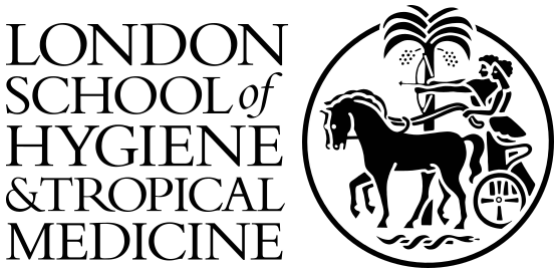

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SYSTEMATIC REVIEW

Costs to Health Services and the Patient of Treating Tuberculosis: A Systematic Literature Review

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Abstract

Background Novel tuberculosis (TB) drugs and the need to treat drug-resistant tuberculosis (DR-TB) are likely to bring about substantial transformations in TB treatment in coming years. An evidence base for cost and cost-effectiveness analyses of these developments is needed.

Objective Our objective was to perform a review of papers assessing provider-incurred as well as patient-incurred costs of treating both drug-susceptible (DS) and multidrug-resistant (MDR)-TB.

Methods Five databases (EMBASE, Medline, the National Health Service Economic Evaluation Database, the Cost-Effectiveness Analysis Registry, and Latin American and Caribbean Health Services Literature) were searched for cost and economic evaluation full-text papers containing primary DS-TB and MDR-TB treatment cost data published in peer-reviewed journals between January 1990 and February 2015. No language restrictions were set. The search terms were a combination of 'tuberculosis', 'multidrug-resistant tuberculosis', 'cost', and 'treatment'. In the selected papers, study methods and characteristics, quality indicators and costs were extracted into summary tables according to pre-defined criteria. Results were analysed according to country income groups and for provider costs, patient costs and productivity losses. All values were converted to $US, year 2014 values, so that studies could be compared.

Results We selected 71 treatment cost papers on DS-TB only, ten papers on MDR-TB only and nine papers that included both DS-TB and MDR-TB. These papers provided evidence on the costs of treating DS-TB and MDR-TB in 50 and 16 countries, respectively. In 31 % of the papers, only provider costs were included; 26 % included only patient-incurred costs, and the remaining 43 % estimated costs incurred by both. From the provider perspective, mean DS-TB treatment costs per patient were US$14,659 in high-income countries (HICs), US$840 in upper middle-income countries (UMICs), US$273 in lower middle-income (LMICs), and US$258 in low-income countries (LICs), showing a strong positive correlation. The respective costs for treating MDR-TB were US$83,365, US$5284, US$6313 and US$1218. Costs incurred by patients when seeking treatment for DS-TB accounted for an additional 3 % of the provider costs in HICs. A greater burden was seen in the other income groups, increasing the costs of DS-TB treatment by 72 % in UMICs, 60 % in LICs and 31 % in LMICs. When provider costs, patient costs and productivity losses were combined, productivity losses accounted for 16 % in HICs, 29 % in UMICs, 40 % in LMICs and 38 % in LICs.

Conclusion Cost data for MDR-TB treatment are limited, and the variation in delivery mechanisms, as well as the rapidly evolving diagnosis and treatment regimens, means that it is essential to increase the number of studies assessing the cost from both provider and patient perspectives. There is substantial evidence available on the costs of DS-TB treatment from all regions of the world. The patient-incurred costs illustrate that the financial

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burden of illness is relatively greater for patients in poorer countries without universal healthcare coverage.

Key Points for Decision Makers

Drug-susceptible tuberculosis treatment cost data are available from the perspective of both providers and patients from various settings around the world.

Multidrug-resistant tuberculosis treatment costs are not widely available, particularly not for middle- and low-income countries.

Productivity losses were presented in 57 % of the papers, for both drug-susceptible and multidrug-resistant tuberculosis. However, methods used varied widely, reflecting the lack of clear guidelines on the best instrument and methods for this estimation.

1 Introduction

The post-2015 World Health Organisation (WHO) *End TB strategy* 2016–2035 has a vision of a 'world free of tuberculosis (TB) (zero deaths, disease or suffering due to TB)' and a goal of 'ending the global TB epidemic' by 2035, defined as an annual incidence of fewer than ten cases per 100,000 of population [1]. These targets are likely to require scaling-up of high-quality drug-sensitive (DS) TB and drug-resistant (DR) TB treatment, but may stretch the resource capacity of national TB programmes far beyond any previous efforts. Country- and context-specific economic evaluations and budget impact analyses are essential for decision making, but obtaining timely cost data can be expensive and labour intensive. Assembling a repository of quality-assessed DS-TB and multidrug-resistant (MDR)-TB treatment costs can facilitate these processes and identify gaps for future targeted cost data collection.

Earlier reviews have investigated TB treatment costs, but these are either incomplete or no longer up to date. We identified eight previous reviews on TB treatment costs. In 1997, Fryatt [2] reviewed cost-effectiveness papers of TB treatment programmes, in 2004, Russell [3] reviewed the economic burden of households due to TB, and, in 2011, Verdier et al. [4] reviewed economic evaluations of TB control in high-income countries (HICs). Three reviews were published in 2012: two on patient-incurred TB treatment costs in sub-Saharan Africa [5, 6] and one on MDR-TB treatment costs [7]. In 2013, Diel et al. [8] published a review determining the costs of TB in the EU, and, in 2014, Tanimura et al. [9] reviewed papers on patient costs in low- and middle-income countries [9]. This present review complements and synthesises the evidence provided in these previous reviews by including papers from all countries, assessing both DS-TB and MDR-TB costs, and evaluating both provider- and patient-incurred costs.

2 Methods

2.1 Search Strategy and Data Extraction

Peer-reviewed papers were eligible for inclusion if mean treatment cost estimates of DS-TB or MDR-TB in adults were reported and based on primary data that originated from 1990 or later. Five databases were searched: EMBASE, Medline, the National Health Service Economic Evaluation Database, the Cost-Effectiveness Analysis Registry, and the Latin American and Caribbean Health Sciences Literature. An initial search was conducted in April 2013 and updated in February 2015. Therefore, the search period was from January 1990 to February 2015. Search terms were a combination of 'tuberculosis', 'multidrug-resistant tuberculosis', 'cost', and 'treatment'. The full search strategies are included in the Electronic Supplementary Material (ESM) Online Resource 1. No language restrictions were applied in the search. To assess relevance, abstracts or papers in Spanish were translated by the authors, and abstracts obtained in French, Hungarian and Russian were translated using electronic translation software (Google Translate) [10]. Reference lists of identified reviews were checked for papers that may have been missed by the database search; references cited in retrieved papers were also examined.

