INT J TUBERC LUNG DIS 23(7):774–782

http://dx.doi.org/10.5588/ijtld.18.0715

STATE OF THE ART SERIES
MDR-TB
Series editors: C Horsburgh, Christoph Lange and Carole Mitnick
NUMBER 5 IN THE SERIES

Tackling drug-resistant tuberculosis: we need a critical synergy of product and process innovations

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SUMMARY

The End TB Strategy diagnostic pillar calls for access to high-sensitivity diagnostic testing and universal rapid drug susceptibility testing (DST). The recommended diagnostic technologies available in low and middle-income, high-burden countries for multidrug-resistant tuberculosis (MDR-TB) are essentially limited to Xpert® MTB/RIF and MTB/RIF Ultra assays, culture DST and the line-probe assays. The primary reasons for slow scale-up are insufficient political will, and therefore, insufficient funding for qualified human resources, and safe laboratory and health system infrastructure. Innovative approaches to enable the private health sector to provide high-quality diagnosis are also needed. The Essential Diagnostics List provides impetus and a standard benchmark for the rational implementation of MDR-TB diagnostics, but the epidemic will ultimately only be favorably impacted by complete end-to-end solutions to patients that address the complete cascade of care, including patient-centered diagnosis and treatment of TB and MDR-TB, management of comorbidities and social protection. By scaling up access to the currently available diagnostics, we lay the groundwork for future innovations for rapid accurate diagnosis of MDR-TB, which in turn will bring us closer to meeting the targets in the End TB Strategy.

KEY WORDS: TB; multidrug-resistant; access; equity

TUBERCULOSIS (TB) is the world's leading cause of death from infectious disease.[1] In 2017, an estimated 10 million people fell ill with and 1.6 million died from TB,[1] and an estimated 558 000 people developed TB that was resistant to rifampicin (RMP), 82% of whom had multidrug-resistant TB (MDR-TB; i.e., in vitro resistance to at least RMP and isoniazid [INH]).[1] MDR-TB claimed an estimated 230 000 lives in 2017,[1] making TB also first as a cause of death attributable to antimicrobial resistance. In 2017, only 30% of the 6.6 million new and previously treated patients notified worldwide were tested for resistance to at least RMP, and only 25% of the estimated 558 000 MDR/RMP-resistant (RR) TB patients started treatment.[1] This tragedy—from the loss of each of these persons to the continued global spread of MDR-TB—is among our most pressing public health crises, and is driven in part by inadequate access to rapid, accurate diagnosis.

On 19 May 2014, the 67th World Health Assembly adopted the End TB Strategy, which includes universal drug susceptibility testing (DST) as a key component.[2] While DST is routinely performed in all TB patients in high-income countries, it is far from being a reality for the majority of TB patients in low- and middle-income countries (LMICs). This lack of

Previous articles in the series: **Editorial:** Horsburgh C. The MDR-TB epidemic—a status report. Int J Tuberc Lung Dis 2019; 23: 121. **Articles: No 1**: Cox V, Cox H, Pai M, Stillo J, Citro B, Brigden G. Health care gaps in the global burden of drug-resistant tuberculosis. Int J Tuberc Lung Dis 2019; 23: 125–135. **No 2**: Nathavitharana R R, Lederer P, Tierney D B, Nardell E. Treatment as prevention and other interventions to reduce transmission of multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 2019; 23: 396–404. **No 3**: Kendall E A, Sahu S, Pai M, et al. What will it really take to eliminate drug-resistant tuberculosis? Int J Tuberc Lung Dis 2019; 23: 535–546. **No 4**: Lange C, Aarnoutse R, Alffenaar J-W, et al. Management for patients with MDR-TB. Int J Tuberc Lung Dis 2019; 23: 645–662.

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Article submitted 22 October 2018. Final version accepted 7 April 2019.

