

# Tuberculosis Pathways to Care and Transmission of Multidrug Resistance in India

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## Abstract

**Rationale:** India is experiencing a regional increase in cases of multidrug-resistant tuberculosis (MDR-TB).

**Objectives:** Given the complexity of MDR-TB diagnosis and care, we sought to address key knowledge gaps in MDR risk factors, care delays, and drivers of delay to help guide disease control.

**Methods:** From January 2018 to September 2019, we conducted interviews with adults registered with the National TB Elimination Program for MDR ( $n = 128$ ) and non-MDR-TB ( $n = 269$ ) treatment to quantitatively and qualitatively study care pathways. We collected treatment records and GeneXpert-TB/RFI diagnostic reports.

**Measurements and Main Results:** MDR-TB was associated with young age and crowded residence. GeneXpert rifampicin resistance diversity was measured at 72.5% Probe E. Median time from symptom onset to diagnosis of MDR was 90 days versus 60

days for non-MDR, Wilcoxon  $P < 0.01$ . Delay decreased by a median of 30 days among non-MDR patients with wider access to GeneXpert, Wilcoxon  $P = 0.02$ . Pathways to care were complex, with a median (interquartile range) of 4 (3–5) and 3 (2–4) encounters for MDR and non-MDR, respectively. Of patients with MDR-TB, 68% had their first encounter in the private sector, and this was associated with a larger number of subsequent healthcare encounters and catastrophic expenditure.

**Conclusions:** The association of MDR with young age, crowding, and low genotypic diversity raises concerns of ongoing MDR transmission fueled by long delays in care. Delays are decreasing with GeneXpert use, suggesting the need for routine use in presumptive TB. Qualitatively, we identify the need to improve patient retention in the National TB Elimination Program and highlight patients' trust relationship with private providers.

**Keywords:** pathways; multidrug-resistant tuberculosis; private sector; delays; National TB Elimination Program

India carries more than a quarter (27%) of the global burden of tuberculosis (TB), with an estimated 2.7 million cases in 2018 (1). Although TB incidence is slowly declining, the emergence and transmission of drug resistance is challenging disease control efforts (2). In 2016, the first Indian national drug resistance survey estimated the proportion of multidrug-resistant TB (MDR-TB, resistant to at least isoniazid

and rifampicin) at 2.8% (95% confidence interval [CI], 2.3–3.5%) among new cases and 6.2% (95% CI, 5.5–6.9%) overall, that is, among new or previously treated TB cases (3). Although estimates at the state level were of lower precision than nationally, the survey suggests Maharashtra is an MDR-TB “hotspot” with a proportion (7.7% among new TB; 95% CI, 4.5–10.9%) more than double the national estimate. A 2007 drug

resistance survey conducted in Maharashtra reported the proportion of MDR at 2.7% of new cases (4), suggesting a large interval increase between 2007 and 2015. There are also several single health center reports in Mumbai, the largest city in Maharashtra, that support an increasing MDR proportion (5–7).

MDR rates may be rising because of new resistance acquisition (i.e., due to

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## At a Glance Commentary

### Scientific Knowledge on the

**Subject:** Multidrug-resistant tuberculosis (MDR-TB) has been a serious concern globally and especially for India, being the country with the highest burden. The pathways to MDR-TB care are complex yet less explored in the Indian context.

### What This Study Adds to the

**Field:** The association of MDR with young age, crowding, and low genotypic diversity raises concerns of ongoing MDR transmission fueled by long delays in care. Delays are decreasing with GeneXpert use, suggesting the need for routine use in presumptive TB. Qualitatively, we identify the need to improve patient retention in the National TB Elimination Program and highlight patients' trust relationship with private providers.

within-patient pathogen evolution under suboptimal antibiotic treatment) or may instead result from primary infection with transmitted MDR-TB. Both of these possibilities are potentiated by delays in MDR diagnosis and effective treatment. There is currently limited quantification of MDR transmission and care delays in India. Available studies report long delays up to 55 days before drug-susceptible TB treatment initiation (8–13). A systematic reassessment of delays and barriers to care is timely given recent TB health system changes. These include the expansion of standardized treatment within the public National TB Elimination Program (NTEP) and the large-

scale rollout of molecular TB tests, such as the GeneXpert MTB/RIF (Xpert) assay that can decrease time-to-result, increase diagnostic sensitivity for TB and MDR-TB, and allow us to approximate the genetic epidemiology of rifampicin resistance mutations (14–16). In addition, timely TB care is hampered by the presence of a vast and weakly regulated private healthcare sector in India, with recent efforts focused heavily on improving notification of TB from this sector and referral to the NTEP (17, 18). There has been limited evaluation of care after referral to the NTEP. Here, we undertook a mixed-methods study among patients registered with the NTEP for treatment of MDR-TB and non-MDR-TB with the following objectives: 1) identify risk factors associated with MDR-TB including rifampicin resistance gene (*rpoB*) diversity, 2) quantify delays to the first healthcare encounter and to diagnosis and initiation of appropriate treatment for TB and MDR-TB, and 3) map patient pathways as they navigate the private/public health system to receive TB and MDR-TB care, and document reasons driving care transitions.

