

Cost and cost-effectiveness of MDR-TB treatment in Estonia and Russian Federation

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Summary

Evidence on the cost and cost-effectiveness of treatment for multidrug-resistant tuberculosis (MDR-TB) is limited, and no published data are available from former Soviet Union countries where rates of MDR-TB are highest globally.

We evaluated the cost and cost-effectiveness of MDR-TB treatment in Estonia and the Russian Federation (Tomsk oblast), comparing cohorts enrolled on treatment according to World Health Organization (WHO) guidelines in 2001 and 2002 with cohorts treated in previous years. Costs were assessed from a health system perspective in year 2003 US\$; effects were measured as cures, deaths averted and DALYs averted. Cure rates when WHO guidelines were followed were 61% (90/149) in Estonia and 76% (76/100) in Tomsk, with a cost per patient treated of US\$ 8,974 and US\$ 10,088 respectively. Before WHO guidelines were followed, cure rates were 52% in Estonia and 15% in Tomsk: the cost per patient treated was US\$ 4,729 and US\$ 2,282 respectively. Drugs and hospitalization accounted for 69–90% of total costs. The cost per DALY averted by treatment following WHO guidelines was US\$ 579 (range 297–902) in Estonia and US\$ 429 (range 302–546) in Tomsk. Treatment of patients with MDR-TB can be cost-effective, but requires substantial additional investment in TB control in priority countries.

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Introduction

The World Health Organization (WHO) estimates that about 440,000 cases of multidrug-resistant tuberculosis (MDR-TB) develop each year [1]. Defined as resistance to at least the two most effective first-line anti-TB drugs, rifampicin and isoniazid, cases of MDR-TB accounted for about 5% of the approximately 8.8 million new cases of TB that occurred in 2010 [1]. While India and China combined account for about half of the world's estimated cases of MDR-TB, the highest rates occur in countries of the former Soviet Union (FSU): Armenia, Azerbaijan, Belarus, Estonia, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, the Republic of Moldova, the Russian Federation, Tajikistan, Turkmenistan, Ukraine, and Uzbekistan. In 2010, these countries had an estimated 66,000 cases of MDR-TB among reported TB patients (out of an estimated total of 290,000 cases among reported TB patients worldwide) and ranked first to thirteenth globally in terms of the percentage of TB cases with MDR, with figures of 9.4%–26% among new cases and 24–65% among previously treated cases [1]. In 2010, the same set of countries notified (i.e. reported) 33,000 cases of MDR-TB to WHO. In the three FSU countries with the largest populations (the Russian Federation, Ukraine and Kazakhstan), 14–18% of new TB cases and 44–46% of previously treated cases were estimated to have MDR-TB in 2010; 26,412 cases of MDR-TB were notified to WHO.

A six-month course of first-line anti-TB drugs can achieve cure rates of about 90% in patients with drug-susceptible TB [1]. However, cure rates with the same regimen for patients with MDR-TB are much lower: 5%–35% for previously treated cases and 12%–60% for new cases [2], with a relapse rate of 24% [3]. Death and treatment failure rates for people with MDR-TB are correspondingly high. Treatment that

includes second-line anti-TB drugs can considerably improve cure rates [4–16], but takes longer, causes more side-effects, requires more complex regimens and has a much higher cost [17–20].

WHO and partner agencies have developed guidelines for the treatment of MDR-TB using first and second-line drugs, most recently in 2011 [17-20]. Key elements include diagnosis based on culture and drug susceptibility testing (DST), treatment with second as well as first-line drugs for 18–24 months, and standardized recording and reporting of treatment outcomes. Projects or programmes that have followed these guidelines in Estonia, Latvia, Peru, the Philippines and the Russian Federation have achieved cure rates of 60–75% [21].

Data on cost and cost-effectiveness are needed to assess whether investment in MDR-TB treatment is justified compared with competing health sector priorities as well as to develop appropriate budgets for implementation if treatment is scaled up. To date, published studies are limited to Peru and the Philippines [4, 22, 23]. In this paper, we present data on the cost and cost-effectiveness of MDR-TB treatment according to WHO guidelines in Estonia and the Russian Federation (Tomsk oblast), from two studies initiated in 2002 and completed in 2006.

Methods

Setting

The Russian Federation had a population of 143 million in 2010 [1], a reduction from 146 million in 2001. The number of TB cases notified to WHO in 2010 was 163,000, with a relatively stable notification rate (per 100,000 population) during the decade 2001–2010 [1]. The estimated number of MDR-TB cases was 40,000 in 2010, third only to China and India [1]. Administratively the country is divided into 88 oblasts. Tomsk oblast is in Siberia, with a land area similar to that of Poland and a population of 1·1 million. The WHO-recommended approach to TB control was introduced in 1997.

Estonia is among the smallest of the FSU countries with a population of 1·3 million in 2010 [1]. In the decade 2001–2010 the number of notified TB cases fell from 708 in 2001 to 283 in 2010, while the number of cases of MDR-TB was around 60–90 each year [1]. The DOTS strategy has been implemented countrywide in Estonia since 1999. Estonia and the Russian Federation are both middle-income countries, with per capita incomes of US\$ 4,450 and US\$ 1,780 respectively in 2001 and US\$ 14,370 and US\$ 9,910 respectively in 2010 [24].

MDR-TB diagnosis and treatment, pre-and post adoption of WHO guidelines

Management of MDR-TB before and after the introduction of WHO guidelines was similar in Tomsk oblast and Estonia. Before WHO guidelines were adopted, all TB cases were routinely tested for MDR-TB. Treatment for MDR-TB was determined by individual physicians, who were often constrained by the limited availability of second-line drugs as well as incomplete information about a patient's susceptibility to

first and second-line drugs (while resistance to isoniazid and rifampicin was confirmed for all patients, data on resistance to other first and second-line drugs was sometimes lacking). Surgery sometimes formed part of treatment. Patients were almost always hospitalized throughout treatment, and discharged when cavity closure was documented.

