TARGET PRODUCT PROFILE

for a rapid test for diagnosis of mycetoma at the primary health-care level

World Health Organization

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1. Introduction

Mycetoma is a chronic granulomatous infection that causes tumorous lesions in the subcutaneous tissue. Most of the infection occurs in the feet, followed by the hands, legs and back *(1, 2)*. Characteristic of this disease is that the causative agent organizes itself in granules (called grains), which can be secreted through sinuses.

2. Epidemiology

Mycetoma is caused by at least 70 different microorganisms of fungal or bacterial origin *(1)*. Fungal mycetoma (eumycetoma) is most often caused by *Madurella mycetomatis, Scedosporium boydii* and *Falciformispora senegalensis*. Bacterial mycetoma (actinomycetoma) is most often caused by Actinomadura madurae, Streptomyces somaliensis, *Actinomadura pelletieri, Nocardia brasiliensis* and *Nocardia asteroides (1)*. Although mycetoma is reported in 102 countries, its etiology differs by region *(1, 3)*. *M. mycetomatis, S. somaliensis* and *A. pelletieri* are highly prevalent in Africa and Asia but hardly found in South America. In South America, *N. brasiliensis* is by far the commonest causative agent, but this species is very rarely encountered in the rest of the world. Only A. madurae has been found to be prevalent on all continents *(1)*.

A hallmark of mycetoma is visible grains. The colour of the grain depends on the causative agent. Generally, eumycetoma causative agents form black (*M. mycetomatis, F. senegalensis*) or white (*S. boydii*) grains *(4)*, whereas actinomycetoma causative agents cause white (*Nocardia spp., Actinomadura madurae*), yellow (*Streptomyces* spp.) or red (*Actinomadura pelletieri*) grains *(4)*.

3. Clinical course and treatment

Although mycetoma has two distinct etiologies based on the causative agent (bacterial for actinomycetoma and fungal for eumycetoma), the clinical presentation is virtually identical. In both cases the infection starts with a small nodule, usually at the site where the microorganism was introduced into the subcutaneous tissue via a minor trauma such as a thorn prick. With time, this painless nodule grows into a larger subcutaneous mass from which sinuses are secreted and grains discharged as purulent or seropurulent material *(2)*. In advanced lesions the bone is also invaded by the microorganism *(2)*. Actinomycetoma is generally more aggressive and destructive and invades the bone earlier than eumycetoma.

Treatment of mycetoma depends on the causative agent. Actinomycetoma is usually treated with a combination of antibiotics, most often trimethoprim and sulfamethoxazole plus amikacin, but other combinations of medicine are also used *(5)*. Actinomycetoma caused by *Nocardia brasiliensis* seems to respond better to these medicines than actinomycetoma caused by *Actinomadura madurae*. Eumycetoma is treated with a combination of antifungal therapy and surgery. Itraconazole is used most often, followed by terbinafine *(5)*.

4. Available diagnostic tools

At present, the diagnosis of mycetoma is often made clinically. The causative agent is usually identified through a combination of histology and culturing *(6)*. For this a deep-seated biopsy is recommended, as the grains secreted from open sinuses are often non-viable *(4)*. With histology, the grain can be easily seen inside the infected tissue, and discrimination between actinomycetoma and eumycetoma can be

made; however, identification to the species level is not possible *(4)*. With culturing, the isolate can be grown and the species identified; however, identification can take up to 6 weeks for a positive culture, and misidentifications are common *(7)*. Molecular diagnostic tests such as polymerase chain reaction are commonly used in research settings but only rarely in regions where mycetoma is endemic *(4)*. Furthermore, specific molecular assays are not available for all species of causative agent.

5. The WHO Diagnostic Technical Advisory Group for Neglected Tropical Diseases

In 2016, mycetoma was added to WHO's list of neglected tropical diseases. The disease is included in the road map for neglected tropical diseases 2021–2030 with a target for control *(8)*. The core strategic intervention is case managment. Strengthening diagnostics is a top priority. The critical actions required to achieve the targets, sub-targets and milestones for 2030 are to develop differential rapid diagnostic tests and effective treatment; establish surveillance for case detection and reporting; develop a standardized field manual for diagnosis and treatment; ensure proper training of health-care workers; and provide access to affordable diagnosis and treatment *(8)*.

Since case management relies on proper diagnosis, the Diagnostic Technical Advisory Group, an advisory group to the WHO Department of Control of Neglected Tropical Diseases, has included mycetoma in its portfolio. To ensure availability of diagnostic assays for clinical staff working in endemic regions, the Group has recommended the development of a target product profile (TPP) for mycetoma.

