Addis Ababa University

College of Health Sciences

School of Public Health

Cost-effectiveness analysis of Gene Xpert test compared to smear microscopy test for diagnosis of suspected tuberculosis patients at health facilities in Arsi zone, Ethiopia.

By: - Abdene Kaso Weya (Bsc, MPH)

Advisor: - Dr. Alemayehu Desalegne Hailu

A thesis paper submitted to the Department of Reproductive Health and Health Service Management, School of Public Health, College of Health Science, Addis Ababa University in partial fulfillment of the requirements for the degree of Master science of Public Health in Health Economics.

October, 2019

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I, the undersigned MPH student, declare that I have submitted my original work on a title 'Cost-effectiveness analysis of Gene Xpert test compared to smear microscopy test for diagnosis of suspected tuberculosis patients at health facilities in Arsi zone, Ethiopia.

Abdene Kaso Weya _____ _____

Principal Investigator Signature Date

We, the undersigned Advisors, declare that this thesis is our original work in partial fulfillment of the requirement for the degree of Master of Science for the stated student above to our best knowledge. We confirmed that this thesis is ready for defense with our approval as the university advisor

Approved by:

1. Alemayehu Desalegne Hailu _____ _____

   Advisor Signature Date

This thesis by Abdene Kaso Weya is accepted in its present form by the board of examiners as satisfying thesis requirement for the degree of Master of Public Health in Health Economics

Internal examiner:

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Name Signature Date

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_____ _____ _____

Name Signature Date

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Acronyms and Abbreviation

AFB	Acid Fast Bacilli
ACER	Average Cost-Effectiveness Ratio
CDR	Case Detection Rate
DOTS	Direct Observed Treatment Short Course
EPTB	Extra Pulmonary Tuberculosis
ETB	Ethiopian Birr
EQC	External Quality Control
GDP	Gross Domestic Product
FMOH	Federal Ministry of Health
HIV	Human Immunodeficiency Virus
ICE	Incremental Cost-Effectiveness
ICER	Incremental Cost Effectiveness Ratio
INMB	Incremental Net Monetary Benefit
LIC	Low-Income Countries
LMIC	Low and Medium-Income Countries
MODS	Microscopic Observation Drug Susceptibility
MDR-TB	Multi-Drug Resistant Tuberculosis
MDR/ RIF	Multi-Drug Resistant Tuberculosis/Rifampicin
MTB	Mycobacterium Tuberculosis
NTCP	National Tuberculosis Control Program
NTLCP	National Tuberculosis and Leprosy Control Program
NPV	Negative Predictive Value
OPHRCBQAL	Oromia Public Health Research Capacity Building & Quality Assurance Laboratory
PPV	Positive Predictive Value
PSA	Probabilistic Sensitivity Analysis
PTB	Pulmonary Tuberculosis
POC	Point Of Care
QC	Quality Control
SOP	Standard Operating Procedure
SM	Smear Microscopy

TB	Tuberculosis
TB/HIV	Tuberculosis/Human immune Virus
TSR	Treatment Success Rate
USD	United State Dollar
WHO	World Health Organization
YLD	Years Lived With Disability
WTP	Willingness To Pay

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Abstract

Background: Tuberculosis remains a global public health problem. It mainly affects the poor and vulnerable populations. Therefore, there is a substantial global and country level effort to detect and treat tuberculosis cases. Early diagnosis of tuberculosis is one of the pillars of the tuberculosis control strategy. Smear microscopy testing is a routine test for the diagnosis of pulmonary tuberculosis in resource-constrained countries. However, the use of rapid molecular tests like Gene Xpert is increasing, and many countries are scaling up the use of Gene Xpert without a clear evaluation of the cost and cost-effectiveness of the technique.

Objective: To evaluate the cost-effectiveness of Gene Xpert test compared to smear microscopy test for diagnosis of tuberculosis patients at health facilities in Arsi zone.

Methods: We developed a decision-analytic model to evaluate the cost-effectiveness of Gene Xpert algorithms compared to smear microscopy for the diagnosis of tuberculosis. Costs were estimated from the health provider perspective in a one-year time frame. We applied an ingredients-based costing approach to identify, measure, and value the cost of the smear microscopy and Xpert algorithm. Effectiveness was measured as the proportion of cases detected for each of the diagnostic strategies. The cost-effectiveness ratio was calculated by dividing the change in cost and change in effectiveness. One-way and probabilistic sensitivity analysis was done by varying different inputs parameters.

Result: The unit cost of Gene Xpert and smear microscopy methods was $12.92 and $3.1 per test respectively. The unit costs of Xpert and smear microscopy were mostly influenced by the cost of cartridge $10.67 (82.58%) and supplies $1.28 (41.29%). The mean cost of smear microscopy and Gene Xpert site was 3.3$ ($2.4-$4.96) and 12.96$ ($12.69-$13.22) respectively. The cost-effectiveness of the Gene Xpert method was $729.82 per proportion of TB cases detected. During one-way sensitivity analysis, TB prevalence was the most influential parameter on ICER (530.56 to 1401.13 per proportion of TB cases detected).

Conclusion: The unit cost of Gene Xpert is high compared to smear microscopy diagnostic method. Our study found that using the Gene Xpert as a routine test is cost-effective compared to one or three times GDP per capita of Ethiopia and can be part of the routine diagnostic testing strategy. TB prevalence was the most influential parameter of the cost-effectiveness of the Gene Xpert method.
Keywords: Cost, Cost-effectiveness analysis, Gene-Xpert, Arsi zone

1. Introduction

1.1. Background

Tuberculosis is an infectious disease caused by a bacillus *Mycobacterium tuberculosis* (MTB) (1). According to the global tuberculosis report, tuberculosis (TB) is a major global health problem. For example, in 2014, there was an estimated 9.6 million new TB cases and 1.5 million death from the disease (2). The number of TB cases is decreasing in most parts of the World Health Organization (WHO) regions but it is increasing in Africa (3). Africa has the highest number of both TB cases and HIV infections with two thirds of TB patients co-infected with HIV (4).

According to the 2016 WHO TB report, Ethiopia was ranked eighth among the world's 22 high burden TB countries. There were an estimated 191 per 100,000 incident cases of TB in 2015 (5). The increasing trends of TB raised the creation of the Directly Observed Treatment Short Course (DOTS) in 1990. After the DOTS strategy launched, Ethiopia started implementing this strategy as a pilot in Arsi and bale zone of Oromia in 1994. At that time, two targets for TB control at the global level were established. 70% case detection rate and 85% cure rate by the year 2000 (6).

However, the multiple drug-resistant tuberculosis (MDR-TB) strains make it difficult to diagnose and treat the disease. So that there was a need to evolve new diagnostic methods that were fast and cost-effective to reduce the transmission (7). In recent years new molecular and advanced techniques have been used that are more specific and sensitive (8).

In more developed countries diagnosis of TB relies on an advanced and highly accurate machine. The main goals for advances in TB diagnostics include enabling point of care (POC) testing for same-day treatment, improving the accuracy of diagnostic tools and support greater access to drug-susceptibility testing (8). Xpert is recommended by WHO to be used as an initial diagnostic test in all adults presumed to have MDR-TB, TB/HIV and in children (9). It is a cheap, rapid and specific test that can help us in distinguishing specific tuberculosis (10). But, in most resource-poor countries, TB diagnosis relies on smear microscopy due to the low cost (11). Microscopy has been known to be less sensitive due to inherent reasons such as the presence of few bacilli to detect bacilli and inadequate specimen quality (12). Therefore, the aim of this study was to evaluate the incremental cost-effectiveness of Gene Xpert compared to smear microscopy for the diagnosis of TB suspected patients.

1.2. Statement of the problem

Regardless of the availability of free and effective treatment and diagnosis, TB remains a major health problem in Ethiopia(13). Smear microscopy has been used as a routine diagnostic tool for TB diagnosis for a decade. It has a sensitivity of 70% and cannot detect MDR-TB from a patient sample. In addition, the low sensitivity of smear microscopy can delay diagnosis and lead to the secondary spread of tuberculosis infection (14). In 2015, the prevalence of MDR-TB was estimated to be 2.7% and 14% among newly treated and retreated patients in Ethiopia (5). However, the National Tuberculosis Control Program (NTCP) requires effective strategies to rapidly detect and treat the infection with resistant organisms (15). To achieve these technologies like Xpert has been endorsed as a frontline test for tuberculosis testing in populations where there is a high burden of HIV and MDR-TB (2).

However, the high cost of Xpert was a great barrier to the introduction of this algorithm as a routine diagnostic tool. A study conducted in India, South Africa, and Uganda found that diagnostic costs of testing all individuals with suspected TB also increase from US$28–US$49 to US$133–US$146 and US$137–US$151 per TB case detected when Xpert is used "in addition to" and "as a replacement of" smear microscopy respectively. Moreover, the result of this study revealed that the introduction of Xpert increased TB case finding from 72%–85% to 95%–99% of the cohort of individuals with suspected TB when compared to the smear microscopy (16). In addition, a study conducted in South Africa on the use of Xpert MTB/RIF versus sputum microscopy demonstrated that the Xpert group has a higher proportion of positive index test results when used as the initial diagnostic test for tuberculosis. After adjustment for baseline imbalance, there was 49% positive index test result in the Xpert group (14). The NTCP also requires advanced technologies that have good diagnostic accuracy to detect more tuberculosis cases. Gene Xpert is one of the advanced diagnostic methods with high diagnostic accuracy(17).

Xpert is more sensitive than sputum smear microscopy in detecting TB, and it has similar accuracy with golden standards like culture (18). National Validation report found that the overall sensitivity and specificity of gene Xpert for detecting MDR-TB was 100% in new cases whereas in retreated cases it was 95.8% and 89.7% respectively. The overall sensitivity and specificity of gene Xpert in detecting MDR cases were 96.8% and 92.9% respectively. In smear-positive cases, the sensitivity was 94.4% and the positive predictive value (PPV) was 93.4% while the sensitivity and specificity were 75.0% and 81.6% in smear-negative

respectively (13). According to the WHO report, Xpert has an overall sensitivity of 88% and specificity of 99.7% when used as an initial TB diagnostic test. Similarly, when used as an add-on test following a negative smear microscopy result, Xpert had a sensitivity of 68% and specificity of 99% (9).

This tool is easy to train health workers in its use, there is no risk of sample cross-contamination and the need for a specific biological safety environment (19). However, the scale-up of new diagnostic tests as routine testing has important economic implications. The new TB diagnostic tool has to be at least as good as smear microscopy and has an acceptable cost. Moreover, many countries are scaling up the use of Gene Xpert without a clear evaluation of the cost and cost-effectiveness of the technique. Currently, the Federal Ministry of Health of Ethiopia (FMOH) proposed to perform all routine testing for tuberculosis using gene Xpert. However, studies conducted before have been done on an eligible group for Xpert testing. But the absence of information on cost-effectiveness analysis of this new technology on routine patients hinders policymakers and government to take part in full decision to scale up services to all facilities in the country. Thus, this research aimed to evaluate the cost-effectiveness of this new diagnostic method for the diagnosis of TB suspected individuals as a routine diagnosis.

1.3. Significance of the study

At the present time tuberculosis has confronted with different health problems. These problems have aggravated by different risk factors from the socio-economic, cultural environment and absence of rapid and effective diagnostic tests. The rapid and early diagnosis of the disease is required to prevent further infection and spread of disease.

However, the use of this advanced diagnostic technology for routine diagnosis needs economic evaluation. Therefore, this study is initially important by availing information on the cost of providing service for the community. It is also aimed to indicate important and scientific evidence on the effectiveness and cost-effectiveness of this diagnostic tool for policymakers, service providers, and stakeholders. Finally, the findings of this study will also provide a recommendation to review the current diagnostic programs offered in the health centers and hospitals in Ethiopia.

