# The Economic Cost of Non-adherence to TB Medicines

## Resulting from Stock-outs and Loss to Follow-up in Kenya

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## Key Words

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

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## ACRONYMS AND ABBREVIATIONS

| | |
|---|---|
| CI | confidence interval |
| CTLC | County TB and Leprosy Coordinator |
| DOT | directly observed treatment |
| DOTS | directly observed treatment, short course |
| DR-TB | drug-resistant TB |
| DS-TB | drug-sensitive TB |
| GFATM | The Global Fund to Fight AIDS, Tuberculosis and Malaria |
| LTFU | loss to follow-up |
| MDR-TB | multidrug-resistant TB |
| MOH | Ministry of Health |
| MSF | Medecins Sans Frontieres |
| MSH | Management Sciences for Health |
| NTLDP | National Tuberculosis, Leprosy and Lung Disease Program |
| OOP | out of pocket |
| OR | odds ratio |
| PMDT | programmatic management of Drug-Resistant TB |
| SIAPS | Systems for Improved Access to Pharmaceuticals and Services |
| TB | tuberculosis |
| USAID | US Agency for International Development |
| WHO | World Health Organization |
| XDR-TB | extensively drug-resistant TB |

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## CONTENTS

# EXECUTIVE SUMMARY

One of the key elements of successful tuberculosis (TB) control programs is adherence to treatment, which is a cornerstone of most international and national policies and guidelines. Non-adherence results in increased length and severity of illness, death, disease transmission, and drug resistance. This has economic consequences in terms of cost, to both individuals and the health system as a whole, as well as lost income for patients and their families.

A common cause of non-adherence is treatment interruption, which may range from short, intermittent periods of days to longer periods of weeks or months, and may even result in complete discontinuation of treatment. Treatment interruption is often due to patient-related factors—classed as loss to follow-up (LTFU)—but can also be a result of provider issues, such as stock-outs of medicines. Interventions to prevent treatment interruption are, therefore, aimed at both treatment providers and patients. On the provider side, actions include ensuring proper prescribing practices and management of side effects, providing good quality medicines, and preventing stock-outs. On the patient side, actions include interventions to encourage patients to use medicines as directed and continue treatment even when they feel better, as well as to remove barriers to treatment, such as transport costs. These actions are believed to be a good investment, but the economic savings have not been clearly defined.

Kenya is among 22 countries considered to have a high burden of TB, including multidrug-resistant TB (MDR-TB). The Kenyan Ministry of Health (MOH) has an extensive TB program that is managed by the NTLDP. The program includes directly observed treatment, short course (DOTS) for TB and DOTS-Plus for MDR-TB. In addition, the NTLDP has strategies and procedures in place to ensure and improve treatment adherence, including patient compliance incentives and supply chain management systems.

Under government devolution in 2013/14, the procurement of TB medicines became the responsibility of the county governments. However, county governments had limited capacity to procure TB medicines due to technicalities involved in the procurement process. As a result, no adult first-line TB medicines were procured for two financial years and stock-outs were a serious concern. The NTLDP, with technical support from the Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program and advocacy from other stakeholders, prepared a compelling, evidence-based case to the national government and key partners. As a result, emergency funding was obtained, which averted the crisis. This situation was selected by SIAPS to illustrate the impact that this crisis could have had on morbidity and mortality, as well as the economic impact, if it had not been averted.

Like many developing countries, Kenya has had challenges with LTFU. According to NTLDP data, the average LTFU in 2014 was 4%, with Samburu and Pokot counties having the highest rates (10% and 12%, respectively) (NTLDP Annual Report, 2015).

The purpose of this study was to estimate the morbidity, mortality, and economic impact of TB treatment interruption due to stock-outs and LTFU. The results are expected to help promote the

benefits of ensuring the availability of good quality medicines and of undertaking interventions to reduce LTFU.

Based on NTLDP data and experiences, three case studies were selected that would have had the greatest economic impact:

1. Averted stock-outs of drug-sensitive TB (DS-TB) Category 1 medicines
2. LTFU of DS-TB patients
3. LTFU of MDR-TB patients

The results of these case studies are summarized as follows.

The interventions to prevent stock-outs are estimated to have saved more than 7,000 lives and prevented the development of more than 1,000 cases of drug-resistant TB (DR-TB) and more than 400 new infections. The interventions also saved more than USD 113 million (USD 25 million in health service costs and USD 88 million in household and society costs) (table 8). These savings translate to more than USD 2,000 per patient.

An estimated 3,317 DS-TB patients who were lost to follow-up in 2015 are likely to have resulted in 70 patients developing MDR-TB, 28 new persons being infected with MDR-TB, and more than 400 deaths. In addition, this LTFU is likely to have resulted in more than USD 7 million in additional costs (USD 1.6 million in health service costs and USD 5.5 million in household and society costs). This translates to a cost of more than USD 2,000 per patient.

An estimated 52 MDR-TB patients who were lost to follow-up in 2015 are likely to have resulted in 5 patients developing extensively drug-resistant TB (XDR-TB), 3 new persons being infected with MDR-TB and 1 new person with XDR-TB, and 3 deaths. In addition, this LTFU is likely to have resulted in approximately USD 380,000 million in additional costs (USD 325,000 in health service costs and USD 55,000 in household and society costs). This translates to a cost of more than USD 7,000 per patient.

The above figures for morbidity, mortality, and economic impact are probably underestimated, as the research team did not take into account all the effects of non-adherence. For example, the team did not include the impact of re-infection, whereby a patient who has been partially treated and become non-infectious has stopped treatment long enough to become infectious again. The results also did not include the productivity losses related to new persons who are infected by non-adherent patients and who then die.

The interventions that were undertaken to prevent DS-TB drug stock-outs undoubtedly cost far less than USD 133 million and represent a massive saving to Kenya's health system, families, and society. Further, interventions to prevent LTFU can probably be implemented for much less than USD 2,159 per DS-TB patient and USD 7,247 per MDR-TB patient.

Based on the results of the analysis, it appears that the supply chain has been robust since the devolution of the budget was resolved. However, priority should be given to reducing DS-TB patient LTFU through improved education and case management, especially in regions where

LTFU is high, and reducing MDR-TB LTFU through improved case management, including better management of the medicines, as adverse side effects are a major reason for LTFU. The global literature review found that little research has been done on the impact of treatment interruption. Additional research would, therefore, be highly beneficial, both in Kenya and internationally, to provide a more robust evidence base.

In summary, it is highly likely that the costs of interventions to prevent stock-outs and LTFU are significantly less than the economic costs incurred as a result of these situations. Taking into account the reduction in hardship for TB sufferers and their families, these interventions are likely to be beneficial investments.

# BACKGROUND

## Tuberculosis Treatment Adherence

One of the key elements of successful TB control programs is adherence to treatment, which 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 drugs is essential to achieving successful program outcomes. Non-adherence results in increased length and severity of illness, death, disease transmission, and drug resistance. This has economic consequences in terms of cost to the health system as well as cost to the individual, such as lost income for patients and their families [7, 8].

A common cause of non-adherence is treatment interruption, which may range from short, intermittent periods of days to longer periods of weeks or months, and may even result in complete discontinuation of treatment. Interventions to prevent treatment interruption are aimed at both treatment providers and patients. On the provider side, actions include ensuring proper prescribing practices and management of side effects, providing good quality medicines, and preventing stock-outs. On the patient side, actions include interventions to encourage patients to use medicines as directed and continue treatment even when they feel better, as well as to remove barriers to treatment, such as transport costs. These actions are believed to be a good investment, but the economic savings have not been clearly defined.

## Kenya

Kenya is situated in East Africa and has a population of 45 million. The country is divided into 47 counties and its capital is Nairobi. In terms of major health indices (2015 estimates), the maternal mortality rate is 510 deaths per 100,000 live births; infant mortality is 39.38 deaths per 1,000 live births; and life expectancy is 63.77 years (ranking it the 30th, 51st, and 185th highest country in the world, respectively).[1] The adult prevalence rate for HIV and AIDS is 5.3% (2014 estimate), making the country 13th highest in the world.

Kenya is one of 22 countries considered to have a high burden of TB [9]. In 2014, it was estimated that Kenya had 9,400 TB-related deaths and 8,100 HIV-positive TB deaths. The prevalence rate was estimated at 266 per 100,000 population[2] and the incidence rate was estimated at 246 per 100,000 (both figures include HIV-positive TB). A total of 88,294 cases were notified in 2014 and 544 patients were started on MDR-TB treatment. In the same year, the treatment success rate was 86% for new cases registered in 2013 and 83% for MDR-TB cases who started treatment in 2012. In 2014, 36% of TB patients were HIV positive. Although Kenya did not meet its prevalence and mortality reduction targets, the country did meet its target for reducing the TB incidence rate in 2015.

[1] CIA Fact Book. https://www.cia.gov/library/publications/the-world-factbook/geos/ke.html

[2] A new prevalence survey is currently in process and may result in a higher estimate of prevalence given the use of improved diagnostics.

Kenya's Ministry of Health (MOH) has an extensive TB program with DOTS[3] for TB and DOTS-Plus for MDR-TB. TB tests and medicines are provided by the government free of charge; however, consultation, inpatient services, and non-TB medicines are not free. Some private-sector providers also provide TB services, including Medecins Sans Frontieres (MSF), which plays a significant role in MDR-TB and XDR-TB treatment.

The MOH has strategies and procedures in place to ensure the availability of TB medicines, including the use of the QuanTB tool for rapid quantification and an Early Warning System, both of which were introduced by SIAPS. Some stock-outs have occurred at the national level with occasional, and mainly short, stock-outs of levofloxacin, pyrazinamide, capreomycin, streptomycin, and pediatric TB medicines. There is no indication, however, that these shortages resulted in treatment interruption.