Data were independently extracted by two authors. Any discrepancies were resolved by re-evaluation of the paper in question. A data extraction sheet was used, the composition of which was informed by the data-extraction guidelines for economic evaluations in the *Centre for Reviews and Dissemination's Guidance for Undertaking Reviews in Health Care* [11] and the *Cochrane Handbook for Systematic Reviews of Interventions* [12]. Variables included the characteristics of the study, as well as provider- and patient-incurred costs. The outcome measure was mean treatment costs per patient. For each paper, all cost items reported, such as drugs, hospitalisation, diagnostic tests and productivity loss, were extracted separately and, where relevant, divided into patient-incurred and provider costs. Patient-incurred costs were further divided into direct costs and productivity losses. Direct patient costs were defined as expenses paid by patients for receiving treatment, such as user fees for health facilities or monitoring or diagnostic

tests, drug expenditures, transportation and other costs, which included food, non-TB drugs, traditional medicine and room and board for patients not resident near the TB treatment facility. Moreover, if costs were aggregated, this total was included in the 'other' category. Productivity losses were defined as the value of paid and unpaid production loss due to time seeking treatment, being ill, or because of premature mortality [13].

Given that our aim was to provide a dataset that best informs the estimation of current TB treatment costs, in papers that compared the costs of more than one treatment delivery strategy, for instance directly observed treatment (DOT) versus self-administered treatment (SAT) [14], we selected the intervention we considered to best reflect the current standard practice in the respective country. This was determined from the paper, or, if not stated, by consulting with TB experts familiar with the respective countries.

2.2 Data Analysis

Costs were converted to 2014 values in the local currency and then to US$ using the International Monetary Fund's average consumer price indices and OANDA's average annual exchange rates [15, 16]. For papers that did not provide the year of cost data, we used the year prior to the publication date.

Results were presented according to 2013 World Bank country income groups. HICs were classified as those with per capita gross national income (GNI) of US$12,746 or greater, upper middle-income countries (UMICs) greater than or equal to US$4126 and less than US$12,746, lower middle-income countries (LMICs) greater than or equal to US$1046 and less than US$4126, and low-income countries (LICs) less than US$1046 [17].

The relationship between provider costs and country GNI per capita was assessed using Pearson's correlation coefficient.

2.3 Study Quality Assessment

Quality assessment focused on methods for estimating and reporting costs; methods used for determining health effects as part of cost-effectiveness studies were not evaluated. Quality appraisal was based on two guidelines; the *Consolidated Health Economic Evaluation Reporting Standards* (*CHEERS*) statement [18] and *The Tool to Estimate Patient's Costs* published by the TB Coalition for Technical Assistance (TBCTA) [19]. Four requirements of the CHEERS statement were used: (1) sources used for resource quantities and unit costs clearly described, (2) dates of estimated resource quantities and unit costs reported, (3) methods for adjusting unit costs to the reporting year and performing currency conversion explained, and (4) mean values for main categories of estimated costs reported [18]. For papers that included patient costs, quality was further evaluated using two requirements of the TBCTA tool: (1) clear description of patient interview procedures given and (2) methods used for valuing productivity losses explained and justified [19]. Additional quality indicators abstracted from all papers were the number of patients included in the study sample in order to provide some indications of representativeness [20, 21]. We also extracted whether any measures of dispersion, such as standard deviation (SD), around the mean cost values were given [22]. The review protocol was not registered in any systematic review database or registry. Two authors independently assessed paper quality, with disagreements resolved through discussion.

3 Results

3.1 Paper Selection

The search identified 4899 papers, and 289 papers were included for full-text review, after which 199 papers were excluded (Fig. 1). Of the excluded papers, 42 presented costs of TB screening in schools or in high-risk individuals, such as immigrants, healthcare workers, individuals with HIV or the elderly. Reporting was insufficient in 28 papers, including only presenting selected cost items or providing costs of a national TB programme without mean treatment costs per patient; 11 papers were excluded because the same primary data were used in an already included paper. A total of 90 papers were included in the analysis; 71 were on DS-TB treatment costs only, nine were on MDR-TB only, and ten included the costs of both.

3.2 Study Characteristics

For DS-TB and MDR-TB, 50 and 16 countries were represented, respectively (Table 1). In this review we distinguished between paper and study to illustrate where a paper included cost values for two or more countries, which would thereby represent two or more studies in one paper. Therefore, a total of 95 studies were represented in this review. The oldest paper was from 1995; six papers were from 2014 and one was from 2015, as of the February 2015 search. Country income groups were relatively evenly represented; 28 % of the papers were from HICs, 32 % from UMICs, 19 % from LMICs, and 21 % from LICs.

In 51 papers, only one type of TB treatment management was evaluated (for example, ambulatory DOT), while the remaining 39 papers compared two or more strategies in either a cost-comparison or a cost-effectiveness analysis.

In 31 % of the papers, only provider costs were included, in 26 % only costs incurred by patients, and in the

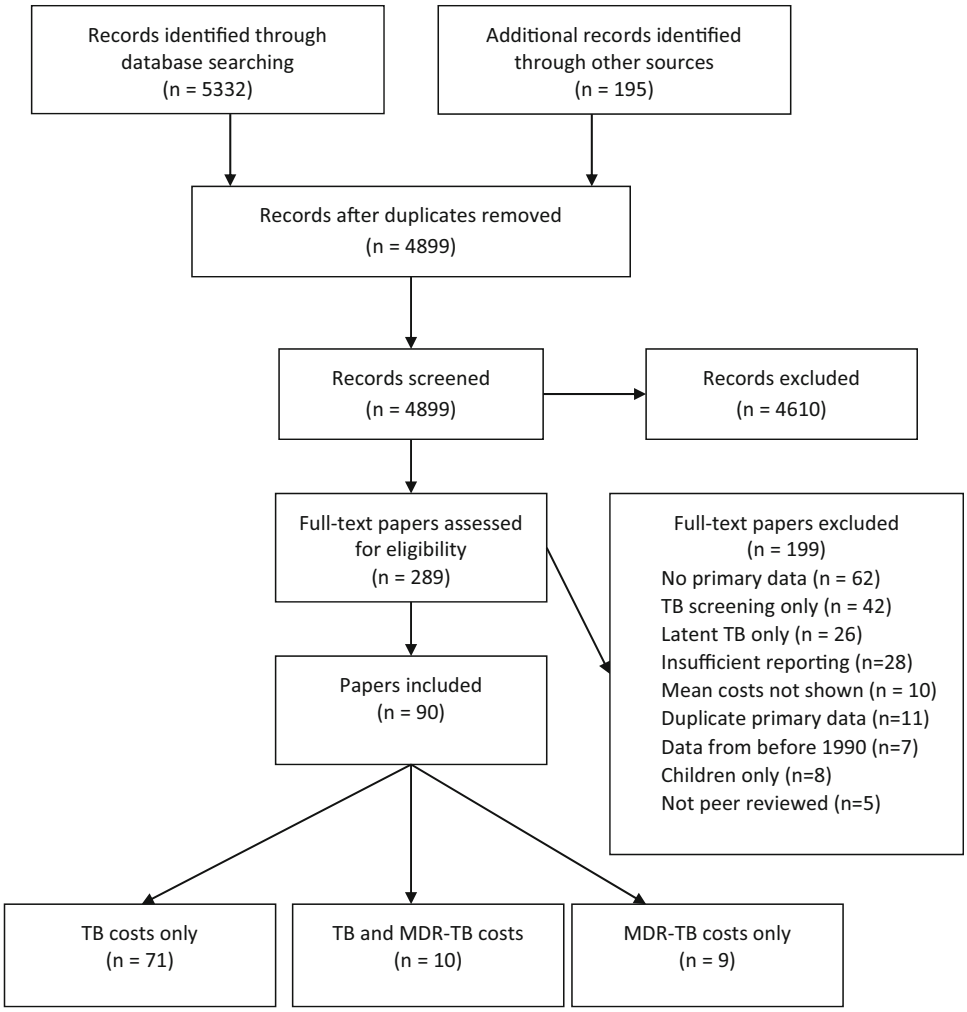

Fig. 1 Literature review flow chart. *MDR* multidrug-resistant, *TB* tuberculosis