With the introduction of treatment for MDR-TB according to WHO guidelines (January 2001 in Tomsk oblast, August 2001 in Estonia), management of patients with MDR-TB changed substantially. All cases diagnosed with MDR-TB were considered for treatment by a small expert committee ("consillium") of 4–5 physicians including both TB and public health specialists. This committee determined which patients should be enrolled, the treatment regimen, and whether patients should be treated in hospital or as an outpatient. In Estonia, the exclusionary criteria defined by the expert committee were a diagnosis of AIDS and a history of repeated defaulting. In Tomsk oblast, the expert committee used more exclusionary criteria, including the presence of another life-threatening condition, high likelihood of default, patient unwillingness to be enrolled and a drug susceptibility test (DST) pattern that suggested treatment would fail (however, as illustrated in the Results, almost all enrolled patients were resistant to ≥ 3 drugs and DST patterns were similar to those among patients enrolled on treatment prior to the adoption of WHO guidelines). In Tomsk oblast, shortages of drugs during the study period also meant that priority was given to the patients who were most seriously ill. It was beyond the scope of our study to assess what happened to those patients who did not meet the inclusion criteria, although we acknowledge that they would have been a source of further transmission of TB in the community.

After the introduction of WHO guidelines, treatment regimens in both Estonia and Tomsk oblast were designed based on DST results for first and second-line drugs, and typically included 6–7 drugs in the intensive phase of treatment, including a second-line injectable and any first-line drugs to which the patient was susceptible. Laboratory tests in Estonia in 2001 and 2002 were quality-assured by laboratories in the UK and Germany as well as by a supranational reference laboratory in Sweden. External quality assurance for the laboratory in Tomsk oblast was provided by the Massachusetts State Laboratory Institute in Boston, USA; this laboratory is part of the supranational laboratory network. In the 12–18 month long continuation phase of treatment, started 6 months after conversion to culture-negative status, the injectable drug was removed from the regimen. All treatment was provided under direct observation. Transport vouchers and food packages were given to outpatients in Estonia, and food parcels or free provision of meals were provided at outpatient facilities in Tomsk oblast. Clinical and laboratory staff in both settings were trained through international and national courses, and in Tomsk oblast technical assistance was provided on a regular basis by Partners in Health (an NGO headquartered in Boston, USA). Patient progress was monitored using periodic X-rays and monthly sputum and culture examinations. A small management team was established to provide overall supervision of clinical and laboratory work and to maintain a TB register in which data on patients including their treatment outcomes were recorded.

Patient cohorts studied

For treatment according to WHO guidelines, we considered the cohorts enrolled in the first 12–19 months after WHO guidelines were adopted. The time period was 1 January 2001–31 July 2002 (19 months) in Tomsk oblast and 1 August 2001–31 July

2002 (12 months) in Estonia. For the period prior to the adoption of WHO guidelines, we considered a cohort of patients enrolled July 1998–December 1999 in Tomsk oblast and a three year cohort enrolled in South Estonia 1995–1997. The Estonian cohort was selected because clinical records were still available and, with DST conducted in a supranational reference laboratory in Sweden, a diagnosis of MDR-TB was considered reliable.

Treatment outcomes

Treatment outcomes were assessed using internationally-agreed consensus definitions [25]. There were six possible outcomes: cured, completed treatment, died, defaulted, transferred out of the district with treatment outcome unknown, and failed treatment.

Cost and cost-effectiveness analysis

Any cost-effectiveness analysis requires comparison of relevant alternative strategies [26]. We compared treatment for MDR-TB according to WHO guidelines with treatment before these guidelines were adopted (as described above). Costs for both strategies were assessed from a health system perspective in year 2003 US\$ (the year in which most patients completed their treatment), using standard methods [27,28]. Patient costs were not considered because it was impossible to establish these costs in the period prior to the adoption of treatment according to WHO guidelines. In addition, after WHO guidelines were adopted costs to patients were small. In Estonia and Tomsk oblast, costs that are often borne by patients in other countries became the responsibility of the health system (e.g. transport costs, which were covered by vouchers in Estonia).

Two types of costs were considered: (a) the average cost of individual components of treatment (e.g. drugs, a visit for direct observation of treatment - DOT); and (b) the average cost per patient treated. The costs of individual components of treatment were calculated using an “ingredients” approach, i.e. the quantity of resources used was multiplied by unit prices. Joint costs (e.g. staff that spent time on TB patients on first-line treatment for drug-susceptible TB and patients being treated for MDR-TB) were allocated according to the time spent on each group of patients. Vehicle and equipment costs were annualised using current replacement prices, the assumption of a five-year life expectancy, and a discount rate of 3% [29]. Start-up training costs were annualised over three years. Building costs per year were based on rental values per month. All local costs were converted into US\$ using the average exchange rate in 2003 (US\$1=14.7 Kr in Estonia, and US\$1= 34.8 Roubles in the Russian Federation). The average cost per patient treated was calculated as the cost of each treatment component multiplied by the average number of times this cost was incurred. Sources of data included expenditure records, interviews with staff and patients, project records and databases and clinical records. The social insurance system was also as source of data on the unit prices of several components of care in Estonia (for example, the cost of different types of laboratory test and the cost of a bed-day in hospital). Data on the cost of second-line drugs were collected from national sources and from the Green Light Committee (GLC). The GLC was a mechanism established by WHO to help countries to access second-line drugs at the lowest-possible price, and it helped to supply second-line drugs to Estonia and Tomsk oblast in the years after WHO guidelines on MDR-TB treatment were adopted.

