



Costs of tuberculosis disease in the European Union: a systematic analysis and cost calculation

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ABSTRACT Without better vaccines it is unlikely that tuberculosis (TB) will ever be eliminated. An investment of ~€560 million is considered necessary to develop a new, effective vaccine in the European Union (EU). However, less is known about the costs of TB disease in the EU. We performed a systematic review of literature and institutional websites addressing the 27 EU members to summarise cost data. We searched MEDLINE, EMBASE and Cochrane bibliographies for relevant articles.

Combining direct and indirect costs, we arrived at an average per-TB case costs in the original EU-15 states plus Cyprus, Malta and Slovenia of €10 282 for drug-susceptible TB, €57 213 for multidrug resistant (MDR)-TB and €170 744 for extensively drug resistant (XDR)-TB. In the remaining new EU states, costs amounted to €3427 for drug-susceptible TB and €24 166 for MDR-TB/XDR-TB. For the 70 340 susceptible TB cases, 1488 MDR-TB and 136 XDR-TB cases notified in 2011 costs of €536 890 315 accumulated in 2012. In the same year, the 103 104 disability-adjusted life years caused by these cases, when stated in monetary terms, amounted to a total of €5 361 408 000.

Thus, the resulting economic burden of TB in the EU clearly outweighs the cost of investing in more efficient vaccines against TB.



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Introduction

Although vaccination with bacille Calmette–Guérin (BCG), the only available vaccine against tuberculosis (TB), has been shown to decrease the risk of severe forms of TB in young children (disseminated TB and TB meningitis) [1], it is ineffective in preventing infectious pulmonary TB, which occurs mainly in adults and remains the primary source of TB transmission. Currently, 12 vaccines have been taken into phase I or II clinical trials, with the aim of replacing the present BCG vaccine or at enhancing immunity induced by BCG [2, 3], and with the hope of licensing at least one new vaccine by 2018 [4].

An investment of ~€560 million is considered necessary to achieve this result in the European Union (EU) [5]. As part of its efforts for funding, the Tuberculosis Vaccine Initiative (TBVI) has proposed an investment model to close the financial gap and speed up the development of those new TB vaccines [6]. The economic calculation that follows shows how the annual cost of TB in the EU clearly outweighs the total cost of developing new vaccines.

Confusion may arise as to the definition of the region when looking at the cost of TB in Europe. A much used estimation of TB-related costs in Europe, the European Academies Science Advisory Council study [7], comes from the European Lung White Book, which placed these in 2003 at €2.1 billion in the European region as defined by the World Health Organization (WHO), *i.e.* comprising 53 member states including the EU, EU-associated and former Soviet Union (FSU) countries [8]. However, some details of that cost calculation have not been provided and thus it is challenging to provide a more explicit, reasonable cost calculation of TB disease focusing on the current 27 member states of the EU (EU-27).

Numerous publications stress the dramatic increase of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB in the world [9, 10]. According to estimates by the WHO, of the total 8.7 million new cases in 2011 an estimated 3.7% had MDR-TB [11], defined as resistance to at least the two most powerful first-line anti-TB drugs, isoniazid and rifampicin, and ~58 000 cases involved XDR-TB, defined as resistance to any fluoroquinolone and at least one of the three injectable anti-TB drugs (amikacin, capreomycin or kanamycin) in addition to MDR.

Of the 22 countries considered “MDR-TB high burden”, 15 are in the WHO Europe region [12]. In 2011 the number of cases tested for MDR-TB in Europe was 84 140, of which 68% delivered a positive bacteriological result [13].

The highest rates of MDR-TB, up to 26% among new cases and up to 65% among previously treated cases, are seen in the countries of the FSU [14, 15], which together had an estimated 31 000 cases in total in 2010 [16].

According to a recent document of the WHO Regional Office for Europe [17] the total number of notified XDR-TB patients in the WHO European region almost tripled, from 132 in 2008 to 344 in 2009.

For 2011, the European Centre for Disease Prevention and Control (ECDC) and WHO Regional Office for Europe surveillance report [18] mentions 1518 MDR-TB cases and 136 XDR-TB cases. This confirms that drug-resistant TB is an important problem, especially because it is well known to be associated with a relatively low treatment success rate [19, 20] and, as shown in our calculations later on, a significant increase in treatment cost. Accordingly, in every economic analysis the increasing cost of MDR-TB has to be included according to its proportion among all TB cases arising in the EU.

