Point of care Xpert MTB/RIF versus smear microscopy for tuberculosis diagnosis in southern African primary care clinics: a multicentre economic evaluation

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Summary

Background Rapid on-site diagnosis facilitates tuberculosis control. Performing Xpert MTB/RIF (Xpert) at point of care is feasible, even when performed by minimally trained health-care workers, and when compared with point-of-care smear microscopy, reduces time to diagnosis and pretreatment loss to follow-up. However, whether Xpert is cost-effective at point of care remains unclear.

Methods We empirically collected cost (US$, 2014) and clinical outcome data from participants presenting to primary health-care facilities in four African countries (South Africa, Zambia, Zimbabwe, and Tanzania) during the TB-NEAT trial. Costs were determined using an bottom-up ingredients approach. Effectiveness measures from the trial included number of cases diagnosed, initiated on treatment, and completing treatment. The primary outcome was the incremental cost-effectiveness of point-of-care Xpert relative to smear microscopy. The study was performed from the perspective of the health-care provider.

Findings Using data from 1502 patients, we calculated that the mean Xpert unit cost was lower when performed at a centralised laboratory (Lab Xpert) rather than at point of care ($23·00 [95% CI 22·12–23·88] *vs* $28·03 [26·19–29·87]). Per 1000 patients screened, and relative to smear microscopy, point-of-care Xpert cost an additional $35 529 (27 054–40 025) and was associated with an additional 24·3 treatment initiations ([–20·0 to 68·5]; $1464 per treatment), 63·4 same-day treatment initiations ([27·3–99·4]; $511 per same-day treatment), and 29·4 treatment completions ([–6·9 to 65·6]; $1211 per completion). Xpert costs were most sensitive to test volume, whereas incremental outcomes were most sensitive to the number of patients initiating and completing treatment. The probability of point-of-care Xpert being cost-effective was 90% at a willingness to pay of $3820 per treatment completion.

Interpretation In southern Africa, although point-of-care Xpert unit cost is higher than Lab Xpert, it is likely to offer good value for money relative to smear microscopy. With the current availability of point-of-care nucleic acid amplification platforms (eg, Xpert Edge), these data inform much needed investment and resource allocation strategies in tuberculosis endemic settings.

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Introduction

Early screening and diagnosis is a key component of tuberculosis control and underpins the post-2015 END TB Strategy aimed at substantially reducing the burden of disease.[1,2] The Xpert MTB/RIF (Xpert) assay is a rapid molecular-based test that has consistently shown its superior sensitivity over smear microscopy in diagnosing pulmonary,[3] extrapulmonary,[4] and paediatric tuberculosis.[5,6] As such, it has been endorsed by WHO[7] and is undergoing a large-scale global rollout.[8]

However, where Xpert should optimally be placed within national tuberculosis programmes (NTPs) remains unclear. Should Xpert, to exploit its portability and user-friendly format, be situated in centralised laboratories or within more peripheral clinics at point of care? WHO endorses implementation at centralised health facilities (district and subdistrict levels), but this implementation limits the potential benefits of Xpert as a rapid diagnostic tool. Indeed, later diagnosis and reporting of results, as a consequence of centralised placement, can delay clinical decisions and hence treatment initiation.[9,10] Moreover, up to 40% of patients in tuberculosis endemic areas contribute to pretreatment loss to follow-up (ie, they do not return to the clinic to start treatment after being informed of a positive result).[11–13] A large randomised controlled trial[14] showed that placing Xpert at point of care within primary care clinics was not only feasible, when performed by a minimally trained health-care worker, but significantly reduced pretreatment loss to follow-up. Given these considerations, a strategic and ideological drive has occurred to move to point-of-care diagnosis—as occurred with HIV, sexually transmitted diseases, and diabetes. Indeed, Xpert

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Research in context

Evidence before this study

We searched PubMed for all studies published between Jan 1, 2010, and Sept 1, 2018, using the search terms "tuberculosis" OR "(TB)" AND ("cost" OR "cost effectiveness") AND ("Xpert MTB/RIF" OR "GeneXpert"). Many studies investigated the cost-effectiveness of Xpert MTB/RIF (Xpert) for tuberculosis diagnosis in several contexts and settings using modelling approaches. Only one South African study estimated the cost-effectiveness of Xpert in a real-world context with the use of primary economic and clinical data. This study found that Xpert was cost neutral and did not improve the cost-effectiveness of routine tuberculosis diagnosis. However, no published studies assessed the cost-effectiveness of Xpert when performed at the point of care with prospectively collected clinical and cost-related data.

Added value of this study

This study used empirical cost data nested within a randomised controlled trial of point-of-care Xpert versus sputum smear microscopy in four African countries, suggesting that point-of-care Xpert is a cost-effective option for tuberculosis diagnosis in settings willing to pay at least US$3820 per additional patient with tuberculosis completing treatment. The volume of testing in each clinic was the most important determinant of cost and cost-effectiveness of the point-of-care Xpert strategy.

Implications of all the available evidence

Data on the cost-effectiveness of Xpert situated at a centralised laboratory remain discordant. However, the available evidence suggests that, in clinics where volume of testing is sufficiently high to offset implementation costs, point-of-care Xpert testing is likely to provide good value for money in high-burden settings in sub-Saharan Africa.

is already being used at the point of care in high burden clinics, mines, and prisons in countries such as Zimbabwe and South Africa.

