Making the most of poor diagnostics: increasing access to tuberculosis treatment through optimized smear microscopy services
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Chapter 1

Introduction
1. **Tuberculosis**

An estimated 9.3 million new cases and 1.8 million deaths due to TB occurred in 2007, of which 1.4 million cases and 0.5 million deaths were in HIV-positive people.\(^1\) An estimated 4.1 million (44%) of the new cases in 2007 would be sputum smear-positive.\(^1\) The prevalence of TB in 2007 was estimated at 13.7 million cases globally.\(^1\) Half a million cases are estimated to be multi-drug resistant TB cases.\(^1\) Twenty-two high-burden countries (HBCs), all low and middle-income countries (LMICs), collectively account for 80% of the global TB burden.\(^7\)

2. **Mycobacterium tuberculosis infection and tuberculosis**

The development of tuberculosis (TB) requires infection by bacteria of the *Mycobacterium tuberculosis complex* (Mtb). Infection with Mtb usually occurs through a potential host being exposed to the bacilli in airborne droplets. Such infectious airborne droplets are produced by someone with active (infectious) pulmonary tuberculosis disease when they cough. The bacilli when inhaled by the potential host can establish an infection in the lung (primary focus).\(^2\) Bacilli may spread from this focus, via the lymphatic or blood circulatory system, to other parts of the body. Host defences form a granuloma around the infecting bacilli in the primary focus, which becomes caseous and necrotic at the centre. In the majority of cases the immunocompetent host is able to arrest the growth of the bacilli within this primary focus, with no obvious signs of illness.\(^2\) However, in some cases the infection is not contained and disease ensues either at the site in the lung, at other sites to which the bacilli spread, or at both. Infectious potential depends upon the site and extent of disease with advanced lung disease (involving cavity formation) being the most common form with high infectious potential. In most cases, infection does not result in disease and the initial lesion resolves and eventually calcifies. Such old lesions may, however, still harbour viable bacilli and the host is considered to have a latent TB infection (LTBI). These latent infections may reactivate later, sometimes many years later, and result in disease.\(^3\)

Exposure to the bacilli does not necessarily lead to infection, and Mtb infection does not necessarily lead to disease (either at the time of infection or through reactivation). Disease does not always lead to infectiousness, nor death. Risk factors are important, and a number of these are described later.\(^4\) The model depicted in Figure 1 provides a framework for understanding the epidemiology of tuberculosis and approaches to control of the disease.

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**Figure 1**

3. Control of tuberculosis for public health and development

The rationale for tuberculosis control is simple. Infection with Mtb is necessary for the development of TB. Mtb infection is newly acquired primarily through the inhalation of Mtb in the air. Since the only major source of infection is patients with tuberculosis who are coughing Mtb into the environment, the key to controlling the disease is to identify cases of tuberculosis as early as possible and treat them effectively. This is also the key to providing the best care to patients.

TB is one of the major infectious diseases of poverty and remains a considerable public health problem in most of the world. Tuberculosis transmission, disease development and progression are driven by poverty through a number of direct and indirect channels, while poverty is as variously generated or exacerbated by tuberculosis. The dynamics are mutually reinforcing. The impact of tuberculosis and other major infectious diseases on poverty and international development is recognized and reflected in the 8 UN Millenium Development Goals (MDGs) declared by the UN General Assembly in 2000. Targets for TB control have been set within the context of the Millenium Development Goals and by the World Health Assembly and the Stop TB Partnership. The impact targets are to halt and begin to reverse incidence of TB by 2015, and to halve prevalence and death rates by 2015 compared to 1990 levels. Mathematical modelling has been used to predict the trajectory of the TB epidemic in the presence of various interventions with various degrees of success. This has been used to identify process targets that must be reached to have the desired impact. These process targets are a) that at least 70% of the estimated new smear positive TB cases are detected and b) that 85% of those that are detected are successfully treated. The case detection rate for new smear-positive cases in DOTS programmes is 63% globally (ie, 2.6 million cases notified of 4.1 million estimated to occur each year). Treatment success rate is 84.7% globally (2006 figures). After a period of impressive increase in the global case detection rate progress in case detection slowed down between 2005 and 2006, and stalled in India and China.

4. Tuberculosis control activities and poverty

The Director-General of the World Health Organization, Dr Margaret Chan, recently warned: “If we want better health to work as a poverty reduction strategy we must reach the poor. Here is where we fail”. Table 1 shows the estimated numbers of poor people (living on <2US$ per day) who are TB cases and are not detected under DOTS in the 22 highest TB burden countries. Undoubtedly, the methodology used to make the estimate, would underestimate the figures, since it considers the percentage of poor people in the general population to be the same as the percentage among undetected TB cases. For many reasons, the percentage of poor people among undetected cases is likely to be higher than in the general population. These reasons may include poor people having a) higher risk of exposure to infection through overcrowded living conditions; b) higher risk of developing infection and or disease due to sub-optimal nutrition or immunosuppressive co-infections; and, c) less access to quality health care. Thus, it may be considered that, based on the figures in Table 1, at least 60% of those people undetected under DOTS in the 22 highest TB burden countries live on less than 2 US$ per day. Initiatives to improve case-finding need to focus on the poor.
### TABLE 1. Minimum estimated TB incidence among the poor in the 22 highest TB burden countries.  

