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Target product profiles: leprosy diagnostics

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Abstract

The World Health Organization (WHO) aims to reduce new leprosy cases by 70% by 2030, necessitating advancements in leprosy diagnostics. Here we discuss the development of two WHO's target product profiles for such diagnostics. These profiles define criteria for product use, design, performance, configuration and distribution, with a focus on accessibility and affordability. The first target product profile outlines requirements for tests to confirm diagnosis of leprosy in individuals with clinical signs and symptoms, to guide multidrug treatment initiation. The second target product profile outlines requirements for tests to detect *Mycobacterium leprae* or *M. lepromatosis* infection among asymptomatic contacts of leprosy patients, aiding prophylactic interventions and prevention. Statistical modelling was used to assess sensitivity and specificity requirements for these diagnostic tests. The paper highlights challenges in achieving high specificity, given the varying endemicity of *M. leprae*, and identifying

target analytes with robust performance across leprosy phenotypes. We conclude that diagnostics with appropriate product design and performance characteristics are crucial for early detection and preventive intervention, advocating for the transition from leprosy management to prevention.

Introduction

Leprosy (Hansen's disease), a neglected tropical disease, is caused by *Mycobacterium leprae* or less often by *M. lepromatosis*¹ The disease is a chronic, moderately infectious condition affecting mostly skin, peripheral nerves, mucosa of upper respiratory tract and eyes.^{2,3} Approximately 200 000 new cases are reported annually from nearly 120 countries.⁴ In 2021, the World Health Organization (WHO) launched the *Towards zero leprosy: global leprosy (Hansen's disease) strategy 2021–2030*, aiming for a global reduction of 70% in new leprosy cases by 2030.⁵ Continued investment in leprosy diagnostics is crucial if we are to achieve the proposed targets.

Leprosy is an important public health problem due to its potential for causing lasting physical impairments and adverse socioeconomic consequences if left undiagnosed.^{6,7} *M. leprae* is moderately contagious and infections can become chronic. Infected contacts can remain asymptomatic for up to 20 years,^{8–10} and indirect evidence suggest that these individuals with subclinical infection could transmit *M. leprae* to close contacts.^{10–13} Therefore, conducting regular contact tracing and testing; and administering prophylactic treatment is crucial to interrupt transmission cycles.¹¹ Despite multidrug treatment availability and global advancements in leprosy treatment, delayed diagnosis remains a substantial concern as it can lead to grade 2 disabilities (ulcers, contractures, foot drop, lagophthalmos, and muscle wasting).^{14,15} The global reduction in leprosy cases,¹⁶ along with less active engagement from health-care professionals in managing the disease, has led to a decline in clinical public-health expertise in diagnosing leprosy, further causing delays in diagnosis.^{15,17,18}

Currently, leprosy diagnosis primarily relies on defined clinical criteria.¹⁹ Microscopic or laboratory-based diagnosis using acid-fast bacilli identification in a slit-skin smear or skin biopsy is used in numerous leprosy programmes and tertiary care settings.¹⁹ Additionally, various point-of-care tests and laboratory assays have been developed to detect *M. leprae* infection directly or indirectly.^{20–22} These include enzyme-linked immunosorbent assays and lateral flow assays for detection of immunoglobulins and polymerase chain reaction for pathogen detection.^{23,24} Both immunodiagnosics and molecular assays are sensitive enough to diagnose multibacillary leprosy²³ as well as some paucibacillary cases.²⁵ Although direct diagnosis of paucibacillary leprosy is challenging, in vitro stimulation followed by detection of immunity against *M. leprae* antigens, increases diagnostic potential.^{26,27}

Variability in leprosy presentation, patient type and diagnostic targets complicate accurate testing.^{28,29} Furthermore, limited awareness about leprosy among health-care workers pose a diagnostic challenge.³⁰ Hence, diagnostic tests that support rapid contact tracing and screening are essential for efficient and comprehensive leprosy control programmes. Easy-to-use diagnostic tests are therefore needed to help reduce delays.

In efforts to achieve better performance, some tests lean on complex instrumentation and expertise that limit their field use, especially in low-resource settings. Additionally, tests requiring invasive sampling are challenging to deploy in a field setting.³¹ These problems underscore the current need for to develop diagnostic tests that should be designed for settings where they are most needed.³² Furthermore, health authority authorized, commercially available in vitro diagnostic assays are limited.

