Cost-Effectiveness of a Medication Event Monitoring System for Tuberculosis Management in Morocco

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Abstract

Background Poor adherence to tuberculosis (TB) treatment can result in community transmission and drug resistance. Digital health technologies have been used to enhance adherence to TB medication for proper management, but the cost-effectiveness of this approach remains unclear.

Methods We used the real data from the study conducted from April 2014 to December 2020 in Morocco to enhance the adherence to drug-susceptible TB treatment using a smart pillbox with a web-based medication monitoring system, called Medication Event Monitoring Systems (MEMS). We applied a Markov model adding Multi-drug resistant (MDR) TB to evaluate the costs and cost-effectiveness of MEMS, compared to the standard of care (modified directly observed treatment and intervention) from the health perspective. The primary outcome was the incremental cost-effectiveness ratio (ICER) per disability adjusted life-year (DALY) averted. We also performed two-way sensitive analysis between treatment success rate of MEMS and standard of care.

Results The average total per-patient health system costs for treating a new TB patient under MEMS versus standard of care were $398.7 and $155.7, respectively. The MEMS strategy would reduce the number of drug-susceptible TB cases by 0.17 and MDR-TB cases by 0.01 per patient over five years. The ICER of MEMS was $434/DALY averted relative to standard of care, and was most susceptible to the TB treatment success rate of both strategies followed by the managing cost of MEMS.

Conclusion MEMS is considered cost-effective for managing infectious active TB in Morocco.

Key Points For Dicision Makers

Digital health technologies and management have been used to enhance adherence to TB medication.

As a digital health technology, Medication Event Monitoring Systems (MEMS) intervention for managing drug-susceptible TB is cost-effective compared to the standard of care in Morocco.

However, the MEMS strategy is most sensitive to the treatment success rate of TB.

1 Introduction

Tuberculosis (TB) is the leading cause of mortality among infectious diseases, accounting for 1.5 million deaths worldwide in 2018 [1]. In high TB burden countries, the successful completion of TB treatment is one of the critical TB control strategies to prevent TB transmission through the community [2]. Poor adherence to TB treatment can increase the risk of treatment failure, relapse, as well as the development of drug resistance [3]. However, adherence to TB treatment is often suboptimal despite various treatment interventions, including directly observed treatment (DOT).

Recently, digital health technologies and management have been used to enhance adherence to TB medication. Many studies have reported that digital adherence technology (DAT) substantially improved adherence [4] and led to cost savings up to 58% compared to traditional DOT [5]. In 2017, the World Health Organization (WHO) reported that DAT for TB treatment can be used as a substitute of traditional DOTS [6] and recommended its implementation as part of national tuberculosis control programs (NTP) [5]. In order to scale up DAT at a national level, it is important to understand the cost-effectiveness of DAT [7], considering TB burden and the strategic TB program in a given setting [8]. Furthermore, financial and case management strategies should be reassessed to accomplish the goals of global TB strategy [9].

In Morocco, where TB incidence in 2018 was 99/100,000 nationwide and 130/100,000 in cities like Kenitra [10], the overall treatment success rate was 84%, and the loss to follow-up (non-compliance) rate was as high as 15% [11]. We previously reported the demonstrable effectiveness of a smart pillbox (SP) with a web-based medication monitoring system, called a Medication Event Monitoring System (MEMS), as a tailored adherence-monitoring intervention to improve patients' adherence to TB treatment among active TB patients in Morocco [12]. We used the epidemiological and cost data from this study to evaluate the cost-effectiveness of MEMS to monitor TB treatment among infectious active TB patients in Morocco.

2. Methods

2.1 KOICA Project in Morocco

The study was conducted in Salé, Morocco by the Korean International Cooperation Agency (KOICA) in collaboration with Global Care International and the Ministry of Health and Welfare of Morocco from April 2014 to December 2020. Briefly, the study enrolled and provided patients a smart pillbox with a web-based medication monitoring system, called MEMS, which reminded patients to take medication at certain times [13]. The system provided regular statistical monitoring results including drug adherence status according to time, region, and patient information to health care workers. When patients failed to take their medication, health care workers made phone calls or home visits to patients.

