# COUNTING ON US:

## AN ANALYSIS OF THE ROOTS OF VARIABILITY IN MORTALITY AMONG TB PATIENT COHORTS IN ETHIOPIA, GHANA, KENYA, MOZAMBIQUE, AND ZAMBIA AND ITS IMPLICATIONS FOR MONITORING & EVALUATION OF TB/HIV CARE

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# 1. EXECUTIVE SUMMARY

Globally, TB mortality has declined by 36% over the past decade, but this preventable, treatable condition still claims too many lives.[1] High tuberculosis mortality is increasingly understood as an indicator of a constellation of problems in the community and the health system. TB is the leading cause of death among PLHA, approximately 13% of TB patients are HIV co-infected throughout the world with >50% co-infection in some settings in Sub-Saharan Africa

A memorandum of understanding recently signed by UNAIDS and the Stop TB Partnership has pledged "To achieve zero deaths from TB among people living with HIV" in the next ten years. Stakeholders are urged to 'take action….to strategically address the intolerable burden of TB mortality borne by people living with HIV'. [2]

This ambitious target represents a challenge for those engaged in monitoring and evaluation of TB/HIV mortality.

It has been known for many years that co-morbid TB patients (i.e. those with HIV, hepatitis, diabetes, etc.) are particularly vulnerable when TB diagnosis and treatment are delayed and/or the quality and timing of clinical care services are suboptimal [3-4]. Addressing the treatment needs of co-morbid TB patients continues to present logistical and clinical dilemmas in high burden settings. This report focuses on the reported mortality among TB patients in five African countries and progress in ensuring the survival of vulnerable TB patients, particularly dual diagnosed TB/HIV patients. The objectives of the analysis were:

1. To assess M&E Officers' ***attitudes*** toward and reported ***usage*** of mortality data by National Tuberculosis Programs in countries with a high burden of TB.
2. To assess the ***accessibility*** and ***quality*** of recording and reporting of mortality in TB HIV co-infected patients by national tuberculosis programs in 5 African countries (Ghana, Ethiopia, Kenya, Mozambique and Zambia).
3. To explore epidemiological and programmatic drivers of **variability in mortality** in routine surveillance data in TB mortality hotspots.
4. To provide inputs to the global ***strategy*** to improve current M&E systems on TB-HIV mortality indicators in high burden countries (To improve National Tuberculosis Program data collection for mortality in TB-HIV patients in order to ensure quality of care and guide policy decisions.)

This project employed a multi-method design to generate a broad understanding of the TB/HIV mortality M&E challenges. Data from a survey of M&E officers in 19 countries as well as an analysis of 24,049 TB records from surveillance systems in five African countries were triangulated to determine the accessibility, quality and utilization of TB patient mortality data for monitoring and evaluation purposes.

Some stakeholders consider TB mortality as a key benchmark of global progress of TB programs but its utility as an M&E indicator has always been contested[5-6].

Assuming that the drivers of TB/HIV mortality could be programmatic, this assessment sought to explore mortality monitoring and evaluation practices through a lens of routine programmatic data in two types of settings: highest performing (i.e. lowest mortality) and least performing (highest mortality).

## ATTITUDES TOWARD AND USAGE OF MORTALITY DATA

We found that although mortality is considered an important benchmark by M&E Officers and there is widespread acknowledgement of its potential utility, the practical hurdles in collecting good data were daunting to M&E officers charged with generating these values. There is a felt need to improve collection and analysis of TB mortality data.

Half of M&E officers reported that there was a demand for mortality information disaggregated by HIV status. However, most were not yet disaggregating by HIV. Only 50%(9/19) reported that they disaggregated mortality data by district, although 63% were able to produce mortality estimates for basic management units (BMU) when requested for this survey. Most were skeptical of the completeness and accuracy of the mortality data they have and report low levels of cooperation with institutions and programs with complementary data.

With the exception of Ghana, few national TB programs are initiating extensive analyses of their paper-based systems to discern trends in TB mortality in their TB cohort. Even countries with electronic patient-based records, such as Kenya, have not initiated extensive analyses of TB/HIV mortality surveillance data to date. Two noteworthy exceptions are the districts of Chókwe and Chalucuane in Gaza province of Mozambique, where TB/HIV patient data are entered into an electronic database that automatically generates a wide range of quarterly program performance indicators and trends are tracked. However, the utility of these analyses are undercut by a large amount of missing data due to high rates of labor migration and loss to follow up among TB patients.

## THE ACCESSIBILITY OF MORTALITY DATA

Most M&E officers surveyed do not collect information on cause of death because data that are available are not valid, and/or relationships with key partners do not permit the timely flow of this information. Only six out of 19 M&E officers (32%) reported that the level of data sharing between TB and HIV programs was “good” or “excellent” in 2011.

In theory, TB surveillance treatment outcome data are widely available in paper-based registers. In practice, they are inaccessible for routine analytic purposes. Even in some NTPs where data are being entered in electronic case-based records, treatment outcome information is inconsistently recorded, rendering the data of limited analytic value. In fact, the 2 electronic databases analyzed had higher rates of missing treatment outcome data than the paper-based systems. The expectation that electronic systems would inevitably lead to greater TB/HIV data access and quality is yet to be fulfilled.

## THE QUALITY OF MORTALITY DATA

M&E officers face many hurdles in obtaining valid TB/HIV mortality estimates from surveillance data (e.g. access, completeness, reliability, missing data). Although M&E officers surveyed are very aware of the value of TB/HIV mortality information for assessing program performance and M&E, most are skeptical of the quality of their mortality data.

There was a large difference in data quality among countries and striking differences among basic management units within the same country.

The proportion of missing values was high for some key parameters, especially HIV status and treatment outcome. Contrary to expectation, the proportion of patients with an unknown treatment outcome was not consistently higher among TB patients with HIV and an unknown HIV status. This finding contrasts sharply with earlier findings [7]. However, missing TB treatment outcomes data were roughly correlated with the back ground HIV prevalence of the district and degree of migration/internal displacement. In the Chókwe district, an area with an HIV prevalence of 27% (2007) and high rates of migration, 32.5% of treatment outcome data were missing[8]. This raises the possibility that mortality estimates are inaccurate. A significant burden of hidden mortality could reside in the groups of patients classified as lost to follow up or 'not evaluated'.

Loss of patients to follow-up and care is an important problem for TB/HIV treatment programs. As mortality is often higher in patients lost to follow up compared to patients remaining in care, TB/HIV programs with high rates of loss to follow-up may substantially underestimate mortality of all patients starting ART[9-10]. This is particularly true in areas of high migration and internal displacement[11].

## MORTALITY

Sample units were selected based on notified mortality in TB cohorts, so this report did not aim to produce generalizable or comparable estimates of mortality. Rather, the sample purposefully selected extreme cases (i.e. best and worst rates). Sampled units ranged from a low of 1.5% mortality among HIV negative TB patients in Nairobi, Kenya to a high of 21.3% among HIV positive TB patients in Gaza Province of Mozambique.

**Sampling Units Deaths by HIV status**

| | **Total Mortality TB patients (%)** | **HIV+ TB patients (%)** | **HIV- TB patients (%)** | **UNKNOWN HIV status (%)** |
|---|---|---|---|---|
| **Ethiopia** | | | | |
| High (n=161) | 17.5 | 19.3 | 19.0 | 12.8 |
| Low (n=183) | 11.4 | 14.1 | 11.2 | 6.0 |
| **Ghana** | | | | |
| High | n/a | 18.0 | 8.0 | 9.8 |
| Low | n/a | | | |

| | | | | |
|---|---|---|---|---|
| **Kenya** | | | | |
| High (n=229) | 11.7 | 18.7 | 8.7 | 7.8 |
| Low (n=107) | 3.3 | 6.1 | 1.5 | 2.2 |
| **Mozambique** | | | | |
| High (n=388) | 20.5 | 21.3 | 14.8 | 12.5 |
| Low (n=65) | 10.2 | 12.2 | 7.7 | 9.8 |
| **Zambia** | | | | |
| High (n=179) | 5.5 | 6.7 | 4.5 | 6.2 |
| Low (n=42) | 4.4 | 4.9 | 4.1 | 3.4 |

### MORTALITY HOT SPOTS

Five areas in three countries were identified as TB mortality "hotspots". Hotspots were defined as any geographic area reporting TB mortality above a 10% threshold in the 2009/2010 TB patient cohorts.

### RISK FACTORS FOR MORTALITY

Conventional wisdom dictates that HIV is the biggest risk factor for mortality in any African TB cohort. However this was not consistently found in this review. HIV was a risk factor for mortality in Ghana, Kenya, and Gaza province of Mozambique, but it did not predict mortality among TB patients in Ethiopia, Zambia, or Zambezia province of Mozambique, suggesting that program management (e.g. timely diagnosis, provision of ART/CPT) and other enabling /environmental factors may mitigate the well-documented relationship between HIV and TB patient mortality. Male gender was consistently found to be a risk factor for mortality, in line with multiple studies pointing to a systematic neglect of the specific health care needs of men[12-14].

## RECOMMENDATIONS FOR M&E

To enhance the utility of data on TB patient mortality we recommend a range of changes to current practice.

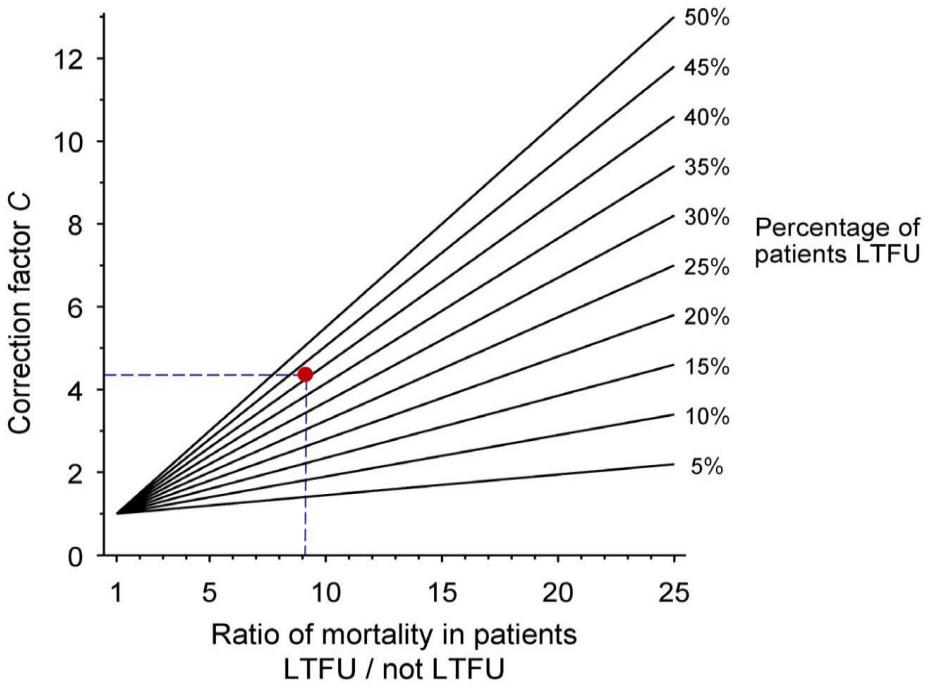
- *Present mortality data in the TB cohort by HIV status.*
  Countries should present all cause mortality during TB treatment by HIV status All-cause mortality differed between HIV positive and HIV negative TB patients. Presenting mortality by HIV status is of additional value, because it would allow a country to evaluate its TB and HIV activities and monitor outcome in these subgroups of TB patients.

- *Improve reporting and recording, especially of treatment outcome.*
  Although this recommendation has been echoed for decades, treatment outcome, date of outcome, and HIV status were missing in a high proportion of patients: up to 10% for treatment outcome and up to 18% for HIV status. We expect a lot of hidden mortality in patients with "unknown treatment outcome" and in patients classified as "OOC" ("out of control"). It is therefore important to improve reporting and recording, especially of HIV status and treatment outcome, in order to make valid estimation of mortality during TB

treatment. For example, the treatment outcome should be checked regularly to confirm that the currently recorded outcome is still up-to-date.

- *Launch a global effort to conduct tracing studies among patients lost to follow up to derive a mortality correction factor for crude mortality estimates from surveillance data*
  More emphasis is needed on preventing initial pre-treatment loss should receive greater emphasis in programs and tracing patients lost to follow up[10, 15]. To help M&E officers to properly interpret the treatment outcome data that they routinely collect, researchers should develop a correction factor (i.e. nomogram) for "loss to follow up" and "transferred out", similar to that developed for ART programs [16]
  An example of how this was done for ART programs is outlined here http://www.iedea-sa.org/

**Figure 1: Sample Nomogram to correct for Loss to Follow up**




- *Integrate National TB and HIV programs.*
  There is a global consensus that National TB and HIV programs should be better integrated and that is the single biggest obstacle to progress. Almost all of the twenty-two TB M&E Officers surveyed reported that they do not have highly collaborative relationships with their HIV M&E counterparts. One frequent legacy of AIDS exceptionalism can be a level of mistrust and cultural differences that may hinder data sharing between programs[17-19]. They want to improve the level of cooperation on data management. Information about a TB-HIV co-infected patient that is missing in the TB registry might be available in the HIV registration, and vice versa, especially information on TB treatment outcome, i.e. mortality.

- *Assess and address both under-counting and double counting of TB patients in TB and HIV programs*

TB and HIV programs should consider the use of a unified unique identifier that combines patient and facility characteristics such as a 17 digit alphanumeric code

*Facility code(3 digits)+ BMU code(3 digits)+date of birth(8 digits)+3 letters of name*

- In the interim, it is important to identify strategies to address duplicate records for patients enrolled in TB and HIV care. One option would be to combine TB & HIV name-based data and remove duplicates. Another would be to implement a compatible unique identification system in both programs. The Inventory Studies Guide (2012) by WHO includes an overview of the underlying theory of linking as well as websites where open-source software, such as Link Plus, can be downloaded to link and de-duplify name-based registers. It is freely available from : http://www.tbcare1.org/publications/toolbox/

- *Conduct periodic death audits in districts with high rates of mortality in a cohort. Take action. Track Results.*
  Measuring the burden of mortality is necessary but insufficient for improving TB patient outcomes. Exploration and analysis of root causes of death among TB patients can lead to a clearer and specific understanding of why the deaths happened and where interventions are likely to make a difference in patient survival. The Death Audit tool "Lessons from Loss" is freely available from: http://www.tbcare1.org/publications/toolbox/

- *To identify issues requiring intervention, routinely disaggregate mortality by:.*
    - Date of death (v.s. date of treatment outcome)
    - HIV status
    - Age
    - Gender
    - Basic management units-regions/provinces/state/districts
    - Location –public, private, mission, NGO/CBO managed cases
    - Date of diagnosis, date of IPT, ART, CPT, and TB treatment initiation
    - Now that the evidence on timeliness is definitive, additional emphasis on M&E of the time interval between TB and HIV diagnoses and initiation of preventive therapies (ART and CPT) is key[20]. All new recording and reporting forms should require the recording of dates of each step on the patient pathway. This is essential so that diagnostic turnaround times can be tracked and delays pinpointed and addressed. New WHO 2013 Case Definitions and reporting Forms recommend dropping the date variable for start of ART from new Tb treatment registers. However the rationale for this deletion is not given and in light of the M&E benefit for programs that these dates provide, this recommendation is of dubious value.

- *Contextualize all mortality findings.*
  While disaggregated analyses of surveillance data for M&E purposes need to be encouraged, crude or simplistic analysis of register data that does not take into account underlying mortality patterns in the population can often yield mistaken conclusions and policy recommendations.[21] For example, it frequently appears that elderly TB patients are underserved by TB programs because mortality is higher. However, these groups have

higher all-cause mortality in many settings and when rates are adjusted there is no significant difference [21].

- *Comprehensive treatment for TB/HIV*

  The provision of antiretroviral therapy (ART) and provision of cotrimoxazole preventive therapy (CPT) to HIV-positive TB patients are two protective treatments that can significantly reduce TB mortality in co-infected patients to rates equivalent to HIV-negative TB patients [3]. The Kenyan data show that HIV+ TB patients who received ART and/or CPT had a mortality rate around 7%, compared to 15-19% in patients who did not receive ART/CPT; similar to the mortality in HIV-negative Kenyan TB patients (6.4%). Both the delivery and the timing of these two interventions should be captured and reported routinely by all countries.

  - Develop better tools to rigorously monitor diagnostic delay. With the GenXpert MTB/RIF platform and other new diagnostics, we can reduce diagnostic delay and reduce delay in effective treatment of RR-TB. All registers need date fields to track turn-around times.

  - These data should be re-analyzed by collapsing the 5 countries into 2 extreme categories. The five cohort mortality hot spots should be compared against "high performance" spots, defined less than 6% mortality in the TB patient cohort to identify correlates of high mortality that cut across contexts.

## CONCLUSION

We assessed the added-value of collecting and analyzing mortality and mortality data to discern if they can be better utilized as a monitoring and evaluation indicator of program performance. We found that in many settings, the current quality of the crude treatment outcome data is too poor to reliably reflect the actual mortality in the cohort. Deaths are widely misclassified as Loss to Follow Up and hence under counted. The quality of recording and reporting needs improvement before mortality can be a valid reflection of performance.

Nevertheless, the results of this assessment suggest that if improvements in data quality and hurdles to collaboration can be overcome, there is insight to be gained from regular analysis of disaggregated TB/HIV mortality data, particularly if it is followed up with death audits to facilitate local decision making on the improvement of care. Efforts to improve monitoring and evaluation systems must also take a "one stop shop" or integrated approach by engaging all partners in data sharing agreements that preserve and protect clients' rights while ensuring the possibility of data-driven programmatic decisions.

The findings of this assessment support the notion that TB patient death rates may one day be a reflection of TB program effectiveness and not simply biological relationships and artifacts of data quality.

# 2. INTRODUCTION

Limited awareness of TB signs and symptoms combined with restricted accessibility and/or poor quality of health services can be deadly combination. Pinpointing basic management units with high mortality and identification of commonalities among those areas, can yield insights on how to target interventions. Not long ago, high mortality in TB/HIV cohorts was taken for granted and TB programs felt powerless to reduce it. However we now know that in settings where the TB/HIV care is well-coordinated and patients are fully supported, outcomes of HIV+ TB patients are no different from the outcomes of HIV negative TB patients.

There is an increasing demand to monitor mortality trends in HIV infected TB patients to assess progress in reaching MDGs, STOP TB Partnership, UNAIDS, and donor targets. Collaborative efforts to serve the TB/HIV population have expanded significantly. Documenting the impact of expanded access to life saving diagnostics and treatments is vital, but challenging[6, 22].

The main goal of TB control is to alleviate TB suffering and prevent ongoing transmission by reducing TB prevalence, incidence and mortality. In 2006, the STOP TB strategy set forth a target-to reduce TB deaths by 50% in 2015 compared to 1990. Reducing TB mortality is highlighted as the main goal of many NTP strategic plans and Global Fund proposals, as well as the MDGs -Goal 6 target 8. The TB CARE I and II initiatives have also identified reducing mortality rates among TB patients as one of their key impact indicators.

Despite the acknowledged need for and prioritization of mortality reduction, the availability of accurate TB/HIV mortality information in sub-Saharan Africa is limited. Data that are available can be challenging to interpret and derive lessons for program improvement due to missing information and lack of certainty as to causes of death[22]. [1] The TB case-fatality rate of HIV-infected TB patients is the subject of many small studies, but it is unknown for most countries[23-24]. The accessibility, usage, and completeness of mortality data disaggregated by HIV status in the region are unknown, but suspected to be low.

