Impact of Xpert MTB/RIF rollout on management of tuberculosis in a South African community

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Background. The Xpert MTB/RIF test shortens the time to microbiological confirmation of pulmonary tuberculosis (TB) under research conditions.
Objective. To evaluate the field impact of Xpert MTB/RIF rollout on TB diagnostic yield and time to treatment in a South African (SA) community.
Methods. We compared TB investigation outcomes for 6-month calendar periods before and after Xpert MTB/RIF rollout in a semi-rural area of SA. The proportion of adult patients who tested positive by sputum smear microscopy, liquid culture or Xpert MTB/RIF and the proportion of positive sputum smear, liquid culture or Xpert MTB/RIF tests were compared. Secondary outcomes included time to laboratory diagnosis and treatment initiation. Data were collected from the National Health Laboratory Service database and from the Western Cape Provincial Department of Health TB register.
Results. Regional rollout of Xpert MTB/RIF testing occurred in 2013. Of the 15 629 patients investigated in the post-rollout period, 7.9% tested positive on GeneXpert, compared with 6.4% of the 10 741 investigated in the pre-rollout period who tested positive by sputum smear microscopy ($p<0.001$). Median laboratory processing time was <1 day for Xpert MTB/RIF (interquartile range (IQR) 0 - 1) compared with 1 day (IQR 0 - 16) for sputum smear microscopy ($p=0.001$). The median time to TB treatment initiation was 4 days (IQR 2 - 8) after rollout compared with 5 days (IQR 2 - 14) before ($p=0.001$).
Conclusions. Patients investigated for suspected pulmonary TB were more likely to be diagnosed after rollout of Xpert MTB/RIF testing, although the benefit to diagnostic yield was modest, and Xpert MTB/RIF testing was associated with a marginal improvement in time to treatment initiation.

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South Africa (SA) is one of the 22 high tuberculosis (TB) burden countries that account for 83% of cases of TB worldwide.[1] Effective and rapid diagnosis of TB is an important strategy for reducing the burden of TB globally through early treatment initiation. Early initiation of treatment can reduce the opportunity for an infectious person to transmit TB within the community and improve patient treatment outcomes.[2,3] Xpert MTB/RIF is a diagnostic test for TB performed with the GeneXpert device (Cepheid, USA) – an automated, cartridge-based, nucleic amplification assay that detects both the *Mycobacterium tuberculosis* (MTB) organism and rifampicin resistance directly from sputum.[4] In ideal conditions, sample processing takes 2 hours, with <20 minutes' hands-on processing time.[5] Sputum testing by the Xpert MTB/RIF test may enable quicker diagnosis and earlier treatment initiation than sputum smear microscopy.[6]

Before availability of the Xpert MTB/RIF test, the diagnosis of pulmonary TB in resource-limited settings was based primarily on detection of acid-fast bacilli by sputum smear microscopy. Additional MTB culture might be performed to diagnose suspected smear-negative TB and to detect suspected drug resistance.[7] Sputum smear microscopy is well suited for low-income countries because it is inexpensive and rapid, requires basic laboratory infrastructure and expertise, and is highly specific. However, sputum smear microscopy has relatively low diagnostic sensitivity and cannot detect drug resistance.[7] Sputum MTB culture in liquid or solid medium is more sensitive than smear microscopy and can detect drug resistance, but MTB culture is too slow to have an immediate impact on clinical management, requiring up to 8 weeks for laboratory processing. Additionally, MTB culture requires expensive equipment, advanced laboratory facilities and highly trained personnel.[4]

Since December 2010, the World Health Organization has recommended global rollout of the Xpert MTB/RIF test for diagnosis of pulmonary TB. In SA, Xpert MTB/RIF testing was officially launched in October 2011 and complete implementation was reported by 2013.[8] Per SA national guidelines, TB diagnosis before Xpert MTB/RIF rollout relied on sputum smear microscopy on two different samples from an individual suspected of having pulmonary TB, taken on different days or on the same day at least 1 hour apart. TB diagnosis after Xpert MTB/RIF rollout relies on a single 'spot' sputum sample. MTB culture was not routinely performed before Xpert MTB/RIF rollout (and is not routinely performed now), but was requested for investigation of HIV-infected individuals who might have paucibacillary TB disease, or if drug resistance was suspected. All sputum samples were collected by staff at local primary healthcare facilities and processed by a regional National Health Laboratory Service (NHLS) laboratory that generated a paper-based result for the clinic.[9]

