Improving tuberculosis mortality estimates

An evaluation of data sources, strategies and new diagnostics in a high tuberculosis and HIV burden setting

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CHAPTER 1

Background
Despite being one of the most ancient diseases affecting humans,[1] tuberculosis (TB) remains as one of the 21st century's the major global health concerns.[2] The existence of effective treatment, sensitive molecular diagnostic tools, a widely-administered vaccine and preventive drugs has not been enough to impact the TB pandemic to a level where it is no longer considered a public health concern. In fact, in many countries, particularly in low-resource settings, TB remains one of the leading causes of morbidity and mortality.[3,4] According to the World Health Organization, TB caused 10 million episodes of disease and 1.6 million deaths in 2017.[5] It is the leading cause of death by an infectious disease and ranks 10th in the list of causes of death.[5] It is also one of the top 5 causes of death among women of reproductive age.[3,6] Most of these deaths are concentrated in low-income countries of sub-Saharan Africa and South East Asia (Figure 1).


The End-TB strategy, launched by the World Health Organization in 2014, outlines the global efforts that need to be made in order to reduce the incidence of tuberculosis by 90% and its mortality by 95% by 2035 (as compared to 2015).[7] It also aims to ensure that no families face catastrophic costs due to this disease. It is clear that not only are new tools (new diagnostics, treatments and vaccines) needed to impact TB incidence and mortality at the needed speed, but also inter-sectoral approaches which urgently need long-term political commitment and sustainable resource mobilisation.[8] Those approaches span from the strengthening of health systems and the enhanced effectiveness of the overall TB cascade of care, to the improvement of universal health coverage and implementation of social protection schemes.[9,10]
The likelihood of dying from an episode of TB disease varies, as expected, depending on whether the patient receives anti-tuberculosis treatment or not. Tuberculosis disease without specific antibiotic treatment leads to death in the majority of the cases. Several studies conducted in the pre-chemotherapy area, before the advent of the first anti-tuberculosis drugs in mid-twentieth century, showed that the aggregate 10-year survival rate for untreated smear positive patients was around 30%.[11] The chances of survival diminish with increasing age of the person experiencing the TB episode and also showed minor differences by sex.[12] Clearly, the prognosis of untreated TB is affected by smear status (sputum bacillary load).[11] Untreated HIV-positive TB patients are also assumed to have an increased case fatality rate (CFR), although no studies reporting direct measurements are available.[13,14] Conversely, treated tuberculosis is associated with much lower mortality, although it varies considerably by HIV status. Pooled estimates from a meta-analysis show CFRs of 9.2% and 3% among HIV-positive and HIV-negative patients respectively.[15] Nonetheless, beyond HIV status and ART treatment, several factors are associated with increased mortality among treated patients (high sputum bacillary load, history of a previous TB episode, low BMI, drug resistance, among others).[16-19] Poor quality of health systems and low socio-economic status are also key determinants which increase the risk of dying from TB.[10,20]

### The importance of measuring TB mortality

One of the key indicators in public health is mortality. Deaths are easily measurable outcomes for many diseases and mortality rates (all-cause or specific-case fatality rates) provide an indicator of the health status of countries. Premature death, that which happens before the average age of death for a certain population, has a strong impact on society at all levels. Although the long term sequelae of TB disease are being increasingly recognized,[21] most of the overall burden of disability adjusted life years (DALYs)[3,22] attributed to tuberculosis are due to premature deaths (in other words, years of life lost, one of the subcomponents of DALYs, another key burden indicator).

From a public health perspective, assessing tuberculosis associated mortality is relevant for a variety of reasons. First, it helps to understand the true magnitude of TB compared to other diseases, and thus, it is critical for planning and prioritization of health interventions and allocating resources. Second, it is fundamental for assessing progress on TB control efforts, which will contribute to the assessment of the End-TB and SDG indicators.[23,24] Third, it is important for evaluating the success of specific interventions aimed at reducing TB mortality, both at the programmatic level and in the context of research. Fourth, the monitoring of the TB case fatality rate (the proportion of deaths due to TB among those who develop tuberculosis disease) could alert us to the substandard implementation of TB care measures or procedures or the existence of a potential outbreak of drug resistant TB.

