Tuberculosis in persons with sudden unexpected death, in Cape Town, South Africa

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A B S T R A C T

Background: Globally, tuberculosis (TB) remains one of the leading causes of death from a single infectious agent, but there has been little work to estimate mortality before the diagnosis of TB. We investigated the burden of diagnosed and undiagnosed TB in adult and child sudden unexpected deaths (SUDs) evaluated at Tygerberg Forensic Pathology Services, South Africa.

Methods: In a retrospective descriptive study spanning 2016, we identified all SUDs where active TB was detected at post-mortem and matched with routine health service data to differentiate decedents who were diagnosed or undiagnosed with TB before death. A patient pathway analysis of the health service activities preceding SUD in adults with active TB was conducted.

Results: Active TB was identified at post-mortem in 6.2% (48/770) of SUDs and was undiagnosed before death in 91.7% (44/48). The prevalence of active TB was 8.1% in adult SUDs (90.1% undiagnosed before SUD) and 1.8% in children (none diagnosed before SUD). Patient pathway analysis was possible for 15 adult SUDs, and this documented primary health care clinic attendances and hospital admissions in the six months preceding death and missed opportunities for TB investigations.

Conclusion: The prevalence of TB among SUDs in the Eastern Metro of Cape Town is high. Most active TB at post-mortem was undiagnosed before death, and multiple missed opportunities for TB investigation and diagnosis were noted. The systematic evaluation of all SUDs for TB could improve the reporting of undiagnosed TB and support risk mitigation for healthcare workers involved with the post-mortem process.

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Background

Infectious airborne Tuberculosis (TB) is one of the leading causes of death globally (World Health Organization, 2020) and the leading cause of death in South Africa (Statistics South Africa, 2018). The World Health Organization (WHO) estimated that 10 million people developed TB disease globally, and South Africa accounted for 3.6% of this burden. HIV accounted for 58% of the estimated incident TB in South Africa. Only 58% of people with incident TB started antituberculosis treatment in 2019 (World Health Organization, 2020). Despite advances in diagnosis and adequate treatment, the WHO estimated that 1.2 million HIV-negative people with TB and a further 208,000 HIV-positive people with TB died globally, with 58,000 deaths estimated to have occurred in South Africa in 2019 (World Health Organization, 2020). The South African population register recorded 47,206 deaths in 2016, which included TB as an underlying or contributing cause of death (Statistics South Africa, 2018).

Quantifying mortality before TB treatment is challenging, as it reflects individuals who have not engaged with the health system

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(undiagnosed TB deaths) or who were lost to follow-up after an initial diagnosis of TB. Estimates of mortality before TB treatment have been made through post-mortem studies and are dependent on the region, the sample population (e.g., hospital vs. community), and the prevalence of TB in the post-mortem population. Most of these studies evaluated in-hospital death, and the prevalence of TB ranged from 0-64%, with undiagnosed TB ranging from 46-67% (Flavin et al., 2007; Garg et al., 2011; Gupta et al., 2015). In a community-based study from Matlosana, South Africa, 31.8% of adults dying at home without an apparent cause had TB diagnosed at post-mortem (Omar et al., 2015).

Sudden unexpected death (SUD) is defined as a death in an individual where a medical practitioner could not certify the cause of death with confidence. It includes individuals with no previous medical history or who had insufficient symptoms preceding their death to adequately explain the cause of death by the attending medical practitioner. In South Africa, all SUDs are by law required to be evaluated by the Forensic Pathology Services (FPS) (South African Government, 1959, 2018). In the Western Cape Province, South Africa, FPS are rendered by 16 facilities across the province, including two academic training centers. Tygerberg FPS, one of the two academic centers, evaluated 816 SUDs among adults between 2001 and 2005 (Tiemensma and Burger, 2012). The burden of undiagnosed TB in adult and child SUDs has not been estimated in this setting. We aimed to estimate the prevalence of TB and quantify the burden of diagnosed and undiagnosed TB in adult and child SUDs routinely evaluated at the Tygerberg FPS in Cape Town, South Africa.

Methods

We conducted a retrospective descriptive study of all SUDs admitted to Tygerberg FPS during 2016 that were documented in the existing FPS register. Data was extracted from retrieved pathology reports into a standard case record form by research assistants using a digital data capture tool. All SUDs were matched with routine data sources for health visits, laboratory information, TB treatment registers, and other health activities preceding death, including primary health care (PHC) attendance or hospital admission. Following linkage with routine data, information on previous TB diagnoses, the time since the previous TB diagnosis, and the most recent TB treatment outcome were documented. For decedents with TB detected at the time of SUD, a detailed account of activities in the six months preceding death was documented.

