Title

Multicomponent strategy with decentralised molecular testing for tuberculosis in Uganda: a cost and cost-effectiveness analysis

Journal

The Lancet Global Health, 11(2)

ISSN

2572-116X

Authors

Thompson, Ryan R
Nalugwa, Talemwa
Oyuku, Denis
et al.

Publication Date

2023-02-01

DOI

10.1016/s2214-109x(22)00509-5

Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Multicomponent strategy with decentralised molecular testing for tuberculosis in Uganda: a cost and cost-effectiveness analysis

Ryan R Thompson, Talemwa Nalugwa*, Denis Oyuku, Austin Tucker, Mariam Nantale, Annet Nakaweesa, Johnson Musinguzi, Tania F Reza, Alexandra J Zimmer, Olivia Ferguson, Stavia Turyahabwe, Moses Joloba, Adithya Cattamanchi, Achilles Katamba, David W Dowdy†, Hojoon Sohn†*

Summary

Background Decentralised molecular testing for tuberculosis could reduce missed diagnoses and losses to follow-up in high-burden settings. The aim of this study was to evaluate the cost and cost-effectiveness of the Xpert Performance Evaluation for Linkage to Tuberculosis Care (XPEL-TB) study strategy, a multicomponent strategy including decentralised molecular testing for tuberculosis, in Uganda.

Methods We conducted a costing and cost-effectiveness analysis nested in a pragmatic cluster-randomised trial of onsite (decentralised) versus hub-and-spoke (centralised) testing for tuberculosis with Xpert MTB/RIF Ultra (Xpert) in 20 community health centres in Uganda. We collected empirical data on the cost of the XPEL-TB strategy (decentralised Xpert testing, workflow redesign, and performance feedback) and routine tuberculosis testing (onsite smear microscopy with specimen transport for centralised Xpert testing) from the health system perspective. Time-and-motion studies were performed to estimate activity-based service costs. Cost-effectiveness was assessed as the incremental cost (2019 US$) per tuberculosis diagnosis and per 14-day treatment initiation.

Findings The XPEL-TB study ran from Oct 22, 2018, to March 1, 2020. Effectiveness and cost-effectiveness outcomes were assessed from Dec 1, 2018, to Nov 30, 2019 and included 4867 women and 3139 men. On a per-test basis, the cost of decentralised ($20·46, range $17·85–25·72) and centralised ($18·20, range $16·58–24·25) Xpert testing was similar. However, decentralised testing resulted in more patients receiving appropriate Xpert testing, so the per-patient cost of decentralised testing was higher: $20·28 (range $17·68–25·48) versus $9·59 (range $7·62–14·34). The XPEL-TB strategy was estimated to cost $1332 (95% uncertainty range $763–5558) per incremental tuberculosis diagnosis and $687 ($501–1207) per incremental patient initiating tuberculosis treatment within 14 days. Cost-effectiveness was reduced in sites performing fewer than 150–250 tests annually.

Interpretation The XPEL-TB strategy facilitated higher rates of Xpert testing for tuberculosis at a similar per-test cost and modest incremental cost per tuberculosis diagnosis and treatment initiation. Decentralised Xpert testing, with appropriate implementation supports, should be scaled up to clinics with sufficient testing volume to support a single-module device.

Funding The National Heart, Lung, and Blood Institute.

Lancet Glob Health 2023; 11: e278–86

See **Comment** page e185

*Co-first authors, contributed equally

†Co-senior authors, contributed equally

Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA (R R Thompson MSPH, O Ferguson MSc, Prof D W Dowdy MD); **Uganda Tuberculosis Implementation Research Consortium, Kampala, Uganda** (T Nalugwa MBA, D Oyuku PGDME, M Nantale BBLT, A Nakaweesa BHRM, J Musinguzi BA, S Turyahabwe MPH, Prof A Cattamanchi MD, A Katamba PhD, Prof D W Dowdy); **Department of Global Health and Population, Harvard T H Chan School of Public Health, Boston, MA, USA** (A Tucker MHS); **Division of Pulmonary and Critical Care Medicine and Center for Tuberculosis, San Francisco General Hospital, University of California San Francisco, San Francisco, CA, USA** (T F Reza MPP, Prof A Cattamanchi); **McGill International Tuberculosis Centre** (A J Zimmer MSPH) **and Department of Epidemiology, Biostatistics and Occupational Health** (A J Zimmer), **McGill University, Montreal, QC, Canada; National Tuberculosis and Leprosy Program, Uganda Ministry of Health, Kampala, Uganda** (S Turyahabwe, Prof M Joloba PhD); **School of Biomedical Sciences, Makerere University College of Health Sciences, Kampala, Uganda** (Prof M Joloba); **Partnerships for Research in Implementation Science for Equity Center, University of California**

Introduction

Tuberculosis caused an estimated 1·6 million deaths in 2021, making it one of the top ten causes of death globally.[1] Gaps in the cascade of tuberculosis diagnosis, including failure to order appropriate diagnostic testing and loss to follow-up while awaiting test results, are major contributors to tuberculosis burden, mortality, and ongoing transmission.[2,3]

Molecular testing—eg, with Xpert MTB/RIF Ultra (Xpert; Cepheid, Sunnyvale, CA, USA)—is globally recommended as the standard of care for tuberculosis diagnosis.[4] Nevertheless, in many high-burden settings, onsite tuberculosis testing in peripheral health centres, if performed at all, is limited to sputum smear microscopy (SSM). To provide access to molecular testing, most high-burden countries have adopted a hub-and-spoke model with onsite sputum collection (and sometimes SSM) and remote Xpert testing at larger centralised facilities.[5] Sputum samples are transported using a specimen transport network to central testing facilities, with results transmitted back to peripheral sites for clinical action—often resulting in delays of many weeks from presentation to treatment initiation.[6,7]

Providing onsite (decentralised) molecular testing has the potential to close gaps in the tuberculosis diagnostic care cascade.[5,8] Until recently, however, this strategy was largely infeasible owing to the scarcity of inexpensive, durable, and battery-powered molecular testing platforms.[9–12] With the development of new platforms, such as the GeneXpert Edge system (Cepheid, Sunnyvale, CA,

