REVIEW ARTICLE

Economic Impact of a Vaccine Preventable Disease: A Scoping Review on Tuberculosis

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ABSTRACT

Using pulmonary tuberculosis (pTB) as an example of a vaccine-preventable disease (VPD), we aimed to gather evidence on the economic impact of treating a case or managing an outbreak of a VPD. A scoping review was conducted. Online databases (MEDLINE and Google Scholar) were used to collate published studies from the year 2015 to 2019 on the management cost of one case or an outbreak of pTB. Keywords used were cost, treatment, outbreak, pulmonary tuberculosis, tuberculosis, economic, economic evaluation. A total of 29 studies were analysed. The costs of pTB treatment for individual patient were higher in high-income countries compared to middle-income and low-income countries. A case of pTB can result in household catastrophic health expenditure; while an outbreak can overwhelm the health system's capacity, and disrupts the economy of a country. Therefore, accessibility of vaccines especially in low-income countries must be ensured. Also, vaccine-hesitant individuals must reconsider their stance on vaccination.

Keywords: Vaccine-preventable diseases, Pulmonary tuberculosis, Economic impact, Vaccine hesitancy

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INTRODUCTION

As of October 2010, there are 11 diseases that are part of the recommended childhood immunization schedule from birth to 18 years. The main vaccine-preventable diseases (VPDs) targeted by the Expended Program on Immunization (EPI) are tuberculosis (TB), diphtheria, tetanus, pertussis, measles, hepatitis B, rotavirus, Haemophilus influenzae type B (Hib), Streptococcus Pneumoniae infection and yellow fever.

According to the World Health Organization (WHO), in 2017 there was an estimated 19.9 million infants worldwide who did not receive routine immunization services such as three doses of the diphtheria, tetanus and pertussis (DTP) vaccine (1). Apart from the recognized problems of access to vaccines in low-income countries, there seems to be a new worrying trend globally, which is vaccine hesitancy (2,3). The WHO in 2019 declared it as one of the Ten Threats of Health (4). The WHO defines vaccine hesitancy as the "reluctance or refusal to vaccinate despite the availability of vaccines" (3). Vaccine hesitancy can contribute to reduced population immunity (or herd immunity), which may result in localized outbreaks or cases of infection in specific groups or populations (7). Regardless of the reasons of no vaccination, the economic costs of managing a case of VPDs is high. Moreover, because VPDs are infectious diseases, their management not only involves the patient, but also the contacts and ultimately the nation. The management of any disease incurs costs, hence preventing people from contracting the disease should be the way forward, as in the case of VPDs. Perhaps if the providers of vaccines and the users are aware of the real-life economic impact of not being vaccinated, this knowledge could be one of the encouraging factors in overcoming the inaccessibility of vaccines and/or the hesitancy in using vaccines.

Therefore, using pulmonary tuberculosis (pTB) as an example of a VPD, we conducted a scoping review to identify and map the available evidence on the economic impact of treating a case or in managing an outbreak of pTB. Specific question was: What are the economic costs and impact, of managing one case of TB, or its outbreak to a community and/or country?

METHODS

This review considered published studies on the cost incurred in the management of one pTB case or

an outbreak of pTB. The design of the search strategy was done according to the broad Population-Concept-Context (PCC) mnemonic recommended by the Joanna Briggs Institute for scoping reviews (8). Population was cases of pTB of any nation, sex and age; Concept was the cost of treating pTB in the specified currency, while Context was the perspective of the economic evaluation, be it providers', patient's or societal. Keywords used for the review were cost, treatment, outbreak, pulmonary tuberculosis, tuberculosis, economic, economic evaluation.

This review consists of three steps. The first step was literature search in databases MEDLINE and Google Scholar, followed by an analysis of the words contained in the title and abstract. The second step was screening of the full text versions of the articles two reviewers separately, to determine whether the articles fulfilled the inclusion criteria. Disagreements of the decisions were resolved through discussion (4). Thirdly, the reference lists of all articles were hand-searched for additional studies. Papers found through snowballing of eligible systematic reviews were also screened and subsequently reviewed.

Eligibility criteria

The inclusion criteria were aimed to find only published studies and papers (of which full-text journal articles were available), limited to materials in the English language and published between the years 2005 and 2019. Editorials, articles on methodological aspects, protocols, reviews, replies, comments, correspondences, conference proceedings, viewpoints, and protocols were excluded.

