve early detection and access to treatment; and (iii) to assess the burden of disease and, when necessary, establish disease control measures *(2)*.

Mycetoma and chromoblastomycosis are included in the road map, which sets global targets and milestones to prevent, control, eliminate or eradicate 20 diseases and disease groups in alignment with the Sustainable Development Goals. For the disease group of mycetoma, chromoblastomycosis and other deep mycoses, the road map defines three foundational pillars which will support global efforts to achieve the targets: accelerate programmatic action (pillar 1), intensify cross-cutting approaches (pillar 2), and change operating models and culture to facilitate country ownership (pillar 3).

The first target set for this group of diseases relates to surveillance. As of 2020, 1 out of 30 countries with a burden of the disease had a national control programme and surveillance systems in place for mycetoma. Additional actions outlined in the road map for mycetoma, chromoblastomycosis and other implantation mycoses include development of point-of-care or close point-of-care diagnostics for mycetoma (differentiating its actinomycetoma and eumycetoma forms) and chromoblastomycosis, and evaluation and standardization of skin testing for diagnosis of sporotrichosis.

Treatment regimen efficacy and design of shorter and higher efficacy regimens for mycetoma and chromoblastomycosis are also indicated in the road map.

Box 1. The CURE ID Internet-based repository of clinical data

CURE ID is an internet-based repository that lets the clinical community report novel uses of existing medicines for difficult-to-treat infectious diseases through a website, a smartphone or other mobile device. The platform enables medical information to be crowdsourced from health care providers to facilitate the development of new treatments for neglected diseases and diseases lacking adequate approved therapies. CURE ID is a collaboration between the United States Food and Drug Administration (USFDA) and the National Center for Advancing Translational Sciences, part of the National Institutes of Health (NCATS/NIH). Both agencies are also collaborating with WHO and the Infectious Diseases Society of America (IDSA) to assess the global utility of CURE ID.

The CURE ID platform serves as a treatment registry and captures clinical outcomes when medicines are used for new conditions, in new populations, in new doses or in new combinations. Healthcare professionals generally may choose to prescribe or use a legally marketed human medicine or medical device for an unapproved or uncleared use when they judge that the unapproved use is medically appropriate for an individual patient. The systematic collection of real-world experience in CURE ID will help identify existing drug candidates for additional study, encourage further drug development and serve as a resource for physicians to share information where no product approved by USFDA exists for the indication. Repurposing approved drugs for new clinical uses can offer an efficient drug-development pathway for treatments of diseases and conditions that have few or no therapeutic options due to limited financial incentives.

See CURE ID: investigating drug repurposing opportunities to treat challenging infections *(5)*.

Box 2. Summary of the implantation (deep) mycoses considered in the survey

Implantation or deep mycoses include a heterogeneous group of fungal diseases that develop at the site of transcutaneous trauma. Also known as "subcutaneous mycoses", some implantation mycoses may involve muscles, fascia, cartilage and bones, beyond the skin and the subcutaneous tissues. Hence the use of the more precise term "implantation mycoses".

Mycetoma results from infection with several microorganisms of bacterial or fungal origin; based on its causative agent the disease is classified as actinomycetoma (bacterial mycetoma) or eumycetoma (fungal mycetoma). The disease causes chronic infection of skin, connective tissue, muscle and bone, eventually leading to deformities and disabilities. The clinical presentation is a combination of a painless subcutaneous mass, multiple sinuses and discharge of grains. Bone invasion is not uncommon, and, in some cases, even repeated surgery cannot control progression of the disease. It is associated with severe morbidity and increased mortality. The mode of transmission is not well understood; the disease affects people of all ages and is more common in men than in women; it affects mainly poor people who work in agriculture (farming and livestock breeding).

Chromoblastomycosis and sporotrichosis are transmitted by traumatic inoculation of relevant microorganisms through broken skin. Chromoblastomycosis is a chronic fungal infection of the skin and subcutaneous tissue caused by a group of fungi; the three most common species are *Fonsecaea pedrosoi, Cladophialophora carrionii* and *Phialophora verrucose*. Chromoblastomycosis causes lesions that are clinically polymorphic, the most frequent being nodular, verrucous and tumoral. Chromoblastomycosis affects poor people working in rural areas in which spiny plants are common and wearing of protective clothing or shoes is lacking.

Sporotrichosis is an infection caused by dimorphic fungi of the genus *Sporothrix*. It occurs in three clinical forms: cutaneous, pulmonary and disseminated. Sporotrichosis causes skin lesions that are commonly single nodules or ulcers or chains of nodules. *Sporothrix brasiliensis*, associated with animal infections and zoonotic transmission through deep scratches and bites from infected animals, mainly cats, is the most prevalent cause of the disseminated infection.

Implantation mycoses are mainly prevalent in tropical and subtropical areas. Mycetoma, chromoblastomycosis and cutaneous sporotrichosis occur mainly among rural populations with low socioeconomic status, and many cases progress because they are not diagnosed and recognized early by most health workers.

2. Methods

The WHO survey was conceptualized using a mix of information sources: published literature on diagnostic and treatment methods, and interviews with key informants. This survey was conducted as part of the WHO collaborative project on CURE ID with USFDA, extending the scope to include the other deep (implantation) mycoses. The initial enquiry was conducted with around 10–12 key informants (international and national experts on the subject) to investigate diagnostic and clinical practices in middle income countries. The survey preparation relied on a 2019 article co-authored by more than 20 experts on implantation mycoses for the diagnostic methods *(6)*.

The draft survey questions were reviewed and improved with feedback provided by WHO, the USFDA, the CURE Drug Repurposing Collaboratory and external WHO advisors for neglected tropical diseases. The survey was designed using multiple-choice lists (as an example for diagnostic methods, pharmacological treatment and non-pharmacological interventions). An option was available for participants to provide additional entries and comments.

The survey was translated into French and Spanish. The preliminary enquiry with key informants indicated that in order to reach the widest possible audience, the survey should be translated to ensure participation from WHO's African and Americas regions. It was created using a WHO official survey tool and opened on 7 January 2022. The survey was disseminated extensively through different channels: key informants of the initial enquiry; global and regional associations on dermatology, mycology and NTDs; working groups on implantation mycoses; experts and authors' articles; and social media.

On 17 February 2022, a webinar was organized to launch and disseminate the survey *(7)*. The survey was closed on 15 March 2022. The preliminary analysis was shared and feedback from WHO, the USFDA, the CURE Drug Repurposing Collaboratory and external WHO advisors on neglected tropical diseases was incorporated. This prompted additional analysis where feasible, such as the sub-analysis on diagnostic methods.

Limitations of the survey

The survey was conceptualized to collect mainly qualitative information on the type of diagnostic methods available in the participant setting, the medicines used, the type of non-pharmacological interventions and the presence of refractory cases, as well as eventual comments on each of these aspects. A question was also included on affordability and availability of medicines in the participant setting to investigate if these had an impact on the selection and use of medicines, and hence on drug repurposing. The survey provided a qualitative indication on all these aspects, which was considered in light of the number and profile of respondents. The survey did not collect direct information on treatment regimens and treatment outcomes. Reference is made to the survey questions in **Annex 1**.

3. Main findings

The global WHO online survey on four implantation mycoses (eumycetoma, actinomycetoma, cutaneous sporotrichosis and chromoblastomycosis) collected information from 142 respondents from 47 countries, from all continents: 60% from middle income countries, with 59% working at the tertiary level of the health system and 30% at the secondary level. The main findings should be considered in light of the respondents' profiles: 85% were from high and middle income countries; hence this analysis is scarcely representative of low-income countries.

In relation to diagnostic methods, in addition to clinical features and visual inspection (86%), fungal culture was the most available method (85%), followed by grains direct microscopy (79%) and histopathology on skin biopsy (72%). Bacterial culture for actinomycetoma was less available (67%). Molecular diagnosis is reported as available to 42%, while serology and epiluminescence microscopy (ELM) are reported to be available at 23%. MALDI-TOF (matrix-assisted laser desorption ionization time-of-flight) was indicated as an additional technique. Disaggregated data show that diagnostic methods for implantation mycoses are available at tertiary and secondary levels, with similar trends. At primary level, there is a generalized trend for lower availability of diagnostic techniques other than visual inspection.

The survey found that there is considerable drug repurposing occurring in all four implantation mycoses, with respondents outlining also medicines that were not included in the survey list. The survey confirms a certain level of repurposing for eumycetoma, chromoblastomycosis and cutaneous sporotrichosis beyond itraconazole as first choice (85–90%) and terbinafine for refractory cases (44–56%). For eumycetoma and chromoblastomycosis, newer generation azoles (posaconazole and voriconazole) were also reported as used (27–41%). Older generation azoles are reportedly still used for eumycetoma (oral ketoconazole at 30%) and for chromoblastomycosis. Amphotericin B injectable is considerably used for eumycetoma (36%). For chromoblastomycosis, there is a lower but consistent use of flucytosine (14%) and topical imiquimod (11%). For cutaneous sporotrichosis, there is considerable use of oral potassium iodide (44%). For actinomycetoma, several antibiotics/antibacterics from several classes are used in oral and injectable forms, suggesting a high level of drug repurposing. Among the used medicines are dapsone (30%), rifampicin oral (27%), carbapenems injectable (23%) and fosfomycin oral (10%).

