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Cost effectiveness analysis of adopting Gene-Xpert® (GX) for the Diagnosis of Tuberculosis in Egypt

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ABSTRACT

Background: Tuberculosis is one of the most devastating infectious diseases worldwide. It constitutes a major global health problem infecting millions of people each year, with a particular heavier burden on the developing world.
Objective: evaluating the cost effectiveness of incorporating Gene Xpert to sputum microscopy compared to sputum microscopy and culture for diagnosis of tuberculosis and multidrug-resistant (MDR) tuberculosis in low- to middle-prevalence settings like Egypt.
Design: An economic evaluation study was conducted using a decision analysis model representing the diagnostic process starting with tuberculosis suspects, continuing to tuberculosis cases, and ending with treatment. The model outcome was the incremental cost per incremental DALYs (Disability Adjusted Live Years) averted between the new GX algorithms incorporated with smear microscopy versus the standard algorithm for detection of suspect TB case.
Results: Xpert testing is estimated to result in additional costs (EGP 2,320) per each
DALY averted compared to sputum microscopy and culture.
Conclusion: The results of this study advocate that GXpert is a cost-effective method of TB diagnosis, compared to a base case of smear microscopy and clinical diagnosis with its ability to substantial increase in case finding. It has also important potential for improving tuberculosis diagnosis and disease control.
Keywords: Cost-effectiveness, Economic analysis, Gene-Xpert®, TB, Tuberculosis

INTRODUCTION

Tuberculosis (TB) is one of the most potentially fatal contagious diseases on the earth [(1).] It is a significant global health concern that infects millions of individuals each year, with the developing world bearing a disproportionately heavy burden [(2).] 9.6 million new tuberculosis instances (133 per 1000 persons) and 1.5 million tuberculosis deaths occurred in 2014, with 0.4 high mortality and morbidity among HIV-positive individuals [(3).]

TB global incidence is waning sluggishly, at a rate compared with fewer than 2% per year. To achieve the TB eradication objective of less than 1 case/1,000,000 population in 2050, the prevalence of TB must decrease by 20% per year [(4).] Diagnoses that are missed or prolonged, as well as issues with access to the highest care, lead to increased risk, boost struggling with devastating financial implications, and delay the eradication of tuberculosis. Such wasted opportunities also make a contribution to individuals' contagiousness lasting longer, allowing transmission to continue [(5,6)] particularly among high density population with poor living and working conditions [(7).] Approximately a third of the determined 9 million people infected with tuberculosis (TB) do not obtain the treatment they need each year [(8).]

In addition, MDR-TB is on the rise, posing a serious threat to global tuberculosis control [(9).] Rifampicin and isoniazid (INH) resistance are both present in MDR-TB (RIF). Diagnostic services, notably for MDR-TB, are difficult to come by in many countries. Furthermore, the consequences of traditional diagnostics can take up to two months to arrive [(8).]

In developing and high-burden countries, WHO suggests employing accurate and rapid molecular diagnostic tests (MTBDR plus) and Gene-Xpert® (GX) to recognise tuberculosis [(10,11).] Egypt is categorized as a country with a low-to-moderate occurrence of tuberculosis (TB), as per WHO estimates. Annually, 11 instances per 100,000 of the population advance pulmonary smear positive stimulated TB, while 24 cases per 100,000 establish all types of TB [(12).]

Almost all cases of tuberculosis can be cured with prompt diagnosis and treatment [**(13).**] For several years, the therapies rate of success among new confirmed cases by National TB Programs has remained consistent at around 85 percent. Multidrug-resistant tuberculosis (about 0.5 million new instances per year) is more difficult to treat in all settings because therapeutic options necessitate protracted therapies with efficient and expensive drugs; the global cure rate in such instances is about 50% [(13).]