Study selection

After the reviewers independently assessed the titles and abstracts, eligible full-text articles were retrieved and again screened against the inclusion criteria. Any disagreements were resolved through discussion or involvement of a third reviewer (2).

Data charting

Methodological features were extracted into the adapted JBI Template Study Details, Characteristics and Results Extraction Instrument (JBI Reviewer's Manual) (9). The study details charted were citation details (e.g. author/s, year of publication, country), population (study population and the conduct of the study), concept (the cost of treating pTB in the specified currency) and context of costs (perspective of the economic evaluation).

Costs remained in local currencies of the year of the study or US dollars (USD) as reported by the original researchers. To put the costs into perspective, some costs were compared against the GDP per capita of the country in which the study was conducted, adjusted to the year of the currency of the cost in the study.

RESULTS

Study characteristics

Systematic searches yielded 423 records. After the assessment, a total of 29 studies were included in the final analysis. All studies were cross-sectional studies, either using prospective and retrospective data collection method. Several studies used secondary data. The outcomes of the evaluations were either the cost of treatment per patient, the costs of management of one out-break or the incidence of catastrophic health expenditure, as summarized in Table I.

Based on the findings of the reviewed studies, the costs of pTB treatment for individual patient in high-income countries ranged from 17% to more than 60% of the countries' per capita growth domestic product (GDP). For example, in the United States of America (USA), a study found that the costs of treating and managing cases of active pTB disease was United States Dollar (USD) 34,600 in 2015 which was more than half (61%) of the per capita GDP the country in that same year (5). Another study in the USA, the average hospitalization expenditure for pTB disease per person (including multiple hospitalization episodes) among privately insured patients was USD 28, 058 (also almost 60% of the per capita GDP) (6). In Cyprus, pTB treatment per person was €12,882 estimated at approximately 52% of their GDP per capita (7). Similarly, in Spain, the mean cost of treatment of a patient involving both direct and indirect costs from diagnosis to rehabilitation in 2014 was € 10,262 (almost 50% of their per capita GDP) (10). In Germany, the mean outpatient costs per case were €11,240 (about 28% of their per capita GDP) (11). In Australia the median cost of treating drug susceptible pulmonary pTB was AUD 11,538 (approximately 17% of the per capita GDP) (12).

As for the middle- and low-income countries, based on the findings of the studies reviewed, treatment of individual pTB cases in these countries constitute lesser percentage of the countries' GDP. In Iran, treatment cost per person was USD 2,588 in the year 2011 (approximately 38% of their GDP per capita) and USD 1,409 in the year 2015 (approximately 26% of their GDP per capita) (13,14).

The pTB treatment costs were found to be lower in Yemen at USD 142 (approximately 11% of their GDP per capita (15). In China the average total cost of inpatient was CNY13007 (approximately 27% of their GDP per capita) (16), while in Malaysia, one study showed that the cost of pTB treatment was USD 726 (9.9% of their GDP per capita) (17), while another study showed that it was USD 916 (18).

The costs of TB treatment for individual patient were higher in high-income countries, which ranged

