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Higher cost of implementing Xpert® MTB/RIF in Ugandan peripheral settings: implications for cost-effectiveness

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SUMMARY

SETTING: Initial cost-effectiveness evaluations of Xpert® MTB/RIF for tuberculosis (TB) diagnosis have not fully accounted for the realities of implementation in peripheral settings.

OBJECTIVE: To evaluate costs and diagnostic outcomes of Xpert testing implemented at various health care levels in Uganda.

DESIGN: We collected empirical cost data from five health centers utilizing Xpert for TB diagnosis, using an ingredients approach. We reviewed laboratory and patient records to assess outcomes at these sites and10 sites without Xpert. We also estimated incremental cost-effectiveness of Xpert testing; our primary outcome was the incremental cost of Xpert testing per newly detected TB case.

RESULTS: The mean unit cost of an Xpert test was US$21 based on a mean monthly volume of 54 tests per site, although unit cost varied widely (US$16–58) and was primarily determined by testing volume. Total diagnostic costs were 2.4-fold higher in Xpert clinics than in non-Xpert clinics; however, Xpert only increased diagnoses by 12%. The diagnostic costs of Xpert averaged US$119 per newly detected TB case, but were as high as US$885 at the center with the lowest volume of tests.

CONCLUSION: Xpert testing can detect TB cases at reasonable cost, but may double diagnostic budgets for relatively small gains, with cost-effectiveness deteriorating with lower testing volumes.

KEY WORDS: tuberculosis; diagnostic tests, routine; molecular diagnostic techniques; cost-benefit analysis

TUBERCULOSIS (TB) is the leading cause of death due to a single infectious agent globally, responsible for 1.5 million deaths in 2014.[1] An estimated 3.6 million cases go unreported every year. Reaching this 'missing 3 million' is among the highest priorities for global TB control.[1] In 2010, the World Health Organization endorsed Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA), a molecular TB diagnostic test that can provide results in 2 h, with minimal human resource requirements, higher sensitivity than sputum smear microscopy, and the ability to identify multidrug-resistant TB (MDR-TB) based on detected resistance to rifampin (RMP).[2,3] Scale-up has been rapid, with more than 10 million cartridges procured under concessional pricing in over 100 countries in 2014.[4,5] However, while sputum smear microscopy costs US$1–3 per test in most high-burden countries,[6] Xpert has been estimated to cost between US$15 and $50 per test.[7–11] A key question is thus whether the improved accuracy of Xpert is worth the additional cost.

Initial economic evaluations suggested that Xpert is cost-effective, although estimations of incremental cost-effectiveness vary.[7,8,11–13] These earlier modeling studies largely assumed efficiently functioning laboratories that served as initial sites of Xpert scale-up. Over time, however, the focus of Xpert implementation has shifted to district and subdistrict levels,[14–16] where the cost of Xpert may be substantially higher due to lower testing volumes or additional costs associated with transport and installation.[17] Previous work in South Africa has suggested that point-of-treatment placement of Xpert could increase Xpert testing cost by 50% or more;[9] whether that additional cost, as well as the linkage between such additional cost and the potential for Xpert to improve diagnostic outcomes, generalizes to high-burden, low-income settings remains uncertain.

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Recent evidence has also suggested that Xpert, as implemented in African primary care settings, may not improve treatment, morbidity, or mortality outcomes as much as initially expected.[18–20] Xpert effectiveness may be further reduced in non-trial settings due to equipment failure, uncertain electrical supply, ongoing calibration requirements, and unanticipated patterns of use (e.g., treatment monitoring).[9,17] It is thus important to collect data on both the costs and outcomes of Xpert implementation in peripheral settings, particularly in high-burden, low-income countries, where funding gaps suggest that the affordability of Xpert remains a key question.[1]

Here, we report on the costs of Xpert testing and corresponding diagnostic outcomes across regional hospitals, district hospitals and subdistrict health centers in Uganda, a typical sub-Saharan African setting with high rates of TB and TB-HIV (human immunodeficiency virus) and the site of prior studies of Xpert's effectiveness[21] and cost-effectiveness.[11]

METHODS

Ethical considerations

The study received approval from institutional review boards at Makerere University College of Health Sciences, Kampala, Uganda, and Johns Hopkins Bloomberg School of Public Health in Baltimore, MD, USA.

