Economic Cost of Non-Adherence to TB Medicines Resulting from Stock-Outs and Loss to Follow-Up in the Philippines

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Key Words

Philippines, TB, tuberculosis, supply chain, stock-out, loss to follow up, default, non-adherence, treatment interruption, cost, economic impact

CONTENTS

ACRONYMS AND ABBREVIATIONS

DOH	Department of Health
DOTS	directly observed treatment short course
DS-TB	drug-sensitive TB
Global Fund	Global Fund to Fight AIDS, Tuberculosis and Malaria
IPT	isoniazid preventive therapy
LTFU	loss to follow-up
MDR-TB	multidrug resistant TB
MSH	Management Sciences for Health
NTP	National Tuberculosis Control Program
OOP	out-of-pocket
PPMD	public-private mix DOTS
RHU	rural health units
SIAPS	Systems for Improved Access to Pharmaceuticals and Services
TB	tuberculosis
USAID	United States Agency for International Development
WHO	World Health Organization
XDR-TB	extensively drug-resistant TB

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EXECUTIVE SUMMARY

A key element of successful tuberculosis (TB) control programs is adherence to treatment, and this is a cornerstone of most international and national policies and guidelines. Non-adherence is often due to patient-related factors but can also be a result of provider issues, such as stock-outs of TB medicines. Non-adherence results in increases in the length and severity of illness, death, disease transmission, and drug resistance, all of which have economic consequences in terms of cost and loss of income for patients and their families and cost to the health system.

Non-adherence is commonly due to treatment interruption, which may be for short, intermittent periods (e.g., days) or for longer periods of weeks or months that may lead to complete discontinuation of treatment. Interventions to prevent treatment interruption are aimed at both patients and providers. On the provider side, actions include ensuring proper prescribing practices and management of side effects, providing good quality medicines, and preventing stock-outs. Actions on the patient side include interventions to encourage patients to continue treatment even when they feel better and use medicines as directed and to remove barriers, such as transport costs. These actions are believed to be a good investment, but the economic savings have not been clearly defined.

The Philippines is among 22 countries considered to have a high TB burden, including multidrug-resistant TB (MDR-TB). The Philippines DOH has an extensive TB program with Directly Observed Treatment Short Course (DOTS) for TB and DOTS-Plus for MDR-TB. In addition to DOTS, the DOH has strategies and procedures in place to ensure and improve treatment adherence, including patient compliance incentives and supply chain management system strengthening, both of which are challenging in a large, decentralized country where health care services are generally managed at the local level and stock-outs and loss to follow-up (LTFU) are common.

In recent years, NTP data and several studies have indicated problems with stock-outs of some TB medicines and LTFU. Both result in treatment interruption, which has an impact on the well-being of patients and their families, on the health system, and on society and the economy in general.

The purpose of this study was to estimate the morbidity and mortality impact and economic costs of non-adherence to TB medicines resulting from treatment interruption due to stock-outs or LTFU. This is expected to be helpful in promoting the benefits of investing in improving patient management and interventions to ensure the availability of good quality medicines and to encourage and aid in patient compliance.

Based on the NTP data and studies, three case studies were selected on the assumption that these probably had the greatest impact:

- Stock-outs of drug-sensitive TB (DS-TB) category 1 medicines
- LTFU of DS-TB patients
- LTFU of MDR-TB patients

Data were obtained from three sources:

- A global literature review aimed at identifying methodologies used to conduct economic studies of the impact of TB treatment interruption as well as details of its health, mortality, and economic impact

- A review of NTP documents and records for information on Philippines treatment norms, numbers of services, and costs

- Interviews with an Expert Group comprising doctors, pharmacists, and NTP staff regarding Philippines treatment decision making, patient pathways, and the impact of treatment interruption on morbidity and mortality

The modeling was developed to quantify the likely impact of the treatment interruption in terms of subsequent treatment or non-continuation of treatment and on the provider and household (out-of-pocket (OOP) costs and lost productivity). The modeling only shows the additional effects of each specific type of treatment interruption and does not show what would have happened in the absence of that interruption. For example, the stock-out model does not include a component showing the likely treatment outcomes and costs if the stock-out had not occurred. In addition, each model only shows the impact of one type of treatment interruption. For example, the stock-out model does not take into account whether there could have been simultaneous LTFU.

Because we were unable to find any existing tools or models suitable for this purpose, we developed a new, spreadsheet-based tool that was used to develop a model for each case study.

The results of the three case studies are summarized as follows.

DS-TB Medicine Stock-outs

Based on a sample patient survey conducted in early 2014, as many as 2,663 DS-TB patients may have been unable to obtain medicines from the public sector for one month or more. The survey did not determine at what stage of treatment the stock-outs occurred, but based on Expert Group guidance, we assumed for the modeling that they occurred three months into treatment. Although some patients experienced the stock-out for more than one month, for the modeling we assumed that it lasted for one month.

Based on Expert Group opinion, we assumed that 53 (2%) of these patients are likely to have had undiagnosed MDR-TB and would have remained infectious during DS-TB treatment. The remaining DS-TB patients would not have been infectious because they should have received and adhered to a one-month supply of intensive-phase medicines at the time they started treatment and would have converted to smear-negative within that month.

The likely impact of this stock-out for the 2,663 patients is that 266 of those with DS-TB would have developed MDR-TB because of poor quality private-sector treatment, poor adherence, or

discontinuation of treatment. These 266 patients are likely to have infected an additional 63 people with MDR-TB. In addition, 588 of the original DS-TB and MDR-TB patients and the other persons infected with MDR-TB are likely to have died. We did not take into account that some DS-TB patients who had become non-infectious before interrupting treatment but did not return to treatment would have become infectious again at some point. We also did not take into account that some of these MDR-TB patients would have developed extensively drug-resistant TB (XDR-TB). In both cases, we were unable to obtain any estimates of what proportion of patients would be affected or how long that might take.

The total additional economic cost resulting from the stock-out is likely to have been as much as USD 21 million, comprising USD 1.5 million in service delivery costs and USD 19.5 million in household costs. This works out to a cost of roughly USD 8,000 per patient whose treatment was interrupted by the stock-out, meaning that an investment of up to that amount to prevent the stock-out for one patient would have resulted in a net savings to society.

DS-TB Patients Lost to Follow-up

In 2014, 8,870 DS-TB patients were reported by the NTP as LTFU. No data were available on the stage of treatment at which the interruption occurred or the length of the interruption. Based on guidance from the Expert Group, we assumed for the modeling that the interruption occurred three months into treatment and lasted for three months for those patients who returned to treatment.

Based on Expert Group opinion, we assumed that 177 (2%) of these patients are likely to have had undiagnosed MDR-TB and would have remained infectious during DS-TB treatment. The remaining DS-TB patients would not have been infectious because they should have received and adhered to a one-month supply of intensive-phase medicines at the time they started treatment and would have converted to smear-negative within that month.

The likely impact of this LTFU for the 8,870 patients is that 887 of those with DS-TB would have developed MDR-TB through poor quality private-sector treatment, poor adherence, or discontinuation of treatment. Those patients are likely to have infected an additional 245 people with MDR-TB. In addition, 1,958 of the original DS-TB and MDR-TB patients and the other persons infected with MDR-TB are likely to have died. We did not take into account that some of the DS-TB patients who had become non-infectious before interrupting treatment but did not return to treatment would have become infectious again at some point. We also did not take into account that some of the MDR-TB patients would have developed XDR-TB. In both cases, we were unable to obtain any estimates of what proportion of patients would be affected or how long that might take.

The total additional economic cost resulting from this LTFU is likely to have been as much as USD 72.2 million, comprising USD 5.8 million in service delivery costs and USD 66.4 million in household costs. This works out to a cost of roughly USD 8,000 per patient who interrupted treatment due to LTFU, meaning that an investment of up to that amount to prevent LTFU for one patient would have resulted in a net savings to society.

MDR-TB Patients Lost to Follow-Up

A study of a 2012 cohort of MDR-TB patients found that 29% were LTFU. We applied that percentage to the 2,680 MDR-TB patients treated in 2014, which gave an assumption that 777 MDR-TB patients would have been LTFU. Data from the NTP indicated that, on average, treatment was interrupted four months after commencement, and we assumed this in the modeling. No data were available on the length of the interruption, but based on guidance from the Expert Group, we assumed for the modeling that it lasted five months for those patients who returned to treatment.

Based on Expert Group opinion, we assumed that 15 (2%) of these patients are likely to have had undiagnosed XDR-TB and would have remained infectious during the MDR-TB treatment. A significant number of the remaining MDR-TB patients would no longer have been infectious at the time of interruption, and we assumed 50% for the modeling.

The likely impact of this LTFU for the 777 patients is that 330 of those with MDR-TB would have developed XDR-TB through poor quality private-sector treatment, poor adherence, or discontinuation of treatment. Those patients are likely to have infected an additional 19 people with XDR-TB. In addition, the MDR-TB patients who were still infectious at the time of interruption are likely to have infected an additional 474 persons with MDR-TB, and 233 people are likely to have died as a result of the LTFU.

We did not take into account that some MDR-TB patients who had become non-infectious before interrupting treatment but did not return to treatment would have become infectious again at some point because we were unable to obtain any estimates of what proportion of patients would be affected or how long that might take.

The total additional economic cost resulting from this LTFU is likely to have been as much as USD 13.4 million, comprising USD 4.5 million in service delivery costs and USD 8.9 million in household costs. This works out to a cost of roughly USD 17,000 per patient who interrupted treatment due to LTFU, meaning that an investment of up to that amount to prevent LTFU for one patient would have resulted in a net savings to society.

