

ECONOMICS OF TUBERCULOSIS DRUG RESISTANCE;

A Case Study in Indonesia*

Development of the research and problems encountered

BACKGROUND

The human quest to infectious disease has been significantly successful with the discovery of antimicrobials, especially in the developed world. However, its success stories are challenged by the occurrence of drug-resistant microbes¹.

Drug resistance in Tuberculosis is a growing problem worldwide². Despite of the high incidence of tuberculosis case in Asia, the magnitude of the drug resistance problem is not yet well known, particularly in the five countries with the greatest estimated incidence of tuberculosis worldwide, namely India, China, Indonesia, Bangladesh and Pakistan³. Current estimates of the number of drug-resistant TB are believed to be only the tip of the iceberg⁴.

Systematic review study shows that there are still very limited studies on the economics of drug resistance in the literature⁵. Those studies are mostly coming from developed countries (predominantly the USA), and do not measure the cost impact of antimicrobial resistance to the health service, patients or society⁶. Although the effect of drug resistance is arguably greater in the developing world, studies in the field of drug resistance to the developing countries are still very limited.

* This paper is based on an ongoing PhD research study conducted in the University of East Anglia, Norwich.

Of the studies primarily concern on the economic of Tuberculosis and TB program, most of those studies have been undertaken in high-income industrialised countries (North America, Western Europe or Japan) on topics that are of high priority in those countries but relatively low priority in, or of no relevance to, high burden countries⁷. There were only two studies in India, one each for China, Indonesia, Bangladesh and Pakistan, which are the countries with the highest burden of Tuberculosis.

Cost studies of TB have mostly been analyses of total or per patient diagnostic and treatment costs from the perspective of health service provider⁷. A societal cost perspective is generally more desirable in an economic analysis of health and health programmes to all resources taken into account of the analysis regardless whose budget is affected⁸. A good example of a study which has tried to exhaustively contain the societal cost perspective was conducted in South Africa by Floyd⁹. The costs to health systems were calculated (including capital and maintenance costs) as well as the costs to patients and the community.

The work of Joesoef in 1989¹⁰ is the only publication recognized in the area of economic studies of Tuberculosis in Indonesia. This study developed an epidemiological model to Tuberculosis using secondary data and enhances it into a cost-effectiveness analysis of different treatment strategies for Tuberculosis in Indonesia. This was done in the pre-Directly Observed Treatment Short Course (DOTS) era, where now all the treatment strategies have already been abandoned. The only cost covered in this analysis was the standard drug provided by the government.

Economic studies on the drug-resistant Tuberculosis are even more limited. Wilton et al.¹¹ created an economic model comparing the treatment of susceptible and Multi-drug resistant Tuberculosis using Directly Observed Treatment (DOT) and conventional strategies in the USA and South Africa using main reference from two published data on probability, costs and health impact. In the modelling, the cost was observed from the provider perspective. While in this paper the use of provider standpoint seems appropriate, it is unsuitable to use this result directly for the area where patients and their family have to bear substantial amount of the costs of the

disease. This is unfortunately the case for most developing countries, where private spending still dominates the healthcare market¹².

Other costs studies of drug-resistant TB have been studies in the developed country and mainly involved hospital-based treatment approach, such as Geerlig's study¹³ in the Netherlands, White¹⁴ and Drobniewsky¹⁵ in the UK, Dasgupta in Canada¹⁶, Burman¹⁷, Heymann¹⁸, Brown¹⁹, and Mahmoudi²⁰ in the USA.

Modelling in the area of Tuberculosis control has been advocated by Brewer²¹, as a low-cost way to compare programmes, programmes evaluation, project future cases, and programme needs. With proper inputs, the model could improve estimation and help planning that otherwise relies on rough extrapolation or guessing.

Walker²² suggested that economic analysis should be conducted to various methods and procedures in detecting Tuberculosis in order to get the most resource-efficient approach especially for the resource poor countries. However, his work has not developed further to explore the issue of detecting drug resistance. Whether detecting drug resistance (by culture or other tests) for all patients in the beginning of treatment would be cost effective or not still is open to debate.

Decision analysis with Monte Carlo simulation of a Markov decision tree have been used to model the impact of DOTS compared with DOTS-plus²³ on multi-drug resistant tuberculosis and its associated death²⁴. This paper has shown that modelling techniques are very useful in assessing the programme which could prove impossible or very difficult to conduct using traditional approaches. Although the risk of re-infection was included in the Markov model, secondary transmission of tuberculosis was not taken into consideration.