San Francisco, San Francisco, CA, USA (Prof A Cattamanchi); **Clinical Epidemiology & Biostatistics Unit, Department of Medicine, Makerere University College of Health Sciences, Kampala, Uganda** (A Katamba); **Department of Preventive Medicine, College of Medicine, Seoul National University, Seoul, South Korea** (H Sohn PhD)

Correspondence to: Prof Hojoon Sohn, Seoul National University College of Medicine, Seoul 03080, South Korea
hsohn@snu.ac.kr

Research in context

Evidence before this study

We searched for studies published in PubMed between Jan 1, 2010, and Oct 31, 2022, using the search terms ("TB" OR "tuberculosis") AND ("Cost" OR "Cost-Effectiveness" OR "Economic") AND ("Xpert" OR "GeneXpert") AND "Decentralised Testing". We found three papers that described the cost-effectiveness of decentralised molecular testing for tuberculosis, although only one used empirical results from a high-burden setting. Few studies have compared the cost and cost-effectiveness of molecular testing for tuberculosis when performed onsite in peripheral clinics versus in centralised laboratories. The Xpert Performance Evaluation for Linkage to Tuberculosis Care (XPEL-TB) trial found that a multicomponent intervention—including decentralised molecular tuberculosis testing, clinic workflow redesign, and performance feedback—increased the number of individuals diagnosed with and treated for tuberculosis. The costs and cost-effectiveness of this strategy remain uncertain.

Added value of this study

In XPEL-TB, a highly pragmatic cluster-randomised trial, the cost of molecular testing for tuberculosis was modestly higher when performed in decentralised way. Cost-effectiveness of the multicomponent intervention (including decentralised molecular testing) was similar to that of other interventions for tuberculosis that have been scaled up, and was sensitive to annual testing volumes in clinics performing decentralised testing. The multicomponent strategy with decentralised molecular testing was less cost-effective in sites that performed fewer than 150–250 tests for tuberculosis per year.

Implications of all the available evidence

As part of a multicomponent strategy, decentralised molecular testing for tuberculosis results in more patients receiving appropriate testing, with only a modest increase in per-test costs and at a reasonable incremental cost per patient diagnosed with or treated for tuberculosis. As such, this strategy should be considered for broader scale-up in health facilities that perform 150–250 tests (or more) for tuberculosis per year.

USA), decentralised molecular testing is now a feasible reality for most high-burden countries.[10–12] However, this strategy's cost-effectiveness has not been well documented using empirical data, an important consideration for decision makers charged with allocating scarce resources. The Xpert Performance Evaluation for Linkage to Tuberculosis Care (XPEL-TB) trial in Uganda[13] showed that, relative to centralised testing, the XPEL-TB strategy—a multicomponent strategy focused around decentralised molecular testing—improved case detection and treatment initiation.[14] As part of the XPEL-TB study, we collected empirical economic data in the context of the trial to evaluate the cost and cost-effectiveness of the XPEL-TB strategy versus routine tuberculosis testing (onsite SSM plus centralised Xpert testing using a hub-and-spoke model).

Methods

Study design and participants

XPEL-TB was a highly pragmatic, cluster-randomised, hybrid implementation-effectiveness trial conducted from Oct 22, 2018, to March 1, 2020, at 20 peripheral health centres within 150 km of Kampala, Uganda. XPEL-TB assessed whether providing decentralised point-of-care molecular testing using the GeneXpert Edge platform, in conjunction with streamlined clinical workflows and performance feedback via monthly report cards, would increase the number of people diagnosed with tuberculosis and reduce pre-treatment loss to follow-up, compared with routine care.[13,14] Ten health centres were randomised to receive this package, and had GeneXpert Edge systems installed onsite. The remaining ten centres were randomised to routine care, with SSM performed onsite and molecular Xpert testing performed at an off-site facility in accordance with national guidelines. The protocol and trial results have been published previously.[13,14]

The study was approved by institutional review boards at the University of California, San Francisco, CA, USA (protocol 17–21505), Makerere University, Kampala, Uganda (protocol 595), and by the Uganda National Council for Science and Technology (protocol HS 2437). All health centre staff who participated in time-and-motion studies provided written informed consent. The primary trial was performed under a waiver of informed consent for extraction of participant data.[13,14]

Procedures

We estimated the costs of the multicomponent intervention—consisting of onsite molecular testing, streamlining workflow for tuberculosis diagnosis and treatment, and performance feedback—from the health system perspective. At four of the ten health centres randomised to receive this decentralised testing package, we collected empirical cost data on all clinical and laboratory testing processes. We also collected costs of SSM at five control health centres and specimen transport at two centralised testing facilities that received samples from control health centres. The cost of Xpert testing itself at the central facilities was taken from a previous study that our team performed in the same area,[15] adjusted for inflation and service volume.

To collect clinic-level cost data on overhead, building expenses, staff salaries, physical space, and operating costs, we adapted a standardised tuberculosis costing tool.[16,17] Sources of estimates included health centre budgets, interviews with key personnel, and staff rosters. Building and overhead data were not available at one intervention site, so mean cost at the other intervention sites was used as a proxy. Equipment (capital assets) and supply (consumable) purchases were prospectively tracked by the research team using procurement logs. Costs were based on purchase price paid and included shipping and customs, when applicable. Implementation costs and activities were tracked centrally and at all ten intervention sites and were categorised into design, initiation, and maintenance costs.[18] For health centres continuing routine (hub-and-spoke) testing, we included estimates for the cost of onsite SSM (in accordance with Ugandan guidelines)[14] and specimen transport to central facilities; these estimates have been published previously.[7] The appendix (p 3) contains detailed costing methods.

An ingredients-based, bottom-up approach was used for the cost analysis. Cost data were collected at the four selected decentralised Xpert testing sites between July 1, 2019, and Feb 28, 2020, approximately 1 year after testing infrastructure was established. We used a health system perspective and assumed implementation over a 5-year time horizon. Research-related costs were excluded. Resource-use data were categorised into implementation, overhead, building, staff, equipment, transportation, and supplies. Costs of developing the clinic streamlining and performance feedback mechanisms were included as implementation costs for decentralised testing and allocated on a per-test basis. All costs were inflated to 2019 prices based on the gross domestic product (GDP) deflator for Uganda and were converted from Ugandan shillings (UGX) to US$ at the median 2019 World Bank conversion rate (1 US$=3704 UGX).[19,20] For capital assets (eg, GeneXpert equipment), costs were annuitised and depreciated linearly based on expected life-years at a 3% annual discount rate.