2. Literature review

2.1. Overview of TB

Tuberculosis remains a considerable global public health concern (20). The recent global burden of disease (GBD) estimated that latent tuberculosis was responsible for 1 out of 4 years lived with disability (YLD) and 1.3 million TB deaths in 2016. About 59% of the estimated number of cases occurred in Asia and Africa (21). Recent evidence demonstrated that TB prevalence and TB death rates were globally decreased after reached a peak. It was estimated that 37 million lives were saved between 2000 and 2013 through effective diagnosis and treatment (22). However, TB case-load continued to grow in Africa (23). Despite significant efforts to control TB, it remained a major health problem in Ethiopia. Ethiopia stands 8th among the world's top 22 TB high-burden countries (6). The estimated TB incidence per 100,000 populations was 163 in 2016. The prevalence of MDR-TB in Ethiopia has been increasing from 1.6 to 2.7% in new cases and 11.8 to 14% in retreated TB cases from 2005 to 2015 (24). Poverty and a rapid spread of HIV were among the risk factors for developing TB, which placed Ethiopia among highly burdened countries (25). Therefore, early diagnosis and effective treatment are needed to tackle transmission of MTB.

2.1. Diagnostic tests for TB diagnosis

Tuberculosis continued to be a major public health threat worldwide despite the availability of highly sensitive diagnostic tools (26). In order to successfully control the spread of MTB, cases must be detected and treated immediately. The detection of cases has been relied on direct smear microscopy in low and middle-income countries (LMIC) (27). It has relatively low sensitivity and can accurately detect TB in 20% to 80% of TB cases (28). Moreover, smear microscopy has little value in extra pulmonary TB (EPTB) and children. For these reasons, microbiological confirmation of childhood tuberculosis relies on a combination of signs, symptoms and radiological findings (29). Therefore, the introduction of new diagnostic tests that have high sensitivity and specificity is needed to alleviate this problem.

In 2010, the WHO endorsed the Xpert MTB/RIF assay, a rapid molecular diagnostic tool for the diagnosis of MDR-TB (30). It is a fully automated molecular assay in which real-time polymerase chain reaction technology is used to detect MTB and RIF mutations in the rpoB gene (31). The availability of Xpert offers the potential for rapid and accurate diagnosis of TB and MDR-TB. This has generated new hope in resource-constrained countries with high

burdens of TB/HIV co-infection like Ethiopia (9). The Gene Xpert result was available within 2 hours (32). According to the WHO, the four-module Xpert instrument has a capacity of 15 - 20 tests per working day. Human resource requirements were considerable, with a minimum of 2 staff needed to process TB tests daily (33)**.** This simple test can be implemented almost in every set up. However, its' cost, environmental limitations, lack of awareness on program guidelines and local repair options were major obstacles in low-income countries (19, 34).

2.2. Cost of providing TB diagnosis

Performing the Xpert assay is relatively simple and involves minimal specimen processing. However, difficulties involved in the supply, calibration, maintenance and programmatic cost requirements associated with the assay caused the implementation to be more challenging than expected (18).

Furthermore, the cost of the diagnostic system may increase due to the high cost of cartridge, number of assays and decreasing testing volume. A study on Xpert MTB/RIF for diagnosis of tuberculosis and drug-resistant tuberculosis found that using Xpert to diagnose MDR-TB would cost US$70–90 million per year globally. In this report, diagnosing TB in HIV-positive people would cost US$90–101 million per year and lower than conventional diagnostics. They also found that testing everyone with TB signs and symptoms would cost US$434–468 million per year globally (28). A cohort study of Pulmonary tuberculosis (PTB) in South Africa primary care clinic indicated that Xpert costs were mainly driven by the costs of the cartridge (47%), cartridge procurement (24%) and equipment (16%) (35). A study from Ugandan peripheral settings also showed that the mean unit cost of the Xpert test was US$21 based on a mean monthly volume of 54 tests (36).

Furthermore, the cost of providing diagnostic services using the Xpert method was high compared to AFB smear microscopy. For example, in South Africa, the mean total cost per study participants for tuberculosis investigation and treatment was US$31,258 in the Xpert group and $29,858 in the microscopy group. The mean health service provider cost in this study was $16,879 for the Xpert group and $16,046 for the microscopy group (37). In Nigeria, a study demonstrated that the cost per positive case detected using smear microscopy test was $52.84 (38). Moreover, a study on incremental cost-effectiveness of the second Xpert MTB/RIF assay to detect MTB reported that the incremental cost of performing a second Xpert was huge. Besides this, the second Xpert assay is beneficial not only for MTB detection but also for MDR-TB diagnosis for smear-negative TB suspects (39).

2.3. Cost-effectiveness studies on the TB diagnostic methods

Introduction of Xpert into the routine diagnostic procedure can lead to an improvement in the quality of care, reduce delay in time for treatment initiation and were cost-effective (40). A number of studies found that Gene Xpert was a cost-effective method for the diagnosis of PTB and reduces TB mortality in comparison to smear microscopy. For example, a study on the impact of Xpert/MTB/RIF on cost and time to treatment for the diagnosis of tuberculosis revealed that initiation with the addition of Xpert to the diagnostic algorithm, increased costs, reduced days to TB treatment initiation and was cost-effective (41).

On the other hand, a study conducted in Hong Kong indicated that Xpert would be the most cost-effective option if the sensitivity of smear microscopy was 74% or less (42). Moreover, in the United States a study demonstrated that compared to existing molecular assays, implementation of Xpert was very cost-effective at willingness-to-pay (WTP) of US$50,000. It can save on average about 51.5 patient-hours in all and up to $11,466 relative to microscopy without a compromise in sensitivity (43, 44). Other previous studies also indicated that the Xpert test was a cost-effective diagnostic technique for the diagnosis of TB (45-48).

On the other hand, the cost-effectiveness of the Gene Xpert test was determined by many factors. A study on the cost-effectiveness of novel diagnostic tools for the diagnosis of tuberculosis in South Africa, Brazil and Kenya revealed that adding novel diagnostic tests for TB was more cost-effective. They observed the cost-effectiveness was sensitive to the specificity, price of the new test, the baseline TB CDR and the discount rate (49). Furthermore, screening with Xpert was found to be cost-effective and determined by the prevalence of TB among patients with HIV and volume of testing in Malawi (50) and by the sensitivity of Xpert in Ethiopia (51). However, there was emerging evidence, that using Xpert in resource-limited health care settings may not be cost-effective or cost-neutral (52, 53).

In Uganda, the study revealed that the algorithm using microscopic observation drug sensitivity (MODS) was more cost-effective compared to the Xpert algorithm for a wide range of parameters. The cost-effectiveness ratio of the algorithm using MODS was US$ 34 per TB patient diagnosed compared to US$ 71 of the algorithm using Xpert (54). Moreover, a study in South Africa showed that Xpert introduction was cost-neutral, and found no evidence that Xpert improved the cost-effectiveness of tuberculosis diagnosis (37).

In general, the scale-up of advanced and novel diagnostic tools for routine TB diagnosis needs information on the cost and cost-effectiveness. Some previous studies in different countries reported that using Xpert for TB diagnosis was cost-effective while others revealed as not cost-effective or cost-neutral. Similarly, they demonstrated that the cost-effectiveness of this test was determined by TB prevalence, willingness to pay (WTP), the accuracy of the test, the volume of the test, and the cost of the cartridge.

3. Objective

3.1. General objective

The general objective of this study was to evaluate the cost-effectiveness of the Gene Xpert test compared to the smear microscopy test as diagnostic methods of suspected tuberculosis patients at public facilities in Arsi zone, Ethiopia.

3.2. Specific Objectives

1. To estimate the cost of providing Gene Xpert and smear microscopy diagnostic services for the diagnosis of suspected tuberculosis patients in public health facilities in Arsi zone.
2. To determine the effectiveness of Gene Xpert and smear microscopy diagnostic methods for detecting tuberculosis among TB suspected individuals in public health facilities in Arsi zone.
3. To evaluate the incremental cost-effectiveness ratio of Gene Xpert test compared to smear microscopy as diagnostic methods of TB suspected patients in Arsi zone facilities.

3.3. Research Questions

- What is the unit cost of providing TB diagnostic services using the Gene Xpert and AFB smear microscopy algorithm?
- Which diagnostic method detects more proportion of TB cases among TB suspected individuals in public health facilities in Arsi zone?
- Is the Gene Xpert cost effective compared to smear microscopy algorithm?

4. Methods

4.1. Study design

Cost-effectiveness analysis using a decision analysis model was conducted to compare tuberculosis diagnostic algorithms. The costing part of this study was done using an institutional based cross-sectional study design.

4.2. Study period

This study was conducted from January 1 to February 30, 2019.

4.3. Target population

The source population of the study was all tuberculosis suspect patients who had presented with signs and symptoms of TB in public health facilities in Arsi zone in 2018/2019.

4.4. Study population

The study population was all tuberculosis suspected patients who had presented with signs and symptoms of TB and sent to the laboratory for diagnosis in selected health facilities of Arsi zone in 2018/2019.

Inclusion criteria: -All patients come with a sign and symptom of TB to selected facilities and who referred from other facilities to these facilities laboratories for diagnosis of TB.

Exclusion criteria: - Patients who have incomplete data on AFB registration logbook and didn't provide sputum after sent from the outpatient department.

4.5. Study setting

A study on the cost-effectiveness analysis of Xpert compared to smear microscopy was conducted in TB laboratory located within Arsi zone health facilities. Arsi zone, which is 175 km far from Addis Ababa comprises of 28 Woreda and two town administrations. The zone consists of a total of 7 hospitals and 102 health centers. In hospitals and health centers Laboratory operates under the National Tuberculosis and Leprosy Control Program (NTLCP) of Ethiopia.

4.6. Comparative strategies

The analysis was conducted from a health provider perspective. We compared two diagnostic methods, the smear microscopy, and Xpert method. In the Xpert algorithm, a single sputum specimen was tested by Xpert for all persons suspected of TB. The test procedure may be used directly on either fresh sputum samples or sputum pellets, which are obtained after decontaminating and concentrating the sputum. In both cases, the test material is combined with the reagent, in a 2:1 ratio for sputum liquefaction and inactivation mixed by hand or vortex. Then it was incubated at room temperature for 15-20 minutes. After incubation, a total of 2 ml of the mixture was introduced into an Xpert MTB/RIF cartridge, which was then loaded into a Gene Xpert instrument for analysis. The instrument generates the test report automatically within 2 hours (9). In the smear microscopy method, all persons would present two sputa for tuberculosis diagnosis.

4.7. Sample size determination

The sample size was calculated by using the formula from the method proposed by Glick et al 2011a (55). The parameter like standard deviations for the effectiveness (1.74 DALY), standard deviations for the cost ($9.07), WTP (505 GDP per capita), the expected incremental effectiveness (0.2 DALY) and the expected incremental cost (1$) were used from a study done in ALERT hospital for calculation of the sample size (51).

$$n= 2*\frac{(Z\alpha+Z\beta)^2 *(Sdc^2+ (W* Sdq)^2- (2W \rho*Sdc\ Sdq)}{(WQ-C)^2}$$

Where:

Zα is the Z-statistic for the level of Type I error (usually set at 95%) =1.96

Zβ is the Z-statistic for the level of Type II error (usually set at 80%) =0.84

Sdq = the standard deviations for the treatment effect.

Sdc = the standard deviations for the treatment effect cost.

W= the Maximum Willingness to Pay.

Q= the expected incremental effectiveness

C= the expected incremental cost =1$

ρ= the expected correlation of the difference in cost *(C)* and effect which assumed to be zero

$$n= 2*\frac{(Z\alpha+Z\beta)^2 [(Sd^2+ (W* Sdq)^2-(2w \rho*Sdc\ Sdq)]}{(WQ-C)^2}$$

$= \frac{2*(1.96+0.84)^2\,[9.07^2 + (505*1.74)^2 - (2*505*0*1.74*9.07)]}{(505*0.2-1)^2} = 1211$

= 1211 per group and considering 10% for incomplete data = 1211+ 121= 1332

The calculated final minimum sample size for this study was 1332 per diagnostic method.

