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 11

Summary
Tuberculosis (TB) is regarded as the single infectious disease which is responsible for the highest number of human deaths. Lowering this mortality burden is one of the main priorities of World Health Organization (WHO)’s End-TB strategy, which aims at reducing 95% of the TB mortality rate in the period 2015–2035. However, mortality estimates are imprecise and there is considerable uncertainty on what the true burden is, especially in countries without vital registration systems, which happen to be those enduring the highest TB burden. It is critical to improve our knowledge on the human toll caused by Mycobacterium tuberculosis in order to prioritize and plan health interventions, as well as being able to measure progress on national and global control targets. The central aim of this thesis is to evaluate different methods, strategies and tools related to TB mortality measurement through different study designs. All original data included in this thesis has been conducted within the context of Southern Mozambique, a low resource setting with high TB and HIV burden.

**PART 1 – INTRODUCTION**

In order to contextualize the different studies presented in this thesis, chapter 1 provides background information on the importance of measuring TB mortality and presents a review on the main methods used to estimate TB mortality. The strengths and limitations of using vital registration systems, treatment outcomes from national TB programmes, verbal autopsies, complete diagnostic autopsies, hospital registries or cohort studies are discussed. This introduction also reviews the current situation of TB control in Mozambique, highlighting the bottlenecks that hinder the availability of good quality TB burden indicators. Lastly, the context where studies described in chapters 3 to 5 were implemented (the district of Manhiça) is briefly described in order to provide a better picture of the particularities of this setting.

Chapter 2 includes a detailed comparison on the TB mortality figures for the year 2015 estimated by the two main institutions providing these data on an annual basis, the World Health Organization (WHO) and the Institute for Health Metrics and Evaluation (IHME). Although both estimates are quite similar for most countries, the results show a global difference of nearly 450 000 deaths (WHO estimating higher global mortality than IHME), with some countries differences higher than 10 000 deaths. A few countries account for the large discrepancy in estimates, being the top 3: Nigeria (216 621), Bangladesh (49 863) and Tanzania (38 272). Given that the magnitude of the difference in estimates might be driven by countries’ TB burden, we standardized the absolute difference by the average number of deaths estimated by both sources. This adjustment showed some other countries (Azerbaijan, Marshall Islands, Egypt, Timor-Leste, Papua New Guinea) with lower burden, but where differences in estimates are considerable. The use of prevalence surveys or case detection rates (in the case of WHO) seem to be associated with the observed differences. These findings constitute a claim for IHME and WHO to take a closer look at the modelling approaches for the countries where the differences are largest. Country specific analysis would contribute to a better understanding of the mortality burden in some low resource settings.
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

Chapter 3 provides some background data on TB and HIV associated TB burden in the district of Manhiça. The lab-confirmed TB case notification rate is very high, especially among HIV positive men, in the age band of 38–47, where it can reach around 1884 per 100,000 male population. The HIV prevalence among new cases in 2011 was 77% with a high proportion of patients dying during treatment (15%). The population attributable fraction associated with HIV was estimated at 62%, meaning that almost two thirds of the TB in the district would be prevented if HIV could be eliminated from the population. The true TB incidence rate in the district of Manhiça might be much higher, given the presumably low case detection rate. Further characterization of the TB epidemic in the district of Manhiça is shown in chapter 4, where the trends on the main programmatic TB related indicators over a 16-year period are presented. From 1997 to 2012, the TB notification rate in the district of Manhiça has increased by 3-fold from 174 to 573 cases per 100,000 population. Mortality rate during TB treatment was higher in HIV-positive patients than in HIV-negative ones (17.3% vs 8.3% respectively). Treatment success rate over the entire period was below 70% and has remained relatively constant over the 16-year period.

The poor treatment outcomes shown in chapter 3 and 4 led to the analysis presented in chapter 5, where factors associated with fatal outcomes during the period 2011–2012 are analyzed. In this two-year period, 15.1% of TB patients died during anti-tuberculous treatment. Being HIV positive (OR 2.73; 95% CI: 1.70–4.38), being male (OR: 1.39; 95% CI: 1.01–1.91) and not having bacteriological confirmation at diagnosis (OR 1.54; 95% CI: 1.12–2.13) were factors associated with dying during the course of TB treatment. The contribution of TB to the overall death burden in the district of Manhiça was 6.5% (95% CI: 5.5–7.6), higher for males than for females (7.8% vs 5.4% respectively). This study shows that TB is a very frequent cause of death in the district, especially among young males and also highlights the importance of improving HIV patient management in order to improve overall treatment outcomes. Chapters 3 to 5 used information from the health and demographic surveillance system at CISM and National Statistics Institute, results from an HIV prevalence survey and data from the National TB Programme. The latter source only reports information which is passively collected, and is subject to data quality and completeness concerns. However, it is useful to analyse trends in main TB indicators and identify broad areas in which implementation of TB and TB/HIV care might be substandard.