We measured the effectiveness for all clinical outcomes assessed in the XPEL-TB trial[13,14] using patient records: number of individuals presenting for tuberculosis diagnostic care, number of individuals receiving Xpert or SSM testing, number of individuals with microbiologically confirmed tuberculosis, and number of individuals treated for tuberculosis within 14 days of presenting for care. Effectiveness and cost-effectiveness outcomes were assessed during a 1-year period from Dec 1, 2018, to Nov 30, 2019. Sex was self-reported by participants as male or female.

Time-and-motion studies provide insight to human-resource needs and costs to provide health services.[21] We conducted time-and-motion studies to estimate the amount of time spent by health workers in tuberculosis diagnostic activities at intervention health centres. Study data were collected through direct observation of consenting health workers from July 9 to Aug 15, 2019, and from Jan 28 to Feb 21, 2020, corresponding with planned visits to study sites. Observers recorded the time health workers spent on nine predefined activities, the number of patients involved (or samples processed) per activity, whether the activity was related to tuberculosis or not, and the locations where each activity was performed. Time-and-motion study data were combined with calculated estimates of the per-minute cost of staff, building, and overhead expenses to estimate the per-patient costs for each activity.[22]

Data on annual patient volumes between Dec 1, 2018, and Nov 30, 2019 were extracted from the Ugandan National Health Management Information System. The number of patients who received tuberculosis diagnostic testing was taken from laboratory records, and GeneXpert machine data were used to estimate the number of tests performed annually. For the routine care (centralised) arm, we used total annual Xpert testing volumes observed at the centralised testing hub (ie, not restricted to health centres participating in the trial), as including only samples from XPEL-TB health centres would underestimate total testing volumes (and thus overestimate unit costs) for centralised facilities.

See Online for appendix

Outcomes

Our primary cost outcomes were the per-patient and per-test cost of the multicomponent decentralised molecular tuberculosis testing strategy. The primary cost-effectiveness outcome was the incremental cost per incremental patient with microbiologically confirmed tuberculosis disease initiating treatment within 14 days of initial presentation, comparing the intervention (decentralised) and routine care (centralised) arms. Our secondary cost-effectiveness outcome was the incremental cost per incremental patient identified with microbiologically confirmed tuberculosis (regardless of 14-day treatment initiation).

Statistical analysis

Using bottom-up cost estimates, we first estimated the cost per test under the intervention (decentralised) Xpert scenario at each of the four health centres in which empirical costing was performed. To estimate the corresponding per-test cost in the routine care arm as a function of service volume, we built a cost function using data from centralised testing facilities in the same area.[15] For both intervention and routine care strategies, we estimated cost per test as the mean per-test cost, weighted by the number of tests performed at each facility. We then apportioned per-test costs into per-patient costs based on the proportion of patients receiving each diagnostic test (SSM, Xpert, or both) in the trial. These per-patient costs are used for all primary cost and

	1-year economic sub-study population*		XPEL-TB full study population†	
	Intervention (n=4135)	Control (n=3871)	Intervention (n=5546)	Control (n=5098)
Sex				
Female‡	2470 (59·8%)	2397 (61·9%)	3289 (59·3%)	3112 (61·0%)
Male‡	1665 (40·2%)	1474 (38·1%)	2257 (40·7%)	1986 (38·9%)
Age, years				
Median (IQR)	40 [30–53]	38 [27–50]	40 [30–52]	38 [27–50]
18–29	950 (23·0%)	1174 (30·3%)	1309 (23·6%)	1539 (30·2%)
30–39	953 (23·0%)	900 (23·3%)	1267 (22·8%)	1149 (22·5%)
40–49	852 (20·6%)	799 (20·6%)	1163 (21·0%)	1060 (20·8%)
≥50	1380 (33·4%)	998 (25·8%)	1807 (32·6%)	1350 (26·5%)
HIV status§				
Positive	1720/3943 (43·6%)	1439/3162 (45·5%)	2285/5273 (43·3%)	1905/4290 (44·4%)
Negative	2223/3943 (56·4%)	1723/3162 (54·5%)	2988/5273 (56·7%)	2385/4290 (55·6%)

Data are n (%), n/N (%), or median (IQR). XPEL-TB=Xpert Performance Evaluation for Linkage to Tuberculosis Care. *1-year economic sub-study population includes all individuals enrolled in the XPEL-TB study from Dec 1, 2018, to Nov 30, 2019. †XPEL-TB full study population includes all individuals enrolled in the XPEL-TB study from Oct 22, 2018, to March 1, 2020.[14] ‡Self-reported. §HIV status unknown for some individuals in both populations; denominators include all individuals with status known.

Table 1: **Patient-level characteristics of the XPEL-TB study**

cost-effectiveness outcomes. Per-test cost estimates are available in the appendix (p 24), as well as a top-down costing analysis (p 26).

To explore key drivers of cost, we performed one-way and probabilistic sensitivity analyses of both primary and secondary cost-effectiveness outcomes. We used Monte Carlo simulation to estimate uncertainty in our trial-based estimates of cost and cost-effectiveness, accounting for simultaneous uncertainty in multiple parameter values. For each parameter (appendix p 35), we constructed a β distribution around the empirically observed point estimate, with the weighted mean serving as the mode of the distribution and range based on the minimum and maximum observed values for each parameter in the trial. We sampled with replacement from these parameters 1000 times to build 95% uncertainty estimates around our estimates of incremental cost-effectiveness.

A second probabilistic sensitivity analysis was performed to illustrate uncertainty under different scenarios of service volume (eg, if decentralised testing were to be implemented only in health centres above a certain size), using four simulated cohorts of health centres with different service volumes: 1–249, 250–499, 500–749, and 750–1000 people evaluated for presumptive tuberculosis annually. At each of these four levels, we estimated the incremental cost-effectiveness under variation of all other parameter values specified above.

In a third sensitivity analysis, we estimated uncertainty under a scenario of implementation across heterogeneous health centres of different sizes in 1000 simulated districts in Uganda, with approximately 5000 patients presenting for care annually in each district. We used Uganda's official list of health centres to estimate the number of centres in each of the four tiers of the health system in each simulated district.[23] We then sampled with replacement from each of the four health centre pools created in the second probabilistic sensitivity analysis to build each district.

