Risk Factors Associated with MDR-TB at the Onset of Therapy among New Cases Registered with the RNTCP in Mumbai, India

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Abstract

Background—Multidrug-resistant TB (MDR-TB) has emerged as a major threat to global TB control efforts in recent years. Facilities for its diagnosis and treatment are limited in many high-burden countries, including India. In hyper-endemic areas like Mumbai, screening for newly diagnosed cases at a higher risk of acquiring MDR-TB is necessary, for initiating appropriate and timely treatment, to prevent its further spread.

Objective—To assess risk factors associated with MDR-TB among Category I, new sputum smear-positive cases, at the onset of therapy.

Materials and Methods—The study applied an unmatched case-control design for 514 patients (106 cases with MDR-TB strains and 408 controls with non-MDR-TB strains). The patients were registered with the Revised National Tuberculosis Control Program (RNTCP) in four selected wards of Mumbai during April 2004-January 2007. Data were collected through semi-structured interviews and drug susceptibility test results.

Results—Multivariate analysis indicated that infection with the Beijing strain (OR = 3.06; 95% C.I. = 1.12-8.38; \(P = 0.029\)) and female gender (OR = 1.68; 95% C.I. = 1.02-2.87; \(P = 0.042\)) were significant predictors of MDR-TB at the onset of therapy.

Conclusion—The study provides a starting point to further examine the usefulness of these risk factors as screening tools in identifying individuals with MDR-TB, in settings where diagnostic and treatment facilities for MDR-TB are limited.

Keywords

India; MDR-TB; RNTCP; Risk factors; Unmatched case-control

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Introduction

Multidrug-resistant tuberculosis (MDR-TB) is emerging as a growing threat to TB control programs in many countries and accounts for 5% of all newly diagnosed patients worldwide. The potentially serious impact of MDR-TB (TB strain resistant to at least isoniazid and rifampicin) has long been recognized; however, the problem is of special concern because second-line drugs required for its treatment are often unavailable, are far more expensive than the first-line drugs, with only 65-75% efficacy, and have side effects that may require hospitalization.

In high-burden countries like India, data on drug-resistant TB and/or MDR-TB are lacking for many regions, largely because of the absence of a surveillance network and limited facilities for its diagnosis and treatment, except a few recently implemented pilot projects in Delhi, Gujarat, and three districts — Ernakulam in Kerala state, Hoogli in West Bengal state, and Mayurbhanj in Orissa State. A study on the surveillance of drug-resistant TB in the state of Gujarat indicated the prevalence of MDR-TB among previously untreated (new) cases as, 2.4 and 17.4% among previously treated cases. Studies in metropolitan Mumbai, in Western India, indicated high levels of MDR-TB in recent years, especially among new cases. Although many of these studies have some limitations being carried out in hospital-based settings, the problem of MDR-TB in Mumbai is particularly a concern for public health because of various predisposing and precipitating factors, such as, high population density (21190 per sq. km), 54% of the population residing in slums, and a substantial migration of people from different parts of India as well as the world.

From the perspective of the public health policy, a study on the screening of risk factors linked to MDR-TB at the onset of therapy, among new cases, is important to identify patients vulnerable to getting infection with MDR-TB strains. This is because patients with MDR-TB strains respond poorly to first-line treatment (DOTS), which has been reported in a multi-country study. Similarly there is a considerable risk of amplification of resistance among MDR-TB patients if treated with first-line drugs. Early identification of new cases infected with MDR-TB strains can prevent patient and health system-induced delays in the initiation of appropriate treatment and those patients can be put on a different, appropriate regimen. This is necessary for breaking the transmission cycle of MDR-TB. This will further reduce the cost of treatment, as well as improve the implementation of the DOTS-based RNTCP. As highlighted by Cobelens and colleagues, scaling up of programmatic management of drug-resistant TB requires targeting of those patients most at risk of having MDR-TB. This is more promising in the light of the current limited availability of rapid molecular assays, for undertaking drug susceptibility testing and strain typing on a large scale.

The literature shows that factors such as young age, migration, unemployment at the time of diagnosis, poor nutritional status (based on low body mass index), history of alcoholism, homelessness, and comorbidities, such as, diabetes, HIV / AIDS, and so on, are associated with MDR-TB. A number of studies have indicated that certain strains of Mycobacterium tuberculosis (for example Beijing / W family) are associated with MDR-TB and are also known to cause its outbreaks in some settings. Although most of these
studies have documented risk factors associated with MDR-TB among the previously treated cases, the literature on new cases is extremely limited.