There was uncertainty about several parameters that influence the effectiveness of treatment for MDR-TB, which in turn affected estimates of both total costs and cost-effectiveness. The effectiveness, cost and cost-effectiveness of treatment for MDR-TB after WHO guidelines were adopted, compared with the pre-guidelines period, was therefore estimated as part of a multivariate uncertainty analysis. For consistency and comparability, this analysis was based on the same principles and much of the data that were used in previously published evaluations of MDR-TB treatment in Peru and the Philippines, full details of which are available elsewhere [4,22] and in the technical appendix. In brief, the analysis was designed to measure the effectiveness of treatment for MDR-TB in terms of cases cured, deaths averted and disability-adjusted life years (DALYs) averted, and to capture both a) effects among the patient cohort treated and b) the effect of treatment of this cohort on transmission, and hence the number of cases, deaths and DALYs averted that occur in the future. An Excel spreadsheet model was used in which treatment paths were defined for the same patient cohort (i.e. 149 patients in Estonia and 103 patients in Tomsk) for the two alternative strategies i.e. treatment for MDR-TB before and after WHO guidelines were adopted (the analysis was undertaken for the same number of patients to avoid distortions caused by different numbers of patients in the cohorts considered before and after the introduction of WHO guidelines). The number of patients following each treatment path, together with their associated costs and effects, was then defined according to (a) the parameters, parameter distributions and data sources listed in the technical appendix [30-39] (b) the costs per patient before and after the adoption of WHO guidelines, reported in this article and (c) treatment outcomes before and after the introduction of treatment according to WHO guidelines, also reported in this article. A Monte Carlo simulation involving 5,000 iterations was used to estimate means and

lower and upper bounds (5th and 95th centiles) for the main outputs of interest i.e. total costs and total DALYs lost for each strategy, total DALYs averted by treatment according to WHO guidelines, and the cost per DALY averted by treatment according to WHO guidelines.

Statistical analysis

We compared the clinical, socio-economic and demographic characteristics of the patient cohorts treated before and after the introduction of treatment for MDR-TB according to WHO guidelines, and also compared the cohorts treated after the introduction of WHO guidelines in Estonia and Tomsk. We used chi-square tests for categorical outcome variables and t-tests for continuous outcome variables. We also used the chi-square test to compare the treatment outcomes of chronic cases, new and re-treatment cases.

Results

Patient enrolment and characteristics

The clinical, socio-economic and demographic characteristics of the patients treated for MDR-TB before and after the introduction of WHO guidelines in Estonia and Tomsk oblast are summarized in Table 1 (further details are available from the authors upon request). For the patient cohorts enrolled after the introduction of WHO guidelines, the numbers of patients considered eligible, enrolled on treatment and considered in our analysis are summarized in Figure 1a and Figure 1b.

From 1 August 2001–31 July 2002, 173 cases were diagnosed with MDR-TB in Estonia, of whom 149 were enrolled on treatment according to WHO guidelines (Figure 1a). The average age of patients was 45, and most were men (109/149, 73%). Alcohol abuse and unemployment rates were high (30% and 42% respectively), and patients had extensive drug resistance (79% were resistant to five or more drugs). Among the 54 patients with MDR-TB treated before the introduction of WHO guidelines in Estonia, 63% were men. The age distribution was similar to the patient cohort treated according to WHO guidelines, but the rate of alcohol abuse appeared to be lower ($p=0.01$ when those for whom no data were available were excluded) and fewer cases were from urban areas ($p=0.005$). Most strikingly, there was less severe drug resistance ($p<0.001$), with only 4% of patients resistant to five or more drugs. Overall, about 60% of patients were tested for HIV in Estonia, and one was HIV-positive.

In Tomsk oblast, 124 patients were considered eligible for treatment for MDR-TB according to WHO guidelines (Figure 1b). Of these, we considered the 100/105

patients from the civilian sector for whom detailed data on their treatment could be retrieved. We were unable to obtain permission to collect data from the prison sector. The average age was 38, and 70% of patients were men. As in Estonia, unemployment and alcohol abuse rates were high. Drug resistance was less severe than in Estonia (29% of patients were resistant to five or more drugs), but 98% of patients were resistant to ≥ 3 drugs.

In the cohort treated before the introduction of treatment according to WHO guidelines, 83% of patients were men and the average age was 46, both significantly higher than the cohort treated after WHO guidelines were followed (Table 1). There were no statistically significant differences between the cohorts for the other variables that we studied, except for the rate of alcohol abuse which was higher in the cohort treated before the introduction of treatment according to WHO guidelines ($p=0.04$). Representative data on HIV status were not available.

Treatment outcomes

Treatment outcomes are shown in Table 2. For the cohorts treated according to WHO guidelines, the cure rate was 76% in Tomsk oblast and 61% (including patients that completed treatment) in Estonia. In the cohorts treated before the introduction of WHO guidelines, the cure rate was 15% in Tomsk oblast and 52% in Estonia. The death rate in Tomsk oblast before WHO guidelines were adopted was high, at 67%, and the remainder of patients (17%) failed treatment. Within the cohort treated according to WHO guidelines in Estonia, failure rates were lower but default rates higher among new cases compared to previously treated cases; in Tomsk oblast, cure rates were

lower and default rates higher in new cases compared with previously treated, chronic cases ($p=0.01$).

