Abstract

Barriers to global tuberculosis (TB) control include multidrug resistance, HIV infection, and weak health systems. Case detection is critical to TB control and is affected by all three of these. Currently, most low- and middle-income countries (LMICs) rely almost entirely on direct sputum smear microscopy (DSSM) for routine TB diagnostic services. This involves the examination of a series of sputum specimens from each patient and requires repeated patient visits to health facilities to submit specimens and to collect results. International guidelines exist for the DSSM-based diagnosis and management of TB suspects, and patients and most countries have adopted these in their national programmes [4,5]. International efforts to control TB, largely based on DSSM, ensure that millions of patients receive treatment and hundreds of thousands of lives are saved each year, but so far these efforts have failed to substantially reduce the annual global incidence [1]. Three major barriers to global TB control have been identified: the weak health systems that exist in many countries, the growing resistance of Mycobacterium tuberculosis (MTB) to the currently used anti-TB drugs, and HIV infection [1].

It is also recognized that inadequate case finding is a major obstacle to global TB control [1]. This inadequacy may be considered both quantitative and qualitative. Case finding may be inadequate, quantitatively, in failing to identify the majority of those in the community with TB. In many countries in recent decades, HIV has compromised quantitative case finding by altering the clinical presentation of TB and mitigating the immunological reaction to infection, which in turn results in a lower sputum bacillary load [6]. Case finding may also be considered qualitatively inadequate in failing to distinguish between TB cases with and without critical patterns of drug resistance that impact upon treatment success and continued transmission. Both forms of
Recent advances

**Current tools for diagnosing TB in resource-poor settings**

Currently, all bacteriological diagnostic tests for TB rely upon microscopically visualizing the characteristic acid-fast bacilli in specially stained sputum smears, growing and identifying MTB in cultures of specimens, or detecting MTB-specific nucleic acids in specimens. Diagnosis through MTB culture or nucleic acid detection is more sensitive than DSSM, and particularly so in HIV-associated TB, in which DSSM is notoriously insensitive [8]. These techniques also have the benefit of making isolates or nucleic acids available for drug susceptibility testing. A disadvantage of these tests is that they take considerably longer than smear microscopy for a result to be available for the management of the patient. This may be because the test itself takes several weeks to complete (culture) and/or because it requires a sophisticated bio-safe laboratory and, unavoidably, a centralized service of some kind. Centralized services and the logistics involved in specimen transport and delivering laboratory reports within a clinically useful time frame are particularly difficult to organize within weak health systems [9,10]. Where these tests have been introduced at the National TB Reference Laboratory (NRL) level, they have been associated with limited impact on TB case management [10].

**Integrating new TB diagnostic tools in resource-poor settings**

Until recently, modern culture methods and nucleic acid detection tests have been considered either too complex or too expensive for implementation in LMICs outside of NRLs. In the past two years, the World Health Organization has endorsed the use of both liquid culture systems (plus new rapid methods for identifying isolates) and molecular line-probe assays for TB control in LMICs [11,12]. There are now considerable global efforts under way to assist National TB Programs (NTPs) in LMICs to build laboratory capacity to introduce these new tools and develop services based on them [13]. It is recognized that that there is no strong evidence that the introduction of these tools will actually improve TB control at the routine programmatic level. Field studies and cost-effectiveness data are needed to better understand the real-world implications of the changes [14]. There are considerable challenges involved in delivering services based on these technologies in LMICs. These challenges are well recognized, but with little prospect that technology platforms will become available in the near future and thus obviate the need for greatly increased laboratory capability/capacity, there is an imperative to act now.

The Retooling Task Force and the New Diagnostics Working Group of the Stop TB Partnership recently described the pipeline of new diagnostic tools for TB [15]. Of eight new tools considered to be in late-stage development and perhaps available within the next few years, one is a nucleic acid detection test (which may be simpler than current line-probe assays for drug resistance detection) and four are culture-based diagnostics. Of the remaining three tools in late-stage development, two are based on improved smear microscopy. The remaining tool is the interferon-gamma release assay, which (though available on the market) has not yet been endorsed by the World Health Organization for use in TB control programmes, as there is considerable uncertainty about its likely contribution to case finding in LMICs [16]. The two improved microscopy tools, being appropriate for the lower levels of poor health services, may have considerably more impact on quantitative case finding in LMICs than either the culture methods or the molecular assays. One of the improved microscopy tools is fluorescent microscopy (FM) systems based on inexpensive battery-powered light-emitting diodes (LEDs) for DSSM [17]. In a recent systematic review, FM was found to have comparable specificity to Ziehl-Neelsen DSSM but with an approximately 10% increase in sensitivity while taking around 25% of the time to examine smears [18]. The benefits for case finding and alleviating heavy workloads in laboratories have not been realizable to date since conventional fluorescence microscopes were complex and very expensive. The LED-FM systems are currently under evaluation in a number of LMICs. The other improved microscopy tool, front-loaded microscopy, is an approach rather than a technological change [19]. A systematic review of the yield of serial sputum specimens has reported that the first two specimens (collected as spot and morning) identify 95–98% of all smear-positive cases [20]. Because a considerable proportion of patients default from the current DSSM diagnostic process (that requires multiple patient visits), front-loaded smear microscopy involves collecting and examining two sputum specimens on the first day a patient presents and referring those patients in whom the sputum is smear-positive immediately for
treatment. Multi-country trials of front-loaded microscopy are ongoing. These optimized smear microscopy tools, though less sensitive than reference laboratory tests, may be more accessible and have a greater public health impact [21]. However, they will not identify drug resistance.

Implications for clinical practice

Using new tools to improve diagnostic services for TB in resource-poor settings

Diagnostic services based on new tools, whether new (or modified) technologies or new approaches to delivery, have the potential to revolutionize TB case finding. The deficiencies in both quantitative and qualitative case findings need to be addressed. Diagnostic services need to identify more TB cases and to identify drug-resistant cases. Such services are unlikely, in the foreseeable future, to be based upon the introduction of a single new diagnostic tool. Rather, they will involve multiple tools being implemented in an integrated way within a tiered health system [15]. The new diagnostic tools, as well as being integrated with the health systems, will need to be carefully integrated with algorithms for the clinical management of cases. Simple new tools for the diagnosis of pulmonary TB at the lowest levels of health services (point-of-care) and for the diagnosis of extrapulmonary and childhood TB are also urgently needed. They are not yet on the horizon.

Abbreviations

DSSM, direct sputum smear microscopy; FM, fluorescent microscopy; LED, light-emitting diode; LMIC, low- and middle-income country; MTB, Mycobacterium tuberculosis; NRL, National Tuberculosis Reference Laboratory; NTP, National TB Program; TB, tuberculosis.

Competing interests

The authors declare that they have no competing interests.

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