Having no prior documentation of risk factors available from Mumbai, this study was aimed at exploring an association of MDR-TB, at the onset of therapy, among new cases, with recognized risk factors, namely, age, gender, glycemic control, occupational status, migration, substance abuse, nutritional status, HIV / AIDS, and infection with specific TB strains.

**Materials and Methods**

**Ethical approval**

The study was approved by the Ethics Committee of the Foundation for Medical Research (FMR), Mumbai (20.07.2001 / 01).

**Study Setting and patient selection**

The study was carried out as a part of a larger epidemiological investigation on MDR-TB in four municipal wards\(^1\) of Mumbai, where the annual TB case detection rate was 190 per 100,000, for the year 2002.\(^2\) These wards (F / N, G / N, H / E, and K / E), covering 38 DOTS centers and approximately 2.4 million population were characterized by a high load of sputum smear-positive cases with moderately suboptimal cure rates ranging between 78-81%. Fifty percent of the wards in Mumbai (11 / 23) displayed similar cure rates, while an additional 20% of the wards displayed further reduced cure rates of 50-74%.\(^3\) These wards with suboptimal performance were selected to minimize the possibility of extreme outcomes due to a selection bias. There was no apparent deviation seen in the RNTCP functioning in these and other wards in Mumbai. The World Health Organization guideline-based questions.\(^4\) were applied for screening of a cohort of new sputum smear-positive cases registered with the RNTCP during April 2004 - January 2007.

**Inclusion and exclusion criteria**

To ensure inclusion of genuinely new cases in the study, Category I new sputum smear-positive cases, who during screening admitted to not having undergone anti-TB treatment continuously for > 1 month in the past, were included. This was done to minimize the selection bias that could be introduced due to erroneous categorization of previously treated cases as ‘new’.\(^5\)

Patients < 15 years and > 70 years of age were excluded because of reasons such as inability to produce sputum and unwillingness for appearing for an interview and laboratory investigations, respectively. Similarly, those who had taken the current anti-TB medication for more than a week were also excluded, as even small amount of treatment doses reduce the bacillary load and could affect their growth in culture for drug susceptibility testing. All the patients were consecutively enrolled.

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\(^1\) One ward for approximately 0.5 million population; however, here four wards covered approximately 2.4 million population. Since the study was carried out during 2004-2007, the RNTCP reports for years 2001-2003 were referred for selection of wards based on high case load.

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\(^3\) These wards with suboptimal performance were selected to minimize the possibility of extreme outcomes due to a selection bias.

\(^4\) The World Health Organization guideline-based questions.

\(^5\) To ensure inclusion of genuinely new cases in the study, Category I new sputum smear-positive cases, who during screening admitted to not having undergone anti-TB treatment continuously for > 1 month in the past, were included.
Being a part of larger epidemiological investigation, the sample size calculation for the larger study was considered. A pilot study on MDR-TB in Mumbai by Mistry et al. revealed that 57% strains were clustered. Based on this observation, to detect 50% clustering with a precision of +7%, the required sample size for the larger study was 200 index (Category I failures) and 1000 secondary (Category I new sputum smear-positive) cases in a 1:5 ratio. Considering the annual case detection rate of 190 per 100,000 per year, we could estimate approximately 70 new smear-positive cases per year (based on the premise that 50 would be new smear-positive cases when the annual case detection rate was 135 per 100,000 as per the RNTCP guidelines). Referring to these calculations, we estimated to have 1680 new smear-positive cases in a year, in these four study wards, covering a population of 2.4 million (24*70). In a three-year period, there would be approximately 5000 new smear-positive cases. During the study period (April 2004 to the study period (April 2004 January 2007), which was less than three years, a total of 4297 new smear-positive cases were registered in these selected four wards. For achieving the target sample size of 1000 secondary cases, we screened 1324 new cases. As per the inclusion criteria and considering the time and resource constraints, we could include a total of 681 cases. About 12% (154 of 1324) of the cases were excluded for having anti-TB treatment for > one month before registering with the RNTCP. Others were excluded for various reasons mentioned in the exclusion criteria.