Overview

We nested this evaluation of Xpert costs and TB diagnoses into a larger observational study of implementing TB diagnostic algorithms in Uganda.[22] Data were collected at 18 rural and urban health facilities from 2012 to 2014, selected to be representative of both geography and health system level: one national referral center (not included in this analysis), four regional referral centers, nine district hospitals, and four subdistrict health centers. Xpert had been implemented at seven sites (plus the national referral center) at the time of evaluation, whereas the remaining 10 sites had laboratories capable of performing sputum smear microscopy. These 10 sites provided Xpert testing only as an offsite referral test from another health center, and only rarely. Here we compared five sites where Xpert was implemented, excluding two sites that served as referral centers, against the 10 sites without Xpert.

Our primary aim was to measure costs and diagnostic outcomes related to Xpert testing as actually implemented in various levels of the Ugandan health care system to explore the primary drivers of Xpert cost-effectiveness in such settings. Because we did not measure treatment costs or outcomes, we did not attempt to estimate cost-effectiveness in terms of cost per disability-adjusted life year (DALY) averted, but rather used cost per diagnostic outcome (diagnosis of TB or RMP-resistant TB) as a more proximal measure for exploring the key drivers of cost-effectiveness in these settings.

Empiric costing

We estimated diagnostic costs from the health system perspective using a unit-based 'ingredients' approach. This method identifies and values all inputs required to perform diagnostic testing to develop a unit cost for each test. At five sites with Xpert implementation (two regional hospitals, one district hospital, and two subdistrict [Level IV] health centers), we collected the costs of overheads, building space, equipment, staff, reagents, and consumables related to Xpert testing and smear microscopy. We used a combination of laboratory personnel interviews, budgetary documentation reviews, procurement guides, and publicly available product information. Overhead costs were allocated based on proportional space required for TB testing and percentage of staff time devoted to TB testing, as appropriate. To determine the allocation of costs of shared resources between Xpert testing and non-Xpert testing, we directly observed time and motion of laboratory procedures at each site. For smear microscopy, we assumed an algorithm consisting of two smears per patient. Costs and diagnostic outcomes of TB culture, which is performed only rarely at these sites, were excluded.

Based on consultation with experts in Uganda, we assumed that one person would require training in Xpert use per site per year, and that Xpert cartridge procurement and transportation would equal 10% of the US$9.97 cartridge list price. The cost of shipping the GeneXpert four-cartridge system was incorporated as a 10.9% markup of the ex-works list price.[23] Annual maintenance of GeneXpert was based on annual warranty cost[24] with a 5-year expected lifetime, whereas we assumed annual maintenance costs of all other durable equipment and building space to be 5% of total cost each year, given an assumed expected lifetime of 30 years. All future costs were discounted at 3% per year.[25] Costs were measured in 2014 currency and converted to US dollars using published exchange rates.

Estimation of diagnoses made

We reviewed 12 months of TB laboratory records, including electronic Xpert instrument logs and laboratory specimen registers, for Xpert testing volume and results of Xpert and smear microscopy at each site, as reported previously.[22] Laboratory results and treatment data for 100 consecutive patients who provided sputum samples were also abstracted at each site to establish linkages between test results and treatment initiation. In order not to underestimate the cost-effectiveness of Xpert in diagnosing smear-negative TB, we assumed that Xpert tests run without a specific reason recorded

