INT J TUBERC LUNG DIS 20(5):611–618

http://dx.doi.org/10.5588/ijtld.15.0455

Cost-effectiveness of the Xpert® MTB/RIF assay for tuberculosis diagnosis in Brazil

M. Pinto,* R. E. Steffen,† F. Cobelens,‡§ S. van den Hof,‡§ A. Entringer,* A. Trajman†¶

***Oswaldo Cruz Foundation, Rio de Janeiro, †Rio de Janeiro Federal University, Rio de Janeiro, Rio de Janeiro, Brazil; ‡KNCV Tuberculosis Foundation, The Hague, §Department of Global Health, Academic Medical Center, and Amsterdam Institute for Global Health and Development, Amsterdam, The Netherlands; ¶McGill University, Montréal, Quebec, Canada**

SUMMARY

INTRODUCTION: The Xpert® MTB/RIF assay is being implemented as a substitute for sputum smear microscopy (SSM) in many low and high tuberculosis (TB) burden countries, including Brazil, a country with low multidrug resistance and moderate human immunodeficiency virus co-infection rates.

SETTING: Brazilian National TB Programme (NTP).

OBJECTIVE AND DESIGN: We estimated the incremental cost-effectiveness ratio (ICER) of Xpert as a substitute for two SSM tests in the diagnosis of drug-susceptible TB. The costs for confirming each additional case and for avoiding treatment due to false-positive empirical diagnoses were estimated.

RESULTS: The ICER was US$943 for each additional TB diagnosis and US$356 for each additional TB diagnosis with bacteriological confirmation, assuming 80% specificity of clinical diagnosis using both strategies. For every 100 000 patients with suspected TB, the NTP would spend an additional US$1.2 million per year to confirm 3344 more TB patients. The model was highly sensitive to specificity of clinical diagnosis after a negative test.

CONCLUSION: Although the NTP has no threshold for cost-effectiveness, our model can provide support for decision makers in Brazil and other countries with a low prevalence of drug resistance among TB patients. Financial benefit can potentially be expected if physicians rely more on a negative Xpert result and empirical treatment is reduced.

KEY WORDS: cost-effectiveness; molecular diagnostic testing; *Mycobacterium tuberculosis*; nucleoside acid amplification test

IN 2013, 9 million people were reported with tuberculosis (TB). According to the World Health Organization (WHO), an estimated 3 million additional cases were either not diagnosed or not reported to national TB programmes (NTPs) worldwide.[1] Sputum smear microscopy (SSM) is the basis of TB diagnosis in low- and middle-income countries, as it is relatively inexpensive and has few technical requirements.[1] Its sensitivity, however, is limited.[2] Low SSM sensitivity delays TB diagnosis, which increases TB-related morbidity, mortality and transmission.[3] In addition, because of the low negative predictive value of SSM, patients with other diseases are often initially treated for TB, thus delaying other diagnoses.

The Xpert® MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) is an automated real-time polymerase chain reaction test for the simultaneous detection of TB and rifampicin (RMP) resistance through the detection of mutations in the *rpo*B gene. It provides results within 2 h, and has minimal biosafety and technical manipulation requirements.[4] Xpert was endorsed in 2010 by the WHO for use in persons with suspected multidrug-resistant TB (MDR-TB) or who were co-infected with TB and the human immunodeficiency virus (HIV).[5,6] In 2014, the WHO extended its recommendation to include the use of Xpert as the initial diagnostic test in individuals presumed to have pulmonary TB, in children and in those with extra-pulmonary TB.[5] However, studies in routine programme conditions suggest that empirical treatment following clinical/radiological diagnosis reduces the impact of Xpert in increasing TB detection.[7–10]

In Brazil, a high TB burden country with low MDR-TB prevalence among new TB cases (<2%) and moderate rates of HIV co-infection (9.7%),[11] 34% of patients who start anti-tuberculosis treatment do not have bacteriological confirmation (D Barreira, NTP coordinator, personal communication). In addition, only 27% of retreatment cases undergo culture and drug susceptibility testing (DST).[11]

While some NTPs quickly embraced Xpert as a new technology,[12] several experts have expressed concerns regarding the cost of the technology and its

Correspondence to: Ricardo Ewbank Steffen, Avenida Prefeito Mendes de Morais, 1500 Bl.1/501, São Conrado, Rio de Janeiro 22610-095, RJ, Brazil. e-mail: ricardo.steffen@gmail.com

Article submitted 9 June 2015. Final version accepted 19 November 2015.

increased demand on existing infrastructure.[6,13–15] In a pragmatic trial in two Brazilian cities with high TB incidence rates, Xpert was shown to improve diagnostic confirmation and reduce the time to treatment.[10] It has been proposed to replace the current standard procedure[13] by a single Xpert test throughout the country. We performed a cost-effectiveness analysis of this change from the NTP perspective in Brazil. We also looked specifically at the economic effects of empirical treatment following a negative Xpert or SSM test.

METHODS

Model structure

We used a deterministic decision-tree simulation model from the NTP perspective to conduct a cost-effectiveness analysis considering a hypothetical cohort of 100 000 individuals with presumptive TB, i.e., those seeking health care for TB-related symptoms, stratified by HIV status, and undergoing all the TB diagnostic procedures.[16] Briefly, the standard of care strategy consists of presumptive TB patients undergoing an initial consultation, a chest X-ray (CXR), two SSM examinations and HIV testing. Those with HIV co-infection undergo culture and DST.[16] If two SSM examinations are negative and clinical and radiological findings are suggestive of TB, a clinical diagnosis is made. Patients diagnosed with TB are treated with the WHO-recommended standard first-line drug regimen. During treatment, monthly follow-up visits are performed.[16] At the end of treatment, another CXR is performed.[16]

In the alternative strategy the SSM testing of two samples was replaced by Xpert testing of one sputum sample; all other diagnostic and treatment procedures remained as in the SSM strategy (Figure 1), including culture and DST for HIV-positive individuals. The main endpoints were additional TB diagnosis and additional bacteriologically confirmed TB cases detected. The secondary endpoint was the number of false-positive TB diagnoses avoided. TreeAge Pro 2011 (TreeAge Software Inc., Williamstown, MA, USA) was used for the cost-effectiveness model.