Commercial liquid culture, rapid speciation strip tests, DST	Culture (growth-based)/phenotypic	2007	✓	✓
Molecular LPAs for first-line anti-TB drug resistance detection	NAAT/genotypic	2008	✓	✓
LED microscopy	Microscopy	2010	✓	
Xpert® MTB/RIF	NAAT/genotypic	2010	✓	✓
Selected non-commercial DST methods (MODS, CRI, NRA)	Phenotypic	2011		✓
Loop-mediated amplification test	NAAT/genotypic	2016	✓	
Urine LAM rapid test	Antigen detection test	2016	✓	
Molecular LPAs for second-line anti-TB drug resistance detection	NAAT/genotypic	2016		✓
Xpert® MTB/RIF Ultra	NAAT/genotypic	2017	✓	✓

Figure WHO-endorsed diagnostic technologies for TB detection and DST. DST = drug susceptibility testing; LPA = line-probe assay; NAAT = nucleic acid amplification test; TB = tuberculosis; LED = light-emitting diode; MODS = microscopic-detection drug susceptibility assay; CRI = colorimetric redox indicator; NRA = nitrate reductase assay; LAM = lipoarabinomannan; WHO = World Health Organization.

universal access to TB DST is an example of the inequities in global health care delivery.

Studies on the TB care cascade show just how complicated the journey is for the symptomatic patient at risk for MDR-TB, apart from the need for access to appropriate diagnostics.[3–5] In the first article of this State of the Art Series, Cox et al. commenced a discussion on the inequities in accessing care (including diagnosis) for drug-resistant TB (DR-TB) at critical points in the cascade, from the number of estimated cases to numbers successfully treated.[6] There are bottlenecks at every step: from initial health-care seeking motivation to access to an informed, enabled health care workforce supported by appropriate national clinical algorithms and adequate diagnostic availability through trained, equipped laboratory services, to a turnaround time that delivers actionable diagnostic results. The patient must then be able to access and complete appropriate treatment, issues that will be addressed in depth by other articles in this State of the Art Series.

HIGH-SENSITIVITY DIAGNOSIS AND UNIVERSAL RAPID DRUG SUSCEPTIBILITY TESTING

The diagnostic pillar of the End TB Strategy calls for access to high-sensitivity diagnostic testing and universal rapid DST.[2] The latter is defined as access to rapid DST for at least RMP for all persons with presumptive TB, and, if RMP resistance is detected, access to DST for at least fluoroquinolones (FQs) and second-line injectable agents.[2] As pointed out in the Global Plan to End TB 2016–2020,[7] and further clarified in an accompanying publication,[8] national governments should implement by 2020 initial diagnostic testing for their presumptive TB patients with a WHO-recommended rapid diagnostic test that can also detect resistance to RMP. Countries with high burdens of TB, MDR-TB and TB-HIV (human immunodeficiency virus) coinfection should have already accomplished this by 2018.[8] By 2025, ≥90% of people should be diagnosed using a WHO-recommended rapid test, and 100% of those diagnosed should have their isolates characterized using DST.[8]

Access to MDR-TB diagnosis is intuitively expected to improve patient care and 'bend the curve' of the MDR-TB epidemic by interrupting community transmission. Mathematical modelling has also been used to predict the impact of rapid DST implementation. In one model calibrated to the TB epidemic in India,[9] if 75% of persons with presumptive TB encountered over 3 years in the public sector had access to rapid DST, we might avert more than 180 000 cases of MDR-TB (95% confidence interval [CI] 44 187–317 077) between 2015 and 2025. The reality is more complicated than these models suggest; nonetheless, it is clear that we are responding too slowly to the health-related targets of the 2030 Sustainable Development Goals and that many countries are 'off target'.[10]

WHAT IS IN THE ARMAMENTARIUM FOR THE DIAGNOSIS OF MDR-TB?

