The economic burden of tuberculosis in Cyprus. A probabilistic cost of illness study

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ABSTRACT

Introduction: Tuberculosis remains a major public health problem with considerable economic burden worldwide. The aim of this study was to estimate the economic burden of tuberculosis in Cyprus during 2009. In addition, this study is part of a major effort to track the economic costs of TB over time.
Methods: A retrospective probabilistic incidence-based cost of illness model was developed to calculate, from the societal perspective, the economic burden of the disease including direct medical costs, direct non-medical costs and indirect costs. The bottom-up approach (person-based data) was used for the calculation of direct costs while for the calculation of indirect costs the approach of human capital was employed. In addition, probabilistic sensitivity analysis with 1000 Monte Carlo simulations was performed in order to calculate a 95% Confidence Interval (CI).
Results: Mean per patient cost of tuberculosis in Cyprus in 2009 was estimated at €12,882 (95% CI: €12,747.35 – €12,964.32). Direct medical costs accounted for 83.07% of the overall expenses, €10,675 per patient (95% CI: €10,462.07 – €10,780.59). Total direct non-medical costs of €355 (95% CI: €353.04 – 364.29) accounted for 2.77% of the overall expenses whereas 14.16% of the overall expenses were associated with the indirect cost of €1,820 (95% CI: €1,815.20 – €1,873.65).
Conclusion: For the first time in Cyprus, the cost of tuberculosis was estimated using a probabilistic incidence-based cost of illness model. Our study confirms that tuberculosis is an expensive disease for the society. In addition, it provides important information to policy makers for the comprehension of the economic consequences of tuberculosis in order to draft the national health policy accordingly and strengthen surveillance of the disease.

Key words: Cost of illness; Tuberculosis; Burden of disease; Cyprus

INTRODUCTION

Tuberculosis (TB) is a major public health problem with high mortality and morbidity. It is estimated that between 19% and 43% of the world population is infected with Mycobacterium tuberculosis [1]. According Houben and Todd, in 2014, the global burden of LTBI was 23.0%, amounting to approximately 1.7 billion people, while

prevalence of recent infection was 0.8% of the global population, amounting to 55.5 (million individuals currently at high risk of TB disease [2]. It has been estimated that every minute there is a new tuberculosis infection worldwide [3].

Tuberculosis is a major significant cause of death from infectious diseases among adults and carries major burden for patients, their families, the community and public budgets(4). Tuberculosis is associated with a significant impact on quality of life, consequent reduction of productive time and economic burden on the society [4]. For a 10% increase in the incidence of tuberculosis worldwide, economic growth is limited at about 0.2-0.4%, which in absolute numbers amounts to 1.4-2.8 billion USD per year [5].

The increase in total costs incurred by a country for treatment, supervision and control of tuberculosis, is a natural consequence arising from the observed increase in cases of tuberculosis in recent years [6]. According to the World Health Organization the financial support required for a response to the global TB epidemic in countries with low or middle income is estimated at about US$ 8 billion per year in 2015 (excluding research and development for new TB diagnostics, drugs and vaccines) [7].

Tuberculosis in Cyprus currently affects a small proportion of the population (incidence 6.2 cases per 100000) [8], thus the disease has a minimal effect on the overall public budget. However, active TB cases have been on the rise in recent years, especially among immigrant groups. The incidence rate increased from 4 cases per 100000 in 2000 to 5.3 per 100000 in 2009 [9]. In addition, in the years between 1999- 2009, a total of 406 cases were reported, of which 261 involved immigrants (64.29%). A possible outbreak of the disease would not only threaten health of the population but the economy as well [4,5,10]. Furthermore, all medical services such as diagnostic procedures, hospitalisation and treatment of the disease are offered free of charge for all patients, exclusively by the public health sector, irrespective of their nationality. Specifically, for year 2009, 81.13% TB cases were foreigners. This comprehensive service provision by the Cyprus Government is part of the policy that aims to monitor, control and restrict the spread of the disease, as well as to prevent relapses and the emergence of resistant forms of the disease.