To facilitate early prophylactic interventions to disrupt the chain of leprosy transmission, the Global Partnership for Zero Leprosy, under the WHO's diagnostic technical advisory group guidance,³³ developed two target product profiles for high-priority leprosy diagnostics. These profiles ensure that the diagnostic products not only meet the necessary performance criteria but also consider the specificities of the intended health-care context and the patient demographic. The first target product profile covers confirmatory diagnostic tests for individuals presenting with clinical manifestations indicative of leprosy, with the goal of initiating multidrug therapy. The second target product profile covers diagnostic assays for the detection of *M. leprae* infection in asymptomatic household or familial contacts of individuals with confirmed clinical leprosy.

Methods

Development process

To create target product profiles and guide product developers, the Global Partnership for Zero Leprosy formed a leprosy-focused diagnostic expert working group to assist the WHO's diagnostic technical advisory group's skin neglected tropical disease subgroup. The working group assisted by clarifying unmet public health needs, determining whether existing available target product profiles or pipeline products are addressing current needs, defining the scope of needed new target product profiles and serving as scientific group to develop new target product profiles.

The Global Partnership for Zero Leprosy included leprosy experts working in laboratory, field research and clinical capacities, as well as community stakeholders who developed target product profiles. The group collaborated with the WHO diagnostic technical advisory group,

WHO Technical Advisory Group for leprosy and consulted experts at the Bill & Melinda Gates Foundation. The original draft version zero criteria were chosen by the Global Partnership for Zero Leprosy's diagnostic working group using methods such as landscape assessments, use case needs analyses and diagnostic performance modelling, all designed through an internal consultative process.

The Global Partnership for Zero Leprosy's diagnostic working group reviewed the need for a leprosy diagnostic test using WHO reports, literature and outcomes of discussions with the experts. We created target product profile version 0.1 using the quality by design planning method,^{34,35} with performance characteristics based on statistical analysis and modelling by expert group members (online repository).³⁶ The target product profile version 0.1 adapted based on feedback from diagnostic technical advisory group members was then published on the WHO website for public consultation (30 November to 30 December 2021). In addition to online public consultation, the WHO Technical Advisory Group on Leprosy Control also reviewed draft version 0.1. Once all comments on Version 0.1 were addressed, the documents were reviewed by the chair of the diagnostic technical advisory group's skin neglected tropical diseases subgroup and a WHO technical staff member before becoming the final version 1.0.

Target product profiles^{9,10}

WHO finalized and disseminated Version 1.0 of the target product profiles on 24 July 2023.^{9,10} Target product profile 1 describes a test to confirm leprosy in individuals presenting with clinical signs and symptoms (hereafter confirmatory test).⁹ The target product profile 2 describes a point-of-care test for the detection of analyte specific to *M. leprae* or host response to *M. leprae* to enable detection of subclinical *M. leprae* infections (hereafter test for subclinical infection).¹⁰

The WHO diagnostic target product profiles define minimal and ideal targets for each profile and organize them into five categories: (i) product use summary; (ii) design; (iii) performance; (iv) product configuration; and (v) product costs and distribution channels. Minimal refers to the lowest acceptable output for a characteristic for the test to be suitable for the intended use, and ideal reflects targets that may be harder to achieve but would accelerate access, adoption and clinical outcomes.

Product use summary

For a confirmatory test, the intended application is at minimum a laboratory-based assay for the qualitative and quantitative detection of biomarkers specific to *M. leprae* and, ideally, *M. lepromatosis*. This test should be able to confirm diagnosis of clinical leprosy in individuals

exhibiting clinical manifestations. In contrast, the subclinical test delineates specifications for a point-of-care, rapid diagnostic tool aimed at identifying biomarkers pertinent to *M. leprae* or the host immune response to *M. leprae* or *M. lepromatosis*. Such a test should be applicable in contact tracing scenarios and facilitate detection of asymptomatic *M. leprae* infections among contacts of leprosy patients. The ideal intended use for both profiles is deployment as point-of-care diagnostics.

A confirmatory test should require minimal infrastructure, characterized by a laboratory setting where technicians with less than one week of additional formal training can perform the assay. The ideal scenario for such test is a point-of-care format executable in health-care settings without any laboratory infrastructure. The ideal intended user profile is health-care professionals, community health workers and volunteers; requiring only a one day, complemented by easy and accessible usage instructions. For test for subclinical infection, the prerequisites for infrastructure, end-user capability and training are consistent with the ideal conditions described for confirmatory tests.

