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Microscopic observation drug-susceptibility assay vs Xpert® MTB/RIF for the diagnosis of tuberculosis in a rural African setting: a cost-utility analysis

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Abstract

Objective: To compare the cost-utility of Microscopic Observation Drug-Susceptibility Assay (MODS) and Xpert®MTB/RIF implementation for TB diagnosis in rural northern Mozambique.

Methods: Stochastic transmission compartmental TB model from the health care provider perspective with parameter input from direct measurements, systematic literature reviews, and expert opinion. MODS and Xpert®MTB/RIF were evaluated as replacement test of smear microscopy (SM) or as an add-on test after a negative SM. Costs were calculated in 2013 USD, effects in Disability Adjusted Life-Years(DALY). Willingness to pay threshold (WPT) was established at once the per capita Gross National Income of Mozambique.

Results: MODS as an add-on test to negative SM produced an incremental cost-effectiveness ratio (ICER) of 5´647.89USD/DALY averted. MODS as a substitute for SM yielded an ICER of 5'374.58USD/DALY averted. Xpert®MTB/RIF as an add-on test to negative SM yielded ICER of 345.71USD/DALY averted. Xpert®MTB/RIF as a substitute for SM obtained an ICER of 122.13USD/DALY averted. TB prevalence and risk of infection were the main factors impacting MODS and Xpert®MTB/RIF ICER in the one-way sensitivity analysis. In the probabilistic sensitivity analysis, Xpert®MTB/RIF was most likely to have an ICER below the WPT, whereas MODS was not.

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Conclusion: Our cost-utility analysis favours the implementation of Xpert®MTB/RIF as a replacement of SM for all TB suspects in this rural high TB/HIV prevalence African setting.

Keywords: *Mycobacterium tuberculosis*; Diagnosis; Cost-Effectiveness analysis; Sub-Saharan Africa

Introduction

Tuberculosis (TB) is a leading cause of mortality worldwide. Together with HIV, it is the primary cause of death from an infectious disease. In 2014 there were an estimated 9.5 million new cases globally, and 1.5 million people died of TB. About 390,000 of those deaths were of people living with HIV (PLWH).[1]

Mozambique is considered by the WHO as a high TB/high HIV burden country. TB incidence is 551 (IC95% 435-680)/100,000 population; representing 150,000 new cases every year (85,000 or 63% among HIV-infected patients) with approximately 45,000 annual deaths. The nationwide HIV prevalence is 12%, and 1.6 million are PLWH.[2] TB is the leading cause of death among PLWH.[3]

Sputum smear microscopy (SM) is the most common TB diagnostic test. However, it is not very sensitive, especially in HIV-infected patients in whom TB often has an atypical clinical presentation and a paucibacillary nature.[4] TB diagnostic delay in HIV-infected patients has been pointed out as one of the main factors for the high mortality of HIV/TB co-infection in high HIV prevalence settings.[5,6] The global priorities for TB care and control are to improve case detection and to detect cases earlier, including cases of smear-negative disease which are often associated with HIV co-infection and young age, and to enhance the capacity to diagnose multidrug-resistant tuberculosis (MDR-TB).[7,8]

Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) is a fully automated cartridge-based real-time DNA-based test that can detect both TB and resistance to rifampicin in less than 2 hours. Xpert® MTB/RIF has been endorsed by WHO and recommended for expansion at a district level in low-income countries. It is recommended as the initial test in all adults and children presumed to have pulmonary MDR-TB or HIV-associated TB. It has also been recommended as the initial diagnostic test (rather than conventional microscopy and culture) in all children and adults suspected of having pulmonary TB although this recommendation remains conditional due to resource implications.[8] It is also considered the preferred initial diagnostic test for TB meningitis and a good replacement test for other forms of extra-pulmonary TB. According to a meta-analysis by the Cochrane Collaboration Group, overall sensitivity for Xpert® MTB/RIF is 88% (CI 82%-92%), decreasing to 76% (CI 63%-85%) in HIV-infected patients and to 61% (CI 40%-81%) in HIV+ smear negative patients.[9] Market prices for Xpert® MTB/RIF are around 50.000 USD for the four cartridge module and computer extension and

65 USD per cartridge. Nevertheless, it is provided at concessional prices to high-burden countries such as Mozambique (17.000 USD for the 4 cartridge module and 9.98 USD for each cartridge) thanks to a contribution of the United States President's Emergency Plan for AIDS Relief (PEPFAR), the United States Agency for International Development (USAID), UNITAID, and the Bill & Melinda Gates Foundation.[10-12]

One of Xpert® MTB/RIF main drawbacks is costs, as actual prices are challenging for many developing countries. Also, its diagnostic accuracy poses some doubts, especially in high HIV prevalence settings. Other limitations are the need for stable electricity supply and stable room temperature, below 30ºC for operation, while a temperature of 2-28ºC is mandatory for cartridge storage.