Since 2007, the WHO has endorsed nine new TB diagnostics (Figure), and six of these technologies detect drug resistance: commercial liquid culture and DST; line-probe assays (LPAs) for first and second-line anti-tuberculosis drug resistance; the Xpert® MTB/RIF assay (Cepheid, Sunnyvale, CA, USA), the Xpert® MTB/RIF Ultra assay (Cepheid); and selected non-commercial DST methods. There are excellent recent reviews of the features of these recommended TB diagnostics,[11] and of progress toward their implementation.[12,13]

Compared with culture-based DST methods, molecular methods potentially offer the trifecta of speed,

accuracy, and improved laboratory safety. These detect mutations in the patient's *Mycobacterium tuberculosis* strain that confer drug resistance. The current impediment to perfect accuracy is that we have neither identified every mutation that confers resistance nor do we know if every mutation identified in phenotypically resistant strains are those that confer resistance. Nonetheless, current tests are able to diagnose >90% of MDR-TB, superbly reviewed in a recent consensus statement that reports the evidence on the definite correlation between certain nucleotide mutations and in vivo drug resistance.[14]

Xpert MTB/RIF and other cartridge-based nucleic acid amplification tests

The Xpert assay is an automated nucleic acid amplification test (NAAT) for rapid and simultaneous TB and RMP resistance detection using the GeneXpert® platform. Xpert has been referred to as a disruptive technology—one that has relatively rapidly displaced other technologies,[15–17] shaken up the status quo of enduring weeks to RMP resistance test results, and provided evidence of a functional approval pathway for other molecular diagnostics. Multiple follow-on technologies are available, including Truenat MTB RIF Dx (Molbio Diagnostics, Goa, India)[18] and the RealTi*me* MTB RIF/INH Resistance assay (Abbott Molecular, Des Plaines, IL, USA),[19] with several other molecular detection technologies under development. Important current technical limitations include the fact that the Xpert assay only tests for RMP resistance, and only tests for this resistance within the RMP resistance-determining region, which misses the Ile491Phe mutations that contribute to some of the RMP resistance in Southern Africa.[20]

Line-probe assays

Compared with phenotypic DST, LPAs substantially reduce the time to the accurate diagnosis of drug-resistant TB.[21] Unlike current versions of the Xpert assay, LPAs are approved to detect resistance to anti-tuberculosis drugs other than RMP,[22] and offer a rapid path for second-line drug resistance testing.[23] However, laboratory conduct of LPA technology is more complex and time-consuming than the Xpert assay. Yet to be recommended by the WHO, the FluoroType® MTBDR (Hain Lifescience, Nehren, Germany) is a new molecular DST method that, compared with LPA, requires less hands-on time, is faster (3 h), and offers the significant benefit of automated interpretation.[24]

Because current LPAs require specialized laboratory facilities and expertise, only patients with access to reference laboratories or whose jurisdictions have robust specimen transport mechanisms can benefit from their use. Assuming that serious innovations in rapid specimen transport are not imminent, similar to the mycobacterial culture and DST methods, LPAs are unlikely to revolutionize global access to universal rapid DST.

Whole-genome sequencing using next-generation sequencing technologies

Whole-genome sequencing (WGS) may be the next transformative molecular DST method in the diagnostic pipeline.[25–27] WGS is already routinely used for public health surveillance in some industrialized countries, and accumulating evidence suggests that WGS sets the highest bar among genotyping methods as an epidemiologic tool.[28,29]

However, the majority of presumptive TB patients presenting in resource-limited, high-burden settings are far from benefiting from routine WGS. To bring WGS to the people most in need, key translational challenges include at least 1) the ability to directly test respiratory samples (i.e., bypass culture); 2) automated methods to extract adequate TB DNA; 3) reduced resource requirements, such as smaller, more robust, user-friendly, but less expensive next-generation sequencing (NGS) platforms; and 4) maintaining parallel methods for DST that detect and correlate emerging resistance mutations to enable accurate WGS interpretation.[30,31] The EUSeqMyTB Consortium is leading the drive to establish standards for WGS methods, nomenclature, and analysis[32] and the WHO has established a centralized data sharing platform and bioinformatics tool called the Relational Sequencing for Tuberculosis Platform (ReSeqTB).[33]

CURRENT ACCESS TO MOLECULAR DRUG SUSCEPTIBILITY TESTING

In 2017, only 24% of new and 70% of previously treated patients had isolates tested for RMP resistance (30% overall).[1] Among patients with MDR-/RR-TB who were notified in 2017, only 50% progressed to DST to both FQs and second-line injectable drugs, although this does represent a considerable increase from the 39% tested in 2016.[1]