Setting

The City of Cape Town is a defined health district with a population of four million people (City of Cape Town, 2017) and includes two geographical service areas, Metro West and Metro East. The population HIV prevalence estimate for Cape Town was 9.5% in 2017 (Simbayi et al., 2019), and the estimated incidence for TB was 596/100,000 (Massyn et al., 2016) in 2015. Tygerberg FPS is responsible for Metro East, including the Khayelitsha, Eastern, Tygerberg, and Northern Health sub-districts, and has 71 PHC facilities and four district hospitals, serving approximately 51% of the city's population (~2.04 million people). During 2016, the City of Cape Town reported 30,114 deaths; 85.5% (25,755/30,114) of all deaths were due to natural causes, and 5.0% (1,296/25,755) of the deaths due to natural causes were due to TB (Statistics South Africa, 2018). FPS in Cape Town received 25.2% (7,596/30,114) of all decedents for evaluation; 49.6% (3,766/7,596) of FPS referrals were received at Tygerberg FPS, and 21.1% (793/3,766) of deaths evaluated by Tygerberg FPS were classified as SUD.

Forensic Pathology Services

Prior to the medico-legal post-mortem examination, a trained Forensic Pathology Officer interviews the next of kin and completes a standard questionnaire. At Tygerberg FPS, each SUD referral is evaluated by a specialist pathologist who decides on the possibility of ascertaining and reporting causes of death through the process of 'view and grant' without autopsy or the need for a complete post-mortem autopsy. All 'view and grant' reports are done by a specialist medical pathologist by reviewing the case history, performing an external clinical examination, and typically including a radiological screening. All post-mortem autopsies are done by a specialist pathologist or a specialist in training under the specialist pathologist's supervision and include a complete autopsy, with the opening of all anatomical regions of the body. In case the cause of death can be ascertained through the history and external examination at post-mortem autopsy, no further investigations are done. Specimens for toxicology, chemistry, microbiology, or histology are taken at the discretion of the pathologist and typically only where the cause of death is uncertain, the autopsy revealed no findings, or for future evidentiary purposes. Every death is then classified as natural or unnatural, and the immediate, underlying and contributory causes of death are recorded in the pathology report. Pathologist reports are submitted to the courts as a specialist medical opinion where a final cause of death is declared by the magistrate, and a decision on further investigation or prosecution is made.

Diagnosis of TB

The diagnosis of TB at post-mortem is made by the pathologist based on the evaluation of the history, external clinical examination (features supportive of TB include wasting, peripheral lymphadenopathy, clubbing), pathological examination of all organs (features supportive of TB include empyema, atypical pustular loculations, caseating nodular lesions, miliary patterns, airway compression by nodes), and any additional investigations. For TB, this may include radiological and histological findings. Macroscopic evaluation of the lungs is extensive, with the complete removal of the thoracic plug, weighing of the lungs, and each lobe being sliced for inspection. Additional specimens for GeneXpert MTB/RIF assay (Xpert; Cepheid, Sunnyvale, CA), microbiological TB culture, or testing for HIV are typically not done post-mortem. When TB is diagnosed by the pathologist, a distinction between active TB versus resolved TB is usually documented based on the pathological findings. 'Active TB' is the pathologist's interpretation of findings reflecting current active TB disease at the time of SUD, including soft, caseating, inflammatory lesions, miliary patterns, or pulmonary consolidation and hilar nodes in children; 'Resolved TB' where the pathologist deemed the findings related to TB to have occurred previously in the decedent's life with subsequent scarring, fibrosis and chronic changes associated with TB; and 'TB at SUD' as the presence of features associated with TB at the time of SUD regardless of whether it was active or resolved TB. When active TB is suspected or diagnosed, no routine link with health services to establish whether these patients were on TB treatment at the time of death is made as FPS currently does not have routine access to the Provincial Health Data Centre (PHDC). Findings of TB at post-mortem do not contribute to TB reporting, as South Africa reports TB via TB treatment registers.

Provincial Health Data Centre (PHDC)

The Western Cape Government: Health Department has a PHDC, established in 2015, which uses a unique health system

patient identifier to harmonize electronic records of attendances and health services provided (laboratory, pharmacy, or diagnostic) at all public sector health care facilities to produce a single patient record (Boulle et al., 2019). Records of all SUDs were matched to the PHDC using the name, surname, date of birth, and death date.

Statistical analysis

Age was stratified based on WHO definitions into two categories: children <15 years and adults ≥15 years. Descriptive statistics for baseline demographics and TB symptoms, features of TB on examination, and histology were stratified by the type of TB noted at post-mortem (active TB or resolved TB). Continuous variables were evaluated, and medians and interquartile ranges (IQR) were presented due to the presence of outliers. For decedents with active TB detected at post-mortem, a detailed patient pathway analysis was completed and depicted graphically. We used SAS software, Version 9.4. Copyright © 2002-2012 SAS Institute Inc., Cary, North Carolina, USA.

Ethics

This study was approved on the National Health Research Database (WC_201809_009) and at Tygerberg Hospital. Ethical approval was received from the Stellenbosch University Health Research Ethics Committee (S17/10/257). A waiver of informed consent was granted.

