Chapter 19

Economic Evaluation of Diagnosis Tuberculosis in Hospital Setting

Luciene C. Scherer

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/54479

1. Introduction

Tuberculosis (TB) is an ancient disease, but not a disease of the past. After disappearing from the world public health agenda in the 1960s and 1970s, TB returned in the early 1990s for several reasons, including the emergence of the HIV/AIDS pandemic and the increase in drug resistance. More than 100 years after the discovery of the tubercle bacillus by Robert Koch, what is the status of TB control worldwide? The evolution of global TB control policies, including DOTS (Directly Observed Therapy, Short course) and the Stop TB Strategy, and assess whether the challenges and obstacles faced by the public health community worldwide in developing and implementing this strategy can aid future action towards the elimination of TB.(Lienhardt, Glaziou et al. 2012) The report of the Commission on Macroeconomics and Health of the World Health Organization has emphasized that tuberculosis is the most common of the infectious diseases. Tuberculosis is one of the most important health problems in the world, causing 1.4 million deaths each year, in 2011. (WHO, 2010)

The most of TB cases (82%) was concentrated in 22 countries around the world. In the year of 2010, in Brazil were detected 81946 cases, with 5000 death (WHO, 2010).

In Rio Grande do Sul, a state in extreme south of Brazil, the incidence of TB in 2011 was 46,1 per 100.000, with 4947 new cases. Porto Alegre, capital of Rio Grande do Sul shows incidence of 116 in 2009.(Sul 2011; Brazil 2012)

Tuberculosis is the first cause of death in patients with AIDS in Brazil. Patients with co-infection HIV/TB have had in treatment of Tuberculosis probability of worst outcome.

Rio Grande do Sul, has had the major incidence of TB/HIV co-infection. The co-infection adversely affects the lives of individuals in both the biological and psychosocial aspects. (Neves, Canini et al. 2012)

Some factors can be considered as risk factors for co-infection of TB and HIV, as the impoverishment of the population, use of injecting drugs, the disruption of services on the epidemiology of TB control, the delay in the diagnosis of TB and increased risk of acquiring multi-drug resistant TB (MDRTB), essentially associated to the expansion of the disease in the world.(Kritski, Lapa e Silva et al. 1998). Multidrug-resistant tuberculosis (MDR-TB) is a major clinical challenge, particularly in patients with human immunodeficiency virus (HIV) co-infection.(Nathanson, Nunn et al. ; Farley, Ram et al. 2011; Arjomandzadegan, Titov et al. 2012; Jain, Dixit et al. 2012; Udwadia 2012)

For the above, in recent years became consensus that the epidemic of TB in developing countries demands the evaluation of broader approaches, described in the Plan STOP-TB/OMS control global TB 2006-2015.

Among them have been prioritizing the implementation of:

a) improvements in access to diagnostic system user health; b) culture for mycobacteria in every patient suspected of TB and HIV positive and all TB patients in retreatment; c) sensitivity test for suspected cases of resistant TB (retreatment cases, treatment failure, contact MDR-TB or have been treated at the Health Unit with a high rate TB-MDR/XDR); d) review and economic evaluation under routine conditions of deployment of new technologies (phenotypic or molecular, automated or not) for the early diagnosis of TB, resistant TB patients with paucibacillary TB, HIV-infected or suspected drug-resistant TB.

Early detection of tuberculosis (TB) is essential for infection control. Rapid clinical diagnosis is more challenging in patients who have co-morbidities, such as Human Immunodeficiency Virus (HIV) infection. Direct microscopy has low sensitivity and culture takes 3 to 6 weeks (Sharma, Mohan et al. 2005; WHO 2006). Diagnostic testing for tuberculosis has remained unchanged for nearly a century, but newer technologies hold promise for a revolution in tuberculosis diagnostics. Tests such as the nucleic acid amplification assays commercial and in house technologies allow more rapid and accurate diagnosis of pulmonary and extrapulmonary tuberculosis.(Rodrigues Vde, Queiroz Mello et al. 2002; Sanchez, Rossetti et al. 2006; Scherer, Sperhacke et al. 2007; Scherer, Sperhacke et al. 2011; Hida, Hisada et al. 2012). Xpert MTB/RIF (Xpert) is actually a promising new rapid diagnostic technology for tuberculosis (TB) which has characteristics that suggests large-scale roll-out.(Vassall, van Kampen et al. 2011). In developing countries, *in house* Polymerase Rhain reaction (PCR) based on amplifying the IS*6110* insertion element can be used for the amplification of *Mycobacterium tuberculosis* (MTB) DNA and offers the potential of a sensitive, specific and rapid diagnostic for ruling out or considering pulmonary tuberculosis (PTB) (Mehrotra, Metz et al. 2002; Sarmiento, Weigle et al. 2003; Schijman, Losso et al. 2004; Flores, Pai et al. 2005).

