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Characterising cause of death among people treated for drug-susceptible TB in India

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Dear Editor,

Annually, 1.5 million people die of TB.[1] India has the highest burden of TB,[1] and in 2020, the case fatality ratio (CFR) among people with drug-susceptible TB was 4.3%.[2] Even after treatment, mortality is more than two-fold higher among people with prior TB compared to the general population.[3,4] However, information about cause of death, particularly in India, is limited. Thus, we sought to characterise cause of death among individuals who accessed TB care.

From 2013 to 2018, we enrolled individuals within 1 week of being diagnosed with drug-susceptible TB at public clinics in Pune and Chennai, India, into two pooled prospective cohorts.[5,6] Participants received care according to India's standard guidelines and were followed up to 18 months post-treatment. Sociodemographic and clinical data were collected

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at enrolment and microbiological results were tracked. Considering low paediatric mortality, participants <18 years were excluded.

Our primary analysis was to characterise cause-specific mortality during follow-up. We collected death narratives from family and clinicians, and used a previously published algorithm for classifying the likelihood of TB-related death.[7] If death was unlikely to be due to TB, we categorised causes according to ICD-10 codes. Cases were reviewed by two independent clinicians and discordant reviews adjudicated by a third. Cause was classified as unknown if all three were discordant. Our secondary analysis was to characterise treatment status at time of death. CFRs were calculated as deaths divided by the total number of participants at the beginning of the period. For mortality rates, person-time included enrolment to last follow-up or death. Differences in baseline characteristics were assessed using Fisher's exact test for categorical, and Wilcoxon rank-sum test for continuous variables. Analyses were conducted using Stata v14.2 (StataCorp, College Station, TX, USA). We received ethical approval from Johns Hopkins University (Baltimore, MD, USA) and each enrolling site. All participants provided written informed consent.

Of 1,290 adults, 832 (64%) were male; the median age was 34 years (interquartile range [IQR] 25–48). Overall, 682 (53%) were underweight (body mass index [BMI] <18.5 kg/m^2), 337 (26%) had diabetes, 55 (4%) were living with HIV, 315 (24%) had unhealthy alcohol use and 283 (22%) were current/former smokers. At entry, 1,125 (87%) had pulmonary TB (PTB), and the median duration of symptoms was 45 days (IQR 30–90). The median follow-up time was 16.5 months (IQR 15.6–22.2).

We documented 99 deaths, 82 (83%) were male, and the median age was 43 years (IQR 32–53); 69 (70%) were underweight, 25 (25%) had diabetes, 8 (8%) were living with HIV, 51 (52%) had unhealthy alcohol use and 43 (43%) were current/former smokers. At entry, 92 (93%) had PTB, and the median symptom duration was 60 days (IQR 30–90). Seventy-five (76%) deaths were TB-related, of which 10 (13%) were bacteriologically confirmed, 34 (46%) probable and 31 (41%) possible TB deaths. Of the 16 deaths unlikely to have been caused by TB, causes included ischaemic heart disease (n = 6), alcohol-associated (n = 2), malignancy (n = 2), diabetes-associated (n = 2), accident (n = 1), HIV-associated (n = 1), suicide (n = 1), abdominal hernia (n = 1) and unknown (n = 8). TB deaths tended to be among younger individuals (median age: 42 years; IQR: 28–50) with lower BMI (median: 15.3 kg/m^2; IQR: 14.0–17.8) compared to other causes (P = 0.029, P = 0.023, respectively).

Deaths occurred at a median of 9.4 months (IQR 3.5–15.8). Forty-seven died after treatment failure or default. Of 77 deaths that occurred prior to completing treatment, 65 (84%) were TB-related. Of 22 deaths after treatment completion, 10 (45%) had TB recurrence (Figure). Of the remaining 12 post-treatment deaths, causes included ischaemic heart disease (n = 4), alcohol-associated (n = 2), diabetes-associated (n = 1) and unknown (n = 5). CFR and mortality rates were estimated as follows: overall, 7.7% (95% confidence interval [CI] 6.3–9.3) and 5.6/100 person-years (py) (95% CI 4.6–6.9); prior to treatment completion, 6.0% (95% CI 4.7–7.4) and 4.4/100 py (95% CI 3.5–5.5); and post-treatment completion, 1.8% (95% CI 1.1–2.7) and 1.3/100 py (95% CI 0.8–2.0). We observed higher unemployment

among those with death due to TB than among those with death due to other causes ($P = 0.015$).

In our study of 1,290 adults with drug-susceptible TB, we found that two-thirds of the 99 deaths were TB-related. This aligns with our finding that nearly half of deaths were among people who had failed or defaulted treatment. This may be partially explained by the 3x weekly treatment regimen recommended during the period of our study. Since then, guidelines in India have shifted to daily treatment. Additional interventions to improve treatment response (e.g., identifying symptomatic individuals earlier, wider application of drug susceptibility testing) and the prevention of default (e.g., stronger adherence support services) could help avert these types of deaths. Additionally, efforts to address comorbidities should be bolstered; a disproportionate number of deaths were among people with modifiable risk factors such as undernutrition, unhealthy alcohol use and tobacco use.

