INT J TUBERC LUNG DIS 21(10):1100–1105

http://dx.doi.org/10.5588/ijtld.17.0372

Missed opportunities for earlier diagnosis of rifampicin-resistant tuberculosis despite access to Xpert® MTB/RIF

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SUMMARY

OBJECTIVE: To assess the proportion of rifampicin-resistant tuberculosis (RR-TB) patients with potential earlier RR-TB diagnoses in Khayelitsha, South Africa.

DESIGN: We conducted a retrospective analysis among RR-TB patients diagnosed from 2012 to 2014. Patients were considered to have missed opportunities for earlier diagnosis if 1) they were incorrectly screened according to the Western Cape diagnostic algorithm; 2) the first specimen was not tested using Xpert® MTB/RIF; 3) no specimen was ever tested; or 4) the initial Xpert test showed a negative result, but no subsequent specimen was sent for follow-up testing in human immunodeficiency virus-positive patients.

RESULTS: Among 543 patients, 386 (71%) were diagnosed with Xpert and 112 (21%) had had at least one presentation at a health care facility within the 6 months before the presentation at which RR-TB was diagnosed. Overall, 95/543 (18%) patients were screened incorrectly at some point: 48 at diagnostic presentation only, 38 at previous presentation only, and 9 at both previous and diagnostic presentations.

CONCLUSIONS: These data show that a significant proportion of RR-TB patients might have been diagnosed earlier, and suggest that case detection could be improved if diagnostic algorithms were followed more closely. Further training and monitoring is required to ensure the greatest benefit from universal Xpert implementation.

KEY WORDS: rapid diagnostics; resistance; diagnostic algorithms; human immunodeficiency virus

RIFAMPICIN (RMP) RESISTANT tuberculosis (RR-TB) is a growing public health concern. Rapid diagnosis and initiation of appropriate treatment are required to improve patient outcomes and curb community transmission.[1] The World Health Organization (WHO) reported 132 120 notified cases of multidrug-resistant tuberculosis (MDR-TB, defined as TB resistant to at least isoniazid [INH] and RMP) globally in 2015.[2] This figure represents 40% of the estimated burden of MDR-TB among notified pulmonary TB patients and only 23% of the estimated incident MDR-TB cases worldwide.[2] While this gap remains substantial, it has decreased since 2010, when the WHO estimated that only 10% of TB patients with MDR-TB were actually being diagnosed.[3]

Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) is a rapid, potentially point-of-care, diagnostic tool which simultaneously detects the presence of *Mycobacterium tuberculosis* and RR-TB, and has assisted in addressing the diagnostic gap for RR-TB.[4–6] Xpert testing does not require complex reference laboratory facilities, thereby improving access to drug susceptibility testing (DST). Moreover, Xpert produces a result more rapidly than culture-based methods, therefore potentially enabling RR-TB patients to start appropriate anti-tuberculosis treatment earlier, with consequent benefits to the individual and the community.[7–9] Xpert has been recommended by the WHO, wherever feasible, as the primary diagnostic tool among individuals with signs and symptoms of TB to improve the detection of TB and RR-TB cases.[10]

In an effort to respond to the TB, RR-TB, and human immunodeficiency virus (HIV) epidemics in South Africa,[11] Xpert was implemented progressively from 2011, allowing universal access to RMP DST for all individuals investigated for TB. Xpert has likely contributed to the dramatic increase in case detection of RR-TB in South Africa, from 7386 cases notified in 2010 to 19 613 in 2015.[2,3] Xpert has also likely contributed to significant reductions in the time to initiation of second-line treatment in South Africa.[12,13] The use of Xpert has been incorporated

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Article submitted 30 May 2017. Final version accepted 30 June 2017.