The historical summary of the Wolfheze workshops and their consensus documents with recommendations on TB control activities in the EU [21] highlights the ultimate target of TB elimination, defined as a TB incidence of less than one case per million population [22]. As it must be recognised, following current trends, Europe is unlikely to achieve elimination of the disease by the target date of 2050 [23, 24], we urgently need new vaccines, as well as improved diagnostics [25, 26] and new drugs [27–29]. With respect to economic considerations, the aim of the present study was to evaluate the costs associated with TB disease in order to determine whether they outweigh the investment needed to generate a new vaccine.

Methods

Calculating direct and indirect costs

First, we performed a systematic literature review, followed by the extraction of direct as well as indirect costs of TB (fig. 1). Direct costs include costs for the medical treatment of TB (medication, laboratory work, hospitalisation and outpatient visits) and indirect costs represent productivity loss because of TB-induced sick days taken off work.

From this we gathered information on the following cost components for drug-susceptible TB, MDR-TB and XDR-TB: 1) duration of hospitalisation and inpatient cost per day; 2) outpatient cost; 3) cost of medication; 4) cost due to loss of productivity; and 5) year in which the costs were assessed or collected.

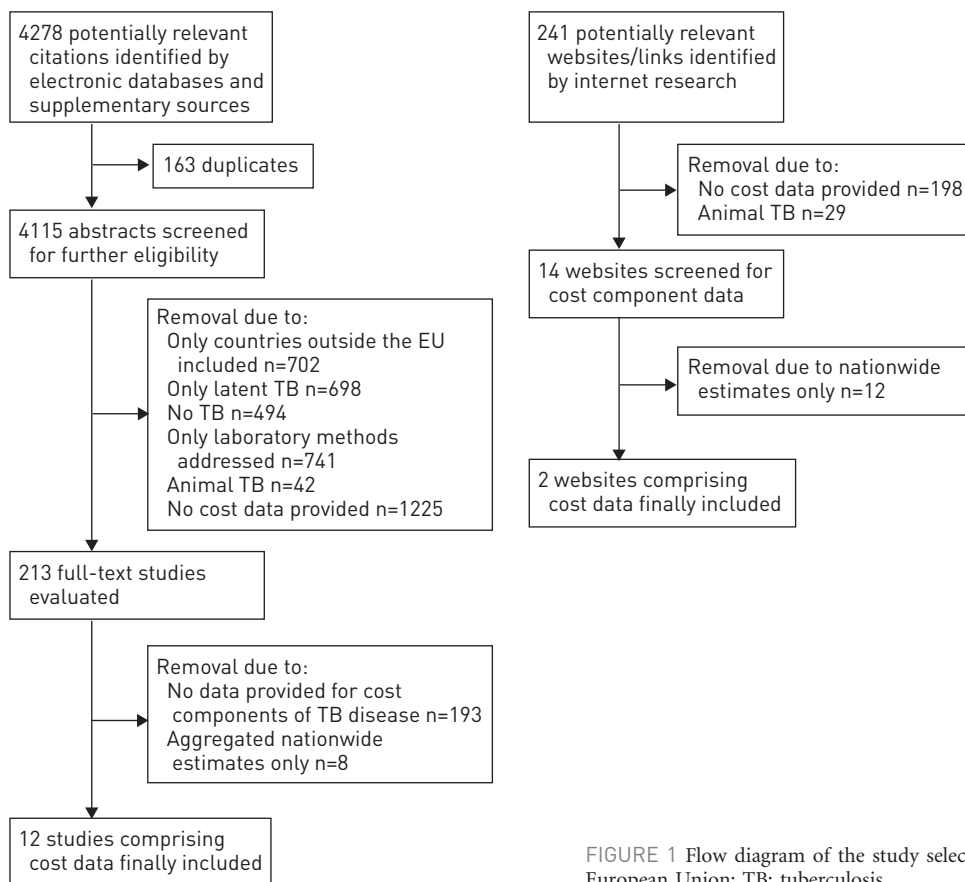


FIGURE 1 Flow diagram of the study selection. EU: European Union; TB: tuberculosis.

If there was more than one cost calculation for a country the most current version was chosen in the review. It was the aim of our study to show current TB costs, so the price year of this study was 2012. Consequently, all costs arisen in different EU countries and years were adjusted to 2012 values using the Harmonised Index of Consumer Prices for the Euro area countries [30] and the results were summarised.

Costs of public health surveillance, especially costs of contact tracing, screening risk groups, preventive treatment of persons latently infected by *Mycobacterium tuberculosis* and the activities of national reference laboratories and institutes were beyond the scope of this analysis.

