Implementing rapid testing for tuberculosis in Mozambique

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Problem In Mozambique, pulmonary tuberculosis is primarily diagnosed with sputum smear microscopy. However this method has low sensitivity, especially in people infected with human immunodeficiency virus (HIV). Patients are seldom tested for drug-resistant tuberculosis.

Approach The national tuberculosis programme and Health Alliance International introduced rapid testing of smear-negative sputum samples. Samples were processed using a polymerase-chain-reaction-based assay that detects Mycobacterium tuberculosis deoxyribonucleic acid and rifampicin resistance. Four machines were deployed in four public hospitals along with a sputum transportation system to transfer samples from selected health centres. Laboratory technicians were trained to operate the machines and clinicians taught to interpret the results.

Local setting In 2012, Mozambique had an estimated 140,000 new tuberculosis cases, only 34% of which were diagnosed and treated. Of tuberculosis patients, 58% are HIV-infected.

Relevant changes From 2012–2013, 1558 people were newly diagnosed with tuberculosis using sputum smear microscopy at intervention sites. Xpert® detected M. tuberculosis in an additional 1081 sputum smear-negative individuals, an increase of 69%. Rifampicin resistance was detected in 58/1081 (5%) of the samples. However, treatment was started in only 82% of patients diagnosed by microscopy and 67% of patients diagnosed with the rapid test. Twelve of 16 Xpert® modules failed calibration within 15 months of implementation.

Lessons learnt Using rapid tests to diagnose tuberculosis is promising but logistically challenging. More affordable and durable platforms are needed. All patients diagnosed with tuberculosis need to start and complete treatment, including those who have drug resistant strains.

Introduction

People infected with human immunodeficiency virus (HIV) are susceptible to tuberculosis. This has led to an HIV-driven tuberculosis epidemic in sub-Saharan Africa over the past two decades.1 Diagnosing tuberculosis is often difficult given the low sensitivity of smear microscopy. Among people infected with HIV, smear microscopy is even less sensitive due to the lower bacterial load in co-infected people.2

Xpert® MTB/RIF (Xpert®; Cepheid, Sunnyvale, United States of America) is a rapid and fully-automated molecular test that uses real-time polymerase chain reaction on sputum samples to simultaneously detect Mycobacterium tuberculosis deoxyribonucleic acid and the genetic sequence indicative of rifampicin resistance.3,4 The test has 88% sensitivity for tuberculosis and 94% sensitivity for rifampicin resistance. Given the high sensitivity, the test is more effective than sputum smear microscopy in diagnosing tuberculosis in HIV-infected people. Therefore the World Health Organization (WHO) has recommended the use of Xpert® for diagnosis of tuberculosis in countries with high prevalence of HIV infection and multidrug-resistant tuberculosis (MDR-TB).5,6 The four-module Xpert® machine and desktop computer retails for 17 000 United States dollars (US$) in low-income countries and each cartridge (one per sample) costs an additional US$ 10.7 This paper describes the introduction of Xpert® in Mozambique.

Local setting

Mozambique has a high burden of tuberculosis. In 2012, WHO estimated an incidence of 552 per 100 000 people, which corresponds to approximately 140 000 new cases. However, only 34% of these estimated cases are diagnosed and notified to the national tuberculosis programme. Most, (94%), new tuberculosis patients are tested for HIV8 and 58% are found to be co-infected. Tuberculosis diagnosis has improved in people reporting a persistent cough, using smear microscopy on sputum samples.8 MDR-TB testing is seldom done since culture of M. tuberculosis is not routinely available.9 New cases typically receive first-line therapy. The treatment success rate is 85% for new sputum smear-positive patients who start treatment at a public treatment centre.7 First-line therapy typically includes isoniazid, rifampicin, ethambutol and pyrazinamide. Second-line therapy typically includes kanamycin, levofloxacin, ethionamide, cycloserine, ethambutol and pyrazinamide.

In 2012, an estimated 3.5% (4900 people) of the new estimated tuberculosis patients had MDR-TB; however, only 213 patients with MDR-TB started appropriate second-line treatment.7 Both in Mozambique and globally, the prevalence of MDR-TB tuberculosis is increasing. Therefore improved MDR-TB diagnostics and access to treatment are priorities for the Mozambican national tuberculosis programme and the global health community.4

Planned intervention

To increase the number of people diagnosed and treated with tuberculosis and to improve MDR-TB detection and treatment, the Xpert® implementation project was approved by the Mozambican Ministry of Health, with support from Health Alliance International. We chose to use a two-step testing algorithm for individuals suspected of having pulmo-
nary tuberculosis. All sputum samples were analysed using smear microscopy and new patients with at least one positive sputum smear out of two separate samples were treated with first-line tuberculosis therapy. Patients with two separate smear negative results were retested using Xpert® on one of the original samples.