[A version in Spanish of this article is available from the Editorial Office in Paris and from the Union website www.theunion.org]

Table 1 Diagnostic algorithm for presumptive TB cases used in Khayelitsha, South Africa

	Presumptive TB case, diagnostic algorithm					
	Sample 1: Xpert conducted					
Sample 1: Xpert result	MTB-positive, RIF-resistant	MTB-positive, RIF-susceptible	MTB-positive, RIF inconclusive	MTB-negative, HIV-positive	MTB-negative, HIV-negative	Xpert unsuccessful
Sample 2: Action	Send for microscopy, culture and LPA	Send for microscopy	Send for microscopy, culture and LPA	Send for culture and LPA	No action needed	Repeat Xpert

TB = tuberculosis; MTB = *Mycobacterium tuberculosis*; RIF = rifampicin; HIV = human immunodeficiency virus; LPA = line-probe assay.

into diagnostic algorithms in South Africa at national and provincial levels.

However, despite these successes, only 59% of RR-TB patients (range 33–83 across South African provinces) were initially diagnosed with Xpert in 2013.[13] Given a sensitivity of 86% in culture-positive TB in South Africa, the percentage of cases diagnosed with Xpert is lower than expected,[4] possibly due to failures in the implementation of the TB diagnostic algorithm.[14,15]

To assess whether Xpert is being utilised to its full potential, we investigated reasons for RR-TB diagnosis using tests other than Xpert, adherence to the diagnostic algorithm, and therefore missed opportunities for earlier RR-TB diagnoses among RR-TB patients in Khayelitsha, Cape Town, South Africa.

STUDY POPULATION AND METHODS

Design

This was a retrospective, descriptive cohort study investigating possible breakdowns in the implementation of the diagnostic algorithm for presumptive TB among patients diagnosed with RR-TB in Khayelitsha between January 2012 and December 2014. The overall proportion of patients for whom the algorithm was not implemented as per policy was determined, and breakdowns in the implementation of the algorithm and possible causes of these breakdowns were described.

The study was covered by pre-existing ethical approval for the evaluation of decentralised drug-resistant tuberculosis treatment in Khayelitsha from the Human Research Ethics Committee of the University of Cape Town, Cape Town. The study met the criteria for exemption from Médecins Sans Frontières ethical review as it was based on the use of routinely collected programmatic data.

Setting

Khayelitsha is a peri-urban township in Cape Town with a population of approximately 450 000, half of whom live in informal settlements.[16] The estimated annual case notification rate of RR-TB in Khayelitsha is 55 per 100 000 population,[17] and the HIV co-infection rate is approximately 70%.[18] Xpert was rolled out in Khayelitsha from November 2011; the impact of Xpert implementation, coupled with the provision of decentralised care for RR-TB in Khayelitsha, has been described previously.[12,17]

Diagnostic algorithm

The diagnostic algorithm for presumptive TB patients implemented in Khayelitsha health care facilities requires the collection of two sputum specimens 1 h apart at presentation for TB investigation. Both sputum specimens should be sent to the laboratory in plastic envelopes joined by a perforated seal, with two laboratory requisition forms. The first specimen should be tested using Xpert, with testing for the second specimen dependent on the Xpert test result (Table 1). According to the algorithm, HIV status should be recorded on the laboratory requisition forms. Furthermore, Xpert testing should not be conducted in patients already undergoing first-line anti-tuberculosis treatment, even if RR-TB is suspected. In late 2014, the Department of Health released a directive for clinicians on the use and interpretation of Xpert results, cautioning them against using Xpert in previously treated patients for up to 2 years following the completion of previous anti-tuberculosis treatment due to the risk of false-positive results.[19] This guidance was not intended to discourage the use of Xpert but instead to alert clinicians to its appropriate use based on symptoms and clinical presentation.

Cohort selection

All patients captured in a prospective database in Khayelitsha and diagnosed with RR-TB from 2012 to 2014 were included. Patients with a history of second-line anti-tuberculosis treatment were excluded, as the likelihood of diagnosing RR-TB after inadequate second-line treatment is increased. These patients are often restarted on RR-TB treatment on a presumptive basis while awaiting DST results. Patients with extra-pulmonary TB (EPTB) were also excluded from the analysis, as guidelines for clinicians on using Xpert in EPTB during the study period were not clear.