Currently, there are two main institutions providing estimates of TB mortality at global, regional and country level. The Global TB Department at the World Health Organization releases the Global Tuberculosis Report[2,25] annually, which includes information on the number of TB deaths reported by countries, and the estimates of TB mortality, disaggregated by HIV status.
age and sex. The other renowned institution that estimates TB mortality figures is the Institute of Health Metrics and Evaluation (IHME) at the University of Washington in Seattle. As part of the Global Burden of Diseases (GBD) project,[26,27] tuberculosis incidence and mortality estimates are included in every update of the main results of the GBD project. In addition, two other analyses with a focus on TB have been released.[28,29] Disaggregated estimates for both the World Health Organization and IHME can be consulted on their respective websites.[30,31] The first formal comparison of published estimates of both institutions was done with data from the year 2013.[32] This assessment showed similar global mortality figures (WHO 1.3 million deaths and GBD 1.4 million), although there were considerable differences at both the national and regional level, and especially among HIV-associated deaths (0.9 and 1.3 million as estimated by WHO and IHME respectively).[28,33] HIV-associated TB is of great concern for mortality measurement, since despite the proportion of new TB cases being HIV positive is “just” 10%, co-infected cases account for 25% of TB associated mortality.[5] The differences in estimates were considered to stem from the use of different data sources and parameters included in the statistical and mathematical models as well as the overall modelling strategy used by each institution.[32] The lack of certainty about TB mortality figures for a given country hinders the understanding of the magnitude of the TB pandemic and thus, the selection of best approaches for TB control.

**Current methods to assess TB mortality**

There are several methods or tools that could be used to assess TB mortality.

- **Vital registration systems (VRS).** These are civil administrative platforms managed at country level by governments and usually regulated by law. VRS routinely collect all births, deaths and causes of deaths (often including fetal deaths and marriages) which occur in a given population or country. The cause of death is usually assigned by the physician issuing a death certificate. VRS are a reliable tool for monitoring TB mortality in high-income countries, which usually have high quality health systems, access to good diagnostic tools and a low burden of tuberculosis. Nonetheless, the completeness of the information on causes of death or the quality of the information included varies widely depending on the setting. Conversely, coverage of VRS in low-income countries (Figure 2), those with the highest burden of TB, is limited and cannot be used for assessing TB mortality.

- **TB treatment outcomes from National Tuberculosis Programs (NTP).** In countries without or with poor VRS, a way of assessing TB mortality is through the CFR derived from treatment outcomes multiplied by the TB incidence.[34,35] However, in settings where this method would be contemplated (low-resource settings) the TB case detection is usually low. Thus, it would entail a series of assumptions about TB case incidence (usually unknown) and on the CFR derived from the NTP registries or from cohorts of TB patients.[22] TB control programs record the outcomes of patients starting treatment, which includes a fatal outcome (death). However, due to the limitations for ascertaining cause of death and the NTP registries themselves, those deaths might not be due to TB. Thus, CFR based on the NTP information would constitute an overestimation of the CFR. The proportion of TB deaths among people dying during treatment is likely to depend on the local epidemiology of TB and the overall
health profile of a country. In addition, some deaths occurring among people who are lost to follow up are not captured, and in this sense, the limitation also constitutes a source of bias. Lastly, the CFR from patients registered in NTPs (i.e. started on TB treatment) is lower than that of TB patients who remain untreated, either because they are never diagnosed or because they are diagnosed but fail to initiate TB treatment. The untreated patients will be the major contributors to TB mortality in settings where case detection is low. Thus, to account for mortality among never-diagnosed patients, beyond the need for estimating the often unknown case detection rate, several assumptions regarding their CFR would need to be made.

Figure 2 | Coverage of death registration (December 2017). Source: Demographic and Social Statistics. United Nations Statistics Division. Available at: https://unstats.un.org/unsd/demographic-social/crvs/

- Hospital based registries. In countries where the quality of VRS regarding cause of death is limited (no cause of death assigned or no health personnel involved in the process), information derived from hospital registries could be used to estimate TB mortality.[36,37] A hospital-based TB mortality rate could be extracted and applied on the overall all-cause mortality from VRS or mortality surveys or censuses to estimate TB mortality in a given region.[37,38] However, this method introduces several biases, given that the population attending a hospital does not usually reflect the general population. In addition, the profile of TB patients dying in hospitals is also different compared to the profile of deaths in the community.