<table>
<thead>
<tr>
<th>Country</th>
<th>Population (millions, 2003)</th>
<th>Estimated incidence: all forms (in thousand, 2003)</th>
<th>Percentage of estimated TB cases detected under DOTS</th>
<th>Percentage of population living on &lt;$US2/day</th>
<th>Estimated number of TB cases not detected under DOTS that are poor (&lt;$US2/day) (in thousands)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afghanistan</td>
<td>24</td>
<td>80</td>
<td>17.5</td>
<td>73.6</td>
<td>49</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>147</td>
<td>361</td>
<td>24.4</td>
<td>82.8</td>
<td>226</td>
</tr>
<tr>
<td>Brazil</td>
<td>178</td>
<td>110</td>
<td>15.5</td>
<td>22.4</td>
<td>21</td>
</tr>
<tr>
<td>Cambodia</td>
<td>14</td>
<td>72</td>
<td>38.9</td>
<td>77.7</td>
<td>34</td>
</tr>
<tr>
<td>China</td>
<td>1304</td>
<td>1334</td>
<td>41.5</td>
<td>46.7</td>
<td>364</td>
</tr>
<tr>
<td>DR Congo</td>
<td>53</td>
<td>195</td>
<td>43.6</td>
<td>84.0</td>
<td>92</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>71</td>
<td>252</td>
<td>46.4</td>
<td>77.8</td>
<td>105</td>
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<tr>
<td>India</td>
<td>1065</td>
<td>1788</td>
<td>46.8</td>
<td>80.6</td>
<td>767</td>
</tr>
<tr>
<td>Indonesia</td>
<td>220</td>
<td>627</td>
<td>28.4</td>
<td>52.4</td>
<td>235</td>
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<tr>
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<td>32</td>
<td>195</td>
<td>47.2</td>
<td>58.3</td>
<td>60</td>
</tr>
<tr>
<td>Mozambique</td>
<td>19</td>
<td>86</td>
<td>33.7</td>
<td>78.4</td>
<td>45</td>
</tr>
<tr>
<td>Myanmar</td>
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<td>85</td>
<td>89.4</td>
<td>82.8</td>
<td>7</td>
</tr>
<tr>
<td>Nigeria</td>
<td>124</td>
<td>363</td>
<td>12.1</td>
<td>92.4</td>
<td>295</td>
</tr>
<tr>
<td>Pakistan</td>
<td>154</td>
<td>278</td>
<td>26.3</td>
<td>73.6</td>
<td>151</td>
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<tr>
<td>Philippines</td>
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<td>237</td>
<td>56.5</td>
<td>47.5</td>
<td>49</td>
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<tr>
<td>Russian Fed</td>
<td>143</td>
<td>161</td>
<td>13.0</td>
<td>7.5</td>
<td>11</td>
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<tr>
<td>South Africa</td>
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<td>242</td>
<td>93.8</td>
<td>34.1</td>
<td>5</td>
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<tr>
<td>Tanzania</td>
<td>37</td>
<td>137</td>
<td>45.3</td>
<td>72.5</td>
<td>54</td>
</tr>
<tr>
<td>Thailand</td>
<td>63</td>
<td>89</td>
<td>61.8</td>
<td>32.5</td>
<td>11</td>
</tr>
<tr>
<td>Uganda</td>
<td>26</td>
<td>106</td>
<td>39.6</td>
<td>58.3</td>
<td>37</td>
</tr>
<tr>
<td>Vietnam</td>
<td>81</td>
<td>145</td>
<td>64.1</td>
<td>82.8</td>
<td>43</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>13</td>
<td>85</td>
<td>62.4</td>
<td>83</td>
<td>27</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>3942</strong></td>
<td><strong>7027</strong></td>
<td><strong>41.5</strong></td>
<td><strong>60.3</strong></td>
<td><strong>2688</strong></td>
</tr>
</tbody>
</table>

### 5. Why don’t interventions reach the poor?

This can be analysed using the Piot model. 8,9,10 The basis of the model is a description of the different stages between a person becoming ill and finally being successfully treated for the illness. At each stage, people may stall and not move on to the next stage, or be detained at particular stages only moving forward after some delay. 