Model parameters and assumptions

The parameters of the model were determined using data on bacteriological confirmation and clinical diagnosis among TB patients derived from the pragmatic trial of Xpert in Brazil,[10] and using TB treatment outcomes from Brazil's National TB Information System (SINAN)[17] (Table 1). The sensitivity and specificity of Xpert and SSM were based on the most recent meta-analysis, stratified by HIV status.[23] Parameter values for the sensitivity and specificity of clinical diagnosis for smear-negative patients were derived from the literature;[21] it was assumed that 80% of presumptive TB patients undergo CXR in Brazil, based on information from SINAN.[17] The proportion of TB among presumptive TB patients was calculated using Xpert-positive results (14%) in the pilot study[10] and the lower range of Xpert sensitivity (76%) in the most recent meta-analysis.[23]

We assumed that 1) all TB patients were new cases, 2) the probability culture and DST is requested for new non-HIV TB cases is 10%, 3) all patients undergo laboratory diagnostic procedures (SSM or Xpert), 4) patients who are initially SSM- or Xpert-negative and remain symptomatic are diagnosed based on clinical and radiological findings, 5) all patients diagnosed with TB are started on standard first-line drug treatment, and 6) the specificity of clinical diagnosis after both tests is the same (80%). The incremental cost-effectiveness ratio (ICER) was calculated to describe the additional cost per detected TB case and per bacteriologically confirmed TB case.

Costs

A micro-costing analysis was carried out and published elsewhere.[24] The National Reimbursement Table (NRT) underestimates true cost, as the micro-costing method yielded cost estimates that were 3.51 times higher than the NRT, both for SSM (our data) and for culture/DST.[25] For other diagnostic cost components, we therefore adjusted the NRT values by multiplying them by 3.51 (Table 2). All costs were converted into US$2014 at the rate of 2.40 Brazilian reais/US$1. No discounting or inflation rate adjustments were applied because of the short time period. Costs were annualised when necessary, and are summarised in Table 2. Treatment costs were estimated based on a previous study[26] and on NTP guidelines.[16] Costs of drug-induced liver injury (DILI) were included into TB treatment costs, assuming an annual incidence of 1%.[18]

Sensitivity analyses

We performed one-way deterministic sensitivity analyses and a Monte Carlo probabilistic simulation to test the robustness of the model (Figure 2A and B, Figure 3). All cost parameters were varied by 50% to 200% of their initial value (Table 2), except for the costs of SSM, where the lower value is the NRT value (US$1.75). A potential benefit of Xpert is that the specificity of clinical diagnosis is higher for TB patients after a negative Xpert result than after a negative SSM result. This is based on the expectation that clinicians will be less inclined to make a TB diagnosis based on a negative Xpert than with a negative SSM result, given the higher negative predictive value of Xpert.[23] In the sensitivity analysis, we explored the possibility that the specificity of clinical diagnosis after Xpert may be higher than the 80% specificity after SSM. A two-

