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A Systematic Review of the Cost and Cost Effectiveness of Treatment for Multidrug-Resistant Tuberculosis

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Abstract

Background: Around 0.4 million cases of multidrug-resistant tuberculosis (MDR-TB) occur each year. Only a small fraction of these cases are treated according to international guidelines. Evidence relevant to decisions about whether to scale-up treatment for MDR-TB includes cost and cost-effectiveness data. Up to 2010, no systematic review of this evidence has been available.

Objective: Our objective was to conduct a systematic review of the cost and cost effectiveness of treatment for MDR-TB and synthesize the available data.

Methods: We searched for papers published or prepared for publication in peer-review journals and grey literature using search terms in five languages: English, French, Portuguese, Russian and Spanish. From an initial set of 420 studies, four were included, from Peru, the Philippines, Estonia and Tomsk Oblast in the Russian Federation. Results on costs, effectiveness and cost effectiveness were extracted. Assessment of the quality of each economic evaluation was guided by two existing checklists around which there is broad consensus. Costs were adjusted to a common year of value (2005) to remove distortions caused by inflation, and calculated in two common currencies: $US and international dollars (I$), to standardize for purchasing power parity.

Data from the four identified studies were then synthesized using probabilistic sensitivity analysis, to appraise the likely cost and cost effectiveness of MDR-TB treatment in other settings, relative to WHO benchmarks for assessing whether or not an intervention is cost effective. Best estimates are provided as means, with 5th and 95th percentiles of the distributions.

Results: The cost per patient for MDR-TB treatment in Estonia, Peru, the Philippines and Tomsk was $US10 880, $US2423, $US3613 and $US14 657, respectively. Best estimates of the cost per disability-adjusted life-year (DALY) averted were $US598 (I$960), $US163 (I$291), $US143 (I$255) and $US745 (I$1059), respectively. The main influences on costs were (i) the model of care chosen (the extent to which hospitalization or ambulatory care were relied upon) and (ii) the second-line drugs included in the treatment regimen. When extrapolated to other settings, the best estimate of the cost of treatment varied from $US3401 to $US195 078, depending on the region and model of care.

The cost per DALY averted was lower than GDP per capita in all 14 WHO sub-regions considered, with better cost effectiveness for outpatient versus inpatient models of care.

Conclusions: Treatment for MDR-TB can be cost effective in low- and middle-income countries. Evidence about the relative cost effectiveness of outpatient versus inpatient models of care is limited and more data are needed from Africa and Asia – especially India and China, which have the largest number of cases. Unless there is strong evidence that hospitalization is necessary to achieve high rates of adherence to treatment, patients with MDR-TB should be treated using mainly ambulatory care.

Key points for decision makers

- Treatment for multidrug-resistant tuberculosis (MDR-TB) can be cost effective in low- and middle-income countries
- Scaling up treatment for MDR-TB towards the 2015 goal of universal access to care will require additional resources for TB care and control
- Outpatient-based models of care can greatly enhance the efficiency of treatment for MDR-TB, and should be used unless there is strong evidence that hospitalization is necessary to achieve high rates of adherence to treatment

Background

Multidrug-resistant tuberculosis (MDR-TB) is defined as TB disease that is resistant to the two most effective and commonly used first-line drugs, isoniazid and rifampicin. MDR-TB is recognized as a major threat to TB control worldwide,[1] with an estimated 440 000 cases emerging each year.[2] In 2009, just under 30 000 of these cases (7% of the estimated incidence) were detected and reported to WHO. Even fewer (around 12 000) were known to be managed according to international guidelines.[3] Reasons for these low numbers include insufficient laboratory capacity to conduct tests for drug resistance, and drug regimens that are much more costly and complex than those for drug-susceptible TB. WHO guidelines[3] recommend chemotherapy for 18–24 months using combinations of first- and second-line drugs that include daily injections for the first 6–8 months; the second-line drugs that are used can result in serious side effects. In contrast, treatment for drug-susceptible TB consists of 6 months of treatment with only first-line drugs, and side effects are unusual.

Drug resistance is mostly the consequence of inappropriate or inadequate treatment. Better management of drug-susceptible cases can help to prevent the development of drug resistance during treatment (termed 'acquired drug resistance'). However, with more than 75% of estimated cases of MDR-TB occurring in people who have not been previously treated for TB, transmission of resistant strains within populations is already a major problem.[1] Control of MDR-TB requires prevention of both acquired drug resistance and transmission, as well as effective diagnosis and treatment for those cases that do occur.

Countries are demonstrating growing commitment to scaling-up the diagnosis and treatment of MDR-TB. For example, at a ministerial conference held in Beijing, China, in April 2009,[4] the 27 countries with the highest burden

of MDR-TB (the so-called 27 high MDR-TB burden countries) committed to develop plans to achieve universal access to diagnosis and treatment by 2015. In May 2009, a resolution on MDR-TB was passed at the WHO annual World Health Assembly,[5] with a similar goal.

Cost and cost-effectiveness data are part of the evidence needed to inform decisions about whether and how to scale-up MDR-TB treatment. Data on costs are important for budgeting and financing the expansion of services, and for analysis of affordability. Data on cost effectiveness are required to assess whether treatment offers good value for money in the context of many competing demands on healthcare resources and, if so, which models of care are most efficient (e.g. outpatient models of care compared with more hospital-oriented treatment).

Objectives

Our primary objective was to review and summarize the available evidence on the cost and cost effectiveness of treatment of MDR-TB. We had two secondary objectives. The first was to identify the main drivers of the cost and cost effectiveness of treatment of MDR-TB. The second was to appraise the cost and cost effectiveness of MDR-TB treatment in different regions of the world.

Methods

The methods used to achieve our objectives had three main components. The first was a systematic literature review. The second was analysis of the evidence identified in the literature review to produce standardized, comparable results for the studies that met our inclusion criteria. The third was use of these standardized results to assess the cost and cost effectiveness of treatment for MDR-TB in a wide range of settings. Full details are provided below.

Data Sources

A search strategy was developed to identify studies (or systematic reviews of studies) of the cost and cost effectiveness of treatment of MDR-TB from health and economics databases, including published and unpublished (grey) literature. Search terms in five languages (English, French, Portuguese, Russian and Spanish) were defined (search terms in Chinese and Arabic were not defined because neither author could review citations in these languages). The search was conducted over 15–16 January 2010 for four languages; the exception was Russian, for which the search was conducted on 21 January 2010. There were no restrictions on the years that were searched.

The search covered eight online databases: PubMed, EMBASE, ISI Web of Knowledge, Centre for Agricultural Bioscience International (CABI) Global Health, Health Economic Evaluations Database, Centre for Review and Dissemination (CRD)/National Health Service Economic Evaluation Database (NHSEED), the Cost-Effectiveness Analysis Registry and the European Network of Health Economic Evaluation Databases. To minimize publication bias in our sources of data, specific efforts were also made to identify grey literature from WHO regional databases and Google Scholar. Each online database required slight adaptations to the search terms; these are presented in detail in Annex 1 (available as Supplemental Digital Content [SDC], http://links.adisonline.com/PCZ/A124).

