HHS Public Access

Author manuscript

Appl Health Econ Health Policy. Author manuscript; available in PMC 2019 August 01.

Published in final edited form as:

Appl Health Econ Health Policy. 2018 August ; 16(4): 537–548. doi:10.1007/s40258-018-0397-3.

Cost analysis of tuberculosis diagnosis in Cambodia with and without Xpert® MTB/RIF for people living with HIV/AIDS and people with presumptive multidrug-resistant tuberculosis

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Abstract

Background: The Xpert® MTB/RIF (Xpert) test has been shown to be effective and cost-effective for diagnosing tuberculosis (TB) under conditions with high HIV prevalence and HIV-TB co-infection but less is known about Xpert's cost in low HIV prevalence settings. Cambodia, a country with low HIV prevalence (0.7%), high TB burden, and low multidrug-resistant (MDR) TB burden (1.4% of new TB cases, 11% of retreatment cases) introduced Xpert into its TB diagnostic algorithms for people living with HIV (PLHIV) and people with presumptive MDR TB in 2012. The study objective was to estimate these algorithms' costs pre- and post-Xpert introduction in four provinces of Cambodia.

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Ethical review: The U.S. Centers for Disease Control and Prevention (CDC), Atlanta, GA, USA, and the Cambodia National Tuberculosis Control Program (CENAT) determined the study to be a program evaluation and not research involving human subjects, and therefore no IRB approval was required.

Conflicts of interest: Sarah Wood Pallas, Marissa Courey, Chhaily Hy, William Perry Killam, Dora Warren, and Brittany Moore declare that they have no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are not publicly available due to them containing information considered procurement sensitive by the Cambodia National TB Program (CENAT). The data are however available on reasonable request from the corresponding author (SWP) and with permission of CENAT.

Author Contributions

Conceptualization and design of the study: SWP, MC, WPK, DW, BM
Acquisition of data: SWP, CH, BM
Analysis of data: SWP, MC
Interpretation of data and analysis: SWP, MC, CH, WPK, DW, BM
Drafting of the manuscript: SWP
Revisions of the manuscript for important intellectual content: SWP, MC, CH, WPK, DW, BM
Final approval of the manuscript for publication: SWP, MC, CH, WPK, DW, BM

Methods: Using a retrospective, ingredients-based microcosting approach, primary cost data on personnel, equipment, maintenance, supplies, and specimen transport were collected at four sites through observation, records review, and key informant consultations.

Results: Across the sample facilities, the cost per Xpert test was US$33.88-US$37.11,clinical exam cost US$1.22-US$1.84, chest x-ray cost US$2.02-US$2.14, fluorescent microscopy (FM) smear cost US$1.56-US$1.93, Ziehl-Neelsen (ZN) smear cost US$1.26, liquid culture test cost US $11.63-US$22.83, follow-on work-up for positive culture results and *Mycobacterium tuberculosis* complex (MTB) identification cost US$11.50-US$14.72, and drug susceptibility testing (DST) cost US$44.26. Specimen transport added US$1.39-US$5.21 per sample. Assuming clinician adherence to the algorithms and perfect test accuracy, the normative cost per patient correctly diagnosed under the post-Xpert algorithms would be US$25-US$29 more per PLHIV and US$34-US$37 more per person with presumptive MDR TB (US$41 more per PLHIV when accounting for variable test sensitivity and specificity).

Conclusions: Xpert test unit costs could be reduced through lower cartridge prices, longer usable life of GeneXpert® (Cepheid, USA) instruments, and increased test volumes; however, epidemiological and test eligibility conditions in Cambodia limit the number of specimens received at laboratories, leading to sub-optimal utilization of current instruments. Improvements to patient referral and specimen transport could increase test volumes and reduce Xpert test unit costs in this setting.

1. Introduction

Globally, an estimated 10.4 million people developed tuberculosis (TB) in 2015, of whom an estimated 11% were co-infected with HIV (1). There were 480,000 estimated new cases of multidrug-resistant (MDR) TB in 2015 (1). Traditional diagnostic procedures of clinical screening, chest x-ray, and sputum smear microscopy often fail to accurately diagnose TB among people living with HIV (PLHIV) and do not diagnose drug resistance, while more accurate diagnostics of culture and drug susceptibility testing (DST) take multiple weeks to complete before results are available for clinicians and patients (2–5). Delayed diagnosis and treatment of TB among PLHIV and of MDR TB increases opportunities for disease transmission and can accelerate disease progression and mortality (1, 6–9).

The Xpert® MTB/RIF (Xpert) rapid test conducted on the GeneXpert® platform (GeneXpert; Cepheid, USA) was developed in response to these challenges. Xpert is a polymerase chain reaction-based test that delivers a result in roughly two hours for both *Mycobacterium tuberculosis* complex (MTB) detection and resistance to one of the first-line anti-TB drugs, rifampicin (RIF) (3, 10). As the test is largely automated, it also addresses concerns about shortages of trained laboratory personnel in low- and middle-income country settings with the highest burdens of TB among PLHIV and MDR TB (10). In 2010, the World Health Organization recommended Xpert use for TB diagnosis in PLHIV and for people with presumptive MDR TB, and in 2013 for pediatric and some types of extrapulmonary TB (3, 11). Previous literature has shown Xpert to have high sensitivity and specificity for the diagnosis of TB and detection of RIF resistance (12–17), and to be cost-effective (18–23). Prior cost-effectiveness studies, however, have focused on settings with high HIV prevalence such as southern Africa using model-based approaches. Less is known

about the costs of Xpert under routine implementation conditions in settings with low HIV prevalence.