Table I: Cost of pTB treatment

Country, year	Study population and the conduct of the study	Perspective	Cost, (currency year)	Note
United States of America, 2017 (5)	Systematic review of the United States of America (USA) literature. Estimated costs of treating and managing cases of active TB disease in California, based on published figures in the USA and operational data of the California Department of Public Health.	Provider	Average direct cost of treating and managing a TB case = US$34,600 (range of average 16,600–61,300), (year 2015).	
United States of America, 2017 (6)	Retrospective review of in-patient claims data on private insurance claims for reimbursement for TB hospital admissions in the 2010-2014 MarketScan® commercial database. Estimated the hospitalization expenditures for tuberculosis (TB) disease among privately insured patients in the United States	Patient	Average hospitalization expenditure per person (including multiple hospitalizations) = USD 28058 (95%CI USD 26632-USD 29484), (year 2014).	
Cyprus, 2018 (7)	A retrospective probabilistic incidence-based cost of illness model developed to calculate direct medical and non-medical costs and indirect costs, Estimated the economic burden of tuberculosis in Cyprus during 2009.	Societal	Mean per patient cost = €12,882 (95% CI: €12,747.35 – €12,964.32), (year 2009) Direct medical costs = €10,675 per patient (95% CI: €10,462.07 – €10,780.59) Indirect cost was €1,820 (95% CI: €1,815.20 – €1,873.65).	Direct medical costs accounted for 83.07% of the overall expenses per patient. Total direct non-medical costs accounted for 2.77% of the overall expenses whereas 14.16% of the overall expenses were associated with the indirect cost.
Spain, 2016 (8)	Prospective multi-centre study. Determined the direct (hospital stays, visits, diagnostic tests, and treatment) and indirect (sick leave and loss of productivity, contact tracing, and rehabilitation) costs of pulmonary TB patients.	Societal	Average total cost = €10,262.62 ±14,961.66, (year 2014-2015)	Costs increased significantly when associated with hospital admission, polymerase chain reaction, sputum smears and cultures, sensitivity testing, chest computed tomography, pleural biopsy, drug treatment longer than nine months, DOT and sick leave.
Germany, 2012 (9)	Retrospective review of documents to estimate the mean direct outpatient and combined in- and outpatient costs of TB, and other attributable costs of the disease. Calculations of the direct costs are based on the rates established by the uniform appraisal scale and Institute for the Hospital Remuneration System data for the German diagnosis-related groups (DRG) system.	Society	The outpatient costs (rounded) per case = €1,197 (adults) and €1,006 (children) for standard therapy (year 2011). The combined in-patient/outpatient costs = €7,364 (adults) and €7,300 (children), respectively (year 2011).	The costs due to loss of productivity = €2,313. Costs per case for rehabilitation = €74 Cost for contact tracing = €922.
Australia, 2017 (10)	Retrospective record review of patients in a single tertiary referral hospital. Estimated cost of treating drug susceptible pulmonary TB enrolled in a single tertiary referral centre.	Provider	Median cost = AUD 11,538 (range 5,820 – 170,119), (year 2012-2014)	Approximately 50% of total costs was derived from inpatient hospitalisation bed days.
Iran, 2014 (11)	Cross-sectional study of patients in health centers of the Ministry of Health and Ministry of Education. Calculated the cost of illness of tuberculosis in Tehran	Societal	The average costs per patient = 28,467,737 Rials (USD 2,588 dollars) for direct medical costs (2011) The average costs per patient = 1,011,360 Rials (92 dollars) for indirect medical costs and The average costs per patient = 5,533,020 (503 dollars) Rials for indirect costs. Overall, average costs per patient was 35,056,170 Rials.	Most of costs were related to hospital costs
Iran, 2017 (12)	Retrospective study of all new smear positive pulmonary TB patients who had been registered at the district's health network between April 2013 and December 2015 and had successfully completed their treatment were entered into the study (45 patients). Treatment costs were estimated using activity-based costing (ABC) method. Estimated the cost of smear-positive drug-susceptible pulmonary tuberculosis treatment of the patients in the Azadshahr district, Golestan Province, Iran.	Provider	The cost of treating a new smear-positive pulmonary TB patient = USD 1,409 (Iranian Rial, 39,438,260) (year 2015).	
Yemen, 2012 (13)	Prospective cross-sectional study. Determined the costs associated with tuberculosis diagnosis and treatment for the public health services and patients in Sana'a, Yemen.	Patient and provider	Patient cost: for pulmonary TB treatment = US$ 108.40 (year 2009) Provider cost: for pulmonary treatment was US$ 34.00 (year 2009)	For pulmonary and extra pulmonary TB, drug treatment represented 59.3% of the total cost to the provider. The greatest proportionate cost to patients for pulmonary TB treatment was time away from work (67.5% of the total cost), and for extra pulmonary TB was laboratory and X-ray costs (55.5%) followed by transportation (28.6%).
China, 2019 (14)	Cross-sectional cost analysis of active TB patients who lived in Jingkou District, Runzhou District, Dantu District, or Xin District who were diagnosed and treated in the No.3 hospital of Zhenjiang City from April 2014 to March 2015. Determined the inpatient service expenditures.	Patient	The average total cost to inpatients = Chinese Yuan 13007.91 ±5205.58 (year 2014-2015)	Despite advances in TB insurance policies, there were substantial costs associated with TB diagnosis and treatment. TB patients still face a heavy financial burden.

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Table I: Cost of pTB treatment (Continued....)