All analyses were performed in Stata (version 15.1) and R (version 4.0.2).

Role of the funding source

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Table 1 presents demographic characteristics of the study population. Over a 5-year time horizon, the cost per Xpert test was similar between arms: $20·46 (range $17·85–25·72) under the decentralised XPEL-TB strategy versus $18·20 (range $16·58–24·25) with centralised testing (table 2). However, since only 1632 (42%) of 3871 individuals received Xpert testing in the routine care arm, versus 4097 (99%) of 4135 individuals in the intervention arm, the per-patient cost of decentralised testing was higher: $20·28 (range $17·68–25·48) versus $9·59 (range $7·62–14·34; table 2). The difference in per-patient costs primarily reflected equipment (especially the GeneXpert Edge device), supplies (mainly Xpert cartridges), and the implementation of the multicomponent decentralised testing strategy ($2·24), which were not offset by increased costs of SSM ($1·93) and specimen transport ($0·58) in routine care.

Service volume was the largest driver of per-test and per-patient costs. With respect to testing volumes, estimated per-patient costs for the decentralised XPEL-TB strategy were $33·94 in sites that evaluated 150 patients annually, $25·26 at 250 patients annually, and $18·75 at 500 patients annually (appendix p 6). At larger patient volumes, per-patient costs stabilised at approximately $15 per patient for the XPEL-TB strategy and $9 for centralised testing.

The total annuitised cost of decentralised testing services under the XPEL-TB strategy for ten peripheral health centres over 1 year was $83 816 (95% uncertainty range [UR] $69 585–111 758) compared with $37 123 (95% UR $27 493–53 343) for the ten health centres receiving routine centralised testing. This difference was largely attributable to more individuals receiving Xpert testing in the decentralised XPEL-TB strategy arm. Decentralised testing cost $294 (95% UR $268–435) per case detected and $339 (95% UR $310–500) per 14-day treatment initiation, compared with $148 (95% UR $143–195) per case detected and $207 (95% UR $204–276) per 14-day treatment initiation for centralised testing. Over 1 year, the XPEL-TB strategy resulted in 35 (95% UR 8–69) additional diagnoses of confirmed tuberculosis (285 *vs* 250) and 68 (95% UR 37–108) additional 14-day treatment initiations for confirmed tuberculosis

(247 *vs* 179), at an incremental cost of $1332 (95% UR $763–5558) per diagnosis and $687 (95% UR $501–1207) per 14-day treatment initiation (table 3).

The largest determinants of incremental cost-effectiveness for the decentralised XPEL-TB strategy were equipment costs (ie, cost of GeneXpert Edge devices), the annual volume of patients evaluated, and the proportion of patients with confirmed tuberculosis initiating treatment within 14 days (figure 1). The estimated incremental cost per additional 14-day treatment initiation declined with increasing patient volume, from $2050 (95% UR $1069–4751) at health centres evaluating fewer than 250 patients per year to $492 (95% UR $355–703) at health centres evaluating more than 750 patients per year (appendix p 8). Extrapolating our trial-based estimates to hypothetical Ugandan districts with a range of health centres reflective of actual clinic sizes,[23] the estimated incremental cost per tuberculosis diagnosis and 14-day treatment initiation were $2182 (95% UR $1741–2790) and $1077 (95% UR $968–1205), respectively (figure 2).

Discussion

These empirical estimates from a large pragmatic trial show that a multicomponent strategy including decentralised molecular testing for tuberculosis can be implemented in peripheral clinics in Uganda at only a 10% increase in per-test cost ($20·46 *vs* $18·20) relative to centralised testing. This increased cost includes the implementation of additional procedures (streamlining of workflows and performance feedback) that, along with decentralised testing, increase the number of people appropriately tested for, diagnosed with, and promptly treated for tuberculosis. Because the decentralised XPEL-TB strategy enabled more than twice as many people to receive Xpert testing, it also more than doubled total costs per patient presenting for evaluation ($20·28 *vs* $9·59). Decentralised testing was more expensive and less cost-effective in clinics with lower service volume; the per-patient cost rose substantially in clinics testing fewer than 150–250 people annually for pulmonary tuberculosis. Taken together with the primary results of the trial, these findings

	Cost per test*		Cost per patient†	
	Decentralised (range)‡	Centralised (range)	Decentralised (range)	Centralised (range)
Supplies	$10·84 (10·82–10·98)	$12·05 (11·67–12·53)	$10·73 (10·71–10·87)	$5·06 (4·90–5·26)
Equipment	$6·79 (5·23–11·20)	$3·80 (2·00–9·83)	$6·72 (5·18–11·09)	$1·60 (0·84–4·13)
Implementation process	$2·26 (1·56–3·80)	..	$2·24 (1·54–3·76)	..
Transport	..	$1·38 (0·27–3·71)	..	$0·58 (0·11–1·56)
Staff	$0·51 (0·19–0·83)	$0·61 (0·09–1·49)	$0·51 (0·19–0·82)	$0·26 (0·04–0·63)
Building	$0·03 (0·02–0·06)	$0·35 (0·18–0·89)	$0·03 (0·02–0·06)	$0·15 (0·08–0·38)
Overhead	$0·03 (0·02–0·05)	$0·01 (0·01–0·03)	$0·03 (0·02–0·05)	$0·01 (0·01–0·02)
Total (Xpert)	$20·46 (17·85–25·72)	$18·20 (16·58–24·25)	$20·26 (17·67–25·46)	$7·66 (5·98–11·98)
Sputum smear microscopy	..	$2·41 (2·05–2·95)	$0·02 (0·01–0·02)	$1·93 (1·64–2·36)
Total (Xpert and smear)	$20·46 (17·85–25·72)	$20·61 (18·63–27·20)	$20·28 (17·68–25·48)	$9·59 (7·62–14·34)

*Weighted mean cost per test. Per-test costs were evaluated according to Uganda Ministry of Health guidelines. Under the guidelines, clinics with centralised Xpert (hub-and-spoke) testing are also supposed to perform sputum smear microscopy for all individuals receiving diagnostic care for tuberculosis. †Weighted mean cost per patient. The per-patient costs are apportioned based on the proportion of individuals receiving diagnostic tuberculosis testing who receive each type of test. For example, only 42% of all individuals who received testing at centralised (hub-and-spoke) sites received an Xpert test, versus 99% of individuals who received diagnostic testing at decentralised (onsite testing) sites. ‡Range is based on the empirically observed minimum per maximum values at costed sites, with the exception of sample transport networks, where the 2·5th and 97·5th percentiles of observed values were used. All costs presented in 2019 US$.

