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Original article

A step up to end tuberculosis: Lessons from a community-based death review of patients with tuberculosis from western India

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ABSTRACT

Understanding factors leading to death following the onset of symptoms of tuberculosis (TB) is important to predict prognosis among patients with TB. With aiming the End TB strategy, mortality is declining not as expected globally and in India. Although India is one of the highest incidence countries globally, India lacks evidence of understanding of the factors for TB death. Thus, this study aims to document the characteristics of deaths due to TB in the Western state of India, Gujarat.

About 74 deaths were randomly documented from 7 different geographic regions of Gujarat through a community-based death review from Oct 2021 to February 2022. The trained researchers administered a semi-structured questionnaire to capture the demographic, socioeconomic, history of comorbidity and addiction, medical history, case records, and chronology of events preceding death.

Most deaths happened within 24 weeks from the onset of symptoms, which reduced to half (12 weeks) in the other cascades, i.e., diagnosis and treatment initiation to the death. Out of 74 reviewed deaths, 47 (64%) deaths had the cause of death as TB, with an average duration of 87 days from onset of symptoms to death. The study observed the time, place, and person distribution on different epidemiological parameters. While analyzing narratives from the relative, the gaps between the system (service provider) and demand (patient perspective) sides were synthesized.

It is recommended to conduct such kind of community-based death reviews in the routine practices of the National TB Elimination Program to ensure the appropriate review of the underlying causes of deaths due to TB. The matrix developed in this study is easy to replicate in any other death reviews to understand the intercept of the supply-demand side determinants for the deaths.

1. Introduction

Tuberculosis (TB) is a communicable disease that is one of the top ten causes of death worldwide and the leading cause of death from a single infectious agent (ranking above HIV/AIDS).[1] The National Strategic Plan to end TB in India (NSP) 2017–2025 set into motion an unprecedented and ambitious attempt to enhance the coverage, quality, equity, efficiency, and effectiveness of the National Tuberculosis Elimination Programme (NTEP). Eight countries accounted for two-thirds of the global total of TB: India, Indonesia, China, the Philippines, Pakistan, Nigeria, Bangladesh, and South Africa. Reduced access to TB diagnosis and treatment has increased TB deaths. The best estimates for 2020 were 1.3 million (1.2–1.4 million) TB deaths among HIV-negative people and an additional 214 000 (187 000–242 000) among HIV-positive people, with the combined total back to the level of 2017.[2] The End TB strategy aims to reduce TB incidence and zeroing mortality in 2035 (compared to 2015 figures).[3]

The annual number of TB deaths is falling globally, but not fast

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enough to reach the 2020 milestone of a 35% reduction between 2015 and 2020. The estimated mortality rate in India declined from almost 60 deaths per hundred thousand population (HIV-negative) in 2000 to 32 per hundred thousand in 2018, while the global mortality rate declined at the same rate, from 30/hundred thousand to 16/hundred thousand.[4] Since the World Health Organization (WHO) defined TB deaths as the number of TB patients dying during treatment, irrespective of cause,[5] the underlying causes of death in TB patients may help to customize existing country-specific interventions. The case fatality ratio (estimated mortality/estimated incidence) in high-income countries is 5%, and it continues to be around 20% in high-burden countries.[2] Risk factors for death may include noninfective comorbidities, human immunodeficiency virus (HIV) infection, alcoholism, and multidrug-resistant TB (MDRTB).[6]

Some studies have investigated the actual causes of death among TB patients.[7–14] Most relied on vital statistics registration or death certificates. Still, there are methodological problems in estimating the mortality in high TB-burden countries that lack universal health coverage and have poor vital registration systems (VRS) and disease reporting systems with inadequate information on the burden of undiagnosed TB. Several autopsy-based studies have revealed that diagnosis is often missed in patients with disseminated and extrapulmonary TB patients with smear-negative tuberculosis. Studies have shown that recorded deaths during treatment; may not be due to TB.[15,16] These data may not apply to the rest of the world and countries such as India, with a high burden of incidence and mortality.[17] This study was conducted to identify the associated factors and provide possible interventions linked with programmatic interventions, this study was conducted to identify various epidemiological, socio-demographic, and programmatic determinants for deaths due to TB in the Western state of India, Gujarat.