2.2 TB guidelines in Morocco

The national TB treatment guidelines of Morocco recommend two months of rifampin, isoniazid, pyrazinamide, and Ethambutol (2RHZE) followed by four months of rifampicin and isoniazid (4RH) for new smear-positive cases [14, 15].

Direct supervision at the treatment site for two months is recommended (modified DOT) before self-administered treatment (SAT). Retreatment regimens include two months of streptomycin, rifampin, isoniazid, pyrazinamide, and Ethambutol (2SRHZE), followed by one month of RHZE and five months of RHE (1RHZE/5RHE). Multi-drug resistant (MDR) TB treatment consists of six months of intensive phase with injectable drugs in addition to levofloxacin, ethionamide, cycloserine, pyrazinamide, and ethambutol, and 18 months of continuation phase without injectable drugs before the WHO TB treatment guidelines were updated in 2018 [15].

2.3 Overview of the Markov Model

We used epidemiology and costing data from the KOICA project to perform a cost-effectiveness analysis from the health system perspective in a hypothetical cohort of infectious TB patients with acid-fast bacilli (AFB) smear-positive results in Morocco. We used a five-health state Markov model to evaluate two strategies for the first line treatment of drug-susceptible TB: 1) standard of care by modified DOT (SoC); or 2) MEMS. Based on the WHO guideline [16], we included five health states for treatment results as follows: treatment success, default (loss to follow up) or failure, death, complete healing, or recurring TB or MDR-TB (Figures 1 and 2). Based on the treatment outcomes and effectiveness of first-line treatment, patients were categorized into the completion of first-line treatment, recurring TB or MDR-TB, or mortality. Since the first two months of the intensive treatment phase is critical for sputum conversion in sputum AFB smear (+) patients, adherence to the initial two months of treatment was separately categorized for the initial health outcomes. The patients lost within the initial two months of treatment were assumed to be recruited again for drug-susceptible treatment. We assumed that drug susceptibility testing did not influence treatment because all treatment regimens were considered standardized medications. We limited our analysis to 5-year time horizons to accommodate the following lengths of treatment: six months for initial treatment regimens, eight months for retreatment regimens, and 24 months for MDR-TB treatment regimens with two cycles. All analyses were performed using TreeAge software (Williamstown, MA, USA).

2.4 Epidemiological Parameters and Cost Measurement

Epidemiological parameters were determined from literature review and real data of the KOICA project (Table 1). We conducted micro-costing for both SoC and MEMS strategies (Table 2). Costs were measured based on the types of resources. Unit cost for TB treatment per patient was calculated according to the Morocco TB guideline, which is practiced in health centers in the Salé area of the Rabat-Sale-Kenitra region in Morocco. For the MEMS strategy, we estimated the costs using both top-down and bottom-up approaches. For human resources, costs were calculated based on the approximate time engaged in the MEMS program.

Table 1
Parameter Estimates for the Cost-Effectiveness Analysis of the Medication Event Monitoring Systems for Tuberculosis