Country, year	Study population and the conduct of the study	Perspective	Cost, (currency year)	Note
Malaysia, 2014 (15)	Prospective, incidence-based study design, in a government outpatient specialist clinic among all new smear positive PTB patients who were diagnosed and successfully completed their treatment at the study site between March 2010 and February 2011. Determined the cost of treatment of smear positive pulmonary tuberculosis patients	Provider and patient	The provider cost was = USD 325.35 per patient) (year 2010-2011) The patient cost = USD 401.90 per patient, (about 5.7% of study respondents' annual family income.).	
Malaysia, 2018 (16)	Retrospective and prospective prevalence-based partial pharmacoeconomic evaluations. All types of direct costs were obtained from different hospital departments while the indirect costs to the patient were estimated by interviewing 30 patients who were randomly selected. Determined the cost of treatment of smear positive pulmonary tuberculosis patients in a government hospital	Societal	The cost of treatment = USD 916/patient (year 2003)	
Tajikistan, 2010 (17)	Cross-sectional study among new pulmonary TB patients enrolled in the DOTS program in 12 districts between 2006 and 2007. Determined the patient costs of TB in the former Soviet Union.	Patient	Average total illness costs per TB episode = Tajik Somonis $1053 ± 1601 (USD 4900 purchasing power parity, PPP) (year 2006-2007).	The illness-related costs of an episode of TB exceed the per capita GDP of $1600 PPP about two-and-a-half times.
China, 2010 (18)	Questionnaire survey of patients currently on treatment in eight TB dispensaries in two provinces and in-depth interviews with providers at the facilities. Measured patient expenditure on additional drugs and tests in public services where tuberculosis (TB) drugs are supplied for free.	Patient	Cost to patients of various drugs and tests prescribed/ month = Chinese Yuan 287 (USD 40)	For patients below the poverty line, drug and test expenditure was 1.85 times their average household monthly income.
Ethiopia, 2016 (19)	Cross-sectional cost-of-illness analysis conducted between September to November 2015 among 576 randomly selected adult TB patients who were on directly observed treatment in 27 public health facilities in Addis Ababa, Ethiopia. Determined treatment cost of adult TB patients on DOTs.	Patient	Direct (Out-of-Pocket) mean cost = $123.00 (± 58.8) (year 2015). Indirect (loss income) mean cost = $54.26 (± 43.5) (year 2015).	Despite the availability of free-of-charge anti-TB drugs, TB patients were suffering from out-of-pocket payments with catastrophic consequences.
Ethiopia, 2018 (20)	Longitudinal study among new TB cases from January 2015 through June 2016 in 10 woredas (districts) of southwestern Ethiopia. Direct out-of-pocket, payments, and lost income (indirect cost) were solicited from patients during the first 2 months and at the end of treatment. Assessed pre- and post-diagnosis costs to TB patients.	Patient	Direct out-of-pocket expenses during the pre-diagnosis periods amount to median (IQR) of US$21.64 (10.23-48.31) (year 2015). Direct out-of-pocket expenses during the post-diagnosis periods respectively amount to median US$35.02 (0-70.04), (year 2015).	
China, 2016 (21)	Retrospective review of data from the baseline survey of the China Government – Gates Foundation TB Phase II program in 2013. Assessed the incidence, intensity of catastrophic health expenditure (CHE) relating to TB care in China.	Patient	The incidence of CHE = 66.8 % using the household income measure (year 2013) The incidence of CHE = 54.7 % using non-food expenditure (capacity to pay) (year 2013)	Households defined as experiencing CHE if their annual expenditure on TB care: (a) exceeded 10 % of total household income; and (b) exceeded 40 % of their non-food expenditure (capacity to pay)
Indonesia, 2018 (22)	Cross-sectional study among adult TB and multidrug-resistant TB (MDR-TB) patients in urban, suburban and rural areas of Indonesia who had been treated for at least one month or had finished treatment no more than one month earlier at primary health centers (PHCs) linked with the country's National TB Program (NTP). Assessed the costs of treatment and the incidence of catastrophic total costs due to TB.	Patient	The median (IQR) of total costs incurred by households =USD 133 (55–576), (year 2016). The incidence of catastrophic total costs in all TB-affected households was 36% (43% in poor households and 25% in non-poor households).	Catastrophic total costs were defined as total costs (direct and indirect costs) incurred by household that exceed 20% of the household's annual income. Households earning below USD 1.9 per capita per day was classified as poor households.
India, 2018 (23)	Mixed-method design among TB patients in Puducherry district, where there was free care for TB under the national tuberculosis program (NTP). Estimated patient costs during diagnosis and intensive phase of treatment and determined the proportion of households experiencing catastrophic costs.	Patient	The median (IQR) total cost of TB care = USD 195 (52.1, 492.9), (year 2016) The median (IQR) direct cost = USD 65.3 (22.3, 156.5), (year 2016) The median (IQR) indirect cost = USD50.2 ((0.9, 295.1), (year 2016).	Catastrophic cost was defined as total tuberculosis care costs exceeding 20% of annual household income. Overall, 32.4% of households experienced catastrophic costs due to TB care.
Burkina Faso, 2013 (24)	Cross-sectional study of smear positive pulmonary TB patients in six rural districts of Burkina Faso between the years 2007and 2008. Determined out-of-pocket expenses (direct costs) associated with TB according to the different stages of their healthcare pathway.	Patient	Median (IQR) direct cost associated with TB =USD 101 (53.1, 172.4), (year 2007-2008) This cost was equal to 2.8 months of household income.	A total of 72% of patients incurred direct costs during the pre-diagnosis stage (i.e. self-medication, travel, traditional healers' services), 95% during the diagnosis process (i.e. user fees, travel costs to various providers, extra sputum smears microscopy and chest radiology), 68% during the intensive treatment (i.e. medical and travel costs) and 50% during the continuation treatment (i.e. medical and travel costs).