Data collection

During recruitment, information pertinent to the study was imparted to patients and a written consent for participation in the study was obtained from each of them. Furthermore, all patients were interviewed using the same precoded structured interview schedule. It included questions related to their socio-demographic profile, years of stay in Mumbai, information on their migration to Mumbai, course of treatment, and substance abuse. Additionally, information related to weight and height (for assessing the body mass index (BMI), glycosylated hemoglobin, and HIV status, was also collected. Hematological tests were carried out at pathological laboratories and HIV tests were carried out at Voluntary Counseling and Testing Centers (VCTCs).

Study design

An unmatched case-control design was used to study the risk factors associated with MDR-TB at the onset of therapy in this setting (Figure 1). The ‘case group’ included MDR-TB patients having strains resistant to at least isoniazid (H) and rifampicin (R), whereas, the ‘control group’ included patients with non-MDR-TB strains. Classification of cases and controls was based on the drug susceptibility test (DST) results; however, their sputum samples were collected prior to the initiation of treatment.

Drug susceptibility testing

Early morning sputum samples collected from patients were processed by modified Petroff’s method and cultured on Lowenstein-Jensen Slants as well as Dubos broth (Himedia, India). Drug susceptibility testing of the samples was performed by the radiorespirometric Buddemeyer technique (a manual modification of the Bactec 460 technique).
After performing DST at the Foundation for Medical Research (FMR), the isolates were retested at the FMR to determine reproducibility of the results, and a random sample of about 5% of the isolates was sent to the Swedish Institute for Infectious Disease Control, Karolinska, for external validity. Similarly more than 10% of the isolates were randomly selected and subjected to internal validity of the results [Table 1]. Based on the Kappa values (> 0.7), a good agreement was seen for the DST results obtained at the FMR and Swedish Institute. Subsequently, genotypic corroboration of rifampicin resistance in a subset of cases was also obtained (k = 0.74, 88% agreement) by the INNO-LiPA (Line Probe Assay), which screens for mutations in the rpoB gene. As the present study was the part of a larger study on MDR-TB, the DST results were referred from the earlier publication of our group (D’Souza et al.) and presented here as Table 1.

Of the 681 cases, results of DST were available for 604 cases in Mumbai. On account of lack of information on some variables, 90 patients were excluded from the analysis leading to the sample of 514 patients, which included 106 cases and 408 controls.

As there was no prior evidence of the potential ‘confounding factors’ (age and sex, which are non-modifiable factors generally used for matching) from this study setting, an unmatched analysis was carried out. This enabled us to further examine their association with MDR-TB. Furthermore, we examined the association of MDR-TB with four major clusters (strains), namely, Beijing (prevalent in China, Far-East-Asia, and also in Middle-East-Central Asia and Oceania), Central Asian Strain (CAS 1 prevalent in Asia), Manu (ancient Indian strain), and East Afican Indian (EAI), which were based on the spoligotype patterns (Spol DB4) obtained from the cohort. As there was previously documented evidence of an association of the Beijing strain with MDR-TB, and CAS and Manu are endemic in India, the association of MDR-TB with these major clusters was examined.

### Analysis

Both, univariate and multivariate analyses were carried out using the SPSS version 16.0 and Epi-info 2002. Multivariate logistic regression analysis was carried out. The strength and the magnitude of the association of MDR-TB with risk factors was expressed in terms of odds ratios (OR) and 95% confidence intervals (CI). The variables were considered significant if 95% CI did not include value 1 with \( P < 0.05 \).

### Results

#### Characteristics of the study population

Nearly 69% patients belonged to the younger (15-35 years) age group with a median age of 26 years (IQR: 20-37 years). About two-thirds of patients (62%) were males. Fifty-six percent of the patients were married. Three-fourths of patients had primary / high school education. Thirty-seven percent of the patients were unemployed and others were involved predominantly in lower services such as paper mill workers, watchmen, courier delivery boys and the like, and women were housewives. More than three-fourths of the patients in

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2WHO / IUATLD supra-national reference laboratory
both the groups had an annual income of less than Rs. 80,000 (US $1860)\(^3\) and resided in crowded localities such as slums and ‘chawls’. More than half of the patients were migrants from other states in India [Table 2].