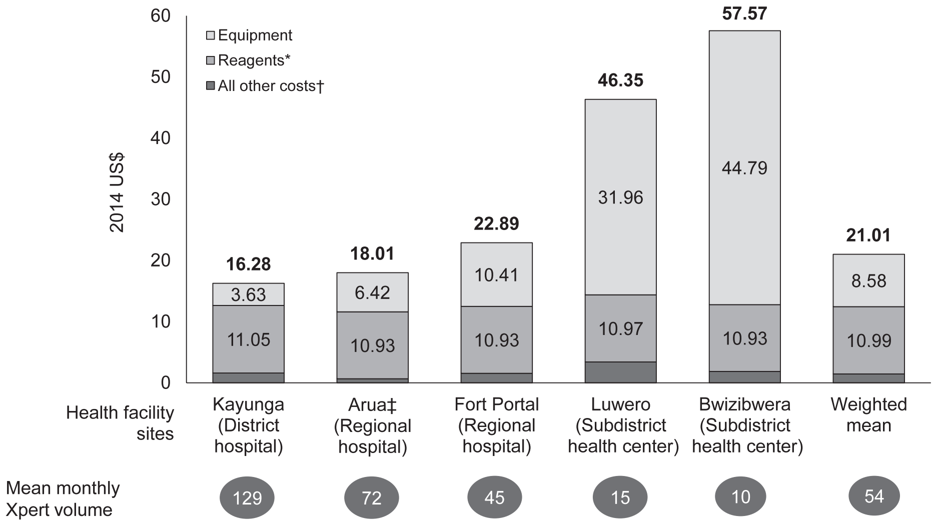

Figure 1 Unit cost of Xpert® MTB/RIF test by input type at each site. The height of each column (at the top of each column) represents the mean unit cost of Xpert at each of the five sites in Uganda; the corresponding observed monthly Xpert volume is indicated in circles below each column. Different shades within each bar represent components of the unit cost. Note that Kayunga, as a district hospital, is at a lower level of the Uganda health care system than Arua and Fort Portal regional hospitals, but had a greater volume of tests.* The cost of reagents includes the Xpert cartridge.† Includes costs of overheads, building space, staff time, and consumables.‡ Because time-motion data for Xpert testing were not collected at Arua, the allocation of resources not directly related to Xpert (i.e., all but GeneXpert system and Xpert cartridge) was based on time-motion studies in Fort Portal; these resources accounted for 9% of costs per Xpert test in Fort Portal.

were performed for the purpose of diagnosing TB over other reasons (e.g., treatment monitoring).

Analysis of outcomes

Primary cost outcomes were the cost per Xpert test performed and the incremental cost of diagnosis of a new TB case due to Xpert. Our primary effectiveness outcome was the number of positive Xpert tests performed in individuals without known pre-existing TB. A secondary effectiveness outcome was the number of Xpert tests indicating RMP resistance among individuals not previously documented as having MDR-TB. The cost per diagnosis made for each Xpert site was calculated based on the mean monthly cost of Xpert testing and the mean number of incremental TB diagnoses. Finally, we compared mean facility-level estimates of monthly diagnostic costs and the number of individuals started on anti-tuberculosis treatment between sites with and without Xpert.

Uncertainty analysis

As we measured costs and diagnostic outcomes directly, we did not need to use parameter values from the literature. Nevertheless, our sample size of five Xpert sites still leads to uncertainty in our estimates as a reflection of other, similar Ugandan clinics. To capture this uncertainty, we adopted a probabilistic approach in which we drew 10 000 samples of testing volume, Xpert unit cost (as a function of testing volume), and the number of newly diagnosed TB and MDR-TB cases (as a function of testing volume). Testing volume was modeled as a gamma distribution to reflect the zero bound and right skew observed in our data. In each simulation, we calculated the diagnostic cost per Xpert test positive for TB and the diagnostic cost per Xpert test positive for RMP resistance. We also compared the cost-effectiveness of TB testing in simulated sets of nine small-volume facilities (<20 tests per month) against single large-volume facilities (>20 tests per month; mean nine times larger than small-volume facilities).

RESULTS

Unit cost of Xpert

Across the five sites evaluated, the mean unit cost of Xpert was US$21 based on an observed mean monthly volume of 54 tests per site (Figure 1). Reagents (including the Xpert cartridge) and equipment comprised 93% of this unit cost, which varied from US$16 to US$58 across sites. The primary driver of this variation was testing volume, which tended to be higher in regional and district hospitals and lower in subdistrict health centers. If all five facilities operated under the lowest-volume conditions observed over the 12-month periods, the estimated mean unit cost would increase to US$65 (Table 1).

