Tuberculosis mortality: quantifying agreement in clinical cause of death assessments

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Mortality is a key statistic recorded by tuberculosis (TB) programs globally and is used as a marker of the overall effectiveness of healthcare services.[1,2] Data on TB mortality are compiled by the World Health Organization and other bodies, and targets for reduction in TB mortality are central to the 'End TB' strategy.[3,4] However, while death is an objectively defined outcome, there are concerns that the classification of whether a death is 'TB-related' may have significant variation between settings and practitioners, particularly in settings where autopsy is infrequently conducted.[5] Although recording of all-cause mortality avoids some issues, it may limit recognition and correction of drivers of poor outcomes.

There are a variety of reasons why mortality data may be inaccurate and classifications vary. Assigning cause of death can be complicated, and clinical judgement frequently plays an important role, particularly in a multisystem condition such as TB that is treated with multiple medications for a prolonged time. While death certificates are generally written by attending doctors or pathologists, in programmatic monitoring, cause of death may be centrally recorded by staff with a variable amount of direct involvement in management. In some published series with detailed review, up to half of deaths among notified TB cases were not considered primarily caused by TB, so incorrect classification may have a substantial impact on mortality and case fatality estimates and result in missed opportunities for targeted prevention measures.[6,7] Understanding variation in classification and the reason for differences is important to improve the reliability and consistency of reported TB-associated mortality, as well as subsequent policy and practice interventions. We aimed, therefore, to survey clinicians and public health practitioners in Australia to explore variability in TB-associated death classification in order to understand how more uniform approaches can be developed.

Abstract

Objectives: Mortality is a key statistic for public health globally, and mortality reduction is a key target of 'End TB' strategy. However, cause of death in relation to tuberculosis (TB) may be controversial, and we aimed to evaluate classification in Australia.

Methods: We surveyed Australian clinicians and public health officers, presenting a variety of scenarios. Respondents were asked to classify each scenario with regards to whether TB was considered causative, contributory or not related to death.

Results: Fifty-nine individuals completed the survey. Respondents were experienced TB clinicians and public health officers (median 14 years of TB care experience), with a majority having recently been involved in death certification/classification. In most scenarios, there was substantial variation, particularly where death was related to TB medications, or if an alternative contributing process was recognised, such as cardiovascular complications. Variation in classification was not evidently associated with classification experience.

Conclusion: We found significant variation in cause of death classification among experienced TB clinicians and public health officers, using representative TB death scenarios.

Implications for public health: Consensus and transparency with regards to classification would assist in more uniform cause of death classification across jurisdictions and allow for better tracking of this critical performance measure.

Key words: mortality, tuberculosis, policy, public health

Methods

The National Tuberculosis Advisory Committee (NTAC) invited Australian TB clinicians and public health officers to participate in a survey of classification of cause of death relating to TB. Potential participants were recruited through jurisdictional TB programs and clinical

networks. As a relatively small group of clinicians and public health officers work in Australian TB services, participation was anonymous, and invitations were secondarily distributed by jurisdictional TB programs to increase participation.

Consenting participants were provided with an online platform to provide non-identifying demographic data, before responding to a series of hypothetical scenarios where death may be TB-associated. Participants were asked to classify cases in both a dichotomous (death was/was not TB-related) and non-exclusive (TB was cause of death/contributed to death/was not related to death) schema. Specific scenarios are listed in Supplementary File 1.

Descriptive statistics were performed to report summary measures, particularly proportions and kappa values. Thematic analysis was performed to consider patterns of responses within/between respondents. Demographic data regarding age, sex and occupation were analysed to consider variation in attitudes and values, and chi-squared testing was performed to compare proportions between groups. Continuous or pseudo-continuous data were analysed (e.g. age) with t-tests to compare group means.

This project was approved by the Biomedical Sciences Human Ethics Advisory Group, University of Melbourne (1955071.1).

Results

Fifty-nine individuals completed the survey. Respondents included doctors (35; 59%), nurses (15; 25%) and public health officials engaged in TB. Respondents were 54% male (32/59), had a median age of 47 years, and had worked in TB care for a median of 14 years. Most (36; 61%) stated that they had been directly involved in assigning TB cause of death in the previous two years.

Survey respondents were asked to estimate the Australian TB case fatality rate. All participants considered it was less than 5%, with 23 reporting that it was <1%, 21 that it was 1–2%, and 15 that it was 2–5%. Respondents also reported how appropriately they considered TB-related death was classified in Australia, with 28 (47%) considering it was "about right", 26 (44%) that it was slightly (21/59) or substantially (5/59) under-reported, and 5 (8%) that it was slightly (5/59) or substantially (0/59) over-reported.