Cost and cost-effectiveness

The average cost per patient treated according to WHO guidelines (in prices for 2003) was US\$ 8,974 in Estonia and US\$ 10,088 in Tomsk oblast. This was considerably more than costs in the period before WHO guidelines were used, which were US\$ 4,729 in Estonia and US\$ 2,282 in Tomsk oblast (Table 3). Drugs and inpatient care were the most important costs in both cohorts and in both sites; when combined, they accounted for 69–90% of total costs. The drug regimens used in Tomsk oblast when WHO guidelines were followed were more expensive than those used in Estonia, at US\$ 3,718 compared with US\$2,219 per patient.

The total costs for each strategy, including both the costs of the cohort enrolled and the costs associated with secondary cases generated through transmission of TB by this cohort, are shown in Table 4. The net increase in total costs associated with treatment for MDR-TB according to WHO guidelines was about US\$ 0.5 million (range, 0.4–0.6 million) in Estonia and US\$1.0 million (range, 0.9–1.1 million) in Tomsk oblast.

These additional costs resulted in a large number of averted deaths and DALYs (Table 4). The mean cost per DALY averted by treatment according to WHO guidelines was US\$ 579 (range 297–902) in Estonia, and US\$ 429 (range 302–546) in Tomsk oblast. The total funding required for treatment according to WHO guidelines of all registered cases of MDR-TB in 2003 was about US\$ 1.3 million in Estonia and US\$ 375 million in the Russian Federation when the costs in Tomsk oblast are extrapolated to the whole of the country (Table 5).

Discussion

The cost of providing treatment for patients with MDR-TB according to WHO guidelines in Estonia and the Russian Federation (Tomsk oblast) was about US\$ 9,000–US\$ 10,000 per patient treated (in prices for 2003), with the dominant cost items being second-line drugs and hospitalization (averaging over 6 months). This was about twice the cost of the treatment previously available in Estonia, and 4–5 times the cost of the treatment previously available in Tomsk oblast. The increase in costs was accompanied by a substantial improvement in the cure rate in Tomsk oblast (76% compared to the previous 15%), and a smaller improvement in Estonia (61% vs. 52%). The cost per DALY averted was about US\$ 400–600.

Previous studies of the cost and cost-effectiveness of treatment for MDR-TB in low and middle-income countries are limited to Peru and the Philippines. The cost of MDR-TB treatment in these countries were low compared to Estonia and Tomsk oblast, at US\$2,500–3,500 per patient [4, 22]. Almost all of the difference was explained by the high cost of hospitalization in Estonia and Tomsk oblast, at US\$ 4,491 and US\$ 3,341 respectively compared to US\$ 107 in the Philippines and no hospitalization in Peru. Drug costs were also higher, particularly in Tomsk oblast (US\$3,718 per patient vs. US\$2,219 in Estonia, US\$1,557 in the Philippines and US\$824 in Peru), which can be explained by more extensive patterns of drug resistance, including to second-line drugs [4,22]. The cost per DALY averted was 2–3 times higher than the approximately US\$ 200 reported in the two studies from Peru and the Philippines that have used the same methodology for the cost-effectiveness analysis. A more recent study for Peru [23] also produced similar results to our study for a strategy in which MDR testing is conducted among all patients that have already

received at least one course of TB treatment with first-line drugs, provided allowances are made for methodological differences (such as the number of years of life gained per death averted). However, results for a theoretical strategy in which all TB cases are tested for MDR - an approach which is directly comparable to the strategies implemented in practice in Estonia and Tomsk oblast - were different. For Peru, this strategy was estimated to cost US\$2,731 per quality-adjusted life year (QALY) gained, much more than we have estimated for Estonia and Tomsk oblast. The explanation for this much higher figure is that compared to Estonia and Tomsk oblast, Peru has much lower rates of MDR among new TB cases, the ratio of costs with MDR testing to costs without MDR testing is much higher, and better treatment outcomes for MDR cases are achieved in the absence of treatment with second-line drugs [26].

Differences in the cure rates achieved in Estonia and Tomsk oblast when WHO guidelines were adopted were mainly due to higher default and death rates in Estonia. The higher death rate in Estonia may be due to more extensive drug resistance, which itself might reflect the after-effects of suboptimal treatment in the period before WHO guidelines were adopted as well as the less stringent enrolment criteria that were applied. The higher default rate is more difficult to explain; possible risk factors such as unemployment and alcohol abuse were present to a similar degree in both cohorts, and social support to encourage treatment compliance was available in both settings. A plausible explanation is that stricter enrolment criteria were used in Tomsk oblast. The particularly high death rate in Tomsk oblast before WHO guidelines were adopted is comparable to the natural history of disease, illustrating the low efficacy of treatment at that time.

Our study has several limitations. There were differences in the socio-economic, clinical and demographic characteristics of the cohorts treated in the period before and after the application of WHO guidelines for the treatment of MDR-TB. In Estonia, there were lower rates of unemployment and alcohol abuse and less extensive drug resistance in the cohort treated before WHO guidelines were followed, and as a result we may have underestimated the improvement in health outcomes associated with treatment according to the WHO guidelines in this setting. In Tomsk oblast, a large number of patients were eligible for treatment but not enrolled. This could lead to over or under-estimation of the increased effectiveness associated with the introduction of WHO guidelines. The fact that priority was given to the most severely ill patients would tend to underestimate the effectiveness of treatment according to WHO guidelines, although the cure rates achieved were high. Both settings have a population of about 1 million people, so the results apply to treatment that is provided on a relatively small scale. We did not collect data on costs to patients in either setting, since reliable data could not be obtained retrospectively for those patients treated before the WHO guidelines were adopted, and in Tomsk we also lacked data on rates of HIV infection and data for patients treated in the prison sector.

