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Point-of-care Xpert® MTB/RIF for smear-negative tuberculosis suspects at a primary care clinic in South Africa

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SUMMARY

OBJECTIVE—To assess the clinical utility and cost of point-of-care Xpert® MTB/RIF for the diagnosis of smear-negative tuberculosis (TB).

DESIGN—Cohort study of smear-negative TB suspects at a South African primary care clinic. Participants provided one sputum sample for fluorescent smear microscopy and culture and an additional sample for Xpert. Outcomes of interest were TB diagnosis, linkage to care, patient and provider costs.

RESULTS—Among 199 smear-negative TB suspects, 16 were positive by Xpert, 15 by culture and 7 by microscopy. All cases identified by Xpert began anti-tuberculosis treatment the same or next day; only one of five Xpert-negative culture-positive cases started treatment after 34 days. Xpert at point of care offered similar diagnostic yield but a faster turnaround time than smear and culture performed at a centralized laboratory. Compared to smear plus culture, Xpert (at US$9.98 per cartridge) was US$3 less expensive per valid result (US$21 vs. US$24) and only US$6 more costly per case identified (US$266 vs. US$260).

CONCLUSION—Xpert is an effective method of diagnosing smear-negative TB. It is cost saving for patients, especially if performed at point of care, but it is costly for health care providers. Data-driven studies are needed to determine its cost-effectiveness in resource-poor settings with diverse diagnostic practices.

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Keywords

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The world health organization (WHO) recommends the Xpert® MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) as the initial diagnostic for human immunodeficiency virus (HIV) associated or multidrug-resistant tuberculosis (TB).[1] Recognizing important resource constraints in high TB burden countries, the WHO also conditionally recommended Xpert as a follow-up diagnostic in smear-negative TB suspects. Smear-negative TB, which constitutes 36% of the global TB caseload,[2] poses a diagnostic challenge, particularly in resource-constrained settings that have poor access to culture and chest X-ray (CXR). This may result in diagnostic delay, poorer patient outcomes and ongoing transmission.[3,4]

The aim of this study was to compare the diagnostic yield, cost and turnaround time of a single Xpert test at point of care to that of a third sputum sample for smear microscopy and culture performed at a central laboratory among smear-negative TB suspects presenting to a primary care clinic in South Africa.

METHODS

We conducted a cohort study at Witkoppen Health and Welfare Centre, a large primary care clinic in Johannesburg, South Africa. Following standard clinic procedures, which differ somewhat from standardized WHO diagnostic algorithms, individuals with prolonged (>2 weeks) cough and/or other TB symptoms provided two sputum samples for fluorescent smear microscopy were given a 5-day course of antibiotics if clinically indicated, and were asked to return within 5–7 days. Upon return, individuals with two negative smear microscopy results provided a third sputum sample, which was sent to a central laboratory for fluorescent smear microscopy and liquid culture. A CXR was requested if clinically indicated, and was performed at a nearby hospital.

A smear-negative TB suspect was defined as a TB suspect (i.e., an individual who initially presented with prolonged [>2 weeks] cough and/or other TB symptoms) who had two recent sputum fluorescent microscopy smear-negative results, irrespective of current clinical symptoms, response to recent antibiotic therapy trial or CXR results. Consecutive smear-negative TB suspects were eligible. Those consenting to study participation provided an additional sputum sample for a single Xpert test performed at point of care by an HIV counselor who received 2 days' training in the Xpert assay.

Demographic, clinical and patient cost data were collected by standardized questionnaire. Clinical status at time of first clinic visit (time of first sputum sample collection) and 2 months thereafter were gathered by chart review. Treatment decisions were made by clinic staff based on the results of smear microscopy, culture, Xpert, CXR and clinical presentation. Individuals with a positive smear microscopy or culture result were routinely traced by phone or home visit.

Provider costs were estimated for both point-of-care Xpert and the approach of a third centralized fluorescent smear microscopy plus liquid culture followed by Ziehl-Neelsen microscopy and GenoType® MTBDR*plus* (Hain Lifescience, Nehren, Germany) for all positive cultures. Costs for sputum collection, communication of results to patients and anti-tuberculosis treatment were not included, as they were assumed to be the same for both approaches.