Among the WHO-recommended molecular DST diagnostics, we only have information on the status of GeneXpert machine and Xpert assay procurement because implementation monitoring was established when it was first endorsed. It is hoped that all access to diagnostic testing will soon be routinely reported, and reflect not only procurement but, more relevantly, patient use and impact. For Xpert, an interactive global map is available to check which countries have procured at least one GeneXpert machine, and the total number of procured modules and Xpert assays.[34] Cepheid, the manufacturer of the Xpert assay, has also regularly reported purchases: as of 31 December 2017, a total of 9449 GeneXpert instru-

ments (comprising 42 392 modules) and 34 422 850 Xpert assays had been procured in the public sector in 130 of the 145 countries eligible for concessional pricing. This translates to an average of only one Xpert assay run per module per working day (excluding South Africa, where machine throughput is relatively high).[1] In a study of 30 sites in 18 countries from 2012 to 2016, only 4% of HIV-infected patients diagnosed with TB had been tested using Xpert, although the majority of sites had access to it.[35]

Another approach to monitor implementation is to assume that the number of sputum acid-fast bacilli (AFB) smears performed will proportionately decrease as Xpert assays are used. Cazabon et al. conducted a trend analysis of the ratio of sputum AFB smears to Xpert assay volumes in the 21 high TB burden countries.[36] Overall, the median ratio decreased from 32.6 in 2014 to 6.0 in 2016, but increased in four countries. None of the 19 countries analyzed were using GeneXpert machines to their full capacity.[36]

REASONS FOR THE UNDERUTILIZATION OF MDR-TB DIAGNOSTICS

The historic obstacle to progress toward universal rapid DST is inadequate investment at all levels—internationally, nationally, and locally. The first UN General Assembly High-Level Meeting on TB, held in New York on 26 September 2018, endorsed a political declaration to accelerate progress towards the End TB Strategy targets.[37] Part of the declaration was committed to diagnosing and successfully treating 1.5 million people with drug-resistant TB, including 115 000 children, by 2022.[37] Although the Meeting was an unprecedented opportunity to recognize improved TB care and prevention as a global public good and a social justice imperative, commitment and accountability remain to be realized.

Performance and platforms

Platform limitations and imperfect performance characteristics are certainly not the primary cause of the incomplete deployment of MDR-TB diagnostics. However, Xpert is undergoing improvements, which may further shift the cost-benefit equation toward programmatic investment. The WHO recently endorsed the Xpert Ultra assay,[38] which is more sensitive than the Xpert assay for diagnosing smear-negative, culture-positive TB and HIV-associated TB.[39] In July 2018, Cepheid released GeneXpert® Edge, a portable single module that obviates the need for a steady supply of electricity and uses already available cartridges. Edge is intended as a near-patient version of the GeneXpert technology for use at lower levels of the health system, such as the nearest clinic or microscopy center with a functioning sputum transport system from the clinic. Although delayed by several months, GeneXpert® Omni is also anticipated as a single portable module, battery-operated and therefore suitable, for lower levels of the health system, which offers greater opportunity for access.[12]

The world anxiously awaits an Xpert MTB/XDR assay capable of testing for resistance to INH, FQs and injectable agents.[40,41] This cartridge would support an accessible algorithm targeting universal rapid DST: a patient at any level of the health system undergoes testing with the Ultra assay on the GeneXpert modular, Edge or Omni platforms and, if RMP resistance is detected, the specimen can be reflexively tested for second-line drug resistance using the MTB/XDR assay. Unfortunately, the release of the Xpert MTB/XDR assay has been delayed.