Perhaps the most obvious limitation is that the data are relatively old, from patients started on treatment in 2001 and 2002. This is due to delays in finalizing the results in the format of a paper for publication in a peer-reviewed journal. Nonetheless, the data are as recent as any other published data on the cost and cost-effectiveness of treatment for MDR-TB in low and middle-income countries, and the numbers of cases of MDR-TB in 2010 were broadly comparable to numbers in 2001. Although recent analyses of the cost of second-line drugs and the regimens used in Estonia and Tomsk oblast

suggest that the cost of the regimens used in 2001–2002 remained at similar levels in 2010 (data not shown), two principal changes have occurred or are likely to have occurred in the years since the data were collected. First, some of the costs associated with treatment are likely to have increased, notably costs (such as those of staff providing care in outpatient facilities or on hospital wards) that are closely related to income levels. Average GNI per capita almost doubled in Estonia and almost tripled in the Russian Federation between the end of 2003 (the year for which we estimated costs in US\$) and 2010, reaching US\$ 14,370 in Estonia and US\$ 9,910 in the Russian Federation in 2010 [24]. Second, the funding available for TB control in both countries grew, especially in the Russian Federation. On the assumption that the cost of the drug regimens has remained unchanged (as suggested by analysis of the cost of the regimens used at current prices quoted by the GLC - data not shown) but that other costs have increased in line with the growth in incomes per capita, the cost per patient treated in 2010 would have been US\$ 20,910 in Estonia and US\$ 22,512 in the Russian Federation and the cost per DALY averted would be US\$ 692–2101 and US\$ 674–1218 respectively. Funding for TB control increased more than the estimated growth in costs in the Russian Federation, reaching US\$ 1.3 billion in 2010. Although the total funding available for TB control in Estonia was not available, the funding available for second-line drugs had increased, to approximately US\$ 3,500 per patient.

Study strengths include the collection of detailed data on health services utilization, costs and treatment outcomes for MDR-TB cases for all patients, and that this is the first study to provide evidence of the cost and cost-effectiveness of treatment for MDR-TB according to WHO guidelines in FSU countries - the part of the world where the problem of MDR-TB is most severe. The results from Tomsk oblast may be

broadly generalizable to other parts of the Russian Federation, given a common approach to TB control across the country, and results from Estonia may be generalizable to the two other Baltic countries (Latvia and Lithuania). Results from Tomsk oblast also have broad relevance to other FSU countries, given similar levels of drug resistance and comparable models of care that remain largely hospital-based.

Our results suggest that treatment for MDR-TB according to WHO guidelines can be cost-effective in both Estonia and the Russian Federation. The cost per DALY averted in both settings was much less than per capita GDP, a threshold which WHO has used to define interventions that are "highly cost-effective" [40]. This would remain the case even if the non-drug costs of treatment have risen in line with GNI per capita since the time the study data were collected. Expanding treatment according to WHO guidelines to all cases of MDR-TB in FSU countries will require a big increase in funding, however. In the Global Plan to Stop TB for the five years 2011–2015, the cost of such expansion has been projected at US\$ 3.5 billion over five years, increasing from US\$ 0.6 billion in 2011 to US\$ 0.8 billion in 2015 [40], compared with reported funding of US\$ 259 million in 2011 [1].

Overall conclusions

Treatment of patients with MDR-TB can be cost-effective in Estonia and the Russian Federation, and results may be broadly generalizable to neighbouring European countries with a high burden of MDR-TB. Scaling up MDR-TB treatment in the 18 priority countries of the WHO European Region in line with targets set in the Stop TB

Partnership's Global Plan to Stop TB, 2011–2015 [41] will require a substantial increase in funding for TB control.

Contributors

All authors were involved in study design. KF provided overall guidance to both studies. KK led data collection and conducted much of the data analysis for the Estonia study, supported by RC, GBM and KF. RH and NK led data collection and analysis in Tomsk, supported by SK and WJ. KF and RC conducted the costs-effectiveness analysis for Estonia; RH and KF conducted the cost-effectiveness analysis for Tomsk. KF produced the first draft and final version of the manuscript. All investigators contributed to the interpretation of the data and revisions to the paper, and agreed upon the final version.

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Conflict of interest statement

None of the authors have any financial or personal relationship with people or organisations that could inappropriately bias the study. The corresponding author had full access to all the data collected for the study.

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Table 1: Clinical, socio-economic and demographic characteristics of patient cohorts pre- and post-WHO guidelines, Estonia and Tomsk oblast (Russian Federation)

Variable	ESTONIA			TOMSK OBLAST, RUSSIAN FEDERATION			P-value, comparison of Estonia and Tomsk (cohorts treated according to WHO guidelines)	P-value, comparison of Estonia and Tomsk (cohorts treated before the adoption of WHO guidelines)
	Post WHO guidelines (n=149)	Pre WHO guidelines (n=54)	P-value	WHO guidelines (n=100)	Pre WHO guidelines (n=103)	P-value		
Age								
15–24	10 (7%)	5 (9%)	0.85	11 (11%)	0 (0%)	<0.001	0.03	0.01
25–34	29 (19%)	13 (24%)		35 (35%)	20 (19%)			
35–39	13 (9%)	3 (6%)		8 (8%)	12 (12%)			
40–49	43 (29%)	14 (26%)		21 (21%)	23 (22%)			
≥ 50	54 (36%)	19 (35%)		25 (25%)	48 (47%)			
Sex								
Male	109 (73%)	34 (63%)	0.16	70 (70%)	85 (83%)	0.04	0.59	0.007
Female	40 (27%)	20 (37%)		30 (30%)	18 (17%)			
Residence								
Urban	113 (76%)	30 (56%)	0.005	58 (58%)	61 (59%)	0.86	0.003	0.66
Rural	36 (24%)	24 (44%)		42 (42%)	42 (41%)			
Employment status								
Employed	32 (22%)	16 (30%)	0.10	27 (27%)	26 (25%)	0.31	0.08	<0.001
Unemployed	63 (42%)	14 (26%)		50 (50%)	61 (59%)			
Other (e.g. retired, student)	54 (36%)	24 (44%)		23 (23%)	16 (16%)			
Alcohol abuse								
Abusing alcohol	44 (30%)	17 (31%)	0.01 excluding those with no data	38 (38%)	54 (52%)	0.04	0.04	0.01
Not abusing alcohol	39 (26%)	37 (69%)		62 (62%)	49 (48%)			
No data	66 (44%)	NA		NA	NA			
Resistance pattern								
2 drugs	1 (1%)	10 (19%)	<0.001	2 (2%)	2 (2%)	0.65	<0.001	<0.001
3 drugs	6 (4%)	11 (20%)		30 (30%)	38 (37%)			
4 drugs	24 (16%)	24 (44%)		40 (40%)	33 (32%)			
5 or more drugs	117 (79%)	2 (4%)		28 (28%)	30 (29%)			