Definitions

'Diagnostic presentation' was defined as presentation to a health care facility where a specimen was given from which RR-TB was diagnosed; 'date of diagnosis' was defined as the date of this specimen collection. If

Table 2 Clinical and demographic characteristics of pulmonary RR-TB patients diagnosed stratified by diagnostic method, 2012–2014

Diagnostic method	Xpert (n = 386, 71%) n (%)	Diagnosed with LPA (n = 157, 29%) n (%)	Total (n =543) P value
Year of diagnosis*			
2012	118 (62)	72 (37.9)	<0.001†
2013	140 (78)	40 (22.2)	0.015
2014	128 (74)	45 (26.0)	0.31
Female sex	191 (50)	74 (47)	0.62
Previous treatment history			
No history	205 (53)	43 (27)	0.000†
Treatment with first-line drugs	181 (47)	114 (73)	
HIV status			
HIV-negative	116 (30)	38 (24)	0.17
HIV-positive	270 (70)	110 (70)	0.98
Unknown	0	9 (6)	0.000†

* Row percentages presented; all other percentages are column percentages.
† Statistically significant ($P < 0.05$)
RR-TB = rifampicin-resistant tuberculosis; LPA = line-probe assay; HIV = human immunodeficiency virus.

Xpert results were received before any other DST result, the patient was diagnosed using Xpert. To assess whether the diagnostic algorithm was implemented as per policy before the RR-TB diagnosis, the diagnostic pathways of patients were investigated retrospectively; 'previous presentation' was defined as presentation at a health care facility for TB investigation >14 days but <6 months before diagnostic presentation. For patients who provided a specimen within this timeframe, but who were undergoing first-line anti-tuberculosis treatment, their diagnostic pathway was followed retrospectively back to their first TB diagnostic sample to determine whether the algorithm had been implemented at the previous presentation according to policy. Patients who presented before the availability of Xpert (November 2011) were excluded from the analysis.

Data collection

Routine RR-TB data were linked to data on first-line anti-tuberculosis treatment to determine whether RR-TB patients initiated first-line anti-tuberculosis treatment before RR-TB diagnosis. A manual search of each patient was conducted in the National Health Laboratory Service (NHLS) database to determine if there had been previous presentations for TB investigation. Patients with no presentation before their diagnostic presentation were categorised as 'screened incorrectly' if Xpert had not been performed. Patients with previous presentations were categorised as 'screened correctly at either or both previous and diagnostic presentations', 'screened incorrectly at either previous presentation or diagnostic presentation' or 'screened incorrectly at both previous and diagnostic presentation'.

The primary outcome measure was the proportion of patients screened incorrectly at any point along the pathway. The total number of breakdowns in algorithm implementation was also estimated (some patients had breakdowns at both previous and diagnostic presentations). Finally, laboratory requisition forms were investigated for specimens representing a breakdown in algorithm implementation to assess the type and possible reasons for breakdown. Breakdowns in algorithm implementation were categorised as follows: Xpert testing not performed as per algorithm; Xpert-negative, HIV-positive patient with no follow-up culture performed as per the algorithm; and no specimen available for testing.

Data analysis

χ^2 tests were conducted to describe differences in clinical and demographic characteristics of those diagnosed using Xpert or the line-probe assay (LPA; Hain LifeScience, Nehren, Germany). Descriptive statistics (frequencies and proportions) were provided to highlight the reasons for the breakdown in algorithm implementation. Data were analysed using STATA/IC v14.1 (StataCorp, College Station, TX, USA).

RESULTS

Diagnosis of rifampicin-resistant tuberculosis

From January 2012 to December 2014, a total of 543 patients were diagnosed with pulmonary RR-TB in Khayelitsha, of whom 386 (71%) were diagnosed using Xpert. The proportion of patients diagnosed using Xpert increased from 62% in 2012 to respectively 78% and 74% in 2013 and 2014, and more patients with no previous anti-tuberculosis treatment were diagnosed using Xpert than patients who had been treated previously (Table 2).