- Verbal autopsies. Verbal autopsies (VA) could be considered in places with poor access to health services and without a good VRS. A verbal autopsy consists of an interview with relatives of the deceased person (usually a few weeks/months after the death) during which
the interviewers ask about signs and symptoms before death and register this information in a structured questionnaire [39] (a WHO VA tool is widely used). VA are traditionally conducted by field workers and later interpreted by 2 physicians (PCVA, physician coded verbal autopsy), assigning the most likely diagnoses with the available information. Results from studies assessing the validity of VA-based diagnosis using clinical diagnosis as gold standard vary widely.[40,41] Recently, different automated software has been developed (SmartVA, InterVA, Random Forest, King Lu, InSilicoVA), in order to avoid the bias introduced by the health care workers interpreting the information on the questionnaires. These automated software programs use algorithms and probabilistic packages which take into account the local epidemiology of the country, although their validity varies widely by disease, setting and age group, among other factors.[42-45] Few studies have assessed the accuracy of verbal autopsies compared to the gold standard (complete diagnostic autopsy) with respect to TB as cause of death. The results of studies in Kenya, South Africa and Mozambique show very poor sensitivity and specificity, concluding that VA might not be a good tool for estimating TB mortality.[43,46-48]

Complete diagnostic autopsies (CDAs). This is, indisputably, the gold standard tool for cause of death ascertainment.[49,50] However, CDAs are seldom performed in low- and middle-income settings due to scarcity of trained pathologists, the majority of patients dying at home, time-consuming procedures and poor acceptability by relatives.[51] As is the case with hospital registries, the proportion of deaths due to TB might also be biased due to the questionable generalizability to the general population, given that the profile of diseases and patients accessing hospitals where CDAs are performed might be different to the general population. In recent years, alternative minimally-invasive post-mortem methods [minimally-invasive autopsies (MIA) or minimally invasive tissue sampling (MITS)-based autopsies], have been developed,[52-56] showing good correlation with the diagnosis obtained through complete diagnostic autopsies (at least for determining TB as cause of death).[57,58] However, the number of TB cases included in many of these post-mortem assessments is limited, and further studies are needed.

The quest for improved diagnostic tools in the field of tuberculosis has yielded some exciting developments in recent years. The advent and quick global roll-out of Xpert MTB/RIF,[59-61] a cartridge based highly sensitive real time PCR which provides results in approximately 2 hours, [62] has allowed improving the proportion of laboratory confirmed patients starting treatment, and reducing diagnostic delays and (probably) increasing the overall number of patients starting treatment.[63-66] Nonetheless, no impact on mortality has been shown after its introduction as a routine diagnostic tool for TB.[67-69]
Table 1 | Overview of main methods, tools or data sources used for mortality estimation

<table>
<thead>
<tr>
<th>Method / Tool</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
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<tbody>
<tr>
<td>Vital Registration Systems</td>
<td>Direct measurement. Usually nationwide systems, although can be implemented at regional level. They usually collect other relevant demographic data.</td>
<td>Various levels of quality. Various levels of coverage. In some countries, no cause of death included or not certified by a physician. Not available in many high TB-burden countries. It is an expensive platform.</td>
</tr>
<tr>
<td>Treatment Outcomes from National Tuberculosis Programmes</td>
<td>Information widely available through National TB programmes for most endemic countries. It uses an existing platform for data collection.</td>
<td>The CFR based on treatment outcome data needs reliable data on TB incidence (often unavailable) in order to assess national TB mortality burden. Lost-to-follow-up patients who died are not captured. Patients with “death” as outcome might die of non-TB related causes. Quality of NTP reporting varies widely. Mortality among undiagnosed / untreated patients not included.</td>
</tr>
<tr>
<td>Verbal Autopsies</td>
<td>Only available method for cause of death ascertainment in some settings.</td>
<td>Validity differs per setting. Less accurate than clinical diagnosis. Only in sub samples of population, many under demographic surveillance systems.</td>
</tr>
<tr>
<td>Registries From Hospitals / Health Facilities</td>
<td>Death usually ascertained by a physician. Information is relatively easy to obtain.</td>
<td>Case fatality rates need to be applied to all cause mortality (from VRS or other sources). Poor generalizability of results due to profile of diseases and patients. No digital registries in many TB endemic countries. Poor quality diagnosis.</td>
</tr>
<tr>
<td>Cohort Studies</td>
<td>Direct measurement. Often embedded in populations under surveillance such us demographic surveillance platforms. Possibility of studying risk factors.</td>
<td>It is not a sustainable / feasible method. Might not be representative for population outside the cohort. Large numbers required. Causes of death might still need ascertainment by a physician or VA.</td>
</tr>
<tr>
<td>Complete Diagnostic Autopsies (CDA)</td>
<td>Gold standard for cause of death ascertainment.</td>
<td>Expensive, time consuming, considerable expertise required, few pathologists in high-TB endemic countries, seldom performed and if so, only in reference hospitals. Not well accepted by relatives.</td>
</tr>
</tbody>
</table>
The role of new diagnostics in post-mortem TB diagnosis