Some of the results of these studies have been previously reported in the form of a preprint ([https://papers.ssrn.com/sol3/papers.cfm?abstract\\_id=3717571](https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3717571)).

## Methods

### Study Setting

We conducted this cross-sectional mixed-methods study from January 2018 to September 2019 in the metropolis Pune Municipal Corporation (PMC) and surrounding industrial belt of Pimpri-Chinchwad Municipal Corporation (PCMC) areas of Maharashtra state. Maharashtra is the second most populous state in India with the 10th highest TB incidence rate (19). The study area spans approximately 7 million

population (9,400 people/km<sup>2</sup>); it includes 564 slums in the PMC region and has a considerable migrant population (20). The region is served by 17 TB units (TUs) under the NTEP; each TU covers a population of 0.3–0.5 million. The PCMC area TUs manage patients from surrounding rural areas. Thus, the study area has urban, industrial, and some rural representation, similar to most Indian states. Until September 2018, Xpert was recommended for retreatment cases or in case of nonresponse to first-line treatment. After that, it was recommended for all sputum smear-positive TB cases and a subset of presumptive TB.

### Approvals

We secured approvals from the Indian Ministry of Health and Family Welfare, Central TB Division, the state and local NTEP, Harvard Medical School's Institutional Review Board, and the institutional ethics committee of Dr. D. Y. Patil Vidyapeeth.

### Xpert Probe Binding

Data collection and analysis of Xpert rifampicin resistance gene, *rpoB*, probe binding are presented separately in Annex 1 in the online supplement.

### Participants Excluding Xpert Probe Analysis

We consecutively recruited patients aged  $\geq 15$  years with microbiologically confirmed TB who were registered and treated in the 17 TUs in the PMC and PCMC area. We used NTEP laboratory records to identify 1) patients with rifampicin-resistant TB diagnosed by Xpert (all were confirmed isoniazid resistant by a line probe assay and are hence MDR) and 2) comparator non-MDR-TB cases registered for first-line therapy after confirmation of sputum smear positivity. These patients either were negative

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This article has a related editorial.

This article has an online supplement, which is accessible from this issue's table of contents at [www.atsjournals.org](http://www.atsjournals.org).

**Table 1.** Sociodemographic Characteristics of Study Participants ( $n = 397$ )

Characteristics	Non-MDR ( $n = 269$ )	MDR ( $n = 128$ )	Total ( $n = 397$ )
Age group			
15–35 yr	165 (61.3)	92 (71.9)	257 (64.7)
36–56 yr	77 (28.6)	35 (27.3)	112 (28.2)
>56 yr	27 (10.0)	1 (0.8)	28 (7.1)
Sex			
M	158 (58.7)	56 (43.8)	214 (53.9)
F	111 (41.3)	72 (56.2)	183 (46.1)
Marital status			
Unmarried	77 (28.6)	41 (32.0)	118 (29.7)
Married	176 (65.4)	80 (62.5)	256 (64.5)
Other (widowed/separated)	16 (5.9)	7 (5.4)	15 (3.8)
Family type			
Nuclear	136 (50.6)	69 (53.9)	205 (51.6)
Joint and extended	119 (44.2)	55 (42.9)	174 (43.8)
Single	8 (3.0)	2 (1.6)	10 (2.5)
Stay with friends	6 (2.2)	2 (1.6)	8 (2.0)
Education			
Illiterate	31 (11.5)	5 (3.9)	36 (9.1)
Primary (1st–4th)	37 (13.8)	13 (10.2)	50 (12.6)
Secondary (5th–10th)	139 (51.7)	58 (45.3)	197 (49.6)
High secondary (11th/12th)	34 (12.6)	25 (19.5)	59 (14.9)
Graduation/PG	28 (10.3)	27 (21.1)	55 (13.9)
Occupation			
Unemployed	55 (20.4)	35 (27.3)	90 (22.7)
Housewife	55 (20.4)	32 (25.0)	87 (21.9)
Student	25 (9.3)	23 (18.0)	48 (12.1)
Skilled laborer	26 (9.7)	15 (11.7)	41 (10.3)
Other	108 (40.1)	23 (17.9)	131 (32.9)
Type of house/locality			
Crowded	202 (75.1)	97 (75.7)	299 (75.3)
Noncrowded	67 (24.9)	31 (24.3)	98 (24.7)

Definition of abbreviation: MDR = multidrug resistant; PG = postgraduation. Data are shown as  $n$  (%).

for rifampicin resistance by Xpert or were not tested but experienced sputum smear conversion to negative on first-line therapy. Eligible patients for enrollment were contacted by phone or in person with the help of TU staff.

