The role that tuberculosis in the home plays in the incidence of multidrug-resistant tuberculosis*

ELIZABETH CLARA BARROSO1, ROSA Mª SALANI MOTA2, ADALGISA C. M. OLIVEIRA3, JOSEFA IVONETE R. CORDEIRO4, JOANA BRASILEIRO BARROSO5 E JORGE LUIS NOBRE RODRIGUES 6

Background: Multidrug Resistant Tuberculosis (MDR-TB) is a matter of worldwide concern. Identifying risk factors related to its development may contribute to controlling this public health problem.

Objective: To determine whether presence of tuberculosis (TB) in the home is a risk factor for the appearance of MDR-TB.

Methods: A retrospective, population-based, case-control study was conducted. Multidrug resistance was defined as resistance to at least rifampin and isoniazid, and susceptible TB (cases in which the first treatment had been given during the same period as the first treatment given to the MDR-TB cases, but which were disease free at the time of the interview). Selection of cases was made based upon records of susceptibility tests carried out at the Laboratório Central de Saúde Pública of the state of Ceará from 1990 to 1999. The proportion method was used. Controls were selected from among bacilliferous on file in the records of the TB Control Program. The history of TB in the family was investigated. These cases were divided into three groups: MDR-TB, non-compliant TB and cured TB.

Results: During the designated period, 266 cases of MDR-TB were diagnosed. We were able to locate only 153 of these patients. Of those, 19 were excluded. Therefore, the study group comprised 134 patients. We selected 185 additional patients to create a control group. Fisher’s exact test disclosed no correlation between MDR-TB and contact with other TB patients in the home (p = 0.119). Analyzing the subgroups, we found that contact with cured TB patients was correlated with susceptible TB (p < 0.0001) whereas contact with either non-compliant TB patients or MDR-TB patients in the home was correlated with MDR-TB (p < 0.016 and p < 0.03 respectively).

Conclusion: Cases of MDR-TB or non-compliance with TB treatment in the home are risk factors for MDR-TB and therefore represent a public health problem.

Key words: Multidrug-resistant tuberculosis. Household contacts. Non adherance to tuberculosis treatment.

*Study carried out as part of a Masters degree course under the orientation of Professor Jorge Luis Nobre Rodrigues, Ph.D. Thesis defended on 10/09/2001. Study conducted at the Hospital de Maracanaú – Department of Health, and at the Hospital de Messejana – Department of Health of the State of Ceará.

1 MS in Medicine and Pulmonologist
2 MA in Statistics
3 Social assistant in the Department of Health
4 Nurse in the Department of Health
5 Undergraduate student in Psychology
6 Ph.D. in Infectious and Parasitic Diseases

Correspondence to: Elizabeth Clara Barroso · Rua Fonseca Lobo 50 apto 402, Aldeota. CEP · 60.175-020 · Fortaleza, CE. Tel (85) 267-1557. E-mail – vbarroso@portalnet.com.br

Submitted: 05/12/2003. Accepted, after revision: 09/10/2003.

Abbreviations used in this paper:
TB – Tuberculosis
BK – Koch’s bacillus
INH – Isoniazid
RIF – Rifampin
PZA – Pyrazinamide
MDR-TB – Multidrug-resistant tuberculosis
ST – Susceptibility test
INTRODUCTION

Drug resistance is a threat to all tuberculosis (TB) control programs worldwide. Patients infected with multidrug-resistant strains are less likely to be cured,\(^{(1-5)}\), especially if they are HIV-positive or suffer from another immune disease. Treatment for such patients is more toxic and 700 times more expensive than for patients infected with drug-susceptible strains.\(^{(6-10)}\)