remaining 43 % both provider and patient costs were evaluated (Table 1). This varied according to country income group. While a provider-only perspective was taken in 15 and 11 of the HIC and UMIC papers (60 and 38 %, respectively), only one LMIC paper (6 %) and one LIC paper (5 %) included provider costs only. Productivity losses were included in 81 % of the papers that measured patient-incurred costs.

3.3 Quality Assessment

Quality assessment of individual papers is included in the ESM (Online Resources 2 and 3). Table 2 presents a summary according to country income group.

3.3.1 Data Collection Methods

The year of cost data and the main cost categories were adequately reported in 77 % of papers (Table 2). In 79 of the 90 papers, cost data were collected from a sample of patients. The mean sample size across these studies were 324 patients (SD 532), ranging from nine in a MDR-TB study from the UK to 3510 patients in a German cost-of-illness study [23, 24]. However, in spite of relatively large sample sizes in many studies, only 30 % presented descriptive statistics showing the spread around the mean cost values.

In ten of the remaining 11 studies, costs were determined by making assumptions about resources needed to treat TB according to national guidelines. For instance, a South African study by Pooran et al. [25] assumed that all DS-TB patients received drugs for 6 months and MDR-TB patients for 24 months, as this was the length of a full recommended treatment course. In the one study [26] that did not follow this approach, annual costs of primary health clinics in a specific area of South Africa were estimated and costs of TB treatment were determined by weighing total costs by the proportion of patients presenting due to TB [26].

Table 1 Summary of treatment cost papers included in review

References	Year	Country	Interventions evaluated in study	Provider costs included	Direct patient costs included	Productivity losses included
HICs ($n = 25$)						
Burman et al. [38][a]	1997	USA	DOT vs. self-administered therapy	X		X
Palmer et al. [92]	1998	USA	Universal vs. partial DOT	X		
Migliori et al. [76]	1998	Russia	New vs. old treatment strategies	X		
Migliori et al. [78]	1999	Italy	DOT vs. DOT with staff incentives	X		X
Marchand et al. [93]	1999	Canada	Hospitalised treatment of elderly	X		
Weis et al. [33]	1999	USA	DOT vs. traditional therapy	X		
Wurtz and White [88]	1999	USA	Traditional therapy	X		
White and Moore-Gillon [23][a]	2000	UK	Hospitalised treatment	X		
MacIntyre et al. [94]	2001	Australia	Inpatient vs. outpatient therapy	X		
Jacobs et al. [30]	2002	Russia	DOTS vs. traditional treatment	X	X	X
Rajbhandary et al. [28][b]	2004	USA	MDR-TB	X		X
Atun et al. [40]	2006	Russia	TB control system	X		
Kang et al. [31][b]	2006	South Korea	MDR-TB	X	X	X
Bocchino et al. [48]	2006	Italy	Integrated in- and outpatient	X		
Burns and Harrison [39]	2007	New Zealand	DOT in non-resident population	X		
Kik et al. [29]	2009	Netherlands	Household costs of immigrants		X	X
Miller et al. [52]	2010	USA	Total TB costs in a Texas county	X		X
Montes-Santiago et al. [65]	2010	Spain	Hospitalisation only	X		
Tu et al. [95]	2011	Taiwan	Comparison of diagnostic methods	X		
Eralp et al. [51]	2012	UK	Screening, diagnosis and treatment	X		
Diel et al. [24][a]	2012	Germany	Hospital and outpatient	X		X
Floyd et al. [55][b]	2012	Estonia, Russia	Traditional vs. WHO approach	X		
Miller et al. [41][a]	2013	Latvia	DOTS and MDR-TB	X		
Marks et al. [56][b]	2014	USA	Hospitalisation	X		X
Diel et al. [87][b]	2014	Germany	WHO guidelines	X		X
UMICs ($n = 29$)						
Masobe et al. [43]	1995	South Africa	Isoniazid prophylactic therapy	X		
Wilkinson et al. [49]	1997	South Africa	DOT vs. traditional treatment	X	X	X
Sawert et al. [77]	1997	Thailand	TB programme improvements	X		X
Dick and Henchie [26]	1998	South Africa	TB programme in Cape Town	X		
Xu et al. [60][a]	2000	China	DOTS vs. traditional treatment	X		
Suarez et al. [62][b]	2002	Peru	MDR-TB 2nd line drug treatment	X		
Kamolratanakul et al. [61][a]	2002	Thailand	Comparison of delivery centres	X		
Moalosi et al. [45]	2003	Botswana	Home-based vs. hospital DOT	X	X	X
Ruiz et al. [96]	2003	Mexico	National costs	X		
Costa et al. [81][a]	2005	Brazil	Treatment in Salvador state	X	X	X
Sinanovic and Kumaranayake [97]	2006	South Africa	Public–private partnership model	X		
Peralta Perez et al. [53]	2006	Cuba	DOTS	X		
Jackson et al. [98]	2006	China	Household costs		X	X
Liu et al. [99]	2007	China	Household costs		X	
Elamin et al. [72]	2008	Malaysia	Costs in Penang state	X	X	X
Cusmano et al. [44]	2009	Argentina	DOTS	X	X	X
Guzman-Montes et al. [100]	2009	Mexico	Household costs		X	X
Fairall et al. [42]	2010	South Africa	Educational outreach services	X	X	