Table 7, which condenses the results, allows for a comparison of the impact on morbidity and mortality. In each case, the likely impact of the treatment interruption is significant, with many more cases of drug-resistant TB and many more deaths.

In each case, the likely economic impact is also significant, with additional costs of USD 21.2 million resulting from DS-TB stock-outs and USD 72.2 million and USD 13.4 million resulting from DS-TB and MDR-TB LTFU, respectively.

These results are only approximate estimates because of the lack of strong evidence for some of the assumptions, and it is possible that the above figures are actually underestimated.

The global literature review found that little research has been done on the impact of treatment interruption, and additional research would be highly beneficial, both for the Philippines and globally, to provide a more robust base of evidence.

Based on the analysis, it is recommended that priority be given to improving supply chain management to prevent stock-outs; reducing DS-TB patient LTFU through better education and case management, particularly in regions with a high prevalence; and reducing MDR-TB LTFU through improved case management, including better management of medicines, because adverse side effects are a major cause of MDR-TB LTFU.

It is clear from these case studies that the cost of treatment interruption in the Philippines is significant and that investing additional resources to resolve the causes of interruption is likely to be extremely worthwhile.

BACKGROUND

Tuberculosis Treatment Adherence

A key element of a successful TB control program is adherence to treatment, and this is a cornerstone of most international and national policies and guidelines [1–6].

Non-adherence is often due to patient-related factors but can also be a result of service delivery issues [5], such as stock-outs of TB medicines. An uninterrupted and sustained supply of quality-assured anti-TB medicines is essential to achieving successful program outcomes. Non-adherence results in increases in the length and severity of illness, death, disease transmission, and drug resistance, all of which have economic consequences in terms of cost and loss of income for patients and their families and cost to the health system [7,8].

Non-adherence is commonly due to treatment interruption, which may be for short intermittent periods (e.g., days) or for longer periods of weeks or months that may lead to complete discontinuation of treatment. Actions to prevent treatment interruption are aimed at both patients and providers. On the provider side, actions include ensuring proper prescribing practices, providing good quality medicines, and preventing stock-outs. Actions on the patient side include interventions to encourage patients to continue treatment even when they feel better and use medicines as directed and the removal of barriers, such as transport costs. These actions are believed to be a good investment, but the economic savings have not been clearly defined.

The Philippines

The Philippines is the second-largest archipelago on the planet, with more than 7,107 islands [9]. In 2010, the population of the Philippines was 92.3 million, with a growth rate of 1.9% per year. There are 80 provinces, 138 cities, and 1,496 municipalities. Half of the population (50.3%) lives in urban areas, and of those, 44% live in slums. Both urban and rural poverty rates are high but decreasing steadily. The population includes 180 ethnic groups and is highly fragmented across the islands. Health services are provided by public and private facilities that provide the entire range of interventions with varying degrees of emphasis at different health care levels. Public services are mostly used by the poor and near-poor, including communities in isolated and deprived areas.

The Philippines is one of 22 countries considered to have had a high TB burden, including MDR-TB, over a number of years [10]. According to 2014 data in the 2015 World Health Organization (WHO) Global TB Report, the Philippines had a TB mortality rate of 10 per 100,000 (excluding HIV+TB); a prevalence rate of 417 per 100,000; an incidence rate of 288 per 100,000 (including HIV+TB); a case detection rate of 85%; and an MDR-TB burden of 2% of new cases and 21% of retreatment cases [11]. On a positive note, the same report noted that the Philippines was one of nine high-burden countries that met the 2015 targets for halting and reversing TB incidence and reducing the TB mortality and prevalence rates.

The Philippines DOH has an extensive TB program with DOTS for TB and DOTS-Plus for MDR-TB. TB services provided by the government, including diagnosis and medicines, are free of charge. The Philippines also has a large private sector that includes thousands of private practitioners and more than 1,000 private hospitals, some of which are accredited by the government's Philippines Health Insurance Corporation (PhilHealth) to provide TB treatment. Anti-TB medicines are widely available on the private market [12].

The DOH has strategies and procedures in place to ensure and improve treatment adherence, including patient compliance incentives and supply chain management system strengthening [13, 14]. Both are challenging, particularly in a large, decentralized country where health care services are mainly managed at the local level. A recent supply chain study, for example, found that stock-outs of first-line medicines resulted in delays starting treatment, interruptions of treatment, and patients having to buy medicines from third-party pharmacies [15]. The study identified several factors that contribute to stock-outs, including insufficient storage capacity, lack of transport resources, and weaknesses in inventory management practices. Purchasing medicines from third-party pharmacies can increase the risk of drug resistance due to medicines being of sub-standard quality or being provided in incomplete or incorrect doses. Interruption of treatment due to stock-outs can also lead to LTFU when patients decide not to return.

LTFU, defined in the Philippines as an interruption of two or more consecutive months, has been a significant issue in the country, particularly in cases of drug-resistant TB, where side effects are a major factor. The NTP reported an LTFU rate of 36% for drug-resistant patients in 2012, which was an improvement over the reported figure of 44% in 2011 but is still a major issue for TB control. A study of a cohort of MDR-TB patients who started treatment in 2014 found an LTFU rate of 29%, indicating that there may have been a further reduction, but the number of patients remains significant [16]. The study identified the primary reasons for stopping treatment as medication side effects or the fear of side effects, followed by the need to work, financial problems, and a lack of money for transportation to the treatment facility.

High LTFU rates for MDR-TB patients are concerning because some have XDR-TB or pre-XDR-TB when treatment begins; drug resistance is sometimes acquired during treatment; and many of those lost to follow-up were culture-positive at last contact, enabling community transmission of strains with more extensive resistance.

The purpose of this study was to estimate the impact on morbidity and mortality and the economic cost of non-adherence to TB medicines due to treatment interruption[1] resulting from both stock-outs and LTFU. This is expected to provide useful evidence for promoting the benefits of investing in improving treatment adherence through actions to ensure the availability of good quality medicines and interventions to encourage and assist patient compliance.

[1] In this report, the term "treatment interruption" is used generically to refer to the cessation of treatment. This is different from the way the term is sometimes used to describe the case where a patient misses a dose of treatment for at least one day and for less than two consecutive months [14].

METHODOLOGY

To gather information on the impact of non-adherence due to treatment interruption, data were collected from three sources:

- A global literature review aimed at identifying methodologies used to conduct economic studies of the impact of TB treatment interruption as well as details of the its morbidity, mortality and economic impact

- A review of NTP plans, policies, reports, and other documents and records for information on Philippines treatment guidelines, numbers of services, and costs

- Interviews with an Expert Group comprising doctors, pharmacists, and NTP staff regarding Philippines treatment decision making, patient pathways, and the impact of treatment interruption on health and mortality

The modeling was developed to quantify the likely impact of treatment interruption in terms of subsequent treatment or non-continuation of treatment, provider and patient costs, and lost productivity. The modeling only shows the additional effects of each specific type of treatment interruption and does not show what would have happened in the absence of that interruption. For example, the stock-out model does not include a component showing the likely treatment outcomes and costs if the stock-out had not occurred. In addition, each model only shows the impact of one type of treatment interruption. For example, the stock-out model does not take into account that there could have been a simultaneous LTFU.

Because we were unable to find any existing tools or models suitable for this purpose, we developed a new, spreadsheet-based tool that was used to develop a model for each case study. This tool was developed by Management Sciences for Health (MSH) through SIAPS, a USAID program. The tool is open source, designed to be user friendly, and free of charge from MSH.

The tool was constructed with a set of assumptions covering the decisions that patients might make in the absence of public-sector medicines or when they are lost to follow-up and the likely impact of those decisions, with each case resulting in eventual cure or death. These are summarized in a simple conceptual framework in figure 1:

- Factor 1: Whether patients are infectious at the time of interruption. Those who are infectious will infect other persons during the interruption period and afterward if they do not return.

- Factor 2: Whether patients are treated by non-accredited private providers[2] during the interruption period or not treated at all.

[2] References to treatment in the private sector in this document refer to treatment by service providers not accredited by PhilHealth.

- Factor 3: Whether patients develop drug resistance during the interruption period.

- Factor 4: Whether patients return to an accredited provider to continue treatment after the interruption period.

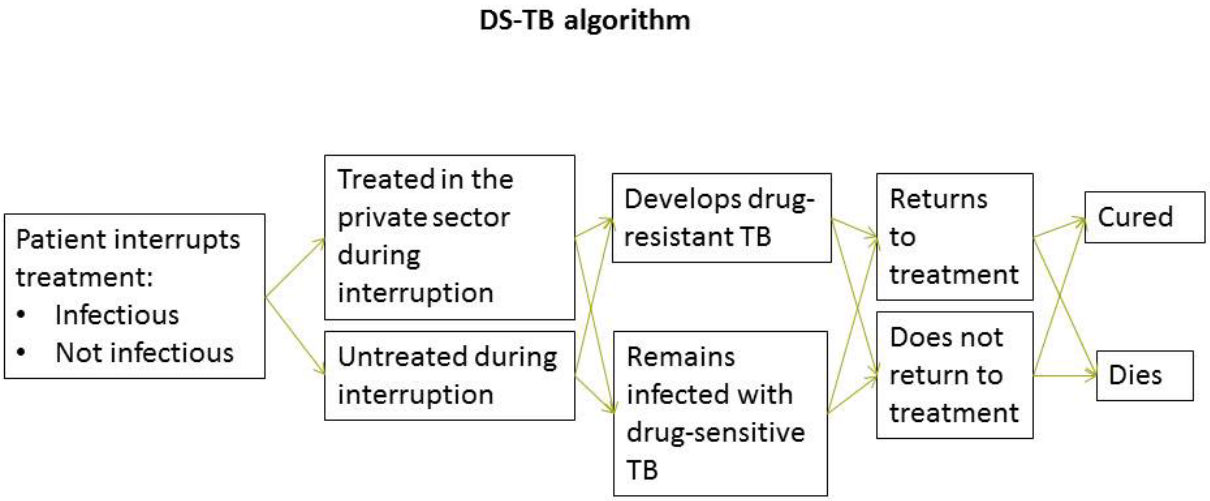

Figure 1. Conceptual framework for treatment interruption

Four types of economic cost are included in the model:

- The cost to the service provider for treating TB
- The OOP cost to the patient for diagnosis and treatment
- The loss of productivity for the patient and household due to illness
- The lifetime loss of productivity due to premature death

Each decision has an impact on the economic cost. For example, those who decide to buy medicines in the private sector incur an OOP expense that they would not have incurred in the public sector, where medicines are free of charge. They may also incur a higher risk of developing drug resistance due to poor quality medicines or incorrect dosages or combinations. People who die as a result of non-adherence to treatment due to stock-outs or LTFU have an economic impact in the form of a loss of productivity due to premature death.