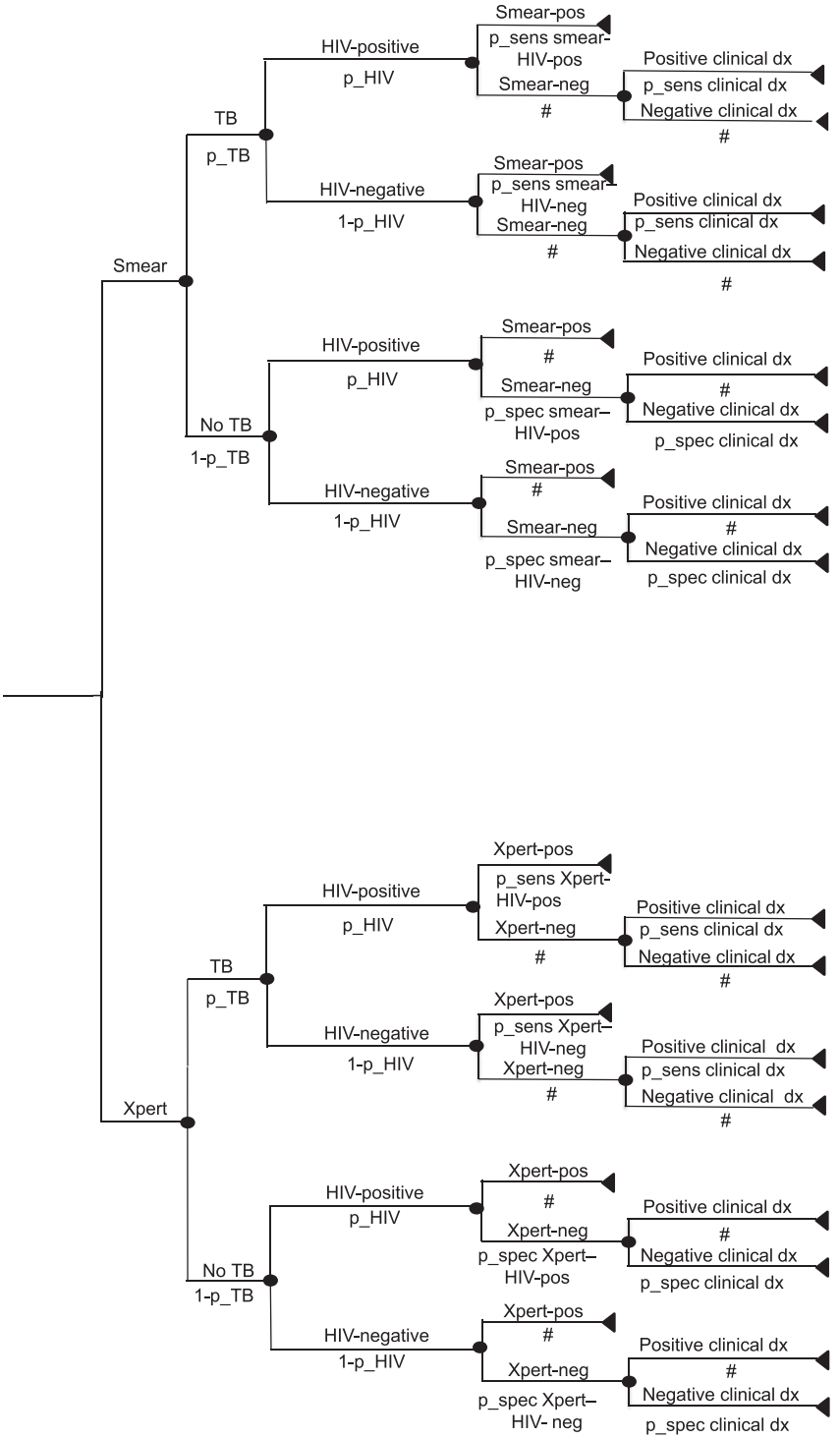


Figure 1 Decision tree diagram of Xpert® MTB/RIF vs. SSM for TB diagnosis. Two diagnostic pathways for the diagnosis of TB are shown, one using Xpert and the other SSM as the diagnostic strategy. Patients with suspected TB are stratified according to HIV status. Those with a negative initial test can receive a TB diagnosis based on clinical suspicion. Outcomes include TB diagnosis with and without bacteriological confirmation. TB = tuberculosis; HIV = human immunodeficiency virus; sens = sensitivity; pos = positive; neg = negative; dx = diagnosis; spec = specificity; SSM = sputum smear microscopy.

way sensitivity analysis was also performed of the varying specificity of clinical diagnosis both after two negative SSMs and after one negative Xpert from 0.70 to 0.95 (Figure 3).

Ethics statement

The study was approved by the National Ethics Board (Comissão Nacional de Ética em Pesquisa #493/2011), the Rio de Janeiro Municipal Health Depart-

Table 1 Model parameter and assumption values used for primary analyses and ranges used for sensitivity analyses*

	Value	Range	Source
Cohort proportions (or input variables)			
Proportion of TB among individuals with suspected TB	0.18	0.10–0.26	Base-case: roll-out implementation study;[10] range: assumption
Proportion of TB-HIV co-infection	0.095	0.09–0.12	[17]
Probability of performing a chest X-ray	0.80	0.75–0.90	[17]
Probability of DILI	0.01	0.005–0.02	[18]
Probability of hospitalisation in DILI cases	0.0001	0.00005–0.0002	[19]
Diagnostic parameters for TB diagnosis			
Sputum smear microscopy			
Sensitivity (two slides), HIV-negative TB cases	0.69	0.67–0.88	[20]
Sensitivity (two slides), HIV-positive TB cases	0.45	0.38–0.52	[20]
Specificity (two slides), HIV-negative TB cases	0.99	0.98–1.00	[20]
Specificity (two slides), HIV-positive TB cases	0.98	0.96–1.00	[20]
Xpert® MTB/RIF			
Sensitivity in HIV-positive patients	0.79	0.70–0.86	[20]
Sensitivity in HIV-negative patients	0.86	0.76–0.92	[20]
Specificity in HIV-positive patients	0.99	0.98–0.99	[20]
Specificity in HIV-negative patients	0.99	0.98–0.99	[20]
Clinical diagnosis			
Sensitivity in HIV-negative patients	0.61	0.55–0.67	[21]
Sensitivity in HIV-positive patients	0.63	0.49–0.66	[22]
Specificity after negative SSM	0.80	0.70–0.90	Assumption
Specificity after negative Xpert	0.80	0.70–0.90	Assumption

* A beta distribution was used for all variables.
TB = tuberculosis; HIV = human immunodeficiency virus; DILI = drug-induced liver injury; SSM = sputum smear microscopy.

ment Review Board (Comitê de Ética em Pesquisa [CEP]/Secretaria Municipal de Saúde #445A/11) and the Amazonas Tropical Medicine Foundation Doutor Heitor Vieira Dourado Review Board (CEP/FMT/HVD 24 November 2011).

