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Morbidity and mortality up to 5 years post tuberculosis treatment in South Africa: A pilot study

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ABSTRACT

Background: A high risk of tuberculosis (TB), chronic lung disease, and mortality have been reported among people with a history of previous TB treatment, but data from high-incidence settings remain limited. The aim of this study was to characterize general morbidity and mortality among adults who had successfully completed TB treatment in the past 5 years in a high-incidence setting in South Africa.
Methods: Adults (≥18 years) who had completed treatment for pulmonary TB between 2013 and 2017 were randomly selected from TB treatment registers. Household visits were conducted to locate and interview former TB (FTB) patients, and bacteriological testing for TB was offered. Additional data sources were used to ascertain the vitality status of FTB patients who could not be located.
Results: Addresses were located for 200 of the 223 FTB patients sampled and 89 FTB patients were contacted of whom 51 agreed to be interviewed. Approximately half reported persistent respiratory symptoms, such as shortness of breath and wheezing, and repeated lung infections. One (3.6%) of 28 patients who provided a sputum sample had culture-positive TB and another two were currently on re-treatment for TB. Fifteen deaths post treatment were ascertained, resulting in a standardized mortality ratio of 3.8 (95% confidence interval 2.3–6.3) after successful TB treatment relative to the general population.
Conclusions: In this high-incidence setting, locating and interviewing FTB patients was challenging. The study findings are consistent with a high rate of respiratory disease, including recurrent TB, and substantially elevated mortality among FTB patients.

Introduction

Tuberculosis (TB), an airborne infectious disease caused by *Mycobacterium tuberculosis*, accounts for considerable morbidity and mortality worldwide, with an estimated 10 million TB cases and 1.6 million TB deaths in 2017 (World Health Organization, 2018).

There is increasing awareness of the severe and potentially life-threatening adverse health consequences of TB after completion of treatment (Harries et al., 2016). Former TB (FTB) patients frequently suffer from pulmonary sequelae, chronic obstructive pulmonary disease (COPD) with impaired lung function, bronchiectasis (Allwood et al., 2018; Hnizdo et al., 2000; Menezes et al., 2007), pulmonary hypertension (Allwood et al., 2018), and residual cavitation with secondary bacterial and fungal infections (Allwood et al., 2018; Hedayati et al., 2015). In addition to non-TB lung disease, there is also a high risk of recurrent TB after successful treatment, associated with the extent of pulmonary involvement during the initial TB episode and residual cavitation (Panjabi et al., 2007; Rosser et al., 2018), and a higher risk of death compared to the general population (Fox et al., 2019; Miller et al., 2015; Shuldiner et al., 2016). Apart from health-related consequences, FTB patients and their families are faced with severe socio-economic challenges. Loss of income (Barter et al., 2012a), catastrophic costs during TB treatment (Tanimura et al., 2014), and lifelong disability with further loss of income may act as a poverty trap (Mudzengi et al., 2017; Barter et al., 2012b Barter et al., 2012b).

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To date, much of the evidence about adverse health consequences post TB treatment has come from countries with a relatively low burden of TB (van Kampen et al., 2018a); there are limited data from high TB incidence settings. Population-based studies in Uganda (van Kampen et al., 2018b) and South Africa (Hnizdo et al., 2000; Amaral et al., 2015; Buist et al., 2007; den Boon et al., 2007) have revealed a high burden of respiratory symptoms, chest X-ray abnormalities, and moderate to severe COPD, associated with a history of previous TB treatment. FTB patients constitute a large group (10/1000 population) in the adult population in several high TB burden communities in South Africa and also account for a considerable fraction of prevalent TB (19%) (den Boon et al., 2007; Marx et al., 2016a Marx et al., 2016a), suggesting opportunities for targeted TB control measures in this population (Marx et al., 2018).

A random sample of adult FTB patients from a community with a high TB incidence, who had successfully completed their TB treatment in the preceding 5 years, were selected for this pilot study. The aim was to determine whether it is feasible to locate, contact, and survey FTB patients on the basis of routine TB treatment records. A description of general and lung health based on self-reported symptoms and sputum testing for TB is given for the patients who were successfully contacted. Ascertainment of vitality status from the field visits, as well as from additional routine electronic data sources, was used to estimate the rate of general mortality post TB treatment in this setting.