Microscopic-Observation Drug-Susceptibility (MODS) assay is a cheap and low-complexity liquid-culture based technique for the diagnosis of TB infection and drug susceptibility testing (DST). It has been evaluated under high-level laboratory conditions in African settings, namely in South Africa, Ethiopia, Zimbabwe, and Uganda. [13-16] WHO has endorsed the assay for DST but has not recommended its implementation at district level. However, it has been shown that technicians from peripheral health centre laboratories without previous experience in TB cultures can learn MODS technique in 3 weeks.[17] Published numbers for the cost per test for the MODS assay have varied, ranging from as little as 0.72 USD to 7.31 USD including labour costs, fixed costs and DST.[18,19] A recent meta-analysis on MODS showed a global sensitivity of 96% (CI 94-98%), with 88.3% (95% CI 86.18–90.2%) in HIV-infected patients and 88.2% (95% CI 86.1–89.9%) in HIV-infected with smear-negative TB.[20,21] Therefore, its lower price per test could make it more cost-effective than Xpert® MTB/RIF. Another advantage is that it is patent-free. Challenges for the implementation of MODS are the need for more complex laboratory equipment (compromising a P2 biosafety cabinet, an inverted optic microscope, a centrifuge and an incubator), a stable electricity supply and 3 weeks of training.

Cost-effectiveness evaluations for TB diagnostics are key to informing policy makers, as the main TB burden worldwide is supported by low-income countries where resources have to be allocated with extreme caution. So far, cost-effectiveness comparisons of Xpert® MTB/RIF and MODS have been limited to short-term evaluation on rather broad regional or country-level impact on TB transmission.[22] Our aim was to evaluate the long-term cost-utility of MODS – which is potentially less expensive and more effective –versus that of Xpert® MTB/RIF for the diagnosis of TB in a rural health centre at a district level in a high HIV burden setting through a mathematical modelling approach.

Material and Methods

Target Population and Setting

The target population was the population of Ancuabe district. Ancuabe is located in Northern Cabo Delgado province, one of the poorest provinces in Mozambique. Cabo Delgado has a population of 1.8 million inhabitants with 51.6% women. 80% of the population lives in rural areas, and the illiteracy rate is around 80% for women and 51% for men. Life expectancy is 54 years and less than 40% have access to health care.[23,24] The prevalence of HIV is 9.4%.[25] HIV infection is responsible for at least 20% of the deaths in the province.[26]

Ancuabe measures 4,606 km^2 and has a population of 118,926 inhabitants. The estimated HIV prevalence is about 5%.[27] In 2013 the district had two Type 1 health centres led by a physician with space for 87 inpatients (Ancuabe Sede and Metoro) and a basic laboratory. In these health centres, a Chronic Diseases Unit/HIV Clinic offered HIV treatment and care. The district also had four Type 2 health centres that only had outpatient services and were led by a non-physician clinician (Meza, Mariri, Minheuene and Ngeue); Meza health centre also provided HIV treatment and care. Most clinical care was provided by non-physician clinicians with 1.5 to 2.5 years medical training. Ancuabe district laboratories were not doing TB culture at the time of this study. All TB diagnoses were based on clinical symptoms and SM, which was only available in the Type 1 health centres. X-rays were only available at Pemba Provincial Hospital, 120 km away.

Diagnostic strategies evaluated

We analysed the use of three different techniques for the evaluation of TB suspects attending Ancuabe health centres: SM, MODS, and Xpert® MTB/RIF.

- SM was used as the base case scenario, as this was the standard of care in the district and it is the most common diagnostic tool for TB diagnosis worldwide. This strategy consisted of two SM examinations followed by a chest x-ray or antibiotic trial in smear-negative TB suspects.
- Xpert® MTB/RIF technique was evaluated in two ways: as a replacement of SM for initial evaluation or as an add-on test for smear-negative cases.
- MODS was also evaluated as a replacement of SM for initial evaluation or as an add-on test for smear-negative cases.

Development of a compartmental Markov TB Model

A stochastic, transmission, Markov TB Model was programmed in R to describe the transmission of TB and the interaction between the patients and the health system.[28] The model was stratified by age group and HIV status in analogy with previous models. Conventions adopted for previous epi-

demic models of major anti-tuberculosis interventions and diagnostics were followed.[29–32] The population was divided into different compartments according to TB disease status. The TB-infected population was further divided into different compartments through the diagnostic pathway as well as treatment states (Figure 1).

Three methods were used to choose the model parameters: information available from a descriptive baseline study of the local TB programme outcomes;[33] a systematic literature reviews with meta-analysis when deemed appropriate, and expert consultation when no other source was available.[21] The total population was maintained stable during the simulation by programming the birth rate equal to the death rate.

For calibration, parameters were given a probability distribution and the model was run 10,000 times. The goodness of fit to WHO 2000-2014 estimates for TB incidence was evaluated with the least squares method. Then, the sets of parameters were resampled with replacement 10,000 times with probability of sampling directly proportionate to the goodness of fit. This way, a "best fit" set of parameters was obtained as well as a posterior distribution for each parameter. The "best fit" set of parameters was used for the cost-utility evaluation. The posterior distribution was used for the PSA.

Model assumptions were: there is no multi-drug resistant TB, HIV incidence stays at the 2014 level throughout the time of the study, patients are not started on TB treatment empirically (i.e. treatment based only on clinical symptoms, without any diagnostic test performed), and individuals show homogeneous mixing within the population.

Cost evaluation

A health care provider perspective was adopted for cost evaluation. A micro-costing approach was used. To estimate the capital costs and equipment costs up-to-date Pro-forma invoices from local and international providers were used. The costs were annualised according to the half-life of the goods. The half-life was estimated by the WHO estimates (www.who.int/choice/costs/prices_t4/en/index.html). As there were no tables available for Mozambique, Kenyan tables were used. In case no source was found for the half-life, the most commonly used value of 5 years was used or different after expert consultation. To estimate the labour costs, the official salary tables for laboratory technicians of the Mozambican Ministry of Health were used. Data from previous publications or expert opinion were used to estimate costs if no better source was found. Costs were measured in 2013 USD. A 3% yearly discount rate was applied to both costs and effectiveness as recommended.[34] Costs were calculated with the model, depending on the population in each state at every time-point.

