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. 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 tuberculosis 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 tuberculosis incidence 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.

Abstracts in عربي, 中文, Français, Русский and Español at the end of each article.

Introduction

In health services in areas with a high burden of tuberculosis, diagnosis can be especially difficult because it takes several weeks or months to obtain the results of mycobacterial culture, which is the gold standard test for the diagnosis of tuberculosis. In such settings, diagnosis is usually based on microscopic examination of at least two sputum smears,[1] but because sputum smear microscopy has low sensitivity, patients are often started on antituberculous therapy based on clinical evidence, without bacteriological confirmation.[2] This leads to the underreporting of tuberculosis 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.[3]

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*).[4] 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.[5,6] In light of these advantages, the World Health Organization has recommended the use of Xpert for the diagnosis of tuberculosis in countries with high prevalences of human immunodeficiency virus (HIV) infection and multidrug-resistant tuberculosis (MDR-TB).[7]

Brazil is considered a high-burden tuberculosis country (90 cases per 100 000 population). However, it is unusual among countries with a high tuberculosis burden in that primary MDR-TB is relatively uncommon (< 2%).[3] Yet despite low rates of HIV co-infection (10%)[3] and MDR-TB, the Brazilian National Tuberculosis Programme has recommended the incorporation of Xpert for the routine diagnosis of pulmonary tuberculosis in the public health system in an effort to increase the notification of cases with bacteriologically confirmed tuberculosis. To monitor the implementation of this new diagnostic test in the routine work of public health services, a roll-out 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.

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(*Submitted: 8 October 2013 – Revised version received: 20 January 2014 – Accepted: 21 January 2014 – Published online: 1 May 2014*)

The field experience

Study design

The roll-out 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 tuberculosis incidence rates (94.4 and 89.3 per 100 000 population, respectively).[3]

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 tuberculosis cases diagnosed with the new technology.[8] 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.[9] The training, which lasted one day, was carried out by a representative of the manufacturer and the municipal tuberculosis programme team. In addition, a four-hour training session was organized by the National Tuberculosis Programme and the municipal tuberculosis programme to teach physicians and nurses how to interpret the results of a resistance signal in a country with a low prevalence of MDR-TB 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.

Box 1. **Summary of main lessons learnt**

- To minimize errors when using Xpert, notification forms have to be adapted and an efficient communication system has to be in place.
- A regular supply of PCR cartridges and the ready availability of spare parts must be negotiated with the manufacturer of Xpert.
- The capacity to perform sputum smear microscopy should be maintained for follow-up tests and for the testing of sputum samples too scanty to run Xpert.

Operational findings

During the study period, several bottlenecks 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.[10] 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.[11] Such problems were attributable to the characteristics of the sputum samples. Among 15 701 samples analysed by Xpert, 1151 (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.[12] 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 tuberculosis 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 tuberculosis 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.[13,14] 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 bacteriologically confirmed TB cases are accurately captured.

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.[6] Before adopting Xpert, national tuberculosis programmes might want to prepare algorithms and technical notes on how to investigate suspected tuberculosis 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 use of 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 record keeping. 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,[15] 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 tuberculosis 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 MDR-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. ■

Acknowledgements

We thank all directors of the clinics and laboratories, as well as laboratory staff. Without them this study would not have been possible.

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Competing interests: None declared.

ملخص

الدروس التشغيلية المستفادة من التنفيذ التجريبي لاختبار التشخيص السريع للسل "Xpert MTB /Rif" في البرازيل

المشكلة اعتمدت منظمة الصحة العالمية اختبار التشخيص السريع للسل "Xpert MTB /RIF" (المعروف اختصاراً باسم Xpert)، وهو اختبار مؤتمت يستند على تفاعل البوليميراز المتسلسل، للتشخيص السريع لداء السل (TB). ومع ذلك، يتطلب الاستخدام واسع النطاق للتكنولوجيا الجديدة التأهب والتكيف.

الأسلوب تم إجراء دراسة للتنفيذ التجريبي في مدينتين في البرازيل لاستكشاف الاستعاضة عن الفحص المجهري للطاخات البلغم باختبار "Xpert". وغطت المختبرات المدرجة 70 ٪ من حالات داء السل التي تم تشخيصها، ولم تشهد تداخلاً في مناطق التجمعات السكانية، وتناولت أعباء العمل المختلفة وتم تحويلها عشوائياً إلى اختبار "Xpert". وتم جمع عينات البلغم من خلال نفس الإجراءات الروتينية. وقبل الدراسة، تم إعداد نظام المعلومات الطبية لتسجيل نتائج اختبار "Xpert". وتم تدريب فنيي المختبرات على تشغيل أجهزة اختبار "Xpert" وتم تعليم العاملين الصحيين كيفية تفسير النتائج.