2. Material and methods

2.1. Study type

This community-based death review study was conducted among the relatives of deceased TB patients who were notified through NI-KSHAY* from Oct 2021 to February 2022. A community-based death review ascertains the personal, familial, community, and quality of care factors that may have contributed to the deaths. As a pre-requisite of the method, sensitivity was ensured in discussing the circumstances of the death.

* NI-KSHAY-(Ni = End, Kshay = TB) is the web-enabled patient management system for TB control under the National Tuberculosis Elimination Programme (NTEP). It is developed and maintained by the Central TB Division (CTD), Ministry of Health and Family Welfare, Government of India.

2.2. Study settings

This study was conducted in the western state of India, Gujarat, with a 60.4 million population scattered across 33 districts. This study was conducted in 7 different geographical regions, i.e., Ahmedabad, Amreli, Anand, Bhavnagar, Dahod, Gandhinagar, and Surat. These areas were selected for two prime reasons: first, because of the high TB death rate ($\geq$5%) in 2020 and second, to represent the state's geographic diversity as agreed upon through participatory workshops representing the government and concerned stakeholders.

2.3. Study definitions

The study followed the case definitions as advised in the NTEP guideline. There are three types of TB cases, i.e., the new cases (drug-sensitive), retreatment cases (drug-sensitive TB patients with a history of the previous episode of TB) and programmatic management of drug-resistant TB (PMDT) cases (drug-resistant TB cases who are on drug-resistant treatment regimen). The key population as per the NTEP guideline is that some patients are at increased risk for tuberculosis due to certain factors. Individuals with these vulnerabilities are included in the key population. These are contacts of TB patients, diabetics, tobacco users, prison inmates, miners, migrants, refugees, urban slum dwellers and health care workers.[18]

2.4. Study sample & sampling

As per the NI-KSHAY 2021, Gujarat has reported approximately 145 812 TB cases from the public and private sectors, with a proportion of approximately 5% TB deaths. The third and fourth quarter notification register of 2021 was extracted from the NI-KSHAY, and all the notified death cases were line listed for the study purpose. There were 830 TB deaths reported from the TB patients who were notified. The sample size was calculated based on the formula of $N = Z21\text{-}\alpha/2P(1\text{-}P)/\varepsilon 2$ on the qualitative variable of a proportion of 5% TB deaths; 68 or more measurements/surveys were needed to have a confidence level of 95% that the real value is within $\pm$5% of the measured/surveyed value. Additionally, the final sample size accounted for a 10% non-response rate, which remained at 74. Simple random sampling was adopted to select the deceased TB cases within the selected geographic areas; however, an adjustment was considered for the unified distribution across the region. Final eligible TB and death cases were listed with the inclusion and exclusion criteria below.

Inclusion criteria: The TB patients notified through the NI-KSHAY, and their current state PHI should be within the selected geographical areas of Gujarat state, the TB patients whose treatment outcome reported as "Died" before initiation of treatment, after initiation of treatment, and post-treatment period. Relatives who provided consent to be part of the study.

Exclusion criteria: TB patients' family who was migrated or untraceable or did not reside in the current PHI surveyed areas or whose relatives didn't provide any consent were excluded from the study.

2.5. Study data collection and analysis

The TB death audit semi-structured tool consists of primary demographic, socioeconomic, history of comorbidity and addiction, medical history, case records, and chronology of events preceding death, with the most recent condition first and the earliest (e.g., the situation that started the sequence of events between normal health and death) last was designed and pilot-tested before the study. The quantitative part aims to collect information on various events associated with TB therapy, whereas the death event was captured through an open-ended qualitative inquiry about the chronology of the events before the death. The trained researcher administered this pre-tested tool in the vernacular language through personal interviews of a relative of the deceased cases by undertaking home visits. All interviews occurred at participants' homes at a time convenient to them. The relative of the randomly selected TB death cases was approached, and those who provided written consent were finally included in the study. Other relatives, who were present during the event of death, were preferred to be a respondent to ensure the maximum valid information regarding the death event.