4.8. Sampling procedure

After examining a year report of the health center and hospitals providing TB diagnosis and treatment services, eight health facilities were selected purposefully. Then the sample was proportionally distributed based on the number of patients treated in that facility. Finally, a systematic random sampling method was used to select study participants from each health facility, with sampling interval k=2 and 1 for Xpert and smear microscopy group respectively. The first participant from the first two was selected by the lottery method using their registration number for each health facility (Figure 1).

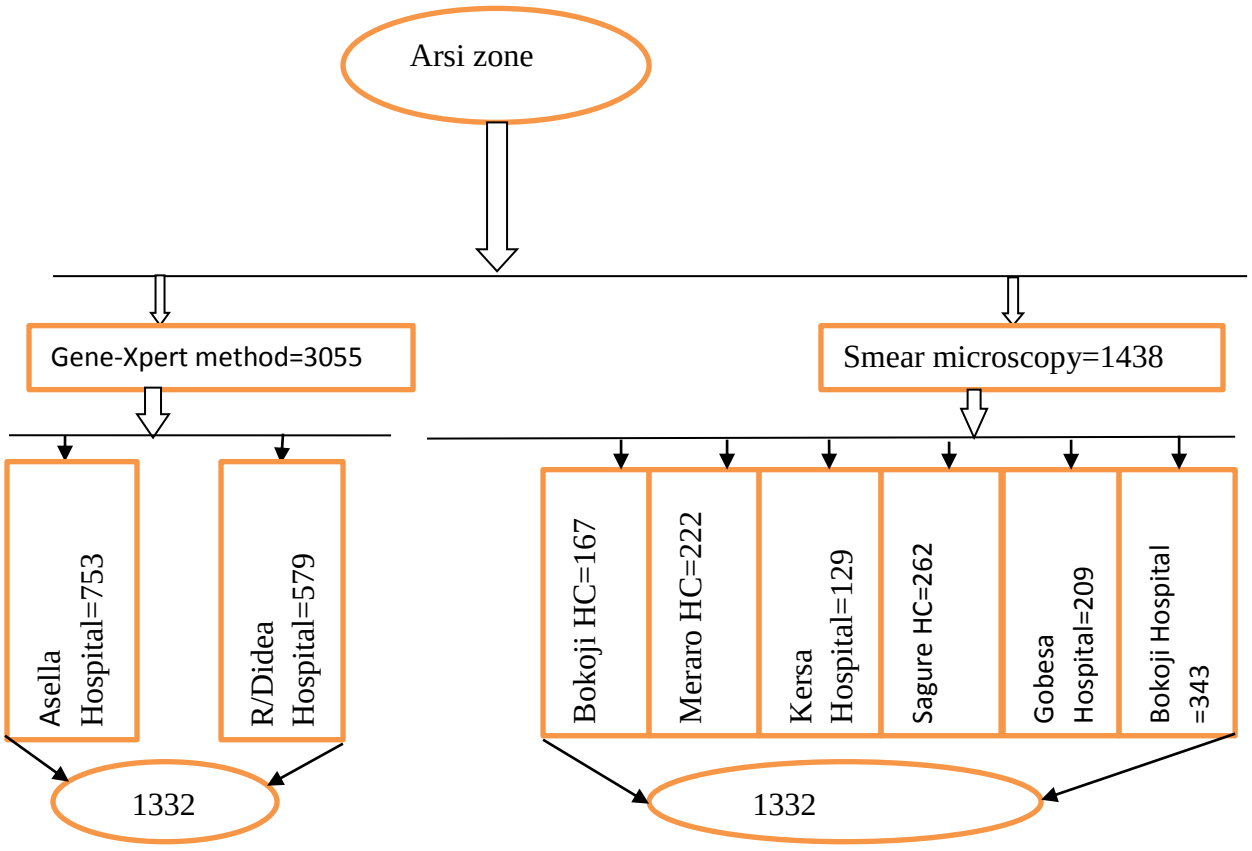

Figure 1:- Sampling frame showing the size of the sample for each selected health facility for evaluation of cost-effectiveness Xpert compared to smear microscopy among TB patients in Arsi zone, Ethiopia in 2018.

4.9. Operational definition

Allocation base: the unit of cost measurement for allocation.

Consumer price index: the current prices of goods and services in terms of the prices during the same period in the previous year to show the effect of inflation on purchasing power.

Exchange rate: Price for which the currency of a country can be exchanged to another common currency.

Sensitivity analysis: Analysis in which key quantitative assumptions and computations are changed systematically to assess their effect on the final outcome.

Cost allocation method: Cost allocation method where the method of allocating one department cost to another specific unit before allocating cost to the final cost centers.

Standard operating procedure: a step by step procedure specific to your operation that describes the necessary activities to be accomplished in accordance with regulations or standards established in the organization.

Probabilistic sensitivity analysis: Type of sensitivity analysis used to understand the influence of parameter uncertainties or assumptions on the model result.

Ingredient based costing: Costing approach that identifies all the inputs required to perform a test, their quantities and values them to arrive at the unit cost.

4.10. Data collection methods and procedures

The data collection tools were developed based on guidelines for cost and cost-effectiveness analysis of tuberculosis control prepared by WHO in 2002(24). The data collection process is coordinated and supervised by a hired supervisor, and the principal investigator. A total of 3 individuals were hired; 1 supervisor and 2 data collectors. The training was given on data collection format before the data collection and pretest was conducted at Asella health center. Based on the feedback from the pretest necessarily correction was made on data collection tools. The data was collected from the review of procurement invoice, patient log book, payrolls of salary, administration report, literature review and estimate of expert and other responsible bodies.

4.11. Diagnostic cost

Identification, measurement, and valuation of the cost of tuberculosis diagnosis techniques were conducted from the health providers' perspective.

4.11.1. Identification of cost

All costs for the diagnosis of TB suspected individuals with smear microscopy and Xpert algorithm were included. For smear microscopy, different costs like building space, equipment, overhead, staff, and training were included in cost-effectiveness analysis. In addition, the cost of quality control conducted every week and during opening new batch reagents were included. However, the cost of the annual calibration of the microscope was not included in the study.

For Gene Xpert, the costs of building space, overhead, Gene Xpert IV module machine, and its accessories were included. Moreover, for this algorithm cost of operating staff and training needed for conducting Xpert diagnosis were included in analysis. Costs of External Quality Control (EQC) and annual calibration of the Xpert module were also accounted for the analysis. However, for both TB diagnostic methods cost of service maintenance was not included due to the absence of cost data.

4.11.2. Measurement of cost

We collected costs of overhead, building space, equipment, staff, reagents, and consumables related to each algorithm from procurement invoice, expert and managers opinion, a systematic review and administration reports available in health facilities. We used an excel spreadsheet to record cost information. The cost types and quantity of each resource used in each diagnostic technique were recorded and calculated.

4.11.3. Valuation of cost

Cost estimation for compared diagnostic methods was estimated for a one-year time frame using an ingredients approach method. The cost of reagent and consumables for smear microscopy was obtained by dividing the gross cost of a given measure of each reagent over the average number of tests that can be performed using that amount. In addition, the cost of the cartridge for the Xpert test obtained from a published source (56). The cost of overhead for each algorithm was calculated by taking 5% of the total health facility overhead cost

based on expert opinion and discussion with laboratory head. For buildings, an expected lifetime of 30 years was used. Laboratory space cost was allocated based on the proportional size required for conducting TB diagnosis. The cost of quality control (QC) for smear microscopy was obtained by identifying all resources needed to perform QC and multiplying by the total QC recommended according to guidelines and SOP in the year. The cost of EQC for Xpert was obtained by multiplying the cost of the cartridge by the amount of cartridge used in four-term proficiency testing. Gene Xpert module annual calibration must be performed every 2000 tests or every 12 months. The cost of the annual calibration was obtained from the Stop TB partnership (57). The cost of EQC per test was obtained by dividing the annual calibration cost over 2000 tests as recommended by the manufacturer when QC should be performed. The cost of equipment for each diagnostic method was obtained by dividing the annualized cost of the equipment over the number of tests performed in that year. The useful life of microscopy was assumed to be 10 years and run five tests per day. Based on expert opinion and observation about 100 % and 40% of microscopy use were allocated for smear microscopy at hospitals and health centers respectively. With regard to the Gene Xpert algorithm, the laboratory utilized four modules Xpert machine operating four simultaneous tests and running for 8 hours per day. The instrument was assumed to have a useful life of 10 years and to process on average 8 sputum samples per day. We valued personnel cost based on an estimated proportion of working time spent on tuberculosis diagnosis by each diagnostic method. The smear microscopy diagnostic procedure assumed to take five minutes per slide for sputum smear preparation, plus 11 minutes from fixing to adding counterpart reagent and an additional seven minutes per slide for manual readings. Moreover, we assumed that all procedures related to testing by the Xpert method would take 25 minutes per test. The number of training days for conducting tests by AFB smear microscopy and Xpert was assumed to be 5 days and 3 days respectively. Data on the cost of training was obtained from OPHRCBQAL (Oromia Public Health Research Capacity Building & Quality Assurance Laboratory). Capital costs such as Gene Xpert machine, fridge, light microscopes, and building costs were annualized using a standard discount rate of 3% per year as used in similar studies (35, 58). Local costs were collected in Ethiopian birr and converted to United States dollars (USD) using exchange rates by Commercial Bank of Ethiopia (1USD= 27.18 birr) (59). All the costs were adjusted for inflation using the consumer price index of the year 2018 as a base year cost.

Table 1:- Value and sources of data relevant to the costing of the Xpert algorithm.

	Value	**Source**
Capital costs		
Gene Xpert Machine (four module) and accessory	Calculated per test	procurement invoice
Building	Space required	Administration and expert opinion
Recurrent costs		
Xpert MTB/RIF cartridge	$9.98	Published price (56) .
Consumables	Calculated per test	Procurement invoice
Salaries	Average staff salary per hour	payroll
Staff time per test	0.25 min/sample	SOP
External quality assessment		Lab report
Annual module calibration	$450	(57)
Training (3 days)	Training compensation	OPHRCBQAL
Overhead cost	calculated per test	Administration report and expert opinion

Table 2:- Value and source of data needed for smear microscopy diagnostic method.

Cost	Valuation method	Source
Capital costs		
Light Microscope	Calculated per test	invoice
Building	Space used	Measurement and expert opinion .
Recurrent costs		
Reagents	Calculated per test	Procurement invoice
Consumables	Calculated per test	Procurement invoice
Salaries	Average salaries/hour	Administration and payroll
staff time per test	Lab: 0.35 min/sample	SOP
Quality control	Calculated per test	SOP and TB guidelines
Training (5 days)	Training compensation	OPHRCBQAL
Overhead cost	Calculated per test	Administration report and expert opinion

4.12. Model structure

A decision analysis model was developed using TreeAge Pro software version 2019 to compare the cost-effectiveness analysis of diagnostic algorithms for the diagnosis of TB (Figure-2). This economic evaluation was conducted from a health system perspective with study participants of 1332 suspected TB patients per diagnostic method. Tuberculosis prevalence was used as the probability of being positive for each algorithm. A positive test result was either a test positive (true positive) or a test negative (false positive) based on the sensitivity of the diagnostic algorithm. A negative test result method was either a test negative (true negative) or a test positive (false negative) based on the specificity of the diagnostic method.

