



**Noncommercial culture and drug-susceptibility testing
methods for screening patients at risk for multidrug-
resistant tuberculosis**

Policy statement

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Abbreviations

CI	confidence interval
CRI	colorimetric redox indicator
DST	drug-susceptibility testing
GRADE	grades of recommendation assessment, development and evaluation
LJ	Lowenstein-Jensen
MDR	multidrug-resistant
MODS	microscopic observation of drug susceptibility
NRA	nitrate reductase assay
STAG-TB	Strategic and Technical Advisory Group for Tuberculosis
TB	tuberculosis
WHO	World Health Organization

Executive summary

Commercial liquid culture systems and molecular line-probe assays have been endorsed by the World Health Organization (WHO) as gold standards for rapid detection of multidrug-resistant (MDR) tuberculosis (TB); however, because of technical complexity, cost and the requirement for sophisticated laboratory infrastructure, use of these techniques has been limited in many resource-constrained settings. Several noncommercial culture and drug-susceptibility testing (DST) methods have been developed specifically for settings with limited access to sophisticated laboratory infrastructure and technical expertise. Several rapid, inexpensive methods have shown initial promise. The most advanced are microscopic observation of drug susceptibility (MODS), colorimetric redox indicator (CRI) methods, thin-layer agar methods, the nitrate reductase assay (NRA) and mycobacteriophage-based assays.

- *MODS*: a microcolony direct method in liquid culture, based on inoculation of specimens into drug-free and drug-containing media, followed by microscopic examination of early growth;
- *thin-layer agar*: a microcolony direct method on solid culture, based on inoculation of specimens into drug-free and drug-containing media, followed by microscopic examination of early growth;
- *CRI methods*: indirect methods based on the reduction of a coloured indicator added to liquid culture medium on a microtitre plate after exposure of *Mycobacterium tuberculosis* strains to anti-TB drugs in vitro;
- *NRA*: a direct or indirect method based on the ability of *M. tuberculosis* to reduce nitrate, which is detected by a colour reaction; and
- *phage-based assays*: assays in which bacteriophages are used to infect and detect the presence of viable *M. tuberculosis* in clinical specimens and culture isolates.

In 2009, the strength of the evidence for these noncommercial methods was assessed by WHO, following standards appropriate for evaluating both the accuracy of new TB diagnostics and their effect on patients and public health. The results showed that the current evidence is insufficient to recommend the use of thin-layer agar or phage-based assays. There was considered to be sufficient evidence for the use of CRI methods, MODS and NRA under clearly defined programme and operational conditions, in reference laboratories and under strict laboratory protocols, and as an interim solution while capacity for genotypic or automated liquid culture and DST is being developed.

Under these conditions, MODS and NRA are recommended for direct testing of sputum specimens. Together with CRI methods, MODS and NRA are also recommended for indirect DST of *M. tuberculosis* isolates grown in conventional culture. The time to detection of MDR-TB may not necessarily be faster with indirect testing, and none of these methods can detect extensively drug-resistant TB. Conventional culture and DST capacity are therefore still required in all settings.

Policy statement

Noncommercial culture and drug-susceptibility testing methods for screening patients at risk for multidrug-resistant tuberculosis

1. Background

Early detection of drug resistance in TB ensures appropriate treatment regimens for patients and therefore better TB control. The spread of drug-resistant strains of *M. tuberculosis* and the management of patients with drug-resistant disease are formidable obstacles faced by national TB control programmes, which are compounded by a lack of appropriate diagnostic tools and vastly inadequate laboratory capacity.

Rapid methods for DST are crucial, in view of the increasing rates of MDR-TB worldwide and the emergence of extensively drug-resistant TB, with high HIV-associated mortality. Conventional culture and DST methods entail long delays for confirmation of mycobacterial growth and for detection of drug resistance, during which time patients may be inappropriately treated, drug-resistant strains may continue to spread, and resistance may be amplified. Rapid diagnosis of TB and drug resistance therefore has obvious benefits for both patients and public health, including better prognosis, increased survival, prevention of acquisition of further drug resistance and reduced spread of drug-resistant strains to vulnerable populations.