The data analysis involved two steps-approach; first, all the descriptive statistics were analyzed through STATA 14.1 and the qualitative narratives through thematic analysis; second, the cause of death analysis was conducted through a consultative participatory approach.

2.5.1. Epidemiological characteristics of deaths

The journey of the TB patient across the TB care cascade was mapped with milestones of service delivery; date of onset of symptoms, first formal consultation, confirmed diagnosis, treatment interruption, and treatment completion. The factors associated with the death event were analyzed qualitatively and mapped through thematic coding. The

epidemiological characteristics are described in the form of the place, person, time, and treatment distribution. The duration of service delivery date to the date of death was calculated to derive median and average days.

2.5.2. Cause of death analysis

As the cause of death analysis requires expertise with the International Classification of Diseases - the 10th revision recommended by WHO, a consultative participatory approach was adopted among the potential experts.[19] The review committee of medical specialists not affiliated with NTEP was constituted to review all the available evidence and code the underlying causes of death, reducing bias when TB program personnel conduct a death audit. A committee of three clinical experts independently reviewed all available evidence to ascertain the underlying cause of death following guidelines. A final assignment of the cause of death required the concurrence of more than two members. If two reviewers did not concur on the cause of death, they would meet the third reviewer and develop a consensus. The committee assigned the underlying cause of death as TB if it had initiated the sequence of illness events leading directly to death. If the underlying cause of death was not TB, the committee also recorded what was believed to be the specific cause of death using codes from the International Classification of Diseases, 10th revision, as recommended by WHO.[19] For patients with a cause of death not directly attributed to TB but that may have resulted from TB or TB treatment (e.g., drug-induced psychosis leading to suicide), TB was listed as an underlying cause of death. The qualitative factors from the demand side and health system side contributed to each TB death based on the verbal response of the study respondents were captured for the TB care cascade matrix.

3. Results

Among the 74 patients with TB who died, 69 died during the treatment or post-treatment phase, 04 died immediately (within 24 h) after the diagnosis, and 01 died within 48 h of treatment prescription (initiation of medication was not started due to the severity of the illness).

3.1. Characteristics of TB deaths

3.1.1. The place distribution of deaths

About 74 TB deaths were captured from the different geographic locations of Gujarat. There were about 27 (35.5%) deaths captured from Ahmedabad Municipal Corporation, followed by 20 (26.3%) deaths from Surat and 12 (16.2%) deaths from the Anand district. About 2–6 deaths were collected from Amreli, Bhavnagar, Dahod, and Gandhinagar. While enquiring about the place of death, it was documented that 52 (68%) of TB cases died at home. Whereas only 17 (22%) deaths were reported at either public/private healthcare facilities and 7 (10%) were in transit either to the healthcare facility or way back home.

3.1.2. The person distribution of deaths

About 42 (56.8%) reported death cases belonging to the key population, and 47 (63.5%) were living in a nuclear family. About 11 (14.9%) cases were single and 26 (35.1%) were illiterate. About 31 (41.9%) were daily labourers, followed by 14 (18.9%) farmers/cultivators. Among all the surveyed TB deaths, 31 (42%) were in the age group of 26–50 years, followed by 31 (42%) in the age group of 51–75 years.

3.1.3. The time distribution of death

As per national guidelines, the TB treatment for drug-sensitive pulmonary TB patients is 24 weeks.[18] The TB treatment varies from 8 months to 24 months for drug-resistant TB patients. The treatment period is based on the site and type of TB case. A differential variability has been observed between the time duration throughout the cascade to the event of death. The cumulative death days of the above three sub-cascades suggests that 80% of deaths happened in 24 weeks in the sub-cascade of onset of symptoms to the death (Figure-1). In contrast, it has reduced to half i.e., 12 weeks in the other two sub-cascade, i.e., diagnosis and treatment initiation to the death.

