Occurrence of active tuberculosis in households inhabited by patients with susceptible and multidrug-resistant tuberculosis*

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Background: Since the first years of antituberculosis chemotherapy, there has been controversy regarding the transmissibility, infectiousness, virulence and pathogenicity of susceptible and drug-resistant strains of *Mycobacterium tuberculosis*.

Objective: To determine the incidence of active tuberculosis (TB) among individuals cohabiting with patients infected with susceptible and multidrug-resistant tuberculosis (MDR-TB).

Methods: A case-control study was conducted. Cases of MDR-TB were defined as those infected with *M. tuberculosis* strains resistant to at least rifampin and isoniazid. Susceptible TB cases (controls) were defined as those first treated at approximately the same time as the first treatment of the MDR-TB cases - and cured by the time of the interview. Study cases were selected on the basis of the results of susceptibility tests, using the proportion method, carried out at the Central Laboratory of Public Health of the State of Ceará. The control group consisted of patients enrolled in the Tuberculosis Control Program between 1990 and 1999.

Results: We evaluated 126 patients and 176 controls. The number of individuals sharing the household with patients was 557 in the MDR-TB group and 752 in the controls. The average number of exposed individuals per index case was 4.42 and 4.27 among patients and controls, respectively. Of the 557 MDR-TB-exposed individuals, 4.49% (25) received antituberculosis treatment after the respective index case had begun treatment, compared to 5.45% (41/752) among the controls (p = 0.4468). Microepidemics of MDR-TB were confirmed in eight families.

Conclusion: Our results suggest that the incidence of active TB is comparable between households inhabited by MDR-TB patients and those inhabited by susceptible-TB patients.

Key words: Tuberculosis, multidrug-resistant/epidemiology. Tuberculosis/trasmission.

*Study carried out at the Hospital de Maracanaú/Ministério da Saúde (Maracanaú Hospital/Health Ministry) and at the Hospital de Messejana/Secretaria da Saúde do Estado do Ceará (Messejana Hospital/Ceará State Department of Health).

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INTRODUCTION

Tuberculosis (TB) is a chronic infectious disease that has afflicted mankind for 5000 years. Its etiologic agent, known as *Mycobacterium tuberculosis* (Mtb) or Koch's bacillus, has caused more deaths in adults than any other infectious disease(1). Chemotherapy is the most effective weapon against TB, leading to a cure in almost all cases. However, various factors may negatively effect outcomes(2). Inappropriate use of medication during treatment is one of the most significant factors, creating resistant strains of the bacteria, or patients with "acquired resistance". Patients who become ill after being infected with strains that have developed resistant to medications never administered (or administered for less than a month) to those patients are designated as cases of "primary resistance"(3). Internationally, multidrug-resistant tuberculosis (MDR-TB) is defined as those cases in which strains are resistant to (at least) the combination of rifampin (RIF) and isoniazid (INH)(3).

In the 1960s and 1970s, various studies conducted in the USA showed that, although strains resistant to antituberculosis drugs had appeared, the expected increase in the incidence of primary resistance due to acquired resistance did not occur. A possible explanation for this could be the fact that multidrug-resistant Mtb strains are either not as readily transmitted or do not cause infection or disease as easily as do susceptible strains(4). Some authors have reported that INH-resistant strains present decreased pathogenicity in laboratory animals, especially in guinea pigs, leading the scientific community to believe that these strains were less likely to cause infection or disease in humans(5).

However, since the first decades of chemotherapy, various studies have proven that strains resistant to INH, streptomycin (SM) and para-amino salicylic acid can indeed be transmitted and lead to development of TB(4). In a study involving a guinea-pig model of the disease, wide variation in virulence was observed among strains, although resistant strains were not shown to be consistently less virulent(6).

The combined prevalence of MDR-TB (primary + acquired) in the state of Ceará increased from 0.82% in 1994 to 1.48% in 1999(7). Between 1995 and 1996, the prevalence was 0.6% for primary MDR-TB and 3.3% for acquired MDR-TB(8).