Parameters (Probability)	Base (Range)	Reference
TB treatment success rate in SoC	0.855 (0.7-0.86)	[13]
TB treatment success rate in MEMS	0.9897 (0.7-0.9948)[a]	[13, 20, 21]
Treatment failure or default rate in SoC before 2 months	0.1298 (0.0604-0.14)	Used WHO Tuberculosis data files [17] [13, 14]
Treatment failure or default rate in SoC after 2 months	0.1298 (0.0604-0.14)	Used WHO Tuberculosis data files [17] [13, 14]
Treatment failure or default rate in MEMS before 2 months	0.0052 (0.0039-0.0065)	Used WHO Tuberculosis data files[17] [13, 14]
Treatment failure or default rate in MEMS after 2 months	0.0052 (0.0039-0.0065)	Used WHO Tuberculosis data files[17] [13, 14]
Compliance rate for the initial 2 months in SoC	0.9924 (0.7443-1.0)	Used WHO Tuberculosis data files[17] [13, 14]
Compliance rate for the initial 2 months in MEMS	1 (0.75-1.00)	Used WHO Tuberculosis data files [17] [13, 14]
TB relapse after complete healing	0.054 (0.028-0.08)	[13, 22, 23]
Treatment failure or default in the first MDR year	0.405 (0.392-0.417)	[24]
Mortality in the first MDR year	0.0405 (0.0393-0.0417)	[7, 9]
Treatment failure or default in the second MDR year	0.405 (0.071-0.405)	[17, 24]
Mortality in the second MDR year	0.0405 (0.0393-0.0417)	[25, 26]
Mortality after MDR treatment success	0.001 (0.00097-0.00103)	[27]
Mortality after completely healing of MDR TB	0.001 (0.00097-0.00103)	[25–27]
Mortality after default or failure for MDR TB treatment	0.0405 (0.0393-0.0417)	[25, 27]
Relapse after MDR treatment	0.0925 (0.04-0.145)	[25–27]
TB re-treatment success rate	0.709 (0.636-0.7365)	[17, 25, 28]
TB re-treatment mortality rate	0.046 (0.0345-0.0575)	[25, 26, 28]
Completely healed after TB re-treatment	0.904 (0.838-0.904)	[17, 25, 28, 29]
Relapse rate after TB re-treatment	0.095 (0.028-0.095)	[23, 25, 28]
Mortality rate after default or failure of TB re-treatment	0.078 (0.046-0.11)	Calculated from [23] [25, 29, 30]
MDR development after treatment failure or default for retreatment	0.1685 (0.122-0.215)	[23, 25, 29, 31, 32]
Mortality and Life Expectancy		
TB or MDR TB (age-specific)	NA	WHO life table [29, 31–33]
Completely healed (age-specific)	NA	WHO life table [27] [29, 31–33]
Disutility		
TB or MDR TB	0.331	[34]

[a]Base value was re-calculated excluding the non-evaluated cases

SoC standard of care, MEMS medication event monitoring system, MDR TB multi-drug resistant tuberculosis, NA non-applicable

Table 2
Unit Costs for the Treatment of Tuberculosis per One Patient in 2018 US$

Cost components	Base (Range)	Reference
Cost for the treatment of a new TB patient (6 months) in MEMS	**398.6 (299.0-498.3)**	[13, 15]
Managing cost for the initial 2 months	**163.9**	
Managing cost for the remaining 4 months	**234.7**	
Cost for MEMS	219.4	Study
Installation and management cost for MEMS	99.8	Study
Staffing (Human Resources) for managing MEMS	77.8	Study
Overhead cost (office equipment and telephone use)	27.0	Study
Transportation	6.8	Study
Training and education, TB campaign (HCWs and patients)	7.9	Study
Diagnosis and first-line treatment	132.0	Guidelines [15]
HCWs for patient care	47.2	Guidelines [15]
Cost for the treatment of a new TB patient (6 months) in SoC	**155.6 (116.7-194.5)**	[14, 15, 35]
For the initial 2 months	**84.8**	
For the remaining 4 months	**70.7**	
Overhead cost (Office equipment and telephone use)	4.8	Guidelines
Transportation	3.4	Guidelines
Diagnosis and first-line TB treatment	132.0	Guidelines
HCWs	15.3	Guidelines
Recruiting TB patients who stopped TB treatment	5.1 (3.83-6.38)	[15]
Cost for TB retreatment (not MDR, 9 months)	**762.2 (571.6-952.8)**	[15, 32]
Diagnosis and treatment	676.5	Guidelines
HCWs	85.7	Guidelines
Cost for MDR Treatment for 24 months[a]	**4437.3 (3327.9-4159.9)**	[15, 24]
For the first year	**2841.6**	
For the second year	**1595.6**	
Diagnosis and treatment per MDR TB	4138.4	Guidelines
Health Care Workers per MDR TB	298.8	Guidelines

[a]This cost was calculated for the outpatient treatment of an MDR-TB patient

TB tuberculosis, MEMS medication event monitoring system, SoC standard of care, MDR TB multi-drug resistant tuberculosis, HCW Health Care Workers

2.5 Model Outcomes

The primary outcome of analysis was the incremental cost-effectiveness ratio (ICER), measured in units of 2018 US$ per disability adjusted life-year (DALY) averted. For DALY calculation, the life table of Morocco and the raw data of the WHO reports were adopted [17]. We also estimated the total number of treatment-related acquired MDR-TB and mortality. Future DALYs and costs were discounted at 3% per year. We performed one- and two-way deterministic sensitivity analyses for all model parameters using a range of parameter values based on the literature review and the project data when available, or ±25% of baseline values.