Research Question:

Although it is assumed that drug-resistant tuberculosis incurs higher costs both to patient and health care providers, quantification of the extra burden of the disease is less established, as well as the lack of information on the strategies to reduce the

occurrence of drug resistant TB. The objective of the study is to assess the economic impacts of Tuberculosis drug resistance in Indonesia and strategies to contain the emergence of drug resistant TB.

METHODOLOGY

This study is using a 'cost of illness' approach using a societal perspective which objective is to itemise, value and sum the cost of a particular problem with the aim of giving an idea of its economic burden²⁵. It can help to focus society's attention on health and assist the decision making process, as well as bringing it to political agenda²⁶. However, the fact that this type of study is not addressing the question on how we allocate resources efficiently^{26 27} has to be noted as a limitation to the study.

A modelling exercise will be conducted to model the impact of drug resistance in Indonesian setting. It helps us to clearly understand the framework of analysis and quickly identify the data required for analysis and allows the research to be conducted using the limited resources available (budget, time, etc). However, it should also be noted that this modelling approach may also have the limitation of using various types of information from different sources in the same model, making it prone to biases inherited from the referenced studies²⁸.

The model will compare the costs and consequences between drug-susceptible and drug resistant patients and try to explore the possible differences among them. By doing the modelling, related policy exercises can be investigated, such as to the decision whether to conduct drug susceptibility test to all smear positive cases, or selectively to previously treated cases, or only conduct tests to the patients whose smears still positive after completing regular treatment.

The data required to construct the model was gathered using several methods. The probabilities figures required for the model would use epidemiological data, published literatures, and expert judgements.

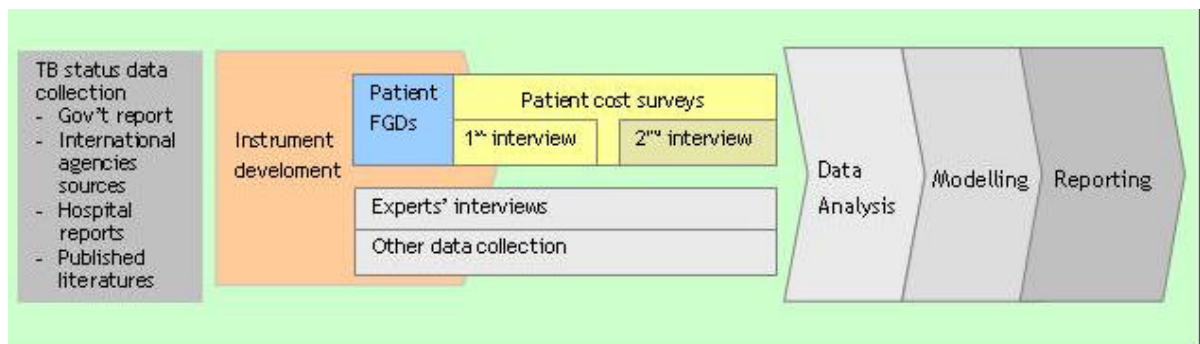
The table below summarises the required costs data and their sources.