RESULTS

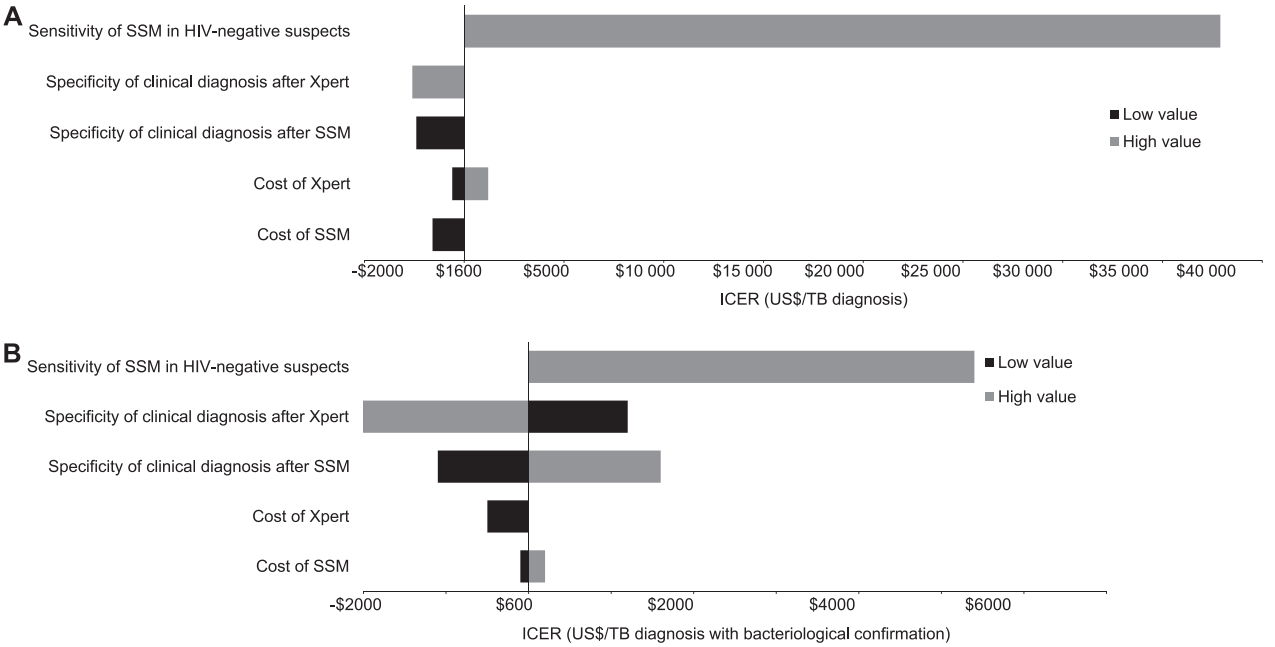
The main costs and outcomes for the cohort of 100 000 are shown in Table 3. Using the primary analysis parameter values and a probabilistic simulation, with the newer Xpert technology the health system spends US$943 (95% uncertainty range [UR] 851–992) for each additional TB diagnosis and US$356 (95%UR 292–641) for each additional TB diagnosis with bacteriological confirmation (Table 4). In other words, using Xpert, for each 100 000 individuals with suspected TB, the NTP would spend an additional US$1.2 million per year to confirm 3344 more TB patients.

The model was highly sensitive to changes in the specificity of clinical diagnosis following laboratory testing. When increasing the specificity of clinical diagnosis after an Xpert test by one percentage point steps, Xpert became dominant (i.e., less costly and more effective) at a specificity of 83% (Table 4). This means that only a small increase in the specificity of the clinical diagnosis after Xpert compared to that after SSM would result in a reduction in empirical treatment that brings potential financial benefit. The two-way sensitivity analyses (Figure 3) showed that Xpert would remain dominant in avoiding false diagnoses if the specificity of the clinical diagnosis

Table 2 Cost of TB diagnostic tests and treatment (in 2014 US$)*

TB diagnosis	NRT	Adjusted primary analysis value†	Range	Source
Sputum smear microscopy (2 samples)	1.75	6.15	1.75–12.30	Base-case: micro-costing analysis; range: MoH
Xpert® MTB/RIF (1 sample)	—	14.69	7.35–29.38	Micro-costing analysis‡
Initial medical visit ($n = 1$)	4.17	14.62	7.31–29.24	Indexed prices
Follow-up medical visits ($n = 3$)	12.51	43.87	21.94–87.74	Indexed prices
Chest radiograph ($n = 1$)	3.95	13.90	6.95–27.80	Indexed prices
Culture (1 sample)	2.35	8.23	4.11–16.46	Indexed prices
Drug susceptibility testing (1 sample)	5.55	19.49	9.75–38.98	Indexed prices
HIV diagnosis cost	19.79	69.47	34.74–138.94	Indexed prices
Anti-tuberculosis treatment costs§	120.63	691.24	345.62–1382.48	[26]

* Probabilistic Monte Carlo simulation using a triangular distribution for all cost variables.
† Primary analysis value was adjusted by multiplying the NRT value by a factor of 3.51.
‡ Includes 6.6% Xpert waste due to inadequate or insufficient volume.
§ Include costs of treatment of adverse reactions and hospitalisation and based on previous publication, adjusted to 2014 US$.[26]
US$ = US dollars; TB = tuberculosis; NRT = National Reimbursement Table; MoH = Ministry of Health; HIV = human immunodeficiency virus.



Figures 2 Tornado diagram summarising one-way sensitivity analyses. The tornado shows the effect of parameter variation on the estimated ICER for Xpert for the two main outcomes. Longer bars represent parameters to which the model is more sensitive. All cost parameters are varied by 50% to 200% of their initial value, except for the costs of SSM, where the lower value is the National Reimbursement Table value. The effect of variation in specificity of clinical diagnosis takes different directions for the Xpert scenario compared to the SSM scenario: increasing specificity increases ICER, while for Xpert it decreases. Costs are in 2014 US$ dollars. **A)** ICER (US$/TB diagnosis) **B)** ICER (US$/TB diagnosis with bacteriological confirmation). ICER = incremental cost-effectiveness ratio.