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Table I: Cost of pTB treatment (Continued....)

Country, year	Study population and the conduct of the study	Perspective	Cost, (currency year)	Note
Nigeria, 2013 (25)	Cross-sectional cost-of-illness study among all new adult smear-positive or smear negative pulmonary TB patients registered in the three rural hospitals between January and August 2011 in southeast Nigeria. Estimated the comprehensive costs of TB diagnosis and treatment (intensive phase) from the patients' perspective in an under-resourced high TB/HIV setting.	Patient	The total cost of TB care per household was $592 (year 2011); corresponding to 37% of median annual household income pre-TB.	Patient and household costs for TB care are potentially catastrophic even where services are provided free-of-charge
China, 2016 (26)	Cross-sectional study of TB cases from three cities selected using a stratified cluster sampling method in Zhenjiang City, Jiangsu Province in eastern China; Yichang City, Hubei Province in central China; and Hanzhong City, Shaanxi Province in western China. Direct non-medical costs related to TB treatment were collected using in-person interviews.	Patient	The median (IQR) non-medical cost = RMB 1429 (424–2793), (year 2013) About 20 % of all respondents had their non-medical costs exceeded 40 % of their non-food expenditure, while 37 % reported that these costs exceeded 10 % of their annual household income.	The non-medical costs typically include payments for transport, accommodation, and the cost of nutritional supplementation during the treatment period.
United States of America, 2012 (27)	Cost analysis of TB outbreak among homeless persons using a Homeless Shelter between the years 2007 and 2011. Estimated the costs of providing supportive resources for 24 patients with TB disease treatment during an outbreak-associated cases.	Provider	Supportive resources alone to provide successful treatment for these 24 patients with TB = $204,500 (year 2011)	Costs excluded the costs of health-care services. All 24 cases completed or were continuing treatment as of December 2011
Peru, 2016 (28)	Cross-sectional prospective study among TB patients in the national TB program which included interventions such as economic support (cash transfers) and social support (household visits and participatory community meetings). Investigated the economic effects of a TB-specific socioeconomic intervention among 32 shantytown communities in Peru.	Provider	Cash transfer total value averaged US$173 (equal to 3.5% of TB-affected households' average annual income) (year 2015-2015)	Cash transfer mitigated 20% of households' TB-related costs. The mitigation impact was higher among poorer households.
Africa, 2016 (29)	Cost-of-illness method. Future non-health GDP losses were discounted at 3%. Estimated future gross domestic product (GDP) losses associated with TB deaths in the African Region for use in advocating for better strategies to prevent and control tuberculosis.	Provider	The average total non-health GDP loss = Int$66 872 per tuberculosis death (year 2014)	Tuberculosis deaths in the African Region in 2014 decreased the non-health GDP by International Dollars (Int$) 50.4 billion.
Denmark, 2015 (30)	Retrospective review of national databases. Evaluated the economic burden of tuberculosis (TB) in Denmark due to health-related costs (health system contacts and –procedures, medications) and socio-economic parameters (foregone earnings and social transfer expenses).	Societal	Employment income deficiency was € 11,635 before vs. € 13,885 after diagnosis.	Excess health costs in the 2 years around diagnosing and treating TB were € 10,509. Cases received an average excess public transfer income of € 3,345 before vs. € 3,121 after diagnosis. Spouses also had lower income, more social transfer, and posed higher health-related costs than matched controls.
Benin, 2014 (31).	A retrospective cross-sectional study among smear positive TB patients ≥15 years old of the selected districts who were enrolled The survey covered the period from onset of TB symptoms to the completion of the DOTS treatment. Patients' expenses related to examination and laboratory tests, consultation fees, drugs, hospital care, transport to healthcare providers, services provided by traditional healers, food supplements, self-medication and traditional remedies. In-kind spending was estimated in local currency by the patients during the interview	Patient	One-half of the households spent over 2.1 months of their income to care for the person with tuberculosis (IQR, 1.0–4.1). The median of the direct economic burden was 17.8% (IQR, 8.4–34.4%) of the annual household income. The median indirect cost was 131 (IQR, 77–207) days lost by the patient because of illness and care-seeking and waiting for consultation; 30 (IQR, 3–87) days were lost by informal caregiver and guardian.	
United States of America, 2017 (32)	Retrospective electronic record review of TB patients in two tertiary hospitals and one community hospital, New York. TB cases in hospitals which had delayed diagnosis were chosen. Estimated person-hour costs required by infection control staff to investigate a single hospital-based TB exposure, in two tertiary hospitals and one Community hospital in a large health care system in metropolitan New York City.	Provider	Used 15-20 hours of work per exposure plus 30 minutes of follow-up for each exposed staff member.	Time from admission to isolation averaged 3.3 days, with a mean of 41 staff exposed per patient.