3. Results

3.1 Treatment-related Costs

Table 2 represents the unit costs and total costs under the MEMS and SoC. The average total per-patient health system costs for treating a new TB patient using the MEMS and SoC were $398.7 and $155.7, respectively. For a new TB patient using the MEMS, the installation and management cost of MEMS was $99.8, while the cost for human resources managing MEMS and overhead costs was $77.8 and $27.0 respectively. The cost of healthcare workers (HCWs) for patient care was $47.2. For both strategies, the cost of diagnosis and treatment was $132.1. The diagnosis and treatment costs including personal expenses for nine months of re-treatment for drug-susceptible TB and 24 months of MDR-TB treatment were $762.2 and $4,437.3, respectively.

3.2 Effectiveness and Cost-effectiveness

Under the SoC strategy, 0.48 drug-susceptible TB cases and 0.03 MDR-TB cases / per patient (first year) would occur over the 5-year time horizon (Table 3). However, under the MEMS strategy, 0.31 drug-susceptible TB and 0.02 MDR-TB cases / per patient (first year) would occur, reducing the number of drug-susceptible TB cases by 0.17 and MDR-TB cases by 0.01 per patient over 5 years. The expected total costs and DALYs per patient over 5 years under the SoC strategy were $619 and 0.52 DALYs, respectively. Under the MEMS strategy, the expected total costs and DALYs per patient over 5 years were $745 and 0.23 DALYs, respectively. The ICER was $434/DALY averted by MEMS relative to SoC.

Table 3
Expected Total Costs, DALY, and Incremental Cost-Effectiveness per Patient Over 5 Years

Strategy	Cost, US$	Number of drug-susceptible TB cases	Number of MDR-TB cases	Deaths	DALYs	Incremental cost/DALY averted US$
SoC	619	0.48	0.03	0.06	0.52	-
MEMS	745	0.31	0.02	0.04	0.23	-
Incremental	125	-0.17	-0.01	-0.02	-0.29	434

DALY disability adjusted life-year, SoC standard of care, MEMS Medication event monitoring system

3.3 Sensitivity Analyses

The ICER of TB management was most sensitive to the TB treatment success rate in MEMS and TB treatment success rate in SoC (Figure 3). At a willingness-to-pay (WTP) of $10,000/DALY averted, when we assumed a TB treatment success rate in MEMS as 70%, the estimated ICER was $26,759/DALY averted. When we assumed a TB treatment success rate in MEMS as high as 82.6%, ICER was always dominant irrespective of the TB treatment success rate in standard of care, and the ICER increased to $35,546/DALY averted at this point. In two-way sensitivity analysis (Figure 4), at a WTP threshold of $3,000/DALY (the per-capital gross national income of Morocco) and $10,000/DALY averted, 74.98% and 83.28% favored TB treatment with the MEMS, respectively.

4 Discussion

We found that MEMS intervention in Morocco would cost $434/DALY averted for managing drug-susceptible TB patients with AFB smear-positive sputum over 5 years of time horizon, compared to SoC. The MEMS strategy would reduce the number of drug-susceptible TB by 0.17 and MDR-TB by 0.01 per patient over 5 years. The result was most sensitive to the treatment success rate of drug-susceptible TB using the MEMS strategy. In light of the GDP of Morocco ($3,000), our study results support that MEMS is considered cost-effective in Morocco.

The strength of our study is that we used micro-costing and measured the detailed costs of implementing MEMS and the standard care of drug-susceptible TB and MDR-TB, including staff salaries, follow-up visits, and costs for monitoring tests and drugs. The estimated total cost of MDR treatment in our study was lower than that reported from other studies [8]. Potential reasons are that we did not include any costs related to in-patient treatment, and the costs for treatment and human resources in Morocco are relatively lower compared to other countries [8].