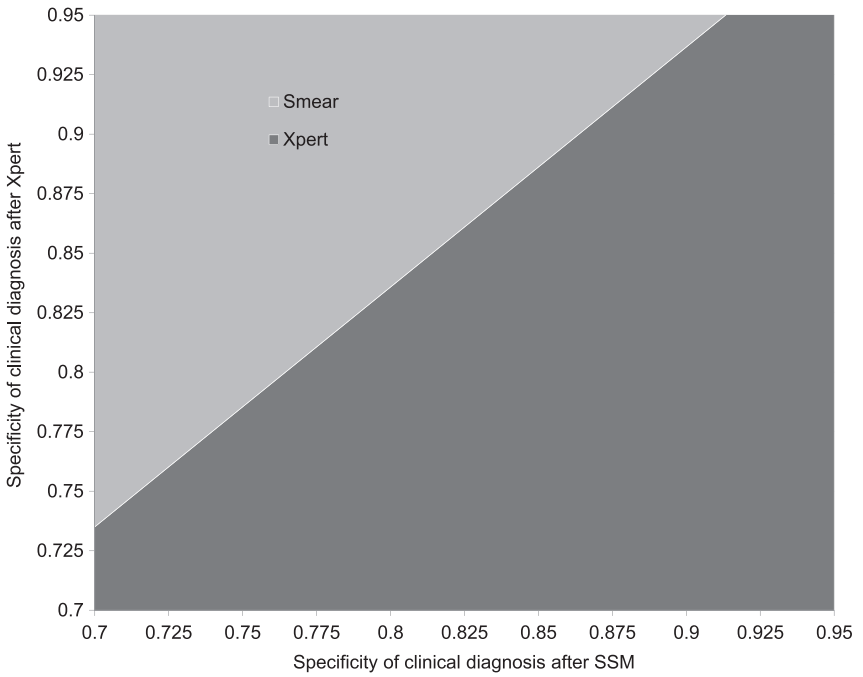


Figure 3 Two-way sensitivity analysis varying specificity of clinical diagnosis following Xpert vs. specificity of clinical diagnosis following SSM. The light grey area represents the values where the Xpert-only strategy is more costly. The dark grey area represents the values where the SSM-only strategy is more costly. Xpert remains less costly than SSM if the specificity of clinical diagnosis after Xpert is 3% greater than the specificity of the clinical diagnosis after SSM. SSM = sputum smear microscopy.

Table 3 Summary of costs and effectiveness in the primary analyses

Effectiveness outcomes	TB diagnoses/100 000 cases with suspected TB		Difference %
	SSM	Xpert® MTB/RIF	
Total TB diagnoses	32 773	34 034	3.9
Total TB diagnoses with bacteriological confirmation	12 836	16 180	26.1
True-positive TB diagnoses (includes correct clinical diagnoses)	15 655	16 978	8.5
False-positive TB diagnoses*	17 118	17 040	–0.5
From incorrect clinical diagnoses*	16 220	16 220	0
From incorrect test results*	898	820	–8.7
True-negative diagnoses	64 882	64 960	0.1
False-negative diagnoses*	2 345	1 022	–56.4
Costs/100 000 cases with suspected TB, US$	37 713 000	38 902 000	3.2

* Effectiveness is the difference between the number of patients diagnosed using Xpert and the number diagnosed using SSM; in the case of avoided false diagnoses, effectiveness is the difference between the number diagnosed using SSM and the number diagnosed using Xpert.
TB = tuberculosis; SSM = smear sputum microscopy.

after a negative Xpert was ⩾3% higher than that after two negative SSM tests.

The model was also sensitive to changes in the sensitivity of SSM in HIV-negative patients and the costs of both tests (Figure 2A and B). Using the NRT value for SSM, the ICER would be US$1597 (95%UR 1510–2585) for each additional TB diagnosis and US$602 (95%UR 597–658) for each additional TB diagnosis with bacteriological confirmation. The Monte Carlo probabilistic simulation yielded a 95% probability of being cost-effective in all ranges of willingness-to-pay threshold to both outcomes (US$100–US$11 000).

DISCUSSION

Xpert is more costly[27] than SSM, but has been shown to be more accurate,[23] and potentially more cost-effective in low-[28] and high-burden countries[29,30] with high MDR-TB and HIV co-infection rates. In a setting with low MDR-TB and moderate HIV co-infection rates such as Brazil, implementation of single-sample Xpert testing replacing two-sample SSM tests would result in a modest increase (US$1.2 million per year, or 1.7% of Brazil's NTP budget) in total health system costs for the additional TB confirmation of 3344 patients. Varying most parameters reduced the ICER. A difference of ⩾3% in the specificity of clinical diagnosis following a negative Xpert compared to that following two negative SSM tests resulted in Xpert becoming dominant over SSM, i.e., less costly and more effective.

Previous studies on the costs and effectiveness of Xpert have shown its potential to reduce TB incidence, morbidity and mortality at the expense of increased costs associated with MDR-TB treatment and HIV care.[20,27,29–32] These studies, however, have not evaluated the cost-effectiveness of this new technology in confirming TB diagnosis and its potential for avoiding false-positive clinical diagnoses. Introducing laboratory assays with increased sensitivity may reduce the number of false-positive clinical diagnoses if it increases clinicians' confidence in a negative test result, in particular for HIV-negative patients. This could raise the threshold for diagnosing TB based on atypical CXRs, thereby increasing the specificity of clinical diagnoses. In our primary analysis, we found a very modest reduction in false-positive diagnoses with Xpert implementation, resulting in a very high ICER (>US$32 000 to avoid one false diagnosis), as we assumed that the specificity of a clinical diagnosis was similar after a negative Xpert and after two negative SSM tests. However, our sensitivity analyses showed that, for a difference in specificity of clinical diagnosis of only

Table 4 Results of one-way sensitivity analyses (ICER) for the two main outcomes

Effectiveness outcomes*	ICER, in 2014 US$								
	Specificity of clinical diagnosis after Xpert						Sensitivity of SSM in HIV-negative individuals		
	80% (base-case)	81%	82%	83%	84%	85%	67%	69% (base case)	88%
Additional TB diagnosis	943†	1 399	–185	420	531	577	923	943†	12 627
Additional TB diagnosis with bacteriological confirmation	356†	187	20	–147	–315	–483	348	356†	1 934

* Effectiveness is the difference between the number of patients diagnosed using Xpert and the number diagnosed using SSM; for avoided false diagnoses, effectiveness is the difference between number diagnosed using SSM and the number diagnosed using Xpert. A negative ICER value means savings per effectiveness unit.
† Dominated values.
ICER = incremental cost-effectiveness ratio; SSM = sputum smear microscopy; HIV = human immunodeficiency virus; TB = tuberculosis.