Methods

Setting

This study was conducted in a community in suburban Cape Town, South Africa, with a population of 60 528 in 2011 (StatsSA, 2018). Local TB services, including diagnosis, standard treatment, and recording and reporting of TB cases, are provided by two local primary health care clinics, in line with South African National TB Programme (SA NTP) guidelines (National Department of Health, 2014). In 2017, 674 TB cases (57% co-infected with HIV) were reported in this community — a TB case notification rate of 1033 per 100 000 population.

Study design

For this cross-sectional study, electronic TB treatment register (ETR.Net) data were extracted for TB cases treated in the community between January 1, 2013 and June 30, 2017. A random sample of 256 adults (age $\geq$18 years) with bacteriologically confirmed pulmonary TB was obtained, whose documented standard TB treatment outcome was either 'cure' or 'treatment complete'. 'Cure' was defined as patients who had bacteriologically confirmed pulmonary TB at the beginning of TB treatment and were then smear- or culture-negative in the last month of treatment and at least one previous occasion during treatment. 'Treatment complete' included patients who had completed their treatment without evidence of bacteriological failure, but with no record of negative smears or cultures as defined in 'cure' (World Health Organization, 2014). Randomization was stratified by year of treatment registration.

Survey and data collection

Based on personal identifiers and recorded addresses, home visits were conducted between March and May 2018, to locate and contact FTB patients. Up to two separate home visits were conducted per address to locate and contact FTB patients. Experienced field staff fluent in the local language (isiXhosa) spoke to household residents and/or neighbours to locate FTB patients. Participants who were successfully contacted and who provided informed consent were interviewed using a standard questionnaire, which included demographic and socio-economic data, medical history of TB and other diseases, current TB and pulmonary symptoms, and common TB risk factors. Participants were further requested to provide a single sputum specimen. Samples were transported to the National Health Laboratory Services and tested using the Xpert MTB/RIF test (Xpert; Cepheid, Sunnyvale, USA) and by culture (BACTEC MGIT; Becton Dickinson, USA).

Use of additional data sources

Two further data sources were used to obtain additional information about deaths (including date of death) among the sampled FTB patients. Data from the patient-level Health Information Exchange (HIE) of the Western Cape Government Health Department were accessed. The HIE uses a unique health system patient identifier and compiles individual routine health-related data across all public health facilities in the province (Heekes et al., 2018). The HIE was also searched for the FTB patients' South African identity numbers, which are not recorded in the TB register. Where obtained, this was used to ascertain the vitality status in the South African population register.

Data analysis and mortality estimation

SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for the data analysis. The analysis included descriptive statistics of survey data and laboratory information obtained.

The rate of general mortality among FTB patients was estimated as the number of TB deaths per 100 person-years following the successful completion of TB treatment. Person-time was calculated for FTB patients who were located during the field work as the time between the documented TB treatment outcome and the interview date, or a single date of the field work for those FTB patients not interviewed. For deceased individuals, the date of death, as recorded in the electronic data sources, was used to ascertain the time since the recorded TB treatment outcome.

The standardized mortality ratio (SMR) was estimated as the ratio of deaths observed after TB treatment and the number of deaths expected in the general population of the same age. For standardization, we relied on age-specific estimates of general mortality projected by the Thembisa model, a deterministic, compartmental, mathematical model of the HIV epidemic in South Africa (Johnson et al., 2016). The model uses age-specific mortality probabilities for 1997–2010 derived from the South African National Burden of Disease study and projects rates from 2011 onwards. At calibration of deaths in those between 20 and 59 years of age, the Thembisa model reported good agreement between the modelled and recorded deaths (Johnson and Dorrington, 2018). For each FTB patient identified in the study, single-year mortality probabilities reflecting years of TB registration, age, and sex were extracted from the Thembisa model. The mortality probability and the person-time (years) between the completion of TB treatment and the study were used to estimate the expected deaths in the general population per FTB patient profile. Two SMR estimates were calculated. The first was based on deaths ascertained exclusively through the survey; the second included deaths ascertained through additional data sources.

Results

Description of the underlying population and sample

Between 2013 and 2017, a total of 2470 adult patients with pulmonary TB (≥18 years) were treated in the study community. Of these, 1734 (70%) had successfully completed their TB treatment and 142 (5.7%) had died during TB treatment; 18.4% of patients were lost to follow-up and 5% were transferred out. The mortality rate during TB treatment was 15 deaths per 100 person-years. A random sample of 256 individuals who had successfully completed TB treatment was obtained; these patients did not differ from those of the underlying cohort when stratified by year of treatment, or clinical and demographic characteristics (Table 1).

