Cost effectiveness of treating multi-drug resistant tuberculosis by adding Deltyba™ to background regimens in Germany

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Summary

Objective: To assess the cost-effectiveness of adding delamanid (Deltyba™) to a background regimen (BR) for treating multidrug-resistant tuberculosis (MDR-TB) in Germany.

Methods: The incremental cost-effectiveness of treating a cohort of MDR-TB patients, 38-years old on average, with Deltyba™ plus BR versus a five drug- BR regimen alone was compared in a Markov model over a period of 10 years. Cost per quality-adjusted life year (QALY) and disability-adjusted life years (DALY) were determined from a societal perspective. Recent data from a German cost calculation on MDR-TB were applied to the 24-month outcome results of patients participating in the placebo-controlled, phase II Otsuka's Trial 204. Costs and effectiveness were discounted at a rate of 3% and subjected to deterministic as well as probabilistic sensitivity analysis in a Monte Carlo simulation.

Results: Based on the current market prices the total discounted cost per patient on BR plus Deltyba™ was €142,732 compared to €150,909 for BR alone. The total discounted QALYs per patient were 8.47 for Deltyba™ versus 6.13 for BR alone. Accordingly, the addition of Deltyba™ proved to be dominant over the BR alone-strategy by simultaneously saving €8177 and gaining 2.34 QALYs. Deltyba™ was cost saving in 73% of probabilistic sensitivity analyses compared to BR alone and 100% cost effective at a willingness-to-pay (WTP) threshold of €10,000.

Conclusions: Under conditions prevalent in Germany, Deltyba™ added to a five drug BR regimen is likely to be cost-saving compared to BR alone under a wide range of assumptions. Adding delamanid remained cost-effective when costs due to loss of productivity were excluded as the QALYs gained by lower lethality and a higher proportion of successfully treated

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Introduction

Although worldwide tuberculosis (TB) incidence rates are decreasing slightly, multidrug-resistant TB (MDR-TB), defined as simultaneous resistance to at least the most powerful anti-TB drugs, isoniazid and rifampicin, remains a major public health challenge in Europe. In 2012, 15 of the 22 countries considered "MDR-TB high burden" belong to WHO European region [1,2] in which the prevalence of MDR-TB among 90,127 new TB cases subjected to first-line testing was 15% [3]. A nearly identical proportion among the 127 MDR-TB cases tested (14.9%) for second line drugs were found to be extensively-drug-resistant (XDR-TB), defined by an additional resistance to at least one fluoroquinolone and to one or more of the injectable drugs [3]. In Germany, where the incidence of MDR-TB had remained stable at approximately 2.2% over the previous decade, an increase in the absolute cases of MDR-TB, from 65 cases in 2012 to 102 cases in 2013, was observed [4].

Compared to drug-susceptible TB, treatment of MDR-TB and XDR-TB requires significantly higher resources. This is due to its longer duration of 20 months and the use of a number of more costly and potentially toxic drugs. Globally, it is reported that only 48% of MDR-TB patients receive successful treatment whilst 28% of cases are reported to be lost to follow-up on [5]. Thus, new drugs that help to improve treatment outcomes in a higher proportion of patients with MDR-TB are urgently needed.

Following positive opinions from the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA), recommending the approval of delamanid and bedaquiline [6,7] the first novel treatment to be licensed for use in MDR-TB by the European Commission was bedaquiline (Sirturo™) in March 2014. One month later, in April 2014, marketing authorization was granted for delamanid (Deltyba™) for use as part of an appropriate combination regimen against pulmonary multidrug-resistant tuberculosis (MDR-TB) in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability. The full course of Deltyba™ is 24 weeks, preferably under directly observed conditions (DOT). To date, three consecutive trials of the drug have been completed. These are: 1) a randomized placebo-controlled trial of two months (Trial 204) of 481 patients; 2) an open-label trial with Deltyba™ lasting six months (Trial 208), performed on 213 patients who completed Trial 204; and 3) a follow-up registry trial (Trial 116) collecting treatment outcomes in 421 patients from Trial 204, 24 months post-randomization. Taken together, the results of these trials show that joint treatment of MDR-TB patients with an optimized background regimen (BR) of anti-tuberculosis drugs and Deltyba™ significantly improved the two-month sputum culture conversion (SCC) rates,

compared to a BR plus placebo. In addition, ≥6-month Deltyba™ treatment was associated with a more highly favorable long-term treatment outcome and lower mortality as compared to ≤2 month placebo or Deltyba™ [8].

Most recently, a cost analysis of the burden of MDR-/XDR-TB in Germany based on the respective strain resistance patterns reported to the National Reference Center for Mycobacteria was published [9]. There, the actual direct medical costs of suitable therapies and the indirect costs of MDR-TB were calculated. The results — shown in the following subsections "Cost of treatment" and "Cost of productivity loss" — as well as the results of Otsuka's Trial 204 provided the basis for our study to investigate the cost-effectiveness of introducing Deltyba™ in terms of quality adjusted life year (QALY) gained by comparing different willingness-to-pay (WTP) thresholds.