**Risk factors associated with MDR-TB**

Univariate analysis included parameters listed in Table 3. It indicated that infection with the Beijing strain was significantly associated with MDR-TB. Although no significant association was seen for other parameters, consistent increase in odds ratio indicated a higher risk of MDR-TB in the older age groups. Nearly three-fourths of the patients had a BMI below normal and glycosylated hemoglobin above 6.5%, indicating their poor nutritional status and poor glucose tolerance, respectively. However, both these factors did not show a significant association with MDR-TB.

Considering the collinearity of variables, multivariate logistic regression analysis was carried out. It indicated a significant association of MDR-TB with the female gender (OR = 1.68; 95% CI = 1.02-2.87; \(P = 0.042\)) and Beijing strain (OR = 3.06; 95% CI = 1.12-8.38; \(P = 0.029\)). Similar to univariate analysis, the multivariate analysis also showed a higher risk of MDR-TB associated with the older age groups. However, interactions among age, gender, and Beijing strain were not significant, implying that these parameters were independent predictors of MDR-TB among new cases, at the onset of therapy, in this setting [Table 4].

As information on HIV status was not available for 47 patients, this variable was not included in the analysis. However, the available data showed that seven of 93 cases (7.5%) and 16 of 374 (4.2%) controls had a HIV seropositive status. As the sample contained a very small number of HIV positive cases; its association with MDR-TB could not be established.

**Discussion**

Applying an unmatched case-control design, this study explored the relationship of various risk factors with MDR-TB at the onset of therapy, among new TB cases.

Some earlier studies reported age below 40 years associated with the risk of getting MDR-TB.\(^{26}\) Although a majority of patients in the present study sample belonged to the younger age group (15-35 years), the risk of MDR-TB was seen to be higher among elderly individuals (age > 45 years), which contrasts with the finding reported by Kimerling and colleagues.\(^{26}\) Although a rigorous screening procedure was followed to minimize the ‘selection bias’ that could be introduced because of erroneous categorization of some previously treated cases as ‘new,’\(^{21}\) it might be possible that some cases did not disclose the history of prior anti-TB treatment, which was a risk factor significantly associated with MDR-TB.\(^{5,20}\) It would be useful to examine the association of age with MDR-TB in a larger sample and other geographical settings for generalizability or elderly patients should be questioned more closely for previous treatment.

\(^3\)This represents ‘lower-middle income group’, the category based on studies by the National Council for Applied Economic Research; cited in Statistical Outline of India 2002-2003, TATA Services Ltd., Mumbai.

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Besides age, gender was found to be associated with MDR-TB. Studies in Western Europe and the Samara region of Russia revealed that males had a significantly higher risk of MDR-TB. A study in France and other parts of Russia, however, revealed a statistically significant association of primary MDR-TB with the ‘female gender’. Similarly, other studies by Cox et al. in central Asia and Vashakidze et al. in Georgia, also identified ‘female gender’ as a significant factor related to MDR-TB infection. Consistent with the latter studies, the present study suggests a higher risk of MDR-TB presentation in new female patients. Furthermore, a gender-based analysis among MDR-TB patients revealed that significantly more women than men were spending the entire day in crowded localities, where ventilation was poor. This supported the finding from Georgia, which also indicated the risk of MDR-TB to be associated with staying in the densely crowded capital. These observations suggest the vulnerability of women for MDR-TB. Nevertheless, the present study indicated no significant association of MDR-TB with any specific occupation group, implying that the MDR-TB can pose a risk to anybody, particularly in settings like Mumbai.

According to Borrell and Gagneux, the variable genetic background of strains belonging to different strain lineages could play a role in the evolution of drug resistance. The same article further reported that the Beijing lineage of M. tuberculosis was repeatedly strongly associated with MDR-TB in different settings, such as, the Soviet Union and South-East Asia. The present study identified only 3.5% of the strains as Beijing, an observation consistent with other studies from India. A low proportion of patients with Beijing strains could be attributed to the competition for transmission between the Beijing strains and other established strains, within defined geographical boundaries. Although the proportion of Beijing was found to be low, its significant association with MDR-TB, as reported here, was consistent with the other studies. The Beijing strain background could be ‘pre-adapted’ to the fitness effects of drug resistance. In this context, as proposed by Borrell and Gagneux, an inquiry into the molecular and evolutionary mechanisms that have contributed to the successful circulation of MDR Beijing strains and determinants of primary drug resistance would be relevant areas for future research.

