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SHORT COMMUNICATION

Xpert® MTB/RIF under routine conditions in diagnosing pulmonary tuberculosis: a study in two hospitals in Pakistan

S. K. Shah,[1] A. M. V. Kumar,[2] O. F. Dogar,[1] M. A. Khan,[3] E. Qadeer,[4] S. Tahseen,[4] F. Masood,[4] A. K. Chandio,[5] M. E. Edginton[6]

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Xpert® MTB/RIF testing was offered to consecutive patients with presumptive tuberculosis (TB) attending two hospitals in Pakistan during April–May 2012, in addition to routine diagnostic protocol (smear microscopy, chest radiography and clinical judgement). We assessed the relative contribution of each tool in detecting pulmonary TB under routine conditions. Of 606 participants, 121 (20%) were detected as pulmonary TB: 46 (38%) by microscopy, 38 (31%) by Xpert alone and 37 (31%) on clinical and radiological grounds; 41 (65%) were detected by both Xpert and microscopy. One patient had rifampicin resistance. Although Xpert detected approximately twice as many TB cases as microscopy (n = 79, 65%), clinical judgement remained favoured by clinicians even when smear and Xpert were negative.

Pakistan is one of the five countries with the highest tuberculosis (TB) burden, with an annual estimated incidence of 231 per 100000 population; it contributes 63% of the TB burden in the Eastern Mediterranean Region (EMRO).[1] Globally, TB control has been successful in terms of high treatment success rates and a consequent reduction in mortality. However, the impact on transmission of TB has not been as significant as expected. Failure in timely interruption of transmission has been attributed to diagnostic and management delays; suboptimal availability of sensitive diagnostic tools has been considered as one of the obstacles in achieving early diagnosis.[2] Sputum smear microscopy, given its advantages of high specificity, low cost and ability to identify the most infectious patients, has been a critical tool in TB control efforts. However, this test misses nearly half of all cases.[3]

A new molecular test for the diagnosis of TB, Xpert® MTB/RIF has shown great promise, with high sensitivity (73%) and specificity (99%), and has been endorsed for use by the World Health Organization.[4] Pakistan's National TB Programme (NTP) is planning to scale up the implementation of Xpert for the diagnosis of pulmonary TB (PTB). Given the high cost per test and concerns regarding the feasibility of its implementation, the use of Xpert needs careful evaluation under routine settings before large-scale implementation.

As a pilot initiative, Xpert was used on all patients with presumptive PTB attending two health facilities in Rawalpindi, Pakistan. In this operational study we assess, among the presumptive TB cases evaluated, 1) the total number (proportion) detected as having PTB under routine conditions, 2) the relative contribution of sputum microscopy, Xpert and clinical judgment (including radiography [CXR]) in the detection of PTB, and 3) the number of patients detected with rifampicin (RMP) resistance. Validation of diagnosis by sputum culture was beyond the scope of this operational study.

METHODS

This was a cross-sectional study involving a review of NTP records and Xpert assay results. Two tertiary care hospitals (one public and one private) in Rawalpindi district were selected purposively based on their close links with the NTP and the availability of a limited number of Xpert cartridges for research purposes. All consecutive presumptive TB patients referred to the laboratories of the two hospitals for diagnostic sputum smear examination between 15 April and 30 May 2012 were informed about the study and their consent sought. Those who consented underwent an Xpert assay on the residual sputum of the initial (spot) microscopy specimen transported to the National Reference Laboratory (NRL) in addition to the routine diagnostic protocol (microscopy, CXR and clinical diagnosis). The results of the Xpert assay were reported back to the treating physicians within 24 hours of specimen collection. Technicians performing the Xpert assay and smear microscopy were blinded to each other's results.

A case of pulmonary TB was defined as a participant who was either smear- or Xpert-positive or judged to be a case of TB by the treating physician based on clinical assessment and CXR findings. Study variables extracted into a structured tool included laboratory number, sex, age, and the results of smear microscopy, Xpert and clinical judgement (including CXR findings).

Data were double-entered and validated using EpiData version 3.1 (EpiData Association, Odense, Denmark), and the numbers and relative proportions of PTB patients diagnosed by each method (sputum smear microscopy, Xpert assay and clinical judgement, including CXR) were calculated.

Ethics approval was obtained from the Ethics Advisory Group of the International Union Against Tuberculosis and Lung Disease, Paris, France.

RESULTS

Of 606 patients with presumptive TB, 307 (51%) were males, 59% were from the private hospital, and ages

AFFILIATIONS
1 Department of Health Sciences, University of York, York, UK
2 International Union Against Tuberculosis and Lung Disease (The Union), South-East Asia Office, New Delhi, India
3 Association for Social Development, Islamabad, Pakistan
4 National Tuberculosis Programme, Islamabad, Pakistan
5 Health Services Academy, Islamabad, Pakistan
6 The Union, Paris, France

CORRESPONDENCE
Sarwat K Shah
Seebohm Rowntree Building
2nd floor
University of York
York, YO10 5DD, UK
Tel: (+44) 190 432 1841
e-mail: sarwatdopasi@hotmail.com

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KEY WORDS
operational research; tuberculosis; Xpert MTB/RIF; diagnosis; Pakistan

