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Abstract

Setting: In 2007, WHO recommended introducing rapid *Mycobacterium tuberculosis (MTB)* culture in the diagnostic algorithm of smear-negative pulmonary tuberculosis (TB).

Objective: To assess the cost-effectiveness of the introduction of rapid non-commercial culture method (Thin Layer Agar) together with Löwenstein Jensen culture to diagnose smear-negative TB at a district hospital in Kenya.

Design: Effectiveness data (number of true TB cases treated) were obtained from a prospective study evaluating the effectiveness of a clinical and radiological algorithm (conventional) with and without (culture-based) MTB culture in 380 smear-negative TB suspects. The costs of each algorithm were calculated using a “micro-costing” or “ingredient-based” method. The cost and effectiveness was compared between conventional and culture-based algorithms and the incremental cost-effectiveness ratio (ICER) was estimated.

Results

The cost of conventional and culture-based algorithms (per smear-negative TB case) was 15,026€ (39.5€) and 54,931€ (144€), respectively. The cost per TB confirmed and treated case was 455.3€ and 915.5€, respectively. The culture-based algorithm allowed to diagnose and treat 27 more cases for an additional cost of 39,905€ (1478€ per case).

Conclusion

MTB culture is cost-effective to diagnose smear-negative pulmonary TB according to WHO standards but did not reduce the cost of overtreatment due to long delay of culture results.

Keywords: Economic Evaluation, smear negative pulmonary, TB diagnosis, Health Technology Assessment

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INTRODUCTION

Tuberculosis is the first cause of death among people living with HIV[1] and perpetuates poverty and inequalities in low-income countries[2-4]. In 2010, 8.8 million of new cases of TB were reported worldwide, of which 350,000 among HIV positive population[5]. In Kenya, in 2008-2009, the HIV/AIDS prevalence rate was 6.3%[6]. This national average masks huge disparities, and the prevalence rate was 13.9% in the Homa Bay district, where MSF intervenes since 1996. At Homa Bay, 70% of TB cases are HIV infected[7].

Smear microscopy has a low sensitivity (50%) compared to the *Mycobacterium tuberculosis* (MTB) culture reference standard[8]. This sensitivity is even more reduced in HIV infected patient[9-11]. In 2007, the WHO reviewed its diagnostic algorithms for smear-negative patients and recommended, when available, MTB culture and an earlier and systematic chest X-ray examination[12]. However, culture requires high infrastructure level, highly qualified staff and scrupulous respect of safety standards[12]. Due to the very low access to the MTB cultures in resource-limited settings, smear-negative TB suspected patient are diagnosed on the basis of clinical examination, chest X-ray and absence of response to an antibiotic trial targeting bacterial pneumonias[13]. The performances of these diagnostic algorithms are disappointing, leading to a sub-diagnosis of true TB cases and overtreatment of non-TB cases[14].

The MGIT liquid culture method is the most sensitive culture but remains expensive and has an increased safety risk compared to methods using solid media[14]. There are non-commercial alternatives, such as Thin Layer Agar culture (TLA)[15], based on the microscopic observation of MTB on agar medium. Sensitivity is close to the Löwenstein-Jensen (LJ) classical method, but faster (10-15days against 30-40 days for LJ)[16-19]. To improve the TB diagnosis in the Homa Bay District, MSF introduced the TLA and LJ cultures in the laboratory of the district hospital[20].

This study aims to address the question whether the introduction of the rapid non-commercial TLA culture together with LJ culture increased the number of true TB patients started on treatment among smear-negative pulmonary TB suspects and for which cost.