The appropriate and affordable use of any of these tests depends on the setting in which they are employed (Perkins 2000; Brodie and Schluger 2005). New tools for TB diagnosis, treatment and control are necessary, especially in health settings with a high prevalence of HIV/TB co-infection.

Although TB is one the greatest causes of mortality worldwide, its economic effects are not well known, especially in Brazil. Despite the fact that the families did not have to

http://dx.doi.org/10.5772/54479

pay for medications and treatment, given that this service is offered by the State, the costs to families related to loss of income due to the disease were very high. The proportion of public service funds utilized for prevention is small. Greater investment in prevention campaigns not only might diminish the numbers of cases but also might lead to earlier diagnosis, thus reducing the costs associated with hospitalization. The lack of an integrated cost accounting system makes it impossible to visualize costs across the various sectors.(Costa, Santos et al. 2005)

To make rational decisions about the implementation of new tools in the medical routine, cost-effectiveness studies are essential(Mitarai, Kurashima et al. 2001; Kivihya-Ndugga, van Cleeff et al. 2003; Hazbon 2004).

A key step in cost-effectiveness analysis is to identify and value cost. The economic concept of opportunity cost is central to cost-effectiveness analysis. When a public health agency spends money to provide health care, this money is not available for housing, education, highway construction, or as a reduction in income taxes. When a health care organization spends money for bone transplantation, this money is not available for example for mammography outreach or something. When an elderly man spends time being vaccinated for influenza, this time is not available to play golf or to work. An overall conceptual goal in cost-effectiveness analysis is comprehensive identification of all costs of the intervention and its alternative, including all of the opportunity costs.

Contributors to cost must be identified before the costs can be valued. The terms used to describe the contributors to cost (e.g. direct costs, indirected costs, opportunity costs) are used in different ways in different textbooks and in published cost-effectiveness analysis.

The definition of cost terms is the opportunity cost is the value of resources in an alternative use, the direct cost is the value of all goods, services, and other resources consumed in the provision of an intervation or in dealing with the side effects or other current and future consequence linked to it and the productivity costs are the costs associated with lost or impaired ability to work or engage in leisure activities and lost economic productivity due to death attributable to the disease. These costs have been substituted for indirect costs. There are several categories of direct costs. The first category of total direct cost is direct health cost, this category include costs with tests, drugs, supplies, personnel, equipment, rent, depreciation, utilities, maintenance and support services. The second category of total direct cost is direct non- health care cost, these cost include for example the cost to patients to partake of the intervention e.g., transportation, child care, parking). The third category of total direct cost is the cost of informal caregiver time, this is the monetary value of the time of family members or volunteers who provide home care. The fourth category of total direct cost is the cost is the cost of the use of patient time. Such studies provide insight into the composition of different cost components, which may be the most important factor from the patient and the health service's perspectives. Recent studies have compared the cost effectiveness of news tools for diagnosis, treatment and control in Tuberculosis.(Amicosante, Ciccozzi et al. ; Kowada, Deshpande et al. ; Baltussen, Floyd et al. 2005; Barbieri, Wong et al. 2005; Bachmann 2006; Dwolatzky, Trengove et al. 2006; Kominski, Varon et al. 2007; Kowada,

Takahashi et al. 2008; Rosen, Taylor et al. 2010; Shi, Hodges et al. 2010; Vassall, van Kampen et al. 2011; Fitzpatrick and Floyd 2012; Lienhardt, Raviglione et al. 2012; Mandalakas, Hesseling et al. 2012). In a recent study we compared the cost-effectiveness of direct microscopy by Ziehl Neelsen staining (AFB smear) with *in house* polymerase chain reaction (PCR) and with culture on the first sputum specimen collection, including staff costs, using culture and clinical evaluation as the gold standard (Scherer, Sperhacke et al. 2009). In contrast to the cost-effectiveness analysis described by van Cleef et al. in a reference ambulatory clinic in Kenya, where only culture for mycobacteria was used as the gold standard (Roos, van Cleeff et al. 1998; van Cleeff, Kivihya-Ndugga et al. 2005). The cost-effectiveness of the AFB smear plus PCR dot-blot strategy described in recent study was similar to other strategies, when lower TB prevalence made PCR more expensive for diagnosis of PTB (Roos, van Cleeff et al. 1998; van Cleeff, Kivihya-Ndugga et al. 2005). (Scherer et. aL., 2009).