Under research conditions, the Xpert MTB/RIF test greatly accelerates the time to laboratory diagnosis compared with MTB culture,[3,10] so that time to TB treatment initiation could potentially be reduced significantly – particularly for patients with sputum smear-negative TB disease, who would rely on MTB culture for diagnosis. Additionally, Xpert MTB/RIF has approximately two-fold

higher sensitivity than sputum smear microscopy.[10,11] For these reasons it was hoped that Xpert MTB/RIF would be a 'game-changer' for TB control.[7] However, the majority of data have been derived from ideal research conditions, and it is unclear what impact Xpert MTB/RIF has had in real-world field settings. Initial reports indicate that the SA Xpert MTB/RIF rollout has not contributed to significant improvement in mortality of patients investigated for pulmonary TB.[12]

Objective

To determine the impact of Xpert MTB/RIF rollout on yield of TB case detection, time to diagnosis and time to treatment initiation in an SA community with a very high incidence of TB.[13,14]

Methods

This before-and-after observational cohort study evaluated the impact of rollout of Xpert MTB/RIF testing on the detection and treatment of new adult pulmonary TB cases in the Cape Winelands East district of the Western Cape Province, SA. The study protocol was approved by the University of Cape Town Human Research Ethics Committee (ref. no. 387/2014). Waiver for individual consent was granted for secondary data analysis of de-identified health systems data. The Cape Winelands East is a semi-rural area with a very high estimated total TB case notification rate of 1 400 per 100 000 population.[14] There are >60 primary healthcare facilities in the district. Data from all adults aged ≥18 years who presented at primary healthcare facilities and were suspected of having pulmonary TB were included for potential analysis. Analyses were conducted for the period May - November in the calendar years 2012 and 2014. These corresponding 6-month periods were selected in order to bracket Xpert MTB/RIF implementation in the Cape Winelands East district, which occurred during 2013, and to adjust for possible seasonal confounders.

Data from the two periods were compared for the proportion of patients investigated for TB who tested positive by sputum smear microscopy, liquid culture or Xpert MTB/RIF, and the proportion of sputum smear microscopy, liquid culture or Xpert MRB/RIF tests that were positive. Median time to laboratory diagnosis of pulmonary TB and median time to TB treatment initiation were compared, by test method and by period.

Data were collected from the electronic NHLS database that records all microbiological tests for TB in the region, including the type of test (sputum smear microscopy, Xpert MTB/RIF or liquid culture) and the result of each test. Unique individuals tested for pulmonary TB were identified by unique laboratory identifiers. For the analysis of proportion of patients investigated who tested positive, the denominator was the total number of individuals in the study period who were tested, and the numerator was the number of patients with a positive test by a particular method (sputum smear microscopy, Xpert MTB/RIF, liquid culture). For analysis of the proportion of positive tests, the denominator was the total number of tests in the study period, and the numerator the number of positive tests by a particular method. Data for the proportion of tests reported as invalid were collected to evaluate differences between sputum smear microscopy and Xpert MTB/RIF laboratory processes. An invalid result was obtained when a sample was lost or when a test was not completed, for whatever reason.

Secondary outcomes evaluated were median time to laboratory diagnosis and median time to TB treatment initiation. Time to laboratory diagnosis was defined as the time in days from when a sputum sample was collected to the time when that test result was reported. Time to TB treatment initiation was defined as the time from when a sputum sample was collected to the time when TB treatment was recorded as being initiated. The dates of sputum collection and generation of the result report were determined from dates captured on the NHLS electronic database. The dates of treatment initiation for individual patients were retrieved from an electronic TB register maintained by the Western Cape Provincial Department of Health.

Statistical tests for comparison of two proportions and Wilcoxon signed rank tests were used, with a threshold for significance of 0.05. Data were analysed using Stata 12 (StataCorp, USA).

Results

A total of 15 629 individuals with suspected TB were screened between May and November 2012 (pre-Xpert MTB/RIF rollout period) and 10 741 between May and November 2014 (post-rollout period). The median age and gender distribution of the patients investigated did not differ between the pre- and post-rollout periods (Table 1).

Of the patients tested for TB in the pre-rollout period, 13 279 (85.0%) had sputum smear microscopy and 1 860 (11.9%) had additional liquid culture performed. Post-rollout, as expected, far fewer patients had sputum smear microscopy (n=2 542, 23.7%; p<0.001) or liquid culture (n=832, 7.7%; p<0.001) performed. The proportion of patients with positive sputum smear microscopy results was similar in the two periods (6.4% v. 6.2%; p=0.40), although the proportion of patients with positive liquid cultures was higher in the pre-rollout period than after rollout (1.5% v. 0.9%; p<0.001). In the post-rollout period, 7.9% of patients tested positive on Xpert MTB/RIF, significantly more than by sputum smear microscopy in the pre-Xpert MTB/RIF period in 2012 (7.9% v. 6.4%; p<0.001).