The fundamental objective of cost of illness studies is to evaluate the economic burden on the society due to the disease. Costs of illness studies are descriptive, aim to classify, give economic value and summarise the costs of a particular disease. The ultimate goal is to give an idea of the economic burden of disease. Therefore, when conducting such studies, researchers should recognise, record and measure the value of costs of the disease [11]. According to Clabaugh and Ward disease costing studies present useful opportunities for communication with both the public and the policy makers about the importance of particular diseases [12] thus, drafting their policies accordingly.

METHODS

Objective

The aim of this study was to identify and estimate the economic burden of tuberculosis in Cyprus for the year of 2009. This includes direct medical costs, the direct non-medical costs borne by patients and the indirect costs relating to the damage caused to society due to absenteeism from work. The costing of tuberculosis is of great importance for the policy makers as well as the doctors involved as it provides important information for the comprehension of the economic consequences of tuberculosis. In this context, this study is part of a major effort to track the economic costs of TB over time. Cyprus has gone through the worst economic recession of its history during 2012 - 2014. Cyprus also suffered from the world economic crisis of 2008. Furthermore, a major healthcare reform with the introduction of the National Health System will be introduced in 2019. For the above reasons, 2009 was chosen as the initial year for this cost of illness study, as it was the first year after the major world recession of 2008 and a follow up cost of illness study is scheduled for the year 2019. Therefore, the ten-year gap between the two studies will be sufficiently enough to identify any possible trend of the economic burden of the disease. In addition, 2019 will be the first year of the implantation of the new national healthcare system of Cyprus and any cost of illness studies during this year will serve as background knowledge for policy makers.

Study Design

This was a retrospective approach cost of illness study, based on incidence, focusing on both direct and indirect costs of the disease. The bottom-up approach (person-based data) was used for the calculation of direct costs (taking into consideration their lifetime costs of disease), while for the calculation of indirect costs; the approach of human capital was employed. The societal perspective is used which covers all aspects of costs such as direct medical and non-medical, and indirect economic costs.

Cost of illness studies based on incidence estimate the number of new cases of the disease in a given year and implement the lifetime cost (usually by cure or death) in these new cases [13]. Studies based on incidence are advantageous when the goal is to identify preventive measures. Studies based on incidence provide estimates of the savings that might occur if precautionary measures are applied and analysis of disease management during a specific period. Through this approach, researchers can develop clinical and treatment guidelines in order to increase efficiency and effectiveness, both overall and in each step of the disease management [14]. On the other hand, a prevalence based approach is not as

appropriate, since all incidences that occur in Cyprus are reported to the National Committee of Surveillance of Infectious Diseases Control.

In order to evaluate the indirect economic burden, a human capital approach was implemented. The human capital approach takes the perspective of the patient and considers every man-hour that was not worked by the patients as a corresponding loss in productivity [16]. Indirect costs of each patient depend on their income as well as the overall number of sick leaves from work. The per capita income as declared by the Ministry of Finance was used to calculate the lost income [16] and for 2009 is estimated as €57.15.

Time Frame and Population

The study population consisted of all active tuberculosis patients on treatment, who commenced hospitalised treatment from January 1 - December 31, 2009. In 2009, 55 new tuberculosis cases were reported in Cyprus. It is worth noting that tuberculosis incidence data correspond to 100% of the reported cases for the year 2009 because all tuberculosis new cases in Cyprus (diagnoses both at the private or public health care sector) are obligatorily reported to the National Committee of Surveillance of Infectious Diseases Control. As part of a continuous effort to ensure complete control of the disease, the overall costs of TB are borne by the Government for all patients diagnosed with tuberculosis [17].

Sample and data

In 2009, 55 new tuberculosis cases were reported in Cyprus. From those, 3 cases that were non-Cypriots refused any treatment and immediately left Cyprus. Of the remaining 52, a simple random sample of 26 cases was selected and their medical records were fully reviewed. Given some difficulties relating to the archive of the medical records, thus requiring several resources to extract all the data, a simple random sampling technique was used. Simple random sampling has the advantage of yielding a representative sample of the population. In order to build confidence for the calculations for the cost of tuberculosis the final sample was cross checked to ensure that it was representative of the population with respect to nationality, gender and age.