Design

For confirmatory tests, at the minimal level, portability requisites for a laboratory-based assay stipulate that transport and portability conditions should not exceed those of standard laboratory apparatus. The test should be designed to use electricity supplied by main lines and laboratory-grade water resources (such as distilled water). Should instrumentation require periodic maintenance and calibration, it should be feasible within the recipient countries and not more than once per calendar year. Acceptable specimen types include capillary blood via fingerstick, venous blood, collected urine, nasal swabs, slit skin smears and punch biopsies, with the latter permitting sub-millimetre tissue collection. Sample processing and transfer should be simple, necessitating a single holding tube with a 500 µL capacity and disposable transfer pipette for one-time use. The maximum sample volume should not surpass 100 µL. Confirmatory tests should aim to detect biomarkers uniquely associated with *M. leprae* and provide semiquantitative analysis of bacterial load or immune response. An instrument-based detection method should incorporate an external process control indicator. All necessary reagents and operational supplies must comply with the basic importation restrictions and ensure the safety of the operator.

In an ideal scenario, confirmatory tests should be done on a highly portable point-of-care device without specialized transport requirements. The device should be battery powered or otherwise not depend on mains power and availability of water, obviating the need for regular

maintenance or calibration. Sample collection is confined to capillary blood via fingerstick, urine or nasal swabs, with straightforward processing and single-use pipette transfer. Ideally, requisite sample volume is less than 10 μ L. The assay should quantitatively determine biomarkers specific to both *M. leprae* and *M. lepromatosis*, assessing bacterial load or immune status. Results should be discernible to the unaided eye, marked by stark contrast and clarity. The required provisions for quality control, necessary supplies, and safety protocols mirror those at the minimal level.

For test for subclinical infection, the prerequisites for portability, and power and water independence are consistent for both minimal and ideal characteristics. The test's portability should negate the need for specialized transportation, mains electricity and water supply. At the minimum level, any field-compatible equipment employed (e.g. sample incubator, reader) should require only basic maintenance or calibration, potentially facilitated through return to the manufacturer or execution of a standard procedure. In the ideal scenario, the reader should require neither maintenance nor calibration. Both minimal and ideal acceptable sample types include capillary blood, collected urine and nasal swabs, with venous blood and slit skin smear included at the minimal level only. Sample volumes are confined to less than 100 μ L for the minimal scenario and less than 10 μ L for the ideal scenario. The minimal requirement is identification of biomarkers indicative of latent *M. leprae* infection, whereas the in ideal scenario the test also identifies *M. lepromatosis*. Both, in minimal and ideal scenario, a qualitative output is favoured, with results clearly visible to the naked eye, and the test must have an internal process control indicator.

Performance

For confirmatory tests, a minimal diagnostic assay should display a clinical sensitivity of $\geq 90\%$ and a specificity of $\geq 99\%$ for the detection of *M. leprae*. The assay should yield results within 4 hours, and these results must maintain their stability for at least 30 minutes post-analysis. Operational throughput should exceed 100 tests per technician per day. Assay stability should be ≥ 18 months when stored at temperatures ranging from 4 to 40 °C and at 75% relative humidity. The testing procedure should be limited to maximum 15 user steps, of which a maximum of five steps should be timed.

An ideal confirmatory test would be capable of detecting both *M. leprae* and *M. lepromatosis*, maintaining a clinical sensitivity of $\geq 90\%$ but with a specificity of $\geq 99.9\%$. A field-deployable version of the assay should deliver results in less than 30 minutes, with the stability of results extending to at least 24 hours. Operational throughput should surpass 10 tests

per technician per hour. The stability criterion for the ideal test should extend to ≥ 24 months under the aforementioned temperature and humidity conditions. Conducting the analysis should be possible by performing maximum five steps, out of which no more than one should be timed.

For test for subclinical infection, the minimal test should have a clinical sensitivity of $\geq 81\%$ and a specificity of $\geq 99.5\%$ for the detection of *M. leprae*. The time to results should be less than 2 hours, and these results should maintain their stability for at least 30 minutes post-analysis. The expected throughput is more than seven tests per tester per hour. The stability of these assays should be no less than 18 months within the temperature range of 4 to 40 °C and at maximum 75% relative humidity. The analysis should be maximum two-timed steps and maximum eight user steps.

An ideal contact tracing test would detect both *M. leprae* and *M. lepromatosis* with a clinical sensitivity of $\geq 94\%$ and a specificity of $\geq 99.9\%$. The test should produce results in less than 30 minutes, with results remaining stable for at least 24 hours. The throughput should be more than 10 tests per tester per hour, with stability guaranteed for ≥ 24 months under the above specified storage conditions. The test should be designed for ease of use, with maximum one timed step and maximum five user steps. Both minimal and ideal tests should yield binary outcomes.

