Making the most of poor diagnostics: increasing access to tuberculosis treatment through optimized smear microscopy services

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Chapter 14.2

Discussion
General Discussion

In 2008, there were an estimated 9.3 million new cases of tuberculosis (TB), the majority occurring in low- and middle-income countries (LMICs). The most recent data indicate that 1.4 million of the TB cases were in people living with HIV/AIDS (PLWHA). Diagnosing TB on the basis of clinical and radiological findings alone is known to be inaccurate, particularly in HIV-associated TB. The definitive diagnosis is bacteriological. Most 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. 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.

Three challenges in the control of TB have been identified: resistance of Mycobacterium tuberculosis (MTB) to the currently-used anti-TB drugs, HIV infection and the weak health systems that exist in many countries. All of these impact negatively upon case-finding, and inadequate case-finding is recognized as one of the major obstacles to global control of the disease. This inadequacy may be considered both quantitative and qualitative. 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 inadequate case-finding are exacerbated by widespread poverty in LMICs. Many poor people who need to be investigated for tuberculosis are financially unable to afford repeated visits to health facilities for smear diagnosis and frequently default during the diagnosis process. Services, based on new tools, that can be delivered within resource-poor health systems, are sensitive to the poverty of many service-users, and result in the increased identification of HIV-associated and drug-resistant TB cases could make a very major contribution to global TB control.

New point-of-care tests for TB are urgently needed but cannot be expected in the near future. Until recently, modern culture methods and nucleic acid detection tests have been considered either too complex or too expensive for implementation in LMICs. Diagnosis through MTB culture or nucleic acid detection is more sensitive than direct sputum smear microscopy (DSSM), and particularly so in HIV-associated TB in which DSSM is notoriously insensitive. These techniques also have the benefit of making isolates or nucleic acids available for drug susceptibility testing and drug resistance detection. 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 (eg 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. Where these tests have been introduced at National TB Reference Laboratory (NRL) level in resource-poor settings they have been associated with minimum impact on TB case management.
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. There are now considerable global efforts under way to assist National TB Programmes in LMICs to build laboratory capacity to introduce these new tools and develop services based on them. The implementation of these technologies in LMICs will present challenges. The challenges are well recognized. However, with little prospect of new technology platforms becoming available in the near future that will obviate the need for greatly increased laboratory capability/capacity, there is an imperative to act now. It remains to be seen whether services based on these tools can be made widely accessible to patients.

The Retooling Task Force and the New Diagnostics Working Group of the Stop TB Partnership have recently described the pipeline of new diagnostic tools for TB. 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. One of the remaining three tools in late stage development is the interferon gamma release assay (IGRA) which, although available on the market, has not yet been endorsed by WHO for use in TB control programmes as there is considerable uncertainty about its likely contribution to case-finding in LMICs. The remaining new diagnostic tools are improvements in sputum smear microscopy. One of the improved microscopy tools is fluorescence microscopy (FM) systems based on inexpensive battery-powered light-emitting diodes (LEDs) for DSSM. The other improved microscopy tool, frontloaded microscopy, is an approach rather than a technological change. These optimized smear microscopy tools, though less sensitive than reference laboratory tests, may be more accessible and have the greater impact on quantitative case-finding in LMICs.

Studies presented in this thesis show that patients in LMICs face many barriers to accessing a TB diagnosis. The barriers identified were mainly socioeconomic or related to health service accessibility. Patients incur major expenses in travelling to health centres and the need to make repeated visits (over two days) to submit specimens and receive results. The anticipation of these expenses result in patients delaying their presentation to healthcare facilities. Diagnostic delay in different settings and the contribution of patients’ financial hardship and other (mainly health service) factors have also been described by other researchers.

Research presented in this thesis indicates that, as of now, there are no commercially-available serological tests that can be used to replace smear microscopy and provide a more rapid TB diagnosis. These findings were confirmed by a laboratory-based evaluation of 19 commercially-available rapid diagnostic tests for tuberculosis conducted by WHO/TDR in collaboration with the Institute of Tropical Medicine, Antwerp. This study also reported poor performance of serological tests with none of those evaluated performing well enough to replace sputum smear microscopy.