Table 2: **Cost of molecular testing for tuberculosis in Uganda**

	Total cost (95% UI)*	Number of patients tested (95% UI)*	Number of patients diagnosed with tuberculosis within 6 months (95% UI)*	Number of patients initiating treatment in 14 days (95% UI)*	Cost per patient (95% UI)*	Incremental cost-effectiveness ratio	
						Cost per additional tuberculosis diagnosis (95% UI)*	Cost per additional treatment initiation in 14 days (95% UI)*
Centralised	$37 123 (27 493–53 343)	3871 (2397–5044)	250 (145–347)	179 (102–247)	$9·59 (9·43–12·55)	..	..
Decentralised	$83 816 (69 585–111 758)	4135 (2540–5426)	285 (165–395)	247 (143–344)	$20·27 (18·90–29·29)	..	..
Difference	$46 693 (40 364–61 646)	264 (126–417)	35 (8–69)	68 (37–108)	$10·67 (8·78–17·04)	$1332 (763–5558)	$687 (501–1207)

UI=uncertainty interval. XPEL-TB=Xpert Performance Evaluation for Linkage to Tuberculosis Care. *The point estimates are based on empiric observations from the XPEL-TB trial for a 1-year period from Dec 1, 2018, to Nov 30, 2019. 95% uncertainty ranges were calculated using a Monte Carlo simulation (1000 iterations), with parameter inputs based on the variability in cost-effectiveness observed in the XPEL-TB trial. All costs presented in 2019 US$.

Table 3: **Total cost, total effectiveness, and incremental cost-effectiveness for 1 year of testing (Dec 1, 2018, to Nov 30, 2019)**

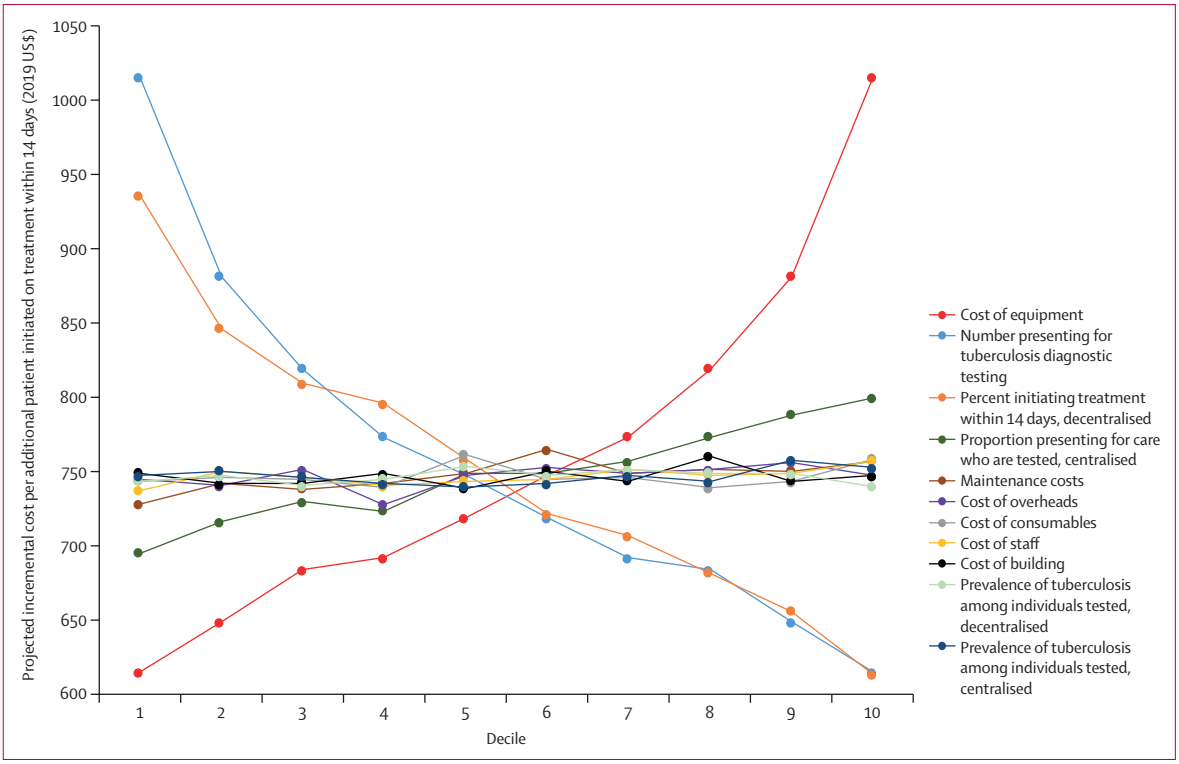

Figure 1: **Factors influencing the cost-effectiveness of a multicomponent strategy including decentralised molecular testing for tuberculosis in Uganda**
The figure depicts how the ICER varies from the lowest to highest deciles of each variable across the probabilistic sensitivity analysis simulations. Each dot represents the median ICER value among all simulations with the specified parameter in that decile. For example, the median ICER per 14-day treatment initiation was $614·82 among simulations with equipment costs in the lowest 10% across all simulations. The most influential parameters on cost-effectiveness are those with the largest variation in incremental cost per incremental treatment initiation between the first and tenth deciles. The number of individuals presenting for tuberculosis diagnostic testing, equipment costs, and the percent initiating treatment within 14 days at decentralised sites were the largest drivers of cost-effectiveness. Estimates are based on the per-patient cost of testing. The analysis included all parameters; only the most influential values are shown here. All costs presented in 2019 US$. ICER=incremental cost-effectiveness ratio (incremental cost per additional patient initiated on tuberculosis treatment within 14 days of presenting for care).

suggest that, in high-burden settings that can afford an increase in total diagnostic costs and evaluate at least three to five people per week for pulmonary tuberculosis, a decentralised molecular testing strategy with appropriate implementation supports can be both epidemiologically and economically viable.