Accordingly, this paper presents results from a cost analysis of Xpert integration into TB diagnostic algorithms for PLHIV and people with presumptive MDR TB in Cambodia, which has an estimated adult HIV prevalence of 0.7% (0.3%−1.5%) but is one of 30 WHO-designated high TB burden countries (1, 24). Cambodia's estimated TB incidence rate is 380 per 100,000 (246–543), and an estimated 2.4% of incident TB cases are co-infected with HIV.(1) MDR TB cases in Cambodia are estimated at 1.8% (0.77%−2.8%) of new TB cases and 11% (1.4%−20%) of retreatment TB cases (1). In 2012, the Cambodian Ministry of Health introduced Xpert testing into its diagnostic algorithms for PLHIV and people with presumptive MDR TB (Supplemental Figures 1–4) and placed 4-module GeneXpert instruments in selected laboratories throughout the country. For PLHIV, the primary change to the algorithm was that PLHIV with a positive symptom screen for TB would initially receive an Xpert test rather than initially receiving clinical exam, chest x-ray, and sputum smear microscopy for TB diagnosis. For patients with presumptive MDR TB, the primary change to the algorithm was to first receive an Xpert test and be started on empirical treatment based on Xpert results while awaiting culture and DST results, rather than waiting for culture and DST results before beginning treatment.

This rollout of Xpert has been the subject of an ongoing program evaluation by the Cambodian National TB Program (CENAT), and the U.S. Centers for Disease Control and Prevention (CDC) (25), which includes assessing the fidelity of implementation of the algorithms and the costs of the diagnostic algorithms before and after Xpert introduction. The objective of the cost analysis was to identify the unit costs of each procedure in the diagnostic algorithms for PLHIV and people with presumptive MDR TB, as well as to estimate the cost per patient diagnosed and to understand the factors influencing TB diagnosis costs in Cambodia. This study – the first cost analysis of TB diagnostics in Cambodia – offers insights into the cost drivers of Xpert introduction and use that are also relevant to a broader range of countries seeking to optimize their use of the GeneXpert platform.

2. Methods

2.1. Study Setting and Site Sample

The study setting was four provinces in northwest Cambodia – Battambang, Banteay Meanchey, Pursat, and Pailin – selected based on the CDC's existing presence there. In 2012, 4-module GeneXpert instruments were placed in two provincial referral hospitals (Battambang Provincial Referral Hospital in Battambang and Mongkol Borei Provincial Referral Hospital in Banteay Meanchey) to provide Xpert testing for the four-province catchment area. Across the four provinces, there are a total of 12 outpatient departments located at provincial or lower-level operational district hospitals, each of which has a TB clinic that screens TB patients and patients with presumptive MDR TB and 10 of which have co-located HIV clinics that screen PLHIV for TB symptoms. PLHIV who screen positive for TB in HIV clinics are referred to TB clinics for TB testing and treatment. Two of the provincial referral hospitals (Battambang and Mongkol Borei) provide MDR TB treatment

to any diagnosed MDR TB patient within the four provinces; MDR TB treatment at CENAT in the capital city of Phnom Penh is also an option. Ten of the hospitals in the catchment area currently have functioning x-ray equipment that could be used for chest x-rays and all have laboratories that are equipped to perform sputum smear microscopy. Public sector TB culture testing is available at the laboratory of the Battambang Provincial Referral Hospital or the CENAT national laboratory in Phnom Penh.

Four sites were included in the sample for the cost analysis: the two provincial referral hospitals in the four-province catchment area in which a GeneXpert instrument had been placed in 2012 (Battambang (BTB) and Mongkol Borei (MKB)), one operational district (OD) hospital in Mong Russey (MR), and the CENAT national laboratory. The BTB and MKB provincial referral hospitals were selected as these were the only two sites in the four-province study setting in which public sector Xpert testing was conducted. Mong Russey OD hospital was selected for convenience based on proximity as a feeder facility to the BTB provincial referral hospital. The CENAT national laboratory in Phnom Penh was selected as the only facility in Cambodia that performs DST and because hospitals in the study setting may choose to send samples for culture to the CENAT laboratory rather than to BTB. Selected sites were not intended to be a representative sample for Cambodia as a whole.

2.2. Study Design

The cost analysis was conducted from a public health sector perspective, considering costs to the publicly-funded health care provider, which for this evaluation includes CENAT, the National HIV/AIDS Program, and other Ministry of Health costs, including costs within the public health sector that may be funded by international donor agencies or non-governmental organizations. This perspective excluded patients' out-of-pocket and opportunity costs, as well as the costs of private sector health care providers, government services outside of the health sector, and health services not directly related to the study populations and diagnostic algorithms being evaluated.

The cost analysis used an ingredients-based, micro-costing approach to obtain the empirical economic costs of each procedure in the TB diagnostic algorithms for PLHIV and people with presumptive MDR TB as implemented in the study sites. These procedures were clinical exam, chest x-ray, fluorescent microscopy (FM) smear, Ziehl-Neelsen (ZN) smear, Xpert, Mycobacteria growth indicator tube (MGIT) liquid culture (MGIT 960, Becton Dickinson, USA), follow-on work-up for a positive liquid culture result and MTB identification, and DST.

