Operational lessons drawn from pilot implementation of Xpert MTB/Rif in Brazil

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Problem The World Health Organization has endorsed the Xpert MTB/RIF (Xpert), an automated polymerase-chain-reaction-based assay, for the rapid diagnosis of tuberculosis (TB). However, large-scale use of a new technology calls for preparation and adaptation.

Approach A pilot implementation study was conducted in two Brazilian cities to explore the replacement of sputum smear microscopy with Xpert. The laboratories included covered 70% of the TB cases diagnosed, had no overlap in population catchment areas, handled different workloads and were randomly shifted to Xpert. Sputum samples were collected through the same routine procedures. Before the study the medical information system was prepared for the recording of Xpert results. Laboratory technicians were trained to operate Xpert machines and health workers were taught how to interpret the results.

Local setting The average annual TB incidence rate in Brazil is around 90 cases per 100,000 population. However, co-infection with the human immunodeficiency virus and multidrug resistance are relatively infrequent (>10% and <2%, respectively).

Relevant changes Of the tested sputum samples, 7.3% were too scanty for Xpert and had to be examined microscopically. Ten per cent of Xpert equipment needed replacement, but spare parts were not readily available in the country. Absence of patient identification numbers led to the introduction of errors in the medical information system.

Lessons learnt For nationwide scale-up, a local service provider is needed to maintain the Xpert system. Ensuring cartridge availability is also essential. The capacity to perform smear microscopy should be retained. The medical information system needs updating to allow efficient use of Xpert.

Introduction

In health services in areas with a high burden of tuberculosis (TB), diagnosis can be especially difficult because it takes several weeks or months to obtain the results of microbiological culture, which is the gold standard test for the diagnosis of TB. In such settings, diagnosis is usually based on microscopic examination of at least two sputum smears, but because sputum smear microscopy has low sensitivity, patients are often started on antituberculous therapy based on clinical evidence, without bacteriological confirmation. This leads to the underreporting of TB cases, unnecessary exposure to therapy with potential toxicity, and delay in the correct diagnosis and treatment of patients. In Brazil, around 26% of new tuberculosis cases are not confirmed with any bacteriological test and culture is not performed in 73% of re-treatment cases.

Xpert MTB/RIF (Xpert), a new nucleic acid amplification test based on polymerase chain reaction (PCR), has been recently developed to detect Mycobacterium tuberculosis DNA and genetic sequences indicative of rifampicin resistance (i.e. mutations of rpoB). The entire PCR assay is performed automatically within a cartridge, where the sample and reagents are mixed. The test, which takes less than two hours, has 88% sensitivity for tuberculosis and 94% sensitivity for rifampicin resistance, as well as 98% specificity for both. In light of these advantages, the World Health Organization has recommended the use of Xpert for the diagnosis of TB in countries with high prevalences of human immunodeficiency virus (HIV) infection and multidrug-resistant TB.

Brazil is considered a high-burden TB country (90 cases per 100,000 population). However, it is unusual among countries with a high TB burden in that primary multidrug resistance (MDR) is relatively uncommon (<2%). Yet despite low rates of HIV co-infection (10%) and MDR, the Brazilian National Tuberculosis Programme has recommended the incorporation of Xpert for the routine diagnosis of pulmonary TB in the public health system in an effort to increase the notification of cases with bacteriologically confirmed TB. To monitor the implementation of this new diagnostic test in the routine work of public health services, a rollout pilot study was conducted. In this paper we report the lessons learnt during the introduction of Xpert in two cities. The results of the pilot study will be used to plan for the national scale-up of Xpert in Brazil and may be useful to other countries that are trying to incorporate this new technology.