The key factor driving a relatively low ICER for MEMS was the higher success rate of TB treatment with MEMS. There has been limited evidence of MEMS effectiveness on percentage of cure and completion as the indicators for treatment success [18]. In a small study in South Africa, the TB cure rate using medication monitors was reported to be 75-100% [7]. In Uganda, the treatment success rate using e-compliance software and mobile phone reminders was 80.6% and 96.7%, respectively [19]. We varied the TB treatment success rate in a reasonably wide range from 0.70 to 0.99 in the sensitivity analysis and found that more than 80% favored the MEMS strategy at the threshold of $10,000/DALY averted.

In addition to the TB treatment success rate, the ICER was also sensitive to the managing costs of MEMS during continuation and intensive phases. In another study in Brazil, the unit cost of TB medication monitor was $423, which was slightly higher than the unit cost per person ($398.6) in our study [8]. More studies are needed to determine the cost-effectiveness of MEMS in settings with different TB burdens, feasibilities for digital health, and costs for TB management in order to scale up the program.

Our study has several limitations. First, MEMS only allows to monitor opening of the pillboxes electronically. Therefore, drug adherence is not guaranteed without virtual confirmation of the medication counts. Second, costs for MDR-TB were assumed based on outpatient clinics only and did not include any costs for in-patient treatment. Third, we did not include bedaquline and delamanid as MDR-TB new drugs. Lastly, actual data were used only for drug-susceptible TB, and we used the data from literature reviews to estimate the costs related to recurring TB and MDR-TB management.

5 Conclusions

Our study demonstrated the cost-effectiveness of MEMS among infectious active TB patients in Morocco. To inform scale-up of digital health intervention as part of TB control strategy, further cost-effectiveness studies are needed under different national tuberculosis programs and TB burdens.

Declarations

Ethical Approval and Consent to participate

This study was approved by the Institution Review Board (IRB) of Mohammed V University (IRB number: Dossier number 48/16)

Consent for publication

All authors consented and approved the final version of the manuscript for publication.

Availability of data and materials

All data generated or analysed during this study are included in this published article. Further specific data is available on request

Competing interests

There are none to be declared by the authors.

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Authors' contributions

J.M. Yang, S.H. Lee, N. Green, and S. Park contributed to the design and implementation of the study. J.M. Yang, H-Y Kim, and S.H. Lee contributed to the analysis and interpretation of the data. S. Park, I. Sentissi, B.K Oh, E Paek, Y.J. Park, and S.H. Lee participated in field surveys. S. Park, I. Sentissi, and B.K Oh contributed to the acquisition of data. H-Y Kim and S.H. Lee contributed to the writing of the manuscript. Y.J. Kim, K.H. Oh, and I-H Oh contributed to the critical revision of the manuscript. S.H. Lee and S. Park had full access to all the data in this study and held final responsibility for the study.