### Procedures and Data Collection Excluding Xpert Probe Analysis

After introduction to the study, patients (and guardians for participants aged 15 to <18 yr) were consented; participants aged 15 to <18 years were assented. Study participants underwent a structured interview followed by an in-depth interview for the majority (Annexes E1 and E2). In the structured interview, we collected sociodemographic data including employment, marital status, family type, education, residence type and locality (crowded if residing in slums or huts and noncrowded if residing in a colony/compound, apartment, or a bungalow), average time spent in a crowded locality per day (24 h or <24 h), history of TB, health providers visited, TB diagnosis for the

current episode, substance abuse, and comorbidities. Additional data collection from the NTEP treatment cards included the type of treatment regimen, sputum smear status, comorbidities, and substance use. Additional interview procedures are provided in the online supplement.

### Quantitative Analysis Excluding Xpert Probe Analysis

Quantitative data was entered in Qualtrics.XM (Qualtrics) and processed using MS-Excel 2013 (Microsoft) and R Statistical Language. We used the chi-square test to compare proportions and the nonparametric Wilcoxon rank-sum to test continuous variables. We performed a multivariable logistic regression analysis to identify risk factors associated with MDR-TB without variable selection unless otherwise stated in the results. We tested for interaction between sex and the variable “24 hours per day spent in crowded locality/slum” and found that this was not statistically significant.

### Qualitative Analysis

Data from in-depth interviews was processed using MAXQDA (VERBI, Version 18). Based on the questions used in the interview guide, a coding list was prepared. Thematic analysis was performed by identifying the most commonly reported themes followed by the less commonly reported themes and conducted separately for the MDR and non-MDR groups. Thematic saturation was reached for both groups (21). We used a convergent parallel design. Further details are provided in Annex E1.

## Results

### Enrollment and Sample Characteristics

During the study period, we identified 448 patients with non-MDR-TB and 235 patients with MDR-TB who met the inclusion criteria and contacted them for enrollment. Of these, 179 patients with non-MDR-TB and 110 patients with MDR-TB were not enrolled. The most common reason for the inability to enroll was the lack of telephone contact numbers or no response (84 [47%] and 51 [46%], respectively) (Annex E3). Death before the telephone contact was noted in 9 (5%) nonenrolled patients with non-MDR-TB and 16 (15%) nonenrolled patients with MDR. The age distribution was similar among nonenrolled patients, patients who died before attempted enrollment, and patients enrolled in this study (Annex E3).

We enrolled a total of 269 patients with non-MDR-TB and 128 patients with MDR-TB detected by Xpert assay (Tables 1 and 2). Of the enrolled patients with TB, 64% were adolescents or young adults (aged 15–35 yr) and 54% were men. A large proportion (75%) resided in crowded localities such as slums or *chawls*. One-third (33%) reported history of prior TB; alcohol use was reported by 21%; 9% reported diabetes and 5% reported HIV coinfection.

### Risk Factors Associated with MDR-TB

We assessed sociodemographic and medical risk factors for MDR-TB infection using the non-MDR-TB group as a reference (Table 3). After multivariable adjustment, MDR-TB was significantly associated with a prior history of TB (adjusted odds ratio [aOR], 4.57; 95% CI, 2.72–7.70;  $P < 0.001$ ) and continuous residence in a crowded locality (aOR, 2.02; 95% CI, 1.12–3.63;

**Table 2.** Self-reported History of TB, Substance Use, and Comorbidities among Study Participants ( $n = 397$ )

Characteristics	Non-MDR ( $n = 269$ )	MDR ( $n = 128$ )	Total ( $n = 397$ )
History of TB			
Yes	65 (24.1)	65 (50.7)	130 (32.9)
No	204 (75.9)	63 (49.3)	267 (67.1)
Number of previous TB episodes ( $n = 130$ )			
1	56 (86.2)	45 (69.3)	101 (77.7)
2	9 (13.8)	20 (30.7)	29 (22.3)
Substance use			
Smoking*			
Yes	27 (10.2)	9 (7.0)	36 (9.2)
No	238 (89.8)	119 (93.0)	357 (90.8)
Chewing tobacco*			
Yes	78 (29.5)	23 (18.0)	101 (25.8)
No	186 (70.5)	105 (82.0)	291 (74.2)
Alcohol*			
Yes	60 (22.6)	25 (19.5)	85 (21.6)
No	206 (77.4)	103 (80.5)	309 (78.4)
Comorbidities			
Diabetes			
Yes	27 (10.0)	10 (7.8)	37 (9.3)
No	242 (90.0)	118 (92.2)	360 (90.7)
HIV*			
Yes	10 (3.7)	9 (7.1)	19 (4.8)
No	259 (96.3)	117 (92.9)	376 (95.2)
Cancer			
Yes	0 (0)	1 (0.8)	1 (0.3)
No	175 (65.1)	72 (56.2)	247 (62.2)
Unknown	94 (34.9)	55 (43.0)	149 (37.5)

Definition of abbreviations: MDR = multidrug-resistant; TB = tuberculosis.

Data are shown as  $n$  (%).

\*Data are missing for some participants.

$P = 0.019$ ). Older age was protective of MDR (aOR, 0.71 for every 10-yr increase in age; 95% CI, 0.57–0.89;  $P = 0.003$ ).

