

Assessment of the patient, health system, and population effects of Xpert MTB/RIF and alternative diagnostics for tuberculosis in Tanzania: an integrated modelling approach

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Summary

Background Several promising new diagnostic methods and algorithms for tuberculosis have been endorsed by WHO. National tuberculosis programmes now face the decision on which methods to implement and where to place them in the diagnostic algorithm.

Methods We used an integrated model to assess the effects of different algorithms of Xpert MTB/RIF and light-emitting diode (LED) fluorescence microscopy in Tanzania. To understand the effects of new diagnostics from the patient, health system, and population perspective, the model incorporated and linked a detailed operational component and a transmission component. The model was designed to represent the operational and epidemiological context of Tanzania and was used to compare the effects and cost-effectiveness of different diagnostic options.

Findings Among the diagnostic options considered, we identified three strategies as cost effective in Tanzania. Full scale-up of Xpert would have the greatest population-level effect with the highest incremental cost: 346 000 disability-adjusted life-years (DALYs) averted with an additional cost of US\$36.9 million over 10 years. The incremental cost-effectiveness ratio (ICER) of Xpert scale-up (\$169 per DALY averted, 95% credible interval [CrI] 104–265) is below the willingness-to-pay threshold (\$599) for Tanzania. Same-day LED fluorescence microscopy is the next most effective strategy with an ICER of \$45 (95% CrI 25–74), followed by LED fluorescence microscopy with an ICER of \$29 (6–59). Compared with same-day LED fluorescence microscopy and Xpert full rollout, targeted use of Xpert in presumptive tuberculosis cases with HIV infection, either as an initial diagnostic test or as a follow-on test to microscopy, would produce DALY gains at a higher incremental cost and therefore is dominated in the context of Tanzania.

Interpretation For Tanzania, this integrated modelling approach predicts that full rollout of Xpert is a cost-effective option for tuberculosis diagnosis and has the potential to substantially reduce the national tuberculosis burden. It also estimates the substantial level of funding that will need to be mobilised to translate this into clinical practice. This approach could be adapted and replicated in other developing countries to inform rational health policy formulation.

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Introduction

The past decade has seen a renewal of activity and funding dedicated to the development of improved tuberculosis diagnostics. Several promising new diagnostic methods and algorithms have been recently endorsed by WHO.^{1–3} For example, Xpert MTB/RIF is a cartridge-based, automated diagnostic test that can identify *Mycobacterium tuberculosis* (MTB) with improved accuracy and resistance to rifampicin (RIF). However, whether these new diagnostics will replace existing methods or will be used in combination with them is not yet clear. Although new diagnostic methods and algorithms have the potential to overcome many of the weaknesses of the present diagnostic processes, they might substantially increase the demands on scarce resources and funds.⁴ Before national tuberculosis programmes can fully scale up new tuberculosis diagnostics, policy makers need to understand the effects on patients, the health system, and

the wider population. Failure to do so could lead to poor performance outcomes, unsustainable implementation, and wasted resources.⁵

Trials of new tuberculosis diagnostic algorithms are essential for measuring their effect.^{6–9} However, these studies provide little quantification of the effect that these methods will have in health systems and epidemiological contexts other than those in which the trials were done. Studies are also unable to predict longer-term effects of these algorithms on disease dynamics and it is usually not possible to predict how these new algorithms will affect the operational performance of the health system. Using an integrated modelling approach that combines detailed operational and transmission components, we assessed the effects and cost-effectiveness of several new tuberculosis diagnostic algorithms for adult pulmonary tuberculosis in Tanzania.

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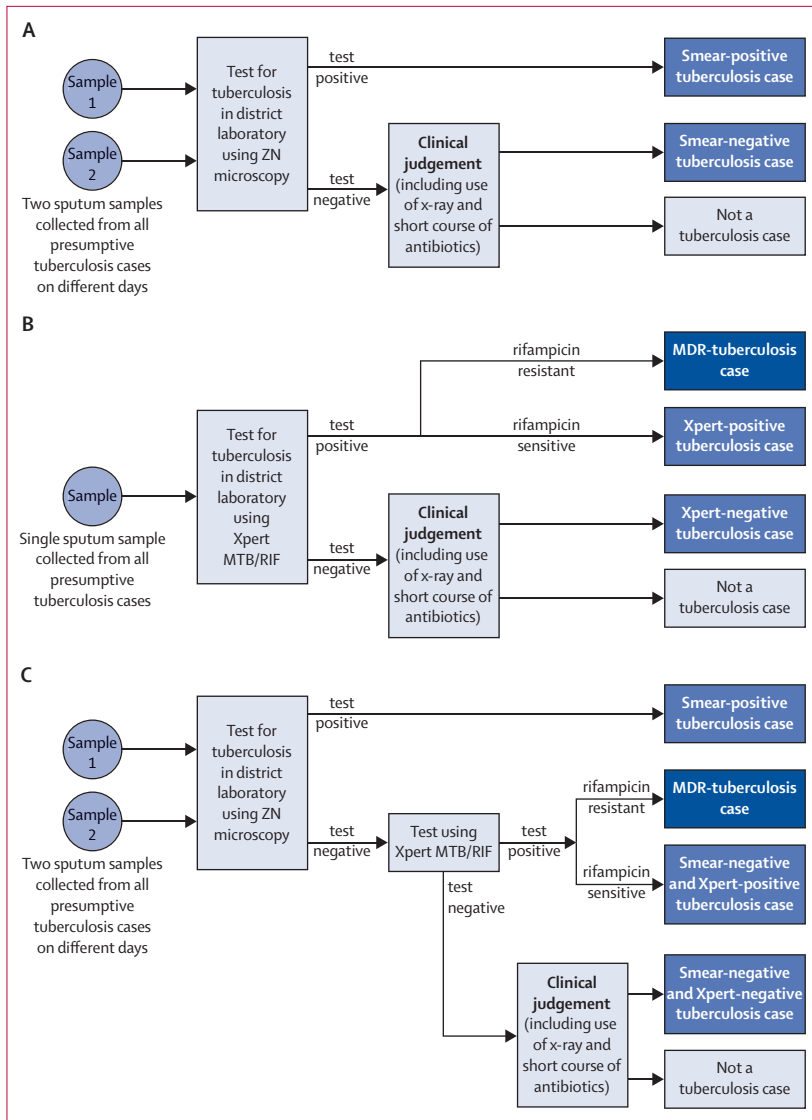


Figure 1: Summary patient pathways for three tuberculosis diagnostic processes
 (A) Sputum smear microscopy. (B) Xpert MTB/RIF replacing microscopy. (C) Xpert MTB/RIF in addition to microscopy. MDR=multidrug resistant.