In terms of non-pharmacological treatments, the survey indicates that surgery is applied in the treatment of eumycetoma (82%), with cryotherapy/hyperthermia also rarely reported (< 3%). For chromoblastomycosis, non-pharmacological interventions are used/applied (53%). In addition to heat therapy (23%), cryotherapy/cryosurgery (14%) and surgery/surgical excision (15%) were found to be also consistently used/applied. The survey provides indications on levels of refractory cases for chromoblastomycosis (68%) and for cutaneous sporotrichosis (34%).

The survey reveals and confirms that the level of drug repurposing is limited by restricted availability and/or affordability of medicines in the respondents' countries.

Although with several limitations, the survey provides interesting indications on diagnostic capacity and treatment trends as well as challenges for implantation mycoses globally, especially but not only in middle income countries. These findings could prompt additional and more in-depth investigations to inform strategies and actions of the road map for the implantation mycoses. The survey confirmed that the CURE ID platform could be a useful tool for collection of clinical case reports for these diseases, considering that in addition to drug repurposing outcomes, the collected data could have a major value in the light of the absence of surveillance systems in countries for these diseases.

4. Analysis

4.1 Respondents' profile: country, setting and role

Of the 318 people who attempted to participate in the online survey, 142 provided complete answers and 138 declared their country (**Annex 2**). The survey respondents were from 47 countries, from all continents: North and sub-Saharan Africa, Asia, Europe, Latin America, Middle East, North America and Oceania (**Table 4.1A**, **Fig. 4.1A**). The analysis of the survey respondents and their countries by WHO region shows that the highest number of respondents were from the Region of the Americas, followed by the African, European and South-East Asia regions. In terms of national coverage, the African Region was the most represented region followed by the Region of the Americas (**Table 4.1B**, **Fig. 4.1B**).

The vast majority of respondents were from upper and lower middle income countries (60%), hence the purpose of the survey to provide information on the level of drug repurposing in middle income countries was achieved. There were also 35 (25%) respondents from 12 high income countries, while respondents from low income countries were only 16 (12%). (**Table 4.1C**, **Fig. 4.1C**).

Some 85% of respondents who completed the survey provided their name and address to be informed of the results of the survey and on additional activities/initiatives related to implantation mycoses.

Table 4.1A. Indication of geographical distribution by continent

Continent	Total no. of countries	Total no. of respondents disclosing country	Percentage
Africa (North and sub-Saharan)	20	36	26%
Asia	6	31	22%
Europe	7	28	20%
Latin America	9	35	25%
Middle East	1	4	3%
North America	1	1	1%
Oceania	2	3	2%

Fig. 4.1A. **Indication of geographical distribution by continent**

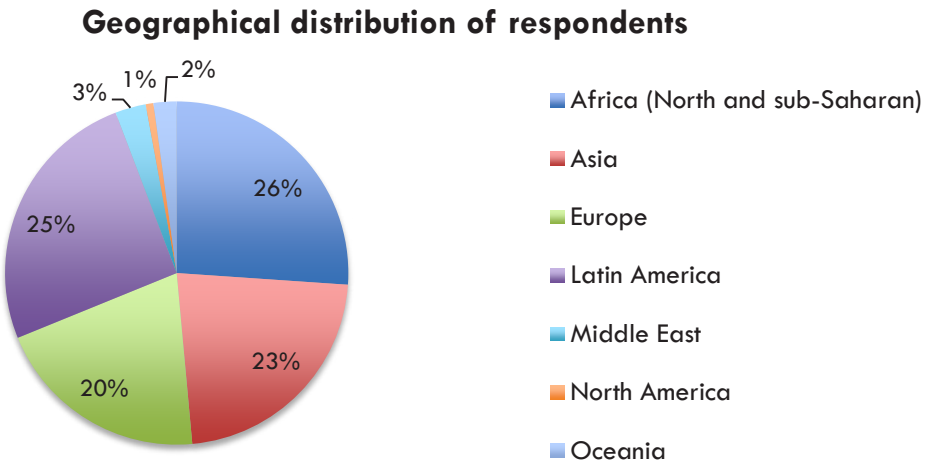
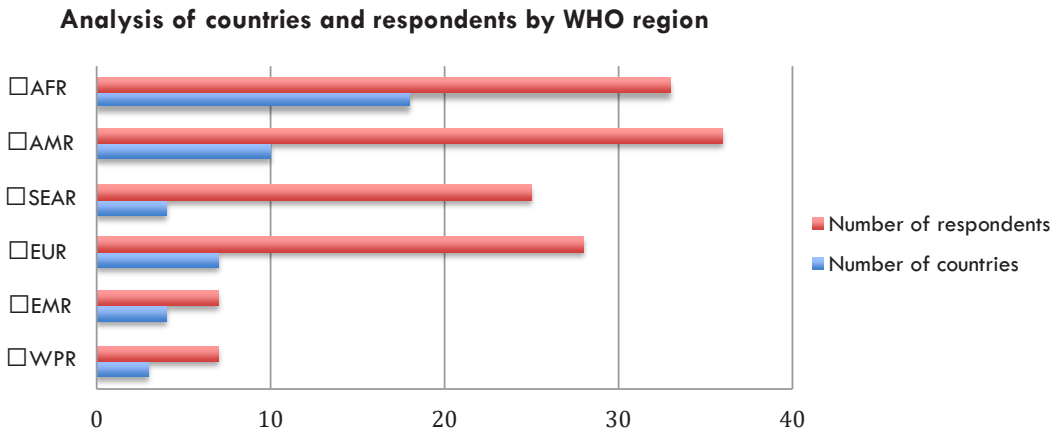


Table 4.1B. **Number of countries and respondents by WHO region**

WHO region	No. of countries	No. of respondents
African	18	33
Americas	10	36
South-East Asia	4	25
European	7	28
Eastern Mediterranean	4	7
Western Pacific	3	7

Fig. 4.1B. Number of countries and respondents by WHO region



AFR: African Region: AMR: Region of the Americas; SEAR: South-East Asia Region; EUR: European Region; EMR: Eastern Mediterranean Region; WPR: Western Pacific Region.

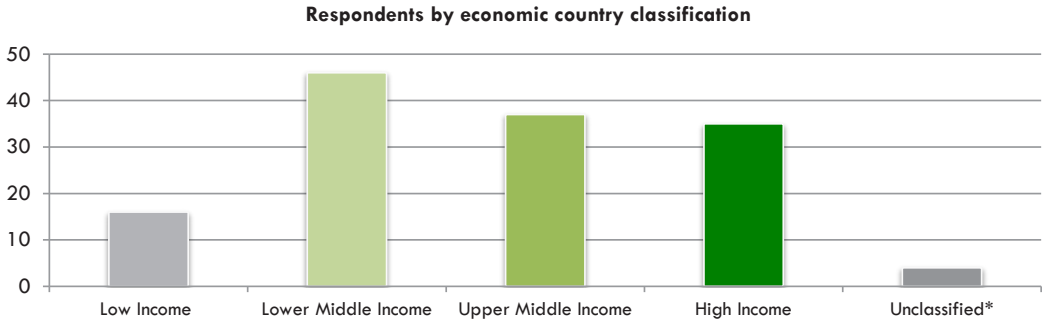
Table 4.1C. Indication of country level income for respondents

World bank country classification (2022–2023)[a]	Total no. of countries	Total no. of respondents disclosing country	Percentage
Low income	8	16	12%
Lower middle income	15	46	33%
Upper middle income	11	37	27%
High income	12	35	25%
Unclassified[b]	1	4	3%

a *Source*: New World Bank country classifications by income level: 2022–2023 (https://blogs.worldbank.org/opendata/new-world-bank-country-classifications-income-level-2022-2023).

b Bolivarian Republic of Venezuela

Fig. 4.1C. Indication of country level income for respondents



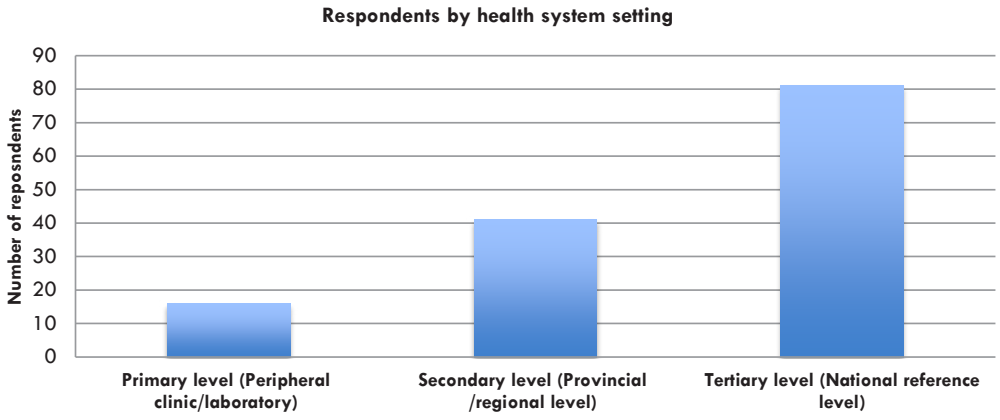
Source: New World Bank country classifications by income level: 2022–2023 (https://blogs.worldbank.org/opendata/new-world-bank-country-classifications-income-level-2022-2023).

