Factors associated with Tuberculosis Mortality in Selected Health Facilities in Lusaka, Zambia, 2016

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ABSTRACT

Introduction: Zambia is among the 30 countries with the highest burden of tuberculosis (TB), with an estimated incidence rate of 346 per 100,000 population in 2018. Lusaka is among the districts with the highest TB incidence in Zambia. In 2015, TB mortality (6%) exceeded the national target of less than 5%. We sought to assess factors associated with TB mortality in selected public health facilities in Lusaka, in order to gain knowledge required to design appropriate strategies for reduction. **Methods:** We conducted a cross-sectional study in three purposively selected public health facilities in Lusaka including a 1st level-hospital, an urban-clinic, and a peri-urban clinic. We used the 2013 World Health Organisation's (WHO), definitions and reporting framework for TB and defined TB mortality as any TB patient who died for any reason during the course of TB treatment. We abstracted data from treatment registers for TB cases on treatment in 2016. Using multivariable logistic regression, we analysed the associations between TB mortality and age, health facility type or HIV status and reported adjusted odds ratios(AOR), and 95% confidence intervals(CI). **Results:** We included 1,537 registered TB patients from the three sites in 2016 (urban-clinic(n=676), 1st-level-hospital(n=630) and peri-urban-clinic(n=231)). The overall mortality rate was 9%, and by facility: 8%(urban-clinic), 11%(1st-level-hospital) and 8%(peri-urban-clinic). The odds of TB mortality were higher among patients >64 years (AOR=7.6, 95%CI:1.97–29.55), TB/HIV co-infected (AOR=3.1, 95%CI:1.91–4.93) and those treated at the 1st-level-hospital (AOR=1.6, 95%CI:1.08–2.40). **Conclusion:** TB mortality in the selected facilities was high compared to the national target. We recommend scaling up of TB treatment and preventive therapy among people living HIV especially those >64 years old in the selected health facilities.

KEYWORDS: Tuberculosis, Death; Lusaka, Zambia

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Introduction

Zambia is among the 30 countries with the highest burden of tuberculosis (TB), with an estimated incidence rate of 346 per 100,000 population in 2018 [1]. Zambia has made good progress in TB control and the prevalence/incidence of TB has been going down over the years. However, the TB burden is still high which could be attributed to high rates of undetected TB cases (42%), delayed diagnosis and low utilization of TB preventive therapy (18%) [2]. Zambia recorded a mortality rate of 74/100,000 population in 2018 [2].

World Health Organisation (WHO), defines TB death as any TB patient who died for any reason during the course of treatment [1]. Death among TB patients is a critical issue that requires special attention in TB control programs as this is the case in the WHO high TB-burdened countries, Zambia inclusive.

Studies in other settings have identified factors associated with TB mortality. A retrospective case-control study done in Cameroon found that TB death occurred in the first two months of TB treatment and factors included HIV/TB co-infection, extra-pulmonary TB, sputum smear-negative pulmonary TB and male sex [3]. Another study in Taiwan found that, age ≥75 years (reference: 65-74 years), male sex, end-stage renal disease (ESRD), malignancy, acid-fast bacilli-smear positivity, TB-culture positivity, pleural effusion on chest radiograph and notification by an ordinary ward or intensive care unit were associated with a higher risk of all-cause death. This study however was only looking at TB mortality in elderly patients [4]. Another study conducted in Ethiopia found that TB death was highest in the first 2 months and declined with time on Antiretroviral therapy (ART) to reach 1 per 100 person years after 24 months on ART. TB was significantly associated with mortality among HIV patients on ART (AHR 2.0, 95% CI 1.47-2.75). In this same study, male gender was associated with mortality among TB/HIV co-infected patients [5].

Although national treatment success rates among new TB cases reached above 85% in 2015 [6], death rates in Lusaka district alone remains high at 5% [6]. Lusaka, the capital city of Zambia, has residential areas that developed as a result of rural-urban migration, as well as a number of industries and private businesses which have made it a destination centre for people looking for employment and petty trade. This could have led to the increase in the number of TB cases reported for the reason that these people tend to live in densely populated areas and hence subjected to poor living conditions [7].

TB mortality studies have been conducted in the past in different settings [8-11]. However there is still need to add to the existing knowledge about the predictors of TB mortality in Zambia [1]. Knowledge of the determinants of TB mortality is critical for informing solutions needed to improve TB outcomes and contain the spread of the disease there by reducing mortality. Information and identification of predictors of TB mortality in mixed practice settings is important to understand contextual problems and, accordingly, design appropriate community/population-based strategies to reduce it. To better understand these factors, we conducted a study to identify factors associated with death among TB patients in selected facilities within Lusaka district for the period 1st January to 31st December, 2016.