LTFU is, however, a significant issue in Kenya, reaching as high as 10% and 12% in Samburu and Pokot, respectively, in 2014 [10]. According to NTLDP data for 2015, an estimated 4.4% of DS-TB Category 1 patients were lost to follow-up. Applied to the total of 74,798 cases treated that year, a total of 3,317 patients would have been lost to follow-up. Additionally, NTLDP data for 2015 estimated that 12% of MDR-TB patients were lost to follow-up. Applied to the total of 438 cases treated that year, a total of 52 patients would have been lost to follow-up.

A common reason for LTFU cited by DST-TB patients is that they feel better after a few months on treatment and decide that there is no need to continue. For MDR-TB patients, the most common reason is dislike of the daily injections together with side effects. Unfortunately, if patients return to treatment at a different health facility (which is reportedly common), there is no ability to link their data with data from previous encounters, and thus the previous treatment of the patient is unknown.

High rates of LTFU for MDR-TB patients are concerning as some may have XDR-TB or pre-XDR TB when treatment is started. The high proportion of patients who also have HIV only adds to these concerns. In addition, drug resistance is sometimes acquired during treatment, and some individuals who are lost to follow-up may remain culture-positive at last contact, enabling transmission of strains with more extensive resistance.

The purpose of this study was to estimate the morbidity and mortality as well as the economic impact of TB treatment interruption[4] due to stock-outs and LTFU. The results are expected to help promote the benefits of ensuring the availability of good quality medicines and of undertaking interventions to reduce LTFU. The case study on stock-outs is hypothetical in that it looks at the potential impact of a major stock-out that could have occurred but was, in fact, prevented. The two case studies on LTFU are based on actual data from 2015 and are most likely to reflect an ongoing problem.

The results of these case studies are expected to provide useful evidence to promote the benefits of investing in improving treatment adherence through interventions to ensure the availability of good quality medicines and to encourage and assist patient treatment compliance.

[3] Directly Observed Treatment, Short Course – the TB control strategy recommended by WHO.

[4] 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 gathered from three sources. The first was 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 morbidity, mortality, and economic impact of such treatment interruption. The second source was a review of NTLDP plans, policies, reports, and other documents and records for information on Kenya's treatment guidelines, numbers of services, and costs. The third source consisted of interviews in Kenya with an expert panel comprising service providers, managers, and NTLDP staff regarding Kenyan treatment decision-making, patient pathways, and the impact of treatment interruption on health and mortality.

A model was developed to quantify the likely impact of the treatment interruption in terms of subsequent treatment or non-continuation of treatment, provider and patient costs, and productivity losses. Notably, the model only shows the additional effects of each type of treatment interruption; it does not show what would have happened in the absence of that interruption. For example, the stock-out model does not include a component that shows 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 problem of LTFU.

For the modeling, the research team used a spreadsheet-based tool that was developed by MSH through USAID's SIAPS Program.[5] This tool was piloted for a similar study conducted by SIAPS in the Philippines [11].

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, resulting in each case ending in either eventual cure or death. These are summarized below in a simple conceptual framework (figure 1):

- The first factor is whether patients are infectious or not at the time of interruption. Those who are infectious will infect other persons during the interruption period and beyond if they do not return to treatment.

- The second factor is if the patients are treated by non-accredited private providers during the interruption period or if they are not treated at all.

- The third factor is if the patients develop drug resistance during the interruption period.

- The fourth factor is whether or not the patient returns to an accredited provider to continue treatment after the interruption period.

[5] The tool is open source and designed to be user friendly. It can be obtained free of charge from MSH.

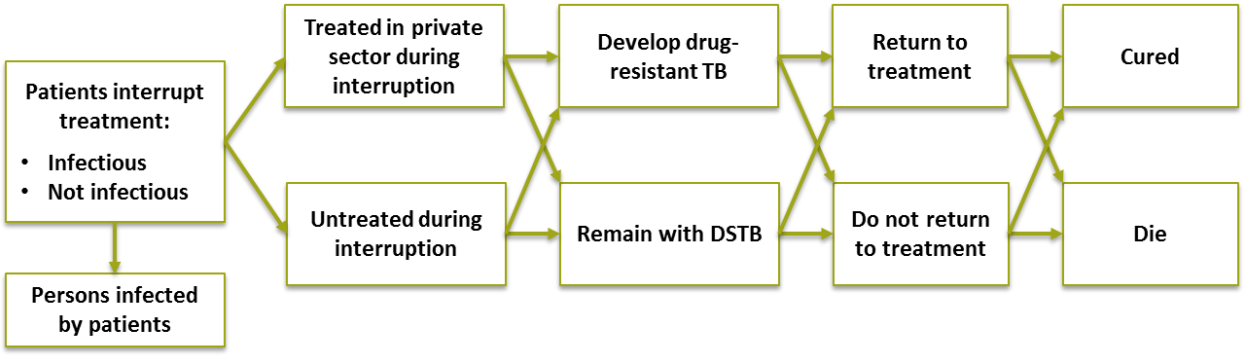


**Figure 1. Conceptual framework for treatment interruption**

Four types of economic cost are included in the model. These are:

- The cost to the service provider of treating TB
- The out-of-pocket (OOP) cost to the patient of seeking and obtaining diagnosis and treatment
- The loss of productivity suffered by 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, persons who decide to buy medicines in the private sector incur an OOP expense that they would not have paid in the public sector (where the medicines are free of charge). Individuals may also incur a higher risk of developing drug resistance due to poor quality medicines or incorrect dosages or combinations. And people who die as a result of non-adherence to treatment due to stock-outs or LTFU represent an economic cost in the form of loss of productivity due to premature death.

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

- Averted stock-outs of DS-TB Category 1 medicines
- LTFU of DS-TB patients
- LTFU of MDR-TB patients

The research team did not estimate the costs of LTFU for retreatment patients, which would require the development of a retreatment model. However, the number of LTFU retreatment patients is estimated at 681 in 2015 (8.9% of the total number of 7,693 patients) and it would be worthwhile calculating the cost related to these patients in the future.

The unit costs used in the study were obtained from various sources, which are shown in annex B.

## 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 interruption.

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. Free text and MeSH keywords were used in combination for two searches:

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

(2) tuberculosis, adherence, and outcome assessment in low- and middle-income countries.

### Search Results

The first search on criteria including "stock-outs" identified a total of 65 published articles. None of the articles covered the impact of stock-outs of TB medicines and so none were included in the results.

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

However, of these 12 papers, 11 discussed the reasons for treatment interruption but not the impact of treatment interruption. Only one paper included anything on the impact of non-adherence; this was a 2014 paper by Ershova et al. on treatment of South African TB patients [12]. This study found that incomplete directly observed treatment (DOT), specifically DOT received 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

Supplementing the above searches with citation searches and consultation with experts, the research team identified a publication by Pablos-Mendez et al. related to a study in New York [13] and publications by Podewils et al. [14], Tupasi et al. [15], Kizito et al. [16], Mauch et al. [17], Muture et al. [18], and Sitienei et al. [19].

The retrospective study by Pablos-Mendez et al. examined a city-wide cohort of 184 patients with TB in New York City (before the strengthening of its control program) who were newly diagnosed by culture in April 1991 and followed through 1994. Non-adherence was defined as

treatment default for at least two months. Eighty-eight (48%) of the 184 patients 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 overall cost of treatment.

Podewils et al. 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 a period of 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 length per interruption was 1.4 days and a total of 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 length interruptions with sporadic variability during the 6–12 month or the 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, excepting the final 18–24 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 prescribed treatment doses. It should be noted that this study focused on treatment interruption that was less than two months and, therefore, did not include patients lost to follow-up, which is operationally defined as periods of two months or greater.

The Tupasi et al. (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. Out of 986 patients who started MDR-TB treatment, 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 case-patients was medication side effects or the fear of side effects, which was reported by 52 (58%) of 89 case-patients who responded to this question. The two other most commonly self-reported reasons for LTFU were 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 useful information on LTFU, but did not examine the impact of LTFU.

Kisito et al. presented the results of a retrospective study conducted between July 2006 and December 2008 to determine the rate of LTFU from the MSF TB program in Kibera and to assess associated clinical and sociodemographic factors. Patients who had missed their appointments were routinely traced under the program and were encouraged to return for treatment. Where possible, reasons for missed appointments were recorded. Cases of LTFU were defined as those patients started on anti-TB treatment in the MSF clinics who missed TB clinic appointments for two consecutive months. LTFU occurred in 146 (13%) of the 1,094 patients registered, with the most significant associations identified as male gender, no salaried

employment, lack of family support, and positive TB smear at diagnosis. Of these cases, 111 were randomly selected and 36 (32.4%) were found to be LTFU in the first two months of treatment (described as early), 34 (30.6%) between the second and the fourth month, and 41 (36.9%) after the fourth month (late). Some of the patients had missed their clinic appointments on several occasions before eventually becoming LTFU. Despite the existence of the MSF's Defaulter Tracing Programme, there was a higher rate of LTFU (13%) in Kibera compared to the Kenyan national average at that time. This was likely due to the mobile nature of the population in Kibera, who often return to their villages "up-country." The rate of LTFU could have been higher had the Defaulter Tracing Programme not managed to contact patients who had missed an appointment and encouraged them to continue with treatment. Nevertheless, since the MSF program had a system in place to trace and follow-up with defaulters, it is reasonable to assume that the LTFU rates found would be lower than those in a place similar to Kibera, which lacks such a system.