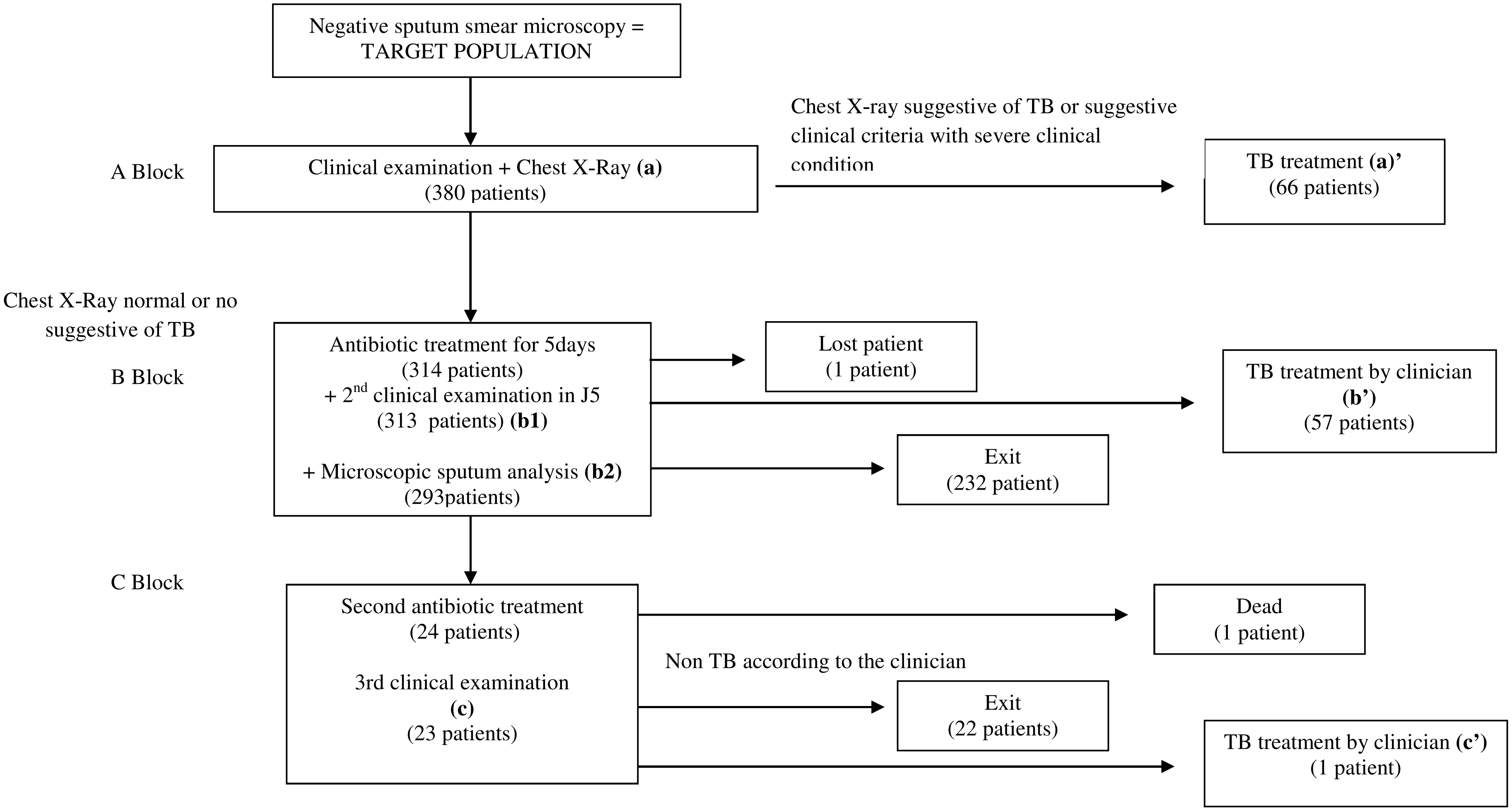
METHODS

Diagnostic algorithms

The conventional diagnostic algorithm based on clinical, radiological features and use of an antibiotic trial is compared with the culture-based algorithm which includes the TLA and LJ cultures in addition to the conventional algorithm (Figures 1 and 2). The diagnostic algorithm included several steps after which some patients could be started on TB treatment.

In the conventional algorithm, when the chest X-ray and/or clinical examination were suggestive of TB, patients were started on TB treatment (A block). Otherwise, they received an antibiotic trial (amoxicilline 1g 3x/j) for five days followed by a second clinical examination and sputum microscopy examination. The decision to start or not a TB treatment was decided by the clinician (B block) who could prescribe a second antibiotic treatment and perform a third clinical examination (C block).

Figure 1: Conventional diagnostic algorithm without culture



In the culture-based algorithm, culture was introduced from the A block for every patients. If the culture was positive and the patient was not already treated for TB the patient was contacted and traced to start the TB treatment. The rest of the management process was the same as in the conventional algorithm.