Results

There were 793 SUDs referred to Tygerberg FPS during 2016. We were able to retrieve 770 (97.1%) pathology reports. The prevalence of active TB (diagnosed and undiagnosed) at post-mortem was 6.2% (48/770); 8.1% (44/543) among adults and 1.8% (4/227) in children (Figure 1). Of the 44 adults with TB, we were able to match 25/44 (56.8%) to the PHDC; 4/44 (9.1%) were diagnosed with TB before their death, and all four were on TB treatment while none of the children were diagnosed before death.

TB and adult SUDs

Where the pathologist was able to classify the nature of death, 355/413 (86.0%) adult SUDs were natural causes of death, including 40/44 (90.9%) SUDs with active TB. The median age among all adult SUDs was 46.8 (IQR: 34.7-60) years and 46.5 (IQR: 35.5-55.9) years in those with TB at SUD. The median BMI among all adult SUDs was 25.7 (IQR: 22.0-30.1) kg/m^2 and 22.4 (IQR: 18.8-27.7) kg/m^2 in those with TB. Among the adult SUDs due to natural causes with active TB, 7/40 (17.5%) did not include TB as a final or contributing cause of death in the post-mortem report. Pathological changes associated with resolved TB were documented in nine adults at SUD and were noted among the causes of death in four of the nine adults. Based on collateral history from family or alternative contact that was interviewed, 16/543 (2.9%) had a history of HIV reported; 50/543 (9.2%%) had ≥1 possible TB symptom, and 19/543 (3.5%) had a medical history of TB before death, but the timing was not specified. Loss of weight preceding death was the most common TB symptom reported in 40/50 (80%) decedents who reported any TB symptoms. The diagnosis of TB at SUD by FPS was based on features of TB on post-mortem examination in 30/543 (5.5%) and features on histology in 22/543 (4.1%) (Table1).

Linkage to the PHDC was possible in 288/543 (53.0%) adults; 19/288 (6.6%) adults linked to the PHDC had a record of TB; 7/19 (41.2%) adults with a record of TB in the PHDC had multiple TB treatment episodes; 8/19 (42.1%) adults with a record of TB in the PHDC were previously lost to follow up after having been diagnosed with TB, a median of 53.0 (IQR: 25.2-91.7) months before death (4/8 previously lost to follow up adult TB patients had initiated TB treatment); and 4/19 (21.1%) adults with a record of TB in the PHDC had their most recent TB episode in the six months preceding death. Of the adults with a record of TB in the PHDC, 1/19 (5.3%) did not have TB detected at SUD by FPS and was excluded from the estimate of TB prevalence at SUD (Figure 2). This patient had a positive mycobacterial culture six days before death but had not started TB treatment. Of the 44 adult SUDs with active TB, 25/44 (56.8%) could be matched to the PHDC; 2/25 had no activity recorded in the PHDC, and 8/25 did not have recent activity (last activity recorded >6 months before death). Of the remaining
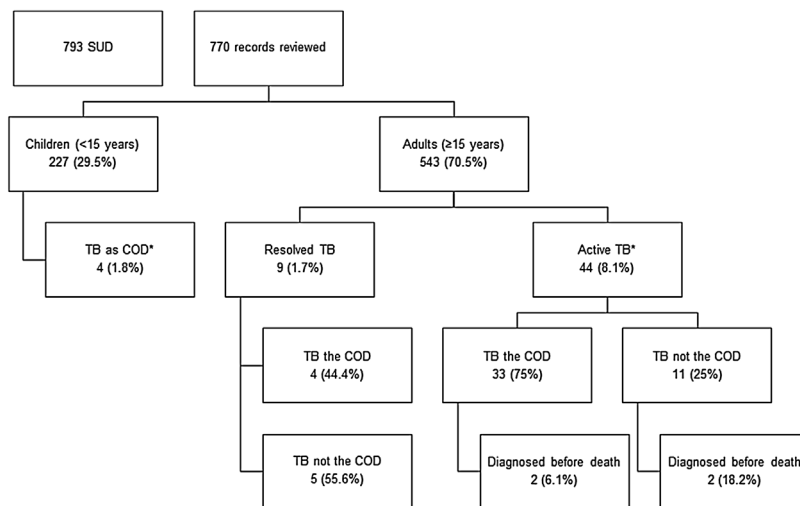

Figure 1. Flow diagram of records extracted of sudden unexpected deaths and tuberculosis as classified by pathologists at Tygerberg Forensic Pathology Services, South Africa, 2016
*1 child and 1 adult were found to have TB following linkage with the Provincial Health Data Centre, and TB was not noted in the post-mortem evaluation. These decedents are not included in the flow diagram
COD: cause of death; SUD: sudden unexpected death; TB: tuberculosis

Table 1
Overall demographic and clinical characteristics of sudden unexpected deaths among adults stratified by tuberculosis status at Tygerberg Forensic Pathology Services, South Africa, 2016 (n = 543).