The number of days to death decreased during each phase of the TB care cascade, where the difference was noted during the treatment phase to death due to the number of TB patients who died before treatment initiation. (Fig. 2). The study revealed that the average number of days for the TB diagnosis to death was less in patients with a history of addiction (48.4 days) than in patients with a history of comorbidity (54.2 days) and adverse drug reactions (63.3 days). The study could not identify the severity of these factors in the absence of valid documents and medical records with respondents.

3.1.4. The treatment distribution of deaths

18% (13) of TB patients visited more than three health facilities for consultations and were diagnosed with TB diseases. About 43 (58.1%) were new TB cases, 23 (31.1%) retreatments (history of the previous episode of TB), whereas only 8 (10.8%) were PMDT (drug-resistant TB) cases; however, 60 (85.7%) patients were under the fixed drug dose regimen as per national guidelines. Although there were 62 (83.8%) pulmonary TB and 12 (16.2%) extrapulmonary cases, only 45 (65%) were microbiologically confirmed as reported by the relatives and cross-verified from the Ni-Kshay portal secondary data. There were 30 (43%) under directly observed treatment, 39 (53%) under ICT-based adherence tool but about 26 (37.7%) cases reported the TB medication interruption. Among 24 (34.8%) cases reported, adverse drug reactions (ADR) during treatment. While enquiring about a history of comorbidities, 28 (37.8%) reported either anyone comorbidity like diabetes mellitus (DM), HIV, hypertension, mental disorders, COVID-19, etc. and 46 (62.1%) reported having one or more addictions such as tobacco, alcohol, etc.

3.2. The underlying cause of TB patients' deaths

Based on history and clinical records, the consultative findings are summarized on the probable cause of death. Out of 74 TB deaths, 47 (64%) patients have tuberculosis being an underlying cause of death if it had initiated the sequence of morbid events leading directly to death, followed by acute myocardial infarction (6%), HIV disease resulting in multiple infections (6%) and malignant neoplasm in (6%) patients. (Table 1). The survival period of patients who died due to TB had average days of 47, and those who died not due to TB had 40 days from diagnosis to death which could be the reason for the severity of non-TB-related complications. The differential pattern of various characteristics were observed across the patients who died with TB as an underlying cause compared to non-TB as an underlying cause of death (Table 2).

3.3. TB care cascade gaps matrix

While developing the TB care cascade gaps matrix, the gaps between the system (service provider) and demand (patient perspective) sides were synthesized and summarized. As per the transcripts, system-side gaps were found in concern with early formal consultation and diagnosis, private sector sensitization, high-risk stratification, availability and access of HR, capacity building of healthcare providers, adverse drug reaction (ADR) management, adherence and follow-up mechanism, and supervision and monitoring (Table 3). Similarly, from the demand-side gaps in awareness of TB, awareness regarding TB complications, care-seeking behaviour for comorbidity and its complication, addiction, access to health services in the COVID-19 pandemic, local beliefs, stigma, and financial issues were found. Most of the gaps in the system side are in the phase of early formal consultation & diagnosis and high-risk stratification, followed by adherence & follow-up mechanism. The prime gaps in the demand side were awareness regarding TB and its complication, followed by healthcare-seeking behaviour toward comorbidities and addictions (Table 3).