The cost categories included were personnel, equipment, equipment maintenance, supplies, and specimen transport directly related to the diagnostic procedures. Costs for general hospital and laboratory administration, facility space, and utilities were not included as these were not expected to differ due to the introduction of Xpert testing in the study sites. Personnel time was valued at average monthly wages and benefits for each position as paid by the Cambodian Ministry of Health, including the costs for personnel hired as full-time government employees and as consultants using international donor funds. Donated equipment and supplies were valued at their replacement cost using current market prices quoted by vendors that regularly supply CENAT and the Ministry of Health. Costs of

transporting centrally procured drugs, supplies, and equipment from the CENAT warehouse in Phnom Penh to sites were not included. Equipment maintenance was defined to include all services and investments required to keep diagnostic procedure equipment in working order (e.g., personnel time, spare parts, calibration services). Specimen transport included the costs of personnel time, courier services, transportation, and per diem.

The time frame for the cost analysis was from the date of GeneXpert placement in 2012 (February for BTB, June for MKB) through the end of the program evaluation in June 2013. When historical cost data were not available, cost data that were current as of the date of data collection (May-July 2014) were used. For each site, a single set of procedure unit costs were calculated, which were then used to calculate the total cost per TB case diagnosed under each algorithm: the pre-Xpert algorithms in use before GeneXpert placement in the evaluation sites in 2012, and the post-Xpert algorithms introduced after 2012. The differences in pre- and post-Xpert algorithm costs at each site therefore only reflect the differences in the type and number of procedures used under each algorithm (i.e., differences in the combination of procedures) and not differences in the unit costs of the individual procedures across algorithms.

2.3. Data Collection Procedures

Primary cost data were collected by CDC staff at the study sites in May-July 2014 using a standard set of Excel-based tools for TB clinic costs, laboratory costs, and CENAT national lab and program costs. Not all procedures were performed at all sites. Cost data were collected only for procedures performed at each site per the diagnostic algorithms for PLHIV and people with presumptive MDR TB in the four-province catchment area. Data were collected through consultation with clinical and laboratory staff at the study sites, procurement and financial staff at CENAT, and private sector vendors that regularly supply CENAT and the Ministry of Health, as well as through observation of laboratory procedures and review of laboratory records. Personnel time was collected through direct observation of laboratory procedures and from clinical and laboratory staff members' self-reports of their time or percent effort spent on each activity. The costs of equipment and supplies that were shared across procedures were allocated on the basis of the reported percent of space or percent of time used for each procedure as reported by laboratory staff at each site. For each site, the data collected included the prices and quantities of inputs used for each procedure, allocation of inputs across procedures, and monthly procedure volumes. Cost data were recorded manually during site visits and then entered into electronic versions of the tools.

2.4. Cost Analysis

The cost analysis had three components: (i) calculation of the unit cost for each procedure included in either the pre- or post-Xpert algorithm for PLHIV and patients with presumptive MDR TB, (ii) calculation of the total costs per TB case diagnosed under the pre- and post-Xpert algorithms for PLHIV and patients with presumptive MDR TB under the hypothetical assumptions of perfect (i.e., 100%) test accuracy and that the algorithms were followed as written, and (iii) calculation of the total costs per TB case diagnosed and treated under the pre- and post-Xpert algorithms for PLHIV accounting for differential sensitivity and specificity of FM smear versus Xpert.

In the first component of calculating the unit cost for each procedure, the purchase price, annual cost, or monthly cost of each input (i.e., each type of personnel, supplies, equipment, and equipment maintenance) was converted to a per-procedure cost (Supplemental Box 1). For personnel, the average monthly salary for a given cadre was multiplied by the share of time that that cadre of personnel spent on the procedure in the evaluation site divided by the number of procedures performed per month in that site (Supplemental Table 2). For single-use supplies (e.g., glass slide, Xpert cartridge), the purchase price was divided by the quantity purchased and multiplied by the quantity used in the procedure. For supplies used across more than one test (e.g., gloves, pens, markers, waste bags), the purchase price was divided by the quantity purchased and the number of tests performed during the time period before the supply needed to be replaced (e.g., per month). For equipment, the purchase price was converted to an annual equivalent cost based on the number of years of useful life of the equipment, the resale value of the equipment at the end of its useful life (assumed to be US $0 in all cases), and an assumed 3% annual discount rate. The annual equivalent cost of each piece of equipment was then divided by the actual average number of procedures performed per year in the evaluation site to obtain the per-procedure cost. For maintenance costs, the reported annual cost of maintenance for each piece of equipment was divided by the average number of procedures performed per year in the evaluation site to obtain the per-procedure cost. The unit cost for each procedure was then calculated as the sum of the per-procedure costs for each input. Costs collected in Cambodian riel were converted to 2014 U.S. dollars at the rate of 4000 riel per dollar, the average current exchange rate at the time of data collection, and subsequently adjusted to 2017 U.S. dollars using the GDP implicit price deflator.(26)

Sensitivity analyses were performed to examine how the unit cost of an Xpert test would change under different scenarios for the useful life of the GeneXpert instrument, the cartridge cost, and the average monthly test volume. These factors were selected for sensitivity analysis because of the Ministry of Health's uncertainty around the performance of GeneXpert under conditions of routine use in Cambodia (as the instruments were new technology placed in 2012, it was not known how long they would last beyond the date of data collection) and the availability of future concessional pricing for cartridges. The effect of varying monthly test volume was explored as a factor that directly impacts the unit cost of an Xpert test and that may be amenable to policy or programmatic intervention. We also examined how the unit costs of other procedures would change if monthly procedure volumes were held constant across sites to examine the degree to which factors besides volume influenced costs.