We searched MEDLINE, EMBASE, the Health Economic Evaluations Database, Centre for Reviews and Dissemination/National Health Service Economic Evaluation Database, the Cost-Effectiveness Analysis Registry, the European Network of Health Economic Evaluation Databases and the Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library 2013, issue 3, through March 15, 2013) for studies published using the following search terms in different combinations: “tuberculosis” OR “TB disease” OR “MDR-TB” OR “drug resistant TB” OR “drug resistant tuberculosis” OR “multidrug resistant TB” OR “multidrug resistant tuberculosis” AND “cost” OR “cost-effectiveness” OR “economic” OR “burden”.

No restrictions were made with respect to language, study design or data collection (prospective or retrospective). Secondary references cited by the studies and review articles retrieved from the databases were reviewed. In addition, the search terms were translated into the respective languages of all 27 EU member states for web research using internet search services provided by Google and Yahoo in order to receive results from country-specific governmental or regional papers from the respective national statistical offices and authorities.

Calculation of disability-adjusted life years and conversion to monetary terms

Disability-adjusted life years (DALYs) represent the loss equivalent to 1 year of full health due to a specific disease, in this case TB. In brief, they are the sum of life years lost (YLL) due to premature mortality, *i.e.* the number of deaths due to TB multiplied by the standard life expectancy at the age at which death occurs, and

of the years lived with the disability (YLD), the latter gained by multiplying incident TB cases by treatment duration and disability weight for the condition: $DALY=YLL+YLD$.

The basic formula for calculation of YLL and YLD on a population basis are as follows: $YLL=[n/r](1-1-e^{-rL})$, where n is the number of deaths, L is the life expectancy at age of death (years) and r is the discount rate; and $YLD=[I \times DW \times L (1-e^{-rL})]/r$, where I is the number of incident cases, DW is the disability weight and L is the duration of disability (years).

For practical purposes we calculated the difference between life expectancy and average age at death from TB, summed across the EU-27 population and incorporated a 3% discount rate as well as a non-uniform age weighting (full equations are shown in the online supplementary material) [31]. In line with the Global Burden of Disease (GDB) study [32] we used an average disability weight for TB disease of 0.271. YLDs were calculated separately for drug-susceptible TB ($L=0.5$ years) and MDR-TB ($L=2$ years).

Finally, the resulting DALYs were multiplied by the long-established estimate of the European Commission of €52 000 as value of 1 life-year lost (VOLY) [33], derived from citizens' responses to willingness-to-pay questionnaires on the topic of air pollution mortality, which remains unadjusted in consideration of the fact that the TB burden weighs more heavily on the poorer EU member states than it does on the former EU core members [34].

Results

Direct costs

In the selection process 4278 citations and 241 websites were identified, of which only 12 scientific articles [35–46] and two websites [47, 48] were eligible for final inclusion, as they contained specific information on at least one of the cost components as listed above. To take into consideration the gaps in gross domestic product (GDP) per capita between the 27 present EU member countries, we presented separately the results for the EU-15 states (member countries of the EU prior to the accession of 12 candidate countries on May 1, 2004 comprising the following 15 countries: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden and the UK) and the other 12 countries that have since joined (table 1 shows figures of total treatment costs and table 2 shows the key features of all 12 studies included in our review).

Total costs of TB treatment for drug-susceptible and/or MDR-/XDR-TB could be obtained from the following countries.

UK

Aggregated governmental National Health Service data were available for the UK, in which a partitioning between hospital inpatients and outpatient visits was not provided, nor was cost of medication separately documented [47]. The total direct cost of treatment of a “normal” case of TB has been calculated to be around £5000 in 2009 (equivalent to €5864) and cost of treatment of a drug-resistant case between £50 000 and £70 000 or >£70 000 per patient (equivalent to €58 624 and €82 096, respectively). This estimate is less

TABLE 1 Countries for which total direct (treatment) costs of tuberculosis (TB) are available

	Costs per case € adjusted to 2012		
	Drug-susceptible TB	MDR-TB	XDR-TB
EU-15 member states			
France	5691	NA	NA
Germany	7751	55 003	188 466
UK	6234	62 343	NA
Netherlands	8340	46 990	148 136
Italy	9294	NA	NA
Finland	8242	NA	NA
Spain	9384	NA	NA
Mean value	7848	54 779	168 310
New EU members			
Estonia	2616	23 355	23 355

MDR: multidrug resistant; XDR: extensively drug resistant; EU: European Union; EU-15: 15 original member states of the EU; NA: not available.