Health outcomes

Using the model, estimates of the number of TB patients, time of permanence in each state, life years lost due to disease, as well as life years lived with disability were obtained. Disease adjusted life years (DALYs) were calculated using the weights for TB of the Global burden of disease study 2010.[35] For the calculation of life-years lost, we used the standard expected years of life lost approach, establishing 82 years as the maximum life expectancy.[34] No age weighting was used.

Cost-utility evaluation

For each run of the model, a total of 90 years (i.e. our time horizon) of TB transmission, diagnosis, and treatment was simulated. During the simulation, costs incurred and DALYs produced were calculated by the model and stored.

For the cost-utility evaluation, the incremental cost-effectiveness ratios (ICER) – i.e. the difference in costs divided by difference in health effects – compared with baseline strategy were calculated. These ICERs were calculated for each one of the different strategies evaluated.

A one-way sensitivity analysis was undertaken to evaluate the impact of the variation of different key parameters on the model output. It was performed for the following variables: TB prevalence, risk of infection sensitivity of the techniques for HIV-infected and not HIV-infected patients, and discount rate. A Monte-Carlo simulation was used for probabilistic sensitivity analysis (PSA), to evaluate the magnitude and impact of parameter uncertainty. The model was run 1,000 times for each strategy. The willingness to pay threshold (WTP) was established at one time the per capita Gross National Income (GNI) of Mozambique in 2013 (590 USD).[36] The CHEERS statement was followed for reporting.[37]

Results

Model

The compartmental TB model is presented in Figure 1. A summary of the main parameters used for smear positive (SP) TB is presented in Table 1; more details of the structure and parameters are described in Appendix 1. The code is available via e-mail to the corresponding author. A summary of costs is presented in Table 2; a more detailed description of the costs is available in Appendix 2.

Base case scenario results

Using smear microscopy as the only TB diagnostic technique the model predicted a total burden of disease of 346,232.8 DALYs, and it cost a total of 758,687.5 USD.

MODS

MODS as an add-on study produced a decrease in DALYs of 2,699.19 with an increase in the cost of 15,244,692 USD yielding an ICER of 5,647.89 USD per DALY averted. MODS as a substitute for smear microscopy produced a decrease in DALYs of 2,699.19 at an increase in the cost of 14,507,004 USD yielding an ICER of 5,374.58 USD per DALY averted.

Sensitivity analyses

In the one-way sensitivity analysis (Figure 2), MODS ICER was mainly affected by the prevalence of TB and the risk of infection, with the ICER inversely affected by the TB prevalence and risk of infection. TB diagnostic test sensitivity was not a big driver of ICER uncertainty.

The sensitivity analysis showed the same trend for both strategies, the add-on strategy, and the substitution strategy, for all the evaluations. A post-hoc sensitivity analysis was done to evaluate the effect of a possible reduction of the probability of completing the diagnostic pathway in the add-on strategy. A 10% reduction was applied, and the ICER raised to 68´644.74 USD/DALY averted.

In the probabilistic sensitivity analysis (Figure 3) MODS fell within the WTP threshold in 2% of the runs.

Xpert® MTB/RIF

Xpert® MTB/RIF as an add-on test to negative SM cases yielded an increase in DALYs averted of 3,206.23 at an increase in the cost of 1,108,441 USD, giving an ICER of 345.71 USD /DALY averted. Xpert® MTB/RIF as a substitute for SM averted 3,206.23 more DALYs than SM alone, at a total increase in the cost of 391,604.9 USD. The ICER was 122.13 USD/DALY averted.

Sensitivity analyses

Results of the one-way sensitivity analysis are shown in Figure 2. The main factors impacting the ICER were, as for MODS, the risk of infection and TB prevalence. A post-hoc sensitivity analysis was done to evaluate the effect of a possible reduction of the probability of completing the diagnostic pathway in the add-on strategy. A 10% reduction was applied, and the ICER did not rise significantly (346.08 USD/DALY averted).In the probabilistic sensitivity analysis (Figure 3), Xpert® MTB/RIF was fell within the WPT in 60.6% of the runs.

Discussion

Our results suggest that in this rural African setting substituting smear microscopy by Xpert® MTB/RIF would be the most cost-effective strategy compared to its implementation as an add-on strategy or MODS implementation. However, the degree of uncertainty is high.

The development of the Xpert® MTB/RIF assay was a landmark event. It provides fast results; it is easy to use and has a low biohazard level that facilitates its implementation in rural settings. Previous modelling studies have already considered it cost-effective in low- and middle-income settings as a replacement test of smear microscopy and clinical diagnosis, and as a screening method in HIV-infected patients initiating ART.[38,39] However, the extent of cost-effectiveness gain to TB programmes depends on current TB diagnostic practices and Xpert® MTB/RIF has been deemed to be too expensive for a point-of-care treatment setting and has been recommended to be installed only at laboratory facilities.[40] MODS was specifically developed and designed to be set up in low-income countries. Nevertheless, its feasibility in rural areas is of concern and WHO has not recommended its implementation at a district level.[41] Information to date raised the possibility of MODS being better than Xpert® MTB/RIF from a cost-effectiveness perspective as MODS is more sensitive in PLWH and its implementation could be less costly tan Xpert® MTB/RIF. However, direct cost-effectiveness comparison to date had only been short time oriented and had been performed evaluat–ing the impact on TB incidence in broad regions. Our study provides, to our best knowledge, the first cost-utility comparison of these two diagnostic techniques in a rural high HIV prevalence low-income setting.