See Online for appendix

Methods

Study setting and diagnostic algorithms

In 2011, the incidence of tuberculosis in Tanzania was 169 per 100 000, and 38% of patients were co-infected with HIV.^{10,11} The estimated proportion of multidrug-resistant (MDR) tuberculosis was 1·1% in patients with new infection and 3·1% in those undergoing retreatment.^{11,12} We assessed the effects of eight WHO-endorsed diagnostic options for patients with presumptive tuberculosis, covering three different processes and three diagnostic methods that might be differently targeted on the basis of HIV status (figure 1, table 1). The first three algorithms (A) use sputum smear microscopy: A1 is the base case scenario of Ziehl-Neelsen (ZN) microscopy; A2

replaces ZN microscopy with light-emitting diode (LED) fluorescence microscopy; and A3 uses LED fluorescence microscopy and two sputum samples provided on the same day.¹ The algorithms in processes B and C represent the possible approaches to the use of Xpert MTB-RIF (Xpert) under present WHO recommendations.² B1 tests all patients with presumptive tuberculosis with Xpert; B2 and B3 target the use of Xpert to patients with presumptive tuberculosis who are HIV-positive. C1 and C2 use LED fluorescence microscopy as the primary method for tuberculosis diagnosis and target Xpert for smear-negative individuals with HIV infection.

The model

To assess the effects of different diagnostic algorithms at the patient, health system, and population levels, we developed a modelling platform that integrates operational and transmission components.¹³ The operational component used the discrete-event simulation approach and incorporated patient and sputum sample pathways based on WHO guidelines and the present diagnostic procedure in Tanzania.^{14–17} We calibrated the model using data from two diagnostic centres in Tanzania (Temeke and Kibong’oto) where different microscopy techniques (ZN and LED fluorescence) were in use and where there were plans to implement Xpert. We validated the outputs from the model against the results from the 2010 National TB and Leprosy Programme (NLP) annual reports (appendix). The transmission component followed previous epidemic modelling approaches and further incorporated the care-seeking pathway of patients with tuberculosis (appendix).^{18–20} The model was calibrated to the epidemiological situation of tuberculosis in Tanzania with Bayesian melding.²¹ Because the operational outcomes can affect transmission, and conversely transmission outcomes can affect operations, the two components were linked, in that output of one served as input to the other component (figure 2).¹³ Key input variables to the operational and transmission component are shown in table 2; other variables are presented in the appendix. The frequency and accuracy of clinical diagnosis (ie, diagnosis without microbiological confirmation) and presumptive treatment will alter the expected effect of new diagnostic methods and algorithms.¹¹ For this study, we estimated the accuracy of such diagnostic practices using the known levels of smear-positive and smear-negative tuberculosis in Tanzania in conjunction with estimates of the sensitivity and specificity of microscopy and the sensitivity of clinical judgment in smear-negative cases from published work^{7,37} (details of these calculations are shown in the appendix). Operational and transmission components of the model have been previously published and can be found in the appendix.^{13,20,37}

Cost-effectiveness analysis

We did cost-effectiveness analyses to compare different diagnostic options. The incremental cost of implementing each alternative diagnostic option was derived from the

	Process (see figure 1)	HIV status		Diagnostic method(s)	Comment
		HIV positive	HIV negative or unknown status		
A1	ZN microscopy base case	A	A	ZN microscopy	Algorithm used in most of Tanzania
A2	LED fluorescence microscopy	A	A	LED fluorescence microscopy	Being rolled out across Tanzania
A3	Same-day LED fluorescence microscopy	A	A	LED fluorescence microscopy	As A2, but sputum samples collected on the same day
B1	Full Xpert rollout	B	B	Xpert MTB/RIF	Xpert used for all presumptive tuberculosis cases
B2	Xpert for known HIV-positive cases	B	A	LED fluorescence microscopy and Xpert MTB/RIF	Xpert targeted to those who have a known HIV-positive status
B3	Xpert for HIV-positive cases with additional HIV testing	B	A	LED fluorescence microscopy and Xpert MTB/RIF	As B2, plus additional HIV testing before tuberculosis testing to increase known HIV-positive numbers
C1	Xpert for smear-negative and known HIV-positive cases	C	A	LED fluorescence microscopy and Xpert MTB/RIF	Initial test LED fluorescence microscopy. If smear-negative and known HIV-positive status use Xpert
C2	Xpert for smear-negative and HIV-positive cases with additional HIV testing	C	A	LED fluorescence microscopy and Xpert MTB/RIF	As C1, but with additional HIV testing for smear-negative cases to increase known HIV status

ZN=Ziehl-Neelsen. LED=light-emitting diode.

