Cost of Tuberculosis in Childhood

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Abstract

Background: Cost of management of tuberculosis (TB) has high expenses from both patient and health insurance perspective.

Methods: A systematic review on cost analysis of TB in children was executed in Ovid-MEDLINE for the period 1991-2011. Search terms were tuberculosis, cost and childhood. Review articles, commentaries, letters were excluded.

Results: The first search resulted 156 articles, after linguistic and content screening 16 articles were considered for further analysis. The topics related to the cost-analysis were latent tuberculosis infection, BCG vaccination, cost-effectiveness of TB control program, TB screening, extrapulmonary TB, TB in resource rich and resource poor countries.

Conclusion: After processing the results of the articles, it was identified that tuberculosis screening among schoolchildren and kindergarteners as well as BCG revaccination is not cost-effective in low-burden countries.

Keywords: Cost-benefit; Cost-Effectiveness; Tuberculosis; Childhood; Latent Tuberculosis Infection; Tuberculin Skin Test; BCG Vaccination; Tuberculosis Control; Extrapulmonary TB; Developed Countries; Developing Countries

Introduction

Management of tuberculosis (TB) can result in significant economic burden in countries with high incidence and prevalence of TB. There were 8.8 million new TB patients and 12.0 million prevalent cases in the world in 2010. Most of the cases in 2010 occurred in resource poor countries such as Asia (59%) and Africa (26%). Smaller proportions of cases were detected in the Eastern Mediterranean Region (7%), the European Region (5%) and the Region of the Americas (3%) [1]. Extrapulmonary manifestation or co-morbidities and drug-resistant TB can cause additional cost-rise in the treatment of TB patients [2]. In 2010, there were 650 000 cases of multidrug-resistant TB (MDR-TB) globally. It is noteworthy that in the high-burden countries, the cost per patient treated is lower than the gross national income (GNI) per capita [1]. The costs of diagnosis and treatment of the disease are significant due to the increasing number of cases with HIV co-infections, MDR-TB and the introduction of directly observed therapy (DOT) [2].

Health economic analyses of TB can be aimed at different end-points. While the health economic studies in developing countries aims to select the patient population infected with TB where the treatment is cost-effective and so affordable, health economic studies in developed countries emphasize cost-optimisation of interventions [3-5].

Health economic analyses can be evaluated according to the perspective of the society, the health service financer or the patients. Categorization of the expenses is shown in Table 1.

Economic studies are represented with an increasing number in the medical literature. Economic analyses can help to maximize welfare and the economic investigations of different health interventions can be used to identify the most effective way of using available resources [6].

The aim of our study was to evaluate and summarize the result of TB health economic studies published in the last 20 years.

Materials and Methods

Systematic review of cost studies was carried out in 4 steps. First, an Ovid-MEDLINE search for the period 1991-2011 was applied using the search terms of cost and tuberculosis and childhood on 20th October 2011.

Second, publications had to meet with the following inclusion criteria: original article, text in English, no conflict of interest of the author that related to the publication and the search was focused on full texts. Review articles, commentaries and a letter were excluded. Third, in the systematic review, some studies were included on account of their key-word, cost" but cost analysis was not carried out or not TB patients or children were investigated in the trial. These publications were also excluded. Finally, co-morbidities (HIV/AIDS) were exclusion criteria on account of their cost-rise effect on the treatment. The remaining studies were categorized according to their topic.

Results

The first search resulted in 156 articles. The majority of trials were written in English but there were a few with an English abstract and a full text in another language (Hungarian:1, Spanish:4, Turkish:1, Portuguese:1, French: 1, Russian: 4, Japanese: 2, Italian:1, Danish:1,