Chapter 6 aims to assess the validity of clinical diagnosis for estimating mortality, using complete diagnostic autopsies as gold standard in 112 adult deaths (excluding maternal deaths) occurring at Maputo Central Hospital, the main reference hospital of Mozambique. Clinico-pathological discrepancies were very frequent, especially in infection related deaths, where 70% of cases showed major discrepancies (those cases where correct identification of the diagnosis before death could have cured or prolonged the survival of the patient). In this
series, TB was the single most important cause of death, with 23 cases. Clinical diagnosis had a very low sensitivity at 34% (95% CI: 16–57) and a positive predictive value of 42% (95% CI: 20–66) for diagnosing TB as cause of death. The proportion of major discrepancies for TB diagnosis as cause of death was 65%. These results show the need for improving patient management, especially with regards to ascertaining diagnosis, and question the reliability of this data source, and by extension of verbal autopsies, for TB mortality estimation, at least in similar settings.

PART 3 – NEW DIAGNOSTIC TOOLS AND STRATEGIES TO ASCERTAIN TB AT DEATH

All the studies presented in this section, as well as that included in chapter 6, are ancillary studies to the CaDMIA research project, which aimed at validating minimally invasive autopsies (MIAs) for cause of death investigation in low resource countries. The quest for having highly sensitive and rapid tools for TB diagnosis at death led to a pilot study (chapter 7) which explored the usefulness of the Xpert MTB/RIF (Xpert) assay in post-mortem tissues (lung, liver and brain). The presence of TB in those tissues was determined by a composite endpoint which included microbiological (a TB specific in-house PCR and LAMP) and histological findings (TB compatible lesions). Xpert had a sensitivity to detect TB in lung tissue of 87.5% (95% CI: 47.3–99.7) and a specificity of 95.7% (95% CI: 78.1–99.9). It also showed perfect concordance of results for brain and tissue. Although the study had a limited sample size (30 deaths and 8 TB cases), the results suggest that Xpert might be a useful, rapid and easy to perform assay for post-mortem TB diagnosis.

Chapter 8 presents a detailed analysis on the TB burden and the validity of clinical diagnosis for determining TB disease at death in a large complete diagnostic autopsy series of 54 children, 112 adults and 57 maternal deaths. The new Xpert MTB/RIF Ultra (Xpert Ultra) assay, a more sensitive version of the Xpert, was used in the algorithm for TB case classification. TB was the cause of death in 31 patients (3 children, 23 adults and 57 maternal deaths). Concomitant TB disease (TB lesions in a patient dying of other causes) was found in 31 additional cases and *M. tuberculosis* DNA was identified by both in-house PCR and Xpert Ultra assay in 18 patients without histopathological evidence of TB. The main clinical diagnosis at death assigned by physicians had a poor overall sensitivity to diagnose the cause of death: sensitivity 19.4% (95% confidence interval: 7.5–37.5). This study shows a high prevalence of TB among deaths occurring in a reference hospital in a high TB HIV burden setting, as well as poor validity of clinical diagnosis for detecting TB both as cause of death and as a concomitant disease at death. The inclusion of Xpert Ultra as part of the diagnostic algorithm allowed to identify forms of TB that would have otherwise been missed.

Minimally invasive autopsies have shown a high sensitivity and specificity to diagnose TB as cause of death when compared to the complete diagnostic autopsies (gold standard). However, the microbiological assays used in previous validation studies rely on traditional diagnostic tools, which might not be very sensitive, are slow and time consuming. In chapter 9
we explored the diagnostic performance of Xpert Ultra performed in lung, serum, cerebrospinal fluid or central nervous system tissue obtained through minimally invasive autopsy procedures to determine TB as the cause of death. MIA samples from all cases with TB findings and a subset of 37 cases without any evidence of TB from the study described in chapter 8 were used. The highest sensitivity was obtained if tested in lung and brain combined (0.85% 95% CI: 0.66–0.96). The highest specificity was observed in single lung (0.98; 95% IC: 0.92–1.00) or serum (0.98; 95% IC 0.91–1:00) samples, with positive predictive values (PPV) of 0.91 (95% CI: 0.72–0.99) and 0.91 (95% CI: 0.71–0.99). Easily accessible samples, such as serum, could help to rule in or rule out TB as CoD using a quick and simple molecular test.

The main strengths and limitations of the research included in this thesis are explained in chapter 10, where the main findings are discussed. This section also aims to identify knowledge gaps on the field and potential new research ideas that might contribute to advance epidemiological assessments of TB mortality burden.