**Xpert rpoB mutation patterns.** We examined mutation patterns among a sample of 233 patients with MDR/rifampicin-

resistant TB diagnosed contemporaneously in our study catchment area (Annex E1). We calculated the frequency of *rpoB* probe binding patterns in these 233 patients as an approximate measure of the diversity of circulating rifampicin resistance isolates

(Table 4). The majority, 72.5%, had a pattern consistent with an S531L, S531W, or L533P *rpoB* mutation.

### Pathways to Care

We collected delays between first symptoms to diagnosis for all enrolled patients using the structured interview ( $n = 128$  MDR,  $n = 269$  non-MDR). We mapped care pathways and more detailed delays for the 128 MDR-TB patients, and for a subset ( $n = 139$ ) of non-MDR-TB with whom we conducted in-depth interviews. Non-MDR-TB patients interviewed in-depth did not differ in sex, age, time spent in crowded locality or annual family income from patients who were not similarly interviewed (Annex 4).

**Time to health system access, diagnosis, and treatment.** The median duration between symptom onset and first encounter with the health system was 15 days (interquartile range [IQR], 9–30) for the MDR-TB group and 10 days (6–15) for the non-MDR group (Wilcoxon  $P < 0.0001$ ) (Table 5). Health system delays between the first encounter and diagnosis were longer among MDR patients, median 80 days (IQR, 44–161), than among non-MDR, median 48 days (IQR, 24–80; Wilcoxon  $P < 0.0001$ ). Delays between the onset of symptoms and diagnosis were longer for MDR (median 90 days; IQR, 60–180) than for non-MDR-TB (median 60 days; IQR, 30–90; Wilcoxon  $P < 0.001$ ). For 29% of MDR patients, the total duration from symptom onset to diagnosis was  $\geq 6$  months. Treatment rapidly followed diagnosis for non-MDR patients (median delay 1 day; IQR, 0–4; data available

**Table 3.** Univariate and Multivariable Logistic Regression Indicating Association of Self-reported Risk Factors and MDR-TB ( $n = 372$ )

Predictors	Crude OR (95% CI)	Crude P Value	Adjusted OR (95% CI)	P Value (Wald)
Sex, F	1.81 (1.17–2.82)	0.008	1.17 (0.63–2.19)	0.614
Age (10-yr increments)	0.75 (0.63–0.90)	0.002	0.71 (0.57–0.89)	0.003
Unemployed*	2.40 (1.51–3.84)	<0.001	—	—
24 h/d spent in crowded locality/slum	2.42 (1.45–4.05)	<0.001	2.02 (1.12–3.63)	0.019
History of TB	3.46 (2.18–5.49)	<0.001	4.57 (2.72–7.70)	<0.001
HIV	1.95 (0.73–5.2)	0.180	1.96 (0.65–5.95)	0.235
Diabetes	0.71 (0.32–1.58)	0.405	1.29 (0.52–3.24)	0.582
Alcohol use	0.82 (0.48–1.42)	0.484	2.15 (0.98–4.72)	0.056
Smoking	0.63 (0.28–1.43)	0.271	0.65 (0.22–1.92)	0.440
Chewing tobacco	0.51 (0.3–0.88)	0.015	0.48 (0.23–0.98)	0.044
Annual family income <sup>†</sup>	1.02 (1.01–1.04)	0.010	1.03 (1.00–1.05)	0.015

Definition of abbreviations: CI = confidence interval; MDR = multidrug-resistant; OR = odds ratio; TB = tuberculosis.

Note:  $n = 25$  had missing data on comorbidities or substance use and were excluded from the regression analysis.

\*Unemployment was excluded from the multivariable model because of strong collinearity with continuous residence in crowded locality and the latter factor being more proximal in the causal pathway.

<sup>†</sup>Annual family income measured in 10,000 Indian rupee increments.

**Table 4.** GeneXpert MTB/RIF Failed or Delayed Probe Patterns

Probe	Binding Failed or Delayed ( <i>n</i> = 233) [ <i>n</i> (%)]	Mutations Targeted
Probe E	169 (72.5)	S531L, S531W, L533P
Probe D	23 (9.9)	H526Y, H526N, H526D, H526C, H526P, H526R, H526L
Probe B	20 (8.6)	Q513K, Q513P, Q513L, D516Y, D516V, D516G, 516-517del
Probe A	13 (5.6)	G510H, L511P, L511R
Probe C	2 (0.9)	S522L S522Q S522W
A + D	4 (1.8)	—
A + E	1 (0.5)	—
A + B	1 (0.5)	—

for 16 of 139), but treatment delay was more substantial for MDR (median 8 days; IQR, 3–14 days; data available for 84 of 126; Wilcoxon  $P < 0.001$ ).