Norwegian:1). After screening the language and the abstracts, our search for full texts resulted in 54 articles of which 17 were a review article. At the end of the search 37 original articles remained. Four articles were eliminated on account of the type of the publication. Nine publications without any original cost analysis and 4 others on account of co-morbidities, 3 proved not to be about TB and 1 article according to age >18 were excluded.
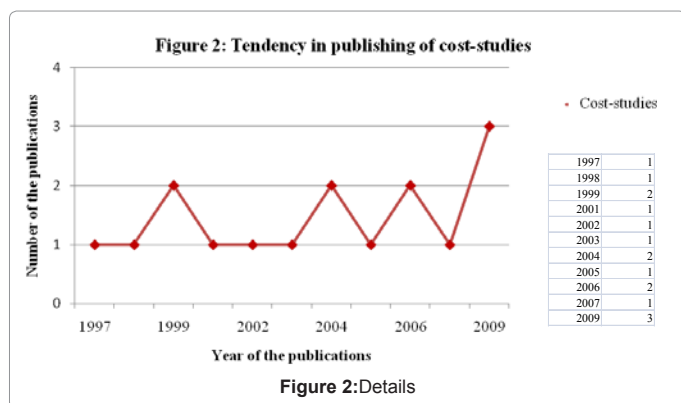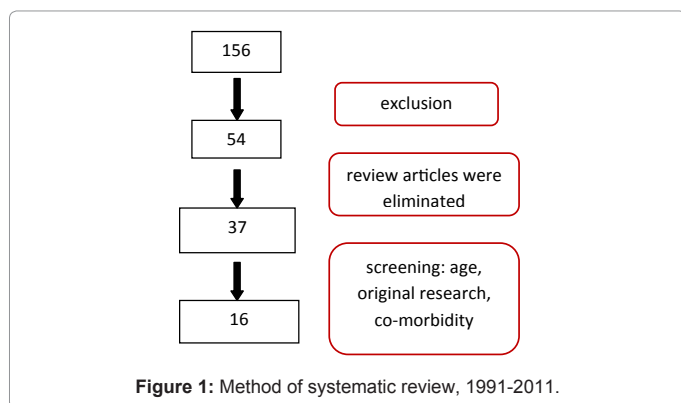
Finally, 16 articles could be considered after the total screening (Figure 1).

Categories of cost analysis were classified as latent tuberculosis infection, Bacille Calmette-Guérin (BCG) vaccination, cost-effectiveness of TB control program, TB screening, extrapulmonary TB, TB in resource rich and in resource poor countries.

The majority of the studies have been carried out in the United States (37.5%) and in developing countries (31.25%). Cost analysis studied mostly the investigation of total and medical direct costs. Indirect costs were analyzed only in few trials.

The investigated types of cost analysis in TB are shown in Table 2.

The most commonly studied topic was the cost of tuberculosis screening (n=4) and BCG vaccination (n=3) (Table 2). There was an increasing tendency in the number of the publications from the year 2004. The majority of cost-studies were published in the year 2009 (n=3) (Figure 2). There were significant differences between the cost of diagnosis and treatment in developing countries than that of developed countries. In developing countries, the cost of a short-course treatment per case was yarning (US $ 10-234). Interestingly cost of prevention resulted the highest expenditure in resource poor countries (Table 3).

Figure 1: Method of systematic review, 1991-2011.

Figure 2: Details

	Medical expenditures	Non-medical expenditures
Direct costs	• Medications • Hospital treatment, diagnostics, salary • Public primary care unit • Inpatient care, meal, heating and lighting charges	• Transportation • Sick pay • Home care
Indirect costs	• Extra costs on account of won life years	• Time lost from work • Community loss by reason of early death

Table 1: Classification of type of costs.

Type of study	Number	Excluded	Included
LTBI	4	2	2
BCG vaccination	3	-	3
TB control	2	-	2
Extrapulmonary TB	2	-	2
Tuberculosis screening	4	-	4
Cost of TB in developed countries	2	1	1
Cost of TB in developing countries	3	1	2
Total	20	4	16

Table 2: Type of the cost studies.