For the economic impact analysis in the Philippines, three case studies were selected on the assumption that these would have the greatest economic impact:

1. Stock-outs of DS-TB category 1 medicines
2. LTFU of DS-TB patients
3. LTFU of MDR-TB patients

Other potential studies that were not explored relate to reported shortages of DS-TB category 2 intensive phase kits needed for retreatment cases and shortages of pediatric TB medicines. We also did not model the costs of retreatment related to LTFU because the Expert Group felt that very few of these patients are reportedly lost because they are afraid of the impact of not adhering to their medicines.

The unit costs used in the study were obtained from various sources (annex A).

LITERATURE REVIEW

The purpose of the literature review was to identify methodologies used to conduct economic studies of the impact of TB treatment interruption and to collect information on the morbidity, mortality, and economic impact of such treatment interruptions.

Resources were identified by searching the MEDLINE database for a period of 10 years from January 2005, with the last search run on February 4, 2015. No limits were applied for language. We used free text and MeSH keywords in combination for two searches:

1) TB, adherence, compliance, stock-out, drug supply, medicine supply, and prescription drugs (supply and distribution) regardless of location

2) TB, adherence, and outcome assessment in low- and middle-income countries

Search Results

The first search on criteria including "stock-outs" identified 65 published articles. None of these covered the impact of stock-outs of TB medicines and therefore they were not included in the results.

The second search on adherence and outcome assessment identified 720 articles. Of these, 708 were eliminated because they did not relate to either TB or the outcomes of non-adherence for TB. This left 12 papers related to non-adherence.

However, 11 of these discussed the reasons for treatment interruption and not the impact of that interruption. Only one paper included anything on the impact of non-adherence, which was on the treatment of South African TB patients [17]. This study found that incomplete DOT, specifically receiving DOT during the intensive phase only, was independently associated with poor treatment outcome. However, the sample size of the patients with incomplete DOT was small and the nature of the "poor outcome" was not defined, although it usually signifies default, failure, or death.

Other Literature

We supplemented the above searches with citation searches and by consulting experts. Through this process we identified a publication by Pablos-Mendez et al., related to a study in New York [18] and additional publications by Tupasi et al., 2006 [19]; Podewils et al., 2013 [14]; and Tupasi et al., 2016 [16].

The study by Pablos-Mendez et al., was a retrospective study of a citywide cohort of 184 TB patients in New York City who were newly diagnosed by culture in April 1991—prior to the city strengthening its control program—and followed up through 1994. Non-adherence was defined as treatment default for at least two months. Of the 184 patients, 88 (48%) were non-adherent. The non-adherent patients took longer to convert to negative culture, were more likely to acquire

drug resistance, required longer treatment regimens, and were less likely to complete treatment. The study concluded that non-adherence may contribute to the spread of TB and the emergence of drug resistance and may increase the cost of treatment.

The study by Tupasi (2006) provides useful information on the cost of treating MDR-TB in the Philippines in 2002, including health system, patient, and household costs. The study reviewed 117 MDR-TB patients enrolled in a DOTS-Plus program[3]. The overall default (LTFU) rate was 14% and was lower among chronic cases compared with new and retreatment cases. Among all cases, 62% were resistant to five or more drugs. Of the 16 patients who defaulted, 53% were bacteriologically negative at the time of default.

Podewils' study looked at the impact of treatment interruption on MDR-TB patients in the Philippines. Treatment interruption was defined as any time that a patient missed a prescribed dose of treatment for at least one day but for less than two consecutive months. The median age of the MDR-TB patients was 37.5 years, and 60.2% of the sample was male. The median was 1.4 days per interruption, and 23 days were missed over the course of treatment. Only 7% of 583 patients completed treatment without interruption. Of the remaining 542 patients, the median time to the first interruption was 2.5 months (70 days). The study concluded that patients who miss more consecutive days of treatment with sporadic interruption patterns or a greater proportion of treatment were at an increased risk for poor treatment outcomes. Patients who had longer interruptions with sporadic variability during a 6–12 month or 12–18 month treatment period had a significantly increased risk for poor outcomes compared to patients who had short, regular interruptions during the treatment course. Poor outcomes were also more likely among patients with short, sporadic treatment interruption patterns during the 12–18 month period. In addition, with the exception of the final 18 to 24 months of treatment, there was an independent and significant effect associated with missing a greater proportion of doses during the period, with a 1.5- to 2-fold increase associated with missing 10% or more of the prescribed treatment doses. It should be noted that this study focused on treatment interruption, which was less than two months, and therefore did not include patients lost to follow-up, which relates to periods of two months or longer.

Tupasi's 2016 study analyzed the status of MDR-TB patients who were lost to follow-up in a cohort of patients who started treatment in 2012. Of the 477 patients who started MDR-TB treatment and were eligible for the study, 136 were lost to follow-up (29%). Most (70 [77.8%]) of the 90 case patients for whom information on length of treatment was available were lost to follow-up during the intensive phase of treatment. The primary reason for stopping treatment most commonly reported by patients was medication side effects or the fear of side effects, reported by 52 (58%) of 89 patients who responded to this question. The two other most commonly self-reported reasons for LTFU were the need to work and financial problems, reported by 25 (28%) of 89 patients, and lack of money for transportation to the treatment facility, reported by 18 (20%) of 89 patients. The study provided very useful information on LTFU but did not look at its impact.

The literature review indicates that there has been little research into the impact of non-adherence to TB medicines due to stock-outs or LTFU.

[3] Of the 171 patients eligible for the DOTS-Plus program, 24 were lost while waiting for treatment; 25 died before starting treatment; and 5 were unwilling, self-medicated, or transferred out, leaving 117 enrolled patients.

RESULTS

Stock-Outs of Drug-Sensitive TB Adult Category 1 Medicines

In response to perceived problems with the supply chain for TB medicines in the Philippines, SIAPS conducted a study in 2014 to identify the locations of and reasons for stock-outs and to analyze and cost solutions. The results of this analysis indicated that a coordinated restructuring of the TB supply chain in the Philippines is necessary and feasible and provided several costed options for this restructuring.[4][15] The study concluded that this restructuring would contribute significantly to reduced stock-outs and waste and would improve the quality of information for decision making.

The analysis included an assessment of stocks of TB medicines at a sample of warehouses and facilities and interviews with a number of patients. A total of 223 government and private facilities accredited by PhilHealth were surveyed, including 181 rural health units (RHUs) and 22 Public Private Mix DOTS (PPMD) facilities. Between December 2013 and May 2014, the surveyed RHUs and PPMDs reported stock-outs in 27.1% and 22.7% of facilities, respectively. In the assessment, stock-out was defined as facilities having zero units on hand of one or more of the commodities included in the study. The first-line commodities most frequently out of stock included Category 2 kits (found in 27.87% of surveyed facilities that normally stock these kits with a mean stock-out period of 92 days), followed by isoniazid preventive therapy (IPT) for children (19.44% and 106 days), streptomycin (13.04% and 112 days), and TB kits for children (10.45% and 95 days). Stock-outs of Category 1/3 TB kits were found in 2.9% of facilities with a mean of 20.5 days and a maximum of 58 days out of stock.[5] The assessment also identified that there were expired medicines at 20 of 223 facilities, with 16 of these being RHUs.

As part of this study, a patient survey was conducted to collect data on the impact of stock-outs on patients. In that survey, 3.81% of the patients interviewed reported that they had missed taking their medicines because of stock-outs at their health facility.[6] Of the 40 patients who stated how long they missed taking their medicines, 12 (30%) missed for 30 days or more (median 58 days; range, 30–222 days). Among these patients, 72% bought the missing medicines from a third-party pharmacy,[7] and the remaining 28% waited until the medicines became available in the public sector.

According to the 2014 WHO TB Report [20], there were 232,941 pulmonary Category 1 DS-TB cases notified in the Philippines in 2014, and we assumed that all of these patients started

[4] At the time of the lead consultant's visit to the Philippines in March 2016, he was informed by the NTP that no decision had been made regarding the implementation of any of the options.
[5] A facility should have a six-month kit for each DS-TB patient who starts treatment, and it is not clear if a measure of stock-out would include any medicines missing from those kits or only additional "non-designated" medicines.
[6] In addition, 17.3% of patients reported delays in starting treatment, with 21.8% of those waiting more than four weeks. Of these patients, 8.7% reported that the reason for the delay was non-availability of medicines.
[7] According to the patient interviews, of the 102 patients who were asked to buy medicines because they were out of stock, the following were bought: anti-TB medicines (44, 45.4%); antibiotics (3, 3.1%); pain killers (2, 2.1%); nutritional supplements and multivitamins (37, 38.1%); cough syrup, anti-histamines (6, 6.2%); and other (maintenance medications, syringes) (5, 5.2%).

treatment. We applied the 3.81% found in the patient survey to that total, which gave an extrapolated total of 8,875 patients who would have missed taking their medicines. Again, based on the survey sample, we assumed that 30% of these 8,875 patients would not have had access to medicines for 30 days[8] or more, for a total of 2,663 patients. There were no data on months of treatment left at the time of the interruption. Based on guidance from the Expert Group, we assumed for the modeling that the interruption occurred on average three months into treatment and that three months of treatment remained. Although some patients in the selected sample experienced the stock-out for more than one month, for the modeling we assumed that it lasted for one month. The main assumptions used in the modeling are shown in annex B.