المواقع المحلية يبلغ متوسط المعدل السنوي للإصابة بداء السل في البرازيل حوالي 90 حالة لكل 100 ألف شخص. إلا أن العدوى بداء السل المقاوم للأدوية المتعددة المصاحبة للعدوى بفيروس العوز المناعي البشري غير متكررة نسبياً (10 ٪ وأقل من 2 ٪، على التوالي).

التغيّرات ذات الصلة كان 7.3 ٪ من إجمالي عينات البلغم التي تم اختبارها ضئيلة بدرجة لم تكف لإجراء اختبار "Xpert" واستدعى الأمر فحص هذه النسبة مجهرياً. وكان لا بد من استبدال عشرة في المائة من معدات اختبار "Xpert" غير أن قطع الغيار لم تكن متاحة بسهولة في البلد. وأدى غياب أرقام تحديد هوية المرضى إلى حدوث أخطاء في نظام المعلومات الطبية.

الدروس المستفادة لزيادة الحجم على الصعيد الوطني، يتعين وجود مقدم خدمة محلي للحفاظ على نظام "Xpert". كما أن ضمان توافر الخرطوشة ضروري. وينبغي الحفاظ على قدرة تنفيذ الفحص المجهري باستخدام اللطاخات. ويتعين تحديث نظام المعلومات الطبية لإتاحة استخدام اختبار "Xpert" بكفاءة.

摘要

巴西试点实施 Xpert MTB/Rif 的经验教训

问题 世界卫生组织已赞同使用 Xpert MTB/RIF（Xpert）（一种基于聚合酶链反应的自动式化验）进行肺结核（TB）快速诊断。然而，大规模使用新技术需要准备和适应。

方法 在两个巴西城市执行试点实施研究以探究用 Xpert 代替痰涂片镜检的情况。所包含的实验室覆盖了所诊断的 TB 病例的 70%，在人口责任区方面没有重叠，处理不同的工作负荷并被随机转移至 Xpert。痰样本通过同样的常规流程收集。在研究之前，准备医疗信息系统以记录 Xpert 结果。培训实验室技术人员来操作 Xpert 机器，教会卫生工作人员如何解析结果。

当地状况 在巴西，每 10 万人口的 TB 平均年发生率为大约 90 例。然而，艾滋病病毒协同感染和多耐药性相对少见（分别为 10% 和 <2%）。

相关变化 在被测的痰样本中，7.3% 因太少而不能进行 Xpert，必须用显微镜检测。有 10% 的 Xpert 设备需要更换，但该国没有现成可用的备件。缺少患者身份证号码导致医药信息系统出错。

经验教训 要进行全国范围的推广，就需要本地服务提供者维护 Xpert 系统。确保药筒供应也非常关键。应保留执行痰片显微镜检查的能力。需要更新医疗信息系统以高效使用 Xpert。

Résumé

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, ne présentaient pas de chevauchement dans les bassins de vie des populations, traitaient différentes charges de travail et basculaient aléatoirement vers l'utilisation de Xpert. Les échantillons d'expectoration étaient recueillis avec les mêmes procédures de routine. Avant l'étude, le système d'informations médicales a été préparé pour l'enregistrement des résultats Xpert. Les techniciens de laboratoire ont été formés à l'utilisation des machines Xpert, et le personnel de santé a appris à interpréter les résultats.

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 multirésistance 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

Проблема Всемирная организация здравоохранения одобрила автоматизированный метод анализа на основе полимеразной цепной реакции Xpert MTB/RIF (Xpert) для быстрой диагностики туберкулеза (ТБ). Однако широкомасштабное использование новой технологии требует подготовки и внедрения.

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, не имели перекрытия районов охвата населения, обрабатывали различные нагрузки и в рандомизированном 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 коинфекция с вирусом иммунодефицита человека и множественная лекарственная устойчивость являются относительно редкими (10% и <2% соответственно).

Осуществленные перемены Из протестированных образцов мокроты 7,3% образцов были слишком скудны для исследования методом Xpert и их пришлось исследовать под микроскопом. 10% устройств Xpert нуждались в замене, однако запасных частей не оказалось в достаточном количестве в стране. Отсутствие идентификационных номеров пациентов привело к появлению ошибок в медицинской информационной системе.

Выводы Для применения метода Xpert в общенациональном масштабе необходимы местные поставщики услуг для обслуживания данных систем. Также важное значение имеет обеспечение наличия картриджей для замены. Возможность лабораторий выполнять микроскопию мазков должна быть сохранена. Необходимо обновление медицинской информационной системы для обеспечения эффективного использования метода Xpert.