The most common reason given for LTFU among the 46 (54%) out of 86 patients contacted was relocation from Kibera to their up-country rural homes. Out of 86 patients, 13 (15%) cited work commitments and lack of time off to attend TB clinic, 6 (7%) had moved from their last known address to locations outside Kibera and were unable to attend their appointments, and 6 (7%) were unwilling to continue with their TB treatment. The remaining 15 (17%) cited various other reasons.

Males were more likely to be lost to follow-up than females; this may be due to the challenges of finding work. Anecdotal reports indicate that most of the males in Kibera work as daily laborers, employed on a casual basis. Although not statistically significant, patients testing positive for HIV were less likely to be lost to follow-up, which may be partly due to MSF's emphasis on HIV treatment literacy.

Mauch et al. presented the results of interviews with 208 patients with TB in 2008 to estimate patient costs. The study found that TB patients in two districts had a substantial burden of direct (OOP; USD 55.80) and indirect (opportunity; USD 294.20) costs due to TB. Inability to work was identified as a major cause of increased poverty. The study concluded that TB had resulted in a "medical poverty trap" situation in the two districts (i.e., expenditures increased while incomes decreased). The authors did not discuss stock-outs of TB medicines or LTFU.

The study by Muture et al. in Nairobi Province in 2006/08 found that of 945 defaulters, 215 (22.7%) and 193 (20.4%) abandoned treatment within the first and second months (intensive phase) of treatment, respectively. Among 120 defaulters interviewed, 20 (16.7%) attributed their default to ignorance, 15 (12.5%) to traveling away from the treatment site, 14 (11.7%) to feeling better, and 13 (10.8%) to side effects. In a multivariate analysis, inadequate knowledge of TB (odds ratio [OR] 8.67; 95% confidence interval [CI] 1.47–51.3), herbal medication use (OR 5.7; 95% CI 1.37–23.7), low income (OR 5.57; CI 1.07–30.0), alcohol abuse (OR 4.97; 95% CI 1.56–15.9), previous default (OR 2.33; 95% CI 1.16–4.68), co-infection with HIV (OR 1.56; 95% CI 1.25–1.94), and male gender (OR 1.43; 95% CI 1.15–1.78) were independently associated with default.

Sitienei et al. reviewed 2012 and 2013 data from the national electronic data recording system and found that out of 106,824 total cases assessed, HIV infection was the single most influential risk factor for default. More than 94% of patients received family-based DOT and were more

likely to default than patients who received DOT from health care workers. Males were more likely to default than females. Caloric nutritional support was associated with lower default rates. Additionally, patients cared for in the private sector were less likely to default than those in the public sector.

While the above studies demonstrate that there has been some research on overall reasons for LTFU, the literature review indicates that there has been little research on the impact of non-adherence to TB drugs due to stock-outs or LTFU.

SIAPS previously conducted a study of the impact of stock-outs and LTFU in the Philippines [11]. The study looked at three case studies with the following findings:

- An estimated 2,663 DS-TB patients interrupting treatment for one month due to stock-outs, which is likely to have resulted 588 deaths and USD 21 million (USD 7,800 per patient) in additional costs

- An estimated 8,870 DS-TB patients lost to follow-up for three months, which is likely to have resulted in 1,958 deaths and USD 72 million (USD 8,100 per patient) in additional costs

- An estimated 777 MDR-TB patients lost to follow-up for five months, which is likely to have resulted in 233 deaths and USD 12 million (USD 16,600 per patient) in additional costs

# RESULTS

## Stock-out of DS-TB Adult Category 1 Medicines

Until financial year 2013/14, funding for the procurement of adult first-line TB medicines was fully provided by the Government of Kenya and funding for second-line medicines was provided by donors. With the introduction of the new constitution, certain functions of government were devolved to 47 county levels. Apart from some services, such as national referral hospitals, health services were transferred to the counties, which also became responsible for the budgets for these services. Funding came from block grants from the National Treasury and from local taxes. There was no earmarking of funding for health services and decisions on allocations to sectors were made by the county governments.

With this change, funding for the procurement of TB medicines became the responsibility of county governments. However, county governments have limited capacity to procure TB medicines due to technicalities involved in the procurement process. As a result, no adult first-line TB medicines were procured for two financial years, and stock-outs became a serious concern.[6] If this transpired, treatment of enrolled adult DS-TB patients would be interrupted for several months, resulting in increased deaths, illness, development of drug resistance, and further transmission of the disease.

The NTLDP, with support from stakeholders, prepared a compelling, evidence-based case to the national government and key partners for emergency support and for the national government to engage in centralized procurement to avoid stock-outs and poor quality medicines.[7] Assistance was provided by SIAPS, notably for quantification using the QuanTB tool and the use of the Early Warning System to generate reports on specific areas of greatest need. As a result of this intervention by the NTLDP and its partners, actions were taken to obtain emergency funding for supplies, thus averting the crisis. These actions included:

- Stop TB Partnership Global Drug Facility agreement to support an immediate order for 50% of the needed adult first-line medicines and a later order for 100% of the needed medicines
- Fast tracking of delivery of medicines from the Global Drug Facility and the Global Fund to Fight AIDS, TB, and Malaria (GFATM)
- GFATM allowing the country to initiate early procurement of 55,000 patient packs planned for year 5
- The Kenya NTLDP obtaining medicines from Malawi
- The Government of Kenya setting aside USD 3 million for the procurement of medicines

[6] The tool is open source and designed to be user friendly. It can be obtained free of charge from MSH.
[7] At the time of this report, the centralization of procurement has remained in place.

This experience was selected by SIAPS to illustrate the impact that this crisis would have had on morbidity and mortality, as well as the economic impact, if it had not been averted. The SIAPS analysis conducted in October 2014 indicated that stocks of first-line medicines would run out in January 2015 if emergency supplies were not obtained. This would result in interrupted treatment for the 52,724 adult patients[8] enrolled in first-line treatment in October 2014.[9] For the purposes of the case study, the research team assumed that all 52,724 patients would have been affected; stock-outs would have occurred three months, on average, into treatment; and stock-outs would have lasted for three months, on average. The main assumptions used in the modeling are shown in annex C.

Based on expert panel opinion, it was assumed that 527 (1%) of these patients are likely to have had undiagnosed MDR-TB at the time they started DS-TB treatment and would have remained infectious during the treatment. The remaining DS-TB patients would not have been infectious since they should have received and adhered to a one-month supply of intensive-phase medicines at the time they started treatment, and thus would have converted to smear-negative within the one month.

The likely impact of this stock-out would have been that 1,107 of those with DS-TB would have developed MDR-TB as a result of the interruption. These 1,107 patients would likely have infected an additional 443 people with MDR-TB. A total of 7,319 additional deaths would have occurred as a result of the interruption. The results did not take into account that some DS-TB patients who had become non-infectious prior to treatment interruption but did not return to treatment would have become infectious again. The results also did not consider that some of the above MDR-TB patients would have developed XDR-TB. In both cases, the research team was unable to obtain estimates of what proportion of patients would be affected and how long it would take to become infectious again in the first case, and to develop XDR-TB in the second case.

**Table 1. Morbidity and Mortality Outcomes of DS-TB Treatment Interruption for Three Months Due to Stock-outs**

| Description | Outcome |
|---|---|
| Total number of DS-TB patients who interrupted treatment | 52,724 |
| Number of patients who would develop MDR-TB as a result of the interruption | 1,107 |
| Number of additional persons who would develop DS-TB as a result of the interruption[10] | 0 |
| Number of additional persons who would develop MDR-TB as a result of interruption | 443 |
| Number of additional persons who would develop XDR-TB as a result of interruption | 0 |
| Number of additional patients who would die as a result of the interruption | 7,319 |

[8] 55,652 total patients less 2,928 children

[9] If new patients had continued to be enrolled after October 2014, the number of patients affected would be higher and stocks would run out sooner.

[10] This figure is zero because the opinion of the expert panel 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. The results 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.

If this stock-out had occurred, the total additional economic cost could have been as high as USD 113.8 million, comprising USD 25.6 million for additional service delivery costs and USD 88.2 million for household costs (table 2). This additional cost is made up of the total cost less the cost that would have been incurred if the patients had adhered to their medicines (i.e., not interrupted treatment). This works out to a cost of approximately USD 2,100 per patient who would have interrupted treatment due to the stock-out.

The biggest element of the additional costs is the USD 76.2 million for productivity losses related to the expected premature death of patients directly affected by the stock-outs. This is based on the following set of assumptions:

- None of the 52,724 patients would have received treatment during the stock-out period as the stock-out would have equally affected the accredited private sector.
    - Of these patients, 1,107 (2.1%) would have developed MDR-TB, 941 (85%) of these would have returned to treatment after the stock-out, and 649 (69%) would have died; 166 (15%) would not have returned to treatment and all would have died.
    - The remaining 97.9% (51,617) would have remained with DS-TB, 85% (43,874) would have returned to treatment and 14% (6,142) of these would have died, while the other 15% (7,743) would not have returned to treatment and all would have died.
    - After deducting 7,381 patients who would have died even if they had not interrupted treatment, that leaves a total of 7,319 additional deaths incurred as a result of the treatment interruption.
- The average age of becoming ill with DS-TB would have been 39 years[11] and it is assumed that untreated patients would live for 3 years, meaning that premature death would take place at the age of 42. Assuming a person is productive until the age of 65, 23 years of productivity would be lost, amounting to a total value of USD 14,456; when discounted using 3% per year, this would result in a value of USD 10,507.