Outcome of household visits

Tracings were completed by the study team for a total of 223 of the 256 FTB patients initially sampled. Addresses were located for 200 of these 223 patients (90%) (Figure 1). Eighty-nine (45%) FTB patients were successfully located, of whom 51 (57%) agreed to participate in the survey. Other FTB patients had moved ($n = 48$; 24%) or could not be located ($n = 52$; 26%). The median time between successful completion of TB treatment and interviewing the FTB patient in this study was 2.6 years (interquartile range (IQR) 0.8–3.4 years). The FTB patients interviewed did not differ significantly from the patients who were not interviewed in terms of baseline demographic and TB characteristics.

Survey results

Of the 51 surveyed participants, 32 (63%) were male, the median age was 40 years (IQR 31–49 years), and 32 (63%) reported some form of employment in the last 12 months. Eighteen (35%) reported having had between two and four prior episodes of TB treatment. About half ($n = 26$; 49%) were recorded as HIV-infected at their last TB treatment. When asked, 36 of 51 were willing to disclose their HIV status, with 19/36 (52%) reporting that they were living with HIV. Fourteen (27%) of the 51 FTB patients reported a current cough and 12 reported coughing for 2 weeks or longer (Table 2). Other respiratory symptoms reported included regular shortness of breath while walking up a hill or when walking fast (28/51, 55%), needing to walk slower due to breathlessness (26/51, 51%), and wheezing (24/51, 47%). In addition, 15/51 (29%) reported at least one severe chest infection in the preceding year (Table 2).

The profile of FTB patients is shown in Table 2: 32/51 (63%) FTB patients had a smoking history, 41/51 (80%) reported previous or ongoing use of alcohol, and 2/51 (4%) had been imprisoned in the last 5 years. Thirty-five (69%) of the FTB patients were reliant on some form of social support grant in the home, the most common being a disability or child support grant.

Evidence of recurrent TB

Sputum was obtained from 28 FTB patients and one specimen was Xpert and culture positive. The one positive specimen was from a FTB patient who was known to local health services and at the end of the second month of TB treatment. Subsequent follow-up with routine health services indicated a good clinical response and negative specimens thereafter. Two other FTB patients, who were Xpert and culture negative, were currently on TB treatment at the local TB clinic.

General mortality in the study sample

The field strategy was completed in 223 of the 256 sampled FTB patients, and 11 (4.9%) deceased FTB patients were recorded. A mortality rate of 2.1 deaths (95% confidence interval (CI) 1.2–3.8) per 100 person-years was estimated, and an SMR of 3.1 (95% CI 1.7–5.5) (Table 3). The electronic databases were searched for mortality information for the 156 FTB patients for whom vitality status could not be confirmed via the survey (Figure 2). An additional four deaths were documented in the HIE, for a total of 15 (5.9%) deaths among the 256 FTB patients. This resulted in an overall mortality rate of 2.5 deaths (95% CI 1.5–4.1) per 100 person-years, and an SMR of 3.8 (95% CI 2.3–6.3) (Table 3).

Figure 3 demonstrates the overlap of the reporting sources for the 15 confirmed deaths. Two thirds of the deceased FTP patients were between 18 and 44 years of age; 9/15 (60%) were male and 12/15 (80%) were HIV-infected. All HIV-infected deceased patients were

Table 1
Comparison of TB treatment register characteristics between former TB patients sampled and not sampled for the study.

Variable	Category	Sampled		Not sampled	
		n	Column %	*n*	Column %
Total		256	100	1478	100
TB treatment registration year	2013	49	19.1	422	28.6
	2014	60	23.4	386	26.1
	2015	57	22.3	338	22.9
	2016	43	16.8	245	16.6
	2017	47	18.4	87	5.9
Age (years)	18–44	209	81.6	1165	78.8
	45–64	41	16.0	277	18.7
	>64	6	2.3	36	2.4
Sex	Female	91	35.6	572	38.7
	Male	165	64.4	906	61.3
TB patient category	New case	172	67.2	974	65.9
	Retreatment	84	32.8	504	34.1
Smear status	Unknown	46	18.0	285	19.3
	Smear-positive	107	41.8	603	40.8
	Smear-negative	103	40.2	590	39.9
HIV status	Unknown	0	0	11	0.7
	Negative	103	40.2	591	40.0
	Positive	153	59.8	876	59.3
TB treatment outcome	Cured	101	39.5	563	38.1
	Treatment completed	155	60.6	915	61.9

TB, tuberculosis.