In the second component of the cost analysis, the normative cost to diagnose TB in a single patient under each of the four diagnostic algorithms (pre- and post-Xpert for PLHIV and pre- and post-Xpert for patients with presumptive MDR TB) was calculated as the sum of each procedure's empirical unit cost multiplied by the normative frequency of that procedure as written in the algorithm, under the hypothetical assumptions that the algorithm was followed as written and that each procedure was perfectly (i.e., 100%) accurate. Although empirical procedure unit costs were used, this is termed a normative cost analysis of the algorithm because it calculates the cost for the algorithm as it should have been implemented (i.e., the algorithm "on paper"), not the actual practice of clinicians in the evaluation sites,

which may have differed from the algorithm. In the third cost analysis component, this normative analysis was repeated for the PLHIV pre- and post-Xpert algorithms replacing the assumption that each procedure is perfectly accurate with sensitivity and specificity values from the literature for FM smear and Xpert to examine the potential implications for treatment costs under the post-Xpert algorithm.

3. Results

3.1. Empirical Unit Costs per Procedure

Unit costs per procedure and average monthly procedure volumes varied by site (reported in Table 1). Unit costs were lower in the facilities with higher test volumes, as the costs of equipment, maintenance, and personnel were amortized over a larger number of tests.

The inputs representing the largest share of the unit cost per procedure at each site were fairly consistent across sites (Table 2), though the exact shares varied based on procedure volume and some differences in available equipment and personnel. Consumables and equipment represented the largest input cost shares for all procedures, with the exception of clinical diagnostic assessment, FM smear at BTB, and DST at the CENAT national lab for which personnel time was among the two most costly inputs.

Specimen transport costs for Xpert, culture, and DST varied by site location and patient type (PLHIV versus people with presumptive MDR TB) and were therefore calculated separately from the unit costs per procedure. In the study's four-province catchment area, for both PLHIV and people with presumptive MDR TB, the cost to transport a set of three sputum samples from lower-level health clinics and operational district hospitals to the two provincial referral hospitals for Xpert testing ranged from US$4.17-US$14.59 (US$1.39-US $4.87 per sample). Samples sent from MKB to BTB for culture testing incurred an additional US$10.42 transport cost (US$3.47 per sample) for both PLHIV and people with presumptive MDR TB. If the lower-level facility referred a patient with presumptive MDR TB to the provincial referral hospital to provide sputum samples there, the patient could receive US$15.63 to cover transport and overnight stay costs (US$5.21 per sample). Specimen transport from the provincial referral hospitals to the CENAT national laboratory for DST for both PLHIV and people with presumptive MDR TB cost US$109.43 per month on average (US$4.72 per sample based on average monthly sample volumes). There were no specimen transport costs for sputum smear microscopy, which can be performed at lower-level health facilities.

Costs for community directly-observed therapy short course (C-DOTS) were calculated as US$11.21 per month for the BTB provincial referral hospital catchment area and US$8.60 per month for the MKB provincial referral hospital catchment area. Differences in C-DOTS costs were due to differences in the personnel and funding models used during the study period in each catchment area. First and second line drug costs were assumed to be the same across all study sites as drugs are centrally procured by CENAT. On average, a category 1 first line regimen of RIF and isoniazid (each for six months) plus pyrazinamide and ethambutol (each for the first two months only) cost US$26.05 per patient, whereas a five- to eight-month category 2 regimen for treatment failure, relapse, and retreatment cases that

added streptomycin cost US$104.22 per patient, and a 24-month regimen of second line drugs (various formulations) for patients with multidrug resistance cost US$3,126.50 per patient. Patients receiving treatment also receive an average of three ZN smears performed at lower-level health clinics or operational district hospitals to monitor their response to treatment.

3.2. Normative Cost Estimates per Patient Diagnosed and Treated

Assuming hypothetical perfect test accuracy, for PLHIV, the cost per patient diagnosed with TB under the post-Xpert algorithm is US$34-US$37 compared to US$9 under the base case pre-Xpert algorithm, whereas for people with presumptive MDR TB, the cost per patient diagnosed with MDR TB under the post-Xpert algorithm is US$169-US$201 compared to US$135-US$164 under the base case pre-Xpert algorithm (Table 3). In this case of perfect test accuracy, the cost per patient diagnosed by these multi-step algorithms is equivalent to the cost per patient tested, assuming no dropout at each stage of testing. Ranges reflect the variation in unit costs per procedures across the study site sample. For comparison, the treatment cost implications for PLHIV were estimated based on the estimated sensitivity and specificity of FM smear (Se: 73%, Sp: 100%) versus Xpert (Se: 88%, Sp: 99%).(11, 27) Under these parameters, the post-Xpert algorithm results in an estimated 1% of patients receiving a false positive diagnosis and 12% receiving a false negative diagnosis following Xpert testing, compared to no false positives and 27% false negatives under the pre-Xpert algorithm. The reduction in false negatives and slight increase in false positives under the post-Xpert algorithm means that more of the PLHIV tested would be initiated on TB treatment under this algorithm than the pre-Xpert algorithm; this increase in treatment costs (US$13-US$16 per PLHIV diagnosed with TB) plus the increase in diagnostic costs (US $25-US$28 per PLHIV diagnosed with TB) increases the total diagnosis and treatment cost of the post-Xpert algorithm byUS$41 per PLHIV diagnosed with TB relative to the pre-Xpert algorithm using FM smear.