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TABLE Results of smear microscopy and the Xpert® MTB/RIF assay among presumptive TB cases in two health facilities, Rawalpindi, Pakistan, April–May 2012 (N = 606)*

Xpert results	Smear microscopy		
	Negative *n* (%)†	Positive *n* (%)†	Total *n* (%)
Negative	444 (79.3)	3 (6.5)	447 (73.8)
Mycobacterium tuberculosis positive	38 (6.8)	41 (89.1)	79 (13.0)
Invalid, error	14 (2.5)	1 (2.2)	15 (2.5)
Missing	64 (11.4)	1 (2.2)	65 (10.7)
Total	560	46	606

*Among presumptive TB cases who were smear-negative and Xpert-negative/invalid/missing (n = 522), 37 were diagnosed and placed on treatment based on clinical judgement/radiographic findings.
†Column percentage.
TB = tuberculosis.

ranged from 6 to 78 years (median 32 years). The microscopy and Xpert results are shown in the Table. Of the 606 patients, 46 (8%) were sputum smear-positive. The Xpert assay could not be performed on 65 sputum samples due to loss before or during transportation to the NRL. Of 560 smear-negative samples (including 65 samples lost for Xpert), 38 (7%) were Xpert-positive. Among 522 cases who were smear- and Xpert-negative or invalid, 37 (7%) were registered based on CXR and clinical judgement. Thus, a total of 121 pulmonary TB cases were detected by all three tools, of which 46 (38%) were contributed by microscopy, 38 (31%) by Xpert and 37 (31%) on clinical and radiological grounds. One participant was found to have RMP resistance on Xpert assay.

DISCUSSION

This is the first study from Pakistan to describe the performance and shortcomings of using the Xpert assay in a programme setting. Although similar studies have been conducted in many countries under well-controlled research settings, they do not reflect performance under routine conditions.[5,6] This study has several implications. First, we found that Xpert detected approximately twice as many TB cases as smear microscopy alone (79 vs. 46/606), clearly demonstrating the value of Xpert in enhancing TB case finding. The impact on TB case finding would have been greater if we had been able to examine the 65 (11%) specimens lost during the process of transportation to the NRL. Future implementation models should take this into account and appropriate measures should be instituted, including strengthening the sputum collection and transport system, to avoid operational losses.

Second, clinical judgment (including good quality CXR) contributed a substantial proportion of detected cases, emphasising its continued preference among clinicians in diagnosing TB.

Third, nearly 3% of the Xpert results were invalid, and would require re-testing; this needs to be taken into account by the programme managers during planning for procurement and supply chain management. It is interesting to note that there were three patients who were smear-positive but Xpert-negative; although the exact reason is not clear, it could be due to non-tuberculous mycobacteria.

The study had some important limitations. First, the almost double yield of Xpert might be due to suboptimal quality of the microscopy. As we did not collect reliable data on microscopy quality, we are uncertain about the incremental yield of the Xpert assay. Second, as this was operational research conducted under routine conditions, we could not use a gold standard to confirm the diagnosis of PTB and RMP resistance, and hence we are unable to comment on the sensitivity and specificity of each tool used. Third, although cost is an important consideration in the decision to scale up Xpert, we did not include it in this study, and it is a topic for future research.

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En plus d'un protocole de diagnostic de routine (examen microscopique des frottis, cliché thoracique et évaluation clinique), on a offert Xpert® MTB/RIF à des patients consécutifs suspects de tuberculose (TB) qui présentaient à deux hôpitaux du Pakistan au cours de la période avril–mai 2012. Nous avons évalué la contribution relative de chaque outil à la détection de la TB pulmonaire dans les conditions de routine. Sur 606 participants, 121 (20%) ont été diagnostiqués comme TB pulmonaire : 46 (38%) par l'examen microscopique, 38 (31%) par Xpert seul, et 37 (31%) sur une base clinique et radiologique ; 41 (65%) ont été détectés par l'examen microscopique et Xpert. Chez un patient, on a trouvé une résistance à la rifampicine. Quoique l'Xpert ait détecté approximativement deux fois le nombre de cas de TB détectés par l'examen microscopique (n = 79, 65%), le jugement clinique reste favorisé par les cliniciens, même lorsque le résultat du frottis et de l'Xpert est négatif.

En dos hospitales de Paquistán se propuso a un grupo de pacientes con presunción de tuberculosis (TB) que acudieron de manera consecutiva entre abril y mayo del 2012 la prueba Xpert® MTB/RIF, además del protocolo diagnóstico corriente (que comportaba la baciloscopia, la radiografía de tórax y la evaluación clínica). Se analizó la contribución relativa de cada instrumento en el diagnóstico de la TB pulmonar en las condiciones corrientes. De los 606 participantes, en 121 (20%) se estableció el diagnóstico de TB pulmonar de la siguiente

manera: en 46 casos (38%) por microscopia, en 38 (31%) mediante la prueba Xpert sola y en 37 casos (31%) con base en las características clínicas y radiográficas; 41 (65%) fueron detectados por microscopia y Xpert. Un paciente exhibió resistencia a rifampicina. Si bien la prueba Xpert permitió el diagnóstico de cerca del doble de casos de tuberculosis que la baciloscopia (n = 79, 65%), el juicio clínico predomina aun en la decisión de los médicos, incluso frente a un resultado negativo de la baciloscopia y la prueba Xpert.

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