Although there is widespread appreciation of the importance of preventing TB mortality, some stakeholders are not yet convinced that TB mortality measurement is feasible, cost-effective, or informative *as an indicator of TB program performance*. Other stakeholders are urging the use of TB mortality as the main indicator of global progress in TB control. A new indicator, called the MN (mortality:notification) ratio, is being discussed by WHO/STOP TB Partnership as a key programmatic indicator in all settings post-2015. This would require heavy reliance on vital registration, verbal autopsy, and/or necropsy on a wider scale despite the multiple feasibility, acceptability, and even reliability issues inherent in these methods.[25-26]

There are four well-documented technical challenges to the use of TB mortality as an indicator (See box).

[1] The WHO currently uses a modeling process to estimate TB mortality but the outcomes have not been validated and the process is being revised.

Although WHO has advocated for disaggregation of TB treatment outcomes by HIV status since 2004, most National TB Programs do not disaggregate by HIV status and many do not disaggregate to region or district[27].

It was therefore worthwhile to assess the quality, accessibility, utilization, and added-value of collecting and analyzing mortality data by HIV-status, to discern if these data offer valuable insights into the main risk factors and intervention opportunities. If TB mortality were shown to be robust and feasible as an indicator (and if valid methods were established to facilitate its collection as part of routine M&E activities), the all-cause TB patient mortality indicator might become an important proxy measure of both effectiveness of early detection efforts and quality of TB/HIV integration efforts and patient care.

These data belong to the national TB programs in Ethiopia, Ghana, Kenya, Mozambique, and Zambia and were analyzed in order to facilitate local decision making on the improvement of monitoring and evaluation by the respective programs as well as to derive lessons for countries facing similar challenges. The Ghana data were available to us as aggregated data; therefore some tables in this report do not contain data from Ghana.

## 3. PROJECT OBJECTIVES

This assessment was undertaken to fulfill three primary aims:

1. To assess M&E Officers' ***attitudes*** toward and reported ***usage*** of mortality data by National Tuberculosis Programs in countries with a high burden of TB.
2. To assess the ***accessibility*** and ***quality*** of recording and reporting of mortality in TB HIV co-infected patients by national tuberculosis programs in 5 African countries (Ghana, Ethiopia, Kenya, Mozambique and Zambia).
3. To provide inputs to the global ***strategy*** to improve current M&E systems on TB-HIV mortality indicators in high burden countries (To improve National Tuberculosis Program data collection for mortality in TB-HIV patients in order to ensure quality of care and guide policy decisions.)

## 4. METHODS

The methods are divided into two sections in accordance with study objectives. Section one pertains to the conduct of the M&E officer survey and section two pertains to the analyses of TB surveillance data in five African countries.

**4 Technical Challenges in M&E of TB/HIV mortality**

1. Counting all the TB/HIV patient deaths (i.e. the numerator)
2. Counting the TB/HIV patient population (i.e. the denominator)
3. Determining the cause of death
4. Interpretation of high mortality

## Study Design Objective 1: attitudes and usage of TB Surveillance data on mortality

### Study Population

Monitoring and evaluation (M&E) officers from the national TB programs of 19 high burden countries were selected.

### Sampling

The countries were drawn by USAID respondents from the countries they support (17 TB CARE I, 1 TB CARE II, and 2 TB2015), the respondents were selected by the NTP Managers.

### Operationalization of variables

A 44-item semi-structured self-administered questionnaire was developed to explore the frequency and challenges to use of TB/HIV mortality information for monitoring and evaluation purposes (see Appendix 3).

### Data collection

Responses were emailed to the authors by the respondents. In some instances the respondents had completed the survey alone. In other cases, they had collaborated in pairs of M&E officers. Survey data were single-entered into an Excel spreadsheet and transferred to STATA for analysis.

### Data analysis plan

The survey data (n=19) were described in frequencies and proportions. Open-ended responses were hand coded.

## Study design Objective 2: Mortality Data in the TB Surveillance System

### Study population

This project focused preferentially on countries with high rates of HIV and TB. Due to resource constraints we limited the universe to 5 countries where the TB/HIV burden is significant but varied: Mozambique, Kenya, Ethiopia, Zambia, and Ghana. The selection of countries was opportunistic. The Namibia NTP was invited, but declined to participate. The provinces and districts selected were not intended to be representative of the country, but rather to reflect trouble spots and high functioning areas that could provide clues useful for monitoring and evaluation of TB/HIV mortality. The TB cohorts from 2009 and 2010 were selected because they were thought to be completed at the time of study implementation (mid-2011).

**Table 1: Comparison of Core Indicators for Countries Included (WHO)**

| **Indicators** | **2011** | | | | |
|---|---|---|---|---|---|
| | **Ethiopia** | **Ghana** | **Kenya** | **Mozambique** | **Zambia** |
| Population (million) | 83 | 25 | 41 | 23 | 13 |
| Estimated TB prevalence (all forms/100,000) | 330 (140-520) | 92 (44–158) | 110 (49-180) | 491 (233-844) | 482 |
| Estimated Mortality per 100,000 (excluding HIV+ TB) | 35 (28-42) | 7.5 (3.5–13) | 17(12-23) | 49(30-74) | 27 |

| | | | | | |
|---|---|---|---|---|---|
| Notified TB cases | 156928 | **15 840** | 106083 | 46174 | 44,879 |
| Treatment Success rate (S/C+) | 84 | 86 | 86 | 85 | 91 |
| Percentage of TB patients tested for HIV | 43 | 79 | 91 | 88 | 77 |
| Percentage of tested TB patients HIV positive | 15 | 23 | 41 | 61 | 67 |
| Percentage of HIV-infected TB patients on ARV | 39 | 28 | 48 | 25 | 42 |
| Percentage of HIV-infected TB patients on CPT | 69 | 71 | 100 | 97 | 64 |

### SAMPLING

Two provinces or regions in each country were selected using extreme case sampling. The high mortality province should have ≥ 10% mortality in the most recent TB patient cohort and the low mortality province should have <5% or the lowest mortality of any province in the country. NTP M&E officers identified the region/province reporting the highest and lowest TB mortality. Within each province/region, a minimum of 2 districts and a maximum of 4 were randomly selected, to obtain a 2009/2010 TB patient cohort of sufficient size to include at least 200 and preferably 300 TB patient deaths per country for analysis (e.g. a total of 1500 deaths).

**Table 2 Mortality in the extreme sampled units**

| | | **Province** | **Total Mortality TB patients in districts (%)** | **Deaths** |
|---|---|---|---|---|
| | **Ethiopia** | | | |
| 1. | High | >10% | 17.5 | 161 |
| 2. | Low | <5% | 11.4 | 183 |
| | **Kenya** | | | |
| 3. | High | >10% | 11.7 | 229 |
| 4. | Low | <5% | 3.3 | 107 |
| | **Mozambique** | | | |
| 5. | High | >10% | 20.5 | 388 |
| 6. | Low | <5% | 10.2 | 65 |
| | **Zambia** | | | |
| 7. | High | >10% | 5.5 | 179 |
| 8. | Low | <5% | 4.4 | 42 |

### OPERATIONALIZATION OF VARIABLES

The primary outcome of interest was death of a TB patient without regard for cause. Causes of death were infrequently recorded and no valid vital registration was available.

Missing data were defined as unfilled variables in registers as well as system missing in electronic databases. If date of death was not given, then the date of end of treatment was used as a proxy.

### DATA COLLECTION

Tuberculosis patient register data (excluding names) were collected from two geographical areas of five African countries: Ethiopia, Ghana, Kenya, Mozambique and Zambia. National TB Programs provided anonymous patient-based data including demographic information (gender, age), clinical data (type of disease, smear status, HIV status, weight, ART and CPT use) and treatment outcome. Data were extracted from the registers in four countries (Ethiopia Ghana, Mozambique (1 province), Zambia) and electronic patient-based records were available in two countries (Mozambique (1 province) and Kenya). Paper-based forms were single-entered in Ethiopia, Mozambique, and Zambia and double-entered in Ghana, due to variation in resources.

### DATA ANALYSIS

Data were described as proportions, means (+standard deviation) or median (+inter-quartile range) where appropriate. For the analysis of the variable *Treatment Outcome*, the category 'died' was used as a proxy for 'all-cause mortality'. For some analyses the following outcome categories were combined: *cured + treatment completed*, and *Transferred out + Failed + Loss to Follow Up + out of control + unknown/missing* treatment outcome. Logistic regression was conducted to analyze the association between treatment outcome and sex, age, HIV status or TB type. The group '*Cured/Completed*' was compared with '*Died*' to identify factors associated with mortality, and compared with 'Other outcomes' to identify factors associated with treatment outcomes that could contain hidden mortality. Data analysis was done using SPSS 19.0. and STATA 9

In some instances where the date of death was not known, then the date of end of treatment was used as a proxy.

### ETHICAL CONSIDERATIONS

To preclude deductive disclosure, all data were collected without patient names. Data were stored on password protected computers and access was limited to researchers trained in international research ethics. The low risk of harm to humans in this analysis of routine program data allowed it to be exempted from formal ethical review. However, to preclude harm to the reputations of district-level TB programs the specific sampled units are not identified by name.

### PROJECT MANAGEMENT

The project was coordinated by KNCV in close collaboration with MSH, FHI360, and the national TB programs themselves.

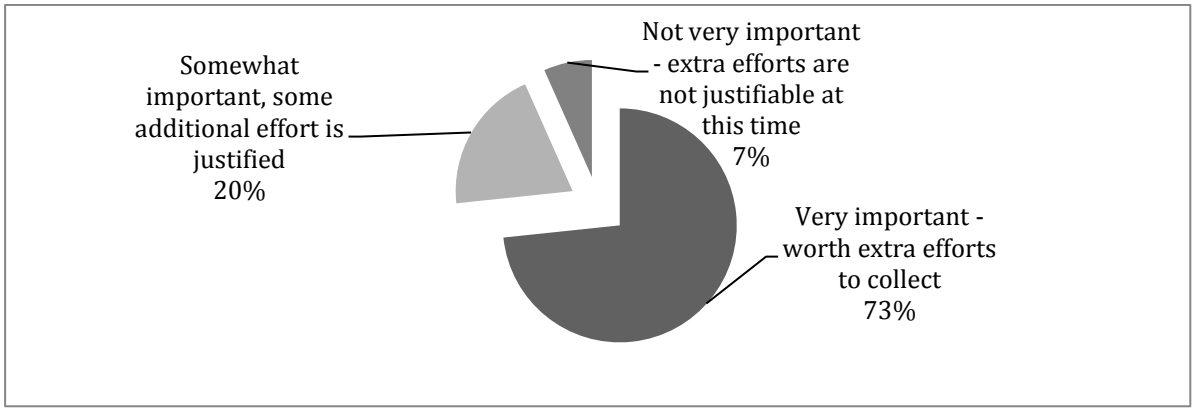
# 5. SURVEY RESULTS

This section summarizes the finding of the small survey of M&E officers. Given the small size (n=19) and varying degrees of missing data, only simple descriptive and exploratory analyses are provided. Findings are illustrative and not generalizable.

## ATTITUDE TOWARD M&E OF TB/HIV MORTALITY

In principle, M&E officers were cognizant of the potential value of robust mortality indicators for tracking their program's performance. When asked "How important is high quality data on TB deaths in your TB program?" 73% felt it merited extra efforts.

**Figure 2: Attitude toward Increasing Efforts to Improve Mortality data**




However, most M&E officers did not understand how mortality data were generated and were unclear on systems of disease classification. Most were unsure how the death of a patient with both TB and HIV would be classified or where it would be reported.

## ACCESSIBILITY OF TB/HIV MORTALITY DATA

The nineteen M&E officers reported the following classical challenges that hamper efforts to render valid mortality information from TB patient cohorts.

**Table 2: Challenges faced by M&E officers in constructing valid TB/HIV Mortality Estimates (n=19)**

| Challenges | n |
|---|---|
| Delays in receiving data from districts | 15 |
| Missing data | 8 |
| Misclassification of treatment outcomes | 5 |
| Difficulties in getting data from partners | 4 |
| High proportion of loss to follow up | 3 |
| High proportion of transfer outs that are unknown | 1 |

M&E officers from 19 countries were asked to indicate the areas with the highest and lowest mortality in their countries over three years. Twelve countries were able to provide estimates

based upon their surveillance data. The degree of intra country variation is striking. Trouble spots were noted in almost all countries and the year to year variation was high.

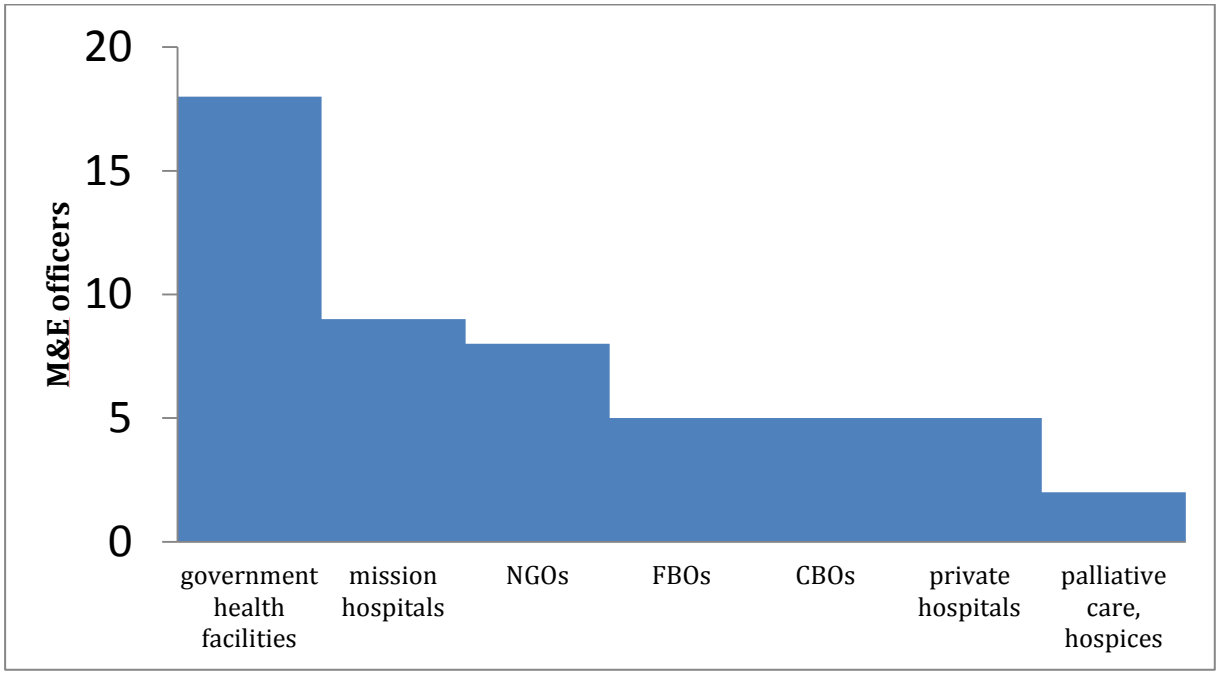
**Table 3: Survey of Intracountry Variation in Mortality among TB Patients (n=12)**

| | 2008 | | 2009 | | 2010 | |
|---|---|---|---|---|---|---|
| **country** | **highest** | **lowest** | **highest** | **lowest** | **highest** | **lowest** |
| Tanzania | 25.3 | 0.53 | 18.8 | 0 | - | - |
| Ghana | 11.8 | 4 | 9.8 | 2 | - | - |
| South Sudan | 19 | 3 | 15 | 4 | 10 | 2 |
| Mozambique | 14.1 | 5.8 | 15.5 | 5.2 | - | - |
| Ethiopia | 5.9 | 1.3 | 5 | 0.9 | 4.2 | 0.2 |
| Nigeria | 10 | 1.6 | 9 | 1.7 | 9 | 1.8 |
| Cambodia | 8 | 0 | 6 | 0 | 6 | 0 |
| Kazakhstan | 8 | 1.9 | 5.8 | 0.7 | - | - |
| Zambia | 7 | 3 | 7 | 2 | | 3 |
| Kenya | 6 | 2 | 13 | 1 | - | - |
| Pakistan | 3 | 0 | 3 | 1 | - | - |
| Dominican Republic | - | - | 16 | 1 | 43* | 1 |

* Unverified.

M&E officers relied primarily on data from government health facilities to estimate mortality in the TB cohort (Figure 3). Very few respondents reported linkages with hospices or palliative care programs or the private sector.

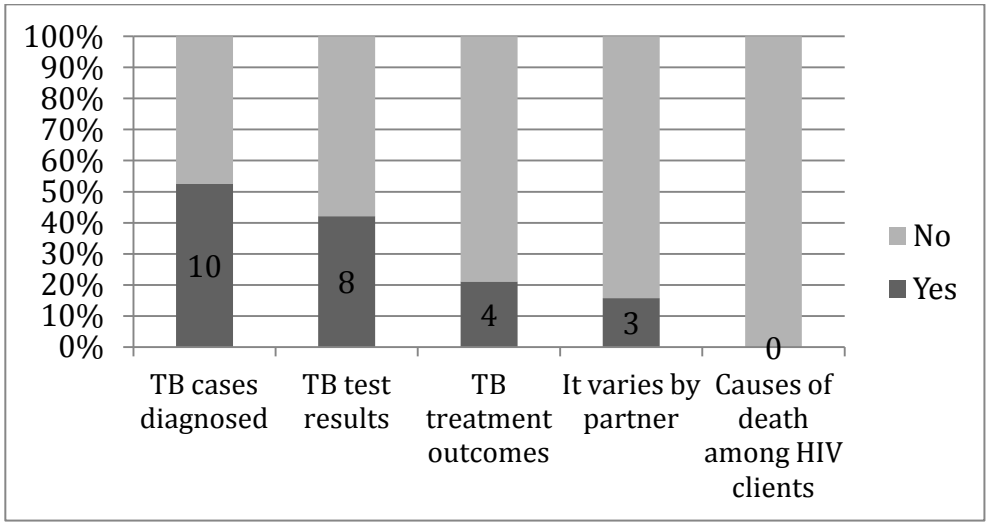
**Figure 3: Sources of Cohort Mortality Information**




Only 4 of 19 TB M&E programs received mortality information (i.e. treatment outcomes) from their corresponding HIV M&E unit (Figure 4). None of the M&E programs received cause of

death information in order to differentiate between deaths due to TB and deaths due to other opportunistic infections.

**Figure 4: Types of data received from HIV programs**




M&E officers prioritized the improvement of data sharing between TB and HIV programs as the most important solution to enhancing M&E of TB/HIV mortality (Table 4).

**Table 4: Potential Solutions to improve M&E of TB/HIV mortality (n=19)**

| | **In Favor** |
|---|---|
| Greater collaboration between TB and HIV programs | 17 |
| A national vital registration system for deaths | 9 |
| Transition to Patient-based TB record keeping | 6 |
| Other- e.g. modify the data collection forms | 1 |
| Routine surveillance of morgues, hospices, and religious institutions | 0 |

# 6. RESULTS OF ANALYSES OF TB SURVEILLANCE DATA

Beginning with an overview of the characteristics of the sample from five African countries, this section describes the accessibility and quality of mortality data. Finally, the section compares all-cause mortality and timing of death in the TB cohorts by age, sex, TB type, HIV status, and ART/CPT status.

## Accessibility of TB/HIV Mortality data

Table 5 gives an overview of the data collected for this assessment. In total 23,404 TB records were collected from five different African countries: Ethiopia, Ghana, Kenya, Mozambique and Zambia. The number of records per country ranged from 2656 (Mozambique) to 8915 (Ghana).