**Delays and Xpert usage.** From September 2018, the Xpert assay was recommended for a wider group of patients including all patients in whom TB was diagnosed and a subset of patients with presumptive TB, namely, children, those coinfecting with HIV, and patients with extra pulmonary symptoms. The majority of enrolled MDR patients received diagnoses before that time (115/128), and we could not assess change in delays in this group. For non-MDR patients, we found a significant decrease in delays: from 60 days (IQR, 30–90;  $N = 220$ ) to 30 days (IQR, 30–60;  $N = 49$ ; Wilcoxon  $P = 0.023$ ) before and after the policy change.

**Pathways to MDR-TB care.** Patients with MDR-TB had their first health encounter in the private sector in 68% (87 of 128) of cases, followed by the NTEP in 26% (33 of 128) and in a pharmacy/chemist in 6% (8 of 128) of cases. Patient-reported reasons for seeing a private sector care provider included an established relationship with a family physician, confidentiality, easy access, or prior good experience. The majority of MDR patients (75%) reported that they had

to shop around for care ( $\geq 3$  visits before TB diagnosis, overall distribution in Figure 1). Of the 57 patients who left the private sector in favor of the NTEP, 44 (77%) reported reasons of no symptomatic relief, and 12 (21%) reported that treatment was not affordable in the private sector. Twelve of 128 patients (9%) reported that they were admitted for “saline therapy” in the private sector. Of the 24 (19%) patients who returned to the private sector after  $\geq 1$  encounter in the NTEP, 18 (75%) reported that they had no symptomatic relief and hence there was a need for a second opinion from their established private provider; four (17%) were unable to provide records on prior TB treatment requested by NTEP staff and their treatment initiation was delayed (by 2 wk or more), prompting their return to the private sector; two patients (8%) needed the private sector for drug susceptibility testing that was not available at the time in the government facility.

The median number of providers visited by patients with MDR-TB was 4 (IQR, 3–5). Only 9 of 128 patients (7%) received their MDR-TB diagnosis at the first healthcare encounter; all of these patients first accessed care in the NTEP. Patients continuing in the private sector, that is, not referred to the NTEP by the second encounter ( $n = 61$ ),

visited an additional median number of 2 providers (IQR, 2–4) before receiving their diagnosis. This was significantly higher than for patients referred to/seeking care in the NTEP at the second encounter ( $n = 57$ , median 1 additional encounter before diagnosis [IQR, 0–1]; Wilcoxon  $P < 0.0001$ ). Only 11 (9%) patients received their MDR diagnosis in the private sector; the remaining received diagnoses at the NTEP.

**Pathways to non-MDR-TB care.** Similar to MDR patients, the majority 100/139 (72%) of patients with non-MDR-TB had their first encounter in the private sector (Figure 2) and for similar reasons. Fourteen patients (10%) first accessed care from a chemist, and the remaining from the NTEP (Annex E5). Pathways to care were also complex, albeit it lesser so than for MDR patients. The median number of providers visited by patients with non-MDR-TB was 3 (IQR, 2–4; Wilcoxon vs. MDR  $P < 0.001$ ; Figure 2), and none of the 139 patients with TB received diagnoses at the first encounter. Eighteen patients (13%) left the NTEP for the private sector after  $\geq 1$  NTEP encounters because of the lack of symptomatic relief. Thirty-six (26%) patients received diagnoses in the private sector.

**Patients with prior TB.** We assessed if patients with prior TB were more likely to access care in the NTEP owing to confidence in the quality of care or familiarity. Although the majority of MDR patients with a first encounter in the NTEP had a history of TB, 26/33 (79%), the reverse was not true as less than half of MDR patients with a history of TB initially accessed care in the NTEP, 26/60 (43%). MDR patients with a prior history of TB were nevertheless more likely to access care in the NTEP than in the private sector (odds ratio, 7.9; 95% CI, 3.0–23.5; chi-square  $P < 0.00001$ ). We observed a similar pattern among patients with non-MDR-TB.

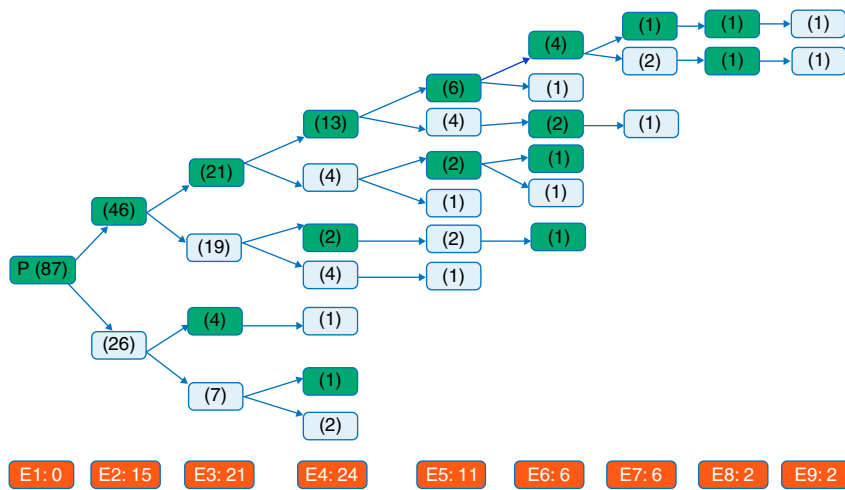
**Healthcare expenditure in the private sector.** We asked patients to approximate out-of-pocket health expenditure in the private