Our results reinforce the WHO conditional recommendation of using Xpert® MTB/RIF as a first line test for every pulmonary TB suspect in rural Sub-Saharan Africa with a long-term utility-based evaluation. The ICER found in our study is within the same range of those found in other studies in other settings, namely South Africa, India and Uganda.[38,42] Whether Xpert® MTB/RIF is such a huge step forward in TB diagnostics that it should replace the 125-year-old smear microscopy as the first TB diagnostic test remains controversial.[8] It has been reported as cost-effective with a very low ICER for many countries with high TB burden and intermediate TB burden.[43–45] Recently it has even been deemed cost-effective in different evaluations undertaken in high-income low-TB burden countries, namely the United Kingdom, as an add-on to present care, and in Germany, as a replacement for sputum smear.[46,47] However, when evaluated in clinical trials, shorter time to TB treatment when using Xpert® MTB/RIF has not translated into lower TB morbidity nor mortality.[48,49] These results suggest that more than better diagnostic techniques are needed to improve outcomes in TB programmes. In our study, we found a high variability in the PSA, with negative ICER in a substantial number of runs. We believe that this is reflecting that multiple factors influence the final outcomes

and not only the sensitivity of the diagnostic techniques. Other interventions along the TB diagnostic and treatment cascade (as improving patients' linkage to care) may be key to improving TB programmes outcomes and should be further analysed. In this setting the suboptimal treatment outcomes may influence substantially and negatively the effectiveness. Also, the health care seeking rate, which was given a wide prior (?? au: please explain) in the PSA as it was considered unknown, could partially explain the high variability.

MODS implementation did not reach the WTP threshold in our analysis and was clearly dominated by Xpert® MTB/RIF. In the one-way sensitivity analysis, only in case of very high TB prevalence or risk of infection, did MODS have an ICER similar to Xpert® MTB/RIF. This finding raises the hypothesis that perhaps in a setting with very high TB prevalence MODS could have its place. Also, the possible added value of DST was not explored as we assumed that there was no MDR-TB. MDR-TB is not very frequent in Mozambique, and thus the expected impact might be small. [50] Nevertheless, treatment cost of MDR-TB is high and full DST provided by MODS could be of advantage. However, the new Xpert® MTB/RIF Ultra with the XDR cartridge might overshadow this possible added value. Further analyses are needed to evaluate this issue.

Our study has certain limitations. We found a lack of precise information about local TB epidemiology, some parameters of the diagnostic pathway and costs that could generate a high degree of uncertainty. However, we believe that we used the best available estimates, and sensitivity analyses were undertaken to minimise the impact of this uncertainty. Costing was based on a thorough budgeting exercise, but no implementation study was undertaken. Therefore, there could be unforeseen costs that have been unaccounted. However, a PSA with a wide prior distribution of costs was undertaken, not impacting the results.

Choosing the WTP at one time the per capita GNI of Mozambique is certainly standard practice, but it has recently been questioned as there is no evidential basis for it. The main issue is that this threshold is arbitrary and may not reflect societal willingness to pay. Other approaches to establish a WTP have been used as benchmark approaches and league tables but also have limitations. We are not aware of any study exploring the societal willingness to pay in Mozambique, so we chose the per capita GNI despite its limitations. However, to answer the study question, we also present a small league table ordering the ICERs of the different interventions and the results still favour the substitution of SM by Xpert® MTB/RIF.

Our results are based on the TB programme of a rural district with high HIV/TB prevalence in Northern Mozambique and are therefore of limited generalizability. Nevertheless, rural African settings, such as Ancuabe district, are very remote and inaccessible and therefore are often not evaluated. So, exploring the implementation of different TB diagnostic techniques in these remote areas is

one of the added values of our study.

In summary, replacing smear microscopy with Xpert® MTB/RIF for the evaluation of all TB suspects was most likely to be cost-effective in this rural and remote African setting. Our results reinforce the WHO recommendation of Xpert® MTB/RIF being the first diagnostic test in every pulmonary TB suspect and adds to a growing body of evidence suggesting that SM is a technique to replace when possible.

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Figure Legends

Figure 1. The structure of the compartmental Markov TB model. Dx: Diagnosis; HC: Health centre; LTFU: Lost to follow-up; SN: Smear negative; SP: Smear positive; TB: Tuberculosis.

Figure 2. Tornado plots for the one-way sensitivity analyses conducted. Bars show the range of possible ICER varying the variable from the lowest value to highest value. DALY: Disease adjusted life-year; DR: Discount rate; ICER: Incremental cost-effectiveness ratios; MODS: Microscopic observation drug susceptibility; RI: Risk of infection; SE: Sensitivity.

Figure 3. A) Cost-effectiveness plane for Microscopic-Observation Drug-Susceptibility assay (MODS) Vs Smear microscopy B) Cost-effectiveness plane for Xpert® MTB/RIF Vs Smear microscopy . Cost differential is in 2013 USD and effectiveness differential in DALYs. The grey area represents the area below the willingness to pay threshold.

Appendix 1. Model Structure description.

