

# Xpert MTB/RIF implementation manual

Technical and operational ‘how-to’:  
practical considerations

NEW DIAGNOSTIC TESTS  
**IMPLEMENTATION MANUAL**  
TUBERCULOSIS  
DIAGNOSIS  
RESISTANCE  
PULMONARY TB  
RIFAMPICIN  
TB  
DRUG-RESISTANCE  
TB/HIV  
RAPID TB TEST  
PERFORMANCE  
ACCURACY  
RECOMMENDATIONS  
MYCOBACTERIUM  
MOLECULAR DIAGNOSTICS



World Health  
Organization

# **Xpert MTB/RIF implementation manual**

Technical and operational ‘how-to’:  
practical considerations



**World Health  
Organization**

## WHO Library Cataloguing-in-Publication Data

Xpert MTB/RIF implementation manual: technical and operational 'how-to'; practical considerations.

1. Tuberculosis, Multidrug-resistant - diagnosis. 2. Tuberculosis - diagnosis. 3. Rifampin - pharmacology. 4. Mycobacterium tuberculosis - isolation and purification. 5. HIV infections - diagnosis. 6. Sensitivity and specificity. 7. Manuals. I. World Health Organization.

ISBN: 978 92 4 150670 0

(NLM classification: WF 310)

© World Health Organization 2014

All rights reserved. Publications of the World Health Organization are available on the WHO web site ([www.who.int](http://www.who.int)) or can be purchased from WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland (tel.: +41 22 791 3264; fax: +41 22 791 4857; e-mail: [bookorders@who.int](mailto:bookorders@who.int)).

Requests for permission to reproduce or translate WHO publications – whether for sale or for noncommercial distribution – should be addressed to WHO Press through the WHO web site ([http://www.who.int/about/licensing/copyright\\_form/en/index.html](http://www.who.int/about/licensing/copyright_form/en/index.html)).

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area, or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by the World Health Organization to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall the World Health Organization be liable for damages arising from its use.

Designed by GPS Publishing

Printed in France

WHO/HTM/TB/2014.1

# Contents

---

<b>1. BACKGROUND</b>	<b>VII</b>
<b>2. POLICY DEVELOPMENT</b>	<b>1</b>
2.1. PROCEDURE FOR DEVELOPING POLICIES	1
2.2. INITIAL POLICY RECOMMENDATIONS AND FOLLOW UP	1
2.3. POLICY UPDATE	2
2.4. SUMMARY OF WHO'S 2013 POLICY RECOMMENDATIONS	3
<b>3. EVIDENCE BASE</b>	<b>5</b>
3.1. EVIDENCE AVAILABLE AT THE END OF 2010	5
3.2. EVIDENCE BASE AS OF FEBRUARY 2013	6
<b>4. POSITIONING THE TEST AND SELECTING A SITE</b>	<b>9</b>
<b>5. TESTING AND MANAGING PATIENTS</b>	<b>10</b>
5.1. SELECTING INDIVIDUALS TO BE TESTED	10
5.2. TEST PERFORMANCE	12
5.3. INTERPRETING RESULTS FROM XPERT MTB/RIF	14
5.4. DIAGNOSTIC ALGORITHMS	16
5.5. MONITORING PATIENTS DURING TREATMENT	18
5.6. USING XPERT MTB/RIF IN DRUG RESISTANCE SURVEYS	18
5.7. USING XPERT MTB/RIF IN TB PREVALENCE SURVEYS	19
<b>6. CASE DEFINITIONS AND PATIENT REGISTRATION</b>	<b>21</b>
6.1. TB CASE	21
6.2. CLASSIFICATION BASED ON TYPE OF DRUG RESISTANCE	21
6.3. REGISTRATION OF TB CASES DIAGNOSED USING XPERT MTB/RIF	21
<b>7. PRACTICAL CONSIDERATIONS</b>	<b>23</b>
7.1. OPERATIONAL CONSIDERATIONS	23
7.2. PREFERENTIAL PRICING AND ELIGIBLE COUNTRIES	28
7.3. IMPLEMENTATION COSTS	29
7.4. PUBLIC HEALTH IMPACT OF XPERT MTB/RIF	29
<b>8. MONITORING AND EVALUATION</b>	<b>32</b>
8.1. ROUTINE MONITORING	32
8.2. MEASURING THE IMPACT	33

<b>9. COLLABORATION AND COORDINATION</b>	<b>35</b>
9.1. KNOWLEDGE SHARING	35
9.2. DONORS SUPPORTING THE ROLL-OUT OF XPERT MTB/RIF	35
 ANNEX 1. COUNTRIES ELIGIBLE FOR PREFERENTIAL PRICING ON EQUIPMENT AND CONSUMABLES.	 37
ANNEX 2. STANDARD OPERATING PROCEDURE (SOP) FOR PROCESSING EXTRAPULMONARY SPECIMENS (CSF, LYMPH NODES AND OTHER TISSUES) FOR XPERT MTB/RIF ASSAY.	39

## Acknowledgements

---

This document was prepared by a writing group under the coordination of the Laboratories, Diagnostics and Drug Resistance unit of WHO's Global TB Programme.

The first edition titled *Rapid implementation of the Xpert MTB/RIF diagnostic test* was based on the outcomes of a Global consultation on implementation and scale-up of the Xpert MTB/RIF assay convened by WHO in December 2010, together with the findings from WHO's first Expert Group Meeting on Xpert MTB/RIF, which had been convened in September 2010. This current edition of the implementation manual has been updated to reflect findings from the Expert Group Meeting convened in May 2013, and the experiences of early implementing countries and technical partners, including those experiences shared at the three annual Global Forums of implementers held by WHO in 2011, 2012 and 2013.

