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Long-term follow-up of persons diagnosed with multidrug-resistant TB in Chennai, India, 2013–2020

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Dear Editor,

India has the largest number of multidrug-resistant TB (MDR-TB) cases, defined as *Mycobacterium tuberculosis* resistant to at least isoniazid (INH) and rifampicin (RIF).[1] However, less than half of all persons with MDR-TB in India successfully complete treatment.[1] Although initial end-of-treatment outcomes offer a standardised time point to assess the effect of treatment, these tend to underestimate the overall burden of unfavourable long-term outcomes among persons treated for TB.[2,3] The long-term outcomes of persons diagnosed with MDR-TB in India, including the proportion with recurrent TB disease or mortality, are unknown. This analysis was conducted under programmatic conditions in a high-burden setting, with no regular check-ups after treatment. The results can be used to show the burden of recurrent illness and death following treatment, and can be used as a benchmark to measure improvement.

We assessed the long-term outcomes of an MDR-TB cohort with diagnostic case isolates stored in Chennai, India, to determine the additional burden of recurrent episodes of TB disease and undocumented mortality. All persons diagnosed with at least RIF-resistant TB

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between 1 January 2013 and 30 December 2016 in Chennai were eligible for enrolment; further details are described elsewhere.[4] Briefly, under routine practice, only persons with a history of previously treated TB, failure of first-line treatment or contacts of persons with MDR-TB were eligible for drug susceptibility testing (DST) using MTBDR*s*/ line-probe assay (LPA; Hain LifeScience, Baden-Württemberg, Germany). If RIF resistance was detected on LPA, patients were admitted to a hospital for a minimum of 2 weeks and started on treatment for presumptive MDR-TB until phenotypic DST results confirmed diagnosis using culture-based methods[5,6] (see Supplementary Data). From February 2018 to February 2020, we attempted to contact eligible participants, initially by phone to verify their current address. If they continued to reside in Chennai and verbally agreed to a home visit, a follow-up appointment was scheduled. After three phone attempts without response, the patient's home was visited to confirm the patient's current residence and interest in study participation. For persons who had died, a family proxy confirmed the date of death either by phone or in person. Participants who were located and provided written, informed consent were interviewed using a standardised form to systematically collect demographic information, TB diagnosis and treatment history, and current TB symptoms (i.e., cough ≥2 weeks, fever ≥2 weeks or unintentional weight loss). Enrolled participants received a chest radiograph. For participants who were symptomatic or had an abnormal chest radiograph, a spot sputum was tested using Xpert® MTB/RIF assay (Cepheid; Sunnyvale, CA, USA), and an early morning sputum were subjected to smear microscopy, culture and whole-genome sequencing (WGS) (see Supplementary Data). In persons with multiple episodes of TB, WGS can distinguish relapse from exogenous reinfection, and identify molecular markers for acquired additional resistance.[7]

A total of 149 stored case-isolates had viable *M. tuberculosis* growth from the baseline collection. Median age was 43 years (interquartile range 32–50 years). Twenty-eight (56%) patients had diabetes and one was HIV co-infected. Of 149 case isolates, 148 (99%) persons initiated MDR-TB treatment. Among these, 43 (29%) had no documented treatment status, 23 (16%) were cured or completed treatment and 82 had unfavourable treatment outcomes—57 were lost to follow-up, 19 died during treatment and 6 had treatment failure (culture-positive after at least 12 months of treatment). [6] Of these, 2 required a regimen change for extensively drug-resistant TB (XDR-TB; defined as resistance to RIF, any fluoroquinolone and at least one of second-line injectable pre-2019, or bedaquiline or linezolid post-2019) (Table). As 19 people died during treatment of the primary episode, 130 were eligible for subsequent follow-up, and 102 (79%) were reached directly or by family proxy. Among those reached, a further 25 (24%) had died after treatment but before follow-up screening. Among 77 surviving patients, 75 (97%) were screened and 8 (11%) had recurrent TB episodes; 3 were classified as relapse (1 with additional acquired resistance, 1 as exogenous reinfection).