Multidrug-resistant tuberculosis (MDR-TB) is internationally defined as tuberculosis in which *Mycobacterium tuberculosis* is resistant to at least rifampin (RIF) and to isoniazid (INH).\(^{(11)}\) In a reference clinic in São Paulo, *M. tuberculosis* primary resistance to RIF was 0.3% in the 1970s, whereas a rate of 1.1% (p = 0.02) was reported in the 1980s.\(^{(3)}\) From 1994 to 1997, the combined world average prevalence of MDR-TB was 5.0% (according to World Health Organization-Lung Disease Working Group on Anti-Tuberculosis Drug Resistance Surveillance), compared to 1.3% in Brazil\(^{(11)}\); and 1.1% in the state of Ceará.\(^{(12)}\) In Ceará, there were 41,073 TB cases reported between 1990 and 1999.\(^{(12)}\)

Although TB rates trended toward a decrease during that period, the annual MDR-TB incidence was increasing, and the combined prevalence of MDR-TB rose from 0.82% in 1994 to 1.48% in 1999.\(^{(12)}\)

Innumerable studies have been published on MDR-TB risk factors since controlling such risks may prevent new cases of MDR-TB. The most significant risk factors are: irregular treatment, previous treatment history, lung cavitation, extensive pulmonary tuberculosis, alcoholism, illicit drug abuse, minimal schooling, low family income, imprisonment, lack of housing, and public shelter use.\(^{(1,9,13-17)}\) Contact with TB patients shows no statistically significant correlation with the occurrence of MDR-TB.\(^{(18-20)}\)

However, studies on risk factors such as imprisonment and extended stays in public shelters or clinics show similar statistical significance as studies on contact with TB patients in the home. All of these risk factors have a common denominator: the risk of MDR-TB transmission. In some studies, a significant correlation between the risk factor and MDR-TB transmission was found.\(^{(13,14)}\)

The presence of a drug-susceptible TB or MDR-TB patient at home is definitely worrying for family members who seek healthcare orientation. In general, contact with TB patients has long been considered a risk factor for new TB cases,\(^{(21)}\) and the nature of this process has been well established. The objective of the present study is to elucidate this situation in relation to MDR-TB.

METHODS

A population-based nested case-control study was conducted. The study group comprised MDR-TB patients only. The international definition for MDR-TB was adopted, in which the bacillus must be resistant to at least the RIF + INH combination. The control group comprised drug-susceptible TB patients. Drug-susceptible TB patients were included in the study if they: had their first treatment during a period proximal to that during which the MDR-TB patients had their first treatment; were diagnosed with bacilliferous TB; had been treated with Regimen I, which is defined as 2RIF+INH+pyrazinamide (PZA)/4RIF+INH; were disease free at the time of the interview.

Case selection was based upon 1500 susceptibility tests (STs) performed at the Laboratório Central between 1990 and 1999. The Laboratório Central is the only
laboratory in the state of Ceará that performs such tests and operates under the auspices of the Centro de Referência Professor Hélio Fraga, a national reference center for STs. The population in the state of Ceará is 6,809,290, and the population of its capital, Fortaleza, is 1,965,513.\(^{(22)}\)

Cases were selected from those attended at the Hospital de Maracanaú, a reference hospital for TB in the state, located in Maracanaú (160,065 inhabitants),\(^{(22)}\) the Hospital de Messejana, a reference center for TB (both in the state of Ceará and in neighboring states) located in Fortaleza and from the Unidade Sanitária Dona Libânia, a reference clinic, also located in Fortaleza.

Control patients were matched to study patients for gender, age and year of first treatment. The mean period between first treatment and MDR-TB diagnosis was 6.5 ± 3 years. The study was conducted in the year 2000. The time necessary for resistance to develop was taken into consideration, and the median was therefore extended an extra year into the past. All bacilliferous TB patients were selected from the records of the TB control program (Hospital de Maracanaú and Hospital de Messejana) from 1993 on. We selected quadruple the required number of patients from each age bracket (10-19, 20-29, etc.) and gender because we believed that many addresses might have changed, some patients might have died, and some patients might refuse to participate. At the end of the selection phase, it was not necessary to exclude any patients to achieve the necessary sample size since the selected number of participants was similar to what had been pre-established. Patients were notified by mail and invited to participate. Participating patients gave written informed consent, and the study design was approved by the Comitê de Ética em Pesquisa da Universidade Federal do Ceará. At the phthisiology clinic, patients were screened by chest radiograph and routine blood tests (including HIV serology if consent was given), as well as sputum smear and culture for acid-fast bacilli if there was expectoration. If the patient was considered cured, a questionnaire was filled out and the data entered into the control database. All questionnaires (study group and control group) were completed by the primary author of the study.