In only one scenario (7) was there uniformity regarding classification, which related to massive haemoptysis (coughing blood) in a young patient with culture-confirmed TB, prior to initiation of therapy. By comparison, participants were divided regarding death due to haemoptysis in an individual who had successfully completed therapy with residual bronchial stenosis, with 34 (58%) considering that TB was the cause of death, and, when non-exclusive classification was permitted, 36 (61%) classifying TB as a contributing factor.

Cardiovascular complications

Several scenarios considered death from a cardiovascular incident during TB treatment. Participants were very likely to attribute death to TB where a vascular complication of TB was considered to have biological plausibility, with 49/59 (83%) considering that cerebral infarction in the setting of TB meningitis was caused by TB (and the remaining 10/59 [17%] that TB was a contributing factor). Conversely, where myocardial infarction occurred during pulmonary TB therapy, most (46/59; 78%) did not consider death TB associated.

Potential treatment-associated mortality

Death apparently due to medication side effects was also variably classified. In each of the three scenarios including potential adverse effects (2, 3 and 11), a majority considered that TB was a contributing factor (35 [59%], 43 [73%] and 44/59 [75%], respectively). When dichotomous classification was required, more significant variation was seen. Death from fulminant hepatitis while on first-line TB treatment was generally (47/59; 80%) attributed to TB, while only one-quarter (16/59; 27%) considered TB as the cause of death in an apparent suicide committed by someone on multidrug-resistant (MDR) TB therapy, and half (30/59; 51%) in an unexpected death during MDR TB therapy with multiple QT-prolonging medications.

Death without confirmed TB

Two scenarios related to cases where TB was not confirmed. In one case, pulmonary TB was clinically suspected and treated despite negative investigations, while in the second, a post-mortem identified consistent histological changes, but confirmatory microbiological tests for TB were not conducted. Respondents were similarly unlikely to attribute cause of death to TB in either of case (15/59 [25%] and 17/59 [29%], respectively).

Alternative causes

Respondents considered one scenario in which TB was diagnosed in the context of an alternative cause of death (metastatic lung cancer). A majority reported that they would consider TB as a contributing factor (46/59; 78%), but not as the primary cause. Only 18/59 (31%) would consider TB as the primary cause of death when dichotomous classification was used.

Comparison of classification between those respondents who had recently been involved in assigning cause of death found no overall difference in the likelihood that TB would be considered causative (p=0.38). There were no significant differences found in overall classification when comparing by gender or occupational groups (doctors vs. other). Given the relatively small number of participants in this survey, subgroup analysis for individual scenarios was not conducted.

Discussion

We found significant variation in TB death classification in scenarios typical of what may be encountered in practice. This variation was evident despite survey respondents being experienced practitioners with direct experience in death classification and accurate understanding of TB mortality. While studies reporting variation in death classification often call for improved data tools or increased education of practitioners, our observed variation seemed to represent a lack of consensus on optimal TB-death assignment.[8]

Thematic analysis identified several areas with larger variability, such as classification in scenarios where a definitive diagnosis of TB had not been established. This is understandable, although reflects the reality of real-world classification challenges. Beyond this, significant variation also existed for classification when another potential cause was present, or where death was related to TB medications. This last point is perhaps the most significant from a policy perspective, as clear guidance regarding the classification of death related to medication side effects could be helpful for increasing uniformity of practice.

We noted that there also appeared to be substantial variation in the degree to which practitioners judged death due to cardiovascular events was TB-associated. There is evidence for increased cardiovascular events during and following TB therapy, both in anatomical association (e.g. TB meningitis and stroke) and general cardiovascular risk (e.g. myocardial infarction within 12 months of TB treatment).[9,10] Whether such events should be considered caused by TB, or with TB as a contributing factor, is a matter of policy but should be clarified and made transparent in classification systems.

Some of this complexity may be resolved by classification allowing multiple contributing factors in assigning cause of death, although there is evidence to suggest that allowing multiple causes of death increases classification error.[11] It may be optimal for national death classification in relation to TB to request both approaches be combined with a narrative review, given the small number of cases overall and existing individual case review procedures undertaken. Alternatively, assigning cause of death may be avoided entirely by reporting all-cause mortality during a defined period, such as within 12 months of notification. This, however, runs counter to existing Australian death classification systems, and may introduce other problems such as under-recognition of secondary conditions contributing to the risk of disease-specific mortality.[12]

While the differences highlighted here reflect several thematic issues, broad consensus on death classification is critical for monitoring this key outcome measure. NTAC intends to develop a national policy statement to contextualise these findings and improve within-jurisdictional and cross-jurisdictional standardisation. Regular national review of all potential TB-associated deaths would improve consensus on classification and identify opportunities for strengthening TB care. Overall, measures should support greater consistency in this important aspect of programmatic performance, leading to stronger services with better outcomes for people with TB.

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Supporting Information

Additional supporting information may be found in the online version of this article:

Supplementary File 1: Scenarios.