Based on the opinion of the Expert Group, we assumed that 53 (2%) of these patients are likely to have had undiagnosed MDR-TB and would have remained infectious during DS-TB treatment. The remaining DS-TB patients would not have been infectious because they should have received and adhered to a one-month supply of intensive-phase medicines at the time they started treatment and would have converted to smear-negative within that month.

The likely impact of this stock-out for the 2,663 patients is that 266 of those with DS-TB would have developed MDR-TB through poor quality private-sector treatment, poor adherence, or discontinuation of treatment. These 266 patients are likely to have infected an additional 63 people with MDR-TB. In addition, 588 of the original DS-TB and MDR-TB patients and the other persons infected with MDR-TB are likely to have died. We did not take into account that some of the DS-TB patients who had become non-infectious before interrupting treatment but did not return to treatment would have become infectious again at some stage. We also did not take into account that some of the MDR-TB patients would have developed XDR-TB. In both cases, we were unable to obtain any estimates of what proportion of patients would be affected or how long that would take.

Table 1. Morbidity and Mortality Outcomes of DS-TB Treatment Interruption for One Month for 2,663 Patients due to Stock-outs

Description	Outcome
Number of patients who develop MDR-TB as a result of the interruption	266
Number of patients who die as a result of the interruption	588
Number of additional persons who develop DS-TB as a result of the interruption[9]	0
Number of additional persons who develop MDR-TB as a result of the interruption	63
Number of additional persons who develop XDR-TB as a result of the interruption	Not estimated

Based on the assumptions used in the model, the total additional economic cost related to the 2,663 patients is estimated to be USD 21 million (USD 7,882 per patient). The additional cost is

[8] Because the median was 58 days and the range was 30 to 222 days, this is probably a conservative estimate.
[9] This figure is zero because the opinion of the Expert Group was that none of the patients with DS-TB should be infectious at the time of the treatment interruption and therefore, no additional people would be infected as a result of the interruption. We did not take into account that some of those patients who interrupted or discontinued treatment could have become infectious again due to lack of evidence with which to estimate such an impact.

the total cost less the cost that would have been incurred if the patient had adhered to the medicines and treatment had not been interrupted.

The total additional cost of USD 21 million comprises USD 20.5 million related to the patients who interrupted treatment because of the stock-outs and USD 0.5 million related to new cases resulting from persons infected by those patients (table 2).

The total additional costs are also broken out by provider and patient costs. The additional provider cost would be USD 1.5 million and the additional cost for the patients and the persons they infect would be USD 19.5 million.

The biggest element of the additional costs is the USD 16 million for lost productivity related to the expected premature death of patients directly affected by the stock-outs. This is based on the following set of assumptions:

- During the stock-out period, 72% (1,917) of the 2,663 patients would get treatment in the unaccredited private sector, 10% (192) of those would not get quality treatment and would develop MDR-TB, and 75 of those patients would die. Of the remaining 90% (1,725) who get good quality private-sector treatment, 30% (518) would not complete treatment after the stock-out period, and 70% of these (362) would die.

- During the stock-out period, 28% (746) of the patients would get no treatment, 10% (75) would develop MDR-TB, and 29 of these would die, while 90% (671) would continue to have DS-TB and 150 of these would die.

- The average age at which patients become ill with DS-TB is 39[10] and it is assumed that untreated patients will live for three years, meaning that premature death would take place at the age of 42. Assuming a person is normally productive until the age of 65, 23 years of productivity with a total value of USD 41,148 would be lost that when discounted using 3% per year would result in a value of USD 29,907.

If the stock-out could have been prevented for one patient, there would have been an average saving to the health system of USD 573 in terms of provider costs and a saving to the household of USD 7,309. If the cost of preventing that stock-out is less than the total additional cost of USD 7,882, there would be net savings to society.

Table 2. Economic Cost of Stock-outs of TB Medicines for One Month for DS-TB Patients

	Total additional costs (USD)	**Additional costs per patient (USD)**
Costs for directly affected patients		
Provider treatment costs	1,136,178	427
Sub-total provider treatment costs	**1,136,178**	**427**
Patient treatment OOP costs	520,839	196

[10] Based on NTP data, this is the average age at enrollment for treatment and is assumed to be the time at which a patient falls ill.

	Total additional costs (USD)	Additional costs per patient (USD)
Patient productivity losses during illness	2,810,403	1,056
Patient productivity losses due to premature death	15,981,514	6,002
Sub-total patient OOP costs and productivity loss	**19,312,756**	**7,254**
Total cost of treating directly affected patients	**20,448,933**	**7,680**
Cost of treating new cases infected by patients		
Provider treatment cost of DS-TB cases	-	-
Provider treatment cost of MDR-TB cases	388,821	146
Provider treatment cost of XDR-TB cases	-	-
Sub-total provider treatment costs	**388,821**	**146**
Patient OOP costs and productivity losses of DS-TB	-	-
Patient OOP costs and productivity losses of MDR-TB cases	147,264	55
Patient OOP costs and productivity losses of XDR-TB cases	-	-
Sub-total patient OOP costs and productivity losses	**147,264**	**55**
Total cost of treating new patients	**536,084**	**201**
Total costs	**20,985,018**	**7,882**
Total provider costs	*1,524,998*	*573*
Total household/society costs	*19,460,019*	*7,309*

Note: Small differences in totals are due to rounding.

Sensitivity Analysis

A sensitivity analysis was conducted see the influence of key variables on the costs (annex E)

The results showed that the costs are not very sensitive to the length of treatment before interruption, the proportion of patients who are infectious at the time of interruption, or the length of the interruption. They are also not very sensitive to the proportion of patients treated by private (unaccredited) providers during the interruption period provided that those patients do not develop MDR-TB as a result of that treatment.

The costs are most sensitive to the proportion of patients who develop MDR-TB as a result of being treated by private providers and to the proportion of patients who develop MDR-TB as a result of being untreated during the interruption period. They are also sensitive to the proportion of patients who return to treatment after the interruption period and to the number of persons infected by patients who then develop active TB. All of these assumptions used in the model are based on expert opinion because there is little or no evidence in the Philippines or elsewhere.

Loss to Follow-Up of Drug-Sensitive TB Patients

The NTP data for 2014 show that 8,870 patients[11] were lost to follow-up out of 216,041 total reported TB cases. Across the regions, the total LTFU cases of all types ranged from 2% to 8% (24 to 1,747) of all patients. No data were available on the stage of treatment at which the interruption occurred or the length of the interruption. Based on guidance from the Expert Group, we assumed for the modeling that the interruption occurred three months into treatment and

[11] This figure reflects 4.2% of 216,041 cases of all types; 98.26 of these were Category 1.

lasted three months for those patients who returned to treatment. The main assumptions used in the modeling are shown in annex C.

Based on the opinion of the Expert Group, we assumed that 177 (2%) of the 8,870 patients are likely to have had undiagnosed MDR-TB and would have remained infectious during DS-TB treatment. The remaining DS-TB patients would not have been infectious because they should have received and adhered to a one-month supply of intensive-phase medicines at the time they started treatment and would have converted to smear-negative within that month.

The likely impact of this LTFU for the 8,870 patients is that 887 of those with DS-TB would have developed MDR-TB through poor quality private-sector treatment, poor adherence, or through discontinuation of treatment (table 3). Those 887 patients are likely to have infected an additional 245 people with MDR-TB. In addition, 1,958 of the original DS-TB and MDR-TB patients and the other persons infected with MDR-TB are likely to have died. We did not take into account that some of the DS-TB patients who had become non-infectious before interrupting treatment but did not return to treatment would have become infectious again at some stage. We also did not take into account that some of the above MDR-TB patients would have developed XDR-TB. In both cases, we were unable to obtain any estimates of what proportion of patients would be affected or how long that would take.

Table 3. Morbidity and Mortality Outcomes of the Three-month DS-TB Treatment Interruption for 8,870 Patients due to LTFU

Number of	Outcome
LTFU patients who develop MDR-TB as a result of the interruption	887
LTFU patients who die as a result of the interruption	1,958
Additional persons who develop DS-TB as a result of the interruption[12]	0
Additional persons who develop MDR-TB as a result of the interruption	245
Persons who develop XDR-TB as a result of the interruption	Unknown

The total additional economic cost of this treatment interruption is estimated to be USD 72.2 million, which comes to USD 8,141 per patient (table 4). The total additional cost of USD 72.2 million includes USD 70.1 million related to patients who interrupted treatment and USD 2.1 million related to new cases resulting from persons infected by those patients.

The total additional costs are also broken out by provider and patient costs. The additional provider costs are estimated at USD 5.8 million, while the additional costs for the patients and the persons they infect are USD 66.4 million.