**Table 5.** Delays to TB Care

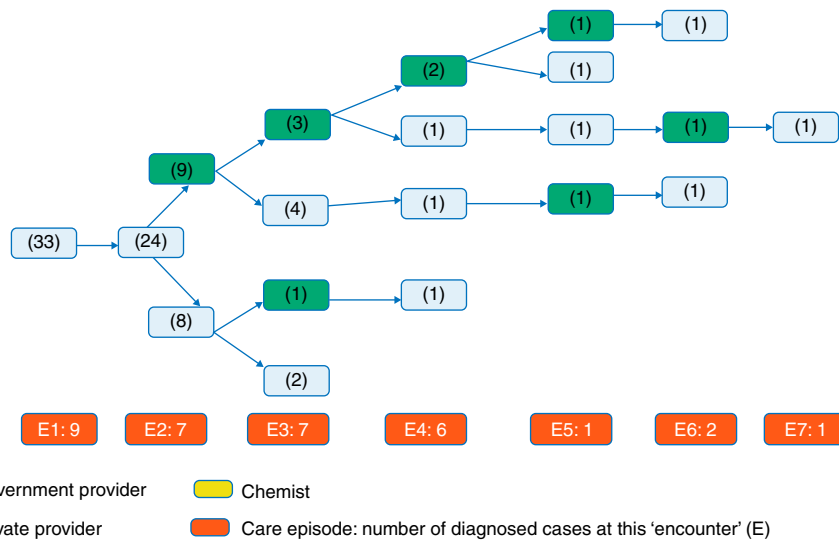
Delay Type	Symptoms to First Encounter (d)	First Encounter to Diagnosis (d)	Onset of Symptoms to Diagnosis of TB or MDR-TB (d)
Non-MDR-TB ( $n = 139$ )	10 (6–15)	48 (24–80)	60 (30–90)
MDR-TB ( $n = 126$ )	15 (9–30)	80 (44–161)	90 (60–180)

*Definition of abbreviations:* MDR = multidrug-resistant; TB = tuberculosis. Data are shown as median (interquartile range).

**A** First encounter in the private sector



**B** First encounter in the public sector (NTEP)



Legend:  
 □ Government provider      □ Chemist  
 ■ Private provider            ■ Care episode: number of diagnosed cases at this 'encounter' (E)

**Figure 1.** Pathways to diagnosis and care among patients with multidrug-resistant tuberculosis. E = episode of care or encounter number. E1, E2, and so on indicate the first episode, second episode, and so on. The total number of patients who received diagnoses and were started on treatment at each care episode is given in the orange box. The total number of patients observed at each care episode in the respective care sector is given in parentheses within each blue or green box. Green designates the private sector. Blue designates the public sector/NTEP. (A) First encounter in the private sector. (B) First encounter in the public sector (NTEP). NTEP = National TB Elimination Program; TB = tuberculosis.

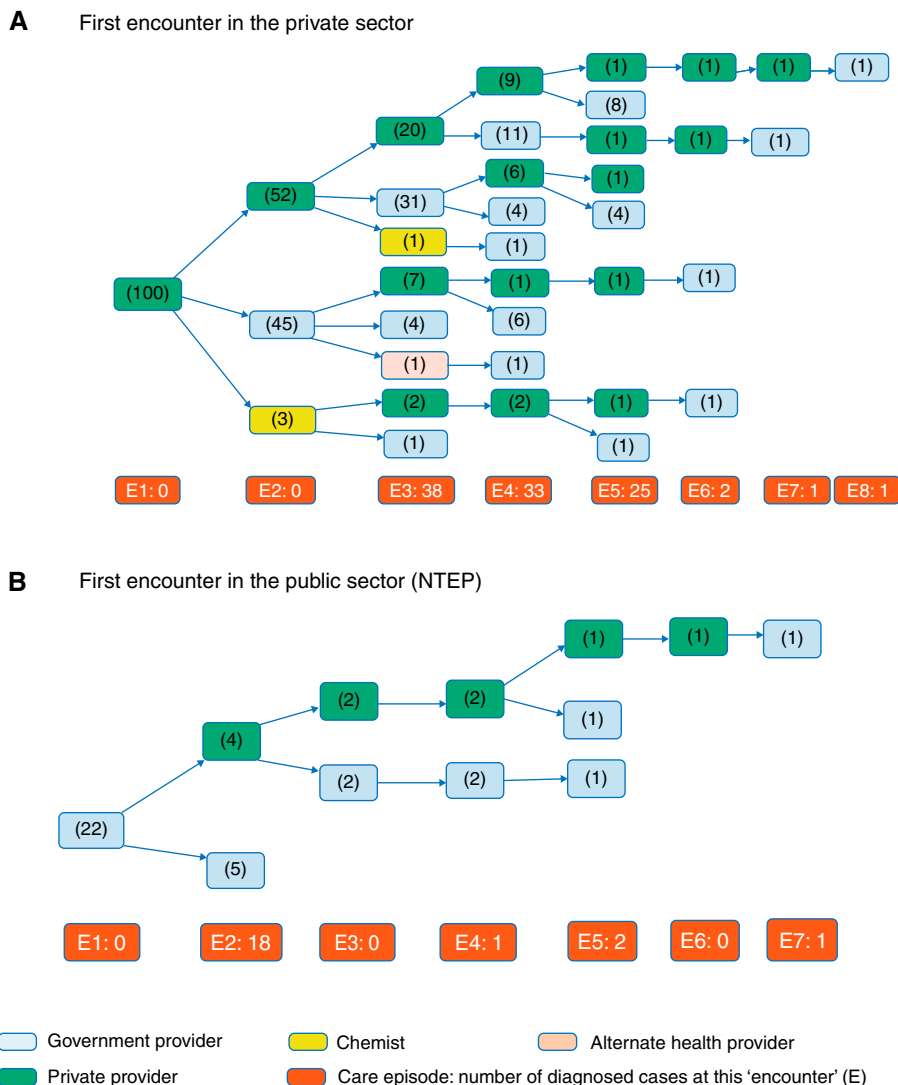
sector before approaching the NTEP (TB care is free in the NTEP). Sixty-two of 128 (49%) patients with MDR-TB provided estimates of expenditure, with the median expenditure being 10,000 Indian rupees (IQR, 3,000–27,000), and 14 (23%) reported catastrophic expenditure >20% of household annual income. For patients with non-MDR-TB, median private sector expenditure was significantly lower at 2,050 Indian rupees (IQR, 975–6,000) (Wilcoxon  $P = 0.001$ , data available for 110 of 139 patients), and