TABLE 2 Characteristics of European Union studies included in the systematic review

Study [ref.]	Year	Country	Method used	Setting	Data available	Reference year for costs	Type of TB assessed	Sampling	Comments
Department of Health [47]	2009	UK	Pooled routine data	Governmental assessment	Total treatment costs	2009	‘‘Normal’’ and drug-resistant TB	NA	No distinction between inpatients and outpatients Local data, not representative of UK
WHITE <i>et al.</i> [35]	2000	UK	Retrospective analysis	Hospital data from St Bartholomew’s Hospital, London	Total treatment costs of adult HIV-negative patients	2000	Drug-susceptible and MDR-TB	9 MDR-TB and 18 drug-susceptible TB patients matched by age group and ethnicity 1996–1999	Local data, not representative of UK
DEUFFIC-BURBAN <i>et al.</i> [36]	2010	France	Modelling per patient	Unit costs were obtained from the French registers and drug costs from the pharmacy records of Tourcoing Hospital, Tourcoing	Total treatment costs	2007	Drug-susceptible TB only	NA	Figures embedded in cost-effectiveness analysis of latent TB infection diagnostics
French National Assembly# [37]	2011	France	Pooled routine data	Governmental assessment	Medication costs only	2009	Drug-susceptible TB, MDR-TB and XDR-TB	NA	
Bocchino <i>et al.</i> [38]	2006	Italy	Retrospective analysis	Division of Respiratory Medicine, University of Tor Vergata, ‘‘L Spallanzani’’, Rome	Total treatment costs of adult HIV-negative patients	2002	Drug-susceptible TB and MDR-TB	Review of the medical records of 92 TB cases 2000–2003	Local data, not representative of Italy
MONTES-SANTIAGO <i>et al.</i> [39]	2004	Spain	Retrospective analysis	Recalculation of governmental data (weighted averaging)	Total treatment costs	2006	Drug-susceptible TB only	Evaluation of routine data	TB patients assigned to the respective diagnosis-related groups
RAJALAHTI <i>et al.</i> [40]	2004	Finland	Retrospective analysis	Combined annual data of two University Hospital Districts (Pirkanmaa and Varsinais-Suomi)	Total treatment costs	2000	Susceptible TB only	27 culture-proven pulmonary TB patients	Local data, not representative of Finland
DIEL <i>et al.</i> [41]	2012	Germany	Modelling per patient	Weighted averaging of cost data, provided separately for children and adults	All types of costs calculated	2010	Drug-susceptible and MDR-TB	All TB cases reported in 2010 included	Epidemiological data and unit costs assessed according to the German public health insurance system

TABLE 2 Continued

Study [ref.]	Year	Country	Method used	Setting	Data available	Reference year for costs	Type of TB assessed	Sampling	Comments
BLAAS et al. [42]	2008	Germany	Retrospective analysis	Averaging of individual cost occurring in the University Hospital Regensburg, Regensburg	Total treatment costs	1998–2003	XDR-TB only	4 XDR-TB patients 1998–2003	
EKER et al. [43]	2008	Germany	Retrospective analysis	27 participating hospitals	Duration of hospitalisation	NA	MDR-/XDR-TB patients only	177 MDR-TB and 7 XDR-TB cases 2004–2006	37% of all culture-confirmed TB cases in Germany included
DE VRIES et al. [44]	2013	The Netherlands	Retrospective analysis	Costs derived from the official National Institute for Public Health and the Environment (RIVM) and Royal Netherlands Tuberculosis Association (KNCV) Tuberculosis Foundation data	Total treatment costs	2009	Drug-susceptible, MDR- and XDR-TB	1138 patients with non-MDR-TB and 20 with MDR-/XDR-TB	Complete country-wide review
Belgian Lung and Tuberculosis Association [48]	2012	Belgium	Pooled routine data	Governmental assessment	Medication costs only	2012	Drug-susceptible TB, MDR-TB and XDR-TB	NA	
RUMETSCHOFER [45]	2008	Austria	Retrospective analysis	Pharmacy records of the Otto Wagner Hospital, Vienna	Medication costs only	2008	Drug-susceptible TB, MDR-TB and XDR-TB	NA	
FLOYD et al. [46]	2012	Estonia	Retrospective cohort analysis	Average cost per patient treated according to World Health Organization guidelines	Total treatment costs	2003	MDR-TB only	Cohort of 149 TB cases (enrolled 2001–2002) followed	

TB: tuberculosis; NA: not available; MDR: multidrug-resistant; XDR: extensively drug-resistant. #: registered June 9, 2011.

than assessed in previous calculations by WHITE *et al.* [35], presenting costs of £6040 for a drug-susceptible TB case and £60 000 for a MDR-TB patient 9 years earlier.