Equitable access to these rapid molecular diagnostics should also be extended to include young children and those who cannot produce sputum. A new stool processing kit for Xpert sample preparation may bypass the need for sputum and, hopefully, reduce the need and resource allocation for gastric lavage.[42]

Appropriate national policies

Even if the planned performance and platform improvements do occur, continued MDR-TB diagnostic underutilization is unavoidable when appropriate national policies and clinical algorithms are not implemented. Among the 48 countries that were classified as high TB, TB-HIV and/or MDR-TB burden, at the end of 2017, only two thirds had adopted national algorithms that correctly positioned Xpert as the initial diagnostic test for all people with presumptive pulmonary TB.[1] According to an in-depth survey of 29 countries representing 82% of the global TB burden, only 52% reported a national recommendation to use Xpert as the initial test for TB, and only seven of these reported that there was widespread access.[43] Of the 28 countries that reported providing initial testing with Xpert to high-risk groups (persons living with HIV and those at risk for MDR-TB), only 54% reported having widely available access.[43] In another report with focus on the 30 high MDR-TB burden countries, only 33% had a national policy recommending Xpert as the initial diagnostic test for all people presumed to have TB.[44]

WHO Essential Diagnostics List

The first Model List of Essential in vitro Diagnostics (EDL) was released on 16 May 2018[45] to complement the WHO Model List of Essential Medicines. The EDL informs governments and health care stakeholders which tests to make available, and, by so doing, clearly declares the value of rational diagnostic approaches, creates sorely needed global

Table 1 The WHO Essential Diagnostics List disease-specific in vitro diagnostics for TB detection and drug-resistant TB*

M. tuberculosis bacteria	For the diagnosis and treatment monitoring of active TB, including drug-resistant TB	Bacterial culture	Multiple specimen types
M. tuberculosis DNA	For the diagnosis of active TB and simultaneous detection of rifampicin resistance	Cartridge-based NAAT	Sputum, CSF and other extra-pulmonary TB specimen types
M. tuberculosis DNA mutations associated with resistance	For the detection of resistance against first-line anti-TB drugs	Molecular LPA	Sputum
M. tuberculosis DNA mutations associated with resistance	For the detection of resistance for second-line anti-TB drugs	Molecular LPA	Sputum
M. tuberculosis culture-based DST	To detect resistance to first-line and/or second-line anti-TB drugs	DST	*M. tuberculosis* isolate

* Adapted from reference[45] (WHO, Geneva, Switzerland).
WHO = World Health Organization; TB = tuberculosis; DNA = deoxyribonucleic acid; NAAT = nucleic-acid amplification test; CSF = cerebrospinal fluid; LPA = line-probe assay; DST = drug susceptibility testing.

diagnostic standards, and guides laboratory strengthening. Countries can use the EDL to benchmark progress[46] and manufacturers can now prioritize product development, which may even drive diagnostic prices down.

The EDL includes 113 diagnostics, of which three are relevant for TB DST: automatic liquid culture and DST MGIT™ (Mycobacterium Growth Indicator Tubes; BD, Sparks, MD, USA), Xpert, and LPAs.[45] For these, the EDL specifies test purpose, format, acceptable specimen type, and the ideal health care facility level for deployment (Table 1). Links to the relevant guidelines, publications and the compendium of WHO policies for TB diagnosis, treatment, and care are also included.

Direct costs

FIND (Foundation for Innovative New Diagnostics) is a non-profit organization that enables the development and delivery of diagnostic tests for poverty-related diseases, including TB. To increase access for people most in need, FIND mitigates the cost of new diagnostics by negotiating preferential pricing with diagnostic suppliers for use in the public sector in LMICs.[47] For each diagnostic, lists of countries eligible for negotiated pricing are maintained, and the public sector is explicitly defined (Table 2).

Table 2 Public sector defined for access to concessionary prices for tuberculosis diagnostics*

Governments or government-funded institutions such as health ministries, associated hospitals, armed forces, or prison services in those countries
Non-governmental organizations and UN-related organizations working for or in eligible countries, such as the International Organization for Migration and United Nations Childrens' Fund
Not-for-profit organizations such as Médecins Sans Frontières, Save the Children, OXFAM and the International Committee of the Red Cross
Global health funding mechanisms such as the Global Drug Facility, UNITAID, President's Emergency Fund for AIDS Relief, US Agency for International Development and the Global Fund, and agencies based outside the country but supporting implementation locally in the country, such as the US Centers for Disease Control and Prevention and the International Union Against Tuberculosis and Lung Disease

* Adapted from reference[47] (FIND, Geneva, Switzerland).
UN = United Nations; OXFAM = Oxford Committee for Famine Relief.