3% favouring Xpert, the new technology would reduce the number of false-positive diagnoses and become less costly than SSM, independently of the assumed value for this specificity.

There is as yet no evidence of such increased specificity due to the limited number of implementation studies conducted to date.[7,10] The actual proportion of false- and true-positive diagnoses avoided with Xpert in the Brazilian trial was unknown, as its primary endpoint was bacteriological confirmation of notified TB cases (which increased by 59% with Xpert).[10] In a recent study in Tanzania, a substantial percentage of treatment episodes were based on a clinical diagnosis in the absence of microbiological confirmation (66% of those treated for TB in the SSM group and 43% of those treated in the Xpert group).[32] Despite the absence of available evidence of this effect, the potential additional advantage of avoiding inadequate empirical treatment is important in the Brazilian setting, where this is common practice. It is plausible that with improved education or improved clinical algorithms, a relatively small change in clinicians' diagnostic behaviour could be achieved, with optimisation of the diagnostic effectiveness of Xpert. The clinical and programmatic implications of these inadequate diagnoses are possibly even more important than the economic aspect,[33] and future implementation studies should address this issue.

Because Brazil does not have a threshold for cost-effectiveness, we cannot affirm that Xpert is (or is not) 'cost-effective'. Using the WHO-recommended benchmark of one gross domestic product per capita per averted disability-adjusted life-year (DALY)—assuming that one TB diagnosis would avert at least one DALY—Xpert implementation would remain cost-effective for a wide range of willingness-to-pay.

Our study has limitations. We did not consider costs associated with HIV treatment for co-infected patients, as in Brazil these costs are not financed by the NTP. Timely TB detection and treatment significantly increases the survival of HIV-infected patients.[34] Previous models have suggested that TB significantly increases costs with HIV care because of antiretroviral therapy and the increased survival of people living with HIV.[30,35] Due to the lack of data for Brazil, our cohort excluded patients with a history of previous anti-tuberculosis treatment, who have a higher risk for resistance. Diagnostic, treatment and follow-up costs are expected to increase significantly with the Xpert strategy in this population, as more cases of resistance will likely be detected. In addition, although according to the Brazilian NTP guidelines culture should be performed in all retreatment cases,[16] this is rarely done, and a positive Xpert result for RMP resistance will be a clear indication of its need. In the Brazilian pilot study, RMP resistance was detected in 7.4% of retreatment cases compared to 3.3% of new cases.[10] Finally, in the sensitivity analysis for clinical diagnosis following a negative Xpert test, we considered a differential in specificity, but not sensitivity. A false-positive clinical diagnosis would be affected by the specificity value only, and similar models have suggested that varying the sensitivity of clinical diagnosis had very limited effect on the cost-effectiveness parameters.[30]

Our study also has specific strengths. We were very cautious not to favour the Xpert strategy. We considered its lowest sensitivity in the primary analysis and we did not consider the costs with hospitalisation that might derive from delayed diagnosis of true disease in those with a false-positive clinical diagnosis in the SSM strategy, which could be significant.[36] We used a micro-costing technique employed to evaluate SSM costs. These costs are typically based on the usual inexpensive reagents and consumables, whereas we found that most costs are derived from human resource costs. In addition, in our analyses we considered costs of both treatment and follow-up, which include follow-up SSM. SSM costs therefore lead to an increase in overall costs of using Xpert, as Xpert detects more cases. Unlike the previous cost-effectiveness analyses,[28,29] which were based mainly on efficacy from demonstration studies, our model incorporates recently published effectiveness data from implementation studies.[8,10,24]

Our results support the Brazilian Ministry of Health's decision to incorporate Xpert into the NTP's diagnostic strategy. Moreover, because of the wide range of parameters and costs used, it is likely that similar results would be found in other countries, although the specific characteristics of the health system, the prevalence of the disease and health care practices should be analysed in each setting before the implementation of a new diagnostic test.

Other non-economic perspectives should be considered by policy makers when incorporating new technologies. This was not the scope of our study. The scale-up of Xpert technology in Brazil and other countries will be an excellent opportunity to follow up on its impact in TB control.

Acknowledgements

The study was supported by the InCo-TB project, a partnership between the Brazilian NTP and the Ataulpho de Paiva Foundation (Rio de Janeiro, RJ, Brazil), with funding from the Bill and Melinda Gates Foundation (Seattle, WA, USA). The funders had no influence on the content of the manuscript or the decision to publish, nor are they responsible for any of the statements in this manuscript.

Conflicts of interest: none declared.