France

In France the direct cost for a drug-susceptible TB case have been calculated at €5231.81 for the year 2007 [36], including medication costs of €268.20.

The cost figure for medication only is in line with the governmental estimation of medication costs [37], which is €250–450 for 6 months of short-course therapy. In addition, for the year 2009, a cost range of €27 330–44 235 is shown for treatment of MDR-TB and €46 614 of XDR-TB. However, these figures only refer to a duration of therapy of 12 months and, therefore, drastically underestimate the costs of a course of therapy as required by the previous [49] and current WHO guidelines [50]. These propose a minimum treatment duration of 18 and 20 months, respectively, after culture conversion for MDR-TB patients, *i.e.* usually a total of 24 months.

Italy

BOCCHINO *et al.* [38] investigated the treatment costs of TB taking into account all “fixed” expenses (€200.45 per day for hospitalisation and €50.12 per day for any outpatient visit) and by adding the cost of drugs, tests and procedures for each case. The resulting annual costs arising in 2002 were a median (interquartile range (IQR)) of €13 413 (€7364–20 194), but these costs also included 19% MDR-TB cases. Thus, the value of the lowest quartile, representing only a quarter of the cost data, *i.e.* €7364, was chosen as the cost of treating drug-susceptible TB.

Spain

For Spain, the cost of hospitalisation and the total TB cost can be extrapolated from the study by MONTES-SANTIAGO *et al.* [39], who calculated an amount of €8175.33, with 77% (€6279.31) for hospitalisation costs in 2006.

Finland

Recalculated from the detailed unit costs given for 2000, the mean costs for a 6-month treatment, which comprised of inpatient stays of only 14 days, amounted to €6673.10 per drug-susceptible TB case [40].

Germany

The most recent data for the direct costs for Germany, calculated by DIEL *et al.* [41], presented combined weighted inpatient/outpatient costs of €7363.99 per patient for drug-susceptible TB and €52 259 per patient for MDR-TB, with an average duration of hospitalisation of 30 days for drug-susceptible cases and 86 days for MDR-TB cases. The costs for XDR-TB patients were not included in this cost analysis, but according to BLAAS *et al.* [42], in 2004–2006 the costs of treating XDR-TB patients in Germany amounted to more than €170 000 per patient. As assessed by another German survey, the mean \pm SD treatment duration of XDR-TB cases as inpatients was 202 ± 130 days [43].

The Netherlands

In a recent retrospective analysis based on 1138 patients with non-MDR-TB and 20 with MDR-TB, DE VRIES *et al.* [44] calculated the total cost per patient. Costs due to drug-susceptible TB amounted to €7854, those due to MDR-TB to €44 250 and those due to XDR-TB to €139 500 [44].

Cost data for TB medication, but no figures for additional inpatient or outpatient costs, were available for the following two countries.

Belgium

According to the Belgian Lung and Tuberculosis Association, the cost of medication per TB case for 2012 ranges from €368 for a drug-susceptible TB case (6 months) to €14 307–41 229 for a MDR-TB case (18–24 months) and to €67 067 for an XDR-TB case (24 months) [48].

Austria

For 2008 there is an estimate of medication costs amounting to €277.50 for drug-susceptible TB and €22 291 for MDR-TB in 2008 [45].

To estimate the TB patient costs of countries for which total cost data are not available we used for the average of the aforementioned costs for susceptible TB. Thus, the assumed average direct costs (after adjusting for 2012) are €7848 for Austria, Belgium, Denmark, Ireland, Greece, Luxemburg, Portugal and

Sweden (table 1). An identical approach with respect to MDR-TB/XDR-TB results in average costs of €54 779 and €168 310, respectively.

Countries where total costs were not available

Estonia

In a recent publication by FLOYD *et al.* [46], in Estonia, one of the smallest of the FSU countries with a population of 1.3 million in 2010, the average costs per patient treated for MDR-TB including XDR-TB were assessed to be US\$8974 or €8530 (US\$1=14.7 kr and €1=15.65 kr) from a health system perspective in 2003. Of note, second-line anti-TB drugs are purchased at favourable conditions for Estonia by the Global Drug Facility (GDF), established by the WHO to help low- and middle-income countries access first- and second-line drugs at the lowest possible price; thus the medication costs per MDR-TB patient were only US\$2219 in 2003 (€2084; €3082 adjusted to 2012). Most EU countries are not eligible for these prices, but new member states such as Estonia, Romania and Bulgaria are. No figures are provided for drug-susceptible TB and XDR-TB. In the analysis by FLOYD *et al.* [46], 192 hospital days for MDR-TB patients were included at US\$30.50 (€28.65) for the first 60 days.