Methods

Model approach

We developed a dynamic, stochastic, cohort-based Markov model simulating the long-term costs and effectiveness parameters of newly diagnosed, adult German MDR-TB patients for both alternatives (BR with and without adding Deltyba™ for 6 months) over a time horizon of 10 years. Following the recommendations of the Panel of Cost-effectiveness in Health and Medicine [10] the comparative performance of the 2 different strategies was calculated by dividing the incremental costs, i.e. the difference between the sums of the costs of each treatment over the 10-year period, with the incremental effectiveness of these interventions. The primary outcome of the analysis was incremental costs per QALY gained to yield a net cost required to increase by 1 QALY compared with the next less costly intervention. Secondary outcomes included the incremental costs per disability-adjusted life years (DALYs) avoided, which is generally used by the WHO for evaluation effectiveness in developing countries. Negative numbers will identify cost savings (i.e., if an intervention costs less and is more effective than its comparator), while positive numbers indicate additional expenditure per outcome unit. That means that the higher the ratio, the less cost-effective the intervention. Each outcome was calculated based on the expected state occupancies through each cycle at the end of a given cycle of a fixed one year-period. Future costs, QALYs, and DALYs were discounted at an annual rate of 3% with varying discount rates in sensitivity analyses. As commonly used, a rough benchmark of $50,000 per QALY, i.e., currently about €37,000 per QALY, as WTP was considered to be the outer range in which an intervention is assumed to be cost-effective. The

epidemiological characteristics of the 65 MDR-TB/XDR-TB patients reported to the German Robert Koch Institute in 2012 were used for calculating the remaining life expectancy in each cycle and for creating distributions to calculate DALYs as described below.

Base case simulations were performed from the societal German perspective including both direct costs arising for the Public Health Insurances well and costs due to loss of productivity. Simulations were performed with the TreeAge Pro 2014 Healthcare Module (TreeAge Software Inc; Williamstown, MA) and version 6 of @risk (Palisade Corp; Middlesex, UK).

Model structure and clinical data

Patients with MDR-TB or XDR-TB started a planned treatment period of 24 months when participating in the randomized placebo controlled Trial 204. The model structure was determined by the core outcomes assessed in the registry Trial 116 at the end of their 24-month MDR-TB therapy.

The estimate of incremental cost-effective analysis was performed accordingly by comparing the outcomes between patients that participated in the open-label Trial 208 and received additional 6-month Deltyba™ treatment with patients not participating in Trial 208 and therefore receiving only 2 months or no Deltyba™ treatment. The raw data from the results of both regimens collected in Trial 116 were normalized in the model to a hypothetical cohort size of 1000, on average 38-year-old MDR-TB/XDR-TB patients according to the data obtained from the Robert Koch Institute (RKI) in 2012 [9]. After 2 years, patients were classified with their respective proportions into one of the following four health states as defined by the WHO (see Table 1):

- Treatment success: "Cure" (five consecutive negative cultures from samples collected at least 30 days apart in the final 12 months of treatment) or "Treatment completed" (MDR-TB patients who completed treatment according to program protocol but did not meet the definition for cure because of lack of bacteriological results)

- Treatment failure ("Failed")
- Lost to follow-up ("Default")
- Death due to TB.

In our simulation, the time horizon for evaluating associated costs and outcomes was extended for a further 8 years to fulfill a chosen total of 10 years which were divided into equal one-year increments. During the 2 years of MDR-TB treatment, all deaths are regarded as caused by TB, using the respective probabilities for mortality as a result of Trial 204 when adding or not adding Deltyba™ (tpDcm_D or tpDcm_noD, see Table 2). MDR-TB/XDR-TB patients achieving "treatment success" with or without a full course of Deltyba™ are assumed to live and die in the years following MDR-TB treatment from background mortality only according to age- and gender-dependent life expectancy as established for the general population, with a probability (tpDn) recalculated in each cycle. In order to avoid overestimation of mortality among MDR-TB patients, background mortality was assumed to be included in the TB-associated probabilities of mortality and was not presented separately.

Once patients are classified as "failed" or "defaulted", they remain in this state for the rest of those 10 years and cannot experience treatment success anymore. Patients who failed received a palliative regimen afterwards in both cohorts, as long as they survived, for the remainder of the 10 years. They were assumed to have the same probability of dying from TB in a given year as the patients who were treated during the first two years of the Trial 204. As failed MDR-TB patients were not expected to differ in the Deltyba™ ≥ 6 months or Deltyba™ ≤ 2 months group after 2 years, the probability of dying from TB under the BR-regimen (tpDcm_noD) was used for patients of both cohorts in order to prevent any bias in favor of the Deltyba™ ≥ 6 months group.