Among the 22 post-treatment deaths, only two were attributable to heart disease. This is in contrast to a recent systematic review, which found that 20% of post-treatment deaths were caused by cardiovascular disease (CVD).[3] However, this estimate was based on data from countries with a different background burden of CVD than India,[8] and from studies with 5–10 years of follow-up.[8] As heart attack is a leading cause of death in India,[9] we may have found additional post-treatment deaths attributable to CVD with a longer follow-up period.

The observed CFR prior to treatment completion of 6.0% is higher than India's most recent nationwide estimate (4.3%).[2] Similarly, a recent review of data from India found that published CFR estimates tended to be higher than nationwide reports,[10] possibly due to selection bias. Among individuals who completed treatment, we observed a CFR of <2%, which is slightly lower than the estimate in the recent review.[10] This may be due to methodological differences, as we restricted post-treatment CFR to treatment-completed individuals. We also found that 10% of deaths were among people who had experienced TB recurrence. With overall recurrence in India at approximately 10%,[11] post-treatment services should be prioritized.

Although our study offers insights into the reasons for death among people treated for TB based on prospectively collected and independently reviewed data, there are some limitations. First, verbal autopsies were not collected. Second, not all TB-related deaths were bacteriologically confirmed. However, <10% had unknown cause. Finally, we only followed patients for 18 months post-treatment.

Understanding the cause of death in patients with TB, and their treatment status at death, can guide more effective strategies for preventing premature mortality. Our findings point to the need for additional interventions at several steps of the TB care cascade. In particular, we observed a high number of TB-related deaths and deaths among patients who failed treatment. Further research is needed to understand the barriers and facilitators for completing TB treatment in India to ensure better adherence, and to reduce TB recurrence and TB-related mortality.

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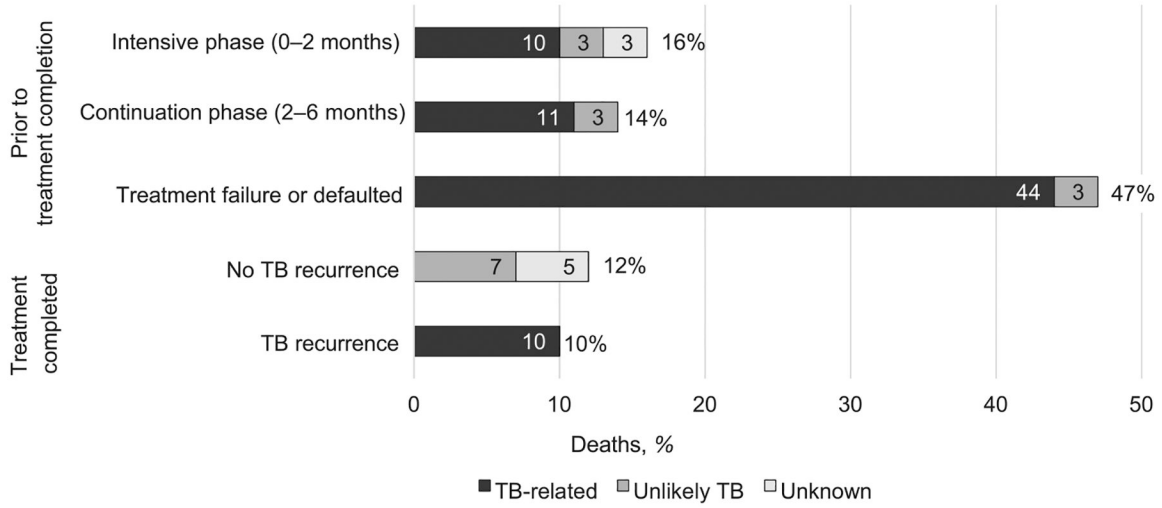

Figure.

TB treatment status at time of death among 99 adults (age: ≥18 years) enrolled in two pooled prospective cohorts in Pune and Chennai, India, between December 2013 and November 2018. Previously published algorithm to classify TB-related deaths, including possible, probable, and bacteriologically confirmed.[7] Mutually exclusive treatment status categories used: intensive phase = treatment ongoing and treatment initiated <2 months prior to death (n = 16); continuation phase = treatment ongoing and treatment initiated 2–6 months prior to death (n = 14); treatment failure = positive on smear or culture during the final 2 months of treatment (n = 35); defaulted = treatment prematurely discontinued (n = 12); confirmed TB recurrence = positive on smear or culture after completing treatment (n = 4); probable TB recurrence=clinical evidence of TB after completing treatment (n = 6).