The mathematical models may be particularly useful for predicting the long term tendency of occurrence of the infection or disease. These models can simulate situations epidemiological and preventive or curative interventions beyond their theoretical impact in reducing the problem. Such predictive models properly formulated and fed with consistent data, may assist the processes of planning and management in public health. Currently several strategies have allowed the use of Multiple Logistic Regression (MLR) in the construction of predictive models. Models of decisions trees are also used for classification decision making or to provide a decision algorithm for the clinical management of infectious diseases.(Aguiar, Almeida et al. 2012)

For developing countries, the emergence of continuous technological innovation represents a double burden. The rapid diffusion of scientific and technical information that are observed now and monetary action multinational companies create a local demand for innovation by health professionals, the media and more informed portions of the population, which further strains the health care system.

Many factors limit the realization of a health technology assessment (HTA) analysis, as the lack of human resources, infrastructure or budget or due to lack of evidence or information costs.

Another obvious problem is that often decisions are based on scientific evidence coming from developed countries and often in settings where the incidence of disease differs effusively of Brazilian and Latin American scenario.

Given this scenario health managers are often between two objectives: they have to incorporate new and more costly technologies to improve the health of the population and at the same time are responsible for the financial sustainability and access equity of this in the system health.(Project 2005)

Beyond the suffering caused directly by the disease, TB is requiring significant portions of the public budget in developing countries. It is estimated that by 2015 they will be required investments around $12 billion for control of diseases such as AIDS, TB and Malaria. The increased costs involved in care and control of TB are due also to the increasing number of

http://dx.doi.org/10.5772/54479

cases of resistant bacteria to different types of chemotherapy. (Polansky, Dymer et al. 1968; Garcia Rodriguez, Marino Callejo et al. 1994; Weis, Foresman et al. 1999; Gomes, Soares et al. 2003; Elamin, Ibrahim et al. 2008; Kik, Olthof et al. 2009; Steffen, Menzies et al. 2010; Vassall, Seme et al. 2010; Pereira, Barreto et al. 2012)

Costs of TB diagnosis and treatment may represent a significant burden for the poor and for the health system in resource-poor countries. Costs incurred by TB patients are high in Rio de Janeiro, especially for those under DOT. The DOT strategy doubles patients' costs and increases by fourfold the health system costs per completed treatment. The additional costs for DOT may be one of the contributing factors to the completion rates below the targeted 85% recommended by WHO (Steffen, Menzies et al. 2010).

Even in a country with a good health insurance system that covers medication and consultation costs, patients do have substantial extra expenditures. Furthermore, our patients lost on average 2.7 months of productive days. TB patients are economically vulnerable. (Kik, Olthof et al. 2009)

In Brazil, the real costs of TB are estimated or poorly known and the overall costs of TB are not perceived by governments, given the fragmentation in the involvement of the three governmental levels: local, state and national.

The purpose of this chapter is to describe the direct and indirect costs for diagnosis and treatment of Pulmonary Tuberculosis in patients infected or not by HIV, admitted to a Hospital Unit of Public Health.

2. Costs of health system of Brazil

In order to describe the costs of Health system of Brazil, we evaluate the costs directs of diagnosis and treatment of screening of 1000 hypothetical patients suspects of Pulmonary Tuberculosis in according with clinical and laboratory Brazilian recommendations for treatment (Tuberculose 2004; Conde, Melo et al. 2009).

The cost components for each clinical and laboratory procedures of screening included costs incurred by the patient, laboratory costs, drugs, consumables and equipment costs. The strategy for screening was the same recommended for Brazilian Public Health System.

Clinical, radiological and laboratory staff costs were calculated from the salary base of Rio Grande do Sul (State of Extreme South of Brazi) in 2011.

For each procedure, costs were attributed based on procedure costs of the Brazilian Public Health System.

Running costs (material costs were used for each 1000 tests evaluated) included all laboratory materials used in procedures.

All costs were expressed in US$, using an exchange rate of US$ 1= R$ 1,72 (REAIS), the average exchange rate from 2010 to 2011. In the treatment costs, those were evaluated related to

the treatment of inpatients and outpatients. To estimate the values that are spent by the public health system of Brazil with the monitoring and control of TB in a hospital and an outpatient unit, we simulated two different scenarios:

a. TB cases diagnosed in hospital wards (hospitalized patients)

b. TB cases diagnosed in outpatient environment (outpatients).

The number of days considered to calculate the costs related to the treatment of inpatients they were considered as the same days that were spent in laboratory procedure.

