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

Tuberculosis remains a major cause of global morbidity and mortality, disproportionately affecting the poorer countries of the world. The control of tuberculosis is dependent upon the early detection and effective treatment of cases. Those patients who are shedding the largest numbers of TB bacilli in their sputum are likely to be most infectious. These patients are also most likely to be sputum smear positive by microscopy. Most national tuberculosis control programmes rely almost entirely upon passive case-finding for control ie. finding cases among symptomatic patients who self-present to healthcare facilities. Direct sputum smear microscopy (DSSM) is often the only diagnostic test available in poorer countries and is used to investigate patients with symptoms suggestive of pulmonary tuberculosis. Diagnostics tests with better laboratory performance, for example TB culture or molecular detection methods, have not become widely available to date because of their cost or technical complexity.

DSSM is relatively insensitive (compared to TB culture, for example), however the sensitivity can vary greatly. Sensitivity is dependent upon the diligence with which specimens are collected, smears are made, and stained smears are examined. The sensitivity of smear microscopy is also compromised in HIV positive patients who, because of altered immunopathology, are often paucibacillary. From the perspective of the service provider DSSM is labour intensive, time-consuming, requires skilled personnel, and requires internal and external quality management. However, it is also cheap and does not depend upon very expensive or delicate instrumentation. This is why DSSM is the most common test available. From the patients’ perspective, the DSSM diagnostic process may in itself be a barrier to diagnosis and treatment access. The need for a laboratory-based diagnostic procedure such as DSSM means that a diagnosis may not be available at the small health centres where most people with tuberculosis present in the first instance. Patients often have to travel to a healthcare facility with a laboratory. Patients furthermore are required to make repeated visits to the healthcare facility to submit multiple sputum specimens and receive test results. This background is described in Chapter 1 of this thesis.

Part One describes a number of systematic reviews of the literature relevant to the optimization of diagnostic services for TB in resource-poor settings. Serological tests, some of them in a simple and rapid test format, are commercially-available and sold widely particularly in low- and middle-income countries. In Chapter 2, we describe two systematic reviews, which focused on the performance of these serological antibody-detection tests. Overall, tests varied widely in their performance as measured by sensitivity and specificity and none performed well enough to replace smear microscopy. The chapter also draws attention to the poor quality of the serological test evaluations, and the lack of studies on the performance of serological tests is HIV positive patients and in children.

The diagnosis of tuberculosis at the lower levels of health services in poorer countries is likely to remain dependent upon sputum smear microscopy for the short to medium term. It is imperative that research identifies and evaluates ways in which DSSM can support efficient and patient-friendly services that will increase the numbers of TB patients accessing treatment. It is also important to explore ways in which smear microscopy can be made more sensitive.

Until 2007, international guidelines recommended the microscopic examination of at least three sputum specimens in the investigation of pulmonary tuberculosis. Chapter 3 describes a systematic review of studies that quantified the diagnostic yield of each of the three sputum specimens that were required. A total of 37 studies were eligible for inclusion in the review. Analysis determined that the average incremental yield and/or increase in sensitivity of examining a third specimen ranged.
between 2% and 5%. The authors argued that reducing the minimum number of specimens examined from three to two could improve case detection by reducing unmanageable workloads in laboratories and indirectly improving the quality of smear microscopy performed. It also suggested that if these two specimens could be examined on the same day, services may be made more convenient for patients. It was recognized that most of the studies included in the systematic review did not adequately ensure that the first, second and third specimens examined were indeed the first, second and third specimen collected. Thus, for services based on two same-day smears it was important to ensure that the second specimen collected (i.e. the “early morning” specimen) was not critical to the sensitivity of such an approach. It was also recognized that the reduction in the number of specimens examined would only negligibly reduce the overall numbers of patients identified as smear-positive so long as this was based on a single positive smear and that smears with only a few bacilli were considered positive. Until 2007, the definition of a smear-positive case (that was based entirely upon smear microscopy) required two positive smears (each graded 1+ or above) and a reduction in the number of specimens examined could considerably reduce the number of confirmatory smears and thus the number of cases defined as smear-positive. In some countries, at that time, access to the best available treatment depended upon being defined as smear-positive.