Latent tuberculosis infection (LTBI)

Definition of LTBI is the presence of *Mycobacterium tuberculosis* as predicted by a positive tuberculin skin test (TST) or interferon-gamma assays (IGRA) result but without clinical signs and symptoms or radiographic or bacteriologic evidence of TB. Without treatment, nearly 5–10% of persons with LTBI will progress to TB disease at some point in their lifetime [7]. It is recommended to screen individuals for LTBI who have an exposure to people with TB infection or have an increase risk of progression from LTBI to TB disease. Preferred treatment regimen of latent TB infection in children according to the Centers of Disease Control (CDC) and the American Thoracic Society (ATS) guidelines is 9 months isoniazid (INH) daily 10-20 mg/kg. Twice weekly isoniazid 20-40 mg/kg for 9 months, 10-20 mg/kg rifampin daily for 4 months can be also used as an alternate regimen. RMP/PZA for 2 months is not recommended because of hepatotoxicity observed in adults and the lack of clinical data in children. Treatment of LTBI may not be necessary in individuals without risk factors [7].

Adequate cost-effectiveness analysis requires information on the side effects of the comparable drugs.

Possible adverse effects of INH are elevated serum liver enzyme concentration (10-20%), drug-induced hepatitis (0.1%) and peripheral neuropathy (0.2%). Possible adverse effects of RMP are hepatotoxicity (0.6%), cutaneous reactions (6%), gastrointestinal symptoms and orange discoloration of body fluids [7].

Previous studies verified the cost-effectiveness of INH chemoprevention in contrast with not intitating long term treatment [8]. Cost of LTBI was examined in 2 studies.

Kandula et al. examined Mexican immigrants. Ten of 16 contact children received rifampin and pyrazinamide for 2 months. Mean age was 6 years and they had no co-morbidities, none were known to be HIV infected. Serious side effect was detected in one case. A 15 year old child developed asymptomatic drug-induced hepatitis. Cost effectiveness of the study was not the primary end point of the investigation. Other limitations of the study were the small patient number, the use of a

Authors	Years	Type of study	Direct cost	Indirect cost	Total cost	Average cost
Finnell et al	2009	A decision model LTBI	Cost of driving:$5 Cost of INH: US $1/month Cost of RMP:US $ 37/month Cost of visit: US $28/month Cost of treating reactivated TB: US$10 871	lost of parental work US $23		Medication, administration treatment of liver failure, TB reactivation RMP: US $1 173 INH: US $ 1 235 INH+RMP: US $ 1 364 No treatment: US $1 413
Kellerman et al.	1994-1995	retrospective, cost-effective analysis TB control program			Total cost of TB Control: US $15 270-28 158	
Pathania et al.	1995-1996	observational cost-benefit analysis BCG revaccination n=134 233	Revaccination: KCR15 million/year Benefit: KCR 13.7 million	Benefit : KCR16.56 million	Total cost of inpatient care: KCR 36 244/case Total cost of outpatient-care: KCR 10 644/case	
Rahman et al.	1996	hypothetical cohort cost-benefit cost-effectiveness analysis BCG revaccination n=2.86 million	Prevention: US $108 378/case TB treatment: US$ 11 576/case Maximum benefit: US $ 23.6 million		Total cost of revaccination: US $ 32.1 million	
Rahman et al.	1996	hypothetical cohort cost-effectiveness analysis BCG universal vaccination n=1.2 million	Cost of prevention: US$35 950-175 862 Cost of side effects: US$ 1.18 million		Total cost of vaccination: US$19.5 million	
Gounder et al.	1991-1995 1996-1998	follow up cost-benefit analysis school-based TB screening (TST) n=788 283	Cost of outpatient TB treatment: US$ 1400-8000/case Cost of hospitalization: US$ 18 588/case		Total cost of TST: US$3 623 550 Total cost of dg workup: US$ 443 800 Total cost of INH prophylaxis: US$1 597 680 ∑ US$5 665 030	
Brassard et al.	1998-2003	retrospective cost-benefit analysis immigrant school-based TB screening (TST) n=2524			Total cost of screening: C$193 461 Total cost of treatment of prevented cases: C$557 384 Total savingvs of school-screening: C$363 923	
Flaherman et al.	2007	cost-effectiveness analysis decision tree model kindergarten-TB screening	Estimated cost of TST: US$ 14.29/case Cost of RQ: US$ 1.41/case		Total cost of targeted TST: US$524 897 Total cost of universal TST: US$ 671 398 Total cost of no screening: US$ 0 Total saving with TT: US$ 1.27 million/year	
Diel et al.	2004	cost-analysis diagnostics and treatment of TB	Outpatient care with medication:€ 828.24 for culturally positive Culturally negative: €699.94 Nurses' salary: €323.06			
Garg	2005	prospective study chronic diarrhea in children abdominal TB n=3/50	charge of outpatient consultation: US $ 0.25			Average cost: cost of consultation, stool microscopic examination, medicines: US $ 10
Jha et al.	1994	cost-analysis cost-effectiveness analysis of forty health interventions in Guinea n= -	Cost of salary: 16% of total in centre, 23% of total in hospital Cost of drugs:73% of total in centre,23% of total in hospital Cost of overheads:11% of total in centre, 54% of total in hospital		Cost of short-course treatment in Centre: US$ 60/case Cost of short-course treatment in hospital:US$234/case	