As shown in table 4, the biggest component of the additional cost is USD 53.2 million for productivity loss related to the expected premature death of patients directly affected by the stock-outs. This based on the same set of assumptions used for the impact of the stock-outs, but

[12] This figure is zero because the opinion of the Expert Group was that none of the patients with DS-TB should be infectious at the time of the treatment interruption and therefore no additional people would be infected as a result of the interruption. We did not take into account that some of those patients who interrupted or discontinued treatment could have become infectious again due to lack of evidence with which to estimate such an impact.

it was assumed that 10% of LTFU patients would use the private sector, compared with 72% of patients affected by the stock-outs.

If LTFU could have been prevented for one patient, there would have been an average savings to the health system of USD 655 in terms of provider costs and a saving to the household of USD 7,485. If the cost of preventing that LTFU is less than the total additional cost of USD 8,141, there would be a net saving to society.

Table 4. Economic Cost of LTFU of Three Months for DS-TB Patients

	Total additional costs (USD)	Additional costs per patient LTFU (USD)
Costs for directly affected patients		
Provider treatment costs	4,297,923	485
Sub-total provider treatment costs	**4,297,923**	**485**
Patient treatment OOP costs	2,141,291	241
Patient productivity losses during illness	10,437,213	1,177
Patient productivity losses due to premature death	53,241,388	6,002
Sub-total patient OOP costs and productivity losses	**65,819,892**	**7,421**
Total cost of treating directly affected patients	**70,117,815**	**7,905**
Cost of treating new cases infected by patients		
Provider treatment cost of DS-TB cases	-	-
Provider treatment cost of MDR-TB cases	1,514,878	171
Provider treatment cost of XDR-TB cases	-	-
Sub-total provider treatment costs	**1,514,878**	**171**
Patient OOP costs and productivity losses of DS-TB	-	-
Patient OOP costs and productivity losses of MDR-TB cases	573,752	65
Patient OOP costs and productivity losses of XDR-TB cases	-	-
Sub-total patient OOP costs and productivity losses	**573,752**	**65**
Total cost of treating new patients	**2,088,631**	**235**
Total costs	**72,206,446**	**8,141**
Total provider costs	*5,812,801*	*655*
Total household/society costs	*66,393,644*	*7,485*

Note: Small differences in totals are due to rounding.

Sensitivity Analysis

A sensitivity analysis was performed see the influence of key variables on the costs (annex F).

The results showed that the costs are not very sensitive to the length of treatment before interruption, the proportion of patients who are infectious at the time of interruption, or the length of the interruption. They are also not very sensitive to the proportion of patients treated by private (unaccredited) providers during the interruption period, provided those patients do not develop MDR-TB as a result of that treatment.

The costs are most sensitive to the proportion of patients who develop MDR-TB as a result of either being treated by private providers or being untreated during the interruption period as well as to the proportion of patients who return to treatment after the interruption period and the number of persons infected by patients who then develop active TB. All of these assumptions are based on expert opinion because there is little or no evidence in the Philippines or elsewhere.

Loss to Follow-Up of MDR-TB Patients

LTFU of MDR-TB patients has been a significant issue in the Philippines for several years. High rates of LTFU among MDR-TB patients are of great concern because death rates are high; many patients have or develop XDR-TB; and many of them can continue to transmit the disease, leading to more extensive resistance.

The NTP reported an LTFU rate of 36% for drug-resistant patients in 2012 (the latest year for which official figures have been released), which is an improvement over the reported figure of 44% for 2011 [21] but is still a major issue for TB control.

The 2016 study by Tupasi et al., of MDR-TB patients, which used data from a cohort who started treatment between July and December 2012, found an LTFU rate of 29% [16]. Most (70) of the 90 patients for whom information on length of treatment was available were lost to follow-up during the intensive phase of treatment. Mean ± SD time receiving MDR-TB treatment for case patients was 7.8 ± 3.4 months (median 7 months; 25th percentile 4 months; 75th percentile 11 months). The study identified one of the main reasons for LTFU as intolerable side effects or fear of side effects,[13,14] and this was confirmed by the Expert Group.

Recent NTP data differed from the study findings and indicated that on average, MDR-TB patients stop treatment four months after initiation, leaving 14 months of treatment remaining (18 months being the total recommended treatment period for MDR-TB in the Philippines). For the modeling, we therefore assumed that the LTFU started four months after treatment initiation, but we also conducted a sensitivity analysis to see the impact of using seven months (the finding from the Tupasi 2016 study [16]). Based on the Expert Group's opinion, we assumed that the length of the LTFU was five months (patients reportedly feel much worse at that stage) and that 50% of patients would be infectious at the time that they stopped treatment.

According to the WHO profile report for the Philippines [20], 2,680 patients started MDR-TB treatment in 2014. Based on the assumption that 29% of patients could have been lost to follow-up, following the 2016 Tupasi study, that equals 777 patients.

Based on the Expert Group's opinion, we assumed that 15 (2%) of these patients are likely to have had undiagnosed XDR-TB and would have remained infectious during MDR-TB treatment.

[13] According to the study, the primary reason for stopping treatment was medication side effects or the fear of side effects, reported by 52 (58%) of 89 patients. The two other most commonly self-reported reasons for LTFU were the need to work and financial problems, reported by 25 (28%) of 89 patients, and lack of money for transportation to the treatment facility, reported by 18 (20%) of 89 patients.

[14] In both cases, improved management of the medication could help address these problems.

The likely impact of this LTFU for the 777 patients is that 330 of those with MDR-TB would have developed XDR-TB due to poor quality private-sector treatment, poor adherence, or discontinuation of treatment (table 5). Those 330 patients are likely to have infected an additional 19 people with XDR-TB. In addition, the MDR-TB patients who were still infectious at the time of interruption are likely to have infected an additional 474 persons with MDR-TB, and 233 people are likely to have died.

We did not take into account that some of the MDR-TB patients who had become non-infectious before interrupting treatment but did not return to treatment would have become infectious again at some stage because we were unable to obtain any estimates of what proportion of patients would be affected or how long that would take.

Table 5. Morbidity and Mortality Outcomes of the MDR-TB Treatment Interruption of Five Months for 777 patients Due to LTFU

Number of	Outcome
LTFU patients who develop XDR-TB as a result of the interruption	330
LTFU patients who die as a result of the interruption	233
Additional persons who develop DS-TB as a result of the interruption	0
Additional persons who develop MDR-TB as a result of the interruption	474
Persons who develop XDR-TB as a result of the interruption	19

The total additional economic cost related to those 777 patients is estimated to be USD 13.4 million (USD 17,296 per patient) (table 6). This additional economic cost reflects the additional costs incurred because the patients interrupted treatment.

The total additional economic cost comprises USD 9.1 million relating to the patients directly affected by the LTFU and USD 4.3 million relating to those infected by these patients. The share of the cost borne by providers would be USD 4.5 million, and the share borne by patients and the persons they infect would be USD 8.9 million.

The biggest single element of the additional cost is USD 6.3 million for productivity losses related to premature death of the patients directly affected by the stock-outs. This was calculated as follows:

- During the stock-out period, 5% (39) of the 777 MDR-TB patients would get treatment in the unaccredited private sector, 90% (35) of those would not get good quality treatment and would develop XDR-TB, and 21 of those patients would die. Of the remaining 10% (4) who get good quality private-sector treatment, 80% (3) would complete treatment and recover while 20% (1) would not complete treatment after the stock-out period and would die.

- During the stock-out period, 95% (738) of the patients would get no treatment, 40% (295) would develop XDR-TB, and 177 of those would die, while 60% (443) would remain with MDR-TB and 135 of those would die.

- The average age of patients who become ill with MDR-TB and XDR-TB is 42,[15] and it is assumed that untreated patients will live for three years, meaning that premature death would take place at the age of 45. Assuming a person is productive until the age of 65, 20 years of productivity would be lost with a total value of USD 36,005 that, when discounted using 3% per year, would result in a value of USD 27,222.

If LTFU could have been prevented for one patient, there would have been an average saving to the health system of USD 5,733 in terms of provider costs and a saving to the household of USD 11,562. If the cost of preventing that LTFU is less than the total of USD 17,296, there would be a net savings to society.

Table 6. Economic Cost of LTFU of Five Months for MDR-TB Patients

	Total additional costs (USD)	**Additional costs per patient LTFU (USD)**
Costs for directly affected patients		
Provider treatment costs	1,377,291	1,772
Sub-total provider treatment costs	**1,377,291**	**1,772**
Patient treatment OOP costs	441,910	569
Patient productivity losses during illness	990,714	1,275
Patient productivity losses due to premature death	6,342,901	8,161
Sub-total patient OOP costs and productivity losses	**7,775,525**	**10,005**
Total cost of treating directly affected patients	**9,152,816**	**11,777**
Cost of treating new cases infected by patients		
Provider treatment cost of DS-TB cases	-	-
Provider treatment cost of MDR-TB cases	2,933,646	3,775
Provider treatment cost of XDR-TB cases	145,014	187
Sub-total provider treatment costs	**3,078,660**	**3,961**
Patient OOP costs and productivity losses of DS-TB	-	-
Patient OOP costs and productivity losses of MDR-TB cases	1,111,103	1,430
Patient OOP costs and productivity losses of XDR-TB cases	99,552	128
Sub-total patient OOP costs and productivity losses	**1,210,656**	**1,558**
Total cost of treating new patients	**4,289,316**	**5,519**
Total costs	**13,442,132**	**17,296**
Total provider costs	*4,455,951*	*5,733*
Total household/society costs	*8,986,181*	*11,562*

Note: Small differences in totals are due to rounding.

Sensitivity Analysis

A sensitivity analysis was carried to see the influence of key variables on the costs (details in table 12, annex G).

[15] Based on the NTP report, that is the average age at enrollment for treatment and is assumed to be the time at which a patient fell ill.