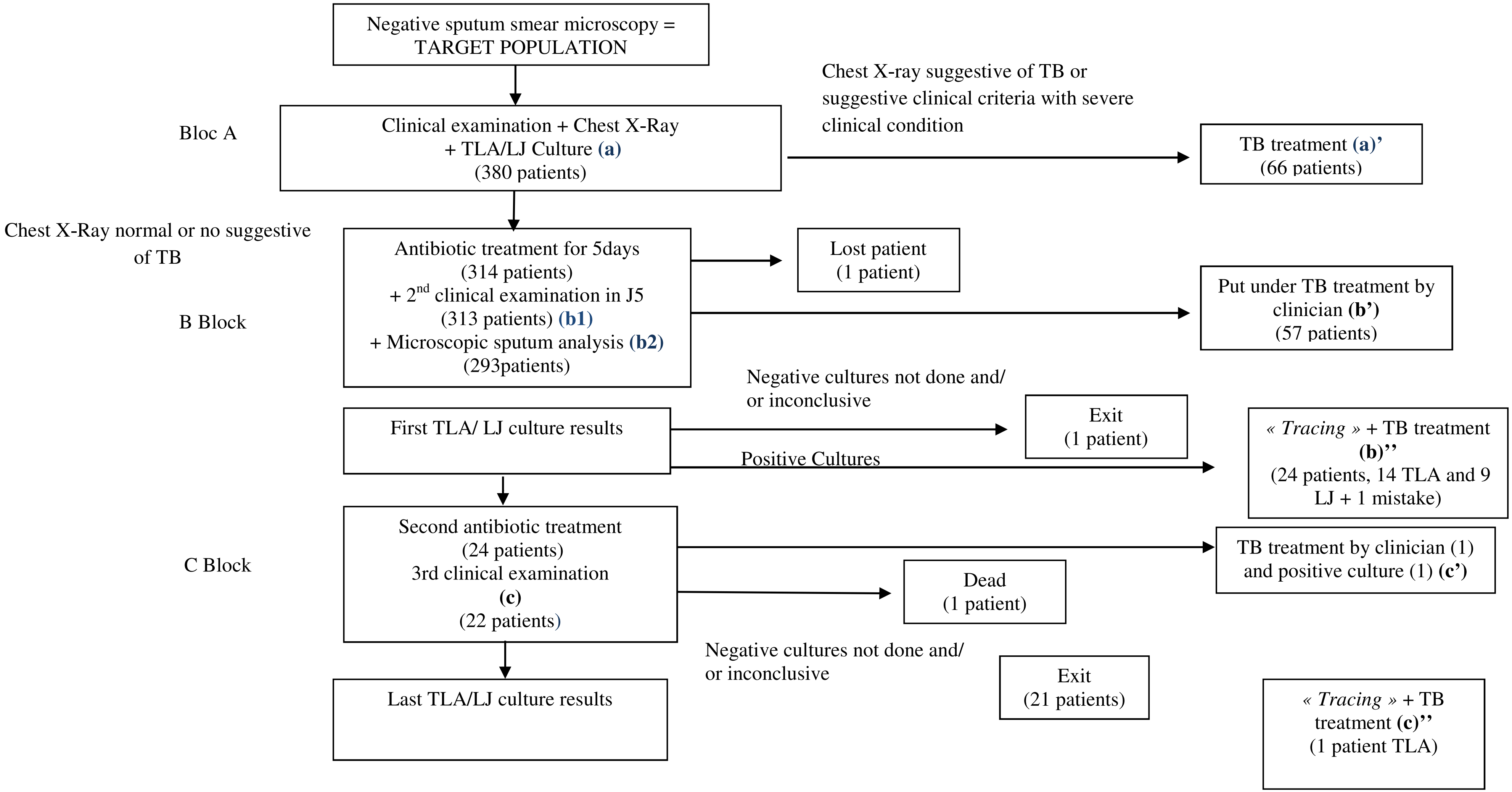


Figure 2: TLA/LJ culture results

The protocol was approved by the Kenya Medical Research Institute Ethical Review Committee and by the Ethical Review Committee at the ''Comite´de Protection des Personnes'', Saint Germain en Laye, in France. Written informed consent was obtained from all study participants as well as from guardians on the behalf of the minor participants before enrolment in the study. The written informed consent was approved by the Ethics Committees.