dg-diagnosis, INH-isoniazid, KCR-Czech Koruna
MDR- multidrug-resistant, RMP-rifampin
RQ-risk factor questionnaire, TB-tuberculosis
TST-tuberculin skin test, TT-targeted tuberculin skin test

Table 3. Selected TB cost and cost-effectiveness studies

non-recommended version of LTBI treatment in children, and the lack of costs of childhood TB preventive treatment. Estimated cost of an uncomplicated course of RMP/PZA was ≤ US $219 per adult, compared to US $122 for 4 months of RMP monotherapy [9].

Finnell et al. calculated direct non medical costs that contain expenses of lost parental work and cost of driving. Total amount of administration was US $28 per monthly visit. Cost of treating reactivation pulmonary TB (US $10 871) and cost of liver failure (US $500 000) were estimated on account of previous studies. *Finnell* found that rifampin for 6 months is the least costly treatment model. It saves administration costs and it is effective against INH resistant bacteria not resistant to RMP. Combined regimen INH for 9 months and RMP for 6 months was slightly more effective than RMP monotherapy for 6 months but exhibited a cost over US $200 more per treatment. Three months of INH and RMP was the least costly (US $988) for all cases with INH resistance of <80% as long as the treatment effectiveness is >50% for susceptible bacteria (Table 3).

In conclusion, it seems that INH chemoprevention is the preferred treatment for LTBI, however, RMP is cheaper and caused hepatotoxicity much more rarely [10].

Extrapulmonary TB

Previous studies established the cost-rising role of extrapulmonary TB [2,11].

Extrapulmonary TB was investigated in 2 articles from developing countries. Van Lierop et al. studied pathological findings in tonsils or adenoids of children. In this study 1 of 172 children had nasopharyngeal tuberculosis. The analysis did not separate the cost of TB from other disorders of adenoids or tonsils [12]. *Garg* evaluated an algorithm for persistent diarrhea in children in North India. Abdominal TB was diagnosed in 6% of the study population. For diagnosis of TB, TST, chest X-ray and/or abdominal ultrasound and drug-susceptibility test were applied. Average cost per treatment was estimated US $10. Method of cost analysis was not explained [13].

Tuberculosis control

Two different studies dealt with TB control in developed and developing countries. Kellerman et al. studied the cost of pediatric TB control in 2 hospitals during a 2-year period. The total cost of TB control programs was US $15 270 and US $ 28 158. No patients with MDR-TB were admitted to the hospitals. Hospital expenditures for TB control interventions were assessed. Children's costs were much lower than estimated on the basis of hospital costs of adults. This study calls the attention to the expenditures for environmental TB controls at hospitals. Infection control personnel was estimated worth US $ 1680. The cost of TB isolation rooms resulted extremely high expenses

(US $20 000) [14]. Dick et al. examined the cost-effectiveness of an alternative TB control program for farm dwellers in South Africa. An increased cost-effectiveness of the role of farm health workers was introduced in TB control [15].