3.3. Sensitivity Analyses

Changes to the useful life of the GeneXpert instrument, the price per Xpert test cartridge, and the average monthly test volume change the unit cost per Xpert test, with alternative unit costs ranging from US$13.23-US$42.32 (Table 4). The actual unit cost was calculated based on an expected 5-year useful life for the 4-module GeneXpert instrument and the reported bulk cartridge procurement price at the time of data collection of US$12.51 per cartridge. The greatest reductions in unit costs were achieved by increases in average monthly test volumes from current levels (40 at BTB and 25 at MKB) to maximum daily utilization of GeneXpert (three runs per day of a 4-module instrument, or 240 tests per month), even when the test cartridge price was increased to commercial levels for non-bulk purchases. Changes to the test cartridge price change the unit cost per Xpert test directly (e.g., if the Cambodian Ministry of Health had to procure cartridges in smaller batches at the commercially available price of US$17.72 per cartridge, the unit cost would increase by US$5.21 per test). Reducing the test cartridge price to US$10.42 per cartridge under concessional pricing that Cambodia currently receives reduces the unit cost per test more than would doubling the useful life of the GeneXpert instrument from five to 10 years.

In a supplemental analysis holding constant average monthly procedure volumes across sites (Supplemental Table 1), unit costs increased when the monthly procedure volumes of the lower volume site were applied to the higher volume site. For chest x-ray, FM smear, and Xpert, the hypothetical unit costs at BTB provincial referral hospital (US$2.28, US$2.54, and US$40.40, respectively) under the lower procedure volumes from MKB provincial referral hospital were higher than the empirical unit costs at either site, reflecting the presence of more expensive personnel and equipment at the BTB laboratory. For liquid culture using MGIT, the hypothetical unit cost at the CENAT national laboratory (US$20.50) under the lower procedure volumes from BTB provincial referral hospital was higher than the empirical unit costs for the CENAT national laboratory but still lower than the empirical unit costs for BTB provincial referral hospital, suggesting that the national laboratory may still have some process efficiencies in performing liquid culture compared to BTB. For follow-on work up for positive MGIT results and MTB identification, the hypothetical unit cost at the CENAT national laboratory (US$16.60) under the lower procedure volumes from BTB provincial referral hospital were higher than the empirical unit costs for both sites.

4. Discussion

This study presents the first cost analysis of tuberculosis diagnostic procedures in Cambodia. Our unit costs are within the range of estimates for these procedures from other countries, falling towards the upper end of previously published estimates (18, 20, 28–32). Prior cost studies do not always report the average volume of tests performed in their settings, however, making it difficult to determine the extent to which test throughput (rather than input prices) explains variation in unit costs. Procedure volume was an important driver of unit costs across the sites sampled for this study as many equipment and supply prices were constant across sites due to centralized government procurement; however, the supplemental sensitivity analysis holding volume constant indicates that this is not the only cost driver. Variations in the number and cadre of personnel and in the allocation of tasks across personnel also partially explained differences in unit costs across study sites. For example, BTB had additional tuberculosis staff at the time of the study as a legacy of other donor-funded projects related to TB-HIV co-infection, whereas such additional clinical staff were not funded at MKB. As another example, sites that used higher-paid temporary contractors (BTB and CENAT) paid by international donor funds to fill in staffing gaps rather than hiring lower-paid full-time government employees had higher unit costs for procedures performed by contractors. Our analysis used the salary rates of these internationally-funded contractors as there was no indication of planned transition of these roles to government-funded staff, and it was not clear if similarly skilled personnel could be recruited and retained at government salary rates. As a hypothetical counterfactual, if the same quality and quantity of tests could have been performed by laboratory staff paid at lower government salary rates, the unit costs for the procedures performed by these staff would have been reduced (BTB FM smear: from US$1.56 to US$1.43; CENAT DST: from US$44.26 to US $36.57) and personnel time would not have been among the two most costly inputs per procedure at these sites; instead, the two inputs contributing the largest shares of the unit cost per test would have been the monetized value of the share of the equipment used for FM smear at BTB (biosafety cabinet, 19% (or US$0.27 per test), and binocular fluorescent

microscope, 15% (or US$0.22 per test)) and supplies for DST at CENAT (sterile filter tips 100–1000 ul, 18% (or US$6.59 per test); sterile filter tips 20–200 ul, 15% (or US$5.48 per test)).

The sensitivity analysis indicates that Xpert unit costs in Cambodia could be reduced through access to further discounted concessional pricing per Xpert cartridge, as had been negotiated through UNITAID (1), or through extending the life of current GeneXpert instruments beyond the five years assumed by program planners in Cambodia. The greatest reductions in Xpert unit cost would come from increasing utilization of current GeneXpert instruments. A primary strategy to increase GeneXpert instrument utilization would be to ensure that all individuals currently eligible for Xpert testing (i.e., PLHIV with a positive TB symptom screen and people with presumptive MDR TB) receive it through strengthened case finding, patient referral, and specimen transport. Given Cambodia's epidemiological context, however, there is a ceiling on the maximum number of Xpert tests that could be performed if Xpert testing continues to be limited to PLHIV with a positive TB symptom screen and people with presumptive MDR TB. Under Cambodia's current diagnostic algorithms for these populations, there are not sufficient numbers of individuals in the four provinces of our study setting who are eligible for Xpert testing to permit the current GeneXpert instruments to be used at their maximum run capacity of 240 tests per month.