In Ethiopia data were collected from two Tigray and Afar regions. In Ghana data were collected from 69 districts in five different regions. In Kenya data were collected from four provinces: Nairobi North, Nairobi South, Nyanza South, and Rift Valley North. Data from Mozambique was collected from Gaza and Zambezia provinces and the Zambian data came from two provinces (Eastern Province and Lusaka). The Ghana data were available to us as aggregated data; therefore some tables in this report do not contain data from Ghana because of this.

All countries were asked to provide two years worth of data and the datasets included TB patients that were reported in 2009 and 2010. The dataset from Ghana included TB patients reported between October 2006 and September 2008 and data were collected in June and July 2009.

**Table 5. Overview of the surveillance sample.**

| Country | provinces | BMU | cases | Deaths in High mortality setting | Deaths in Low mortality setting | Time period | Data source |
|---|---|---|---|---|---|---|---|
| **Ethiopia** | 2 | 5 | 2527 | 161 (17.5) | 183 (11.4) | 2009-2010 | Paper TB registers |
| **Ghana** | 5 | 69 | 8915 | | | 1/10/2006 - 30/09/2008 | Paper TB registers |
| **Kenya** | 2 | 4 | 5245 | 229(11.7) | 107 (3.3) | 2009-2010 | Electronic patient-based records |
| **Mozambique** | 2 | 5 | 2656 | 388(20.5) | 65(10.2) | 2009-2010 | Electronic patient-based records & TB registers |
| **Zambia** | 2 | 3 | 4941 | 179(5.5) | 42(4.4) | 2009-2010 | Paper TB registers |

BMU= basic management unit

### DATA QUALITY

To assess the data quality we analyzed the completeness of data, particularly treatment outcome disaggregated by HIV status, as well as inconsistencies within records and common TB logic checks (e.g. epidemiological ratio) that often hint at quality problems.

COMPLETENESS OF ALL-CAUSE TB MORTALITY DATA

As expected, not all data records were complete. Table 6 gives an overview of missing data for the main variables used in the analysis. Percentage of missing data varied between countries and between variables, but was generally below 5%. For key variables such as HIV status and treatment outcome, the proportion missing values was high (>10%) in some countries. Treatment outcome was missing in 11% of the Ethiopian records. HIV status was missing in 14% of Ethiopian records and 19% of Ghana records.

**Table 6: Missing values from TB Treatment Register Data**

| | **Ethiopia** | | **Ghana** | | **Kenya** | | **Mozambique** | | **Zambia** | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **N=2527** | | **N=8915** | | **N=5245** | | **N=2860** | | **N=4941** | |
| **Variable** | **N** | **%** | **N** | **%** | **N** | **%** | **N** | **%** | **N** | **%** |
| Sex | 4 | 0.2 | 181 | 2.0 | 0 | 0 | 2 | 0.0 | 0 | 0 |
| Age | 17 | 0.7 | 83 | 0.9 | 0 | 0 | 0 | 0 | 2 | 0.0 |
| Type of patient | - | - | 76 | 0.9 | 0 | 0 | 0 | 0 | 0 | 0 |
| TB classification (PTB, EPTB) | - | - | 81 | 0.9 | 0 | 0 | 3 | 0.1 | 0 | 0 |
| Initial smear results* | 20 | 0.8 | 478 | 5.4 | 428[£] | 8.2 | 15 | 0.5 | 0 | 0 |
| Date of start of treatment | 20 | 0.8 | 317 | 3.6 | 0 | 0 | 4 | 0.1 | 30 | 0.6 |
| Treatment category | - | - | 358 | 4.0 | - | - | - | - | - | - |
| Treatment outcome | 269 | 10.6 | 466 | 5.2 | 255 | 4.9 | 0 | 0 | 66 | 1.3 |
| Date of treatment outcome | - | - | 3350 | 38 | - | - | 487[#] | 27.4 | 185 | 3.7 |
| HIV status | 343 | 13.6 | 1674 | 18.8 | 750 | 14.3 | 11 | 0.4 | 458 | 9.3 |
| ART status ** | 0 | 0 | - | | 235 | 13.2 | 0 | 0 | 1733 | 58.3 |
| CPT status** | 0 | 0 | - | | 48 | 2.7 | 0 | 0 | 1066 | 35.9 |

**Legend**: PTB=pulmonary TB; EPTB=extrapulmonary TB; ART=antiretroviral therapy; CPT=cotrimoxazole preventive treatment. * Smear result is not applicable in patients with extrapulmonary TB (therefore not missing). ** For ART and CPT use, missing values are presented for HIV positive patients only. [£] Smear result =is not done in 428 pulmonary TB patients (=missing). [#] 478/487 with missing date of outcome are 'still on treatment'; probably outcome has not been updated.

Completeness of treatment outcome disaggregated by HIV status is shown in Table 7. The proportion of patients with missing treatment outcome varies between HIV positive, HIV negative and HIV unknown TB patients. In Ethiopia and Kenya the proportion of missing treatment outcome was very high in patients with unknown HIV status (20% and 32% respectively). Completeness of treatment outcome could not be disaggregated by HIV status for Ghana.

**Table 7. Missing Treatment Outcome Data by HIV status**

| | **Ethiopia** | | **Kenya** | | **Mozambique** | | **Zambia** | |
|---|---|---|---|---|---|---|---|---|
| **N and % missing** | **High N=1607** | **Low N=920** | **High N=1958** | **Low N=3287** | **N=2216** | **N=644** | **High N=4182** | **Low N=759** |
| | **n,%** | **n, %** | **n,%** | **n, %** | **n,%** | **n, %** | **n,%** | **n, %** |
| **HIV negative** | 85 (5.3) | 83 (9.0) | 0 (0) | 1 (0) | 0 (0) | 0 (0) | 10 (0.2) | 14 (1.8) |
| **HIV positive** | 11 (0.7) | 22 (2.4) | 0 (0) | 1 (0) | 0 (0) | 0 (0) | 13 (0.3) | 16 (2.1) |
| **HIV unknown** | 17 (1.1) | 51 (5.5) | 70(3.6) | 183 (5.6) | 0 (0) | 0 (0) | 1 (0) | 12 (1.6) |

### INCONSISTENCIES IN THE DATA

All records were checked for inconsistencies. In the Mozambique data, 479 patients were 'still on treatment' in 2011 although their TB treatment had started in 2009. As it is not likely that so many patients were still on treatment (the moment of data collection) we assumed that the treatment outcome had not been updated yet and assume these patients are lost to follow-up ('out of control' OOC).

## LOGIC CHECKS TO EXPLORE COMMON TB EPIDEMIOLOGICAL RATIO

To explore the TB epidemiological ratio the proportion of patients with sputum smear positive pulmonary TB, the proportion of HIV positive patients among those tested and the proportion of patients under 15 years of age are shown in Table 8(when available).
The proportion of pulmonary smear positive patients was within the expected range (25-35%) in Kenya, Mozambique and Zambia, but high (69%) in Ghana. According to the WHO [ref TB Report 2011], the HIV prevalence among tested TB patients is 15% in Ethiopia (18% in our database), 23% in Ghana (24% in our data), 41% in Kenya (40% in our data), 61% in Mozambique (83% in our data) and 65% in Zambia (66% in our data).

**Table 8. Logic checks to explore common TB epidemiological ratio**

| **Variable** | **Ethiopia** | | **Kenya** | | **Mozambique** | | **Zambia** | |
|---|---|---|---|---|---|---|---|---|
| | **High (1607)** | **Low (920)** | **High (1958)** | **Low (3287)** | **High (2216)** | **Low (644)** | **High (4182)** | **Low (759)** |
| | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| Proportion smear positive | 246 (15.3) | 161 (17.5) | 377 (35.7) | 648 (33.6) | 692 (31.2) | 351 (54.5) | 1137 (27.2) | 579 (76.3) |
| Proportion HIV positive among tested | 262 (17.4) | 137 (20.2) | 613 (35.0) | 1164 (43.0) | 1792 (81.5) | 297 (57.2) | 2593 (68.2) | 380 (56.1) |
| Proportion under 15 years of age | 145(9.0) | 124(13.7) | 238(12.2 | 284(8.6) | 273(12) | 33(5.1) | 438(11) | 80(10.6 ) |

The data from Ethiopia, Mozambique, and Zambia contained patients with a negative or unknown HIV status who were using antiretroviral treatment (ART) or cotrimoxazole preventive treatment (CPT). ART and CPT are prescribed exclusively for people with HIV. In Ethiopia two patients with unknown HIV status were using ART and CPT, in Mozambique 295 HIV negative patients were listed as taking ART, and in Zambia 5 HIV negative patients and 11 patients with unknown HIV status were on ART. These illogical combinations indicate that either HIV status is not recorded or updated properly or that ART use is recorded incorrectly.

### PATIENT CHARACTERISTICS

Although these proportions are not generalizable to the country itself, the patient characteristics from the two areas were combined in Table 8. The female:male ratio ranged from 0.39 in

Ethiopia to 0.51 in Ghana. The mean age ranged from 32 years in Ethiopia and Zambia to 41 years in Ghana. The proportion of HIV positive TB patients among those who were tested ranged from 18% in Ethiopia to 83% in Mozambique. In Ghana very few TB patients were diagnosed with extrapulmonary TB (4%) compared to other countries, e.g. Kenya (23%).

**Table 9. Characteristics TB cohorts from two areas of five countries**

| | **Ethiopia** | | **Ghana** | **Kenya** | | **Mozambique** | | **Zambia** | |
|---|---|---|---|---|---|---|---|---|---|
| | **high** | **low** | **N=8915** | **high** | **low** | **high** | **low** | **high** | **low** |
| **Sex, n (%)** | n(%) | N(%) | | n(%) | n(%) | n(%) | n(%) | n(%) | n(%) |
| Male | 982 (61.1) | 550 (59.8) | 5791 (65.0%) | 1067 (54.5) | 1867 (56.8) | 1254 (56.6) | 346 (53.7) | 2505 (59.9) | 438 (57.7) |
| Female | 623 (38.8) | 368 (40) | 2943 (33.0%) | 891 (45.5) | 1420 (43.2) | 960 (43.3) | 298 (46.3) | 1677 (40.1) | 321 (42.3) |
| F:M ratio | 0.63 | 0.67 | 0.51 | 0.84 | 0.76 | 0.77 | 0.86 | 0.67 | 0.73 |
| **Age**, mean (SD) | 32.63 (±16.4) | 30.83 (16.0) | 40.9 (±17.3) | 34.5 (±18.0 ) | 32.4 (13.6) | 33.6 (±16.1 | 33.4 (14.1) | 31.6 (±14.0) | 34.0 (16.5) |
| **TB type, n (%)** | | | | | | | | | |
| Pulmonary sm+ | - | - | 6138 (68.9%) | 712 (36.4) | 1120 (34.1) | 690 (31.1) | 347 (53.9) | 1127 (26.9) | 494 (65.1) |
| Pulmonary sm- | - | - | 2283 (25.6%) | 595 (30.4) | 952 (29.0) | 855 (38.6) | 223 (34.6) | 2613 (62.5) | 101 (13.3) |
| Extrapulmonary | - | - | 395 (4.4%) | 345 (17.6) | 854 (26.0) | 471 (21.3) | 29 (4.5) | 442 (10.6) | 164 (21.6) |
| Unknown | - | - | 99 (1.1%) | 306 (15.6) | 361 (11.0) | 200 (9.0) | 45 (6.9) | 0 (0) | 0 |
| **HIV status, n (%)** | | | | | | | | | |
| Negative | 1245 (77.5) | 540 (58.7) | 2118 (23.8%) | 1140 (58.2) | 1543 (46.9) | 0(0) | 0(0) | 1212 (29.0) | 298 (39.3) |
| Positive | 262 (16.3) | 137 (14.9) | 661 | 613 (31.3) | 1164 (35.4) | 408 (18.5) | 222 (34.5) | 2593 (62.0) | 380 (50.0) |
| Unknown | 100 (6.2) | 243 (26.4) | 6136 | 70 (3.6) | 183 (5.6) | 0(0) | 0(0) | 377 (9.0) | 81 (10.7) |
| **HIV positive in tested, n/N (%)** | 262/1507 (17.4%) | 137/677 (20.2) | 661/2779 (23.8%) | 613/ 1753 (35.0%) | 1164/2707 (43.0) | 1792/2200 (81.5) | 297/519 (57.2) | 2593/3805 (68.2) | 380/678 (56.1) |

SAMPLE VARIATION IN MORTALITY DURING TB TREATMENT

Sites were purposely selected using extreme sampling in order to maximize variation in TB treatment outcomes (Table 10). The all-cause mortality (treatment outcome = 'Died') ranged from 3.3% in the Nairobi area to 20.5% in Gaza province of Mozambique. The cells shaded in pink indicate proportions that were higher than expected, and where hidden mortality might be present.

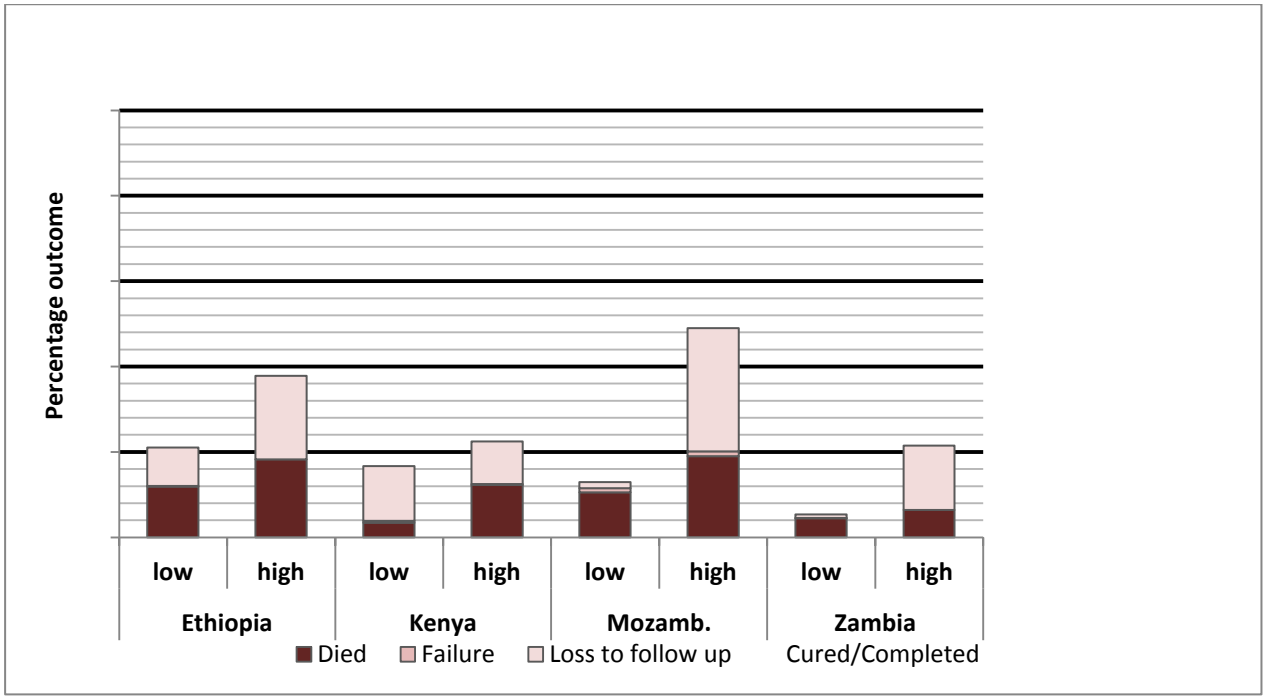
**Table 10. TB treatment outcome by country (N=23,404)**

| | Ethiopia | | Kenya | | Mozambique | | Zambia | |
|---|---|---|---|---|---|---|---|---|
| | **low** | **high** | **high** | **low** | **high** | **low** | **high** | **low** |
| **Treatment outcome** | n(%) | n(%) | n(%) | n(%) | n(%) | n(%) | n(%) | n(%) |
| Cured | 170, (10.6) | 66 (7.2) | 618 (31.6) | 850 (25.9) | 340 (17.9) | 303 (47.4) | 975 (23.3) | 276 (36.4) |
| Treatment completed | 1044 (65.0) | 482 (52.4) | 833 (42.5) | 1745 (53.1) | 680 (35.9) | 235 (36.8) | 2788 (66.7) | 236 (31.1) |
| **Died** | **183 (11.4)** | **161 (17.5)** | **229 (11.7)** | **107 (3.3)** | **388 (20.5)** | **65 (10.2)** | **179 (4.3)** | **42 (5.5)** |
| Transferred out | 69 (4.3) | 39 (4.2) | 87 (4.4) | 173 (5.3) | 28 (1.5) | 4 (0.6) | 205 (4.9) | 107 (14.1) |
| Failure | 2 (0.1) | 0(0) | 4(0.2) | 14 (0.4) | 59 (3.1) | 6 (0.9) | 3 (0.1) | 0 (0) |
| Lost to Follow Up | 26 (1.6) | 16 (1.7) | 117 (6.0) | 213 (6.5) | 26 (1.5) | 21 (3.3) | 8 (0.2) | 56 (7.4) |
| Not evaluated | 113 (7.0) | 156 (17.0) | 70 (3.6) | 185 (5.6) | 0 (0) | 0 (0) | 24 (0.6) | 42 (5.5) |

Many patients described as 'lost to follow up, 'Transferred out' or with an 'Not evaluated' treatment outcome are likely to be deceased, but the proportion varies by country. This misclassification could lead to under-counting of the burden of TB/HIV mortality in the population. A recent study by Egger and colleagues on ART programs shows that mortality misclassification is highly variable across countries, and can result in a highly distorted view of program effectiveness[28].

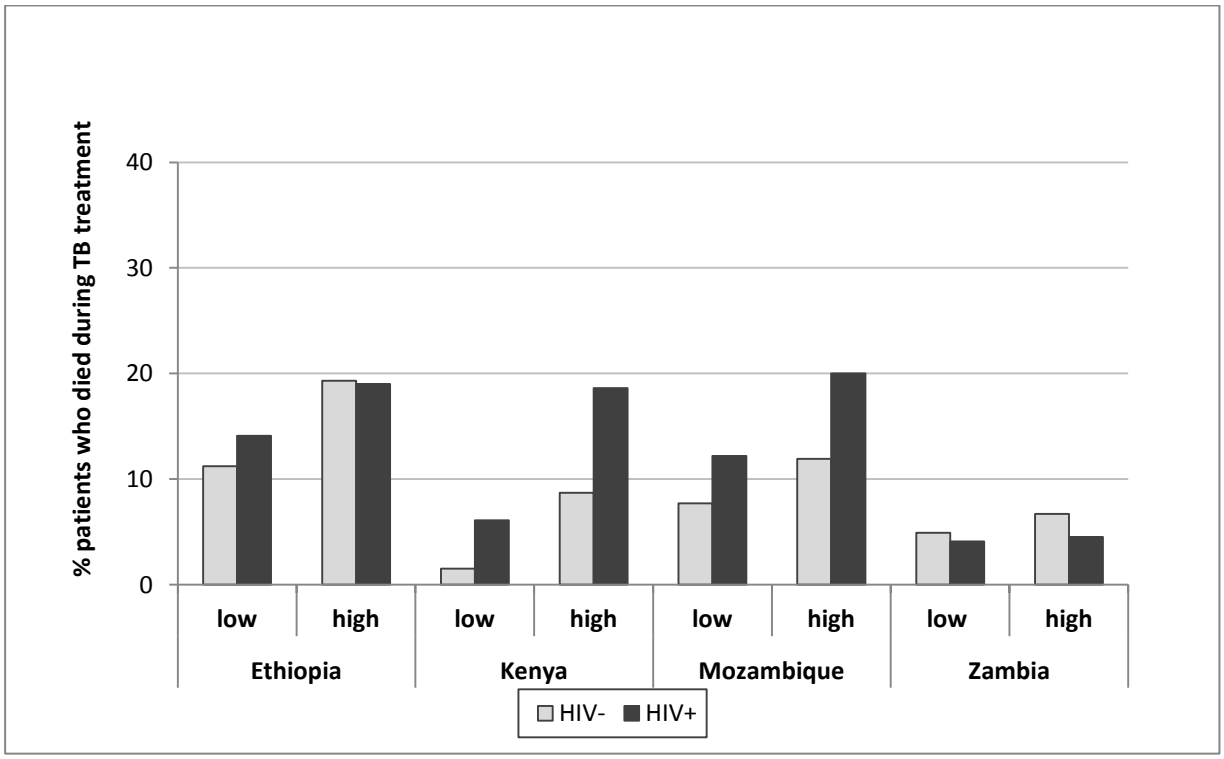
Figure six sums the treatment outcome categories died, transferred out, default, failure, and unknown. The values given refer to the number of patients with an unknown treatment outcome. In the high mortality settings (hot spots), these combined outcomes reflected between 25% and 50% of the entire TB cohort. This suggests that the M&E challenges in these settings extend beyond mortality.