Table 1: Tuberculosis diagnostic algorithms modelled

Tanzanian health system perspective, and included the additional annual running costs (eg, consumables, tuberculosis and MDR-tuberculosis drugs, radiographs, equipment maintenance, and laboratory personnel) and the investment costs (eg, microscopes and the equipment related to Xpert implementation) (table 2, appendix). Following advice from the NTLF, other overhead costs were assumed to be unaffected by a change in the diagnostic algorithm. Patients' costs were not collected or included in this study, but an indication of how they could be used in the model is given in the appendix. Because the introduction of new tuberculosis diagnostics is expected to improve the survival of patients co-infected with tuberculosis and HIV, we estimated the incremental costs from additional antiretroviral therapy (ART) on the basis of the projected number of deaths from tuberculosis and HIV co-infection. The population effect on tuberculosis epidemiology was summarised using disability-adjusted life-years (DALYs) without age weighting.^{36,38} Costs and DALYs were calculated over 10 years with an annual discount rate of 3%.³⁹ We calculated the average cost-effectiveness ratio (ACER) by comparing each alternative diagnostic option to the base case scenario (A1, table 1). Because the alternative diagnostic options are mutually exclusive interventions that compete for the same resources, we also calculated the incremental cost-effectiveness ratios (ICER) to compare one option with the next less-effective option.⁴⁰ The estimated ICER was compared with the willingness-to-pay threshold for Tanzania (US\$599 based on gross domestic product [GDP] per capita in 2012).^{41,42}

Uncertainty and sensitivity analysis

We did an uncertainty analysis using 1000 posterior simulations to estimate the 95% credible intervals (95% CrI) of the population-level effect on incidence,

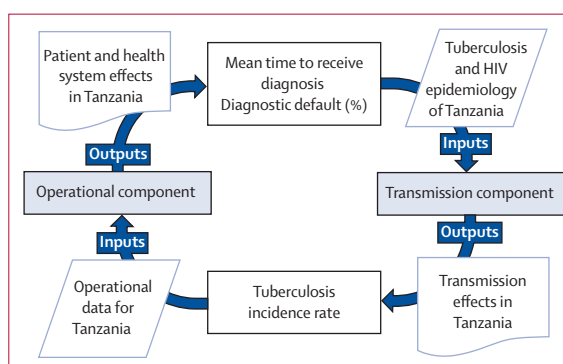


Figure 2: Linkage between the operational and transmission component of the integrated model

prevalence, mortality, and DALYs. The 95% CrIs are the Bayesian framework equivalent of confidence intervals in the frequentist framework.⁴³ We did one-way sensitivity analyses to explore the effect of input variables on ACER and ranking of diagnostic options using 1000 posterior simulations (appendix).

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. IL and H-HL had full access to all data in the study. Together with SBS they had final responsibility for the decision to submit for publication.

Results

Full rollout of Xpert (B1) would have the greatest patient-level benefits among the alternative diagnostic options (table 3). The improved diagnostic sensitivity and the need for only one sputum sample for Xpert reduces mean patient visits for diagnosis by 1·2 (95% CrI 1·1–1·3) visits, time to start treatment by

	Value	Source
Operational component		
Base case		
Annual smear-positive and tuberculosis cases per district	47–500*	NTLP operational data and the annual report 2010 ²²
Proportion of presumptive smear-positive tuberculosis cases	10.0–12.5%*	As above
Proportion of smear-negative tuberculosis cases	34.0–53.9%*	As above
Proportion of tuberculosis cases needing re-treatment	6.1–9.1%*	As above
Proportion of HIV-positive tuberculosis cases	13.6–41.4%*	As above
Proportion of smear-negative presumptive tuberculosis cases that had radiograph and antibiotic trial	70.0%	As above
MDR tuberculosis in new tuberculosis cases	1.1%	WHO, 2012 ²¹
MDR tuberculosis in retreated tuberculosis cases	3.1%	Tanzania Ministry of Health ¹²
Diagnostic lost to follow-up rate	15.0%	Squire and colleagues, 2005 ²³
Sensitivity and specificity		
Sensitivity of ZN microscopy for HIV-positive cases	44.6%	Boehme and colleagues, 2011 ⁷
Sensitivity of ZN microscopy for HIV-negative cases	72.3%	As above
Specificity of ZN microscopy for HIV-positive cases	100.0%	As above
Specificity of ZN microscopy for HIV-negative cases	99.4%	As above
Sensitivity of clinical diagnosis	51.9%	Swai and colleagues, 2011 ²⁴
Sensitivity improvement of LED fluorescence microscopy over ZN microscopy	+6.0%	WHO, 2011 ²⁵
Specificity improvement of LED fluorescence microscopy over ZN microscopy	0.0%	As above
Sensitivity improvement of same-day LED fluorescence microscopy over ZN microscopy	–2.8%	WHO, 2011 ¹
Specificity improvement of same-day LED fluorescence microscopy over ZN microscopy	0.0%	As above
Sensitivity of Xpert for tuberculosis in smear-positive HIV-negative cases	98.4%	Boehme and colleagues, 2011 ⁷
Sensitivity of Xpert for tuberculosis in smear-negative HIV-negative cases	79.3%	As above
Sensitivity of Xpert for tuberculosis in smear-positive HIV-positive cases	97.7%	As above
Sensitivity of Xpert for tuberculosis in smear-negative HIV-positive cases	71.8%	As above
Specificity of Xpert for tuberculosis in HIV-negative cases	98.9%	As above
Specificity of Xpert for tuberculosis in HIV-positive cases	99.2%	As above
Sensitivity of Xpert for MDR tuberculosis	94.0%	Steingart and colleagues, 2013 ²⁶
Specificity of Xpert for MDR tuberculosis	98.0%	As above
Cost variables		
LED fluorescence microscope	\$1250.0	FIND negotiated price, 2012 ²⁷
Xpert cartridge cost per test	\$9.98	As above
Xpert MTB/RIF machine 4 cell	\$17500.0	As above
Xpert annual maintenance 4 cell	\$1800.0	As above
Drug sensitivity cost per test	\$19.0	Tanzania NTLP, 2011
Microscopy cost per test	\$1.5	As above
Radiograph	\$6.9	As above
Monthly drug cost for standard regimen	\$3.0	As above
Monthly drug cost for retreatment regimen	\$17.8	As above
Monthly drug cost for MDR tuberculosis regimen	\$119.4	As above
Annual employment costs for a laboratory technician	\$3200.0	As above
Annual employment costs for a laboratory assistant	\$2240.0	As above
ART cost per year	\$430.5	Ministry of Health and Social Welfare Tanzania and US CDC, 2011 ²⁸
Transmission component†§		
Transmission variable, smear-positive cases	5.9 per year (3.3–10.5); 7.7 per year (5.3–11.0)	Fitted to the observed tuberculosis epidemic before DOTS implementation. ²⁹ Also consistent with Trunz and colleagues, 2006 ³⁰
Relative magnitude of transmission variable, smear-negative cases (compared with smear-positive cases)	0.2 per year (0.13–0.36); 0.21 per year (0.11–0.31)	Behr and colleagues, 1999 ³¹
Primary progression rate, HIV-negative case	0.03 per year (0.0095–0.094); 0.021 per year (0.012–0.041)	Vynnycky and colleagues, 1997 ³²