		Total (N=543)		No TB (n=490)		Resolved TB (n=9)		Active TB (n= 44)	
		n	(col%)	n	(col%)	n	(col%)	n	(col%)
Demographic characteristics									
Age	15-24 years	31	(5.7%)	29	(5.9%)	0		2	(4.5%)
	25-34 years	106	(19.5%)	98	(20.0%)	0		8	(18.2%)
	35-44 years	119	(21.9%)	107	(21.8%)	1	(11.1%)	11	(25.0%)
	45-54 years	103	(19.0%)	90	(18.4%)	2	(22.2%)	11	(25.0%)
	55-64 years	106	(19.5%)	96	(19.6%)	4	(44.4%)	6	(13.6%)
	65+ years	78	(14.4%)	70	(14.3%)	2	(22.2%)	6	(13.6%)
Sex	Female	175	(32.2%)	159	(32.4%)	2	(22.2%)	14	(31.8%)
	Male	368	(67.8%)	331	(67.6%)	7	(77.8%)	30	(68.2%)
Collateral medical history									
HIV reported		16	(2.9%)	15	(3.1%)	0		1	(2.3%)
Previous TB		19	(3.5%)	8	(1.6%)	1	(11.1%)	10	(22.7%)
Any symptoms of TB*		50	(9.2%)	40	(8.2%)	2	(22.2%)	8	(18.2%)
	Cough	12/50	(24.0%)	10/40	(25.0%)	0		2/8	(25.0%)
	Loss of weight	40/50	(80.0%)	30/40	(75.0%)	2/2	(100.0%)	8/8	(100.0%)
	Night sweats	4/50	(8.0%)	4/40	(10.0%)	0		0	
Post-mortem findings									
Classification of death*	Natural	354	(65.2%)	306	(62.4%)	9	(100.0%)	39	(88.6%)
	Unnatural	59	(10.9%)	56	(11.4%)	0		3	(6.8%)
	Undetermined	130	(23.9%)	128	(26.1%)	0		2	(4.5%)
Completed autopsy		529	(97.4%)	482	(98.4%)	8	(88.9%)	39	(88.6%)
Macroscopic features of TB		30	(5.5%)	0		4	(44.4%)	26	(59.1%
Histological features of TB		22	(4.1%)	0		6	(66.7%)	16	(36.4%)
Health information linkage with PHDC									
Linked successfully		288	(53.0%)	257	(52.4%)	6	(66.7%	25	(56.8%)
Previous TB investigations		46/288	(16.0%)	36/257	(7.3%)	2/6	(33.3%)	8/25	(32.0%)
Previous TB treatment record		19/288	(6.6%)	10/257	(2.0%)	3/6	(50.0%)	6/25	(24.0%)

*The classification of death is as reported by the forensic pathologist.
**Any symptoms of TB included a summary of decedents with either, cough, loss of weight or night sweats.
FPS: Forensic Pathology Services; PHDC: Provincial Health Data Centre; TB: tuberculosis.
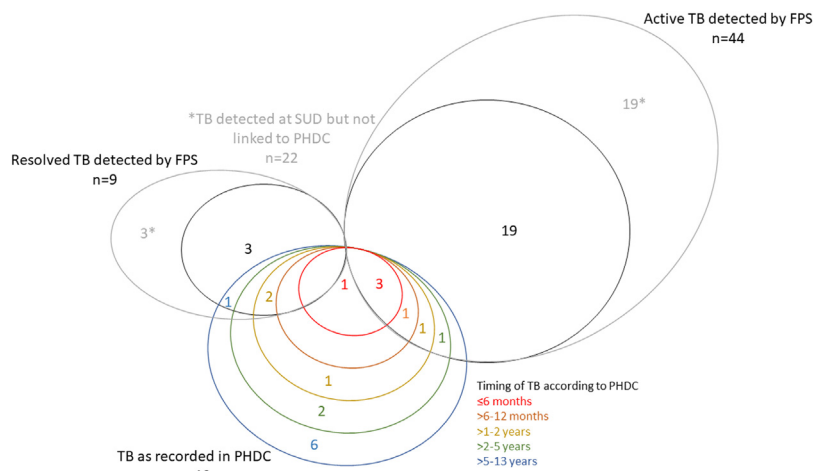

Figure 2. The overlap of sudden unexpected deaths with TB detected at post-mortem, and the timing of TB diagnosed before death as reported in the Provincial Health Data Centre.
FPS: Forensic Pathology Services; PHDC: Provincial Health Data Centre; SUD: sudden unexpected death; TB: tuberculosis.

individuals, 15/25, 60%) had details of attendance at health services in the public sector in the six months preceding death (Figure 3). In the time preceding death, we identified, among others, a 16-year-old female who had three attendances at PHC clinics with the receipt of antibiotics on each occasion, but no record of TB investigations; three patients who were hospitalized, including admission to the intensive care units in two and a diagnosis of lower respiratory tract infection in the third, of which only one had a single Xpert sample (recorded as negative); and two HIV-positive patients who returned to the PHC clinics following absences of

more than one year, were not investigated for TB and died with disseminated TB (Figure 3).