In the beginning of February 2012, four Xpert® machines were deployed at two district and two urban public hospitals in four districts in Sofala and Manica provinces. We developed a transportation network to transfer smear negative sputum samples from three of the 10 surrounding health centres to the two urban hospitals. Eight remote health facilities routinely transferred samples to the two district hospitals via existing sputum transport networks. This covered approximately 5% of all sputum samples from three of the 10 provinces. We developed a transport network to transfer smear negative sputum samples out of two separate sputum samples from the four hospitals had sputum smear positive results. Of the 10 951 people with sputum smear negative results, 8631 (79%) were tested using Xpert® and 1081 (13%) were positive for tuberculosis. Thus, during this intervention Xpert® testing increased the diagnosis of bacteriologically-confirmed pulmonary tuberculosis by 1081/1558 (69%). Rifampicin resistance was detected in 58/1081 (5%) samples. Overall, 1019 (12%) of tests failed because of machine errors, and invalid or no results due to energy shortages.

We reviewed the records of 445 newly-diagnosed patients from the four hospitals in the second quarter of 2012 and found that 26% [115/445] had not been started on treatment (18% [35/200] of those diagnosed by microscopy and 33% [80/245] diagnosed using Xpert®). For patients with rifampicin resistance, 53% [31/58] were not started on second-line treatment. Three patients with rifampicin resistance were mistakenly initially started on first-line treatment but were converted to second-line treatment.

During 2012, 5076 people were placed on treatment in the four intervention districts, an increase of 632 patients (14.2%) over the baseline yearly average for these districts which was 4444 patients (15 554 patients were treated in these districts during the 3.5 years before implementation).

### Challenges

Despite encouraging outcomes, there were several programmatic and operational challenges in implementing and maintaining the Xpert® machines (Table 1).

One computer failed within six months, despite being attached to a surge protector/current stabilizer. Twelve of the original 16 (75%) Xpert® modules broke or failed calibration within 15 months and had to be replaced. In early 2013, Xpert® cartridges and calibration kits were back-ordered, resulting in several days without Xpert® cartridges despite ample lead-time in ordering. Updating antivirus software and operating systems and transferring data from the local computer to Cepheid in California, USA, was also difficult. Cepheid depends on Xpert® machines being connected to the internet to be able to diagnose problems remotely – this was not feasible in Mozambique and caused significant delays. Over time, shipments of cartridges and customer service improved as Cepheid employees and our team learned how to work with each other. However, importing consumables to Mozambique and clearing customs remained challenging, expensive and time-consuming.

The lack of a notification system to report positive Xpert® results to the national tuberculosis programme and no ability to automatically upload results electronically to a central secure database made it challenging to assess the impact of this intervention. It was difficult to remotely monitor Xpert® testing and notify key individuals in a timely fashion – such as provincial MDR-TB care coordinators when a patient tested positive for rifampicin resistance. WHO guidance on recording and reporting test results should allow national tuberculosis programmes to better monitor performance.

The current two-step testing algorithm likely caused delays in tuberculosis diagnosis relative to using Xpert® as a first-line test. Some patients returned after 24 hours for their smear results, but did not get their subsequent Xpert®
result. The need for repeat visits to establish a diagnosis may have led to higher pretreatment loss to follow-up. In the beginning, sites did not routinely collect patient contact information so it was impossible to reach these primary defaulters. Initially there was no protocol to routinely reconcile laboratory and treatment registries to ensure that all patients diagnosed with tuberculosis were started on treatment. Efforts are ongoing to improve the entire tuberculosis care cascade and to increase treatment initiation rates.

Lessons learnt

Our small-scale implementation project allowed us to gain important practical experience about the strengths and limitations of this new diagnostic technique (Box 1). Rapid tests have the potential to improve the diagnosis of tuberculosis and identify drug resistance. However, the tools are expensive and we experienced problems with the machines, data transfer, linkage to tuberculosis treatment initiation, reporting and follow-up. If the use of rapid diagnostic tests for tuberculosis is expanded to the national level, system improvements are needed to prevent these problems from occurring at a larger scale.

The national tuberculosis programme is committed to effective care of all tuberculosis patients in Mozambique. Improving diagnosis is a part of this commitment and, therefore, rapid tests like Xpert® will be provided to more health centres. However, affordable and durable tuberculosis diagnostic platforms that can handle the stresses of laboratory environments in low-resource settings are still needed.