The field experience

Study design

The rollout pilot study, registered at www.clinicaltrials.gov (NCT01363765) and approved by the National Ethics Board-
CONEP (#494/2011), was a stepped wedge randomized clinical trial. It was conducted between February and October 2012 in Rio de Janeiro and Manaus, two large state capitals with high TB incidence rates (94.4 and 89.3 per 100,000 population, respectively). In total, 15 four-slot Xpert systems were implemented in 14 laboratories covering 70% of the TB diagnosis in Rio de Janeiro (n = 11) and Manaus (n = 3). The laboratories were chosen because they had different workloads and their population catchment areas did not overlap. Every month, two laboratories migrated overnight from two-sample smear microscopy diagnostics to a one-sample Xpert test. There were no changes to the patient’s routine management and standard clinical guidelines; two sputum samples continued to be collected from each patient (despite the switch to Xpert) and the same information systems remained in place. If an Xpert result was positive, regardless of a rifampicin resistance signal, the Xpert assay was repeated on a new sputum sample. If a positive rifampicin resistance was detected, culture and drug-susceptibility tests were performed. If resistance was confirmed, the patient was referred to the MDR centre for further evaluation and treatment.

Preparing for implementation of Xpert

For reporting purposes, the existing national electronic laboratory information system, Gerenciador de Ambiente Laboratorial (GAL), had to be modified to include TB cases diagnosed with the new technology. A new item was added to the notification forms (PCR results) of both GAL and the national reporting system. Training of laboratory technicians on the use of Xpert was conducted two weeks before the laboratory entered the intervention phase. The training, which lasted one day, was carried out by a representative of the manufacturer and the municipal TB programme team. In addition, a four-hour training session was organized by the National Tuberculosis Programme and the municipal TB programme to teach physicians and nurses how to interpret the results of a resistance signal in a country with a low prevalence of MDR such as Brazil. The recommendation given was to put patients on four-drug combination therapy – i.e. rifampicin, isoniazid, pyrazinamide and ethambutol – until the results of conventional drug susceptibility tests were available.

Operational findings

During the study period, several bottle-necks and opportunities for strengthening the health-care system were identified. In informal discussions, the health staff said that the GAL system was a very useful tool but pointed out that the lack of a unique patient identifier number in the Brazilian health system resulted in the need to manually enter each patient’s information when requesting a test or a laboratory result – a problem identified in an earlier study. Apart from being time consuming, this practice often led to minor errors that resulted in truncated information and misidentification of samples or double entries for the same patient. It also led to the misuse of PCR cartridges. In some cases two diagnostic samples from the same patient or follow-up samples were processed by mistake. Certain problems came up, in addition to errors involving Xpert syringes, probes and signals previously described by the manufacturer of Xpert. Such problems were attributable to the characteristics of the sputum samples. Among 15,701 samples analysed by Xpert, 1,151 (7.3%) had insufficient volume (less than 1 mL) and 200 (1.3%) had heavy traces of blood or food residuals. Thus, 8.6% of the Xpert samples had to be examined by smear microscopy.

The training of laboratory technicians without computer skills was straightforward and the learning curve was quick. A previous study has shown that Xpert performance is less subject to the influence of user skills, motivation or workload than sputum smear microscopy. In one laboratory with a very high volume of samples, a change in the working shift of one employee was sufficient to enable the processing of all samples.

To confirm rifampicin resistance and investigate resistance to other drugs, it became necessary to expand reference laboratory capacity, especially in performing mycobacterial culture and drug-susceptibility tests, which are not routinely performed in Brazil. Despite frequent energy shortages in Manaus, Xpert machines were able to complete the PCR cycles with support from additional, uninterrupted power supplies. Nonetheless, the maintenance of Xpert equipment consumed much time and energy because spare modules and replacement parts were not immediately available in Brazil. We were able to use parts from Xpert modules that weren’t yet being used in the study, but this is not a good solution in a routine laboratory. During the short pilot study, six of the 60 modules had to be replaced, along with a defective computer that could not be replaced locally on account of software requirements.

Lessons learnt

As newer and more accurate technologies for TB diagnosis are developed, understanding the factors that facilitate or hinder their implementation becomes important. Health system staff should carefully consider the many factors involved in incorporating a new technology when seeking to maximize clinical impact and minimize the TB burden in their settings (Box 1).

Ensuring an efficient laboratory information system is essential. Such a system can lead to improved health outcomes through several mechanisms, including increased adherence to guideline-based care, enhanced disease surveillance and monitoring and fewer medication errors. Above all, laboratory information systems can expedite the reporting of test results. A patient identifier number would reduce the probability of errors.