Most of the studies assessing Xpert MTB/RIF diagnostic performance have been conducted among symptomatic patients reporting at health facilities (“TB presumptive cases”), but its applicability for TB diagnosis at death has been underexplored. The field of post-mortem diagnosis of TB has traditionally relied on finding gross macroscopic lesions (mostly nodular lesions or masses with multiple foci of caseous necrosis) which are later analyzed under the microscope looking for acid fast bacilli (AFB) or the existence of a granulomatous reaction (caseous or non-caseous).[70] In populations with less typical forms of TB such as in contexts of high HIV prevalence, a proportion of TB disease at death (as cause of death or as a concomitant finding at death) may be missed. In some autopsies, mostly in the context of research studies, molecular tools (in-house, real time PCRs) have been used,[71] but they are tedious to perform, need considerable equipment investments and expertise, and are time consuming. Thus, new rapid tools with improved sensitivity might improve postmortem TB diagnosis. In 2018, the WHO endorsed the Xpert MTB/RIF Ultra assay,[72,73] which has improved sensitivity compared to the previous version of the Xpert MTB/RIF cartridge for *M. tuberculosis* detection, especially among smear-negative culture-positive patients and among HIV-positive patients,[74] although with slightly lower specificity. The combination of new strategies for ascertaining cause of death (such as minimally-invasive autopsies) and the introduction of novel molecular diagnostic assays for post-mortem TB diagnosis could contribute to a better picture of the TB burden at death in low-resource settings.

Setting the stage

Much of the work presented in this thesis was done in, or relates to, Mozambique. Mozambique is severely affected by the TB epidemic and faces enormous challenges to achieve its control.[75] In a population of 28 million inhabitants, the annual TB incidence rate is 551 cases per 100,000 population.[25] The country is included by WHO in the high TB, HIV-TB and MDR-TB burden country lists and is one of the few African countries which has not reversed the TB epidemic, although TB incidence figures seem to be levelling off in recent years. Around 45% of all TB cases were found to be HIV positive in 2016 and the overall estimated case fatality ratio is 37%. [25] The estimated low TB case detection rate of 45% in 2016, is one of the lowest in the world and urgently demands sustainable active case finding interventions and broad implementation of improved diagnostics, among others. One of the problems of estimating the number of TB deaths derives from the lack of certainty of TB incidence figures, obtained by applying an unknown case detection rate (generated by expert opinion) to the reported number of cases. Ultimately, the World Health Organization applies a specific case fatality rate to the estimated number of incident cases. This lack of certainty on incident cases is assumed to be improved by the data derived from the first ever national TB prevalence survey, which will take place in 2018.

This low TB case detection rate reflects several bottlenecks that impact the measurement of the overall TB burden. The majority of the population in Mozambique lives in rural areas with poor road and transport infrastructure. Distance to health centers is a commonly reported factor for diagnostic delays and non-adherence to the national TB care recommendations.[76-78] In
addition, the high poverty levels (Mozambique ranks 180 of 189 on the UN human development index)[79] are an added obstacle for accessing care. Lack of access to health care affects the TB case detection rate (in the living, but also in the dead, as an unidentified cause of death in those without a premortem TB diagnosis). In addition, people living with HIV are thought to carry the majority of the TB burden, at least in Southern Mozambique.[25,80] TB diagnosis among people living with HIV is challenging,[81] and despite the progress in rolling out Xpert, sputum smear (a low-sensitivity tool for TB diagnosis) remains the main TB diagnostic test in many settings of the country.[82] A high rate of HIV co-infection contributes to a low case detection rate, especially in some areas in Southern Mozambique, where HIV prevalence among adults could be as high as 40%.[83] Moreover, high rates of undiagnosed TB in children account for the lack of certainty on pediatric TB estimates.[84]

Many people in Mozambique believe that transmission of infectious diseases is driven by ritual and magical factors, which further hinders health seeking behaviours through the national health system networks.[85] Misperceptions about TB (about etiology, transmission and prevention of TB) have been linked to under-diagnosis or delayed diagnosis in the region. [86] The lack of knowledge in the community is aggravated by the fact that more than half of the diseased go to traditional healers before going to the national health system. In addition, poor training of health workers can contribute to the inadequate TB diagnostic work-up. Reporting and TB registries have not been updated in many years (although planned, no electronic reporting to the NTP exists yet), and might contribute to poor quality surveillance. All these circumstances might impact case notification rates and overall TB burden measurement.