Study population

The effectiveness criterion, expressed in terms of true TB cases (positive culture) started on treatment, were obtained from the prospective study of Huerga *et al* conducted between September 2009 and February 2011[7]. The study included 380 patients of 15 years and older, living within a radius of 10kms from the hospital, having at least a cough of two weeks and with two negative smears. Two sputa per patient were collected for TLA and LJ cultures. Due to the delay of the TLA culture results, the effectiveness criterion was independently assessed in the same patients without taking into account the therapeutic decision based on the culture result for conventional algorithm and using culture results for the culture-based algorithm (Figures 1 and 2).

Costs estimation

The collection of data (Appendix Table A) started on site in 2011 and covers the period from September 2009 to February 2011. The cost per patient was estimated for every block of each algorithm. The number of patients in each block of the culture-based algorithm is the observed numbers and those of the conventional algorithm were derived from the culture-based algorithm (Figure 2). Costs, whether direct (resources entirely consumed by the service or joint (shared between different services), included variables costs and fixed costs (provisions of depreciation reserve of equipment and buildings). Infrastructure costs of the existing laboratory before introduction of culture were not considered. Variable costs estimation was based on expenditures, established a posteriori from quantities actually used (consumables, fuel, medicine, actual working time) and the price obtained in the Kenyan market in 2009, using a conversion rate of 108,7 KES for 1€[21]. Joint costs were calculated based upon allocation keys.

The staff (clinician, nurse, lab technician) cost was calculated by either multiplying the time spent in the activity by the cost of a unit (minute) of work time or from the average number of patients per day. The work time of the laboratory technicians in charge of the culture was not easily observable hence we adopted the productivity approach[22]. In 2009, 1195 cultures were carried out at the laboratory, equivalent to an average of two tested patients per day (with 2 samples per patient) for each of the three laboratory technicians. The unit cost of supervisor work of and maintenance worker was calculated by dividing their wages by the total number of cultures. The unit cost of the person in charge of patients' « tracing » was estimated by dividing his wage by the number of searched people from the study period. For follow-up of TB treatment, patients had weekly nursing consultations (6 minutes) during first two months and monthly consultation during last four months. For HIV-positive patients (74%), there were additional medical consultations (15 minutes) once every two weeks during first two months and once per month thereafter.

The materiel and furniture cost includes the cost of treatment, X-Ray, and laboratory equipment. The cost of the first (0.87€) and second (4.4€) antibiotics treatment and TB treatment (22€ for 6 months rifampicin based regimen) was based on a lump sum estimated by MSF. The cost of chest X-ray was based on a lump sum of 1.84€ per X-ray. The cost of small equipment and furniture for microscopy (0.442€ per blade) was based on a previous study in Kenya[23]. For the culture, the equipment and supplies cost included all medical consumables (autoclave pipette, bunsen …), non-medical (gas lighter, lamp, sink, strainer …) and reagents expenditures.

For the running cost, the culture laboratory shared the waste water treatment and waste management with the hospital. We allocated 4.06% of this cost to the culture laboratory, using the surface area as allocation key. The investment cost included medical and non-medical equipment cost and the depreciation of the vehicle used (Table A1). For joint fixed costs, the allocation key was the activity for the TB diagnosis linking to the hospital activity. They were allocated into three services, 10.5% for microscopy, 59.5% for laboratory equipment or the culture laboratory and 30% for the general laboratory. Based on the nomenclature used by the city of Lyon,[24] the lifetime for depreciation estimation is 10 years for laboratory equipment, 15 years for air-conditioning, seven years for fridges, 25 years for buildings and three years for motorcycles.

The total cost was estimated by adding the cost of all different categories listed above according to their use in the conventional and culture-based algorithms, respectively (Table 1).