(Table 2 continues on next page)

	Value	Source
(Continued from previous page)		
Slow reactivation rate, HIV-negative cases	0.0003 per year (0.000021–0.0042); 0.00096 per year (0.000099–0.0023)	Vynnycky and colleagues, 1997 ³²
Partial immunity that decreases probability of fast progression after reinfection, HIV-negative cases	0.65 (0.56–0.75); 0.65 (0.59–0.72)	Cohen and colleagues, 2006 ³³
Proportion smear-positive among incident cases of pulmonary tuberculosis, HIV-negative cases	0.88 (0.85–0.92); 0.89 (0.85–0.92)	Calibrated manually to tuberculosis notification data
Natural cure rate, HIV-negative cases	0.20 per year (0.12–0.34); 0.23 per year (0.13–0.34)	Dye and colleagues, 1998 ¹⁸
Death rate of those with active tuberculosis disease, smear-positive and untreated, HIV-negative cases	0.22 per year (0.13–0.36); 0.22 per year (0.16–0.31)	Adapted from Hughes and colleagues, 2006 ³⁴
Death rate of those with active tuberculosis disease, smear-negative and untreated, HIV-negative cases	0.19 per year (0.11–0.32); 0.18 per year (0.13–0.32)	Adapted from Hughes and colleagues, 2006 ³⁴
Relapse rate after cure, HIV-negative cases	0.001 per year (0.00011–0.0096); 0.0022 per year (0.00019–0.010)	Cohen and colleagues, 2006 ³³
Effect of ART on HIV mortality and tuberculosis natural history variables	Assume a reduction of excess risk by (0.50–1.00) compared with no ART; 0.72 (0.54–1.00)	Assumption, and based on Lawn and Churchyard, 2009 ³⁵
Disability weight, active tuberculosis	0.33 (0.23–0.46); same as prior value	Salomon and colleagues, 2012 ³⁶
Disability weight, HIV-positive with low CD4 cell count	0.55 (0.40–0.69); same as prior value	Salomon and colleagues, 2012 ³⁶

For Transmission components, values in parentheses are 95% ranges from log-normal or logit-normal distributions or lower and upper bound from uniform distribution for prior values, and 95% CrIs for posterior values. All costs are in US dollars. MDR=multidrug-resistant. LED=light-emitting diode. ZN=Ziehl-Neelsen. NTLP=National TB and Leprosy Programme. *Value depends on the size and HIV prevalence of the district (see appendix). †Values are prior values; posterior values. §Source for prior value.

Table 2: Key input variables to the integrated model

	Diagnosis and treatment initiation compared with base case (A1)			Diagnosis and treatment success	
	Reduction in visits to the diagnostic centre (mean, SD)	Reduction in time to start treatment (mean days, SD)	Reduction in diagnostic LTFU rate (%)	Tuberculosis cases diagnosed without a positive sputum test (%)	Likelihood of a true tuberculosis patient completing diagnosis and treatment (%)
A1 ZN microscopy base case	46%	62%
A2 LED fluorescence microscopy	0.0 (0.1)	1.1* (0.4)	0%	40%*	64%
A3 same-day LED fluorescence microscopy	0.9* (0.1)	1.6* (0.6)	6%*	42%*	68%*
B1 full Xpert rollout	1.2* (0.1)	6.6* (0.7)	7%*	14%*	80%*
B2 Xpert for known HIV-positive cases	0.2* (0.1)	1.8* (0.9)	0%	36%*	67%
B3 Xpert for HIV-positive cases with additional HIV testing	0.5* (0.1)	3.5* (0.8)	2%*	28%*	72%*
C1 Xpert for smear-negative or known HIV-positive cases	0.1 (0.1)	1.7* (0.6)	0%	36%*	66%
C2 Xpert for smear-negative or HIV-positive cases with additional HIV testing	0.1 (0.1)	2.8* (0.9)	0%	28%*	69%*

ZN=Ziehl-Neelsen. LED=light-emitting diode. LTFU=lost to follow-up. *Significant difference from base case at 95% level.

Table 3: Patient-level effects of new diagnostic algorithms

6.6 (95% CrI 5.9–7.3) days, and the diagnostic lost to follow-up rate by 7% (95% CrI 6–9), resulting in an 18% increase in the likelihood that a patient with tuberculosis will successfully complete diagnosis and treatment (80% [95% CrI 76–83] compared with 62% [95% CrI 59–65] in the base case). The next best algorithms from the patient perspective include targeting of Xpert to HIV-positive cases alongside additional HIV testing (B3) and same-day LED fluorescence microscopy (A3).