NA: Not Applicable

Table 2a: Treatment outcomes for patients enrolled on treatment for MDR-TB in Estonia, before and after the adoption of WHO guidelines

Treatment outcome	WHO guidelines			Pre WHO guidelines
	Entire cohort (n=149)	Re-treatment cases (n=84)	New cases (n=65)	Entire cohort (n=54)
Cured	80 (54%)	45 (54%)	35 (54%)	23 (43%)
Completed treatment	10 (7%)	5 (6%)	5 (8%)	5 (9%)
Treatment failed	15 (10%)	14 (17%)	1 (2%)	2 (4%)
Died	19 (13%)	12 (14%)	7 (11%)	13 (24%)
Defaulted	25 (17%)	8 (10%)	17 (26%)	11 (20%)
Transferred out	-	-	-	-
All	149 (100%)	84 (100%)	65 (100%)	54 (100%)

Table 2b: Treatment outcomes for patients enrolled on treatment for MDR-TB in Tomsk oblast, Russian Federation, before and after the adoption of WHO guidelines

Treatment outcome	WHO guidelines				Pre WHO guidelines			
	Entire cohort (n=100)	Chronic cases (n=42)	Re-treatment cases (n=18)	New cases (n=40)	Entire cohort (n=103)	Chronic cases (n=52)	Re-treatment cases (n= 26)	New cases (n=25)
Cured	76 (76%)	34 (81%)	13 (72%)	29 (72.5%)	15 (14.6%)	4 (7.7%)	5 (19.2%)	6 (24%)
Completed treatment	-	-	-	-	-	-	-	-
Treatment failed	12 (12%)	5 (12%)	3 (17%)	4 (10%)	17 (16.5%)	10 (19.2%)	5 (19.2%)	2 (8%)
Died	4 (4%)	1 (2%)	1 (5.5%)	2 (5%)	66 (64.1%)	37 (71.2%)	13 (50.0%)	16 (64%)
Defaulted	8 (8%)	2 (5%)	1 (5.5%)	5 (12.5%)	-	-	-	-
Transferred out	-	-	-	-	5 (4.9%)	1 (1.9%)	3 (11.5%)	1 (4%)

Table 3: Average cost per patient treated for MDR-TB before and after the introduction of WHO guidelines in Estonia and Tomsk oblast, Russian Federation, in 2003 US\$ (% column total)*

Cost item	Estonia		Tomsk oblast, Russian Federation	
	WHO guidelines	Pre WHO guidelines	WHO guidelines	Pre WHO guidelines
Hospitalization†	4491 (51%)	3366 (71%)	2987 (30%)	1113 (49%)
Drugs‡	2219 (25%)	911 (19%)	3718 (37%)	576 (26%)
DOT visits to day-stay hospital ward§	NA	NA	783 (8%)	341 (15%)
DOT visits to outpatient facilities , including nutritional support**	891 (10%)	61 (1%)	252 (3%)	97 (4%)
Programme management and supervision	615 (7%)	-	416 (4%)	-
Technical assistance	-	-	370 (4%)	-
Laboratory support	-	-	200 (2%)	-
Laboratory tests (smears, cultures, DST)††	195 (2%)	155 (3%)	166 (2%)	35 (2%)
Training	128 (2%)	-	302 (3%)	-
Advocacy	-	-	288 (3%)	-
X-rays, CT scans and clinical laboratory tests	119 (1%)	128 (3%)	91 (1%)	20 (1%)
Adverse events	12 (0.1%)	2 (0.04%)	54 (1%)	-
Other	304 (1%)	106 (2%)	460 (5%)	72 (3%)
Total	8974	4729	10 088	2253

* The exchange rates used to convert costs in local currency to US\$ were US\$1=14.7 Kr (Estonia) and US\$1= 34.8 Roubles (Russian Federation).

† In Estonia, 192 days for WHO guidelines and 132 days for the period before WHO guidelines were adopted at US\$30.5 for the first 60 days, and US\$15.5 for any days thereafter; in Tomsk, 321 days for WHO guidelines and 120 for the period before WHO guidelines were adopted at US\$ 9.3 per bed day.

‡ In Estonia, the typical patient received the following drugs: Am 42g; Amx 82g; Ca 82g; Cla 43g; Cy 220g; E 341g; Et 23g; H 99g; KA 33g; Of 320g; PAS 1550g; Pt 233g; R 126g; S 33g; Z 1164g. In Tomsk, the typical patient received the following drugs: H 100g; R 596g; Z 530g; E 166g; S 32g; AM 64g; CAP 245g; Cla 32g; Cy 335g; Et 143g; K 215g; MB 39g; Of 419g; PAS 3771g; RB 4g; AMO 59g.