However, inpatient costs per day as low as €28.65 are very unlikely to cover the up-to-date costs of 2012. For 2005, the WHO figures [51] show inpatient bed costs per day (representing the “hotel” component of hospital cost only, *i.e.* excluding drugs and diagnostics) for Estonia of US\$95.24, US\$124.25 and US\$169.71 for primary, secondary and tertiary levels, respectively, corresponding with €76.57, €99.90 and €136.45, respectively (according to an average exchange rate of US\$1=€0.804 in 2005). Adjusted to 2012, hospitalisation costs in Estonia are €105.59 per day at a primary level. Therefore, we use the Estonia figure of €105.59 per hospital day at a lowest (primary) level as an average cost estimate; direct cost of treating a MDR-TB or XDR-TB patient in Estonia consequently adds up to 192 days multiplied by €105.59 (€20 273) plus medication costs of €3082, *i.e.* a total of €23 355.

Cost estimates for susceptible TB patients are completely lacking in the new EU states. According to the European Hospital Morbidity Database [52], the average length of hospital stay due to TB varies between 28 days (Slovakia) and 91 days (Lithuania), but there is no information on which proportion of TB patients are hospitalised, and data for Estonia, Romania and Bulgaria are not assessed at all; in addition, medication costs are mentioned nowhere in the literature.

A reasonable approach to cost estimation would be to compare the gross domestic product (GDP) between EU countries; the EU-15 that were part of the EU before 2004, and Cyprus, Malta and Slovenia have a comparable GDP. The average GDP per capita in 2011 for these countries was €28 979, varying between €16 100 for Portugal and €82 000 for Luxemburg [53]. In the nine remaining countries, on average, the GDP per capita is about a third of that, amounting to €9358 [54].

Accordingly, we estimate the total costs of treating a susceptible TB case in the new EU member states to be one-third of the mean in the old EU member states (€7848), *i.e.* €2616.

Charging for indirect costs

To arrive at total cost, a sum for the loss of productivity caused by TB must be added to these figures for direct treatment costs. The only precise calculation for loss of productivity due to TB in Europe was found in a study of the cost of TB in Germany by DIEL *et al.* [41]. In this study, loss of productivity is calculated at €2313 per case (€2434 adjusted to 2012) regardless of drug susceptibility, since drug-resistant cases only represent 2.1% of the total number of cases and some MDR-TB patients might go to work when still undergoing treatment. As different figures are not provided by any other study, it seems reasonable to use this amount as average for all cases in countries that were part of the EU before 2004 and Cyprus, Malta and Slovenia; the latter three have GDPs closer to the EU-15 than the newer members and are usually seen as belonging to the “high-income” European countries [53].

To calculate cost of productivity loss for the nine remaining countries we considered a third of the amount we used for the 18 other EU members as shown above for direct cost, *i.e.* €811, to be added for each patient to the respective direct cost.

Combining direct and indirect TB cost

For the EU-18 (EU-15 plus Cyprus, Malta and Slovenia) the calculations shown earlier would result in the following total average cost of TB per case, including cost of treatment and loss of productivity: drug-susceptible cases €10 282, MDR-TB €57 213, and XDR-TB €170 744.

The total average cost of TB in the nine remaining “new” countries then becomes: drug-susceptible cases €3427, MDR-TB €24 166, and XDR-TB €24 166.

Original cost data, as presented in the respective publications and the averages mentioned in the calculations earlier, were used to calculate the total cost of TB in the EU as shown in table 3. According to these calculations, the cost of TB in the EU adds up to over €537 million per year. It is conspicuous that in the “new” EU member states (as far as any assessment is possible) the cost of treating an XDR-TB case is only approximately one-seventh of that in the other EU states. This is largely due to the fact that more expensive medications such as linezolid, used to treat XDR-TB in wealthier countries, are not available at a discount and are therefore not affordable to the newer EU members. However, this does not have much influence on the total costs because of the low number of 136 XDR-TB cases notified in the whole EU. Beside the lower medication cost, the main reason for the difference is the much lower inpatient costs in those countries. Whereas the number of inpatient treatment days is comparable, e.g. 202 days in Germany and 192 days in Estonia, the inpatient cost of €296.31 per day in Germany differs substantially from the €105.59 per day in Estonia. It can be expected that in the future inpatient per-day costs, and consequently the cost of treating XDR-TB in the EU, will increase; considering the current gap between inpatient costs for TB patients and those assigned to other diseases. According to an analysis of Organisation for Economic Co-operation and Development data by FARRELL *et al.* [54], the average inpatient costs per day in the EU-15 states, irrespective of the type of disease, are in general much higher, varying between €533 (Germany) and €1639 (Denmark).