No significant associations were seen between MDR-TB and habits such as smoking or alcoholism. This might be due to the ‘reporting bias’ associated with these sensitive issues. In our opinion, it would be useful to explore the training methodologies of such inquiries into behavioral aspects, to retrieve more authentic information.

The study provides a starting point to further examine the usefulness of these risk factors as screening tools (with satisfactory sensitivity and specificity) to identify individuals having a high probability of getting infected with MDR-TB strains. This approach is useful in settings with limited diagnostic and treatment facilities for MDR-TB.

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**References**

1. WHO Report 2008. Global Tuberculosis Control. Surveillance, Planning, Financing. World Health Organization; Geneva: 2008. Rep. WHO/HTM/TB/2008.393
2. Iseman MD. Tailoring a time-bomb. Am Rev Respir Dis. 1985; 132:735–6. [PubMed: 3931520]
3. Cobelens F, Heldal E, Kimerling M, Mitnick CD, Podelwils LJ, Ramachandran R, et al. Scaling up programmatic management of drug-resistant tuberculosis: A prioritized research agenda. PLoS Med. 2008; 5:e150. [PubMed: 18613746]
4. Partners in Health (PIH). Medical management of MDR-TB. Partners in Health; Boston, USA: 2003.
5. World Health Organization/International Union against Tuberculosis and Lung Disease (WHO/ IUATLD). Global Project on Anti-tuberculosis Drug Resistance in the World. Prevalence and Trends. World Health Organization; Geneva: 2008. p. 394
6. Ramachandran R, Nalini S, Chandrasekar V, Dave PV, Sanghvi AS, Wares F, et al. Surveillance of drug-resistant tuberculosis in the state of Gujarat, India. Int J Tuberc Lung Dis. 2009; 13:1154–60. [PubMed: 19723407]
7. Almeida D, Rodrigues C, Udwadwa Z, Lalvani A, Gothi GD, Mehta P, et al. Incidence of multidrug-resistant tuberculosis in urban and rural India and implications for prevention. Clin Infect Dis. 2003; 36:e152–4. [PubMed: 12802779]
8. D’souza DT, Mistry NF, Vira TS, Dholakia Y, Hoffner S, Pasvol G, et al. High levels of multidrug-resistant tuberculosis in new and treatment-failure patients from the Revised National Tuberculosis Control Programme in an urban metropolis (Mumbai) in Western India. BMC Public Health. 2009; 9:211. Available from: http://www.biomedcentral.com/1471-2458/9/211. [PubMed: 19563647]
9. Mistry NF, Iyer AM, D’souza DT, Taylor GM, Young DB, Antia NH. Spoligotyping of Mycobacterium tuberculosis isolates from multiple drug-resistant tuberculosis patients from Bombay, India. J Clin Microbiol. 2002; 40:2677–80. [PubMed: 12089307]
10. Director of Census Operations.. Census of India. Maharashtra, Mumbai: 2001.
11. Dye C, Williams BG, Espinal MA, Raviglione MC. Erasing the World’s slow stain: Strategies to beat multi drug-resistant tuberculosis. Science. 2002; 295:2042–6. [PubMed: 11896268]
12. Farmer P, Kim JY. Community based approaches to the control of multidrug-resistant tuberculosis: Introducing DOTS-Plus. BMJ. 1998; 317:671–4. [PubMed: 9728004]
13. Anonymous. Ivano oblast. Vol. 48. MMWR; Russia: 1999. Primary multidrug-resistant tuberculosis; p. 661-3.
14. Farmer, P. Infections and Inequalities: The Modern Plagues. University of California Press; Berkeley CA: 1999. Immodest claims of causality; p. 231-61.
15. Gordin FM, Nelson ET, Mads JP, Cohn DL, Ernst J, Benator D, et al. The Impact of Human Immuno deficiency Virus infection on drug resistant tuberculosis. Am J Respir Crit Care Med. 1996; 154:1478–83. [PubMed: 8912768]
16. Cox H, Kubica T, Doshetov D. The Beijing genotype and drug resistant tuberculosis in the Aral Sea region of Central Asia. Respir Res. 2005; 6:134. [PubMed: 16277659]
17. Narvskaya O, Otten T, Limeschenko E, Sapozhnikova N, Graschenkova O, Steklova L, et al. Nosocomial outbreak of multidrug-resistant tuberculosis caused by a strain of Mycobacterium tuberculosis W-Beijing family in St. Pertsburg, Russia. Eur J Clin Microbiol Infect Dis. 2002; 21:596–602. [PubMed: 12226690]
18. [Last accessed on 2008 Dec 29] RNTCP report. 2003. Available from: http://www.tbcindia.org
19. RNTCP quarterly reports. Mumbai District TB Control Society; Mumbai: 2001.
20. World Health Organization/International Union against Tuberculosis and Lung Disease (WHO/ IUATLD). Global Project on Anti-tuberculosis Drug Resistance in the World. Prevalence and
Trends. Geneva: 2000. Anti-tuberculosis drug resistance in the world, Report No. 2WHO/CDS/TB/2000.278