The prevention of the stock-out resulted in an average saving of USD 486 per patient for the health system, in terms of provider costs, and a saving of USD 1,674 for each household. If the cost of preventing that stock-out was less than the total additional cost of USD 2,159 there would have been a net saving to society.

[11] Based on NTLDP data, this is the average age at enrollment for treatment and is assumed to be the time they fell ill.

**Table 2. Economic Cost of Stock-outs of TB Medicines for Three Months for DS-TB Patients (USD)**

| | Total additional costs | | Additional costs per patient | |
|---|---|---|---|---|
| **Costs for directly affected patients** | | | | |
| Provider treatment costs | $ | 19,708,244 | $ | 374 |
| **Sub-total provider treatment costs** | **$** | **19,708,244** | **$** | **374** |
| Patient treatment OOP costs | $ | 2,114,237 | $ | 40 |
| Patient productivity losses during illness | $ | 9,394,508 | $ | 178 |
| Patient productivity losses due to premature death | $ | 76,274,375 | $ | 1,447 |
| **Sub-total patient OOP costs and productivity losses** | **$** | **87,783,121** | **$** | **1,665** |
| **Total cost of treating directly affected patients** | **$** | **107,491,365** | **$** | **2,039** |
| | | | | |
| **Cost of treating new cases infected by patients** | | | | |
| Provider treatment cost of DS-TB cases | $ | - | $ | - |
| Provider treatment cost of MDR-TB cases | $ | 5,890,325 | $ | 112 |
| Provider treatment cost of XDR-TB cases | $ | - | $ | - |
| **Sub-total provider treatment costs** | **$** | **5,890,325** | **$** | **112** |
| Patient OOP costs and productivity losses of DS-TB cases | $ | - | $ | - |
| Patient OOP costs and productivity losses of MDR-TB cases | $ | 475,690 | $ | 9 |
| Patient OOP costs and productivity losses of XDR-TB cases | $ | - | $ | - |
| **Sub-total patient OOP costs and productivity losses** | **$** | **475,690** | **$** | **9** |
| **Total cost of treating new patients** | **$** | **6,366,015** | **$** | **121** |
| | | | | |
| **Total costs** | **$** | **113,857,380** | **$** | **2,159** |
| *Total provider costs* | *$* | *25,598,570* | *$* | *486* |
| *Total household/society costs* | *$* | *88,258,810* | *$* | *1,674* |

## LTFU of DS-TB Patients

NTLDP data for 2015 shows that 2,668 patients were lost to follow-up, which represents 4.43% of the 60,168 DS-TB cases evaluated. Applying this percentage to the total number of 74,798 new DS-TB patients in 2015 produces an estimate of 3,317 LTFU cases.

No data were available on the stage of treatment at which the interruption occurred or the length of the interruption. However, based on guidance from the expert panel and for the purposes of modeling, the research team assumed that the interruption occurred three months into treatment and lasted for three months,[12] for those patients who returned to treatment. The main assumptions used in the modeling are shown in annex D.

Based on expert panel opinion, it was assumed that 33 (1%) of the 3,317 patients were 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 as they should have received and adhered to a one-month supply of intensive-phase medicines at the time they started treatment; as a result, they would have converted to smear-negative within the one month.

[12] Patients are only categorized as LTFU after two months of interruption, so the estimate of three months may be conservative.

The likely impact of this LTFU is that the 3,317 patients would have all been untreated during the interruption period, since proper treatment is not available from unapproved private-sector providers.[13] Out of these patients, 70 (2.1%) would have developed MDR-TB, 59 (85%) would have returned to treatment, and 10 (15%) would not have returned to treatment. Of the 3,247 (97.9%) of patients who remained with DS-TB, 2,760 (85%) would have returned to treatment while 487 (15%) would not. A total of 460 additional deaths would have resulted from the treatment interruption.

The results did not take into account that some of the DS-TB patients who had become non-infectious prior to treatment interruption, but who did not return to treatment, would have become infectious again at some stage. The results also did not take into account that some of the above MDR-TB patients would have developed XDR-TB. In both cases, the research team was unable to obtain any estimates of what proportion of patients would be affected and how long it would take to become infectious again in the first case and to develop XDR-TB in the second case.

**Table 3. Morbidity and Mortality Outcomes of DS-TB Treatment Interruption for Three Months Due to LTFU**

| Description | Outcome |
|---|---|
| Total number of DS-TB patients who interrupted treatment | 3,317 |
| Number of LTFU patients who would develop MDR-TB as a result of the interruption | 70 |
| Number of additional persons who would develop DS-TB as a result of the interruption[14] | 0 |
| Number of additional persons who would develop MDR-TB as a result of interruption | 28 |
| Number of persons who would develop XDR-TB as a result of interruption | Unknown |
| Number of LTFU patients who would die as a result of interruption | 460 |

The total additional economic cost of this treatment interruption is estimated at approximately USD 7.1 million, which amounts to approximately USD 2,100 per patient (table 4). The total additional cost of USD 7.1 million is comprised of USD 6.7 million related to patients who interrupted treatment and USD 0.4 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 1.6 million, while the additional costs for patients and the persons they subsequently infect are estimated at USD 5.5 million.

As can be seen in table 4, the most significant element of the additional costs is the USD 4.7 million for productivity losses related to the expected premature death of patients directly affected by the stock-outs. This is based on the same set of assumptions used in the DS-TB stock-outs model, which were explained above.

[13] A number of private providers are approved by the government to provide TB services; they report to the NTLDP. The LTFU figures would, therefore, include patients of approved private-sector providers.

[14] This figure is zero because the expert panel opinion 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. The research team 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.

If LTFU could have been prevented for one patient, there would have been an average saving of USD 486 for the health system, in terms of provider costs, and a saving of USD 1,674 for each household. If the cost of preventing that LTFU is less than the total additional cost of USD 2,159 there would have been a net saving to society.

**Table 4. Economic Cost of LTFU for Three Months for DS-TB Patients (USD)**

| | Total additional costs | | Additional costs per patient LTFU | |
|---|---|---|---|---|
| **Costs for directly affected patients** | | | | |
| Provider treatment costs | $ | 1,239,895 | $ | 374 |
| **Sub-total provider treatment costs** | **$** | **1,239,895** | **$** | **374** |
| Patient treatment OOP costs | $ | 133,012 | $ | 40 |
| Patient productivity losses during illness | $ | 591,032 | $ | 178 |
| Patient productivity losses due to premature death | $ | 4,798,614 | $ | 1,447 |
| **Sub-total patient OOP costs and productivity losses** | **$** | **5,522,658** | **$** | **1,665** |
| **Total cost of treating directly affected patients** | **$** | **6,762,533** | **$** | **2,039** |
| | | | | |
| **Cost of treating new cases infected by patients** | | | | |
| Provider treatment cost of DS-TB cases | $ | - | $ | - |
| Provider treatment cost of MDR-TB cases | $ | 370,575 | $ | 112 |
| Provider treatment cost of XDR-TB cases | $ | - | $ | - |
| **Sub-total provider treatment costs** | **$** | **370,575** | **$** | **112** |
| Patient OOP costs and productivity losses of DS-TB cases | $ | - | $ | - |
| Patient OOP costs and productivity losses of MDR-TB cases | $ | 29,927 | $ | 9 |
| Patient OOP costs and productivity losses of XDR-TB cases | $ | - | $ | - |
| **Sub-total patient OOP costs and productivity losses** | **$** | **29,927** | **$** | **9** |
| **Total cost of treating new patients** | **$** | **6,400,502** | **$** | **121** |
| | | | | |
| **Total costs** | **$** | **7,163,055** | **$** | **2,159** |
| *Total provider costs* | *$* | *1,610,471* | *$* | *486* |
| *Total household/society costs* | *$* | *5,552,585* | *$* | *1,674* |

## LTFU of MDR-TB Patients

LTFU of MDR-TB patients can be a significant issue as death rates are high; many patients can have or develop XDR-TB; and many can continue to transmit the disease, leading to more extensive resistance.

According to NTLDP data, in 2015, an estimated 12.0% of the 92 evaluated MDR-TB patients were lost to follow-up. Applied to the total of 438 cases treated in that year, this would have resulted in a total of 52 patients lost to follow-up. According to the expert panel, most LTFU occurs at five months, which is when many patients can no longer stand the injections. No data were available on the length of the interruption. However, based on guidance from the expert panel and for the purposes of modeling, the research team assumed that, for those patients who returned to treatment, the LTFU lasted for five months.

Based on expert panel opinion, the research team assumed that 1 (1%) of these patients is likely to have had undiagnosed XDR-TB and would have remained infectious during the MDR-TB treatment. Additionally, it was assumed that 3 (5%) of the remaining MDR-TB patients would have been infectious at the time of interruption.

The expert panel believed that the one patient with XDR-TB would have infected one other patient, but that none of the 51 patients with MDR-TB would have developed XDR-TB as a result of the treatment interruption, because they would all have died or resumed treatment beforehand. Two additional deaths would have occurred as a result of the interruption and three additional persons would have been infected with MDR-TB.

The results did not take into account that some of the MDR-TB patients who had become non-infectious prior to treatment interruption, but who did not return to treatment, would have become infectious again at some stage. The research team was unable to obtain any estimates of what proportion of patients would be affected and how long it would take to become infectious again in the first case, and to develop XDR-TB in the second case.

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

| Description | Outcome |
|---|---|
| Number of patients who interrupted treatment | 52 |
| Number of LTFU patients who would develop XDR-TB as a result of the interruption | 5 |
| Number of additional persons who would develop DS-TB as a result of the interruption | 0 |
| Number of additional persons who would develop MDR-TB as a result of interruption | 3 |
| Number of persons who would develop XDR-TB as a result of interruption | 1 |
| Number of LTFU patients who would die as a result of interruption | 3 |

The total additional economic cost related to these 52 patients is estimated at approximately USD 380,000 (USD 7,200 per patient) (table 6). This additional economic cost reflects the additional costs incurred due to patients' treatment interruption.