Studies in English, French, Spanish and Portuguese were assessed directly by at least one of the authors. For studies in Russian, abstracts were first translated using online translation software (Google Translate) to assess their likely relevance. If the study was relevant but not available in other languages, it was translated before being assessed in the same way as the non-Russian studies.

When searches conducted in any of the five languages returned an article in another language, the study was translated and reviewed. In practice, two such studies were reviewed: one in Turkish and the other in Macedonian.

We also checked whether articles from the ISI Web of Knowledge had been cited in more recent studies. On 1 February 2010, a search of systematic reviews of treatment outcomes for MDR-TB was undertaken. Annex 2 (see the SDC) explains the databases and search terms used. References in the two systematic reviews[6,7] identified in this way were checked for any additional studies.

Finally, one of the authors (KF) provided one unpublished manuscript and associated presentations and briefing papers that included results from two further studies.

The search strategy and preliminary list of articles were peer reviewed by a multidisciplinary expert panel (Guideline Development Group) convened by WHO for an update to the *WHO Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis*.[8] We did not receive any suggestions for additional studies that should be included.

Time constraints prevented us from hand searching and from contacting authors for papers that were not available electronically.

Citations were collected and managed electronically using EndNote Web 2.7 (online) and EndNote X (offline). A total of 502 citations were imported, among which 82 duplicates were automatically identified by EndNote. This left a total of 420 studies to be assessed for inclusion in the final list of studies.

Study Selection

Studies were screened in three stages. Figure 1 is a diagrammatic illustration including the numbers of studies included and excluded (with reasons) at each stage.

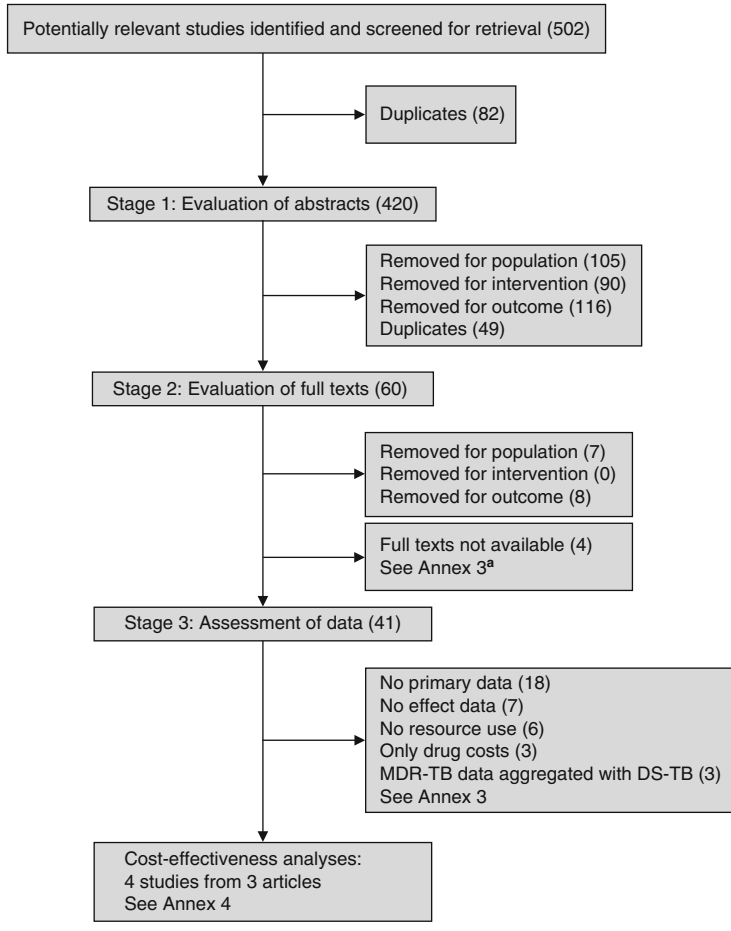

Fig. 1. Flow of included studies. **a** Annexes can be found in the Supplemental Digital Content, http://links.adisonline.com/PCZ/A124. **DS-TB** = drug susceptible tuberculosis; **MDR-TB** = multidrug-resistant tuberculosis.

In the first stage, abstracts of the 420 studies identified through the initial literature search were reviewed. Studies were retained if (i) the study population included cases that met the definition of MDR-TB (i.e. resistance to at least isoniazid and rifampicin); (ii) interventions for MDR-TB treatment were defined; and (iii) outcomes in terms of treatment effectiveness were reported. Examples of studies that were excluded at this stage included those referring to mono drug resistance or resistance of the individual to the disease; studies that considered only diagnosis, infection control, chemoprophylaxis or treatment of latent infection; and studies that referred only to 'fitness costs', to the cost of not treating MDR-TB or to costs in a general way (e.g. commenting that treatment of MDR-TB is likely to have higher costs than treating drug-susceptible TB). We did not apply any restrictions to patient characteristics (e.g. their drug-resistance profile, age, sex or HIV status). After this first screening of the abstracts, 60 studies remained.

In the second stage, full versions available for 56 of the 60 studies were reviewed and 15 were excluded on the basis of the same three above-mentioned criteria.

In the third stage, we critically reviewed each of the remaining 41 studies. To be included in the final list, studies needed to meet the definition of an economic evaluation, i.e. ''the comparative analysis of alternative courses of action in terms of both costs (resource use) and consequences (outcomes, effects).''[9,10] In the terminology of economic evaluation, such studies include cost-effectiveness analyses, cost-utility analyses and cost-benefit analyses.[10] Studies conducted from a patient, healthcare provider or societal perspective were included. We included studies that contained primary data on costs combined with effectiveness data from other studies, but excluded 18 studies that relied on secondary data to assess both costs and effects. Other exclusions at this third stage included seven studies in which no data on effects were reported; six studies in which resource use was not described, and/or costs were not reported with the necessary disaggregation or sensitivity analyses to say anything about their applicability to other settings; three studies in which only the cost of drugs was reported; and three studies in which data for MDR-TB cases were not disaggregated from those for other types of TB cases.

After this third screening, only four studies remained.[11-13] These were studies conducted in Peru, the Philippines, Estonia and the Russian Federation (Tomsk Oblast). A full list of excluded studies, together with the reason(s) for exclusion, is provided in Annex 3 of the SDC. The outcome of interest in all four included studies was the cost per disability-adjusted life-year (DALY) averted. The DALY is the standard metric used for estimation of the global burden of disease in WHO work on the cost effectiveness of healthcare interventions and in the most recent publication that assessed the cost effectiveness of healthcare interventions in low- and middle-income countries.[14-16] No studies reporting alternative measures of cost effectiveness, as sometimes seen in the literature (e.g. cost per death averted, cost per life-year gained, cost per QALY gained), met our other inclusion criteria.

Included Studies

The main characteristics of the four studies[11-13] identified in our review are summarized in table I and presented in greater detail in Annex 4 of the SDC.