The eventual need for changes in national notification systems when incorporating a new technology should also be considered in advance. For instance, it will be necessary to modify reporting forms to ensure that bac-
Training also needs careful planning. In the case of Xpert, it is particularly important to make physicians understand that the test’s negative and positive predictive values for tuberculosis and rifampicin resistance depend on the local prevalences of both and should be adapted accordingly. Before adopting Xpert, national TB programmes might want to prepare algorithms and technical notes on how to investigate suspected TB cases and how to handle positive rifampicin resistance. In addition, since Xpert is not currently recommended for testing follow-up samples, to avoid wasting PCR cartridges health-care workers should be trained in how and when to request the test and laboratory staff should be shown how to manage the flow of samples obtained for different purposes (diagnosis versus follow-up).

It is important to ensure that laboratory technicians feel comfortable with the new technologies, including the simple computer-based tasks they require. A short adaptation period should be planned in advance to allow them time to learn to use the equipment and to gradually shift from paper-based to electronic recordkeeping. With advances in technology, it will be necessary to ensure that health workers, especially in low-resource settings, have the training and support required to effectively operate computers and other equipment. Furthermore, since Xpert cannot be performed from time to time because of inadequate samples or other technical difficulties, it is important to retain the laboratory capacity to perform good quality sputum smears. Moreover, countries where mycobacterial culture is not routinely performed in patients suspected of having TB should be prepared to expand their laboratory capacity to process samples with a positive rifampicin resistance signal, as well as the capacity to manage patients suspected of having multidrug-resistant TB.

Plans for scaling up the use of Xpert should include negotiations with the manufacturer for the maintenance of equipment and the regular supply of cartridges, syringes and other necessities. It is critically important to have available spare parts and local technicians trained to quickly solve occasional technical problems, together with a sustainable and regular supply of cartridges. Hopefully, some of the issues identified in this pilot exercise will help Xpert manufacturers to provide users with effective technical support. Lastly, countries planning to scale up Xpert nationwide should conduct health system research, which plays an essential role in the implementation of new technologies.

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Leçons opérationnelles tirées de la mise en œuvre pilote de Xpert MTB/RIF au Brésil

Problème L’Organisation mondiale de la Santé a approuvé Xpert MTB/RIF (Xpert), un test automatisé basé sur l’amplification en chaîne par polymérase, pour le diagnostic rapide de la tuberculose (TB). Cependant, l’utilisation à grande échelle d’une nouvelle technologie exige une préparation et une adaptation préalables.

Approche Une étude de mise en œuvre pilote a été menée dans deux villes du Brésil pour étudier le remplacement de l’examen au microscope des frottis d’expectoration par Xpert. Les laboratoires inclus couvraient 70% des cas de TB diagnostiqués, mais les pièces de rechange n’étaient pas facilement disponibles dans le pays. L’absence de numéros d’identification des patients a conduit à l’apparition d’erreurs dans le système d’informations médicales.

Environnement local Le taux moyen annuel d’incidence de la TB au Brésil est d’environ 90 cas pour 100 000 habitants. Cependant, la co-infection avec le virus de l’immunodéficience humaine et la résistance croissante aux médicaments sont relativement peu fréquentes (10% et >2%, respectivement).

Changements significatifs Parmi les échantillons d’expectoration testés, 7,3% étaient insuffisants pour Xpert et ont dû être examinés par microscope. Dix pour cent de l’équipement Xpert a dû être remplacé, mais les pièces de rechange n’étaient pas facilement disponibles dans le pays. L’absence de numéros d’identification des patients a conduit à l’apparition d’erreurs dans le système d’informations médicales.

Leçons tirées Pour un déploiement à l’échelle du pays, un prestataire de service local est nécessaire pour la maintenance du système Xpert. Assurer la disponibilité des cartouches est également indispensable. La capacité à effectuer les examens des frottis par microscope doit être maintenue. Le système d’informations médicales doit être mis à jour pour permettre l’utilisation efficace de Xpert.