It was hypothesized that the time to detect *Mycobacterium tuberculosis* in sputum culture from patients with pulmonary tuberculosis may be a better indicator for the duration of time of hospitalization(Ritchie, Harrison et al. 2007).

The time to detect *M. tuberculosis* in the culture was 30 days in this study. This cohort is the same as previous published by our group [20]. This value was used as the standard at which release from isolation could be permitted (Scherer, Sperhacke et al. 2007)

The time spent on laboratory procedure to provide access to the result of the laboratory technique was assumed to be 30 days for AFB smear plus culture. The number of days considered to calculate costs was the same as those spent on laboratory procedure. The number of days considered to calculate the cost of patient travel costs was assumed to be 2 days for AFB smear plus culture.

Total treatment included clinical officer and hospital costs, assuming cost per pill, to be US$ 0.22, using 3 pills per day, during 180 days; hospital room costs, US$ 7/day; costs with salary of clinical staff and clinical consultation, US$ 2.52 per patient and clinical nursing consultation, US$ 2.52 per patient.

Assuming that, during the treatment (6 months), in ambulatory situation, 6 AFB smear test, 6 chest radiographs, 6 consult of nurse and 2 consult of clinical were performed, we used this parameters to estimate the costs of ambulatory following the Brazilian recommendations for treatment (Tuberculose 2004).

Assuming that, during the hospitalization (30 days), 4 AFB smear tests, 4 chest radiographs, 30 nurse and physician consultations were performed, we used these parameters to estimate the costs of inpatient assistance in hospital, following the Brazilian recommendations for treatment (Tuberculose 2004; Conde, Melo et al. 2009). Staff salaries for the physician, nurse and radiologist were considered to be US$ 11,163 per year, and for the chest radiograph technician, the salary was US$ 4,988 per year. The work days were considered 20 days for all staff.

The days of admission to the hospital were considered to be the same number of days spent on each laboratory procedure. All estimated costs reflect an estimative of the public health system of Brazil expenses with the monitoring and control of TB.

The costs were expressed per 1000 suspects, according to the specific bibliographic references for economic analyses, thus, allowing the best decision for investment to be made (Petitti 2000).

http://dx.doi.org/10.5772/54479

Table 1A shows the costs at the health service level and Table 1B shows costs due to laboratory investment. The AFB smear plus Culture require (US$ 39,535) for equipment. Table 1C shows costs incurred by patients.

A. Health service costs

	Staff Number	Salaries of all staff per year (US$)	Staff Cost per day (US$)	Time spent until access to result (days)
AFB smear plus Culture	2	16,151	67	30

B. Laboratory costs

	Equipment (US$)	Annualization Years	Running costs per 1000 suspects (US$)	Running costs per examination (US$)
AFB smear plus Culturea	39,535	5	12,507	12.50

C. Estimated costs incurred by patients, including costs for travel, food and income loss[d]

	AFB smear plus Culture (US$) (outpatients and inpatients)
Travel	1,390
Food	10,000
Income Loss[c]	310,000
Total patients Cost	341,000

[a] Microscopic and Laminar Flow Cabinets[,]. Other equipments were not included[,]

[b] Income loss of patients was calculated from monthly salary base of Brazil (US$207) and was based on proportional days spent by patients until access to the result of each laboratory procedure. Patient costs were estimated using the average of two visits to the laboratory for AFB smear and culture procedures for outpatients; Travel cost was considered as US$ 1.4 (one bus ticket). Food was considered as US$ 10 per meal. Base salary in Brazil was considered (US$ 10 per day /20 days of the work). For inpatients was considered just income loss; Staff costs in the laboratory were based on proportional days spent on each laboratory procedure; Costs of consumables and equipment were provided by the program as well as by the manufacturer.

Table 1. Estimative of Costs in US$ in Tuberculosis Diagnosis in Brazil

We annualized the capital cost of the equipment for 5 years, according to the literature [25]. Building costs were not included. Opportunity costs were not applicable.