Table 1: Cost calculation process

<table>
<tr><td></td><td>Cost without TLA/LJ culture</td><td>Cost with TLA/LJ culture</td></tr>
<tr><td>A BLOCK</td><td>C(a) = Cost of clinical examination + cost of chest X-Ray</td><td>C(a) = Cost of clinical examination + cost of chest X-Ray + cost of culture</td></tr>
<tr><td></td><td colspan="2">C (a’) = C(a) + cost of TB treatment</td></tr>
<tr><td>B BLOCK</td><td colspan="2">C(b) = C(a) + cost of antibiotic treatment + cost of second clinical examination + cost of sputum smear microscopy</td></tr>
<tr><td></td><td colspan="2">C (b’) = C(b) + cost of TB treatment</td></tr>
<tr><td></td><td></td><td>C (b’’) = C(b) + cost of « tracing »+ cost of TB treatment</td></tr>
<tr><td>C BLOCK</td><td colspan="2">C(c) = C(b) + cost of 2^{nd} antibiotic treatment + cost 3rd clinical examination</td></tr>
<tr><td></td><td colspan="2">C (c’) = C(c) + cost of TB treatment</td></tr>
<tr><td></td><td></td><td>C(c’’) = c(c) + cost of « tracing »+ cost of TB treatment</td></tr>
</table>

TLA: Thin Layer Agar Culture
LJ: Löwenstein Jensen Culture
TB: tuberculosis

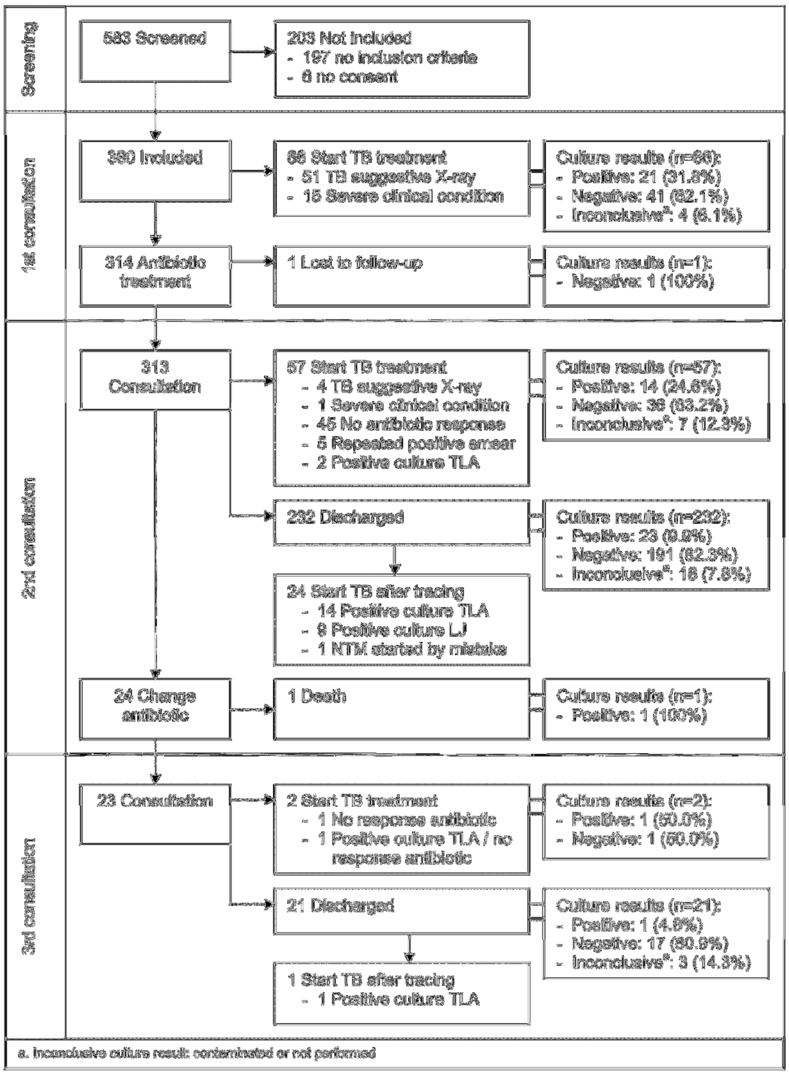
Economic Evaluation

The efficiency of TLA/LJ culture was estimated by calculating the incremental cost-effectiveness ratio (ICER) for the conventional and culture-based diagnostic algorithms (Cost (cult) - Cost / (result (cult) - result) [25]. The effectiveness outcome was the number of true TB cases (positive culture) starting on treatment. There were 33 patients when using the conventional algorithm compared to 60 patients when using the culture-based algorithm. Univariate sensitivity analysis was performed on the number of TB suspects (1680, as the total number of patients screened at the Homa-Bay laboratory in 2009) and on the proportion of true TB cased identified by the culture-based algorithm who were started on treatment after been traced. In study condition, the proportion was 100% whereas it was close to 75% in programmatic condition[7]. We used a tracing coverage rate of 75% and 50% for the sensitivity analysis.