Table 1 continued

References	Year	Country	Interventions evaluated in study	Provider costs included	Direct patient costs included	Productivity losses included
Rouzier et al. [86][a]	2010	Ecuador	Household costs		X	X
Steffen et al. [14]	2010	Brazil	DOTS vs. non-DOTS	X	X	X
Prado et al. [80]	2011	Brazil	Guardians vs. heath workers	X	X	X
Samandari et al. [101][a]	2011	Botswana	DOTS for DS-TB and MDR-TB	X		
Nieto et al. [102]	2012	Colombia	Increased guardian supervision	X	X	
Schnippel et al. [57][b]	2013	South Africa	Hospitalised management	X		
Pooran et al. [25][b]	2013	South Africa	MDR-TB	X		
Zou et al. [103]	2013	China	DOTS incentives vs. no incentive	X	X	X
Pan et al. [63]	2013	China	DOTS		X	X
Wei et al. [104]	2014	China	DOTS		X	
Foster et al. [105]	2015	South Africa	DOTS		X	X
LMICs ($n = 17$)						
Rajeswari et al. [106]	1999	India	Household costs		X	X
Khan et al. [47]	2002	Pakistan	Health worker vs. family	X	X	X
Vassall et al. [46]	2002	Egypt, Syria	DOTS vs. previous strategies	X	X	X
Nganda et al. [66]	2003	Kenya	Increased community involvement	X	X	X
Peabody et al. [107]	2005	Philippines	Economic burden of TB	X	X	
Tupasi et al. [58][b]	2006	Philippines	DOTS-Plus MDR-TB	X	X	
Floyd et al. [34]	2006	India	Public-private mix DOTS	X	X	X
El-Sony et al. [54]	2006	Sudan	Comparison of HIV+ and HIV−	X		
Aspler et al. [108]	2008	Zambia	Household costs		X	X
Muniyandi et al. [83]	2008	India	DOTS vs. non-DOTS		X	X
Pantoja et al. [32]	2009	India	Public-private mix DOTS	X	X	X
John et al. [82]	2009	India	DOTS		X	X
Vassall et al. [35]	2009	Ukraine	DOTS implementation	X	X	
Mahendradhata et al. [79]	2010	Indonesia	Private practitioner referral	X	X	X
Mauch et al. [109]	2011	Kenya	Household costs		X	X
Umar et al. [110]	2012	Nigeria	Household costs		X	
Mauch [68]	2013	Dom. Republic[c], Ghana, Vietnam	Household costs		X	X
LICs ($n = 19$)						
Saunderson [50]	1995	Uganda	Hospital vs. ambulatory care	X	X	X
Maponga et al. [89]	1996	Zimbabwe	TB/HIV co-epidemic	X		
Gibson et al. [111]	1998	Sierra Leone	Household costs		X	
Wyss et al. [67]	2001	Tanzania	Household costs		X	X
Islam et al. [73]	2002	Bangladesh	CHW vs. no CHW	X	X	X
Floyd et al. [36]	2003	Malawi	Increased community involvement	X	X	X
Okello et al. [37]	2003	Uganda	Increased community involvement	X	X	X
Wandwalo et al. [85]	2005	Tanzania	Community vs. health facility	X	X	X
Jacquet et al. [64]	2006	Haiti	DOTS expansion	X	X	X
Karki et al. [112]	2007	Nepal	Public–private partnership	X	X	X
Mirzoev et al. [113]	2008	Nepal	Community vs. family observation	X	X	X
Aye et al. [69]	2010	Tajikistan	Household costs		X	X
Datiko et al. [84]	2010	Ethiopia	Health extension workers	X	X	X
Vassall et al. [74]	2010	Ethiopia	Collaborative TB-HIV		X	X

Table 1 continued

References	Year	Country	Interventions evaluated in study	Provider costs included	Direct patient costs included	Productivity losses included
Pichenda et al. [59][a]	2012	Cambodia	Early diagnosis and non-hospital	X	X	X
Laokri et al. [114]	2013	Burkina Faso	Household costs		X	
Yitayal et al. [71]	2014	Ethiopia	DOTS		X	X
Laokri et al. [115]	2014	Benin	DOTS		X	
Gospodarevskaya et al. [75]	2014	Bangladesh, Tanzania	DOT female community worker; DOT family		X	X

X indicates the category of cost (Provider, Direct patient, or Productivity losses)

CHW community health worker, *DOT* directly observed treatment, *DOTS* directly observed treatment—short course, *DS-TB* drug-susceptible tuberculosis, *HIC* high-income country, *LIC* low-income country, *LMIC* lower-middle income country, *MDR-TB* multidrug-resistant tuberculosis, *UMIC* upper-middle income country, *WHO* World Health Organization

[a] Both DS-TB and MDR-TB costs

[b] MDR-TB costs only

[c] Dominican Republic is an upper-middle income country

Table 2 Quality assessment: percent of papers[a,b]

	Mean number of patients in study sample[c]	Ingredient approach used for provider costs	Resource use and unit costs clearly described	Year of cost data reported	Main cost categories clearly separated	Descriptive statistics presented	Patient interviews	Methods for valuing productivity loss clearly explained	Sources for productivity losses assumptions justified
Papers with provider costs only ($n = 28$)									
HIC ($n = 15$)	307	73	60	80	73	20	NA	NA	NA
UMIC ($n = 11$)	384	100	73	91	82	9	NA	NA	NA
LMIC ($n = 1$)	1797	0	0	0	100	0	NA	NA	NA
LIC ($n = 1$)	300	100	0	100	0	0	NA	NA	NA
Papers with patient costs included ($n = 62$)									
HIC ($n = 10$)	475	89	82	82	82	45	18	82	64
UMIC ($n = 18$)	305	91	78	61	83	22	94	61	56
LMIC ($n = 16$)	345	63	94	88	81	50	94	69	50
LIC ($n = 18$)	154	73	78	78	89	33	100	56	44
All papers	324	81	76	77	80	30	83	65	52

HIC high-income countries, *LIC* low-income country, *LMIC* lower-middle income country, *NA* not applicable, *UMIC* upper-middle income countries

[a] These results are shown for each study in the Electronic Supplementary Material (Online Resources 2 and 3)

[b] Data are presented as % unless otherwise indicated

[c] Among the studies with patient-level data

3.3.2 Provider Costs

The ingredient approach, which entails determining resource quantities and unit costs separately, is generally viewed as the most robust and transparent method for provider cost estimation [27]. This approach was transparently used in 54 of the 67 studies that included provider costs. While the method may also have been partly used in the remaining 13 studies, techniques were not clearly described, and resource quantities and unit costs were not separately presented in these papers.

3.3.3 Patient-Incurred Costs

Patient interviews were conducted in 52 of the 62 studies that included a patient perspective. The mean sample size was 298 (SD 527) patient interviews, ranging from 13 patients in a US study to 3510 in the German cost-of-illness study [24, 28]. Patient interviews were more common in LICs and middle-income countries than in HICs. While ten studies from HICs included patient-incurred costs, interviews were only conducted in two of these, a study from Holland assessing costs among immigrant TB patients and an economic evaluation of the Russian TB treatment scheme and short-course chemotherapy [29, 30]. In the other eight studies, productivity losses (and transport costs in a study from South Korea [31]) were the only type of patient costs included and these were estimated without data from interviews.