Siglas e abreviaturas utilizadas neste trabalho:
TB – Tuberculosis
INH – Isoniazid
RIF – Rifampicin
SM – Streptomycin
PZA – Pyrazinamide
HIV – Human immunodeficiency virus
MDR-TB – Multidrug-resistant tuberculosis
Mtb – *Mycobacterium tuberculosis*
ST – Susceptibility test

Chemoprophylaxis is one of the most efficacious resources in TB treatment. The Brazilian Department of Health recommends the use of INH as a prophylactic agent in order to prevent the development of active TB in individuals cohabiting with patients with TB. In the case of index cases diagnosed with MDR-TB, there is no objective recommendation, since there has been no consistent, conclusive research to justify such a recommendation(9).

The theory that resistant strains were less pathogenic was highly accepted during the first decades of antituberculosis chemotherapy. In the 1990s, institutional epidemics of MDR-TB in human immunodeficiency virus (HIV)-positive patients were reported(3), evoking debate regarding this theory. Transmissibility of TB, especially MDR-TB, continues to be a cause of great concern among health professionals, patient families and the general population.

The objective of this study was to determine the incidence of active TB among individuals cohabiting with patients infected with susceptible TB or MDR-TB

METHODS

The present study was carried out in the state of Ceará, where 41,073 TB cases were reported between 1990 and 1999(7). The population of the state is 6,809,290(10), and the population of its capital, Fortaleza, is 1,965,513(10). Of the total number of cases reported, 50% occurred in Fortaleza.

A case-control study was conducted. Cases of MDR-TB were defined in accordance with the previously mentioned international standard.

Controls were defined as those cases that were initially treated at approximately the same time as the first treatment of MDR-TB cases. Controls were required to have had active TB at the beginning of treatment, have been cured by the time of the interview (susceptible TB) under Regimen I, which consists of 2 months of RIF-INH-pyrazinamide (PZA), followed by 4 months of RIF-INH.

Case selection was based on the results of susceptibility tests (STs) performed at the *Laboratório Central do Estado do Ceará* (Ceará State Central Laboratory), the only laboratory in the state that performs such tests. The laboratory operates under the auspices of the *Centro de Referência Professor Hélio Fraga*, a national reference center for STs. Some cases were selected from among patients examined at the *Hospital de Maracanaú* (a state reference hospital for TB), located in the city of Maracanaú (near Fortaleza). Others were patients from the *Hospital de Messejana* (a state and regional reference hospital and outpatient clinic for TB) located in Fortaleza, while still others were from the *Unidade Sanitária Dona Libânia* (Dona Libânia Health Clinic), a reference clinic that is 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, although the median was extended an extra year into the past. All active TB patients were selected from the records of the TB control program (at the *Hospital de Maracanaú* and *Hospital de Messejana*) from 1993 on. 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* (Ethics-in-Research Committee of the Federal University of Ceará). At the phthisiology clinic, patients were screened through chest X-rays 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.

Various characterizations were made through applying the questionnaire. Cured TB, TB treatment non-compliance and contact with TB were defined according to the criteria established by the 1st Brazilian Tuberculosis Consensus(9). The authors defined a micro-epidemic of MDR-TB as 2 or more cases of MDR-TB in the same household, confirmed by ST. Number of previous treatments was defined as the number of treatments prior to MDR-TB diagnosis (study group) or as the number of treatments prior to patient interview (control group).

Löwenstein-Jensen culture media was used. The proportion method on solid media was used for the ST. Resistance was defined as at least 1% colony growth in critical concentrations of INH (0.2 µg/mL), ethambutol (2 µg/mL) or RIF (40 µg/mL), or at least 10% colony growth in critical concentrations of ethionamide (20 µg/mL), PZA (100 µg/mL) or SM (4 µg/mL).

The chi-square test was used in the statistical analysis and values of $p < 0.05$ were considered statistically significant. Statistical evaluations were performed with the aid of the Excel for Windows and Word for Windows programs.

RESULTS

Of the 1500 STs evaluated at the *Laboratório Central do Estado do Ceará* in the 1990s, 266 strains were resistant to at least the RIF-INH combination. Of the 266 patients from whom those samples were obtained, 153 were located and a standard questionnaire was filled out. Of those 153 patients, 27 were excluded for various reasons: 5 were infected with atypical mycobacteria, 2 did not meet the criteria for a diagnosis of MDR-TB, 6 had had no contact, 4 belonged to families already included in the study (only index cases were exempted from exclusion), and 10 did not provide reliable information on the treated contacts. Therefore, the study group comprised a total of 126 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 those 188, 12 were excluded for various reasons: 1 was diagnosed with MDR-TB, 4 belonged to families already

included in the study (only index cases were exempted from exclusion), 2 were asymptomatic, and 5 did not provide reliable information on the treated contacts. Therefore, the control group comprised a total of 176 patients.