The various characterizations made on the questionnaire were defined as follows. Any situation in which there was co-habitation with a TB patient was considered household contact with a TB patient. Household contacts were classified as being with cured TB patients (those having had no recurrence of the disease, according to the case report or the control, most having been previously treated by the authors), non-compliant TB patients (those who had abandoned treatment, according to the case report or the control) or MDR-TB patients (those with ST confirmed MDR-TB). Only people who slept in the home were included in the “number of people in the household” variable. Bathrooms were included in the “number of rooms” variable, although porches and balconies were excluded. Family income was expressed in number of minimum salaries. As far as educational background is concerned, patients were divided into only 2 categories. The “no education” category included those who were illiterate (unable to read and write, even if capable of signing their names) or who had not completed at least 4 years of study. The “some education” category included patients who had completed at least 4 years of study in elementary school. The presence of running water and sanitation facilities in the home was also taken into consideration. Cure and non-compliance were defined according to the First Brazilian Tuberculosis Consensus.\(^{(23)}\) Number of previous treatments was defined as the number of treatments until MDR-TB was diagnosed (study group), or as the number of treatments until patients were interviewed (control group). Adequate treatment of TB was defined as compliance with the treatment regimen, non-compliance for periods of less than 5 consecutive days, or noncompliance for less than 10 nonconsecutive days within the same month. Inadequate treatment of TB was defined as noncompliance for more than 5 consecutive
days, or noncompliance for more than 10 nonconsecutive days within the same month, as long as it had not been discontinued for more than 30 days. Lung cavitation was considered extensive when cavities larger than 4 cm were found in chest radiographs. Alcoholism and tobacco dependence were defined according to O’Connor(32) and Fahn(33), respectively. Chronic obstructive pulmonary disease (COPD) was defined according to Andreoli et al.(34) Patients were categorized as HIV-positive (HIV+) if confirmed through serology. Patients were considered diabetic if they so reported or if their blood glucose level was higher than 127 mg/dL. Illicit drug abuse, history of mental illness and controlled drug use were noted if reported by the patient, their family members or other reliable sources.

Löwenstein-Jensen culture media was used. The proportion method on solid media was used for the ST. Resistance was defined as either at least 1% colony growth in critical concentrations of the following drugs: isoniazid (0.2 µg/mL), ethambutol (2 µg/mL) or rifampin (40 µg/mL), or at least 10% colony growth in critical concentrations of: ethionamide (20 µg/mL), pyrazinamide (100 µg/mL) or streptomycin (4 µg/mL).

Statistical analysis to compare case and control groups were performed using Fisher’s exact test for dichotomized independent variables and logistic regression for continuous independent variables. Odds ratio (OR) estimates and 95% confidence interval (95% CI) were calculated. A value of p < 0.05 was considered statistically significant. Statistical evaluations were performed with the aid of SPSS version 10.0 software program.

RESULTS

From 1990 to 1999, 41,073 TB cases were reported in the state of Ceará.(12) Collected data indicate that TB incidence was decreasing during that period,(24) whereas MDR-TB incidence was on the rise.(12) The state has a population of 6,809,290 inhabitants.(23) Fortaleza, the capital, has 1,965,513 inhabitants(23) and is responsible for 50% of the reported cases of TB in the state. Most of the patients in the present study were first treated at the Hospital de Maranacau, a state reference hospital for TB located in Maranacau, a city near Fortaleza with a population of 160,065 inhabitants.(23) Some other patients had been previously treated at the Unidade Sanitária Dona Libânia or the Hospital of Messejana, two reference clinics for TB in the state.