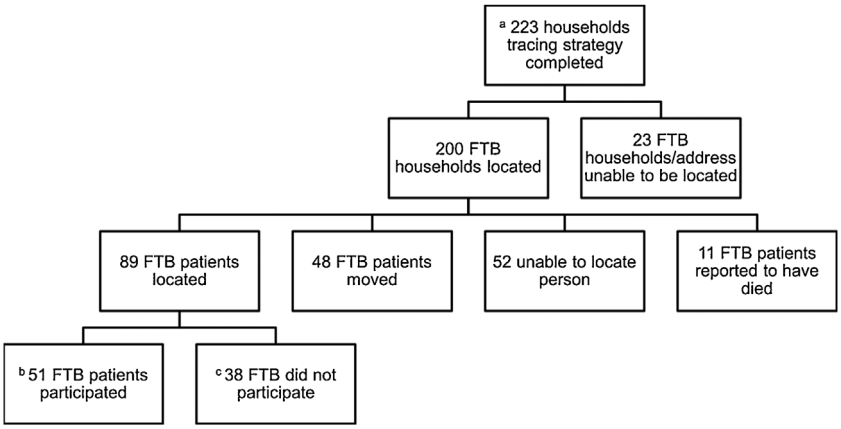

Figure 1. Overview of sampled former TB patients and the outcome of tracing activities. TB, tuberculosis; FTB, former TB.
[a]Two hundred and fifty-six FTB patients were sampled, but due to time and logistical constraints, the pre-specified household tracing strategy could only be completed for 223 individuals.
[b]An ongoing subsequent study in the same community has provided additional feedback: four of the 51 FTB participants interviewed in the present study were reported dead.
[c]Of the 38 who did not participate, one was too ill to participate, one denied having previous TB, and 14 cited time constraints due to work.

Table 2
Demographic, socio-economic, and self-reported respiratory symptoms of 51 former TB patients interviewed, stratified by the HIV status recorded at the time of their last TB treatment episode.

			HIV-uninfected		HIV-infected		Total	
			n	Column %	*n*	Column %	*n*	Column %
Demographics	Age category at the time of interview (years)	18–44	15	60	18	69	33	65
		45–64	9	36	8	31	17	33
		>64	1	4	0	0	1	2
	Sex	Female	6	24	13	50	19	37
		Male	19	76	13	50	32	63
Self-reported chest illness and respiratory symptoms	Current cough	No	17	68	20	77	37	73
		Yes	8	32	6	23	14	27
	Duration of current cough ($n = 14$)	<2 weeks	2	25	2	33	4	29
		≥2 weeks	6	75	4	66	10	71
	Severe chest illness in the last 12 months	No	18	72	18	69	36	71
		Yes	7	28	8	31	15	29
	Shortness of breath while walking up hill or fast	No	11	44	12	46	23	45
		Yes	14	56	14	54	28	55
	Needing to walk slower due to breathlessness	No	12	48	13	50	25	49
		Yes	13	52	13	50	26	51
	Wheeze	No	14	56	13	50	27	53
		Yes	11	44	13	50	24	47
Socio-economic profile	Ever smoked	No	8	32	11	42	19	37
		Yes	17	68	15	58	32	63
	Alcohol use	Have never drunk	6	24	4	15	10	20
		Daily drinker	0	0	1	4	1	2
		Occasional drinker	13	52	18	69	31	61
		Ex-drinker	6	24	3	12	9	18
	Imprisoned in the last 5 years	No	25	100	24	92	49	96
		Yes	0	0	2	8	2	4
	Type of social support grant in home if applicable ($n = 35$)	Disability grant	7	44	8	42	15	43
		Child support grant	7	44	12	63	15	43
		Grants for older persons	3	19	2	11	3	9
		Foster care grant	2	13	1	5	2	6
		Care dependency grant	0	0	2	11	2	6

TB, tuberculosis.

recorded as having been on antiretroviral therapy (ART) and co-trimoxazole prophylaxis during the TB episode. Thirteen patients had a confirmed date of death; the median time to death was 1.43 (IQR 0.48–2.16) years after successful completion of TB treatment. The date of death was unknown for two deceased FTB patients, and the average person-time of the 13 other deceased FTB patients was used to estimate the time between TB treatment and death.

Discussion

This study showed that tracing and locating FTB patients was time-consuming and difficult, despite available records of addresses in the electronic TB treatment register. Although it was possible to locate households from the addresses stored in the register, a large proportion of FTB

Table 3
Mortality rates and standardized mortality ratios for former TB patients using the vitality status as determined by two different search strategies.