In the study group, the mean period between first treatment and MDR-TB diagnosis averaged 6.5 ± 3 years. In the control group, the mean period between first treatment and the interview was 6.5 ± 5 years. Considering all study participants, the mean period between diagnosis of MDR-TB and the study onset was 4.1 years.

In the study group, 79 (62.7%) of the participants were male, compared to 110 (62.5%) in the control group. Mean age was 39 ± 25 in the study group and 41 ± 14 years in the control group. In the study group, 78 (62%) of the 126 were tested for HIV, as were 97 (55%) of the 176 patients in the control group. All HIV test results were negative.

As can be seen in Table 1, the total number of index cases was 302 and the total number of patients having contact with those cases was 1309. The distribution of families in relation to the number of treated patients is shown in Table 2.

Not all "index cases" were treated prior to treatment of the patients who came into contact with them, i.e. some of these were not true index cases. This occurred in both groups. The incidence of contact treatment, whether prior to or after treatment of the corresponding index case, is shown in Table 3. In patients with active tuberculosis, there was a statistically significant difference between the two groups in the percentage of those treated prior to the treatment of index cases, predominantly when they cohabited with the MDR-TB index cases. No such difference between the two groups was found for those patients who were treated after treatment of the index cases.

We identified 8 households, comprising a total of 20 patients, in which ST-confirmed micro-epidemics of MDR-TB occurred (Table 4). Eight index cases generated 12 new MDR-TB cases. In 4 (33%) of these, the resistance profile of the strains involved differed from those isolated in the respective index cases, although they were also multidrug resistant.

TABLE 1
Distribution of index cases and contacts treated in three reference centers for tuberculosis in the state of Ceará between 1990 and 1999. Two groups of are represented: active susceptible tuberculosis (control group) and multidrug-resistant tuberculosis patients (study group)

Group	Index cases	Contacts	Contacts/index cases
Control	176	752	4.27
Study	126	557	4.42
Total	302	1309	4.33

TABLE 2
Distribution of families in the control and study groups in relation to the number of patients per family treated in three reference centers for tuberculosis in the state of Ceará between 1990 and 1999

Number of treated patients per family	Families in control group		Families in study group		Total number of families	
	N	%	N	%	N	%
0	149	84.7	109	86.5	258	85.4
1	19	10.8	12	9.5	31	10.3
2	5	2.8	3	2.4	8	2.6
3	1	0.6	1	0.8	2	0.7
4	1	0.6	1	0.8	2	0.7
5	1	0.6			1	0.3
Total	176	100.0	126		302	100.0

TABLE 3
Incidence of patients per group treated prior to/after, prior to, or after index cases in three reference centers for tuberculosis in the state of Ceará between 1990 and 1999

Treated patients	Control group	Study group	P*
Prior to/after index case	(70/752) 9,3%	(86/557) 15,4%	0,0010
Prior to index case	(29/752) 3,95%	(61/557) 10,9%	<0,0001
After index case	(41/752) 5,45%	(25/557) 4,49%	0,4468

*Chi-square test.

TABLE 4
Distribution of MDR-TB micro-epidemics in relation to the number of MDR-TB cases per family treated in three reference centers for tuberculosis in the state of Ceará between 1990 and 1999

Number of MDR-TB cases (in the same household)	Number of MDR-TB micro-epidemics*	Total
	N	N
2	6	12
3	1	3
5	1	5
Total	8	20

*MDR-TB micro-epidemic is defined as the existence of 2 or more new MDR-TB cases in the same household, confirmed by susceptibility tests.
MDR-TB: multidrug-resistant tuberculosis.

Of the 126 cases of MDR-TB, 114 had developed acquired multidrug resistance and 12 had primary multidrug resistance. Eleven of these patients were unlikely to have generated new TB cases. For 1 patient, there was no information on individuals who may have come into contact.