6. Purpose of the TPP

As indicated in the road map and by experts in the field, point-of-care diagnostic tests are urgently needed to improve early detection at primary health-care level. This assay should not only detect mycetoma but also differentiate between actinomycetoma and eumycetoma to allow initiation of appropriate therapy. Furthermore, since currently it is not apparent when treatment can be stopped, a point-of-care test of cure is also needed.

7. Audiences engaged and external consultations to develop the TPP

In order to initiate the development of TPPs for mycetoma, Dr Wendy van de Sande and Dr Noah Fongwen gathered together a group of nine experts on mycetoma. The group was divided into a group of clinical experts on mycetoma and a group of experts on diagnostics. After discussions, a draft TPP was developed by Dr Wendy van de Sande and Dr Noah Fongwen. The draft was submitted to the D-TAG group chair, Dr Patrick Lammie, for comments before finalization and publication for the online consultation and adapted based on their comments.

The final draft was published on the WHO website for public consultation from 25 October to 29 December 2021 and feedback was received from Dr Neal Stone from the University College London hospitals and the NHS foundation trust. The comments on the plausibility of a single test of cure were noted and discussed but not incorporated in the TPP. The changes were incorporated by Dr W. van de Sande. The final draft was reviewed and approved by the chair of the DTAG subgroup on skin NTDs, Dr Isra Cruz, and WHO staff, and incorporated when relevant.

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Mycetoma Diagnosis TPP – Stop treatment

1. Product use summary	Minimum	Ideal	Background, annotation re requirement risk, etc.
1.1 Intended use	An in vitro laboratory-based test that detects mycetoma analyte(s) for the purpose of deciding if a mycetoma patient on treatment is free of disease so that treatment can be stopped.	An in vitro point-of-care test that detects mycetoma analyte(s) for the purpose of deciding if a mycetoma patient on treatment is free of disease so that treatment can be stopped.	
1.2 Target population	All ages and gender of individuals	All ages and gender of individuals	
1.3 Lowest infrastructure level	For a laboratory-based test, tests can be performed in a peripheral health facility/referral centre, regional or national diagnostic testing laboratory.	The test will be performed under "zero-infrastructure" conditions in the field.	
1.4 Lowest level user	For a laboratory-based test, the test will be performed by trained laboratory technicians.	For a point-of-care test, the test will be performed by health personnel, community health workers, and community volunteers.	
1.5 Training requirements	For a laboratory-based test, < 5 days for trained laboratory technicians; testing job aid/instructions for use should be downloadable via the Internet (i.e. publicly available).	For a point-of-care test, ≤ 2 days for health personnel, community volunteers and lay people; testing job aid/instructions for use should be made downloadable via the Internet (i.e. publicly available).	**Note**: It is not a requirement to have Internet access to obtain job aids/instructions for use since these must be included with the test itself (per requirement 4.5), but rather that job aids/instructions for use should always be available via the Internet.
2. Design	Minimum	Ideal	Annotation
2.1 Portability	For a laboratory-based test, specific portability and transport requirements should not be beyond those associated with standard laboratory equipment.	For a point-of-care test, highly portable with no specialized transport needs.	"Portability" implies those characteristics described in 2.2–2.4 as well as no locational limitations as to where the test can be performed.
2.2 Instrument/ power requirement	For a laboratory-based test, access to mains power is acceptable.	For a point-of-care test, self-contained kit operates independently of any mains power. Battery should be easily replaced after > 1 day in the field.	
2.3 Water requirement	For a laboratory-based test, access to laboratory grade water is acceptable.	For a point-of-care test, self-contained kit operates independently of any water supply.	
2.4 Maintenance and calibration	For a laboratory-based test, periodic maintenance and calibration of any instrumentation must be available in the countries, and should not be needed more frequently than once a year.	For a point-of-care test, no maintenance required (i.e. disposable) and no calibration required.	