The district of Manhiça

Part of the work presented in this thesis has been conducted in the district of Manhiça, Mozambique, in collaboration with the Manhiça Health Research Center (Centro de Investigação em Saúde de Manhiça, CISM). The CISM was created in 1996 to fight disease and safeguard the health of vulnerable populations through research, health care assistance and training.[87] Since then, the center has developed a comprehensive research agenda, and trained researchers and technical personnel. The CISM is located in Manhiça, a village located approximately 80 km from Maputo City, in the northern portion of the Maputo province (South of Mozambique), an area of high TB and HIV burden.[88,89] Since early 2000s, the CISM has been conducting studies in the area of tuberculosis and has participated in different large observational studies and trials (vaccine and drug clinical trials).[84,90-92] The CISM also runs a health and demographic surveillance system (HDSS)[93] and is a founding member of the INDEPTH network,[94] a consortia of 42 HDSS sites which aims to monitor new health threats, track population changes through fertility rates, death rates, migration, morbidity and measure the effect of policy interventions on communities of low-income countries. The HDSS data source has contributed to a better understanding of the population characteristics and estimates in the district of Manhiça and has been used as a data source for part of the work presented in this thesis.
AIM AND OUTLINE OF THIS THESIS

The central aim of this thesis is to evaluate different strategies and approaches related to TB mortality measurement through different study designs and within the context of Southern Mozambique, a low-income setting with a high TB and HIV burden.

MAIN THESIS RESEARCH QUESTIONS

This thesis aims to answer the following research questions:

- How do global and national TB mortality estimates vary depending on the institution which estimate them (World Health Organization or Institute for Health Metrics and Evaluation)? What are the drivers of the differences?
- What is the incidence of HIV-associated TB in a sub-rural district of Southern Mozambique? What are the trends in fatal outcomes in a high TB- and HIV-burden district of Southern Mozambique based on data from National TB control program?
- What is the contribution of TB associated deaths to the overall mortality burden in a sub-rural district of Southern Mozambique? What are the factors associated with fatal outcome during TB treatment?
- What is the accuracy of clinical diagnoses (premortem) to determine the cause of death (post-mortem) in a high TB-HIV burden setting in Mozambique? What is the diagnostic performance of clinical judgement to diagnose TB disease at death?
- What is the diagnostic performance of Xpert MTB/RIF to detect *M. tuberculosis* in post-mortem tissues?
- What is the diagnostic performance of Xpert MTB/RIF Ultra in detecting TB in post-mortem tissues obtained through minimally-invasive autopsies? What could be its added value in complete diagnostic autopsies?

SCOPE AND STRUCTURE OF THIS THESIS

PART 1 – Introduction

Chapter 1 - Background

PART 2 – Tuberculosis mortality in a high TB- and HIV-burden setting in Southern Mozambique. Limitations of using data from National Tuberculosis Programs and Hospital Registries

The objective of this part of the thesis is to provide estimates on TB incidence and mortality in a rural area of Southern Mozambique, using data sources such as the National Tuberculosis Program, the Mozambican National Statistics Institute, the Health and Demographic Surveillance System (HDSS) of the CISM and data from an HIV prevalence survey. It also estimates the accuracy of clinical premortem diagnosis from a reference hospital in Maputo, Mozambique's capital city.

Chapter 3 aims to estimate the background HIV-associated TB incidence and the population attributable fraction of HIV in the district of Manhiça, Southern Mozambique.

Chapter 4 includes background data on programmatic TB indicators (including case notification rates and treatment outcomes) over a 16-year period in the district of Manhiça.

Chapter 5 has a 3-fold objective: a) to evaluate treatment outcomes among TB patients; b) to analyze factors associated with a fatal outcome; and c) to determine the proportion of deaths associated with TB in the district of Manhiça.

In Chapter 6, we assess the accuracy of clinical diagnoses to establish cause of death by comparing them with the post-mortem diagnoses (gold standard). This is a study performed in adults in Maputo Central Hospital, a tertiary hospital in sub-Saharan Africa (Mozambique).

PART 3 – New diagnostic tools and strategies to ascertain TB at death

Chapter 7 aims to assess the role of Xpert MTB/RIF for TB diagnosis in post-mortem tissues.

Chapter 8 is a detailed analysis of the burden of tuberculosis in a series of 223 deaths (part of them are also included in chapter 6), with the novelty of using a the new Xpert MTB/RIF Ultra assay in the post-mortem TB diagnostic algorithm.

Chapter 9 aims to establish the diagnostic performance of Xpert MTB/RIF Ultra applied in different tissues obtained during minimally-invasive autopsies (MIAs) to determine tuberculosis as cause of death.

PART 4 – Discussion of the main findings

Chapter 10 provides a synthesis of the main findings of this thesis and discusses future perspectives in the field, as well as policy implications and recommendations.
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