Of the 142 respondents, 138 disclosed their work settings: 59% (81) reported working at tertiary level (national reference level), 30% (41) working at secondary level (at provincial/regional level) and 11% (16) reported working at primary level (peripheral clinic or laboratory). Four (3%) respondents did not answer this question (**Table 4.1D**, **Fig. 4.1D**).

Table 4.1D. Respondents by health system setting

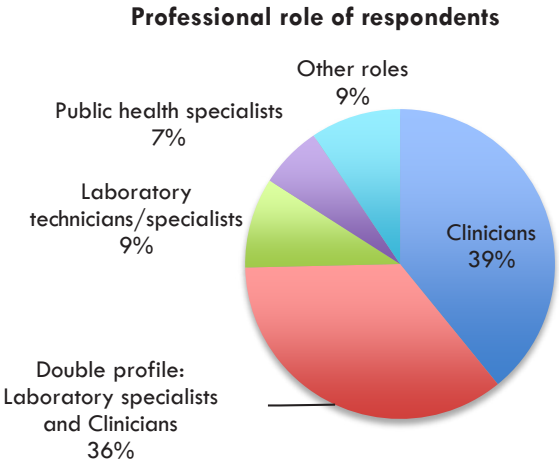
Setting	No. of respondents (138)	Percentage of respondents
Primary level (peripheral clinic/laboratory)	16	11%
Secondary level (provincial /regional level)	41	30%
Tertiary level (national reference level)	81	59%

Fig. 4.1D. Respondents by health system setting



Of the 142 respondents, 138 disclosed their professional role: 39% (54) categorized themselves as clinicians, 36% (49) as having a double profile as laboratory specialists and clinicians, 9% (13) as laboratory technicians/specialists, 7% (9) as public health specialists, and 9% (13) categorized themselves as having other roles (pharmacist, mycologists, researchers, consultant, professor) (**Fig. 4.1E**).

Fig. 4.1E. Respondents by professional role



4.2 Diagnostic techniques

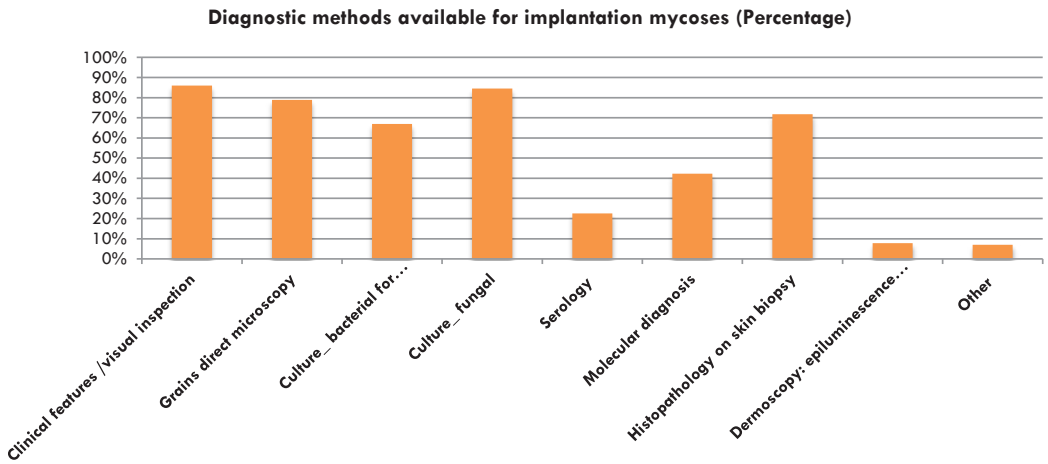
The respondents provided data on the diagnostic techniques available in their setting for the diagnosis of implantation mycoses: 86% use clinical features/visual inspection; grains direct microscopy and histopathology on skin biopsy are available for respectively 79% and 72% of respondents. Bacterial culture for actinomycetoma is available to 67% of respondents, while fungal culture to 85%. Molecular diagnosis is reported as available to 42%, while serology to 23%. Dermoscopy: epiluminescence microscopy is reported as available for 23% of respondents. Of the other techniques not listed but indicated by 11/142 respondents (8%), MALDI-TOF was listed by four respondents (from Cameroon, Colombia, India and Uruguay). (See **Table 4.2A** and **Fig. 4.2A**.) Some 33 respondents provided comments on the techniques available in their setting. The comments highlighted the need to have referential system for molecular diagnosis and for drug susceptibility testing. A few mentioned that while techniques may be available in their setting, reagents and specific primers may not be available. Sequencing was also mentioned by two respondents (from Brazil and China).

Table 4.2A. Diagnostic methods available for implantation (deep) mycoses indicated by respondents

Diagnostic methods	Indicated use by respondent	Percentage
Clinical features /visual inspection	122	86%
Grains direct microscopy	112	79%
Culture – bacterial for actinomycetoma	95	67%
Culture – fungal	120	85%
Serology	32	23%
Molecular diagnosis	60	42%
Histopathology on skin biopsy	102	72%
Dermoscopy: epiluminescence microscopy	33	23%
Other:	11	8%
• MALDI-TOF[a]	4	

a Matrix-assisted laser desorption/ionization time-of-flight.

Fig. 4.2A. Diagnostic methods available for implantation mycoses indicated by respondents



The data collected on available diagnostic methods for implantation mycoses has been further analysed to see if there were different patterns of availability by health system level. This analysis shall be considered in view of the fact that 85% of respondents are from high and middle income countries; hence this analysis is poorly representative of low income countries. The disaggregation of data by number of respondents and

as percentage shows that a number of diagnostic methods for implantation mycoses are available at tertiary and secondary levels with similar trends. At primary level, there is a generalized trend for lower availability of diagnostic techniques other than visual inspection. Grains direct microscopy is indeed available only at 56%, bacterial culture for actinomycetoma available at 38%, molecular diagnosis and histopathology on skin biopsy at 31%, and epiluminescence microscopy at 13%. From this survey, serology seems barely available and used in the diagnosis of implantation mycosis across the three levels (range of 21– 25%) (**Table 4.2B**).

Table 4.2B. Disaggregated data on diagnostic methods available by level of the health system

Diagnostic methods	Tertiary level		Secondary level		Primary level	
	Indicated use by respondent (81)	Percentage	Indicated use by respondent (41)	Percentage	Indicated use by respondent (16)	Percentage
Clinical features/visual inspection	70	86%	38	93%	14	88%
Grains direct microscopy	66	81%	37	90%	9	56%
Culture – bacterial for actinomycetoma	58	72%	31	76%	6	38%
Culture – fungal	72	89%	36	88%	12	75%
Serology	17	21%	11	27%	4	25%
Molecular diagnosis	38	47%	17	41%	5	31%
Histopathology on skin biopsy	65	80%	32	78%	5	31%
Dermoscopy: epiluminescence microscopy	22	27%	9	22%	2	13%
Other	9	11%	2	5%	0	0%

The above analysis and the comments provided by the respondents, the majority of whom work at tertiary or secondary levels, suggest that national diagnostic capacity should be investigated further in low and middle income countries in terms of referral systems (for molecular diagnosis as an example), running capacity (availability of reagents/specific primers) and additional needs (drug susceptibility testing).

Consideration for the CURE ID platform: The survey's answers confirm that a case report form tailored to implantation mycoses shall include these diagnostic techniques to facilitate data entry (including MALDI-TOF).