Resumen

Lecciones operativas extraídas de la implementación piloto de Xpert MTB/RIF en Brasil

Situación 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 microscopia 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 médica con objeto de registrar los resultados de Xpert. Se capacitó 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 necesitó 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

1. Stop TB Partnership. Global Laboratory Initiative. Briefing Note: TB Diagnostics and Laboratory Strengthening [Internet]. Geneva: World Health Organization; 2014. Available from: http://www.stoptb.org/wg/gli/assets/documents/BRIEFING%20NOTE%20LABS%20for%20GC.pdf [cited 2014 Feb 14].
2. Global tuberculosis report 2012. Geneva: World Health Organization; 2013. Available from: http://www.who.int/tb/publications/global_report/en/ [cited 2014 Feb 14].
3. Barreira D. Programa Nacional de Controle da Tuberculose [Internet]. Brasília: Ministry of Health, Brazil; 2013. Available from: https://docs.google.com/file/d/0B0CE2wqdEaR-VG1fa0JJMi1qa0U/edit [cited 2013 Mar 3]. Portuguese.
4. Boehme CC, Nabeta P, Hillemann D, Nicol MP, Shenai S, Krapp F, et al. Rapid molecular detection of tuberculosis and rifampin resistance. N Engl J Med. 2010;363:1005-15. doi: http://dx.doi.org/10.1056/NEJMoa0907847 PMID: 20825313
5. Chang K, Lu W, Wang J, Zhang K, Jia S, Li F, et al. Rapid and effective diagnosis of tuberculosis and rifampicin resistance with Xpert MTB/RIF assay: a meta-analysis. J Infect. 2012;64:580-8. doi: http://dx.doi.org/10.1016/j.jinf.2012.02.012 PMID: 22381459
6. Steingart KR, Schiller I, Horne DJ, Pai M, Boehme CC, Dendukuri N. Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. Cochrane Database Syst Rev. 2014;1:CD009593. PMID: 24448973
7. Rapid implementation of the Xpert MTB/RIF diagnostic test. Geneva: World Health Organization; 2011. Available from: http://whqlibdoc.who.int/publications/2011/9789241501569_eng.pdf [cited 2013 Feb 28].
8. GAL – Gerenciador de Ambiente Laboratorial [Internet]. Sala: Ministério da Saúde; 2014. Available from: http://gal.datasus.gov.br/GAL/default.php]. [cited 2014 Feb 17]. Portuguese.
9. Toouli G, Georgiou A, Westbrook J. Changes, disruption and innovation: an investigation of the introduction of new health information technology in a microbiology laboratory. J Pathol Inform. 2012;3:16. doi: http://dx.doi.org/10.4103/2153-3539.95128 PMID: 22616028
10. Telles MA da S, Menezes A, Trajman A. Bottlenecks and recommendations for the incorporation of new technologies in the tuberculosis laboratory network in Brazil. J Bras Pneumol. 2012;38:766-70. doi: http://dx.doi.org/10.1590/S1806-37132012000600013 PMID: 23288123
11. Stop TB Partnership. Implementation and roll-out of Xpert MTB/RIF. Update May 2013 [Internet]. Geneva: World Health Organization; 2013. Available from: http://www.stoptb.org/wg/gli/assets/documents/Xpert%20MTB-RIF%20UPDATE%20May%202013.pdf [cited 2014 Feb 17].
12. Boehme CC, Nicol MP, Nabeta P, Michael JS, Gotuzzo E, Tahirli R, et al. Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study. Lancet. 2011;377:1495-505. doi: http://dx.doi.org/10.1016/S0140-6736(11)60438-8 PMID: 21507477
13. Buntin MB, Burke MF, Hoaglin MC, Blumenthal D. The benefits of health information technology: a review of the recent literature shows predominantly positive results. Health Aff (Millwood). 2011;30:464-71. doi: http://dx.doi.org/10.1377/hlthaff.2011.0178 PMID: 21383365
14. Chaudhry B, Wang J, Wu S, Maglione M, Mojica W, Roth E, et al. Systematic review: impact of health information technology on quality, efficiency, and costs of medical care. Ann Intern Med. 2006;144:742-52. doi: http://dx.doi.org/10.7326/0003-4819-144-10-200605160-00125 PMID: 16702590
15. Raizada N, Sachdeva KS, Sreenivas A, Vadera B, Gupta RS, Parmar M, et al. Feasibility of decentralised deployment of Xpert MTB/RIF test at lower level of health system in India. PLoS ONE. 2014;9:e89301. doi: http://dx.doi.org/10.1371/journal.pone.0089301 PMID: 24586675