Table 1 Unit cost of Xpert test by monthly volume

	Weighted mean cost of Xpert test (2014 US$)*		
Input type	At minimum monthly volume	At median monthly volume	At maximum monthly volume
Overhead	0.03	0.03	0.03
Building space	1.79	1.35	0.15
Equipment	50.94	9.44	4.33
Staff	0.40	0.40	0.37
Reagents	10.97	10.98	10.99
Consumables	0.67	0.72	0.75
Total	64.80	22.92	16.62

* Calculated by adding variable monthly costs of building space and equipment with constant monthly costs of all other input types as would be required to attain the minimum, median, or maximum volume observed in each site. These total unit costs were then weighted according to the site volume observed in each scenario, as follows: minimum monthly volume: Kayunga, 15; Arua, 17; Fort Portal, 8; Luwero, 4; Bwizibwera, 1. Median monthly volume: Kayunga, 109; Arua, 68; Fort Portal; 46; Luwero, 16; Bwizibwera, 9. Maximum monthly volume: Kayunga, 275; Arua, 132; Fort Portal, 83; Luwero, 23; Bwizibwera, 28.

Xpert diagnostic costs and outcomes

The estimated monthly incremental diagnostic cost of Xpert testing at each site ranged from US$590 to US$2098 (Table 2). Regional and district-level hospitals had higher total costs for the overall Xpert testing program per month due to larger volumes of Xpert testing. On average, of the 54 Xpert tests per site per month, 9.6 were positive for TB and 0.5 indicated RMP resistance; however, variations across sites were substantial. The diagnostic cost per positive Xpert test for patients not known to have TB averaged US$119 (range US$80–885), whereas the diagnostic cost per positive test for RMP resistance among those without known pre-existing resistance averaged US$1383 (range US$896–7081), reflecting the smaller number of RMP-resistant cases diagnosed. Cost per positive diagnosis was highest in sites with lowest volumes of testing.

Figure 2 presents the estimated incremental costs and diagnoses due to Xpert by comparing costs, number of diagnoses, and number started on treatment at Xpert vs. non-Xpert sites. The total cost of TB diagnosis per month averaged US$1679 per Xpert site. Total TB diagnostic costs were 2.4-fold higher in clinics with Xpert testing than in those without (US$702, based on our empiric estimate of US$1.41 per sputum smear). However, Xpert resulted in an estimated 5.3 incremental diagnoses per site per month, an incremental yield of only 12%. While treatment initiations were 31% higher in Xpert vs. non-Xpert sites, rates of treatment initiation after diagnostic testing at Xpert and non-Xpert sites were similar, at respectively 87% and 89%.

Uncertainty analysis

Figure 3 presents the distribution of costs per Xpert test positive for TB and per test positive for RMP resistance across 10 000 simulated months of testing. The median cost per Xpert test positive for TB was

Table 2 Total costs and associated diagnostic impact of Xpert implementation at each site

		Cost	Associated diagnostic impact			Cost per diagnosis made	
Health facility site	Health facility level	Total diagnostic cost of Xpert program/month (2014 US$)	Mean number of Xpert tests run/month	Mean number of new TB-positive Xpert tests/month*	Mean number of RMP-positive Xpert tests/month†	Diagnostic cost per new TB-positive Xpert test (2014 US$)	Diagnostic cost per RMP-positive Xpert test (2014 US$)
Arua	Regional hospital	1291	71.7	14.0	1.1	92	1191
Fort Portal	Regional hospital	1021	44.6	5.7	0.7	180	1531
Kayunga	District hospital	2098	128.9	26.2	0.0	80	NA
Luwero	Subdistrict health center	672	14.5	1.3	0.8	538	896
Bwizibwera	Subdistrict health center	590	10.3	0.7	0.1	885	7081
Mean‡	NA	1134	54.0	9.6	0.5	119	1383

* Excludes TB-positive results of Xpert tests run on individuals already diagnosed with TB, but includes those where the reason for testing is not recorded.
† Includes RMP-positive results of Xpert tests run on individuals already diagnosed with TB, and RMP-positive results where the reason for testing was not recorded.
‡ Weighted mean used in cost calculations, where the data from each site were weighted by the number of patients diagnosed.
TB = tuberculosis; RMP = rifampicin; NA = not available.