The GX-MTB/RIF test is a two-hour automated nucleic acid amplification experiment for tuberculosis diagnosis. GX also necessitates little in the way of laboratory equipment, space, and technician duration. It also allows for the early detection of rifampin resistance, enabling for more effective treatment of drug-resistant tuberculosis. On smear positive samples, specificity and sensitivity for tuberculosis and drug resistance have been found to be >97%, On the other hand, sensitivity on smear-negative specimens can be as high as 70%–80% [(14).] GX has the best sensitivity and specificity for rifampicin mono-resistance, with a 100 percent match to the reference test MGIT 960.

GX is accessible at a reduced cost in low-income areas; however, its purchase price in areas with low TB

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predominance is unidentified [15,16]. In Egypt, no prior economic analysis studies on the cost-effectiveness of GX in TB diagnosis have been performed.

AIM OF THE STUDY

The goal of this study was to see how cost-effective it would be to use the new diagnostic algorithm, (incorporating Gene Xpert to sputum microscopy) compared to the standard algorithm namely (sputum microscopy and culture) for TB and MDR-TB diagnosis in Egypt as a low- to middle-prevalence setting.

METHODS

Study design:

A decision analysis model was developed starting with tuberculosis suspects, moving on to tuberculosis cases, and finishing with therapies (including the associated complications). The model outcome was the incremental cost per incremental DALYs (Disability Adjusted Live Years) averted between the new GX algorithm incorporated with smear microscopy versus the standard algorithm (smear microscopy and culture) for detection of suspect TB case.

Sampling and study population:

The model followed a hypothetical cohort of 10,000 HIV-negative people suspected of having tuberculosis through the diagnostic and therapeutic procedure. These paths were used to approximate costs and consequences.

- The test sensitivities in the diagnostic pathway determine the likelihood of being diagnosed as TB cases among individuals with suspicious TB.
- Similar manner, the likelihood of persons with suspected tuberculosis (who are not TB cases) being misdiagnosed as positive TB instances is determined by the test specificities of the pathway.

Treatment for tuberculosis would follow the diagnosis. Suspected tuberculosis cases completed the pathway and were either successfully treated, defeated therapies, deceased, or stayed tuberculosis-free.

Diagnostic scenarios:

Two different diagnostic scenarios were contrasted according to Egyptian guidelines for suspect cases, namely the first scenario (smear and culture) and incorporation of GeneXpert to base-case.

i- According to the Egyptian guidelines for suspect cases [2] the base-case is determined as having three consecutive sputum acid fast bacilli microscopy examinations (AFB microscopy) accompanied by treatment as smear positive pulmonary TB patient, in case of 3 or 2 positive smears.

ii- However, if the three specimens were negative, broad spectrum antibiotics would be used followed by repeated AFB microscopy, in case of no improvement; radiological and clinical judgment is used to differentiate between confirmed TB case (treat as smear negative pulmonary TB and rolling out the diagnosis).

iii- In case with only one positive smear, it should be complemented by clinical judgment, where TB case would be diagnosed, or AFB microscopy would be recommended to be repeated.

The alternative scenario involving GeneXpert (GX) testing after direct smear microscopy on three smear specimens, if the result of smear microscopy was negative, then it was accompanied by GX on a single sputum specimen (‘‘incorporated").

Each scenario used either traditional drug susceptibility testing (DST) or GX to assess drug resistance in heretofore treated patients [8].

- All people diagnosed with tuberculosis were regarded according to WHO guidelines. For new patients awaiting DST results, first-line therapies (pyrazinamide [Z], isoniazid [H], rifampicin [R], and ethambutol [E]) were started for two months, accompanied by HR for four months. All patients who had formerly been treated for tuberculosis (relapse, treatment after interruption, and therapies after failure) were given two months of HRZES, one month of HRZE, and when a DST result of rifampicin resistance was available, and five months of HRE before being transitioned to second-line treatment [17] If GX detected rifampicin resistance, conventional DST affirmed it.

For this study, a non-probability convenience sample of 22 patients (represented 25% of all the inpatients at this time period), already present at Abassyia Chest Hospital inpatient wards were included. Patients were interviewed using a tailored validated data collection form [18] for estimating the out of pocket payment they incur during their hospital stay.