8% reported catastrophic expenditure (7/84 with data on household annual income).

**Discussion**

We studied risk factors associated with MDR-TB and quantified delays in care with analysis of patients' pathways and perceptions. We confirm the known strong association between previous episodes of TB and MDR (22). This association is

commonly believed to result from recent acquisition of *de novo* antibiotic resistance; however, it can also result from failure of inappropriate first-line treatment in patients with unrecognized transmitted MDR. We made several observations that support a high proportion of MDR-TB resulting from recent transmission. First, we observe a strong association between continuous residence in a crowded locality and MDR-TB, a result suggestive of MDR transmission in these localities. We observe that younger



**Figure 2.** Pathways to diagnosis and care among patients with non-multidrug-resistant tuberculosis. E = episode of care or encounter number. E1, E2, and so on indicate the first episode, second episode, and so on. The total number of patients who received diagnoses and were started on treatment at each care episode is given in the orange box. The total number of patients observed at each care episode in the respective care sector is given in brackets within each blue or green box. Green designates the private sector. Blue designates the public sector/NTEP. (A) First encounter in the private sector. (B) First encounter in the public sector (NTEP). NTEP = National TB Elimination Program; TB = tuberculosis.

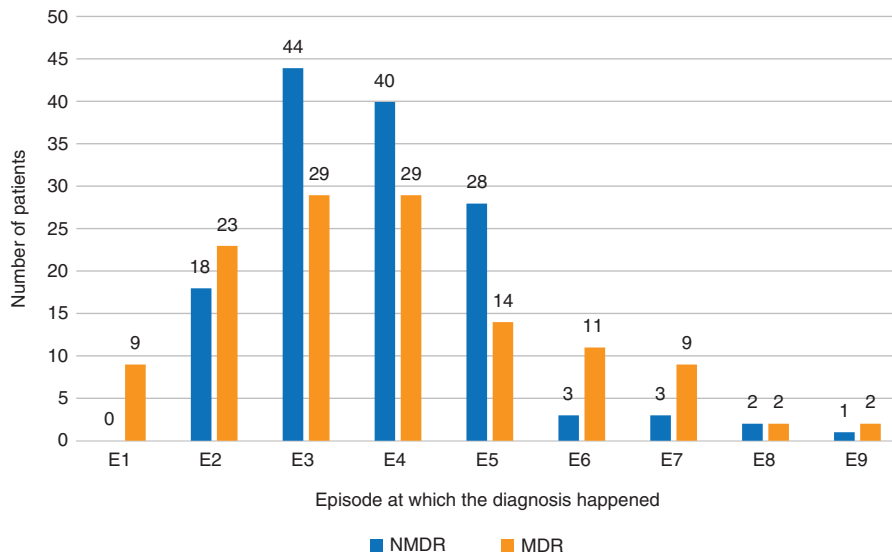
patients are more likely to have MDR-TB. An association of MDR with young age in other high-prevalence settings has been interpreted to be consistent with MDR community transmission, as TB reactivation is more common among older patients (2). In univariate analysis, we found women to be overrepresented among MDR cases. Although active TB disease has a higher incidence in males, MDR-TB was associated previously with female sex in India and several former Soviet Union countries including Estonia (23, 24). This association is yet to be explained but has been postulated to relate to higher MDR transmission to women (25). Our

multivariable model supports this possibility, as sex's effect on MDR appears to be confounded by continuous residence in crowded localities.