Patients who are lost to follow-up without any medication may experience a higher rate of mortality (tpDcm_default) than patients who fail to complete treatment but received palliative care. Therefore — although we used the same probability of mortality for defaulted patients as for patients with treatment failure in base case analysis (see Table 3) — we increased in our sensitivity analysis the range of their annual probabilities of dying

Table 1	Results of MDR-TB treatment in Trial 204 (Trial 116).

Treatment outcome	MITT solid total N = 421	
	BR (placebo or delamanid ≤ 2 months)	Delamanid ≥ 6 months
	Consent to trial 116 N = 229	Consent to trial 116 N = 192
Favorable treatment outcome	126 (55.0%)	143 (74.5%)
Unfavorable treatment outcome	103 (45.0%)	49 (25.5%)
Cured	111 (48.5%)	110 (57.3%)
Treatment completed	15 (6.6%)	33 (17.2%)
Failed	26 (11.4%)	32 (16.7%)
Defaulted	58 (15.3%)	15 (7.8%)
Died	19 (18.3%)	2 (1.0%)

MDR-TB = multidrug resistant tuberculosis; MITT = modified intent-to-treat.

Table 2 Input variables for cost effectiveness analysis.

Variables category	Distribution[a]	Value	Reference
Starting age of cohort (mean)	Fixed	38 yrs	[9]
Total cost of treatment (Deltyba™ plus BR)	Fixed	€77,922.61	[9]
Total cost of treatment (BR-only)	Fixed	€68,201.10	[9]
Loss of productivity (24 weeks) given treatment success	Lognormal	€17,721.60	[9]
Loss of productivity per year	Lognormal	€26,951.60	[9]
Market price for Deltyba™	Lognormal	€25,200	According to manufacturer's info
Probability of cure (Deltyba™ plus BR)	Fixed	0.573	Trial 204
Probability of cure (BR-only)	Fixed	0.4845	Trial 204
Probability of treatment completed (Deltyba™ plus BR)	Fixed	0.172	Trial 204
Probability of treatment completed (BR-only)	Fixed	0.0655	Trial 204
Probability of failure (Deltyba™ plus BR)	Fixed	0.653	Trial 204
Probability of failure (BR-only)	Fixed	0.252	Trial 204
Probability of default (Deltyba™ plus BR)	Fixed	0.306	Trial 204
Probability of default (BR-only)	Fixed	0.563	Trial 204
Probability of mortality (BR-only), tpDcm_noD	Fixed	0.1844	Trial 204
Probability of mortality (Deltyba™ plus BR), tpDcm_D	Fixed	0.0408	Trial 204
Probability of mortality after default, tpDcm_default	Fixed	0.1844	Assumption
Cost of palliative care	Lognormal	€17,113.07	Calculated
Probability of secondary cases by transmission (per year)	Beta	0.03	[9]
Utility during intensive treatment	Beta	0.58	[13]
Utility during continuous treatment	Beta	0.68	[14]
Utility following treatment failure	Beta	0.68	Assumption
Utility following default	Beta	0.58	Assumption
Utility following treatment completed or cure	Fixed	1	Assumption

[a] In probabilistic sensitivity analysis.

from MDR-TB (up to 50%). A simplified decision tree is depicted in Fig. 1.

Patients who achieve sputum culture conversion may experience a subsequent relapse defined as a switch from a negative to a positive sputum culture status over the course of a treatment program. However, no data specific for Deltyba™ were available in the Trial 204 during the 2 years of monitoring, and also no published relapse data are available for MDR-TB patients in Germany. Accordingly, relapse of TB could not be considered as a comparative outcome between the two treatment options in the model. In addition, patients who had reached the "treatment success" state were assumed to be free from exposure to the risk of relapse during the following years.

Patients who were lost to follow-up were assumed not to exhaust any further healthcare resources regarding treatment of MDR-TB/XDR-TB. As with patients who died, no additional costs were assigned to them for the remaining years in the model. Patients lost to follow-up were assumed to suffer permanently the same reduction in quality of life as patients at the start of treatment, thus the lowest utility of 0.58 per remaining life year (see below) was assigned to them.

Transmission dynamics

Most transmission of MTB infections to contact persons of an infectious TB patient is thought to occur prior to diagnosis and beginning of treatment; it will as a rule be halted by established precautionary procedures such as initial isolation in hospital and the wearing of masks. We assumed that the foregone incidence of MTB infections was the same at the onset of the treatment alternatives, and that further spread of MTB would only differ as a function of the respective proportion of defaulting patients without access to second line drugs. These remain continuously infectious. Estimating that the annual risk of progression of recently infected contact persons to active TB is at least 0.3% [11,12] and given that a typical MDR-TB patient on average transmits LTBI to 10 contacts per year of infectiveness, 0.03 new secondary cases of MDR-TB may be produced per year in treatment defaulters. We collected the resulting costs in base-case analysis. As that figure may, however, substantially differ depending on the number of the contacts and on the degree of infectiousness, it was subjected to sensitivity analysis including zero infected contacts.