In many LMICs, however, it is the private sector that plays a dominant role in TB diagnosis. A 13-country patient-pathway analysis showed that about 60% of all TB patients seek care in the private health sector.[5] Although this would mean empowering private providers to provide high-quality TB diagnosis, treatment, and reporting,[48] negotiated pricing for TB diagnostics may not be available within the private sector. Surveys of 12 highly privatized health markets in 2015, and again in 2018 show that, in five countries, Xpert was not available through the private sector.[49,50] The average price patients were charged in the private setting was much higher than in the public sector and even increased between surveys.[49,50]

Strategies enabling the private sector to offer negotiated prices to their patients are already in place. For example, there is a policy facilitating private hospitals and clinics to access negotiated pricing if the health ministry approves the private organization with 'a mission in line with humanitarian principles'.[47] The manufacturer then allows negotiated pricing on a case-by-case basis in consultation with local and global stakeholders. In addition, any health provider within a for-profit model can access the negotiated prices, as long as mark-up to patients does not exceed 20% of the negotiated preferential price.[47]

There are innovative approaches to increase access to TB diagnostics among patients of private practitioners who do not qualify for negotiated pricing under these rules. In the aforementioned survey of countries with highly privatized health markets, India reported the lowest private sector price for Xpert.[50] This is, in part, attributable to the establishment of a network of over 200 private laboratories that offer Xpert testing through IPAQT: the Initiative for Promoting Affordable and Quality TB Tests.[51] IPAQT accessed the negotiated prices for the private sector which, as a prerequisite, agreed to charge patients no more than pre-negotiated ceiling prices.

In another pilot program for DST access through

the private sector in India, free Xpert testing was available to all children with presumptive TB in Chennai, Delhi, Hyderabad, and Kolkata.[52] Participating private providers were linked through rapid specimen transport and result reporting mechanisms, and their patients submitted specimens for testing using the public sector GeneXpert machines. Initial findings show an increase in bacteriologically confirmed pediatric TB and RR-TB cases, and better private-public integration as patients moved from the private to public sector for appropriate reporting and treatment.[52] In a qualitative program review, however, providers used 'an alarming diversity of GeneXpert utilization strategies', highlighting the parallel need for clinician education regarding TB diagnostic algorithms.[53]

Beyond direct costs

Xpert roll-out has provided valuable lessons for any rapid DST diagnostic in the pipeline. Successfully implementing Xpert—whether at a single clinic or throughout an entire jurisdiction—requires an actionable and sustainable plan for instrument import and maintenance, technician training, specimen transport mechanisms, cartridge supply chains, reporting systems, modified clinical algorithms that are clearly communicated to front-line clinicians, quality assurance, linkages to care, adequate funding and demonstration of patient and epidemic impact.[54,55]

Decentralization

Diagnostics for rapid DST must be available to patients seeking care at lower levels of the health system, such as microscopy centers, to achieve universal access. Such decentralization is daunting. A survey of basic infrastructure and logistic capacities at microscopy centers in Brazil, the Russian Federation, India, China, South Africa and LMICs found a uniform lack of sufficient skilled staff.[56] The survey also identified substantial inequalities between these settings, particularly regarding temperature control, access to steady electricity, and general laboratory equipment.[56]

BEYOND PRODUCTS: THE NEED FOR PROCESS INNOVATIONS

Diagnostic policies and recommendations and the implementation of rapid molecular diagnostics are only part of the solution to increase MDR-TB case finding and improve patient outcomes. Even the best diagnostic cannot compensate for a weak health system. Strong, sustainable national TB programs must have organizational and administrative features that reduce the TB burden without exceeding resource limitations, recognizing that the available molecular diagnostics are not yet operationally or fiscally feasible for all settings.