For the purpose of the study five types of data were recorded: a) incidence of tuberculosis in 2009, b) demographic data, c) medication consumption data, d) medical services utilisation and e) days of absenteeism from work.

Diagnosis of the disease

Diagnosis was defined according to the ICD-10 classification system, codes A15-A19 [18].

Cost Components

Direct Costs

The direct medical costs of active tuberculosis consist of hospitalisation, hospital outpatient care (visits to the doctor, either specialist or general practitioner), non-pharmacological interventions (inpatient and outpatient laboratory and radiology tests), pharmacological treatment, hospitalisation monitoring and nursing at home. For example, the overall cost of hospitalisation of tuberculosis patients throughout the treatment period was obtained by multiplying the total number of nights with the cost per night. The health professionals in this study included all staff dealing with tuberculosis patients, during the treatment and hospitalisation period as well as the treatment at home. For unit costs the market prices were used because of their reflection of the cost to society. In Cyprus healthcare services provision at public sector are substantially subsidized by the government, therefore the governmental hospital price list does not reflect the actual costs but merely hospital charges. On the other hand, all costs of anti-tuberculosis drugs as well as laboratory and radiology tests were calculated according to the standard government price list because the treatment is only offered by the government and no market prices exist.

The direct non-medical costs include transportation, meals and possible co-payment of medical treatment and drugs by the patients. As already mentioned, the treatment of tuberculosis in Cyprus is offered free of charge for all residents, exclusively by the public healthcare sector, thus no co-payment for medical treatment exists. The government rate of transportation provided by the Ministry of Finance was used to calculate the total cost of transportation by multiplying the distance from home to the hospital (both ways) for each patient with the cost per kilometre which is around €0.24/Km. The overall cost of food was estimated by multiplying the total number of visits with the average cost per meal of €5.00.

It is worth noting that only costs of diagnosis and treatment of active tuberculosis were included in the study and not any prevention costs. The reason for this is the nature of the disease. As tuberculosis is an infectious disease, individuals exposed to patients with pulmonary TB need to take chemoprophylaxis but this is dependent on each person's decision. That is why prevention costs are viewed as discretionary and they are not normally included in the cost of illness studies [19,20].

Indirect Costs

From the societal point of view, cost estimates of losses in productivity due to the disease have to be included in the cost of illness study. The Human Capital Method is the most common approach used to

calculate the indirect costs of an illness [21]. The human capital can be seen as the investment target through formal education and informal training that formulate the skills, the competencies, as well as the experience of an individual. The above constitutes the individual's productivity to the society. Historically, Cyprus enjoyed low unemployment rates. Especially for 2009 the unemployment rate was 5.4%. Furthermore, Cyprus had a well-educated work force with the university graduates to constitute the 34.1% and only 27.7% of the workforce of 2009 had an education level of lower secondary and below [22]. According to the human capital approach, indirect costs represent the loss of production for the economy due to the absence from the workplace on sick leave by a patient. Given the almost balanced, with respect to education, work force of Cyprus (as described above) and the difficulties to use the Friction Cost method due to unavailable data as well as the Willingness to Pay method due to extensive surveys that had to take place in order to find the stated preferences of the individuals, the human capital method was used to calculate the indirect costs. The Hanover Consensus states that any losses in productivity due to the disease should be estimated without consideration of any differences in the occupation, gender or age, using the average gross income for the period studied [23]. Thus, indirect costs included production loss due to sick leaves, and hospitalizations. The cost of production loss was estimated from an average salary of €57.15 per day in the Cypriot population [16].

Premature mortality

Premature mortality costs are derived by valuing potential years of life lost (PYLL) due to tuberculosis before the age of 65, the usual Cyprus retirement age. Dividing the potential years of life lost with the number of deaths gives an estimate of average years of life lost per death. On the other hand, high degree of uncertainty affects premature mortality due to illness and it is considered biased valuation of lost life [20,24]. Thus, costs relating premature mortality due to illness should be avoided or if calculated, they should be reported separately [20]. In 2009, only two patients died because of tuberculosis, thus a high degree of uncertainty surrounds this small number. Therefore, the productivity loss due to premature death is not included in the calculations for the overall costs of tuberculosis.

