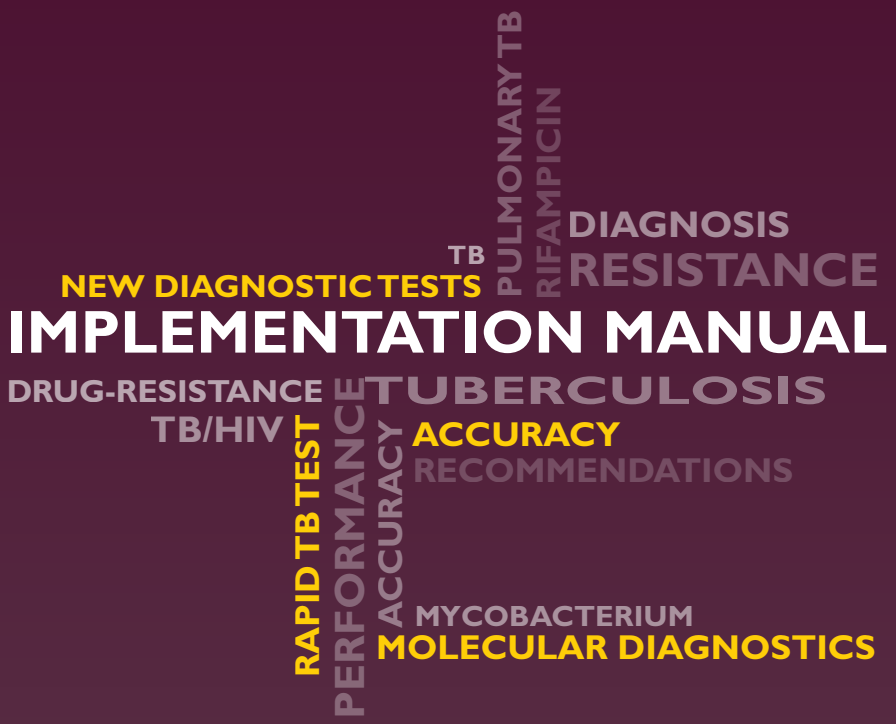
Xpert MTB/RIF
implementation manual

Technical and operational 'how-to':
practical considerations



World Health Organization

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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.

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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
rpoB	gene encoding for the ß-subunit of the DNA-dependent RNA polymerase of *Mycobacterium tuberculosis*
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 coinfected 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[1] 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