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Table I: Cost of pTB treatment (Continued....)

Country, year	Study population and the conduct of the study	Perspective	Cost, (currency year)	Note
Australia, 2013 (33).	Retrospective cost analysis study. Determined the costs of treating TB after a medical officer working in a metropolitan New South Wales (NSW) neonatal intensive care unit (NICU) was diagnosed with active pulmonary tuberculosis (TB). Involved 125 neonates, 165 of their relatives and 122 health care workers.	Provider	The estimated total cost to the hospital for this screening investigation = AUD 128 430 (year 2011).	Cost of time nurses spent on neonatal screening cost = AUD 24 489 (year 2011) Cost of Chest Clinic registered nurses also conducted the relative and health care worker screening = AUD 14 913. Cost of neonatologists and paediatricians reviewed the neonates at the screening and medical review clinics = AUD 19 059. Cost of respiratory physicians interviewed and counselled the families of exposed neonates at the initial screening clinics = AUD 9148.

AUD – Australian Dollar CHE – Catastrophic Health Expenditure DOT – Directly Observed Therapy IQR – Interquartile Range NTP – National TB Program
PHC – Primary Health Centre PPP – Purchasing Power Parity US – United States USD – United States Dollar

from 17% to more than 60% of the countries' GDP, compared to middle- and low-income countries (9.9% to 38% of the countries' GDP), could be due to the absence of highly subsidised national TB programs in the high-income countries, in addition to the fact that healthcare costs are generally higher in richer countries compared to poorer countries. Nonetheless, despite the lower costs of pTB treatment in low- and middle-income countries, people in these still face financial difficulties in getting treatment for pTB. Therefore, in these countries, apart from determining the cost TB treatment per person, studies also focused on how the treatment of TB resulted in catastrophic health expenditure among the households of TB patients. For example, in Tajikistan, illness-related costs of an episode of pTB was about two-and-a-half times more than their per capita GDP of $1600 purchasing power parity (PPP) (19), while in China among patients who were below the poverty line, drug and test expenditure was almost twice of their average household monthly income (20). In Ethiopia, the mean total cost of pTB illness to patient was USD 177, which USD 123 was direct out-of-pocket cost to the patients. This direct cost was catastrophic for 63% of pTB patients (21). Another study in Ethiopia noted that the direct and indirect out-of-pocket costs of TB was approximately USD 56 (22). In China, TB treatment resulted in 55% of households experience catastrophic health expenditure (21); in Indonesia 43% of poor households and 25% of non-poor households (24) and in India it was 32.4% (25). In Burkina Faso, the pTB treatment cost was also high, equivalent to 2.8 months' worth of household income (26), while in Nigeria one study showed that the median total cost of pTB care per household was USD 592; corresponding to 37% of median annual household income pre-TB (27). The abovementioned studies showed that despite the availability of highly subsidised or free-of-charge pTb treatment, pTB patients can suffer from out-of-pocket payments with catastrophic consequences.