Extrapolation of costs to society

The study used bottom-up approach (person-based data) to quantify costs. Bottom-up approach assigns monetary value to the resources use and the productivity loss of individuals with the disease. A random sample was selected, thus, mean per-person costs can be extrapolated to the whole population bearing the disease using the appropriate incidence data [20]. The study includes a sample of 26 patients out of 52 that were diagnosed in 2009 and their characteristics are representative of the total incidence data. Therefore, given that tuberculosis incidence data correspond to 100% of the reported cases as mentioned above and a probabilistic sensitivity analysis aiming to capture any other potential unaccounted effects, an extrapolation of costs to society was performed.

Sensitivity Analysis

Sensitivity analysis is always recommended when uncertainty exists [25] and the results of such analysis must always be reported and evaluated in cost of illness studies [26]. Incidence-based studies include a number of assumptions and estimates, thus introducing a level of uncertainty [27,28]. Consequently, it is of great importance, a sensitivity analysis to be conducted that considers alternative values for all important cost parameters and assumptions in the study. Furthermore, another objective of the sensitivity analysis was to create a 95% Confidence Interval for the estimates as recommended by bibliography [20]. Point estimates are especially useful to describe and bring attention to the costs of an illness. On the other hand, an interval of possible costs has more trustworthiness for health policy analysis [29,30].

For the purpose of this study a probabilistic sensitivity analysis with 1000 Monte Carlo simulations was performed on all cost components using the gamma and the lognormal distributions that are appropriate for modelling costs [31,32] by applying a risk of ±25% on the mean cost values [33], a risk that Cyprus Government also recommends [34]. As, to the best of our knowledge, this is the first study involving probabilistic incidence based costing of tuberculosis in Cyprus, thus no prior information on distributions of costs is available or known. Therefore, separate sensitivity analysis was performed with the two above mentioned distributions but the confidence intervals reported are based on Gamma distribution [35].

In order to estimate costs Microsoft Excel 2007 [36] was used for the analysis. Monte Carlo simulations for sensitivity analysis were performed in R v.3.2.2 [37].

Ethics approval

Permission from the Ministry of Health (Ref No: Y.Y.21.11.49(4)) was obtained for data use for the purpose of the study.

TABLE 1. Demographic characteristics of tuberculosis patients (N=26) in Cyprus, in 2009

	N	PERCENT
Gender		
Male	16	61.54
Female	10	38.46
Type of Tuberculosis		
Pulmonary	15	57.69
Extra pulmonary	11	42.31
Nationality		
Cypriot	3	11.54
Immigrant	23	88.46
Age Range		
< 14 years old	2	7.69
≥ 14 years old	24	92.31

RESULTS

Selected patients' medical files were examined and their demographic characteristics are presented in Table 1. The majority were males (61.54%) and 57.69% had pulmonary tuberculosis. Cypriots represented 11.54% of the study sample and immigrants 88.46%. Finally, 92.31% were above the age of fourteen. No drug-resistant cases were reported in 2009.

Cost estimates

Table 2 demonstrates the total costs per patient (direct and indirect) born by Cyprus Healthcare Services and the patients. More specifically, direct medical expenses account for 83.07% of the overall expenses, €10,675 per patient. Direct medical costs consist of Visits to the doctor (€323 average per patient), Laboratory Tests and radiology (€2655 average per patient), drugs (€330 average per patient), Nursing at home (€345 average per patient), Hospitalization (€6369 average per patient) and finally Medical Attention per day spent at the hospital (€653 average per patient). Direct non-medical costs include transportation to the hospital and back home and meal consumption and they average at €355 per patient.

As mentioned above, the human capital approach was used to estimate the indirect costs. An average of €1,820 of lost income per patient was estimated which consists of 14.16% of the total tuberculosis cost.

The aggregated total economic burden of tuberculosis to the society for 2009 is represented in Table 3. The overall cost of tuberculosis to the Cypriot society is estimated at €668,226. Direct medical expenses are estimated at €555,114. The most important expense is the overall hospitalisation cost estimated at €331,200. Direct non-medical expenses amount €18,480. Finally, losses in productivity are estimated at €94,632, giving an overall cost of tuberculosis for the society of €668,226.