In all studies, a project or programme for the treatment of MDR-TB was implemented. The design of these projects or programmes varied in terms of the drug regimen chosen and the model of care adopted (specifically, a lengthy period of hospitalization at the outset of treatment vs predominantly outpatient care). A standardized regimen was used in Peru, whereas individualized regimens (i.e. regimens determined on an individual basis according to drug susceptibility test [DST] results for first- and second-line drugs) were used in the Philippines, Tomsk and Estonia. The drug regimen used in Peru would, by today's standards, be considered substandard (in particular, kanamycin and ciprofloxacin were part of the regimen, while capreomycin and ofloxacin, respectively, would have been preferred had cost and affordability not been important considerations

Table I. Summary characteristics of included studies[11-13]

Characteristic	Estonia	Tomsk	The Philippines	Peru
Number of confirmed MDR-TB cases in intervention cohort	149	100	117	298
Time period	Aug 2001–Aug 2002	Jan 2001–Jul 2002	Apr 1999–Mar 2002	Oct 1997–Mar 1999
Type of cases	New and re-treatment	Chronic, new, re-treatment	77% chronic	All chronic
Regimen	Individualized	Individualized	Individualized	Standardized
Location for directly observed therapy	Hospital ward, health clinic	Hospital ward, health clinic	Clinic and patient's home	Clinic
Hospitalization during treatment	Yes, lengthy (average 192 days)	Yes, lengthy (average 239 days)	Limited (average 7 days)	None
Resistance pattern/risk factors	95% resistant to ≥4 drugs; alcohol abuse	69% resistant to ≥4 drugs; alcohol abuse	81% resistant to ≥4 drugs	54% resistant to ≥4 drugs
Age and sex	Mostly men, mostly aged 40–49 y	Mostly men, mostly aged 25–34 y	Mostly men, mostly aged 35–44 y	Mostly men, mostly aged 25–34 y

MDR-TB = multidrug-resistant tuberculosis.

at the time the regimen was defined). In Peru and the Philippines, treatment was delivered using a clinic-based, outpatient-oriented model of care. In Tomsk and Estonia, treatment was delivered using a hospital-based, inpatient-oriented model of care, with an average length of stay of 239 and 192 days, respectively.

There was comparatively little difference among study settings in the methods used for diagnosis (including DST), the number of months of treatment after which a patient had converted to culture-negative status and directly observed therapy (DOT). There was some variation in terms of adjunct therapies, patient education, socioeconomic support, psychosocial and emotional support, management of side effects and monitoring systems. For example, food packages were provided in Estonia and Peru but not in the Philippines, while transport vouchers were used to facilitate access to treatment in Estonia but not in Peru and the Philippines. In all four settings, most patients were men and most were aged between 25 and 50 years.

Data Extraction

Data were extracted using methods consistent with those outlined in the *Cochrane Handbook*,[9] notably chapter 15, which discusses the integration of critical reviews of health economic studies into systematic reviews. Assessment of the quality of each economic evaluation was guided by checklists developed by Drummond et al.[10] and the Consensus Health Economic Criteria (CHEC) list.[17] Unfortunately, no CRD/NHSEED structured abstracts were available for comparison.[18] Data were entered into Microsoft® Excel for multivariate uncertainty analysis using the @Risk 5.5 add-in.[19] Further details are provided in the Data Synthesis section.

The major variables for which data were extracted are listed in column 1 of table II. These data were necessary to standardize the cost results from each of the four studies to a common base year of prices, and then to construct a model that would allow the cost per DALY averted results to be generalized beyond Estonia, Peru, the Philippines and Tomsk.

Wherever feasible, we also documented two additional outcomes: the cost per patient compliant with treatment and the cost per death averted (including secondary, default and relapse cases). These intermediate outcomes are reported only in Annex 5 of the SDC because they are implicitly reflected in the cost per DALY averted results.

The quality of the overall evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach and associated GRADE profiler

(GRADEpro) software v.3.2.2.[24] A GRADE profile and summary of findings (SoF) table was produced and is available in Annex 5 of the SDC. We also assessed this paper using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and MOOSE (Meta-analysis Of Observational Studies in Epidemiology) checklists for systematic reviews and meta-analyses of observational studies.[25,26]

Data Synthesis

Cost

Cost data from the four studies were adjusted to remove or mitigate the distortionary effect of inflation and purchasing power on the comparability of results.[10] Costs per patient were standardized to year 2005 values because this is the base year used in WHO estimates of the unit costs of hospital stays and clinic visits, which were used to generalize results from the four studies to 14 sub-regions (see 'Extrapolating Cost Effectiveness to Other Settings' section). For most resources, costs in the original studies were adjusted to year 2005 values using GDP-implicit price deflators combined with nominal or purchasing power parity (PPP) exchange rates (for $US and international dollars [I$], respectively), available from UNData.[20] [1] For the cost of first- and second-line drugs, standardization was carried out using a Uniform distribution of discount rates, between 0% and 6% per annum (table II).

The various components of each of the MDR-TB treatment programmes were summarized and grouped according to a common set of six cost categories, defined as follows: drugs; hospital stay (number of bed-days and day-stays); outpatient clinic visits; laboratory and other diagnostic or monitoring tests (including smears, cultures and DST, x-rays and CT scans); programme management and supervision; and miscellaneous (including treatment for adverse events, advocacy, contact tracing, laboratory support, nutritional support, technical assistance and training).

Effectiveness

All studies compared the MDR-TB treatment intervention with the situation that applied before the project or programme was introduced. In Peru and the Philippines, this was essentially equivalent to a 'do nothing' alternative in which treatment with second-line drugs was not available. However, in Estonia and Tomsk, the comparison was with treatment provided before the new programme was introduced. We standardized results by comparing each intervention with a common null of no intervention at all. This null is modelled on the basis of the epidemiological assumptions and parameters used in the Peru study, as outlined in table II and described in greater detail in the original study.[11] We used the reported mean, 5th and 95th percentile values for the number of deaths under the intervention and assumed a Trigen distribution, to derive a distribution of plausible values for the number of deaths averted. The discount rate used for the number of deaths averted in the four studies was standard, at 3% per annum. To remove differences between the studies in the average age of patients and life expectancy of the general population, a standard Normal distribution of the number of DALYs averted per death averted was then used to derive mean, 5th and 95th percentile values of the total number of DALYs averted in each of the four studies.

Cost Effectiveness

The distribution of standardized cost per patient treated was multiplied by the total number of patients considered (all index cases in the patient cohort, plus all secondary cases resulting from transmission) to obtain the total intervention cost in each of the studies. The cost of the 'do nothing' alternatives was taken to be nil in each of the studies. The distribution of incremental cost was divided by the distribution of the number of DALYs averted in probabilistic uncertainty analysis using a Monte Carlo simulation with 10 000 iterations.

1 In any given country, I$1 is worth what $US1 could have bought in the US in 2005; in other words, costs in I$ allow for the fact that the real value of $US1 (i.e. what $US1 can buy in terms of goods and services when converted at official exchange rates) varies among countries.