References

1 World Health Organization. Global tuberculosis control, 2014. WHO/HTM/TB/2014.08. Geneva, Switzerland: WHO, 2014.

2 Steingart K R, Ng V, Henry M, et al. Sputum processing methods to improve the sensitivity of smear microscopy for

tuberculosis: a systematic review. Lancet Infect Dis 2006; 6: 664–674.
3 Uys P W, Warren R M, van Helden P D. A threshold value for the time delay to TB diagnosis. PLOS ONE 2007; 2: e757.
4 Cepheid. Two-hour detection of MTB and resistance to rifampicin. Xpert® MTB/RIF. Go from test and wait to test and treat. Sunnyvale, CA, USA: Cepheid, http://www.cepheid.com/en/component/phocadownload/category/3-healthcare-impact?download=85: xpert_mtbrif%20brochure%20eu%200089-02%20lor Accessed January 2016.
5 World Health Organization. Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children: policy update. WHO/HTM/TB/2013.16. Geneva, Switzerland: WHO, 2013.
6 Weyer K, Mirzayev F, Migliori G B, et al. Rapid molecular TB diagnosis: evidence, policy making and global implementation of Xpert MTB/RIF. Eur Respir J 2013; 42: 252–271.
7 Theron G, Peter J, Dowdy D, Langley I, Squire S B, Dheda K. Do high rates of empirical treatment undermine the potential effect of new diagnostic tests for tuberculosis in high-burden settings? Lancet Infect Dis 2014; 14: 527–532.
8 Theron G, Zijenah L, Chanda D, et al. Feasibility, accuracy, and clinical effect of point-of-care Xpert MTB/RIF testing for tuberculosis in primary-care settings in Africa: a multicentre, randomised, controlled trial. Lancet 2014; 383: 424–435.
9 Diel R, Loddenkemper R, Zellweger J P, et al. Old ideas to innovate tuberculosis control: preventive treatment to achieve elimination. Eur Respir J 2013; 42: 785–801.
10 Durovni B, Saraceni V, van den Hof S, et al. Impact of replacing smear microscopy with Xpert MTB/RIF for diagnosing tuberculosis in Brazil: a stepped-wedge cluster-randomized trial. PLOS Med 2014; 11: e1001766.
11 Brazil Ministério da Saúde, Secretaria de Vigilância Epidemiológica. Boletim epidemiológico: especial tuberculose. Brasilia, Brazil: Ministério da Saúde, 2012. [Portuguese]
12 World Health Organization. WHO monitoring of Xpert MTB/RIF roll-out. Geneva, Switzerland: WHO, 2016. http: //who.int/tb/laboratory/mtbrifrollout/en/. Accessed January 2016.
13 Dowdy D W, Dye C, Cohen T. Data needs for evidence-based decisions: a tuberculosis modeler's 'wish list'. Int J Tuberc Lung Dis 2013; 17: 866–877.
14 Kirwan D E, Cardenas M K, Gilman R H. Rapid implementation of new TB diagnostic tests: is it too soon for a global roll-out of Xpert MTB/RIF? Am J Trop Med Hyg 2012; 87: 197–201.
15 Zwerling A, Dowdy D. Economic evaluations of point of care testing strategies for active tuberculosis. Expert Rev Pharmacoecon Outcomes Res 2013; 13: 313–325.
16 Brasil Ministério da Saúde, Secretaria de Vigilância em Saúde, Departamento de Vigilância Epidemiológica. Manual de recomendações para o controle da tuberculose no Brasil. Brasilia, Brazil: Ministério da Saúde, 2011. [Portuguese]
17 Brasil Ministério da Saúde, Secretaria de Vigilância em Saúde. Sistema de Informação de Agravos de Notificação SINAN. Brasilia, Brazil: Ministério da Saúde, 2013. [Portuguese]
18 Saukkonen J J, Cohn D L, Jasmer R M, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. Am J Respir Crit Care Med 2006; 174: 935–952.
19 Schwartzman K, Menzies D. Tuberculosis screening of immigrants to low-prevalence countries. A cost-effectiveness analysis. Am J Respir Crit Care Med 2000; 161: 780–789.
20 Boehme C C, Nicol M P, Nabeta P, 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: 1495–1505.
21 Mello F C, Bastos L G, Soares S L, et al. Predicting smear negative pulmonary tuberculosis with classification trees and logistic regression: a cross-sectional study. BMC Public Health 2006; 6: 43.
22 Wilson D, Mbhele L, Badri M, et al. Evaluation of the World Health Organization algorithm for the diagnosis of HIV-associated sputum smear-negative tuberculosis. Int J Tuberc Lung Dis 2011; 15: 919–924.
23 Steingart K R, Schiller I, Horne D J, Pai M, Boehme C C, Dendukuri N. Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. Cochrane Database Syst Rev 2014; 1: CD009593.
24 Pinto M F T, Entringer A, Steffen R, Trajman A. Cost analysis of nucleic acid amplification for diagnosing pulmonary tuberculosis, within the context of the Brazilian Unified Health Care System. J Bras Pneumol 2015; 41: 1–3.
25 Dowdy D W, Davis J L, den Boon S, Walter N D, Katamba A, Cattamanchi A. Population-level impact of same-day microscopy and Xpert MTB/RIF for tuberculosis diagnosis in Africa. PLOS ONE 2013; 8: e70485.
26 Steffen R, Menzies D, Oxlade O, et al. Patients' costs and cost-effectiveness of tuberculosis treatment in DOTS and non-DOTS facilities in Rio de Janeiro, Brazil. PLOS ONE 2010; 5: e14014.
27 Pantoja A, Fitzpatrick C, Vassall A, Weyer K, Floyd K. Xpert MTB/RIF for diagnosis of tuberculosis and drug-resistant tuberculosis: a cost and affordability analysis. Eur Respir J 2013; 42: 708–720.
28 Choi H W, Miele K, Dowdy D, Shah M. Cost-effectiveness of Xpert® MTB/RIF for diagnosing pulmonary tuberculosis in the United States. Int J Tuberc Lung Dis 2013; 17: 1328–1335.
29 Vassall A, van Kampen S, Sohn H, et al. Rapid diagnosis of tuberculosis with the Xpert MTB/RIF assay in high burden countries: a cost-effectiveness analysis. PLOS MED 2011; 8: e1001120.
30 Menzies N A, Cohen T, Lin H H, Murray M, Salomon J A. Population health impact and cost-effectiveness of tuberculosis diagnosis with Xpert MTB/RIF: a dynamic simulation and economic evaluation. PLOS MED 2012; 9: e1001347.
31 Winetsky D E, Negoescu D M, DeMarchis E H, et al. Screening and rapid molecular diagnosis of tuberculosis in prisons in Russia and Eastern Europe: a cost-effectiveness analysis. PLOS MED 2012; 9: e1001348.
32 Langley I, Lin H H, Egwaga S, et al. Assessment of the patient, health system, and population effects of Xpert MTB/RIF and alternative diagnostics for tuberculosis in Tanzania: an integrated modelling approach. Lancet Glob Health 2014; 2: e581–591.
33 Andrews J R, Lawn S D, Dowdy D W, Walensky R P. Challenges in evaluating the cost-effectiveness of new diagnostic tests for HIV-associated tuberculosis. Clin Infect Dis 2013; 57: 1021–1026.
34 Golub J E, Cohn S, Saraceni V, et al. Long-term protection from isoniazid preventive therapy for tuberculosis in HIV-infected patients in a medium burden tuberculosis setting: the TB/HIV in Rio (THRio) Study. Clin Infect Dis 2014; 60: 639–645.
35 Dowdy D W, O'Brien M A, Bishai D. Cost-effectiveness of novel diagnostic tools for the diagnosis of tuberculosis. Int J Tuberc Lung Dis 2008; 12: 1021–1029.
36 Dowdy D W, Cattamanchi A, Steingart K R, Pai M. Is scale-up worth it? Challenges in economic analysis of diagnostic tests for tuberculosis. PLOS MED 2011; 8: e1001063.