In Chapter 4, we summarized two additional systematic reviews, that considered the evidence that smear microscopy could be optimized by: a) fluorescence microscopy (FM); and b) prior chemical and physical sputum processing methods. The FM review found that: a) direct fluorescence microscopy was on average 10% more sensitive than direct Ziehl-Neelsen (ZN) microscopy, with comparable specificity; b) that, to achieve the same sensitivity, FM took approximately 25% of the time required for ZN microscopy; and c) that FM may have particular value in the investigation of paucibacillary HIV-positive patients. It was noted however that conventional FM was complex and expensive and that there had been considerable difficulties experienced implementing it in resource-poor settings. On the positive side it highlighted the development of new, simple and robust FM systems based on light-emitting diodes that may become available for evaluation soon. The specimen processing review found that a) sputum processing (mainly with bleach or sodium hydroxide) yielded an average 18% increase in sensitivity over DSSM with comparable specificity; b) that sputum subjected to overnight sedimentation preceded by treatment with ammonium sulphate or bleach, was on average 23% more sensitive with comparable specificity; and c) that evidence for chemical processing sputum followed by centrifugation also increased sensitivity, with comparable specificity, but concerns were raised about the feasibility and safety of methods requiring centrifugation of digested sputum in resource-poor settings. The results of this review, and of others, led to calls for the wide-spread adoption of bleach microscopy for case-finding in national TB control programmes. In Chapter 5 we cautioned against this, highlighting deficiencies in the scope and detail of the available evidence for bleach microscopy, flaws in the design of evaluations to date and offering advice on the design of future evaluations.

**Part Two** describes studies exploring the limitations of conventional DSSM. Using the Piot Model described in the introduction several aspects of the diagnostic service that may be amenable to optimization were identified and investigated. Firstly, it is clear that patients often delay seeking medical help for the symptoms associated with TB, and sometimes these delays can be protracted. In Chapter 6 the results of a study on delayed presentation to TB services that was conducted in Cameroon were compared with the results of an identical study previously conducted in Ethiopia. Patient delay was less common and less protracted in Cameroon than in Ethiopia. In both locations financial inadequacy was reported to be a cause of protracted delay. The use of traditional healers was also associated with delay to medical health services and this was the case in both Cameroon and Ethiopia. Our research suggests that in both countries, despite the economic and cultural
differences, interventions aimed at involving traditional healers in healthcare structures and encouraging the referral of patients with TB symptoms to medical healthcare facilities for smear microscopy may reduce delay and increase the number of TB cases detected.

In Chapter 7 the direct patient costs associated with seeking a TB diagnosis were assessed in two studies in Nepal and Yemen. These costs were found to be considerable. A key finding of these studies was 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 we often think of a smear diagnosis as free, 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.

In Chapter 8 a further limitation of sputum smear microscopy was identified: a major reason for the poor sensitivity of DSSM is the inadequate time invested in smear microscopy under routine conditions. In a district hospital in Cameroon smears were examined for a median time of 2 minutes 6 seconds. Re-examining the smears for the internationally-recommended duration of examination (up to 10 minutes) increased case detection by up to 70%. However, it was conceded that the workload and human resource constraints facing many health laboratories particularly in sub-Saharan Africa make this impossible in practice.

Part Three describes studies that identified and evaluated ways in which smear microscopy services could be optimized. Chapter 9 describes an evaluation of a bleach overnight sedimentation method that stems directly from the work described in Chapters 4 and 5. This study was conducted in a TB/HIV Clinic in Mathare, Nairobi (Kenya). This study sought to avoid the flaws in the design of previous evaluations and to address identified deficiencies in the available evidence. Specimens were collected under guidance of trained staff, DSSM was of a demonstrated high quality, and all microscopy was conducted by the same staff in the same facility with the same microscopes. Furthermore, microscopists were “blind” to other microscopy results. A major improvement was that the processing method was standardised: “bleach” was identified as sodium hypochlorite (3.5% NaOCl); NaOCl was stored in accordance with evidence-based recommendations; and the activity of the NaOCl was chemically monitored on regular basis. In the high HIV prevalence setting of Mathare it was found that the standardized sodium hypochlorite bleach method was inexpensive and achieved gains in case detection of up to 23% over direct smear microscopy.