Although deployment of Xpert at the point of care can deliver same-day diagnosis[14–16] and other benefits, as outlined, the associated diagnostic test and clinical infrastructure upgrade costs are not insignificant.[9,17,18] Thus, crucial questions for policy makers, and of prime importance to resource allocation planning, are (1) how does the cost of Xpert performed by a minimally trained nurse at point of care compare with when performed by a trained technician at a centralised laboratory; and (2) is point-of-care placement of Xpert cost-effective? Although multiple studies[17,19–26] have examined the economic implications of using Xpert in endemic settings, few have focused on the costs or cost-effectiveness when deployed at point of care,[22,25,26] and no studies have calculated cost-effectiveness using clinical outcome data obtained from a pragmatic real-world prospective study.[19–22,24,25] To address these questions, we analysed prospectively collected cost and clinical outcome data from a large randomised control parent trial that recruited patients from primary care clinics in four southern African countries (South Africa, Zambia, Zimbabwe, Tanzania).[14]

Methods

Clinical trial design

We used data obtained from the TB-NEAT trial,[14] which has been described in detail elsewhere. The trial was a randomised, two-group, parallel-group study of 1502 participants with presumptive tuberculosis recruited from periurban primary health-care clinics located in four southern African countries, including South Africa (Cape Town and Durban), Zimbabwe (Harare), Zambia (Lusaka), and Tanzania (Mbeya). Briefly, patients presenting at the clinics with symptoms suggestive of tuberculosis between April 12, 2011, and March 30, 2012, were recruited into the study and randomly assigned to either same-day smear microscopy (n=758; the smear microscopy group) or Xpert MTB/RIF performed at the point of care (n=744; the Xpert group). Specific inclusion and exclusion criteria for patient recruitment can be found in the TB-NEAT paper.[14] Two spot expectorated sputum samples were collected for the index test (smear microscopy or Xpert) and mycobacteria growth indicator tube liquid culture (BD Diagnostics, Sparks, MD USA). Smear microscopy was performed by a qualified technician in a laboratory linked to the clinic. In Cape Town, smear microscopy was done at a centralised laboratory close to the clinic in accordance with South African national diagnostic practices. Auramine fluorescence smear microscopy was instituted at all study sites except Tanzania, which instead used direct light microscopy with Ziehl-Neelsen staining. Xpert was done by a trained nurse (except in Zimbabwe where national policy required Xpert to be performed by a certified technician) using a four-module GeneXpert machine that was situated at each clinic specifically for the trial. An additional Xpert was performed on a stored sputum sample at a centralised laboratory (Lab Xpert) by a qualified technician, and liquid culture was performed at a reference laboratory at each study site. Patients were asked to wait until smear microscopy or Xpert results became available. If results were positive, patients were referred directly to the tuberculosis treatment office in the clinic. Patients with negative results were referred for routine clinical assessment and chest x-ray. Initiation of empirical treatment was decided by the attending clinician. Patients were subsequently followed up for 6 months after diagnosis.

	Test costs				Clinic costs		
	Smear microscopy	Xpert MTB/RIF at clinic (point-of-care Xpert)	Xpert MTB/RIF at centralised laboratory (Lab Xpert)	Chest x-ray	Tuberculosis screening	HIV testing and counselling	Treatment initiation
Mbeya, Tanzania							
Consumables	$1·24	$11·10	$11·10	$1·80	$0·00	$1·27	$0·00
Staff	$0·97	$0·75	$0·58	$0·66	$2·68	$3·56	$2·28
Equipment	$0·52	$22·59	$9·84	$2·34	$0·00	$0·00	$0·00
Quality control	$0·03	$0·22	<$0·01	$0·00	$0·00	$0·00	$0·00
Overhead	$0·20	$1·04	$0·31	$1·74	$0·08	$0·63	$3·10
Transport	$0·00	$0·00	$1·56	$0·00	$0·00	$0·00	$0·00
Total	$2·96	$35·70	$23·40	$6·54	$2·76	$5·46	$5·37
Lusaka, Zambia							
Consumables	$1·05	$11·03	$11·03	$0·00	$0·00	$0·74	$0·00
Staff	$0·33	$1·02	$0·57	$0·47	$4·91	$2·06	$1·81
Equipment	$0·35	$10·61	$9·78	$5·63	$0·00	$0·00	$0·00
Quality control	$0·05	$0·10	$0·02	$0·00	$0·00	$0·00	$0·00
Overhead	$0·12	$1·98	$0·16	$0·21	$0·36	$0·29	$0·24
Transport	$0·00	$0·00	$1·63	$0·00	$0·00	$0·00	$0·00
Total	$1·90	$24·74	$23·18	$6·31	$5·27	$3·08	$2·05
Harare, Zimbabwe							
Consumables	$1·29	$10·72	$10·31	..	$0·00	$1·19	$0·00
Staff	$0·31	$0·48	$0·51	..	$1·88	$1·32	$1·70
Equipment	$0·39	$18·97	$10·12	..	$0·00	$0·00	$0·00
Quality control	$0·35	$0·12	$0·16	..	$0·00	$0·00	$0·00
Overhead	$0·21	$0·65	$3·52	..	$0·48	$0·17	$2·59
Transport	$0·00	$0·00	$5·95	..	$0·00	$0·00	$0·00
Total	$2·55	$30·93	$30·59	$5·48*	$2·36	$2·68	$4·29
Cape Town, South Africa							
Consumables	..	$10·44	..	$1·03	$0·00	$1·39	$0·00
Staff	..	$1·68	..	$1·27	$1·42	$2·33	$4·95
Equipment	..	$13·51	..	$8·34	$0·00	$0·00	$0·00
Quality control	..	$0·33	..	$0·00	$0·00	$0·00	$0·00
Overhead	..	$1·28	..	$3·40	$1·37	$1·71	$3·12
Transport	..	$0·00	..	$0·00	$0·00	$0·00	$0·00
Total	$2·52†	$27·25	$17·91†	$14·04	$2·79	$5·43	$8·07
All							
Total (95% CI)‡	$2·39 (2·28–2·50)	$28·03 (26·19–29·87)	$23·00 (22·12–23·88)	$9·29 (7·94–10·64)	$3·34 (3·29–3·38)	$4·08 (3·98–4·18)	$5·32 (4·90–5·73)

Costs given in US$, 2014. *X-ray costs in Zimbabwe were taken from the literature[32] because empirical data collection was not possible. †The costs of smear microscopy and Xpert MTB/RIF performed at a centralised laboratory in South Africa were taken as the per-test charge from the National Health Laboratory Services because empirical data collection was not possible. ‡Weighted average of costs across all sites (95%CI), weighted by the number of patients screened at each site.