At the health-system level, full scale-up of Xpert (B1) would reduce the required number of sputum samples by 34% (or 441 000 [95% CrI 404 000–479 000] compared with 730 000 [95% CrI 705 000–769 000] samples per year) and require only 45% of the laboratory staff time that is needed by the base case (table 4). New diagnostics have only a marginal effect on tuberculosis notification, because the increase in cases diagnosed through the improved primary test are counterbalanced by the true-positive and false-positive cases identified by the less specific secondary

	Laboratory outcomes				Patients starting tuberculosis treatment per year (n)		Complete cures per year	
	Sputum samples tested for tuberculosis per year (000s)	Xpert	Total	Staff used on tuberculosis diagnosis* (%)	Standard regimen	MDR tuberculosis regimen	Including false positive	Excluding false positive
A1 ZN microscopy base case	730	0	730	100%	49787	113	44 476	31 801
A2 LED fluorescence microscopy	725	0	725	100%	48 366	110	43 208	32 742
A3 same-day LED fluorescence microscopy	752	0	752†	108%	51 113	116	45 807	33 679†
B1 full Xpert rollout	132	309	441†	45%†	48 441	1285†	42 838	37 639†
B2 Xpert for known HIV-positive cases	681	25	707†	98%	48 605	356†	43 446	33 475†
B3 Xpert for HIV-positive cases with additional HIV testing	580	78	658†	95%	48 700	537†	43 399	34 982†
C1 Xpert for smear-negative and known HIV-positive cases	722	22	744	100%	48 357	337†	43 245	33 283†
C2 Xpert for smear-negative and HIV-positive cases with additional HIV testing	719	66	785†	101%	47 832	447†	42 608	34 344†

Laboratory outcomes include both diagnostic and treatment follow-up testing. MDR=multidrug-resistant. ZN=Ziehl-Neelsen. LED=light-emitting diode. *Assuming laboratory staff is 100% utilised. †Significant difference to base case at 95% level. ‡Patients that start MDR tuberculosis treatment might later transfer to drug-sensitive treatment after contradictory results from drug susceptibility testing from the central reference laboratory.

Table 4: Health-system-level effects of new diagnostic algorithms: mean per year in first 10 years

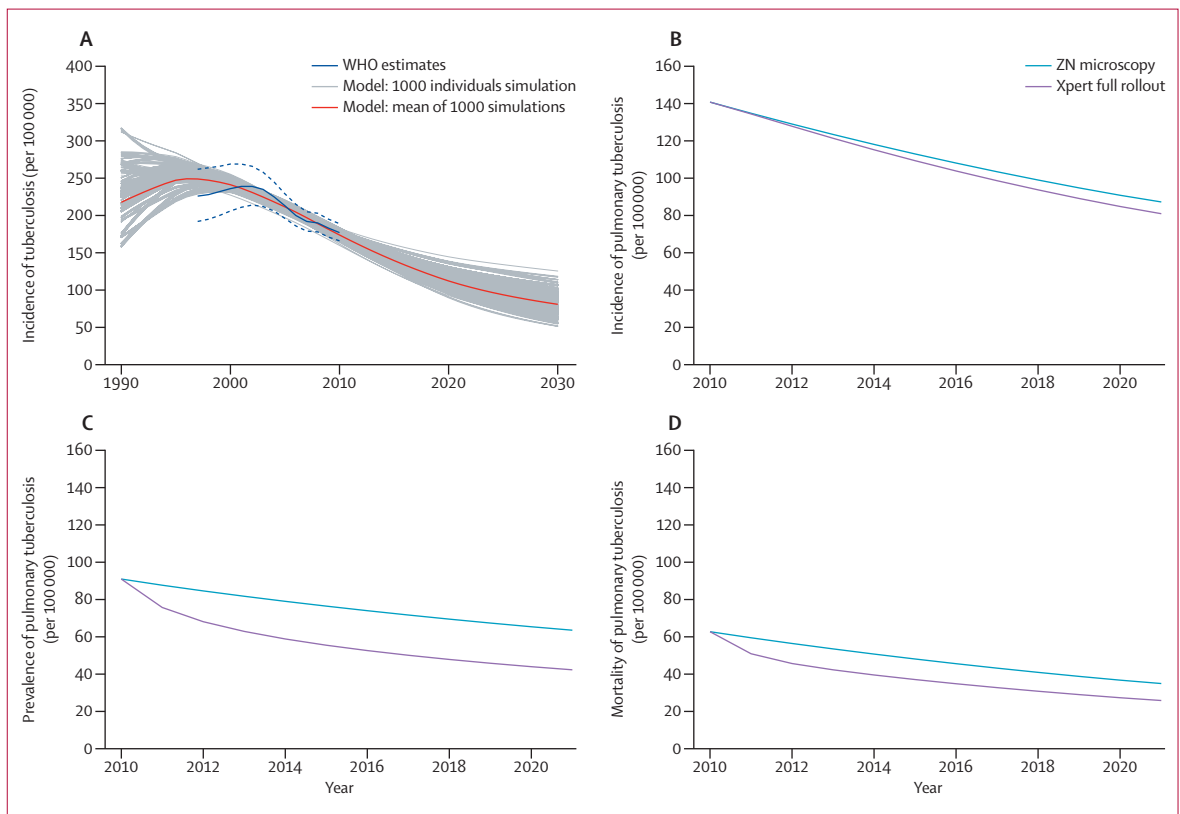


Figure 3: Model calibration and projected effects of full rollout of Xpert MTB/RIF on tuberculosis incidence, prevalence, and mortality
 (A) Model calibration to the observed incidence of tuberculosis in Tanzania. Point estimates and 95% confidence intervals of estimated incidence of tuberculosis in Tanzania reported by WHO. The 1000 posterior simulations after calibrating the transmission component to the observed incidence and the mean of the 1000 posterior simulations are shown. Projected effect on tuberculosis incidence (B), prevalence (C), and mortality (D) comparing the baseline scenario (Ziehl-Neelsen microscopy) with the full rollout of Xpert MTB/RIF.