Study setting and data collection:

Chest Hospital at Abassyia, tertiary hospital located in Cairo, with more than 400 beds was the venue of data collection from patients, hospital staff and reviewing National reports.

- Calculating estimates of costs of each pathway:

1- From the standpoint of a health service, assessments of the economic costs of each pathway were made. All costs were measured using a combination of activity-based costing and macro costing. To estimate cost per test per patient, all required inputs were identified, and their quantities were calculated, then multiplied together to get the cost estimate.

2- Diagnostic costs, such as key necessary items and equipment for each diagnostic test, staff wages and

salaries, quality control and preservation, and calibration inputs, were gathered at one demonstration site (Al Abassia Chest Hospital).

3- Price estimates for devices and tests acquired from suppliers in addition to literature review sources, calibration of equipment, cost of training estimated from technicians.

4- Treatment cost of the used drugs was estimated using tender price list from the Ministry of Health and Population. Estimates for treatment associated complications were based on assumption. To verify the premeditated estimates, a review of past costing studies has been done. Furthermore, validation of the decision analysis model of India case in South Africa study **(16)** was done.

- The model Key input parameters were accessed through the available national data reports. From available national reports and literature reviews, MDR incidence, sensitivity, and specificity variables for all diagnostic tests and treatments were calculated [19,20] taking reference standard from sputum culture. Critical appraisal of relevant studies (published cohort studies, meta-analyses of clinical trials, and systematic reviews) was performed **(Annex I and II).**
- Quality studies was used in estimating DALYs for each pathway of patients being cured, failed treatment, died and also, treatment outcome utilities and probabilities.

  Then, using the standard formula DALY=YLL+YLD, DALYs were calculated for each pathway of patients who were cured, ended in failure treatment, or died. By multiplying the number of deaths by the standard average lifespan at the time of death, the YLL was measured. The equation YLL=N*L was used to define YLL.

  Where: N = number of deaths, L = standard life expectancy at age of death in year

  YLD=I*DW*L, where I denotes the number of incident cases, DW denotes the severity of the disability, and L denotes the average duration of the case until remission or death (years).
- Treatment outcome utilities and probabilities were calculated using cohort studies, meta-analyses of clinical trials, and systematic reviews published in the literature **(21)**. Future DALYs were discounted at 12.5 percent and were calculated based on period with/without active TB and/or anti-TB therapies.

Time Horizon of the follow up was till the end of the treatment course, whether 8 or 24 months according to the different treatment strategies. The added expense for any extra DALYs averted by GXpert over the base-case was calculated using an incremental cost efficiency ratio (ICER). The ICER was then especially in comparison to the WHO's recommended willingness to pay (WTP) thresholds for each country, which is estimated for Egypt to be three times GPD/capita/year.

Data collection tools:

Patients were interviewed using a tailored validated data collection form [17] for measuring direct and indirect costs of TB patients were used, including sociodemographic variables, comorbidities, and out of pocket payment incurred.

Data management and statistical analysis:

- Data collected were entered using Microsoft Excel software (windows 10), then cleaned and revised. Data were presented using tables and graphs, the decision-making tree was constructed using Microsoft Excel software for Window 10.
- To assess the model's robustness, Microsoft Excel software for Windows 10 was used to undertake one-way sensitivity analysis and probabilistic sensitivity analysis (randomly sampling each parameter in our model from their probability 1000 times to produce confidence intervals around our estimates of incremental cost per DALY averted).
- To characterize the increased expense for any additional DALYs averted by GXpert over the base case, an incremental cost efficiency ratio (ICER) was calculated. The ICER was then contrasted to the WHO's proposed country-specific willingness to pay (WTP) threshold, which is three times GPD/capita/year in Egypt. Because the ICER was less than this, the intervention was deemed cost-effective.