Methods

Study Design, Site and Population

A cross-sectional study design was conducted, which involved a review of TB (bacteriologically-confirmed and clinically-diagnosed) case records at three purposively selected different types of health facilities in Lusaka District for 2016.

Zambia´s healthcare system is decentralized, therefore it is broken up into three different levels; hospitals, health centers and health posts. Hospitals are divided into; primary (district or 1st level Hospital), secondary (provincial 2nd Level Hospital) and tertiary (central or university teaching hospital). This study purposively selected 2 health centres (one urban and one peri-urban) and one 1st level hospital because all these offer primary health care.

Lusaka District had a total catchment area population of 2,330,200 as of 2016. The study population included all confirmed cases of TB and clinically-diagnosed for all ages in the selected facilities in Lusaka.

Definitions of TB Treatment Outcomes

Using the WHO definition [12], a TB case was defined as either (1) a bacteriologically-confirmed biological specimen positive by either smear microscopy, culture, or Gene Xpert, or (2) clinically diagnosed with TB by a clinician or other medical practitioner who has decided to give the patient a full course of TB treatment. TB death was defined as a TB patient who died for any reason during the course of treatment. Lost-to-follow-up was a patient who did not start treatment or treatment was interrupted for 2 consecutive months or more. We also defined treatment failure as a patient with a positive sputum smear or culture at month 5 or later during treatment, and patient not evaluated as a patient who has no treatment outcome reported in the TB treatment register. Thus, it was not clear if a "not evaluated" patient has been transferred out to another treatment unit, or if their treatment outcome is truly unknown. A cured patient was defined as a pulmonary TB patient with bacteriologically-confirmed TB at the beginning of treatment who was smear- or culture-negative in the last month of treatment and on at least one previous occasion. The definition of "treatment completion" was a TB patient who completed treatment without evidence of failure, but with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable. An urban clinic was defined as a TB treatment and diagnostic centre that exists in a planned area in the city that was designed through town and country planning by the local authority while peri-urban clinic was a TB treatment and diagnostic centre which exists in an unplanned settlement which resulted from rural urban migration and are subjected to poor economic status [12].

Data Collection and Variables

We abstracted variables from the TB treatment registers that were related to the study objectives. Patients´ age, gender, health facility type, type of TB, treatment category, and HIV-status were the main independent variables. Data on other variables such as comorbidities, ART status, nutritional status, marital and employment status was not available in the registers and, hence, not included in the study. We classified mortality as a dichotomous variable, i.e., dead (patient died) versus not dead (cured, treatment completion, loss to follow-up, failure or not evaluated) outcomes. The continuous variable age which was normally-distributed was categorised to see the various effects in different age categories. Categorical data such as sex was reported using numbers and percentages.

We included patients with either bacteriologically-confirmed or clinical-diagnosed pulmonary tuberculosis (PTB), as well as extra pulmonary tuberculosis (EPTB), and excluded all drug-resistant TB patients because they are reported separately from drug-susceptible TB.

Sampling and Sample Size

The sample size of 384 was estimated by using the following formula for survey sample estimation at 95% level of confidence based on the assumption that 50% of the population had unfavourable outcomes due to an unknown prevalence. All the TB diagnostic centres in Lusaka district were put into three categories: hospitals, urban clinics and peri-urban clinics. We, therefore, purposively selected one 1st level hospital, one urban-clinic and one peri-urban clinic. Despite having a sample size of 384, we did a complete review and abstraction of all records for confirmed TB cases on treatment during the year 2016 from the standard paper TB treatment registers, and verified the recorded information with individual patient TB treatment cards.

Ethical clearance was obtained from Excellence in Research Ethics and Science (ERES) Ethics Committee (Ref: 2017-June-013), and permission to conduct a study was obtained from National Health Research Authority and the Zambia Ministry of Health.

Data Analysis

We entered abstracted data from paper-based TB treatment registers into an electronic MS Excel 2010 data entry form and exported to Stata Version 13 analysis software for cleaning and analysis. A histogram age as a continuous variable was used to graphically check for normality. Chi-square tests were used to ascertain associations with TB mortality. Odds ratios (OR) were reported as a measure of association for all categorical variables with TB mortality using logistic regression.