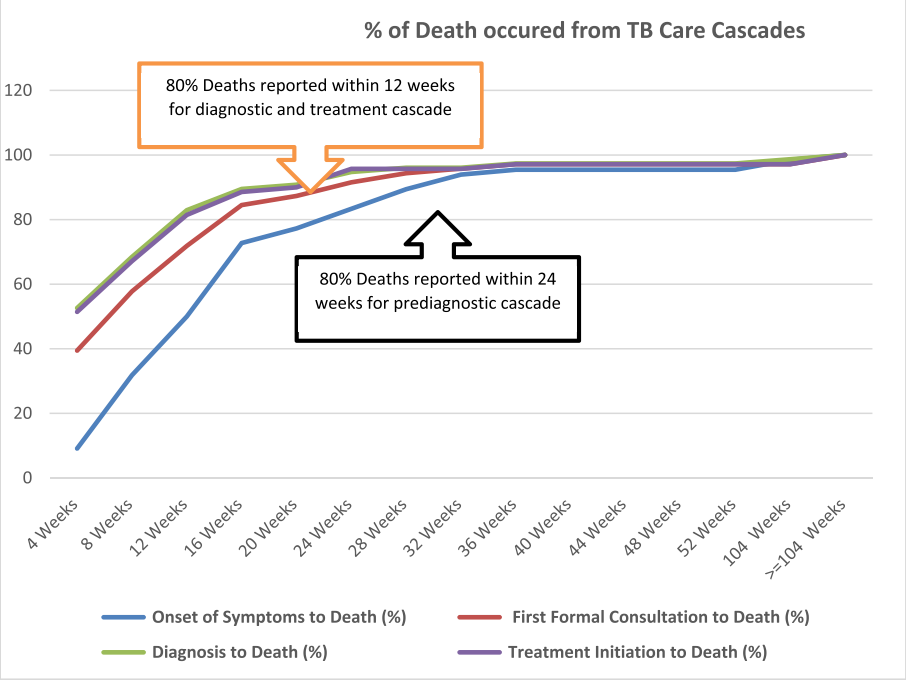

Fig. 1. The duration between milestone to death days with inter variability in the TB care cascade in Gujarat, India.

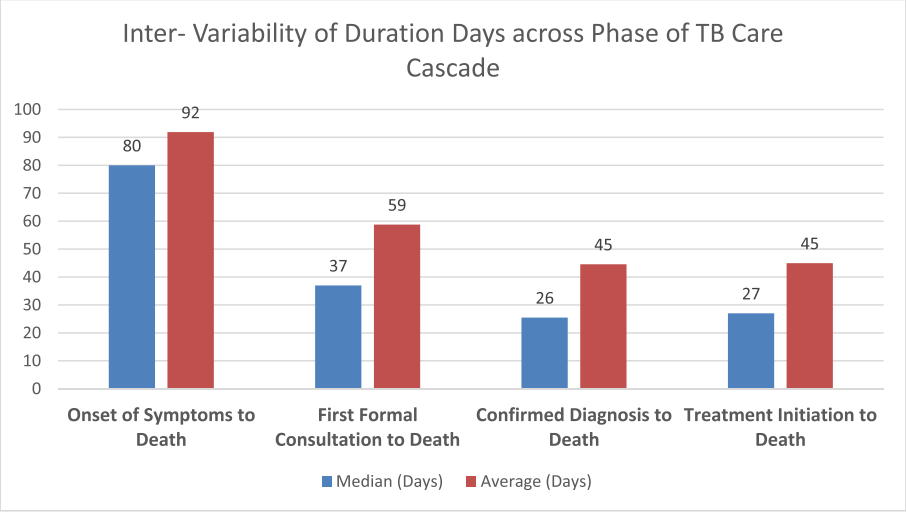

Fig. 2. Distribution of days between different phases of TB care cascade to the event of death in Gujarat, India.

4. Discussion

Our study has confirmed a substantial number of deaths associated with TB, even in the era of effective anti-TB medication. Among the 47 (64%) patients, tuberculosis was the primary underlying cause of death. In contrast, other causes of mortality were acute myocardial infarction (6%), HIV disease resulting in multiple infections (6%), and malignant neoplasm in (6%) predicted mortality in all TB deaths. Similar patterns also have been observed across the globe,[8,20] and it is directly proportionate to the TB incidence in the country. It was observed that the average number of days between the onset of symptoms to death in non-TB deaths was higher compared to patients with TB deaths. This could be due to the studied deaths being selected from the specific TB elimination program, which notifies the TB patient only; a more generalised death review study may provide a considerable comparison.