2.5 Sample type/ collection	Venous blood, finger blood or urine	Finger blood or urine	
2.6 Sample preparation/transfer device	· Sample preparation should not exceed transfer of the sample to a sample processing tube holding no more than 500 µL of processing buffer, an aliquot of which is transferred to the testing device after a defined period of time. · Transfer of the sample volume to the testing device shall occur by use of a predefined and provided single-use transfer device (e.g. inverted cup, disposable fixed-volume transfer pipet).	· Sample preparation should not exceed transfer of the sample to a sample processing tube holding no more than 500 µL of processing buffer, an aliquot of which is transferred to the testing device after a defined period of time. · Transfer of the sample volume to the testing device shall occur by use of a predefined and provided single-use transfer device (e.g. inverted cup, disposable fixed-volume transfer pipet)	
2.7 Sample volume	1–100 uL	1–10 uL	"Sample volume" represents that volume which is introduced to the test device itself.
2.8 Target analyte	**Biomarker(s) specific for eumycetoma or actinomycetoma**	**Biomarker(s) specific for eumycetoma and actinomycetoma.**	**Note**: More promise is expected with a good immune test that can be used in any setting. Isolation of antigens is in progress. More research is ongoing on how to extract antigens from urine. There is an immune test (in the form of enzyme-linked immunosorbent assy) that corroborates well with *Nocardia* (treatment stop when lesions are healed and antibody titre drops to background level) and seems to work for actinomadura as well. Barriers still exist in the optimization of such a test. Getting sera from actively infected patients on treatment is a challenge. In another ongoing study funded by the Global Health Innovative Technology Fund, transcriptomic markers are also identified for the most common causative agents in both plasma and serum. The discovery of antigens and miRNA in urine that can be used as markers for deciding when to stop treatment but will be expensive (although onwards it will be an ideal point-of-care test for patients in endemic areas). For this reason, this is a **moderate-risk** requirement.
2.9 Type of analysis	Quantitative	Quantitative	

2.10 Detection	For laboratory-based tests, may include instrument-based detection of a signal that provides unambiguous determination of a qualitative measure.	For point-of-care tests, results shall be of high contrast, clear to the naked eye, with indoor and outdoor reading of a signal that provides a definitive result without the need for color discrimination.	**Note**: More promise is expected with a good immune test that can be used in any setting. Isolation of antigens is in progress. More research is ongoing on how to extract antigens from urine. There is an immune test (in the form of enzyme-linked immunosorbent assy) that corroborates well with *Nocardia* (treatment stop when lesions are healed and antibody titre drops to background level) and seems to work for actinomadura as well. Barriers still exist in the optimization of such a test. Getting sera from actively infected patients on treatment is a challenge. In another ongoing study funded by the Global Health Innovative Technology Fund, transcriptomic markers are also identified for the most common causative agents in both plasma and serum. The discovery of antigens and miRNA in urine that can be used as markers for deciding when to stop treatment but will be expensive (although onwards it will be an ideal point-of-care test for patients in endemic areas). For this reason, this is a moderate-risk requirement.
2.11 Quality control	· Internal process control indicator	· Internal process control indicator · Colorimetric or other indicator to identify excessive heat/humidity exposure	For further consideration (i.e. beyond the scope of this TPP): definition of how endogenous positive controls should/would be used if they are to be included with a test, e.g., will there be a community-wide quality panel, centralized reporting of results, etc.
2.12 Supplies needed	All reagents and supplies included in test kit, including those needed for sample collection and processing, with minimal import restrictions (e.g. animal-free).	All reagents and supplies included in test kit, including those needed for sample collection and processing, with minimal import restrictions (e.g. animal-free).	
2.13 Safety	Normal use of the test does not create any additional hazards to the operator when observing universal blood safety/body fluid precautions.	Normal use of the test does not create any additional hazards to the operator when observing universal blood safety/body fluid precautions.	

3. Performance	Minimum	Ideal	Annotation
3.1 Species differentiation/ detection	***Eumycetoma* spp. *(Madurella spp.)* and *Actinomycetoma* spp. *(Nocardia* spp.*, Actinomadura* spp.*, Streptomyces* spp.*)***	***Eumycetoma* spp. *(Madurella spp.)* and *Actinomycetoma* spp. *(Nocardia* spp.*, Actinomadura* spp.*, Streptomyces* spp.*)***	There should be no interference/non-specific signals as a result of other infections.
3.2 Diagnostic/ clinical sensitivity	> 90%	> 95%	Due to drug toxicities, it will be better to unneccessarily keep on treating fewer people as possible. Amikacin can cause hearing problems. The antifungal agents can damage the liver but there are more toxic treatments for other diseases than these medicines.
3.3 Diagnostic/clinical specificity	> 75%	> 90%	More laxity on specificity because the follow-up for mycetoma is long and patients will be seen more than once. This means if they stop treatment and there is recurrence, they will be placed back on treatment. Definition of cure: clear of disease for a 24 month period of follow-up (for eumycetoma) and for 12 months follow-up for Nocardia.
3.4 Time to results	<for a lab based test, within a day	< 0.5 h to developed test result	
3.5 Stability of results	Developed test result remains stable for 0.5 h	Developed test result remains stable for 24 h	Ability to interpret final test results in a manner not constrained by timed steps helps greatly in resource-constrained settings
3.6 Throughput	For laboratory-based tests, ≥ 100 tests/day per tester	For point-of-care tests, ≥ 10 individuals tested/h per tester	"Throughput" represents how many tests can be run in parallel within 1 h and is *separate from* the time to results.
3.7 Target shelf-life/ stability	≥ 18 months, 2–40 °C, 75% relative humidity (no cold chain required); temperature excursion/prolonged deviation of 50 °C for 2 weeks acceptable.	≥ 24 months, 2–40 °C, 75% relative humidity (no cold chain required); temperature excursion/prolonged deviation of 50 °C for 2 weeks acceptable.	
3.8 Ease of use	For laboratory-based tests, ≤ 5 timed steps; ≤ 15 user steps; instructions for use should include diagram of method and results interpretation.	≤ 1 timed step; ≤ 5 user steps; instructions for use should include diagram of method and results interpretation. For point-of-care tests, must be able to use in an unprotected external environment.	This is in relation to the test operation only.
3.9 Ease of results interpretation	For laboratory-based tests, a definitive "Yes/No" result can be interpreted by a suitable instrument that meets requirements defined in 2.10 "Minimum".	For point-of-care tests, a definitive "Yes/No" result can be interpreted by eye that meets requirements defined in 2.10 "Minimum".	
3.10 Operating temperature	15–40 °C, 75% relative humidity	15–40 °C, 75% relative humidity	