RESUME

INTRODUCTION : Le test Xpert® MTB/RIF est en train d'être mis en œuvre en tant que substitut de la microscopie de frottis de crachats (SSM) dans de nombreux pays faiblement ou lourdement affectés par la tuberculose (TB), dont le Brésil, un pays où la résistance aux médicaments reste faible et le taux de co-infection au virus de l'immunodéficience humaine modéré.

CONTEXTE : La perspective du Programme National brésilien de TB (PNT).

OBJECTIF ET SCHÉMA : Nous avons estimé le ratio coût-efficacité différentiel (ICER) d'Xpert en tant que substitut de deux SSM afin de diagnostiquer une TB pharmacosensible. On a estimé les coûts visant à confirmer chaque cas supplémentaire et à éviter le traitement de faux positifs ayant eu un diagnostic empirique.

RÉSULTATS : L'ICER a été de US$943 pour chaque diagnostic de TB supplémentaire et de US$356 pour chaque cas supplémentaire de diagnostic de TB avec confirmation bactériologique, en estimant à 80% la spécificité du diagnostic clinique avec ces deux stratégies. Pour chaque 100 000 cas présumés de TB, le PNT dépenserait US$1,2 million de plus par an afin de confirmer 3344 patients tuberculeux de plus. Le modèle s'est avéré très sensible à la spécificité du diagnostic clinique après un test négatif.

CONCLUSION : Bien que le PNT n'ait pas de seuil de rapport coût-efficacité, notre modèle peut soutenir les décideurs au Brésil et dans d'autres pays à prévalence faible de pharmacorésistance parmi les patients tuberculeux. On peut attendre un bénéfice économique potentiel si les médecins se fient davantage à un résultat d'Xpert négatif et si le traitement empirique est donc réduit.

RESUMEN

INTRODUCCIÓN: En la actualidad, se está introduciendo la prueba Xpert® MTB/RIF como sustituto del examen microscópico del esputo en muchos países con alta o baja carga de morbilidad por tuberculosis (TB), incluido el Brasil, donde se observan bajas tasas de TB multidrogorresistente y tasas moderadas de coinfección por el virus de la inmunodeficiencia humana.

MARCO DE REFERENCIA: Una perspectiva del Programa Nacional contra la Tuberculosis (PNT) del Brasil.

OBJETIVOS Y MÉTODO: Se estimó la razón de costoefectividad adicional (ICER) de la prueba Xpert, como sustituto de dos baciloscopias de esputo, en el diagnóstico de la TB normosensible. Se calculó el costo de confirmación de cada caso adicional y el ahorro al evitar el tratamiento de los casos positivos falsos, tras un diagnóstico empírico.

RESULTADOS: La ICER fue $943 US por cada caso suplementario de TB y $356 US por cada caso diagnosticado con confirmación bacteriológica, al suponer una especificidad de 80% del diagnóstico clínico con ambos métodos. Por cada 100 000 casos con presunción clínica de TB, el PNT gastaría 1,2 millones de dólares adicionales por año a fin de confirmar el diagnóstico de 3344 casos más de TB. El modelo fue muy susceptible a la especificidad del diagnóstico clínico tras un resultado negativo de la prueba.

CONCLUSIÓN: Aunque en el PNT del Brasil no se ha definido el umbral para los análisis de costoefectividad, es posible afirmar que el presente modelo podría respaldar la toma de decisiones en el país y en otros países donde la prevalencia de farmacorresistencia en los pacientes con TB es baja. Se prevé una posible ventaja económica si los médicos confían más en un resultado negativo de la prueba Xpert y se disminuyen los tratamientos empíricos.