RESULTS

A total of 380 smear-negative pulmonary TB patients were included in the study[7]. Following the first clinical examination and chest radiography, 66 patients were treated for TB and 314 received an antibiotic trial. Among the last ones, 57 were started on TB treatment based on clinical and microscopy results, 232 were not considered as TB and withdrawn and 24 patients received a 2nd antibiotic trial (Figure 1). In total, 25 patients were secondarily started on treatment after been traced due to a positive culture result (Figure 2 and Figure 3).

Figure 3: Diagnostic and treatment pathway for smear-negative TB suspects (N= 380).



The costs detail is presented in Tables A1 to A3 in the Appendix. The overall cost of the care of the 380 smear-negative TB suspects was 15,026€ and 54,931€ with the conventional and culture-based algorithms, respectively. In the conventional algorithm, the main costs were human resources' cost (72%), followed by the anti-TB drugs cost (18.2%). The chest radiography represented only 4.6% of the total cost. With the culture-based algorithm, the human resources' cost represented only 39.4% of the overall cost, while the cost of materials and supplies participated for almost half of the cost (42.8%). The average cost per screened TB suspect was 39.5€ and 144.5€ for the conventional and culture-based algorithms, respectively. The cost per true TB case started on treatment was 455.3€ when using the conventional algorithm compared to 915.5€ when using the culture-based algorithm (Table 2). As shown by the ICER, the culture allowed starting TB treatment in 27 additional true TB cases for a total additional cost of 39,905€, equivalent of 1,478€ per new true TB case started on treatment (Table 3).

Table 2: Cost-effectiveness of screening negative TB cases with and without TLA / JL culture

Diagnostic algorithms	Cost (euros)	Effectiveness (Screened and treated cases)	Cost-effectiveness ratio
P1Algorithm without TLA/LJ culture, 380 patients	15026	33	455,2
P2Algorithm with TLA/LJ culture, 100% of tracing coverage, 380 patients	54931	60	915,5
P2'Algorithm with TLA/LJ culture, 75% of tracing coverage, 380 patients	53710	52	1032,9
P2''Algorithme with TLA/LJ culture, 50% of coverage tracing, 380 patients	52498	45	1166,6
P3Algorithme without TLA/LJ culture, 1680 patients	66380	146	454,7
P4Algorithm with TLA/LJ culture, 100% of coverage tracing, 1680 patients	200802	265	757,7
P4'Algorithm with TLA/LJ culture, 75% of coverage tracing, 1680 patients	195823	230	851,4
P4''Algorithm with TLA/LJ culture, 50% of tracing coverage, 1680 patients	183910	199	924,2

Using 75% and 50% of proportion of culture positive patients effectively started on treatment after tracing, the average cost per screened patient was 141.3€ and 138.1€, respectively euros. The ICER indicates that the cost per new true TB case started on TB treatment was 2036€ for a tracing coverage of 75% and 3122.7€ for a tracing coverage of 50% (Table 3).

When the number of patients is increased to 1680, the average cost per screened patient using the conventional algorithm was 39.5€ (Table A2). Using the culture-based algorithm with a tracing coverage of 100%, 75% and 50%, the average cost per screened patient was 119.5€, 116.5€ and 109.4€, respectively (Tables 2 and A3). The ICER per new true TB case started on treatment was 1129.6€, 1541€ and 2217.5€ with the respective tracing coverage of 100%, 75% and 50% (Table 3).