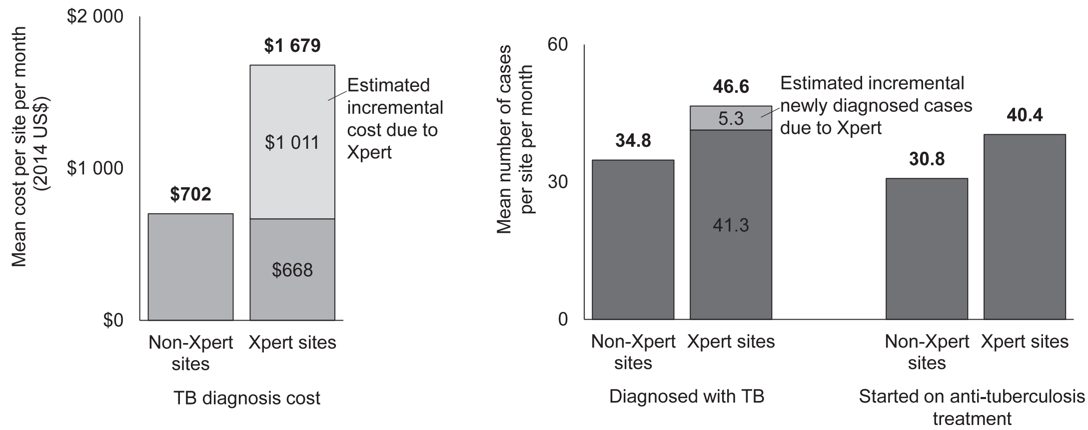

Figure 2 Incremental costs and associated diagnostic and treatment impact of Xpert® MTB/RIF implementation. The left graph shows the costs of diagnosis from the health care setting in sites without and with on-site Xpert testing, while the right graph shows the corresponding outcomes: the number of cases diagnosed and number of cases started on treatment. Incremental newly diagnosed cases due to Xpert (light gray) were estimated by applying the observed proportion of newly diagnosed cases with a previous positive Xpert result (Table 2) to the mean number of new TB diagnoses diagnosed by Xpert per month in sites with on-site Xpert testing available. The remaining TB cases at Xpert sites were either detected using smear microscopy or started on treatment before a positive Xpert result. TB = tuberculosis.

US$106. Among simulations in which Xpert testing volume was less than 20 per month per site, this median diagnostic cost was $918 vs. $138 among simulations in which monthly testing volume was at least 20.

DISCUSSION

This economic investigation of Xpert implementation across regional, district, and subdistrict health centers in Uganda suggests that the costs and impact of Xpert testing vary widely across sites and levels of the health system, with a strong dependence on testing volume. For example, the diagnostic cost per positive Xpert test ranged from US$80 at the site with the highest volume to US$885 in the lowest-volume site. Xpert testing accounted for more than 60% of all diagnostic costs, but was responsible for no more than 12% of new TB diagnoses. As Xpert is increasingly implemented in lower-volume settings, it may become less cost-effective.

Consistent with previous studies performed under conditions of greater resource availability,[19,26] we found that implementation of Xpert in Uganda—a country with fewer resources and outside a trial setting—led to few incremental TB diagnoses relative to the current standard based on sputum smear. We augment this understanding by correlating diagnostic