The results show that the costs are not very sensitive to the proportion of patients treated by private (unaccredited) providers during the interruption period or to the proportion of those patients who develop XDR-TB as a result of that treatment.

The costs are most sensitive to the length of treatment before interruption, the proportion of patients who are infectious at the time of interruption, the length of the interruption period, and the proportion of patients who develop XDR-TB as a result of being untreated during the interruption period. They are also quite sensitive to the proportion of patients who return to treatment after the interruption period and to the numbers of persons infected by patients who then develop active TB. Many of these assumptions are based on expert opinions because there is limited evidence in the Philippines or elsewhere.

LIMITATIONS

There is not a lot of existing knowledge on the impact of non-adherence to TB medicines in the Philippines or elsewhere, and time and resources were insufficient to conduct primary research. There are, therefore, a number of limitations that should be taken into account.

1. In addition to LTFU, which is defined as interruption of two months or more, there are challenges of sporadic treatment interruption. This was not taken into account in the modeling due to the lack of sufficient data and a greater degree of complexity in terms of possible outcomes.

2. We were unable to include the impact of delays in starting treatment, which is also a challenge (17.3% of patients (DS-TB and MDR-TB combined) delayed treatment due to unavailability of medicines according to the Options Study patient interviews, with 21.8% delayed by more than four weeks).

3. The cost of treating extra-pulmonary TB has not been taken into account, and this is usually higher than the cost of treating pulmonary TB due to the need for additional diagnostic tests.

4. Figures were not available in the Philippines for the cost of public-sector diagnosis and consultation costs for DS-TB, OOP costs incurred by DS-TB patients, or the number of days lost due to illness. Data from Indonesia were used instead.

5. The impact of missing some, but not all, of the combination of medicines has not been taken into account.

6. The impact of missing Vitamin B complex vitamins or medicines for side effects has not been taken into account.

7. The impact of treatment interruption on patients with co-morbidities, such as AIDS or diabetes, has not been taken into account.

8. Persons infected by non-adherent patients could also not adhere to their treatment, develop drug-resistant TB, and infect additional persons. This has not been included in the models due to complexity.

9. Discounting was not applied to the cost of future treatment in people who are infected by patients who interrupt treatment or patients who develop MDR-TB or XDR-TB as a result of the interruption. This was because the length of time that it takes is not known in the context of the Philippines, as noted above. However, it is likely that the effect of inflation on the cost of treatment would cancel out the effect of discounting.

10. Data on the number of patients who experienced stock-outs and the length of those stock-outs were derived from patient surveys in the Options Study, and the number of responses was quite small.

11. Patients who were not infectious at the time the interruption started and who do not return to treatment after the interruption are likely to become infectious again. However, it is not known how many patients will convert back or how long that will take, and therefore we did not take this into account in estimating either outcomes or costs.

12. There are no estimates for the Philippines for the numbers of persons infected by an active TB case in one year, the proportion of these persons who develop active TB, or how long that would take. We used international estimates, but these are broad and the figures for the Philippines may be quite different.

13. We have not included the premature mortality costs for persons infected by the patients because of the lack of certainly of the length of time that it takes for persons to be infected, the proportion of persons who will develop active TB, and the time that would take.

CONCLUSIONS

Stock-outs of key TB medicines and LTFU of TB patients are significant problems in the Philippines. Treatment interruption results in the continuing spread of the disease, the increasing development of drug resistance, a burden on the health system, and hardship and loss of productivity for patients and their families.

In the three case studies reported here, it is clear that the impact on morbidity and mortality is likely to have been significant. Many patients are likely to have developed MDR-TB or XDR-TB; many are likely to have died; and many more are likely to have been infected with TB, including MDR-TB and XDR-TB (table 7).

Table 7. Impact of Treatment Interruption on Morbidity and Mortality

Number of	**DS-TB stock-outs of 1 month**	**DS-TB LTFU of 3 months**	**MDR-TB LTFU of 5 months**
Patients whose treatment was interrupted	*2,663*	*8,870*	*777*
Patients who develop MDR-TB as a result of the interruption	266	887	0
Patients who develop XDR-TB as a result of the interruption	Not estimated	Not estimated	330
Patients who die as a result of the interruption	588	1,958	233
Additional persons who develop DS-TB as a result of the interruption[16]	0	0	0
Additional persons who develop MDR-TB as a result of the interruption	63	245	474
Additional persons who develop XDR-TB as a result of the interruption	Not estimated	Not estimated	19

The economic cost of non-adherence is also likely to have been significant, with a total additional cost of USD 21.0 million related to DS-TB stock-outs, USD 72.2 million related to DS-TB LTFU, and USD 13.4 million related to MDR-TB LTFU (table 8). These are probably underestimates of the economic costs because we have not taken into account all effects of non-adherence. For example, we have not included the impact of reinfection where a patient who has been partially treated and become non-infectious has then stopped treatment for long enough to become infectious again. In addition, we have not included the productivity loss related to new persons who are infected by the non-adherent patients and who then die.

[16] In both DS-TB case studies, the opinion of the Expert Group was that no patients with DS-TB should be infectious at the time of the treatment interruption and, therefore, no additional people would be infected as a result of the interruption. We did not take into account that some of those patients who interrupted or discontinued treatment could have become infectious again due to lack of evidence with which to estimate such an impact.

Table 8. Economic Costs of Treatment Interruption

	DS-TB stock-outs of 1 month	DS-TB LTFU of 3 months	MDR-TB LTFU of 5 months
Number of patients whose treatment was interrupted	*2,663*	*8,870*	*777*
Total additional cost (USD)			
Provider cost	$1.5 million	$5.8 million	$4.5 million
Household cost	$19.5 million	$66.4 million	$8.9 million
Total	**$21.0 million**	**$72.2 million**	**$13.4 million**
Additional cost per affected patient (USD)			
Provider cost	$573	$655	$5,733
Household cost	$7,309	$7,485	$11,562
Total	**$7,882**	**$8,141**	**$17,296**

If the stock-out could have been prevented for one DS-TB patient, there would have been an estimated saving to the health system of up to USD 573 in terms of provider costs and up to USD 7,309 in household costs (patient OOP costs and lost productivity). Likewise, if the LTFU could have been prevented for the DS-TB and MDR-TB patients, there would have been estimated savings of up to USD 655 and USD 5,733 in terms of provider costs and up to USD 7,485 and USD 11,562 in household costs, respectively.

Expressed in another way, a 10% reduction in stock-outs could result in savings of USD 2.1 million for providers and households, and a 10% reduction in DS-TB and MDR-TB LTFU could result in savings of USD 7.3 million and USD 1.4 million, respectively.

It is therefore highly likely that the cost of interventions to prevent stock-outs and LTFU is less than the economic cost incurred as a result of them, and taking into account the reduction in hardship for TB sufferers and their families, these are likely to be very beneficial investments.

RECOMMENDATIONS

Several studies have been done on the reasons for treatment interruption in the Philippines and elsewhere, although these have focused more on the subject of LTFU than on medicine supply issues.

Although knowing the economic impact of treatment interruption is important for advocating for greater efforts to prevent it, very little research has been done internationally. A few studies have looked at the impact on immediate patient outcomes, but none have explored the more widespread impact or economic consequences.

As a result, many of the assumptions used in these three case studies are based on expert opinion in the Philippines because there is little or no evidence. Additional research, in both the Philippines and other countries, would help to build a body of evidence that would strengthen the case for investing in preventing treatment interruption.

Research Recommendations

Key areas where additional research would be useful in the Philippines include:

- The reasons why stock-outs of DS-TB kits/medicines have been reported when patients are not supposed to start treatment unless the full six-month kit is available, the average length of treatment before they are affected by the stock-outs, the care-seeking behavior of affected patients, and the proportion who return to the public sector for treatment after the stock-outs

- The proportion of patients who start DS-TB treatment who actually have MDR-TB and the proportion of patients who start MDR-TB treatment who actually have XDR-TB

- The length of time that a patient (DS-TB and MDR-TB) undergoes treatment before becoming LTFU, their care-seeking behavior while LTFU, the proportion of patients who return to the public sector to resume treatment, and the length of time before they return

- The proportion of DS-TB and drug-resistant TB patients who return to treatment after LTFU and resume and extend treatment versus restarting treatment

Areas of research that would be important in the Philippines and globally include:

- The rate at which patients who receive treatment in the non-accredited private sector develop MDR-TB and XDR-TB and how long that takes

- The length of time after starting treatment that it takes for DS-TB and MDR-TB patients to stop being infectious

- The proportion of DS-TB patients who develop MDR-TB or XDR-TB when untreated and how long that takes

- The numbers of persons infected by a person with active DS-TB or active MDR-TB in one year, the proportion of these who develop active TB, and the period of time over which they develop active TB

- The proportion of patients who become infectious again after converting to smear-negative but then interrupt or stop treatment and the time that it takes to become infectious again

- The proportion of untreated MDR-TB patients who develop XDR-TB and how long that takes

- The proportion of untreated MDR-TB patients who die and how long that takes

General Recommendations

Given the high degree of suffering and economic burden related to stock-outs and LTFU in the Philippines, the following general recommendations are made regarding the TB control program:

- The supply chain improvements recommended in the Options Study [15] should be high on the agenda of interventions

- Ways to improve rational medicine use and management of medicines for MDR-TB should be explored to address the side effects and reduce LTFU

- Priority should be given avoiding LTFU of MDR-TB patients by using a set of comprehensive interventions identified in the 2016 Tupasi study and reinforced and expanded in the draft 2016 Joint Program Review, including greater assistance from the TB program, better TB knowledge, and higher levels of trust in and support from physicians and nurses