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Figures

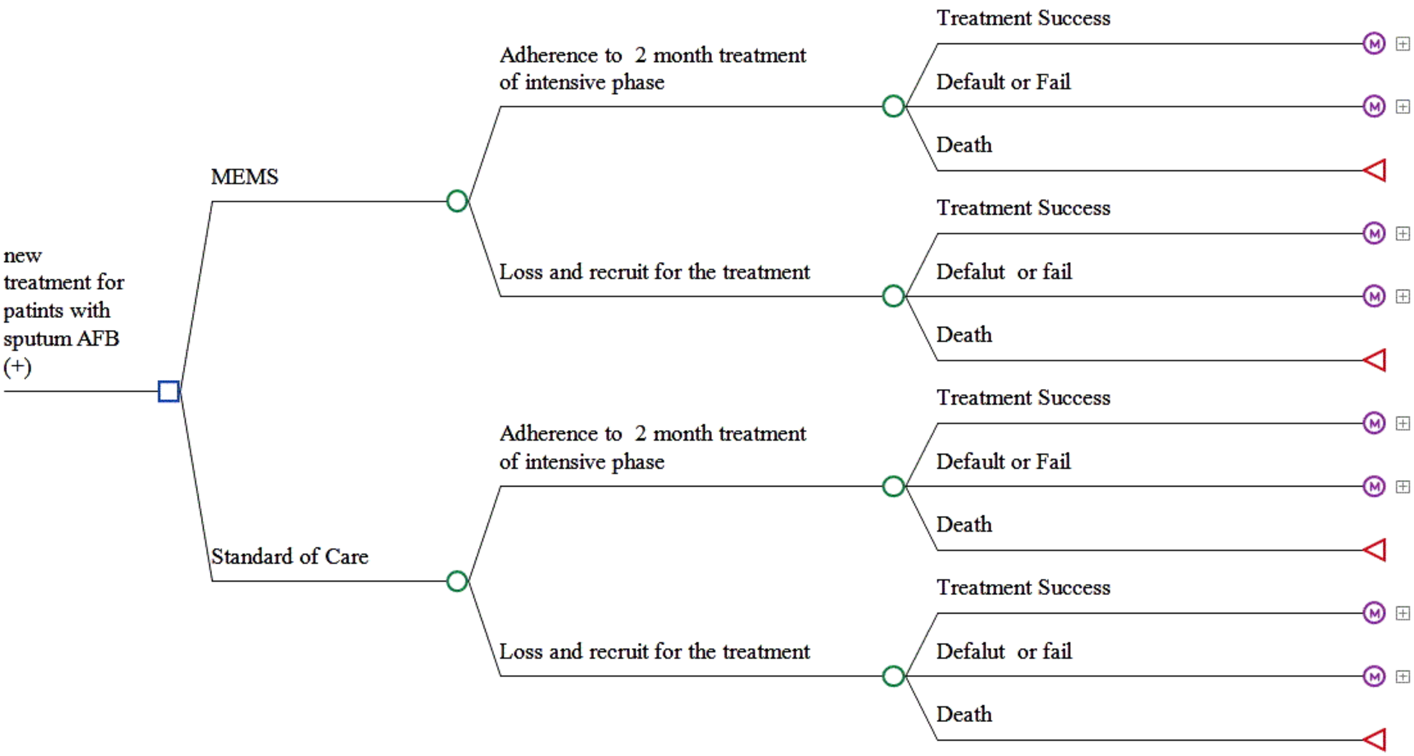

Figure 1

Decision analytic models that represent different Markov health statuses. Diagrams end in Markov nodes (circled M) and terminal nodes (triangles). Markov nodes denote additional subtrees as described in Fig. 2 AFB acid-fast bacilli, MEMS, medication event monitoring system