Sensitivity Analysis

Table 4 shows the 95% Confidence interval of the probabilistic sensitivity analysis that was performed on each cost component using two different distributions. The two assumed distributions demonstrate similar confidence intervals that are robust. Based on Gamma Distribution total direct medical expenses estimated at €10,675 per patient have a 95% CI of €10,462.07 – €10,780.59. Similarly, total direct non-medical costs of €355 (95% CI: €353.04 – 364.29) and indirect cost of €1,820 (95% CI: €1,815.20 – €1,873.65). The overall burden of the disease has a corresponding 95% CI of €12,742.35 – €12,964.32.

DISCUSSION

This is the first study performed in Cyprus that attempted to evaluate the economic burden of tuberculosis from the social perspective, with a probabilistic incidence-based approach. The objective of this study was to identify and estimate the economic burden of tuberculosis in Cyprus. The study found that the total cost of illness per patient is estimated at €12,882 (95% CI: 12,745.37 – 12,964.35). This cost includes medical direct costs (€10,675/patient, 95% CI: €10,462.07 - €10,780.59) and indirect costs (€1,820/patient, 95% CI: €1,815.20 – €1,873.65). Results of the study are different from those reported by Adamidi et al. [17] that estimated the mean per person cost of tuberculosis at €6,479.35. The difference can be attributed to the fact that Adamidi et al. used the hospital perspective consequently the costs estimated were based on hospital charges [17]. This study estimated the cost from the social perspective and market prices were used for the cost of illness.

In a literature review for the cost of tuberculosis in several European Union (EU) countries including Cyprus, it was reported that in 2012 the average cost per drug-susceptible TB incident was €10,282 [38]. Their methodology, however was not based on any Cyprus health data but on other's European countries overall costs of tuberculosis, adjusted for the Cyprus GDP.

Several EU countries have also calculated the overall costs of TB, such as France, Italy, Spain, Finland, the Netherlands and Germany. More specifically, in the UK the cost of tuberculosis was estimated at £5.000 (€ 5.864), in 2009, while for the MDR and extensive resistance tuberculosis costs, amounted to £ 50.000 to £70.000 (€ 58.624 - € 82.096) [39]. In France, in

TABLE 2. Direct and indirect costs of tuberculosis patients during 2009

TYPE OF COST	UNIT COST	ANNUAL NO.†	MEAN COST PER PATIENT (€)	
Direct Medical				**83.07%**
Visits to the doctor	€50.00/visit	168	323	
Medical Tests‡	n.a	n.a	2,655	
Medication‡	n.a	n.a	330	
Nursing at home	€17.00/hour	528	345	
Hospitalisation	€200.00/day	828	6,369	
Medical Attention Per day	€20.50/day	828	653	
Total			10,675	
Direct non-medical				**2.77%**
Travelling	€0.24/Km	35000	323	
Meals	€5.00	168	32	
Total			355	
Indirect				**14.16%**
Lost Income	€57.15/day	828	1,820	
Overall Total			13,206	

†Based on the sample

‡Includes all the relevant tests/ drugs of various prices

n.a: not applicable

TABLE 3. Annual total direct and indirect costs of tuberculosis during 2009, in Cyprus

TYPE OF COST	ANNUAL COST (€)
Direct Medical	
Visits to the doctor	16,800
Medical Tests	138,078
Medication	17,136
Nursing at home	17,952
Hospitalisation	331,200
Medical Attention Per day	33,948
Total	555,114
Direct non-medical	
Travelling	16,800
Meals	1,680
Total	18,480
Indirect	
Lost Income	94,632
Overall Total	668,226

2007, the costs were estimated at €5.231,81 [40], while in Italy in 2002 the total average per patient costs amounted to €7.364, per year [41]. Similarly, in Spain the total cost of the disease in 2006 was €8.175,33 per patient/year [42]. In Finland, the burden of the disease was calculated at €6.673,10 per patient [38] whereas in the Netherlands estimated the cost per patient, in 2013, was €7.854 per year [43]. Finally, in a recent study in Germany in 2012, the cost of TB was estimated at €11.239,71 per patient [44].