Under these conditions, placing additional GeneXpert instruments at lower-level health facilities may not be efficient, as doing so would only further reduce the testing volume at the current provincial referral hospital laboratories and increase per test costs. In addition, TB control program officials in Cambodia and other countries should consider carefully whether high-volume procurement of Xpert cartridges to secure more favorable pricing is warranted when the population eligible for Xpert testing is limited, so as to avoid oversupply and expiration of cartridges. Exploring additional options for pooled procurement, including at the regional level, may be a way to obtain lower prices for smaller volumes appropriate to the country's epidemiological profile and Xpert testing eligibility criteria. Improvements in sample transport and patient referral may also facilitate increased utilization of current GeneXpert instruments to ensure that all patients who are currently eligible for Xpert testing receive it. As the WHO has recommended expansion of Xpert testing to pediatric patients and patients presumed to have some types of extrapulmonary TB, there may be scope to increase the utilization of current GeneXpert instruments in Cambodia through expansions in the eligibility guidelines to cover children with presumptive TB, HIV-associated TB, and drug-resistant TB. WHO also has a conditional recommendation for the use of Xpert as a follow-up test to microscopy in settings in which HIV and MDR TB are of lesser concern, which may also suggest options for broader use of existing GeneXpert instruments in Cambodia.

In addition, our illustrative normative cost estimates do not account for health system cost savings due to reduced TB transmission in the community or for the societal benefits of improved quality of life and survival for PLHIV with TB. For people with presumptive MDR TB, the post-Xpert algorithm does not offer any cost savings per patient diagnosed or treated as Xpert testing is added on to the existing diagnostic tests of culture and DST. In theory, it is possible that the post-Xpert algorithm could still be more cost-effective than the

pre-Xpert algorithm for this population when the benefits of reduced MDR TB transmission and earlier treatment initiation on quality of life and survival are taken into account; however, this cost analysis does not assess the algorithms' cost-effectiveness.

4.1. Limitations

The cost analysis results should be interpreted in light of several limitations. First, the site sample is not a representative sample of all health facilities in Cambodia, limiting the generalizability of the results. Second, historical cost and procedure volume data were not available in all cases; our results therefore do not capture changes in unit costs before and after Xpert placement that might reflect changes in laboratory workflow or efficiencies from learning the new Xpert testing procedure. Third, the value of personnel time was based on self-reported time or percent effort by clinical and laboratory staff. Some validation of these reports was conducted through observation of staff performing diagnostic procedures at the CENAT and BTB labs; however, it is possible that what was reported and what was observed by data collectors does not reflect how time is spent in routine practice without observation. Fourth, the normative analysis of cost per patient diagnosed under each algorithm, while based on empirical unit costs per procedure, relied on assumptions of test accuracy and clinician guideline adherence that are not expected to represent actual programmatic implementation conditions in Cambodia; this normative analysis helps isolate the variation in algorithm costs due to the combination of procedures used in each algorithm but does not necessarily predict what the actual empirical cost per patient diagnosed will be in this setting. Fifth, our estimates excluded overhead costs, which may be relevant in other settings. Finally, the perspective of the analysis did not include patient costs, and therefore does not capture changes in patient's out-of-pocket costs to provide sputum specimens or obtain test results and health care due to changes in the diagnostic algorithms.

5. Conclusions and Implications for Future Research

As a high-burden TB country with low HIV prevalence, Cambodia offers a distinct epidemiological context in which to examine the costs and cost-effectiveness of Xpert implementation, contributing to the existing literature on Xpert costs in settings with higher prevalence of HIV and TB among PLHIV. Our initial normative cost estimate shows that the use of Xpert for diagnosing TB and RIF resistance in PLHIV and people with presumptive MDR TB is more expensive than previous diagnostic algorithms without Xpert; however, a full cost-effectiveness analysis is needed to weigh these increased costs against Xpert's benefits of more timely and accurate diagnoses given that a major rationale for Xpert adoption is the reduced time to diagnosis and treatment and, by extension, the reduced number of new TB infections. This cost analysis did not consider the differential effectiveness of the pre- and post-Xpert algorithms in terms of disease transmission, morbidity, or mortality; these cost data are intended as inputs to cost-effectiveness analyses and should not be interpreted as a recommendation in favor or against Xpert use without consideration of Xpert's potential public health impacts. The empirical cost per patient diagnosed will depend on the observed sensitivity and specificity of each procedure as well as the proportion of patients receiving each procedure in the study sites, as actual clinical practice may deviate from the algorithms; these data are forthcoming from the broader

program evaluation. Nevertheless, our cost analysis results can inform future planning to optimize GeneXpert placement and use within Cambodia and to project the costs that the Ministry of Health may need to assume in the future if the sources of external aid that supported the initial GeneXpert rollout decrease. Our study also contributes to the literature on the costs of Xpert in routine implementation settings. Future research should examine the relative costs and benefits of placing GeneXpert instruments at lower-level versus more centralized health facilities and how improvements in patient referral and specimen transport may be able to increase test volumes with existing instruments. Future research should also examine the costs and cost-effectiveness of Xpert testing using the Xpert® MTB/RIF Ultra test with higher sensitivity and specificity for smear-negative TB and if other tests using the GeneXpert platform (such as HIV viral load) are available, which could increase the population health benefits derived from existing GeneXpert investments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

The authors would like to acknowledge the input and feedback received from staff at the Cambodia National TB Program (CENAT), Dr. Kanara Nong and Mr. Huot Uong of CDC/Cambodia, and respondents at cost data collection sites in Battambang Provincial Referral Hospital, Mongkol Borei Provincial Referral Hospital, Mong Russey Operational District Hospital, and the CENAT National Laboratory.