**Figure 6. Treatment outcome, by country and province**




Although HIV+ TB patients tend to experience high mortality rates compared to their HIV-negative peers, this does not seem to fully explain the variance in mortality among TB patients in the high and low mortality areas (Figure 7).

**Figure 7: All-Cause Mortality in TB cohort by HIV status by extreme sample unit**



Curiously TB mortality appears higher in HIV negative TB patients in three out of eight sampled units. That is very unlikely. In the following sections treatment outcome is presented as 'Cured/completed', 'Died' (i.e. all-cause mortality) and 'Other' (i.e. combination of: transferred out, default, failure, out-of-control and unknown outcome). The association between sex, HIV status and TB type with mortality was presented as odds ratio (95% confidence interval).

## RISK FACTORS FOR MORTALITY

This study was based on self-administered surveys and routine surveillance data and did not collect or compare the patient level records for individual deaths. Therefore it was not possible to explore many important risk factors for death beyond socio-demographic and TB diagnostic and treatment variables. Fortunately, many recent studies have looked in more detail and reported that the wide-ranging mortality rates in HIV-infected TB patients are a function of the time at diagnosis, quality of drug regimen, co-morbidities, and variation in quality of care [29]. A recent systematic review by Waitt also identified other patient characteristics such as advancing immunosuppression, smear negative disease and malnutrition[30]. There is also evidence that TB mortality among HIV-infected patients may be disproportionately high among sub-populations, including women and children, who are not traditionally targeted by TB programs [31-33].

## IMPACT OF ART AND CPT USE ON MORTALITY

The vital importance of TB diagnosis and treatment for the well being of HIV-infected populations has been clear since 1991[34-36]. All HIV-infected persons benefit significantly from the timely provision of CPT, ART, IPT, routine screening for TB, and proactive provision of appropriate TB treatment [36-37]. In contemporary contexts where quality-assured ART, clotrimoxizole, and TB drugs are provided usually yield all-cause mortality rates well below 10% [38-39].

### EXTENT OF ART AND CPT PROVISION IN HIV POSITIVE TB PATIENTS

In 2012 the Joint United Nations Programme on HIV/AIDS (UNAIDS) reported that there has been a further 13% reduction in tuberculosis TB-associated HIV deaths in the last 2 years. The reduction has been attributed to a sharp increase in the numbers of people with HIV and TB co-infection accessing antiretroviral therapy (ART)––a 45% increase between 2009 and 2011, but still only 52% of those eligible.[2]

The provision of antiretroviral therapy (ART) and cotrimoxazole preventive treatment (CPT) among HIV infected TB patients varied between the countries (Table 11). In Ethiopia all HIV positive TB patients were reportedly on ART, compared to 52% in Kenya and 42% in Zambia. According to the WHO TB Report of the 2009 cohort as a whole, 39% of Ethiopian HIV positive TB patients are on ART and 69% on CPT; in Kenya 48% of HIV positive TB patients are on ART and 100% on CPT; in Mozambique 25% of the HIV positive TB patients are on ART and 97% on CPT, and in Zambia 47% of HIV positive TB patients are on ART and 77% on CPT[WHO,2010].

**Table 12. ART and CPT use in HIV positive TB patients.**

| | Ethiopia | | Kenya | | Mozambique | | Zambia | |
|---|---|---|---|---|---|---|---|---|
| **No of HIV+ patients** | **High (262)** | **Low (137)** | **High (613)** | **Low (1164)** | **High (1792)** | **Low (297)** | **High (2593)** | **Low (380)** |
| | **n(%)** | **n(%)** | **n(%)** | **n(%)** | **n(%)** | **n(%)** | **n(%)** | **n(%)** |
| **ART** | | | | | | | | |
| Yes | 262 (100) | 137 (100) | 234 (38.2) | 695 (59.7) | 1008 (55.6) | 78 (26.3) | 1039 (40.0) | 201 (52.9) |
| No * | - | - | 285 (46.5) | 328 (28.2) | 784 (43.8) | 219 (73.7) | 1554 (59.9) | 179 (47.1) |
| Unknown | 0 | 0 | 94 (15.3) | 141 (12.1) | | | | |
| **CPT** | | | | | | | | |
| Yes | 262 (100) | 137 (100) | 519 (84.7) | 1095 (94.1) | 839 (46.8) | 286 (96.3) | 1723 (66.4) | 184 (48.4) |
| No * | - | - | 62 (10.1) | 53 (4.6) | 953 (53.2) | 3 (1.0) | 870 (33.6) | 196 (51.6) |
| Unknown | 0 | 0 | 32 (5.2) | 16 (1.4) | | 8 (2.7) | | |
| **Both ART and CPT** | 262 (100) | 137 (100) | 229 (37.4) | 692 (59.5) | 448 (25) | 74 (25) | 983 (37.9) | 155 (40.8) |

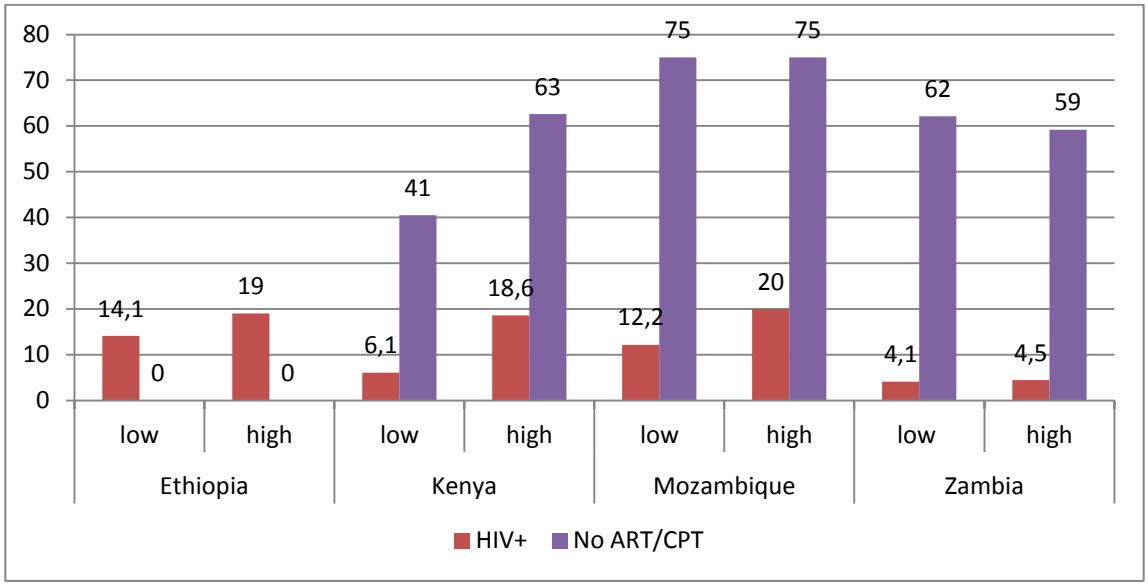
Legend: * In the Kenyan data, the variables ART and CPT were recorded as yes/no/unknown, whereas in Ethiopia, Mozambique and Zambia the options were 'yes' or 'unknown' only.

The following table shows the all-cause mortality by provision of preventive treatment (ART and CPT). In Ethiopia and Mozambique, all HIV positive TB patients were using ART and CPT. In Kenya and Zambia there were HIV positive TB patients that did not use ART and CPT (Kenya) or where ART/CPT use was unknown (both Kenya and Zambia). The mortality in these patients was higher than in patients that did use ART and/or CPT.

**Table 13. Mortality in HIV+ TB Patients by ART and CPT Status**

| | **Ethiopia** | | **Kenya** | | **Mozambique** | | **Zambia** | |
|---|---|---|---|---|---|---|---|---|
| **No of HIV+ patients** | **N=399** | | **N=1777** | | **N=2014** | | **N=2973** | |
| | **N used** | **n(%) died** | **N used** | **n(%) died** | **N used** | **n(%) died** | **N used** | **n(%) died** |
| **ART** | 399 | 63 (15.8) | 929 | 64 (6.9) | 929 | 165 (17.7) | 1240 | 36 (3.1) |
| **CPT** | 399 | 63 (15.8) | 1614 | 160 (9.9) | 705 | 156 (22.1) | 1907 | 77 (4.0) |
| **ART + CPT** | 399 | 63 (15.8) | 921 | 64 (6.9) | 387 | 71 (18.4) | 1138 | 30 (2.6) |
| **No ART or CPT** | - | - | 102 | 19 (18.6) | - | - | - | - |
| **ART-CPT unknown** | - | - | 53 | 6 (11.3) | 583 | 110 (18.9) | 1733 | 88 (5.1) |

**Figure 8: Mortality among HIV/TB Patients and Unmet Need for ART/CPT**




The data from Ethiopia and Zambia were very hard to interpret. It was difficult to explain such low mortality in Zambia given the low levels of CPT/ART of coverage. Similarly, it was difficult to account for such high mortality in Ethiopia in the presence of reported 100% CPT/ART coverage. The quality of the data was increasingly called into question.

The Kenyan data are most illustrative of the effect of ART and CPT on mortality. The Kenyan dataset contained the most detailed information regarding ART and CPT use, because ART and CPT use is recorded as 'yes', 'no' or 'unknown'. Patients that did not use ART or CPT had a higher mortality than those who did use ART and/or CPT. The difference in mortality between patients that do or do not use ART or CPT is substantial: 7% vs. 15% for ART use, 10% vs. 19% for CPT use. Mortality was lowest in patients that were both using ART and CPT (7%) and worst for those who did not use CPT (19%) or who did not use CPT nor ART (also 19%). The risk on mortality is decreased by the use of ART (OR 0.39; 95% CI 0.28-0.55; P<0.001) and CPT (OR 0.42; 95% CI 0.25-0.89; P=0.001). The combined use of ART and CPT has the largest effect on mortality (OR 0.29; 95% CI0.16-0.52) compared to patients that do not use ART nor CPT.

## TIMING IS EVERYTHING: THE VALUE OF DATE VARIABLES IN TB SURVEILLANCE SYSTEMS

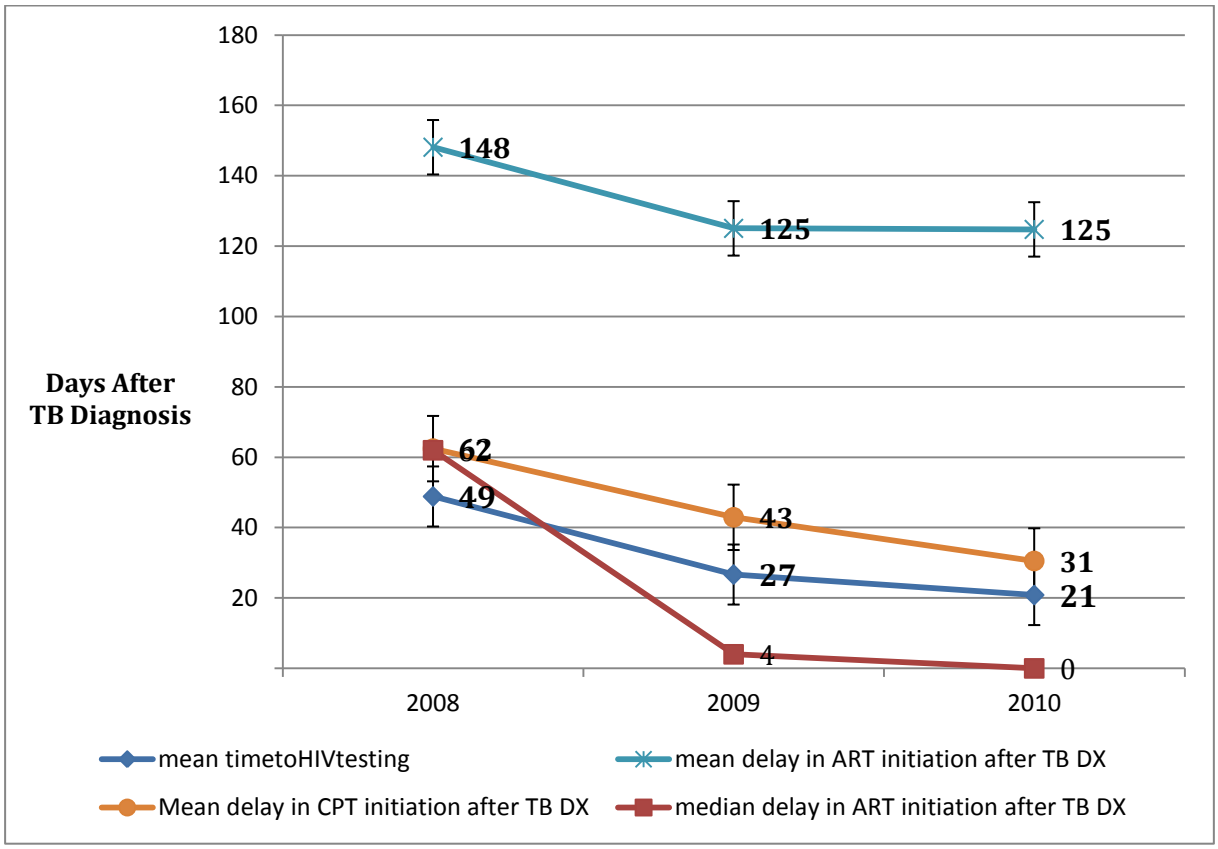
Delay in starting ARVS and CPT results in morbidity and mortality among TB patients. The WHO WHO 2013 Revised Case Definitions and Reporting Forms recommends dropping the date variable for start of ARVs from TB surveillance systems. The value of the start date(s) is unknown and its use in policy making and program management was unclear. We sought to explore if measurement of time intervals (delays) offered insights on program performance.

The integration of TB/HIV/STI/SRH has many obvious benefits, but one of the technical M&E challenges has been making sense of the diverse patient itineraries in simple R&R forms.Although a seemingly mundane political concern about which programs get "credit" for a

particular client's care, there are also underlying public health rationales for wanting to know how patients navigate the health care maze and where they may get lost, stalled or misdirected along the way. The question of timing is perhaps most critical when it comes to providing ARVs which are both powerful TB prevention tool as well as a potent therapeutic agent.

We analyzed routine surveillance data from 4 districts of Kenya from 2008-2010 (n=1222), to calculate the mean and median time from TB diagnosis to implement HIV testing and CPT and ART initiation if warranted. In addition to increases in CPT and ART coverage among HIV+ TB patients, delay in HIV testing declined by 53%, and delays in initiating CPT and ART declined by 50% and 16% respectively.

**Figure K1: Declines in Diagnostic and Treatment Delays in Kenya 2008-2010**




We conclude that the date variable(s) in TB surveillance systems provide key information for monitoring and evaluation of service delivery and should not be eliminated from the TB recording and reporting system.

## TIME BETWEEN TB TREATMENT START AND DEATH

The time between TB treatment start and moment of death (i.e. time to death) during TB treatment was available for Ghana, Mozambique and Zambia.
For Mozambique and Zambia the date of death was not known, but the date of end of treatment was used as a proxy instead. The duration of treatment was calculated using the dates 'start of

treatment' and 'end of treatment' and we considered the duration of treatment as a proxy for the time to death after the start of treatment in the patients who died during treatment.

Overall, 888 (10%) of the TB patients from Ghana died during treatment. For 621 (70%) patients the time between start of treatment and moment of death was available (time to death). In Mozambique, 333 (18.8%) of patients died during TB treatment; time to death (i.e. duration of treatment) was available for 323 (97%) of those patients. In Zambia, 221 (4.5%) of patients died during TB treatment; time to death was available for 184 (83%) of those patients.

Table 14 shows the median time to death for patients who died during TB treatment by sex, HIV status and TB type for Ghana, Mozambique and Zambia. Overall, the median time to death was 23 days (inter-quartile range [IQR] 6-49) for Mozambique, 40 days (IQR 9-88) in Zambia, and 45 days (IQR 12-103) in Ghana. Time to death was longer in pulmonary smear negative patients compared to pulmonary smear positive patients in both Ghana (median 57 vs. 32 days; Mann-Whitney U test, P<0.001) and Zambia (median 53 vs. 27 days; P<0.001). Sex and HIV status were not associated with time to death in any of the three countries.

**Table 14. Time to death by sex, TB type and HIV status for patients who died during TB treatment in Ghana Mozambique and Zambia.**

| | **Ghana** | | **Mozambique** | | | **Zambia** | | |
|---|---|---|---|---|---|---|---|---|
| | **N** | **Time to death, median days (IQR)** | **N** | **Time to death, median days (IQR)** | | **N** | **Time to death, median days (IQR)** | |
| | | | | **high** | **low** | | **high** | **low** |
| **Overall** | 621 | 45 (12-103) | 399 | 24 (7-51) | 90 (43-127) | 184 | 39 (9-78) | 59(6-152) |
| **Sex** | | | | | | | | |
| Male | 410 | 42 (11-101) | 265 | 24 (6-52) | 89 (42-137) | 114 | 36 (14-70) | 59(14-91) |
| Female | 201 | 48 (13-103) | 134 | 23 (8-49) | 95 (67-127) | 70 | 40 (7-91) | 61(1-53) |
| Unknown | 10 | 66 (58-145) | - | | | | | |
| **TB type** | | | | | | | | |
| Pulm sm+ | 220 | 32 (9-76) | 106 | 28 (7-52) | 65(29-95) | 59 | 26 (8-63) | 59(6-152) |
| Pulm sm- | 360 | 57 (15-123) | 156 | 24 (8-61) | 96 (68-125) | 105 | 53 (15-98) | 7(0-14) |
| EP | 33 | 40 (8-100) | 76 | 19 (8-43) | 76 (24-127) | 20 | 16 (1-31) | 83 (36-260) |
| Unknown | 8 | 23 (0-80) | 61 | 24 (4-50) | 372 (372-372) | - | | |
| **HIV status** | | | | | | | | |
| Negative | 138 | 45 (11-106) | 349 | 23 (6-50) | 101 (67-137) | 63 | 49 (11-92) | 25(14-59) |
| Positive | 96 | 43 (13-84) | 45 | 28 (13-70) | 43(24-88) | 109 | 36 (8-67) | 86(6-153) |
| Unknown | 387 | 48 (12-104) | 3 | 14 (4-23) | 95(95-95) | 12 | 38 (21-102) | - |

Table 15 shows the time to death presented as proportion of patients who died within a week, a month and two months after the start of treatment by sex, HIV status and TB type. It gives the appearance that HIV was not a risk factor for very early death, raising concerns about the data quality and/or clinical care.