No single test currently satisfies all the demands for 'quick', 'cheap', and 'easy' kits. Commercially available liquid culture systems and molecular line-probe assays for rapid detection of MDR-TB have been endorsed by WHO; however, because of their complexity and cost and the requirement for sophisticated laboratory infrastructure, uptake has been limited in many resource-constrained settings.

Several noncommercial culture and DST methods have been developed, specifically for use in laboratories that lack access to more sophisticated infrastructure and techniques. Of these, MODS, CRI methods, thin-layer agar methods, the NRA and mycobacteriophage-based assays have shown initial promise as being rapid and inexpensive. These tests were recently assessed by WHO, and the results are summarized below.

- *MODS*: a microcolony direct method in liquid culture, based on inoculation of specimens into drug-free and drug-containing media, followed by microscopic examination of early growth;
- *thin-layer agar*: a microcolony direct method on solid culture, based on inoculation of specimens into drug-free and drug-containing media, followed by microscopic examination of early growth;
- *CRI methods*: indirect methods based on the reduction of a coloured indicator added to liquid culture medium on a microtitre plate after exposure of *M. tuberculosis* strains to anti-TB drugs in vitro;
- *NRA*: a direct or indirect method based on the ability of *M. tuberculosis* to reduce nitrate, which is detected by a colour reaction; and
- *phage-based assays*: assays in which bacteriophages are used to infect and detect the presence of viable *M. tuberculosis* in clinical specimens and culture isolates.

There was considered to be sufficient evidence for the use of CRI methods, MODS and NRA under clearly defined conditions, as outlined below.

2. Evidence for policy formulation

2.1 Synthesis of evidence

In September 2009, WHO assessed the evidence base for selected noncommercial culture and DST methods in a systematic, structured way. The first step was a systematic review and meta-analysis of published and unpublished data with standard methods appropriate for studies of diagnostic accuracy. The second step was the convening of an expert group to evaluate the strength of the evidence, recommend operational and logistical considerations for using noncommercial culture and DST methods within national TB control programmes and identify gaps to be addressed by future research. The third step was presentation of draft recommendations to the WHO Strategic and Technical Advisory Group for Tuberculosis (STAG-TB) for endorsement.

In accordance with current WHO standards for evidence assessment in the formulation of policy recommendations, the grades of recommendation assessment, development and evaluation (GRADE) system (1) was used by the Expert Group to assess the findings of the systematic review. This approach provides a systematic, structured framework for evaluating the accuracy of new interventions and their impact on patients and public health.

The Expert Group's findings and the final GRADE evaluation (2) were presented to STAG-TB in November 2009. STAG-TB recognized the evidence base on CRI methods, MODS and NRA and advised WHO to proceed with policy recommendations under clearly defined premises and conditions. STAG-TB also asked WHO to prepare an overarching policy framework to guide the use of new TB diagnostics, methods and approaches at country level (3).

This document provides a pragmatic summary of the evidence and recommendations related to CRI methods, MODS and NRA, and should be read in conjunction with the detailed findings from the Expert Group report (which include the GRADE tables) and the WHO framework for using TB diagnostics (2). The framework gives the context for use of one or more of the currently approved WHO diagnostic tools and methods in relation to country infrastructure, resources, TB epidemiology and TB policy reform.

The existing TB diagnostic tools are not mutually exclusive: they can be used in various combinations in country screening and diagnostic algorithms, which are highly setting- and resource-specific. Expert laboratory input is therefore needed to define the most cost-effective and efficient algorithms for individual countries, guided by WHO standards (e.g. for laboratory biosafety) and procedures and in the context of overall, integrated, laboratory strengthening.

2.2 Management of declarations of interest

Expert Group members were asked to submit completed declaration of interest forms, which were reviewed by the WHO secretariat before the Expert Group meeting. None of the members declared any conflict of interest. The declaration of interest statements were summarized by the co-chair of the Expert Group meeting at the start of the meeting. No additional declarations were made.

Selected individuals with intellectual or research involvement in the methods reviewed were invited as observers to provide technical input and answer technical questions. These individuals did not participate in the GRADE evaluation and were asked to leave the meeting during the final discussions, when the recommendations were developed. They were also not involved in writing the final meeting report, nor in preparation of the STAG-TB documentation or the final WHO policy statements.