DISCUSSION

The total number of TB cases reported in the state of Ceará decreased from 43,508 during the 1980s to 41,073 during the 1990s and has been steadily decreasing during this decade as well(8). This might reflect underreporting of TB cases, since the number of MDR-TB cases actually increased during the 1990s(7).

Before commenting on the results, we would like to highlight several limitations of the present study. First, this was a retrospective study. In addition, data were collected exclusively from medical records, without conducting patient interviews, in 25% of the cases evaluated. However, since these were chronic cases, admitted various times and generating multiple medical charts, there was an abundance of data, and these patients were well known to the hospital staff, including the author of this study. In order to avoid bias due to lack of information or unreliability of the data, nurses and social caseworkers, who were responsible for the majority of the information entered in the medical records, were interviewed. The other 75% of patients had been treated by the author for the last decade and answered the questionnaire in person. Data on control group subjects were collected from patient interviews and medical records, allowing for comparison and verification of data. Furthermore, owing to the fact that this was a retrospective study, we were unable to determine the transmission time of either susceptible or MDR-TB.

We should also be aware of limitations inherent to studies involving volunteers, who are supposedly more responsible and, consequently, more often adhere to treatment and may present better health status.

The fact that STs for antituberculosis drugs are not part of the routine in the initial diagnosis of TB in our state may have contributed to the fact that only 12 primary-MDR-TB cases were identified, in contrast with 114 acquired-MDR-TB cases.

Finally, we should highlight the fact that 38% of the patients in the study group were not tested for HIV. This was because this test is not part of our routine, especially for outpatients. Most of the hospitalized patients were tested. All volunteers in the control group were outpatients, and all were offered HIV tests, but 45% refused. Although we may have missed a positive case among these, there was no evidence of HIV risk factors among these patients

Due to discrepancies found in the literature[12,13], we believed that variations in gender or age could lead to misinterpretations. Therefore, gender-matched and age-matched controls were selected.

In 1979, Siminel et al. published a study comprising 3189 children who had had close contact with TB cases[14]. Of the 931 index cases, 676 were infected with INH-susceptible strains and 255 with INH-resistant strains. In order to avoid bias, the authors investigated several variables, including the ages of the children, duration of exposure, and severity of the index cases. Statistical analysis confirmed the hypothesis that the sources of INH-resistant Mtb were less pathogenic, not only to laboratory animals but to humans as well. This study involving children was very important because adults are more likely to become infected outside their homes, especially in countries such as Brazil, where there is a high prevalence of TB. The present study shows that the percentage of patients treated after susceptible and MDR-TB index cases are statistically similar between the study group and control group (Table 3). If duration of exposure had been stratified, we might have found similar results, that is, a smaller percentage of patients treated among those who had MDR-TB.

In 1985, Snider et al. published a study comprising 1352 contacts, of which 398 were infected with strains resistant to INH or SM. The authors matched these 398 patients for age, race, gender and geographic location to the same number of patients diagnosed with strains susceptible to 9 drugs. No evidence of lower risk of infection was found among patients exposed to INH-resistant or INH+SM-resistant strains[4]. The same authors, using logistic regression analysis, found a significantly higher risk of infection in individuals having close contact with patients infected with resistant strains when those patients had a history of one or more previous treatments. The can be explained by the fact that these individuals were family members and therefore were exposed for longer periods.

From 1994 to 1998, Teixeira et al. carried out a case-control study in Vitória (in the state of Espírito Santo) on the prevalence of infection and active tuberculosis in households inhabited by patients with susceptible TB and MDR-TB. This study comprised 408 individuals cohabiting with 78 TB patients, 26 infected with resistant strains and 52 with susceptible strains. The authors concluded that the prevalence of infection and the progression to active tuberculosis among those exposed to susceptible and MDR-TB was similar, despite the longer duration of exposure in individuals with MDR-TB index cases[15]. The authors included duration of exposure in their analysis and hypothesized that longer duration of exposure compensates for the lower pathogenicity of resistant strains, resulting in the percentage of new TB cases from contact with susceptible TB cases being equal to that from contact with MDR-TB cases.

All three of these (Siminel et al., Snider et al. and Teixeira et al.) were case-control studies, determining the prevalence of infection and disease in individuals cohabiting with patients with susceptible-TB and MDR-TB patients. However, each was carried out during different periods within the past 3 decades and employed different chemotherapeutic drugs. Nevertheless, they can be compared. Determining the duration of exposure was a common difficulty faced by all of these authors.