TB in child SUDs

Overall, 227/770 (29.5%) SUDs occurred in children (<15 years), with 190/227 (83.7%) occurring in infants (<1 year of age). Based on the post-mortem evaluation, four children had active TB at the time of SUD, two with pulmonary TB and two with disseminated and extrapulmonary TB, which included TB meningitis and
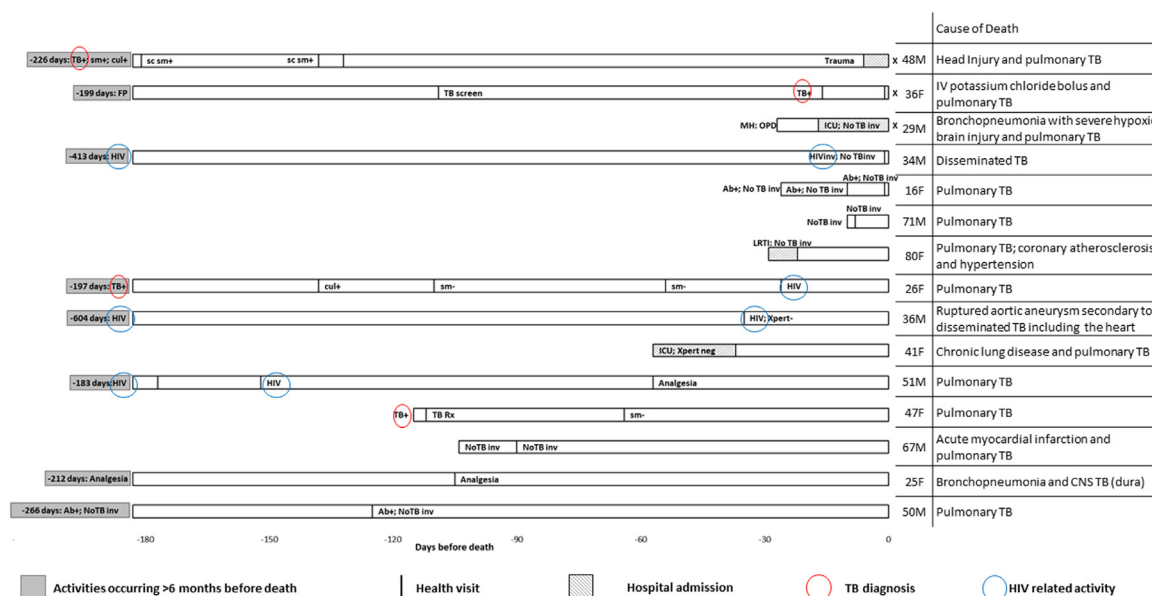
Figure 3. Patient pathway analysis of 15 adults with sudden unexpected death and tuberculosis documenting the details of public health service activities in the six months preceding death.

All health service activities depicted were at primary health care except when denoted as hospital outpatient department or hospital admission;

Ab+: antibiotics issued; CNS: central nervous system; Cul: culture; F: female: ICU: intensive care unit; Inv: investigations; IV: intravenous; LRTI: lower respiratory tract infection; M: male; MH: Mental health; OPD: outpatient department; sc: scanty; sm: smear; TB: tuberculosis; X: In-hospital death; Xpert: Xpert MTB/RIF; +: positive; -: negative

mesenteric adenitis. Only two children with active TB could be matched to the PHDC; there was limited attendance at routine health services in the time preceding death (Table 2). Through matching, 122/227 (53.7%) child SUDs were linked to the PHDC, and 4/122 (3.3%) were found to have a record of TB in the PHDC. One child had TB > 9 years before death, two children had TB detected by FPS at SUD (Table 2), and one child, six months old, was diagnosed with TB 34 days before dying. The diagnosis was based on a culture result; the child had not started TB treatment; TB was not detected at post-mortem evaluation by FPS, and the child was not included in the estimate of TB prevalence in children with SUD.

Discussion

Despite a lack of systematic evaluation for TB in all persons with SUD in this high-burden TB setting in South Africa, we document a high prevalence of active TB at post-mortem in individuals with SUD, 8.1% in adults (90.1% undiagnosed before death), and 1.8% in children (none diagnosed before death). A small number of SUDs (n = 9) had resolved TB detected at SUD and in nearly half, resolved TB was listed as part of the causes of death. Matching to routine health data sources was limited, but identified one adult and one child in whom TB was not detected by FPS during the post-mortem evaluation despite TB being diagnosed before SUD (but neither had

Table 2
Detailed description of children with sudden unexpected death and with tuberculosis at post-mortem evaluation at Tygerberg Forensic Pathology Services, South Africa, 2016 (n = 4)[a].

