SYSTEMATIC REVIEW

Cost-effectiveness of treating multidrug- and extensively drug-resistant tuberculosis: A systematic review

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Abstract

Objective: Tuberculosis (TB), along with the human immunodeficiency virus, is one of the leading causes of death from infectious diseases. Its prevalence has rendered the treatment of drug-resistant TB a major public health problem that threatens the progress made in TB care and control worldwide. Our objectives were to conduct a systematic review of the cost-effectiveness of treatment for multidrug-resistant and extensively drug-resistant TB (MDR-TB/XDR-TB) and to synthesise available data from scientific research.

Methods: Using English keywords, we searched for papers over reputable databases, such as Scopus, PubMed, Cochrane and Google Scholar, from Jan. 23 to Mar. 23, 2019.

Results: The search and screening yielded 13 articles, whose results were extracted and reviewed to draw conclusions on the cost-effectiveness of MDR-TB/XDR-TB treatment. The data extraction table used to cull and categorise the results comprised the characteristics of a given study, as well as its objectives, the perspectives used to guide the investigation, methods and results (outcome, sensitivity analysis). The measured outcome was the incremental cost-effectiveness ratio.

Conclusion: The review indicated that MDR-TB/XDR-TB treatment can be very cost-effective in countries with low to high incomes, regardless of whether minimal or considerable disease burdens exist.

Keywords: Cost-effectiveness, economic evaluation, multidrug-resistant tuberculosis, extensively drug-resistant tuberculosis, systematic review. (JPMA 69: S-131 (Suppl. 2); 2019)

Introduction

Tuberculosis (TB) drug resistance is a major public health problem that threatens the progress achieved in global TB care and control.[1] In particular, three major categories that require global surveillance and treatment are multidrug-resistant, extensively drug-resistant and rifampicin-resistant tuberculosis (MDR-TB, XDR-TB and RR-TB, respectively).[2] In 40 countries that grapple with considerable burdens from TB, MDR-TB or both, the proportion of new MDR-TB cases increased slightly in 2010 to 2015. Global statistics showed that the year 2017 saw the identification of 160,684 cases of MDR-TB and RR-TB (up from 153,119 in 2016) and the enrolment of 139,114 cases in treatment (up from 129,689 in 2016).[2]

As a response to the above-mentioned problems, the World Health Organization (WHO) established the Sustainable Development Goals and the End TB Strategy to provide a framework for national and international efforts intended to eliminate the TB epidemic over the period 2016 to 2030.[2] An additional initiative was the widespread implementation of directly observed therapy (DOT), whose efficacy was supported by a cost-effectiveness analysis (CEA) in 1997.[3] Despite the substantial initial costs incurred from DOT, it is a more practical strategy than self-administered treatment because it achieves a higher cure rate after primary intervention and thereby reduces the treatment costs associated with therapeutic failure and acquired drug resistance. In the past few years, studies have been conducted on the cost-effectiveness of MDR-TB treatment, related interventions and care models. Accordingly, we performed a systematic review to update evidence on anti-TB drug resistance as the data contained in previous studies can serve as useful guidelines in the design of policies for the effective management of MDR-TB.

Methods

A systematic search for studies that delved into the cost-effectiveness of treating MDR-TB or XDR-TB was conducted from January 23 to March 23, 2019 in Scopus, MEDLINE (using PubMed), Google Scholar and Cochrane. The earliest research identified was