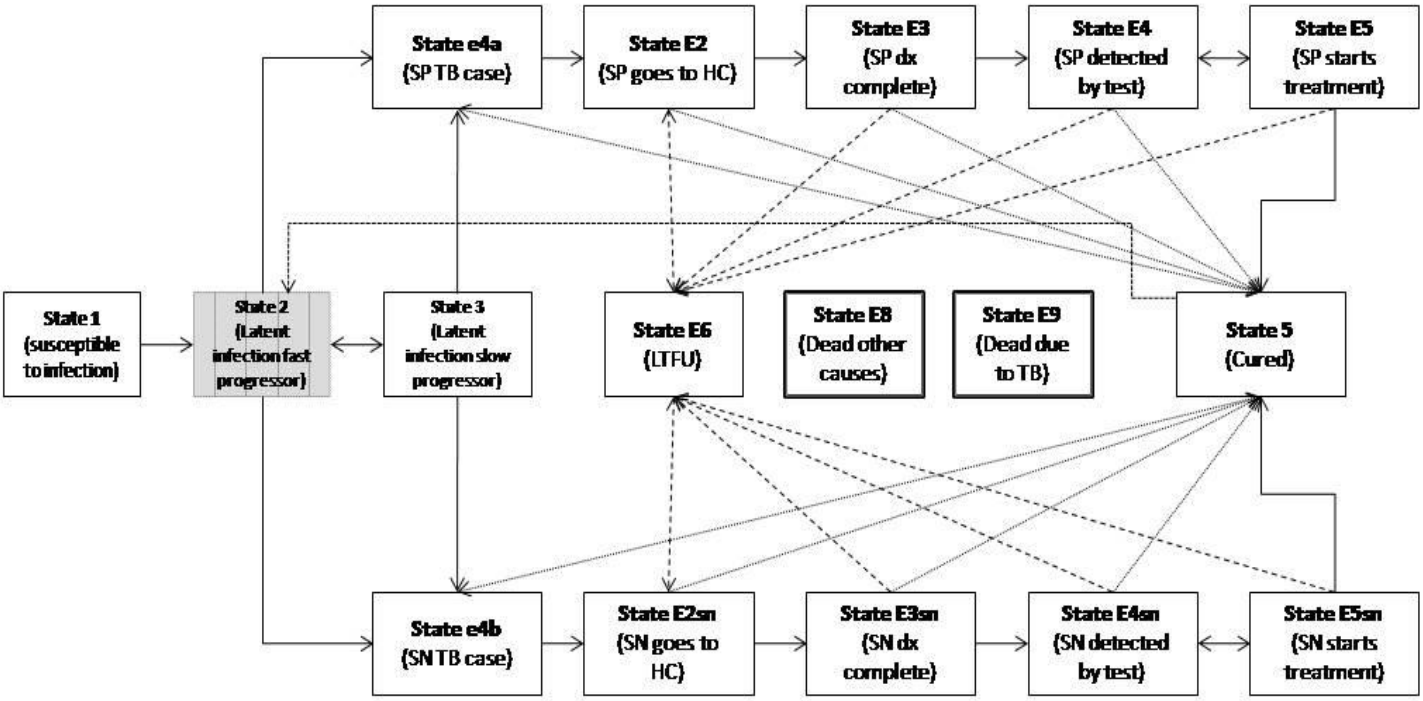

Figure 1. The structure of the compartmental Markov model. Dx: Diagnosis; HC: Health centre; LTFU: Lost to follow-up; SN: Smear negative; SP: Smear positive; TB: Tuberculosis.

State 1: People not infected with TB and thus susceptible to infection
State 2: People recently infected with TB and thus more likely to progress to active TB (fast progressors). This state has five sub-states as it takes five years to transit from being a fast progressor to a slow progressor.
State 3: People infected with TB but who are slow progressors.
State e4a: Smear positive (SP) TB case.
State e4b: Smear negative (SN) TB case.
State E2: SP cases that go to the health centre.
State E2sn: SN cases that go to the health centre.
State E3: SP cases that complete diagnostic pathway.
State E3sn: SN cases that complete diagnostic pathway.
StateE4: SP cases that are diagnosed as TB by the test.
StateE4sn: SN cases that are diagnosed as TB by the test.
StateE5: SP cases that start treatment.
State E5sn: SN cases that start treatment.
StateE6: Lost to follow-up patients.
StateE8: TB infected and not TB infected people that die due to other causes than TB.
State E9: Patients that die because of TB.
State 5: Cured patient. This patient can get re-infected and go back to state 2.

Variable	Description	Input Value	Prior Distribution	Source of data
PrevTBbaseline	Prevalence of TB at baseline	642/100000	Log-Normal	WHO report on TB 2013(1) Lin et al. 2012(2)
state1	Population susceptible to infection	(1-PrevLTBI)*population* (1- PrevHIV)		**Population:** Ancuabe district statistics(3) **Prevalence of latent TB (**PrevLTBI**):** Van Rie et al.(4) Adams et al.(5) Jensen et al.(6) Lebina et al.(7) Machingaidze et al. (8) Mahomed et al.(9) Mandalakas et al.(10) Nkurununngi et al.(11) Shakak et al.(12)
k12	Risk of TB infection	Prevalence*R_0/Population		**TB prevalence:** WHO report on TB 2013(1) **R_0:** Sanchez et al. 1997(13) Lin et al. 2012(2) **Population:** Ancuabe district statistics (3)
R_0	Basic reproductive number	Min 3.6 Max9.6 Mode 8	Triangle	Lin et al. 2012(2) Sanchez et al. 1997(13)
Relative value of R_0 for SN		0.22		Lin et al. 2012(2) Behr et al. 1999(14)
state2 (with 5 substates)	Latent infection fast progressors	PrevLTBI*Prev_LTBI_F* Population*(1-Prev_HIV)		Brooks et al.(15) **Population:** Ancuabe district statistics (3)
K222 K223 K224 K225 k23	Transition rate from fast to slow progressors. It takes five years to transit to slow progressors. Transition rates between the substates of the 5 years.	1-K24 (e2→e22) 1-k24*0.41(e22→e23) 1-k24*0.13(e23→e24) 1-k24*0.086(e24→e25) 1-K24*0.028(e25→e3)		Vynnycky et al. 1997(16) UK MRC BCG trial(17)
state3	Latent infection slow progressors	PrevLTBI* Prev_LTBI_S* Population*(1-Prev_HIV)		Vynnycky et al. 1997(16)