Age (months)	Sex	Symptoms before death	Length (cm)	Mass (kg)	Z score WHO weight for length	Physique	Nutrition	Road to health booklet and vaccinations	Cause of death	Data from routine services
3	Female		60.0	4.2	−3.9	Well built	Well-nourished	Book available BCG recorded; Vaccinations incomplete HIV status unknown	Pulmonary TB and left-sided pleural empyema	At birth – no further contact with public health services
9	Female	Cough and runny nose	69.0	4.52	−7.0	Poor and emaciated	Undernourished	Book available BCG recorded; Vaccinations incomplete HIV status unknown	Pneumonia against the background of malnutrition and pulmonary TB	PMTCT provided at birth, 2 visits to PHC after birth. No visits after age 2.5 months
14	Female		71.0	6.4	−3.1	Emaciated	Dehydrated	RTHB not available	Consistent with TB meningitis	No routine records
36	Male	Stomach problems	100.0	23	>2	Good	Good	RTHB not available	Consistent with TB mesenteric adenitis,	No routine records

BCG: *bacille Calmette-Guérin*; HIVe: HIV exposure; PHC: primary health care; PMTCT: prevention of mother to child transmission; RTHB: the road to health booklet; TB: tuberculosis; WHO: World Health Organization.

[a] One child who did not have TB detected at post-mortem evaluation was found to have TB diagnosed before death according to matching with the PHDC and was not treated. This child is not included in the above.

received TB treatment). In adults with active TB at SUD, we have identified multiple interactions with health services preceding death, presenting missed opportunities to investigate TB.

In Cape Town in 2016, 85.5% of all deaths were due to natural causes, and 5.0% of natural deaths were due to TB (Statistics South Africa, 2018). The overall prevalence of active TB in adults and children with SUD in our study was 6.2%, and as seen in earlier work from this setting, it differed considerably by age. In research from India (a high TB, low HIV prevalence setting), published in 2011, the prevalence of TB at post-mortem was 8.7%, with 60% of cases undiagnosed before post-mortem (Garg et al., 2011). In a systematic review and meta-analysis of health facility-based post-mortem studies of HIV-positive individuals, the prevalence of TB differed by age, with an adult TB prevalence of 39.7% and 4.5% in children, with 45.8% of TB undiagnosed before death (Gupta et al., 2015). A much higher prevalence is expected as the review was restricted to HIV-positive deaths, included mostly in-hospital deaths, and spanned 1992-2012 (Gupta et al., 2015), the period during which the incidence of TB in South Africa peaked and before the scale-up of antiretroviral therapy for HIV (Osman et al., 2020). In Matlosana, South Africa, with a population HIV prevalence of 13.3% and annual TB incidence of 937/100,000, a community-based study using minimally invasive autopsies in a series of adults dying at home with no apparent cause of death, the prevalence of TB was 31.8% (27/85) (Omar et al., 2015). The context differs from our study in several respects: in 2012 Matlosana had a higher background prevalence of TB (937/100,000) compared to 741/100,000 in Cape Town (Massyn et al., 2013)), the period of study (2012 vs. 2016) differs, and the method of ascertainment of TB diagnosis differs, the Matlosana study using Xpert and culture on all decedents (Omar et al., 2015). At Tygerberg FPS, between 2001-2005, the prevalence of TB among adults with SUD was 37/601 (6.2%) but did not differentiate active or resolved TB at SUD, the proportion of TB undiagnosed before SUD, nor the health-seeking patterns of decedents with active TB at SUD (Tiemensma and Burger, 2012). In our study, the TB prevalence among adults was 8.1% but included six times more adults with TB disease (n = 44 in one year vs. n = 37 in five years (Tiemensma and Burger, 2012)). The persistent high prevalence of TB at SUD in Cape Town raises concerns about implementing case-finding strategies, adequate case detection, and treatment initiation in this setting.

In the patient pathway analysis, we documented the interactions of 15 adults with TB detected at SUD in the six months preceding their death and highlighted the multiple missed opportunities for TB investigation at PHC clinics and during hospital admissions. In a systematic review of patient pathways following presentation for TB at health facilities, symptom screening was very poorly done, and only 38% (IQR: 22-45%) of symptomatic patients were offered TB investigation (preprint) (Divala et al., 2020). In a recent study in our setting, using a standardized patient methodology, with a defined minimum level of case management for TB, including TB sputum testing and offering an HIV test, only 43% received the minimum standard (Christian et al., 2018). This study focussed on gaps in clinical practice at PHC, which are also evident in our study. Missed opportunities for TB investigation need to be addressed, especially in hospitals, where the mortality is exceptionally high (Ford et al., 2016). Undiagnosed TB in healthcare and post-mortem facilities place healthcare workers at an added risk of exposure to infectious TB (Baussano et al., 2011; Grobler et al., 2016).

Our study observed a TB prevalence of only 1.8% (4/227) in children with SUD. In earlier work, the population-adjusted prevalence of TB disease at autopsy in Zambia was 18.8%, but this was based on children admitted with respiratory illness to a large teaching hospital between 1997 and 2000 (Chintu et al., 2002), where one would have expected the prevalence of TB to be much higher than among SUD. Future work is needed to systematically evaluate all child SUDs and children with respiratory disease at post-mortem for TB. For 2/4 children with TB at SUD, we could ascertain the vaccination status, and while bacilli Calmette-Guérin (BCG) had been given, the vaccination record was incomplete and indicates a gap in health service engagement. In our study, the youngest children had severe pulmonary TB, while the two older children had disseminated TB. Opportunities for earlier TB and HIV diagnosis and treatment in children must be prioritized and are available within existing health services. South Africa implements the expanded program of immunization (Dlamini and Maja, 2016), and the Western Cape has implemented "the first 1000 days" to focus on children under two years (English et al., 2017). Both these programs present opportunities for regular interaction with infants and children. Case studies using peer educators to screen for TB at post-natal clubs have been well described (Bamford, 2019), but integration into routine services is lacking.