Table II. Variables used in probabilistic uncertainty analysis of generalized results[a] [I$, year 2005 values]

Variable [distribution: parameters]	Model of treatment and care				Source/reference
	Estonia	Tomsk	Peru	Philippines	
Cost[b]					
General					
year of valuation of costs in study	2003	2003	2000	2002	KF,[c][11,12]
viewpoint	Health system	Health system	Health system	Health system and societal[d]	KF,[11,12]
time horizon (y)	Indefinite	Indefinite	Indefinite	Indefinite	KF,[11,12]
exchange rate, period average (local/$US)	13.85	29.45	3.5	50.9	[11,12,20]
GDP-implicit price deflator for non-traded resources, 2005 (base year = year of valuation in study)	8%	37%	15%	15%	[20]
inflation rate for traded resources (i.e. drugs) [Uniform: min–max]	0–6% p.a.	0–6% p.a.	0–6% p.a.	0–6% p.a.	Arbitrary; reflects uncertainty about changes in drug prices over time
PPP exchange rate (local/I$), 2005	8.79	13.39	1.65	24.18	[20]
GDP per capita	15 730	11 570	5920	3170	[20]
Per patient costs, drugs [PERT: most likely (min–max)]	3008 (2463–4552)	7210 (6391–8669)	514 (414–2130)	4695 (4041–6205)	KF,[11,12,21][e]
Resource use (quantity of units per patient), GHS and diagnostics					
hospital bed days	192	321	0	7	KF,[11,12]
hospital day stays	0	250	18	0	
clinic visits	171	85	450	253	
smear tests	14.5	48	14	37	
culture tests	21.4	46.5	9.2	27	
drug susceptibility testing	2.6	3.9	1	2	
Unit cost, GHS [Log-Normal: mean (SD); correlations (x) & (y)]					
(a) hospital bed day	91.60 (134.11); (a) & (b) = 1.00, (a) & (c) = 0.73				[22]; distribution of unit costs for 193 WHO Member States
(b) hospital day stay	37.76 (64.60); (b) & (c) = 0.73				
(c) clinic visit (50–95% coverage)	6.93 (5.41); (c) & GDP per capita = 0.95				
Unit cost, diagnostics [Log-Normal: mean (SD); correlations]					
(d) smear test	2.45 (1.27); (d) & (e) = 1.00, (d) & (f) = 1.00				Average of KF,[11,12]; adjusted for inflation (GDP price deflator) and PPP exchange rate
(e) culture test	10.38 (5.25); (e) & (f) = 1.00				
(f) drug susceptibility testing	17.17 (10.99)				

Continued next page

Table II. Contd

Variable [distribution: parameters]	Model of treatment and care				Source/reference
	Estonia	Tomsk	Peru	Philippines	
Per-patient costs, other non-drug resources					
adverse events	Yes	Yes	Yes	No	KF,[11,12]; total costs were adjusted for inflation (GDP price deflator), purchasing power (PPP exchange rate); also adjusted for GDP per capita (I$, 2005), as a proxy for the quantity and complexity of inputs required; the distribution is given by estimated costs in the 171 countries for which GDP per capita data were available
advocacy	No	Yes	No	No	
contact tracing	No	No	No	Yes	
laboratory support	No	Yes	No	No	
nutritional support	Yes	Yes	Yes	No	
programme management and supervision	Yes	Yes	Yes	Yes	
technical assistance	No	Yes	No	No	
training	Yes	Yes	Yes	Yes	
x-rays and CT scans	Yes	Yes	Yes	Yes	
total [Log-Normal: mean (SD)]	1346 (1541)	6261 (7167)	3248 (3717)	11 898 (13 620)	
Effect					
Both intervention and no intervention					
time horizon (y)	Indefinite	Indefinite	Indefinite	Indefinite	KF,[11,12]
DALYs averted per death averted [Normal: mean (SD)]	26.5, 3.3	26.5, 3.3	26.5, 3.3	26.5, 3.3	[23]
discount rate for deaths averted in the future	3% p.a.	3% p.a.	3% p.a.	3% p.a.	[11,15]
Intervention					
long-term[f] deaths per index case [Trigen: most likely (5%, 95%)]	0.49 (0.42, 0.58)	0.35 (0.26, 0.44)	NR	0.55 (0.40, 0.74)	KF,[12]
No intervention					
number of secondary cases produced in next generation [Uniform: min–max]	0.5–1.0 per index case	0.5–1.0 per index case	0.5–1.0 per index case	0.5–1.0 per index case	[11]
generation time (y) [Uniform: min–max]	2–4	2–4	2–4	2–4	[11]
long-term death rate [Uniform: min–max]	0.60–0.99	0.60–0.99	0.60–0.99	0.60–0.99	[11]

a These are the assumptions used to obtain the results displayed in figures 2, 3 and 4 and the (global) generalized results presented in Annex 5 in the Supplemental Digital Content [SDC], http://links.adisonline.com/PCZ/A124. For the (subregional) generalized results of table IV (and Annex 6), sub-region-specific means and standard deviations were used for the distribution of unit costs for GHS; these can be obtained from Annex 7 in the SDC.

b Only costs related to the intervention are presented; the cost of the hypothetical null set (no intervention) was assumed to be nil.

c Data on file for studies conducted by one of the authors in Estonia and Tomsk.[13]

d For the comparability of results across studies, only results expressed from the health system perspective were used in the data synthesis.

e Drug quantities were multiplied by high, low and median buyer prices for 2009 and converted to year 2005 values at 3% per annum; for the Philippines, for which drug quantities were NR, drug cost was replaced by the weighted average of the individualized regimens used in Estonia and Tomsk.

f Long-term death rate includes deaths among defaulting patients, patients for whom treatment fails, patients who are cured but later relapse, as well as secondary cases that are infected by the index cases.

DALY = disability-adjusted life-years; **GHS** = general healthcare services; **I$** = international dollars; **KF** = Katherine Floyd; **NR** = not reported; **p.a.** = per annum; **PERT** = Program Evaluation and Review Technique; **PPP** = purchasing power parity.

Extrapolating Cost Effectiveness to Other Settings

Going beyond the four original studies, we used the results from Peru, the Philippines, Estonia and Tomsk to assess the likely cost and cost effectiveness of MDR-TB treatment in a wide variety of settings. We conducted probabilistic uncertainty analysis using a Monte Carlo simulation with 10 000 iterations, in which the unit costs from the four studies were substituted with a distribution of unit costs estimated for 14 sub-regions (covering 193 countries) defined by WHO (the list of countries included in each sub-region is provided in table III). While the results of such analyses are not good substitutes for rigorous economic evaluations of similar models of care in other settings, they do serve two important purposes. First, they illustrate the extent to which variation in the cost of resource use affects the conclusions that can be drawn from the studies in Peru, the Philippines, Estonia and Tomsk. Second, in the absence of rigorous economic evaluations, the modelled results provide ranges of plausible costs that countries can use as they plan and budget for MDR-TB scale-up, whatever their chosen model of care.