Table 1: **Component and total costs of diagnostic tests and clinic visits in four primary care clinics in southern Africa**

Economic evaluation overview

We used clinical and cost data empirically collected from each study site to compare the unit cost of point-of-care Xpert and Lab Xpert at different test volume capacities and to assess the cost-effectiveness of point-of-care Xpert compared with smear microscopy. We performed the economic analysis according to well established cost-effectiveness analysis guidelines.[27,28] A completed checklist of the essential components[27] required for doing an economic analysis is provided in the appendix.

Measures of cost

We calculated tuberculosis diagnosis and treatment costs from the health-care provider perspective in each trial country. We calculated the cost per test for smear microscopy, point-of-care Xpert, Lab Xpert, and chest x-ray. At the time of the study, South Africa was using Xpert for routine tuberculosis diagnosis within the NTP; we measured Lab Xpert costs at the remaining study sites (Zambia, Zimbabwe, and Tanzania) in the respective clinics, but after trial completion (within the context of other ongoing

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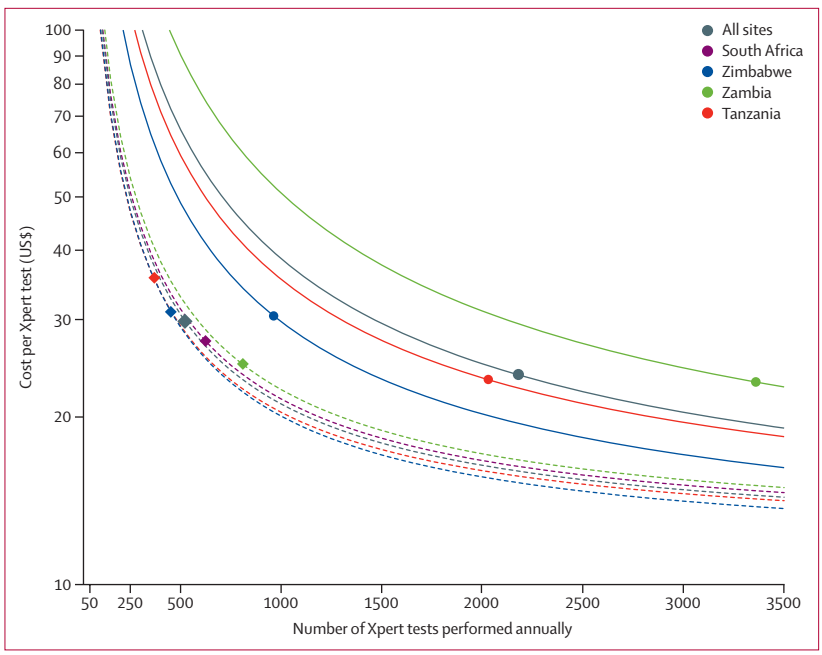

Figure 1: **Estimated unit cost per Xpert test**
Costs (US$, 2014) estimated according to annual test volume either at the clinic (point-of-care Xpert; dashed lines) or central laboratory (Xpert Lab; solid lines) for each individual study site. The overall weighted average of all sites is shown by the grey lines. The cost per Xpert test on the y-axis is expressed on a logarithmic scale. The observed annual number of Xpert tests done at the laboratory (circles) and at the clinic (diamond) in each of the four study sites are indicated. The Xpert Lab is not presented for South Africa as no empirical cost data were collected for this site. For individual and all sites, the observed annual testing frequency was greater at the laboratory compared with the clinic, resulting in a lower Xpert Lab unit cost. However, if the annual number of Xperts performed annually were the same for a given site, the unit cost of point-of-care Xpert would be less than Xpert Lab. Xpert=Xpert MTB/RIF.

studies). We also assessed the cost per clinic visit for tuberculosis screening, HIV testing, and counselling and tuberculosis treatment initiation. We estimated the weighted mean (weighted by volume of testing) for the cost per test and cost per clinic visit across all trial sites. We converted local costs to 2014 US$ at exchange rates of $1=R9·65 (South African rand), K5·35 (Zambia kwacha), or TSh1584·05 (Tanzanian shilling) according to Oanda historical exchange rates. At the time of the study, Zimbabwe had already adopted US$ as their national currency. We adjusted costs to the year of analysis as necessary using country-specific consumer price indices provided by The World Bank. We annualised capital costs (building, vehicles, and equipment) at a discount rate of 3%. We estimated expected lifeyears of buildings at 50 years, whereas the expected lifeyears of vehicles and equipment ranged from 3–10 years depending on their frequency of replacement as indicated by staff. Further details on costing methods can be found in the appendix.