4.3 Eumycetoma

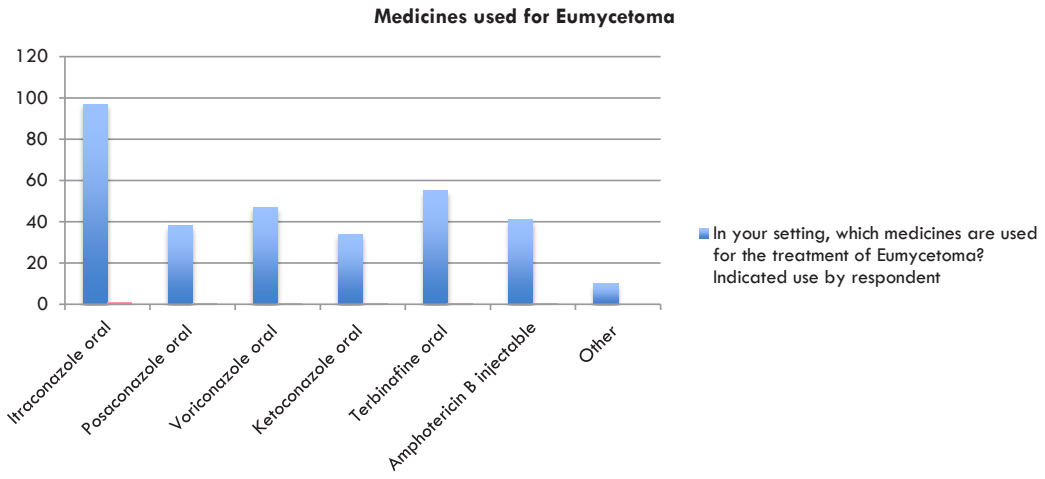
4.3.1 Medicines used for treatment

Some 28 of the total survey respondents (142) did not treat this disease. Itraconazole is the most used medicine (85%) followed by terbinafine (48%). However, as indicated by the percentages, the respondents treating this disease do not use itraconazole in all settings. Posacolazole and voriconazole are indicated as used by respectively 33% and 41% of respondents mainly in high-income countries and certain middle income countries. Interestingly, oral ketoconazole is still used by 30% of respondents, despite its toxicity. Among "other medicines used", fluconazole and also griseofulvin have been listed, although at the development of the survey we did not expect these medicines to be used. Amphotericin B injectable is indicated as used by 36% of respondents; one respondent also indicated the use of its liposomal form. (See **Table 4.3A** and **Fig. 4.3A**.)

Table 4.3A. Medicines used to treat eumycetoma

Medicine	Indicated use by respondent (114)	Percentage
Itraconazole oral	97	85%
Posaconazole oral	38	33%
Voriconazole oral	47	41%
Ketoconazole oral	34	30%
Terbinafine oral	55	48%
Amphotericin B injectable	41	36%
Others:	10	9%
• Fluconazole oral (3)		
• Griseofulvin (2)		
• Liposomal amphotericin B injectable		
• Isavuconazole		
• Dapsone		
• Olorofim		

Fig. 4.3A. Medicines used for eumycetoma



The respondents' comments related to the medicines used for eumycetoma indicated that while itraconazole is the first option, it is very expensive and not always available. In one setting, the respondent indicated that itraconazole is ordered overseas for patients who can afford it. Also terbinafine, used for refractory cases, is indicated by a few comments as expensive. Affordability is mentioned in several instances in the comments, explaining as an example that fluconazole and ketoconazole are indeed used because they are more affordable than other antifungal agents.

"Itraconazole and terbinafine are often unavailable and expensive. Because of these, patients are often started on or switched to available and less expensive antifungals; ketoconazole or fluconazole, even though these drugs are not recommended for treatment of eumycetoma."

The data and comments to this answer confirm that itraconazole is the most used medicine, although not in all settings due to lack of availability and/or affordability. Surprisingly, ketoconazole is still used in a considerable manner (30%), probably due to its low cost in relation to other azoles. Posaconazole and voriconazole seem available in high-income countries and certain middle income countries. Amphotericin B injectable is also used considerably (36%). The survey confirms a certain level of drug repurposing beyond itraconazole as first choice and terbinafine for refractory cases.

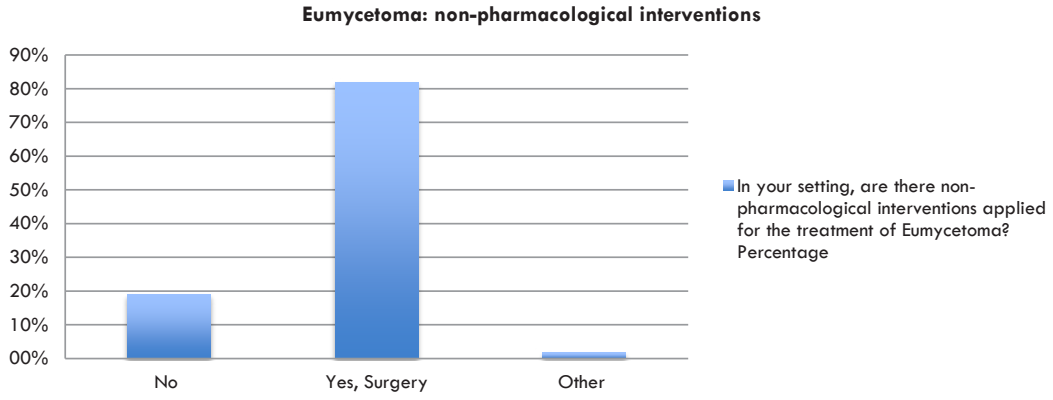
4.3.2 Non-pharmacological interventions

Some 32 of the total survey respondents (142) did not answer this question: 82% indicated that surgery is applied in their setting for the treatment of eumycetoma. Three respondents indicated the use of other non-pharmacological interventions: cryotherapy, hyperthermia and debridement (**Table 4.3A**, **Fig. 4.3B**).

Table 4.3B. Non-pharmacological interventions applied for the treatment of eumycetoma

Answer	Indicated use by respondent (110)	Percentage
None	21	19%
Surgery	90	82%
Others:	3	3%
• Hyperthermia and/or cryotherapy		
• Cryotherapy		
• Wound care, debridement		

Fig. 4.3B. Non-pharmacological interventions applied for the treatment of eumycetoma



In the comments, a few respondents indicated that surgery is applied jointly with pharmacological treatment in difficult cases. Surgical excision is applied jointly (in 2–3 phases) during pharmacological treatment. Amputation was also mentioned in two comments for cases, which presented too late to treatment, with one comment indicating that amputation may not be resolutive.

The survey confirms that surgery (and very rarely cryotherapy and/or hyperthermia) is applied in the treatment of eumycetoma in over 80% of the settings. Nevertheless, the extent and modality of surgical applications for eumycetoma cannot be defined through the survey and it shall be investigated further.

Consideration for the CURE ID platform: The survey's answers confirm that a case report form tailored to implantation mycoses shall also include or facilitate data entry for surgical techniques applied for eumycetoma cases and that additional investigation to categorize these techniques and the patient disease stage may be needed to understand the outcomes of the combination treatment (pharmacological/non-pharmacological).

4.4 Actinomycetoma

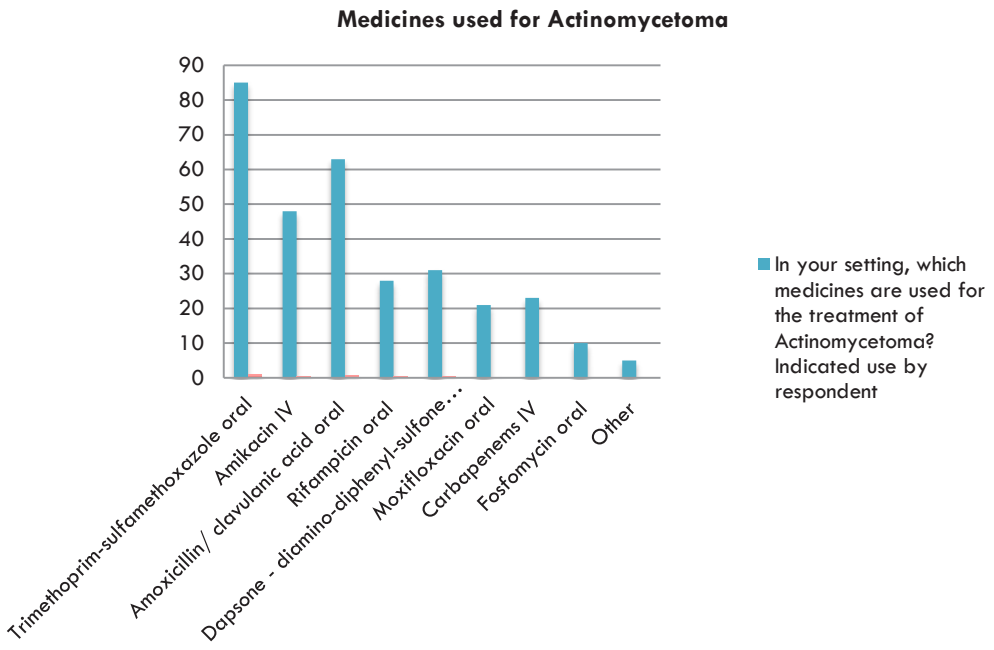
4.4.1 Medicines used for treatment

Some 40 of the total survey respondents (142) did not treat this disease. The medicines most used to treat actinomycetoma include trimethoprim–sulfamethoxazole oral (83%) and amoxicillin/clavulanic acid oral (62%). Amikacin IV is used by 47% of respondents; dapsone and rifampicin are used respectively by 30% and 27% of respondents. There is also a considerable use of injectable carbapenems (23%), moxifloxacin oral (21%) and fosfomycin oral (10%). Among other medicines used for actinomycetoma, five respondents indicated levofloxacin oral, clindamycin oral, gentamicin intravenous, doxycycline oral, rifampicin oral and isoniazid oral. (**Table 4.4A** and **Fig. 4.4A**.)