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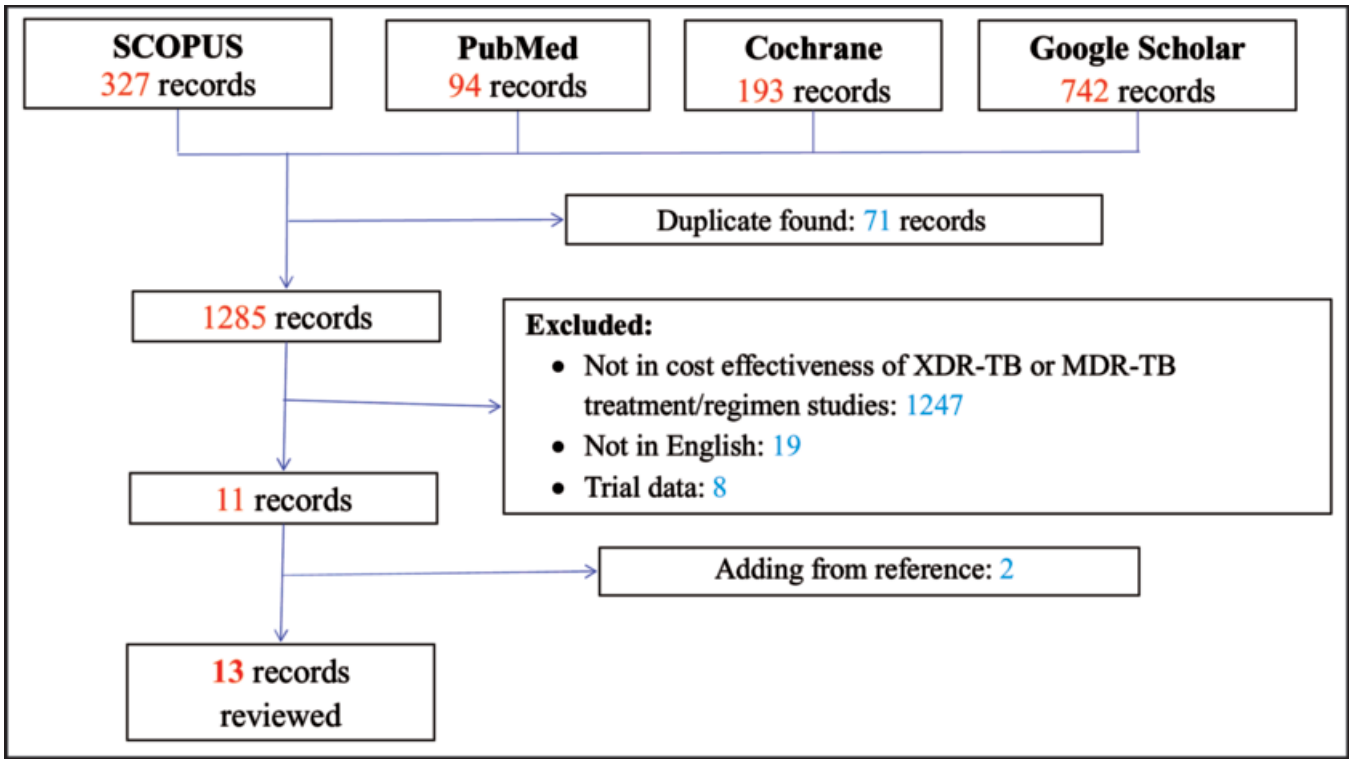

Figure-1: Flow chart of abstract and article selection.

carried out in 1997; thus, the search period chosen was 1997 to March 2019. For the search, the terms 'multidrug-resistant tuberculosis', 'extensively drug-resistant tuberculosis' and 'cost-effectiveness' were combined with the words 'treatment' and 'regimen'. The search techniques implemented were the use of connectives (AND, OR) and field specifications (title, abstract, all fields), checking for duplication and a comparison between articles and criteria. The PubMed database automatically links to MeSH terms and subheadings. The references mentioned in the preliminarily identified articles were checked and added to the final sample of papers in case they pointed to relevant studies that were missed in the database search.

Titles, abstracts and full texts were screened by four reviewers divided into two groups, with consensus aimed for at each stage of the screening. The main reviewer was consulted to resolve disagreements in each group and between the two groups. All cost-effectiveness or economic evaluation articles on drug-resistant TB treatment were included in the review. The exclusion criteria were as follows: studies wherein no cost-effectiveness or economic evaluation of MDR-TB or XDR-TB treatment was conducted, research on trial regimens and those published in non-English journals. The search and selection process is illustrated in Figure-1.