- Action should also be taken to prevent LTFU among DS-TB patients, particularly in regions where this is high, including better provider and patient education, case management, and follow-up

- Consideration should be given to carrying out similar analyses of the extent and impact of reported shortages of DS-TB Adult Category 2 kits, IPT for children, kits for TB in children, and streptomycin, and also of LTFU among retreatment patients

ANNEX A. ECONOMIC COSTS AND SOURCES

Table 9. Economic Costs and Sources

Cost Type	Cost Estimate (USD)	Source
Cost of private sector treatment per month (USD)		
• Consultation	8.79	Dr. Hilton Lam – personal communication PHP 300 – 500. Confirmed by Expert Group
• Diagnostics	6.50	SIAPS/Philippines
• DS-TB medicines – monthly	13.24	SIAPS/Philippines
• MDR-TB medicines	na	Not available in private sector
• XDR-TB medicines	na	Not available in private sector
Public sector provider cost[17] per course of treatment:		
• DS-TB Category 1	183	Indonesia diagnosis and treatment costs [22] and Philippines medicine costs from SIAPS/Philippines
• MDR-TB	6,188	NTP estimate for Global Fund (excludes hospitalization)
• XDR-TB	7,647	NTP estimate for Global Fund (excludes hospitalization)
Patient OOP cost per course of treatment:		
• DS-TB	100	
• MDR-TB	1,473	No data from Philippines. Indonesia Patient Cost study USD 100 [23] Tupasi, Gupta et al., 2006. Costs were for clinic visits, hospitalization, and, in some cases, board and lodging. The figure was updated by inflation.[18] MDR-TB figure of USD 1,473 extrapolated from 20 to 24 months
• XDR-TB	1,768	
Minimum wage	6.59	http://www.nwpc.dole.gov.ph/pages/statistics/stat_current_regional.html
Productive days lost due to illness:		
• Treated DS-	81	Indonesia Economic Burden study [25]

[17] Costs of diagnostics, medicines, ancillary medicines, clinician, nursing, and running the facility

[18] A publication by Marks et al., in 2014 on MDR-TB and XDR-TB with data from the US between 2005 and 2007 [24] found that the direct costs (service delivery), which were mostly covered by the public sector, averaged USD 134,000 per MDR-TB patient and USD 430,000 per XDR-TB patient. In comparison, the estimated cost per non-MDR-TB patient was USD 17,000. Nearly three-quarters of the MDR-TB and XDR-TB patients were hospitalized, 78% completed treatment, and 9% died during treatment.

Cost Type	Cost Estimate (USD)	Source
TB • Untreated DS-TB • Treated MDR-TB • Untreated MDR-TB • Treated XDR-TB • Untreated XDR-TB	 792 132 792 528 792	 Indonesia Economic Burden study [25]. Expected to live for three years – 36 months x 22 days. Intensive period – 6 months x 22 days. Indonesia Economic Burden study [25]. See above. 24 months Same as untreated MDR-TB
Average number of productive days per month	22	
Average years of life lost from DS-TB	23	Average age at which patient contracted DS-TB is 39.[19] Would live for three years if untreated.[26] Age at which patient ceases to be productive is 65.
Average years of life list – MDR-TB and XDR-TB	20	Average age at which patient contracted MDR-TB or XDR-TB is 42.[20] Would live for three years if untreated.[26] Age at which patient ceases to be productive is 65.
Discount rate	3%	
Average exchange rate 2015 - Pesos to USD	45.49	1 Peso = USD 0.021981 Forex website

[19] Source: NTP. Because the age at which a person contracts TB affects the value of the productive years of life lost, it would be better to use the median for each quartile of patients. Consideration should be given to removing children from the data set before determining the medians. Unfortunately, none of these figures were available at the time of writing this report.
[20] Ibid.

ANNEX B. DS-TB STOCK-OUT MODEL ASSUMPTIONS

1. No DS-TB patients were assumed to be infectious at the start of the interruption period because they are all supposed to have received a one-month supply when they start treatment and it is assumed that they all take the medicines as intended and stop being infectious during that month. There is some evidence from other countries that not all patients stop being infectious within 30 days, but that is not the opinion in the Philippines.

2. We assumed that 2% of patients who start treatment for DS-TB actually have MDR-TB according to the opinion of the Expert Group, and these patients will remain infectious because the DS-TB treatment will not be effective. We assumed that all of those patients would infect others during the interruption period and that the 30% of those who do not return to treatment after the interruption period would continue to infect others for three years until they die.

3. There was no information on the average length of treatment of a DS-TB patient before he or she stopped taking medicines due to stock-outs. The Expert Group agreed to assume three months on average. Because the course of treatment for DS-TB is six months, three additional months would be needed to complete treatment.

4. Based on the survey sample conducted for the Options Study, we assumed that 30% of the DS-TB patients who missed taking their medicines due to stock-outs did not have access to medicines for 30 days. This is a conservative estimate because the median number of days without medicines for those patients was 58 days and the range was 30 to 222 days. However, the sample size was small.

5. Based on the survey sample conducted for the Options Study, 72% of the DS-TB patients who missed taking their medicines due to stock-outs went to the private sector for treatment. The Expert Group opined that 50% of these patients would get consultations and diagnosis in a public facility and the other 50% would pay for those services in the private sector. All patients would buy medicines in the private sector.

6. The Expert Group felt that on average 10% of the DS-TB patients who receive treatment in the non-accredited private sector could develop MDR-TB due to poor quality medications, incorrect dosages or combinations, or non-adherence to treatment guidelines.[21]

7. The Expert Group felt that all DS-TB patients who return to the public sector after the period of interruption would resume and extend treatment because the interruption period was assumed to be only one month.

[21] An interesting study published in 2013 of private-sector TB medicines in the Philippines concluded that an enormous quantity of anti-TB medicines was channeled through the private market outside the purview of the Philippine NTP, suggesting significant OOP expenditures, severe under-reporting of TB cases, and/or misuse of medicines due to over-diagnosis and over-treatment. [12]

8. In the 2016 study by Tupasi et al., it was noted that only 70% of MDR-TB patients returned to treatment after the period of interruption. The Expert Group felt that this is a reasonable assumption for DS-TB patients who interrupt due to stock-outs and for those patients who develop MDR-TB.

9. We assumed that 13% of all patients who develop or have MDR-TB and are treated will die, based on NTP data for 2012.

10. We assumed that all patients who develop or have MDR-TB and are untreated will die.

11. We assumed that 30% of the patients who remain with DS-TB and do not return to treatment will self-cure, based on a study by Tiemersma et al. [26]

12. We assumed that an infectious person infects one other person per month and that 10% of those cases would become active TB over the lifetime of the infected person.[22] With a compromised immune system, as many people have in the Philippines due to poverty, the risk of falling ill would probably be higher, with progression to illness taking as little as 10 years.[23]

13. Patients who were not infectious at the time the interruption started and who do not return to treatment after the interruption are likely to become infectious again. However, it is not known how many patients will convert back or how long that will take, and therefore we did not include this in estimating the outcomes or costs.

[22] People infected with TB bacteria have a 10% lifetime risk of falling ill with TB. However, persons with compromised immune systems and active TB can infect 10 to 15 other people through close contact over the course of a year. Without proper treatment, 45% of HIV-negative people with TB on average and nearly all HIV-positive people with TB will die. WHO. Tuberculosis Fact sheet N°104. Reviewed March 2016 http://www.who.int/mediacentre/factsheets/fs104/en/.

[23] According to the CDC Morbidity and Mortality Weekly Report of June 9, 2000, a report entitled Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection noted that persons infected with Mycobacterium tuberculosis are at greatest risk for developing disease in the first two years after infection has occurred.

ANNEX C. DS-TB LTFU MODEL ASSUMPTIONS

1. No DS-TB patients were assumed to be infectious at the start of the interruption period because they are all supposed to receive a one-month supply when they start treatment, and it is assumed that they all take the medicines as intended and stop being infectious during that month.

2. We assumed that 2% of patients who start treatment for DS-TB actually have MDR-TB, based on the opinion of the Expert Group, and they will remain infectious. We assumed that all of those patients would infect others during the interruption period and that the 30% who do not return to treatment after the interruption period would continue to infect others for three years until they die.

3. There was no information on the average length of treatment of a DS-TB patient before being LTFU, but the Expert Group agreed that we would assume that patients stop treatment on average at three months. Since the course of treatment for DS-TB is six months, three additional months would be needed to complete treatment.

4. There was no information on the average length of the period of interruption for the LTFU DS-TB patients. Because a patient is declared LTFU only two months after stopping treatment, the Expert Group agreed that we would assume that the period of interruption is three months.

5. We assumed that 10% of the LTFU DS-TB patients would go to the private sector for treatment during the period of interruption, based on the opinion of the Expert Group.

6. The Expert Group felt that on average, 10% of the DS-TB patients who receive treatment in the non-accredited private sector would develop MDR-TB due to poor quality medications, incorrect dosages or combinations, or non-adherence to treatment guidelines.[24,25]

7. The Expert Group felt that all DS-TB patients who return to the public sector after the period of interruption would restart treatment because the interruption period is assumed to be three months.

8. In the 2016 study by Tupasi et al., it was noted that only 70% of MDR-TB patients returned to treatment after the period of interruption. The Expert Group felt that this is a reasonable assumption for DS-TB patients who interrupt due to LTFU and for those patients who develop MDR-TB.

[24] An interesting study published in 2013 of private-sector TB medicines in the Philippines concluded that an enormous quantity of anti-TB medicines was channeled through the private market outside the purview of the Philippine NTP, suggesting significant OOP expenditure, severe under-reporting of TB cases, and/or misuse of drugs due to over-diagnosis and over-treatment. [12]

[25] The NTP felt that it might take 10 years for a person with MDR-TB to develop XDR-TB.