Technological innovations often improve surrogate endpoints but may fail to meaningfully improve clinical outcomes, in part, because such outcomes improve only when a series of causal events are improved or completed. Often, the entire cascade of events in health care needs to improve; merely improving one or two steps (e.g., diagnosis or process of care) may not lead to improvement in overall outcomes or result in sustained benefit.[57]

For example, if clinicians do not screen patients seeking care for TB-related symptoms, it does not matter what diagnostic is available. In an observational study at 20 primary care clinics in a high-burden district of South Africa where Xpert was established as the first-line diagnostic test, only 79% of 607 patients seeking care for TB-related symptoms were screened for TB.[58] A larger study conducted at 40 primary health clinics in four provinces in South Africa measured TB screening before and after the transition from smear microscopy to Xpert.[59] Only 22.7% of about 3600 consecutive adults experiencing at least one TB symptom reported having been asked to submit a sputum. Although a higher proportion of adults were asked for sputum after Xpert became available (26% vs. 19.8%), this difference was not statistically significantly different (95%CI 0.78–2.20).[59]

This need for improvement in the entire care cascade might explain the only modest impact observed in randomized trials that have evaluated the use of Xpert vs. sputum smear microscopy as initial TB diagnostic. Five of these trials including 8567 adults in five LMICs were subject to an individual patient data meta-analysis.[60] Compared with sputum smear microscopy, Xpert was not associated with a shorter time to TB diagnosis, or a greater likelihood of or less time to TB treatment. Diagnosis using Xpert, rather than smear microscopy, reduced the odds of death by a best estimate of 12%, but the associated 95% CIs were 0.68–1.14 ($P = 0.34$).[60]

Functional, well-performing clinics are often the ones eligible to participate in such trials; these clinics further improve with trial training, attention to supply chain, and strengthened reporting. Clinicians in the study settings may have a lower threshold to start empiric treatment, which dilutes detectable diagnostic impact. The authors of the meta-analysis[60] and those of an associated commentary[61] also note that diagnostic intervention trials are often underpowered, and may exclude some populations that might uniquely benefit from Xpert compared with sputum smear, such as in-patients who are more ill, children, and those with TB meningitis.

There was a slight indication for a modest reduction in time to death among HIV-positive adults diagnosed with Xpert compared with sputum smear (hazard ratio [HR] 0.76, 95% CI 0.60–0.97; $P =$

0.03).[60] In a more recent cluster randomized trial of TB screening among adults newly diagnosed with HIV who experience TB symptoms, 12 primary health clinics in rural Malawi performed either point-of-care Xpert or light-emitting diode fluorescence microscopy (LED FM).[62] TB was diagnosed in twice as many individuals enrolled in clinics randomized to Xpert compared to those using LED FM (2.4% of 1001 adults vs. 1.2% of 841 adults). All-cause mortality was 22% lower in the Xpert arm than in the LED FM arm (6.7 vs. 8.6 per 100 person-years; risk ratio [RR] 0.78, 95%CI 0.58–1.06). Effects were even greater for participants with more advanced HIV disease (RR 0.43, 95% CI 0.22–0.87).[62]

The quality of the DST offered also matters. A recent study comparing molecular or phenotypic DST results at the local level in Côte d'Ivoire, the Democratic Republic of the Congo, Kenya, Nigeria, South Africa, Peru and Thailand, with results obtained in a reference laboratory at the Swiss National Center for Mycobacteria,[63] reported that drug susceptibility tests were discordant for 19% of 634 adult patients, and inaccurate DST (compared to the reference standard) had led to undertreatment of DR-TB and increased mortality.[63]

These studies underscore the need to improve overall quality of TB care, and not just increase the availability of TB and MDR-TB diagnosis. Indeed, the Lancet Commission on TB (https://www.thelancet.com/global-health/commissions), which reviews progress to date and provides a roadmap for countries and their development partners to achieve global commitments towards ending the epidemic, has identified the achievement of universal, high-quality person-centered and family-centered care as a top policy and budget priority.[64]

CONCLUSION

Improved access to molecular diagnostic technologies plays an important role in controlling the MDR-TB epidemic, but LMICs are essentially currently limited to the use of Xpert and Ultra, with centralized culture DST, LPAs, and rarely WGS. Until an accurate molecular diagnostic for full rapid DST is developed for use at the peripheral level, national TB programs should optimize the use of currently available MDR-TB tests within their context and strengthen the laboratory networks, including effective specimen and patient referral mechanisms. By scaling up access to currently available diagnostics and strengthening national TB programs to improve quality of TB care, we lay the groundwork for future innovations of rapid accurate diagnosis of MDR-TB.