DETECTION	Number of services/treatment/activities		Unit cost	
	Data required	Source	Data required	Source
TB and resistance detection				
Smear test – hospital	Number of tests	Patient interviews	Unit cost of test	Hospital calculation/ alternative protocol
Smear test – primary health centre	Number of tests	Patient interviews	Unit cost of test	PHC calculation/ alternative protocol
X-Rays	Number of X-Rays	Patient interviews	Unit cost of X-Ray	Hospital calculation/ alternative protocol
Blood tests	Number of tests	Patient interviews	Unit cost of test	Hospital calculation/ alternative protocol
Sputum culture	Number of tests	Patient interviews	Unit cost of test	Hospital calculation/ alternative protocol
Outpatient Services				
Doctors – Private	Number of visits	Patient interviews	Unit cost service	Patient interviews
Doctors – Health Centres	Number of visits	Patient interviews	Unit cost service	PHC calculation/ alternative protocol
Specialists – Private	Number of visits	Patient interviews	Unit cost service	Patient interviews
Doctors/specialist in Hospital	Number of visits	Patient interviews	Unit cost service	Patient interviews/ hospital calculation
Allied health personnel	Number of visits	Patient interviews	Unit cost service	Patient interviews
Traditional services	Number of visits	Patient interviews	Unit cost service	Patient interviews
Drugs regimen				
Oral drug consumed – actual	Length of treatment	Patient interviews	Cost of drug	Patient interviews
Intravenous drugs – actual	Number of treatment	Patient interviews	Cost of drug	Patient interviews
Drug required – normative				
▪ A new smear-positive TB patient	Length of treatment	Experts interview	Cost of drug	Drug price survey/DOTS cost
▪ A new smear-negative TB patient	Length of treatment	Experts interview	Cost of drug	Drug price survey/DOTS cost
▪ A re-treatment smear positive TB patient (drug resistance unknown)	Length of treatment	Experts interview	Cost of drug	Drug price survey/DOTS cost
▪ A single-drug resistant patient	Length of treatment	Experts interview	Cost of drug	Drug price survey/DOTS cost
▪ An MDR TB patient	Length of treatment	Experts interview	Cost of drug	Drug price survey/DOTS cost
▪ A Chronic MDR TB patient	Length of treatment	Experts interview	Cost of drug	Drug price survey/DOTS cost
In Patient Services				
Emergency unit	Number of admission	Patient interviews	Unit cost of service	Hospital calculation/ Alternative protocol
Bed cost	Length of stay	Patient interviews	Unit cost of bed-day	Hospital calculation/ Alternative protocol
Intensive care / Isolation	Length of stay	Patient interviews	Unit cost of bed-day	Hospital calculation/ Alternative protocol
Extra medication taken	Length of treatment	Patient interviews	Cost of drug	Patient interviews
Extra tests taken	Number of test	Patient interviews	Cost of test A	Patient interviews
PERSONAL AND PRODUCTIVITY COST				
Travel cost	Number of visits	Patient interviews	Travel cost	Patient interviews
	Time spent each visit	Patient interviews	Lost of earning	Patient interviews
Hospitalisation	Length of stay	Patient interviews	Lost of earning	Patient interviews

Non-active days due to sickness (non hospitalisation)	Disability days	Patient interviews	Lost of earning	Patient interviews
Quality of Life	Length of disease	Patient interview/ experts interview	QoL score	FGDs/Patient interviews
Family Cost				
Travel cost	Number of visits	Patient interviews	Travel cost	Patient interviews
	Time spent each visit	Patient interviews	Lost of earning	Patient interviews
TB PROGRAM				
DOTS	Number of Visits of Health Personnel	Patient interviews	Unit cost of a visit	Travel cost
Drugs on National TB Program	Drugs procured	Ministry of health data	Unit cost of packages	Ministry of health data

KEY ACTIVITIES

The activities described below have been designed to fulfil the required data for the model.



Secondary data collection

In order to gain overall magnitude and better understanding of tuberculosis disease and its control in Indonesia, data from known institutions in tuberculosis program has been gathered. The data collected are the current surveillance data on tuberculosis cases in Indonesia, and the drug resistance cases in Indonesia.

Total reported incidence and prevalence of TB cases was gathered from the ministry of health of the Indonesian government. However the estimate of population based incidence and prevalence of TB case was gathered from published literature.

Achievement of past and current tuberculosis control program is also gathered from those institutions.

Toward the drug resistant TB cases, data are collected from WHO Collaborating Centre for Tuberculosis located in Persahabatan Hospital, Jakarta. However, the data is limited towards the cases from only several hospitals/centres referred to this laboratory.

The table below are the test result from the laboratory from the year 2002.

No of positive culture tests	: 1697
Drug susceptible TB	: 1259 (74.19%)
Drug resistant TB results – any drugs	: 438 (25.81%)
MDR* TB	: 167 (9.84%)
Resistance to = 2 drugs	: 259 (15.26%)

Data from published literature, locally unpublished reports studies were also gathered to provide estimates of the incidence of drug resistant TB cases.

Cost of disease surveys

The costs associated both to receptive and drug resistant TB cases are collected to find out the differences among the two groups. A social-perspective of the cost is used in this study. The costs of receptive TB cases are used as a base to the costs of drug resistant TB to show the extra burden of resistant TB.

Ideally, patient treatment information should be gathered from medical records to obtain complete case report of the patient. However, as patients are free to choose where to get treatment, and each institutions have their own medical records system (or no records at all at private practices), tracing cases documentation is very difficult. It is aggravated with the poor practice in maintaining and recording medical records.

* Defined as resistance to at least Isoniazid and Rifampicin²

As an alternative the costs data were gathered from patients. Surveys were conducted in gathering information from both drug receptive and drug resistant tuberculosis patients. One hundred cases drug-resistant TB cases and one hundred drug-susceptible TB cases were targeted to be interviewed.