Costs

Inpatient and outpatient cost, which include treatment monitoring, weighted drug costs already tested for different BR treatment options, unit cost for Deltyba™ and indirect costs were gathered. According to data received from the RKI for 2012, 57 of 65 MDR-TB patients were hospitalized (87.69%) and accrued hospital care costs for an average 89 days, after which they received ongoing secondary outpatient care until completion of the recommended 20 months' treatment [9]. All costs were estimated using figures for the year 2013, and are reported in Euro (€).

Table 3 Result of base case and univariate sensitivity analysis.

Base case analysis	Treatment	Cost per patient (€)	Effectiveness gained	Incremental cost per incremental effectiveness unit
QALY gained	Deltyba™ plus BR	142,731.96	8.47	Dominates (−€3494)
	BR-only	150,908.69	6.13	
DALY avoided	Deltyba™ plus B	142,731.96	7.26	Dominates (−€1825 per DALY avoided)
	BR-only	150,908.69	11.74	

Parameter varied	Variation	Treatment	Cost per patient (€)	QALYs gained	Incremental cost per incremental QALY
Probability of dying from MDR-TB after default	+20%	Deltyba™ plus BR	141,852.49	8.45	Dominates (−€2607)
		BR-only	148,052.01	6.07	
	+50%	Deltyba™ plus BR	140,751.37	8.43	Dominates (−€1534)
		BR-only	144,475.40	6.00	
Cost of palliative care after failure	+20%	Deltyba™ plus BR	144,979.28	8.47	Dominates (−€3803)
		BR-only	152,133.06	6.13	
	−20%	Deltyba™ plus BR	140,484.64	8.47	Dominates (−€3190)
		BR-only	149,378.22	6.13	
Secondary cases due to transmission per year	0.00	Deltyba™ plus BR	142,102.00	8.47	Dominates (−€2891)
		BR-only	148,862.48	6.13	
	0.06	Deltyba™ plus BR	143,361.92	8.47	Dominates (−€4102)
		BR-only	152,954.90	6.13	
Discount rate	0%	Deltyba™ plus BR	146,744.60	8.03	Dominates (−€7346)
		BR-only	156,070.46	6.76	
	6%	Deltyba™ plus BR	139,330.62	9.04	Dominates (−€2099)
		BR-only	146,553.27	5.61	
Market price for Deltyba™	+20%	Deltyba™ plus BR	145,430.64	8.47	Dominates (−€2343)
		BR-only	150,908.69	6,13	
	−20%	Deltyba™ plus BR	140,038.28	8.47	Dominates (−€4651]
		BR-only	150,908.68	6.13	
Disutility for living with MDR-TB	Utilities set to 1 (no disutility)	Deltyba™ plus BR	142,731.96	8.41 (LYG)	Dominates (−€3866)
		BR-only	150,908.69	6.30 (LYG)	
Time horizon	20 years	Deltyba™ plus BR	149,233.42	17.54	Dominates (−€1430)
		BR-only	159,272.05	10.52	
Probability of treatment success when adding Deltyba™	+10%	Deltyba™ plus BR	128,974.95	8.93	Dominates (−€9976)
		BR-only	156,908.69	6.13	
	−10%	Deltyba™ plus BR	156,488.97	8.01	€2974/QALY gained
		BR-only	150,908.69	6.13	
Payer perspective	No loss of productivity considered	Deltyba™ plus BR	89,789.18	8.47	€5084/QALY gained
		BR-only	77,899.66	6.13	

All costs reported in 2013 Euros.
QALYs: quality adjusted life-years; DALYs: disability adjusted life-years; LYG: life year gained; BR: background regimen; TB: tuberculosis.

Cost of treatment

As recently published [9], the total treatment costs of MDR-TB weighted according to the strain resistance patterns of MDR-TB patients in 2012, amounted to €64,429.23. The mean weighted costs for medication as BR for primary outpatients or after initial hospitalization were €51,113.23 and €38,440.00, respectively. The mean reimbursement for hospital treatment was €26,000.76, whilst the costs of diagnosing and monitoring MDR-TB cases as primary outpatients amounted to only €2192.13. Costs of monitoring MDR-TB patients following hospitalization and until end of treatment were even lower with €1550.04.