For **Oanda historical exchange rates** see https://www.oanda.com/fx-for-business/historical-rates

For **World Bank consumer prices** see http://data.worldbank.org/indicator/FP.CPI.TOTL.ZG

Measures of effectiveness

We derived effectiveness measures from clinical outcomes reported in the TB-NEAT trial.[14] We reported outcomes for each individual trial site and subsequently combined for all sites. We only included participants with a valid culture result in the analysis. The measures of effectiveness calculated in each study group (smear microscopy and Xpert) included the number of culture-positive tuberculosis cases: (1) diagnosed by the index test, (2) initiating antituberculosis treatment, (3) initiating antituberculosis treatment on the same day as diagnosis, (4) completing antituberculosis treatment, and (5) having improved morbidity (measured by a numerical tuberculosis score). Completing antituberculosis treatment refers to patients who completed a full 6-month course of antituberculosis treatment and excluded those who were not treatment-adherent, who had died, or who were lost to follow-up (participants started on antituberculosis treatment who were not retained in the study). Improved morbidity refers to patients who started antituberculosis treatment and showed a 25% or more decrease in the well validated tuberculosis score at the end of treatment compared with baseline (see TB-NEAT[14] and Wejse and colleagues[29] for more details on tuberculosis score determination). The TB-NEAT trial was not powered to examine differences in mortality between the two groups. As such, this measure was not included in our analysis. We also reported effectiveness measures 1–5 as a proportion of all individuals clinically suspected of having tuberculosis based on symptom screening. Outcomes were normalised to 1000 people with suspected tuberculosis screened in each study group. Incremental effectiveness (per 1000 people with suspected tuberculosis screened) was also reported. We used incremental costs and outcomes to calculate the incremental cost-effectiveness ratio (ICER) for selected outcomes among culture-positive cases. Further details regarding assumptions used in the analysis can be found in the appendix.

Sensitivity analysis

We did univariate sensitivity analyses to calculate the effect of varying specific parameter inputs on the cost per test of point-of-care Xpert and the incremental cost per culture-positive patient starting treatment. We also did a probabilistic sensitivity analysis to calculate the uncertainty around ICERs given the challenges in estimating their confidence intervals.[30] This analysis involves simultaneously varying cost and effectiveness parameter inputs with the use of 10 000 randomly sampled estimates drawn from their defined probability distributions. We confirmed that 10 000 simulations would be sufficient for model convergence around the uncertainty using a previously published approach.[31] Briefly, we generated ICERs for each outcome using two separate sets of 10 000 randomly sampled estimates to ensure that the mean values of each set of simulations fell within the 95% CI range of the corresponding set (appendix). We also doubled the number of simulations from 10 000 to 20 000 to confirm the width of the 95% CIs were effectively unchanged (appendix). We calculated ICERs for each estimate and used them to construct a cost-effectiveness acceptability curve to establish the

probability that point-of-care Xpert would be considered cost-effective compared with smear microscopy over a range of willingness-to-pay thresholds.

Statistical analysis was done using GraphPad Prism version 6.0 and Microsoft Excel 2016.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or the writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The cost per Xpert assay performed at the clinic (ie, point-of-care Xpert) and at a centralised laboratory (ie, Lab Xpert) was calculated at each study site to allow for cost comparisons at different levels of programmatic implementation. Component costs included consumables, staff, equipment, overheads, quality control, and transport. Under observed conditions, the cost of point-of-care Xpert ranged from $24·74 in Zambia to $35·70 in Tanzania, whereas Lab Xpert costs ranged from $17·91 in South Africa to $30·59 in Zimbabwe (table 1). Across all sites, the weighted mean Lab Xpert unit cost was lower than for the point-of-care Xpert ($23·00 [95% CI 22·12–23·88] *vs* $28·03 [26·19–29·87]). Under observed conditions, Lab Xpert test volumes were 2–5 times higher than the point-of-care Xpert at any given testing facility. Point-of-care Xpert became less costly than Lab Xpert under the assumption that annual test volume estimates were equivalent (figure 1; appendix). Unit test and clinic costs, including the cost breakdown, are reported in table 1.

Figure 2A and 2B (appendix) show differences in clinical outcomes comparing point-of-care Xpert to smear microscopy, both among culture-positive patients and symptomatic patients. For example, when comparing point-of-care Xpert to smear microscopy, the difference in culture-confirmed tuberculosis cases starting antituberculosis treatment was 24·3 cases per 1000 people screened (95% CI –20·0 to 68·5) and in those completing antituberculosis treatment was 29·4 cases per 1000 people screened (–6·9 to 65·6). In terms of incremental costs, point-of-care Xpert was more expensive than smear microscopy, with costs ranging from $28 503 per 1000 people screened in Zimbabwe to $53 280 in Tanzania. Across all study sites, the incremental cost amounted to $35 528 per 1000 people screened (27 053–40 024) and was strongly associated with the unit cost of point-of-care Xpert (figure 2C).

The cost-effectiveness of point-of-care Xpert for the individual and combined study sites is reported as the incremental cost per selected outcome among culture positive tuberculosis cases (table 2). Cost-effectiveness estimates varied widely across study sites, with cost per treatment initiation ranging from $984 in South Africa to $2699 in Zambia (weighted mean of $1464 per treatment initiation) and cost per treatment completion ranging from $465 per treatment completed in Zambia to $8485 in South Africa (weighted mean $1211 per treatment completed). We also compared our cost-effectiveness estimates to other estimates of tuberculosis interventional strategies, in terms of disability-adjusted life-years (DALYs) averted,