Table 3: Incremental Cost Effectiveness Ratio

Program	Costs (euros) (C)	Screened and treated cases (E)	ΔC	ΔE	ICER
P1	15026	33	15026	33	455,3
P2	54931	60	39905	27	1478,0
P2'	53710	52	38684	19	2036,0
P2"	52498	45	37472	12	3122,7
P3	66 380	146	66 380	146	454,7
P4	200802	265	134 422	119	1129,6
P4'	195823	230	129 443	84	1541,0
P4"	183910	199	117 530	53	2217,5

DISCUSSION

The cost analysis was considered from the district hospital perspective and does not include the cost for the patient. The culture-based algorithm was more expensive than the conventional algorithm. Indeed, it requires expensive equipment and many supplies whereas the conventional algorithm without culture depends mainly on human resources. The use of thresholds in decision-making has met some criticism, such as, among others, the risk of uncontrolled growth in health-care expenditure. However, thresholds represent the societal willingness-to-pay for health-care, and for that, this decision rule is considered more appropriate for societal decision-makers[26]. Moreover, budget impact analysis can complement cost-effectiveness analysis. The WHO[27], considers cost-effective a strategy, which the cost-effectiveness ratio is less than three times the GDP per inhabitant of the country where the strategy is implemented.

Despite a higher global cost, the culture-based algorithm was cost-effective. The cost per true TB case started on treatment (915.5€) was less than three times the GDP per capita of Kenya (1668€ in 2009)[28]. The sensitivity analysis showed that the cost-effectiveness of the culture algorithm improved (757.7€) if we multiply, given the available resources of the studied laboratory, by four the number of screened patients. When the tracing coverage rate drops to 50%, the culture-based algorithm remained cost-effective (924.2€, by true TB case started on treatment) regardless of the total number of screened patients. The additional cost per true TB case started on treatment with a tracing rate of 100% is not excessive (1478€) compared to the average cost (915€). It remains true when the tracing rate decreases to 75%.

The total cost for the diagnosis of presumed smear-negative TB increased from 15,026€ (without culture) to 54,931€ (with culture), which would require to multiply by 3.5 or 4 the amount of financial resources. The adoption of the 2007 WHO revised algorithm at the national scale would imply the creation of several laboratories with high-level of infrastructure and staff with expertise[12]. It is therefore important to first ensure that the introduction of the culture is consistent with financial sustainability/affordability at the medium and long term, without risk to the financial situation of Kenya.

Cost-effectiveness studies about algorithm with culture in limited resources countries are relatively scarce[15] and we do not know any of the TLA culture. In addition, the comparison is difficult, the effectiveness outcome being not always the same[29]. Mueller *et al.* in a study on Zambia found a cost per detected case of 134€ with the MGIT culture and 231€ with the LJ culture[30]. When they focused on the smear negative TB suspects, the cost was 413€ with MGIT.

In this study, the culture contributed to put under treatment 27 patients who had escaped the clinical and radiological diagnosis who represented 42% of all TB confirmed patients. However, it requires an effective tracing of patients with a positive culture. Also, the long delays of culture results limit the impact of culture on the therapeutic decision. Therefore, the use of culture does not allow to reduce the potentially proportion of patients wrongly started on treatment based on clinical and radiological findings. A test with a similar sensitivity to the culture, but much faster would have more impact on the treatment decision, and would be probably more cost effective. Among the currently available tests, the XpertMTB/RIF assay is the one that comes closest to this ideal test with a sensitivity of 70% in smear-negative TB suspects compared with culture and results available in 2h[31]. This test has also the advantage of requiring infrastructure and expertises that are close the ones required by microscopy[32].

CONCLUSION

This study is one of the few studies documenting the cost-effectiveness of a diagnostic algorithm for pulmonary TB using the rapid culture of MTB in a district hospital of an area with high HIV prevalence and limited resources. Although cost-effective according to the WHO criteria, the use of MTB culture remains an expensive examination with a too long delay for results increasing the risk of over-diagnose patients.

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Appendix

Table A: Identification and cost valorisation

Costs type	Identification	Measure method	Valorisation	Data source
A. Variable Costs Staff	Clinical staff Culture staff Tracing staff Sputum smear microscopy staff Training staff	Actual working time per patient Time spent in training (<1an)	Net wage	MSF RH
Materials and furniture	Drugs Reagent, radio film Consumables Laboratory supplies (spatula, tube…) Small medical equipment Small non-medical equipment	Daily quantity consumed, lump	Market prices	Bills recorded in accounting records
Functioning and maintenance of building	Electricity Cleaning Plumbing Painting Building renovation Medical maintenance Non-medical maintenance Water treatment	Quantity consumed Based on the area	Market prices	Bills recorded in accounting records
Functioning and maintenance of vehicles	Fuel	Quantity consumed	Market prices	Bills recorded in accounting records
B. Fixed costs Medical equipment	Autoclave, incubator, precision scale, water distiller, biosafety cabinet, X-Ray…	Depreciation calculation	Market prices & lifetime	Bills recorded in accounting records
Non-medical equipment	Air conditioning, fridges, computer…			
Infrastructures	Building electrical and plumbing system			
Vehicles	Vehicle purchased			