Monetary value of DALYs

In 2010, the most recent year for which data are available, the mean age of TB patients (notified cases) was 45.1 years, unchanged since 2001 [12]. Life expectancy in the EU-27 states, combined for both sexes, was 79.7 years [55]. Mortality in new, laboratory-confirmed pulmonary TB cases has been reported to be 6.6% as a treatment outcome and 13% for culture confirmed new MDR-TB cases after treatment duration of 24 months in the ECDC/WHO report [12]. Thus, the number of deaths due to drug-susceptible TB and MDR-TB/XDR-TB were 4642 ($70\,340 \times 0.066$) and 211 (1624×0.13), respectively, totalling 4854 deaths (rounded) in 2012.

The calculated YLL (detailed formula are provided in the online supplementary material) were 90 478.56 and the calculated total of YLD was 11 592.032 (drug-susceptible TB) plus 1033.026 (MDR-/XDR-TB). Multiplication of the aggregated 103 104 DALYs (rounded) by €52 000 per VOLY resulted in a total of €5 361 408 000.

Discussion

Our objective was to review and summarise the available evidence on cost and the cost components of TB and MDR-TB/XDR-TB in the EU. However, despite of a growing flood of epidemiological publications on TB and MDR-TB, aggregated TB costs in the individual EU member countries are sparse and information on the attributable cost components that may act as cost drivers is often incomplete.

Due to different health systems in the EU, there are considerable differences in refunding expenditures of diagnostics and treatment, and what makes the assessment of TB costs even more complicated methodologically is the fact that every country has its own way of monitoring and registering costs. Furthermore, the countries clearly depend on the generally differing pricing of pharmaceutical companies for identical drugs and the degree of eventual sponsoring by nonprofit organisations such as the GDF. Thus, with respect to the target cost components listed earlier, the data provided are quite heterogeneous. Indeed, there are only two studies providing weighted cost data both for drug-susceptible TB and for MDR-/XDR-TB [41, 44] in which the cost components had been comprehensively deduced from all the country-specific economic sources. For the majority of countries there were no data available at all, making extrapolation necessary.

Nevertheless, despite the limitations of our review, the best available cost data are part of the evidence needed for budgeting for and financing the expansion of TB services, especially with respect to scaling-up MDR-TB treatment. The increase of the number of cases of MDR- and XDR-TB is a real health threat but also raises an important concern about the rise of the cost of TB globally as well as in the EU. TB represents a high cost for the EU; summing nearly €537 million each year according to our conservative cost calculations and based on the ECDC/WHO Regional Office for Europe number of cases in the year 2011. Although TB rates are decreasing slightly, drug-resistant strains are on the rise, bringing an increase in treatment costs. No mention is made of MDR-TB and XDR-TB for 2011 in either Malta or Slovenia, and XDR-TB cases are reported in only 12 out of the 27 EU countries, although we can assume that such cost-driving cases were present in at least some of those countries.

We are aware that our calculations underestimate the real overall cost of TB in the EU. The study of DE VRIES *et al.* [44], the only one fully assessing costs due to TB cases as well as general costs, demonstrates that

TABLE 3 Pooled costs of tuberculosis (TB) disease including direct costs and loss of productivity in the European Union[#]