Ethical considerations:

The study was accepted by Egypt National TB Programme and approved by the National and International Institutional Review Boards (IRBs). Patients were recruited after obtaining a written informed consent. The costing and cost-effectiveness assessments were outlined in the study protocol reviewed by the IRBs. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

RESULTS

The mean $\pm$ standard deviation of estimate of the daily cost per patient (using activity-based costing approach) was 432.29 ±170.5 (Table 1). All cost items were presented in Egyptian Pound year 2017.

Table (1): Total diagnostic, hospitalization, treatment and complications costs according to each scenario of TB diagnosis

Scenario	Cohort	Total Diagnostic Costs (EGY 2017)	Hospitalization cost (EGY 2017)	Treatment costs (EGY 2017)	Costs of complications (EGY 2017)*
Base-case (Algorithm1)	Tuberculosis (MDR)	1,510.21	274889.21	175913.78	36716.74
	Tuberculosis (no MDR)	29,023.17	2384873.03	338416.47	631203.75
	No tuberculosis	203160.43	-	-	
	Total	233693.81			
In addition to smear (Algorithm 2)	Tuberculosis (MDR)	17966.23	841371.52	538430.91	112,381.36
	Tuberculosis (no MDR)	336,960.07	1469342.03	208501.47	316,358.34
	No tuberculosis	8,461,295.25	-	-	
	Total	8816221.56			

MDR= Multi-drug resistance TB, *Cost of complication incurred by treated patients was based on assumption

For the 22 interviewed inpatient TB cases, the mean± standard deviation (SD) age was 37.7 ± 15.6 years, 27% of them were females and 73% were males. All patients were smear +ve pulmonary TB and HIV negative; 27% of them receive category 1 treatment, 18% were MDR (Category 4), 54% were receiving category 2 treatment. Mean± SD length of stay (LOS) was 124 ±197 days for MDR patients and 7±5 days for other TB patients. Mean out of the pocket payment (OOP) was 15.7 ± 2.5 Egyptian pounds (LE).

The following can be proved in terms of laboratory and health-care system costs for tuberculosis diagnostic algorithms:

- Laboratory costs of the new diagnostic algorithm (GXpert + smear) are shown in table 2. The total laboratory costs were 251.7 LE per diagnosed MDR- TB patient in case of algorithm 1, (smear testing without GXpert) compared to 1197.7 LE per MDR- TB patient in case of using the 2nd algorithm (GXpert + smear).
- For TB cases (not MDR), the total laboratory costs were 142.27 LE per patient in the base-case scenario, compared to 905.8 LE per patient in the alternative scenario (GXpert + smear testing).

Case finding:

- The use of GXpert in addition to smear microscopy (Algorithm 2), considerably increased TB case finding of MDR- TB patients from 28.5% to 71,5% and from 53.8% to 98.1% in TB patient (not MDR), when compared with the base case (Table 2).

Table (2): Cohort of TB cases detected according to each diagnostic scenario

Scenario	Cohort	No. of individuals among the cohort who have *	Total TB cases detected	% of TB and TB-MDR cases detected in those having actually disease	False –ve cases (according to diagnostic tests sensitivities)	False +ve cases (according to the diagnostic tests specificities)
Base case	Tuberculosis (MDR)	21	6	28.5	200	556
	Tuberculosis (no MDR)	379	204	53.8		
	No tuberculosis	9600				
	Total	10000	210			
In addition to smear	Tuberculosis (MDR)	21	15	71.5	22	96
	Tuberculosis (no MDR)	379	372	98.1		
	No tuberculosis	9600				
	Total	10000	387			

MDR=Multi-drug Resistance TB -

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* No. of cases according to the disease prevalence from National TB programme (Egypt).

When the alternate solution scenario was used, the number of false positives encountered in the base case was reduced due to low clinical diagnosis. Total treatment costs (hospitalization together with costs of complications) were reduced by about 53.4%. Where number of false positive cases decreased from 556 cases in the base case scenario compared to 96 in the alternative scenario. The ICER for using GXpert ‘‘in addition to’’ smear microscopy compared to the base case was 2,320 LE per DALY averted, found to be well below the WTP threshold, which is assumed to be three times the GDP/capita.