Table 4.4A. Medicines used to treat actinomycetoma

Medicine	Indicated use by respondent (102)	Percentage
Trimethoprim + sulfamethoxazole oral	85	83%
Amikacin IV	48	47%
Amoxicillin + clavulanic acid oral	63	62%
Rifampicin oral	28	27%
Dapsone - diamino-diphenyl-sulfone (DDS) oral	31	30%
Moxifloxacin oral	21	21%
Carbapenems IV	23	23%
Fosfomycin oral	10	10%
Other	5	5%

Fig. 4.4A. Medicines used for actinomycetoma



Of the 12 respondents who provided comments, three indicated that the drug combination or choice of medicines is based on culture strain identification or other diagnostic identification technique (microscopy, culture, polymerase chain reaction) and drug susceptibility testing. One comment indicated that treatment is tailored to the type of patient and his or her commitment to treatment. A few comments related to the affordability and availability of medicines. One respondent indicated that amoxicillin + clavulanic acid is available but too expensive in its setting. Two comments indicated difficulty in sourcing dapsone as well as amikacin injectable. The availability of dapsone and rifampicin was also mentioned as linked to disease-specific treatments (leprosy multidrug therapy and antituberculosis regimens respectively). Two comments indicated the toxicity of amikacin for massive lesions or/and long treatment duration (6–12 months).

The survey confirms that there is a certain level of drug repurposing happening for treatment of actinomycetoma. The collection of data (both retrospective and prospective) on treatment combinations, up-front drug susceptibility testing and etiological agents may help inform better outcomes of treatment and possibly constitute observational data to inform treatment guidelines and clinical research. The survey cannot draw conclusions, other than confirming the use of the listed medicines (ranging from 83% to 10%), and also a considerable use of injectable medicines (amikacin at 47%, carbapenems at 23%).

4.5 Chromoblastomycosis

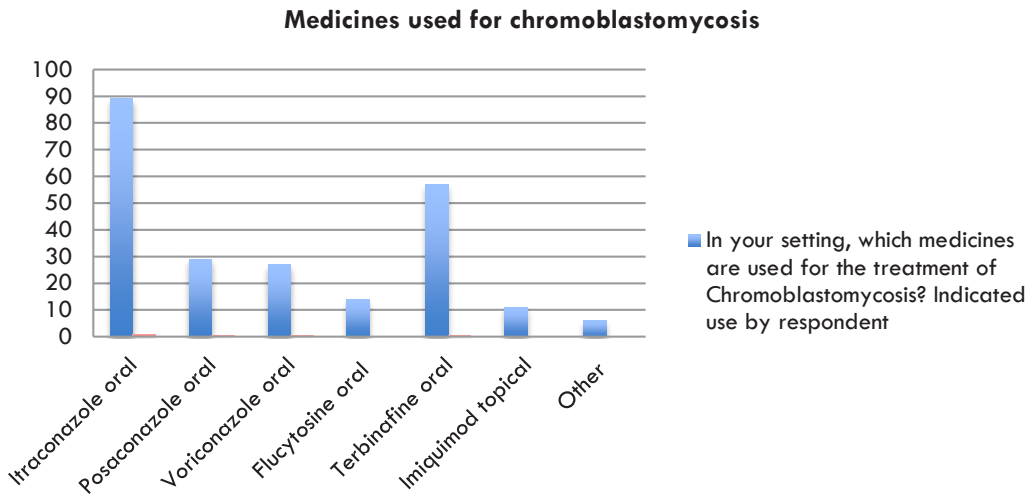
4.5.1 Medicines used for treatment

Some 41 of the total survey respondents (142) did not treat this disease. Itraconazole is the medicine most used to treat chromoblastomycosis (88%), followed by terbinafine (56%); posaconazole (29%) and voriconazole are also used (27%). The respondents reported also a lower but consistent use of flucytosine (14%) and topical imiquimod (11%). Another five medicines were listed by respondents: potassium iodide, isavuconazole, fluconazole, fluorouracil topical and amphotericin B. (See **Table 4.5A**, **Fig. 4.5A**.)

Table 4.5A. Medicines used to treat chromoblastomycosis

Medicine	Indicated use by respondent (101)	Percentage
Itraconazole oral	89	88%
Posaconazole oral	29	29%
Voriconazole oral	27	27%
Flucytosine oral	14	14%
Terbinafine oral	57	56%
Imiquimod topical	11	11%
Other	5	6%
• Potassium iodide	2	

Fig. 4.5A. Medicines used for chromoblastomycosis



The comments provided to this question by around 25 respondents relate to the reporting that often chromoblastomycosis pharmacological treatment is combined with cryosurgery or surgery, with cryosurgery applied for small lesions. One respondent also indicated that itraconazole is prescribed as the first choice and terbinafine as the second choice. One indicated that relapse cases are prescribed a combination of medicines. A few comments also related to lack of availability, non-inclusion in health system schemes and out-of-pocket expenses for patients.

The survey confirms a certain level of drug repurposing beyond itraconazole as first choice and terbinafine for refractory cases. In addition to other antifungal azoles (posaconazole and voriconazole), the survey highlights repurposing of flucytosine oral and imiquimod topical for treatment of chromoblastomycosis.

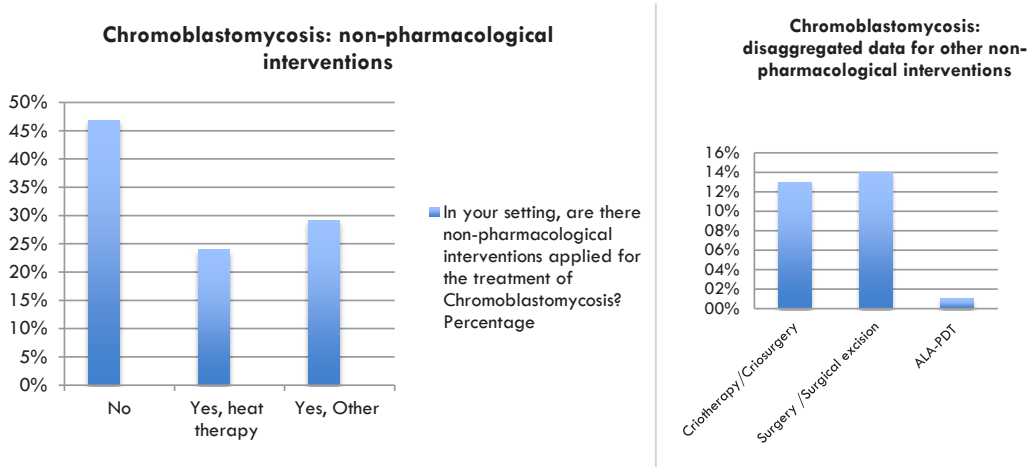
4.5.2 Non-pharmacological interventions

Some 42 of the total survey respondents (142) did not treat this disease. The information collected through the survey indicates that for 47% of respondents only pharmacological interventions are applied for treatment of chromoblastomycosis; for the remaining 53% non-pharmacological interventions are also used. In addition to heat therapy (24%), cryotherapy/cryosurgery (14%) and surgery/surgical excision (15%) are also used. One respondent from China also indicated 5-aminolevulinic acid photodynamic therapy (ALA-PDT). (See **Table 4.5B** and **Fig. 4.5B**).

Table 4.5B. Non-pharmacological interventions applied for the treatment of chromoblastomycosis

Answer	Indicated use by respondent (96)	Percentage
None	45	47%
Heat therapy	23	24%
Other	28	29%
• Cryotherapy/cryosurgery	13	14%
• Surgery/surgical excision	14	15%
• 5-aminolevulinic acid photodynamic therapy (ALA-PDT)	1	1%

Fig. 4.5B. Non-pharmacological interventions applied for the treatment of chromoblastomycosis



The comments provided indicated that cryosurgery is used in combination with itraconazole and/or terbinafine, which is a valid method for small individual lesions combined with oral treatment when monotherapy is not working well. Comments indicated also that cryotherapy is used instead of increasing dosage and toxicity, in selected cases. One comment seems to suggest that use of non-pharmacological methods should be considered in light of itraconazole and terbinafine, being often unavailable and too expensive. Two comments indicated that some patients with a long treatment history and large lesions may need surgery as adjuvant therapy.

The survey confirms that non-pharmacological interventions including heat therapy, cryotherapy/cryosurgery and surgery are applied for treatment of chromoblastomycosis in 53% of settings. Nevertheless, the extent and modality of their applications for chromoblastomycosis shall be investigated further.