Various sources of data and assumptions were used to identify distributions of unit costs in the 14 sub-regions. Drug costs were based on the mid-, high- and low-range buyer prices for 2009, as cited in the International Drug Price Indicator Guide database,[21] multiplied by the quantities of used resources reported in the four studies, and then deflated to year 2005 values at a rate of 3% per annum. The unit costs of hospital bed days, hospital day stays and 10-minute clinic visits were estimated using sub-regional distributions of unit costs available in the WHO-CHOICE (CHOosing Interventions that are Cost Effective) database.[22] In WHO-CHOICE, a standard utilization rate of 80% is implicitly assumed in the unit cost for hospital bed days, and unit costs are estimated for primary-, secondary- and tertiary-level hospitals. We allowed for hospitalization (inpatient or day stays) to take place at any of these three levels. Estimates of the unit costs of clinic visits are available for population coverage levels of

Table III. List of countries by WHO sub-region[a]

AFR D	Algeria, Angola, Benin, Burkina Faso, Cameroon, Cape Verde, Chad, Comoros, Equatorial Guinea, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Madagascar, Mali, Mauritania, Mauritius, Niger, Nigeria, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, Togo
AFR E	Botswana, Burundi, Central African Republic, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Eritrea, Ethiopia, Kenya, Lesotho, Malawi, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Uganda, United Republic of Tanzania, Zambia, Zimbabwe
AMR A	Canada, Cuba, USA
AMR B	Antigua and Barbuda, Argentina, Bahamas, Barbados, Belize, Brazil, Chile, Colombia, Costa Rica, Dominica, Dominican Republic, El Salvador, Grenada, Guyana, Honduras, Jamaica, Mexico, Panama, Paraguay, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Suriname, Trinidad and Tobago, Uruguay, Venezuela
AMR D	Bolivia, Ecuador, Guatemala, Haiti, Nicaragua, Peru
EMR B	Bahrain, Cyprus, Iran (Islamic Republic of), Jordan, Kuwait, Lebanon, Libyan Arab Jamahiriya, Oman, Qatar, Saudi Arabia, Syrian Arab Republic, Tunisia, United Arab Emirates
EMR D	Afghanistan, Djibouti, Egypt, Iraq, Morocco, Pakistan, Somalia, Sudan, Yemen
EUR A	Andorra, Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland, UK
EUR B	Albania, Armenia, Azerbaijan, Bosnia and Herzegovina, Bulgaria, Georgia, Kyrgyzstan, Poland, Romania, Slovakia, Tajikistan, the Former Yugoslav Republic of Macedonia, Turkey, Turkmenistan, Uzbekistan, Yugoslavia
EUR C	Belarus, Estonia, Hungary, Kazakhstan, Latvia, Lithuania, Republic of Moldova, Russian Federation, Ukraine
SEAR B	Indonesia, Sri Lanka, Thailand, Timor-Leste
SEAR D	Bangladesh, Bhutan, Democratic Peoples Republic of Korea, India, Maldives, Myanmar, Nepal
WPR A	Australia, Brunei Darussalam, Japan, New Zealand, Singapore
WPR B	Cambodia, China, Cook Islands, Fiji, Kiribati, Lao People's Democratic Republic, Malaysia, Marshall Islands, Micronesia (Federated States of), Mongolia, Nauru, Niue, Palau, Papua New Guinea, Philippines, Republic of Korea, Samoa, Solomon Islands, Tonga, Tuvalu, Vanuatu, Viet Nam

a The WHO regions are as follows: **AFR** = Africa; **AMR** = the Americas; **EMR** = the Eastern Mediterranean; **EUR** = Europe; **SEAR** = South-East Asia; **WPR** = Western Pacific. WHO sub-regions are classified according to mortality strata: **A** = very low child, very low adult; **B** = low child, low adult; **C** = low child, high adult; **D** = high child, high adult; **E** = high child, very high adult. Note that no region has every possible mortality stratum.

50–95%. Correlations between these unit costs and GDP per capita were also derived from WHO-CHOICE data.

The unit costs of laboratory tests (smears, cultures and DST) were generalized using the distribution of plausible values reported in the four studies, adjusted to a common year of values using GDP-implicit price deflators. Conversions to I$ were conducted using PPP exchange rates. The unit costs of these different laboratory tests were assumed to be highly correlated among themselves (with a correlation coefficient of 0.75). All other non-drug cost categories (i.e. those categories for which quantities had not been reported in the studies) were assumed to be driven by the cost of non-traded commodities, with costs from the four studies extrapolated to other countries using GDP per capita as a proxy for the complexity and quantity of inputs required. These remaining non-drug costs were adjusted to a common year of values using GDP-implicit price deflators and converted to I$ using PPP exchange rates.

In the absence of information to the contrary, we assumed that there was no correlation between unit costs and effect sizes. For equity reasons, we also assumed the same distribution of DALYs averted per death averted for each of the 14 sub-regions, regardless of differences in life expectancy among regions. Detailed assumptions (including distribution parameters) for all variables used in the probabilistic uncertainty analysis are given in table II. Best estimates are provided as means, with 5th and 95th percentiles of the distributions.

Results

Estonia, Peru, the Philippines and Tomsk

The main results from the four studies in Estonia, Peru, the Philippines and Tomsk are summarized in figures 2–4.

The MDR-TB treatment interventions evaluated in the four studies reduced the number of deaths (including deaths averted by prevented transmission) from MDR-TB in all sites, especially Tomsk (figure 2). The number of deaths averted was smallest in Estonia, where the pre-intervention standard of care achieved higher cure rates than that in Tomsk and the self-cure rates assumed in the absence of treatment in Peru and the Philippines. When all four interventions were compared with a counterfactual scenario of no treatment, the result for Estonia was closer to that of Tomsk. With the exception of Peru (where a suboptimal regimen was in use), differences in the mean treatment outcomes were statistically insignificant at the 95% confidence level.

The cost per patient for MDR-TB treatment varied substantially (from $US2423 in Peru to $US14 657 in Tomsk; figure 3). If the suboptimal regimen in Peru were replaced with that used in the Philippines, the cost per patient treated in Peru would increase to $US3611, approximately equal to that in the Philippines. The items that accounted for most of the total cost were hospi-

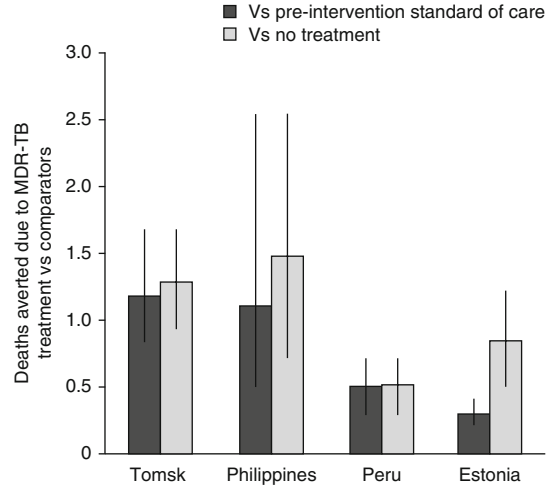

Fig. 2. Deaths averted per index cases, multidrug-resistant tuberculosis (MDR-TB) treatment in study cohorts vs pre-intervention standard of care and vs no treatment. Vertical lines represent the 95% CI of the estimate. The comparison with no treatment is modelled from data used in the Peru study;[11] deaths averted are estimated as the difference between the deaths that occurred in the post-intervention cohort and those that would have occurred in a similarly sized cohort that received no treatment. While the 'pre-intervention' standard of care in Peru and the Philippines is, to all intents and purposes, equivalent to 'no treatment', we nonetheless have small differences in the results for the two comparisons. For all studies, differences between the 'pre-intervention' and 'no treatment' comparisons are due to (i) the modelling of health outcomes under no treatment, based on results from Peru; and (ii) standardization using a common number of disability-adjusted life-years averted per death averted.