	Number of tuberculosis events averted (000s)		Additional ART person-years (000s)	DALYs averted (000s)				Additional health system costs over 10 years (US\$ million)			Cost-effectiveness ratio† (US\$ per DALY averted)		
	Incident cases	Death cases		YLL	YLD	DALY	DALY _p ‡	TB	ART	Total	ACER	ICER	ICER _p ‡
A2 LED fluorescence microscopy	1.3	7.3	3.9	57.5	0.4	57.9	5.7	0.0	1.7	1.7	29 (6–59)	29 (6–59)	37 (10–71)
A3 same-day LED fluorescence microscopy	10.3	16.6	8.0	148.6	3.1	151.7	14.6	2.2	3.5	5.7	38 (20–62)	45 (25–74)	299 (170–602)
B1 Full Xpert rollout	17.0	39.7	19.6	340.8	5.2	346.0	33.6	28.3	8.6	36.9	109 (72–144)	169 (104–265)	1491 (973–2523)
B2 Xpert for known HIV-positive cases	2.5	11.7	6.5	84.0	0.8	84.8	8.7	10.2	2.9	13.1	163 (98–246)	Dominated	Dominated
B3 Xpert for HIV-positive cases with additional HIV testing	6.5	24.0	13.8	160.8	2.1	162.8	17.3	16.1	6.0	22.1	140 (92–192)	Dominated	Dominated
C1 Xpert for smear-negative and known HIV-positive cases	1.4	9.6	5.4	68.3	0.5	68.8	7.1	10.2	2.4	12.6	203 (110–366)	Dominated	Dominated
C2 Xpert for smear-negative and HIV-positive cases with additional HIV testing	1.5	15.2	9.3	94.1	0.6	94.7	10.3	15.5	4.1	19.6	240 (127–501)	Dominated	Dominated

Estimates are based on the incidence approach unless otherwise specified. YLL=years of life lost. YLD=years lost due to disability. DALY=disability-adjusted life-year. ART=antiretroviral therapy. ACER=average cost-effectiveness ratio. ICER=incremental cost-effectiveness ratio. LED=light-emitting diode. *Compared with the base case scenario of ZN microscopy (A1). †Numbers in parentheses are 95% credible intervals. ‡DALY_p and ICER_p are DALY estimates using the prevalence approach.

Table 5: Incremental population-level effect and cost-effectiveness analysis of new diagnostic algorithms*

tests (clinical judgment, including chest radiograph) in the base-case algorithm (A1). After false-positive cases are excluded, Xpert is projected to increase the number of true tuberculosis cures by 5838 per year (or 37639 [95% CrI 35 992–39 286] compared with 31801 [95% CrI 30 311–33 394] per year) (table 4). The use of Xpert would identify 1285 (95% CrI 1119–1437) rifampicin-resistant cases during the diagnostic process (compared with only 113 [95% CrI 97–129] MDR tuberculosis cases identified during treatment), although the positive predictive value for MDR tuberculosis in new tuberculosis cases is only 35% (see appendix for calculation). This low predictive value for rifampicin resistance in the Tanzanian context implies that most identified rifampicin-resistant cases (65%) will not need a full course of second-line treatment after confirmatory drug sensitivity testing.

Similarly, full rollout of Xpert (B1) would have the greatest effect at the population level. The epidemiological effect is projected to be the greatest on tuberculosis prevalence, followed by tuberculosis mortality, and tuberculosis incidence (figure 3). Compared with the baseline algorithm (A1), full implementation of Xpert (B1) would prevent 17000 (95% CrI 8800–26600) cases of incident tuberculosis and 39700 (95% CrI 27600–53000) tuberculosis deaths over 10 years (table 5). In addition to the effect on tuberculosis epidemiology, new diagnostics would increase the number of people on ART because of improved survival of patients co-infected with tuberculosis and HIV. Assuming that the coverage of ART would gradually reach 80% in 10 years,¹⁰ different diagnostic options would result in 3900 (95% CrI 600–8900) (A2) to 19600 (95% CrI 3300–34600) (B1) additional person-years

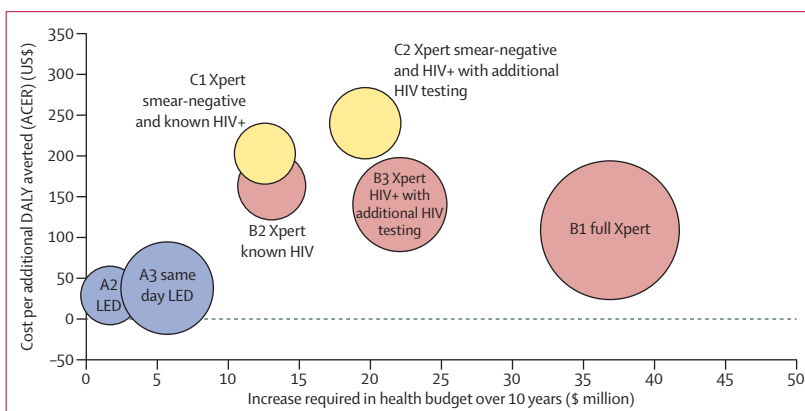


Figure 4: Sustainability versus cost-effectiveness (average cost-effectiveness ratio, ACER) versus disability-adjusted life-years (DALYs) averted

The size of the circles shows the scale of benefits from each intervention measured in DALYs averted over 10 years relative to the base case of Ziehl-Neelsen microscopy. LED=light-emitting diode.

on ART. Compared with the baseline algorithm, full implementation of Xpert (B1) would prevent the largest number of DALYs (346 000, 95% CrI 247 000–475 000) over 10 years (table 5). Other diagnostic algorithms would have less effect on DALYs, with the benefits ranging from 57 900 (A2) to 162 800 (B3) DALYs averted.

In the cost-effectiveness analysis, the ACER of alternative diagnostic options ranged from \$29 to \$240 per disability-adjusted life-year (DALY) averted compared with ZN microscopy (A1), with the incremental cost varying between \$1.7 million and \$36.9 million (table 5, figure 4). In the analysis of ICER, options of targeted use of Xpert (B2, B3, C1, C2) are dominated by

same-day LED fluorescence microscopy (A3) and Xpert full rollout (B1) because they produce DALY gains at a higher incremental cost (appendix). The ICER of Xpert full rollout is \$169 per DALY averted (95% CrI 104–265), followed by same-day LED fluorescence microscopy (\$45, 95% CrI 25–74) and LED fluorescence microscopy (\$29, 95% CrI 6–59) (table 5). The ICERs for all three alternative algorithms are below the willingness-to-pay threshold for Tanzania (\$599).