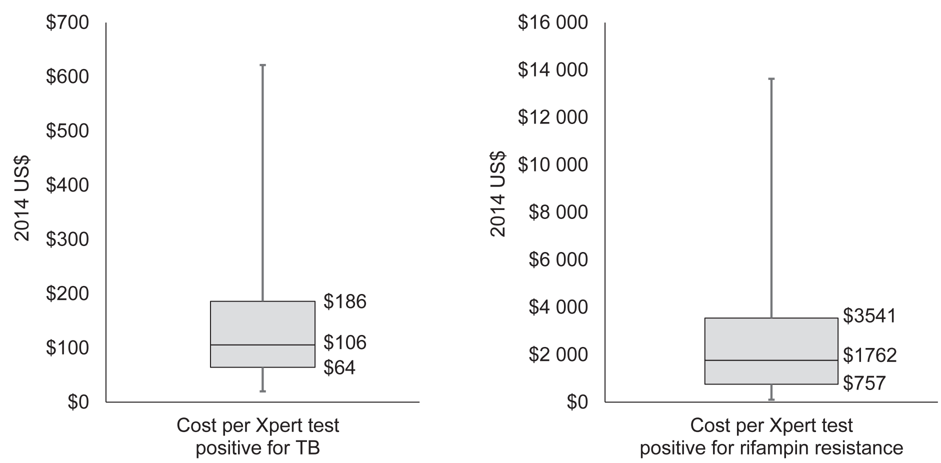

Figure 3 Distribution of cost per positive Xpert test across 10 000 probabilistic simulations. Box plots represent the distributions of cost-effectiveness estimates in probabilistic sensitivity analyses considering the cost per Xpert test positive for tuberculosis (left panel) or rifampin resistance (right panel). Boxes represent interquartile ranges; whiskers represent the 5th and 95th percentiles (not including simulations for which Xpert did not increase the number of positive tests [17% of simulations] or lead to any individuals being diagnosed with rifampin resistance [13% of simulations]).

outcomes with the incremental cost of Xpert, which constituted over 60% of diagnostic costs in sites utilizing Xpert. In our uncertainty analysis simulations, the median cost per new TB case detected was US$106; however, this increased when considering Xpert implementation in sites with low testing volume. These findings may help inform decision-makers about the appropriateness of Xpert deployment in different settings.

Previous analyses have estimated the mean unit cost of Xpert to vary within the range of US$20–$30 depending on the country in which it is deployed,[11] while others have also noted that testing volume is an important contributor to cost variations.[9,10] Our analysis builds on this by describing the degree of variability that could be observed even within the same health system. This research suggests that there is likely a threshold testing volume—and thus, a threshold level of health care system—at which Xpert should be implemented. Such thresholds may raise concerns about trade-offs between equity and efficiency in peripheral settings, especially as some apparent cost savings from a more centralized referral system may in fact represent costs shifted away from the health system and instead toward patients, who would have to travel further, wait longer for results, and delay treatment initiation. The cost-effectiveness of Xpert testing at lower-volume centers could potentially be improved with increased volume of patients referred for testing, such as through facility-based screening and other intensified case-finding initiatives.[27,28] Alternatively, referral networks could be further developed to deliver sputum specimens efficiently to more centralized sites,[29,30] an approach that must take into account the quality of available transport networks and the potential for pre-treatment loss to follow-up while awaiting results. Novel lower-cost platforms for Xpert testing, such as Xpert Omni (Cepheid; http://www.cepheid.com/us/genexpert-omni) and Alere q (Alere, Orlando, FL, USA; http//www.alere.com/en/home/products-services/brands/alere-q.html), may also aid in cost-effective decentralization of testing. Future research should evaluate the appropriate health care level for Xpert implementation in different economic and epidemiological settings, investigate the economic impact of alternative approaches in peripheral settings, and evaluate trade-offs between patient costs and health care system costs when placing Xpert centrally vs. peripherally.

Our study has several limitations. First, we included only costs of Xpert and sputum smear microscopy in estimating diagnostic costs, excluding the costs of ancillary evaluations such as chest X-ray or antibiotic trials. As a result, we likely underestimate the true diagnostic program cost at both Xpert and non-Xpert sites. Second, we took as our primary effectiveness outcome the observed number of positive Xpert tests not performed on those with known TB, which may overestimate the incremental value of Xpert. Third, HIV status was not reliably logged in patient records. We were therefore unable to evaluate the differential costs and impact on diagnoses from Xpert testing within this important subgroup.[31] Finally, we measured costs from the health care perspective and did not incorporate patient costs. Including patient costs would increase the overall estimates of diagnostic and treatment costs, although the incremental cost due to Xpert might differ according to the diagnostic algorithm (e.g., whether testing is same-day).