Search process	Total number of former TB patients	Number confirmed dead[a]	Observation time (person-years)	Mortality rate[a] (95% CI)	Number of expected deaths[b]	Standardized mortality ratio (95% CI)
Field work	223	11	525.5	2.1 (1.2–3.8)	3.6	3.1 (1.7–5.5)
Using additional electronics searches	256	15	608.8	2.5 (1.5–4.1)	4.0	3.8 (2.3–6.3)

TB, tuberculosis; CI, confidence interval. The mortality rate is expressed as the number of deaths per 100 person-years of follow-up. The standardized mortality ratio is calculated as the number of observed deaths/expected deaths.
[a] An ongoing subsequent study in the same community has provided additional feedback: four of the 51 former TB participants interviewed were reported dead; these deaths, which occurred after the present study, are not included in the estimates.
[b] 'Expected deaths' reflects the number of deaths that should have occurred based on the mortality probability in the Thembisa model for the Western Cape.

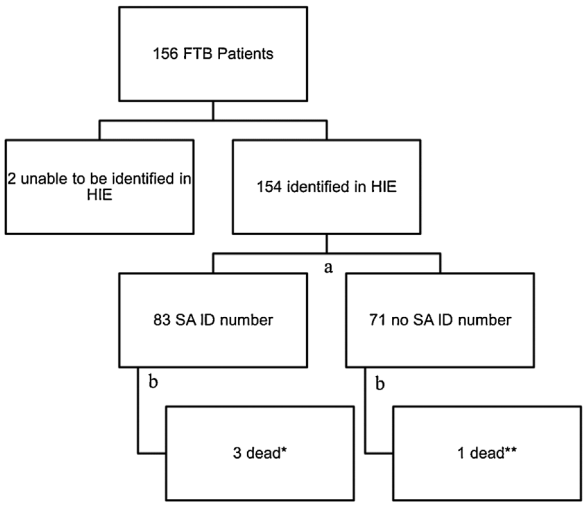

Figure 2. Overview of the search of additional electronic sources for vitality status of former TB patients not definitively ascertained in the field work ($n = 156$). HIE, health information exchange; TB, tuberculosis; SA, South Africa; ID, national identity number.
[a]HIE searched for South African identity numbers.
[b]HIE searched for mortality.
*Two of the three deceased were documented in the SA population register as deceased.
**The SA population register could not be searched as it is dependent on the use of an SA ID number.
Recorded as dead is as applied in the electronic register. Not dead does not automatically imply alive status but rather not recorded as dead.

patients had moved away or they were otherwise unable to participate.

Breathlessness and lung function loss after TB treatment are well documented (Ross et al., 2010; Allwood et al., 2013; van Kampen et al., 2019), and patients with chronic lung disease who have previously had TB have been shown to have chronic respiratory symptoms and recurrent hospital admissions (Mkoko et al., 2019). In the BOLD study, TB and smoking were associated with increased shortness of breath (Grønseth et al., 2014), and an earlier work showed that a chronic productive cough among South African adults was associated with previous TB, smoking occupational exposures, and domestic fuel exposure (Ehrlich et al., 2004). A systematic review has confirmed the increased risk of TB among smokers (Lin et al., 2007). In the present study, it was noted that 63% of interviewed FTB patients had a smoking history, and while lung function was not objectively measured and no attempt was made to classify chronic lung disease, it was possible to confirm that FTB patients who were successfully located commonly reported respiratory symptoms such as shortness of breath and wheezing, as well as repeated lung infections, consistent with chronic pulmonary impairment.

This study included three FTB patients with (recurrent) active TB; all had been detected by routine health services and initiated re-treatment. This finding of recurrent TB is consistent with earlier studies reporting a high prevalence of TB among FTB patients, who may also account for a high proportion of prevalent TB overall in communities (den Boon et al., 2007; Marx et al., 2016b Marx et al., 2016b). A recent modelling study suggested that active case finding and secondary prevention among FTB patients could substantially decrease TB morbidity and mortality in high-incidence settings (Marx et al., 2018), but trials of such targeted approaches have not been conducted.