Data Extraction

A data extraction table was used to filter the insights required for the review. The table consisted of the characteristics of a given study, the objectives pursued in the research, the perspectives that guided the investigation, the methods adopted by the researchers and the results derived (outcome, sensitivity analysis). The measured outcome was the incremental cost-effectiveness ratio (ICER), which was determined using two main approaches, namely, cost-effectiveness and cost utility analyses. The results of the reviewed studies were compared using an instrument similar to the tool employed to assess the cost-effectiveness of MDR-TB or XDR-TB treatment. We were also concerned about what care model was used in treatment and when a given study was conducted.

For each of the reviewed studies, total costs were summarised on the basis of direct and indirect expenditures. Direct treatment costs covered many items, including medical expenses (TB drugs, hospitalisation,

laboratory tests, medical services) and non-medical expenses (transportation, meals, accommodations, devices). Indirect costs were defined as the value of paid and unpaid production losses due to the time spent seeking treatment or being ill or premature mortality.

Results

A total of 1,285 articles (excluding duplicates) were found in the search (Figure-1). Out of these studies, 1,247 did not enquire into the cost-effectiveness of MDR-TB and XDR-TB treatment, 19 were not written in English and 8 were trial studies. These were therefore excluded from the review, leaving us with 11 articles, to which 2 more that were determined from the survey of the studies' references were added. Table-1 indicates that 10 of the studies involved CEA, 4 carried out cost-utility analysis (CUA) and 1 performed justice-enhanced CEA (JE-CEA).

Experience and data on the cost-effectiveness of MDR-TB regimens were limited until 2005, after which similar studies on the cost-effectiveness of DOT were conducted in low- and middle-income countries, such as Ukraine, Africa and nations in Southeast Asia.[4-6] These investigations shed some light on the treatment of MDR-TB patients via short-course DOT (DOTS) or DOTS-Plus, reporting that individual drug regimens may be feasible, relatively effective and cost-effective in low- and middle-income countries. For chronic TB patients, treatment with second-line drugs intended for highly MDR-TB can be feasible and cost-effective in middle-income countries, provided that a strong TB control programme is in place; a typical example is discussed in a study conducted in Peru in 2002.[7]

Interest in reducing the time devoted to MDR-TB treatment and improving its effectiveness has prompted a number of initiatives to treat patients with shorter regimens or interventions featuring a combination of other drug classes. Amongst the reviewed studies, nine that were conducted from 2015 to 2019 revolved around the cost-effectiveness of incorporating bed aquiline into treatment regimens for MDR-TB in Germany,[8] the Republic of Korea,[9] China[10] and other high-burden countries. The results of these studies suggested that in most countries, bed aquiline combined with a standard regimen is a more practical MDR-TB (and XDR-TB) treatment than standard regimens alone.

Tables-2 to 5 present data on the ICER per disability-adjusted life year (DALY) or per quality-adjusted life year (QALY), as extracted from the reviewed studies.

The WHO's DOTS strategy for TB and MDR-TB patients was piloted in two Ukrainian cities, Mariupol and Kyiv, which both showed improvement in terms of cost-effectiveness. The summarised results for these countries are shown in Tables-2 and 3. The cost per case cured declined by more than 50% in Mariupol (from US$2,729 to US$1,333) and by 62% in Kyiv (from US$6,504 to US$2,414). The cost for each DALY for the new method ranged from US$55 to US$100 in 2009.[6] The DOTS for smear-negative and extra-pulmonary cases and the DOTS-Plus treatment for cases of multidrug resistance were also highly cost-effective in

Table-1: Number of publications using different methods.

Method	Number of publication
CEA	10
CUA	4
CEA/JE-CEA	1

CEA: Cost-effectiveness analysis
CUA: Cost utility analysis
JE-CEA: Justice enhanced cost effectiveness analysis.