Among the patients, 431 (79%) had no presentations at health care facilities before their diagnostic presentation and 112 (21%) had at least one presentation before their diagnostic presentation. Overall, 95/543 patients (43+38+5+9, 18%) were screened incorrectly at some point: 48 at diagnostic presentation only, 38 at previous presentation only, and 9 at both previous and diagnostic presentation (Figure).

Breakdown in algorithm implementation

There were 104 instances among the 18% (n = 95) of persons incorrectly screened in which the algorithm was not implemented according to policy; instances in which patients were screened incorrectly at previous presentation and diagnostic presentation were not mutually exclusive.

In 85% (89/104) of the instances, Xpert was not conducted as outlined in the algorithm; in 40% (36/89) of these instances, the patient had undergone

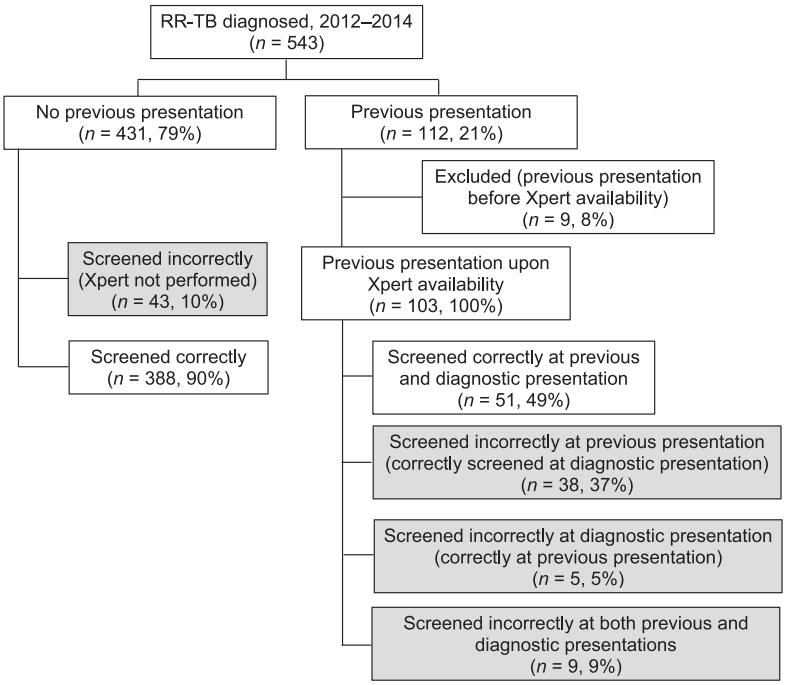

Figure RR-TB diagnostic pathway for patients diagnosed in Khayelitsha, South Africa, 2012–2014. RR-TB = rifampicin-resistant tuberculosis.

first-line anti-tuberculosis treatment within 2 years before RR-TB diagnosis. In 8% (8/104) of the instances, the Xpert result was negative and the patient was HIV-positive, but follow-up culture was not performed. In the final 7% (7/104) of instances, no specimen was ever tested: the specimen had leaked and there was no evidence that another sample was sent ($n = 2$), or no specimen was sent for testing and the patient was started on presumptive treatment with first-line drugs ($n = 5$). Among the 104 instances, laboratory request forms could be retrieved for 68 of the 99 instances in which a specimen was received by the laboratory (Table 3).

DISCUSSION

Xpert diagnostic testing could improve case detection in RR-TB and reduce the often lengthy delays to initiating appropriate second-line treatment.[4,13,20,21] The proportion of RR-TB patients diagnosed using Xpert in Khayelitsha was 71%, which is higher than the national average but lower than expected if all patients had been diagnosed according to the algorithm. However, the proportion of patients diagnosed using Xpert improved between 2012 and subsequent years, suggesting improved implementation of the algorithm over time.