The initial data underlying the evidence base for the Xpert MTB/RIF assay were provided by FIND (Foundation for Innovative New Diagnostics). Subsequent evidence on the performance of Xpert MTB/RIF has been based on operational experiences and the body of work published by implementers and researchers from around the world. The development of the document was coordinated by Fuad Mirzayev, who also prepared the first draft.

The development and publication of this document has been made possible with the support of the Global Fund to Fight AIDS, Tuberculosis and Malaria, the United States Agency for International Development (USAID), UNITAID, the United States President's Emergency plan for AIDS Relief (PEPFAR) and WHO.

### Writing Group

The writing group comprised Fuad Mirzayev, Wayne van Gemert, Christopher Gilpin and Karin Weyer.

### The following individuals also contributed to the writing and review of this manual

Heather Alexander (Centers for Disease Control and Prevention, United States), Vineet Bhatia (WHO Headquarters), Daniela Maria Cirillo (TB Supranational Reference Laboratory, Italy), Jacob Creswell (Stop TB Partnership), William Coggin (Office of the United States Global AIDS Coordinator, United States), Armand Van Deun (TB Supranational Reference Laboratory, Belgium), Dennis Falzon (WHO Headquarters), Philippe Glaziou (WHO Headquarters), Ernesto Jaramillo (WHO Headquarters), Sanne van Kampen (KNCV, Netherlands), Richard Lumb (TB Supranational Reference Laboratory, Australia), Knut Lönnroth (WHO Headquarters), Alberto Matteelli (WHO Headquarters), Ikushi Onozaki (WHO Headquarters), Daniel Orozco (FIND, Switzerland), Suvanand Sahu (Stop TB Partnership), Rohit Sarin (National Institute of TB & Respiratory Diseases, India), Thomas Shinnick (Centers for Disease Control and Prevention, United States), Wendy Stevens (National Health Laboratory Service, South Africa), Mukund Uplekar (WHO Headquarters), Francis Varaine (Médecins Sans Frontières, France), Fraser Wares (WHO Headquarters), Matteo Zignol (WHO Headquarters).

## Abbreviations

---

AFB	acid-fast bacilli
CFU	colony-forming unit
CI	confidence interval
CrI	credible interval
CRS	composite reference standard
CSF	cerebrospinal fluid
DR-TB	drug-resistant TB
DST	drug-susceptibility testing
FIND	Foundation for Innovative New Diagnostics
GRADE	Grading of Recommendations Assessment, Development and Evaluation
LED	light emitting diode
LPA	line probe assay
MDR-TB	multidrug-resistant tuberculosis
MGIT	mycobacterial growth indicator tube
NPV	negative predictive value
NTM	non-tuberculous mycobacteria
NTP	National Tuberculosis Programme
PCR	polymerase chain reaction
PEPFAR	United States President's Emergency Plan for AIDS Relief
PPV	positive predictive value
RRDR	Rifampicin Resistance Determining Region
<i>rpoB</i>	gene encoding for the $\beta$ -subunit of the DNA-dependent RNA polymerase of <i>Mycobacterium tuberculosis</i>
RR-TB	rifampicin-resistant TB
STAG-TB	Strategic and Technical Advisory Group for TB
USAID	United States Agency for International Development
UNITAID	Innovative Financing to Shape Markets for HIV/AIDS, Malaria and Tuberculosis
WHO	World Health Organization
XDR-TB	Extensively drug-resistant tuberculosis

## 1. Background

The global priorities for tuberculosis (TB) care and control are to improve case-detection and to detect cases earlier, including cases of smear-negative disease which are often associated with coinfection with the human immunodeficiency virus (HIV) and young age, and to enhance the capacity to diagnose multidrug-resistant tuberculosis (MDR-TB). MDR-TB poses formidable challenges due to the complex requirements for diagnosis and treatment, and HIV-associated TB is often misdiagnosed due to the limitations of conventional diagnostic techniques. Alarming increases in MDR-TB incidence, the global emergence of extensively drug-resistant TB (XDR-TB), documented institutional transmission, and rapid mortality in patients with MDR-TB or XDR-TB who are coinfecting with HIV have highlighted the urgent need for rapid diagnostic methods.

No single diagnostic test currently satisfies all the demands of “rapid”, “affordable”, and “easy”. The World Health Organization (WHO) has endorsed the use of commercially available liquid culture systems and molecular line probe assays (LPAs) to rapidly detect MDR-TB; however, due to the tests’ complexity and cost, as well as the need for sophisticated laboratory infrastructure and trained personnel, uptake has been limited in

to manipulating *Mycobacterium tuberculosis*. In addition, commercial nucleic acid amplification tests (NAATs) have proved to be less sensitive than microbiological culture, especially in cases of smear-negative TB. Moreover, culture largely remains necessary as a precursor to phenotypic drug-susceptibility testing (DST), and scaling up conventional culture and DST services is still slow and expensive, compounded by huge demands on laboratory infrastructure and human resources.

During 1996-2010, with support from the United States National Institutes of Health<sup>1</sup> and the Bill and Melinda Gates Foundation, the Foundation for Innovative New Diagnostics (FIND) partnered with Cepheid (Sunnyvale, CA, United States) and the University of Medicine and Dentistry of New Jersey to develop an automated, cartridge-based NAAT for TB that is based on the GeneXpert® multidisease platform. The GeneXpert system was launched in 2004, and it simplifies molecular testing by fully integrating and automating the three processes required for real-time PCR-based molecular testing (that is, specimen preparation, amplification and detection). The system consists of an instrument, personal computer, barcode scanner and preloaded software; single-use disposable cartridges contain lyophilized

预览已结束，完整报告链

<https://www.yunbaogao.cn/report/index/r>