We observe low molecular diversity in Xpert *rpoB* probe binding patterns with 72.5% of MDR isolates having a pattern consistent with the S531L, S531W, or L533P *rpoB* mutation. In a recent study with sampling enriched for MDR-TB in Peru, a setting known for ongoing MDR-TB transmission, this proportion was lower at 62% (26). The proportion in Pune was similar to that in the North-West region of Pakistan (77%), a region recently identified to have MDR-TB transmission by whole

genome sequencing (27). In contrast, in China, reported to have a restrained MDR-TB epidemic (28), this proportion was lower and estimated at 41% in clinical isolates (29). Overall, the observed low diversity is consistent with a sizable proportion of MDR-TB disease resulting from recent transmission in Pune.

Delays in diagnosis and the subsequent initiation of effective therapy may be important drivers of MDR-TB transmission (30). A recent study of patients with drug-susceptible TB in the United States demonstrated the risk of TB infection among household members to be 5% higher with every day increase in care delay (31).



**Figure 3.** MDR tuberculosis and NMDR tuberculosis cases diagnosed at sequential healthcare encounters. MDR = multidrug-resistant; NMDR = non-MDR.

The same study also demonstrated a higher rate of TB complications including hemoptysis, aspergillosis, bronchiectasis, and pneumothorax with longer delays. We observed long delays between the first healthcare encounter and diagnosis for both patients with TB and those with MDR-TB. Targeting the long delays in this portion of the care cascade is likely to have a major impact on overall delays. In more detail, pathway to care analysis revealed the private sector to be the point of first contact for most patients, even when they previously have had TB. This is despite the NTEP being the nationally endorsed provider of TB and MDR-TB care. Reasons underlying this preference most notably include a trust or established relationship with a private practitioner that can even result in “bounce back” to the private sector after referral to the NTEP in 13–19% of patients. Pathway analysis also revealed that 23% of patients with MDR-TB had catastrophic expenditure before reaching the NTEP and the provision of questionable therapies (e.g., saline) in the private sector. This is consistent with findings from prior studies in Maharashtra that identified poor knowledge of MDR-TB and its treatment among private practitioners (32, 33). Overall, MDR patients report not only a prolonged path to diagnosis but also a complex one with multiple encounters often across both private and public sectors (Figure 3).

Our study was not without limitations. We enrolled patients in Pune City and the surrounding industrial belt. Although likely

representative of other urban and suburban industrial settings in India, our findings may not be generalizable to all contexts in India (e.g., rural settings where TB is prevalent). We relied on patient reports, and there might have been recall bias and associated over- or underestimation of delays in care. Sampling or survivor’s bias is another concern, and the effect of this on the risk factor analysis is difficult to assess. The sex and age distribution of our patients with TB is consistent with national and statewide data for TB (34). To minimize sampling and survivor’s bias, we tracked the age of patients with MDR-TB we approached for study enrollment but who had died, were unreachable, or otherwise declined to participate. We found that our sample had a similar age distribution to patients not enrolled. The majority of deaths before enrollment (75%) were among adolescents to young adults aged 15–35 years, arguing against the association of MDR with age being due to a survivor’s bias and providing further reason for concern about MDR-TB disease in young adults (Annex E3). Finally, our assessment of delays and pathways only applies to patients eventually treated in the public sector. Based on the Indian TB Report 2020, 14% of MDR patients are notified and treated in the private sector in Maharashtra, compared with 86% in the NTEP (16). We attempted to reach patients treated in the private sector during our study period, but we were not able to enroll them, as the majority voiced fear of disclosure of their TB status.

In conclusion, the accumulation of evidence indicating transmission of MDR-TB in Pune emphasizes the need to shorten patients’ infectious period by tackling the observed long delays in care. The observed reduction of delays with expanded Xpert use suggests the need for routine molecular testing, especially among presumptive TB cases with identified risk factors for MDR. We characterize young age (<35 yr) and continuous residence in crowded localities to be new risk factors for MDR over non-MDR-TB, and these populations should be targeted. Our data support the need for outreach efforts like the Joint Effort for Elimination of Tuberculosis designed to incentivize and boost referral from the private sector to the NTEP (18). They also emphasize the need for direct private practitioner education and support, as private practitioners are and will likely continue to be established providers for a large section of the population. In addition to boosting referral, investment in patient retention efforts in the NTEP is needed, including a more patient-centered approach attentive to persistent symptoms. Reassessing NTEP processes of care to decrease patient burden may also be helpful (e.g., requiring that the private practitioners transfer care records upon referral rather than turn patients away when they cannot provide these records). Given the pressing need, the direct empowerment of patients via either in-person or virtual support communities or alternatively through the assignment of care navigators may be the best short-term solution until system reforms



are implemented. As effective treatment is the only path to interrupting MDR-TB transmission, these system interventions should be prioritized within TB control efforts in India. ■

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