21. Atre SR, D’Souza DT, Dholakia YN, Mistry NF. Observations on categorization of new TB cases: Implications for controlling drug resistance. Int J Tuberc Lung Dis. 2007; 11:1152–3. [PubMed: 17966562]

22. Jureen P, Werngren J, Hoffner S. Evaluation of the Line Probe Assay (LiPA) for rapid detection of rifampicin resistance in *Mycobacterium tuberculosis*. Tuberculosis. 2004; 84:311–6. [PubMed: 15207806]

23. Brudey K, Driscoll JR, Rigouts L, Prodinger WM, Gori A, Al-Hajjoj SA, et al. *Mycobacterium tuberculosis* complex genetic diversity: Mining the fourth international spoligotyping database (Spol DB4) for classification, population genetics and epidemiology. BMC Microbiol. 2006; 6:23. Available from: http://www.biomedcentral.com/1471-2180/6/23. [PubMed: 16519816]

24. Glynn JR, Whiteley J, Bifani PJ, Kremer K, van Soolingen D. Worldwide Occurrence of Beijing/W Strains of *Mycobacterium tuberculosis*: A Systematic Review. Emerg Infect Dis. 2002; 8:843–9. [PubMed: 12141971]

25. Singh UB, Suresh N, Bhanu NV, Arora J, Pant H, Sinha S, et al. Predominant Tuberculosis Spoligotypes, Delhi, India. Emerg Infect Dis. 2004; 10:1138–42. [PubMed: 15207071]

26. Kimerling ME, Slavuckij A, Chavers S, Peremtin GG, Tonkel T, Sirotkina O, et al. The risk of MDR-TB and polyresistant tuberculosis among the civilian population of Tomsk city, Siberia. Int J Tuberc Lung Dis. 2003; 7:866–72. [PubMed: 12971671]

27. Ruddy M, Balabanova Y, Graham C, Fedorin I, Malomanova N, Elizarova E, et al. Rates of drug resistance and risk factor analysis in civilian and prison patients with tuberculosis in Samara region, Russia. Thorax. 2005; 60:130–5. [PubMed: 15681501]

28. Robert J, Trystram D, TrufLot-Pernot C, Jarlier V. Multidrug-resistant tuberculosis: Eight years of surveillance in France. Eur Respir J. 2003; 22:833–7. [PubMed: 14621093]

29. Vashakidze L, Salakaia A, Shubladze N, Cynamon M, Barbakadze K, Kikvidze M, et al. Prevalence and risk factors for drug resistance among hospitalized tuberculosis patients in Georgia. Int J Tuberc Lung Dis. 2009; 13:1148–53. [PubMed: 19723406]

30. Atre, S. Drug resistance: A biosocial perspective-a study among tuberculosis patients in Maharashtra, India [Ph.D. Thesis]. University of Pune; 2007.

31. Borrell S, Gagneux S. Infectiousness, reproductive fitness and evolution of drug-resistant *Mycobacterium tuberculosis*. Int J Tuberc Lung Dis. 2009; 13:1456–66. [PubMed: 19919762]

32. Singh UB, Arora J, Suresh N, Pant H, Rana T, Sola C, et al. Genetic diversity of *Mycobacterium tuberculosis* isolates from patients with pulmonary tuberculosis in India. Infect Genet Evol. 2007; 7:441–8. [PubMed: 17317334]

33. Singh UB, Suresh N, Bhanu NV, Arora J, Pant H, Sinha S, et al. Predominant tuberculosis spoligotypes, Delhi, India. Emerg Infect Dis. 2004; 10:1138–42. [PubMed: 15207071]