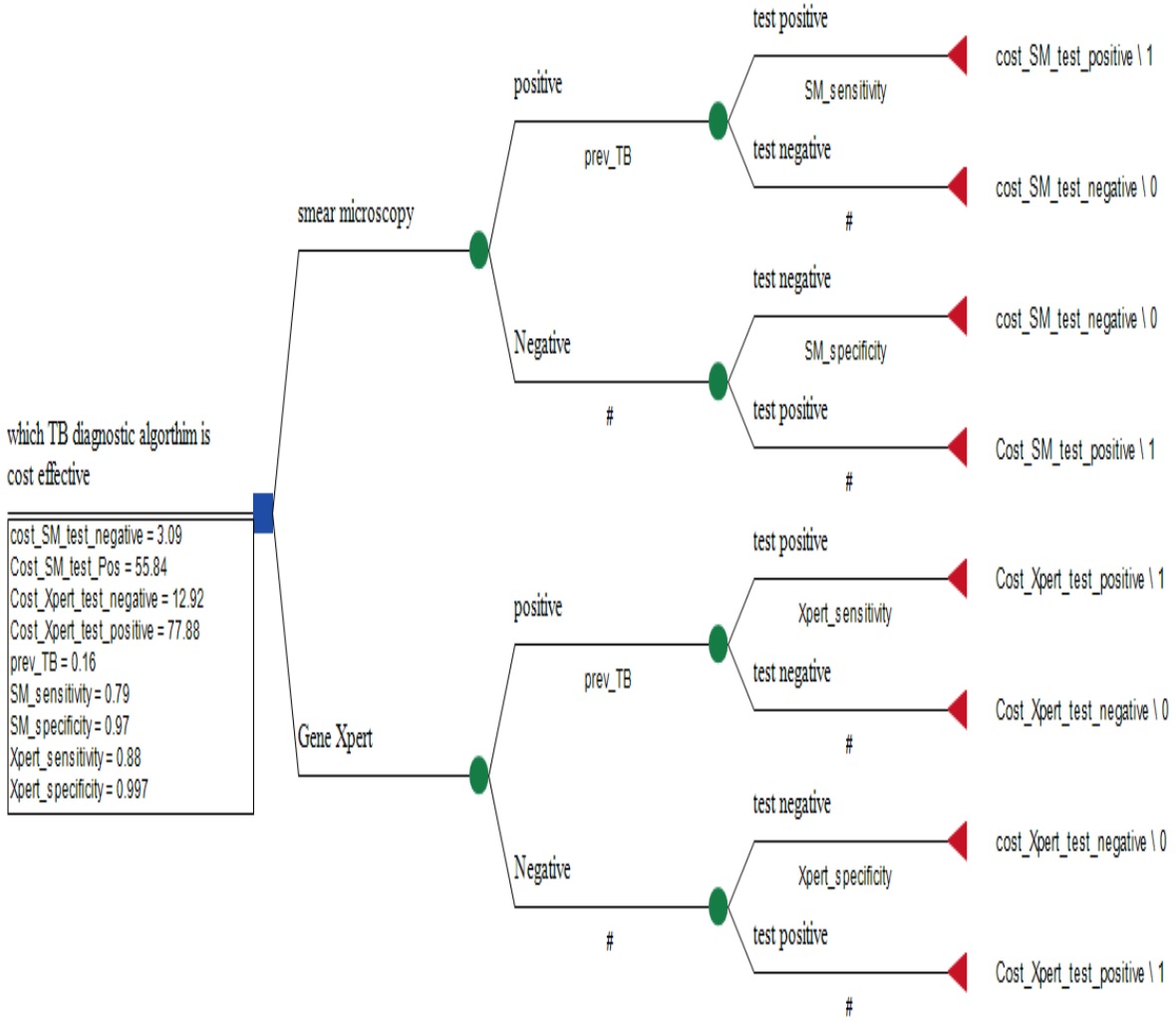

Figure 2:- Decision tree analysis model for diagnosis of pulmonary tuberculosis suspect patients using SM or Xpert at Arsi zone in 2018.

4.13. Model parameters

The epidemiological parameters included in the decision analytic model were the prevalence of TB and the estimates of diagnostic accuracy for tuberculosis diagnosis. Input parameters for each method were obtained from the published data on the sensitivity and specificity of TB diagnostic methods and TB prevalence. We used the pooled values as the base estimates and the 95 % confidence interval values as the outer limits for the diagnostic accuracy of the tests. For cost data, we assumed the lower boundary and the upper boundary to be 20% more or less than the base cases. However, to assist the generalizability of our results we assumed 95% CI of TB prevalence to be 50% above or below the base case result.

Table 3:- Model parameters assumption for tuberculosis using smear microscopy or Gene-Xpert in 2018 at Arsi Zone.

Model input	Value	Min	Max	type data	source
# Test sensitivity Xpert	0.88	0.84	0.92	Beta	(9, 13)
# Test specificity Xpert	0.997	0.97	1.00	Beta	(9, 13)
# Test sensitivity of Two smear	0.79	0.52	0.82	Beta	(27, 60, 61)
# Test specificity of Two smear	0.97	0.94	0.99	Beta	(27, 60, 61)
# TB prevalence	0.16(62)	0.08	0.24	Beta	primary and ± 50%
Cost of smear test negative	3.09	2.48	3.72	Gamma	primary and + 20%
Cost smear test positive	55.84	44.67	67.01	Gamma	primary and ± 20%
Cost of Xpert test positive	77.84	62.3	93.46	Gamma	primary and ± 20%
Cost of Xpert test negative	12.92	10.34	15.5	Gamma	primary and ± 20%

4.14. Effectiveness data

The model's primary outcome measure was the proportion of positive cases detected when each diagnostic method was used for TB diagnosis in suspected tuberculosis individuals.

4.15. Data Analysis

Cost and effectiveness data were entered and analyzed with Microsoft Excel. TreeAge Pro software version 2019 was used to build the decision model and for cost-effectiveness and sensitivity analyses.

4.15.1. One way sensitivity analysis

We performed a one-way sensitivity analysis using a tornado diagram of the model based on adjustments of parameters used in the model using the minimum and maximum values obtained from a different source. A tornado diagram is a graphical presentation of a one-way sensitivity analysis. It used to indicate the influence of model parameters based on the

magnitude of their effects on the ICER. In addition, the scenario analysis was conducted for low and high values of parameters used in the model.

4.15.2. Probabilistic sensitivity analysis

We conducted Probabilistic Sensitivity Analysis (PSA) for the distribution of selected variables using Monte Carlo simulation. It considers model inputs were specified as a distribution and varied to see what difference they created on the incremental cost-effectiveness ratio (ICER). The result of the analysis was presented using cost-effectiveness acceptability frontiers and incremental cost-effectiveness (ICE) scatter plot. Moreover, the PSA result was presented by Incremental Net Monetary Benefit (INMB). The INMB is used as a sensitivity analysis tool on the willingness to pay. It is calculated by multiplying the difference in effectiveness by WTP and subtracts the difference in cost of the two interventions (63). Gamma distribution was used for cost while beta distribution was utilized for probabilities.

4.15.3. Cost-effectiveness Analysis model`

A decision-analytic model was developed using TreeAge Pro software version 2019 to estimate the cost-effectiveness of the routine diagnostic procedures for the diagnosis of TB. A cost-effectiveness analysis was performed by putting the diagnostic accuracy, TB prevalence, proportion of case detected and costs of each method into the software. The diagnostic method had payoff one for case detected while cases that were not detected had a payoff of zero. In all diagnostic techniques, the cost payoffs were the costs for the diagnostic method for TB diagnosis. Even though there isn't universally accepted WTP for this intermediate outcome, we utilized the WHO recommended WTP. The estimated ICER was compared with the WTP for Ethiopia (US$891 based on the gross domestic product (GDP) per capita in 2018) (64). According to WHO recommendation, interventions having ICER less than one GDP per capita were considered as "very cost-effective", between one and three times GDP per capita as "cost-effective" and greater than three-times GDP per capita as "not cost-effective" (63).

4.16. Data Quality assurance and Management

Data were collected by trained laboratory technicians after giving two day training on data collection format. The supervisor was supervised every activity of data collectors and filled

formats. The extracted data were cross-checked using the TB register which was also kept in the same unit. At the end of each day of data collection, the data collected was checked by the principal investigator for completeness.

4.17. Ethical Approval

Ethical approval was obtained from the Addis Ababa University School of Public Health Institutional Review Board. Permission letter to conduct the study in Arsi Zone was obtained from the Oromia Regional Health Bureau Research ethical clearance unit. As data were collected from patients' logbook, the consent of patients was obtained from health facilities administrations. Patient information was handled anonymously to ensure confidentiality.

4.18. Result dissemination plan

The result of the study will be disseminated to responsible bodies such as Addis Ababa University, Arsi Zonal health Beraue, woreda Health office from which health facility selected as well as Health facilities administrations. The study finding will be also submitted to professional journals on health for publication to serve as a data source for further studies.

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5. Results

5.1. Socio-demographic and clinical characteristics of patients

Among 1332 study participants diagnosed by smear microscopy, 692 (52%) were male and 640 (48%) were female respectively. Out of patients diagnosed by AFB smear microscopy, 1258(94.4%) had smear-negative results while 74 (5.6%) had smear-positive. Moreover, about 724 (54.4%) males and 608 (45.6%) females were tested by the Xpert method. Out of patients diagnosed by the Xpert algorithm, 221 (16.6%) had tuberculosis while about 1111 (83.4%) were negative for tuberculosis (Table 4).

Table 4:- Socio-demographic and clinical characteristics of TB suspected patients diagnosed by smear microscopy and Xpert methods at public health facilities in Arsi Zone in 2018.

Algorithm	Category	Percentage
Smear microscopy	Male	692(52%)
	Female	640(48%)
	Smear positive	74(5.6%)
	Smear negative	1258(94.4%)
	.	
Gene Xpert	Male	724(54.4%)
	Female	608(45.6%)
	Positive	221(16.6%)
	negative	1111(83.4%)

5.2. Cost of Gene Xpert and AFB smear microscopy diagnostic algorithm

The unit cost of smear microscopy and Gene Xpert methods varies from facility to facility. In the smear microscopy site, the mean cost of the test was $3.3. The unit cost ranges from $2.4 to $4.96 based on the annual volume of testing and level of health facilities. Furthermore, the mean cost of the Gene Xpert method site was $12.96. The unit cost of the Gene Xpert method was $12.69 and $13.22 for high and low volume testing health facilities respectively (Table 5).

Table 5:- Cost type and unit cost of smear microscopy and Xpert diagnostic method among selected public health facilities in Arsi zone, Oromia, Ethiopia, in 2018/2019.

Health facilities	Supplies	Overhead and space	equipment	Staff cost	Unit cost	Mean cost (range)
Smear microscopy site						
Total cost	$1,637.3	$490.28	$749.89	$1,191.9	$3.1	3.3 $ (2.4-4.96$)
Bokoji HSP	$312.30	$106.74	$210.70	$265.54	$2.79	
Bokoji HC	$240.98	$59.32	$64.58	$190.29	$3.32	
Kersa HSP	$214.14	$103.34	$151.88	$170.16	$4.96	
Sagure HC	$312.30	$59.39	$67.95	$189.95	$2.40	
Gobesa HSP	$271.97	$103.28	$188.01	$192.33	$3.62	
Meraro HC	$285.58	$58.21	$66.77	$183.61	$2.68	
Gene Xpert site						
Total cost	$14,207	$232.2	$1,761.3	$1,009.5	$12.92	12.96$ (12.7-13.2$)
Asella HSP	$8,002.7	$130.18	$882.2	$543.37	$12.7	
R/Didea HSP	$6,204.2	$102.06	$879.1	$466.1	$13.22	

5.3. Cost per test for tuberculosis diagnostic method

Costs per test conducted were USD 12.92 for Xpert and USD 3.1 for smear microscopy respectively. The smear microscopy costs were largely attributable to consumables USD 1.28 (41.29%) per test. Similarly, most drivers of the unit cost of Xpert were consumables and cost of Xpert cartridges USD 10.67 (82.58%) per test. Overhead costs associated with performing Xpert were low (USD 0.17 per test) compared to smear microscopy (USD 0.37 per test) (figure 3).