Of the 1500 STs performed in the Laboratório Central do Ceará during the 1990s, 266 tested positive for strains that were resistant to at least RIF + INH. Of the 266 patients from who those samples were obtained, 153 were located and a standard questionnaire was filled out. Some patients were excluded from this study: 5 because they were infected with atypical mycobacteria, and 2 because they did not meet the criteria established for a diagnosis of MDR-TB. Of the remaining 146 patients, 12 had no previous treatment history (primary MDR-TB) and were also excluded since this study was originally designed to evaluate patients with acquired MDR-TB. Therefore, the study group comprised a total of 134 patients.

In the control group selection, 615 medical records were reviewed and information on the study was mailed to 504 patients. For a variety of reasons (death, relocation, etc.), the mailing was not sent to the remaining 111 patients. Of the 504 letters mailed, 114 were returned because the addressee could not be located, and 188 affirmative replies were received. Of the 188, there was 1 who was diagnosed with MDR-TB and included in the study group and 2 who showed symptoms of TB and were excluded because we could not wait for BK culture and ST results. Therefore, the control group comprised 185 patients.
The period between first treatment and MDR-TB diagnosis averaged 6.5 ± 3 years in the study group, and the period between first treatment and the interview averaged 6.5 ± 4 years in the control group. Parity between averages was achieved. Gender and age distribution and their correlation with MDR-TB are shown in Table 1, where parity can be observed. There were no HIV+ cases in either group.

Group distribution in relation to household contact with TB patients and to any of the 3 defined subgroups (cured, non-compliant and MDR-TB) are shown in Table 2.

The odds of a patient developing MDR-TB from household contact with a non-compliant TB patient when compared to those of a patient whose household members complied with treatment are, according to the odds ratio (OR) system, OR = 3.63 (95% CI = 1.29-10.19). Therefore, the odds of a patient developing MDR-TB from household contact with a non-compliant TB patient are 3.63 times higher than are those for a patient who had no such contact. The odds of a patient developing MDR-TB from household contact with an MDR-TB patient when compared to those for a patient whose had no MDR-TB patients among his/her household members are OR = 3.83 (95% CI = 1.15-12.76). Therefore, the odds of a patient developing MDR-TB from household contact with an MDR-TB patient are 3.83 times higher than are those for a patient who had no contact with MDR-TB patients (Table 3).

**DISCUSSION**

The authors of this study would like to highlight the limitations of retrospective studies, in which bias may result from the review of medical records and of questionnaires (as well as the reliability thereof). Questionnaires, even if filled out together with the patients, depend upon the accuracy of their memory. In this study, patients were asked to recall events that transpired more than 6 years prior. In the study group, 75% of the patients were interviewed, so data on the remaining 25% was taken exclusively from medical records. However, since these were chronic cases, admitted during various periods and having several medical charts, there was an abundance of data. In order to avoid bias due to lack of information or reliability problems, the authors interviewed nurses and social caseworkers who knew the patients very well due to the numerous examinations and admissions, and who were responsible for the majority of the information in the medical records. The other 75% of the patients had been attended by the authors for the last decade and answered the questionnaire in person. Data on patients in the control group were collected from the patients themselves and from their medical records, allowing for the comparison and verification of data.

Gender-matched and age-matched controls were selected because it was believed that these variables could lead to misinterpretations, due to discrepancies found in the literature.\(^\text{[15-17]}\)

In 1997, Boudville et al. published a case-control study in Singapore to investigate MDR-TB risk factors.\(^\text{[19]}\) In that study, 10 (7%) of the 134 subjects in the study group had a history of contact with TB patients (9 cases of household contact and 1 case of workplace contact), as did 17 (8%) of the 207 subjects in the control group. Therefore, no statistically significant difference was found.

In a study published in 2000, Natal et al. performed a case-control study at 23 health centers in the state of Rio de Janeiro to evaluate risk factors for anti-tuberculosis drug resistance. The authors found no correlation between MDR-TB and a history of contact with TB patients.\(^\text{[20]}\)
In the present study, we found that 57 (30.8%) of the 128 patients in the control group and 52 (39.7%) of the 131 patients in the study group had had household contact with TB patients. These results are, statistically speaking, quite similar (p = 0.1190).