Cost estimation for Xpert was performed using an ingredients approach, based on a price of US$9.98 for Xpert cartridges[5] and US$17 500 for a 4-module instrument, discounted at 5% per annum. The instrument was assumed to have a useful life of 5 years and to process on average 35 sputum samples per week from smear-negative patients. Labor costs were estimated at 20 min per test for a clinic staff member with high school education and computer literacy, included the costs of a 2-day training, and assumed that an existing staff member performed Xpert as an added responsibility while continuing other responsibilities. Other costs included use of electricity, water, and space, medical waste disposal, N-95 masks, sputum collection bottles and surface disinfectant.

Costs for microscopy, culture and GenoType MTBDR*plus* were based on public sector laboratory charges, which included laboratory equipment, test consumables, staff, specimen transport and overheads. Cultures with missing results were assumed to have the same rate of growth and contamination as samples for which results were available. All costs in South African Rand (ZAR) were converted to 2010 US dollars at the rate of 7.33 ZAR to US$1; value added tax was excluded.

The cost for Xpert or smear plus culture were calculated in three ways: cost per test performed, cost per valid result (cost per test adjusted for errors or contamination) and cost per case diagnosed (cost per valid test × number of tests performed/number of tests positive for *Mycobacterium tuberculosis*).

Standard descriptive statistics were used to characterize the study population. Univariate logistic regression was used to explore predictors of a positive Xpert result. Sensitivity and specificity were calculated using liquid TB culture as the gold standard.

This study was approved by institutional review boards at the University of North Carolina, USA, and the University of the Witwatersrand, South Africa.

RESULTS

Between April and October 2010, 199 smear-negative TB suspects who returned for their smear microscopy result were enrolled. The majority (72%) were HIV-infected, of whom 26% were on antiretroviral treatment (ART). Employment rates were low (54%), median household income was US$272 per month (interquartile range [IQR] 136–409), and 31% were of non-South African nationality (Table 1).

Tuberculosis diagnosis and treatment

Although a sputum specimen was sent for culture for all participants, valid results were only available for 160 (80.4%). The culture grew *M. tuberculosis* in 15 (7.5%), was negative in

143 (71.9%), contaminated in 12 (6%), positive for non-tuberculous mycobacteria in 3 (1.5%) and missing in 26 (13.1%).

Individuals returned to the clinic for their results after a median of 8 days (IQR 6–22) following collection of the first two sputum samples. Xpert was positive in 16 (8%) individuals, and was repeated in 2 participants because of invalid results. All Xpert-positives were started on treatment, 15/16 on the same day, corresponding to a median time lag of 0 days after collection of the third sputum. Xpert-positive individuals were both HIV-negative and -positive, presented with a wide range of CD4 counts (7–503 CD4 cells/mm^3), and were predominantly ART-naïve (Table 2). A third smear microscopy result was available for 195 (98%) participants, and was positive for acid-fast bacilli in 7 (4%). Two microscopy results were likely false-positive (culture and Xpert-negative), 3 were culture and Xpert-positive, 1 was culture-positive and Xpert-negative, and 1 was Xpert-positive with a missing culture result. None of the three smear-positive Xpert-negative patients started treatment, due to unsuccessful tracing. Of the 86 (43%) participants in whom a CXR was performed, 43 (50%) had radiological signs suggestive of TB: 4 of these were Xpert and culture-positive, 1 was Xpert-positive with missing culture, and 1 was culture-positive, Xpert-negative. Among the 38 Xpert-negative patients with a suggestive CXR, 19 (50%) started treatment a median of 13 days (IQR 7–27) after presenting for sputum results. Among the 5 culture-positive Xpert-negative patients, only 1 was started on treatment 34 days after sputum collection; the remaining 4 were lost to follow-up. One patient without microbiological or radiographic evidence of TB was started on treatment 2 days after presenting for smear microscopy results. Overall, 37 (18.6%) smear-negative TB suspects were started on anti-tuberculosis treatment. Median time to treatment initiation was shorter among Xpert-positive patients than among those diagnosed by other methods (0 days, IQR 0–0 vs. 13 days, IQR 10–20, $P < 0.001$).