Our estimates of cost-effectiveness are comparable with those of other tuberculosis diagnostic and case-finding interventions. For example, a trial of point-of-care Xpert testing versus SSM in four African countries estimated that point-of-care Xpert would cost $1464 per incremental treatment initiation relative to SSM (range $984–2699), somewhat higher than our estimate of $687 (95% UR $501–1207) per incremental 14-day treatment initiation for the XPEL-TB strategy.[16] Likewise, a review of 29 active case-finding interventions for tuberculosis estimated a cost of $332 per treatment initiation (range $123–10 608),[24] similar to our estimate of $339 per treatment initiation. Although these comparisons cannot be used to benchmark cost-effectiveness of the XPEL-TB strategy against an external standard (eg, cost per disability-adjusted life-year averted), they suggest the cost-effectiveness of XPEL-TB is comparable with tuberculosis diagnosis and case-finding interventions that have been implemented in other health systems.

Innovation and contextual adaptation could improve the cost-effectiveness of the XPEL-TB strategy beyond our estimates. For example, pooling of sputum could reduce per-patient Xpert costs, and the XPEL-TB strategy could be integrated with the diagnosis of other diseases.[25] The GeneXpert system can also test for other infectious diseases including COVID-19 and human papillomavirus,[26,27] and the difference in per-test costs for decentralised versus centralised testing could be recovered by reducing equipment costs for this system (table 2). Thus, to the extent that investing in such infrastructure could stimulate availability of rapid molecular testing for other infectious diseases or lead to sharing of equipment costs, decentralised molecular testing for tuberculosis could potentially be cheaper on a per-test basis than centralised testing.[26] Emerging low-cost alternatives to the GeneXpert system (eg, Truenat [Molbio Diagnostics, Verna, Goa, India])[28] could make this more of a reality.

Importantly, since decentralised testing increases the use of guideline-based but more expensive molecular

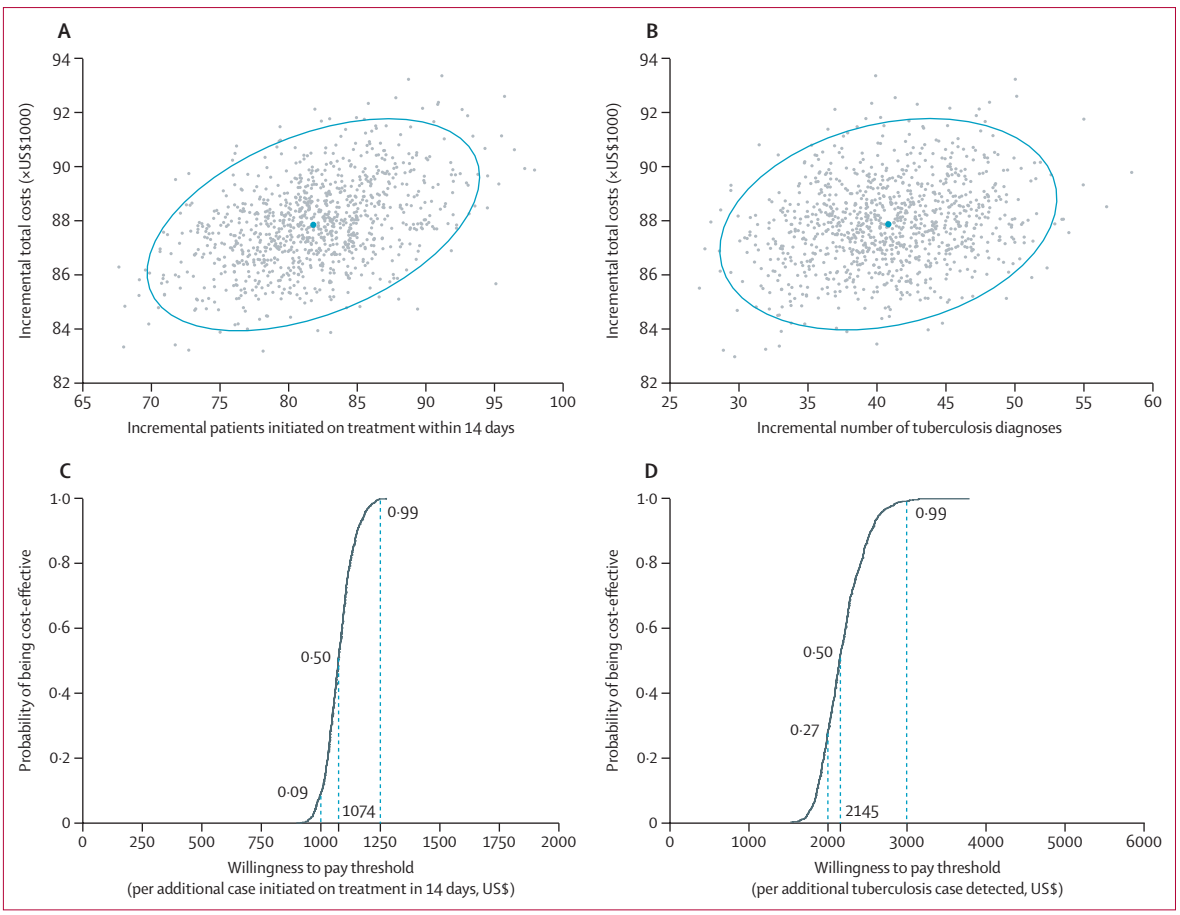

Figure 2: **Incremental cost-effectiveness of a multicomponent strategy including decentralised testing for tuberculosis over 1 year in simulated districts in Uganda**

