Progress towards improved tuberculosis diagnostics for developing countries

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The lack of accurate, robust, and rapid diagnostics for tuberculosis impedes management of patients and disease control. For individual patients, the cost, complexity, and potential toxicity of 6 months of standard treatment demands certainty in diagnosis. For communities, the risk of transmission from undetected cases requires widespread access to diagnostic services and early detection. Unfortunately, diagnostic services in most places where tuberculosis is endemic fail both the individual and the community. Patients are often diagnosed after weeks to months of waiting, at substantial cost to themselves, and at huge cost to society. Many patients are never diagnosed, and contribute to the astonishing number of yearly deaths from tuberculosis worldwide.

The core diagnostic technology enshrined in current control strategies is sputum microscopy, which was developed in the 1880s and has remained essentially unchanged since then. Microscopy is an attractive technology for public-health programmes: it requires one piece of equipment, can be used for more than one purpose, provides visual evidence not only of tuberculosis, but of bacterial burden, and in most instances is specific enough that no confirmatory testing is needed. However, only tiny amounts of material are examined—as little as 0.2 μL even when viewing more than 100 microscopic fields—so bacteria must be present in high concentrations to be visible—typically over 10 000 acid fast bacilli per mL. The low sensitivity of the technology, which only detects roughly half of all active cases of tuberculosis when properly used, is compounded by its complexity. Though routinely described as a simple test, it is highly dependent on the training and diligence of the microscopist, requires multiple examinations, and in programmatic conditions takes days rather than hours to complete, so that many patients drop out during the diagnostic process.1 As an indicator of the difficulty of implementing quality microscopy services, fewer than 45% of predicted incident smear-positive cases of tuberculosis are detected and notified to WHO.2

By definition, microscopy cannot detect smear-negative disease. Although such disease has a lower transmission potential, it contributes importantly to global tuberculosis morbidity and mortality. In areas struck by epidemic HIV, smear-negative disease is disproportionately common.3 Reduced bacterial burden and less obvious radiography findings4 make tuberculosis more difficult to diagnose in these populations, but not less fatal. In a study in Malawi,5 the 8-month mortality in a group of patients with a diagnosis of smear-negative tuberculosis was 40%. Paediatric tuberculosis is also difficult to detect with microscopy, and has become an important killer of children in sub-Saharan Africa.6 Thus, precisely in the areas of the world where microscopy has the poorest performance, the need for early detection of tuberculosis is the greatest.

More than one type of test is needed. International workshops on diagnostics for tuberculosis have emphasised the need to: replace or improve microscopy with a simpler technology to detect smear-positive tuberculosis; develop a faster alternative to culture to detect smear-negative tuberculosis; improve antibiotic susceptibility testing; and develop tests for the detection of latent infection at risk for relapse. Table 1 shows the diagnostic priorities, in roughly rank order of importance to global tuberculosis control.

An industry survey undertaken in the late 1990s identified more than 50 companies (mostly small) with an interest in diagnostics for tuberculosis. This commercial interest, coupled with significant recent technical advances in diagnostics and mycobacteriology, was expected to lead to the development of a series of new methods to meet the stated needs. To facilitate the relevant commercial activity, WHO, and later its Special Programme for Research and Training in Tropical Diseases (TDR), established an enabling infrastructure for industry that included banks of reference materials, diagnostic trial sites, and market research. Unfortunately, this work alone could not ensure that new methods would
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Once developed, high quality laboratory and clinical assessments of the tests in populations of intended use are necessary to ensure that performance characteristics are well understood, with narrow confidence intervals. Such data are often lacking, even for marketed products. Results from trials of tuberculosis serology tests indicate the degree to which performance data provided by the manufacturer can be misleading. A Diagnostics Evaluation Expert Panel, convened by WHO/TDR and FIND, is developing guidelines for the performance of diagnostic trials for tuberculosis and other diseases that are intended to establish quality standards for clinical testing.

Finally, good performance under trial conditions does not always translate into effectiveness after implementation. Demonstration projects must be established to assess the feasibility, bearing, and cost-effectiveness of new diagnostic interventions after scale-up in national control programmes. The outcome of these projects, which are an essential feature of FIND’s diagnostics development activities, should provide evidence for policy, so that useful technologies can be rapidly adopted, and impractical or ineffective ones improved or dropped.

Tuberculosis control programmes in endemic countries have benefitted little from decades of biotechnology progress. New public-sector mechanisms to harness this progress toward better methods for diagnosis of tuberculosis could change that. Donor agencies and research institutions should make investment in diagnostics a priority.

Conflict of interest statement
We declare that we have no conflict of interest.

References

Table 2: Possible diagnostic technologies suitable for various health system levels

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<thead>
<tr>
<th>Health post</th>
<th>Screening for tuberculosis</th>
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<tbody>
<tr>
<td>Referral laboratory</td>
<td>Detect smear-negative tuberculosis</td>
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<tr>
<td>Microscopy centre</td>
<td>Test for tuberculosis in individuals with inconclusive screening result</td>
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M. tuberculosis = multidrug-resistant tuberculosis.