The total additional economic cost comprises USD 318,000 relating to patients directly affected by LTFU and USD 62,000 relating to persons infected by those patients. The share of the cost borne by providers would be USD 325,000, whereas the share borne by patients and the persons they infect would be USD 55,000.

The biggest single element of the additional costs is USD 266,400 for provider treatment costs. This was calculated as follows:

- All 52 patients would be untreated during the interruption period. Of these, 40 (85%) would return to restart MDR-TB treatment. These patients would receive 20 months of treatment compared with the 15 months remaining treatment that they would have received. This would result in an additional five months of treatment, at a rate of USD 665 per month for 45 patients. In addition, four patients would be treated for XDR-TB.

If the LTFU could have been prevented for one patient, there would have been an average saving of USD 6,194 for the health system, in terms of provider costs, and a saving of USD 1,054 for each household. If the cost of preventing that LTFU is less than the total of USD 7,247 there would be a net saving to society.

**Table 6 . Economic Cost of LTFU for Five Months for MDR-TB Patients (USD)**

| | Total additional costs | | Additional costs per patient LTFU | |
|---|---|---|---|---|
| **Costs for directly affected patients** | | | | |
| Provider treatment costs | $ | 266,417 | $ | 5,087 |
| **Sub-total provider treatment costs** | **$** | **266,417** | **$** | **5,087** |
| Patient treatment OOP costs | $ | 5,459 | $ | 104 |
| Patient productivity losses during illness | $ | 13,642 | $ | 260 |
| Patient productivity losses due to premature death | $ | 32,228 | $ | 615 |
| **Sub-total patient OOP costs and productivity losses** | **$** | **51,329** | **$** | **980** |
| **Total cost of treating directly affected patients** | **$** | **317,746** | **$** | **6,067** |
| | | | | |
| **Cost of treating new cases infected by patients** | | | | |
| Provider treatment cost of DS-TB cases | $ | - | $ | - |
| Provider treatment cost of MDR-TB cases | $ | 36,219 | $ | 692 |
| Provider treatment cost of XDR-TB cases | $ | 21,731 | $ | 415 |
| **Sub-total provider treatment costs** | **$** | **57,950** | **$** | **1,107** |
| Patient OOP costs and productivity losses of DS-TB cases | $ | - | $ | - |
| Patient OOP costs and productivity losses of MDR-TB cases | $ | 2,925 | $ | 56 |
| Patient OOP costs and productivity losses of XDR-TB cases | $ | 918 | $ | 18 |
| **Sub-total patient OOP costs and productivity losses** | **$** | **3,843** | **$** | **73** |
| **Total cost of treating new patients** | **$** | **61,794** | **$** | **1,180** |
| | | | | |
| **Total costs** | **$** | **379,539** | **$** | **7,247** |
| *Total provider costs* | *$* | *324,367* | *$* | *6,194* |
| *Total household/society costs* | *$* | *55,172* | *$* | *1,054* |

## SENSITIVITY ANALYSIS

A sensitivity analysis was carried out to examine the influence of key variables on costs (details in annexes C–H).

### DS-TB Treatment Interruption

The results of the sensitivity analysis for treatment interruption from stock-outs and LTFU show that additional costs are only significantly sensitive to changes in timing of the interruption if it affects the degree to which patients are still infectious. If the time on treatment before interruption is so short that patients are still infectious (i.e., usually less than one month), the impact on cost is significant. If, for example, 99% of the DS-TB patients were infectious instead of 0%, the additional total cost would increase by 18% (57% for provider costs and 6% for household costs). Other variables that are sensitive in terms of additional total costs are as follows:

- An increase from 1% to 2% in the percentage of DS-TB patients who actually have MDR-TB would result in an increase of 5.6% in total additional costs.
- An increase from 2.1% to 4.2% in the percentage of patients who develop MDR-TB during the period of interruption would result in an increase of 16% in total additional costs.
- A decrease from 85% to 75% in the percentage of DS-TB patients who return to treatment after interruption would result in a 44% increase in total additional costs.[15]
- A decrease from 86% to 76% in the success rate of treating returned DS-TB patients would result in an 8.1% to 9.1% decrease in total additional costs.[16]
- A doubling in the number from 1.2 to 2.4 per year of persons who become infected and who develop active TB would increase total additional costs by 5.6%.

Total additional costs were not very sensitive to changes in other variables.

A sensitivity analysis of unit costs showed that only changes in the value of lost productivity (the number of years, the minimum wage used, or the discount rate) has a significant impact on the total additional costs. A 10% increase in the unit cost results in a 6.1% increase in additional total costs.

[15] This increase of 44% is largely because a significant additional number of patients would die prematurely, since it is assumed that all the patients who do not return to treatment would die.

[16] A lower treatment success rate and corresponding higher death rate affects the number of persons who would have died without the interruption as well as those who interrupted, and the new effect is fewer additional deaths.

## MDR-TB Treatment Interruption

The expert panel believed that most MDR-TB patients who become LTFU interrupt treatment at approximately five months because this is the time when they can no longer stand the injections. The expert panel believed that by this time, only 5% of patients would still be infectious. If the time of interruption is later, there is a significant impact on costs. For example, increasing the interruption from five to six months would result in an 8.7% increase in total additional costs; if the rate were 10% instead of 5%, the total additional costs would be 10.3% higher. The impact on cost is much greater, however, if the interruption occurs four months or less into treatment because most patients would still be infectious. If, for example, 99% of the MDR-TB patients were infectious at the time of treatment interruption, the additional total costs would increase by 194%, with the additional provider costs increasing by 210% and the additional household costs increasing by 100%.

Other sensitive variables in terms of additional total costs are as follows:

- If the percentage of patients being treated for MDR-TB that are actually XDR-TB increases from 1% to 2%, total additional costs would increase by 6%.

- If the percentage of MDR-TB patients who develop XDR-TB during the interruption period increases from 10% to 20%, total additional costs would increase by 34.3%.

- If the percentage of MDR-TB patients who return to treatment decreases from 85% to 75%, total additional costs would decrease by 31.6%.

- A doubling in the number from 1.2 to 2.4 per year of persons who become infected and who develop active TB would increase total additional costs by 16%.

The expert panel thought that none of the patients who would have remained with DS-TB and who would not have returned to treatment would have self-cured. The panel also felt that the 30% self-cure estimate made by Tiemersma et al. [26] would not be relevant in Kenya. A sensitivity analysis showed that applying a self-cure rate of 30% would result in a 21.9% decrease in total additional costs under the DS-TB scenarios and a 6.0% decrease under the MDR-TB scenario.

The sensitivity analysis of unit costs showed that only changes in the cost of treatment for MDR-TB and XDR-TB would have a significant impact on total costs: a 10% increase in the unit costs of MDR-TB and XDR-TB treatments would result in 6.1% and 5.3% increases in additional total costs, respectively.

The sensitivity analysis shows that the economic impact of treatment interruption depends partly on the difference between the cost of treating TB and of not treating TB. This is particularly true for MDR-TB and XDR-TB where the treatment costs are high, especially in developing countries where the value of lost production is deemed to be low. However, the impact on families and society is not adequately reflected in such economic measures, and policy and programmatic decisions on the advisability of treatment should not be made solely on economic terms.

## LIMITATIONS

There is not a large amount of existing knowledge on the impact of non-adherence to TB medicines in Kenya or elsewhere, and there was neither sufficient time nor resources 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 for 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. The research team was unable to include the impact of delays in starting treatment, which may also be a challenge.

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

4. Figures were not available in Kenya for OOP costs incurred by MDR-TB patients and for the number of days lost due to illness. Data from other countries 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 or medicines for side effects has not been taken into account.

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

8. Persons infected by non-adherent patients may also not adhere to their treatment and as a result develop DR-TB and infect yet more people. This has not been included in the models due to the complexity of the issue.

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

10. Patients who were not infectious at the time of interruption and who do not return to treatment after interruption are likely to become infectious again. However, it is not known how many patients will convert back and how long it will take. Therefore, this was not taken into account when estimating the outcomes and costs.

11. There are no estimates for either the number of people in Kenya who are infected by an active TB case in a year or the proportion of these people who develop active TB and how long that would take. International estimates were used, but these are broad and the specific figures for Kenya may be different.

12. The premature mortality costs for people infected by patients were not included due to a lack of certainty regarding the length of time it takes for people to be infected as well as the proportion of people who will develop active TB and the time that would take.

## CONCLUSIONS

In late 2014, the NTLDP, with support from SIAPS and other donors, made a significant effort to prevent major stock-outs of key TB medicines. The impact of these interventions is estimated to have saved more than 7,000 lives and prevented the development of more than 1,000 cases of DR-TB and more than 400 new infections (table 7). These interventions saved more than USD 113 million (USD 25 million in health service costs and USD 88 million in household and society costs) (table 8), which translates to savings of more than USD 2,000 per patient.

In 2015, an estimated 3,317 DS-TB patients were lost to follow-up. This is likely to have resulted in 70 patients developing MDR-TB, 28 new persons being infected with MDR-TB, and more than 400 deaths. In addition, it is likely to have resulted in more than USD 7 million in additional costs (USD 1.6 million in health service costs and USD 5.5 million in household and society costs), translating to more than USD 2,000 per patient.