Product configuration

A minimal confirmatory test must adhere to the relevant standards, such as ASTM International (ASTM) D4169–05 and international standard organization (ISO) 11607–1:2006, or their equivalents. Test components or consumables for laboratory use should be able to be stored and shipped at temperatures ranging from 0–4 °C. Cold storage is an acceptable condition for any laboratory-based assays. For laboratory-based tests, support should be available from the equipment manufacturer for problem-solving and use of the equipment.

All materials included in the assay should be universally compatible with standard laboratory biohazard waste management protocols. Labelling and instructions must comply with the pertinent CE Mark under In Vitro Diagnostic Regulation stipulations (or other recognized regulatory authorities, such as the United States Federal Drug Administration under 21 CFR 820), alongside guidelines set forth by the WHO prequalification processes.³⁷

The ideal product configuration for confirmatory tests and both the minimal and ideal scenarios for test for subclinical infection have the same requirements. These assays should be point-of-care tests that adhere to the specified ASTM and ISO standards or their accepted

equivalents, eliminating the need for cold-chain transport. They should be storable at ambient temperatures ranging from 2 to 40 °C without requiring service interventions. The assays must not include any materials that are not compatible with standard biohazard waste disposal procedures in a laboratory environment. Packaging must consider daily throughput to minimize unnecessary waste. Finally, the labelling and usage instructions should align with those established for the minimal requirements for confirmatory tests.

Product cost and channels

The minimal requirements for the cost of a confirmatory test are below 3 United States dollars (US\$). Capital expenditure for the deployment of such tests should remain within a threshold of US\$ 5 000. The anticipated lead time for product availability should be less than eight weeks. The market introduction should be focused on countries with endemic leprosy, with regulatory prerequisites encompassing: (i) compliance with CE Mark under In Vitro Diagnostic Regulation or other relevant stringent regulatory authorities; (ii) export certifications from the country of manufacture; (iii) WHO prequalification, contingent upon necessity and relevance; and (iv) national registration in accordance with the regulatory demands of target countries.

The pricing for an ideal confirmatory test is set at below US\$ 1, not accounting for additional expenses like logistics, storage and other operational costs related to national procurement for neglected tropical diseases programmes. Capital costs for these laboratory-based tests should not exceed US\$ 5 000 in a minimal scenario; however, ideally, given the point-of-care nature of the test, no capital investment would be required. The expected lead time for the product should be less than six weeks. The target markets and required registrations for launch should match those outlined for the minimal test.

For test for subclinical infection, the financial and distribution criteria remain consistent with those for the ideal confirmatory test, with the stipulation that capital costs can go up to US\$ 2 000 for both the minimal and ideal versions. Minimally, the contact tracing test is specifically designed for countries that are actively involved in leprosy contact tracing and post-exposure prophylaxis programmes.

Comparative analysis

When comparing 38 requirements across the five categories for both minimal and ideal requirements, we found that 10.5% (4/38) of the requirements were identical for both profiles, regardless of whether we were looking at the minimal or ideal criteria. When comparing the ideal confirmatory test with both levels of test for subclinical infection, 36.8% (14/38) of the

requirements were the same. Furthermore, 34.2% (13/38) of the requirements were alike for both types of tests when considering either the minimal or ideal scenario. Only 18.4% (7/38) of the requirements were different between the two types of tests (Fig. 1).

Discussion

Here we have outlined the minimal and ideal requirements listed in the target product profiles for a confirmatory test and contact tracing test for leprosy.^{9,10} Development of new test complying with the requirements could improve testing outcomes, avoiding complications such as unethical treatment, emotional and physical effects, social exclusion and higher costs.³⁸

Three high-risk factors must be considered to ensure the successful development of a diagnostic test for leprosy, as highlighted for both target product profiles. First, the diagnostic tests aim to identify biomarkers indicative of active infection with *M. leprae* and *M. lepromatosis*. However, *M. leprae* may remain dormant for years and reactivate under certain immune conditions, complicating the identification of recent infections. Despite the challenges and time required to qualify and validate new markers, it is crucial to advance test development using the currently available analytes to prevent delays in development. Second, due to the similar clinical presentations of other mycobacterial infections (like *M. tuberculosis*) and skin disorders prevalent in the same areas as leprosy is prevalent, the tests must differentiate between these conditions. The development of multiplex assays, which can detect multiple diseases simultaneously, could streamline patient care and diagnostics. Third, even in highly endemic areas, the prevalence of leprosy cases is so low that it poses unique diagnostic challenges; the specificity requirements are high³⁹ and the tests must be highly specific to avoid false positives and unnecessary treatment. While test developers may find these performance targets challenging, they are crucial to achieve to maintain low rates of both false positives and false negatives, especially as diseases approach elimination. Perfect accuracy is rarely possible with a single test. However, using multiple tests together, either serial testing or parallel testing, can improve the overall accuracy. Serial testing uses a sequence of more precise tests to confirm a diagnosis, while parallel testing checks for several disease indicators at once to enhance the detection process.³⁹

The target product profile outlines that the one of minimal requirements for a confirmatory test is high specificity for all types of leprosy, including manifestations with low bacilli level. While such specificity can be difficult to achieve, some studies demonstrated adequate sensitivity across paucibacillary and multibacillary leprosy.^{40–43} To ensure adequate performance across

leprosy manifestations, clinical validation studies should be set up at multiple sites worldwide to demonstrate that acceptance criteria are met for all types of leprosy.