Consideration for the CURE ID platform: The survey's answers confirm that a case report form tailored to implantation mycoses shall also include or facilitate data entry for non-pharmacological interventions applied for treatment of chromoblastomycosis. Also in this case, it may be worth categorizing or defining these techniques and the patient's disease stage in order to standardize data entry and to better understand the outcomes of combination treatment (pharmacological/non-pharmacological).

4.5.3 Refractory cases

Some 68% of the respondents to this question reported refractory cases of chromoblastomycosis in their setting (**Table 4.5C**). Comments related to refractory cases suggest that they are caused by disease severity, late diagnosis, and interruptions of treatment (also due to cost and length), which result in increased severity of the lesions and relapses. Refractory cases do not seem linked to antifungal resistance as per the provided comments. Comments were also made on the incapacity to perform tests and diagnose at peripheral level. Two comments made scientific considerations on refractory forms.

Table 4.5C. Refractory cases of chromoblastomycosis

Answer	Indicated by respondent (83)	Percentage
Yes	56	68%
No	26	32%

"After treatment for about 2 years, most of the skin lesions have subsided, and the patients stop taking drugs by themselves, and the skin lesions relapse and aggravate. So we need plus surgery, hyperthermia and cryotherapy."

"In refractory cases we increase the drug dosage, associate two different drugs, perform combined treatment with surgical excision and/or cryotherapy."

The survey's respondents reported a very high percentage of refractory cases of chromoblastomycosis (nearly 70%) with an indication through the provided comments that these cases are caused primarily by late diagnosis and interruption of treatment.

Consideration for the CURE ID platform: A tailored case report form shall also include features to capture refractory form definition and causes (if feasible).

4.6 Cutaneous sporotrichosis

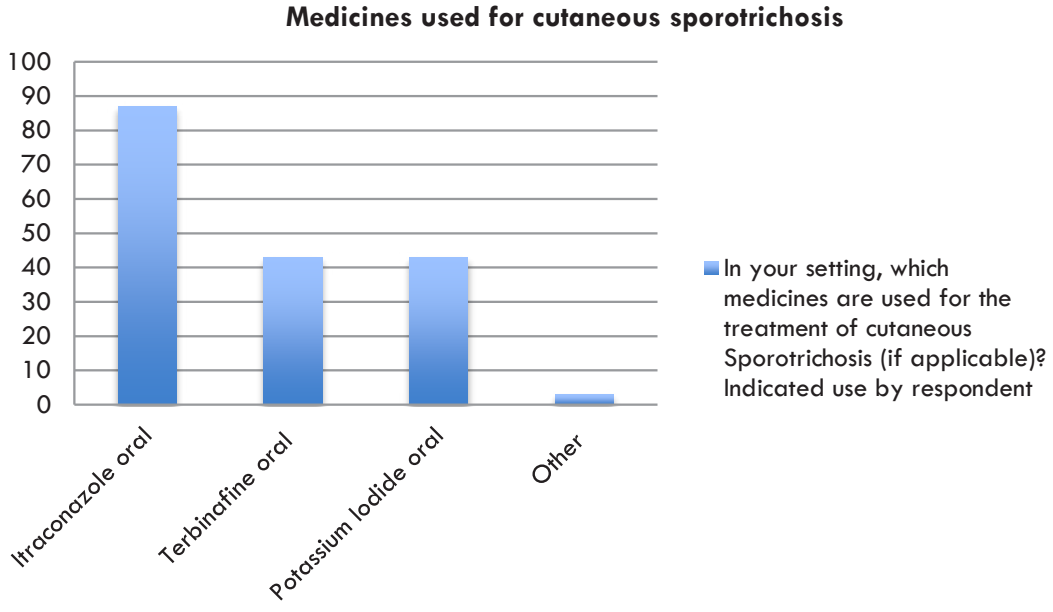
4.6.1 Medicines used for treatment

Some 45 of the total survey respondents (142) did not treat this disease; 90% reported using itraconazole and also indicated considerable use of both terbinafine oral and potassium iodide oral (both at 44%). The respondents indicated minor use of additional medicines (two indicated using alternative azoles and one liposomal amphotericin B). One respondent also indicated the use of cryotherapy as a non-pharmacological intervention (**Table 4.6A** and **Fig. 4.6A**).

Table 4.6A. Medicines used to treat cutaneous sporotrichosis

Medicines	Indicated use by respondent (97)	Percentage
Itraconazole oral	87	90%
Terbinafine oral	43	44%
Potassium iodide oral	43	44%
Other	3	3%
• Fluconazole		
• Voriconazole or/and posaconazole (if itraconazole is not tolerated)		
• Liposomal amphotericin B		

Fig. 4.6A. Medicines used for chromoblastomycosis



Some 68% of the respondents to this question reported refractory cases of chromoblastomycosis in their setting (Table 4.5C). Comments related to refractory cases The comments provided related to different aspects: geographical distribution of the disease, therapeutic protocols as well as availability and affordability of medicines. Two comments highlighted that sporotrichosis is hyperendemic in certain regions of Brazil. China seems to have a standardized protocol for treatment of chromoblastomycosis.[1] One comment indicated use of cryotherapy in combination with oral treatment, with reported success and a publication expected by the end of 2022.

A few comments concerned the affordability and/or availability of medicines. One respondent from China indicated the incapacity to obtain potassium iodide oral as it is not procured through a commercial pharmaceutical company. Terbinafine is also reported as not available in one country.

4.6.2 Refractory cases

Some 34% respondents to this question reported refractory cases of cutaneous sporotrichosis in their setting (**Table 4.6B**). A few respondents provided comments on refractory cases of sporotrichosis. Two comments suggest investigating the disseminated cases of sporotrichosis. From the comments, it seems that also for cutaneous sporotrichosis some cases are refractory due to interruption of treatment (high cost/long duration) or late diagnosis. Potassium iodide and terbinafine are used for treatment of refractory cases, alone or in combination with first-line itraconazole (at higher dosage). One comment referred also to heat therapy use for refractory cases.

One respondent indicated that several studies are ongoing in a specialized clinic in Rio de Janeiro (Brazil) concerning diagnostic methods and treatment options for zoonotic sporotrichosis transmitted by cats, caused by infection with *Sporothrix brasiliensis*.

Table 4.6B. Refractory cases of cutaneous sporotrichosis

Answer	Indicated use by respondent (87)	Percentage
Yes	29	34%
No	57	66%

The survey confirms a certain level of drug repurposing beyond itraconazole as first choice, with oral terbinafine and oral potassium iodide also used considerably to treat cutaneous sporotrichosis.

The comments indicate that medicines may be combined in refractory cases. They suggest the use of non-pharmacological interventions (cryotherapy, heat therapy) is some cases.

Consideration for the CURE ID platform: A case report form for sporotrichosis shall be tailored to distinguish various sporotrichosis forms (cutaneous, disseminated).

[1] Itraconazole (200 mg) twice daily, the first-line therapy for sporotrichosis, may be combined with terbinafine (250 mg) twice daily, but 10% potassium iodide is reported as effective when itraconazole and terbinafine are not effective.

4.7 Availability and affordability of medicines

On the question of availability and/or affordability of medicines in the respondents' setting, 44% (60/135) answered that medicines were available and affordable, and 56% (75/135) that medicines were not available and/or affordable in their setting (**Table 4.7A**). The respondents also indicated the medicines that are not available and/or affordable in their setting. **Table 4.7B** indicates the medicines that were quoted by respondents as not available and/or not affordable in their setting. Interestingly, itraconazole – the first-line treatment for eumycetoma, chromoblastomycosis and sporotrichosis – is among the medicines most listed as not available and/or affordable, followed by second-generation azoles (posaconazole, voriconazole). Availability/affordability is reported as a problem also for flucytosine, terbinafine, amphotericin B (including the liposomal form) and potassium iodide. A number of medicines used for treatment of actinomycetoma have also been listed and reported as problematic to access (dapsone, amikacin, streptomycin, carbapenems, rifampicin). Hence, the level of drug repurposing is also limited by restricted availability and/or affordability of medicines in countries. Moreover, this seems to affect outcomes of treatment as several comments through the survey indicated that even first-line medicines may not be available and/or affordable to patients (not included in health insurance schemes, out-of-pocket purchase by patients, unavailability in the country).

Table 4.7A. Availability and/or affordability of medicines in respondents' settings

Answer	Indicated use by respondent (135)	Percentage
Yes (not available and/or not affordable)	75	56%
No	60	44%

Table 4.7B. Medicines indicated as unavailable and/or unaffordable in the open comment question

Medicine indicated as unavailable and/or unaffordable	No. of respondents (>)
Itraconazole oral	17
Posaconazole oral	24
Voriconazole oral	23
Terbinafine oral	4
Potassium iodide oral	2
Flucytosine oral	7
Dapsone	5
Rifampicin	1
Amphotericin B IV	5
Liposomal amphotericin B	7
Streptomycin IV	3
Amikacin IV	4
Carbapenems IV	1
Imiquimod topical	1

The question as formulated in the survey did not provide an option for respondents to distinguish between availability and affordability of medicines. The collected data combines both concepts related to access to medicines. The main purpose of this question was to determine whether there were barriers to accessing and using medicines and their repurposing due to lack of availability or unaffordability of available medicines in countries. The survey confirms that use of medicines is influenced by their availability and/or affordability in countries. Access barriers to medicines used in implantation mycosis would require further investigation.