4. Product configuration	Minimum	Ideal	Annotation
4.1 Shipping conditions	For laboratory-based tests, conformance with applicable requirements of ASTM D4169-05 and ISO 11607-1:2006 (or equivalent); cold-chain shipping (e.g. 0-4 °C) is acceptable for any test components/ consumables used in the laboratory.	For point-of-care tests, conformance with applicable requirements of ASTM D4169-05 and ISO 11607-1:2006 (or equivalent); no cold-chain shipping required.	
4.2 Storage conditions	For laboratory-based tests, cold storage is acceptable for any *laboratory-based* testing components/ consumables.	For point-of-care tests, ambient storage conditions, 2–40 C; no cold storage required.	
4.3 Service and support	For laboratory-based tests, support must be available from manufacturer for any laboratory-based equipment and/or procedures.	For point-of-care tests, none required.	
4.4 Waste disposal	Does not include material that cannot be disposed of in normal laboratory biohazard waste streams.	Does not include material that cannot be disposed of in normal laboratory biohazard waste streams.	
4.5 Labelling and instructions for use	Compliance required per in vitro diagnostic regulation requirements and WHO guidance on prequalification (see WHO TGS-5: *Designing instructions for use for in vitro diagnostic medical devices*); product insert shall be available in relevant local language(s) and shall include instructions for use for the test. Must provide accurate material safety data sheet information on components that are potentially toxic.	Compliance required per in vitro diagnostic regulation requirements and WHO guidance on prequalification (see WHO TGS-5: *Designing instructions for use for in vitro diagnostic medical devices*); product insert shall be available in relevant local language(s) and shall include instructions for use for the test. Must provide accurate material safety data sheet information on components that are potentially toxic.	WHO prequalification label/guidance on instructions for use should be applied regardless of whether the test is prequalified by WHO or not.

5. Product cost and channels	Minimum	Ideal	Annotation
5.1 Target pricing per test	< 1 week of appropriate therapy	< US$ 1	Actual price details will depend on other factors separate from the test itself, including shipping, storage, quantities purchased and other factors commonly encountered in national procurement for neglected tropical disease programmes.
5.2 Capital cost	For laboratory-based tests, capital costs may vary but should not exceed US$ 5000.	For point-of-care tests, none required.	
5.3 Product lead times	< 8 weeks	< 6 weeks	"Lead time" includes fulfillment and delivery of ordered tests to procurer. **Note**: May be adjusted to longer lead times provided shelf-life is of sufficient duration, e.g. 2 years. The purpose of information is to address design decisions that can impact line/process design for production, and hence impact lead times.
5.4 Targeted countries	WHO prioritized countries	WHO prioritized countries	
5.5 Product registration (i.e. substantiation to regulatory body of product claims)	· CE mark/in vitro diagnostic requirement (or other safety risk assessment) as *relevant* · Any registration required for export from country of origin (e.g. MFDS from Republic of Korea) · WHO prequalification, if *required/applicable* · Country-level registration (if required/applicable for target countries)	· CE mark/in vitro diagnostic requirement (or other safety risk assessment) as *relevant* · Any registration required for export from country of origin (e.g. MFDS from Republic of Korea) · WHO prequalification, if *required/applicable* · Country-level registration (if required/applicable for target countries)	Need to confirm that WHO prequalification will process dossiers for diagnostics for neglected tropical diseases.

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