Also in 2015, an estimated 52 MDR-TB patients were lost to follow-up. This is likely to have resulted in five patients developing XDR-TB, three new persons being infected with MDR-TB and one new person with XDR-TB, and three deaths. In addition, it is likely to have resulted in approximately USD 380,000 million in additional costs (USD 325,000 in health service costs and USD 55,000 in household and society costs), translating to more than USD 7,000 per patient.

**Table 7. Impact of Treatment Interruption on Morbidity and Mortality**

| | DS-TB stock-outs of 3 months[a] | DS-TB LTFU of 3 months | MDR-TB LTFU of 5 months |
|---|---|---|---|
| Percent of patients | 100% | 4.4% | 12% |
| Number of patients | 52,724 | 3,317 | 52 |
| Number of patients who develop MDR-TB as a result of interruption | 1,107 | 70 | 0 |
| Number of patients who develop XDR-TB as a result of interruption | Not estimated | Not estimated | 5 |
| Number of additional persons who develop DS-TB as a result of interruption[17] | 0 | 0 | 0 |
| Number of additional persons who develop MDR-TB as a result of interruption | 443 | 28 | 3 |
| Number of additional persons who develop XDR-TB as a result of interruption | Not estimated | Not estimated | 1 |
| Number of patients who die as a result of interruption | 7,319 | 460 | 3 |

[a] Hypothetical example

[17] In both DS-TB case studies, the opinion of the expert panel was that none of the patients with DS-TB would be infectious at the time of treatment interruption and, therefore, no additional people would be infected as a result of the interruption. The research team did not take into account that some of the 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 (USD)**

| | DS-TB stock-outs of 3 months[a] | DS-TB LTFU of 3 months | MDR-TB LTFU of 5 months |
|---|---|---|---|
| *Number of patients whose treatment was interrupted* | *52,724* | *3,317* | *52* |
| **Total additional cost** | | | |
| Provider cost | $25.5 million | $1.6 million | $324,000 |
| Household cost | $88.3 million | $5.5 million | $55,000 |
| **Total** | **$113.8 million** | **$7.1 million** | **$379,000** |
| | | | |
| **Additional cost per affected patient** | | | |
| Provider cost | $486 | $486 | $6,194 |
| Household cost | $1.674 | $1,674 | $1,054 |
| **Total** | **$2,159** | **$2,159** | **$7,247** |

[a] Hypothetical example

The above figures for morbidity, mortality, and economic impact are probably underestimated, as the research team did not take into account all the effects of non-adherence. For example, the team did not include the impact of re-infection, whereby a patient who has been partially treated and become non-infectious has stopped treatment long enough to become infectious again. The results also did not include the productivity losses related to new persons who are infected by non-adherent patients and who then die.

The interventions to prevent DS-TB drug stock-outs undoubtedly cost far less than the total of USD 133 million, and represent a massive saving to the Kenya's health system, families, and society. A net saving would result in Kenya if LTFU could be prevented for less than USD 2,159 per DS-TB patient and USD 7,247 per MDR-TB patient.

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

The estimated costs per patient in Kenya are lower that the costs estimated for the Philippines, which were approximately USD 7,800–USD 8,100 per DS-TB patient and USD 16,600 per MDR-TB patient. This difference exists for two main reasons. First, the minimum wage used to estimate the value of productivity losses was USD 2.32 in Kenya compared to USD 6.59 in the Philippines. Second, the Kenyan expert panel believed that no TB patients in Kenya would self-cure compared with an assumed 30% self-cure rate in the Philippines.

# RECOMMENDATIONS

The current situation of TB medicine supply in Kenya is reportedly good, with no significant problems of stock-outs. Findings from the study exploring the potential impact of the prevented major stock-out in 2014 clearly demonstrate the importance of maintaining good systems to ensure a steady supply.

LTFU is, however, a significant and ongoing problem in Kenya, both for DS-TB and MDR-TB patients. Reasons for LTFU documented in the study carried out in Kibera [16] were relocation to "up-country" rural homes and work commitments. The study by Muture et al. in Nairobi Province identified ignorance, travel away from the treatment site, feeling better, and side effects as the main reasons for LTFU. Sitienei et al. found that assessed HIV infection was the single most influential risk factor for LTFU.

It is likely that most of the patients included in these studies were DS-TB patients and that additional reasons for LTFU of MDR-TB patients include the longer treatment period and the negative physical effects of MDR-TB medicines. It is also likely that the situation in rural areas is different and the high rates of LTFU in Samburu and Pokot (10% and 12% reported in 2014) illustrate the importance of conducting research in rural areas.

The Kenya study on patient costs [17] did not look at LTFU, but found that DS-TB patients incur an average of USD 55 in OOP costs and USD 294 in opportunity costs for accessing diagnosis and treatment. For patients who are poor, this could be an important reason for LTFU.

Additional research on reasons for LTFU in Kenya will be important in determining what interventions are needed to reduce these rates.

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

As a result, many of the assumptions used in these case studies are based on expert opinion in Kenya since there is little or no evidence, except for the previous study conducted in the Philippines. Additional research, both in Kenya and internationally, would help build a body of evidence that would strengthen the case for investing in prevention of treatment interruption.

## Research Recommendations

Some of the key areas where additional research would be useful in Kenya are as follows:

- 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 lost to follow-up, 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 DR-TB patients who return to treatment after LTFU who resume and extend treatment versus restart treatment

- The reasons for LTFU, especially in areas where rates are high

- Since 36% of TB patients have been identified as also having HIV, and the Sitienei et al. study identified HIV as the single largest risk factor, further research is needed to help identify solutions to LTFU for this cohort

The following areas of research would be important in Kenya and globally:

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

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

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

- The annual number of people infected by a patient with active DS-TB and active MDR-TB, the proportion who develop active TB, and over what period of time they develop active TB

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

- The proportion of untreated MDR-TB cases who develop XDR-TB, and how long it takes

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

## General Recommendations

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

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

- Priority should be given to avoiding LTFU of MDR-TB patients by developing and using a set of comprehensive interventions

- Action should be taken to prevent LTFU among DS-TB patients, especially in counties where this is high, including interventions such as better provider and patient education, case management, and follow-up

- Priority should be given to tracing patients who are LTFU while still infectious in order to reduce onward transmission

- In the longer term, there is a need for a system to trace patients who are lost to follow-up and then return to treatment at another facility, which is reportedly common. This is important to help address challenges with LTFU, but also to ensure that patients' treatment histories are known to providers at different facilities. Priority should be given to MDR-TB patients, patients who are still infectious, and patients with HIV co-morbidity, who may be the population most likely to be lost to follow-up.

## ANNEX A. REFERENCES


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## ANNEX B. ECONOMIC COSTS AND SOURCES

**Table 9. Economic Costs and Sources (USD)**

| Cost Type | Cost Estimate | Source |
|---|---|---|
| Cost of private-sector treatment per month | N/A | Approved private providers are included with government service costs – private sector not involved per expert panel |
| Public-sector provider cost[18] per course of treatment: | | |
| • DS-TB Category 1 | 335 | NTLDP |
| • MDR-TB | 13,300 | NTLDP |
| • XDR-TB | 39,300 | NTLDP – assumed three times cost of MDR-TB |
| Patient out-of-pocket cost per course of treatment: | | |
| • DS-TB | 55.80 | Mauch et al. |
| • MDR-TB | 386 | Assumed 6.9 times DS-TB cost based on Ethiopia (van den Hof et al.) |
| • XDR-TB | 463 | 24/20 months times MDR-TB cost |
| Minimum wage | 2.32 | Unskilled agricultural worker http://www.africapay.org/kenya/home/salary/minimum-wages |
| Productive days lost due to illness: | | |
| Treated DS-TB | 30 | NTLDP |
| Untreated DS-TB | 792 | Expected to live for 3 years, so 36 months x 22 days |
| Treated MDR-TB | 297 | NTLDP |
| Untreated MDR-TB | 792 | Expected to live for 3 years, so 36 months x 22 days. |
| Treated XDR-TB | 528 | 24 months x 22 days |
| Untreated XDR-TB | 792 | Expected to live for 3 years, so 36 months x 22 days |
| Average number of productive days per month | 22 | |
| Average years of life lost – DS-TB | 23 | Average age at which contracted DS-TB at 39.[19] Would live for 3 years if untreated [20]. Age at which cease to be productive = 65. |
| Average years of life lost – MDR-TB and XDR-TB | 20 | Average age at which contracted MDR-TB or XDR-TB at 42.[20] Would live for 3 years if untreated [20]. Age at which cease to be productive = 65. |
| Discount rate | 3% | |
| Average exchange rate 2015 - Pesos to USD | 98.55 | http://fx-rate.net/KES/?date_input=2015-06-30 |

[18] Diagnostics, medicines, ancillary medicines, clinician, nursing, facility running costs
[19] Source: NTLDP
[20] Ibid.

## ANNEX C. DS-TB STOCK-OUT MODEL ALGORITHM ASSUMPTIONS

Details of the sensitivity analysis are shown in annex F. Note that the sensitivity analysis was partial, only taking into account one change.

1. DS-TB treatment in Kenya is for six months: two months intensive and four months continuation.

2. This is a hypothetical situation and there was no information on the average time of interruption of a DS-TB patient due to stock-outs. The expert panel agreed to assume three months, on average. Since the course of treatment for DS-TB is six months, three months more would, therefore, be needed to complete treatment. Sensitivity analysis: Increasing from three to four months would result in a 5.2% increase in total additional costs.

3. The research team assumed that patients would not have had access to the medicines for three months because stock-outs would take some time to resolve. Sensitivity analysis: Increasing from three to four months would result in a 0.7% increase in total additional costs.