TableA2: Cost components of screening (tracing = 100%), with and without TLA / LJ culture, in € and (%), 2009

	Algorithm			
	380 patients		1680 patients	
Cost components	Without TLA/LJ culture	With TLA/LJ culture	Without TLA/LJ culture	With TLA/LJ culture
Staff	10833,5	21617,3	47850	66266,3
	(72,1)	(39,4)	(72,1)	(33,0)
Staff training	0	117,1	0	184,1
	(0)	(0,2)	(0)	(0,1)
Chest X-Ray	695,4	695,4	3074,5	3074,5
	(4,6)	(1,3)	(4,63)	(1,5)
Antibiotic treatment	372,5	372,5	1643,9	1663,8
	(2,5)	(0,7)	(2,48)	(0,8)
Functioning	40,9	1943,2	181,2	3199,1
	(0,3)	(3,5)	(0,27)	(1,6)
Material and furniture	301,5	23507,1	1332,6	104105,9
	(2,0)	(42,8)	(2,01)	(51,8)
Medical equipment	20,4	1863,7	90,6	2997,4
	(0,1)	(3,4)	(0,14)	(1,5)
Non-medical	34,2	269	151,2	2211,5
equipment	(0,2)	(0,5)	(0,23)	(1,1)
TB treatment	2728	3300	12056	14652
	(18,2)	(6,0)	(18,16)	(7,3)
Infrastructure	0	1082	0	1707,3
	(0)	(2,0)	(0)	(0,9)
Motorcycle	0	104	0	472
depreciation	(0)	(0,2)	(0)	(0,2)
Motorcycle	0	60	0	271,3
maintenance	(0)	(0,1)	(0)	(0,1)
Total	15026	54931	66380	200802
Cost per patient	39,5	144,5	39,5	115,5

Table A3: Cost components of screening (tracing = 75% an 50%) with and without TLA / LJ culture, in € and (%), 2009

	Algorithm			
	75% tracing		50% tracing	
Cost components	With TLA/LJ culture 380 patients	With TLA/LJ culture 1680 patients,	With TLA/LJ culture 380 patients	With TLA/LJ culture 1680 patients
Staff	20937,8 (39,0)	64113,2 (32,7)	20493 (39,0)	55136,9 (30,0)
Staff training	115,5 (0,2)	181 (0,1)	113,4 (0,2)	177,8 (0,1)
Chest X-Ray	686,2 (1,3)	3021,2 (1,5)	673,4 (1,3)	2967,8 (1,6)
Antibiotic treatment	372,6 (0,7)	1633,5 (0,8)	357,8 (0,7)	1592,2 (0,9)
Functioning	1916,8 (3,6)	3142,2 (1,6)	1880 (3,6)	3083,4 (1,7)
Material and furniture	23191,7 (43,2)	102340,1 (52,3)	22750,4 (43,3)	100511,3 (54,7)
Medical equipment	1838,6 (3,4)	2945,6 (1,5)	1803,7 (3,4)	2891,9 (1,6)
Non-medical equipment	264,6 (0,5)	2171,7 (1,1)	259 (0,5)	2130,5 (1,2)
TB treatment	3190 (5,9)	14036 (7,2)	3036 (5,8)	13398 (7,3)
Infrastructure	1066,7 (2,0)	1678,7 (0,9)	1046,7 (2,0)	1649,1 (0,9)
Motorcycle depreciation	82,7 (0,2)	355,9 (0,2)	53,8 (0,1)	236 (0,1)
Motorcycle maintenance	47,5 (0,1)	204,6 (0,1)	30,9 (0,1)	135,7 (0,1)
Total	53710,8 (100)	195823,4 (100)	52498,7 (100)	183910,5 (100)
Cost per patient	141,3	116,5	138,1	109,4