A large percentage of the total cost of illness is linked with direct medical costs (83.07%) at a mean cost per patient of €10,675 (95% CI: €10,462.07 – €10,780.59). This is similar to the results of Hasoumi et al. [45] that estimated the percentage of direct medical costs of TB in Tehran, in 2011 at 81.30%. It also compares with Germany that estimates the direct medical expenses at around 70% of the total burden of the disease [44].

Not many studies have included direct non-medical expenses in their calculations although it is recommended in the methodology for estimating the cost of illness [46]. Our study estimated this cost at €355 per person (95% CI: €353.04 – €364.29) accounting for 2.77% of the overall economic cost of tuberculosis, a finding similar to the result in Tehran of 2.90% [45]. On the other hand, it is considerably low if compared with a study done in Penang, Malaysia where the corresponding percent is 9.9% [47].

Furthermore, this study reveals that indirect costs are significant and should not be overlooked. The indirect cost associated with tuberculosis in Cyprus was estimated €1,820 (95% CI: €1815.20 – €1873.65) accounting for 14.16% of the overall costs. This is similar to the above mentioned studies with ranges in their estimates between

TABLE 4. Mean per person cost, 95% Confidence Interval based on Gamma and Lognormal distributions

TYPE OF COST	MEAN COST PER PATIENT (€)	95% CONFIDENCE INTERVAL GAMMA DISTRIBUTION (€)		95% CONFIDENCE INTERVAL LOGNORMAL DISTRIBUTION (€)	
Direct Medical					
Visits to the doctor	323	318.93	329.14	319.23	329.00
Medical Tests	2,655	2,662.77	2,745.96	2,590.86	2,672.67
Medication	330	324.14	334.40	316.86	327.01
Nursing at home	345	340.42	350.63	341.15	351.98
Hospitalisation	6,369	6,204.18	6,390.07	6,296.03	6,495.38
Medical Attention Per day	653	645.13	665.62	644.12	663.89
Total	10,675	10,462.07	10,780.59	10,545.19	10,886.03
Direct non-medical					
Travelling	323	318.70	328.70	317.76	328.12
Meals	32	31.52	32.50	31.68	32.69
Total	355	353.04	364.29	350.18	360.69
Indirect					
Lost Income	1,820	1,815.20	1,873.65	1,825.46	1,884.27
Overall Total	12,882	12,747.35	12,964.32	12,772.32	12,995.85

12.9% [47] to 20.6% [44]. In addition, the study in Tehran [45] estimated the indirect cost at 15.80%, almost matching our finding.

Several countries have estimated the cost of tuberculosis in their territory. The results of these estimates vary widely, because of the differences in their methodology, in data collection, the resources included, the monetary valuation of these resources, the patients concerned and the way they collected their sample. To make matter worse, prices in healthcare are different between the countries. Therefore, it is inappropriate to compare the costs in each study. On the other hand, these studies increase our knowledge of the financial and economic consequences of tuberculosis and provide important information for further economic analyses of dealing with the disease and its medication [48].

As with all cost of illness studies, this study also has limitations. The availability of data in Cyprus is scarce and if available heterogeneous. That is why it is typical to depend on sample data for health related research in Cyprus. However, probabilistic sensitivity analysis was conducted in order to account for the differences in the sample used. Another limitation of the study is that it only took into consideration for the calculation of indirect costs the absenteeism from work. The productivity lost when employees do get to work but do not optimally perform due to the illness was not taken into consideration. It is worth noting that in Cyprus a person will have to overcome the disease in order to get clearance to return to work. Nevertheless, some indirect costs of this kind do occur but were not taken into consideration due to lack of information.

CONCLUSION

This was the first study in Cyprus, which used probabilistic incidence-based cost of illness model to estimate the cost of tuberculosis. Our study confirms that tuberculosis is an expensive disease for the society. Furthermore, it provides important information to policy makers for the comprehension of the economic consequences of tuberculosis so as they can draft the national health policy accordingly and strengthen surveillance of the disease. A follow-up study will be performed in 2019 in order to examine whether there will be a rise of the economic burden of tuberculosis given the fact that Cyprus went into a severe economic crisis from 2012 -2014 and a new healthcare reform is scheduled to take place in 2019.

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