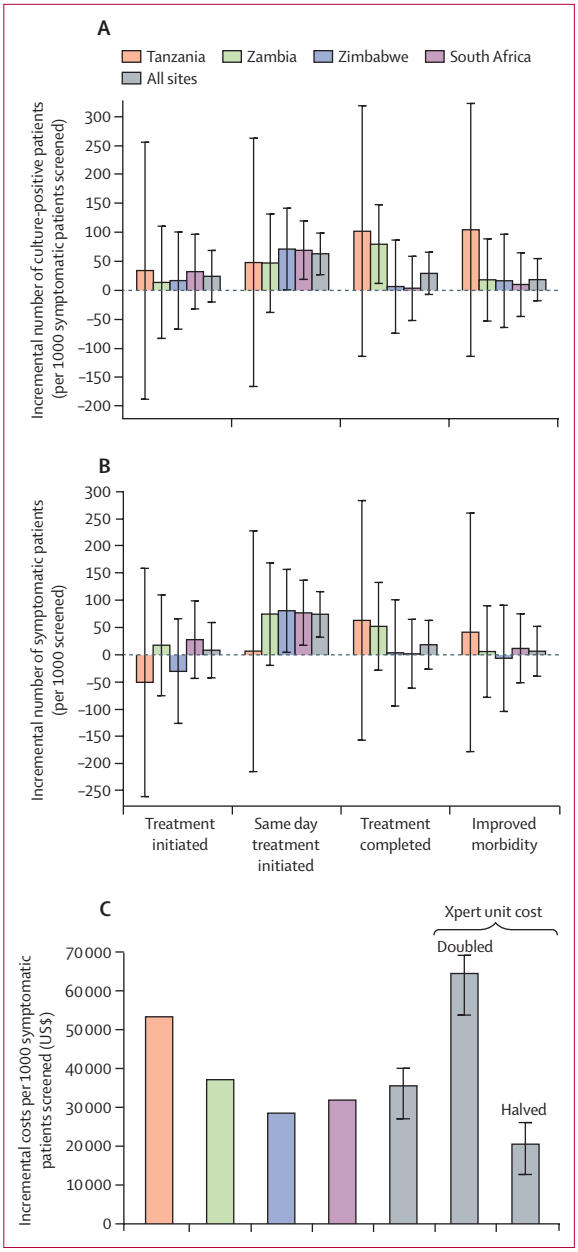

Figure 2: **Differences in clinical outcomes comparing point-of-care Xpert to smear microscopy in culture-positive patients and symptomatic patients**
Error bars indicate 95% CIs. All outcomes and costs are normalised to 1000 patients in each study group. (A) The estimated incremental outcomes for patients ultimately found to have culture-confirmed tuberculosis. (B) Corresponding outcomes in all patients. (C) The estimated incremental costs (US$, 2014); estimates are shown under the assumption that the unit cost of Xpert at all sites can be doubled or halved. Xpert=Xpert MTB/RIF.

	Tanzania	Zambia	Zimbabwe	South Africa	All sites*
Diagnosed by index test	$4254	Point-of-care Xpert†	$1675	$1373	$4186
Starting treatment	$1554	$2699	$1685	$984	$1464
Starting treatment on same day as diagnosis	$1107	$785	$399	$46	$561
Completing treatment	$521	$465	$4309	$8485	$1211
Improved morbidity	$508	$2024	$1710	$3101	$1918

Costs are in $US, 2014. *Weighted average of costs and outcomes across all sites, weighted by the number of patients screened and number of clinical outcomes observed at each site. †Indicates that point-of-care Xpert was both more expensive and less effective than smear microscopy for that particular clinical outcome.

Table 2: **Incremental cost-effectiveness ratios, defined as the incremental cost per selected clinical outcome among culture positive cases**

from the published literature (appendix).[24,33,34] In this comparison, our baseline cost-effectiveness estimates, in most cases, decreased to less than 3 times the gross domestic product (GDP) per capita per DALY averted in each country.

In one-way sensitivity analysis, the expected useful life, purchase price, and annual test volume of the Gene Xpert machine had the greatest influence on the point-of-care Xpert unit cost (figure 3A). A similar pattern was observed on the incremental cost per treatment initiation and treatment completion among culture-positive patients. However, the largest influence on cost per treatment initiation was the proportion of culture-positive patients starting treatment. In the point-of-care Xpert group of the trial,