In one-way sensitivity analyses, the variables having most effect on ICER were the natural history variables of tuberculosis and HIV (eg, reactivation rate, natural cure rate, duration of infectiousness, and the transmission variable) whose prior and posterior ranges of uncertainty were wide, showing insufficient understanding of these variables (appendix). Overall, the estimated ICERs were robust to uncertainty of most input variables. We also changed the assumption on ART so that the coverage increased to 80% in 5 years, and the results were similar (appendix). We further set the variables with greatest effect in the sensitivity analysis to the extreme values (2.5 and 97.5 percentile of the posterior distribution), and found that the ranking of diagnostic options remained unchanged (appendix).

Discussion

We have assessed the effect of several promising tuberculosis diagnostic options that are being considered by many national tuberculosis programmes, and have identified three cost-effective strategies in the context of Tanzania: full rollout of Xpert MTB/RIF (B1) at \$169 per DALY averted, followed by same-day LED fluorescence microscopy (A3) at \$45, and LED fluorescence microscopy (A2) at \$29 per DALY averted.

According to the updated recommendations from WHO, Xpert should be used as the initial diagnostic test in individuals suspected of having HIV-associated tuberculosis (strong recommendation).² In settings such as Tanzania where the prevalence of HIV infection is high, all presumptive tuberculosis cases can be considered as presumptive cases of HIV-associated tuberculosis, justifying the full rollout of Xpert as the initial diagnostic test. However, many HIV-endemic countries (eg, Tanzania) might see the previous recommendation as suggesting Xpert should be used only on presumptive tuberculosis cases with known HIV infection. In Tanzania, because of the high cost of the test, Xpert was seen as a follow-on test to microscopy rather than a replacement test. Our analysis showed that, in settings similar to that in Tanzania, targeted use of Xpert in HIV-positive presumptive tuberculosis cases (B2 and B3) and in HIV-positive and smear-negative cases (C1 and C2) is not cost-effective compared with full rollout of Xpert or same-day LED fluorescence microscopy.

The reason for the inferior cost-effectiveness performance of targeted implementation is that the projected gains in DALYs in most cases are lower than

those projected from implementing same-day LED fluorescence microscopy, and the projected cost is substantially higher. The targeted approaches considered in our analysis focused on HIV-positive presumptive tuberculosis cases. Because the life expectancy of HIV-positive individuals is shorter than that of HIV-negative individuals, the potential gain in life-years (and DALYs) of preventing a death from tuberculosis in a HIV-positive patient would be smaller than that of preventing a death from tuberculosis in a HIV-negative patient. Much of the ART cost would be preserved in the targeted approach, resulting in inferior cost-effectiveness of the targeted approach, showing that if the benefit of new diagnostic algorithms is measured by the overall improved years of healthy life (ie, DALYs averted), the effect (or lack of effect) on the HIV-negative population is an essential element of any assessment. Nonetheless, our results did not suggest that access to improved diagnosis (Xpert) should be denied to the HIV-infected population. In fact, full rollout of Xpert is the only way to ensure all HIV-positive patients receive Xpert diagnosis in the context of Tanzania, because most HIV-positive individuals do not know their HIV status at the point of tuberculosis diagnostic testing.

Among the cost-effective diagnostic options, the decision on which one to use will depend on the cost-effectiveness ratio of other health interventions being considered in Tanzania. If the health-related budget in Tanzania can afford a health intervention with a cost-effectiveness ratio of \$599 (GDP per head in Tanzania, 2012) per DALY, the government should consider full scale-up of Xpert (B1), which has an average ICER of \$169 (95% CrI 104–265) per DALY. We note that cost-effectiveness does not necessarily imply that the interventions are affordable or sustainable. The ICER of each intervention needs to be weighed against the associated incremental costs. The projected 10-year incremental cost to the tuberculosis programme of Xpert scale-up (\$28.3 million) represents an increase of about 25% in funds to the present tuberculosis programme. Additionally, an incremental cost of \$8.6 million to the HIV programme will be needed as a result of the additional cost of ART (see appendix for a breakdown). Without a major ongoing injection of funds into the Tanzanian NTLP, the full scale-up of Xpert appears to be unsustainable at present. Appropriate funding will need to be mobilised to translate this into clinical practice.

By contrast with the findings from the present study, Theron and colleagues⁴⁴ reported that the use of Xpert was not associated with lower tuberculosis-related morbidity in a multicentre randomised trial from four African countries. A substantial percentage of treatment episodes in this field trial were based on clinical diagnosis in the absence of microbiological identification of *Mycobacterium tuberculosis* (66% of those treated for tuberculosis in the smear microscopy group and 43% of those treated in the Xpert group). In settings where the

rate of empirical treatment is high, most individuals with tuberculosis coming for diagnosis will receive treatment, whichever diagnostic method is used. Therefore, the ability of any new diagnostic methods and algorithms to identify additional tuberculosis cases will be limited.^{20,45} Because empirical treatment decisions are not routinely taken in Tanzania, the difference in effect of Xpert between our study and the Theron study might be explained by different rates of empirical treatment. Additionally, the cost-effectiveness of an intervention will depend on the accuracy (sensitivity and specificity) of empirical diagnosis in smear-negative cases. If the specificity were lower than assumed in our study (<95%), the benefits of Xpert (B1) would be increased and the ICER reduced because of a larger reduction in false-positive diagnosis of tuberculosis.