				Ancuabe district statistics (3)
k24	Transition from fast progressors to TB case, weighted for SP and SN cases	Pdis_prim* (1-Prev_SP_TB)	Log-Normal	Vynnycky et al. 1997(16) WHO report on TB 2013(1) Seddon et al. 2014(18)
K34	Transition from slow progressors to TB case; weighted for SP and SN cases	Pdis_End*(1-Prev_SP_TB)	Log-Normal	Vynnycky et al. 1997(16) WHO report on TB 2013(1) Seddon et al. 2014(18)
State4a	Active SP TB cases	PrevTBbaseline*Prev_SP_TB)* Population*(1-Prev_HIV)		By definition
State4b	Active SN TB cases	PrevTBbaseline*Prev_SP_TB)* Population*(1-Prev_HIV)		By definition
Pdead	Mortality of TB patients not on treatment	0.16(0.14,0.29) year $^{-1}$ 0.22(0.15,0.33) year $^{-1}$ 0.31 binomial IC95%(0.28,0.33) year $^{-1}$	Beta	Lin et al. 2012(2) Hughes et al.(19) Tiemersema et al. 2011(20) Berg et al. 1939(21)
NCR	Natural cure rate of TB HIV negative	0.23 year^{-1} (0.13-0.31) 0.2(0.13,0.31) 0.2(0.15,0.25)	Log-Normal	Tiemersema et al. 2011(20) Dye et al. 1998(22) Dye et al. 2000(23)
Bgd_Mort	Background mortality	Age-varying		WHO Global Health Observatory.(24)
Health system transition constants for SP TB				
ACC	Health care seeking rate	0.5 0.21(90/422) 0.43(22/51) 0.25(120/389)	Uniform	Lin et al. 2012(2) Esmael et al. 2013(25) Vanthoog et al. 2011(26) Abebe et al. 2010(27)
f1	Initial lost to follow-up	0.2	Beta	Keeler et al. 2006(28)
f3	Sensitivity of the technique for SP TB	1 for SP		By definition
PTreat	Probability of starting treatment	0.82	Beta	McPherson et al. 2014(29)
Pcure	Probability of finishing treatment and get cured	0.85	Dirichlet	WHO report on TB 2013(1)

	Treatment success rate			
Plost	Probability of being LTFU	0.14	Dirichlet	
Pfail	Probability of being SP at end of treatment	0.01	Dirichlet	
K6E1	Returning from default rate	0.2 $year^{-1}$	Uniform	Assumption
Health system transition constants for SN TB				
ACCsn	Health care seeking rate	0.5 0.2(11/54)	Uniform	Lin et al. 2012(2) Vanthoog et al. 2011(26)
f1sn	Initial lost to follow-up	0.2	Beta	Keeler et al. 2006(28)
f3sn	Sensitivity of the technique for SN TB	0.14	Log-Normal	Lin et al. 2012(2)
PTreatsn	Probability of starting treatment	0.82	Beta	McPherson et al. 2014(29)
Pcuresn	Probability of finishing treatment and get cured Treatment success rate	0.85	Dirichlet	WHO report on TB 2013(1)
Plostsn	Probability of being LTFU	0.14	Dirichlet	
Pfailsn	Probability of treatment fail	0.01	Dirichlet	
K6E1sn	Returning from default rate	0.2 $year^{-1}$	Uniform	Assumption
Natural History Variables for HIV/TB				
state1h	Population susceptible to infection	(1- Prev_LTBI)* Population*Prev_HIV		**Population:** Ancuabe district statistics (3) **Prevalence of latent TB (**PrevLTBI**):** Van Rie et al.(4) Adams et al.(5) Jensen et al.(6) Lebina et al.(7) Machingaidze et al. (8) Mahomed et al.(9) Mandalakas et al.(10) Nkurunungi et al.(11) Shakak et al.(12)

k12h	Risk of infection	Prevalence*R_0/Population		**Population:** Ancuabe district statistics (3) **Prevalence of latent TB (**PrevLTBI**):** Van Rie et al.(4) Adams et al.(5) Jensen et al.(6) Lebina et al.(7) Machingaidze et al. (8) Mahomed et al.(9) Mandalakas et al.(10) Nkurununngi et al.(11) Shakak et al.(12)
R_0	Basic reproductive number	Min 3.6 Max9.6 Mode 8	Triangle	Lin et al. 2012(2) Sanchez et al. 1997(13)
Relative value of R_0 for SN		0.22		Lin et al. 2012(2) Behr et al. 1999(14)
state2h(with 5 substates)	Latent infection fast progressors	PrevLTBI* Prev_LTBI_F*Population* PrevHIV		Vynnycky et al. 1997(16) Ancuabe district statistics (3)
k23h	Transition rate from fast to slow progressors. It takes five years to transit to slow progressors. Transition rates between the substates of the 5 years.	1-K24h* (e2h→e22h) 1-k24h*0.41 (e22h→e23h) 1-k24h*0.13 (e23h→e24h) 1-k24h*0.086 (e24h→e25h) 1-K2h4*0.028 (e25h→e3h)		Vynnycky et al. 1997(16) UK MRC BCG trial(17)
state3h	Latent infection slow progressors	Prev_LTBI* Prev_LTBI_S* Population* Prev_HIV		Brooks et al.(15) Ancuabe district statistics (3)
k24h	Transition from fast progressors to TB case; weighted for SP and SN cases	Pdis_prim *(1-Prev_SP_TB)		Vynnycky et al. 1997(16) WHO report on TB 2013(1)
K34h	Transition from slow progressors to TB case; weighted for SP and SN cases	Pdis_End * (1-Prev_SP_TB)		Vynnycky et al. 1997(16) WHO report on TB 2013(1)
State4ah	Active SP TB cases	PrevTBbaseline*Prev_SP_TBh*		By definition