Methods used for estimating productivity losses varied in six different ways in the 51 papers that included these: (1) patients were interviewed about their loss of income ($n = 15$); (2) patients were interviewed about productive time lost and on their income before falling ill; productivity losses were then calculated by multiplying mean income across the patient sample with reported time loss ($n = 12$); (3) patients were interviewed about productive time lost, which was multiplied by an official wage rate ($n = 11$); (4) assumptions were made about the length of time patients were not able to work, which was valued using an official wage rate ($n = 7$); (5) a value was placed on death based on average lifetime income or GNI per capita, which was multiplied by estimated life-years lost ($n = 4$); and (6) methods were not clear ($n = 2$). Across the 51 studies, only

Table 3 Mean drug-sensitive and multidrug-resistant tuberculosis provider treatment costs according to country income group[a]

Income group	Hospitalisation	Outpatient visits	Drugs	Diagnostic and monitoring tests	Other[b]	Total[c]	SD[d]
DS-TB							
HIC ($n = 19$)	11,283 (8)	1471 (5)	1392 (6)	961 (7)	3413 (5)	14,659 (19)	13,594
UMIC ($n = 19$)	380 (5)	218 (10)	107 (14)	69 (11)	386 (9)	840 (19)	1105
LMIC ($n = 10$)	215 (4)	75 (6)	39 (6)	48 (8)	25 (5)	273 (10)	212
LIC ($n = 11$)	128 (2)	61 (5)	49 (8)	19 (3)	50 (8)	258 (11)	352
All income groups (papers = 58[e])	4909 (19)	396 (26)	329 (32)	453 (26)	744 (27)	6667 (59)	10,105
Proportion, %	73.6	5.9	4.6	4.1	11.7	99.9	
MDR-TB							
HIC ($n = 10$)	53,078 (10)	18,720 (7)	19,887 (8)	1201 (6)	1841 (3)	83,365 (10)	64,825
UMIC ($n = 7$)	6056 (2)	622 (3)	2052 (6)	350 (5)	823 (5)	5284 (7)	3420
LMIC ($n = 1$)	207 (1)	218 (1)	2930 (1)	397 (1)	52,567 (1)	6313 (1)	NA
LIC ($n = 1$)	NI	NI	NI	NI	NI	1218 (1)	NA
All income groups (papers = 18[f])	41,776 (13)	12,102 (11)	11,623 (15)	779 (12)	1356 (9)	46219 (19)	61,027
Proportion, %	61.8	17.9	17.2	1.2	2.0	100.1	

Data are presented as US$, year 2014 values (number) unless otherwise indicated

DS drug susceptible, *HIC* high-income country, *LIC* low-income country, *LMIC* lower-middle income country, *MDR* multidrug-resistant, *NA* not applicable, *NI* cost not itemised, *TB* tuberculosis, *UMIC* upper-middle income country

[a] These are shown for each study in the Electronic Supplementary Material (Online Resources 4–7)

[b] Other provider costs include start-up costs, treatment supervision, staff salary and training, advocacy, adverse effects, contact tracing, supplies and transportation; or in some papers, where costs were not disaggregated, the total treatment costs to the provider, including supervision, training, supplies and drugs

[c] Total ≠ sum of categories because some papers did not itemise costs and only reported total costs

[d] Vassall et al. [46] (2002) presented two LMIC studies (Egypt and Syria) in one paper

[e] Floyd et al. [55] (2012) presented two HIC studies (Estonia and Russia) in one paper

[f] Standard deviation for total mean provider treatment costs

Table 4 Mean drug-sensitive and multidrug-resistant tuberculosis direct patient costs and productivity losses according to country income group[a]

Income group	Clinic visits and clinical tests user fees	Drugs	Transport	Other[b]	Total direct costs[c]	SD[d]	Productivity losses	SD[e]
DS-TB								
HIC ($n = 6$)	107 (1)	NI	260 (1)	379 (1)	373 (2)	106	2801 (6)	2018
UMIC ($n = 19$)	221 (9)	62 (4)	120 (13)	491 (12)	603 (18)	868	600 (12)	847
LMIC ($n = 17$)	55 (9)	21 (7)	9 (4)	47 (10)	84 (17)	90	238 (11)	320
LIC ($n = 19$)	49 (13)	38 (5)	45 (10)	96 (16)	155 (19)	164	248 (14)	266
All income groups (papers = 53[f, g, h])	101 (32)	36 (16)	82 (28)	212 (39)	432 (36)	544	700 (43)	1229
Proportion, %	23.3	8.5	19.1	49.1	100.0			
MDR-TB								
HIC ($n = 5$)	CNI	CNI	21 (1)	CNI	21 (1)	NA	49,204 (5)	51,216
UMIC ($n = 2$)	12 (2)	NI	178 (2)	470 (2)	660 (2)	394	3532 (2)	4578
LMIC ($n = 1$)	909 (1)	NI	NI	707 (1)	1616 (1)	NA	CNI	NA
LIC ($n = 1$)	103 (1)	NI	18 (1)	285 (1)	406 (1)	NA	1256 (1)	NA
All income groups (papers = 9)	259 (4)	NI	99 (4)	483 (4)	672 (5)	621	28,260 (8)	45,605
Proportion, %	30.8	0.0	11.7	57.4	99.9			

Data are presented as US$, year 2014 values (number) unless otherwise indicated

CNI cost not included, *DS* drug susceptible, *HIC* high-income country, *LIC* low-income country, *LMIC* lower-middle income country, *MDR* multidrug-resistant, *NA* not applicable, *NI* cost not itemised, *SD* standard deviation, *TB* tuberculosis, *UMIC* upper-middle income country

[a] These are shown for each paper in the Electronic Supplementary Material (Online Resources 4–7)

[b] Other patient costs typically include direct medical costs (non-TB drugs, hospitalisation) and direct non-medical costs (food, drink, vitamins, traditional medicine, and accommodation), or in some papers, where costs were not disaggregated, the total costs during pre-diagnosis, diagnosis, intensive treatment and continuation treatment phases

[c] Total ≠ sum of categories because some papers did not itemise costs and only reported total costs

[d] Mauch et al. [68] (2013) presented one UMIC study (Dominican Republic) and two LMIC studies (Ghana and Vietnam) in one paper

[e] Vassall et al. [46] (2002) presented two LMIC studies (Egypt and Syria) in one paper

[f] Gospodarevskya et al. [75] (2014) presented two LIC studies (Bangladesh and Tanzania) in one paper

[g] SD for total mean patient costs

[h] SD for mean productivity losses

65 % clearly explained the methods used for productivity losses, and 52 % justified the sources used for these estimates.

3.4 Mean Costs Per Patient

Mean provider and patient-incurred costs per patient are summarised in Tables 3 and 4 according to country income groups. These data are presented for each study in the ESM (Online Resources 4–7).

3.4.1 Drug-Susceptible (DS) Tuberculosis (TB) Provider Costs

DS-TB provider costs were positively correlated with GNI per capita ($r = 0.73$, $p < 0.001$). A scatterplot illustrates the relationship (Fig. 2). Mean DS-TB treatment costs per patient were 57 times higher in HICs [US$14,659 (SD 13,594)] than in LICs [US$258 (SD 352)]. A high degree of variability was observed in income group cost values, with the SD being almost as large as the mean provider costs in HICs and larger for LICs.