In recent years there have been a number of reports describing drop-out (initial default) during the diagnostic process among those listed in the laboratory register with at least one positive sputum smear. Diagnostic drop-out rates among smear positive patients have been reported from: Andhra Pradesh, India (5%); Ho Chi Minh City, Viet Nam (8.3%); Ntcheu, Malawi (15%); Western Cape Province, South Africa (16%); Stellenbosch, South Africa (17%); Gabarone, Botswana (27%); Karachi, Pakistan (28%). High mortality within weeks of smear-diagnosis has been reported among initial defaulters. In addition, some studies have looked at diagnostic drop-out among TB suspects being investigated by smear microscopy. Drop-out rates among TB suspects in different settings have been reported from Chennai, India (13%); Lilongwe, Malawi (37%) and...
Lusaka, Zambia (95%). As in the case of diagnostic delay, accessibility and acceptability of health services are the most important factors in patient adherence to the diagnostic pathway. A key finding of studies in this thesis were that direct costs associated with each day of the two day process were similar so that completing the diagnostic process in a single day would approximately halve the direct costs to patients. The other major finding was that although smear diagnosis is often considered to be available free in national TB programme activities, a substantial component of the direct costs were clinic fees and other payments made in the healthcare facility. Thus further opportunities to optimize smear microscopy services, suggested by the research, would be to reduce the time required for the diagnostic process to a single day and to waive clinic fees associated with an investigation for tuberculosis. The Stop TB Partnership’s TB and Poverty Sub-Group and others are calling for broad advocacy campaigns to ensure that patients who require investigations for TB can access a smear-based diagnostic service free of charge at the time and place of need.

The research also identified heavy laboratory workloads and inadequate smear examination times as additional barriers to smear-based diagnosis of TB.

This thesis has suggested 5 approaches through which case-detection based on smear microscopy may be improved:

1. Reducing the thresholds for defining a positive smear and a smear-positive case;
2. Reducing the workload and improve efficiency of the service by reducing the minimum number of sputum specimens examined in the investigation of suspected pulmonary TB, from three to two.
3. Reducing the number of patient visits required (and potentially reducing patient drop-out during diagnosis) through “frontloading” microscopy services and examining two specimens on the same day the patient presents.
4. Increasing the sensitivity of smear microscopy and reducing smear examination times through introducing low-cost fluorescence microscopy systems.
5. Increasing the sensitivity of smear microscopy through introducing an overnight bleach sedimentation method.

The results of this, and other, research were presented to the WHO in 2007 through a process described in Chapter 14.1. The WHO was advised by its Strategic and Technical Advisory Group on TB (STAG-TB) that there was sufficient evidence to influence policy. This led directly to changes in global policy recommendations in which the thresholds for defining a positive smear and a smear-positive case were lowered, and the minimum number of specimens to be examined in the investigation of pulmonary tuberculosis was reduced from three to two. Thus Approaches (1) and (2) have been WHO-endorsed and are recommended to national TB programmes for implementation.

The studies presented in this thesis to support Approaches (3), (4) and (5), alone do not provide sufficient evidence to change policy.

WHO/TDR has commissioned a large multi-centre pragmatic randomized trial of frontloaded microscopy (Approach 3) versus conventional microscopy in 4 countries and involving some 6,500 patients. Searches of the literature and requests for information from research colleagues would suggest that this is the only study of front-loaded microscopy being undertaken by any group. Recruitment to this study has finished. Analysis will be completed and available for inclusion in a
systematic review of the approach commissioned by the WHO Stop TB Department. The systematic review and other evidence will be the subject of a WHO Expert Meeting on Optimizing Smear Microscopy scheduled for the 3rd Quarter of 2009. The implications for research and policy will be considered.