4.7.1 Other considerations by survey respondents

The survey allowed the respondents to provide comments for each question. Several comments were provided in relation to availability and/or affordability of medicines. Several respondents highlighted that access to treatment is a major problem in their setting. The majority of patients do not have an economic possibility to pay for treatment, have either low income or are in "extreme poverty". Patients have to pay partially or totally for treatment, which is a major barrier to complying with a treatment that is often long. One respondent indicated that their institution/association tries to overcome the high cost barrier for patients by providing medicines using samples or donations. More than one respondent indicated the choice of suboptimal prescribed treatment in order make it affordable to patients. The economic barriers affect the capacity of patients to comply with the prescribed treatment and, in certain settings, even a barrier to affording the transportation costs to come to the medical consultation.

Price barriers may affect patients ("imported cases", i.e. migrants from endemic countries) in high-income countries, as reported by two respondents. National health insurance schemes in such countries may not recognize treatment for implantation mycosis (due to lack of disease classification within the health system). In high-income countries where private insurance schemes are used, migrants may not be insured. One comment suggests that not only cost, but also procurement of certain medicines, may be challenging in high-income countries for treatment of "imported cases".

Treatment capacity to prescribe medicines is linked to availability of diagnostic methods. Identification of the microbiological agent is important in deciding the medication of choice. Several respondents highlighted diagnostic capacity as a major problem in correctly diagnosing and prescribing medicines. The need for training of health professionals and clinicians was also pointed out by respondents. The inclusion of medicines in the List of Essential Medicines was also called upon jointly with a request to deliver them free of charge to patients and make medicines available and affordable to low and middle income countries. A few comments called for the development of treatment guidelines for all subcutaneous and implantation mycoses. Comments suggest also that in certain middle income countries these diseases are not recognized or prioritized by governments and health ministries, hence the lack of procurement and supply schemes for free treatment applied for other diseases.

"Earlier suspicious and adequate therapy are crucial for the successful therapy of the implantation mycoses."

"Pathogen isolation, identification and drug sensitivity test determine the diagnosis, treatment and curative effect of patients. General doctors lack relevant clinical and laboratory knowledge, so there is an urgent need to carry out professional training for clinicians and laboratory testers in order to improve their diagnosis and treatment level. Due to the diversity of strains involved and the difficulty of culture and identification, a highly specific and sensitive examination method is needed. Patients usually have unclear medical history, long course of disease, disability and poverty, and need to provide strong support and guarantee, such as free medical treatment by the state and government, social security provided by relevant welfare institutions, etc. Scientific research should focus on rapid identification of strains, evaluation and improvement of

patients' immune status. It is hoped that WHO can formulate corresponding guidelines or suggestions."

"Most of the treatments that we prescribe have to be acquired either partially or totally by the patient and as most of them are low income or in extreme poverty will not always be in the position to continue in long term basis."

"Most of the used antifungal (itraconazole/terbinafine) are very expensive and as the management is challenging and takes a long period of time, the patients comes back as defaults and with recurrences or extension of the disease."

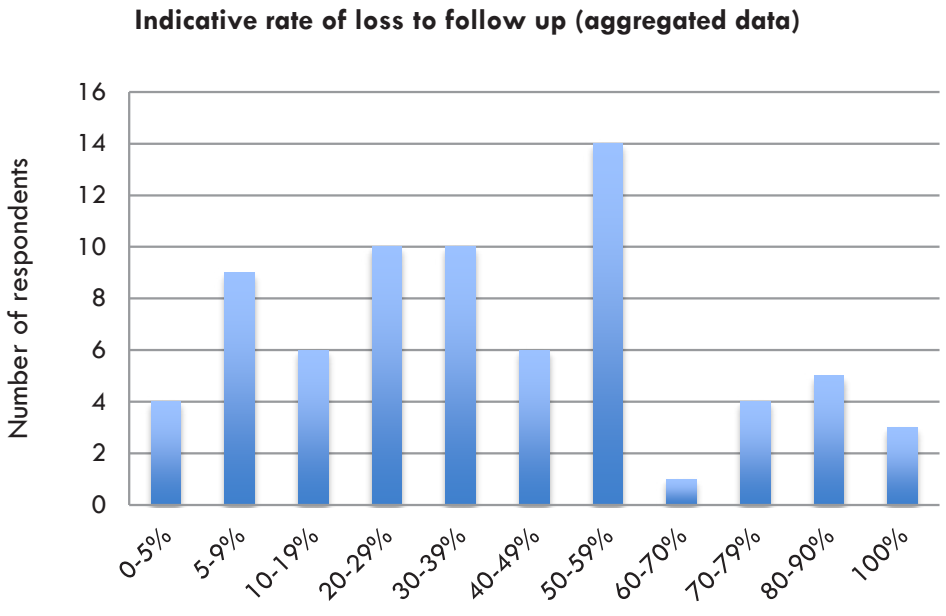
"The real problem in Italy is that these diseases are not covered in terms of healthcare by the national insurance. Patients should cover partially costs of care. Invalidity and NHS insurance is difficult to have for patients with mycetoma although frequently seen in migrants." (Italian respondent)

"Most medicines that are FDA approved are readily available. The limiting factor is patient cost for outpatient use of expensive medications when patients are uninsured. We also have the ability to obtain some meds via IND that are only available via CDC or WHO" (USA respondent).

4.8 Loss to follow up

Around half of the survey respondents (72/142) provided information on the indicative rate of loss to follow up in their setting (**Table 4.8A**). The aggregated data show that there is considerable loss to follow up of patients with diagnosed implantation mycosis in many settings. While some of the reasons may be inferred from the comments provided by the participants for earlier questions, these aggregated data suggest that there is an urgent need to tackle these diseases.

Fig. 4.8A. Indicative rate of loss to follow up by range



5. Discussion

Although this survey has limitations, it provides interesting information on the diagnostic capacity and treatment trends, as well as challenges for treatment of implantation mycoses globally, especially but not only in middle income countries. These findings could prompt additional and more in-depth investigations to inform strategies and actions in support of the road map for implantation mycoses.

The survey confirmed that the CURE ID platform could be a useful tool for collecting clinical case reports for these diseases given that, in addition to drug repurposing outcomes, the data collected could have added value in light of the absence of surveillance systems in countries for these diseases. The first survey, which attempted to determine the burden of disease for mycetoma, was performed by WHO between December 2016 and April 2017 *(8)*. As reported in the road map, as of 2020 only 1 out of 30 countries had a surveillance system in place for mycetoma. The spontaneous collection of case report data through an openly accessible platform could support collection of data on pathogen microorganisms, diagnostic methods, medicines and, where applicable, non-pharmacological interventions used for these diseases. It could allow reporting and analysing treatment outcomes with an indication of the gravity of the disease at patient enrolment. One of the main objectives of the road map is to identify shorter, more effective treatments for this group of diseases in addition to early detection through point-of-care or near point-of-care diagnostic methods. Treatment efficacy for implantation mycoses is low. As an example, for actinomycetoma the cure rate with antibiotics is 60–90%, and for eumycetoma with antifungals is generally low (< 30%) *(4, 9)*.

It is also noted that during the initial landscape analysis and the dissemination of the survey, the scientific and community of practice showed great interest in collaboration and in focusing attention on these particularly neglected diseases. While one phase II proof-of-concept trial is ongoing to test a new azole for the treatment of eumycetoma by the Drugs for Neglected Diseases *initiative* and the WHO Collaborating Centre on Mycetoma in Sudan (the Mycetoma Research Centre of the University of Khartoum), there are no other clinical trials evaluating new chemical entities for these diseases *(10)*. There is one registered study, a single arm observational study for the use of a non-pharmacological intervention in chromoblastomycosis (ALA-DPD) at the Southern Medical University in Guangzhou, Guangdong, China *(11)*. The research and development pipeline for new treatments is empty, with current ongoing efforts focused on identifying new chemical entities with new modes of action using an open-source drug discovery approach *(9, 12)*.

It shall be noted that there are no internationally recognized evidence-based treatment guidelines for these diseases, and the collection of evidence in the absence of clinical trials (as is the case for implantation mycoses) would need to rely on the systematic

review of non-randomized trials and observational studies, including case series and case reports.[1] In this context, the use of a readily accessible platform where clinicians could input case report information for implantation mycoses would constitute an important resource as a global treatment registry. The use of the CURE ID platform would also serve to collect the data in a consistent and structured manner, enabling higher-quality information to be gathered and facilitating aggregation of the case experiences.