§ In Tomsk, 250 day-stays for WHO guidelines and 109 for the period before WHO guidelines were adopted. at a cost of US\$ 3.1 per day-stay.

** In Estonia, 171 visits at US\$ 5.20 per visit. In Tomsk, 85 visits at US\$ 1.4 per visit. Nutritional support not provided before the adoption of WHO guidelines. In Tomsk, nutritional support was about US\$ 130 per patient, or 52% of outpatient costs; in Estonia, these data were not recorded separately from other costs.

†† In Estonia, on average each patient required 21.4 (liquid media) cultures at US\$ 5.5 each , 2.6 DST (liquid media) at US\$ 17.5 each and 14.5 smears at US\$ 2.0 each. In Tomsk, on average each patient required 46.5 cultures at US\$ 2.5 per culture, 3.9 (first and second-line) DST at US\$ 4.0 each and 48.0 smears at US\$ 0.5 each.

Table 4: Cost, effectiveness and cost-effectiveness indicators, alternative strategies*

Indicator	Estonia		Tomsk oblast (Russian Federation)	
	WHO guidelines	Pre WHO guidelines	WHO guidelines	Pre WHO guidelines
<i>Cost indicators</i>				
Total health system costs for patient cohort (n=149 in Estonia and n=100 in Tomsk), including costs of treating secondary cases (US\$ millions)	1.62 (1.50, 1.74)	1.13 (0.95, 1.35)	1.49 (1.30,1.70)	0.45 (0.35,0.62)
<i>Effectiveness indicators</i>				
Deaths among patient cohort†	56 (49,64)	74 (69,79)	25 (19,30)	75 (72,77)
Deaths among secondary cases generated by patient cohort	17 (10,24)	44 (25, 67)	10 (6,15)	77 (39,131)
Total deaths	73 (62,86)	118 (97, 143)	35 (26, 44)	152 (113,206)
Total deaths averted by treatment for MDR-TB according to WHO guidelines	44 (31, 61)	NA	117 (82,167)	NA
Total DALYs averted by treatment for MDR-TB according to WHO guidelines	790 (551,1088)	NA	2516 (1763,3591)	NA
<i>Cost-effectiveness indicators</i>				
Cost per DALY averted by treatment for MDR-TB according to WHO guidelines (US\$)	579 (297,902)	NA	429 (302,546)	NA

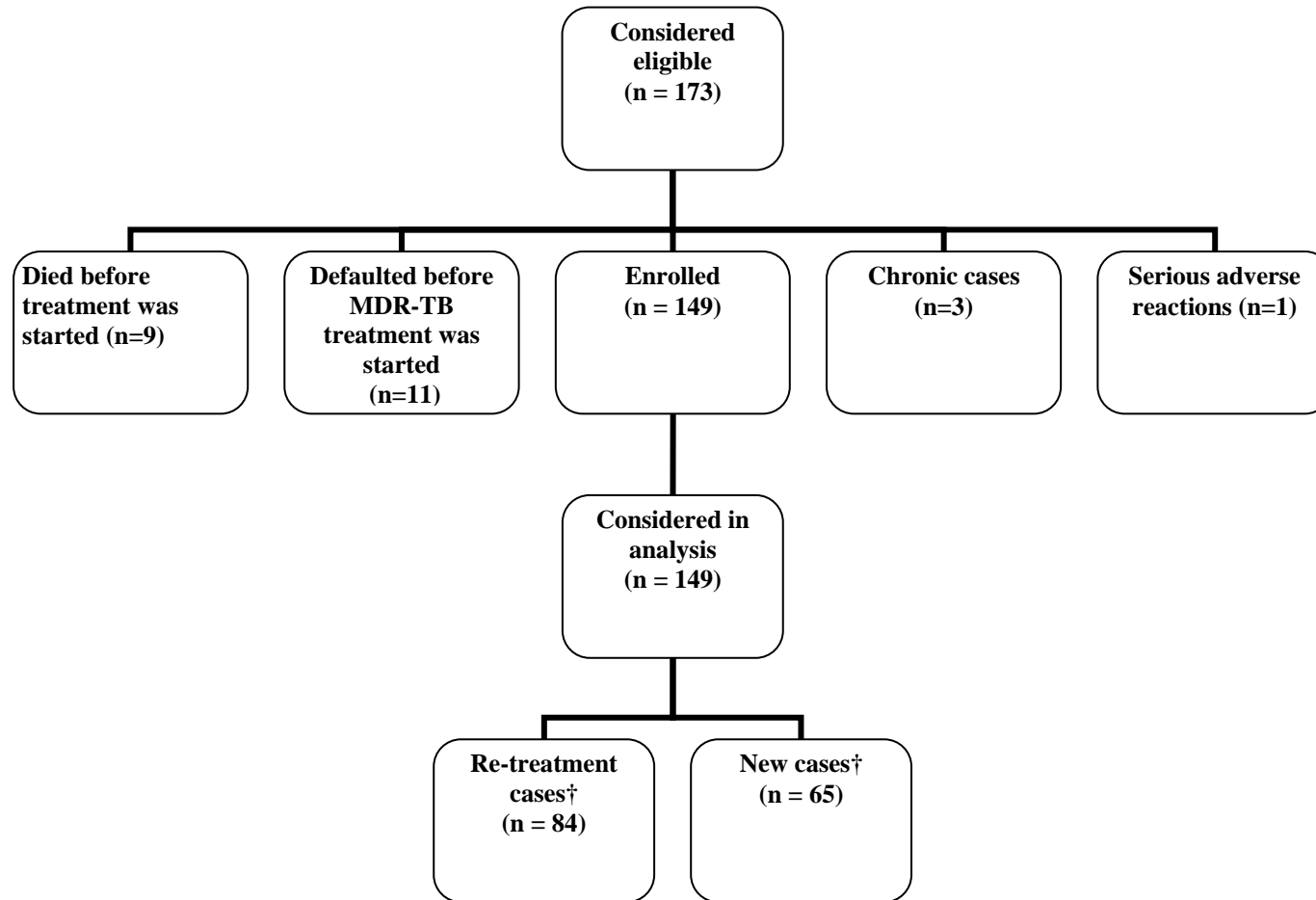
* Shown as means with 5th and 95th centiles in uncertainty analysis.