The process for evidence synthesis and policy development was reviewed by the WHO Guidelines Review Committee, and the policy recommendations were approved in June 2010.

The target date for review is 2015.

2.3 Premises for adopting new diagnostic tools and methods

- The current gold standards for culture and DST (conventional solid and automated liquid culture and DST systems, molecular line-probe assays) should be phased in and scaled up as a matter of urgency and priority.
- Genotypic (molecular) methods have considerable advantages in scaling up programme management and surveillance of drug-resistant TB because of the speed of diagnosis, standardized testing, potentially high through-put and biosafety.
- Rapid DST methods applied directly on sputum specimens are of greatest benefit for patients and public health. Rapid DST is essential to identify patients at risk for MDR-TB and should be a first priority in screening strategies.
- Rifampicin resistance is a reliable proxy for MDR-TB. Once MDR-TB has been confirmed, additional first- and second-line DST should be performed on the basis of current WHO recommendations and available laboratory capacity.
- Noncommercial methods are less expensive, make laboratories independent of single-test commercial providers and may be an incentive to commercial providers to lower prices. Noncommercial methods are, however, prone to error due to lack of standardization and local variations in methodology.
- The evidence base for selected noncommercial culture and DST methods has been reviewed and the performance of these methods found to be acceptable for use under stringent laboratory protocols in reference or national laboratories in selected settings.
- Techniques and methods for culture and DST are not mutually exclusive. Molecular line-probe assays and the selected noncommercial culture and DST methods are suitable for direct application on smear-positive specimens only. Conventional culture is still required for smear-negative specimens, while conventional DST is needed to detect extensively drug-resistant TB.

3. Summary of results

3.1 Colorimetric redox indicator methods

CRI methods are indirect tests, done on *M. tuberculosis* isolates grown from conventional culture. The time to diagnosis of MDR is therefore not faster than with conventional phenotypic DST in liquid culture or genotypic testing with line-probe assays.

CRI methods are highly sensitive (pooled estimate, 98%; 95% confidence interval [CI], 96–99%) and specific (pooled estimate, 99%; 95% CI, 99–100%) for the detection of rifampicin resistance and also isoniazid resistance (pooled sensitivity, 97%; 95% CI, 96–98%; pooled specificity, 98%; 95% CI, 97–99%).

In comparison with the conventional indirect proportion DST method on Lowenstein-Jensen (LJ) medium, CRI methods require additional staff skills, similar equipment but additional consumables that may be difficult to obtain. In comparison with the conventional indirect proportion method in liquid culture medium, CRI methods require similar staff skills, less equipment and consumables that may be readily available.

CRI methods have been standardized, and testing protocols are available (4). The methods require manipulation of concentrated suspensions of mycobacteria, with a high risk for aerosol creation. CRI methods should therefore be performed under laboratory biosafety level 3 conditions.

CRI methods are suitable for use at reference laboratory level; scale-up and decentralization to lower-level laboratories are not recommended.

3.2 Microscopically observed drug susceptibility

MODS can be performed as a direct or an indirect test, by observing microcolony growth and typical cord formation of *M. tuberculosis* in sealed microtitre plates containing liquid culture medium, through an inverted microscope.

Studies on the accuracy of combined (direct and indirect) use showed that MODS is highly sensitive (pooled estimate, 98%; 95% CI, 95–99%) and specific (pooled estimate, 99%; 95% CI, 96–100%) for the detection of rifampicin resistance and slightly less so for isoniazid (pooled sensitivity, 91%; 95% CI, 87–95%). High sensitivity and specificity are retained in direct MODS testing.

Initial concerns about microscopic differentiation of *M. tuberculosis* from nontuberculous mycobacteria were addressed by a revised MODS platform that includes a microtitre well containing *p*-nitrobenzoic acid. *M. tuberculosis* fails to grow in the presence of this compound. Absence of growth combined with cord formation in wells that do not contain *p*-nitrobenzoic acid are therefore indicative of *M. tuberculosis* (similar to current WHO recommendations for use of *p*-nitrobenzoic acid in conventional solid culture and DST methods). Addition of a *p*-nitrobenzoic acid-containing well to the microtitre plate also obviates reopening of the plate and consequently reduces the biosafety risk.