The first two graphs show the incremental cost per incremental 14-day treatment initiation (A) or per incremental tuberculosis diagnosis (B) of decentralised testing for tuberculosis over 1 year in simulated Ugandan districts. Each dot in these panels represents a simulated district with a mean of 5000 symptomatic patients presenting for tuberculosis evaluation annually across health centres of different sizes. Blue dots represent the mean value ($1077 per additional 14-day treatment initiation, $2182 per additional tuberculosis diagnosis), and the blue ellipse represents the 95% confidence region that contains 95% of simulated districts. The second two graphs show the cost-effectiveness acceptability curves for 14-day treatment initiation (C) and tuberculosis diagnosis (D) in the simulated districts. These graphs show the probability of decentralised testing being cost-effective at different willingness-to-pay thresholds, compared with centralised testing. For example, at a willingness to pay of $1000 per additional case initiating treatment within 14 days of presenting for care, the XPEL-TB decentralised testing strategy will be considered cost-effective 9·0% of the time (C). All costs presented in 2019 US$. XPEL-TB=Xpert Performance Evaluation for Linkage to Tuberculosis Care.

testing, this strategy does increase overall costs for tuberculosis diagnosis. Furthermore, in health centres with very low patient volume (fewer than three to five individuals per week), decentralised testing rapidly becomes more expensive on a per-test basis, owing to the fixed cost of installing a GeneXpert Edge device. By contrast, if peripheral health centres evaluate around 500 patients for tuberculosis annually (two patients per operating day), the per-test cost of decentralised Xpert testing approaches that of centralised testing. Notably, introducing onsite molecular testing might increase testing volume, lowering per-patient and per-test costs. This increased testing volume favourably affects cost-effectiveness but increases total costs (ie, affordability).[13]

A strength of this study is the collection of empirical cost and implementation data in the context of a highly pragmatic trial. As such, there is reasonable confidence that these estimates will approximate the real-world programmatic costs of implementing decentralised molecular testing in many resource-limited settings. Costs and cost-effectiveness will vary, however, in settings with different economic (eg, South Africa) or epidemiological (eg, southeast Asia) conditions, or if different molecular tests are implemented. Our numerical estimates will therefore not directly generalise to these settings—highlighting the need for further economic and implementation research similar to the XPEL-TB trial in different contexts. Decentralised testing was implemented as part of a multicomponent strategy that also included streamlining clinic workflows and performance feedback, and these other components might have contributed to the observed effectiveness of the intervention. We incorporated the costs of initiating these procedures, and the ongoing costs of generating

performance feedback reports and streamlining clinic workflows were observed to be small on a per-patient basis. Nevertheless, by focusing on the cost of decentralised testing, our analysis might have marginally underestimated the cost of these additional components.

As with any pragmatic economic evaluation, our findings have important limitations. First, our measures of effectiveness were based on the primary trial outcomes, which did not include patient-level health outcomes such as tuberculosis mortality or health utility. Although estimating effectiveness in terms of health utility (eg, disability-adjusted life-years averted) would enable cleaner comparison with other health interventions, we intentionally limited our effectiveness outcomes to those measured in the trial so as not to require assumptions regarding outcomes (eg, effect on transmission) not measured in the trial itself. Second, the scope of our study was limited to the costs of implementation and diagnosis and did not include costs of tuberculosis treatment or patient support that would occur after diagnosis or treatment initiation. To the extent that decentralised testing would lead to more tuberculosis diagnoses and treatment initiations, these downstream costs would increase as well. Third, owing to the pragmatic trial design, we were unable to collect patient or other societal costs, limiting our analysis to the health system perspective. Fourth, although we inflated costs accordingly, our cost data were collected at different times for intervention and standard-of-care sites. Finally, while inclusion of itemised costs of implementation represents a strength of this study, assessment of implementation costs was performed retrospectively, and prospective evaluation of decentralised testing costs was limited to four sites owing to resource constraints—thereby reducing our ability to assess variations in costs across all ten intervention sites. This limitation was partially addressed through the evaluation of key determinants of clinic-level costs, construction of cost functions, and performance of probabilistic sensitivity analyses. Future research could address these limitations by performing follow-up for longer-term outcomes, evaluating costs along the full cascade of care, incorporating patient-level and other societal costs, and prospectively collecting costs of implementation across a variety of epidemiological and economic contexts.

In conclusion, in this highly pragmatic trial in Uganda, the decentralised XPEL-TB strategy increased the number of patients appropriately tested for, diagnosed with, and promptly started on treatment for tuberculosis with a 10% increase in the per-test cost of Xpert testing. To the extent that equipment costs could be shared or reduced, or more patients would be tested for tuberculosis as part of efforts to increase case detection, decentralised testing could be performed at a lower per-test cost than centralised testing. However, since this strategy led to more than twice as many people receiving recommended molecular testing, it was also associated with more than doubling of total tuberculosis diagnostic costs. These results support the expansion of national and donor budgets for tuberculosis diagnosis to enable decentralised testing, along with appropriate implementation supports, in high-burden clinics that routinely test for tuberculosis on a daily basis.

Contributors

AT, AC, AK, DWD, and HS conceptualised the study. RRT, TN, AT, OF, AC, AK, DWD, and HS developed the methodology for the paper. TN, DO, AT, MN, AN, JM, AJZ, OF, ST, MJ, and AK were involved in investigation for the project. The project was administered by TN, DO, MN, AN, JM, TFR, AC, AK, DWD, and HS. Study resources were procured and administered by TN, DO, MN, AN, JM, ST, MJ, and AK. Supervision of the project was provided by TN, ST, MJ, AC, AK, DWD, and HS. Data was curated by RRT, TN, AT, TFR, and AJZ, and these co-authors conducted the formal analysis with assistance from DWD and HS. RRT, DWD, and HS performed data validation, and visualised the data with assistance from TN and AT. The original draft of the manuscript was prepared by RRT, TN, DWD, and HS. All authors contributed to review and editing of the manuscript. AC and AK acquired funding to support the study. All authors read and approved the final version of the manuscript. All authors had full access to all data in the study and had the responsibility to decide to submit the manuscript for publication. RRT, TN, and HS all directly accessed and verified the underlying data reported in the manuscript.

Declaration of interests

We declare no competing interests.

Data sharing

All data and model code necessary for this analysis are available via Github at https://github.com/tbteam1/XPEL-TB-Cost-Data.

Acknowledgments

We would like to thank the staff, patients, and administration at participating health centres for their support, and the XPEL-TB research team for their involvement and oversight of the study. We are grateful for all the assistance and collaborative efforts provided by the Uganda National Tuberculosis and Leprosy Program, the district health offices, the district tuberculosis focal persons, and health centre staff in implementing the XPEL-TB trial. This project was supported by the National Heart, Lung, and Blood Institute, Bethesda, MD, USA, through grant number R01HL130192.