Case selection is based on laboratory-confirmed drug resistance status of Tuberculosis patients. This comes from Persahabatan Hospital in Jakarta as the national reference for Lung Diseases and housed the WHO collaborating centre for Tuberculosis. The laboratory conducts drug resistance test to all of smear-positive Tuberculosis patients as well as highly suspected Tuberculosis patients. This is the only laboratory known to be conducting regular drug resistance test in Indonesia.

From June 2002 to January 2003, a total of 350 names and addresses of the patient tested for drug resistance in the Persahabatan Hospital was gathered using a special form. This was administered by staff of the laboratory who was instructed to fill the form and ask the patient of their willingness to participate in the study.

To avoid bias, respondent are subject to these criteria:

- Above primary school age. This is to ensure that respondents understand all the questions and provide answers with minimum interference from family members, etc.
- Have no other major compounding disease (HIV, etc). This would prevent the occurrence of major confounding factor that might bias the result.
- Still under or had finished TB treatment not more than 3 months prior to interview. This is done to limit recall bias.

The interview uses a cost questionnaire that has been constructed using references from a cost questionnaire developed by Floyd²⁹. Although the primary respondent were the patients themselves, information from other member of the family such as the head of the patient's family was also used. This is to ensure that all cost data could be collected that a patient might not know otherwise. Along with cost questions, factors related to TB and MDR-TB epidemiology are also raised. The issues posed in the questionnaire were validated in a Focus Group Discussion.

Along with the researcher, interviews are performed by trained interviewers, which were recruited from students of the School of Public Health University of Indonesia. Interview training and questionnaire familiarisation has been done prior to the interviews. Several interview trials were done receive feedbacks from respondents to improve the questionnaire. It was also done to ensure common understanding on the procedure and the way questions posed from the interviewers.

Quality control of the interviews was done by randomly selecting respondents already interviewed, and re-examining the answers given. When necessary, further visits or telephone calls to selected respondents were done to check and ensure that the interviews were conducted properly and respondents' answers were relevant.

137 patients so far interviewed. Only 27 of those are drug resistant patients, 10 being MDR TB. The interviewers are still trying to get more respondents from the patients list. Focus is taken on the patients who are resistant to TB drugs.

Data on the electronic forms are still requiring data cleaning. All questionnaires are available for further data checking.

Focus Group Discussion

Focus group discussion was made to serve different purposes in this research:

- validating the questions and issues brought up in the draft questionnaire,
- exploring qualitatively the perceived impacts of tuberculosis to patients,
- exploring the possibility to conduct Quality of Life measurement methods for tuberculosis patients in Indonesian context,
- understand the reasons behind patients' behaviour in spending, purchasing, and consuming TB medication,
- elaborate qualitatively the drug consumption practice, which thought to be a major component attributing to the development of drug resistance in TB.

The respondent in the session were drug resistant tuberculosis patients or non-compliance tuberculosis patients. It was attended by 11 participants.

It is thought that a patient with tuberculosis is experiencing some negative impacts towards their quality of life. This issue was qualitatively explored in the focus group discussion. Attempts were done to elicit whether there are any quality of life differences between drug susceptible tuberculosis patients and MDR-TB patients. Assessment of the acceptance and usability of quality of life elicitation were explored.

The focus group discussion was conducted by the researcher, with the help of local lung specialist trainee doctor. The discussions were recorded and transcribed.

Experts Interviews

Interviews on tuberculosis problems in Indonesia as well as experience in dealing with MDR-TB were conducted to key person in tuberculosis program in Indonesia, which include the director of directly-transmitted communicable disease program of the ministry of health, director of tuberculosis program of the ministry of health, WHO Indonesia tuberculosis program officer, Indonesian Tuberculosis Control Association, Indonesian Lung Doctors Association Chairman, and Director of Persahabatan Hospital Lung Clinic.

Drug Prices Surveys

The questions in the patient's questionnaire are believed only to give a rough estimate of the direct cost spent on medication. More detailed information on the costs of drugs prescribed to patient is needed to construct the model. A drug price survey was conducted to assess the cost of drug prescribed to patients with several scenario prescriptions.

One or two-week prescription for adult tuberculosis patients with no major other diseases and/or any other specific conditions were asked to be produced from the experts interviewed previously. As it is known that doctors often prescribed medicine

according to the patient's economic capacity to buy drugs, three different prescriptions were asked to reflect:

- generic drugs prescription
- most commonly prescribed drugs
- the 'branded' drugs prescribed for well-off patients

This was made for the whole drug regimens necessary to complete TB treatment (intensive phase, continuation phase) for both drug-receptive and drug-resistant TB cases.