In Germany, costs of administering Deltyba™ amount to €25,200 per full course of 168 days (188 tablets á 50 mg). In cases where MDR-TB patients were treated as primary outpatients, these costs have to be added in full to the figure of €51,113.23, increasing it to €76,313.23. The costs due to administering Deltyba™ following initial hospitalization (168 days minus 89 days of hospital stay = 79 remaining days) were calculated as follows: €37.50 (price per tablets) × 4 tablets × 79 days = €11,850. This figure has to be added to the €38,440.00 as stated above, increasing it to €50,290.00.

The total costs for treating MDR with a BR plus Deltyba™ are accordingly: ([€76,313.23 + €2192.13] × 0.1231)

$+ ([\text{€}50,290.00 + \text{€}1550.04 + \text{€}26,000.76] \times 0.8769)$
$= \text{€}9664.00 + \text{€}68,258.60 = \text{€}77,922.61.$

As 156 of 229 patients in trial 116 did not receive placebo, but Deltyba™ up to 2 months at the start of the 20 month MDR-TB treatment course, treatment costs for the BR-only group have to be weighted accordingly, resulting in a figure on total costs for the BR-only group of €68,201.10.

Routine data on the frequency and severity of possible side effects of MDR-TB treatment and the resulting adjuvant medication or procedures are at this writing not available, thus the respective costs were not included in our calculations.

The most serious side effect of Deltyba™, QT prolongation, may lead to heart rhythm disorders such as ventricular tachycardia. No clinical events, however, have yet been reported as resulting from such prolongation. Studies to determine whether QT-prolongation due to moxifloxacin and clofazimine treatment in combination with Deltyba™ leads to additive effects on heart rhythm or whether the drugs can safely be used together are also inexistent. Consequently, no costs regarding side effects of Deltyba™ were considered in the cost-effectiveness analysis.

Cost of palliative care

For practical purposes, the costs of palliative care following treatment failure are the respective drug costs for the BR minus the costs of injectable group 2 drugs plus costs for outpatient care. Thus, the costs of palliative care are €51,113.23 plus €2192.13 minus the cost for the least expensive injectable drug amikacin (€16,842.24 plus €7908), amounting to a total of €28,555.12 per 20 months. Normalized to 12 months, the costs add up to €17,113.07 per year.

Cost of productivity loss (indirect cost)

In accordance with the human capital approach, the weighted productivity loss per day for TB patients was established at €73.84 [9]. That figure has to be multiplied by the estimated number of days off work. In base case we restricted the sick leave duration to the intensive phase of 240 days for those patients who achieved treatment success; in this case the indirect costs amount to: €17,721.60 (€73.84 × 240 days). In contrast, in the case of treatment failure and default and death, the whole 2 years (730 days) of observation must be taken into account (€53,903.20), and then productivity loss of each additional year (€26,951.60).

Health utilities for QALYs and disability weights

Utility weights for assessing QALYs were taken from two studies, of which only one reported EuroQol (EQ-5D) based utility weight that could be applied within the health state structure of the model:

For weighting the quality of life of MDR-TB patients in the 8 month-intensive phase of treatment, which is dominated by physical health impairment and discomfort from invasive medical investigations, the utility of 0.58 as reported in a study by Resch et al. [13] was used. The utility of 0.58 was assumed equal to that of patients lost to follow-up, under the assumption that they were left untreated again and increasingly suffered from severe TB symptoms. After finishing the intensive phase the utility for regularly treated patients was assumed to increase by 10 percentage points to 0.68, according to Guo's review [14], for the continuous phase of MDR-TB. The combined total utility for the treatment period of 24 months was weighted between the utilities for the intensive and continuous phase according to the time spent in the two phases.

The quality of life of MDR-TB patients who had passed the intensive phase but finally failed therapy and subsequently received palliative treatment was assumed equal to patients in the continuous phase with a utility of 0.68. No disutility was provided for treatment success (cure or treatment completed) after 2 years, thus a utility of 1 (100%) was linked with the life years gained of successfully treated MDR-TB patients in the following years of the time horizon. For XDR-TB utilities the same utility values identified for patients with MDR-TB were used, because XDR-therapy does not necessarily differ from MDR-TB.

DALYs are the sum of the present value of future years of lifetime lost through premature disability (YLL), and the years lost by the disease by weighting the time spent with the disease by its average severity (YLD). The disability weight for TB of 0.331, which does not differ between different states nor between TB and MDR-TB, was sourced from the latest global burden of disease study reported by Salomon et al. [15]. The disability weight changed again to zero (i.e. to non-disability) after treatment completion. In our model, the calculation of DALYs followed the approach detailed by Fox-Rushby and Hanson [16] and Diel and Lampenius [17]. Age, gender and the age of TB-related death were taken from the 65 MDR-TB patients reported to the RKI in 2012 for creating distributions around epidemiological averages coupled with a Monte Carlo simulation for 1000 MDR-TB patients to address uncertainty.