		Population*Prev_HIV		
State4bh	Active SN TB cases	PrevTBbaseline*(1-Prev_SP_TBh)* Population*Prev_HIV		By definition
Pdeadh	Mortality of TB patients not on treatment	0.9 year $^{-1}$	Triangle	Lin et al.(2) Hughes et al.(19) WHO report on TB 2013(1)
NCRh	Natural cure rate of TB/HIV co-infected	0.1 year^{-1}(0.05-0.19)	Log-Normal	Lin et al.(2)
PrevTBbaseline h	Prevalence of TB in general	553/100.000 population		WHO report on TB 2013(1)
Bgd_Morth	Background mortality* relative risk of mortality among HIV-infected	Age-varying*5		Ancuabe district statistics (3) Lin et al. 2012(2)
Health system transition constants for SP TB/HIV				
ACCh	Health care seeking rate	0.5	Uniform	Lin et al. 2012(2)
f1h	Initial lost to follow-up	0.2	Beta	Keeler et al. 2006(28)
f3h	Sensitivity of the technique for SP TB	Sensitivity, 1 for SP by definition		By definition
PTreath	Probability of starting treatment	0.82	Beta	McPherson et al. 2014(29)
Pcureh	Probability of finishing treatment and get cured Treatment success rate	0.85	Dirichlet	WHO report on TB 2013(1)
Plosth	Probability of being LTFU	0.14	Dirichlet	
Pfailh	Probability of treatment fail	0.01	Dirichlet	
K6E1h	Returning from default rate	0.2 year^{-1}	Uniform	Assumption
Health system transition constants for SN TB/HIV				
ACCsnh	Health care seeking rate	0.5	Uniform	Lin et al. 2012(2)
f1snh	Initial lost to follow-up	0.2	Beta	Keeler et al. 2006(28)

f3snh	Sensitivity of the technique for SN TB	0.14	Log-Normal	Lin et al. 2012(2)
PTreatsnh	Probability of starting treatment	0.82	Beta	McPherson et al. 2014(29)
Pcuresnh	Probability of finishing treatment and get cured Treatment success rate	0.85	Dirichlet	WHO report on TB 2013(1)
Plostsnh	Probability of being LTFU	0.14	Dirichlet	
Pfailsnh	Probability of treatment fail	0.01	Dirichlet	
K6E1snh	Returning from default rate	0.2 $year^{-1}$	Uniform	Assumption
HIV epidemiology				
HIV incidence	Time varying	0 1.63 (1.42-1.91) 1 1.64(1.42-1.9) 2 1.59(1.38-1.85) 3 1.45(1.26-1.67) 4 1.36(1.18-1.58) 5 1.27(1.1-1.48) 6 1.15 (1.0-1.34) 7 1.05 (0.9-1.24) 8 0.98 (0.83-1.17) 9 0.93(0.77-1.11) 10 0.88 (0.72-1.07) 11 0.84 (0.69-1.03) 12 0.81 (0.66-1.00) 13 0.74 (0.59-0.93) 14		UNAIDS, Aidsinfo(30)

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Appendix 2. Cost-Analysis.

Costs were calculated by updated Pro-forma invoices, Mozambican official salary scales, and published costs. Items lifetime was estimated using WHO tables. As estimates for Mozambique did not exist those for Kenya were used. When items did not appear on the list other published estimates were used. When no source was available in the literature expert opinion was used. Resource use has been estimated by direct measurement for smear microscopy and by an interview with experts for the other two techniques. In this table, the discounting has not been applied as this was done during the model simulation. Costs are presented in 2013 USD. Values have been corrected for inflation where applicable.

Capital costs	ITEMS	Unit cost (in 2013 USD)	Useful life (in years)	Units	Total cost (in 2013 USD)
	MODS				624119.728
	Cabinet	12405.33	5	18	223295.94
	Centrifuge	10000	5	18	180000
	Microscope	1896	5	18	34128
	Incubator	2203.266	5	18	39658.788
	UPS	2500	7	12.85	32125
	Autoclave	6384	5	18	114912
	GeneXpert				626849.5
	Device+computer	21165	4	22.5	476212.5
	Air conditioning	400	10	9	3600
	UPS	2500	7	12.85	32125
	Autoclave	6384	5	18	114912
	Microscopy				20016.828
	Microscope	1112.046	5	18	20016.828
Material and Equipment					
	MODS				144000
	Lab equipment	8000	5	18	144000
	GeneXpert				9000
	Lab equipment	100	1	90	9000
	Microscopy				9000
	Lab equipment	100	1	90	9000
Laboratory rehabilitation					
	MODS	1000	20	4.5	4500
	GeneXpert	1000	20	4.5	4500