Compliance with Ethical Standards

Funding: This work was supported by funding provided by the U.S. Agency for International Development and the U.S. Centers for Disease Control and Prevention, in addition to funding from the President's Emergency Plan for AIDS Relief (PEPFAR) through the U.S. Centers for Disease Control and Prevention. The findings and conclusions in this presentation are those of the authors and do not necessarily represent the official position of the U.S. Centers for Disease Control and Prevention.

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Key Points for Decision Makers

- Across 4 provinces in Cambodia, Xpert MTB/RIF costs were US$33.88-US $37.11 per test.
- Tuberculosis diagnostic algorithms with Xpert were more expensive than pre-Xpert.
- Increasing use of existing GeneXpert instruments would decrease Xpert test costs.
- Test eligibility and specimen referral practices may limit optimal GeneXpert use.

Table 1.

Unit costs per procedure and average monthly procedure volumes by site (costs in 2017 U.S. dollars)

Procedure		BTB	MKB	MR OD	CENAT
Clinical diagnostic assessment	Unit Cost	US$1.84	US$1.22		
	Procedure Volume	*500*	*500*		
Chest x-ray, automatic development (*manual development)	Unit Cost	US$2.02	US$2.14 (US$2.06*)		
	Procedure Volume	*275 (chest) 531 (all x-rays)*	*200 (chest) 350 (all x-rays)*		
Smear Microscopy – FM	Unit Cost	US$1.56	US$1.93		
	Procedure Volume	*500*	*300*		
Smear Microscopy – ZN	Unit Cost			US$1.26	
	Procedure Volume			*140*	
Xpert	Unit Cost	US$33.88	US$37.11		
	Procedure Volume	*40*	*25*		
Liquid Culture – MGIT	Unit Cost	US$22.83			US$11.63
	Procedure Volume	*112*			*350*
Follow-on work up for positive MGIT results and MTB identification	Unit Cost	US$14.72			US$11.63
	Procedure Volume (Follow-on work-up)	*23*			*85*
	Procedure Volume (MTB identification)	*28*			*45*
DST	Unit Cost				US$44.26
	Procedure Volume				*23*

• **BTB:** Battambang Provincial Referral Hospital; **MKB**: Mongkol Borei Provincial Referral Hospital; **MR OD:** Mong Russey Operational District Hospital; **CENAT:** National TB Control Program Lab

• At the time of the study, the GeneXpert instruments did not operate at maximum possible capacity every day at either the BTB or MKB site due to low specimen volumes received.

Table 2.

Inputs representing largest share of unit costs per procedure by site

Procedure	BTB	MKB	MR OD	CENAT
Clinical diagnostic assessment	**Clinician time (49%), Nurse time (35%)**	**Clinician time (74%), Nurse time (18%)**		
Chest x-ray, automatic development	**X-ray film (52%), X-ray machine (14%)**	**X-ray film (49%), X-ray machine (21%)**		
Smear Microscopy – FM	**Lab technician time (17%), Biosafety cabinet (16%)**	**N95 mask (24%), Microscope (18%)**		
Smear Microscopy – ZN			**Reagent kit (41%), Sputum cup (15%)**	
Xpert	**Xpert cartridge (37%), GeneXpert instrument (24%)**	**GeneXpert instrument (36%), Xpert cartridge (34%)**		
Liquid Culture – MGIT	**MGIT 960 instrument (32%), MGIT 7mL tube (10%)**			**MGIT 7mL tube (20%), MGIT 960 instrument (14%)**
Follow-on work up for positive MGIT results and MTB identification	**MTB identification test (22%), Autoclave (12%)**			**MTB identification test (29%), Autoclave (15%)**
DST				**Lab specialist (contractor) time (21%), Sterile filter tips (15%)**

• **BTB:** Battambang Provincial Referral Hospital; **MKB**: Mongkol Borei Provincial Referral Hospital; **MR OD:** Mong Russey Operational District Hospital; **CENAT:** National TB Control Program Lab

Table 3.

Procedure volume and estimated normative cost per patient diagnosed and treated under Cambodia's TB diagnostic algorithms for PLHIV and people with presumptive MDR TB (costs in 2017 U.S. dollars)