Regardless of the findings of the WHO Expert Meeting further research should be considered to strengthen the evidence that front-loaded microscopy services, either alone or in combination with other approaches, lead to increased access to TB treatment under routine NTP conditions in LMICs. A key area of interest would be the effect of introducing frontloaded microscopy on initial default rates in different settings, and whether the would-be initial defaulters who initiate treatment are able to adhere to it. Studies could also focus on identifying barriers preventing patients from completing the frontloaded TB diagnostic process, and the changes that would be required in health service delivery systems to overcome them.

A number of large-scale trials of Approach (4), low cost fluorescence microscopy systems based on light-emitting diodes (LEDs) are either underway or have recently been completed. These include studies commissioned by WHO/TDR, the Foundation for Innovative New Diagnostics (FIND), and the International Union Against Tuberculosis and Lung Diseases. Several small studies have already been published. A key area of interest would be the effect of introducing frontloaded microscopy on initial default rates in different settings, and whether the would-be initial defaulters who initiate treatment are able to adhere to it. Studies could also focus on identifying barriers preventing patients from completing the frontloaded TB diagnostic process, and the changes that would be required in health service delivery systems to overcome them.

Recruitment in the large multi-centre WHO/TDR trial has been completed and analysis begun. A report of the results will be available for inclusion in a systematic review of this technology commissioned by the WHO Stop TB Department. The systematic review and other evidence will be the subject of a WHO Expert Meeting on Optimizing Smear Microscopy scheduled for the 3rd Quarter of 2009. The implications for research and policy will be considered. Regardless of the findings of the WHO Expert Meeting further research should be considered to strengthen the evidence that LED-based fluorescence microscopy, either alone or in combination with other approaches, lead to increased access to TB treatment under routine NTP conditions in LMICs. Considerable research may be required to permit the development of adequate quality assessment schemes for LED-FM. The re-examination of fluorochrome-stained smears through blinded re-checking may be possible using automatic smear readers. These are unlikely to be capable of smear microscopy that is as sensitive as a trained microscopist, but factoring in a decrease in sensitivity may allow adequate EQA to be done in an efficient way. This subject urgently needs further research. Prospective studies of the workload and staff requirements of optimized microscopy are urgently needed. Data from such studies may be used to adjust the model described in Chapter 12 of this thesis.

Research on sputum processing using bleach and other chemicals followed by centrifugation or sedimentation continues to furbish widely varying results. A major limitation of the study described in Chapter 9 was the absence of TB culture as the Gold Standard. A large-scale multi-country evaluation of Approach (5), a standardized bleach sedimentation method, that was commissioned by WHO/TDR is nearing completion in Bangladesh, Cameroon, Madagascar and Rwanda. Solid TB culture was used as the Gold Standard in this evaluation. Analysis will be completed and a report available for inclusion in a systematic review of the technique commissioned by the WHO Stop TB Department. The systematic review and other evidence will be the subject of a WHO Expert Meeting on Optimizing Smear Microscopy scheduled for the 3rd Quarter of 2009. The implications for research and policy will be considered. Even if the multi-centre TDR study to show
the considerably increased sensitivity found in the original Mathare study, the variability of this kind of method in actual laboratory practice may not auger well for successful implementation in NTP activities.

These optimized smear microscopy tools, though less sensitive than reference laboratory tests, may be more accessible and have a greater public health impact in terms of quantitative case-finding. However, they will not identify drug resistance.

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 finding 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. The new diagnostic tools, as well as being integrated with the health systems, will need to be carefully integrated with algorithms for clinical management of cases.

Simple new tools for the diagnosis of pulmonary TB at the lowest levels of health services (point-of-care) are urgently needed. They are not yet on the horizon. In the meantime, optimized smear microscopy services must be considered an essential part of diagnostic services for TB. A number of major initiatives aiming to increase diagnostic capacity for tuberculosis have recently been funded including a major collaboration of the Global Laboratory Initiative, the Foundation for Innovative New Diagnostics, the Global Drug Facility and UNITAID in 27 high-burden countries. It is imperative that such initiatives support the introduction of optimized microscopy services at the lower levels of the health services as well as more advanced diagnostics in central laboratories. Only in this way can the maximum public health impact of new diagnostic tools be realized.

References