Compared with ZN microscopy, we estimated that the ACER for full rollout of Xpert (B1) would be \$109 (95% CrI 72–144) per DALY averted. Vassall and colleagues⁴⁶ estimated the ACER of Xpert to be \$52–138 per DALY in 1 year using decision analytical models of tuberculosis in India, South Africa, and Uganda.⁴⁶ In another calibrated, dynamic mathematical model of five southern African countries (Botswana, Lesotho, Namibia, South Africa, and Swaziland), Menzies and colleagues⁴⁷ reported the ACER of Xpert to be \$959 (95% CrI 633–1485) per DALY over a 10-year period (panel). In addition to the expected difference in ACER due to different epidemiology of tuberculosis and HIV, we note that these ACER estimates cannot be directly compared for a number of reasons. First, our study and the Menzies study applied epidemic models that incorporated the effect on tuberculosis transmission, whereas the Vassall study used static models that did not account for transmission effects (and therefore might underestimate the overall effect). Second, when measuring DALYs averted by new diagnostics, our study and the Vassall study included the effect on future disease burden (eg, a tuberculosis death averted in a patient with a life expectancy of 20 years would contribute 20 years of DALY), whereas the Menzies study accounted for the effect on prevalent disease burden over the study period (in the previous example, the DALY contribution would be 10 years if the study period is 10 years). We repeated our ICER analysis using a similar prevalence approach as Menzies and colleagues⁴⁷ and found that the estimated ICER increased from \$169 (95% CrI 104–265) to \$1491 (95% CrI 973–2523) (table 5). Third, our study and the Menzies study included the cost of ART in the analysis, whereas the Vassall study did not.

Although we focused only on Tanzania in the present analysis, our key findings on the rank of alternative diagnostic options should be generalisable to countries of similar operational and epidemiological situations (eg, countries with high HIV and low MDR tuberculosis, and similar health system infrastructures). In other settings, the approach in our study, which includes important details related to both infrastructure and epidemiology,

Panel: Research in context

Systematic review

A systematic review of tuberculosis diagnostic modelling was done in April, 2013, by the TB Modelling and Analysis Consortium (TB MAC).⁴⁸ The review focused on modelling studies of new diagnostics for active tuberculosis disease. 31 studies were identified, including 16 cost-effectiveness analyses using decision analytical modelling or epidemic modelling methods. Seven studies assessed the effect of Xpert MTB/RIF when it is used in people with HIV initiating antiretroviral therapy or people with presumptive tuberculosis. Most of these modelling studies focused on the population-level effect of new diagnostics, and none examined the effect at the patient level or the health system level. No modelling studies compared alternative algorithms of Xpert use suggested by WHO.

Interpretation

Our study is the first modelling study to investigate the potential effects on the patient, the health system, and the population for a range of tuberculosis diagnostic methods and algorithms. Our results provide a wish list for policy makers when deciding to deploy new diagnostics in a country. The engagement with partners from the Tanzania National TB and Leprosy Programme throughout the modelling study enabled the results to be communicated to and considered by the policy makers.

allows countries to make the best use of modelling to inform local decision making. As this type of approach is applied in additional settings we might learn more generalisable lessons about which alternatives do best in different settings.

The operational component of this study has enabled the detailed interactions and bottlenecks of the health system to be modelled, which helps to understand the effect of each option on staff use, the number of Xpert machines and microscopes, the level of diagnostic lost to follow-up, and the time to start treatment. This detailed approach will be of particular value for the prioritisation and rollout of new diagnostics to individual districts in Tanzania. Additionally, when combined with data collection from patients, the operational component would help to assess how the observed reductions in patient visits affect patient costs (how this analysis could be done is shown in the appendix).

The robustness of conclusions from this study is affected by the uncertainty of variables and assumptions on model structure. Data availability and accuracy can be a constraint with modelling. In this study some country-level input data and natural history variables had a high degree of uncertainty. We did a sensitivity analysis to explore the effect of this uncertainty on the estimated ICERs. Results of the sensitivity analysis suggest that the ranking of diagnostic options is robust to uncertainty in the input variables. We also note that a full health system

costing model was not constructed in this study; instead unit cost estimates were largely provided by experts from the national tuberculosis programme. A more detailed health system costing model could provide better information to estimate the ICERs and sustainability of different diagnostic options. One limitation of the study is that MDR tuberculosis was not explicitly considered in the transmission component in view of the low prevalence of MDR tuberculosis in patients with tuberculosis. Therefore, we assumed that the proportion of MDR tuberculosis in incident tuberculosis cases remained unchanged over the projection period. Our analysis might have underestimated the cost-effectiveness of Xpert because the use of Xpert could reduce the transmission of MDR tuberculosis. National policy makers should take account of other local infrastructural factors, such as availability of robust power supplies, when considering alternative diagnostic algorithms, because a modelling analysis cannot account for all the practical challenges that might arise from implementation of a new method such as Xpert. Additionally, to gain the benefits outlined in this study, strong project management, good supply chains, commitment from all staff, and adherence to revised diagnostic processes are all necessary. Lastly, there are technical limitations in doing real-time linkage of two models. In particular, linkage across both components has not been possible in the uncertainty analysis. Further research is necessary to fully integrate the two components on one single modelling platform.

We have investigated the effects of alternative diagnostic approaches on the patient, the health system, and the wider community. This study is the first of its kind to bring such comprehensive information to national policy makers and other interested stakeholders. An important next step is to undertake a policy transfer analysis to prospectively understand whether and how this new knowledge will be used to inform the actual decision-making process at the programme level. Meanwhile, as a way of validating the approach, the programme must monitor the key operational (level of empirical treatment, diagnostic lost to follow-up rate, and time from diagnosis to treatment) and epidemiological (incidence, prevalence, and mortality) indicators after the implementation of the selected diagnostic option.

Contributors

IL, HHL, MM, TC, and SBS designed the study. IL and HHL conducted data analysis and wrote the first draft of the Article. All authors reviewed and approved the final report.

Declaration of interests

We declare no competing interests.

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