	AFB smear plus Culture
Laboratory Costs	
Labor Costs[a]	3,743
Investment costs	37
Running costs	3,700
Staff Costs per day	
Cost laboratory staff [b]	1,434
Cost of staff related to the treatment of patients[b]	2,791
Costs of chest radiograph staff related to the treatment of patients	404
Treatment Costs per day	
Costs of diagnostic service related to the treatment of no-hospitalized patients	2,771
Costs of diagnostic service related to the treatment of hospitalized patients	4,686
Treatment costs (hospitalized patients plus no- hospitalized patients)[c]	7,456
Income Loss	190,000
Total Patient costs	190,000
Total Health Service costs	9,479,033
Total Screening costs	9,668,815

[a] For each procedure, costs were attributed based on procedure costs of the Brazilian Public Health System (US$ 1,4 for AFB smear and US$ 1,9 for Culture) and from CDCT/FEPPS (US$ 11,7 for PCR dot-blot), assuming investment laboratory equipment for 5 years; [b]Staff salary was considered; for laboratory technician, US$2,860 per year; for Laboratory technologist, US$6,400 per year. Staff costs in the laboratory were based on proportional days spent on each laboratory procedure; Staff salary was considered for clinical physician, nurse and radiologist; US$6,400 per year; for the X-RAY technician, salary was US$2,860 per year. [c]The days of admission to the hospital were considered as the same as the days spent on each laboratory procedure. The time spent on each laboratory procedure until access to the result of the laboratory technique was assumed to be 30 days for AFB smear plus Culture. Total treatment included clinical officer and hospital costs, assuming US$ 0,22 cost per pill, using 3 pills for day, during 180 days; hospital room costs, US$ 4,16/day; costs of salary of staff clinical; clinical consultation cost, US$2,52 per patient; clinical nursing consultation, US $2,52 per patient. Assuming that during the treatment of inpatients (4 months) 4 ZN and 4 chest radiograph were performed, and during the treatment of no- hospitalized patients (6 months) 6 AFB smear and 6 chest radiograph were performed, following the Brazilian recommendations for treatment (Tuberculose 2004);

[d] Travel was considered 2 days for AFB smear plus Culture strategy. Food and income loss for AFB smear plus Culture strategy was considered 30 days

The health service costs analysis was based on processing 50 AFB smear slides and 14 cultures per day. AFB smear plus Culture was performed by two trained staff.

Running costs were calculated from investments required to examine 1000 smears.

Table 2. Total cost of screening for 1000 suspects. The total screening costs to AFB smear plus Culture were US$ 9,668.815.

The total cost (in US$) related to the treatment (no hospitalized patients) for AFB smear plus Culture was US$ 2,771. The cost related to the treatment of hospitalized patients, for AFB smear plus Culture strategy was US$ 4,686. The cost related to the treatment of (no hospitalized patients) and (hospitalized patients), for AFB smear plus Culture strategy was US$ 7,456.

However, in a context of advanced technologies for the diagnosis of tuberculosis, economic resources has always limited the incorporation and diffusion of new technologies produced and validated by the academy. It is a challenge for health systems worldwide, and in many cases, the cause of serious sustainability problems.(Taylor, Drummond et al. 2004; King, Griffin et al. 2006; Mason, Weatherly et al. 2007; Hughes, Tilson et al. 2009; Weatherly, Drummond et al. 2009; Shi, Hodges et al. 2010)

The decisions related to incorporation, acquisition, reimbursement or coverage of new technologies and those that determine the way in which they should be used are the most important in the health system and should be taken in general and the management of health services in particular.(Greenberg, Peterburg et al. 2005)

The health systems of different countries are diverse with respect to decisions about incorporating technologies and expectations of service users. Tough choices are faced by managers at all levels of the health system. This reality makes the TB every year, become more difficult for the system to provide the user with the most effective intervention theoretically available, depending on the pressures placed on the health system in relation to increased costs, the training of human resources, needs updating certification and regulatory instruments, and investment in physical infrastructure (Newhouse 1992)

Attempts to improve the acceptability of resource allocation decisions around new health technologies have spanned many years, fields and disciplines. Various theories of decision making have been tested and methods piloted, but, despite their availability, evidence of sustained uptake is limited. Since the challenge of determining which of many technologies to fund is one that healthcare systems have faced since their inception, an analysis of actual processes, criticisms confronted and approaches used to manage them may serve to guide the development of an 'evidence-informed' decision-making framework for improving the acceptability of decisions.(Stafinski, Menon et al. 2011)

Author details

Luciene C. Scherer

Lutheran University of Brasil-ULBRA, Canoas/ RS/, Brazil

References

[1] WHO (2010). "Global tuberculosis control: key findings from the December 2009 WHO report." Wkly Epidemiol Rec 85(9): 69-80.

[2] (2010). "WHO global tuberculosis control report 2010. Summary." Cent Eur J Public Health 18(4): 237.

[3] Aguiar, F. S., L. L. Almeida, et al. (2012). "Classification and regression tree (CART) model to predict pulmonary tuberculosis in hospitalized patients." BMC Pulm Med 12(1): 40.

[4] Amicosante, M., M. Ciccozzi, et al. "Rational use of immunodiagnostic tools for tuberculosis infection: guidelines and cost effectiveness studies." New Microbiol 33(2): 93-107.