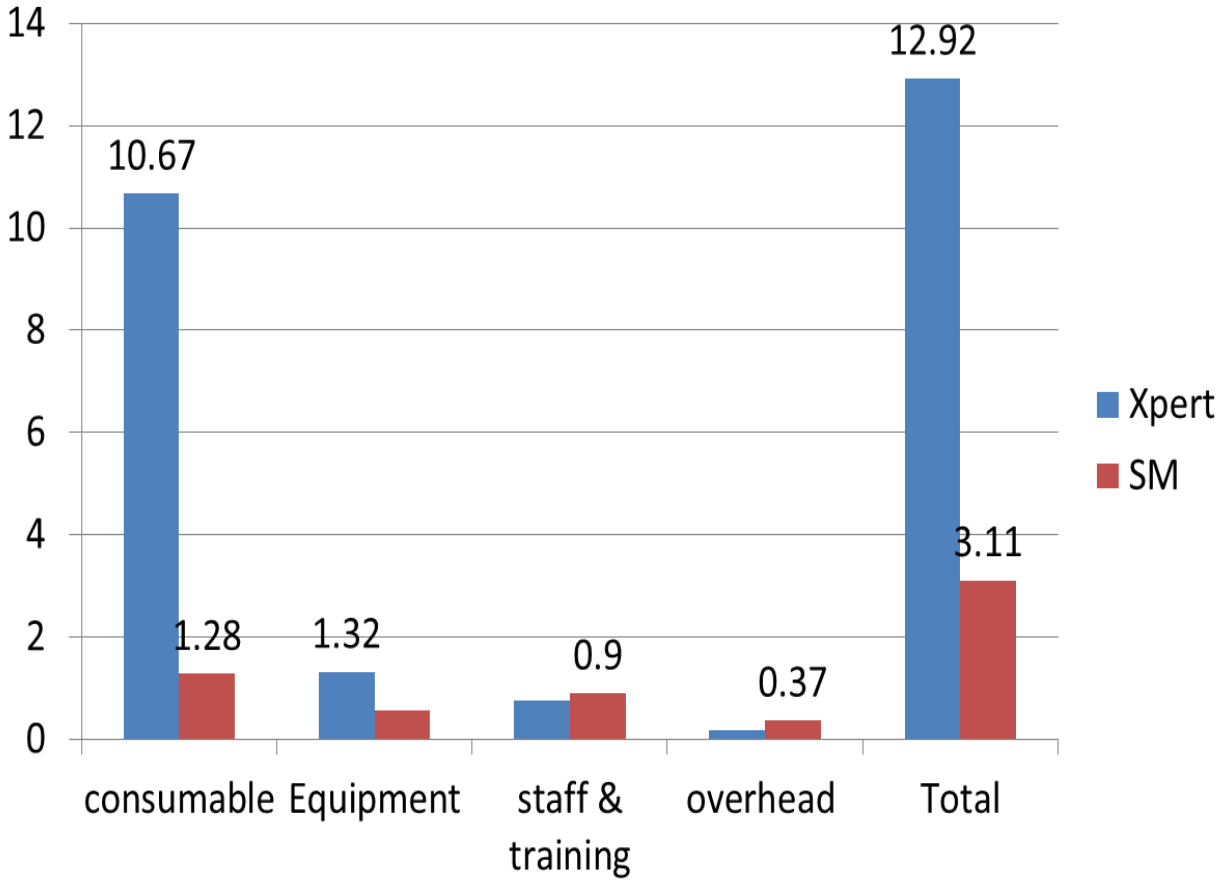


Figure 3:- Unit cost per test for smear microscopy versus Xpert diagnostic method among TB suspected individuals in Arsi zone, Ethiopia, 2018/2019.

5.4. Cost per tuberculosis case detected for diagnostic method

The cost per TB case detected for smear microscopy diagnostic method was USD 55.84. Out of this, the cost of consumable accounts for USD 22.97 (41.14%) and the cost of staff accounts for USD 16.11(28.85%) of the total cost. Overhead and equipment cost accounts for 30.01% of the total unit cost. Moreover, the cost per TB case detected for the Xpert algorithm was USD 77.88. A higher percentage is attributed to the cost of consumable (cartridge) USD 64.29(82.55%) and equipment USD 7.97(10.23%) (Figure 4).

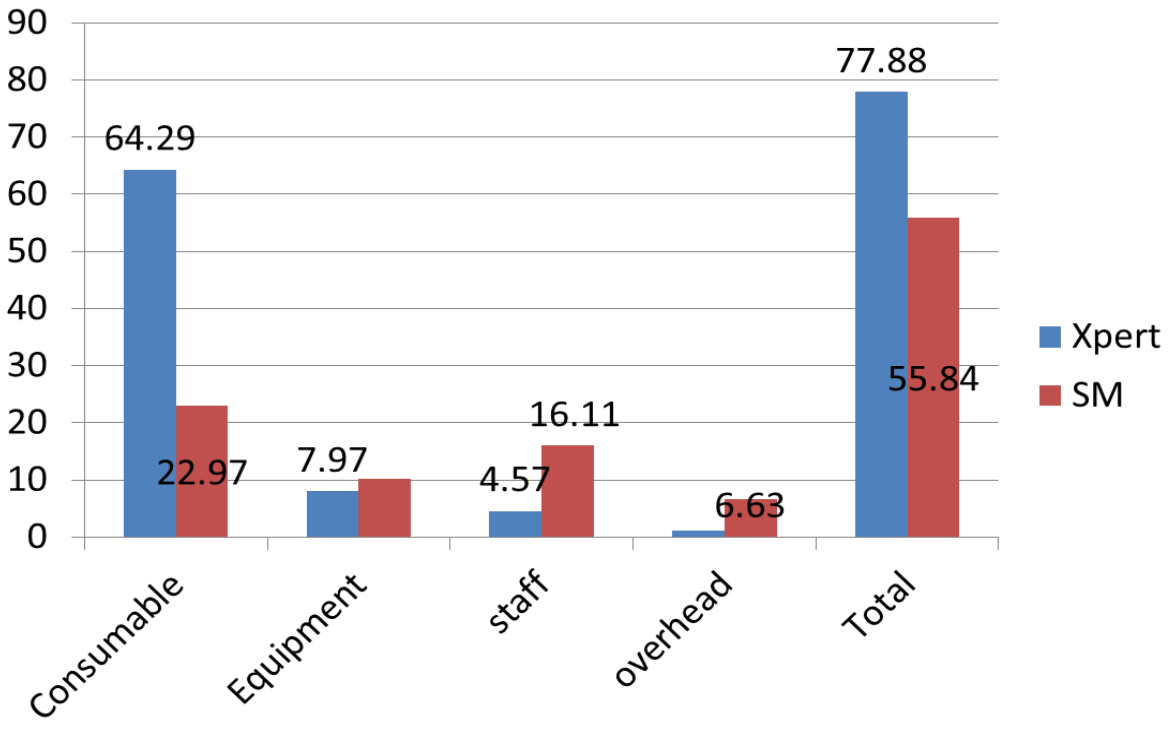


Figure 4:- Unit cost per TB case detected for smear microscopy versus Xpert diagnostic method among TB suspected individuals in Arsi zone, Ethiopia, 2018/2019.

5.5. Impact of different scenario assumptions on the cost of Smear microscopy and Xpert algorithm

In the smear microscopy diagnostic method, reducing the useful life of the capital equipment from ten to five years increased the cost of the test to US$ 3.59. If the number of tests performed per day increased to ten, the cost of the test would decrease by 16.13%. Furthermore, allocating 100 % of microscopy use at health centers to smear microscopy increased the cost of the test to US$ 3.32.

In the Gene Xpert technique, reducing the cartridge price by 10% and increasing the number of tests performed per day to sixteen from eight, lowered the unit cost of Xpert per test to US$ 11.66 and US$ 11.87 respectively. However, reducing the useful life of the Gene Xpert machine and another item to five years increased the cost of Gene Xpert by 7.04% (Table 6).

Table 6:- Impact of different base-case assumptions on cost diagnostic methods to diagnosis TB suspected patients at public health facilities in Arsi zone, Oromia Region, Ethiopia, in 2018/2019.

Type of test/parameter	Impact on unit cost per test	Percentage (%)	Impact on cost per case detected
Smear microscopy ($3.1)			
Reduce useful life of capital equipment from 10 to 5 years	$3.59	+15.81	$64.58
Increase number of tests to 10 per day	$2.60	-16.13	$46.74
Allocate 100 % of microscopy to smear microscopy at health center	$3.32	+7.10	$59.73
Gene Xpert ($12.92)			
Reduce the useful life of capital equipment from 10 to 5 years	$13.83	+7.04	$83.35
Increase number of tests to 16 per day	$11.87	-8.13	$71.55
Reduce price of cartridge by 10%	$11.66	-9.75	$70.28

5.6. Cost-effectiveness analysis

The cost-effectiveness analysis showed that the Xpert diagnostic method has high expected cost and effectiveness compared to smear microscopy. The expected cost of the smear microscopy technique was 11.09 USD while the expected cost for the Xpert algorithm was 22.23 USD. As a result, the ICER of Gene Xpert was $729.82 per proportion of cases detected compared to smear microscopy diagnostic algorithm (Table 7).

Table 7:- Output of cost-effectiveness analysis in order of increasing Costs for Xpert strategy compared to smear microscopy among TB suspected patients in public health facilities in Arsi zone, Oromia, Ethiopia, 2018/2019.

Diagnostic Algorithm	**Cost**	**Incremental Cost**	**Effectiveness**	**Incremental Effectiveness**	**ICER**	ACER
Smear microscopy	11.09	Reference	0.009	Reference	Reference	1218.88
Xpert	22.23	11.14	0.024	0.015	729.82	912.4

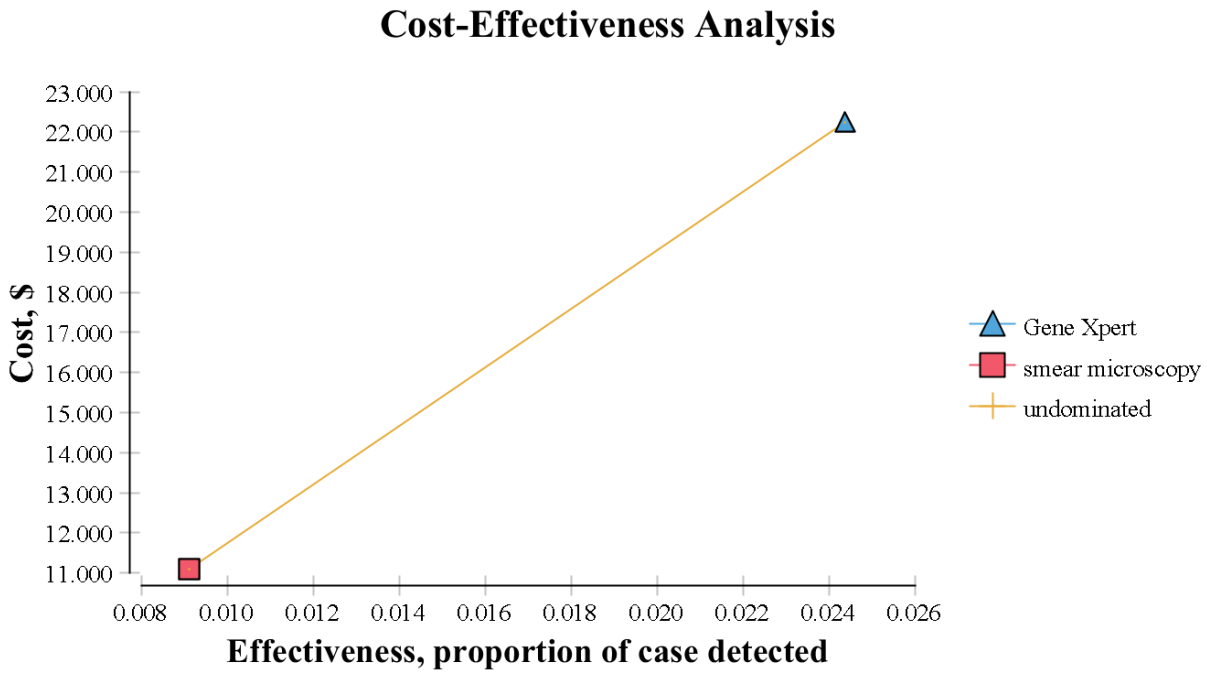


Figure 5:- Graph showing the Cost-effectiveness analysis of the Gene Xpert compared to smear microscopy technique.