**Table 15: Proportion of patients who died within 2 weeks, 1 month and 2 months after start of treatment by sex, TB type and HIV status, in Mozambique and Zambia.**

| | **Mozambique** | | | | | | **Zambia** | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **% Died during treatment** | | | **% Died during treatment** | | | **% Died during treatment** | | | **% Died during treatment** | | |
| | **High (Gaza) n=388** | | | **Low (Zambezia) n=65** | | | **High (Lusaka) n=172** | | | **Low(Eastern) n=42** | | |
| **Time to death** | **<2 wk (%)** | **<1 mo (%)** | **<2 mo (%)** | **<2 wk (%)** | **<1 mo (%)** | **<2 mo (%)** | **<2 wk (%)** | **<1 mo (%)** | **<2 mo (%)** | **<2 wk (%)** | **<1 mo (%)** | **<2 mo (%)** |
| **Overall** | 37 | 53 | 73 | 0 | 1 | 2 | 26 | 40 | 54 | **3** | **3** | **4** |
| **Sex** | | | | | | | | | | | | |
| Male | 36 | 52 | 72 | 0 | 1 | 2 | 25 | 39 | 56 | 4 | 4 | 4 |
| Female | 37 | 56 | 74 | 1 | 1 | 1 | 29 | 41 | 51 | 3 | 3 | 4 |
| **TB type** | | | | | | | | | | | | |
| Pulm sm+ | 33 | 50 | 72 | - | 1 | 3 | 31 | 51 | 61 | 5 | 5 | 5 |
| Pulm sm- | 36 | 53 | 68 | 1 | 1 | 1 | 23 | 31 | 50 | 2 | 2 | 2 |
| EP | 39 | 55 | 79 | - | 1 | 1 | 30 | 50 | 55 | 5 | 5 | 10 |
| Unknown | 41 | 57 | 48 | - | - | - | | | | | | |
| **HIV** | | | | | | | | | | | | |
| Negative | 38 | 54 | 74 | - | 0 | 0 | 27 | 38 | 46 | 5 | 5 | 6 |
| Positive | 27 | 47 | 60 | 2 | 4 | 7 | 26 | 40 | 58 | 3 | 3 | 3 |
| Unknown | - | - | - | - | - | - | 25 | 42 | 67 | - | - | - |

In both of the high mortality hot spots where date of treatment outcome was recorded, the patients deaths occurred very early in treatment. In Gaza province, more than half of TB patients who died did so within the first month of treatment, suggesting that the problem is late diagnosis and not problems with TB management.

To identify potential risk factors for early death, the odds ratios for dying within one month after start of treatment are presented for subgroups in Mozambique and Zambia. There were no risk factors identified.

**Table 16 Risk factors for dying within 1 month after start of TB treatment, Mozambique and Zambia**

| | **Mozambique** | | | | | | **Zambia** | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **High (Gaza) n=388** | | | **Low (Zambezia) n=65** | | | **High (Lusaka) n=172** | | | **Low(Eastern) n=42** | | |
| | **Died <1mo (%)** | **OR (95% CI)** | **P-value** | **Died <1mo (%)** | **OR (95% CI)** | **P-value** | **Died <1mo (%)** | **OR (95% CI)** | **P-value** | **Died <1mo (%)** | **OR (95% CI)** | **P-value** |
| **Sex** | | | | | | | | | | | | |
| Male | 52 | Ref | | 1 | ref | | 39 | ref | | 4 | ref | |
| Female | 56 | 1.20(0.78-1.85) | 0.41 | 1 | 1.0(0.07-13.4) | 1.0 | 41 | 1.15(0.61-2.15) | 0.67 | 3 | 0.63(0.07-5.34) | 0.67 |
| **TB type** | | | | | | | | | | | | |
| Pulm sm+ | 50 | ref | | 1 | ref | | 51 | ref | | 5 | ref | |
| Pulm sm- | 53 | 1.17(0.7-1.96) | 0.54 | 1 | 0.45(0.02-8.8) | 0.60 | 31 | **0.35(0.17-0.69)** | **0.002** | 2 | - | - |
| EP | 55 | 1.16(0.64-2.13) | 0.62 | 1 | 5(0.15-166) | 0.37 | 50 | 1.83(0.51-6.62) | 0.36 | 5 | 0.27(0.02-3.65) | 0.32 |
| Unknown | 57 | 1.24(0.65-2.37) | 0.51 | - | - | - | | - | - | - | - | |
| **HIV** | | | | | | | | | | | | |
| Negative | 52.5 | ref | | 6.7 | ref | | 38 | ref | | 5 | ref | |
| Positive | 56.3 | 1.17 | 0.65 | 40 | 9.33(0.62-140) | 1.0 | 40 | 1.08(0.56-2.09) | 0.82 | 3 | 0.5(0.06-4.15) | 0.52 |
| Unknown | 100 | - | - | 0 | - | | 42 | 0.98(0.28-3.47) | 0.98 | - | - | |

Among contributing factors may be delays in diagnosis and treatment of TB/HIV patients. There are four different delays: (1) Delays in the decision to seek care; (2) Delays in arrival at a health facility; (3) Delays in the diagnostic process; and (4) Delays in provision of adequate care and effective treatment. Unfortunately, the data collected from the five countries did not allow us to analyze the role of these different types of delays.

# MORTALITY IN 2009-2010 TB COHORTS WITHIN TWO AREAS OF ETHIOPIA

Ethiopia is ranked 7th among the 22 TB High Burden Countries (HBCs). TB is the second cause of death with estimated mortality of 66 per 100,000. In 2009, there were an estimated 210,000 (265 per 100,000) incident cases with a total of 148,936 notified TB patients. Ethiopia has generalized HIV epidemic with HIV prevalence of 2.1%. In 2009 only 37% of TB patients were tested for HIV with 15% of TB patients who are HIV positive. According to Ethiopia national TB reports, there 4,748 TB deaths in 2009 representing about 3% of all TB patients. A total of 2527 TB cases of TB were sampled for this project

In Ethiopia data was collected from Tigray and Afar regions. Tigray was the region with highest TB mortality in 2009 and Afar was the region with lowest TB mortality. Data were collected from 5 districts; Sahret, Alamata and Mekele in Tigray region while in Afar region data were collected in Mile and Asaita districts

The following table shows the treatment outcome in the two Ethiopian regions disaggregated by sex, age-group and HIV status. The overall all-cause mortality was 11% in Region 1 and 18% in Region 2. This is in sharp contrast with the district reports which give proportions of 5% and less than 1% respectively. In Tigray male patients had a higher risk of mortality than female patients (OR 0.61; 95% CI 0.44-0.86; P=0.005). HIV status was not associated with mortality. TB type is not shown for Ethiopia because the variable 'pulmonary or extrapulmonary TB' was not available in the dataset.

**Table E1. Treatment outcome by region disaggregated by sex, age and HIV status, Ethiopia (N=2527)**

| **Region:** | **Region 1 Tigray** | | | | | | **Region 2 Afar** | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Total** | **Cured/ completed** | **Other** | **Died** | **Died vs. cured/completed** | | **Total** | **Cured/ completed** | **Other** | **Died** | **Died vs. cured/completed** | |
| | **N** | **%** | **%** | **%** | **OR (95%CI)** | **P-value** | **N** | **%** | **%** | **%** | **OR (95%CI)** | **P-value** |
| **Total** | 1607 | 75.5% | 13.1% | 11.4% | | | 920 | 59.6% | 22.9% | 17.5% | | |
| **Sex** | | | | | | | | | | | | |
| Male | 982 | 73.5% | 13.3% | 13.1% | Ref. | | 550 | 59.6% | 22.7% | 17.6% | Ref. | |
| Female | 623 | 79.0% | 12.4% | 8.7% | **0.61 (0.44-0.86)** | **0.005** | 368 | 59.2% | 23.4% | 17.2% | 0.99 (0.69-1.42 | 0.97 |
| Unknown | 2 | 0 | 100% | 0 | - | - | 2 | 0 | 100% | 0 | - | - |
| **Age group** | | | | | | | | | | | | |
| 0-4 years | 20 | 80.0% | 20.0% | 0% | - | | 39 | 53.8% | 33.3% | 12.8% | 0.88 (0.32-2.39) | 0.80 |
| 5-14 years | 125 | 81.6% | 11.2% | 7.2% | 0.55 (0.27-1.11) | 0.09 | 85 | 67.1% | 17.6% | 15.3% | 0.84 (0.44-1.60) | 0.60 |
| 15-49 years | 1172 | 75.1% | 12.8% | 12.1% | Ref | | 641 | 61.6% | 21.7% | 16.7% | Ref | |
| ≥50 years | 288 | 75.0% | 13.9% | 11.1% | 0.92 (0.61-1.39) | 0.67 | 140 | 50.0% | 28.6% | 21.4% | **1.58 (0.98-2.55)** | **0.06** |
| Unknown | 2 | 0% | 100% | 0% | - | | 15 | 33.3% | 26.7% | 40.0% | **4.43 (1.33-14.80)** | **0.02** |
| **HIV status** | | | | | | | | | | | | |
| Negative | 1245 | 76.9% | 11.9% | 11.2% | Ref. | | 540 | 60.0% | 20.7% | 19.3% | Ref. | |
| Positive | 262 | 71.4% | 14.5% | 14.1% | 1.35 (0.91-2.01) | 0.13 | 137 | 58.4% | 22.6% | 19.0% | 1.01 (0.62-1.66) | 1.01 |
| Unknown | 100 | 70.0% | 24.0% | 6.0% | 0.59 (0.25-1.37) | 0.22 | 243 | 59.3% | 28.0% | 12.8% | 0.67 (0.43-1.05) | 0.08 |

## MORTALITY IN 2007-2008 TB COHORTS WITHIN AREAS OF GHANA

The following table shows the overall all-cause mortality for Ghana by sex and HIV status. There was no mortality difference between male and female patients. Mortality was higher among HIV positive patients compared to HIV negative patients. Because only aggregated and readily analyzed data was available from Ghana, we could not calculate odds ratios for association between the different characteristics and mortality.

**Table G1. Treatment outcome by sex, age, TB type and HIV status, Ghana (N=8915)**

| Characteristic | N | Cured/ completed, % | Died, % | Other, % |
|---|---|---|---|---|
| **Sex** | | | | |
| Female | 2943 | 77.3% | 9.7% | 13.0% |
| Male | 5791 | 75.2% | 10.1% | 14.7% |
| Unknown | 181 | 76.2% | 8.8% | 14.9% |
| **Age**, mean (SD) †‡ | 8832 | 40.4 (17.1) | 45.2 (18.3) | 40.4 (17.3) |
| **Disease classification** (PP vs. PN†‡) (EP vs. PP¶) | | | | |
| Pulm sm+ (PP) | 6138 | 76.9% | 8.7% | 14.4% |
| Pulm sm- (PN) | 2283 | 75.1% | 13.1% | 11.8% |
| EP | 395 | 68.4% | 11.4% | 20.3% |
| Unknown | 99 | 63.6% | 11.1% | 25.3% |
| **HIV status** †# | | | | |
| Positive | 661 | 67.0% | 18.0% | 15.0% |
| Negative | 2118 | 82.2% | 8.0% | 9.8% |
| Unknown | 6136 | 74.7% | 9.8% | 15.5% |

**Legend**: PP, pulmonary smear positive; PN, pulmonary smear negative; EP, extrapulmonary TB. *Other includes: default, transferred, other, unknown.

† $P<0.01$ for difference between those who were treated successfully and those who died.

‡ $P<0.01$ for difference between those who died and those with other outcomes;

¶ $P=0.019$ for difference between those who were treated successfully and those who died.

# $P=0.023$ for difference between those who died and those with other outcome.

**Table G2: Proportion of patients who died within 2 weeks, 1 month and 2 months after start of treatment by sex, TB type and HIV status in Ghana**

| | N | % Died during treatment | | |
|---|---|---|---|---|
| **Time to death** | | **<2 wk** | **<1 mo** | **<2 mo** |
| **Overall** | 621 | 20% | 40% | 59% |
| **Sex** | | | | |
| Male | - | - | - | - |
| Female | - | - | - | - |
| **TB type** | | | | |
| Pulm sm+ | 360 | 18% | 34% | 53% |
| Pulm sm- | 220 | 21% | 48% | 70% |
| EP | - | - | - | - |
| Unknown | - | - | - | - |
| **HIV** | | | | |
| Negative | 138 | 21% | 38% | 56% |
| Positive | 96 | 18% | 42% | 64% |
| Unknown | - | - | - | - |

## MORTALITY IN 2009-2010 TB COHORTS WITHIN TWO AREAS OF KENYA

In Kenya data were collected from four large health areas with two provinces. For this data analysis the districts Nairobi North + Nairobi South were selected to represent "lowest mortality" (3.3%) and Nyanza South + Rift Valley North were selected as the "highest mortality"(12%) districts.

The following table shows the all-cause mortality for the regions Nairobi North & Nairobi South and Nyanza South & Rift Valley North in Kenya. All-cause mortality during TB treatment is 3% in the Nairobi North & Nairobi South regions and 12% in Nyanza South & Rift Valley North. In Nyanza South + Rift Valley North mortality was lower in female patients compared to male patients (OR 0.57; 95% CI 0.43-0.77; P<0.001). Mortality was higher in patients with extrapulmonary TB or TB type unknown compared to pulmonary smear positive patients in both regions. In both regions, 43% of patients with unknown HIV status had an 'other' treatment outcome, suggesting hidden mortality may be high in these subgroups. In Kenya

Data were sampled from the electronic record data base, which had information on 5 provinces.

1. The data were extracted from an Access dbase into 2 excel files National (n=55,668) and Embakasi (n=4,060).
2. 23 variables were not extracted because they were not deemed pertinent to the mortality analysis or would compromise anonymity.
3. Two excel datasets were merged yielding 59,725 cases
4. The 47-variable data set was imported into SPSS 17.0 using the wizard (x=59,725)
5. Categorical variables that could be converted from string variables to numerical variables were converted.
6. A SPSS syntax was developed to further clean the dataset since one province was missing for 2010 and treatment outcomes were absent in 83% of the cases.
7. The years 2009 and 2010 and 4 "provinces" out of five were selected, the rest were discarded.
8. Treatment outcome was missing for approximately 83% of the data set. Those with missing outcomes were compared with those having outcomes in terms of seven factors (year, province, sex, HIV status, Patient type, smear status, ART status). The only statistically significant difference was in the proportion of TB/HIV patients, which was higher in the missing data. Given the absence of broader patterns of missingness, it was decided that the treatment outcome information was likely to be missing at random. This assumption allowed researchers to include the data with treatment outcomes as part of the five country analysis. However, caution should be taken in the interpretation of the Kenyan data, as they are only a small fraction of the total picture, and can be misleading.

**Table K1 Comparison of Excluded vs Included TB patients**

| | TB patients excluded from the analysis | | TB patients included in the analysis | | p-value |
|---|---|---|---|---|---|
| | **n** | **%** | **n** | **%** | |
| New patients | 46614 | 87,0% | 5313 | 86,9% | .723 |
| | | | | | |
| smear positive | 19099 | 35,6% | 2191 | 35,8% | .53 |
| | | | | | |
| Male | 30423 | 56,8% | 3421 | 55,9% | .111 |
| Female | 23185 | 43,2% | 2696 | 44,1% | |
| HIV+ | 21711 | 40,5% | 2291 | 37,5% | **.000** |
| ART | 8525 | 15,9% | 1201 | 19,6% | .5 |

**Table K2. Treatment outcome by region by sex, age, TB type and HIV status, Kenya (N=5245)**

| Region: | Nairobi North + Nairobi South | | | | | | Nyanza South + Rift Valley North | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Total | Cured/ completed | Other | Died | Died vs. cured/completed | | Total | Cured/ completed | Other | Died | Died vs. cured/completed | |
| | N | % | % | % | OR (95%CI) | P-value | N | % | % | % | OR (95%CI) | P-value |
| **Total** | 3287 | 78.9% | 17.8% | 3.3% | | | 1958 | 74.1% | 14.2% | 11.7% | | |
| **Sex** | | | | | | | | | | | | |
| Male | 1867 | 78.9% | 17.7% | 3.4% | Ref. | | 1067 | 71.4% | 14.4% | 14.2% | Ref | |
| Female | 1420 | 79.0% | 17.9% | 3.1% | 0.92 (0.62-1.36) | 0.67 | 891 | 77.3% | 13.9% | 8.8% | **0.57 (0.43-0.77)** | <0.001 |
| **Age group** | | | | | | | | | | | | |
| 0-4 years | 89 | 82.0% | 16.9% | 1.1% | 0.37 (0.05-2.73) | 0.33 | 66 | 78.8% | 12.1% | 9.1% | 0.81 (0.34-1.92) | 0.63 |
| 5-14 years | 195 | 85.6% | 10.8% | 3.6% | 1.15 (0.52-2.52) | 0.74 | 172 | 81.4% | 8.7% | 9.9% | 0.85 (0.50-1.45) | 0.55 |
| 15-49 years | 2689 | 79.2% | 17.9% | 2.9% | Ref | | 1332 | 73.6% | 15.8% | 10.5% | Ref | |
| ≥50 years | 314 | 71.7% | 21.7% | 6.7% | **2.55 (1.54-4.21)** | <0.001 | 338 | 71.6% | 11.3% | 17.0% | **1.66 (1.21-2.29)** | 0.002 |
| **TB type** | | | | | | | | | | | | |
| Pulm sm+ | 1120 | 82.9% | 15.0% | 2.1% | Ref. | | 712 | 76.3% | 13.3% | 10.4% | Ref. | |
| Pulm sm- | 952 | 83.2% | 12.7% | 4.1% | 1.90 (1.13-3.19) | 0.15 | 595 | 80.2% | 8.7% | 11.1% | 1.02 (0.71-1.45) | 0.93 |
| EP | 854 | 80.1% | 16.3% | 3.6% | **1.75 (1.02-3.01)** | 0.04 | 345 | 71.3% | 14.5% | 14.2% | **1.46 (0.99-2.16)** | 0.06 |
| Unknown | 361 | 52.9% | 43.5% | 3.6% | **2.63 (1.13-5.26)** | 0.006 | 306 | 60.5% | 26.5% | 13.1% | **1.59 (1.04-2.41)** | 0.03 |
| **HIV status** | | | | | | | | | | | | |
| Negative | 1543 | 87.2% | 11.3% | 1.5% | Ref. | | 1140 | 81.1% | 10.2% | 8.7% | Ref. | |
| Positive | 1164 | 80.2% | 13.7% | 6.1% | **4.44 (2.76-7.17)** | <0.001 | 613 | 69.5% | 11.9% | 18.6% | **2.50 (1.87-3.35)** | <0.001 |
| Unknown | 580 | 54.3% | 43.4% | 2.2% | 2.42 (1.21-4.82) | 0.12 | 205 | 48.8% | 43.4% | 7.8% | 1.50 (0.85-2.64) | 0.17 |

The Kenyan data are most illustrative of the effect of ART and CPT on mortality. The Kenyan dataset contained the most detailed information regarding ART and CPT use, because ART and CPT use is recorded as 'yes', 'no' or 'unknown'. Patients that did not use ART or CPT had a higher mortality than those who did use ART and/or CPT. The difference in mortality between patients that do or do not use ART or CPT is substantial: 7% vs. 15% for ART use, 10% vs. 19% for CPT use. Mortality was lowest in patients that were both using ART and CPT (7%) and worst for those who did not use CPT (19%) or who did not use CPT nor ART (also 19%).