BCG vaccination

Three publications demonstrated cost analysis on BCG vaccination. Two studies investigated the cost-effectiveness of BCG revaccination. Pathania et al. found that direct costs of BCG revaccination exceed the benefits, especially in outpatient care in the low TB incidence Czech Republic. Their study was made from the perspective of health care financer. 134 233 children were examined. The direct cost of revaccination included the cost of the purified protein derivate (PPD) testing and the cost of revaccination. Direct benefit of revaccination was the marginal cost of treating the future cases of TB among tuberculin-negative children. Indirect costs included absence from work or school, the costs of TB morbidity and TB mortality. Cost of TB mortality meant the value of lost earnings due to TB mortality in young adults. The cost of TB morbidity meant the value of work loss or absence from school due to TB infection. Limitation of the study were provided that all costs were in Czech Koruna (KCR), and in turn they could not be compared to other studies created in USD. Direct costs of revaccination were about KCR 15 million annually, maximum benefits were KCR 13.7 million if treatment included hospitalization. If outpatient treatment was used, benefits of revaccination decreased to KCR 4 million. Direct cost of revaccination without testing was estimated to be KCR 12.45 million. The direct benefit was KCR 0.41-5.24 million [16].

Rahman et al. measured direct costs in Japan but indirect costs were not assessed in their study. A total of 2.86 million schoolchildren were investigated. Total cost of the revaccination program was US $32.1 million (Table 3). Cost of treating pulmonary TB was estimated to be about US $11 576 which was much less than estimated cost for prevention (US $108 378). Indirect benefit (loss of the work due to TB morbidity) was estimated to be US $1.6 million. Maximum benefits were US $23.6 million. The cost-benefit ratio was much less than one. The cost of BCG revaccination resulted much higher expenses than its benefits [17].

Rahman et al. investigated cost of BCG vaccination in Japanese infants. This study found very similar results to the above mentioned revaccination study (Table 4). They estimated cost of vaccination with a hypothetical cohort for 1.207 million infants. It was estimated that the efficacy of BCG vaccine could be around 40-60 %, cost of vaccination was US $35 950-175 862 to prevent a single case of TB which was 8 to 16 times higher than the cost required to treat one patient who had developed TB [18].

Rahman et al. 2000 **Revaccination** n=2.86 million	Direct cost		Direct cost	Rahman et al. 2002 **Infant vaccination** n=1.207 million
personnel	US $ 19.1 million		US $ 10.0 million	
BCG vaccines	US $ 5.0 million			
Multiple puncture disk	US $ 3.9 million		US $ 6.98 million	
PPD test kits	US $ 3.1 million		US $0.98 million	
PPD follow-up	US $ 1.0 million			
Treatment of BCG side effects	US $ 1.159 million		US $ 1.18 million	
Total	**US $ 32.1 million**		**US $ 19.5 million**	

Table 4: Cost of revaccination and infant vaccination.

Tuberculosis screening

Three of 4 clinical trials investigated the cost-effectiveness of tuberculin skin testing (TST) programs among schoolchildren. TST was used in both studies for TB screening. Gounder et al. measured the prevalence of LTBI and the cost-benefit of TST in new school entrants in New York. In this survey, low risk of TST positivity was found in primary school entrants [19]. Another Canadian trial suggested the cost-effectiveness of targeted immigrant children's school-screening with TST [20]. Comparing the screening expenditures, the cost of hospitalization of treated patients resulted in the highest costs (Table 5).

Kahn et al. found that the median days missed following TST administration were 3 days among schoolchildren. The state-funded average daily attendance was US $33 per student/per day [21].

Flaherman et al. examined the cost-effectiveness of TB screening before kindergarten entry. Cost-effectiveness of universal TST, risk factor questionnaire (RQ) and targeted TST (TT) for children with positive result for >1 risk factor and no screening was compared. They found that using TT instead of universal testing would save US $1.27 million annually. TB screening would be necessary in older age groups, in which the prevalence of TST positivity, the risk of developing active disease and the risk of transmitting disease were higher. According to their findings, TB screening among children who enter kindergarten was not recommended, and savings should be redirected to other cost-effective TB prevention methods [22].