We have shown that the number of adults referred with SUD to FPS has increased 3-fold from 826 over five years (2001-2005) (Tiemensma and Burger, 2012) to 543 in one year, and the number of adult SUDs with TB has increased 6-fold with 37 over five years (Tiemensma and Burger, 2012) compared to 44 cases in one year. The impact of this change on workload, the working environment, time to conclusion of post-mortem evaluation, and the increased risk of occupational exposures to TB should be considered. Access to routine health service data provides critical insights around a decedents' prior health status. If treating medical practitioners were provided with access to routine health service data as accessed through the PHDC, referrals to FPS for SUD evaluation may be reduced, and pathologists could make more complete evaluations of each SUD before post-mortem with risk mitigation. We found that collateral history of symptoms was not helpful, and non-specific TB symptoms or a history of previous TB was seen in SUDs with and without active TB. In a research setting, using a trained nurse, minimally invasive techniques (lung core biopsies through a single one cm incision in each axilla) with Xpert as the diagnostic tool applied to biopsy specimens, M. tuberculosis was confirmed in 13/20 TB cases (Omar et al., 2015). Consideration of this technique's feasibility and yield is required as part of a systematic approach for evaluating all SUDs in the standard setting. In Ireland, following a prevalence of 0.3% of TB disease at autopsy, concern about the exposure of healthcare workers to TB was raised, and a call for protective strategies was made (Flavin et al., 2007). A systematic review of healthcare workers and TB exposure has documented a high burden of TB among South African healthcare workers and suggested a greater risk of transmission could be due to the burden of undiagnosed TB (Grobler et al., 2016). This review and more recent qualitative work at a large tertiary hospital in South Africa did not specify the forensic setting as a high-risk location (Grobler et al., 2016; Malotle et al., 2017). Based on the high prevalence of undiagnosed TB, measures to implement and support the occupational health and safety standards to protect healthcare workers in the forensic setting are needed.

This study is restricted to a specific population of SUDs referred to FPS. It excludes unnatural deaths (including injuries) with an apparent cause of death and natural deaths where a medical practitioner could ascertain the cause of death. While access to care may differ by socioeconomic status, earlier work has shown that homeless people in urban settings of South Africa were able to access health facilities and were satisfied with the treatment they received (Seager and Tamasane, 2010). Considering this and the network of health facilities available in this setting, this sample of SUDs is unlikely to be biased towards the homeless or indigent population. Our study's limitation is that specimens were not

collected and tested for HIV, reflecting the setting where specimens and testing for routine evaluation or academic purposes are not done. The reporting of 'resolved TB' in our study is likely an underestimate for multiple reasons. Firstly, resolved TB is not specifically ascertained; secondly, where changes are minimal, pathology reports may not include isolated features such as apical pleural adhesions. Finally, individuals who have previously had TB with good resolution may not have findings easily identifiable at macroscopic post-mortem examination. A further limitation of this study is the small sample size and findings, which may not be generalizable to broader contexts, especially for the child SUDs with TB. This study is further limited by the poor matching of SUDs to the routine health data. This may be due to individuals never accessing care in the Western Cape Province before death, possibly unwell individuals in other provinces who arrived in the Western Cape just before death.

Further work to investigate the patterns and reasons for patient movement is required. Differences in names, surnames, dates of birth, and the failure to use the health identifier in FPS also likely contributed to poor matching. Utilization of the routine unique health identifier for each SUD seen in FPS should be considered, combined with a field study to interview families and search medical records for any history of public or private health service engagement before death. Despite the limited number of records matched, this study provides the first rich patient pathway analysis in SUDs with TB.

We have described a significant burden of TB among SUDs in Cape Town, Metro East. Most of the TB detected at post-mortem was undiagnosed before death, and we highlight several missed opportunities for TB diagnosis and treatment. Improved and regular access to routine data sources for clinicians before referral to FPS and FPS staff before evaluating SUDs is a simple intervention that needs to be implemented as a priority. The use of non-invasive techniques and rapid diagnostics as part of a systematic evaluation of all SUDs is a potential intervention for FPS consideration. It may facilitate a reduction in occupational exposure and the expedited evaluation of some SUDs. The notification of TB for public health reporting and contact investigation should still be enforced, despite the ongoing medico-legal death investigation, as TB remains a reportable disease. Health system interventions beyond FPS are critical to close the gaps identified for timely TB investigation and diagnosis.