We calculated the death rates using the number of deaths as the numerator and the total TB confirmed cases as denominator. Bivariate and multivariable logistic regression were performed.

For the logistic regressions performed, an alpha of 0.05 was used, and odds ratios and corresponding 95% confidence intervals were calculated for the various associated factors. Variables whose P-value was <0.05 in the bivariate analysis were included in the multivariable analysis. We performed a backward stepwise multivariable logistic regression. Selection of the best model was guided by the likelihood ratio test (P-Value >0.05), after estimation of the nested model by eliminating variables one at a time.

Results

We included 1,537 registered TB patients from the urban-clinic (n=676), 1st level hospital (n=630) and peri-urban-clinic (n=231). Overall mortality rate was 9% and by facility: the urban-clinic 8%, 1st level hospital 11% and peri-urban-clinic 8%. The ratio of male-to-female TB patients that died was 1:1. The mean age for those who died was 39 years, standard deviation (SD= 15.10) and the majority were aged above 64 years **Table 1**. Patients with extra-pulmonary TB had a 10% mortality rate compared to pulmonary TB patients with 9%. Relapse patients had 12% while new and relapse patients had 8% and 7% mortality rates respectively. The treatment outcomes according to types were distributed as follows cured 20%, died 9%, lost-to-follow-up 6%, not evaluated 21%, treatment completion 44%.

Bivariate logistic regression analysis **Table 2** revealed that TB patients above 64 years old had higher odds (unadjusted OR =6.9, 95% confidence interval (CI): 1.89, 25.93) of mortality compared to those aged 0-14 years. HIV co-infected TB patients had a statistically significant increased chance of mortality compared to HIV negative TB patients (OR = 2.5, 95% CI: 1.60-3.91). Patients who sought treatment at the 1st-level referral hospital were more likely to die compared to those who sought treatment at the urban clinic (OR = 1.6, 95% CI: 1.02-2.16). Relapse patients had increased odds of mortality compared to new patients (OR = 1.5, 95% CI: 1.08-2.23). Pulmonary TB patients compared to extra-pulmonary TB patients had a reduced chance of mortality (OR = 0.86, 95% CI: 0.55-1.36) however this association had no statistical significance.

The multivariable logistic regression **Table 3** showed that the odds of mortality was significantly higher among patients aged above 64 years (Adjusted Odds Ratio (aOR) = 7.6, 95% CI: 1.97-29.55) compared to those aged 0-14 years after adjusting for, health facility, and HIV status. The odds of mortality were higher among HIV-TB co-infected patients compared to HIV-negative TB patients after adjusting for all other factors (aOR = 3.1, 95% CI: 1.91-4.93). Patients who sought treatment at the 1st-level hospital were more likely to die compared to those that sought treatment at the urban clinic after adjusting for all other factors (aOR = 1.6, 95% CI: 1.08-2.40).

Discussion

TB mortality in three Lusaka health facilities was high. This study found an overall mortality rate of 9% for the three facilities selected, and this was higher than the 5% reported for the entire Lusaka district. This finding may indicate that there could be a possible under reporting of mortality. Possible contributing factors could be high rates of missing TB cases (42%) and low utilization of TB preventive therapy (18%) in Zambia [2]. Data quality issues could also possibly be the reason that explains the difference in the mortality rates found in this study and that which was reported to the national TB program. On the other hand of missing data as evidenced in the not evaluated category (21%) reported in this study may be the reason for the increased mortality estimate. This is also indicative of poor data capturing and reporting issues in the standard TB registers. High TB mortality leads to people dying early and affects the country's productivity. The overall mortality rate found was similar to a study done in southern province Zambia [11] and lower than a study conducted using national data [8]. These differences could be attributed to the different study settings and different study designs. This study has highlighted factors associated with tuberculosis mortality among TB patients in selected health facilities in Lusaka, Zambia, 2016. The study has shown that TB patients that were HIV co-infected, above 64 years old and those who sought

treatment from the 1st level hospital had increased odds of death from TB.

The WHO has set standards for reporting outcomes of anti-tuberculosis treatment [12]. Mortality rate is a major indicator in the assessment of performance of a national TB programme [13]. In this study, the ratio of male-to-female TB patients that died was 1:1 and this finding is different from what other studies have found where males were more likely to die than females [14,15]. This could possibly be attributed to the selection of a few facilities which may not have been generalizable. Patients aged above 64 years and HIV-positive TB patients were more likely to die in our study. This finding is in line with what other studies have found elsewhere [3,15-19].