The CEA graph is a graphical representation of the results of the cost-effectiveness analysis. It shows the expected cost and effectiveness of diagnostic strategies and graphed on a cost-effectiveness plane. The expected cost was graphed on the Y-axis and the expected proportion of cases detected by the diagnostic method was graphed on the X-axis (figure 5). The ICER for Gene Xpert compared to smear microscopy method was $729.82 per proportion of cases detected. This makes the Xpert algorithm a very cost-effective strategy at one time GDP per capita of Ethiopia which was $891 in 2018 (64).

5.7. Sensitivity analysis

5.7.1. One way sensitivity analysis

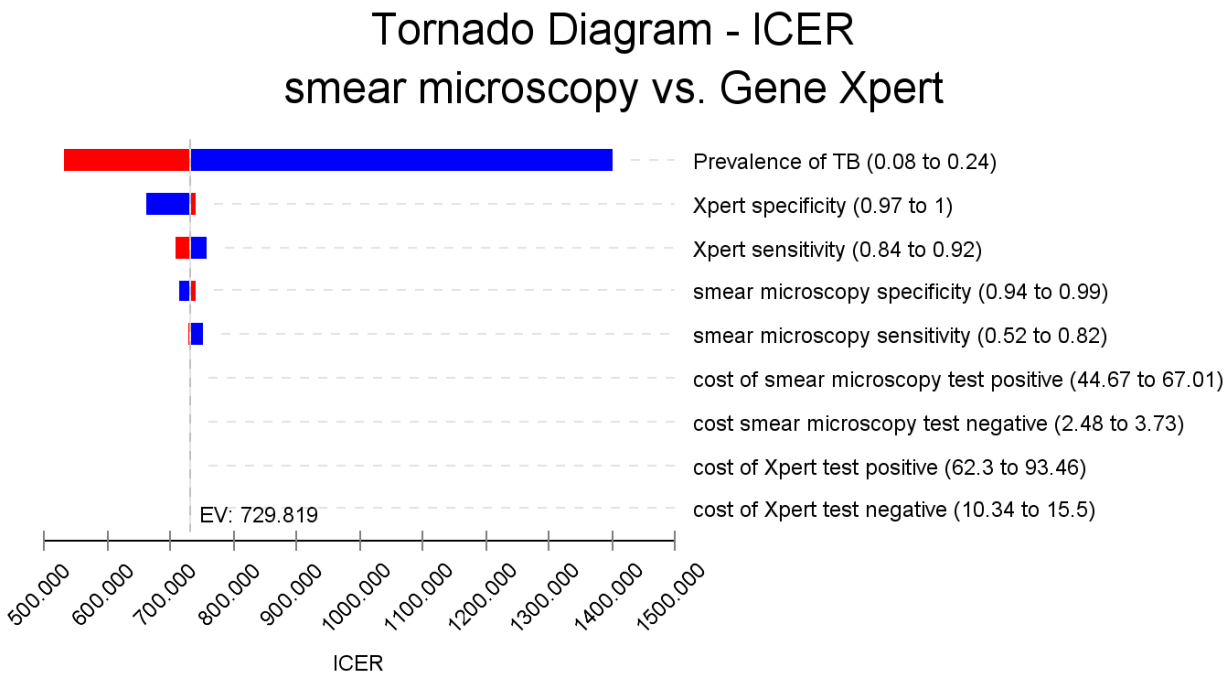
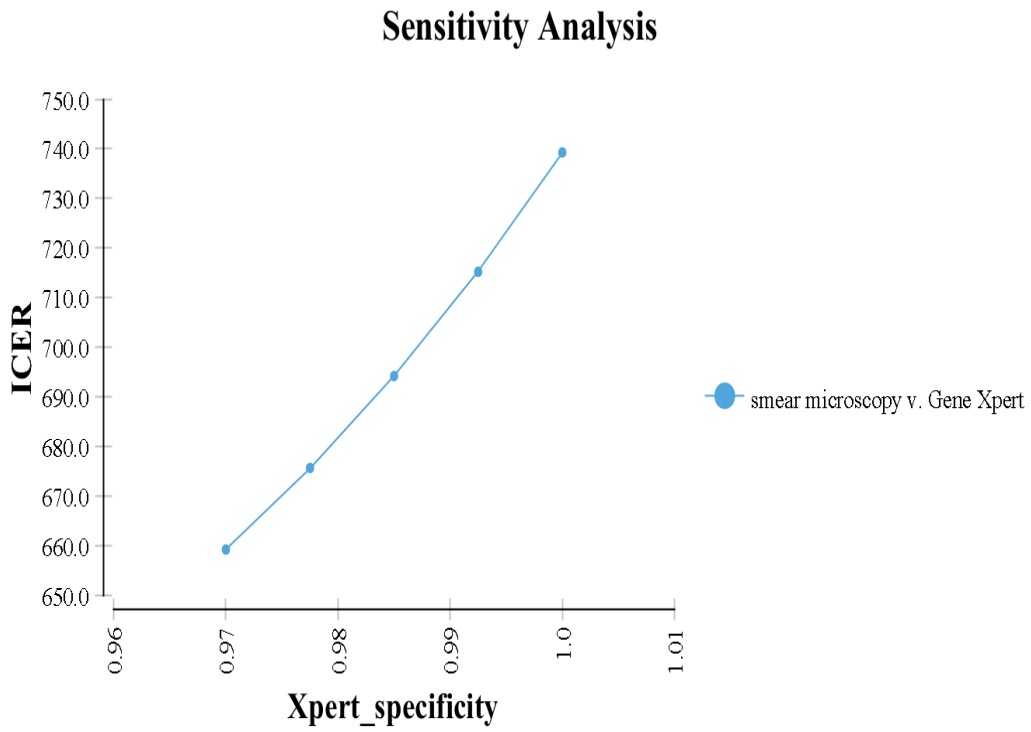


Figure 6:- One-way sensitivity analysis of ICER comparing Xpert to smear microscopy Algorithm using tornado diagram

In one way sensitivity analysis, the prevalence of tuberculosis was a strong driver of the incremental cost-effectiveness of Xpert. When the sensitivity analysis was done by altering the prevalence of tuberculosis infection 50% above and below the base case; the ICER of the Xpert algorithm decreased with an increase in prevalence and vice-versa. The incremental cost-effectiveness ratio increases from $530.57 to $1401.13 per proportion of cases detected for TB prevalence from 0.24 to 0.08. Other variables with a moderate influence on the model were the specificity and sensitivity of the Xpert diagnostic methods. For the specificity of Xpert ranges from 97% to 100%, the ICER would range from $659.72 to $739.86. Moreover, the ICER ranges from $756.50 to $706.69 for Xpert sensitivity ranges from 0.84 to 0.92. The specificity of smear microscopy has also a notable influence on the ICER of Xpert. As the specificity of smear microscopy increases, the ICER also increases and vice versa (Figures 6 and 7).



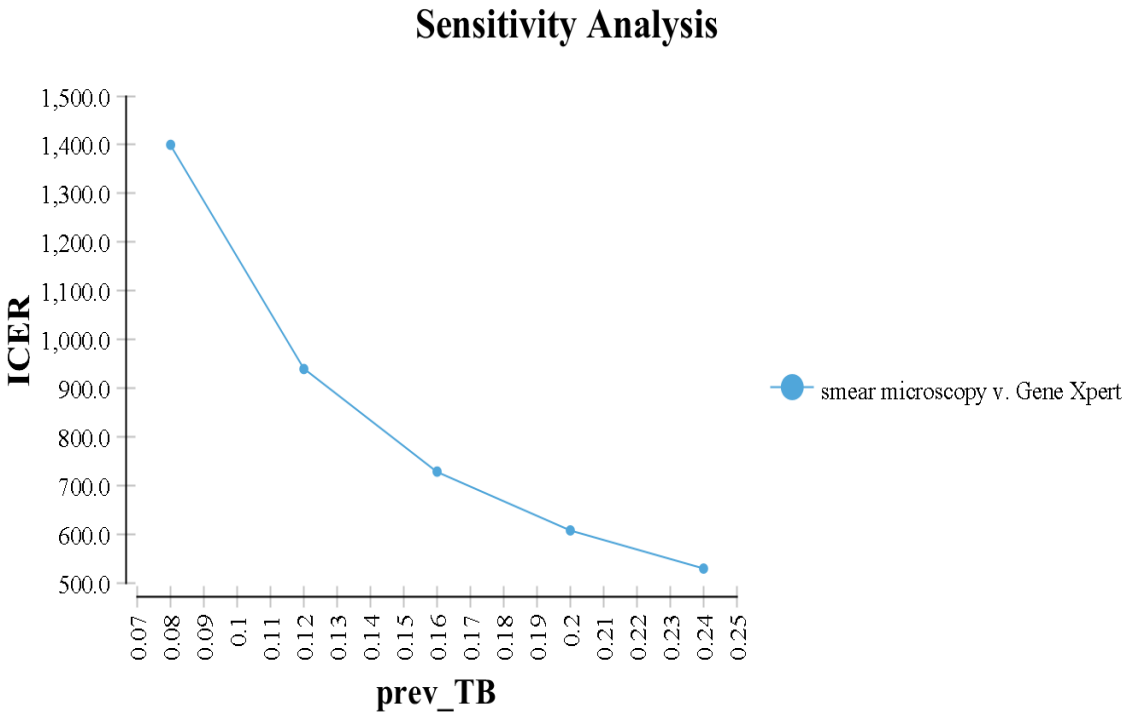


Figure 7:- One-way sensitivity analysis of selected parameters for comparing smear microscopy to Xpert Algorithm.

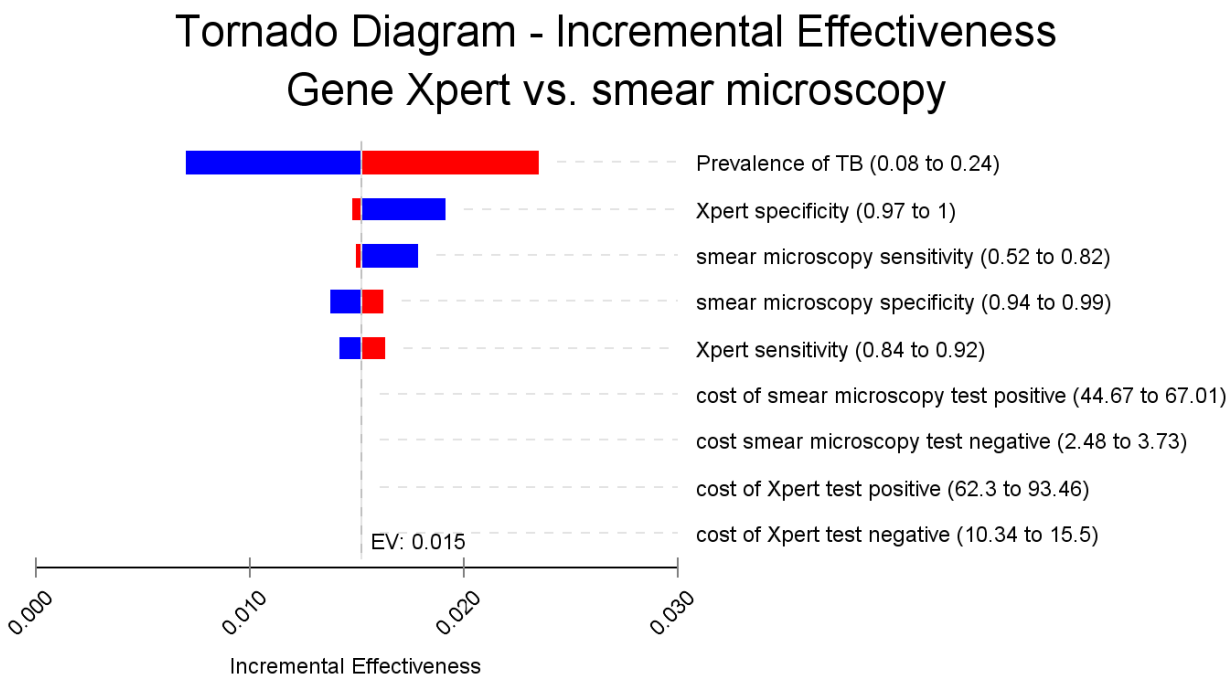


Figure 8:- One-way sensitivity analysis of incremental proportion case detected comparing Xpert Algorithm to smear microscopy among suspected patients in public health facilities in Arsi zone, Oromia, Ethiopia in 2018/2019.