A total of 21 392 samples for TB investigation were processed in the pre-rollout period, compared with 14 858 in the post-rollout period. The proportion of sputum smear microscopy-positive samples was similar before and after rollout (5.7% v. 5.0%; p=0.002), the proportion of positive liquid cultures was higher in the pre-rollout period (3.2% v. 1.8%; p<0.001), and the proportion of positive Xpert MTB/RIF results (5.7%) in the post-rollout period was similar to the proportion of positive sputum smear microscopy results in the pre-rollout period (5.7%; p=0.95).

The median time to laboratory diagnosis for sputum smear microscopy in the pre-rollout period was 1 day compared with <1 day for Xpert MTB/RIF in the post-rollout period. The median time to laboratory diagnosis by MTB culture was also slightly longer before than after rollout (39 v. 38 days; p<0.001). The median time to treatment initiation was 5 days before Xpert MTB/RIF rollout, compared with 4 days after rollout (p<0.001) (Table 2).

Discussion

We demonstrated that in a community-based study of the impact of Xpert MTB/RIF rollout in a high-burden primary healthcare setting in SA, patients with pulmonary TB were more likely to be diagnosed in the post-rollout period, when both Xpert and liquid culture were available, than in the pre-rollout period, when only sputum smear microscopy and liquid culture were available. Although the additional benefit to diagnostic yield was modest, it was also associated with a small improvement in time to laboratory diagnosis and time to TB treatment initiation, saving 1 day to start of treatment after Xpert MTB/RIF rollout, compared with the period in which sputum smear microscopy was the primary diagnostic modality. Although minor, this improvement in time to treatment may be clinically important in view of the very high incidence of TB disease in this region (1 400/100 000 population per year).[14] Our findings are consistent with other studies[6,15,16] that have shown that application of Xpert

Table 1. Patients investigated for suspected pulmonary TB*

	Individuals with suspected TB			Sputum samples	
Variable	**May - November 2012**	**May - November 2014**	***p*-value**	**May - November 2012**	**May - November 2014**
Denominator, *N*	15 629	10 741	0.11	21 392	14 858
Sex, *n* (%)					
Male	8 065 (51.6)	5 833 (54.3)		11 030 (51.6)	7 949 (53.5)
Female	7 179 (45.9)	4 731 (44.1)		9 857 46.1)	6 693 (45.1)
Unknown	385 (2.5)	216 (2.0)		505 (2.4)	216 (1.5)
Age (yr), median (IQR) (range)	37 (28 - 47) (18 - 87)	36 (28 - 46) (18 - 87)		36 (28 - 47) (18 - 90)	36 (28 - 46) (18 - 87)
Xpert MTB RIF, *n* (%)					
Xpert done	n/a	6 336 (59.0)		n/a	6 336 (42.6)
Xpert negative	n/a	5 471 (50.9)		n/a	5 471 (36.8)
Xpert invalid	n/a	14 (0.1)		n/a	14 (0.1)
Xpert positive	n/a	851 (7.9		n/a	851 (5.7)
Sputum smear, *n* (%)					
Smear done	13 279 (85.0)	2 542 (23.7)		15 620 (73.0)	3 609 (24.3)
Smear negative	11 498 (73.6)	1 286 (12.0)		13 369 (62.5)	1 716 (11.5)
Smear invalid	775 (5.0)	592 (5.5)		1 029 (4.8)	1 155 (7.8)
Smear positive	1 006 (6.4)	664 (6.2)	0.40	1 222 (5.7)	738 (5.0)
MTB culture, *n* (%)					
Culture done	1 860 (11.9)	832 (7.7)	<0.001	4 245 (19.8)	2 209 (14.9)
Culture negative	1 471 (9.2)	664 (6.2)		3 187 (14.9)	1 748 (11.8)
Culture invalid	152 (1.0)	72 (0.7)		367 (1.7)	189 (1.3)
Culture positive	237 (1.5)	96 (0.9)	<0.001	691 (3.2)	272 (1.8)

TB = tuberculosis; IQR = interquartile range; n/a = not applicable.
*May - November 2012 represents the pre-rollout period before Xpert MTB/RIF implementation and May - November 2014 the post-rollout period after implementation.