But meaningful impact will only come from improvements in the entire cascade of care. Long-term benefits require provision of a complete end-to-end solution to patients, and this includes diagnosis, novel treatment regimens, support with treatment completion, management of comorbidities, as well as social protection.[57] This solution must encompass susceptible and resistant TB, because simultaneous prevention of MDR-TB is needed for the diagnosis and treatment of MDR-TB to have the intended impact and bring us closer to meeting the End TB Strategy targets.

Conflicts of interest: none declared.

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RÉSUMÉ

Le pilier du diagnostic de la stratégie Mettre fin à la TB exige un accès à des tests diagnostiques de sensibilité élevée et à des tests de pharmacosensibilité (DST) universels rapides. Les techniques de diagnostic de la tuberculose multirésistante (MDR-TB) recommandés et disponibles dans les pays à revenu faible et moyen très frappés par la TB sont pratiquement limités aux tests Xpert® MTB/RIF et Xpert® MTB/RIF Ultra, au DST sur culture et aux tests de sonde en ligne. Les raisons principales de la lenteur de l'expansion sont l'insuffisance d'engagement politique et donc le financement de ressources humaines qualifiées et des infrastructures de laboratoire et de système de santé fiables. Des approches innovantes permettant au secteur de santé privé de fournir un diagnostic de qualité élevée sont également requises. La liste de diagnostics essentiels donne une impulsion et à des normes standard pour la mise en œuvre d'un diagnostic rationnel de la MDR-TB. Mais l'impact sur l'épidémie viendra finalement d'une solution globale pour les patients, comprenant toute la cascade de la prise en charge, notamment un diagnostic et un traitement centrés sur le patient de la TB et de la MDR-TB, la prise en charge des comorbidités et la protection sociale. En intensifiant l'accès aux diagnostics actuellement disponibles, nous jetons les bases des innovations futures en vue d'un diagnostic rapide et précis de la MDR-TB ce qui nous rapprochera des objectifs de la stratégie Mettre fin à la TB.

RESUMEN

El pilar diagnóstico de la Estrategia Fin a la Tuberculosis exige el acceso a pruebas diagnósticas de gran sensibilidad y a pruebas de sensibilidad (DST) rápidas a los antituberculosos para todos. Los métodos recomendados de diagnóstico de la tuberculosis multirresistente (MDR-TB) al alcance en los países con ingresos bajos y medianos, con una alta carga de morbilidad se limitan a las pruebas Xpert® MTB/RIF y Xpert® MTB/RIF Ultra, las DST fenotípicas y los ensayos con sondas en línea. Las principales razones de la lenta ampliación de escala son una escasa voluntad política y la consiguiente insuficiencia de financiamiento destinado a recursos humanos competentes e infraestructuras seguras de laboratorio y del sistema de salud. Asimismo, se necesitan enfoques innovadores que faciliten al sector privado la prestación de diagnósticos de gran calidad. La lista de pruebas diagnósticas esenciales infunde impulso y aporta criterios de referencia a la introducción racional de medios diagnósticos de la MDR-TB. Sin embargo, el efecto sobre la epidemia vendrá en último término de una solución integral completa para los pacientes, que aborde el proceso continuo de atención, incluido el diagnóstico y tratamiento de la TB y la MDR-TB centrado en el paciente, el manejo de las enfermedades concomitantes y la protección social. Al ampliar la escala del acceso a los medios diagnósticos disponibles, se sientan las bases de innovaciones futuras para el diagnóstico rápido y exacto de la MDR-TB, que a su vez nos acercarán al cumplimiento de las metas de la Estrategia Fin a la Tuberculosis.