Sensitivity analysis

Deterministic sensitivity analysis was performed to prove robustness of outcomes, varying input variables along their reasonable ranges. With respect to QALYs we assessed the impact of extending the initially chosen time horizon of the mode to 20 years. We varied several cost parameters and the market price of Deltyba™ by 20%, set all disutility weights to zero, doubled the discount rate from 3% to 6% or set it to zero and also removed loss of productivity. Also, the probability of dying for untreated patients lost to follow-up was increased by 20% and 50%. As the probabilities of treatment success are important variables for determining incremental cost-effectiveness, we varied the fixed probability of treatment success when adding Deltyba™ by 10% and performed a threshold analysis for calculating the probability level below which the Deltyba™ regimen should not fall in order to dominate the BR-only-regimen. Furthermore, in order to capture the interactions between multiple inputs we provided a probabilistic sensitivity analyses (PSA) by assigning an appropriate statistical (probability) distribution for all parameters that were not fixed values. We then ran the model a large number of times in a Monte Carlo simulation. Thus an
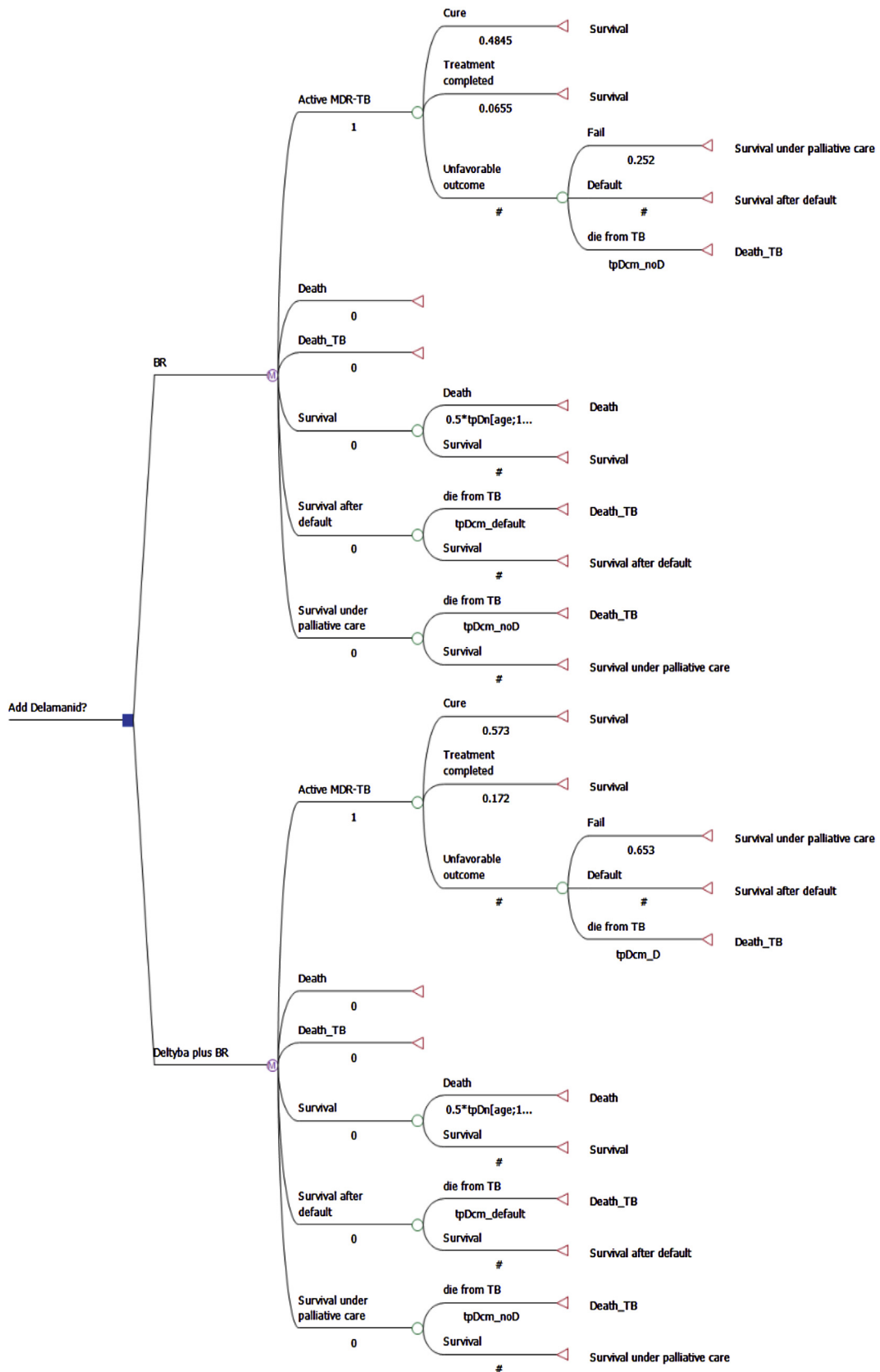
Figure 1 Markov cohort decision tree of the cost-effectiveness model. Simplified Markov model for predicting the total costs and the occurrence of deaths from MDR-TB. A decision node (□) is the decision to add or not to add Deltyba™ to a background regimen (BR) for a cohort of 38-year-old MDR-TB patients. Branches from a Markov node (M) represent the possible different health states. Branches from a change node (○) represent the possible outcomes of an event. A terminal node (◄) represents a state from which