Procedure		PLHIV Pre-Xpert Algorithm (no drug resistance)	PLHIV Post-Xpert Algorithm (no drug resistance)	MDR TB Pre-Xpert Algorithm	MDR TB Post-Xpert Algorithm
Clinical diagnostic assessment	Procedure Frequency	1 time			
	Unit Cost	*US$1.22-US$1.84*			
Chest x-ray, automatic development	Procedure Frequency	1 time			
	Unit Cost	*US$2.02-US$2.14*			
Smear Microscopy – FM	Procedure Frequency	3 tests			
	Unit Cost	*US$1.56-US$1.93*			
Xpert® MTB/RIF	Procedure Frequency		1 test		1 test
	Unit Cost		*US$33.88-US$37.11*		*US$33.88-US$37.11*
Liquid Culture – MGIT	Procedure Frequency			2 tests	2 tests
	Unit Cost			*US$11.63-US$22.83*	*US$11.63-US$22.83*
Follow-on work up for positive MGIT results and MTB identification	Procedure Frequency			2 tests	2 tests
	Unit Cost			*US$11.50-US$14.72*	*US$11.50-US$14.72*
Drug Susceptibility Testing (DST)	Procedure Frequency			2 tests	2 tests
	Unit Cost			*US$44.26*	*US$44.26*
DIAGNOSTIC TEST COSTS per TB+ patient (assuming perfect accuracy)*		**US$8.56-US$9.14**	**US$33.88-US$37.03**	**US$134.77-US$163.62**	**US$168.65-US$200.65**
Community Directly Observed Therapy Short Course (C-DOTS)	Procedure Frequency	6 months	6 months		
	Unit Cost (per month)	*US$8.60-US$11.21*	*US$8.60-US$11.21*		
First Line Drugs (6 months)	Procedure Frequency	6 months	6 months		
	Unit Cost (per month)	*US$4.35*	*US$4.35*		
Treatment Monitoring Smear Microscopy – ZN	Procedure Frequency	3 tests	3 tests		
	Unit Cost	*US$1.26*	*US$1.26*		
TREATMENT COSTS per TB+ patient (assuming perfect test accuracy)		**US$81.42-US$97.12**	**US$81.42-US$97.12**		
Scenario without perfect test accuracy					
False positive rate (1-specificity)[1]		0%	1%		
False negative rate (1-sensitivity)[1]		27%	12%		
Necessary treatment costs per patient due to true positives		US$59.43-US$70.90	US$71.65-US$85.47		
Unnecessary treatment costs per patient due to false positives		US$0.00	US$0.81-US$0.97		
Treatment cost increase per patient under post-Xpert algorithm compared to pre-Xpert algorithm (without perfect test accuracy, using assumed sensitivity and specificity)			US$13.03-US$15.54		
Diagnostic cost increase per patient under post-Xpert algorithm compared to pre-Xpert algorithm (without perfect test accuracy, using assumed sensitivity and specificity)			US$25.32-US$27.89		
Total increase in diagnosis and treatment costs per patient under post-Xpert algorithm compared to pre-Xpert algorithm (without perfect test accuracy, using assumed sensitivity and specificity)			US$40.86-US$40.92		

*Range in costs is due to the variation in unit costs per procedure across study sites.

1.Based on assumed sensitivity of 73% and specificity of 100% for FM smear and sensitivity of 88% and specificity of 99% for Xpert (11, 27).

Table 4.

Unit cost of Xpert test under different scenarios for GeneXpert useful life, cartridge prices, and monthly test volume (costs in 2017 U.S. dollars)

Scenario	Useful life of GeneXpert instrument	Price per Cartridge	Average Monthly Xpert Test Volume	BTB Xpert Unit Cost	MKB Xpert Unit Cost
Alternative scenario 5	5 years	**US$10.42 (concessional pricing)**	**Max utilization (BTB:240; MKB:240)**	US$14.22	US$13.23
Alternative scenario 11	**10 years**	US$12.51 (current bulk purchase pricing)	**Max utilization (BTB:240; MKB:240)**	US$15.65	US$14.67
Alternative scenario 2	5 years	US$12.51 (current bulk purchase pricing)	**Max utilization (BTB:240; MKB:240)**	US$16.30	US$15.31
Alternative scenario 4	5 years	**US$10.42 (concessional pricing)**	**Double current levels (BTB:80; MKB:50)**	US$21.25	US$22.85
Alternative scenario 10	**10 years**	US$12.51 (current bulk purchase pricing)	**Double current levels (BTB:80; MKB:50)**	US$21.41	US$21.86
Alternative scenario 8	5 years	**US$17.72 (commercial pricing)**	**Max utilization (BTB:240; MKB:240)**	US$21.51	US$20.52
Alternative scenario 1	5 years	US$12.51 (current bulk purchase pricing)	**Double current levels (BTB:80; MKB:50)**	US$23.33	US$24.94
Alternative scenario 7	5 years	**US$17.72 (commercial pricing)**	**Double current levels (BTB:80; MKB:50)**	US$28.54	US$30.15
Alternative scenario 9	**10 years**	US$12.51 (current bulk purchase pricing)	Current levels (BTB:40; MKB:25)	US$30.05	US$30.96
Alternative scenario 3	5 years	**US$10.42 (concessional pricing)**	Current levels (BTB:40; MKB:25)	US$31.80	US$35.03
Actual study unit costs	5 years	US$12.51 (current bulk purchase pricing)	Current levels (BTB:40; MKB:25)	US$33.88	US$37.11
Alternative scenario 6	5 years	**US$17.72 (commercial pricing)**	Current levels (BTB:40; MKB:25)	US$39.09	US$42.32

Notes: Bold cells indicate dimensions that are varied compared to the actual study unit costs. Max utilization: maximum utilization of three runs per day of a 4-module GeneXpert instrument (12 tests per working day). All unit costs include costs of annual calibration kit (1 kit per instrument, US$521/kit), but not for replacement cartridges or sending instruments abroad for servicing as these were not reported during the study period.