The following table shows the association between ART and CPT use and the risk of death among Kenyan HIV positive TB patients. Mortality was highest in patients that did not use CPT nor ART (19%) and lowest in patients that used both ART and CPT (7%). The mortality in the subgroup CPT 'Unknown' is probably low (6%) because of overlap with ART use.
The risk of mortality is decreased by the use of ART (OR 0.39; 95% CI 0.28-0.55; P<0.001) and CPT (OR 0.42; 95% CI 0.25-0.89; P=0.001). The combined use of ART and CPT has the largest effect on mortality (OR 0.29; 95% CI0.16-0.52) compared to patients that do not use ART nor CPT.

**Table K3. Risk of Death in HIV+ TB Patients by ART and CPT Status, Kenya (N=1777)**

| | **N** | **% died** | **OR (95%CI)** *(Died vs. Cured/Completed)* | **P-value** |
|---|---|---|---|---|
| **ART** | | | | |
| No | 613 | 15% | Ref. | |
| Yes | 929 | 7% | **0.39 (0.28-0.55)** | **<0.001** |
| Unknown | 235 | 13% | 0.89 (0.57-1.38) | 0.59 |
| **CPT** | | | | |
| No | 115 | 19% | Ref | |
| Yes | 1614 | 10% | **0.42 (0.25-0.70)** | **0.001** |
| Unknown | 48 | 6% | 0.25 (0.07-0.89) | 0.03 |
| **ART-CPT use** | | | | |
| None | 102 | 19% | Ref | |
| Only CPT | 693 | 14% | 0.69 (0.40-1.20) | 0.19 |
| Only ART | 8 | 0% | - | - |
| Both CPT and ART | 921 | 7% | **0.29 (0.16-0.52)** | **<0.001** |
| ART and CPT unknown | 53 | 11% | 0.55 (0.20-1.49) | 0.24 |

## MORTALITY IN 2009-2010 TB COHORTS WITHIN TWO AREAS OF MOZAMBIQUE

Due to extensive cross-border travel, Mozambique shares many features with its nearest neighbor South Africa: high TB prevalence as well as significant levels of drug resistant TB. However unlike its neighbor, Mozambique has a finite and nascent laboratory, managerial, and human resource capacity to deliver the early detection, diagnosis, treatment services, and support that the country's highly-mobile patient population requires.

In Mozambique, Zambezia province was purposefully chosen as the province with lowest mortality (10.1%) whereas Gaza province was selected for its high mortality (20.2%). The provinces have very different underlying epidemiologic drivers of TB as well as distinct TB control challenges.

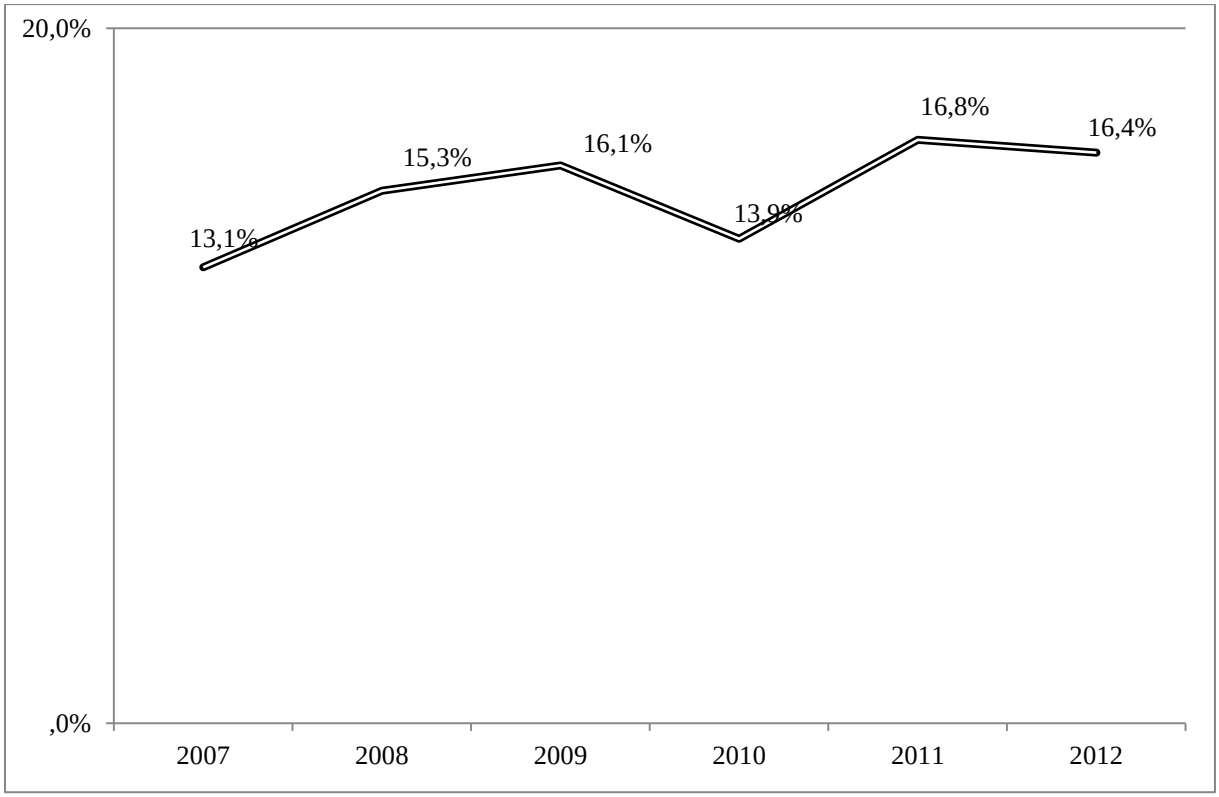
**Table M1 Overview of the abstracted patient-based data (n=2860)**

| **Provinces** | **Districts** | **TB Cases (%)** | **Time periods** |
|---|---|---|---|
| **Gaza** | Chókwe | 1976 (89) | 2009,2010 |
| | Chibuto | 134 (6) | 2009,2010 |
| | Others (10) | 72(3) | 2009,2010 |
| **Zambezia** | Maganja da Costa | 341 (53) | 2010 |
| | Nicolada | 103 (13) | 2010 |
| | Mocuba | 200 (31) | 2010 |
| **Total** | | 2860 (100) | |

In the Chókwe district, Gaza Province, an area with an HIV prevalence of 27% (2007) and high rates of migration, 32.5% of treatment outcome data were missing[8]. This raises the possibility that a significant burden of hidden mortality resides in the groups of TB patients classified as 'out-of-control' (OOC), patients lost to follow up or 'treatment outcome unknown'.

Gaza province is of particular interest because it borders South Africa and has a very dynamic population, with significant cross-border labor migration. TB patient mortality has been high for years, but the reasons for high mortality have been unclear.

**Figure M1: Mortality Patterns in Chókwe 2007-20012**




Chokwé made significant early gains in adding CPT and ART to TB patient care.

**Figure M2: Provision of CPT and ART to HIV+ TB Patients (2006-2012)**

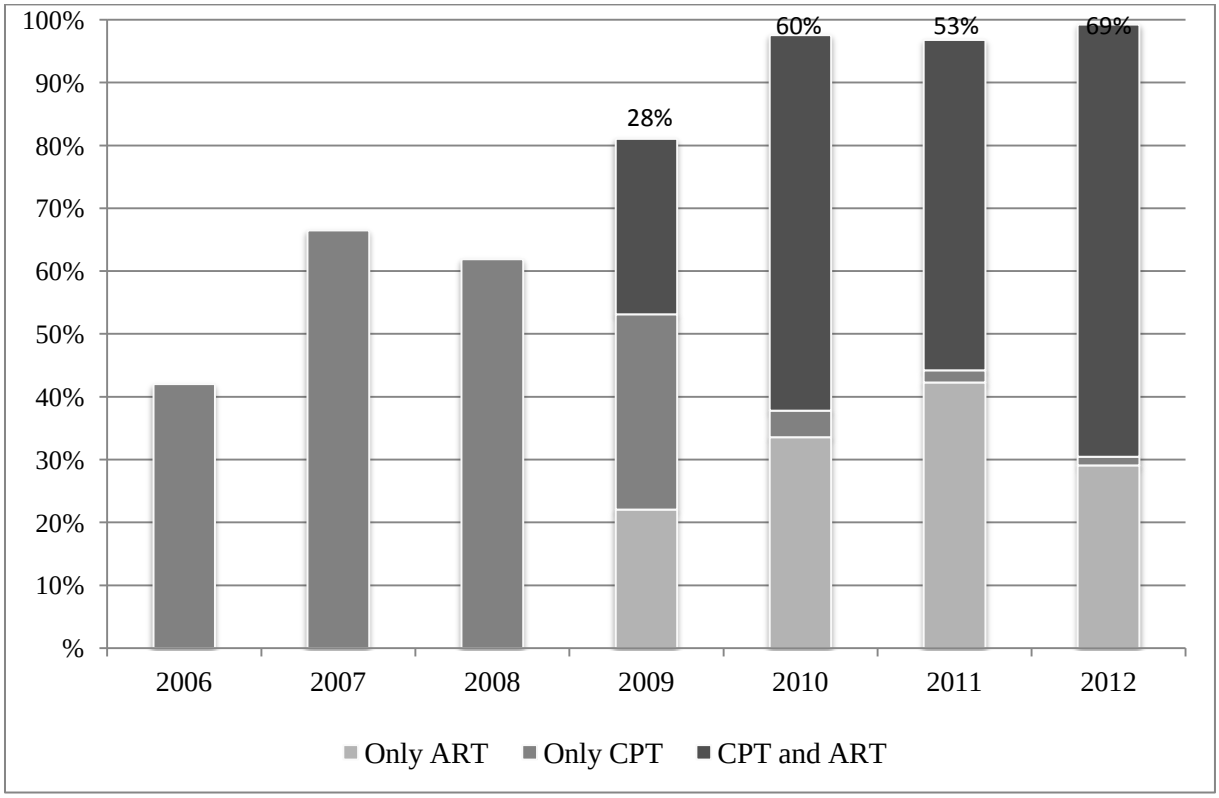


**Table M2 Treatment Outcomes in by Provinces**

| | Gaza | | | Zambezia | | |
|---|---|---|---|---|---|---|
| | n | % | % Excluding missing | n | % | % Excluding missing |
| Cured | 340 | 15.3 | 17.9 | 303 | 47.0 | 47.4 |
| Completed | 680 | 30.7 | 35.9 | 235 | 36.5 | 36.8 |
| Failure | 59 | 2.7 | 3.1 | 6 | .9 | .9 |
| Abandon | 1 | .0 | .1 | 21 | 3.3 | 3.3 |
| Death | 388 | 17.5 | 20.5 | 65 | 10.1 | 10.2 |
| Transfer | 28 | 1.3 | 1.5 | 4 | .6 | .6 |
| Missing | 400 | 18.1 | 21.1 | 5 | .8 | .8 |
| Total | 1896 | 85.6 | 100.0 | 639 | 99.2 | 100.0 |
| Missing | 320 | 14.4 | | 5 | .8 | |
| **Total** | **2216** | **100.0** | | **644** | **100.0** | |

Table M3 shows the treatment outcome by sex, age, TB type and HIV status for Gaza province. Overall mortality in Gaza was 20%, but mortality in subgroups was even higher, such as male patients, pulmonary smear negative, HIV positive and HIV unknown. Almost half of patients with an unknown HIV status had a treatment outcome that could reflect hidden mortality.

**Table M3 Treatment Outcome Data by Serostatus in Two Provinces of Mozambique**

| Province | | | | HIV status | | | Total |
|---|---|---|---|---|---|---|---|
| | | | | negative | positive | unknown | |
| Gaza | | Cured | Count | 94 | 246 | 0 | 340 |
| | | | % | 34.7% | 15.3% | .0% | 17.9% |
| | | Completed | Count | 114 | 563 | 3 | 680 |
| | | | % | 42.1% | 35.0% | 18.8% | 35.9% |
| | | Failed | Count | 14 | 45 | 0 | 59 |
| | | | % | 5.2% | 2.8% | .0% | 3.1% |
| | | Default | Count | 0 | 1 | 0 | 1 |
| | | | % | .0% | .1% | .0% | .1% |
| | | Death | Count | 40 | 343 | 5 | 388 |
| | | | % | 14.8% | 21.3% | 31.3% | 20.5% |
| | | Transfer | Count | 9 | 19 | 0 | 28 |
| | | | % | 3.3% | 1.2% | .0% | 1.5% |
| | | Missing | Count | 0 | 392 | 8 | 400 |
| | | | % | .0% | 24.4% | 50.0% | 21.1% |
| | Total | | Count | 271 | 1609 | 16 | 1896 |
| | | | % | 100.0% | 100.0% | 100.0% | 100.0% |
| Zambezia | | Cured | Count | 140 | 93 | 70 | 303 |
| | | | % | 63.3% | 31.5% | 56.9% | 47.4% |
| | | Completed | Count | 54 | 152 | 29 | 235 |
| | | | % | 24.4% | 51.5% | 23.6% | 36.8% |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | Failed | Count | 1 | 3 | 2 | 6 |
| | | | % | .5% | 1.0% | 1.6% | .9% |
| | | Default | Count | 7 | 6 | 8 | 21 |
| | | | % | 3.2% | 2.0% | 6.5% | 3.3% |
| | | Death | Count | 17 | 36 | 12 | 65 |
| | | | % | 7.7% | 12.2% | 9.8% | 10.2% |
| | | Transfer | Count | 0 | 4 | 0 | 4 |
| | | | % | .0% | 1.4% | .0% | .6% |
| | | Missing | Count | 2 | 1 | 2 | 5 |
| | | | % | .9% | .3% | 1.6% | .8% |
| | Total | | Count | 221 | 295 | 123 | 639 |
| | | | % | 100.0% | 100.0% | 100.0% | 100.0% |

As expected, mortality for HIV+ TB patients (21.3%) is significantly higher than HIV- patients (14.8%) (OR3.2895% CI 2.19-4.91). The group with unknown status had 31.3% mortality, exceeding that of the HIV+ group, suggesting that this "missing data" population may reflect those who are diagnosed when severely ill, who succumb prior to HIV testing. It may also reflect a significant proportion who are HIV+ who are not tested because they already know their positive status.

**Table M3 A Comparison of Treatment Outcomes by HIV+ vs HIV Negative TB Patients**

| Province | | | | HIV status | | HIV+ vs. HIV- Total | |
|---|---|---|---|---|---|---|---|
| | | | | negative | positive | OR (95%CI) | P-value |
| Gaza | | Cured | Count | 94 | 246 | ref | |
| | | | % | 34.7% | 15.3% | | |
| | | Completed | Count | 114 | 563 | 1.89(1.38-2.58) | <0.001 |
| | | | % | 42.1% | 35.0% | | |
| | | Failed | Count | 14 | 45 | 1.23(0.64-2.34) | 0.53 |
| | | | % | 5.2% | 2.8% | | |
| | | Default | Count | 0 | 1 | - | |
| | | | % | .0% | .1% | | |
| | | Death | Count | 40 | 343 | 3.28(2.19-4.91) | <0.001 |
| | | | % | 14.8% | 21.3% | | |
| | | Transfer | Count | 9 | 19 | 0.81(0.35-1.85) | 0.61 |
| | | | % | 3.3% | 1.2% | | |
| | | Missing | Count | 0 | 392 | - | |
| | | | % | .0% | 24.4% | | |
| | Total | | Count | 271 | 1609 | 1.23(1.12-1.35) | <0.001 |
| | | | % | 100.0% | 100.0% | | |
| Zambezia | | Cured | Count | 140 | 93 | ref | |
| | | | % | 63.3% | 31.5% | | |
| | | Completed | Count | 54 | 152 | 0.24(0.16-0.35) | <0.001 |
| | | | % | 24.4% | 51.5% | | |
| | | Failed | Count | 1 | 3 | 0.22(0.02-2.16) | 0.19 |
| | | | % | .5% | 1.0% | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | Default | Count | 7 | 6 | 0.78(0.25-2.38) | 0.66 |
| | | | % | 3.2% | 2.0% | | |
| | | Death | Count | 17 | 36 | 0.31(0.17-0.59) | <0.001 |
| | | | % | 7.7% | 12.2% | | |
| | | Transfer | Count | 0 | 4 | - | |
| | | | % | .0% | 1.4% | | |
| | | Missing | Count | 2 | 1 | 1.33(1.12-14.86) | 0.82 |
| | | | % | .9% | .3% | | |
| | Total | | Count | 221 | 295 | 1.00(0.98-1.02) | 0.93 |
| | | | % | 100.0% | 100.0% | | |

As expected, HIV+ TB patients who received both ART and CPT were more likely to survive than those who only got CPT. This was true even in Gaza Province Chokwé district where mortality was extremely high among all patient groups regardless of treatments provided.