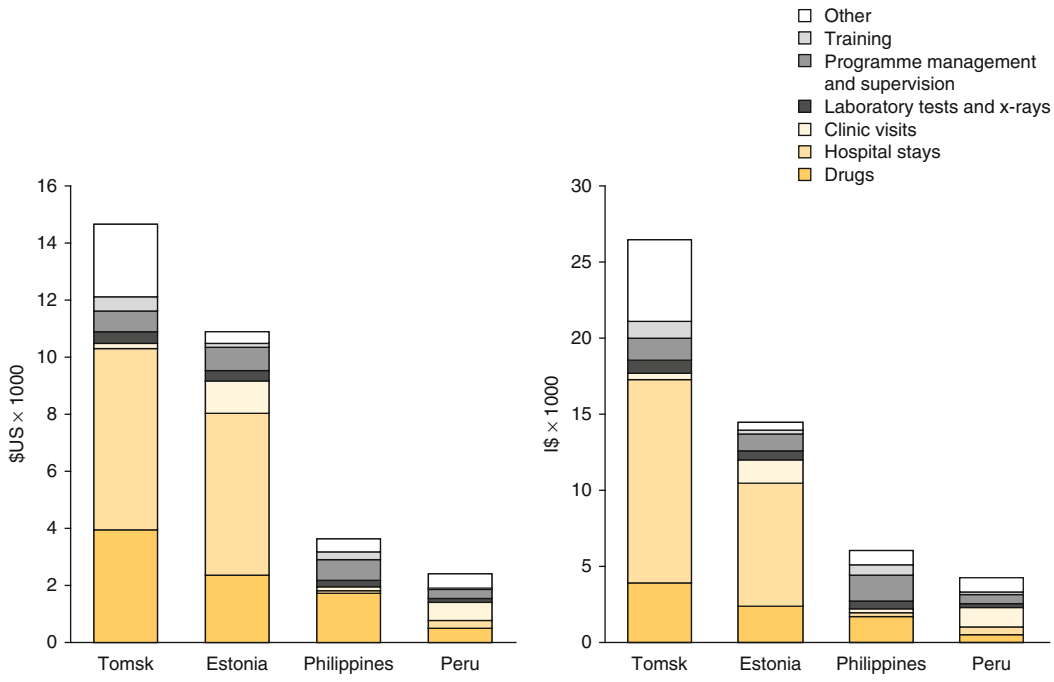

Fig. 3. Health system cost per patient with multidrug-resistant tuberculosis treated, by major cost component. All results have been standardized to year 2005 values. **I$** = international dollars.

talization (Estonia and Tomsk), drugs (the largest or second largest cost in all four settings) and clinic visits for outpatient treatment (Estonia and Peru). Much higher costs in Estonia and Tomsk than in Peru and the Philippines were due to extensive hospitalization (just over 6 months in Estonia and approximately 8 months in Tomsk), which accounted for 43% and 52%, respectively, of the total cost of treating an MDR-TB patient in these settings; and comparatively high costs for drugs ($US3944 per patient in Tomsk and $US2354 in Estonia vs $US1701 in the Philippines). Other costs (e.g. laboratory tests, programme management and supervision) were mainly for non-traded resources (i.e. labour).

The cost per DALY averted was less than GDP per capita in all four settings, in both $US and I$ (figure 4). The best estimate of the cost per DALY averted was $US163 in Peru and $US143 in the Philippines, compared with per capita GDP figures of $US2852 in Peru and $US1156 in the Philippines. If the suboptimal regimen in Peru were replaced with the regimen used in the Philippines, the cost per DALY averted in Peru would increase to $US191 (conservatively assuming no change in the number of deaths averted). In Estonia and Tomsk, the best estimates of the cost per DALY averted were $US598 and $US745. After adjustments for PPP, the cost per DALY averted was slightly higher in Tomsk than in Estonia, but otherwise the rank order was consistent. The uncertainty intervals suggest that there was no statistical difference between the Tomsk and Estonia results, or between the results for the Philippines and Peru. The results were consistent whether the comparison was with a pre-intervention standard of care that included treatment with at least some second-line drugs or with a 'no treatment' scenario in all four settings.

Other Settings

The results of our appraisal of the likely cost and cost effectiveness of MDR-TB treatment in

14 sub-regions for the two main models of care used in the four original studies (i.e. inpatient-based and outpatient-based treatment), are shown in table IV (and Annex 6 of the SDC – results in I$). For each sub-region, the cost per patient treated and the cost per DALY averted are plausible ranges given the local prices of inputs in these regions, on the assumption that the health effects achieved for the outpatient model in Peru and the Philippines and the inpatient model in Estonia and Tomsk are achievable elsewhere.

Outpatient models of care will incur lower costs than inpatient models in a wide range of countries; therefore, unless outcomes achieved are significantly different from those achieved in Estonia, Peru, the Philippines and Tomsk, outpatient models will also be more cost effective (see last two rows of table IV and Annex 6 of the SDC).

Globally, the outpatient model costs an average of $US13 259 (5th–95th percentiles 2797–42 040) per patient treated; the inpatient model costs an average of $US34 599 (6959–109 154) per patient treated. See Annex 5 in the SDC for unit cost results in I$. In terms of cost effectiveness, the outpatient model costs an average of $US725 (5th–95th percentiles 120–2370) per DALY averted, or I$589 (137–1689); the inpatient model costs an average of $US1812 (327–5683) per DALY averted, or I$1859 (401–5445). Outpatient-based models could lower the cost per DALY averted relative to inpatient-based models by as much as 54% (5th–95th percentiles 7–82) in $US or 62% (22–86) in I$.

Discussion

Summary of Main Findings

This is the first systematic review of the cost and cost effectiveness of treatment for MDR-TB. Based on the four studies that met the inclusion criteria for our review, and extrapolation of