Reducing TB mortality in the End TB Strategy can be achieved if TB deaths are considered predictable and preventable, requiring programs to examine and address critical gaps in understanding the distribution and determinants of TB mortality. Although it was difficult to state the statistical significance of the determinants, this study highlighted the characteristics of different epidemiological variables of TB patients, including key population, gender, type and site of TB, visit health facilities, presence of comorbidities and addiction (Table 2). It is also evident in the literature that belonging to the key population increases the risk of death.[21] The study failed to find any significant distribution of death across age groups. Literature indicates a higher burden of TB mortality in younger age groups in the LMICs; in patients in the age group of 15–44 years in rural South India, the number of deaths due to TB was found to be 12 times higher than those expected in the general population.[22] According to the results of the GBD study, the age-standardized mortality and incidence of TB in males are twice that in females.[23] This study also failed to find any significant differences

Table 1
Underlying cause of death for TB patients who died during treatment (N = 74).

The underlying cause of death (ICD-10 code)			
Causes of Death	Codes	No. of Patients	Average Days from Diagnosis to Death
Infectious Diseases	**A00-B99**		
Tuberculosis	A15	**47**	**47**
Sepsis, unspecified	A41.9	**1**	**4**
Human immunodeficiency virus [HIV] disease	**B20–B24**		
HIV disease resulting in multiple infections	B20.7	**4**	**12**
Malignant neoplasms	**C00–C97**		
Malignant neoplasms of digestive organs	**C15–C26**		
Malignant neoplasms of the Oesophagus	C15	**1**	**6**
Malignant neoplasm of bronchus and lung	C34	**3**	**47**
Diseases of the nervous system	**G00-G99**		
Epilepsy	G40	**2**	**51**
Transient cerebral ischaemic attacks and related syndromes	G45	**3**	**43**
Endocrine, nutritional and metabolic diseases	**E00-E90**		
Type 2 diabetes mellitus with multiple complications	E11.7	**3**	**91**
Disease of the Circulatory System	**I00–I99**		
Hypertensive Heart Failure	I11	**1**	**33**
Acute Myocardial Infarction	I21	**4**	**39**
Chronic lower respiratory diseases	**J40-J47**		
Chronic obstructive pulmonary disease with acute lower respiratory infection	J44	**2**	**73**
Diseases of the Digestive System	**K00–K93**		
Alcoholic Liver Disease	K70	**2**	**19**
Acute Hepatic Failure, not otherwise specified.	K72	**1**	**9**

Table 2
Determinants pattern differentiated with TB as the cause of death and compared with other diseases as the cause of death in Gujarat, India.

Variables	Types	Non-TB as the cause of death n = 27 (%)	TB as the cause of death n = 47 (%)
Gender	Female	7 (25.9)	10 (21.3)
	Male	20 (74.1)	37 (78.7)
Family Type	Joint	10 (37)	17 (36.2)
	Nuclear	17 (63)	30 (63.8)
Key population	No	9 (33.3)	23 (48.9)
	Yes	18 (66.7)	24 (51.1)
Education	Illiterate	9 (33.3)	17 (36.2)
	Primary	13 (48.1)	16 (34)
	Secondary	5 (18.5)	12 (25.5)
	Higher and above	0	2 (4.3)
No. of health facilities visited prior to death	Don't Know	4 (14.8)	8 (17)
	>3	9 (33.3)	4 (8.5)
	1	11 (40.7)	21 (44.7)
	2–3	3 (11.1)	14 (29.8)
Type of TB	New	17 (63)	26 (55.3)
	PMDT	2 (7.4)	6 (12.8)
	Retreatment	8 (29.6)	15 (31.9)
Sire of TB	Extrapulmonary	2 (7.4)	10 (21.3)
	Pulmonary	25 (92.6)	37 (78.7)
H/O of comorbidity	No	9 (33.3)	37 (78.7)
	Yes	18 (66.7)	10 (21.3)
H/O of addiction	No	10 (37)	18 (38.3)
	Yes	17 (63)	29 (61.7)
H/O of ADR	No	18 (66.7)	32 (68.1)
	Yes	9 (33.3)	15 (31.9)
Place of death	Home	14 (51.9)	36 (76.6)
	Facility/In transit	13 (48.1)	11 (23.4)
Average of Days between Onset of Symptoms to Death		100	87
Average of Days between First Formal Consultation to Death		61	56
Average of Days between Diagnosis to Death		40	47
Average of Days between Treatment Initiation to Death		57	46

Table 3
The TB death Audit Matrix: Identified Gaps across the TB Care Cascade of TB Patients.