Predictors of an Xpert-positive result

At presentation for sputum microscopy results, all 15 Xpert-positive culture-positive individuals (100%, one-sided 97.5% confidence interval [CI] 78–100) had persistent TB symptoms, whereas only 2/5 culture-positive, Xpert-negative individuals (40%, 95%CI 5–85) had persistent symptoms. Persistence of symptoms despite antibiotic treatment was a strong predictor of a positive Xpert result (odds ratio [OR] 8.79, 95%CI 1.15–68.05). Compared to participants with a negative Xpert result, individuals who were HIV-infected or reported recent TB exposure had a 2.8 times higher odds of being Xpert-positive, but these estimates were not statistically significant (OR 2.83, 95%CI 0.62–12.89 for HIV infection; OR 2.80, 95%CI 0.71–11.01 for recent TB exposure). Level of immunosuppression (CD4 count ≤ 200 cells/mm^3, OR 1.42, 95%CI 0.51– 4.00) and a history of anti-tuberculosis treatment (OR 0.65, 95%CI 0.14–3.01) were not associated with a positive Xpert result.

Sensitivity and specificity of TB diagnostics in smear-negative TB suspects

Among the 160 individuals (80%) with a valid result for third smear microscopy, culture and Xpert, the sensitivity and specificity of the third sputum smear microscopy was respectively 27% (95%CI 8–55) and 99% (95%CI 95–100). The sensitivity and specificity of a single

Xpert test was respectively 67% (95%CI 38–88) and 99% (95%CI 96–100). Among the 66 individuals with a CXR and valid culture result, the sensitivity of CXR was 83% (95%CI 36–100) and specificity 54% (95%CI 41–67). Among the 170 individuals who received antibiotics (77% amoxicillin, 14% erythromycin and 9% other), 159 had a valid culture result. The sensitivity of non-response to an antibiotic trial was 80% (95%CI 52–96), and specificity was 37% (95%CI 29– 45).

Patient costs

The mean number of health facility visits was lower for Xpert-positive than for Xpert-negative participants (1.1, 95%CI 0.9–1.2 vs. 1.7, 95%CI 1.5–1.9, $P < 0.001$). Similarly, the mean number of one-way trips was lower among Xpert-positive than Xpert-negative participants (2.1, 95%CI 1.9–2.4 vs. 5.0, 95%CI 4.7–5.4, $P < 0.001$).

The average patient cost per visit was US$9.28 (IQR US$4.37–US$9.28), which included transportation, clinic fee for those able to pay and food purchased at the clinic. The majority (92%) took a public taxi, for an average cost of US$1.91 (IQR US$1.91–US$2.18). Most (73%) of the patients paid clinic fees; the average clinic fee was US$5.46 (IQR US$4.77–US$5.46). Among the 43 individuals buying food during their clinic visit, the average cost was US$2.18 (IQR US$1.09–US$2.73). Only 18/109 (17%) employed individuals lost income, for an average of US$13.64 (IQR US$8.19–US$19.10). All diagnostics and treatments were provided free of charge.

Provider costs

The total provider cost per Xpert test was US$21.19 (Table 3). The error rate was very low (1%), resulting in a cost per valid result of US$21.40. The total cost per TB case diagnosed by Xpert was US$266. Xpert costs were mainly driven by the costs of the cartridge (47%), cartridge procurement (24%) and equipment (16%).

The average provider cost of smear microscopy plus culture was US$19.31 per smear-negative suspect, ranging from US$15.45 to US$44.83 depending on culture growth (Table 4). Due to the high proportion of missing (13%) and contaminated (6%) results, the average cost per valid culture result increased to US$24.47. The cost per case diagnosed by smear and/or culture was US$260.

DISCUSSION

This study provides evidence that a single Xpert test at point of care is a rapid and accurate diagnostic in smear-negative TB suspects. Similar to other observations among smear-negative, culture-positive TB suspects,[6] we observed a sensitivity of 67% of a single Xpert test. The sensitivity of Xpert was higher than the sensitivity of a third smear microscopy (27%), but lower than that of CXR (83%) or an antibiotic trial (80%). The specificity of Xpert (99%) was, however, much higher than for CXR (54%) or antibiotic trial (37%).

Providing Xpert at point of care had important advantages. Results were available the day of the clinic visit, allowing immediate treatment initiation and eliminating the need for a return visit. This reduced the cost borne by patients, who spent on average almost US$10, or 4% of

their monthly household income, per clinic visit. Xpert at point of care could also reduce the time spent by health care workers on diagnostic work-up, and eliminates the need to trace patients in the community when a positive result is received from the central laboratory.