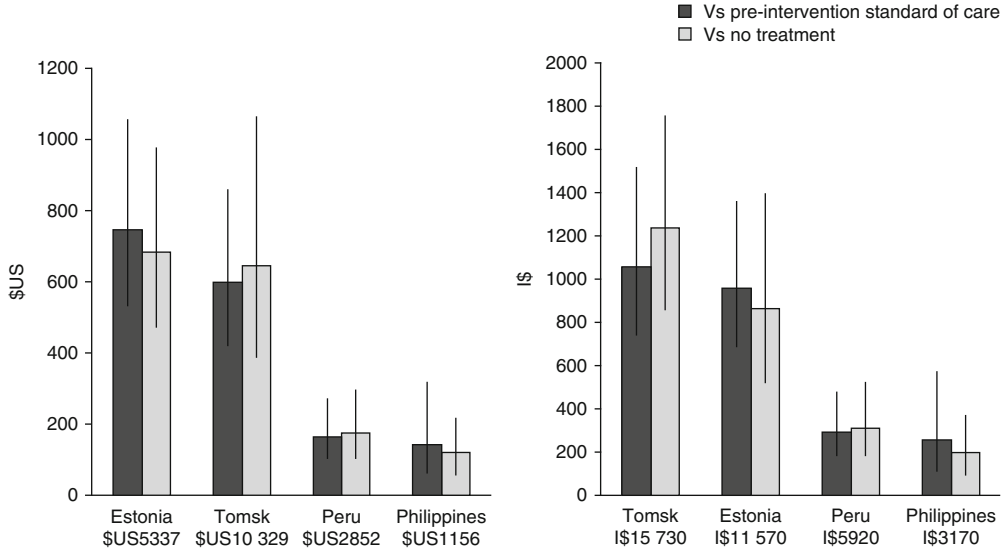

Fig. 4. Health system cost per disability-adjusted life-year (DALY) averted vs pre-intervention standard of care and vs no treatment, year 2005 values. Vertical lines represent the 95% CI of the estimate. The figure below each set of bars is the country's GDP per capita. Following the recommendations of the WHO Commission on Macroeconomics and Health,[27] a cost per DALY averted of less than per capita GDP is considered 'very cost effective'; a cost per DALY averted of less than three times GDP per capita is considered 'cost effective'.[28] The result of the comparison with the 'pre-intervention' standard of care may differ slightly from that reported in a given study because (i) all results have been standardized to year 2005 values; (ii) there may be imprecision in these standardized estimates as a result of the reporting of rounded values and/or of the non-reporting of the distribution of confidence intervals in the studies. While the 'pre-intervention' standard of care in Peru and the Philippines was, to all intents and purposes, equivalent to 'no treatment', we nonetheless have small differences in the results for the two comparisons. For all studies, differences between the 'pre-intervention' and 'no treatment' comparisons are due to (i) the assumption of zero cost for 'no treatment' and the modelling of health outcomes under no treatment, based on results from Peru;[11] and (ii) standardization using a common number of DALYs averted per death averted. **$I** = international dollars.

Table IV. Generalized cost effectiveness of outpatient vs inpatient models of care, by WHO sub-region[a] ($US, year 2005 values)[b]

WHO sub-region	Average GDP per capita[c]	Cost per patient treated		Cost per DALY averted		Absolute difference in cost per DALY averted[d]: inpatient models – outpatient models	Relative difference in cost per DALY averted (%)[d]: (inpatient models – outpatient models)/inpatient models
		outpatient model	inpatient model	outpatient model	inpatient model		
AFR D	2042	4941 (2416–12028)	11570 (5815–25348)	258 (90–655)	600 (260–1372)	342 (85–851)	0.56 (0.2–0.78)
AFR E	1240	3993 (2298–7644)	9411 (5670–17788)	205 (84–444)	487 (250–965)	282 (89–626)	0.57 (0.26–0.78)
AMR A	38811	41225 (28896–62047)	195078 (42865–551746)	2216 (1143–4051)	10131 (2047–28986)	7915 (508–25795)	0.65 (0.23–0.9)
AMR B	5189	9083 (4776–15481)	22198 (11127–41315)	492 (216–944)	1151 (511–2255)	658 (160–1510)	0.54 (0.23–0.75)
AMR D	1702	5033 (3152–7618)	11648 (7431–18631)	267 (127–490)	603 (333–1036)	336 (112–677)	0.54 (0.25–0.75)
EMR B	10957	17673 (6102–37749)	46992 (14996–108902)	987 (281–2238)	2434 (702–5875)	1447 (207–4046)	0.55 (0.19–0.79)
EMR D	1029	3680 (2875–4814)	8872 (6641–12434)	187 (105–311)	459 (283–721)	272 (108–494)	0.58 (0.32–0.76)
EUR A	35388	39654 (18371–69565)	95612 (40561–184086)	2150 (864–4148)	4923 (1907–9892)	2773 (523–6563)	0.53 (0.2–0.75)
EUR B	3384	6057 (2955–11692)	15505 (8063–29015)	316 (123–672)	801 (371–1571)	485 (162–1051)	0.59 (0.32–0.78)
EUR C	5632	8050 (3860–13207)	21334 (10523–39156)	421 (167–810)	1101 (493–2138)	681 (209–1489)	0.6 (0.32–0.79)
SEAR B	1388	4106 (2775–5797)	9969 (6747–15353)	210 (108–365)	516 (297–872)	306 (114–591)	0.58 (0.31–0.76)
SEAR D	937	3401 (2310–5287)	8207 (5653–13324)	170 (83–314)	424 (243–741)	255 (96–497)	0.59 (0.31–0.77)
WPR A	30351	34748 (29204–41259)	80879 (54247–116872)	1891 (1141–3025)	4175 (2405–6729)	2284 (627–4543)	0.52 (0.22–0.73)
WPR B	2733	6347 (2950–15912)	16282 (7174–36644)	341 (118–848)	844 (328–1996)	504 (118–1300)	0.58 (0.25–0.79)

a See table III for the WHO regions and mortality strata.

b Generalized cost-effectiveness results have been generalized for regional distributions of unit costs. This table presents the mean and the 5th and 95th percentiles (in parentheses) of the distribution. In addition, results have been standardized for the number of DALYs averted per death averted, for inflation to a common base year (2005), and for comparison with no treatment at all.

c Cost-effectiveness thresholds are based on GDP per capita; if cost per DALY averted is <GDP per capita, intervention is considered 'very cost effective'. The average GDP per capita is presented here to give an impression of variation in the thresholds across sub-regions.

d The cost per DALY averted for outpatient-based models of care is compared with the cost per DALY averted for inpatient-based models of care for each iteration of the simulation. The mean, 5th and 95th percentiles of the differences are extracted and presented. The mean difference will not necessarily equal the difference between columns 5 and 6 because the mean of the differences is not equivalent to the difference of the means.

DALY = disability-adjusted life-years.

results to 14 sub-regions, our results suggest that treatment for MDR-TB can be very cost effective. WHO has suggested that a healthcare intervention is highly cost effective if the cost per DALY averted is less than per capita GDP, and cost effective if less than three times per capita GDP.[28] On the basis of our models, we find that the cost per DALY averted for MDR-TB treatment could be less than per capita GDP in all sub-regions. The results also indicate that outpatient models of care are more affordable and cost effective than models of care that rely on hospitalization for several months of treatment. An outpatient model could cost from $US84–444 per DALY averted in low-income African countries to $US1143–4051 in the highest income countries of the Americas. An inpatient-based model could cost from $US250–965 per DALY averted to $US2047–28 986 in these same regions. For the average country, the outpatient-based model of care could reduce the cost per DALY averted by over 50%.