The study also found old age to be associated with mortality and many studies have shown this association in TB treatment [4,20-22]. This finding could be attributed to an increased risk of lower immunity, making them more susceptible to infections, as a person grows older which may lead to poor outcomes [23,24]. Another factor that may be attributed to this finding is that older patients are more likely not to adhere to treatment compared to young patients which may be due to them fearing that they may experience side effects (although other studies do not agree with this finding) and some other factors which may be associated with physical fitness and nutrition status of old aged people [24-27]. Comorbidities are also another possible contributing factor to this finding. However, our study used secondary data, so we could not control for the age-associated co-morbidities [19,22,28].

In this study, receiving care from the 1st level hospital was found to be associated with mortality. This study was conducted in three health facilities, a peri-urban, urban clinic and one 1st level referral hospital, the higher death rates in hospitals might be due to hospitalization of more critical TB patients in hospitals than in health centres [16]. Different study designs also may account for the differences in the death rates among countries and within countries in different study settings. These finding call for a prospective study to get into details as why this difference in mortality exists in different types of health facilities.

Similar to other studies, [17-19, 29-34] this study found HIV-positive TB patients to be associated with TB mortality. HIV is known to affect the immune system of individuals making them more susceptible to opportunistic infections such as TB [35-37]. This, therefore, suggests the need to scale up TB preventive therapy (TPT) among people living with HIV (PLHIV) in order to prevent mortality. Studies have also shown that poor uptake of anti-retro viral therapy (ART) in HIV-positive TB patients is associated with mortality [30,38]. This study however did not analyse the association between ART and mortality among HIV positive TB patients due to missing information from the registers. Therefore, this calls for improved action in ensuring that health facilities record and report all TB treatment outcomes. Failure to do so may lead to missing very important information required for effective service delivery in the diagnosis and treatment of TB.

Limitations

This study was subject to several limitations. We classified as not dead any person with TB disease who did not have evidence of mortality, including persons who were lost to follow-up and not evaluated; some of these persons may indeed have been dead or not dead and just not captured by the data source, underestimating or overestimating TB mortality in our results. We reviewed register data in the three selected health facilities and sociodemographic information such as drinking habits, education levels, marital status and employment were not available. Any bias introduced by lack of availability of this data, may have affected the association between potential risk factors and mortality. Our study design of purposively sampling three health facilities may affect the generalization of results for Lusaka District and beyond. The analyses included all deaths irrespective of the cause of death therefore there might be have a possible misattribution of the cause of death as being related to TB, overestimating the mortality truly due to TB disease. However, we applied the standard case definition for TB mortality utilized by WHO member states for comparability reasons. The study did not assess disease severity and this may be a possible confounder as TB in patients who went to the 1st level hospital could have been more critically-ill compared to those that went to clinics.

However, this study was able to identify the potential factors associated with mortality in the treatment of TB and selected all the three different categories of TB diagnostic health facilities in Lusaka with a larger sample size to give enough details on the issue. These findings may help the national TB programme to lay a baseline for a prospective study to find out the differences in mortality according to different levels of the health care system in Zambia. For the HIV positive and elderly TB patients a more focused attention to be paid in the treatment process as they are more likely to die compared to other patients

Conclusion

The aim of this study was to identify factors associated with death among TB patients in selected facilities within Lusaka district. TB mortality in the selected facilities was high compared to the national target, particularly among patients >64 years old and among PLHIV. These findings add evidence for scaling up of TPT in Zambia. There is also need for increased efforts in data capturing using the TB treatment registers at health facility level.

What is known about this topic

- TB mortality is associated with being >64 years old and being HIV co-infected TB patient. However, little research reports on risk factors for TB in Zambia

What this study adds

- TB mortality in three Lusaka-based health facilities was higher than average Zambia
- Tuberculosis mortality in Lusaka Zambia is more likely to occur at a 1st Level referral hospital compared to an urban clinic and this calls for detailed analysis to find out why this difference occurs
- It is important to make sure all TB patient information is correctly filled and captured in the standard TB registers for programmatic performance tracking

Competing interests

The authors declare no competing interests.

Authors' contributions

FHN, SC, CCK, NL designed the study, performed the statistical analyses and data interpretation, and wrote the manuscript. NS contributed to study design and analyses and supervised this study. All authors reviewed and approved the final manuscript.