3.4.1.1 Hospitalisation and Outpatient Care Across all 59 studies, hospitalisation accounted for 74 % of all DS-TB provider costs (Table 3). Hospitalisation accounted for 63 % in HICs (US$11,283), 51 % in LMICs (US$215) and LICs (US$128), but only 12 % in UMICs (US$380). However, within the income groups, the proportion of hospitalisation costs varied widely between studies, with 2 % for an unreported number of hospital days in a public-private sector implementation scenario in India to 81 % in a study on DOT in Texas, USA, with 23 hospital days [32, 33]. Among LMICs, India consistently had the lowest costs for hospitalisation and the other cost categories [32, 34]. In LMIC costs, Ukraine had the highest hospitalisation and outpatient costs, at approximately twice the average income group costs [35]. Only two of the 11 LIC studies

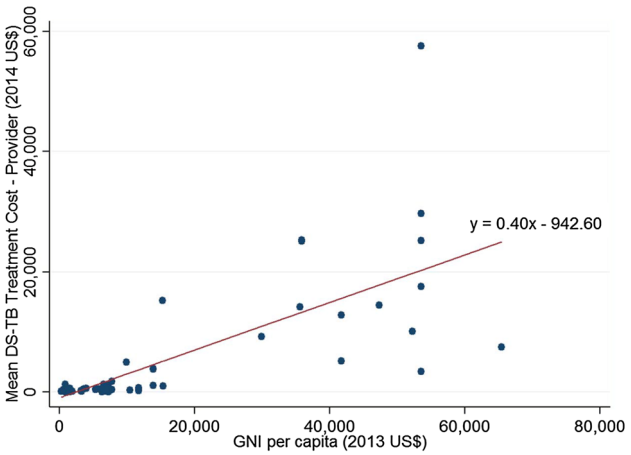

Fig. 2 Mean tuberculosis provider treatment costs per patient (US$, year 2014 values) according to GNI per capita ($US, year 2013 values)

reported hospitalisation costs, with US$75 (60 %) in Malawi [36], and US$181 (50 %) in Uganda [37].

Mean outpatient treatment costs were 12 times less than hospitalisation costs and accounted for only 6 % of total costs. However, the importance of outpatient costs varied substantially among country income groups. In HICs, only five of 19 studies reported any outpatient costs [24, 38–41]. Of the ten UMIC studies that reported these costs, Argentina and South Africa had the lowest values of around US$20 per patient [42–44] and Botswana the highest at US$658 per patient [45]. Egypt was an outlier among the LMICs, reporting outpatient costs of US$187 [46], which was 15–25 times more than in Pakistan (US$11) and India (US$6) [32, 47]. In LICs, five studies reported outpatient costs, with a mean of US$61.

3.4.1.2 Drugs Costs of DS-TB drugs were, on average, 5 % of total costs, but varied widely between settings, from a mean of US$49 across LICs to US$1392 in HICs. Within the HICs, drug costs were US$311 in a US study [38], US$654 in another US study [33], and as much as US$4055 for an unstated combination of DS-TB and MDR-TB drugs in Italy [48]. Within this group of countries, it is difficult to discern whether drug costs have decreased or increased over time because only six of the 19 studies presented disaggregated drug costs. In upper middle-income South Africa, drug costs appear to have decreased from US$46 in 1994 [49] to US$3 in 2003 [42]. In LMICs and LICs, drug costs were lowest in India at approximately US$15 between 2002 and 2005 and highest in Uganda at US$166 in 1992 [32, 34, 50]. Without these outliers, mean drug costs in LMICs and LICs were US$51 and US$33, respectively, with data from between 1992 and 2007.

3.4.1.3 Diagnostics and Monitoring Tests Unlike the costs of drugs and hospitalisation, mean costs per patient for diagnostics and monitoring tests were relatively similar across income groups. In the UK, costs of TB tests in a population of healthcare workers were US$157 [51]. In three US studies on urban DOT programmes by Miller et al. [52], Burman et al. [38] and Weis et al. [33], costs per patient were reported as US$124, US$635 and US$1505, respectively. In the Miller et al. [52] study, only one acid-fast bacilli (AFB) smear and culture was included, while the other studies typically included at least two chest X-rays, four sputum cultures and one tuberculin skin test (TST). Burman et al. [38] additionally included five serum bilirubin tests and five aspartate aminotransferase tests. Interferon-Gamma Release Assay was used instead of sputum culture in the UK study by Eralp et al. [51]. Although this review excluded latent TB, some studies presented aggregated costs for diagnosis of latent TB together with tests for diagnosis and monitoring of active TB, in which case the cost of the latent TB tests could not be excluded.

Mean diagnostics and monitoring costs in UMICs were US$69, with Cuba being the only outlier at US$289 in 2002 [53]. A Sudanese study that compared the costs of managing HIV-positive and HIV-negative TB patients reported the largest monitoring costs within this income group at US$135 per patient [54].

3.4.2 Multidrug-Resistant-TB (MDR-TB) Provider Costs

Mean provider costs for MDR-TB treatment were US$83,365 (SD 64,835) for the ten included studies and far less for the seven UMICs at US$5284 (SD 3420). A large variation in costs was observed for both groups; measures of spread were not available for the LMIC and LIC groups as there was only one study included in each of these categories.

3.4.2.1 Hospitalisation and Outpatient Care MDR-TB hospitalisation represented the highest proportion of provider costs in HICs, contributing to 64 % (Table 3). Even though patients were hospitalised for an average of 192 days in Estonia, hospitalisation represented only 50 % of total costs at US$8007 [55]. In the USA Burman et al. [38] reported hospitalisation costs four times higher than those reported by Rajbhandary et al. [28] because the length of stay decreased from an average of 90 days in 1994 to 28 days in 2000 (US$181,909 vs. 41,612) [28, 38]. The mean length of MDR-TB hospitalisation in the USA in 2010, as reported by Marks et al. [56], remained 28 days, but the cost, US$87,619, more than doubled the 2000 value calculated by Rajbhandary et al. [28].

In Russia, hospitalisation and outpatient care accounted for 37 and 3 %, respectively, if treatment is delivered according to WHO guidelines [55]. This Russian study reported an average of 321 days in hospital, costing US$6493, which was the second lowest value in the HIC group. In South Korea, hospitalisation costs were the least per patient (US$3521), but the length of stay was only 8 days, by far the shortest stay for any HIC or UMIC [31].

In South Africa, Schnippel et al. [57] reported a mean hospitalisation period of 105 days, contrasting greatly with Pooran et al. [25], who estimated costs according to prevailing guidelines, which recommended complete outpatient care for smear-negative MDR-TB patients [25, 57]. Pooran et al. [25] estimated that surgery, which we presented as a hospital cost, amounted to US$97 (2 %) per patient, while outpatient visits totalled US$712 (17 %). Schnippel et al. [57] reported no outpatient costs, but hospitalisation accounted for 95 % of total MDR-TB costs (US$12,666). Both treatment scenarios are present in South Africa, but only 10 % of MDR-TB patients are thought to require hospitalisation [25].

Only the Philippines were represented in the LMIC group. In a DOT short-course plus pilot programme, hospitalisation for 7 days amounted to 3 % and outpatient visits to 4 % of total costs [58]. In the LIC group, no disaggregated data were included for the one country represented, Cambodia, but the total MDR-TB cost was the lowest value of any country at US$1218 [59].