34. Almeida D, Rodrigues C, Ashavaid TF, Lalvani A, Udawadia ZF, Mehta A. High incidence of the Beijing genotype among multidrug-resistant isolates of *Mycobacterium tuberculosis* in a tertiary care centre in Mumbai, India. Clin Infect Dis. 2005; 40:881–6. [PubMed: 15736024]
Figure 1. Unmatched case-control design
Table 1
External and internal validity of drug susceptibility testing for individual first-line drugs

| Drugs | External\(^a\) (n = 45) | Internal\(^b\) (n = 70) |
|-------|--------------------------|------------------------|
|       | Concordance (%) | Kappa values | Sensitivity (%) | Specificity (%) | Concordance (%) | Kappa values |
| H     | 91             | 0.773         | 86             | 94             | 95             | 0.893       |
| R     | 93             | 0.762         | 100            | 93             | 97             | 0.919       |
| Z     | 87             | 0.557         | 100            | 87             | 91             | 0.819       |
| E     | 89             | 0.487         | 80             | 91             | 90             | 0.759       |

\(^a\)Performed at Swedish Institute for Infectious Disease Control, Stockholm;

\(^b\)Repeated at FMR; H: Isoniazid; R: Rifampicin; Z: Pyrazinamide; E: Ethambutol; Source: D’Souza et al.\(^8\)
Table 2
Socio-demographic profile of study population

| Parameters                  | Cases (n = 106) | Controls (n = 408) | Controls (n = 514) |
|-----------------------------|-----------------|-------------------|-------------------|
|                             | No   | %    | No   | %    | No   | %    |
| Marital status              |      |      |      |      |      |      |
| Never married               | 41   | 38.7 | 177  | 43.4 | 218  | 42.4 |
| Married                     | 62   | 58.5 | 228  | 55.9 | 290  | 56.4 |
| Widowed                     | 3    | 2.8  | 2    | 0.5  | 5    | 1.0  |
| Separated                   | 0    | 0    | 1    | 0.2  | 1    | 0.2  |
| Education                   |      |      |      |      |      |      |
| Illiterate                  | 20   | 18.9 | 57   | 14.0 | 77   | 15.0 |
| First – Fourth std.         | 14   | 13.2 | 65   | 15.9 | 79   | 15.4 |
| Fifth – seventh std.        | 25   | 23.6 | 97   | 23.8 | 122  | 23.7 |
| Eighth – tenth std.         | 36   | 34.0 | 147  | 36.0 | 183  | 35.6 |
| Eleventh / Twelfth std.     | 6    | 5.7  | 33   | 8.1  | 39   | 7.6  |
| Degree                      | 5    | 4.7  | 9    | 2.2  | 14   | 2.7  |
| Household Income (rupees / year) |      |      |      |      |      |      |
| <40000                      | 44   | 41.5 | 196  | 48.0 | 240  | 46.7 |
| 40001 – 80000               | 43   | 40.6 | 162  | 39.7 | 205  | 39.9 |
| 80001 – 120000              | 14   | 13.2 | 32   | 7.8  | 46   | 8.9  |
| 120001 – 160000             | 5    | 4.7  | 15   | 3.7  | 20   | 3.9  |
| 160001 and above            | 0    | 0.0  | 3    | 0.7  | 3    | 0.6  |
| Occupational status         |      |      |      |      |      |      |
| Unemployed                  | 33   | 31.1 | 160  | 39.2 | 193  | 37.5 |
| Student                     | 0    | 0.0  | 3    | 0.7  | 3    | 0.6  |
| Housewife                   | 24   | 22.6 | 71   | 17.4 | 95   | 18.5 |
| Laborer                     | 3    | 2.8  | 14   | 3.4  | 17   | 3.3  |
| Artisan                     | 4    | 3.8  | 21   | 5.1  | 25   | 4.9  |
| Lower services              | 38   | 35.8 | 128  | 31.4 | 166  | 32.3 |
| Trade                       | 2    | 1.9  | 9    | 2.2  | 11   | 2.1  |
| Higher services / profession| 2    | 1.9  | 2    | 0.5  | 4    | 0.8  |