Резюме

Практические уроки, извлеченные из реализации пилотного проекта по применению метода Xpert MTB/RIF в Бразилии

Поблема Всемирная организация здравоохранения одобрила автоматизированный метод анализа на основе полимеразной цепной реакции Xpert MTB/RIF (Xpert) для быстрой диагностики туберкулеза (TB). Однако широкомасштабное использование новой технологии потребует подготовки и вложений.

Подход Для изучения замены микроскопии мокроты методом Xpert в двух бразильских городах проводилось исследование по реализации пилотного проекта. Включенные в исследование лаборатории охватывали 70% выявленных случаев туберкулеза, но имели очень небольшую площадь охвата населения, обрабатывали различные нагрузки и в случайном порядке переводились на систему Xpert. Процедуры сбора образцов мокроты при этом оставались неизменными. Медицинская информационная система была подготовлена к регистрации результатов, собранных по методу Xpert, до начала исследования. Лаборанты были обучены работе с установками Xpert, а медицинские работники прошли обучение методам интерпретации результатов.

Местные условия Среднегодовой уровень заболеваемости туберкулезом в Бразилии составляет около 90 случаев на 100 000 населения. При этом инфицированность с вирусом иммунодефицита человека и множественная лекарственная устойчивость являются относительно редкими (10% и <2% соответственно).

Осуществленные перемены Из протестированных образцов мокроты 7,3% оказались слабыми, но в исследовании методом Xpert их пришлось исследовать под микроскопом. 10% устройств Xpert нуждались в замене, однако запасных частей не оказалось в достаточном количестве в стране. Отсутствие числа библиографических ссылок привело к появлению ошибок в медицинской информационной системе.

Выводы Для применения метода Xpert в общенациональном масштабе необходимо местные поставщики услуг для обслуживания данных систем. Также важно значение имеет наличие картриджей для замены. Возможность лабораторий выполнять микроскопию мазков должна быть сохранена. Необходимо обновление медицинской информационной системы для обеспечения эффективного использования метода Xpert.
Situation: La Organización Mundial de la Salud ha aprobado Xpert MTB/RIF (Xpert), un ensayo automatizado basado en la reacción en cadena de la polimerasa para el diagnóstico rápido de la tuberculosis (TB). Sin embargo, el uso a gran escala de una tecnología nueva requiere una preparación y adaptación.

Enfoque: Con objeto de examinar la sustitución de la microscopía de frotis de esputo con Xpert, se llevó a cabo un estudio piloto de implementación en dos ciudades brasileñas. Los laboratorios participantes incluyeron el 70 % de los casos de tuberculosis diagnosticados, no se produjo ningún solapamiento en las zonas de captación de población, manejaron cargas de trabajo distintas y se asignaron a Xpert de forma aleatoria. Las muestras de esputo se recogieron a través de los mismos procedimientos rutinarios. Antes del estudio, se preparó el sistema de información médico con objeto de registrar los resultados de Xpert. Se capacitaron a los técnicos de laboratorio para operar máquinas Xpert y se enseñó a los trabajadores sanitarios cómo interpretar los resultados.

Marco regional: La tasa de incidencia anual media de la tuberculosis en Brasil es de unos 90 casos por cada 100 000 habitantes. Sin embargo, la coinfección con el virus de la inmunodeficiencia humana y la multirresistencia son relativamente poco frecuentes (10 % y < 2 %, respectivamente).

Cambios importantes: De las muestras de esputo sometidas a prueba, el 7,3 % fueron demasiado escasas para Xpert y tuvieron que ser examinadas con microscopio. El diez por ciento de los equipos Xpert necesitaron piezas de repuesto, pero estas no estaban disponibles en el país. La ausencia de números de identificación de pacientes dio lugar a la introducción de errores en el sistema de información médica.

Lecciones aprendidas: La expansión nacional del sistema Xpert necesita un proveedor de servicios local que se haga cargo del mantenimiento del sistema. También es fundamental garantizar la disponibilidad de los cartuchos, y debería conservarse la capacidad de realizar microscopias de frotis. El sistema de información médica debe mantenerse actualizado para permitir un uso eficiente de Xpert.

References