[5] Arjomandzadegan, M., L. P. Titov, et al. (2012). "Determination of principal genotypic groups among susceptible, MDR and XDR clinical isolates of Mycobacterium tuberculosis in Belarus and Iran." Tuberk Toraks 60(2): 153-159.

[6] Bachmann, M. O. (2006). "Effectiveness and cost effectiveness of early and late prevention of HIV/AIDS progression with antiretrovirals or antibiotics in Southern African adults." AIDS Care 18(2): 109-120.

[7] Baltussen, R., K. Floyd, et al. (2005). "Cost effectiveness analysis of strategies for tuberculosis control in developing countries." BMJ 331(7529): 1364.

[8] Barbieri, M., J. B. Wong, et al. (2005). "The cost effectiveness of infliximab for severe treatment-resistant rheumatoid arthritis in the UK." Pharmacoeconomics 23(6): 607-618.

[9] Brazil (2012). "Ministry of Health-Epidemiological Report- Tuberculosis 2011."

[10] Brodie, D. and N. W. Schluger (2005). "The diagnosis of tuberculosis." Clin Chest Med 26(2): 247-271, vi.

[11] Conde, M. B., F. A. Melo, et al. (2009). "III Brazilian Thoracic Association Guidelines on tuberculosis." J Bras Pneumol 35(10): 1018-1048.

[12] Costa, J. G., A. C. Santos, et al. (2005). "[Tuberculosis in Salvador, Brazil: costs to health system and families]." Rev Saude Publica 39(1): 122-128.

[13] Dwolatzky, B., E. Trengove, et al. (2006). "Linking the global positioning system (GPS) to a personal digital assistant (PDA) to support tuberculosis control in South Africa: a pilot study." Int J Health Geogr 5: 34.

[14] Elamin, E. I., M. I. Ibrahim, et al. (2008). "Cost of illness of tuberculosis in Penang, Malaysia." Pharm World Sci 30(3): 281-286.

[15] Farley, J. E., M. Ram, et al. (2011). "Outcomes of multi-drug resistant tuberculosis (MDR-TB) among a cohort of South African patients with high HIV prevalence." PLoS One 6(7): e20436.

[16] Fitzpatrick, C. and K. Floyd (2012). "A systematic review of the cost and cost effectiveness of treatment for multidrug-resistant tuberculosis." Pharmacoeconomics 30(1): 63-80.

[17] Flores, L. L., M. Pai, et al. (2005). "In-house nucleic acid amplification tests for the detection of Mycobacterium tuberculosis in sputum specimens: meta-analysis and meta-regression." BMC Microbiol 5: 55.

[18] Garcia Rodriguez, J. F., A. Marino Callejo, et al. (1994). "[Hospital costs of tuberculosis]." Med Clin (Barc) 102(15): 596-597.

[19] Gomes, C., S. Soares, et al. (2003). "[The cost of tuberculosis care: in-patient estimated costs]." Rev Port Pneumol 9(2): 99-107.

[20] Greenberg, D., Y. Peterburg, et al. (2005). "Decisions to adopt new technologies at the hospital level: insights from Israeli medical centers." Int J Technol Assess Health Care 21(2): 219-227.

[21] Hazbon, M. H. (2004). "Recent advances in molecular methods for early diagnosis of tuberculosis and drug-resistant tuberculosis." Biomedica 24 Supp 1: 149-162.

[22] Hida, Y., K. Hisada, et al. (2012). "Rapid Diagnosis of Tuberculosis by using quenching probe PCR (GENECUBE(R))." J Clin Microbiol.

[23] Hughes, D. A., L. Tilson, et al. (2009). "Estimating drug costs in economic evaluations in Ireland and the UK: an analysis of practice and research recommendations." Pharmacoeconomics 27(8): 635-643.

[24] Jain, A., P. Dixit, et al. (2012). "Pre-XDR & XDR in MDR and Ofloxacin and Kanamycin resistance in non-MDR Mycobacterium tuberculosis isolates." Tuberculosis (Edinb) 92(5): 404-406.

[25] Kik, S. V., S. P. Olthof, et al. (2009). "Direct and indirect costs of tuberculosis among immigrant patients in the Netherlands." BMC Public Health 9: 283.

[26] King, S., S. Griffin, et al. (2006). "A systematic review and economic model of the effectiveness and cost-effectiveness of methylphenidate, dexamfetamine and atomoxetine for the treatment of attention deficit hyperactivity disorder in children and adolescents." Health Technol Assess 10(23): iii-iv, xiii-146.