The survey also indicates that the availability and affordability of medicines do influence treatment options in several countries, particularly in view of the fact that treatment for implantation mycoses is long and often inaccessible to patients through national health systems. Implantation mycoses mainly affect low income patients working in rural settings. The comments provided by survey respondents indicate that availability and affordability influence the medicine of choice, even when diagnostic capacity allows identification of the causative agent and, in principle, tailoring of the pharmacological approach. Access to medicines is reported as a challenge by nearly half (44%) of the survey respondents. Itraconazole is among the medicines most frequently listed as not available/affordable, with second-generation azoles listed as the less available/affordable (posaconazole, voriconazole). Lack of availability and/or affordability seem to affect the entire spectrum of medicines listed in this survey.

[1] According to the 2014 *WHO handbook for guideline development:* "non-randomized trials and observational studies, including interrupted time-series analyses, cohort and case–control studies, cross-sectional studies and other types of studies, such as case series and case reports" *(13)*.

6. Conclusion and recommendations

In 2017, WHO conducted a survey on mycetoma to understand the global epidemiological and control status in an attempt to address the request by the World Health Assembly in resolution WHA69.21 *(2)*. This survey is the second attempt by WHO to collect data on diagnostic and treatment capacity for mycetoma and the first to collect such data for chromoblastomycosis and sporotrichosis. An extensive effort was made to disseminate this global WHO survey and to reach the widest possible audience, mobilizing several players. The scientific community and community of practice for these diseases remain fragmented in institutional, national and regional dimensions, although a number of overarching working groups have been created and a number of international organizations are active on these diseases. The survey succeeded in collecting information from respondents from 47 countries in less than 3 months. There is the potential to build a cross-country network to work towards the objectives set by the road map for implantation mycoses. The pilot testing and use of the CURE ID platform, supported by the implantation mycoses community of practice, could offer a repository of data on case reports in the form of a treatment registry that could be of significant value, given the dearth and challenge of conducting randomized controlled trials.

The survey findings suggest that evidence-based guidelines for these diseases are warranted and should address the entire spectrum of pharmacological and non-pharmacological interventions used for these implantation mycoses. The highlighted challenges of availability and affordability of medicines represent a constraint for effective treatment and for drug repurposing. Barriers to accessing medicines to treat implantation mycoses require further investigation and should be considered while prompting and using the generated real-world data to support clinical research hypotheses for drug repurposing. Policies and procurement schemes to ensure access to medicines should be an integral part of global and national actions to tackle this new group of neglected diseases.

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Annexes

Annex 1. List of survey questions (English version)

1) **Which is your country of practice?**
   a. DROP-DOWN MENU COUNTRY NAMES
   b. Region/Province: ¬¬¬ INSERT

2) In which setting do you work?
   a. Primary level (Peripheral clinic/laboratory)
   b. Secondary level (Provincial/regional level)
   c. Tertiary level (National reference level)

3) What is your role?
   a. Clinician
   b. Laboratory specialist/clinician
   c. Laboratory technician/specialist
   d. Public health specialist
   e. Other: INSERT

4) In your setting, which types of diagnostic techniques are available for subcutaneous mycosis? (FILL ALL THAT APPLY)
   a. Clinical features /visual inspection
   b. Grains direct microscopy
   c. Culture_ bacterial for Actinomycetoma
   d. Culture_ fungal
   e. Serology
   f. Molecular diagnosis (PCR)
   g. Histopathology on skin biopsy
   h. Dermoscopy: epiluminescence microscopy (ELM),

i. Other: (INSERT)
j. Comment:

5) In your setting, which medicines are used for the treatment of <u>eumycetoma</u>? (FILL ALL THAT APPLY)

a. Not applicable (if you don't treat this disease)
b. Itraconazole oral
c. Posaconazole oral
d. Voriconazole oral
e. Ketoconazole oral
f. Terbinafine oral
g. Amphotericin B injectable
h. Other: (INSERT)
i. Comment: (INSERT)

6) In your setting, are there non-pharmacological interventions applied for the treatment of <u>eumycetoma</u>?

a. Not applicable (if you don't treat this disease)
b. No
c. Yes, Surgery
d. Yes, other: (INSERT)
e. Comment: (INSERT)

7) In your setting, which medicines are used for the treatment of <u>actinomycetoma</u>? (FILL ALL THAT APPLY)

a. Not applicable (if you don't treat this disease)
b. Trimethoprim-sulfamethoxazole oral
c. Amikacin IV
d. Amoxicillin/clavulanic acid oral
e. Rifampicin oral
f. Dapsone - diamino-diphenyl-sulfone (DDS) oral
g. Moxifloxacin oral
h. Carbapenems IV
i. Fosfomycin oral
j. Other (INSERT)
k. Comment: (INSERT)

8) In your setting, which medicines are used for the treatment of chromoblastomycosis (if applicable)?

a. Not applicable (if you don't treat this disease)
b. Itraconazole oral
c. Posaconazole oral
d. Voriconazole oral
e. Flucytosine oral
f. Terbinafine oral
g. Imiquimod topical
h. Other: (INSERT)
i. Comment: (INSERT)

9) In your setting, are there non-pharmacological interventions applied for the treatment of chromoblastomycosis?

a. Not applicable (if you don't treat this disease)
b. No
c. Yes, heat therapy
d. Yes, other: (INSERT)
e. Comment: (INSERT)

10) In your setting, are there refractory cases of chromoblastomycosis?

a. Not applicable (if you don't treat this disease)
b. Yes
c. No
d. Comment: (INSERT)

11) In your setting, which medicines are used for the treatment of cutaneous sporotrichosis (if applicable)?

a. Not applicable (if you don't treat this disease)
b. Itraconazole oral
c. Terbinafine oral
d. Potassium Iodide oral
e. Other: (INSERT)
f. Comment: (INSERT)

12) In your setting, are there refractory cases of cutaneous sporotrichosis?

a. Not applicable (if you don't treat this disease)
b. Yes
c. No
d. Comment: (INSERT)

13) In your setting, are there medicines that you are not able to use because not available or/and not affordable?

a. Yes
b. No
c. If Yes, please specify which medicines and for which disease form:
d. Comment: (INSERT)

14) Please add any comment or information that you may think is important to explain medicines' availability, affordability or factors influencing the clinicians' capacity to prescribe the most appropriate treatment according to the identified etiological agents for Eumycetoma, Actinomycetoma, Chromoblastomycosis and Sporotrichosis.

(INSERT)

15) What is the indicative rate of loss to follow up for subcutaneous mycosis' patients in your treatment center?

(INSERT) %

16) Would you like to leave your name to be contacted and participate in follow-up discussions, webinars, etc.?

Name:
Email:

Annex 2. Numbers of survey participants by country

Continent	Country	Country classification	No. of respondents
Africa	Algeria	Lower MIC	1
Latin America	Argentina	Upper MIC	7
Oceania	Australia	HIC	2
Asia	Bangladesh	Lower MIC	4
Europe	Belgium	HIC	1
Latin America	Brazil	Upper MIC	8
Africa	Cameroon	Lower MIC	1
Africa	Chad	LIC	1
Latin America	Chile	HIC	2
Asia	China	Upper MIC	4
Latin America	Colombia	Upper MIC	5
Africa	Congo	Lower MIC	1
Latin America	Cuba	Upper MIC	1
Africa	Democratic Republic of the Congo	LIC	1
Africa	Ethiopia	LIC	3
Europe	France[a]	HIC	15
Africa	Gabon	Upper MIC	1
Europe	Germany	HIC	1
Africa	Ghana	Lower MIC	1
Asia	India	Lower MIC	19
Middle East	Islamic Republic of Iran	Lower MIC	4
Europe	Italy	HIC	1
Africa	Kenya	Lower MIC	2
Africa	Madagascar	LIC	4
Africa	Mali	LIC	1
Africa	Mauritania	Lower MIC	1
Latin America	Mexico	Upper MIC	6
Africa	Mozambique	LIC	2
Asia	Nepal	Lower MIC	1

Europe	Netherlands (Kingdom of)	HIC	5
Oceania	New Zealand	HIC	1
Africa	Nigeria	Lower MIC	4
Asia	Pakistan	Lower MIC	2
Latin America	Peru	Upper MIC	1
Africa	Senegal	Lower MIC	2
Africa	South Africa	Upper MIC	2
Europe	Spain	HIC	1
Africa	Sudan	LIC	2
Asia	Thailand	Upper MIC	1
Africa	Tunisia	Lower MIC	1
Africa	Uganda	LIC	2
Europe	United Kingdom	HIC	4
Africa	United Republic of Tanzania	Lower MIC	3
North America	United States of America	HIC	1
Latin America	Uruguay	HIC	1
Latin America	Venezuela (Bolivarian Republic of)	Not classified	4
	Not declared	4	4
	Total	142	4

[a] Including Martinique (1), Guadeloupe (1) and Guyana (1).

HIC: high income country; MIC: middle income country.

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