Cost of TB in resource rich countries

Diel et al. established the direct outpatient, hospital and treatment costs of lung TB in Germany. Cost of diagnosis contained expenses of TST, chest X-ray, bacteriological confirmation with microscopic verification and/or culture with drug-susceptibility testing. In children the cheapest antituberculosis drug was INH (€0.26/day). The most expensive drug was RMP (€1.84/day). Outpatient therapy had much lower direct costs of € 785.47 for children, because of the lack of the long inpatient care which was an average of 50 days. Expenses on children were much lower than adults' outpatient costs (€ 785.47 vs € 1 225.98) [23].

Cost of TB in resource poor countries

Communicable diseases are the leading cause of hospital admissions in developing countries. TB has an important impact on the direct costs of hospitals. In a survey from Ugandas, the longest inpatient care was observed for patients with TB, accounting for about one-fifth (20.8%) of the total hospitalization time. HIV/AIDS and TB were the leading causes of death between the age of 15 and 54 years in a hospital in Uganda [24].

Two trials investigated the cost-effectiveness of the immunization and health interventions, subjects were not separated into children and adults. Total costs were estimated for both. According to Jha et al., majority of the costs of the interventions of a health center came from drugs, supplies and equipment (73%) and costs of salary (16%). Majority of the expenses were from overheads (54%), drugs (23%) and salary (23%) related to hospital interventions. The expenses of treatment of TB were about 4 times higher in hospitals than in a health center. Compared to other communicable diseases (malaria, pneumonia, diarrhea), curing of TB in hospital had the highest costs. The effectiveness of short-course therapy, cost per year of life saved were higher in hospital than in health centre, however the efficacy was the same. Costs of travel and of time lost from work were not calculated [25]. Peny et al. studied the financial requirements of immunizations against diphtheria, pertussis, tetanus, hepatitis B, Haemophilus influenza type b, yellow fever, meningitis A and C, rotavirus, human papilloma virus, malaria, Streptococcus pneumonia and tuberculosis. For vaccination a cumulated sum of US $30 billion were estimated from 2004 to 2014 in developing countries. Separated cost of TB vaccine was not calculated [26].

Discussion

The results of this systematic review show that there is an increasing tendency in the number of the economic publications from the year 2004, in line with the observation of previous studies [6]. The most commonly studied topic was the cost of tuberculosis screening and BCG vaccination.

In low TB incidence countries direct costs of BCG revaccination exceed the benefits, especially in outpatient care from the perspective of health care financer. However total cost of the revaccination may reach US $32.1 million.

Tuberculosis screening among schoolchildren and among kindergarteners proved to be non cost-effective in resource rich countries. However, TB screening could be more cost-effective for immigrant children and in elderlies.

It was demonstrated that outpatient care of TB can be more cost-effective than hospitalization [19,23] as previous studies suggested [2,27,28].

Some controversial results were found in the studies regarding with the cost of LTBI. According to ATS/CDC guidelines INH for 9 months is the preferred treatment but in this paper it was verified that RMP for 6 months can be more cost-effective than INH. However, only 2 articles evaluated the cost of LTBI in our review. More comparable cost-effective studies should be undertaken to identify the cost-benefit model of LTBI in the future.

There is an important contrast between the availability and affordability of the health care services and resources in TB treatment between developing and developed countries.

However, our study has some limitations, only one database was used for the systematic review and consequently a small number of studies was included.

In conclusion, it was identified that tuberculosis screening among schoolchildren, kindergarteners and BCG revaccination is not cost-

Gounder et al.1991-1998		n=788 283	Brassard et al. 1998-2003	n=2524
Outpatient cost of TB treatment	US$ 1 400-8 000/case		Total cost of DOT:C$ 1228/case	
Hospitalization	US$ 18 588/case		Total cost of hospitalization: C$ 10 848/case	
Total cost of TST program	**US$ 5 665 030**		**Total cost of screening C$ 193 461**	
Cost per case prevented	US$ 123 153		Total cost of treatment of prevented cases: C$ 557 384	

Table 5: Comparison of cost of school-screening.

effective in low-burden countries. The low number of papers indicates the need of more cost-benefit and cost-effectiveness analyses in the future to identify the cost-effective procedure in countries with limited resources.

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