estimate of the joint parametric uncertainty of both incremental costs and effectiveness was provided, allowing us to determine the probability of how often Deltyba™ plus BR could be considered cost-effective versus the BR alone-strategy at various WTP-thresholds. Input parameters are shown together with their probabilistic distributions in Table 2 and the univariate variations of the respective parameters in Table 3.

Results of the base case model

Following a 10-year time horizon, the total discounted costs per MDR-TB/XDR-TB-patient who had been treated with Deltyba™ for 6 months plus BR amounted to €142,732 including costs arising from productivity loss, while during the same period 8.47 QALYs were gained. In contrast, the total discounted costs and discounted QALYs for BR alone were €150,909 and 6.13 QALYs (Table 2). Accordingly, in base case analysis, the addition of Deltyba™ proved to be dominant over the BR alone-strategy by simultaneously saving €8176.73 and gaining 2.34 QALYs.

Due particularly to the lower number of years of premature life lost, treatment with Deltyba™ caused only 7.26 DALYs compared to 11.74 DALYs when using BR alone per single patient. The incremental cost per DALY avoided with Deltyba™ plus BR versus BR alone was on average −€1825. Of note, following the BR-only treatment 378 out of the cohort of per 1000 MDR-TB/XDR-TB patients had died after 10 years, whilst only 207 died following the Deltyba™-plus regime, saving a total of 155 (15.5% of the cohort) lives within the period of 10 years.

Results of sensitivity analysis

Deltyba™ was cost saving in 73% of probabilistic sensitivity analyses compared to BR alone and 100% cost effective at a willingness-to-pay (WTP) threshold of €10,000. Cost-effectiveness remained unchanged when disutilities were set to zero resulting in a cost-saving of €3866 per life year gained. Differences in incremental savings brought about by assuming no secondary MDR-TB cases following infections caused by untreated patients were negligible. In this case, outperformance of the BR-alone strategy by the Deltyba™ plus BR-strategy diminished by only about €3060 per patient over ten years in our cohort of 1000 MDR-TB/XDR-TB patients but did not significantly change the cost-effectiveness ranking.

When the probability of treatment success by adding Deltyba™ — fixed in base case analysis as a result of trial 204 — was assumed to be 10% lower, i.e. only 67.05% instead of 74.5%, the ICER was €2974 per QALY gained, but clearly remained cost-effective. Threshold analysis at a WTP of zero € showed that even when the probability of successful

treatment of Deltyba™ plus-strategy was reduced to 70.1% it was still cost saving compared to the BR-only strategy.

If the economic perspective was restricted to the public health insurance, Deltyba™ plus BR was not cost saving compared to BR alone but amounted on average to €5084 per QALY gained.

Discussion

Only very few incremental cost-effectiveness analyses on different MDR-TB treatment options have been published, and those refer to low- or middle-income countries where routine sputum culturing and drug susceptibility testing is not always available.

Resch and colleagues [13] evaluated five different treatment programs for previously treated MDR-TB patients including DOTS in Peru. There, a DOTS-plus strategy (individualized treatment with second-line drugs following drug susceptibility testing) would be most-effective by preventing 4.8 deaths per 100,000 over a horizon 30 years and producing incremental costs of $720 per QALY gained compared to DOTS-alone.

Fitzpatrick and Floyd in their review [19] compared MDR-TB interventions in Estonia, Peru, Philippines and Russia (Tomsk Oblast). While the costs of treatment per patient differed greatly between the regions, the costs per DALY averted were lowest at $163 in Peru where outpatient care using a standardized regimen without drug testing was principally employed.

On behalf of the WHO, Vassal performed a preliminary and officially unpublished WHO "exploratory" cost-effectiveness analysis on the practice of adding Sirturo™ [20] to the MDR-TB treatment regimen in six low to middle-income countries (China, Estonia, Nepal, Philippines, Peru and Russia). Although the time horizon of the study was restricted to a period of only 20 months Sirturo™ plus BR was considered to be cost-effective compared to a BR-alone strategy.