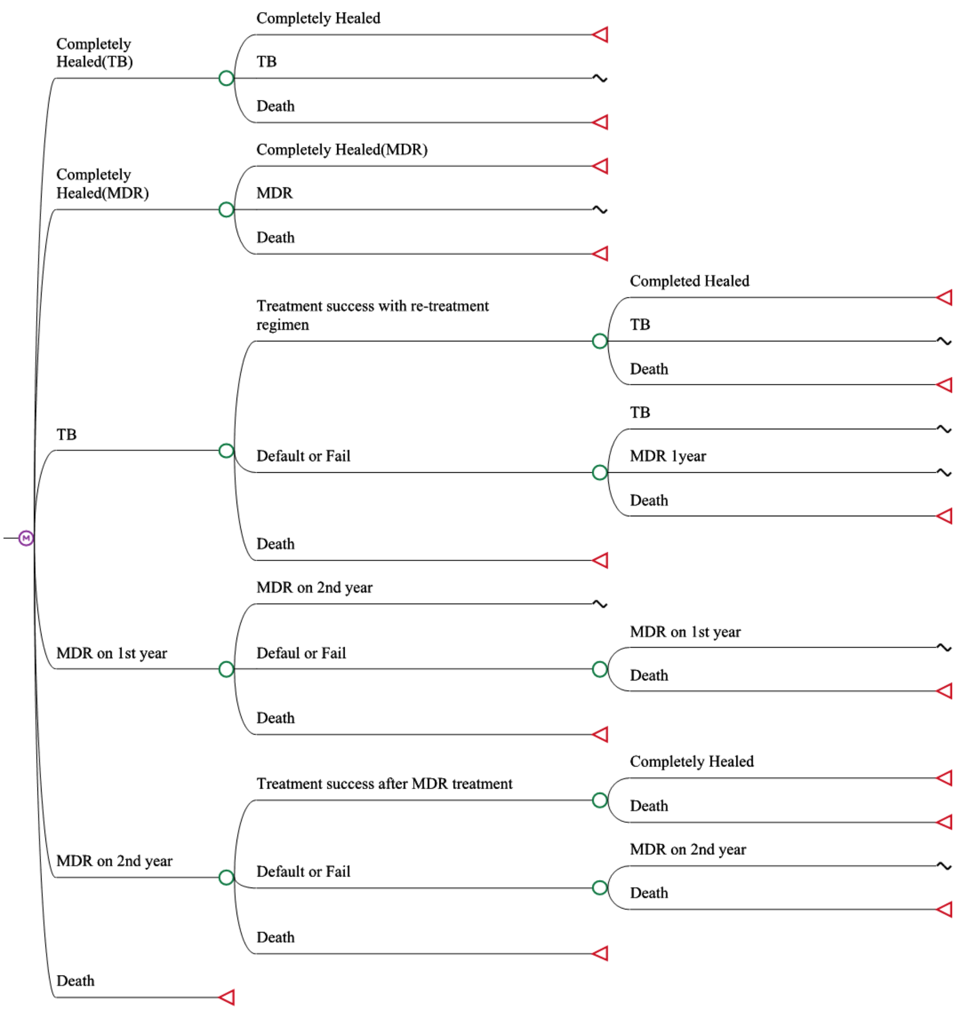

Figure 2

Markov model representing health states and possible transitions between states. Initial probabilities were varied to model the progression of each sub-group through the Markov models TB tuberculosis, MDR multi-drug resistant tuberculosis

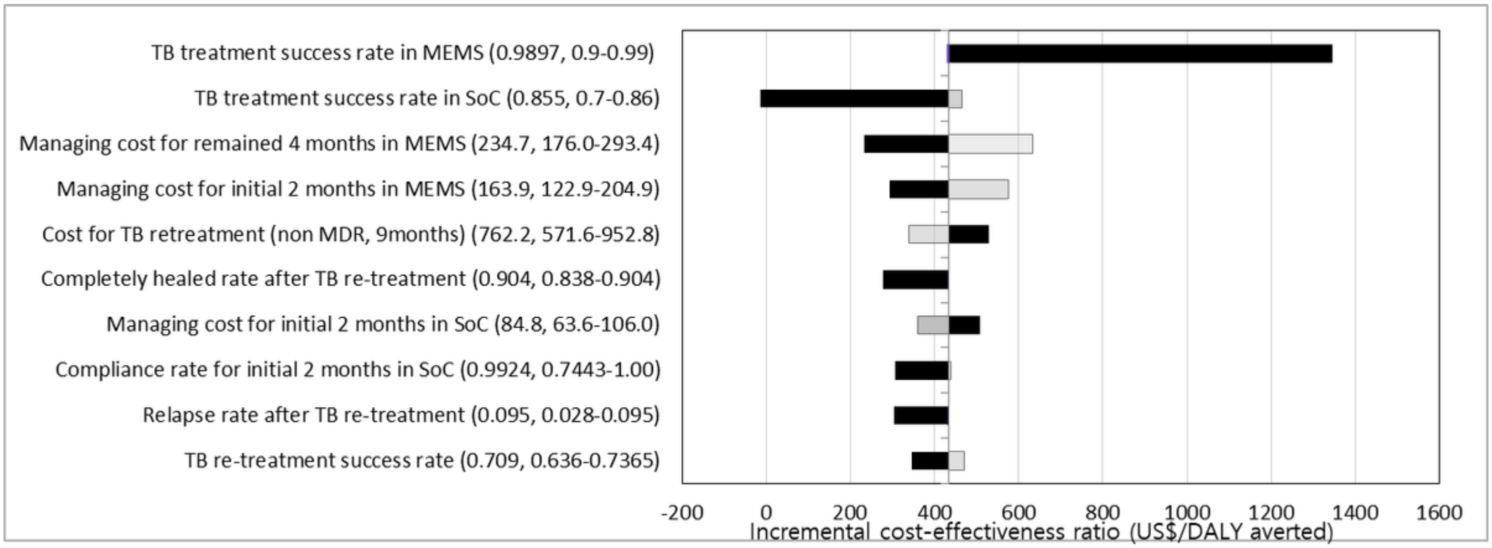

Figure 3

One-way sensitivity tornado diagram comparing routine treatment and MEMS. Bars represent the incremental cost-effectiveness ratio under the low (black) and high (light gray line) bounds associated with each parameter TB tuberculosis, MEMS medication event monitoring system, SoC standard of care, MDR multi-drug resistant tuberculosis, DALY disability adjusted life-year