**Figure M3: Timing of Initiation of ART and Treatment Success**

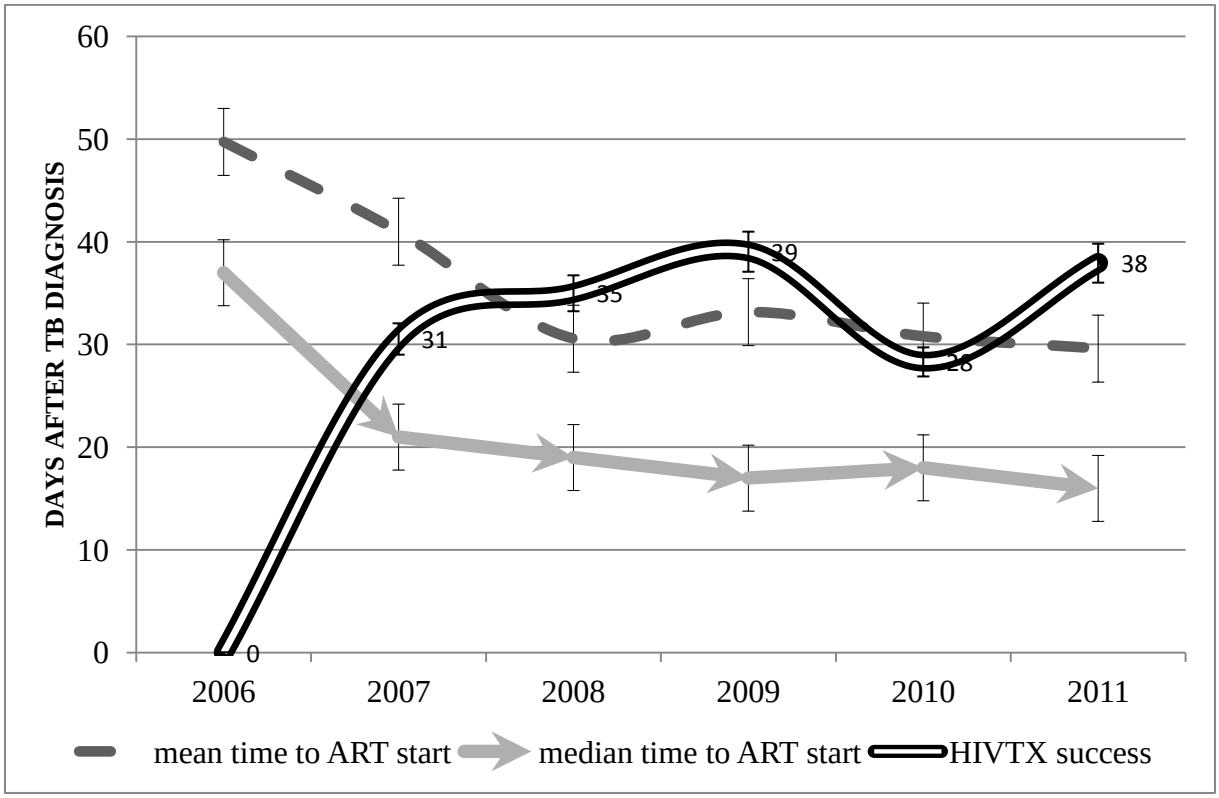


**Table M4. Treatment outcome by sex, age and HIV status, Gaza Province Mozambique ( N=2860)**

| | N | Cured/ completed, % | Other, % | Died, % | Died vs. cured/completed | |
|---|---|---|---|---|---|---|
| | | | | | **OR (95%CI)** | **P-value** |
| **Total** | 2216 | 46.0% | 36.5% | 17.5% | | |
| **Sex** | | | | | | |
| Male | 1254 | 42.0% | 37.6% | 20.4% | Ref. | |
| Female | 960 | 51.3% | 34.9% | 13.8% | **0.55 (0.43-0.70)** | <0.001 |
| **Age group** | | | | | | |
| 0-4 years | 167 | 38.9% | 44.9% | 16.2% | 1.09 (0.68-1.74) | 0.72 |
| 5-14 years | 106 | 57.5% | 39.7% | 2.8% | **0.13 (0.04-0.41)** | 0.001 |
| 15-49 years | 1589 | 46.4% | 35.9% | 17.7% | Ref | |
| ≥50 years | 354 | 44.4% | 33.8% | 21.8% | 1.29 (0.95-1.75) | 0.11 |
| **TB type** | | | | | | |
| Pulm sm+ | 690 | 48.6% | 35.7% | 15.7% | Ref. | |
| Pulm sm- | 855 | 45.0% | 37.7% | 17.3% | 1.24 (0.93-1.66) | 0.15 |
| EP | 471 | 46.9% | 37.2% | 15.9% | 1.09 (0.78-1.54) | 0.61 |
| Unknown | 200 | 39.5% | 30.0% | 30.5% | **2.49 (1.67-3.71)** | <0.001 |
| **HIV status** | | | | | | |
| Negative | 408 | 51.0% | 39.2% | 9.8% | Ref. | |
| Positive | 1792 | 45.1% | 35.8% | 19.1% | **2.20 (1.54-3.16)** | <0.001 |
| Unknown | 16 | - | - | 12.5% | **-** | |

The role of ARVs in protecting HIV+ TB patients from mortality is clearly demonstrated for Gaza, but not for Zambezia. This is probably due to small numbers, lower HIV rates in general and limited provision of CPT and ART of HIV+ TB patients.

**Table M5: Mortality by ART and CPT Status in Two Areas of Mozambique(n=992)**

| Province | | | | Cured/completed | Died | Died vs. cured/completed OR (95%CI) | P-value |
|---|---|---|---|---|---|---|---|
| **Gaza** | | **Only CPT** | n=210 | 124 | 86 | ref | |
| | | | % | 59.0% | 41.0% | | |
| | | **CPT and ART** | n=270 | 198 | 72 | 0.52(0.36-0.77) | 0.001 |
| | | | % | 73.3% | 26.7% | | |
| | | **unknown** | n=488 | 352 | 136 | 0.56(0.39-0.78) | 0.001 |
| | | | % | 72.1% | 27.9% | | |
| | **Total** | | N=968 | 674 | 294 | 0.95(0.92-0.99) | 0.02 |
| | | | % | 69.6% | 30.4% | | |
| **Zambezia** | | **Only CPT** | n=205 | 174 | 31 | ref | |
| | | | % | 84.9% | 15.1% | | |
| | | **CPT and ART** | n=68 | 63 | 5 | 0.45(0.17-1.19) | 0.11 |
| | | | % | 92.6% | 7.4% | | |
| | | **unknown** | n=325 | 296 | 29 | 0.55(0.32-0.94) | 0.03 |
| | | | % | 91.1% | 8.9% | | |
| | **Total** | | N=598 | 533 | 65 | 0.94(0.87-1.00) | 0.06 |
| | | | % | 89.1% | 10.9% | | |
| **Total** | | **Only CPT** | n=415 | 298 | 117 | ref | |
| | | | % | 71.8% | 28.2% | | |
| | | **CPT and ART** | n=338 | 261 | 77 | 0.75(0.54-1.05) | 0.09 |
| | | | % | 77.2% | 22.8% | | |
| | | **unknown** | n=813 | 648 | 165 | 0.65(0.49-0.85) | 0.002 |
| | | | % | 79.7% | 20.3% | | |
| | **Total** | | N=1566 | 1207 | 359 | 0.95(0.92-0.99) | 0.004 |
| | | | % | 77.1% | 22.9% | | |

In Gaza, high mortality occurs among all age groups, but is more common among the youngest and oldest TB patients, whereas in Zambezia it reflects more traditional age distributions.

**Table M6: Mortality by Age and Province**

| Age | | High mortality setting N=388 | Low mortality setting N=65 |
|---|---|---|---|
| < 5 | N | 26 | 1 |
| | % | 23.0% | 11.1% |
| 5-14 | N | 4 | 2 |
| | % | 4.7% | 8.7% |
| 15-50 | N | 281 | 56 |
| | % | 20.1% | 10.6% |
| >55 | N | 77 | 6 |
| | % | 25.8% | 7.5% |

| | | | |
|---|---|---|---|
| Total | N | 388 | 65 |
| | % | 20.5% | 3.3% |

As shown in Table M7 a strikingly high proportion of TB patients succumb within the first two weeks of care, suggesting that patients are diagnosed very late in their disease. Improvements in quality of TB treatment within the facility is unlikely to benefit these patients very much.

**Table M7: Proportion of TB patient deaths that occur within 2 weeks of diagnosis by Area, Socio-demographic, and clinical characteristics**

| | | | Died =< 2 weeks | |
|---|---|---|---|---|
| | | | N | Row N % |
| Gaza | Sex | Male | 96 | 38.2 |
| | | Female | 50 | 39.4 |
| | TB type PP PN EP | Pulm smear+ | 35 | 35.0 |
| | | Pulm smear- | 56 | 38.9 |
| | | EP | 30 | 40.5 |
| | | Unknown | 25 | 41.7 |
| | HIV_status_2 | Negative | 12 | 30.0 |
| | | Positive | 132 | 39.5 |
| | | Unknown | 2 | 50.0 |
| | Age groups | 0-4 years | 8 | 30.8 |
| | | 5-14 years | 2 | 50.0 |
| | | 15-49 years | 108 | 39.4 |
| | | ≥50 years | 28 | 37.8 |
| Zambezia | Sex | Male | 0 | .0 |
| | | Female | 1 | 14.3 |
| | TB type PP PN EP | Pulm smear+ | 0 | .0 |
| | | Pulm smear- | 1 | 8.3 |
| | | EP | 0 | .0 |
| | | Unknown | 0 | .0 |
| | HIV_status_2 | Negative | 1 | 20.0 |
| | | Positive | 0 | .0 |
| | | Unknown | 0 | .0 |
| | Age groups | 0-4 years | 0 | .0 |
| | | 5-14 years | 0 | .0 |
| | | 15-49 years | 1 | 5.6 |
| | | ≥50 years | 0 | .0 |

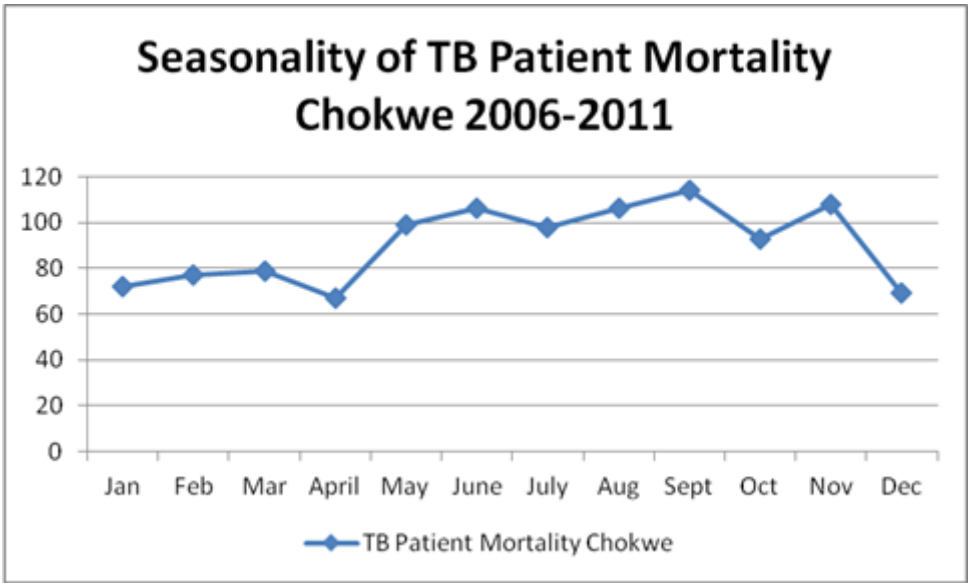
**Table M8:Mean and Median Time to Death in Two Areas of Mozambique**

| | | | time_to_death | | |
|---|---|---|---|---|---|
| | | | Valid N | Mean | Median |
| GAZA | Age groups | 0-4 years | 26 | 939.04 | 23.00 |
| | | 5-14 years | 4 | 40.75 | 33.00 |
| | | 15-49 years | 274 | 41.14 | 24.00 |

| | | | | | |
|---|---|---|---|---|---|
| | | ≥50 years | 74 | 41.69 | 22.50 |
| | Sex | Male | 251 | 135.51 | 24.00 |
| | | Female | 127 | 38.76 | 23.00 |
| | HIV_status_2 | Negative | 40 | 633.92 | 27.50 |
| | | Positive | 334 | 40.44 | 23.00 |
| | | Unknown | 4 | 18.25 | 13.50 |
| | TB type PP PN EP | Pulm smear+ | 100 | 44.58 | 27.50 |
| | | Pulm smear- | 144 | 202.94 | 23.50 |
| | | EP | 74 | 41.00 | 18.50 |
| | | Unknown | 60 | 37.02 | 23.50 |
| Zambezia | Age groups | 0-4 years | 1 | 24.00 | 24.00 |
| | | 5-14 years | 0 | . | . |
| | | 15-49 years | 18 | 136.72 | 98.00 |
| | | ≥50 years | 2 | 36.00 | 36.00 |
| | Sex | Male | 14 | 121.71 | 89.00 |
| | | Female | 7 | 121.86 | 95.00 |
| | HIV_status_2 | Negative | 5 | 110.60 | 43.00 |
| | | Positive | 15 | 127.27 | 101.00 |
| | | Unknown | 1 | 95.00 | 95.00 |
| | TB type PP PN EP | Pulm smear+ | 6 | 112.67 | 64.50 |
| | | Pulm smear- | 12 | 113.17 | 95.50 |
| | | EP | 2 | 75.50 | 75.50 |
| | | Unknown | 1 | 372.00 | 372.00 |

There appears to be some mortality patterns that may be seasonal, but the pattern is counter intuitive. Normally we would expect to see higher death in the December –April period due to malaria transmission during the rainy season, but the mortality is the opposite.

**Figure M1: Seasonality of TB Patient Mortality in Chokwé 2006-2011**



## MORTALITY IN 2009-2010 TB COHORTS WITHIN TWO AREAS OF ZAMBIA

Zambia has one of the highest incidence rates of TB per capita in the world. The sputum-smear positive (SS+) case notification rate in Zambia is 193 cases per 100,000 population, It also has the 10th highest TB incidence rate in the world. Zambia has achieved 100 percent DOTS coverage and about 74 percent case detection for all forms of TB. The treatment success rate has also continued to rise since 2003 and is at the World Health Organization (WHO) target of 85 percent. Unfortunately, the TB-HIV/AIDS co-infection rate is high in the country, and HIV is a major contributor to increasing numbers of TB cases. Seventy percent of all new TB patients in Zambia are co-infected with HIV, and Zambia has the seventh highest rate for prevalence of co-infection rate in the world

In 2009, the national TB program in Zambia reported a total of 3,709 TB deaths representing 8% of all TB cases. Data were collected from two provinces; Lusaka and Eastern, the provinces were selected because they represent a higher TB and HIV mortality (Lusaka) and a low TB mortality (Eastern). Data was derived from Lusaka district and Chipata and Chadiza districts in Eastern province. Data were collected 2009 TB cohort in 6 health facilities, 2 in Lusaka and 4 in Eastern province. A total of 4961 TB cases were assessed for this study.

Table Z1 shows the treatment outcome by sex, age, TB type and HIV status for the two Zambian provinces. Curiously, the extracted data did not match the mortality figures used to select the provinces. In fact, the "low" and "high" provinces were actually reversed. Mortality was 6% in the Eastern Province and 4.3% in Lusaka. There were no major differences in mortality between any of the subgroups. The proportion 'other' treatment outcome was higher in pulmonary smear negative patients compared to pulmonary smear positive TB patients. In the Eastern province, about a third of HIV positive patients and almost half of HIV unknown patients had a 'other' treatment outcome, suggesting that mortality may be higher than indicated in these subgroups.

**Table Z1. Treatment outcome by sex, age and HIV status, by province, Zambia (N=4941)**

| **Region:** | **Lusaka Province** | | | | | | **Eastern Province** | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Total** | **Cured/ completed** | **Other** | **Died** | **Died vs. cured/completed** | | **Total** | **Cured/ completed** | **Other** | **Died** | **Died vs. cured/completed** | |
| | **N** | **%** | **%** | **%** | **OR (95%CI)** | **P-value** | **N** | **%** | **%** | **%** | **OR (95%CI)** | **P-value** |
| **Total** | 4182 | 90.0% | 5.7% | 4.3% | | | 759 | 67.5% | 27.0% | 5.5% | | |
| **Sex** | | | | | | | | | | | | |
| Male | 2505 | 89.2% | 6.4% | 4.4% | Ref. | | 438 | 67.4% | 26.7% | 5.9% | Ref. | |
| Female | 1677 | 91.1% | 4.8% | 4.1% | 0.92 (0.67-1.25) | 0.58 | 321 | 67.6% | 27.4% | 5.0% | 0.84 (0.44-1.60) | 0.59 |
| **Age group** | | | | | | | | | | | | |
| 0-4 years | 229 | 86.9% | 9.2% | 3.9% | 0.99 (0.50-1.97) | 0.97 | 41 | 53.7% | 39.0% | 7.3% | 2.00 (0.56-7.12) | 0.28 |
| 5-14 years | 209 | 96.2% | 0.5% | 3.3% | 0.76 (0.35-1.65) | 0.49 | 39 | 61.5% | 30.8% | 7.7% | 1.84 (0.52-6.49) | 0.34 |
| 15-49 years | 3399 | 90.5% | 5.4% | 4.1% | Ref | | 563 | 70.5% | 24.7% | 4.8% | Ref | |
| ≥50 years | 334 | 83.1% | 10.5% | 6.4% | **1.68 (1.05-2.67)** | **0.03** | 115 | 59.1% | 33.0% | 7.8% | 1.95 (0.88-4.32) | 0.10 |
| **TB type** | | | | | | | | | | | | |
| Pulm sm+ | 1127 | 87.2% | 7.8% | 5.0% | Ref. | | 494 | 72.3% | 23.3% | 4.5% | Ref. | |
| Pulm sm- | 2613 | 91.0% | 4.9% | 4.1% | 0.80 (0.57-1.11) | 0.18 | 101 | 56.4% | 37.6% | 5.9% | 1.71 (0.66-4.40) | 0.27 |
| EP | 442 | 91.0% | 5.7% | 3.4% | 0.66 (0.37-1.17) | 0.15 | 164 | 59.8% | 31.7% | 8.5% | 2.32 (1.14-4.70) | 0.20 |
| **HIV status** | | | | | | | | | | | | |
| Negative | 1212 | 90.6% | 4.5% | 4.9% | Ref. | | 298 | 72.1% | 21.1% | 6.7% | Ref. | |
| Positive | 2593 | 89.7% | 6.2% | 4.1% | 0.86 (0.62-1.19) | 0.35 | 380 | 68.7% | 26.8% | 4.5% | 0.70 (0.36-1.37) | 0.30 |
| Unknown | 377 | 89.9% | 6.6% | 3.4% | 0.71 (0.39-1.32) | 0.28 | 81 | 44.4% | 49.4% | 6.2% | 1.49 (0.53-4.23) | 0.45 |

# 7. DISCUSSION

These two surveys provide important insights into the operational challenges and the limited inferences that can be made from current M&E data on TB patient mortality.

### ATTITUDES TOWARD MORTALITY DATA

TB M&E officers are keen to have valid TB/HIV mortality data but are at a loss as to how to stimulate their collection within the current framework.

### UTILIZATION OF MORTALITY DATA

Few TB programs are making full use of mortality data to drive programmatic improvements because key variables are missing, data are incomplete, and/or disaggregation and analysis of surveillance data has yet to become routine.

### ACCESSIBILITY OF MORTALITY DATA

Paper-based data are theoretically accessible in many settings, but digitizing them represents a hassle for many M&E Officers. As electronic patient-based records become more available, the ability to appreciate both the data quality challenges as well as the mortality challenges will improve. However the problem is not simply technological. There is a historical distrust and lack of data sharing among TB and HIV programs that must be overcome.

### QUALITY OF MORTALITY DATA

There was a marked difference in data quality between the countries and between the different regions within countries. The proportion of missing values was high for some key parameters, especially HIV status and treatment outcome.

However, there may also have been a significant proportion of hidden mortality in the groups of patients classified as 'out-of-control' (OOC) or 'treatment outcome unknown'. The proportion of patients with an "unknown" treatment outcome was much higher amongst those with an unknown HIV status, suggesting that these patients may die before a full work up is possible. Improvement of reporting and recording of TB registry data is therefore essential and highly recommended.

Loss of patients to follow-up and care is an important problem for TB/HIV treatment programs. As mortality is higher in these patients compared to patients remaining in care, TB/HIV programs with high rates of loss to follow-up may substantially underestimate mortality of all patients starting ART. This is particularly true in areas of high migration – such as Southern Mozambique where the male and female population participate in labor migration to the South African mines and urban areas or in countries where there is a large population of internally displaced populations (IDPs) such as Western Kenya in 2008-9 .

Presenting national TB mortality data by HIV status would be of additional value, because it allows a country to evaluate its TB and HIV activities and monitor outcome in these subgroups of TB patients.