[27] Kivihya-Ndugga, L. E., M. R. van Cleeff, et al. (2003). "A comprehensive comparison of Ziehl-Neelsen and fluorescence microscopy for the diagnosis of tuberculosis in a resource-poor urban setting." Int J Tuberc Lung Dis 7(12): 1163-1171.

[28] Kominski, G. F., S. F. Varon, et al. (2007). "Costs and cost-effectiveness of adolescent compliance with treatment for latent tuberculosis infection: results from a randomized trial." J Adolesc Health 40(1): 61-68.

[29] Kowada, A., G. A. Deshpande, et al. "Cost effectiveness of interferon-gamma release assay versus chest X-ray for tuberculosis screening of BCG-vaccinated elderly populations." Mol Diagn Ther 14(4): 229-236.

[30] Kowada, A., O. Takahashi, et al. (2008). "Cost effectiveness of interferon-gamma release assay for tuberculosis contact screening in Japan." Mol Diagn Ther 12(4): 235-251.

[31] Kritski, A. L., J. R. Lapa e Silva, et al. (1998). "Tuberculosis and HIV: renewed challenge." Mem Inst Oswaldo Cruz 93(3): 417-421.

[32] Lienhardt, C., P. Glaziou, et al. (2012). "Global tuberculosis control: lessons learnt and future prospects." Nat Rev Microbiol 10(6): 407-416.

[33] Lienhardt, C., M. Raviglione, et al. (2012). "New drugs for the treatment of tuberculosis: needs, challenges, promise, and prospects for the future." J Infect Dis 205 Suppl 2: S241-249.

[34] Mandalakas, A. M., A. C. Hesseling, et al. (2012). "Modelling the cost-effectiveness of strategies to prevent tuberculosis in child contacts in a high-burden setting." Thorax.

[35] Mason, A., H. Weatherly, et al. (2007). "A systematic review of the effectiveness and cost-effectiveness of different models of community-based respite care for frail older people and their carers." Health Technol Assess 11(15): 1-157, iii.

[36] Mehrotra, R., P. Metz, et al. (2002). "Comparison of in-house polymerase chain reaction method with the Roche Amplicor technique for detection of Mycobacterium tuberculosis in cytological specimens." Diagn Cytopathol 26(4): 262-265.

[37] Mitarai, S., A. Kurashima, et al. (2001). "Clinical evaluation of Amplicor Mycobacterium detection system for the diagnosis of pulmonary mycobacterial infection using sputum." Tuberculosis (Edinb) 81(5-6): 319-325.

[38] Nathanson, E., P. Nunn, et al. "MDR tuberculosis--critical steps for prevention and control." N Engl J Med 363(11): 1050-1058.

[39] Neves, L. A., S. R. Canini, et al. (2012). "[Aids and tuberculosis: coinfection from the perspective of the quality of life of patients]." Rev Esc Enferm USP 46(3): 704-710.

[40] Newhouse, J. P. (1992). "Medical care costs: how much welfare loss?" J Econ Perspect 6(3): 3-21.

[41] Pereira, S. M., M. L. Barreto, et al. (2012). "Effectiveness and cost-effectiveness of first BCG vaccination against tuberculosis in school-age children without previous tuberculin test (BCG-REVAC trial): a cluster-randomised trial." Lancet Infect Dis 12(4): 300-306.

[42] Perkins, M. D. (2000). "New diagnostic tools for tuberculosis." Int J Tuberc Lung Dis 4(12 Suppl 2): S182-188.

[43] Petitti, D. B. (2000). "Meta analysis, Decision Analysis, Cost-Effectiveness analysis. Methods for quantitative synthesis in medicine. ." New York Oxford University 2 ed.

[44] Polansky, F., O. Dymer, et al. (1968). "[Costs of tuberculosis control]." Cesk Zdrav 16(10): 543-549.

[45] Project, O. H. (2005). " Health Technologies and Decision Making. Organisation For Economic Co-Operation And Development. Paris, France."

[46] Ritchie, S. R., A. C. Harrison, et al. (2007). "New recommendations for duration of respiratory isolation based on time to detect Mycobacterium tuberculosis in liquid culture." Eur Respir J 30(3): 501-507.

[47] Rodrigues Vde, F., F. C. Queiroz Mello, et al. (2002). "Detection of Mycobacterium avium in blood samples of patients with AIDS by using PCR." J Clin Microbiol 40(6): 2297-2299.

[48] Roos, B. R., M. R. van Cleeff, et al. (1998). "Cost-effectiveness of the polymerase chain reaction versus smear examination for the diagnosis of tuberculosis in Kenya: a theoretical model." Int J Tuberc Lung Dis 2(3): 235-241.