4. None of the patients with DS-TB would have been infectious at the start of the interruption period because they are all supposed to receive and take a one-month supply upon starting treatment; this should be sufficient to stop them from being infectious. Sensitivity analysis: Increasing from 0% to 1% would result in a 0.2% increase in total additional costs. If the assumption that patients would not get at least a one-month supply is not correct and 99% of the patients were infectious at the time of interruption, it would have resulted in an increase of approximately 58% in additional provider costs, 6% in additional household costs, and 18% in total additional costs.

5. According to the expert panel, 1% of patients who started treatment for DS-TB would have actually had MDR-TB and would have remained infectious during the period of interruption as the DS-TB treatment would not have been effective. The research team assumed that all of those patients would have infected others during the interruption period and that 15% of them would not have returned to treatment after the interruption period, continuing to infect others for three years until they died. Sensitivity analysis: Increasing from 1% to 2% would result in a 5.6% increase in total additional costs.

6. The expert panel believed that patients would not have been able to get treatment in the private sector during the period of the stock-out. Approved private providers would have been affected by the stock-out since they have the same sources as the public sector. Unapproved private providers are not supposed to provide TB treatment. Therefore, 100% of the patients who would have interrupted treatment due to the stock-out would have been untreated during the interruption period. No sensitivity analysis was conducted.

7. According to NTLDP data, and confirmed by the expert panel, it was assumed that 2.1% of patients with DS-TB who were untreated for three months would have developed MDR-TB and the remaining 97.9% would have remained with DS-TB. Sensitivity analysis: Increasing from 2.1% to 4.2% would result in a 16% increase in total additional costs.

8. The expert panel believed that 85% of the patients with MDR-TB would have returned to treatment after the period of interruption and the remaining 15% would not. Sensitivity analysis: Reducing from 85% to 75% would result in a 1% decrease in total additional costs.

9. According to NTLDP data, and confirmed by the expert panel, it was assumed that 31% of patients with MDR-TB who would have returned to treatment after the interruption period would been successfully treated while the remaining 69% would have died. Of the MDR-TB patients who did not return to treatment, 100% would have died. Sensitivity analysis: Increasing from 31% to 62% would result in a 2.5% decrease in total additional costs.

10. The expert panel believed that 85% of patients with DS-TB would have returned to treatment after the period of interruption and the remaining 15% would not. Sensitivity analysis: Reducing from 85% to 75% would result in a 44% increase in total additional costs.[21]

11. The expert panel believed that all the DS-TB patients who would have returned to the public sector after the period of interruption would have restarted (not resumed) treatment, since the interruption period was assumed to be three months. No sensitivity analysis was conducted. If the period of interruption is less than two months, the provider may decide to resume and extend treatment, but the difference in cost for a DS-TB patient would be small.

12. According to NTLDP data, and confirmed by the expert panel, it was assumed that 86% of patients who remained with DS-TB and who returned to treatment would have been successfully treated while the remaining 14% would have died. Of the DS-TB patients who did not return to treatment, 100% would have died. Sensitivity analysis: Reducing from 86% to 76% would result in a 9.1% decrease in total additional costs.[22]

13. The expert panel believed that none of the patients who would have remained with DS-TB and MDR-TB and who would not have returned to treatment would have self-cured. The panel thought that the 30% self-cure estimate made by Tiemersma et al. [26] was not relevant in Kenya. Sensitivity analysis: Increasing from 0% to 30% would result in a 21.9% decrease in total additional costs.

[21] This increase of 44% is largely because a significant additional number of patients would die prematurely, since it is assumed that all the patients who do not return to treatment would die.

[22] A lower treatment success rate and corresponding higher death rate affects the number of persons who would have died without the interruption as well as those who interrupted; the new effect is fewer additional deaths.

14. The research team assumed that an infectious person infects one other person per month and that 10% of those cases (1.2 per year) would become active TB over the lifetime of the infected person.[23] With a compromised immune system, as many people would have in Kenya due to poverty and HIV and AIDS, the risk of falling ill would be higher, with progression to illness taking as few as 10 years.[24] Sensitivity analysis: Increasing this rate from one to two persons per month, or from 10% to 20%, would result in a 5.6% increase in total additional costs.

[23] People infected with TB bacteria have a 10% lifetime risk of falling ill with TB. However, persons with compromised immune systems have a greater risk. People with 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/)

[24] According to the CDC Morbidity and Mortality Weekly Report 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. DS-TB LTFU MODEL ALGORITHM ASSUMPTIONS

Details of the sensitivity analysis are shown in annex G. Note that the sensitivity analysis was partial, only taking into account one change.

1. DS-TB treatment in Kenya is for six months: two months intensive and four months continuation.

2. There was no information on the average length of treatment of a DS-TB patient before being LTFU, but it was agreed upon with the expert panel that the research team would assume that patients stop treatment at three months, on average. Since the course of treatment for DS-TB is six months, three months more would, therefore, be needed to complete treatment. Sensitivity analysis: Increasing from three to four months would result in a 5.2 % increase in total additional costs.

3. There was no information on the average length of the period of interruption for LTFU DS-TB patients. Because a patient is declared LTFU only after two months of stopping treatment, the period of interruption would have to be greater than two months. It was agreed upon with the expert panel that the research team would assume that the period of interruption is three months. Sensitivity analysis: Increasing from three to four months would result in a 0.7% increase in total additional costs.

4. None of the patients with DS-TB would have been infectious at the start of the interruption period because they are all supposed to receive and take a one-month supply upon starting treatment; this should be sufficient to stop them from being infectious. Sensitivity analysis: Increasing from 0% to 1% would result in a 0.2% increase in total additional costs. If this assumption is not correct and 99% of the patients were infectious at the time of interruption, it would result in an increase of approximately 57% in additional provider costs, 6% in additional household costs, and 18% in additional total costs.

5. According to the expert panel, 1% of the patients who started treatment for DS-TB would have actually had MDR-TB and would have remained infectious during the period of interruption as the DS-TB treatment would not have been effective. The research team assumed that all of those patients would have infected others during the interruption period and that 15% of them would not have returned to treatment after the interruption period, continuing to infect others for three years until they died. Sensitivity analysis: Increasing from 1% to 2% would result in a 5.6% increase in total additional costs.

6. The expert panel believed that patients would not have been able to get treatment in the private sector during the period of the stock-out. Approved private providers would have been affected by the stock-out since they have the same sources as the public sector. Unapproved private providers are not supposed to provide TB treatment. Therefore, 100% of the patients who would have interrupted treatment due to the stock-out would have been untreated during the interruption period. No sensitivity analysis was conducted.

7. According to NTLDP data, and confirmed by the expert panel, it was assumed that 2.1% of patients with DS-TB who were untreated for three months would have developed MDR-TB and the remaining 97.9% would have remained with DS-TB. Sensitivity analysis: Increasing from 2.1% to 4.2% would result in a 16% increase in total additional costs.

8. The expert panel believed that 85% of patients with MDR-TB would have returned to treatment after the period of interruption and the remaining 15% would not. Sensitivity analysis: Reducing from 85% to 75% would result in a 1% decrease in total additional costs.

9. According to NTLDP data, and confirmed by the expert panel, it was assumed that 31% of the patients with MDR-TB who would have returned to treatment after the interruption period would have been successfully treated and the remaining 69% would have died. Of the MDR-TB patients who did not return to treatment, 100% would have died. Sensitivity analysis: Increasing from 31% to 62% would result in a 2.5% decrease in total additional costs.

10. The expert panel believed that 85% of patients with DS-TB would have returned to treatment after the period of interruption and the remaining 15% would not. Sensitivity analysis: Reducing from 85% to 75% would result in a 44% increase in total additional costs.[25]

11. The expert panel believed that all DS-TB patients who return to the public sector after the period of interruption would restart (not resume) treatment, since the interruption period is assumed to be three months. No sensitivity analysis was needed.

12. According to NTLDP data, and confirmed by the expert panel, it was assumed that 86% of patients who remained with DS-TB and who returned to treatment would have been successfully treated while the remaining 14% would have died. Sensitivity analysis: Reducing from 86% to 76% would result in an 8.1% decrease in total additional costs.[26]

13. The expert panel believed that none of the patients who would have remained with DS-TB and who would not have returned to treatment would have self-cured. The panel thought that the 30% self-cure estimate made in by Tiemersma et al. [26] was not relevant in Kenya. Sensitivity analysis: Increasing from 0% to 30% would result in a 21.9% decrease in total additional costs.

[25] This increase of 44% is largely because a significant number of additional patients would die prematurely, since it is assumed that all the patients who do not return to treatment would die.

[26] A higher death rate affects the number of people who would have died without the interruption as well as those who interrupted; the new effect is fewer additional deaths.

14. The research team 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.[27] With a compromised immune system, as many people would 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. [28] Sensitivity analysis: Increasing this rate from one to two persons per month or from 10% to 20% would result in a 5.6% increase in total additional costs.

[27] People infected with TB bacteria have a 10% lifetime risk of falling ill with TB. However, persons with compromised immune systems have a greater risk. People with 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/)

[28] According to the CDC Morbidity and Mortality Weekly Report 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. MDR-TB LTFU MODEL ALGORITHM ASSUMPTIONS

Details of the sensitivity analysis are shown in annex H. Note that the sensitivity analysis was partial, only taking into account one change.