### LEVELS OF MORTALITY WITHIN COUNTRIES

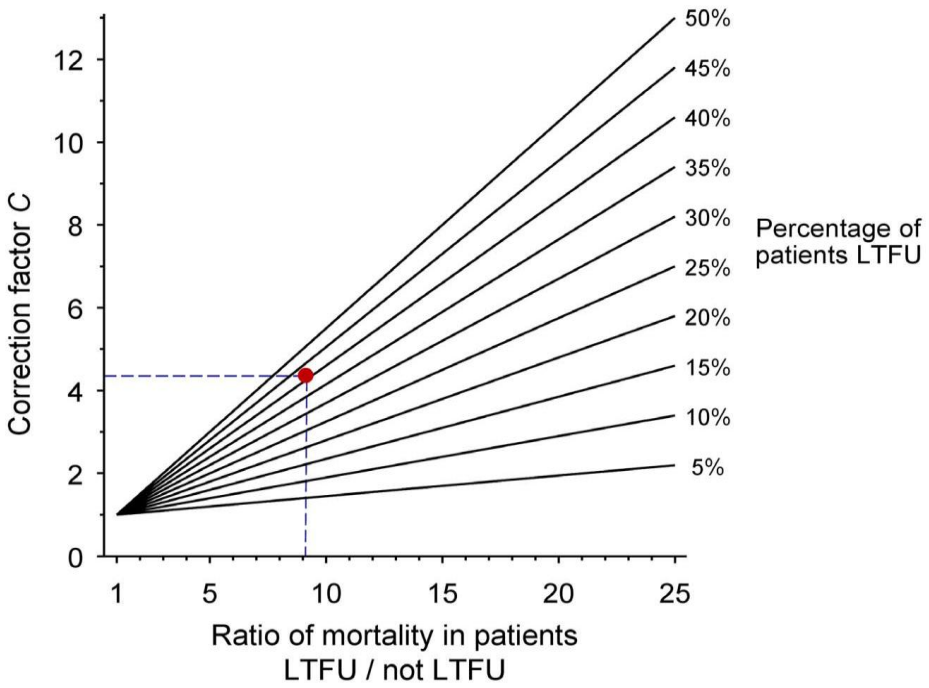
Notified all-cause mortality among treatment cohorts in the five countries ranged from 3% in Nairobi to 21% in Gaza province in Mozambique. Deaths in areas of high mortality often occurred very early in the course of treatment and suggest delays to diagnosis more than inadequate care. Mortality hot spots with early deaths among TB patients should consider introducing strategies to stimulate earlier diagnosis such as active case finding. In settings within Ethiopia, Kenya, and Mozambique, male TB patients appeared to be at higher risk for death, suggesting the need for more gender-sensitive approaches.

### RECOMMENDATIONS FOR IMPROVING M&E OF MORTALITY AMONG TB PATIENTS

- *Present TB mortality by HIV status.*
  Countries should present all-cause mortality during TB treatment by HIV status All-cause mortality differed between HIV positive and HIV negative TB patients. Presenting mortality by HIV status is of additional value, because it would allow a country to evaluate its TB and HIV activities and monitor outcome in these subgroups of TB patients.

- *Improve reporting and recording, especially of treatment outcome.*
  Treatment outcome, date of outcome, and HIV status were missing in a high proportion of patients: up to 10% for treatment outcome and up to 18% for HIV status. We expect hidden mortality in patients with "unknown treatment outcome" and in patients classified as "OOC"( out of control). It is therefore important to improve reporting and recording, especially of HIV status and treatment outcome, in order to make valid estimation of mortality during TB treatment. For example, the treatment outcome should be checked regularly to confirm that the currently recorded outcome is still up-to-date.

- *Launch a global effort to conduct Loss to Follow UPer Tracing studies to derive a mortality correction factor*
  To help M&E officers to properly interpret the treatment outcome data that they routinely collect, researchers should develop a correction factor (i.e. nomogram) for "loss to follow up" and "transferred out", similar to that developed for ART programs [16]
  An example of how this was done for ART programs is outlined here http://www.iedea-sa.org/




- *Integrate National TB and HIV programs.*
  National TB and HIV programs should be integrated more. Information about a TB-HIV co-infected patient that is missing in the TB registry might be available in the HIV registration, and vice versa, especially information on TB treatment outcome, i.e. mortality.

- *Assess and address double counting of TB patients in vertical TB and HIV programs*
  TB and HIV programs should consider the use of a unified unique identifier that combines patient and facility characteristics such as a 17 digit alphanumeric code

  *Facility code(3 digits)+ BMU code(3 digits)+date of birth(8 digits)+3 letters of last name*

  In the interim, M&E need training to combine TB & HIV name-based data and remove duplicates
  Microsoft SQL "Fuzzy Logic" and "Fuzzy Look-up" database matching programs can match patients despite spelling or phonetic differences that are very common in treatment registers.
- *Conduct death audits in districts with high rates of mortality.*
  Exploration and analysis of root causes of death among TB patients can lead to a clearer and specific understanding of why the deaths happened and where interventions are likely to make a difference in patient survival. The Death audit tools are available from : http://www.tbcare1.org/publications/toolbox/

- *To identify issues requiring intervention, routinely disaggregate mortality by .*
  - Date of death-important to distinguish poor access from poor quality of care
  - HIV status-to monitor the impact of TB/HIV interventions
  - Age
  - Gender
  - Location-Regions/Provinces/State/districts

- Develop better tools to rigorously monitor diagnostic delay. With the GeneXpert platform and other new diagnostics, we can reduce diagnostic delay and reduce delay in effective treatment of RR-TB

### OTHER RECOMMENDATIONS

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### LIMITATIONS

The TB registry data that were used for this assessment were intentionally collected from regions or provinces with atypical characteristics and are not intended to be representative for the country.

There were significant missing data for key variables, such as treatment outcome and HIV status. In some settings, data were single entered due to budget constraints. A data quality audit of key variables identified a keystroke error rate as high as 11.7% for some variables. This is a reminder that single-entry performs poorly for these exercises.

Finally, crude analysis of register data that does not account for the underlying mortality patterns in the population can often yield misleading information and policy recommendations.[40] For example, it may appear that elderly and/or male TB patients are underserved by TB programs when in fact it is simply that these groups have higher all-cause mortality in many settings.

## 8. CONCLUSION

These data offer a window into the data quality issues inherent in countries with large TB and HIV burdens. Both qualitative and quantitative findings offer complementary perspectives on the challenges of capturing and using TB/HIV data to influence the mortality trend.

We assessed the added-value of collecting and analyzing mortality and mortality data to discern if they can be better utilized as a monitoring and evaluation indicator of program performance. We found that in most cases, the current quality of the crude treatment outcome data is too poor to reliably reflect the actual mortality in the cohort—deaths are widely misclassified as Loss to Follow Ups and under counted. The quality of recording and reporting needs improvement before mortality can be a valid reflection of performance. A recent study by Hermans et al (2012) echoes this concern, showing that in a Ugandan hospital where TB/HIV care was fully integrated and improved, corresponding improvements in reporting and reporting systems gave the false impression that TB mortality had risen[20].

In the interim, to track progress in this arena, programs could consider the use of a nomogram/correction factor to adjust crude mortality rates in ways that take into account the probability of death among those who are lost to follow-up[28, 41].

We found that although TB and TB/HIV mortality is considered important by M&E Officers and there is widespread acknowledgement of its utility, the practical hurdles in collecting good data have not received enough attention in many NTPs and by global TB policy makers. There is a need to improve TB mortality data collection and analysis. This can be done both routinely and through special evaluation and extrapolation. Analysis of TB mortality in surveillance data should be planned as part of regular M&E through NTP and projects budget.

# 9. APPENDICES

## APPENDIX 1 GLOSSARY OF ACRONYMS AND TERMS

| | |
|---|---|
| AIDS | acquired immunodeficiency syndrome |
| ART | antiretroviral therapy |
| ARVs | Antiretrovirals |
| CBO | community-based organization |
| CFR | Case fatality rate |
| CPT | cotrimoxazole preventive therapy |
| DLTLD | Division of Leprosy, Tuberculosis and Lung Disease |
| DOTS | the internationally recommended strategy for TB control |
| HIV | human immunodeficiency virus |
| IEC | information, education and communication |
| IDP | internally displaced populations |
| IPT | isoniazid preventive therapy |
| M&E | monitoring and evaluation |
| MDG | Millennium Development Goal |
| NACP | national AIDS control programme |
| NGO | nongovernmental organization |
| NTP | national tuberculosis programme |
| OI | Opportunistic Infections |
| OOC | 'out of control' |
| PDA | Personal Data Assistants |
| PLWHA | people living with HIV/AIDS |
| PMTCT | prevention of mother-to-child transmission of HIV |
| QOC | Quality of Care |
| TB | tuberculosis |
| TB/HIV | the intersecting epidemics of TB and HIV |
| TBPT | tuberculosis preventive therapy |
| UNAIDS | Joint United Nations Programme on HIV/AIDS |
| VCT | voluntary counselling and testing (for HIV) |
| WHO | World Health Organization |

# APPENDIX 2: SURVEY INSTRUMENT

Questionnaire for NTP M&E Officers

MISSING DATA ==99

| | |
|---|---|
| Country | |
| Name | |
| Position | |
| Contact telephone | |
| E-mail | |
| Date | |

KNCV Tuberculosis Foundation in coalition with MSH is implementing TB CARE I Core project "Assessment TB/HIV Mortality data". Objectives of the Project are: To assess the availability and quality of recording and reporting of mortality in TB HIV co-infected patients by National Tuberculosis Programs (NTP) in 5 TBCARE I countries; To assess the usage of mortality data by National Tuberculosis Programs in 16 TBCARE I countries; To develop a strategy to improve current M&E systems on TB-HIV mortality indicators in TBCARE I countries.

In order to achieve our objectives, we need your support; we kindly ask you to read the questionnaire with patience and compile the information at your convenience. These data will be aggregated with the responses of 20 other countries and presented as regional estimates, so confidentiality can be maintained.

Please fill in this table using the information in the NTP surveillance system. In some cases, the data may not be available. Please indicate where data are not available. **PLEASE TYPE OR WRITE LEGIBLY**

| | | **2008** | **2009** | **2010** |
|---|---|---|---|---|
| | What was the number of smear positive TB cases notified in the following years? | | | |
| | What was the total number of all forms of TB patients notified in the following years? | | | |
| | What was the number of smear positive TB/HIV+ cases notified in the following years? | | | |
| | What was the number of deaths in the annual cohort? | | | |
| | How many of the deaths in the cohort were HIV+ TB patients? | | _____ | _____ |
| | Do you calculate TB mortality rates by district? | 0=No 1= Yes<br>77I don't know | 0=No 1= Yes<br>77I don't know | 0=No 1= Yes<br>77I don't know |
| | What was the ***highest*** mortality rate in the country reported by geographical area ***or*** district? | %:___ | %:___ | %:___ |
| 7b | The name of the area with the **highest** mortality rate | | | |
| | What was the ***lowest*** mortality rate in the country reported by geographical area or district? | %:___ | %:___ | %:___ |
| 8b | The name of the area with the **lowest** mortality rate | | | |

| | | |
|---|---|---|
| | What are some of the challenges you face in collecting TB treatment outcome data? *(tick all that apply)* | ☐Missing values = 1<br>☐Delays in receiving information from districts = 2<br>☐Difficulty in receiving information from partner organizations = 3<br>☐Misclassification of treatment outcomes = 4<br>☐High proportions of "loss to follow-up" that are unknown =5<br>☐High proportions of patients that "transfer out" with status unknown =6<br>☐High proportions of patients lost to follow up with status unknown =7<br>☐Other (specify) q9open:_____<br>☐Other (specify): q9open2_____<br>☐I don't know =77 |
| | What specific TB mortality information was collected in 2008 by the TB program? | |

| | | |
|---|---|---|
| | Date of death? | No= 0 Yes= 1 I don't know=77 |
| | Underlying cause of death? | ☐ |
| | Direct cause of death? | ☐ |
| | Place of death? | ☐ |
| | What is the source of data of TB and TB/HIV death? | Please, indicate: |
| | Are all deaths of TB patients on treatment assumed to be caused by TB? | ☐ No ☐ Yes ☐ I don't know<br>No= 0 Yes= 1 I don't know=77<br>Comment: |
| | If you answered "yes" to either Q. 11 or Q.12, do you have concerns about the accuracy of the cause of death information that you receive? | ☐ No ☐ Yes ☐ Not applicable – 88 we do not collect it<br>No= 0 Yes= 1 |
| | How do you feel about the completeness of the TB mortality information that you currently receive? ***(please tick one answer)*** | ☐Confident of the completeness =1<br>☐Somewhat skeptical of the completeness=2<br>☐Very doubtful of the completeness=3<br>☐Other (specify):44_____<br>Comment: (EXPLAINQ17) |
| | What kind of data does your TB program receive from HIV/AIDS services? ***(tick all that apply)*** | ☐ TB tests performed on HIV+ clients=1<br>☐ TB cases diagnosed among HIV+ clients=2<br>☐ TB treatment outcomes (including mortality) of HIV+ clients=3<br>☐ Causes of death among HIV+ clients=4<br>☐ It varies by HIV program and coordinating partner=5<br>☐ I don't know exactly= 77 |
| | How is the level of data sharing between the two programs (TB and HIV/AIDS) in your country? ***(please tick one answer)*** | ☐Excellent =1<br>☐Good =2<br>☐Fair =3<br>☐Poor =4<br>☐I don't know=77<br>☐I choose not to answer= 88<br>Comment: (EXPLAIN Q19) |
| | If an HIV+ person dies from TB, will that death be registered as a death due to HIV/AIDS or TB? ***(please tick one answer)*** | ☐HIV death =1<br>☐TB death =2<br>☐TB/HIV death (i.e. both)=3<br>☐I don't know=77 |
| | Have you ever been asked to try to disaggregate TB treatment outcomes by HIV status? | ☐ No ☐ Yes ☐ I don't know No= 0 Yes= 1 I don't know=77 |
| | If yes, in what context was this request made (i.e. what was the purpose of looking at treatment outcomes by HIV status)? | Comment: |
| | If you worked on disaggregating the data, what challenges (if any) have you encountered? ***(tick all that apply)*** | ☐No challenges encountered =1<br>☐Missing HIV status information on patients =2<br>☐Missing treatment outcome information =3<br>☐Other =4 |
| | Have you been asked to disaggregate mortality data by HIV status?<br>**If no, skip to Q.26** | ☐ No ☐ Yes ☐ I don't know No= 0 Yes= 1 I don't know=77 |
| | If yes, how were you able to do it? | ☐We have patient-based records =1 |

| | | |
|---|---|---|
| | | ☐We made estimates=2<br>☐We entered the TB register data as part of a special study=3<br>☐We queried at the district level=4<br>☐Other (explainQ25):_____ |
| | Do hospitals report TB/HIV mortality to the TB program? **If no, skip to Q.28** | ☐ No ☐ Yes ☐ I don't know No= 0 Yes= 1 I don't know=77 |
| | If yes, do they also report causes of death? | ☐ No ☐ Yes ☐ I don't know No= 0 Yes= 1 I don't know=77 |
| | How important is high quality data on TB deaths to your TB program? | ☐Very important – worth extra efforts to collect=1<br>☐Somewhat important – some additional effort is justified=2<br>☐Not very important – extra collection efforts are not justifiable at this time=3<br>☐I don't know=77 |
| | What strategies would help to improve the collection of information on TB/HIV mortality? ***(tick all that apply)*** | ☐Greater collaboration between TB and HIV programs=1<br>☐Transition to patient-based TB record keeping=2<br>☐Routine surveillance of morgues, hospice, religious institutions=3<br>☐A national vital registration system for deaths=4<br>☐Other =5(specify):_(EXPLAIN q29)_____<br>☐I don't know=77 |
| | From what institutions do you receive TB treatment outcome data? ***(tick all that apply)*** | ☐Non-governmental organizations (NGOs)=1<br>☐Faith-based organizations (FBOs)=2<br>☐Community based organizations (CBOs)=3<br>☐Palliative care/hospice/end of life case centers=4<br>☐Mission Hospitals=5<br>☐Private hospitals=6<br>☐Government health facilities=7 |
| | Do private sector facilities report TB mortality to the TB program? **If no, skip to Q.33** | ☐ No ☐ Yes ☐ Some do, some do not No= 0 Yes= 1 some do, some don't= 33, I don't know=77<br><br>☐ I don't know<br>Comments: |
| | In your estimation, how complete is the mortality information you receive from the private sector? | ☐ very complete= 1 ☐ varying completeness= 2<br>☐ I don't know= 77<br>Comments: |
| | Do religious institutions (e.g. temples, churches, mosques, etc.) maintain own records of number of deaths? | ☐ No ☐ Yes, they all do ☐ some do, some do not<br>No= 0 Yes= 1 some do, some don't= 33, I don't know=77<br>☐ I don't know<br>Comments: |
| | Do religious institutions (e.g. temples, churches, mosques, etc.) maintain records on *causes of death* as well? | ☐ No ☐ Yes, they all do ☐ some do, some do not<br>No= 0 Yes= 1 some do, some don't= 33, I don't know=77<br>☐ I don't know |

| | | |
|---|---|---|
| | | Comments: |
| | What other data sources are available in your country that could be used to monitor TB-HIV mortality indicators *(tick all that apply)* | ☐Vital registration system (national statistical institute)=1<br>☐Sentinel sites (research cohorts)=2<br>☐Demographic surveillance sites=3<br>☐Social security – insurance system=4<br>☐Pension system=5<br>☐I don't know=77 |
| | What (if any) special TB/HIV mortality studies have been conducted in your country? | **Names of investigators: _36A_____ date: __36B___**<br>**Title (if known): _____36C_____** |
| | Does your country have a National Health Information Management System (HMIS)? *( If No, skip to Q.39)* | ☐ No ☐ Yes ☐ I don't know No= 0 Yes= 1 I don't know=77 |
| | Are TB mortality statistics included as part of a national Health Information Management System (HMIS)? | ☐ No ☐ Yes ☐ I don't know No= 0 Yes= 1 I don't know=77 |
| | Does your TB program collect any patient-based data?<br>***If no, the survey ends here. If yes, please complete the next section.*** | ☐ No ☐ Yes ☐ I don't know No= 0 Yes= 1 I don't know=77 |

**PLEASE COMPLETE THIS SECTION for 2010 *ONLY IF YOUR PROGRAM COLLECTS AND ANALYZES INDIVIDUAL PATIENT-BASED TB RECORDS (i.e. NOT AGGREGATED BY DISTRICT)***

| | |
|---|---|
| 40 Is TB patient mortality disaggregated by HIV status? | ☐ No ☐ Yes ☐ I don't know No= 0 Yes= 1 I don't know=77 |
| # of deaths of HIV+ TB patients | |
| # of deaths of HIV negative TB patients | |
| 41 Is TB patient mortality information disaggregated by time of death and phase of treatment? | ☐ No ☐ Yes ☐ I don't know No= 0 Yes= 1 I don't know=77 |
| # of deaths in intensive phase | |
| # of death in continuation phase | |
| # of deaths in follow-up phase | |
| 42 Are TB mortality data disaggregated by age? | ☐ No ☐ Yes ☐ I don't know No= 0 Yes= 1 I don't know=77 |
| # of deaths 0-4 | |
| # of deaths 0-14 | |
| # of deaths 15-24 | |
| # of deaths 25-34 | |
| # of deaths 35-44 | |
| # of deaths 45-54 | |
| # of deaths 55-64 | |
| # of deaths over 65 | |
| 43 Are TB mortality data disaggregated by sex? | ☐ No ☐ Yes ☐ I don't know No= 0 Yes= 1 I don't know=77 |
| # of deceased males | |
| # of deceased females | |
| | |
| 44 Are TB mortality data disaggregated by place of death? | ☐ No ☐ Yes ☐ I don't know No= 0 Yes= 1 I don't know=77 |

| | |
|---|---|
| Death in hospital? | |
| Death in hospice? | |
| Death in communities (home)? | |

Thank you very much for your cooperation. We will analyze the information you provided confidentially and keep you informed regarding further developments.

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