3.4.2.2 Drugs In Estonia, 18 months of first- and second-line drugs amounted to half of the hospitalisation costs (192 hospital days) [55] (ESM Annex 5). The 2004 US study by Rajbhandary et al. [28] did not separately report costs of drugs, tests and personnel, but the 1997 US study by Burman et al. [38] calculated MDR-TB drug costs as amounting to approximately US$12,000 per patient (6 %) [28, 38].

3.4.2.3 Diagnostic and Monitoring Tests Mean costs per MDR-TB patient for diagnostics and monitoring tests were US$779 (1 %) across the 12 studies reporting these data. This accounted for less than 1 % of total treatment costs in both the USA and the UK [23, 38]. In the South Korea study, diagnostics and monitoring test amounted to 24 % of total costs [31]. The costs reported in the UK were for drug monitoring only, while Estonia, Germany, South Korea and the USA (Burman et al. [38]) each included at least one drug susceptibility test, 13 sputum culture tests and a combination of audiograms (USA), sputum smear tests (Estonia), X-rays, liver function and blood count tests.

The mean costs of diagnostics and monitoring tests were US$350 in UMICs, ranging from US$82 in China to US$1013 in South Africa [25, 60]. With the exception of the South African study by Schnippel et al. [57], all studies reported at least eight sputum smear tests. Costs of sputum culture tests were included in all studies, with for instance three tests per patient in 24 months in Thailand and 18 tests per patient in 18 months in Peru [61, 62]. Costs of at least four chest X-rays per patient were included in all UMIC studies, except in South Africa where only one chest X-ray was included and all patients were hospitalised during the intensive phase of treatment [57]. Drug-susceptibility tests were reported in Thailand and in the two studies from South Africa [25, 57, 61]. In the only LMIC, the Philippines, costs of 34 smear tests, 27 culture tests, two drug-susceptibility tests and three X-rays were estimated at US$397 per patient, equivalent to 6 % of total costs [58].

3.4.3 DS-TB Patient Costs

Across all 61 studies, in 57 papers, mean direct costs incurred by patients was US$432 (SD 544), ranging from US$4 in Egypt to US$3525 in China (Table 4) [46, 63]. Approximately half of patient costs, the highest proportion, was recorded in the 'other' category, which mainly consisted of non-TB drugs and food while hospitalised, or aggregated direct (medical and/or non-medical) patient costs. User fees comprised 23 %, drugs 9 %, and transportation 19 % of total costs. In contrast to provider costs, there was no clear relationship between patient-incurred costs and GNI per capita. UMIC studies reported the highest mean patient costs (US$603), followed by two HIC studies (US$373), LICs (US$155), and LMICs (US$84).

3.4.3.1 User Fees The user fees category comprised costs incurred by patients for medical consultations or examinations when attending clinics or other health facilities during treatment, or for diagnostic or monitoring tests. Mean user fees payments were similar in high-income Netherlands and upper-middle income Botswana at around US$105. In the Netherlands, user fees accounted for 22 % of patient payments, but only for 11 % in Botswana [29, 45].

Patients in upper-middle income Mexico and low-income Haiti paid the highest user fees of US$344 and US$299, respectively [64, 65]. The greatest proportion of total direct costs spent on user fees were in India (80 %), Kenya (69 %), South Africa (68 %) and Tanzania (66 %) [34, 42, 66, 67]. In general, user fees appeared to constitute the greatest proportion of patient costs in LMICs and smallest in UMICs.

3.4.3.2 Drugs No out-of-pocket payments were paid for drugs in HICs. Patients in Vietnam paid the least for drugs (US$1), followed by the patients in the Dominican Republic (US$5) [68]. Studies in Tajikistan and China

reported the highest payments of US$126 and US$118, respectively [69, 70]. In most LMICs, drug expenses were around US$20, ranging between US$1 and US$63. Only five studies reported payments for drugs in LICs, ranging from US$4 in Ethiopia to US$126 in Tajikistan [69, 71].

3.4.3.3 Transportation The only HIC study that reported transportation costs was in Russia, with US$260 [30]. Transportation costs in UMICs accounted for 1 % of direct costs in the Dominican Republic and as much as 85 % in Malaysia [68, 72]. In LMICs, patients paid an average of US$9, accounting for between 2 and 28 % of total direct costs. Ten of the 19 LIC studies reported transportation costs, accounting for 80 % of direct costs in Bangladesh and between 22 and 44 % in Ethiopia, Tajikistan and Tanzania [67, 69, 71, 73–75].

3.4.3.4 Productivity Losses Time lost due to seeking treatment and being ill with DS-TB was reported as 81 days in the Netherlands, 60 days in Thailand, 30 days in Italy, 25 days in the USA, 14 days in Malaysia, and 50 % disabled for 2 months in Haiti [29, 64, 72, 76, 77].

DS-TB productivity losses increased with increasing GNI per capita, but amounts varied widely within country income groups (SD 1229) with a mean loss of US$700 per patient for 43 studies. In HICs, values varied from US$450 in Russia to US$6246 in Italy [30, 78]. In UMICs, the range was between US$46 in Argentina and US$3048 in China [44, 63]. In LMICs, an Indonesian study reported productivity losses of US$12 per patient compared with US$996 in Vietnam [68, 79]. In LICs, costs were US$11 in Bangladesh versus US$775 in Tajikistan [69, 73]. Studies from similar countries also showed quite different productivity loss estimates, such as US$11 and US$332 in Brazil [80, 81], US$52 and US$636 in India [82, 83], US$9 and US$200 in Ethiopia [71, 84], and US$18 and US$825 in Tanzania [67, 85].

3.4.4 MDR-TB Patient Costs

Mean direct costs incurred by MDR-TB patients were US$672 (SD 621) across five studies (Table 4). The 'other' category constituted 57 % of total costs, which included food, non-TB medication, follow-up tests and ventilation improvements to family homes. No patient costs were reported for MDR-TB drugs in any studies.

3.4.4.1 User Fees Similar to DS-TB user fees, MDR-TB user fees incurred by patients were for medical consultations or examinations at health facilities or to obtain diagnostic or monitoring tests. The mean MDR-TB user fees were US$259, which were almost three times higher than for DS-TB. The Philippines reported the highest user fees at US$909, accounting for 56 % of all direct MDR-TB patient costs [58]. The user fees in low-income Cambodia (US$103) were around eight times more than in UMICs (US$4–20) [59]. No user fees were reported in HICs.

3.4.4.2 Transportation Mean transport costs incurred from receiving DS-TB treatment were US$99 across the four studies. The highest costs were reported in the two UMICs, Brazil and Ecuador, at US$90 and US$266, respectively [81, 86]. Studies from high-income South Korea and low-income Cambodia each reported around US$20 per patient [31, 59].