1. MDR-TB treatment in Kenya is for 20 months: 8 months intensive and 12 months continuation.

2. The expert panel felt that most MDR-TB patients who become LTFU interrupt treatment at around five months because this is the time when they can no longer stand the injections. Sensitivity analysis: Increasing from five to six months would result in an 8.7% increase in total additional costs. If the interruption starts at less than four months into treatment, then the majority of patients would still be infectious. If, for example, 99% of the MDR-TB patients are infectious at the time of treatment interruption, the additional total cost would increase by 194%, with the additional provider cost increasing by 210% and the additional household cost increasing by 100%.

3. There was no information on the average length of the period of interruption for LTFU DS-TB patients. Because a patient is declared LTFU only after two months of stopping treatment, the period of interruption would have to be more than two months. It was agreed upon with the expert panel that the research team would assume that the period of interruption is five months. Sensitivity analysis: Increasing from five to six months would result in a 1.6% increase in total additional costs.

4. The expert panel believed that most MDR-TB patients convert at approximately four months, but 5% of the MDR-TB patients would have remained infectious if the interruption starts at five months. Sensitivity analysis: Increasing from 5% to 10% would result in a 10.3% increase in total additional costs.

5. According to the expert panel, 1% of patients who started treatment for MDR-TB would have actually had XDR-TB and would have remained infectious during the period of interruption because the MDR-TB treatment would not have been effective. The research team assumed that all of those patients would have infected others during the interruption period and that 15% of them would not have returned to treatment after the interruption period, continuing to infect others for three years until they died. Sensitivity analysis: Increasing from 1% to 2% would result in a 6% increase in total additional costs.

6. The expert panel believed that patients would not have been able to get treatment in the private sector during the period of the stock-out. Approved private providers would have been affected by the stock-out since they have the same sources as the public sector. Unapproved private providers are not supposed to provide TB treatment. Therefore, 100% of patients who would have interrupted treatment due to the stock-out would have been untreated during the interruption period. No sensitivity analysis was needed.

7. According to NTLDP data, and confirmed by the expert panel, it was assumed that 10% of patients with MDR-TB who were untreated for three months would have developed XDR-TB and the remaining 90% would have remained with MDR-TB. Sensitivity analysis: Increasing from 10% to 20% would result in a 34.3% increase in total additional costs.

8. Based on NTLDP data and expert panel opinion, the research team assumed that 85% of XDR-TB patients would return to treatment and the remaining 15% would not. Sensitivity analysis was not conducted as the expert panel thought that most XDR-TB patients would die quickly and the cost of treatment would be more than the costs incurred due to onward infection.

9. According to NTLDP data, and confirmed by the expert panel, it was assumed that 10% of patients with XDR-TB who would have returned to treatment after the interruption period would have been successfully treated and the remaining 90% would have died. Sensitivity analysis was not conducted as the numbers are too small to model changes.

10. According to the expert panel, 100% of the XDR-TB patients who did not return to treatment would have died. No sensitivity analysis was conducted.

11. Based on NTLDP data and expert panel opinion, the research team assumed that 85% of MDR-TB patients who were untreated during the interruption period would return to treatment and 15% would not. Sensitivity analysis: Reducing from 85% to 75% would result in a 31.6% decrease in total additional costs.

12. The expert panel believed that all MDR-TB patients who return to the public sector after the period of interruption would restart (not resume) treatment because the interruption period is assumed to be five months. No sensitivity analysis was needed.

13. According to NTLDP data, and confirmed by the expert panel, it was assumed that 31% of patients with MDR-TB who would have returned to treatment after the interruption period would have been successfully treated and the remaining 69% would have died. Of the MDR-TB patients who did not return to treatment, 100% would have died. Sensitivity analysis: Increasing from 31% to 62% would result in a 9.6% increase in total additional costs. [29]

14. The expert panel believed that none of the patients who would have remained with MDR-TB and who would not have returned to treatment would have self-cured. The panel thought that the 30% self-cure estimate made in by Tiemersma et al. [26] was not relevant for MDR-TB patients in Kenya. Sensitivity analysis: Increasing from 0% to 30% would result in a 6% decrease in total additional costs.

[29] Increasing the treatment success rate results in a lower death rate, which affects the number of persons who would have died without the interruption as well as those who interrupted; the net effect is more additional deaths.

15. The research team 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.[30] With a compromised immune system, as many people would have in Kenya due to poverty and HIV and AIDS, the risk of falling ill would be higher, with progression to illness taking as few as 10 years. [31] Sensitivity analysis: Increasing this rate from one to two persons per month, or from 10% to 20%, would result in a 16% increase in total additional costs.

[30] People infected with TB bacteria have a 10% lifetime risk of falling ill with TB. However, persons with compromised immune systems have a greater risk. People with 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/)

[31] According to the CDC Morbidity and Mortality Weekly Report 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 F. 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 provider costs (table 10). The degrees of change are hypothetical.

**Table 10. Sensitivity Analysis on Key Variables for DS-TB Stock-outs**

| Description | Change | 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 | From 3 to 4 months | +5.2% | +9.8% | +3.9% |
| Proportion of patients who are infectious with MDR-TB at the time they interrupt treatment | From 1% to 2% | +5.6% | +23% | +0.5% |
| Proportion of DS-TB patients who are infectious at the time they interrupt treatment | From 0% to 1% | +0.2% | +0.6% | +0.1% |
| Length of treatment interruption | From 3 to 4 months | +0.7% | +2.7% | +0.1% |
| Percent of patients treated in the private sector | Not applicable in Kenya | N/A | N/A | N/A |
| Percent of patients who develop MDR-TB while treated in the private sector | Not applicable in Kenya | N/A | N/A | N/A |
| Percent of patients who develop MDR-TB during the interruption period through not being treated | From 2.1% to 4.2% | +16% | +47% | +7% |
| Percent of MDR-TB patients who return to treatment | From 85% to 75% | -1% | -5.7% | +0.3% |
| Percent of MDR-TB patients who return to treatment who are cured | From 31% to 62% | -2.5% | 0% | -3.2% |
| Percent of DS-TB patients who return to treatment | From 85% to 75% | +44.2% | -3.4% | +58% |
| Percent of DS-TB patients who return to treatment who are cured | From 86% to 76% | -8.1% | 0% | -10.4% |
| Number of persons who are infected by patients per month and who develop active TB | From 0.1 to 0.2 | +5.6% | +23% | +0.5% |
| Percent of persons with DS-TB and MDR-TB who self-cure | From 0% to 30% | -21.9% | 0% | -29.2% |

## ANNEX G. 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 provider costs (table 11). The degrees of change are hypothetical.

**Table 11. Sensitivity Analysis on Key Variables for DS-TB LTFU**

| Description | Change | 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 | From 3 to 4 months | +5.2% | +9.8% | +3.9% |
| Proportion of patients who are infectious with MDR-TB at the time they interrupt treatment | From 1% to 2% | +5.6% | +23% | +0.5% |
| Proportion of patients who are infectious with DS-TB at the time they interrupt treatment | From 0% to 1% | 0.2% | +0.6% | +0.1% |
| Length of treatment interruption | From 3 to 4 months | +0.7% | +2.7% | +0.1% |
| Percent of patients treated in the private sector | Not applicable in Kenya | N/A | N/A | N/A |
| Percent of patients who develop MDR-TB while treated in the private sector | Not applicable in Kenya | N/A | N/A | N/A |
| Percent of patients who develop MDR-TB during the interruption period through not being treated | From 2.1% to 4.2% | +16% | +47.7% | +6.8% |
| Percent of MDR-TB patients who return to treatment | From 85% to 75% | -1% | -5.7% | +0.3% |
| Percent of MDR-TB patients who return to treatment who are cured | From 31% to 62% | -2.5% | 0% | -3.2% |
| Percent of DS-TB patients who return to treatment | From 85% to 75% | +44.2% | -3.4% | +58% |
| Percent of DS-TB patients who return to treatment who are cured | From 86% to 76% | -8.1% | 0% | -10.4% |
| Number of persons who are infected by patients per month and who develop active TB | From 0.1 to 0.2 | +5.6% | +23% | 0.5% |
| Percent of persons with DS-TB and MDR-TB who self-cure | From 0% to 30% | -21.9% | 0% | -29.2% |

## ANNEX H. 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 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 Tupasi et al. study [16]. All other changes are hypothetical.

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

| Description | Change | 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 | From 5 to 6 months | +8.7% | +9.1% | +5.9% |
| Proportion of patients who are infectious with XDR-TB at the time they interrupt treatment | From 1% to 2% | +6% | +6.7% | +1.7% |
| Proportion of patients who are infectious with MDR-TB at the time they interrupt treatment | From 5% to 10% | +10.3% | +11.2% | -5.3% |
| Length of treatment interruption | From 5 to 6 months | +1.6% | +1.7% | +0.7% |
| Percent of patients treated in the private sector | Not applicable in Kenya | N/A | N/A | N/A |
| Percent of patients who develop XDR-TB while treated in the private sector | Not applicable in Kenya | N/A | N/A | N/A |
| Percent of patients who develop XDR-TB during the interruption period through not being treated | From 0% to 10% | +47% | +51% | +27% |
| Percent of XDR-TB patients who return to treatment | Not conducted | N/A | N/A | N/A |
| Percent of XDR-TB patients who return to treatment who are cured | Not conducted | N/A | N/A | N/A |
| Percent of MDR-TB patients who return to treatment | From 85% to 75% | -31.6% | -38.8% | +10.8% |
| Percent of MDR-TB patients who return to treatment who are cured | From 31% to 62% | +9.6% | 0% | +66.1% |
| Number of persons who are infected by patients per month and who develop active TB | From 0.1 to 0.2 | +28% | +31% | +10% |
| Percent of persons with DS-TB and MDR-TB who self-cure | From 0% to 30% | -5.9% | 0% | -40.8% |