The results of our study indicate that Deltyba™ is generally cost-effective in the current German setting when compared to BR alone. From the societal perspective, Deltyba™ dominates (incurs more benefits at lower costs) the BR comparator in terms of incremental cost per QALY in 71% of all probabilistic assumptions as shown in Table 3. This result was also mirrored for the incremental cost per DALY avoided. Use of Deltyba™ leads to a higher number of patients achieving treatment success, which translates into savings on indirect costs and costs for palliative care following treatment failure. The savings gained by using Deltyba™ outweigh the increased drug acquisition costs associated with its full use of 24 weeks.

From the payer-perspective only, Deltyba™ treatment is not cost-saving using the German list price for Deltyba™ of €25,200 per course, but is still clearly cost-effective, even

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a patient will jump to the next cycle. Only the state "death" is an absorbing one from which departure is excluded. tpDn: probability of death due to causes other than MDR-TB ("background mortality"). tpDm_noD: probability of death due to MDR-TB in patients receiving no Deltyba™ (BR-only). tpDm_D: probability of death due to MDR-TB in patients receiving Deltyba™ plus BR. tpDcm_default: probability of death due to MDR-TB in patients after default. #: Complementary probability (all probabilities of chance node's branches to sum to 1.0).

if the lower threshold for cost-effectiveness of £20,000 (currently equivalent to about €25,093) as requested by NICE [18] was proposed.

As our model was only based on the patient-level data representing the outcomes of Otsuka's trial 204, it has some limitations. There were MDR-TB patients solely from outside of Germany enrolled; their treatment outcomes cannot be directly compared to those of the German MDR-TB population. For example, treatment success of MDR-TB patients under standard of care-treatment in Germany reported for 2012 [21] was higher with 63% than the 55% of patients without Deltyba™ in Trial 204, but it must be considered that in such small study populations — here $N = 65$ MDR-TB patients — minimal numerical changes may have important impact on percentages.

Secondly, we did not include the costs associated with relapse (reversion) following sputum culture conversion, a parameter that was not monitored in Trial 204. In the Sirturo™ C208 trial, however, a relapse was shown in only 4 of 66 patients in the bedaquiline arm compared to 10 patients suffering from relapse in in the equally large placebo group [22]. Assuming a similar risk reduction for Deltyba™, cost-effectiveness of adding Deltyba™ in our study may be underestimated.

A third limitation is the assumption that patients who were once lost to follow-up remained lost over the complete time horizon of the analysis and did not gain specific MDR-TB treatment at a later date. An audit of initially-lost TB patients between 2004 and 2008 in West Yorkshire in the UK reported that 16% of patients recommenced treatment within a period between 12 and 24 months after starting therapy, but this observation did not refer to MDR-TB [23]. Therefore, the proportion of MDR-patients in Germany with eventual re-treatment and the resulting outcomes must yet be evaluated from future TB surveillance data.

The model also expects, for both outcome parameters — QALYs as well as DALYs — that patients who achieved treatment success did not experience any lasting disutility (in terms of quality of life) or disability (in terms of calculation of DALYs). Although this is probably an overly optimistic assumption with respect to eventual TB sequelae [24] the impact of differences in utility weights assigned to the respective health states on outcomes in our study was limited, showing cost effectiveness of adding Deltyba™ even if quality of life was considered 100% in sensitivity analysis for all life years counted in the model over the time horizon.

In Germany, Deltyba™ plus BR can be shown to be a likely dominant strategy versus BR alone, when taking loss of productivity into consideration. Although the number of MDR-/XDR-TB patients in Germany in 2012 is relatively limited, no data were available with respect to the real time of sick leave days on an individual basis. As it can hardly be assumed that MDR-TB patient is fully capable of working for an average of 8 h a day under the difficult conditions that taking injectable drugs twice daily creates, we used the recommended period of 8 months for administering injectable drugs as the period of sick leave days. This conservative approach, however, may underestimate the true number of sick leave days. If we assume that impairment caused by the disease itself and the probable side-effects of the other drugs that have still have be taken beyond that period, productivity would continue to be drastically reduced. Of note, the CDC recently considered indirect cost for the full treatment period of at least 20 months to amount to USD 126,000 [25].

Trial 204 was not designed as a pivotal study, so the effects of adding Deltyba™ to BR are currently being investigated in greater depth, under Trial 213. There, the exact dates of default and death will be addressed as well as relapses within a period of one year after finishing the MDR-TB treatment. Of even more importance is finding an answer to the question of whether sputum smear culture conversion occurs earlier with Deltyba™ and if in thus-treated patients the total treatment duration may be shortened. The results of that trial may be considered in future model simulations.

In conclusion, the results of our analysis show that treatment with Deltyba™ for 24 weeks added on to a five-drug BR is cost-saving in 73% of all probabilistic assumptions from a societal perspective compared to BR alone, even with a 20% increase of its current market price. These results strongly support the application of Deltyba™ in treating MDR-TB patients.

Conflict of interest

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