Review Limitations

Our paper has several limitations. According to the GRADE methodology used by WHO for the development of guidelines, the quality of evidence about the comparative cost effectiveness of inpatient and outpatient models of care for MDR-TB is 'very low' overall (SDC, Annex 5). The principal reason is that none of the four studies included in our study were conducted alongside a randomized controlled trial (RCT). In the GRADE methodology, data from an RCT or an 'exceptionally strong' observational study are required in order for evidence to be rated as 'high' quality; otherwise, the only two possible grades are 'low' or 'very low' quality. This is problematic in the case of economic evaluations, since they are often not conducted in association with an RCT or an 'exceptionally strong' observational study, but may still score highly according to well established and standard checklists for assessing the quality of an economic evaluation (all four of the studies included in our review scored well according to these checklists, and indeed could not have been included in our review had they not done so). As a result, the GRADE framework does not allow for a very nuanced assessment of the quality of the evidence available from economic evaluations. In this context, it is worth highlighting that, of the 75 economic evaluations of tuberculosis interventions cited with full abstracts in the NHSEED, only one contains a reference to an RCT. In addition, virtually all of the evidence available to the WHO Guideline Development Group (a multidisciplinary expert panel on the prevention and management of MDR-TB) on the programmatic management of MDR-TB was rated as 'low' or 'very low' quality, highlighting the virtual absence of RCTs related to MDR-TB.[8]

Another reason for the 'very low' quality grading is that none of the original studies included compared different models of care within the same setting. This is not a fault of the studies themselves, but rather reflects that only one model of care was implemented in each setting (thus precluding the possibility of comparing alternative models of care implemented during the same time period).

We assumed that the effectiveness of the outpatient and inpatient models of care would be reproduced in other settings when we made comparisons of the two models and generalized results to 14 sub-regions. In practice, the effectiveness of hospital-based treatment may be lower in some countries than in Estonia and Tomsk; similarly, outpatient treatment may be less effective in some countries than in the Philippines and Peru. This assumption is not trivial, as we were unable to control for differences among study populations in basic demography, socioeconomic characteristics, epidemiology and the previous treatment history of patients included in the study cohorts. We recognize that patterns of drug resistance will vary across settings and that the drug costs incurred and the cure rates achieved will therefore also vary.

Only one of the studies (that from the Philippines[12]) considered costs to patients. Nonetheless, it is clear from the resource use described in all studies that a patient will spend more time accessing treatment and care when an inpatient model of care is used. For example, using data from the four studies and assumptions described

in Annex 5 of the SDC, approximate calculations suggest that patients will spend 365–468 hours away from families and/or jobs when outpatient treatment is used, and 3158–5429 hours when inpatient care is relied upon for the first few months of treatment.

Other limitations include that the literature search did not cover publications in Chinese or Arabic. It is also possible that countries will adopt lower- or higher-cost approaches to treatment for MDR-TB than the models of in- and outpatient care employed in the four studies reviewed. Evidence about the cost and cost effectiveness of community-based models of outpatient care was lacking.

Review Strengths

Our review has several strengths. The systematic review was carefully and thoroughly conducted using established methods. Uncertainty in parameters and resulting estimates of cost and cost effectiveness was explicitly considered. The four studies that were included in our review and that formed the basis for extrapolation of results to other settings used established methods for economic evaluation and scored well on related checklists.[10,17] Appropriate adjustments were made to standardize results and the analysis of likely costs and cost effectiveness was able to draw on a comprehensive WHO database that included estimates of relevant unit costs for 14 sub-regions. Our review was conducted in four languages in addition to English and considered the grey literature. We compared the studies that were included in our review with those considered in a systematic review of the effectiveness of treatment[6,7] and found nothing to suggest the presence of effect-size bias in the included studies.

Comparisons with Other Studies

The findings from this review are consistent with two previous publications[16,29] that assessed the likely cost effectiveness of MDR-TB treatment at a regional level. The Disease Control Priorities in developing countries Project (DCPP),[16] which used unit costs for six World Bank regions as well as a standardized epidemiological framework for estimating effectiveness, produced cost per DALY averted estimates of $US200–400 in all regions except Europe and Central Asia ($US800–1300). The DCPP focused on low- and middle-income countries and did not consider high-income countries (those with per capita Gross National Income [GNI] of ≥$US12 196 in 2009), and hence does not include results that can be directly compared with three of the regions (AMR A, EUR A and WPR A [see table III for definitions and countries]) considered in our modelling. A second study, which focused on the African and South-East Asia regions (the AFR E and SEAR D sub-regions considered in our modelling), estimated that the cost per DALY averted for MDR-TB treatment was in the range of I$100–200 (year 2000 values).[29] This compares with best estimates of around I$250 in our analysis.

Policy Implications

If the findings from our review are robust, it is clear that outpatient-based models of care can greatly enhance the efficiency of treatment for MDR-TB. Considerable amounts could be invested in incentives and enablers (such as food packages and transport vouchers) to minimize the risk of default from outpatient treatment before costs would come close to those for inpatient care. Although the cost of second-line drugs represents a large share (around 20–50%) of the total cost per patient treated, it is likely to be differences in the utilization and associated costs of inpatient and outpatient care that drive differences among countries in the cost per DALY averted.

In their own specific settings, managers of national TB programmes (NTPs) will need to consider whether a given model of care is feasible with the existing allocation of resources (for example, whether there are enough hospital beds to provide inpatient care, and whether primary care facilities have the required healthcare workers and social support services to promote adherence to outpatient treatment). NTPs will also have to consider whether effect sizes are likely to be replicated given the demographic, socioeconomic and epidemiological profile of the country, compared with those observed in Peru, Estonia, the

Philippines and Tomsk. Nonetheless, if countries were to consider adopting lengthy hospitalization as part of their model of treatment and care, it would need to demonstrate a very large effect size in terms of DALYs averted compared with outpatient care. Until then, outpatient treatment should be the default model of care for resource-limited NTPs, especially those that are just beginning to scale-up treatment.

The relatively favourable cost effectiveness of MDR-TB treatment in terms of the cost per DALY averted is an argument for allocating more resources to TB control in general. However, it does not suggest that MDR-TB treatment is more cost effective than other TB control interventions. NTPs with limited resources will have to benchmark the cost effectiveness of MDR-TB treatment against the expansion and enhancement of diagnosis and treatment for drug-susceptible TB.

What New Evidence is Needed?

Empirical evidence on the cost effectiveness of MDR-TB treatment is currently limited to one middle-income country in Latin America, two upper-middle-income countries that were part of the former Soviet Union and one lower-middle-income country in Asia. More data are needed, especially from (i) the two countries that, in combination, account for about 50% of the world's cases of MDR-TB – China and India; (ii) the African region; and (iii) low-income countries. Three studies known to the authors that are nearing completion (Nepal), underway (China) or at the planning stage (Cameroon) will provide important new evidence and, once this is available, the results published in this review will need to be updated. Operational research to identify the conditions under which outpatient-based models of care may fail, such as among transient populations and substance abusers, or, alternatively, the conditions required for outpatient models to succeed (including among these sub-populations), is also crucial. Further research may also shed light on whether hospitalization is more cost effective for those with close contacts who are immunosuppressed, or for those who are themselves immunosuppressed.

Conclusions

To date, few studies have examined the cost and cost effectiveness of treatment for MDR-TB. The evidence that does exist suggests that treatment for MDR-TB can be cost effective in low- and middle-income countries. The data also indicate that outpatient treatment should be the default model of care unless there is strong evidence that lengthy inpatient care is necessary to achieve high rates of adherence to treatment. This conclusion has been supported by the WHO Guideline Development Group in a conditional recommendation that "MDR-TB patients should be treated using mainly ambulatory care rather than models of care based principally on hospitalization."[8] Looking forward, more data from Africa and Asia – especially India and China, which have the largest number of cases – as well as more comparisons of alternative models of care within the same setting, are needed.

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