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Tables

Table 1: Socio-Demographic and Clinical Characteristics of Registered TB patients (N = 1537) by outcome at three Health Facilities in Lusaka District, Zambia, 2016.
Table 2: Bivariate Association between Demographic /Clinical Characteristics and Tuberculosis Mortality among TB Patients in Lusaka, Zambia, 2016
Table 3: Multivariable Analysis of Factors Associated with Tuberculosis Mortality among TB Patients in Lusaka, Zambia, 2016

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Table 1: Socio-Demographic and Clinical Characteristics of Registered TB patients (N = 1537) by outcome at three Health Facilities in Lusaka District, Zambia, 2016

Characteristic	**Died n(%)**	**Did not Die n(%)**	**Total n**	**P-Value**
TOTAL (n)	138 (9)	1339 (91)	1537	
SEX				0.80[a]
Male	88 (9)	907 (91)	995	
Females	50 (9)	492 (91)	542	
AGE GROUP				0.002[a]
0-14	3 (4)	71 (96)	74	
15-34	59 (8)	642 (92)	701	
35-54	55 (9)	582 (91)	637	
55-64	8 (12)	60 (88)	68	
> 64	13 (23)	44 (77)	57	
Patient type				<0.25[a]
New	101 (8)	1110 (92)	1211	
Relapse	35 (12)	259 (88)	294	
Treatment Resume	2 (7)	26 (93)	28	
HIV Status				<0.001[a]
Positive	108 (11)	866 (89)	974	
Negative	25 (5)	501 (95)	526	
Health Facility Type				<0.13[a]
Urban Clinic	51(8)	625 (92)	676	
1st Level Hospital	67 (11)	557 (89)	624	
Peri-Urban Clinic	20 (8)	217 (92)	237	

[a]**Chi-square test.**

Table 2: Bivariate Association between Demographic /Clinical Characteristics and Tuberculosis Mortality among TB Patients in Lusaka, Zambia, 2016

Characteristic	Total Number	Number died (%)	UOR (95% CI)	P-Value
Sex				
Male	995	88 (9)	1.00	
Female	542	50 (9)	1.04 (0.73, 1.51)	0.80
AGE GROUP				
0-14	74	3 (4)	1.00	
15-34	701	59 (8)	2.1 (0.66-7.12)	0.20
35-54	637	55 (9)	2.2 (0.68-7.34)	0.18
55-64	68	8 (12)	3.2(0.80-12.43)	0.10
> 64	57	13 (23)	6.9(1.89-25.93)	0.004
Patient Type				
New	1211	101 (8)	1.00	
Relapse	294	35 (12)	1.5 (1.08-2.23)	<0.05
Treatment Resume	28	2 (7)	0.8 (0.19-3.61)	0.82
TB Type				
Extra Pulmonary	249	25 (10)	1.00	
Pulmonary	1286	113 (9)	0.86 (0.55, 1.36)	0.52
HIV Status				
Negative	526	25 (5)	1.00	
Positive	974	108 (11)	2.5 (1.60-3.91)	<0.001
Health Facility				
Urban-Clinic	676	51(8)	1.00	
1st Level Hospital	630	67 (11)	1.5(1.01-2.16)	<0.05
Peri-Urban-Clinic	231	20 (8)	1.1(0.66-1.94)	0.67

CI; Confidence interval; uOR, Unadjusted Odds ratio;

Table 3: Multivariable Analysis of Factors Associated with Tuberculosis Mortality among TB Patients in Lusaka, Zambia, 2016

Characteristic		**Total Number**	**Number Died(%)**	**AOR (95% CI)**
Age Group	0-14	74	3 (4)	1.00
	15-34	701	59 (8)	2.1 (0.62-6.81)
	35-54	637	55 (9)	1.8 (0.54-5.90)
	55-64	68	8(12)	2.6 (0.64-10.69)
	>64	57	13 (23)	7.6 (1.97-29.55)
HIV Status	Negative	526	25 (5)	1.00
	Positive	974	108 (11)	3.1 (1.91-4.93)
Health Facility	Urban-Clinic	676	51(8)	1.00
	1st Level Hospital	630	67 (11)	1.6 (1.08-2.40)
	Peri-Urban-Clinic	231	20 (8)	1.1 (0.63-1.92)
Patient Type	New	1211	101 (8)	1.00
	Relapse	294	35 (12)	1.4 (0.89-2.80)
	Treatment Resume	28	2 (7)	0.4 (0.04-3.09)

CI; Confidence interval; aOR, Adjusted Odds ratio;