The effectiveness of Xpert was superior to culture, as Xpert detected a similar number of cases (15 culture-positive, 16 Xpert-positive), had 98% valid results compared to 80% valid culture results, and more than a quarter of Xpert-positive results were in patients with missing or contaminated culture results. Furthermore, the majority (4/5) of those diagnosed by culture only did not start treatment as they were lost to follow-up by the time the culture results became available.

The cost per Xpert was only US$1.88 higher than the cost for smear microscopy and culture, and US$14.05 higher than smear microscopy only. Due to the low error rate, the cost per valid Xpert result was US$3.28 lower than the cost per valid smear microscopy plus culture result. The cost per case diagnosed was similar for both strategies (US$266 vs. US$260). A prior decision analytic modeling study assessed the impact of Xpert on the cost and cost-effectiveness of TB care in three countries.[7] The results suggested that, in smear-negative TB suspects, Xpert is a cost-effective TB diagnostic compared to smear microscopy plus clinical diagnosis (which might include CXR and antibiotic trial). A limitation of this modeling study is the assumption that Xpert and clinical diagnosis are used in isolation. In many settings, an antibiotic trial is started while awaiting smear microscopy results, i.e., prior to performing the Xpert assay. We collected data on actual practice, and showed that 20/37 smear-negative TB suspects receiving treatment were initiated based on clinical or radiological findings despite having a negative Xpert result. It is unknown how many Xpert-positive cases would have been started on treatment based on clinical grounds had Xpert not been available. Our data therefore suggest that one may only be able to determine the true cost-effectiveness of Xpert for the diagnosis of smear-negative TB in the setting of a randomized trial. The cost-effectiveness may also depend on whether Xpert is performed at point of care or in a centralized laboratory.

Even if Xpert is truly cost-effective, this does not imply affordability, particularly in low-income countries. Our results suggest that a targeted approach limiting Xpert testing to those remaining symptomatic after antibiotic treatment, those with recent TB exposure and those infected with HIV, may improve the cost-effectiveness and financial feasibility of Xpert for smear-negative TB suspects.

Although the findings of this study provide promising evidence for the use of point-of-care Xpert as a follow-up to smear microscopy, our results need to be interpreted in the light of study limitations. The study was performed at a single site, and the sample size was small. The clinic did not strictly follow the WHO algorithm for diagnosis of smear-negative TB. The presence of participation bias is possible, as only those TB suspects who returned for results of the initial sputum smear microscopy tests were enrolled. Costs from a provider perspective were only calculated for laboratory diagnostics, and included the use of culture, which is not available in most resource-poor settings. Provider costs could differ between settings, depending on the diagnostic algorithm used, the volume of tests performed and the qualifications of the individual performing the Xpert assay. Any costs from the patient

perspective are highly context-specific. Finally, because we did not perform a randomized trial due to ethical concerns, we could not include the costs of CXR and health care worker assessment as their use depended on the outcome of the Xpert assay. We could therefore only estimate the costs and effectiveness of Xpert as compared to smear microscopy plus culture.

CONCLUSIONS

The Xpert MTB/RIF assay is an effective method of diagnosing smear-negative TB; it can be cost saving for patients, especially if performed at point of care, but it is costly for the health care provider. Data-driven studies are needed to determine its cost-effectiveness in resource-poor settings with diverse diagnostic practices.

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Table 1

Socio-demographic and clinical characteristics of 199 smear-negative TB suspects

	n	%
Age, years, median [IQR]	36 [30– 44]	
Female sex	113	57
Nationality		
South African	138	69
Zimbabwean	43	22
Other	16	8
Employed	108	54
Monthly household income, US$, median [IQR]	261 [131–392]	
History of anti-tuberculosis treatment	35	18
HIV status		
Infected	144	72
Non-infected	40	20
Unknown/refused	15	8
Among HIV infected (*n* = 144)		
CD4 count, cells/mm^3, median [IQR]	198 [89–333]	
On ART at first TB suspect visit	37	26
On cotrimoxazole prophylaxis	96	67

TB = tuberculosis; IQR = interquartile range; HIV = human immunodeficiency virus; ART = antiretroviral therapy.