The incremental proportion of TB cases detected comparing Xpert testing to smear microscopy algorithm was mostly influenced by the prevalence of tuberculosis infection. The incremental proportion of cases detected ranges from 7 per 1000 TB suspects to 23.6 per 1000 TB suspects for TB prevalence of 8% to 24% among TB suspects. However, as the specificity of the Xpert diagnostic method increases from 97% to 100%, the incremental effectiveness will declines from 19.1 per 1000 TB to 14.8 per 1000 TB suspects (Figure 8).

5.7.2. Probabilistic sensitivity analysis output

A thousand iteration of PSA was done on costs, data accuracy (sensitivity and specificity) and prevalence of tuberculosis. The average result of PSA for thousands of iteration was almost similar to the baseline value of the diagnostic algorithm (Table 8).

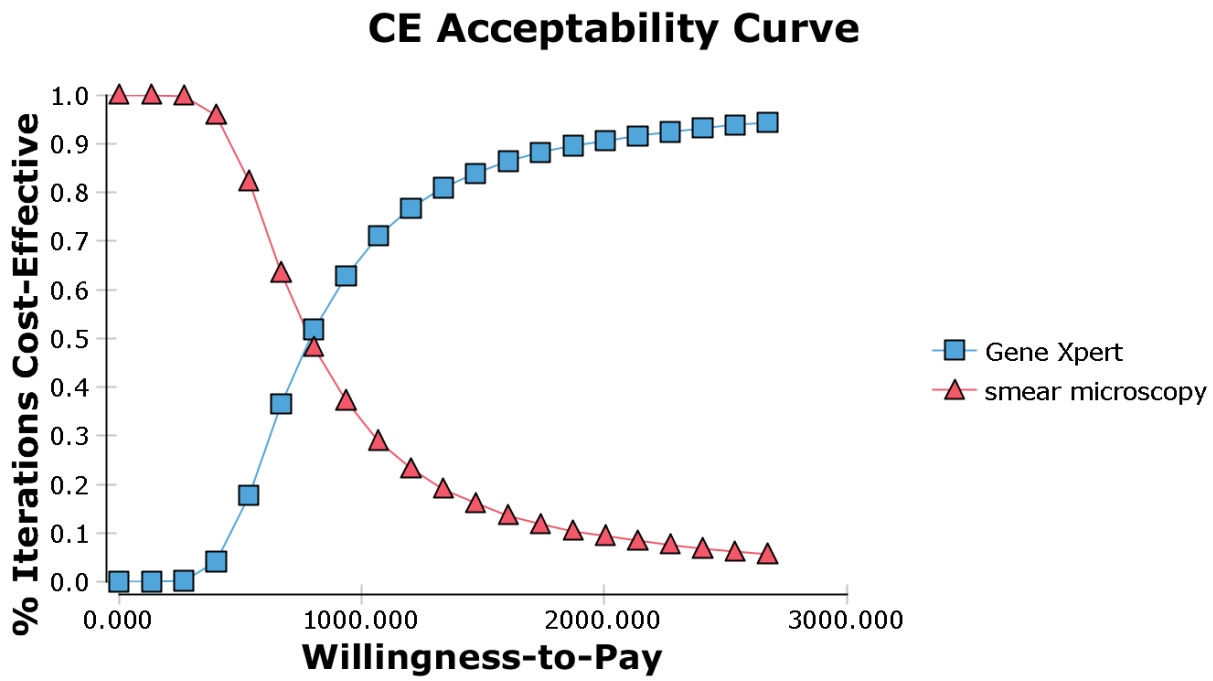


Figure 9:- Cost-effectiveness acceptability curve comparing Xert diagnostic algorithm compared to smear microscopy technique.

The ICER of Gene Xpert algorithm was USD 726.78 per proportion of TB cases detected. The probabilistic sensitivity analysis results found that the ICER of the Xpert algorithm was around the baseline value. At a WTP threshold of three times GDP per capita of Ethiopia, the probability of the Xpert diagnostic method to be cost-effective is 94% compared to smear microscopy diagnostic algorithm (Figure 9 and Table 8).

Table 8:- probabilistic sensitivity analysis output of ICER for Xpert compared to smear microscopy algorithm.

Diagnostic Algorithm	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	ICER	ACER
Smear microscopy	11.07	Reference	0.009	Reference	Reference	1219.79
Xpert	22.29	11.22	0.024	0.015	726.78	909.25

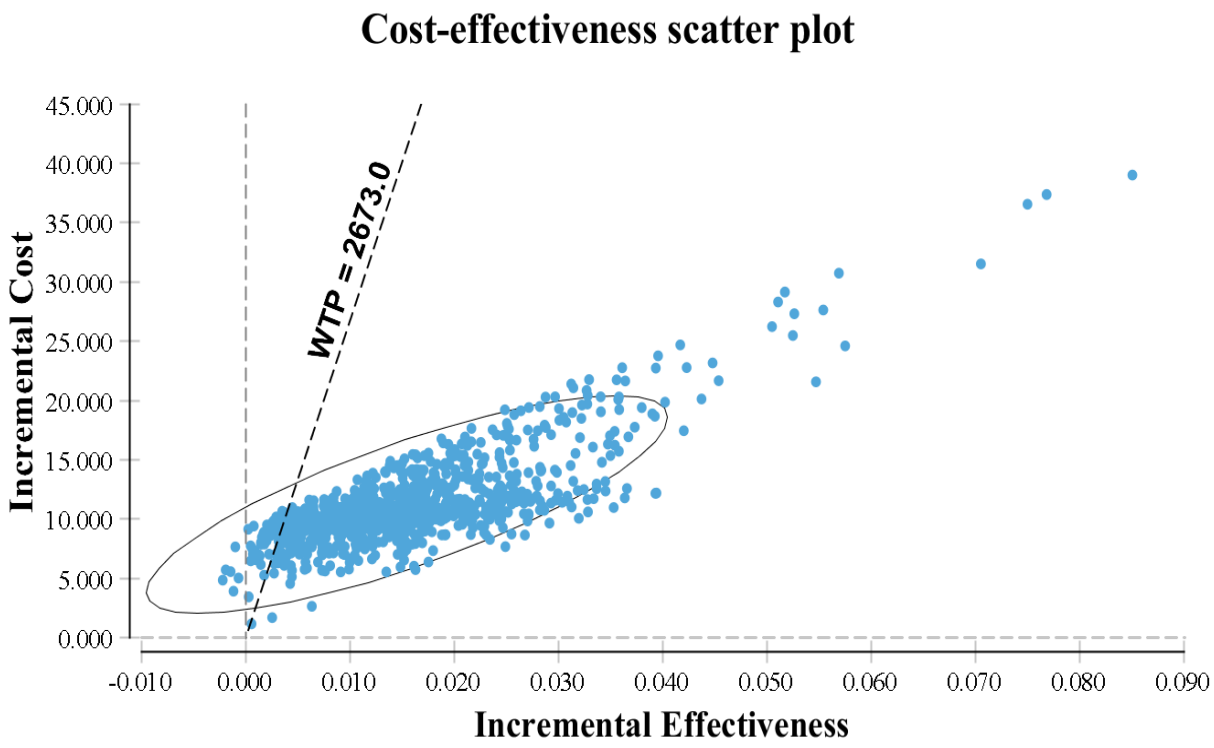


Figure 10: ICE Scatterplot graph for the Xpert method compared to the AFB smear microscopy algorithm.

The scatter plot in Figure 10 presented the ICE result of PSA output for Xpert compared to smear microscopy diagnostic algorithm. It showed that the Xpert algorithm is nearly more costly and more effective method compared to the baseline algorithm. The region below and to the right of the WTP line were the points where the Gene Xpert is more cost-effective than the smear microscopy technique. Moreover, it indicated that the Xpert algorithm is the optimal strategy compared to AFB smear microscopy at a WTP of three times GDP per capita of Ethiopia.

The incremental net monetary benefit

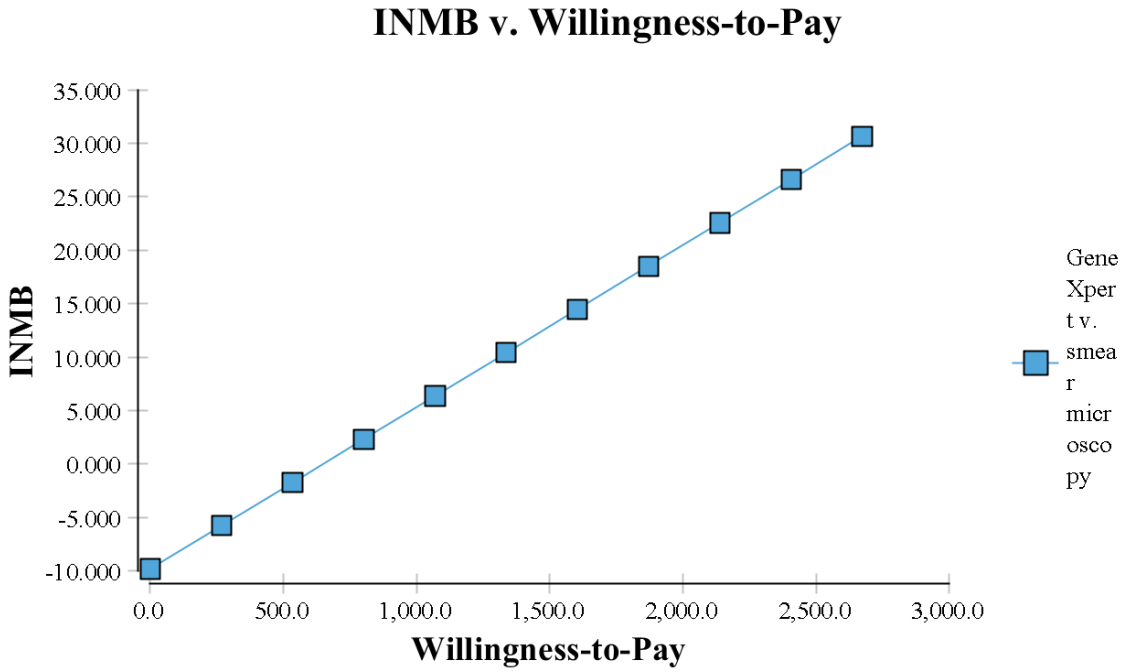


Figure 11:- probabilistic sensitivity analysis output of INMB versus WTP for Gene Xpert and smear microscopy diagnostic algorithm.

The INMB is used as a decision tool to decide on what WTP the TB diagnostic method will detect one more tuberculosis case. The INMB for the Gene Xpert is positive above USD 729.82 on the willingness to pay threshold. The positive INMB shows at WTP above USD 729.82, the Gene Xpert diagnostic technique is the optimal strategy for detecting more tuberculosis cases (Figure 11).

6. Discussion

Tuberculosis is the public health threat despite the availability of advanced diagnostic tools (26). In order to successfully control the spread of MTB, cases must be detected and treated immediately. Gene Xpert is one of the advanced diagnostic tools enabling POC for the same day diagnosis and treatment. The aim of this study is to evaluate the cost-effectiveness of Gene Xpert compared to smear microscopy test using decision-analytic model. To provide relevant cost and cost-effectiveness information for the economic evaluation, the ingredient-based costing approach was employed. The study found that the Gene Xpert algorithm is costly than AFB smear microscopy technique even though it detected more TB cases. Diagnosis of TB suspected patients with Xpert method was cost-effective at ICER of USD 729.82 per proportion of cases detected which is less than one times or three times GDP per capita for Ethiopia.