In a multi-hospital transversal study of anti-tuberculosis drug resistance conducted in 1996 in Madrid, Peña et al. included contact with TB patients in the epidemiological characteristics of patients. However, only descriptive information was given, revealing that 65 (14%) of the 467 patients had a history of contacts of TB patients.18

Seiscento et al., in a 1993-1994 study involving 70 MDR-TB patients at the Instituto Clemente Ferreira de São Paulo, found that 6 (8.6%) of the 70 had a history of contact with MDR-TB patients.4

From 1995 to 1999, Melo et al. conducted a cohort study of patients with MDR-TB at the above-mentioned institute.24 The authors studied 170 cases, and found 129 to be of unknown etiology. Of the 41 cases in which etiology was determined, 34 were found to have resulted from household contact with TB patients (83%) and 7 from institutional TB contact (17%). Of the 34 household contact cases, 15 were from contact with drug-susceptible TB patients and 19 from contact with MDR-TB patients. In the present study, 29 from the primary MDR-TB group and 12 from the persistent MDR-TB group were cured. There seems to be a correlation between cured TB and MDR-TB. However, as can be seen through comparative analysis with the control group, the correlation is actually between MDR-TB and household contact with MDR-TB patients.

Other studies on risk factors such as imprisonment and length of stay in public shelters or clinics were reviewed. These risk factors are virtually identical in nature to TB in the home, since what they have in common is the risk of MDR-TB transmission. Some of these studies demonstrated significant correlations.13,14

The division into 3 groups (cured, non-compliance, and MDR-TB) was essential to explaining why contact with TB patients in general is not a risk factor for MDR-TB. Table 2 shows that the percentage of household contact incidence is very similar between the study and control groups. However, when the results are stratified, household contact with cured TB patients is quite significantly related to drug-susceptible TB in control group patients (p < 0.0001), whereas household contact with non-compliant TB patients or MDR-TB patients correlate with MDR-TB (p < 0.0160 and p < 0.0300, respectively). According to OR interpretation, the odds for developing MDR-TB through household contact with non-compliant TB or MDR-TB patients are about 4 times greater than when these risk factors are absent.

We can then conclude that, if TB is correctly treated and cured, there is no risk of contracting MDR-TB from household contact. However, household contact with a TB patient who has fallen out of compliance with treatment or is an MDR-TB patient does constitute a risk factor and is therefore a public health problem. Measures to protect and guide family members of non-compliant TB patients must be established. Patients must be motivated to comply with the treatment regimen. Health professionals should, among other things, convince families that their support in encouraging patient compliance to the treatment is fundamental, since non-compliance is a risk for all the family members. An alternative could be compulsory admission. Finally, a prophylactic regimen for family members of MDR-TB patients must be provided.