No significant difference between controls and cases
### Table 3
Univariate analysis of risk factors associated with MDR-TB among new cases

| Risk Factors                      | Cases (n = 106) | Controls (n = 408) | Odds Ratio (OR) | 95% C.I. | P-value |
|-----------------------------------|----------------|-------------------|----------------|---------|---------|
| Age groups (years)                |                |                   |                |         |         |
| 15 – 24                           | 38             | 186               | Ref            |         |         |
| 25 – 34                           | 29             | 100               | 1.42           | 0.80 – 2.52 | 0.20   |
| 35 – 44                           | 21             | 68                | 1.51           | 0.79 – 2.87 | 0.17   |
| 45 and above                      | 18             | 54                | 1.63           | 0.82 – 3.23 | 0.13   |
| Gender                            |                |                   |                |         |         |
| Male                              | 61             | 59                | Ref            |         |         |
| Female                            | 45             | 149               | 1.28           | 0.81 – 2.03 | 0.26   |
| Native state                      |                |                   |                |         |         |
| Maharashtra                       | 44             | 187               | Ref            |         |         |
| Non-Maharashtra                   | 62             | 221               | 1.19           | 0.76 – 1.88 | 0.42   |
| Occupational status               |                |                   |                |         |         |
| Unemployed                        | 57             | 231               | Ref            |         |         |
| Employed                          | 49             | 177               | 1.12           | 0.71 – 1.76 | 0.59   |
| Body Mass Index (BMI) Kg / m^2    |                |                   |                |         |         |
| Normal (>18.5)                    | 31             | 113               | Ref            |         |         |
| Below Normal (<18.5)              | 75             | 295               | 0.93           | 0.56 – 1.53 | 0.75   |
| Glycosylated Hemoglobin (%)       |                |                   |                |         |         |
| < 6.5                             | 33             | 149               | Ref            |         |         |
| ≥ 6.5                             | 73             | 259               | 1.27           | 0.79 – 2.07 | 0.30   |
| Smoking                           |                |                   |                |         |         |
| No                                | 87             | 346               | Ref            |         |         |
| yes                               | 19             | 61                | 1.24           | 0.68 – 2.25 | 0.45   |
| Alcohol consumption               |                |                   |                |         |         |
| No                                | 90             | 334               | Ref            |         |         |
| yes                               | 16             | 74                | 0.80           | 0.43 – 1.49 | 0.46   |
| Strain 1                          |                |                   |                |         |         |
| Other strains                     | 99             | 398               | Ref            |         |         |
| Beijing                           | 7              | 10                | 2.81           | 1.04 – 7.57 | 0.03 * |
| Strain 2                          |                |                   |                |         |         |
| Other strains                     | 96             | 363               | Ref            |         |         |
| Central Asian                     | 10             | 45                | 0.84           | 0.38 – 1.81 | 0.63   |
| Strain (CAS)                      |                |                   |                |         |         |
| Strain 3                          |                |                   |                |         |         |
| Other strains                     | 80             | 303               | Ref            |         |         |
| Manu                              | 26             | 105               | 0.94           | 0.55 – 1.58 | 0.79   |
| Other strain                      | 100            | 386               | Ref            |         |         |
| EAI                               | 6              | 22                | 1.05           | 0.37 – 2.83 | 0.91   |

Note: First Category: Reference category [Strain 1: Beijing; Strain 2: Central Asian Strain (CAS) Strain 3: Manu (ancient Indian strain) Strain 4: EAI]

* P < 0.05; BMI = [Wt. in kg/(Height in meters)^2]
### Table 4
Multivariate logistic regression analysis of risk factors associated with MDR-TB among new cases

| Risk factors     | Adjusted odds ratio | 95% C.I.  | P-value |
|------------------|---------------------|-----------|---------|
|                  | Lower Limit | Upper Limit |         |
| Age groups (years) |           |           |         |
| 25 – 34          | 1.44       | 0.83      | 2.49    | 0.19    |
| 35 – 44          | 1.68       | 0.90      | 3.12    | 0.10    |
| 45 and above     | 1.83       | 0.94      | 3.53    | 0.07    |
| Female gender    | 1.68       | 1.02      | 2.87    | 0.042*  |
| Beijing strain   | 3.06       | 1.12      | 8.38    | 0.029*  |

*P < 0.05; Note: Here binary logistic regression analysis was carried out, where DST status was taken as a dichotomous dependent variable with categories – Non-MDR-TB and MDR-TB; The variable age group has multiple categories.