Overall, 18% of RR-TB patients were not screened according to the diagnostic algorithm at either the initial or diagnostic presentations. Given that this was a retrospective analysis of patients already diagnosed with RR-TB, similar levels of failure to implement the diagnostic algorithm among all presumptive TB patients are likely to contribute to lower overall RR-TB case detection. Among the 18% of patients screened incorrectly, it is likely that the diagnosis of

Table 3 Reasons for the 104 instances of breakdown in algorithm implementation among the 95 cases incorrectly screened

Instances of algorithm implementation breakdowns ($n = 104$)	Forms available ($n = 68$) n (row %)	Reasons ascertained from available forms
No Xpert performed ($n = 89$, 86%)	61 (69)	The two specimens sent to different laboratories (unclear which was specimen 1) ($n = 17$) Xpert not requested on laboratory requisition form ($n = 55$) Conflicting information on the two laboratory requisition forms ($n = 37$) Use of non-standard laboratory requisition forms ($n = 16$)
Xpert-negative, HIV-positive and no follow-up culture (with LPA) ($n = 8$, 8%)	5 (63)	HIV status not indicated on the laboratory requisition form ($n = 3$) HIV-positive indicated on the laboratory requisition form ($n = 1$) HIV status unknown indicated on the laboratory requisition form ($n = 1$)
No specimen tested ($n = 7$, 7%)	2 (29)*	Sample leaked and no evidence that two samples were sent ($n = 2$)

* There were no forms for the remaining 5 (71%) patients as they were started on presumptive anti-tuberculosis treatment.
HIV = human immunodeficiency virus; LPA = line-probe assay.

RR-TB could have been made sooner, potentially contributing to improved individual patient outcomes and reduced community transmission.

In 40% of the instances in which Xpert testing was not performed as it should have been, the patient had received first-line treatment in the previous 2 years. Although the directive cautioning against Xpert use among patients with a history of anti-tuberculosis treatment was only released in late 2014, there was much discussion on the directive before its issue.[22] Uncertainty regarding the interpretation of Xpert results among previously treated patients is therefore a likely contributor. While all diagnostic tests should be interpreted according to the clinical presentation of each individual, such nuanced advice is often difficult to apply in practice for clinicians inexperienced in TB management.

Although the diagnostic algorithm in use in this setting might appear simple at first glance, it is contingent upon clinicians to send two sputum samples in the appropriate laboratory specimen bags and with the laboratory request forms correctly completed. The laboratory requires that the correct test be requested, along with the indication for that test. In addition, the algorithm specifies a different pathway for the second specimen if the initial Xpert test is negative and the patient is HIV-positive. This algorithm is not reflected in the laboratory request form, and in this setting several non-standard request forms are in use. The standard laboratory request form does not include a specific request for the HIV status of the patient, and there is no section on the form in which to indicate the number of specimens sent. Furthermore, there are no instructions to indicate how to complete the various sections of the form. Finally, there is a lack of clarity regarding reflex laboratory testing (i.e., follow-up tests of Sample 2). It is not clear (for either clinicians or laboratory staff) whether the laboratory should conduct follow-up tests as per the algorithm in the absence of, or in contradiction to, the clinician's request. The laboratory request forms should be simplified and a standard operating procedure should be implemented to detail the processes for form completion.

This study was subject to the limitations inherent in routinely collected data from a programmatic setting. Although laboratory data were collected from the NHLS, laboratory data from outside the province were not reviewed. Among patients who presented before the diagnostic presentation, it was not known whether resistance was present at the presentation before diagnosis or whether it was acquired following a previous presentation. Finally, we were unable to ascertain the accuracy of the information given in the forms for the analysis of breakdowns in algorithm implementation.

Although there has recently been debate about the ability of Xpert to affect TB notification rates and outcomes, Xpert remains one of the most powerful diagnostic tools available for early diagnosis of RR-TB.[23] Incorrect implementation of the TB diagnostic algorithm recommending Xpert as the primary diagnostic test in this setting highlights the need for simplified algorithms and continued education and training on the use of new diagnostics. Clarification of the tasks involved in algorithm adherence and reflex laboratory testing are needed to extract the greatest benefit from implementing new diagnostics such as Xpert.