Table 1. Responses to technical and logistical challenges encountered when implementing rapid tests for tuberculosis, Mozambique 2012–2013

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Reason</th>
<th>Response</th>
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<tbody>
<tr>
<td>High testing error rates</td>
<td>Laboratory technicians unfamiliar with Xpert®</td>
<td>Targeted training of technicians at facilities with high error rates. Error rate decreased from 12% in first year to 6% in the second year</td>
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<td></td>
<td>Higher (20%) cartridge error rates when cartridges were stored in non-air conditioned rooms</td>
<td>Installed air conditioners in cartridge storage areas</td>
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<td>Loss to follow-up</td>
<td>Laboratory registries were not routinely reconciled with tuberculosis treatment registries</td>
<td>Developed monthly meetings to reconcile laboratory and treatment registries</td>
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<td></td>
<td>Current two-step testing algorithm for tuberculosis delays patient results, decreasing the percentage of patients started on tuberculosis treatment</td>
<td>Ensured that laboratories collect patient addresses and phone numbers</td>
</tr>
<tr>
<td>Loss to follow-up for patients with rifampicin resistance</td>
<td>Some technicians did not initially understand that Xpert® tested for tuberculosis and rifampicin resistance</td>
<td>Pilot a remote monitoring system to immediately notify key individuals by SMS when a patient tests positive for rifampicin resistance</td>
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<td>Lack of real-time monitoring and evaluation</td>
<td>Xpert® originally designed to transmit data via Ethernet cables, not cell phone-based data connections that are widely available in low-income countries</td>
<td>Ministry of Health and national tuberculosis programme reporting systems need to be adapted to incorporate test results</td>
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<td></td>
<td>Limited ability to access test results and aggregate these by district, province or national level</td>
<td>Pilot a remote monitoring system for Xpert® that automatically transmits test results to a central database</td>
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<td>Determining an appropriate testing algorithm</td>
<td>Balancing the high cost of Xpert® with increased sensitivity for detecting tuberculosis and rifampicin resistance</td>
<td>Start using Xpert® as a first-line test for high risk patients (those with HIV infection, diabetes, cancer, children) and those at risk for MDR-TB</td>
</tr>
<tr>
<td>Xpert® durability</td>
<td>Poor understanding of routine maintenance requirements in dusty, non-temperature controlled remote laboratories</td>
<td>Use Xpert® at health centres with adequate staff and maintenance support</td>
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<tr>
<td>Lusophone staff struggling with English software</td>
<td>Software was initially only available in English</td>
<td>A new version was released that supports several languages, including Portuguese</td>
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HIV: human immunodeficiency virus; MDR-TB: multi-drug resistant tuberculosis; SMS: short message service.

Box 1. Summary of main lessons learnt

- **Xpert® MTB/RIF (Xpert®)** testing increased the number of confirmed bacteriologically positive tuberculosis cases. However, one third of patients diagnosed by Xpert® did not receive tuberculosis treatment, highlighting the need to strengthen the overall tuberculosis care cascade.
- Implementation and maintenance of Xpert® machines are costly and logistically challenging, which creates a need for more affordable and durable molecular testing platforms.
- Of the tuberculosis patients diagnosed with Xpert®, 5% were resistant to rifampicin, highlighting the need to develop a multi-drug resistance tuberculosis programme in Mozambique.
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Remote monitoring and evaluation of rapid testing systems may improve with the use of platforms such as GxAlert, XpertSMS and the Cepheid cloud system. Finally, while innovation in diagnostic tests is important, this is only one part of the tuberculosis care cascade. When increasing the number of people diagnosed with tuberculosis, attention is needed to ensure they receive the appropriate treatment, care and support.

Acknowledgement
Health Alliance International is a centre within the Department of Global Health, University of Washington, Seattle, USA.

Competing interests: None declared.

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Aplicación de la prueba de detección rápida de la tuberculosis en Mozambique

**Resumen**

La tuberculosis pulmonar se diagnostica principalmente mediante la baciloscopia del esputo. No obstante, la sensibilidad de este método es insuficiente, especialmente en las personas infectadas con el virus de la inmunodeficiencia humana (VIH). Pocas veces se somete a los pacientes a pruebas para la tuberculosis resistente a medicamentos.

El programa nacional contra la tuberculosis y Health Alliance International han introducido la prueba rápida de muestras de esputo de frotis negativo. Se analizaron las muestras mediante un análisis basado en la reacción en cadena de la polimerasa que detecta el ácido desoxirribonucleico de la *Mycobacterium tuberculosis* y una mutación que indica resistencia a la rifampicina. Xpert® MTB/RIF (Xpert®) detectó la prueba rápida. Se instalaron cuatro máquinas en cuatro hospitales públicos junto con un sistema de transporte de esputo para transferir las muestras de los centros de salud seleccionados. Se capacitó a los técnicos de laboratorio para operar las máquinas y a los médicos se les enseñó a interpretar los resultados.

En 2012, Mozambique presentó aproximadamente 140 000 casos nuevos de tuberculosis, de los cuales solo se diagnosticó y trató el 34 %. De los enfermos de tuberculosis, 58 % estaba infectado por el VIH.
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References