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Conflict of interest

Author contributions

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References

Bamford L. In: Shung-King M, Lake L, Sanders D, Hendricks M, editors. The first 1,000 days: Ensuring Mothers and Young Children Thrive. South African Child Gauge 2019; 2019.

Baussano I, Nunn P, Williams B, Pivetta E, Bugiani M, Scano F. Tuberculosis among health care workers. Emerg Infect Dis 2011;17(3):488–94.

Boulle A, Heekes A, Tiffin N, Smith M, Mutemaringa T, Zinyakatira N, et al. Data centre profile: the provincial health data centre of the Western Cape Province, South Africa. Int J Popul Data Sci 2019;4(2).

Chintu C, Mudenda V, Lucas S, Nunn A, Lishimpi K, Maswahu D, et al. Lung diseases at necropsy in African children dying from respiratory illnesses: a descriptive necropsy study. Lancet 2002;360(9338):985–90.

Christian Cs, Gerdtham Ug, Hompashe D, Smith A, Burger R. Measuring quality gaps in TB screening in South Africa using standardised patient analysis. Int J Environ Res Public Health 2018;15(4).

City of Cape Town. In: Research Branch: Organisational Policy & Planning, editor. 2016 Community Survey Cape Town Trends 1996 to 2016. Cape Town, South Africa.

Divala TH, Lewis J, Bulterys M, Lutje V, Corbett E, Schumacher S, et al. Missed opportunities for diagnosis and treatment in patients with tuberculosis symptoms: a systematic review. Res Square 2020;.

Dlamini NR, Maja P. The expanded programme on immunisation in South Africa: a story yet to be told. S Afr Med J 2016;106(7):675–7.

English R, Peer N, Honikman S, Tugendhaft A, Hofman KJ. 'First 1000 days' health interventions in low- and middle-income countries: alignment of South African policies with high-quality evidence. Glob Health Action 2017;10(1)1340396.

Flavin RJ, Gibbons N, O'Briain DS. Mycobacterium tuberculosis at autopsy–exposure and protection: an old adversary revisited. J Clin Pathol 2007;60(5):487–91.

Ford N, Matteelli A, Shubber Z, Hermans S, Meintjes G, Grinsztejn B, et al. TB as a cause of hospitalization and in-hospital mortality among people living with HIV worldwide: a systematic review and meta-analysis. J Int AIDS Soc 2016;19(1):20714.

Garg M, Aggarwal A, Singh S, Kataria S. Tuberculous lesions at autopsy. J Indian Acad Forensic Med 2011;33(2).

Grobler L, Mehtar S, Dheda K, Adams S, Babatunde S, van der Walt M, et al. The epidemiology of tuberculosis in health care workers in South Africa: a systematic review. BMC Health Serv Res 2016;16(1):416.

Gupta RK, Lucas SB, Fielding KL, Lawn SD. Prevalence of tuberculosis in post-mortem studies of HIV-infected adults and children in resource-limited settings: a systematic review and meta-analysis. AIDS 2015;29(15):1987–2002.

Malotle MM, Spiegel JM, Yassi A, Ngubeni D, O'Hara LM, Adu PA, et al. Occupational tuberculosis in South Africa: are health care workers adequately protected?. Public Health Action 2017;7(4):258–67.

Massyn N, Day C, Dombo M, Barron P, English R, Padarath A, et al. District Health Barometer 2012/13. Durban, South Africa: Health Systems Trust; 2013.

Massyn N, Peer N, English R, Padarath A, Barron P, Day C. District Health Barometer 2015/16. Durban: Health Systems Trust; 2016.

Omar T, Variava E, Moroe E, Billioux A, Chaisson RE, Lebina L, et al. Undiagnosed TB in adults dying at home from natural causes in a high TB burden setting: a post-mortem study. Int J Tuberc Lung Dis 2015;19(11):1320–5.

Osman M, du Preez K, Naidoo P, Bock P, Rabie H, Dlamini SS, et al. Key changes in the public health response to TB and HIV in South Africa. Int J Tuberc Lung Dis 2020;24(8):857–9.

Seager JR, Tamasane T. Health and well-being of the homeless in South African cities and towns. Development Southern Africa 2010;27(1):63–83.

Simbayi L, Zuma K, Zungu N, Moyo S, Marinda E, Jooste S, et al. South African National HIV Prevalence, Incidence, Behaviour and Communication Survey 2017. Cape Town: HSRC Press; 2019.

South African Government. The Inquests Act 58 of 1959. Government Gazette; 1959.

South African Government. National Health Act. 2003 (Act No. 61 of 2003). Regulations Regarding the Rendering of Forensic Pathology Services. Government Gazette; 2018.

Statistics South Africa. Mortality and causes of death in South Africa, 2016: Findings from death notification. Pretoria, South Africa: P03093; 2018.

Tiemensma M, Burger EH. Sudden and unexpected deaths in an adult population, Cape Town, South Africa, 2001-2005. S Afr Med J 2012;102(2):90–4.

World Health Organization. Global Tuberculosis Report 2020 Geneva, Switzerland. 2020.