In comparison with the conventional indirect proportion DST method on LJ medium, MODS requires additional staff skills, an additional inverted microscope and additional consumables that may be difficult to obtain. In comparison with the conventional indirect proportion method in liquid culture medium, MODS requires additional staff skills, less equipment and consumables that may be readily available.

MODS has been standardized, with testing protocols and online support available through a dedicated website. The biosafety risk associated with use of the revised MODS platform is considered to be similar to that of conventional culture on solid medium and therefore requires biosafety level 2 precautions.

MODS is suitable for use at reference laboratory level; scaling-up and decentralization to lower-level laboratories is not recommended.

3.3 Nitrate reductase assay

The NRA can be used as a direct test on smear-positive sputum specimens or as an indirect test on *M. tuberculosis* isolates grown from conventional solid culture. Indirect testing with NRA is therefore not faster than conventional phenotypic DST with liquid media.

Studies on combined (direct and indirect) use showed that NRA is highly sensitive (pooled estimate, 97%; 95% CI, 95–98%) and specific (pooled estimate, 100%; 95% CI, 99–100%) for the detection of rifampicin resistance and for isoniazid resistance (pooled sensitivity, 97%; 95% CI, 95–98%; pooled specificity, 99%; 95% CI, 99–100%). The diagnostic accuracy of NRA by direct testing alone did not differ significantly from that of combined testing, although the sensitivity values in individual studies showed wider variation (range, 85–100%), and the data were limited.

The reagents for NRA are nonproprietary and relatively inexpensive. In comparison with the conventional indirect proportion DST method on LJ medium, NRA requires similar staff skills, similar equipment and no additional consumables; in comparison with the conventional indirect proportion method in liquid culture medium, NRA requires fewer staff, equipment and consumables.

Procedures for NRA have been standardized, and testing protocols are available (4). As NRA involves solid culture media, the biosafety requirements are similar to those for conventional solid culture (biosafety level 2); however, addition of NRA reagent requires regular opening of tubes, which poses a significant risk for aerosol generation. This should therefore be done inside an appropriate biological safety cabinet.

NRA is suitable for use at reference laboratory level; scaling-up and decentralization to lower-level laboratories should not be considered until those laboratories have demonstrated proficiency in performing solid culture.

4. Policy recommendations

The GRADE process confirmed that there is sufficient generalizable evidence to recommend the use of selected noncommercial culture and DST methods as an interim solution in resource-constrained settings, under clearly defined programme and operational conditions, while capacity for genotypic or automated liquid culture and DST is being developed.

With due consideration of the issues raised under section 2.2 above, WHO recommends the selective use of one or more of the following noncommercial culture and DST methods in reference laboratories, under strict laboratory protocols:

- *CRI methods*, as indirect tests on *M. tuberculosis* isolates from patients suspected of having MDR-TB, recognizing that the time to detection of MDR-TB is not faster (but less expensive) than with conventional DST methods with commercial liquid culture or molecular line-probe assays;
- *MODS*, as direct or indirect tests for rapid screening of patients suspected of having MDR-TB; and
- *NRA*, as direct or indirect tests for screening patients suspected of having MDR-TB, recognizing that the time to detection of MDR-TB in indirect application is not faster than with conventional DST methods with liquid culture.

To ensure testing standards and consistency, WHO will:

- review existing documents on technical procedures, standard operating procedures and biosafety requirements for each method; and
- prepare and disseminate procedures for internal quality control and external quality assurance for each method.

5. Intended audience

This policy statement should be used to guide use of noncommercial culture and DST methods for TB diagnosis in national TB control programmes. It is intended for use by national TB control programme managers and laboratory directors, in coordination with external laboratory consultants, donor agencies, technical advisors, laboratory technicians, laboratory equipment procurement officers, warehouse managers, other service providers, other relevant government officials and implementing partners involved in country-level TB laboratory strengthening. People responsible for programme planning, budgeting, resource mobilization and training for TB diagnostic services may also benefit from reading this document.

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3. http://www.who.int/tb/advisory_bodies/stag/en/index.html
4. <http://www.tbevidence.org/rescentre/sop.htm>

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