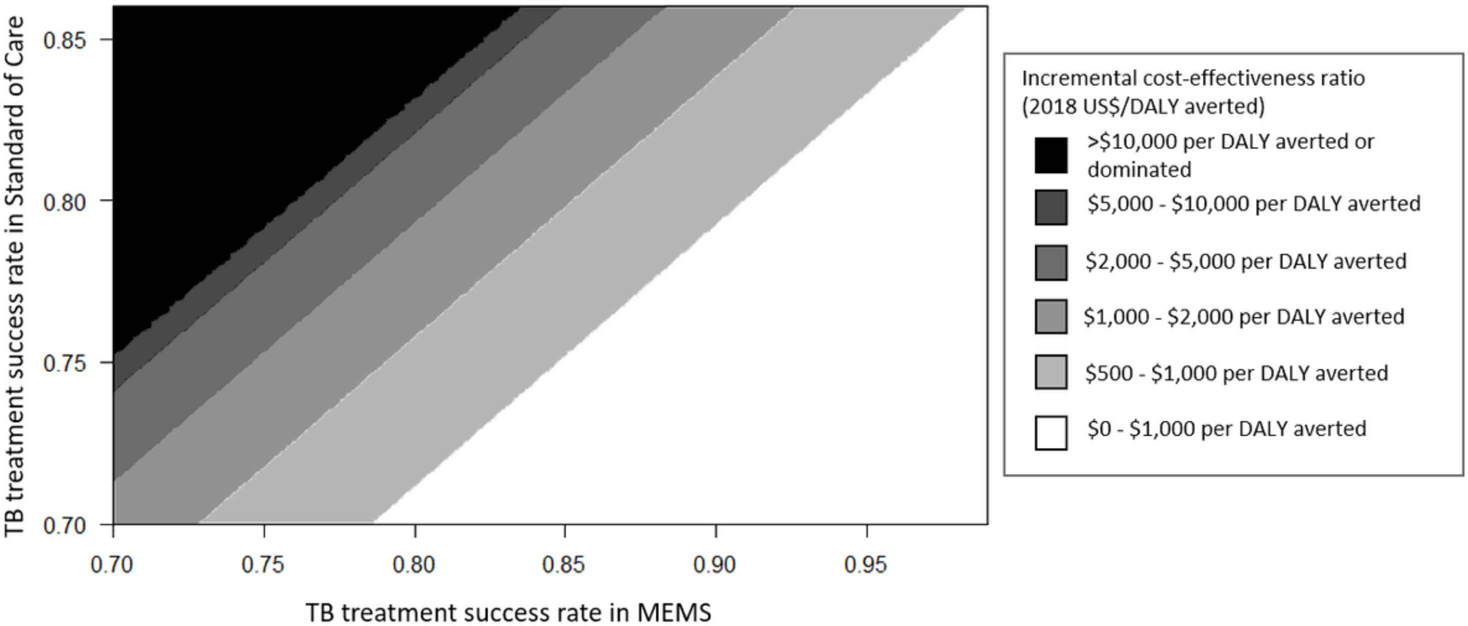

Figure 4

Incremental cost-effectiveness of TB treatment according to the treatment success rate of MEMS versus routine treatment. Each shaped region corresponds to a range of incremental cost-effectiveness ratios (in 2018 US$/DALY averted) for the TB treatment success rate in MEMS relative to that in routine treatment. The x-axis denotes the different probabilities of TB treatment success rates in MEMS, and the y-axis for routine treatment. The different line border denotes the border of willingness to pay threshold, and the lighter area favors TB treatment with MEMS at each willingness to pay threshold MEMS medication event monitoring system, DALY disability-adjusted life-year

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CHEERSchecklist.pdf