As leprosy incidence decreases, confirmation of diagnosis happens in environments that can support moderately complex evaluations, laboratory-based tests need to satisfy the basic requirements for a confirmatory diagnosis of leprosy. Given the strict clinical sensitivity and specificity requirements, laboratory-based tests might be more suitable than point-of-care tests to meet these performance criteria. On the contrary, to perform WHO-recommended contact tracing for individuals diagnosed with *M. leprae* infection, a test that can be implemented at the point-of-care is essential for to ensure usefulness in field settings. In all cases, ensuring immediate availability of appropriate medical interventions following the detection of leprosy or *M. leprae* infection is crucial for ethical reasons.

Currently, WHO only recommends use of single dose rifampicin for post-exposure-prophylaxis.¹¹ However, in household contacts of newly diagnosed leprosy cases, a single dose of rifampicin may not suffice, as the observed risk reduction for developing leprosy is only 50–60% and this protection lasts for merely two years after administration.^{44,45} Thus, additional tools to detect *M. leprae* infection, together with improved post-exposure-prophylaxis, is desirable. Close collaboration, coordination and alignment is required with teams working on other post-exposure-prophylaxis regimens to ensure concurrent availability of these regimens along with the appropriate diagnostic tools. Two trials are currently ongoing: one in Bangladesh, Brazil, India and Nepal and another in the Comoros.^{46,47} In these trials, field teams closely collaborate with researchers developing and evaluating immunodiagnostic and molecular tests for monitoring the direct and longitudinal effects and efficacy of various forms of post-exposure-prophylaxis on development of leprosy.^{46,47} Clinical validation studies of both diagnostics and treatment interventions may depend on and benefit from each other.

A factor not covered in this research is the impact of stigma associated with leprosy, leading to discrimination against affected individuals and their families, which can hinder timely diagnosis and treatment. Long standing stigmas associated with leprosy necessitate diagnostic approaches that also consider social factors such as privacy and discretion, similar to contact tracing efforts undertaken in human immunodeficiency virus testing.

In conclusion, investing in diagnostics for both disease and infection is critical to significantly reduce new cases of leprosy worldwide. WHO target product profiles for leprosy

diagnostics can help guide development of appropriate tools. The goal is to not only manage leprosy but also to prevent it, thereby reducing its global burden.

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Fig. 1. **Comparative analysis matrix for target product profiles for leprosy diagnostics**

Category				
Product use summary	Design	Performance	Product configuration	Product cost and channels
Intended use	Portability	Species differentiation or detection	Shipping conditions	Target pricing per test
Target population	Instrument or power requirement	Diagnostic or clinical sensitivity	Storage conditions	Capital cost
Lowest infrastructure level	Water requirement	Diagnostic or clinical specificity	Service and support	Product lead times
Lowest level user	Maintenance and calibration	Time to results	Waste disposal	Target launch countries
Training requirements	Sample type/collection	Result stability	Labelling and instructions for use	Product registration (substantiation to regulatory body of product claims)
	Sample preparation or transfer device	Throughput		
	Sample volume	Target shelf-life or stability		
	Target analyte	Ease of use		
	Type of analysis	Ease of results interpretation		
	Detection	Operating temperature		
	Quality control			
	Supplies needed			
	Safety			

Color legend

- Unique to each target product profile and performance level (4 of 38 requirements)
- Same between both target product profiles for ideal tests and/or minimal tests separately (13 of 38 requirements)
- Same between ideal test in confirmatory test and both minimal and ideal tests in test for subclinical infection (14 of 38 requirements)
- Same between both target product profiles for both ideal and minimal tests together (4 of 38 requirements)
- Same between ideal and minimal test in one or both the both target product profiles (3 of 38 requirements)

Note: Target product profile 1 is a diagnostic test to confirm leprosy in individuals presenting with clinical signs and symptoms⁹ and target product profile 2 is a diagnostic test to identify *Mycobacterium leprae* infection in asymptomatic household and familial contacts of diagnosed leprosy patients.¹⁰