Table 2

Characteristics of cases of TB confirmed by Xpert® MTB/RIF, culture and/or smear microscopy*

Xpert	Culture	Smear microscopy	HIV	CD4 count cells/mm^3	ART	Chest X-ray	Cough	Loss of weight	Fever	Night sweats
+	+	+	−	NA	NA	ND	−	−	−	+
+	+	+	+	223	No	ND	+	+	−	−
+	+	+	+	106	No	Suggestive	+	+	−	+
+	Missing	+	+	77	No	ND	+	+	−	+
+	+	−	−	NA	NA	ND	+	−	−	−
+	+	−	+	503	No	Suggestive	+	−	−	−
+	+	−	+	333	Yes	Suggestive	+	+	−	−
+	+	−	+	261	No	ND	+	+	−	+
+	+	−	+	210	No	ND	+	−	−	−
+	+	−	+	201	No	ND	+	+	−	−
+	+	−	+	12	Yes	Suggestive	+	+	−	−
+	Contaminated	Missing	+	73	No	ND	+	+	−	+
+	Missing	−	+	576	No	ND	+	−	−	+
+	Missing	−	+	89	No	ND	−	−	−	−
+	Missing	−	+	7	No	Suggestive	+	+	−	+
+	−	−	+	75	No	ND	+	+	−	+
−	+	−	−	NA	NA	NA	−	−	−	−
−	+	−	+	319	Yes	ND	−	−	−	−
−	+	−	+	194	Yes	Suggestive	+	−	−	−
−	+	−	+	149	No	ND	−	−	−	−
−	+	−	+	142	No	ND	+	+	−	−
−	+	+	−	NA	NA	ND	−	−	−	−
−	−	+	−	NA	NA	ND	−	−	−	−
−	−	+	+	304	Yes	ND	+	−	−	−

*Symptoms listed are those present at the time of the patient's return to the clinic to collect the smear microscopy results. All patients enrolled in the study had prolonged cough and/or other symptoms of TB at the time of collection of the first sputum specimen.

TB = tuberculosis; HIV = human immunodeficiency virus; ART = antiretroviral treatment; + = positive; − = negative; NA = not applicable; ND = not done; Suggestive = radiological signs suggestive of active TB.

Table 3

Costing of the Xpert® MTB/RIF approach to TB diagnosis in smear-negative TB suspects

Cost component	Cost US$ (2010)	% of total
Xpert cartridges*	9.98	47
Cartridge—local procurement†	5.03‡	24
Labor‡	1.30	6
Equipment§	3.42	16
Overheads¶	1.17	5
Other consumables#	0.30	1
Total cost per Xpert test	21.19	
Adjustment for Xpert errors	0.21	1
Total cost per valid Xpert test	21.40	100
Total cost per TB case diagnosed by Xpert	266.00	

*Per the international price announced in August 2012.

†Includes international air freight, customs duties, insurance, local delivery, logistics fees and exchange rate losses due to the weaker ZAR at the time of international price announcements.

‡Estimated at 20 min per test for a non-medical staff member with high school education, computer literacy and 2 days' training in the use of Xpert.

§Includes GX4 instrument, international freight, annual module calibration, laptop computer, desktop printer, barcode reader, uninterrupted power supply unit and insurance against theft. Equipment is discounted at 5% per annum for an assumed useful life of 5 years. The average weekly number of tests performed was assumed to be 35.

¶Includes electricity, water, space used and medical waste disposal.

#Includes N-95 masks, sputum collection bottles and surface disinfectant.

TB = tuberculosis, ZAR = South African Rand.

Table 4

Costing of the smear microscopy and culture approach to TB diagnosis in smear-negative TB suspects

Cost item	Cost US$ (2010)
Fluorescent smear microscopy	3.57
Liquid culture (growth)	13.48
Liquid culture (no growth)	11.89
Ziehl-Neelsen smear microscopy (after culture growth)	2.06
Line-probe assay (after culture growth)	25.72
Total cost for sample with no culture growth	15.45
Total costs for sample with culture growth	44.83
Average total cost per smear and culture	19.31
Total cost per valid smear and culture result	24.47
Total cost of case diagnosed by smear and/or culture	260.00

TB = tuberculosis.