Table 2. Median time to pulmonary TB diagnosis (TTD) and TB treatment initiation (TTI) in patients screened for suspected pulmonary TB*

	May - November 2012	**May - November 2014**	***p*-value**
Xpert MTB/RIF			
TTD (d), median (IQR)	n/a	0 (0 - 1)	
Sputum smear			
TTD (d), median (IQR)	1 (0 - 16)	2 (1 - 22)	<0.001
Culture			
TTD (d), median (IQR)	39 (37 - 40)	38 (37 - 40)	<0.001
TTI (d), median (IQR)	5 (2 - 14)	4 (2 - 8)	<0.001

TB = tuberculosis; IQR = interquartile range; n/a = not applicable.
*May - November 2012 represents the pre-rollout period before Xpert MTB/RIF implementation and May - November 2014 the post-rollout period after implementation.

MTB/RIF in a primary healthcare programmatic setting can improve the rate of TB case detection and reduce time to TB diagnosis.

We also observed a reduction in the number of sputum samples sent for testing (30.5% less) and the number of persons tested for TB (31.3% less) after Xpert MTB/RIF rollout (Table 1), with a consequent reduction in workload for TB clinic staff and laboratory staff in the latter period. However, we could not determine whether this decline reflected a true decline in the community burden of TB disease, and a corresponding reduction in persons presenting to the primary healthcare clinics with suspected TB, or was due to a change in TB screening practices, since pre-rollout sampling required two sputum samples. As expected, fewer sputum samples were sent for smear microscopy in the post-rollout period, but the proportion of positive smear results in both analysis periods was similar, implying that the rate of TB disease among investigated patients did not change, and therefore that the higher proportion of detected TB cases in the post-rollout period was due to more sensitive diagnostic testing using Xpert MTB/RIF. However, although the proportion of individuals screened for TB who had MTB culture performed was higher before than after Xpert MTB/RIF rollout, the MTB culture positivity rate followed the same trend (1.5% v. 0.9%; $p<0.001$). This finding might be explained if patients in the later period were slightly more paucibacillary, but not sufficiently so to make an impact on the rate of sputum smear positivity. A consequence of Xpert MTB/RIF rollout was decreased demand for MTB culture testing, which we hypothesise may be due to increased diagnostic confidence in Xpert MTB/RIF and/or the fact that Xpert MTB/RIF tests for rifampicin susceptibility, with less reliance on MTB culture to exclude drug-resistant organisms.

The rollout of Xpert MTB/RIF testing at primary healthcare level was reportedly completed in this community by 2013, with a corresponding change in the recommended TB testing algorithm from sputum smear microscopy to Xpert MTB/RIF. However, we observed that almost a quarter of individuals with suspected TB who underwent screening in the post-rollout period still underwent sputum smear microscopy and not Xpert MTB/RIF testing. This finding indicates incomplete uptake of the new guidelines,[16] possibly owing to a GeneXpert cartridge shortage in 2013.[15] A forecast

cartridge price reduction in 2012 caused some countries to delay shipments, with a resultant break in supply and temporary reversion to first-line sputum smear microscopy testing.[15] Creswell *et al.*[15] also identified lack of or poor infrastructure and interrupted power supply as key barriers to Xpert MTB/RIF implementation. Additional local infrastructure improvements to address issues of uninterrupted electricity supply, climate control, work-space security, ventilation and dust control were required to set up GeneXpert machines. Unlike smear and culture testing, Xpert testing requires an uninterrupted power supply for the duration of the testing cycle.[15]

Study strengths and limitations

The main strengths of our study are that it was pragmatic, based on actual TB programmatic data in a field setting, and represents translation value at primary healthcare level in an endemic community. The benefits, or lack of benefit, of programmatic rollout of Xpert MTB/RIF at community level cannot be assumed from national-level statistics. However, one limitation of our study was that we could not identify the number of tests and the types of tests performed on each individual with suspected TB in this community; rather, we measured the total number of individuals investigated and number of samples processed. While efforts were made to merge databases that captured individual patient-level sputum smear microscopy, Xpert MTB/RIF, and MTB culture results, this was not always technically possible. For example, since all Xpert MTB/RIF laboratory identifiers were unique, we could not link Xpert MTB/RIF laboratory identifiers to individual patient sputum smear microscopy or MTB culture results. Another limitation of our study was the non-availability of HIV incidence for our study periods, with the latest HIV transmission rate only known for 2016 in the Western Cape (1.4%). It is unclear whether the decline in TB testing with Xpert MTB/RIF may be related to improved control of the HIV epidemic.

Conclusion

In summary, we found that rollout of Xpert MTB/RIF in an SA community with a very high TB burden led to a modest improvement in the rate of detection of pulmonary TB and slightly more rapid treatment initiation among individuals screened at primary healthcare clinics. These benefits were associated with a reduced TB investigation workload for clinic and laboratory staff. These findings support continued use of this diagnostic test in the TB control programme and continued attempts to facilitate universal implementation in SA communities, where marginal systemic improvements may translate to major individual patient benefit.

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