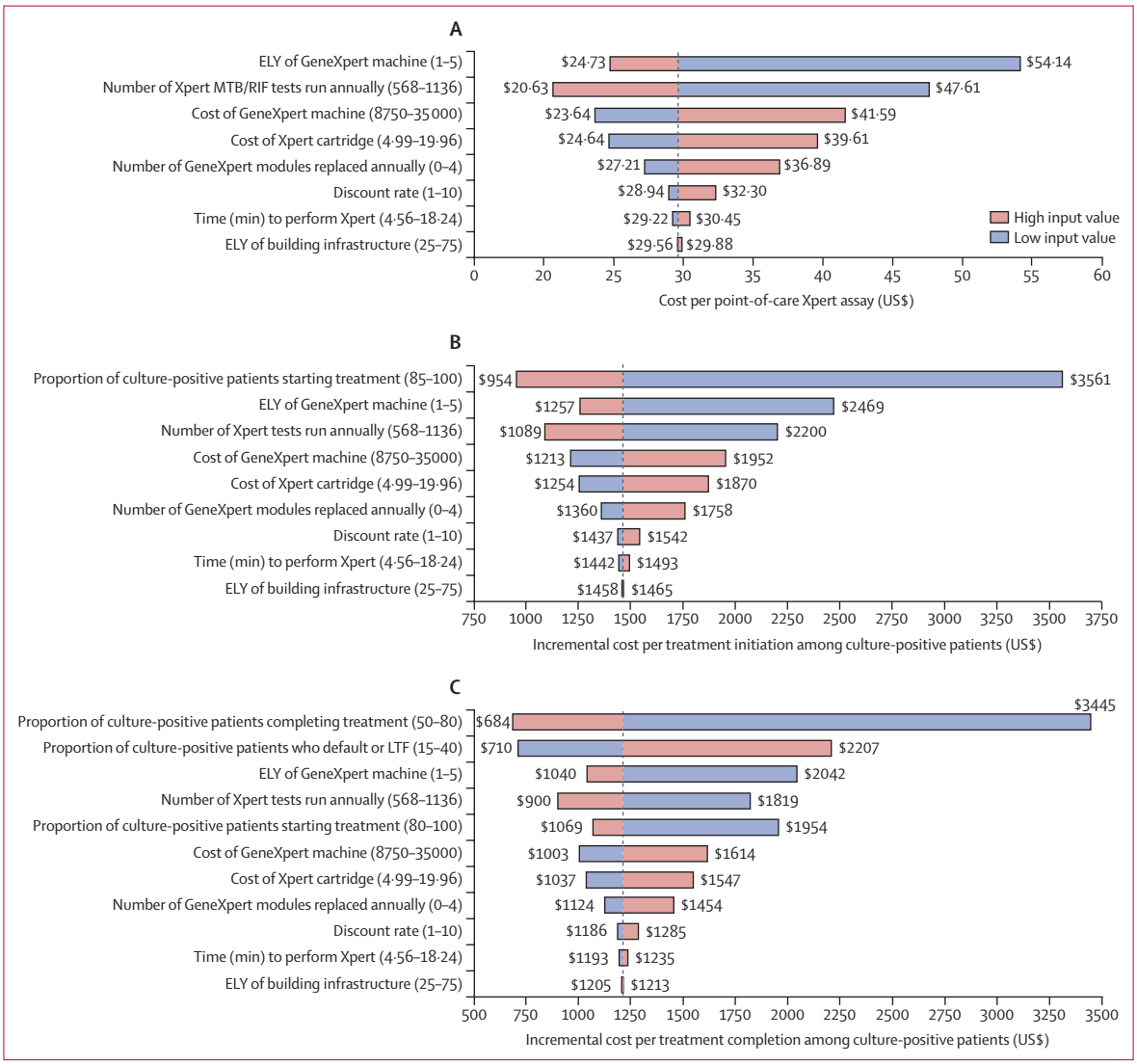

Figure 3: **Univariate sensitivity analysis**

Tornado diagrams showing the effect of changing individual cost parameters on the cost (US$, 2014) per Xpert assay performed at the point of care (A), the incremental cost per treatment initiation (B), and the incremental cost per treatment completion among culture-positive patients across all sites (C). Low and high estimates of each input parameter are shown in parentheses on the left side of each figure. ELY=expected life years. LTF=lost to follow up. Xpert=Xpert MTB/RIF.

91% of culture-positive patients started treatment. If this proportion fell to 85%, then the estimated incremental cost per treatment initiation increased from $1464 to $3561 (figure 3B). Similarly, reducing the proportion of culture-positive patients completing treatment from 60% to 50% increased the estimated cost per treatment completion from $1211 to $3445. A similar pattern was also observed if the number of patients who were lost to follow-up was varied (figure 3C).

Figure 4 shows the willingness-to-pay thresholds at which point-of-care Xpert would be preferred over smear microscopy across 10 000 probabilistic simulations. Assuming that a 90% probability of cost-effectiveness might make an effective decision threshold, point-of-care Xpert would be preferred at this threshold in settings willing to pay $9450 per culture positive patient diagnosed, $4450 per patient starting treatment, $1600 per patient starting treatment on the same day as diagnosis, $3820 per patient completing treatment, or $5840 per patient with improved morbidity. Willingness-to-pay thresholds at other cost-effectiveness probability estimates are shown in the appendix.

Discussion

The primary findings of this economic evaluation, nested within a clinical trial across four Southern African countries, is that point-of-care Xpert, while more costly than smear microscopy, is likely to be cost-effective (in >90% of simulations) in settings willing to pay at least $4500 per treatment initiation or $3800 per treatment completion among culture-positive patients. High test volume capacity at primary care clinics is probably necessary for Xpert point-of-care placement to be economically feasible in many settings.

Few studies have estimated the economic effect of implementing Xpert at the point of care[22,25,26] and all have used modelling analyses rather than prospectively obtained trial data to assess cost-effectiveness.[19,20,24,25,35] In most of these modelling studies, Xpert was cost-effective either as a full replacement[19,24,25,35] or in conjunction with other diagnostic tests[20,21] compared with the standard of care (smear-microscopy). However, some of these studies did not incorporate empirical treatment and thus might have overestimated the effectiveness of Xpert.[24,25] Our estimates of cost-effectiveness account for levels of empirical treatment observed in the TB-NEAT trial and require fewer modelling assumptions than these previous analyses but might, therefore, underestimate the effectiveness of point-of-care Xpert by not explicitly accounting for effects on secondary transmission. Conversely, clinical trials can provide direct and real-world data on patient important outcomes related to Xpert implementation. For example, the XTEND trial[15] assessed the effect of Xpert relative to smear microscopy on patient morbidity and mortality when placed at central laboratories within the context of the South Africa national Xpert rollout. Similar to TB-NEAT, no significant differences were observed in terms of patient morbidity or mortality. A subsequent follow-up cost-effectiveness analysis showed that the South African Xpert rollout was cost neutral and failed to improve the cost-effectiveness of tuberculosis diagnosis, probably due to the trial finding no benefits to mortality.[23] Conversely, in our study we used clinical endpoints from the TB-NEAT trial rather than mortality or health utility (eg, DALYs as more direct measures of effectiveness). We estimated that, relative to smear microscopy, point-of-care Xpert is likely to cost $1464 per treatment initiation and $1211 per treatment completion among patients with culture-confirmed tuberculosis.