As pTB treatment requires frequent visits to the healthcare facility, the Out-of-Pocket expenditure incurred by the patients for non-medical items could be high. For example, in a study in China, it was found that about 20 % of all respondents reported that their non-medical costs were more than 40 % of their non-food expenditure, while for 37 % of the respondents, the costs exceeded 10 % of their annual household income (28).

Treatment of TB requires that the patient is adherent to the treatment regime. In order to ensure adherence to treatment, some countries provide social assistance to TB patients. Social assistance included housing support, cash, food, transportation or treatment for TB disease by directly observed therapy. These assistance costs are high in TB treatment. For an example, in ensuring homeless patients complete their pTB treatment, the United States Communicable Disease Center (US CDC) spent approximately USD 8,520 per person on social assistance during an outbreak of TB involving 24 individuals in a shelter for the homeless (29). In Peru, the government gave cash transfer to pTB patients in 32 shanty towns, in order to prevent pTB patients from experiencing CHE. The total cash transfer was equivalent to 3.5% of TB-affected households' average annual income (30).

Treatment of TB affects not only the individual patient and his/her contacts, but also the country. Due to the prolonged nature of the disease, the productivity of the patient and even the country could be negatively affected. For example, the average total non-health GDP loss was estimated as International Dollars 66,872 per tuberculosis death in Africa. As a result, TB deaths in the African Region in 2014 decreased the non-health GDP by International Dollars 50.4 billion (31). In Germany, the mean cost due to loss of productivity per patient was estimated as €2,313 in year 2009 (11). Similarly, in Denmark, an average employment income deficiency was € 11,635 before diagnosis of pTB versus € 13,885 after diagnosis (32). The study in Benin also showed that the median indirect cost was 131 days lost by the patient because of illness and care-seeking and waiting for consultation; 30 days were lost by informal caregiver and guardian (33).

These studies also showed that outbreak management

of TB cases used a substantial amount of resources, particularly human resource and laboratory tests, as pTB outbreak management also includes contact tracing, contact screening and provision of post-exposure prophylaxis. In circumstances where TB was missed as a possible diagnosis, the health care facility involved could face calamitous consequences. For example, a study showed that an additional workload of almost 40 hours was required for managing a contact of a pTB index-case (34). Another study of a TB case in health care facility also described the extensive use of resources, in addition to high levels of anxiety for the relatives of the patients. In that study, the diagnosis of one infected neonatal intensive care unit (NICU) staff resulted in the contact tracing and screening of 125 neonates, 165 relatives of the neonates and 122 health care workers (35).

CONCLUSION

The findings in this review illustrate the magnitude of economic impact faced by an individual, community and country in managing pTB. The costs of treating pTB in one individual can be more than half of the country's GDP per capita. Even when the treatment costs are not very high because of the availability of highly subsidised or free-of-charge treatment, an episode of pTB can put the patient's household into catastrophic health expenditure, whereas an outbreak can overwhelm the health system's capacity to carry out daily activities and manage the outbreak. Additionally, productivity of the individuals affected by the outbreak are reduced, and at a macro level this can disrupt the economy of the country including trade and travel.

The most cost-effective way to prevent the economic impact of TB or its outbreak is to ensure adequate and timely vaccination of the target groups. The unavailability of vaccines in several low-income countries must be addressed urgently. Additionally, as vaccine hesitancy is an additional burden to a persisting problem of vaccine unavailability, the realization of the economic impact of VPD should encourage vaccine-hesitant individuals to reconsider their stance on vaccination.

The major limitation to this review is that the studies were not nationally representative. Instead they were conducted in one or several health facilities, or in one or several parts of a country. Therefore, the results of the studies could only be limited to those study sites and not generalizable. It is recommended that a nationwide costing study is conducted especially in countries where TB incidence is high.

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