REFERENCES
TABLE 1
Gender and age distribution in 319 pulmonary tuberculosis patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cases (n = 134)</th>
<th>Controls (n = 185)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male – nº (%)</td>
<td>81 (60.40)</td>
<td>116 (62.70)</td>
<td>0.7270*</td>
</tr>
<tr>
<td>Av. age – years ± SD</td>
<td>39.78 ± 13.26</td>
<td>41.22 ± 14.14</td>
<td>0.3591</td>
</tr>
<tr>
<td>Lived in another state – #/total (%)</td>
<td>29/139 (22.30)</td>
<td>39/183 (21.31)</td>
<td>0.8900*</td>
</tr>
<tr>
<td>Some educational background</td>
<td>46/120 (38.30)</td>
<td>95/185 (51.40)</td>
<td>0.0340*</td>
</tr>
<tr>
<td>Av. # minimum salaries in family ± SD</td>
<td>2.03 ± 2.08</td>
<td>3.27 ± 2.39</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Av. # people in household ± SD</td>
<td>5.12 ± 2.88</td>
<td>5.23 ± 2.92</td>
<td>0.7267*</td>
</tr>
<tr>
<td>Av. # people per room ± SD</td>
<td>1.1 ± 1.1</td>
<td>1.3 ± 0.9</td>
<td>0.3147</td>
</tr>
<tr>
<td>Households contact with TB – #/total (%)</td>
<td>52/131 (39.70)</td>
<td>57/185 (30.80)</td>
<td>0.1190*</td>
</tr>
<tr>
<td>Some educational background</td>
<td>46/120 (38.30)</td>
<td>95/185 (51.40)</td>
<td>0.0340*</td>
</tr>
<tr>
<td>Av. # minimum salaries in family ± SD</td>
<td>2.03 ± 2.08</td>
<td>3.27 ± 2.39</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Av. # people in household ± SD</td>
<td>5.12 ± 2.88</td>
<td>5.23 ± 2.92</td>
<td>0.7267*</td>
</tr>
<tr>
<td>Av. # people per room ± SD</td>
<td>1.1 ± 1.1</td>
<td>1.3 ± 0.9</td>
<td>0.3147</td>
</tr>
<tr>
<td>Running water in household – #/total (%)</td>
<td>86/124 (69.30)</td>
<td>163/185 (88.10)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Sanitation facilities in household – #/total (%)</td>
<td>62/124 (50.00)</td>
<td>129/185 (69.70)</td>
<td>0.0010*</td>
</tr>
<tr>
<td>Alcoholism – #/total (%)</td>
<td>48/133 (36.10)</td>
<td>34/185 (18.40)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Tobacco dependence – #/total (%)</td>
<td>78/130 (60.00)</td>
<td>78/185 (42.20)</td>
<td>0.0200*</td>
</tr>
<tr>
<td>Illicit drug abuse – #/total (%)</td>
<td>11/133 (8.30)</td>
<td>10/185 (5.40)</td>
<td>0.3630*</td>
</tr>
<tr>
<td>HIV+ – #/total (%)</td>
<td>11/131 (8.40)</td>
<td>18/185 (9.70)</td>
<td>0.4360*</td>
</tr>
<tr>
<td>Diabetes – #/total (%)</td>
<td>15/133 (11.30)</td>
<td>12/185 (6.50)</td>
<td>0.1550*</td>
</tr>
<tr>
<td>Mental illness – #/total (%)</td>
<td>101 (75.40)</td>
<td>36 (19.50)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>TB with cavitation – #/total (%)</td>
<td>107/123 (87.00)</td>
<td>74/161 (46.00)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Non-compliance – # (%)</td>
<td>65 (50.00)</td>
<td>29 (15.70)</td>
<td>&lt;0.0001*</td>
</tr>
</tbody>
</table>

Av. = average; SD = standard deviation; *Fisher’s exact test; †logistic regression

TABLE 2
Distribution of patients with pulmonary tuberculosis, by group, in relation to household contact with TB patients in general and with each of the 3 subgroups: cured TB, non-compliant TB, and MDR-TB

<table>
<thead>
<tr>
<th>Household contact</th>
<th>Controls N (%)</th>
<th>Cases N (%)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>128 (69.2)</td>
<td>79 (60.3)</td>
<td>0.1190</td>
</tr>
<tr>
<td>Yes</td>
<td>57 (30.8)</td>
<td>52 (39.7)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>185 (100.0)</td>
<td>131 (100.0)</td>
<td></td>
</tr>
<tr>
<td>Cured TB</td>
<td>3 (5.3)</td>
<td>23 (44.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Non-compliance TB</td>
<td>51 (89.5)</td>
<td>36 (69.2)</td>
<td>0.0160</td>
</tr>
<tr>
<td>MDR-TB</td>
<td>53 (93.0)</td>
<td>40 (76.9)</td>
<td>0.0300</td>
</tr>
</tbody>
</table>

*Fisher’s exact test.

TABLE 3
Odds Ratio (OR) estimate, odds for developing MDR-TB through household contact with non-compliant or MDR-TB patients

<table>
<thead>
<tr>
<th>Contact</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-compliant patient</td>
<td>3.63</td>
<td>[1.29-10.19]</td>
</tr>
<tr>
<td>MDR-TB patient</td>
<td>3.83</td>
<td>[1.15-12.76]</td>
</tr>
</tbody>
</table>

TB: tuberculosis; MDR-TB: multidrug-resistant tuberculosis; 95% CI: 95% confidence interval