Chapter 10 describes an evaluation of different thresholds for defining a positive sputum smear and a smear-positive case and was conducted in direct response to the policy-relevant research questions raised in Chapter 3. This study, also conducted in the Mathare TB/HIV Clinic and in the high-quality DSSM and research context described above, evaluated the impact of reducing the number of specimens examined (from three to two) on smear-positive TB case detection and laboratory workload. A smear positive case detection rate based on finding one positive smear with ≥4 AFB/100 HPF increased the yield of cases detected by up to 17% compared with other definitions currently in use in national TB control programmes. The number of smears examined would be reduced by 36% using a one positive smear case definition. An important finding, relevant to the proposed examination two sputum specimens on the same day, was that the morning specimens in this study, although likely to be quantitatively more positive (i.e. a higher grade of positive smear) than a spot specimen, and more likely to be considered positive with the then-current definition of a positive smear, were not more likely to be considered positive with the lowered threshold.
In Chapter 11, building on the findings of Chapters 3 and 10, we explored “frontloading” smear microscopy services in which at least two smear examinations occur on the first day. We compared conventional approaches involving 3 specimens (as spot-morning-spot collections) and two specimens (as spot-morning collections) and compared then with a frontloaded equivalent, spot-spot morning and spot-spot, respectively. We found no difference between the conventional and frontloaded 3-specimen approaches, nor between the conventional and frontloaded 2-specimen approaches. We concluded that frontloaded microscopy services combined with the reduced thresholds for case definitions and the reduced number of specimens examined could be a way of diagnosing TB cases and referring for treatment on the same day they present. This might reasonably be expected to reduce the high rates of drop-out experienced in a number of national TB programmes and reduce the financial burdens experienced by patients and described in Chapters 6 and 7.

In Chapter 12, using data from the laboratory register of a busy district hospital in Malawi, we modelled the potential of the WHO policy changes related to smear microscopy (lowered threshold for a positive smear, changed definition of a smear positive case and the reduction in minimum number of specimens examined), combined with the introduction of fluorescence microscopy, to improve smear microscopy services. We found that the combined implementation of the new policy recommendations and LED-based fluorescence microscopy could result in substantial increases in smear-positive case detection through:

a) increases in smear-positive case detection directly related to the lowered thresholds for the new case definition; and

b) reducing workload to allow the adequate smear examination times (equivalent to a 10 minute ZN smear examination) that have been reported in Cameroon to be associated with increases in case detection of up to 70%.

The increases associated with the equivalent of a 10 minute ZN examination had been described in Chapter 8, but had been recognized as impossible with the then-current policies and technology. The study described in Chapter 12 indicates that not only is it possible with the new policies and technologies, it can be achieved with existing staff and minimal additional expenditure on equipment.

In Chapter 13 we interrogated the data from the Nairobi study to determine whether patients submitting specimens that would be considered poor quality would particularly benefit from the lowered thresholds for defining a positive smear and a smear positive case. Since women, in several countries, have been reported to submit poor quality specimens more frequently than men we investigated whether women would be more likely to be defined as smear positive cases with a revised case definition. In this study it was found that even where patients were well-instructed in sputum collection and where microscopy services were of high quality, lowering the thresholds resulted in more female patients being considered smear positive cases. This was linked to the submission of specimens that were considered of poor quality which was more common in women. The effects of HIV on case detection with different case definitions still requires further study.

During the period of this research the WHO developed a process for reviewing evidence related to new tools for TB control and for making recommendations on policy. The details of this WHO policy process has been made public and will greatly facilitate the development, evaluation and WHO endorsement of new tools. This policy process and the current evidence base for TB diagnosis is described in Chapter 14.1. A general discussion in Chapter 14.2 ends the main body of the thesis.