In summary, this analysis demonstrates that the diagnostic costs and impact of Xpert on TB and MDR-TB diagnoses made can vary widely at different levels of the same health care system, with cost-effectiveness deteriorating substantially in low-volume settings. As Xpert is scaled up to sites with increasingly lower testing volumes, more attention should be paid to proper placement within the health care system and the development of alternative strategies to make peripheral implementation more cost-effective. Future policy guidance for Xpert and emerging TB diagnostic tests[32] should consider the economic realities of testing in peripheral settings carefully when recommending implementation strategies.

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RESUME

CONTEXTE : Les évaluations initiales du rapport coût-efficacité de l'Xpert® MTB/RIF pour le diagnostic de la tuberculose (TB) n'ont pas totalement pris en compte les réalités de sa mise en œuvre dans des contextes périphériques.

OBJECTIF : Evaluer les coûts et les résultats diagnostiques du test Xpert mis en œuvre à divers niveaux de soins de santé en Ouganda.

SCHÉMA : Nous avons recueilli des données empiriques de coût émanant de cinq centres de santé utilisant l'Xpert pour le diagnostic de la TB en employant une approche par ingrédients. Nous avons revu les dossiers du laboratoire et des patients afin d'évaluer les résultats dans ces cinq sites ainsi que dans 10 sites sans Xpert. Nous avons également estimé le rendement incrémentiel du test Xpert ; notre résultat essentiel a été le coût incrémentiel du test Xpert par nouveau cas de TB détecté.

RÉSULTATS : Le coût unitaire moyen d'un test Xpert a été de 21 $US en se basant sur un volume mensuel de 54 tests par site, bien que le coût unitaire ait largement varié (16 à 58 $US) et qu'il ait été déterminé en premier lieu par le volume des tests. Le coût total des diagnostics a été 2,4 fois plus élevé dans les centres Xpert par comparaison aux centres non Xpert, bien que l'Xpert ait seulement accru les diagnostics de 12%. Les coûts du diagnostic de l'Xpert ont été autour de 119 $US par nouveau cas de TB détecté, mais ont atteint 885 $US dans le centre qui avait le plus faible volume de tests.

CONCLUSION : Le test Xpert peut détecter les cas de TB à un prix raisonnable mais peut doubler le budget du diagnostic pour un gain relativement faible, avec une détérioration du rendement lorsque les volumes de tests sont plus faibles.

RESUMEN

MARCO DE REFERENCIA: Las evaluaciones iniciales de la rentabilidad de la prueba Xpert® MTB/RIF en el diagnóstico de la tuberculosis (TB) no tuvieron en cuenta plenamente las realidades de su ejecución en los entornos periféricos.

OBJETIVO: Evaluar los costos y el rendimiento diagnóstico de la prueba Xpert en los diversos niveles de la atención de salud en Uganda.

MÉTODOS: Se recogieron los datos empíricos sobre los costos en cinco centros de atención de salud que utilizan la prueba Xpert en el diagnóstico de TB, aplicando un enfoque de ingredientes. Se examinaron los registros de laboratorio y las historias clínicas de los pacientes, con el fin de evaluar los desenlaces en estos centros y los 10 centros que no practican la prueba Xpert. Se estimó también el incremento adicional de la rentabilidad con la prueba Xpert; el criterio primario de evaluación fue el costo diferencial con la prueba Xpert por cada caso nuevo de TB diagnosticado.

RESULTADOS: El promedio del costo unitario de la prueba Xpert fue $21, con base en un volumen mensual promedio de 54 pruebas por centro, pero el costo unitario fue muy variable (de $16 a $58) y el principal factor determinante fue el volumen de pruebas. El costo total del diagnóstico fue 2,4 veces más alto en los consultorios que utilizaban la prueba Xpert que en los consultorios que no la utilizaban; sin embargo, la prueba solo aumentó los diagnósticos un 12%. El costo diagnóstico promedio de la prueba Xpert fue $119 por cada caso nuevo de TB detectado, pero pudo aumentar hasta $885 en el centro con menor volumen de actividad.

CONCLUSIÓN: La prueba Xpert detecta los casos de TB con un costo aceptable, pero puede duplicar el presupuesto del diagnóstico, con un beneficio relativamente pequeño, lo cual reduce su rentabilidad en los centros con bajo volumen de actividad.