Those prescriptions were checked for its prices in chemists/drug dispensaries in government and private hospitals, chain and local chemists, and also drug stores. The prices in other cities and areas than Jakarta is also planned to be collected.

Other activities

As some of the cost borne by hospitals, medical centres, and some other institutions are subsidised by the government and/or other sources, the cost to the patient is not the true cost to the society. Related cost data of treating TB patients in hospital and health centres were gathered for the purpose of constructing the model.

Official Programmes in Eliminating TB

Past, present and future programs in eliminating TB have also been qualitatively explored with interviews conducted to key personnel. National program indicators were also collected.

Special attention was taken to the DOTS program as this approach is widely accepted as the best method of eliminating TB and reducing the occurrence of MDR-TB. Current practice in conducting DOTS program in Indonesian setting was elaborated by interviewing experts and field personnel. Information on the costs of running the DOTS program was elaborated, especially the costs to procure antituberculous drugs.

PROBLEMS

There are a number of limitations recognised in the current data set. Some of which are embedded in the choice of methodology used.

- Drug susceptibility data is only gathered from one source (Persahabatan Hospital). This hospital is the country's referral centre for Lung diseases. This is predicted to have a bias toward higher rate of drug resistance as well as tend to point more ill patients as they are referred to or had chosen to be treated in this Lung-reputable hospital. Ideally, data source should be from primary health centres, with resistance data confirmed from a reference laboratory. Having one source for drug resistance data however can maintain the reliability of resistance test. Persahabatan Hospital Microbiology Laboratory serves as WHO collaborating centre for Tuberculosis research and uses recommended WHO method to detect resistance.
- Patients still have to pay for the drug susceptibility testing. Some poorer patients were simply not able to pay for the tests. A government scheme 'social safety net' is in place that allows patients to get free consultation, tests, and treatment upon presenting a 'health card'. However, this program has not covered the whole population in need, as also showed by the experience of one participant in the Focus Group Discussion. This will make a tendency toward limiting the poor from being identified as drug resistant, which is quite complicating to the research as deprivation is thought to be a key factor to drug resistance.
- Complete case report can not be obtained. This ideally be gathered using medical records. The resources used to treat the patient can be traced and calculated as well as outcome data can be gathered. However, due to the poor quality of medical records available, this could not be done.
- Low number of cases being registered using the special form developed to recruit respondents. Many cases are actually not recorded in the special form developed for this research. This is partly out of my control as recording was done by the hospital system. The low success rate (response rate) of the interviews was further worsened the number of sample successfully interviewed.
- This low success rate is a result of several causes: Patients gave wrong or inaccurate address/telephone number, their addresses were too far or hard to reach

(outside Jakarta), patients have moved, unwilling to participate, too ill to be interviewed, had passed away or simply were not at home. Records were made on the reasons of unsuccessful interview visits and will be evaluated to assess possible pattern in those patients who were unsuccessfully interviewed.

- Other limitations are also remarked: limited information available on the hospital costing process, limited data on the costs of National TB Control program, and more importantly, limited data on the prevalence of anti-tuberculosis drug resistance in Indonesia.

Proposed Solution

As the number of drug resistant patients interviewed so far has not reached the proposed number, a follow-up interview is planned as an important part to complement the result. This will give a more descriptions on the costs and outcome of the respondents at least 6 months after the first interview.

All drug resistant patients already interviewed with a corresponding number of drug-receptive patients are planned to be re-interviewed using a modified questionnaire from the original questionnaire.

Nevertheless the difficulty of having only a small sample in the analysis will still prevail. Especially that the model would incorporate effectively three different classifications: receptive, single drug resistant, and MDR group of patients.

More qualitative data is also needed. This is to be done by doing another Focus Group Discussion focussing on the qualitative side of patients having TB and drug resistant TB. Preferably, this will be conducted in another location/setting with the previous one. The follow-up interview will also put more attention to the qualitative aspect of the cost having TB and its medications.

ISSUES RAISED:

- I expect to have 100 drug resistant cases and 100 drug susceptible cases for the patient samples. However, to date, I could only interview 27 drug resistant cases. How many respondents are 'minimum' for this case do you think? Analysis of the variance of their answer seems to be quite large (e.g. some patients treated with 'branded' second line drugs, while some others treated with 'generic' drugs which have significant cost differences).
- Would you think this second (follow up) interview be useful? Should I focus to obtain more drug resistant patients instead? Please note that significant time would be required to accomplish this.
- How can qualitative response from the respondents and other informants be incorporated in the modelling study?

Your comments and suggestions (on these issues and beyond) are highly appreciated.

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