Acknowledgements

The authors thank the City of Cape Town Health Department (Cape Town), Western Cape Government Health (Cape Town), the NHLS (Johannesburg), and the Department of Health (Pretoria) staff dedicated to working with RR-TB patients in Khayelitsha facilities.

Conflicts of interest: none declared.

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RESUME

OBJECTIF : Evaluer la proportion de patients atteints de tuberculose résistante à la rifampicine (RR-TB) qui auraient dû bénéficier d'un diagnostic potentiellement plus précoce de la RR-TB à Khayelitsha, Afrique du Sud.
SCHÉMA : Nous avons réalisé une analyse rétrospective parmi les patients RR-TB diagnostiqués de 2012 à 2014. Les patients ont été considérés comme ayant manqué une opportunité de diagnostic plus précoce si : 1) ils ont été incorrectement dépistés selon l'algorithme de diagnostic du Cap Ouest ; 2) le premier échantillon n'a pas été testé avec l'Xpert® MTB/RIF ; 3) aucun échantillon n'a jamais été testé ; ou 4) l'Xpert initial a eu un résultat négatif mais aucun autre échantillon n'a ensuite été envoyé pour suivre le dépistage chez les patients positifs pour le virus de l'immunodéficience humaine.
RÉSULTATS : Parmi 543 patients, 386 (71%) ont été diagnostiqués grâce à l'Xpert et 112 (21%) étaient venus en consultation dans une structure de santé au moins une fois au cours des 6 mois précédant la consultation au cours de laquelle la RR-TB a été diagnostiquée. Au total, 95/543 (18%) patients ont été dépistés incorrectement à un moment quelconque : 48 seulement lors de la consultation de diagnostic, 38 seulement lors de la consultation précédente et 9 dans les deux consultations.
CONCLUSION : Ces données montrent qu'une proportion significative de patients atteints de RR-TB pourrait avoir été diagnostiquée plus tôt et suggèrent que la détection des cas pourrait être améliorée si les algorithmes de diagnostic étaient suivis de plus près. Davantage de formation et de suivi sont requis pour obtenir le plus grand bénéfice de la mise en œuvre universelle de l'Xpert.

RESUMEN

OBJETIVO: Evaluar la proporción de pacientes con tuberculosis (TB) resistente a rifampicina (RR) que podría presentar un antecedente de diagnóstico de TB-RR en Khayelitsha, Sudáfrica.
MÉTODOS: Se llevó a cabo un análisis retrospectivo de los pacientes con TB-RR diagnosticados del 2012 al 2014. Se consideró que los pacientes habían perdido oportunidades para un diagnóstico más temprano en los siguientes casos: 1) cuando su detección sistemática fue incorrecta con respecto al algoritmo diagnóstico del Cabo Occidental; 2) cuando la primera muestra no se examinó mediante la prueba Xpert® MTB/RIF; 3) cuando no se examinó ninguna muestra; o 4) cuando la primera prueba Xpert dio un resultado negativo, pero no se envió una nueva muestra para seguimiento, en los pacientes positivos frente al virus de la inmunodeficiencia humana (VIH).
RESULTADOS: De los 543 pacientes incluidos, en 386 se estableció el diagnóstico con la prueba Xpert (71%) y 112 habían acudido por lo menos en una ocasión a un establecimiento de salud en los últimos 6 meses, antes de la consulta que dio lugar al diagnóstico de TB-RR (21%). En general, en 95 de los 543 pacientes la detección fue incorrecta en algún momento (18%); en 48 casos fue incorrecta solo en la consulta en la cual se estableció el diagnostico, en 38 pacientes solo en una consulta anterior y en 9 pacientes en ambas oportunidades.
CONCLUSIÓN: Estos datos ponen de manifiesto que existe una alta proporción de pacientes con TB-RR que hubiesen podido recibir antes el diagnostico e indican que es posible mejorar la detección de casos, si se cumplen con mayor precisión los algoritmos diagnósticos. Se precisa mejorar la capacitación y aumentar el seguimiento a fin de alcanzar las máximas ventajas de la aplicación generalizada de la prueba Xpert.