3.4.4.3 Productivity Losses Productivity loss amounted to US$28,260 per patient across the eight studies that included these values. As with DS-TB, productivity losses increased with income group, ranging from US$295 in Brazil to US$136,802 in the USA and an overall SD of US$45,605 [56, 81]. Only three studies, two from the USA and one from Germany, clearly stated productive time lost for MDR-TB, which was 6, 24 and 8 months, respectively [38, 56, 87].

4 Discussion

Costs of TB treatment vary substantially globally, with LICs adopting comparatively low-cost ambulatory methods of treatment delivery and benefitting from lower drug regimen prices than HICs. Provider costs are strongly correlated with GNI per capita. The cost of treating DS-TB from the provider perspective ranged from US$45 in Zimbabwe to US$57,559 in one of the US studies [88, 89]. Provider costs of MDR-TB treatment are substantially higher than those for DS-TB and varied from US$1218 in Cambodia to US$204,876 in the USA [38, 59]. It should be noted that many MDR-TB patients are primarily infected with transmitted MDR-TB strains and do not acquire the disease through misuse of their first-line regimen, so on the individual level these are not always alternative treatments. However, at a population level, the origins of MDR-TB lie in the misuse of TB drugs, and the improved delivery of first-line treatment can potentially reduce the level of comparatively high MDR-TB treatment costs [90, 91].

We also observed substantial cost variation within country income level groups. In the case of DS-TB, very low comparative costs were observed in LICs and LMICs using community-based models of care. While this suggests that devolvement of TB treatment at the community level may be efficient, the cost of community provision of TB treatment depends strongly on whether community workers are paid, and the valuation of their time. In the case of MDR-TB treatment, the variation in costs within country income level groups was also substantial. Lower

cost treatment within groups was observed where primarily ambulatory models of care are adopted, with hospitalisation being a major driver of total cost. Across DS-TB treatment, there is a clear reduction in costs over time due to the extent of hospitalisation decreasing as countries moved towards ambulatory DOTS, although in countries such as Germany, Spain, the USA and Latvia high hospitalisation costs were still reported between 2010 and 2013 [24, 41, 52, 65] (DS-TB patients were hospitalised for an average of 115 and 72 days in Latvia and the USA, respectively). Care should therefore be taken when using costs from this review to estimate current costs for any one setting to ensure that the cost applied reflects the current mix of hospitalisation and ambulatory treatment. In particular, while the majority of MDR-TB treatment is currently provided in hospital, several countries are now piloting ambulatory models of care, so these costs may fall in coming years.

The costs of DS-TB drugs were reported in 34 studies. When compared with DS-TB treatment, drug costs remain a substantial component of MDR-TB treatment, and are particularly high in countries using individualised MDR-TB regimens and/or with high levels of extensively drug-resistant (XDR) TB, or not accessing concessionary prices. In the Philippines, MDR-TB drugs accounted for 46 % of total provider costs in 2006 [58].

While there has been substantial research on direct costs incurred by TB patients in low- and middle-income countries, these were only included in two HIC studies, possibly highlighting a lesser interest in the poverty impact of TB in countries with higher income levels and more comprehensive social protection and health insurance systems. Nevertheless some patient costs were found. Kik et al. [29] reported that immigrant DS-TB patients in Holland paid, on average, US$486 to receive treatment [29]. In contrast, in poorer countries, substantial attention has been paid to patient-incurred costs. Although TB treatment is provided free in many settings, it incurs a high economic burden, either through out-of-pocket/direct payments (in some settings 'under-the-counter' payments), but also through substantial productivity loss. DS-TB direct patient costs were, on average, US$603 in UMICs, US$84 in LMICs and US$155 in LICs. The high values in LICs were noted by many studies to be catastrophic, and are primarily driven by costs captured in the 'other' category, which included out-of-pocket payments made by patients and their social networks for non-TB drugs, food and specialised diets, traditional healers, and accommodation, among other costs. The respective direct patient costs for MDR-TB patients were US$660, US$1616 and US$406. There was substantially less evidence on the patient cost of MDR-TB. The few studies found highlight the potential of MDR-TB to have a substantially higher catastrophic impact than DS-TB. More research is required in this area, particularly to better understand how these costs are incurred over time, and how patient cost is affected by different levels of hospitalisation.

Well defined estimates of productivity losses were included in 81 % of DS-TB papers and 75 % of MDR-TB papers. As a proportion of DS-TB patient costs, productivity losses comprised 96 % in HICs, 68 % in UMICs, 98 % in LMICs and 74 % in LICs. The methods used to estimate productivity loss vary widely; nevertheless, it can be seen that this is an important component of the economic impact. Therefore, by excluding this cost, the majority of reported TB patient costs are substantially underestimating the impact of TB on patients. The difference in methodological approaches taken also makes it challenging to draw general conclusions about the key drivers of patient-incurred costs, and for analysts to use this review to extrapolate patient costs across settings or over time. It is therefore recommended that, although the costs presented in this review provide some guidance, the measurement of setting-specific costs that are comprehensive may still be required in economic analyses of TB control interventions for some time to come.

We captured 90 papers in all income groups. The review of economic evaluations in TB control published by Verdier et al. [4] in 2011 included 118 papers from HICs only. This large volume was due to the inclusion of mathematical modelling papers and multiple papers using the same primary data. For MDR-TB, 16 countries were included in our review, compared with only four countries captured by Fitzpatrick and Floyd in 2012 [7]. Quality assessment is crucial for systematic reviews, but only three of the previous reviews completed this [2, 4, 5]. Using the CHEERS and TBCTA guidelines, we identified several key methodological issues that suggest further standardisation is required in order to further develop a set of costs that can be used globally. First, even when the ingredient approach to costing was used, cost items were insufficiently separated in several studies, hindering our ability to observe cost drivers and analyse trends such as drug costs over time. The lack of reporting of disaggregated costs was also an issue for patient-incurred costs. Second, methods for calculating productivity losses were not clearly explained in more than one-third of the studies that included these costs, and disparate approaches were used between studies, which led to widely different estimates within the same country. The lack of standard methods for identification, measurement and valuation of productivity losses have frequently been acknowledged in the wider literature on the measurement of costs, and minimum standardised approaches are urgently required to enable comparisons across settings, particularly in light of the increased global attention on social protection [13]. Third, even though cost

data were collected from a relatively large number of patients, insufficient statistical analyses were undertaken in most studies. In addition to mean values, descriptive statistics, such as SD, minimum and maximum values must be presented and any outliers in the patient sample should be highlighted.

5 Conclusion

In summary, literature on the costs of DS-TB treatment to both providers and patients is extensive. However, evidence is still scarce on the costs of treating MDR-TB, and how these costs may vary by mode of delivery and setting. MDR-TB treatment is rapidly evolving; a recent global guideline change recommends Xpert® MTB/RIF diagnostics, which is more sensitive and also detects rifampicin resistance, therefore identifying more cases. In addition, recent global investment in further testing of existing MDR-TB drugs as well as development of new drugs has been substantial. More data are urgently required to estimate the budgetary impact of these changes and to support economic evaluations of new MDR-TB control approaches.

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