Our study reveals that within 6 years of MDR-TB diagnosis, almost a third of the cohort had died or suffered an additional episode of TB disease. Persons with an unfavourable end-of-treatment outcome had a higher probability of death, and recurrent TB during follow-up. Overall, the case-fatality rate was high (30%), and an important finding was that the majority of deaths occurred after treatment (25/44, 57%) and was substantially greater than was reported as a standard end-of-treatment outcome alone (19/44, 43%). These rates were

similar to post-treatment outcomes of persons with XDR-TB from the Republic of Georgia.[7] In South Korea, fewer deaths during treatment (10%) and post-treatment deaths (12%) occurred during 3−7 years of post-treatment follow-up.[8] To note, a substantial number of our cohort who started treatment did not have documented treatment success. This could have been due to the current availability of a 2-year category IV treatment, with documented low treatment success and tolerability.[9] Given this intense treatment regimen, we hypothesise that many patients left treatment against medical advice, or were not traced by the local TB programme. Moreover, our study team offered follow-up services at a location closer to their residence and included screenings for their household contacts. This may account for our relative success during the follow-up period, especially among those previously thought to be lost.

Our study had several limitations. First, our cohort was a convenience sample and may not reflect the experiences of all persons with MDR-TB in Chennai. An unknown proportion of people were likely missed prior to diagnosis or treatment, and some proportion of these individuals may have experienced multiple TB episodes or premature mortality. Second, about a third of our cohort had no documented treatment outcome for the primary episode and could lead to a potential underestimation of loss to follow-up, and outcome-specific proportions. Furthermore, 20% of persons eligible for follow-up were not reached, and we could not accurately assess the primary outcomes. It is thus possible that we are not accurately accounting for the cumulative impact of recurrent episodes and death toll due to the disease. Finally, we did not assess cause of death, and some proportion of mortality may not have been due to TB. However, a research study involving a similar group of individuals with MDR-TB in India reported that 66% of deaths were due to TB or its treatment.[10]

CONCLUSION

This cohort of MDR-TB patients, observed under programmatic conditions in India, had high post-treatment mortality. This additional burden would have remained unrecognised without continued follow-up. As India expands access to all-oral MDR-TB regimens, treatment outcomes are expected to improve; however, the full benefit may not be realised without systematic post-treatment monitoring. For persons with MDR-TB, extending services to include more frequent clinical interactions and monitoring beyond treatment completions are important to document, and may improve overall clinical outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table.

End-of-treatment outcomes, recurrent TB episodes, and death after treatment among persons diagnosed for MDR-TB in Chennai, India (2013–2020).

	Primary episode ***n***	**Primary episode outcome (2013–2016)** ***n*** **(%)**[*]	**Reached for follow up (2018–2020)** ***n*** **(%)**[†]	**Died after treatment** ***n*** **(%)**[†]	**Recurrent TB** ***n*** **(%)**[†]
No documented treatment initiation	1	—	0	0	0
Initiated MDR-TB treatment	148				
Treatment status not documented		43 (29)	26 (60)	11 (26)	2 (5)
PMDT, cured or completed[‡]		23 (16)	23 (100)	2 (9)	0
PMDT, died during treatment		19 (13)	—	—	—
PMDT, lost to follow up		57 (39)	47 (82)	11 (19)	3 (5)
PMDT, treatment failure		6 (4)	6 (100)	1 (17)	3 (50)
Total	149	148 (99)	102 (69)[§]	25 (17)[§]	8 (5)[§]

[*] Column percentage.

[†] Row percentage.

[‡] Includes one person who transferred out who died after treatment.

[§] Among those who initiated MDR TB treatment (n = 148).

MDR-TB = multidrug-resistant TB; PMDT = programmatic management of drug-resistant TB.