In deciding whether point-of-care Xpert would be cost-effective, there is no consensus on appropriate

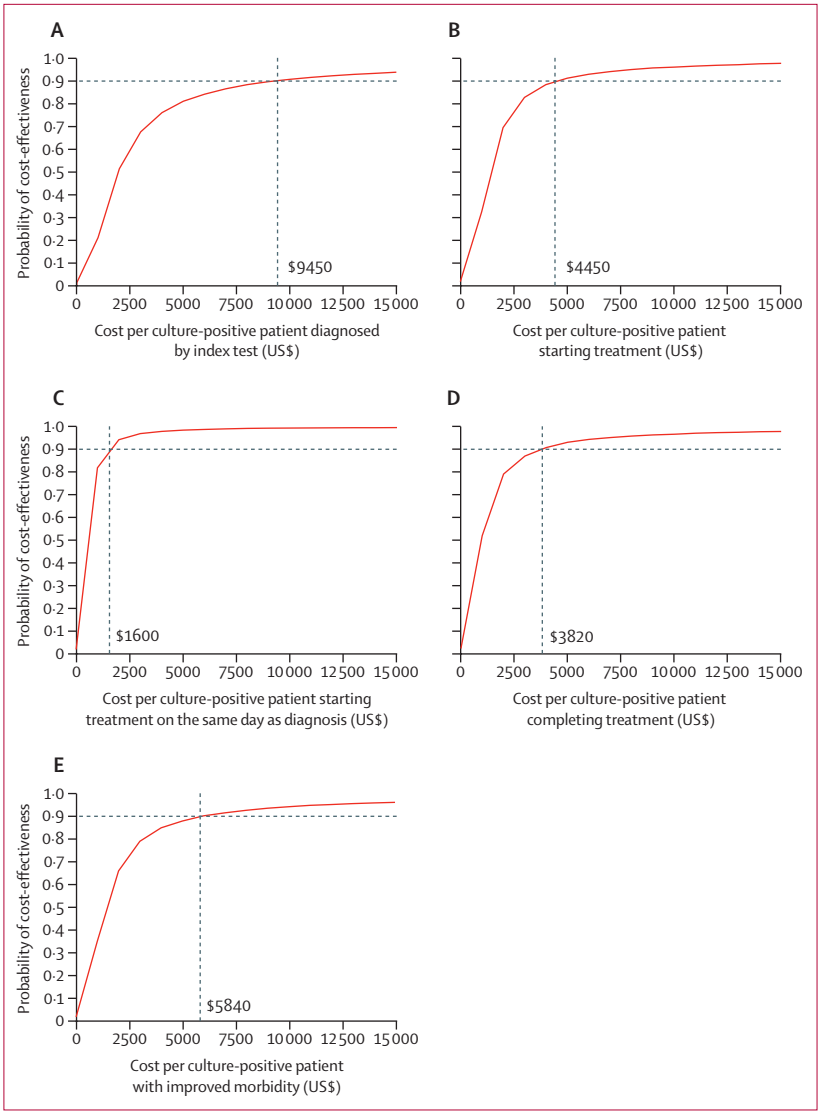

Figure 4: **Cost-effectiveness acceptability curves for selected incremental cost-effectiveness ratios**
The probability of point-of-care Xpert, relative to smear microscopy, being cost-effective was plotted as a function of willingness to pay per culture-positive patient diagnosed by the index test (A), starting treatment (B), starting treatment on same day as diagnosis (C), completing treatment (D), and experiencing improved morbidity for all sites combined (E). The arrow indicates the willingness-to-pay threshold, at which the probability of cost-effectiveness is 90%. Xpert=Xpert MTB/RIF.

willingness-to-pay thresholds, and the use of generic thresholds have been largely criticised.[36–38] Cost-effectiveness thresholds provide no information on affordability and do not have the disease-specific context in which scale-up of point-of-care Xpert could have major implications on resource allocation within the NTP. Nonetheless, a commonly used metric for highly cost-effective interventions is the per-capita GDP (or gross national income) per DALY averted (or 3 times this value for cost-effective interventions). To keep our analysis faithful to trial-measured outcomes (with a minimum of modelling assumptions), we did not measure outcomes in terms of DALYs averted. However, we did compare our results to those of other model-based economic evaluations from which a ratio could be calculated of clinical outcomes (as calculated in this study) to DALYs averted (appendix).[24,33,34] Our estimates in these comparisons were substantially less favourable toward point-of-care Xpert (eg, incremental cost-effectiveness ratio 10 times higher than reported by Vassall and colleagues),[24] probably because our estimates incorporate the levels of empirical treatment observed in the TB-NEAT trial. Nevertheless, our estimates of point-of-care Xpert cost-effectiveness in most cases come below a threshold of 3 times per-capita GDP per DALY averted, suggesting cost-effectiveness of this intervention according to this classical willingness-to-pay threshold. These results do not speak to the affordability of point-of-care Xpert under existing budget constraints, but they do suggest that the cost-effectiveness of point-of-care Xpert is likely to be at least equivalent to that of many other interventions that have been characterised as cost-effective in the scientific literature up to now.

Another useful metric to assess cost-effectiveness and willingness to pay is the potential health gains if provided with a fixed monetary sum. For example, if an additional $10 000 was provided to the NTP for the Xpert point-of-care strategy, the expected gains over smear microscopy would be an additional four tuberculosis cases diagnosed, 12 cases starting treatment, 30 cases starting same-day treatment, and 14 cases completing treatment (appendix). Thus, policy makers can directly compare these values to other tuberculosis diagnostic strategies to assess the relative expected value of investment in point-of-care Xpert.

The TB-NEAT trial showed an increase in the number of Xpert-positive culture-negative individuals that were placed on treatment. Conversely, a Brazilian study[35] showed a reduction in these Xpert false positives (with culture as a gold standard) compared with smear microscopy. Such discrepancies between Xpert and culture could represent false-negative culture results but might also reflect false-positive Xpert results due to residual *Mycobacterium tuberculosis* DNA, particularly in people previously (and successfully) treated for tuberculosis.[39] If some of these individuals who start treatment do indeed represent Xpert false-positives, it will be important to establish the extent of such Xpert-based overtreatment in various settings because the cost of such overtreatment ($113 per patient in our analysis) is not inconsequential.

The TB-NEAT study also showed much higher smear microscopy-based empirical treatment decisions compared with Xpert and probably explains why no incremental morbidity benefit was observed in the trial. To the extent that such empirical diagnoses represent people without underlying tuberculosis, the true cost-effectiveness of point-of-care Xpert might be even more favourable than reported here.