The present study reinforced the findings of the two latter studies (Snider et al. and Teixeira et al.) Duration of exposure was not investigated in our study, but we found that the number of previous treatments in the study group averaged 2.8 (prior to diagnosis of MDR-TB) and 1.3 in the control group (prior to the interview). The mean interval between diagnosis of MDR-TB and study onset was 4.1 years. This indicates that the duration of exposure was considerably longer. We must remember that, for every treatment of a susceptible-TB case, infectivity time

corresponded to the duration of symptoms plus 15 days after the beginning of the appropriate therapy[16]. In contrast, there is no therapy that has proven highly efficacious in cases of MDR-TB. It has been demonstrated that conversion of sputum smear microscopy and culture to negative occurs in only 65% of properly treated cases, and the incidence of recurrence is quite high[17], thereby increasing the likelihood of transmission.

In a survival study carried out in the state of Ceará, the 5-year survival of MDR-TB patients who had not adhered to treatment was 73%, compared to 32% for those who had no access to proper treatment[8]. This gives an indication of the duration of exposure among individuals cohabiting with MDR-TB patients. However, the incidence of active TB resulting from close contact with MDR-TB patients is similar to that resulting from such contact with susceptible-TB patients. This suggests that the pathogenicity of multidrug-resistant strains is actually lower. Nevertheless, this does not lessen our concern regarding this type of exposure since the proportions of active TB within the two groups converges after some time, creating a cumulative risk for the development of primary MDR-TB.

We studied the proportion of individuals having close contact with a TB patient and receiving treatment prior to treatment of the corresponding index case (Table 3). We observed this was significantly predominant in the study group, leading us to speculate that MDR-TB patients are the real victims and are less able to transmit the disease. This was reinforced by the fact that, for 11 of the 12 patients with primary MDR-TB, there was little evidence that these patients generated new cases of TB.

Melo et al., in a cohort study conducted from 1995 to 1998 at a reference clinic in the city of São Paulo, reported 4 MDR-TB outbreaks (3 or more individuals) within families[18]. Vidal et al. carried out a prospective study from 1989 to 1994 in a general hospital in Barcelona, Spain, with the objective of studying the increased risk of TB transmission during micro-epidemics within families. They considered 3 or more individuals with TB in one household a micro-epidemic, since 2 or more new TB cases within a family is a greater number than expected[19]. Since the proportion of MDR-TB to TB was, on average, 1.48% in 1999 in the state of Ceará(7), we considered 2 cases of MDR-TB in the same household to be greater than expected. This definition allows us call attention to MDR-TB, a disease that represents a very serious health threat.

In our study, a discordance of 33% was found between the susceptibility profiles of Mtb strains isolated from new MDR-TB cases and those of Mtb strains isolated in the index cases from the same households. This has also been reported in other studies.

Kritski et al. reported that 54% of the 13 strains isolated from patients who had had contact with 12 index patients had different susceptibility profiles, and that 3 (23%) of them were susceptible to all drugs tested(20). Mean age in the group studied by the authors was 35.6 years.

Teixeira et al. reported a discordance of only 17% in the susceptibility profiles of 6 strains isolated from patients who cohabited with MDR-TB index cases(15). The strain was susceptible to the drugs tested, but its DNA fingerprint was identical to that isolated from the respective index patient. Mean age of the patients studied was 39.5 years.

In a follow-up to a previous study, Schaaf et al. conducted a prospective study involving children younger than 5 years of age cohabiting with adult pulmonary MDR-TB patients and monitored (between 1994 and 2000) for 30 months. They authors reported that 25% of the clinically isolated strains presented different resistance profiles, although also multidrug resistant. The DNA fingerprinting confirmed that the isolated strains were not the same as those of the index cases. No other source of contagion was identified, although the multidrug-resistant strains isolated were prevalent in the community in which the children lived[21, 22].

We conclude that the incidence of treatment of TB patients is similar between those cohabiting with susceptible-TB patients and those cohabiting with MDR-TB patients. This is extremely serious and demands that, as soon as possible, protective measures and proper chemoprophylaxis be made available to individuals cohabiting with patients with MDR-TB.

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