[49] Rosen, V. M., D. C. Taylor, et al. (2010). "Cost effectiveness of intensive lipid-lowering treatment for patients with congestive heart failure and coronary heart disease in the US." Pharmacoeconomics 28(1): 47-60.

[50] Sanchez, J. I., L. Rossetti, et al. (2006). "Application of reverse transcriptase PCR-based T-RFLP to perform semi-quantitative analysis of metabolically active bacteria in dairy fermentations." J Microbiol Methods 65(2): 268-277.

[51] Sarmiento, O. L., K. A. Weigle, et al. (2003). "Assessment by meta-analysis of PCR for diagnosis of smear-negative pulmonary tuberculosis." J Clin Microbiol 41(7): 3233-3240.

[52] Scherer, L. C., R. D. Sperhacke, et al. (2011). "Comparison of two laboratory-developed PCR methods for the diagnosis of pulmonary tuberculosis in Brazilian patients with and without HIV infection." BMC Pulm Med 11: 15.

[53] Scherer, L. C., R. D. Sperhacke, et al. (2007). "PCR colorimetric dot-blot assay and clinical pretest probability for diagnosis of Pulmonary Tuberculosis in smear-negative patients." BMC Public Health 7: 356.

[54] Scherer, L. C., R. D. Sperhacke, et al. (2009). "Cost-effectiveness analysis of PCR for the rapid diagnosis of pulmonary tuberculosis." BMC Infect Dis 9: 216.

[55] Schijman, A. G., M. H. Losso, et al. (2004). "Prospective evaluation of in-house polymerase chain reaction for diagnosis of mycobacterial diseases in patients with HIV infection and lung infiltrates." Int J Tuberc Lung Dis 8(1): 106-113.

[56] Sharma, S. K., A. Mohan, et al. (2005). "Miliary tuberculosis: new insights into an old disease." Lancet Infect Dis 5(7): 415-430.

[57] Shi, L., M. Hodges, et al. (2010). "Good research practices for measuring drug costs in cost-effectiveness analyses: an international perspective: the ISPOR Drug Cost Task Force report--Part VI." Value Health 13(1): 28-33.

[58] Stafinski, T., D. Menon, et al. (2011). "To fund or not to fund: development of a decision-making framework for the coverage of new health technologies." Pharmacoeconomics 29(9): 771-780.

[59] Steffen, R., D. Menzies, et al. (2010). "Patients' costs and cost-effectiveness of tuberculosis treatment in DOTS and non-DOTS facilities in Rio de Janeiro, Brazil." PLoS One 5(11): e14014.

[60] Sul, S. o. H. P. o. S.-R. G. d. (2011). "Epidemilogical Report of Infective Diseases 2011."

[61] Taylor, R. S., M. F. Drummond, et al. (2004). "Inclusion of cost effectiveness in licensing requirements of new drugs: the fourth hurdle." BMJ 329(7472): 972-975.

[62] Tuberculose, I. C. B. d. (2004). "Diretrizes Brasileiras para Tuberculose." Jornal Brasileiro de Pneumologia 30(1).

[63] Udwadia, Z. F. (2012). "MDR, XDR, TDR tuberculosis: ominous progression." Thorax 67(4): 286-288.

[64] van Cleeff, M., L. Kivihya-Ndugga, et al. (2005). "Cost-effectiveness of polymerase chain reaction versus Ziehl-Neelsen smear microscopy for diagnosis of tuberculosis in Kenya." Int J Tuberc Lung Dis 9(8): 877-883.

[65] Vassall, A., A. Seme, et al. (2010). "Patient costs of accessing collaborative tuberculosis and human immunodeficiency virus interventions in Ethiopia." Int J Tuberc Lung Dis 14(5): 604-610.

[66] Vassall, A., S. van Kampen, et al. (2011). "Rapid diagnosis of tuberculosis with the Xpert MTB/RIF assay in high burden countries: a cost-effectiveness analysis." PLoS Med 8(11): e1001120.

[67] Weatherly, H., M. Drummond, et al. (2009). "Methods for assessing the cost-effectiveness of public health interventions: key challenges and recommendations." Health Policy 93(2-3): 85-92.

[68] Weis, S. E., B. Foresman, et al. (1999). "Treatment costs of directly observed therapy and traditional therapy for Mycobacterium tuberculosis: a comparative analysis." Int J Tuberc Lung Dis 3(11): 976-984.

[69] WHO (2006). "Global tuberculosis control - surveillance, planning, financing" WHO Report 2006: 362.