This study also speaks to the cost implications of placing Xpert at the point of care versus a centralised facility. In our analysis, test capacity was a major influence driving the unit cost of Xpert. However, despite annual test volumes being 2–5 times higher when Xpert was positioned in the laboratory, point-of-care Xpert was only slightly more expensive on a per-test basis in some settings due to reductions in sample transport and overhead costs (table 1). Additionally, the variation in Lab Xpert test costs across study settings reflects the different laboratory setups at each site. For example, more GeneXpert machines were in use at the centralised laboratory in Zambia accounting for the higher Lab Xpert costs at that site.

In most countries, Xpert has been positioned at subdistrict level laboratories within the NTP rather than at the peripheral level, probably due to the financial and logistical limitations of point-of-care placement. A 2011 South African study[17] projected that national implementation of Xpert at the point of care would cost 51% more than lab placement, equivalent to an estimated $36 million per year. This cost represents a major hurdle to point-of-care placement, especially in other high burden countries where NTP budgets are under severe financial constraints.[40] However, these costs should be interpreted within the overall context of the economic effect of tuberculosis; one report[41] estimated that, over the next 15 years, economic losses due to tuberculosis would amount to about $300 billion in the African region (equating to about 2–3% of the GDP in the case of some African countries, including South Africa) and close to $1 trillion globally. The cost implications on patients can also be substantial, especially in low-income countries where tuberculosis disease can consume close to 60% of an individual's income.[42] Additional concerns of point-of-care placement include the need for a stable electricity supply, temperature control, and adequate storage facilities.[9,18] However, placement of Xpert at centralised facilities diminishes its potential to improve patient outcomes.[9] One potential solution might involve targeting point-of-care Xpert placement at specific primary care facilities where cost and health benefits can be maximised. For example, point-of-care implementation of Xpert might first be prioritised to clinics (1) in tuberculosis hotspots—ie, periurban slums where the disease burden is high, (2) where transportation of samples to central laboratory facilities is difficult and delays in result

reporting are common, (3) where empirical treatment initiation is uncommon, and (4) where the incidence of drug resistance and rates of loss to follow up are high. Any implementation strategy will need to be assessed in the context of newer Xpert technologies, such as the more point-of-care-friendly Xpert Edge instrument (recently released and uses the more sensitive Xpert Ultra cartridge),[43] and point-of-care molecular platforms in development (eg, QuantuMDx. etc).[44]

Our study had several limitations. First, we did not account for rifampicin (RIF) resistance detection, a major advantage of Xpert, in our analysis. The parent trial was not powered for detection of drug resistance, and the additional effectiveness gained by RIF resistance detection is not directly comparable to smear microscopy without incorporating another method of drug resistance testing, such as line probe assay, which was not performed in the study. Incorporation of RIF resistance detection might make Xpert more cost-effective by reducing the time to treatment in positive cases but might also favour smear microscopy because of the possibility for false-positive diagnosis of RIF resistance by Xpert. Second, our results are difficult to directly compare with those that used single utility metrics, such as DALYs. However, we chose to compare costs using hard data and real-world clinical outcomes (obtained from several settings) rather than to estimate a measure (eg, DALYs), which requires extensive assumptions about the downstream consequences of a diverse array of clinical outcomes based on sparse data. We also did not attempt to estimate effects on secondary transmission for similar reasons; thus, our findings, like for resistance detection, might be biased against point-of-care Xpert, which significantly shortened time to diagnosis in the trial. Third, economic evaluation within the context of a clinical trial has inherent limitations. Although able to provide direct data in specific settings compared with modelling, resource use and patient recruitment is often restricted to the selection criteria of the trial protocol.[45] However, TB-NEAT was designed with pragmatic implementation in mind, which might mitigate this concern to some degree, and empirical cost data was collected in a standardised way from multiple high-burden settings, which might not have been possible outside the context of a clinical trial. The cost of Lab Xpert used in our analysis (figure 1) was taken from the National Health Laboratory Service (NHLS) in South Africa but might be lower than if estimated with the use of empirically collected cost data.[46] The NHLS Lab Xpert cost estimate was chosen because it represents the cost charged to the South African government and thus represents the actual cost incurred from the health-care provider perspective. Several other studies[47–49] have used this estimate for similar reasons. Finally, some limitations were also related to measurement uncertainty of costs and outcomes. The large differences in incremental cost-effectiveness observed between the different study sites was primarily driven by differences in effectiveness measures. However, these differences should be interpreted with caution because of the low recruitment number at any given site (eg, wide 95% CIs were reported for patient outcomes in Tanzania) and that the TB-NEAT clinical trial was not powered to detect differences across the various study site.

In summary, we have estimated the cost-effectiveness of implementing Xpert at the point of care in four different African settings. Overall, our results indicate that a point-of-care-based Xpert can offer good value for money relative to other tuberculosis diagnostic strategies, though the cost-effectiveness of this strategy is likely to be even higher given that transmission reduction and drug resistance detection were not factored into the analysis. These findings will facilitate decision making about public health strategy and resource allocation by NTPs so that cost savings and health benefits can be maximised.

Contributors

APo, GT, LZ, DC, PC, HS, MH, APy, JP, KD, and DD conceived and designed the study. APo, GT, LZ, DC, PC, HS, MH, APy, JP, KD, and DD implemented the study. APo, LZ, DC, PC, LM, FM, PL, and JM collected economic data. APo, GT, HS, and DD analysed the data. All authors interpretated the data and gave important intellectual input. APo, GT, KD, and DD wrote the first draft of the manuscript and all authors provided input on the initial and subsequent drafts of the manuscript.

Declaration of interests

We declare no competing interests.

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