Table-2: Data extraction based on ICER.

Intervention vs. comparator	Novel treatment compared with standard regimen for drug-resistant TB patients	Implementation of DOTS for TB and MDR-TB patients in Kyiv and Mariupol, Ukraine	Treatment with second-line drugs compared with first-line medications for chronic TB with high multidrug resistance in Peru	Comparison of the clinical, socioeconomic and demographic characteristics of patient cohorts in Estonia and Russia treated before and after the introduction of MDR-TB treatment in accordance with WHO guidelines	Four treatment strategies: (1) standard WHO-recommended treatment strategy, (2) addition of EMB throughout a 6-month treatment of new cases, (3) use of a strengthened standardised retreatment regimen and (4) use of a standardised MDR-TB treatment upon failure of initial treatment Treatments administered to smear?positive TB patients
Result	Cost per life year gained for novel treatment: US$1,000 (2017)[11]	Cost per DALY for new method: US$55 to US$100 (2009)[6]	Mean cost per DALY gained: US$211 (1997-1999), US$484 (2001)[7]	Cost per DALY averted by treatment: US$579 in Estonia and US$429 in Tomsk Oblast (2012)[12]	Cost per DALY gained: US$2,857 to US$5,745 (2014)[13]

Table-3: Data extraction based on ICER (cont.).

Intervention vs. comparator	Comparison of the cost-effectiveness of five care models on the basis of actual implementation and individual patient data on MDR-TB patients in KwaZulu-Natal, South Africa	Bedaquiline plus standard regimen compared with standard regimen alone for patients with MDR-TB or XDR-TB in Korea Treatment decision based on approved indications of bedaquiline	Deltyba plus BR compared with a five- drug BR regimen alone for MDR-TB patients (38-years old on average) in Germany	Second-line drug regimen following first-line treatment compared with first-line drugs only for MDR-TB patients in Peru	
Result	Mobile model more effective but more costly than clinical model: ICER= US$402 (2018)[14]	Incremental cost/utility ratio: 11,638,656 KRW/QALY (2016)[9]	Addition of Deltyba™ outperformed the BR alone strategy, generating a savings of €8,177 and resulting in 2.34 QALYs (2015)[15] → ICER = -3,494	STR2 compared with DOTS: US$720 per QALY (US$8,700 per averted death) ITR1 compared with STR2: US$990 per QALY (US$12,000 per averted death) ITR2 compared with ITR1: US$11,000 per QALY (US$160,000 per averted death) (2006)[16]	
Intervention vs. comparator	Treatment in a DOTS-Plus project and individualised regimen compared with no intervention for patients admitted to the Makati Medical Center in Manila, Philippines	Comprehensive programme versus baseline programme for DR-TB patients in China	Cost and cost-effectiveness of treatments for MDR-TB patients	Treatment of smear-positive, smear-negative and extra-pulmonary cases in DOTS programmes and treatment of MDR cases in DOTS-Plus programmes for smear-positive TB patients in countries of sub-Saharan Africa and Southeast Asia Countries involved had high adult and child mortality rates	
Result	Mean cost per DALY gained via the DOTS-Plus project: US$242 (range: US$85-US$426) (2006)[5]	Cost incurred from comprehensive programme: US$639 (range: US$112-US$1,322) per DALY averted (2012)[17]	Costs per DALY averted were $US598 (I$960), $US163 (I$291), $US143 (I$255) and $US745 (I$1059), respectively, in Estonia, Peru, the Philippines and Russia (2012)[18]	New cases of smear-positive TB in DOTS programmes: $Int6-$Int8 per DALY averted in Afr-E; $Int7 per DALY averted in Sear-D In Afr-E, addition of treatment for smear-negative and extra-pulmonary cases: $Int95 per DALY averted; addition of DOTS-Plus treatment for MDR cases: $Int123 In Sear-D, costs were $Int52 and $Int226, respectively (2005)[4]	

*Standardised second-line treatment for confirmed MDR-TB cases (STR2).
* Individualised second-line drug treatment for MDR-TB following first-line failure (ITR1).
*A more aggressive version of the individualised treatment strategy (ITR2).
* Sear-D includes the following countries: Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Maldives, Myanmar, Nepal, Timor Leste.
* Afr-E includes the following countries: 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.