When this model is used at a population level to evaluate the pathway to successful TB treatment it may be seen that people drop-out at various stages, with only a relatively small proportion of patients being detected and successfully treated. Once patients get on to TB treatment there are many obstacles to staying on treatment and these have been discussed elsewhere.11,12,13,14 These obstacles may include social, economic, health systems and geographical barriers. The major steps to accessing TB treatment, and the potential for drop-out, are described in Figure 2. Six drop-out stages during the diagnostic process are described and three stages either before or after the diagnostic process. The pre-diagnostic drop-out is essentially that before presentation to healthcare services. Non-presentation or delay in presentation may be multi-causal and affected by social, economic, cultural and geographical factors. It is a serious problem as it can jeopardize
treatment success in individual patients and lead to increased transmission of infection in the community. There may, however, be systemic weaknesses in the delivery of health services that increase the likelihood that these factors contribute to drop-out. Drop-out during the diagnostic process may also be due to the same or similar factors that affect pre-diagnostic drop-out but weaknesses in health service delivery and particularly weaknesses in the way that diagnostic technologies are applied, may increase the likelihood of drop-out. The framework in Figure 2 also recognizes two post-diagnostic drop-out stages where the patient is identified by the laboratory as a TB case, the patient returns to the health facility but does not get access to anti-TB treatment.

**Figure 2:** Pathway to TB treatment access (on left) and major drop-out stages (on right).
Operational and diagnostics research can be used to determine which stages are most problematic, identify the barriers at each stage, and the effect of the barrier in terms of numbers of patients being stopped, and the likely contribution of the barrier to inadequate case-detection. Research may also be able to identify barriers that particularly affect the poor. Research can also suggest interventions that may be used to remove barriers.

6. Poor diagnostics as an obstacle to TB treatment for the poor.
HIV-associated TB and drug resistant TB (particularly multi-drug resistant TB and extensively-drug resistant TB, MDR-TB and XDR-TB respectively) present challenges to both diagnosis and treatment.\textsuperscript{15,16,17} This is important both in terms of control targets and the adequate care of the patient. In most parts of the world smear microscopy is usually the only diagnostic test available for TB. HIV-associated TB is more likely to be paucibacillary and smear-negative by direct sputum microscopy.\textsuperscript{15} As well as compromising progress towards the case detection rate target, this leaves the patients without definitive diagnoses and reduces their chances of being treated for TB. Smear microscopy moreover gives no information about the drug susceptibility profile of an infecting strain of Mtb and in settings where drug-resistant TB is common cannot adequately guide treatment. Diagnostics, currently available, that are more sensitive than smear microscopy and/or can detect drug resistant TB require advanced laboratory skills and levels of laboratory infrastructure rarely available in the poorer countries at present.\textsuperscript{17} Examples of these diagnostic tests include Mtb culture and drug susceptibility (in solid or liquid media) and molecular diagnostics such as line-probe assays. Most molecular diagnostics are generally not more sensitive than culture and provide less potential information regarding drug resistance profiles, but have the advantage of being more rapid than culture.\textsuperscript{15} Building the laboratory infrastructure for expanding use of these tests will be challenging.\textsuperscript{17}

New simple rapid accurate diagnostics for TB that could identify cases at health centres closer to communities would almost certainly improve access to diagnosis and treatment. Such tests are urgently needed but cannot be reasonably expected to be widely available to TB control programmes in the next 5 to 10 years.\textsuperscript{18} Regardless of the format of any new test the improvement in case detection is unlikely to be achieved through the technology alone, but through the introduction of the test into strengthened patient-centred health services.

Unfortunately, at least in the short to medium term, national TB control programmes will have to diagnose tuberculosis without the aid of new diagnostic tools. Given this reality, how can diagnostic services be made more convenient for patients? What tools currently available could be used to replace or support smear microscopy? What could be done to improve the quality of smear microscopy services? How can the results of research related to these questions be used to change policy and practice? These are the research questions that have led to this thesis.

Research objectives
A. To describe patient healthcare-seeking behaviour and both patient and health service barriers to direct smear-based diagnosis of TB. (Chapters 6 & 7)

B. To evaluate the potential of commercially-available diagnostics, with test formats appropriate for use at the lower levels of health services in LMICs, to replace smear microscopy. (Chapter 2)

C. To evaluate approaches to optimizing sputum smear microscopy services. This included
1. evaluating the efficiency of current approaches to smear microscopy (Chapters 3 and 8);
2. Evaluating the definition of a positive smear and a smear positive case (Chapters 10 and 13);
3. Evaluating the requirement for sputum specimens to be collected over two days (Chapter 11);
4. Evaluating the potential of new technologies or sputum processing methods to improve smear microscopy performance (Chapter 4);
5. Evaluating the potential of combinations of approaches and technologies to improve case detection (Chapter 12);
6. Developing and evaluating a standardized sputum concentration method (Chapters 5 and 9).

D. To describe the process by which results of this research were translated into policy into practice (Chapter 14.1).

References