The results of the probabilistic sensitivity analysis (Monte Carlo simulation) is depicted in table 3, the median (CI) of ICER was 6456.1 (range 818.3-51181.4)/DALY averted, denoting that GXpert continued to be cost effective with probabilistic sensitivity analysis.

Table (3): Cost per DALY according to each scenario of TB diagnostic algorithm

Scenarios	Total Cost	Total DALYs	Cost per DALY	Incremental cost effectiveness ratio (ICER Compared to base-case	Monte Carlo Simulation ICER, Median (C.I. 2.5-97.5)
Base-Case	6,319,290	3413.87	1851.1	2,320	6456.1 (818.3-51181.4)
In addition to smear	13,070,652	503.46	25961.4		

Deterministic sensitivity analyses illustrated that ICER of the alternative algorithm compared to the base case sill cost effective (Figure 1).

When the parameters for the suspect population and the performance of the base-case change, as shown in figure 1, the ICER varies.

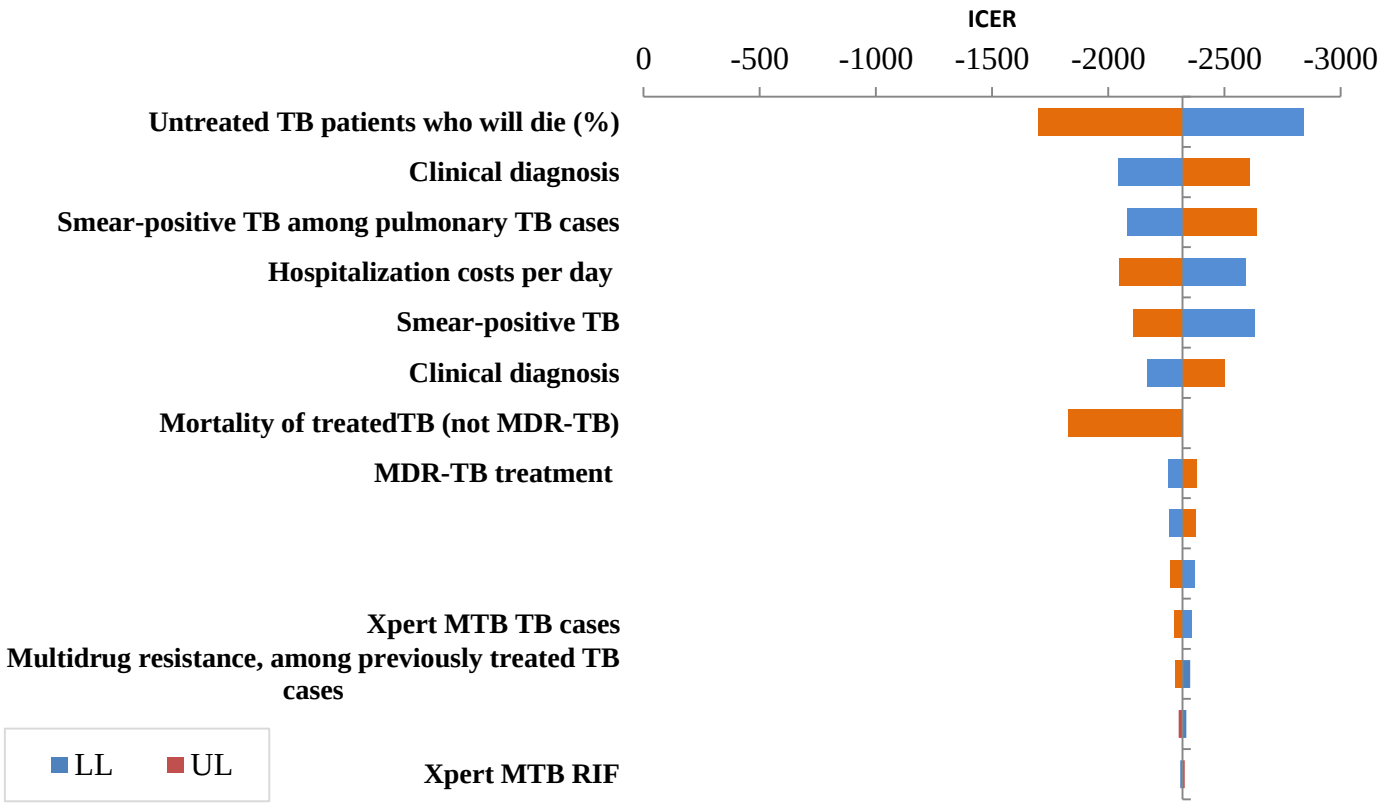

Figure (1): ICER deterministic sensitivity analysis

UL: is upper limit of confidence interval
LL: is lower limit of confidence interval
The negative sign of cost denoting DALYs averted.

ICER of the alternative algorithm compared to the base-case (smear microscopy and culture) was slightly worsened when the probability of death among untreated TB patients becomes 70%. However, varying the treatment success rate among TB cases and varying the specificity or sensitivity of GXpert in detecting MDR or MDR-RIF cases in the included cohort has little effect on our results.

DISCUSSION

GXpert is highly probable to become more cost-effective than a base-case of smear microscopy and culture for suspect HIV negative-TB persons, according to the findings of this study. A number of model inputs indicated the amount and type of cost-effectiveness benefit from deploying GXpert. The achievement of existing TB diagnostic practice is the most important of these factors. In case with low sensitivity of the current practice coupled with high specificity, GXpert can significantly impact effectiveness. While current practice had a high sensitivity but a low specificity, GXpert would reduce care money by minimizing the number of false positives.

The results also revealed that the total treatment costs (hospitalization together with costs of complications) were reduced by about 53.4% as the number of false positive cases, decreased from 556 cases in the base-case scenario compared to 96 in the alternative scenario.