Afr-E and Sear-D. The costs incurred from the DOTS of smear-positive TB treatment were US$6 to US$8 per DALY averted in Afr-E and $Int in Sear-D; the treatment of negative and extra-pulmonary cases cost $Int95 in Afr-E and $Int123 in Sear-D. Supplementary DOTS-Plus in Afr-E and Sear-D cost $Int52 and $Int226 in 2005, respectively.[4] Despite these positive outcomes, however, DOTS does not always work as expected for patients with chronic TB. For example, DOTS is unavailable for chronically ill patients in health facilities in the public sector, and those seeking treatment from private facilities have an insufficient ability to pay for such intervention. As a means of addressing this problem, a pilot DOTS-Plus project was initiated in the Philippines, where the mean cost per DALY gained in 2006 was US$242 (US$85-US$426) — a value that demonstrated the cost-effectiveness of the strategy in low-and middle-income nations.[5]

The treatment of TB with second-line drugs was highly cost-effective and feasible in middle-income countries,

Table-4: Cost per DALY and GDP per capita by nation and year.

Study	Country-Year	Cost per DALY	GDP per capita (World Bank Group [US])
Ref. 12	Estonia-2012	US$579 (US$297-US$902)	US$17,421.89
Ref. 12	Russia-2012	US$429 (US$302-US$546)	US$15,434.57
Ref. 5	Philippines-2006	US$242 (US$85-US$426)	US$1,391.77
Ref. 7	Peru-2001	US$484 (US$285 -US$737)	US$1,981.24
Ref. 6	Ukraine-2009	US$55-US$100	US$2,545.48
Ref. 17	China-2012	US$639 (US$112-US$1322)	US$6,337.88

Meanwhile, the cost-effectiveness threshold as determined by WTP for one additional QALY gained varied noticeably depending on country or the region. Table 5 illustrates these variations.

Table-5: Cost-effectiveness threshold by nation.[20]

Region/Country	Cost-effectiveness threshold based on WTP
The UK	£23,000 per QALY gained
The US	US$62,000 per QALY gained
Australia	AU$64,000 per QALY gained
Taiwan	NT$2,100,000 per QALY gained
Japan	JPY5,000,000 per QALY gained
Republic of Korea	KRW68,000,000 per QALY gained

such as Peru. In the reviewed studies, two kinds of novel drugs were administered to patients. One is bed aquiline, which was used in the Republic of Korea as a supplement to the standard regimen for MDR-TB and XDR-TB treatment.[9] The results showed that the incremental cost/utility ratio was 11,638,656 KRW/QALY and that the incremental cost-effectiveness ratio was 10,822,991 KRW/life-year gained (2016).[9] The other drug used for treatment was delamanid, sold under the trade name Deltyba™, which was used in Germany as a supplement to a five-drug BR regimen. BR plus Deltyba™ treatment (€142,731) cost less than BR intervention alone (€150,909), indicating that the addition of Deltyba™ enhanced cost-effectiveness by simultaneously generating a savings of €8,177 and a gain of 2.34 QALYs at an ICER of -3,494 (2015).[15] The summarised results are shown in Tables-2 and 3.