This study reports a mortality rate after TB treatment exceeding that of the general population by several-fold, despite the successful course of TB treatment. The findings are consistent with those of an earlier study in a low burden setting, which followed FTB patients for a median of 5.9 years and documented an SMR of 3.7 (Shuldiner et al., 2016). More recently, an SMR of 4.0 (95% CI 3.7–4.2) for mortality after the start of TB treatment was reported in Vietnam, but this included mortality both during and after TB treatment (Fox et al., 2019). In that study from Vietnam, two thirds of deaths occurred after patients had been discharged from TB treatment (Fox et al., 2019). In a study conducted in Zimbabwe, Chin et al. noted that successfully treated TB patients had a 6-fold increased rate of mortality compared to the HIV-infected population and 15-fold increased rate of mortality compared to the general population in the first year after TB treatment (Chin et al., 2019). In the present study, a high proportion of those who were confirmed dead were HIV-infected, and although documented as on ART during treatment, this included those on ART prior to TB treatment and those starting ART during the TB treatment episode. The role of HIV, compliance with ART, and the degree of viral load suppression in the final cause of death could not be ascertained.

This was a pilot study of limited size and has important limitations. While it was possible to locate 90% of addresses of FTB patients, it was only possible to contact and interview less than half of the FTB patients. The ability to definitively locate FTB patients may vary depending on migrant patterns of specific communities and should be investigated further. Of the FTB patients located, a large number declined participation due to competing commitments. Interviewed patients did not differ from those who declined participation in terms of baseline characteristics. However, it is not possible to exclude the possibility that those who declined participation represented healthier individuals. While more objective measures of lung function or radiographic examinations were not performed, this study provided the basis for a more comprehensive study in the same location to quantify the loss of lung function. Following the field survey component of the study, additional data sources were used to obtain information on mortality. It was noted that neither strategy was complete and that deaths were missed in field work and electronic data searches. The reported mortality rates are documented for each strategy and likely represent underestimates, as it was assumed that FTB

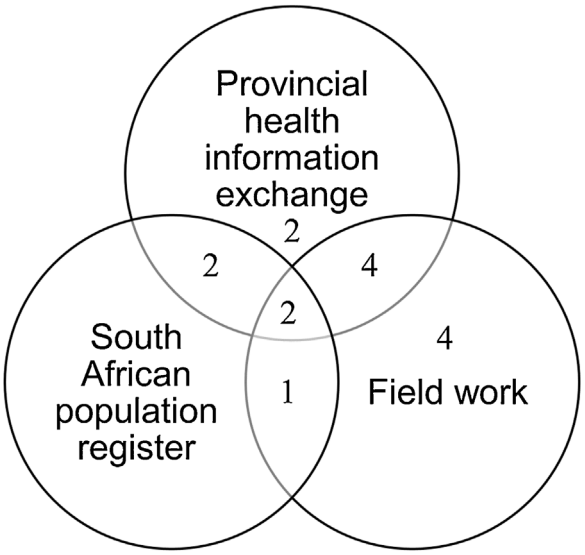

Figure 3. Venn diagram documenting the overlapping mortality sources in the confirmation of death and the number of deaths recorded through each source for the 15 documented deaths among former TB patients.

patients were alive when vitality status could not be ascertained. This has likely resulted in conservative estimates of mortality after TB treatment. It was not possible to determine the definitive cause of death or disentangle the effect of HIV and ART on mortality and it is acknowledged that we report all-cause mortality after TB treatment.

In conclusion, this study highlights a substantial burden of prevalent TB, symptoms of chronic lung impairment, and general mortality among FTB patients. Additional research and public health efforts are also needed to ensure proper management of adverse health consequences post TB in order to minimize these consequences, especially in high TB burden settings. The fact that FTB patients are in contact with the health system for the duration of TB treatment creates opportunities for secondary prevention, including appropriate education, follow-up, and treatment for individuals with lung impairment.

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Ethics statement

The study was approved by the Ethics Committee of the Faculty of Medicine and Health Sciences of Stellenbosch University (Reference N18/01/004). The Cape Town City Health Directorate (Reference 7952) and the Western Cape Government Health Department (Reference WC_201804_013) approved the use of routine data sources and individual identifiers. All participants provided written informed consent.

Conflict of interest

All authors declare no conflict of interest.

Author contributions

MO, AW, ACH, and FM conceived and designed the study. MO, FM, RD, RB, and GH developed the implementation plan for the study and oversaw all data collection and validation. MO, AW, and FM developed the data analysis plan. All authors provided critical input for the interpretation of data and contextualization of results. MO and FM produced the first draft of the manuscript. All authors reviewed the manuscript and provided critical input. All authors have reviewed the final version of the manuscript and approve of its content and submission for publication.

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