9. We assumed that 13% of all patients who develop or have MDR-TB and are treated will die, based on NTP data for 2012.

10. We assumed that all patients who develop or have MDR-TB and are untreated will die.

11. We assumed that 30% of the patients who remain with DS-TB and do not return to treatment will self-cure, based on a study by Tiemersma et al. [26]

12. We assumed that an infectious person infects one other person per month, and 10% of those cases would become active TB over the lifetime of the infected person.[26] With a compromised immune system, which many people have in the Philippines due to poverty, the risk of falling ill would probably be higher, with progression to illness taking as little as 10 years.[27]

13. Patients who were not infectious at the time the interruption started and who do not return to treatment after the interruption are likely to become infectious again. However, it is not known how many patients will convert back or long that would take, and therefore we did not include this in estimating the outcomes or costs.

[26] People infected with TB bacteria have a 10% lifetime risk of falling ill with TB. However, persons with compromised immune systems and active TB can infect 10 to 15 other people through close contact over the course of a year. Without proper treatment, 45% of HIV-negative people with TB on average and nearly all HIV-positive people with TB will die. WHO. Tuberculosis Fact sheet N°104. Reviewed March 2016 http://www.who.int/mediacentre/factsheets/fs104/en/.

[27] According to the CDC Morbidity and Mortality Weekly Report of June 9, 2000, a report entitled Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection noted that persons infected with Mycobacterium tuberculosis are at greatest risk for developing disease in the first two years after infection has occurred.

ANNEX D. MDR-TB LTFU MODEL ASSUMPTIONS

1. There were mixed opinions on the length of time that MDR-TB patients remain infectious after starting treatment. Data from the NTP showed that MDR-TB patients become non-infectious two months after initiating treatment.[28] However, the Expert Group felt that all patients are still infectious after four months and that 50% are still infectious after seven months.

2. We assumed that 2% of patients who start treatment for MDR-TB actually have XDR-TB according to the Expert Group, and these patients will remain infectious.

3. Recent NTP data showed that on average, MDR-TB patients who become LTFU stop four months into treatment. The 2016 study conducted by Tupasi et al. with data from 2012 to 2014 found that LTFU MDR-TB patients stop at seven months on average. We decided to assume the figure of four months but conducted a sensitivity analysis to show the impact of using seven months.[29]

4. There was no information on the length of the period of interruption for LTFU MDR-TB patients, so we assumed five months based on the opinion of the Expert Group.

5. Based on the Expert Group's opinion, we assumed that 5% of the LTFU MDR-TB patients would go to the private sector for treatment during the interruption period.

6. We assumed that 90% of the LTFU MDR-TB patients who go to the non-accredited private sector for treatment during the interruption period would develop XDR-TB because MDR-TB medicines are not available in the non-accredited private sector.[30,31]

7. We assumed that 80% of patients who are treated in the private sector and who develop XDR-TB would return to the public sector for treatment based on the opinion of the Expert Group. We assumed the same for patients who are untreated during the interruption period.

8. We assumed that 40% of patients who are untreated during the interruption period will develop XDR-TB.

9. We assumed that 13% of all patients who remain with MDR-TB and are treated will die, based on NTP data for 2012.

[28] It would be better to use the median for each quartile of patients, but this was not available at the time of writing the report.
[29] It would be better to use the median for each quartile of patients, but this was not available at the time of writing the report.
[30] A study published in 2013 noted that key second-line medicines are not available in the private market in the Philippines, making it impossible to design an adequate treatment regimen for MDR-TB in the private sector. It also concluded that that an enormous quantity of anti-TB medicines was channeled through the private market outside the purview of the Philippine NTP, suggesting significant OOP expenditures, severe under-reporting of TB cases, and/or misuse of medicines due to over-diagnosis and over-treatment. [12]
[31] The NTP felt that the development of XDR-TB might take five years.

10. We assumed that 50% of patients who developed XDR-TB and return to the public sector for treatment would be cured and the remainder would die. This is based on limited international studies and was agreed upon by the Expert Group.

11. We assumed that all patients who have MDR-TB and all who develop or have XDR-TB and are untreated will die, based on the opinion of the Expert Group.

12. We assumed that all MDR-TB and XDR-TB patients who were infectious at the start of the interruption period would infect others during the interruption period and that 20% of those patients who do not return to treatment after the interruption period would continue to infect others for three years until they die. [26]

13. We assumed that an infectious person infects one other person per month and 10% of those cases would become active TB over the lifetime of the infected person.[32] With a compromised immune system, which many people have in the Philippines due to poverty, the risk of falling ill would probably be higher, with progression to illness taking as little as 10 years. [33]

14. Patients who were not infectious at the time the interruption started and who do not return to treatment after the interruption are likely to become infectious again. It is not known how many patients will convert back or long that would take, and therefore we did not take this into account in estimating the outcomes or costs.

[32] People infected with TB bacteria have a 10% lifetime risk of falling ill with TB. However, persons with compromised immune systems and active TB can infect 10 to 15 other people through close contact over the course of a year. Without proper treatment, 45% of HIV-negative people with TB on average and nearly all HIV-positive people with TB will die. WHO. Tuberculosis Fact sheet N°104. Reviewed March 2016 http://www.who.int/mediacentre/factsheets/fs104/en/.

[33] According to the CDC Morbidity and Mortality Weekly Report of June 9, 2000, a report entitled Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection noted that persons infected with Mycobacterium tuberculosis are at greatest risk for developing disease in the first two years after infection has occurred.

ANNEX E. SENSITIVITY ANALYSIS FOR DS-TB STOCK-OUTS

A partial sensitivity analysis was carried out on key single variables to see which had the greatest influence on total costs and on provider costs (table 10). The degrees of change are hypothetical.

Table 1. Sensitivity Analysis on Key Variables for DS-TB Stock-outs

Description	Change from	Impact on total additional cost	Impact on additional provider cost	Impact on additional household cost
Length of treatment before the interruption, assuming no change in the proportion of patients who are infectious at the time of interruption	3 to 4 months	+4%	0%	+4%
Proportion of DS-TB patients who are infectious at the time they interrupt treatment	0% to 10%	1%	4%	1%
Length of treatment interruption	1 to 2 months	0%	+2%	0%
Percentage of patients treated in the private sector	72% to 36%	0%	0%	0%
Percentage of patients who develop MDR-TB while being treated in the private sector	10% to 20%	+11%	+53%	+8%
Percentage of patients who develop MDR-TB during the interruption period through not being treated	10% to 20%	+5%	+21%	+3%
Percentage of MDR-TB patients who return to treatment	70% to 35%	+11%	-10%	+12%
Percentage of DS-TB patients who return to treatment	70% to 35%	+92%	0%	+99%
Number of persons who are infected by patients per month and develop active TB	0.1 to 0.2	+2%	+25%	+1%

ANNEX F. SENSITIVITY ANALYSIS FOR DS-TB LTFU

A partial sensitivity analysis was carried out on key single variables to see which had the greatest influence on total costs and on provider costs (table 11). The degrees of change are hypothetical.

Table 2. Sensitivity Analysis on Key Variables for DS-TB Stock-outs

Description	Change from	Impact on total additional cost	Impact on additional provider cost	Impact on additional household cost
Length of treatment before the interruption, assuming no change in the proportion of patients who are infectious at the time of interruption	3 to 4 months	+4%	+3%	+5%
Proportion of patients who are infectious at the time they interrupt treatment	0% to 10%	0%	+1%	0%
Length of treatment interruption	3 to 4 months	0%	+2%	0%
Percentage of patients treated in the private sector	10% to 20%	0%	0%	0%
Percentage of patients who develop MDR-TB while being treated in the private sector	10% to 20%	+2%	+6%	+1%
Percentage of patients who develop MDR-TB during the interruption period through not being treated	10% to 20%	+15%	+58%	+11%
Percentage of MDR-TB patients who return to treatment	70% to 35%	+10%	-9%	+11%
Percentage of DS-TB patients who return to treatment	70% to 35%	+87%	-4%	+95%
Number of persons who are infected by patients per month and who develop active TB	0.1 to 0.2	+3%	+26%	+1%

ANNEX G. SENSITIVITY ANALYSIS FOR MDR-TB LTFU

A partial sensitivity analysis was carried out on key single variables to see which had the greatest influence on total costs and on provider costs (table 12). The change in the variable for length of treatment before interruption is based on the alternative figure of seven months identified in the 2016 Tupasi study [16]. All other changes are hypothetical.

Table 12. Sensitivity Analysis on Key Variables for MDR-TB LTFU Patients

Description	Change from	Impact on total additional cost	Impact on additional provider cost	Impact on additional household cost
Length of treatment before the interruption, assuming no change in the proportion of patients who are infectious at the time of interruption	4 to 7 months	+9%	+14%	+6%
Proportion of patients who are infectious at the time they interrupt treatment	50% to 25%	-16%	-33%	-7%
Length of treatment interruption	5 to 3 months	-5%	-11%	-2%
Percentage of patients treated in the private sector	5% to 10%	+2%	+1%	+2%
Percentage of patients who develop XDR-TB while being treated in the private sector	90% to 45%	-2%	0%	-2%
Percentage of patients who develop XDR-TB during the interruption period through not being treated	40% to 20%	-13%	-4%	-18%
Percentage of XDR-TB patients who return to treatment	80% to 40%	+11%	-5%	+20%
Percentage of MDR-TB patients who return to treatment	80% to 40%	+69%	-71%	+68%
Number of persons who are infected by patients per month and who develop active TB	0.1 to 0.2	+33%	+69%	+14%

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