In another model of care, cohorts enrolled in treatment in accordance with WHO guidelines were compared to evaluate the cost-effectiveness of MDR-TB treatment in Estonia and Russia. As can be seen in Tables-2 and 3, the costs per DALY averted because of treatment were US$579 in Estonia and US$429 in Tomsk Oblast in 2012, indicating that the treatment can be cost-effectiveness but that additional investment in TB control is required in middle-income countries.[12] In China during that same year, the comparison of comprehensive and baseline programmes for DR-TB patients uncovered a cost per DALY averted of US$639 (out of a range of US$112-US$1,322).[17] For the MDR-TB patients in South Africa, the mobile care model generated better results than did the clinical model because it was more cost-effective, as evidenced by its 2018 ICER of US$402.[14]

Discussion

Our review demonstrated the cost-effectiveness of numerous treatments applied globally for the past 17 years on the basis of ICER values per DALY or QALY. The 13 studies corroborated the potential practicality of MDR-TB/XDR-TB treatment. According to the WHO's cost-effectiveness threshold based on willingness to pay (WTP), a cost-effective healthcare intervention is one that produces a cost per DALY averted that is no larger than three times the annual gross domestic product (GDP) per capita of a country, and a highly cost-effective therapy is one that generates a cost per DALY averted that is no larger than the annual GDP per capita.[19]

A precise scrutiny of the results of the 2012 study conducted in Estonia and Russia (Tomsk Oblast), where treatment based on WHO guidelines was applied in 2001 and 2002 for MDR-TB patients, indicated that the mean costs per DALY averted were US$579 (US$297-US$902) and US$429 (US$302-US$546), respectively.[12] Statistical data from the World Bank Group (US) reflected that Estonia and Russia's GDPs per capita in 2012 were US$17,421.89 and US$15,434.57, respectively. These findings suggested that in the two studied countries, the cost per DALY averted stemming from MDR-TB treatment in 2012 was significantly lower than the GDP per capita that year; the value is classified as constituting high cost-effectiveness on the basis of the WHO assessment threshold.

Another reflection of the considerable cost-effectiveness of MDR-TB treatment with DOTS-Plus and an individualised regimen was presented in a 2006 study in the Philippines,[5] where the mean cost per DALY gained was US$242 (US$85-US$426) amid a GDP per capita of US$1,391.77 (World Bank Group [US]). Additional comparisons of costs per DALY and GDPs per capita in different countries are shown in Table-4.

The 2016 study conducted in the Republic of Korea, which evaluated the cost-effectiveness of a combined bed aquiline and standard treatment, found an incremental cost per utility of 11,638,656 KRW/QALY. On the basis of the threshold of the country (i.e. 68,000,000 KRW/QALY), this medical intervention is highly cost-effective.

Several limitations of our review are worth discussing. One of the major drawbacks was that only 17 countries have publicised their official cost effectiveness threshold, suggesting that the majority of the world is neglectful of formal healthcare decision-making and use common thresholds that are unsupported by explicit scientific evidence. This assessment, however, is not absolute setting as there are countries which have reasonable explanations for foregoing the implementation of justifiable thresholds. In particular, Germany has not proposed an official threshold because of the incompatibility of such an index with its history and legislative policies. Nevertheless, instances such as this are somewhat negligible. Owing to this limitation, we could not fully use all the statistical data presented in the reviewed works. As a specific example, we could not

thoroughly evaluate the cost-effectiveness of adding Deltyba™ to a background MDR-TB regimen in Germany. Moreover, certain stakeholders regard the WHO's suggested threshold as misconceived and lacking in methodological evidence.[21]

Another limitation that should be taken under consideration is that most of the studies reviewed did not compare discrete healthcare models in the same setting but only interpreted one in each context. In addition, articles that were not written in English were excluded, but such research satisfied our inclusion criteria. There is a possibility that these excluded articles might have provided more objective and clearer results.

Conclusion

In summary, treatments for MDR-TB/XDR-TB patients can be very cost-effective in countries with low to high incomes, regardless of whether they are suffering from minimal or substantial TB-related burdens. Bed aquiline should be considered for use along with standard regimens as it features remarkable cost-effectiveness and can therefore lead to major improvements in health-related quality of life amongst patients afflicted with MDR-TB/XDR-TB.

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