TB Death Audit Matrix - Gaps Identified throughout the TB Care Cascade		
Themes	System Side Gaps	Demand Side Gaps
Codes	Early Formal Consultation and Diagnosis	Demand Generation in General
	Private Sector Sensitization	Awareness of TB
	High-Risk Stratification	Awareness regarding TB Complication
	Availability and Access of HR	Care Seeking behaviour for comorbidity and its complication
	Capacity Building of HCPs	Addictions
	ADR Management	Access to Health Services during the COVID-19 Pandemic
	Adherence & Follow-up Mechanism	Local Beliefs and Stigma
	Supervision and Monitoring	Financial Issues

across gender. Therefore, age, gender, and educational status are independent of TB deaths, as per the findings of this study.

Comorbidities and TB-associated deaths are highly evident in the literature.[6,20,24] About 36% of deaths are associated with TB and other comorbidities resulting in death. People with HIV or other respiratory disorders are prone to higher mortality.[8] This is also evident in the frequency distribution shown in the current study. The current study also highlights that new pulmonary TB cases with any comorbidities tend to die from non-TB causes and have travelled to multiple healthcare facilities before the diagnosis. It also adds value that the death of such cases has taken place in the health facilities compared to higher TB death cases.

A number of limitations are highlighted. When generalizing findings, it should be considered that this analysis was limited to a few districts and might not be as appropriate for all the death registered under the NTEP program. The existing community-based death review was not undertaken immediately after all reported death, so this delay could have resulted in some of the missing information obtained from the respondents. Another limitation is excluding the migrated TB deaths, which hinders knowing the exact cause of the death in terms of geographic access.

There remains a need for prospective clinical studies, mainly focusing on deaths occurring during the first months of anti-tuberculosis treatment. Efforts should be made to ensure the completeness of reporting of treatment outcomes among TB patients, using information from vital registration to complete reporting of deaths where possible. It is also recommended to establish such kind of community-based death review system in the routine practices of the NTEP program to ensure immediate actions on programmatic gaps that lead to death.

5. Conclusion

This study highlights the determinants of TB death in the western state of India, Gujarat. We conclude that a review of deaths due to TB highlighted important system and demand side gaps in the TB care cascade which can be addressed. The study recommends focusing on

early diagnosis, risk stratification and differential care, patient educational efforts regarding the severity of comorbidities and TB and counselling to avoid addictions. The TB death surveillance and response system should be established to ensure the system-strengthening approach with equal emphasis on community empowerment. The matrix developed in this study is easy to replicate in any other death reviews to understand the intercept of the supply-demand side determinants for death and direct the policymakers to design the appropriate public health actions.

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Disclaimer

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Data sharing statement

All relevant data supporting this study's findings are within the manuscript.

Ethics approval and consent to participate

Approval for carrying out the study was obtained from the Institutional Review Board of the Indian Institute of Public Health, Gandhinagar, Gujarat. The permission for carrying out the study was obtained from the State TB Office, Government of Gujarat.

Author contributions (CrediT author statement)

All authors contributed equally to the development of this study. All authors approved the final draft. All authors contributed to data analysis, drafting, or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

HD Shah, S. Yasobant, Deepak Saxena, PD Nimavat, S Makwana: Conceptualization, Methodology, Software. KM Narkhede, Jay Patel, Priya Bhavsar: Data curation, HD Shah, S. Yasobant- Original draft preparation. HD Shah, S. Yasobant, Somen Saha, AK Sinha, Tapasvi Puwar: Visualization, Investigation. Dixit Kapadia: Supervision.: HD Shah, S. Yasobant, Jay Patel, KM Narkhede: Software, Validation HD Shah, S. Yasobant, Deepak Saxena, PD Nimavat, S Makwana: Writing-Reviewing and Editing.

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cegh.2022.101205.

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