Country	TB cases 2011 [†]	Drug-susceptible TB cases	MDR-TB cases [†]	XDR-TB cases [†]	Cost per drug-susceptible TB case €	Cost per MDR-TB case €	Cost per XDR-TB case €	Total cost due to drug-susceptible TB cases €	Total cost due to MDR-TB cases €	Total cost due to XDR-TB cases €	Overall total cost €
Austria	687	662	19	6	10 282	57 231	170 744	6 806 684	1 087 389	1 024 464	8 918 537
Belgium	1044	1026	15	3	10 282	57 213	170 744	10 549 332	858 195	512 232	11 919 759
Bulgaria	2407	2352	55	NA	3427	24 166	24 166	8 060 304	1 329 130	NR	9 389 434
Cyprus	54	53	1	NA	10 282	24 166	170 744	544 946	24 166	NR	569 112
Czech Republic	600	591	7	2	3427	24 166	24 166	2 025 357	169 162	48 332	2 242 851
Denmark	381	378	3	NA	10 282	57 213	170 744	3 886 596	171 639	NR	4 058 235
Estonia	341	249	78	14	3427	24 166	24 166	853 323	1 884 948	NA	2 738 271
Finland [#]	325	320	5	NA	10 676	57 213	170 744	3 416 320	286 065	NR	3 702 385
France	4942	4902	40	NA	8668	57 213	170 744	42 490 536	228 8520	NR	44 779 056
Germany [#]	4316	4260	56	NA	10 185	57 487	190 880	43 388 100	3 219 272	NR	46 607 372
Greece	489	482	5	2	10 282	57 213	170 744	4 955 924	286 065	34 1488	5 583 477
Hungary	1445	1438	7	NA	3427	24 166	24 166	4 928 026	169 162	NR	5 097 188
Ireland	425	422	3	NA	10 282	57 231	170 744	4 339 004	171 693	NR	4 510 697
Italy	3521	3434	81	6	11 728	57 213	170 744	40 273 952	4 634 253	1 024 464	45 932 669
Latvia	885	778	95	12	3427	24 166	24 166	2 666 206	2 295 770	289 992	5 251 968
Lithuania	1904	1555	296	53	3427	24 166	24 166	5 328 985	7 153 136	1 280 798	13 762 919
Luxembourg [#]	26	24	2	NA	10 282	57 213	170 744	246 768	114 426	NR	361 194
Malta	33	33	NA	NA	10 282	24 166	170 744	339 306	NR	NR	339 306
The Netherlands [#]	1007	992	15	NA	10 774	49 424	150 570	10 687 808	741 360	NR	11 429 168
Poland	8478	8436	41	1	3427	24 166	24 166	28 910 172	990 806	24 166	29 925 144
Portugal	2540	2518	22	NA	10 282	57 213	170 744	25 890 076	1 258 686	NR	27 148 762
Romania	19 212	18 682	500	30	3427	24 166	24 166	64 023 214	12 083 000	724 980	76 831 194
Slovakia	399	396	3	NA	10 282	24 166	24 166	4 071 672	72 498	NR	4 144 170
Slovenia	192	192	NA	NA	3427	24 166	24 166	657 984	NR	NR	657 984
Spain	6762	6720	41	1	11 818	57 231	170 744	79 416 960	2 346 471	170 744	81 934 175
Sweden	586	569	17	NA	10 282	57 213	170 744	5 850 458	972 621	NR	6 823 079
UK	8963	8876	81	6	8558	64 777	170 744	75 960 808	5 246 937	1 024 464	82 232 209
Total	71 964	70 340	1488	136	NA	NA	NA	480 568 821	49 855 370	6 466 124	536 890 315

Data are presented as n, unless otherwise stated. MDR: multidrug resistant; XDR: extensively drug resistant; NA: no data available; NR: not reported. [#]: cost of 2011 TB cases adjusted to the year 2012; [†]: data from [18].

the costs due to TB of €29.49 million in 2009 in the Netherlands are mainly (61%) due to surrounding costs such as surveillance, screening of high-risk groups, follow-up and treating of contacts and BCG vaccination. The “net” cost in the UK only for detecting and treating latent TB infection and BCG vaccination in 2006 were estimated to be GBP 10.405 million (€15.264 million adjusted to 2012) by the calculations of the National Institute for Health and Clinical Excellence [56], indicating that costs directly linked to TB disease are meaningful but represent only a fraction of its whole financial impact.

Without new tools to control the disease, it is unlikely that the cost of TB will go down. With respect to the development of new vaccines, TBVI’s funding model proposes an investment of €560 million spread over 10 years. This cost is only slightly higher than the current cost of TB disease in the EU for 1 year based on 2011 cases, but, using a minimal discount rate of 3%, the net present value of an investment of €537 million at the end of 10 years would be ~€722 million.

Furthermore, taking into account the monetary equivalent of more than €5.3 billion for the 103 104 DALYs caused by the TB cases notified in 2011, there is no doubt that the economic burden of TB provides a good rationale for investing in the development of new, safe and efficacious vaccines. In line with the new EU standards for TB care [57], such an investment could clearly contribute to fulfil the goal of eliminating TB in the future.

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