References

1 WHO. Global Tuberculosis Report 2022. 2021. https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022 (accessed Nov 2, 2022).
2 MacPherson P, Houben RMGJ, Glynn JR, Corbett EL, Kranzer K. Loss of follow-up before treatment of tuberculosis patients in low- and middle-income countries and in high-burden countries: a systematic review and meta-analysis. *Bull World Health Organ* 2014; **92:** 126–38.
3 Getnet F, Demissie M, Assefa N, Mengistie B, Worku A. Delay in diagnosis of pulmonary tuberculosis in low- and middle-income settings: systematic review and meta-analysis. *BMC Pulm Med* 2017; **17:** 202.
4 WHO. WHO operational handbook on tuberculosis. Module 3: diagnosis-rapid diagnostics for tuberculosis detection, 2021 update. 2021. https://www.who.int/publications/i/item/9789240030589 (accessed Nov 10, 2021).
5 Boehme CC, Nicol MP, 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:** 1495–505.
6 Dowdy DW. Minding the gap: specimen referral systems for diagnosis of infectious diseases. *Clin Infect Dis* 2017; **64:** 804–05.
7 Tucker A, Oyuku D, Nalugwa T, et al. Costs along the TB diagnostic pathway in Uganda. *Int J Tuberc Lung Dis* 2021; **25:** 61–63.
8 Cox HS, Daniels JF, Muller O, et al. Impact of decentralized care and the Xpert MTB/RIF test on rifampicin-resistant tuberculosis treatment initiation in Khayelitsha, South Africa. *Open Forum Infect Dis* 2015; **2:** ofv014.

9 Clouse K, Page-Shipp L, Dansey H, et al. Implementation of Xpert MTB/RIF for routine point-of-care diagnosis of tuberculosis at the primary care level. *S Afr Med J* 2012; **102:** 805–07.

10 WHO. Molecular assays intended as initial tests for the diagnosis of pulmonary and extrapulmonary tuberculosis and rifampicin resistance in adults and children: rapid communication. Policy update. 2020. https://www.who.int/publications/i/item/9789240000339 (accessed Nov 28, 2021).

11 Sohn H, Kasaie P, Kendall E, et al. Informing decision-making for universal access to quality tuberculosis diagnosis in India: an economic-epidemiological model. *BMC Med* 2019; **17:** 155.

12 Drain PK, Garrett NJ. The arrival of a true point-of-care molecular assay—ready for global implementation? *Lancet Glob Health* 2015; **3:** e663–64.

13 Reza TF, Nalugwa T, Farr K, et al. Study protocol: a cluster randomized trial to evaluate the effectiveness and implementation of onsite GeneXpert testing at community health centers in Uganda (XPEL-TB). *Implement Sci* 2020; **15:** 24.

14 Cattamanchi A, Reza TF, Nalugwa T, et al. Multicomponent strategy with decentralized molecular testing for tuberculosis. *N Engl J Med* 2021; **385:** 2441–50.

15 Hsiang E, Little KM, Haguma P, et al. Higher cost of implementing Xpert(®) MTB/RIF in Ugandan peripheral settings: implications for cost-effectiveness. *Int J Tuberc Lung Dis* 2016; **20:** 1212–18.

16 Pooran A, Theron G, Zijenah L, et al. Point of care Xpert MTB/RIF versus smear microscopy for tuberculosis diagnosis in southern African primary care clinics: a multicentre economic evaluation. *Lancet Glob Health* 2019; **7:** e798–807.

17 Tucker A, Tembo T, Tampi RP, et al. Redefining and revisiting cost estimates of routine ART care in Zambia: an analysis of ten clinics. *J Int AIDS Soc* 2020; **23:** e25431.

18 Sohn H, Tucker A, Ferguson O, Gomes I, Dowdy D. Costing the implementation of public health interventions in resource-limited settings: a conceptual framework. *Implement Sci* 2020; **15:** 86.

19 The World Bank. Inflation, GDP deflator (annual %)–Uganda. 2021. https://data.worldbank.org/indicator/NY.GDP.DEFL.KD.ZG?locations=UG (accessed April 20, 2021).

20 The World Bank. Official exchange rate (LCU per US$, period average)–Uganda. 2021. https://data.worldbank.org/indicator/PA.NUS.FCRF?locations=UG (accessed April 20, 2021).

21 Tampi RP, Tembo T, Mukumba-Mwenechanya M, et al. Operational characteristics of antiretroviral therapy clinics in Zambia: a time and motion analysis. *BMC Health Serv Res* 2019; **19:** 244.

22 Ministry of Public Service. Uganda. Circular Standing Instruction No. 5 of 2018–Salary Structure for FY 2018/19. 2018. https://publicservice.go.ug/download/csi-no-5-of-2018-salary-structure-for-fy-2018-19/ (accessed June 3, 2021).

23 Ministry of Health. Uganda. National Health Facility Master List 2018. 2018. https://health.go.ug/sites/default/files/Signed%20n%20final%20mfl.pdf (accessed July 7, 2021).

24 Gomes I, Dong C, Vandewalle P, et al. Comparative assessment of the cost-effectiveness of Tuberculosis (TB) active case-finding interventions: a systematic analysis of TB REACH wave 5 projects. *PLoS One* 2022; **17:** e0270816.

25 Cuevas LE, Santos VS, Lima SVMA, et al. Systematic review of pooling sputum as an efficient method for Xpert MTB/RIF tuberculosis testing during the COVID-19 pandemic. *Emerg Infect Dis* 2021; **27:** 719–27.

26 Rakotosamimanana N, Randrianirina F, Randremanana R, et al. GeneXpert for the diagnosis of COVID-19 in LMICs. *Lancet Glob Health* 2020; **8:** e1457–58.

27 Einstein MH, Smith KM, Davis TE, et al. Clinical evaluation of the cartridge-based GeneXpert human papillomavirus assay in women referred for colposcopy. *J Clin Microbiol* 2014; **52:** 2089–95.

28 Lee DJ, Kumarasamy N, Resch SC, et al. Rapid, point-of-care diagnosis of tuberculosis with novel Truenat assay: cost-effectiveness analysis for India's public sector. *PLoS One* 2019; **14:** e0218890.