The current results are based on several assumptions, e.g. 50% of the untreated cases will die after 2 years, mortality rate for treated MDR-TB patients was estimated to be 14% [22], while mortality rate of treated TB cases was estimated to be 2.9% [16] and its assumed that cost of death is incurred in the year of diagnosis (wasn't discounted).

Owing to lack of data, we couldn't make micro-costing for GXpert test. The cost/test was estimated through average cost from different suppliers.

Additionally, the model started with HIV negative cohort, which might impact the results and overstate cost effectiveness, influenced by higher mortality, morbidity rates and higher disability weights for TB, HIV-positive cases. Our model was concerned with costs from the Health Sector perspective, while full societal evaluation would make the alternative algorithm (GXpert in addition to smear) fair better as Xpert is likely to require less patient visits. Moreover, GXpert can help patients get a better diagnosis and save money before they have to go to the doctor[23].

Nonetheless, our analysis is hampered by a number of assumptions. Initially, assuming no transmission impacts or extra death advantage from early diagnosis is a cautious approach that will undervalue GXpert's price, particularly where GXpert's introduction is extremely huge of drug-resistant patients treated appropriately and quickly. Also, in this study the deterministic sensitivity analysis showed that greater prevalence of TB cases in the suspect population improves the cost-effectiveness of GXpert**.** Furthermore, the probabilistic sensitivity analysis, illustrated that the median (95%CI) of ICER was 6456.1 (818.3-51181.4)/DALY averted, which was still cost effective (but still below Egypt's WTP threshold) [24].

CONCLUSION

Despite the fact that our model is robust in light of current data and evidence, critical data, particularly on the characteristics of TB suspect communities and the viability of implementing GXpert at scale, remains lacking. Moreover, we are unable to anticipate the costs associated with GXpert scale-up at this time. The model in this study strongly suggests that GXpert will be cost effective in a variety of settings; nevertheless, scaling up GXpert will massively boost TB diagnostic costs, entailing additional cost efficiency research in this area.

DECLARATIONS

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