In this study, the unit cost per test for smear microscopy diagnostic technique was 3.1$ while the unit cost per case detected was 55.5$. The most driver of unit cost for this method was reagent and consumable cost 1.28$ (41.3%). This finding was consistent with a study conducted in Zambia US$0.25 (61%) (65) and in Nigeria around US$ 3.24 (68.5%) (38) that indicated the majority of the cost of smear microscopy was attributed by supplies used for testing. Moreover, AFB smear microscopy has low cost compared to the Gene Xpert algorithm.

In our study, the average unit cost of Gene Xpert was $12.92 per test. This is higher than the unit cost per test of a study conducted on cost and cost-effectiveness in India (12.29$) (66) and Uganda ($12.41) (54). However, this is lower than studies in South Africa (US$21.19) (35) and Uganda's peripheral settings (US$21) (36). The observed variation may be due to the cost of cartridge used, costing method used in these studies and utilization rate of capital equipment.

Moreover, the unit cost per test was high for Gene Xpert-based algorithm compared to the conventional smear microscopy technique. This is consistent with studies conducted in Brazil and India (66, 67), and South Africa (68). This may be the Xpert algorithm requires expensive equipment and cartridge and high maintenance cost compared to the smear microscopy diagnostic method. The most driver of the unit cost was cartridge and consumable cost (80%). The scenario analysis result also indicated that if the cost of cartridge

reduced by 10%, the unit cost would reduce by 9.75% below the base case. This was similar to a study conducted in South Africa (47%) (35), and Uganda (54) that indicated the high price of the cartridge have a significant influence on the cost of Xpert algorithm during implementation. This indicates the high cost of cartridge raises the issue of sustainability even though using Xpert as a routine test is cost-effective in several high burden TB countries. For the full scale-up of this technology, controlling financial sustainability by reducing cartridge price is needed as indicated in another study (28).

This study found that in low testing volume health facilities the cost of smear microscopy and Xpert was $4.96 and $13.22 respectively. Moreover, our scenario analysis result revealed that the cost of both diagnostic algorithms was reduced from the base case estimate by increasing the volume of tests per day. This is in line with a study conducted in sub-Sahara Africa (50) and Uganda (36) on cost and cost-effectiveness of the Xpert diagnostic test. According to the result of these studies, the cost of the test method was high in health facilities where their testing volume was low. This may be due to the decreasing cost of capital equipment per volume of tests performed.

Even though smear microscopy was the preferred alternative in cost, the Xpert has several advantages in regard to the detection of drug-resistant bacilli, biosafety, the volume of space required, and proportion of case detected (10). In our finding, Xpert detected 16.6% of positive cases while smear microscopy detected 5.6% of positive cases among total cases. This indicated that testing using the Xpert algorithm detected more positive cases compared to AFB smear microscopy method. This was consistent with finding from the USA on the cost-effectiveness of Xpert MTB/RIF testing in hospitalized patients with presumptive pulmonary tuberculosis (44). Another study also indicated, the introduction of Xpert into the routine diagnostic procedure lead to an improvement in the quality of care, avoid both unnecessary hospitalizations and treatments (45). Moreover, a study conducted in five South African countries found that the introduction of Xpert reduced tuberculosis morbidity and mortality through improved case-finding (69). This indicates the expansion of advanced technology like Xpert has the potential to reduce the burden of disease. This is because the Xpert technology has significantly increased sensitivity for the detection of TB as compared to the AFB smear microscopy technique. However, scaling up of this algorithm should be considered with great care as it increases both the number of TB cases diagnosed and the cost of TB diagnosis (70).

The transmission of tuberculosis is still the problem of developing countries due to MDR-TB and poor case detection rate. This forced countries to raises their concern about using advanced laboratory diagnostic methods (71). However, advanced technology should have an acceptable cost and cost-effectiveness to be used as a routine diagnostic procedure. Our study result demonstrated that Xpert testing among patients with suspected TB is very cost-effective at one times GDP per capita of Ethiopia ($729.82 per proportion of cases detected) (64). This is in line with a study conducted in China (39) and United States (44) that found incorporating Xpert in the TB diagnostic algorithms was highly cost-effective. Moreover, the result of this study was in agreement with a study on the cost-effectiveness of Xpert in South Africa (48) that found that using novel diagnostic test (Xpert) for TB diagnosis was cost-saving and cost-effective. However, this result was inconsistent with the study conducted in Uganda that found Xpert was not cost-effective compared to MODS (54). This may be due to algorithm sensitivity and specificity as MODS has almost similar diagnostic accuracy and low cost compared with the Xpert diagnostic method.

In our study, the cost-effectiveness of Xpert algorithm was indicative of the potential use of this method for the routine diagnosis of TB suspected patients. However, the cost-effectiveness of this advanced technique depends on the prevalence of TB and the diagnostic accuracy of compared algorithms. In one way sensitivity analysis, the ICER of Xpert was more sensitive to the prevalence of tuberculosis. As the prevalence of TB increases, the Xpert algorithm will become the best optimal strategy compared to smear microscopy technique despite the higher cost. In addition, the ICER of Xpert was moderately influenced by specificity and sensitivity of the Xpert diagnostic algorithm. Similarly, studies on the cost-effectiveness of Xpert indicated that the most driver of ICER was the prevalence of TB (47, 51). Other studies results demonstrated that the diagnostic accuracy of Xpert was the most influential parameter on the cost-effectiveness of this test (15, 43). This indicates if the prevalence of the disease increases, the probability of Xpert to detect more cases increases. This is because the sensitivity of the test algorithm was dependent on the prevalence of tuberculosis (72).

7. Strength and limitation of the study

7.1. Strength of the study

This study is the first of its kind measuring the cost-effectiveness of Xpert compared to smear microscopy in Ethiopia, and one of the few studies in the world. This study tried to detect cost-effectiveness of Gene Xpert in routine patients by including all relevant costs. In this study, we used the ingredient-based costing method, which will avoid overestimation or underestimation of diagnostic cost. The way the data collected from each facility was also with close supervision of the principal investigator and with strong support from health facilities administration and staff. Therefore, this will increases the reliability of the data collected. In addition, we used a standardized checklist adapted from WHO which enables us not to miss essential health provider costs needed for this economic evaluation study. Furthermore, we conducted a probabilistic sensitivity analysis to account for uncertainty in our model.

7.2. Limitation of the study

Our study has some caveats that need careful interpretation of the results. First, the use of intermediate outcome i.e. the proportion of cases detected might pose difficulty in comparing with other interventions which are not reported with the same outcome measure. In addition, as the outcome data is collected from secondary data, it is impossible to check the accuracy of the result. Consequently, this can overestimate or underestimate the result of each method during diagnosis. The way effectiveness measured may also impose difficulty on our result as the proportion of case detected used. Moreover, the test performance parameters used in our model was used from different pooled systematic analysis and meta-analysis. The golden standard used in those studies for diagnostic accuracy analysis may lead to overestimation of the sensitivity and underestimation of the specificity of the test algorithm. Even though this study used WTP of 1X or 3X recommended by WHO as in similar studies to decide the cost-effective strategy, this can influence the implementation of the result of our study. Failure of the cost-effectiveness analysis to indicate the affordability of the cost-effective strategy as we didn’t conduct budget impact analysis can also influence the full implementation of our study result.

8. Conclusion

The unit cost per test was $3.1 for smear microscopy and $12.92 for the Xpert diagnostic method. The unit cost of Gene Xpert is higher than that of the AFB smear microscopy technique. The high cost of the Gene Xpert was a result of the cost of cartridges and the cost of equipment. However, the unit costs of both techniques can be reduced by increasing the testing volume per day. On the other hand, the result of this study demonstrated that Xpert diagnostic method identified more cases (16.6%) compared to smear microscopy algorithm (5.6%). The use of Gene Xpert as a routine test for all suspected TB patients compared to standard care have ICER of 729.82 per proportion of cases detected. This study suggests that the introduction of Xpert technology as the routine is very cost-effective or cost-effective compared to the conventional smear microscopy method at willingness to pay threshold of 1X or 3X GDP per capita of Ethiopia respectively. However, the cost-effectiveness of this technology was more influenced by the prevalence of tuberculosis during sensitivity analysis. As the prevalence of tuberculosis increases, the Xpert algorithm becomes a more optimal strategy and vice-versa.

9. Recommendation

Even though the findings of our study provide paramount evidence for the use of Xpert at point-of-care as a replacement to smear microscopy is cost-effective, the high cost of diagnosis should be reduced. Therefore, the FMOH and Regional Health Bureau, as well as different stakeholders, should consider facilities testing volume and prevalence of TB during the distribution of the Xpert machine.

This study result also suggested that, wherever the Xpert algorithm has a higher cost compared to standard care, this technique can be cost-effective by detecting more cases. Therefore, efforts should be undertaken by the FMOH and Regional Health Bureau, as well as different stakeholders, to increase access to this advanced diagnostic method for use in all patients suspected for TB. On the other hand, the cost-effectiveness of this algorithm does not mean it is affordable. So, the FMOH and other researchers should conduct studies on affordability and the impact of using the Xpert algorithm for routine testing in the health system.

It should also be noted that, although the Xpert algorithm appears to be a cost-effective technique, the high cost of cartridge had a substantial impact on its feasibility. So, the national TB control programs have to consider different ways of getting the less expensive cartridge in case of donor phase-out. This would considerably increase the affordability and sustainability of the technique. Moreover, researchers should also conduct full economic evaluation studies using a societal perspective and final outcome to generate more evidence on the use of Xpert diagnostic technique as a routine diagnostic test. On the other hand, health facilities and health professionals working on TB should use their maximum efforts to increase utilization of this service at every point of care.

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11. Annex

11.1. Annex I: English Version information sheet and consent format

Hello my name is _____, I am a laboratory expert working here in TB laboratory and I am now collecting data from patients TB logbook for the research being conducted to evaluate cost-effectiveness analysis of smear microscopy compared to the Xpert MTB/RIF method for diagnosis of suspected tuberculosis patients at public facilities in Arsi, Ethiopia, by Abdene Kaso who is a Health economics student in Addis Ababa University. The Hospital/health center is selected as one of the study areas. The researcher employed me for data collection to maintain your data strictly confidential. Anyone outside me cannot access your result. We believe that the finding of this study will have paramount importance for the evaluation of the recent TB diagnostic algorithm and health service system delivery. As the study will be conducted through medical records review alone, it will not inflict any harm as far as the confidentiality is kept. The information will be taken when you give permission. Your willingness for TB record information will help us to achieve the stated benefits of the study. Name and personal identifiers of the patients will not be recorded on a data collection form. The information that we utilize will be kept confidential and will also be used for this study purpose alone. If you have any questions about this study you may ask me or the principal investigator.

Abdene Kaso (Tel: 0910400038/0912821018 and E-mail: abdannekaso@gmail.Com.)

Signature that shows the Hospital/ health center administration has consented written or verbal on behave of patients to collect data necessary for this study _____

11.2. Annex II: Format for collection of cost data

Name of Health facilities: _____ Date of data collection:_____

Name of data collector:_____ Name of supervisor_____

Type of diagnostic method at site_____

Section 1: - Staff time collection format

S.N	Health facilities	Type of lab professional	No who work on TB	Annual cost	The proportion spent working on TB	Total annual cost

Section 2: - Building costing format

No.	Health facilities	Cost to build a laboratory	Annual cost	Percentage of allocation	Annual cost

Section 3: - Equipment costing format

Health facilities	Type of equipment	Cost to buy new equipment	Expected years of life span	Annualized cost	The proportion used for TB only	Annualized cost

Section 4:- Format for collecting supplies cost

Health facilities	Supplies used	The unit cost of supplies	Number of tests done	Total annual cost

Section 5:- Format for calculating the average cost of a diagnostic method.

Cost item	Total annual cost		The average cost per algorithm	
	Xpert	Smear microscopy	Xpert	Smear microscopy
Equipment				
Staff and training				
Reagent and consumable				
Building				
Other overhead				

Section 6:- Format for collecting effectiveness data from health facilities

S.N	Health facility	Algorithm used	Number of TB diagnosed	Total		Total	
				Male	Female	positive	Negative