† Numbers for treatment according to WHO guidelines higher than shown in tables 2a and 2b because they allow for deaths among defaulting patients, patients who fail treatment, and deaths among patients who are cured but later relapse.

Table 5: Total costs and affordability of treatment according to WHO guidelines in the context of funding for TB control in 2003

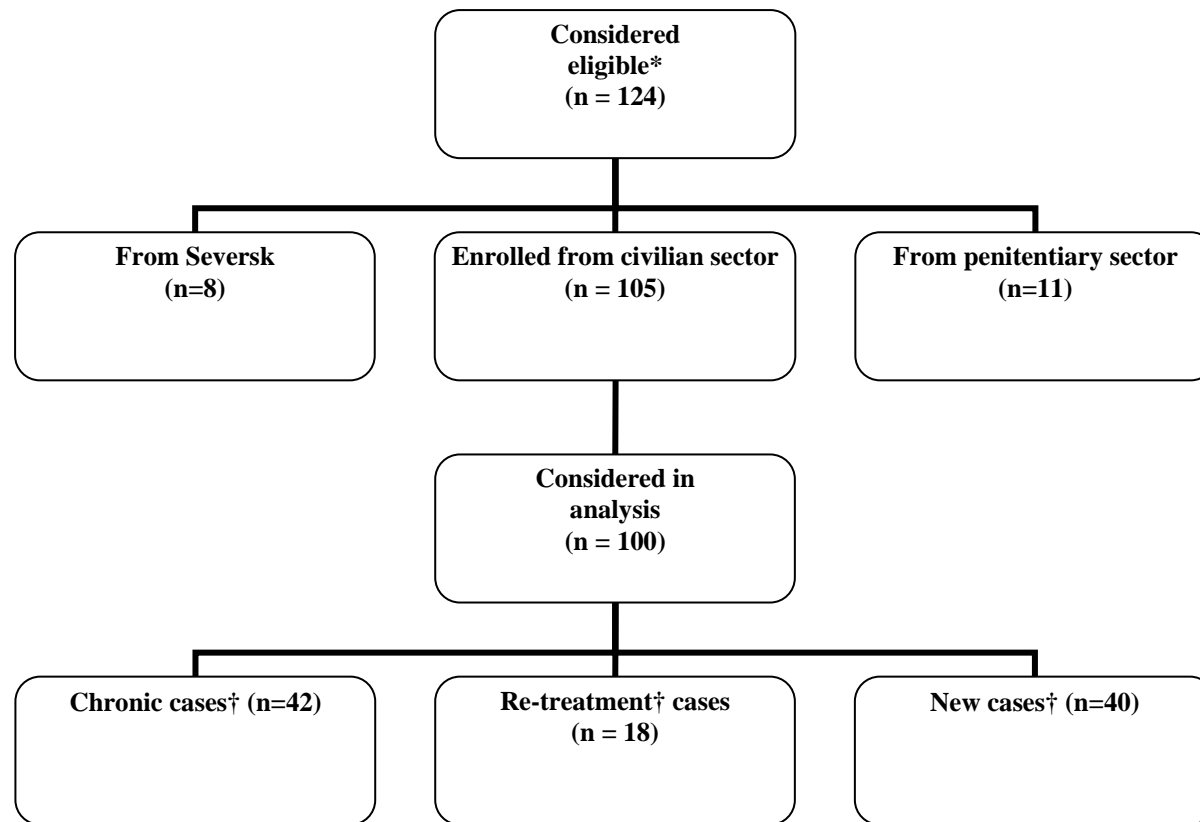
Indicator of cost, funding or affordability	Estonia	Russian Federation
Estimated number of cases of MDR-TB	150	34,029
Cost per patient treated (US\$)	8974	10,088
Total cost (US\$ millions, nominal values)	1.3	343
Total funding for TB control (US\$ millions)	3.1	375
Cost as % total funding for TB control	43%	91%

Figure 1a: Patient enrolment in treatment according to WHO guidelines in Estonia, 1 August 2001 to 31 July 2002



† Re-treatment cases are patients who had been treated for TB before, and who had failed or defaulted from the treatment regimen. New cases were patients who had not been previously treated for TB.

Figure 1b: Patient enrolment in treatment according to WHO guidelines in Tomsk oblast, Russian Federation, 1 January 2001 to July 31 2002



*There were 1314 patients identified with MDR-TB during the study period. The big difference between this number and the 124 patients that were considered eligible was due to several factors. Anyone with severe concurrent pathology (for example, diabetes, severe mental pathology, or ulcer) was excluded, as were pregnant women. Rural residents were enrolled only if they lived in an area where a health worker was available to oversee treatment after discharge from hospital. Given the limited supply of second-line drugs, priority was given to patients whose condition was life-threatening. The programme was new and unproven, and not all cases were willing to consider treatment in it. Staff capacity was also a limiting factor, as there was a shortage of physicians considered to have the necessary competence to treat and manage side-effects associated with second-line drugs.

†Chronic cases are patients who had already received at least two treatments with first-line drugs (a treatment regimen for a new case, and a re-treatment regimen). Re-treatment cases are patients who had been treated for TB before, and who had failed or defaulted from the treatment regimen. New cases were patients who had not been previously treated for TB.