	Microscopy	1000	20	4.5	4500
Transport					
	MODS	956.25	5	18	17212.5
	GeneXpert	1730.55	4	22.5	38937.375
	Microscopy	650	5	18	11700
Training					
	MODS				175545
	Flight	1800	3	30	54000
	Fee	2551.5	3	30	76545
	Housing	500	3	30	15000
	Technicians	1000	3	30	30000
	GeneXpert				51000
	Flight	800	3	30	24000
	Fee	750	3	30	22500
	Housing	45	3	30	1350
	Technicians	105	3	30	3150
	Microscopy				0
	None				
Human Resources					
	MODS				
	Technician	29250	1	90	2632500
	GeneXpert				
	Technician	17550	1	90	1579500
	Microscopy				
	Technician	17550	1	90	1579500
Implementation					

	MODS				Ppat 6.48
	MODS Kit1000/year	5947.3	1	90	535257
	Transport	537.38	1	90	48364.2
	GeneXpert				Ppat 12.92
	Cartridges/year	12425.1	1	90	1118259
	Transport	500	1	90	45000
	Microscopy				Ppat 1.33
	Reagents	1093.89	1	90	98450.1
	Transport	238.87	1	90	21498.3
Maintenance					
	MODS				137232.9
	Hepa filters	524.81	1	90	47232.9
	Quality Control	1000	1	90	90000
	GeneXpert				40500
	Calibration	450	1	90	40500
	Microscopy				9000
	Quality Control	100	1	90	9000
Treatment costs					
	Per TB patient diagnosed				68.13 (1)

UPS: Uninterruptible power supply.

Bibliography

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Model Variables	Description	Input Value	Prior Distribution
PrevTBbaseline	Prevalence of TB at baseline	642/100000	Log-Normal
k12	Risk of TB infection	Prevalence*R_0/Population	
R_0	Basic reproductive number	Mode 8(Min 3.6, Max9.6)	Triangle
Relative value of R_0 for SN		0.22	Log-Normal
K222 **K223** **K224** **K225** **k23**	Transition rate from fast to slow progressors. Takes 5 years to transit to slow progressors. Transition rates between the substates of the 5 years.	1-K24 (e2→e22) 1-k24*0.41(e22→e23) 1-k24*0.13(e23→e24) 1-k24*0.086(e24→e25) 1-K24*0.028(e25→e3)	
k24	Transition from fast progressors to TB case, weighted for SP and SN cases	Age varying	Log-Normal
K34	Transition from slow progressors to TB case, weighted for SP and SN cases	Age varying	Log-Normal
Pdead	Mortality of TB patients not on treatment	0.31 (0.28,0.33) $year^{-1}$	Beta
NCR	Natural cure rate of TB HIV negative	0.23 $year^{-1}$ (0.13-0.31)	Log-Normal
ACC	Health care seeking rate	0.5	Uniform
f1	Initial lost to follow-up	0.2	Beta
f3	Probability of being detected by the test	Sensitivity, 1 for SP	
PTreat	Probability of starting treatment	0.82	Beta
Pcure	Probability of being cured Treatment success rate	0.85	Dirichlet
Plost	Probability of being LTFU	0.14	Dirichlet
Pfail	SP at end of treatment	0.01	Dirichlet
K6E1	Returning from default rate	0.2 $year^{-1}$	Uniform

Table 1. Model parameters for smear-positive tuberculosis (TB) cases. LTFU: Lost to follow-up; SP: Smear Positive.

Cost estimates	MODS	Xpert MTB/RIF®	Smear micros-copy
Capital costs 2013 USD , 90 years	624119.72	626849.5	20016.82
Small material and equipment 2013 USD , 90 years	144000	9000	9000
Laboratory rehabilitation 2013 USD , 90 years	4500	4500	4500
Equipment transport 2013 USD , 90 years	17212.5	38937.37	11700
Training 2013 USD , 90 years	175545	51000	0
Human resources 2013 USD , 90 years	2632500	1579500	1579500
Reagents(ppt) 2013 USD	6.48	12.92	1.33
Maintenance 2013 USD , 90 years	137232.9	40500	9000
Treatment costs (pTBct) 2013 USD	68.13	68.13	68.13

Table 2. Total cost estimates for the implementation during 90 years of the three different techniques in the Ancuabe district. Units are in 2013 USD. As the reagents consumed and the treatment costs depend on the simulation results (i.e. the number of patients tested and number of patients diagnosed during model simulation), these are presented as the individual cost per patient tested and per patient treated. MODS: Microscopic Drug Susceptibility assay; ppt: per patient tested; pTBct: per TB case treated.

Intervention	ICER USD/DALY averted	Cost(USD) per patient diagnosed	Cases detected
Xpert® MTB/RIF as a substitute for SM	122.13	1´354.89	641
Xpert® MTB/RIF as an add-on test to negative SM	345.71	1´346.98	641
MODS as a substitute for SM	5'374.58	22´767.52	658
MODS as an add-on test to negative SM	5´647.89	22´763.60	658

Table 3. League table, costs per patient diagnosed, total costs during the 90 years simulation period and case detection rates for each intervention addressed. ICER: Incremental cost-effectiveness ratio; MODS: Microscopic drug susceptibility assay; SM: Sputum smear microscopy; USD: 2013 United States Dollars.

Tuberculosis transmission model with patient and health system interaction