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Drug-resistant tuberculosis in six hospitals in Rio de Janeiro, Brazil

R. C. Brito,* F. C. Q. Mello,† M. K. Andrade,†‡ H. Oliveira,§ W. Costa,¶ H. J. Matos,# M. C. Lourenço, V. C. Rolla,** L. Fonseca,† A. Ruffino Netto,†† A. L. Kritski†**

***Programa de Controle da Tuberculose, Secretaria de Estado de Saúde e Defesa Civil do Rio de Janeiro, Rio de Janeiro, †Programa Acadêmico de Tuberculose, Faculdade de Medicina da Universidade Federal do Rio de Janeiro, Rio de Janeiro, ‡Hospital Raphael de Paula Souza, Secretaria Municipal de Saúde da Prefeitura do Rio de Janeiro, Rio de Janeiro, §Hospital Estadual Santa Maria, Secretaria de Estado de Saúde e Defesa Civil do Rio de Janeiro, Rio de Janeiro, ¶Instituto Estadual de Doenças do Tórax Ary Parreiras, Secretaria de Estado de Saúde e Defesa Civil do Rio de Janeiro, Rio de Janeiro, #Hospital dos Servidores do Estado, Ministério da Saúde, Rio de Janeiro, **Instituto de Pesquisa Evandro Chagas, FioCruz, Rio de Janeiro, Rio de Janeiro ††Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, São Paulo, São Paulo, Brazil**

SUMMARY

SETTING: Tuberculosis (TB) drug resistance survey in six hospitals in Rio de Janeiro, Brazil.

OBJECTIVE: To estimate resistance to at least one drug (DR) and multidrug resistance (MDR) and identify associated factors.

DESIGN: One-year cross-sectional survey. Hospitals were included as a convenience sample.

RESULTS: Of 595 patients investigated, 156 (26.2%) had previously undergone anti-tuberculosis treatment, 433 (72.8%) were not previously treated and information on the remaining 6 was not available. Overall, DR and MDR rates were high, at respectively 102 (17.1%, 95%CI 14.3–20.5) and 44 (7.4%, 95%CI 5.5–9.9) cases. Among individuals not previously treated, 17 had MDR (3.9%, 95%CI 2.4–6.3) and diagnosis in a TB reference hospital was independently associated with MDR (prevalence ratio [PR] 3.3, 95%CI 1.2–8.7) after multivariate analysis. Among previously treated individuals, 27 had MDR (17.3%, 95%CI 11.7–24.2). MDR-TB was independently associated with diagnosis in a TB reference hospital (PR 3.6, 95%CI 1.5–8.7), male sex (PR 2.3, 95%CI 1.2–4.4) and dyspnoea (PR 0.3, 95%CI 0.1–0.7).

CONCLUSION: We found high levels of DR- and MDR-TB. Our study design did not permit us to determine the contribution of community versus nosocomial transmission. Further studies are needed to establish this. Nevertheless, hospitals should be recognised as a potential source of transmission of resistant TB strains and urgent measures to avoid nosocomial TB transmission should be taken.

KEY WORDS: *M. tuberculosis*; drug resistance; MDR-TB; epidemiology; hospitals

TUBERCULOSIS (TB) control remains a great challenge for public health globally, with high incidence, mortality, association with human immunodeficiency virus (HIV) infection, multidrug-resistant TB (MDR-TB) and, more recently, extensively drug-resistant TB (XDR-TB).[1,2] The World Health Organization (WHO) estimated that 489 139 (95% confidence limits [CLs] 455 093–614 215) MDR-TB cases emerged in 2006 and that the proportion of resistance among all TB cases globally was 4.8% (95%CL 4.6–6.0) of the 10 229 315 new cases of TB.[2]

The modern era of TB control has also been characterised by serious nosocomial events.[3–5] In industrialised and developing countries, several nosocomial MDR-TB outbreaks have been described, including a large number of HIV co-infected patients, leading to high case fatality and affecting health care workers.[1,6,7]

A number of resistance surveys based in hospital settings have been published in the last two decades. In general, the levels of drug resistance have varied according to hospital profile, and mainly according to local epidemiological features. University hospitals in Madrid, Spain, and Paris, France, reported MDR rates of respectively 1.2% and 1.4%,[8,9] while in a university hospital in Manila, Philippines, and in a prison hospital in Tula, Russia, these figures were respectively 53.5% and 71.2%.[10,11]

Although nosocomial events are important factors in the context of drug resistance, little attention is given to these health care settings and the potential for transmission of infection is underestimated by TB

Correspondence to: Rossana Coimbra Brito, Programa de Controle da Tuberculose, Secretaria de Estado de Saúde e Defesa Civil do Rio de Janeiro, Rua México 128, Sala 411, Centro, Rio de Janeiro 20031 142, RJ, Brazil. Tel: (+55) 21 2299 9188. Fax (+55) 21 2299 9750. e-mail: rossanacb@terra.com.br

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control programmes, mainly in resource-limited countries with a high prevalence of TB disease and inadequate implementation of measures to prevent nosocomial transmission of TB. Furthermore, despite the microbiologically confirmed evidence of drug-resistant TB (DR-TB) in these regions,[2] few comprehensive reports of well-conducted drug resistance studies of inpatients have been described.

Brazil ranks fifteenth among the world's 22 TB high-burden countries, with a TB mortality rate of 7.5 per 100 000 population according to WHO estimates.[12] Rio de Janeiro State has the highest TB incidence (100/100 000/year) and mortality (5.2/100 000/year) rates in Brazil, as well as 43% of the MDR-TB cases registered nationally. Approximately 15 000 cases are reported each year, 20% of them in hospital units.[13]

Culture and drug susceptibility testing (DST) are not routinely performed for TB diagnosis in Brazil. Among 83 089 TB cases reported in 2007, DST was performed for only 5266 patients (6.3%). The last national survey held in 1996 reported a primary MDR-TB rate of 0.9%. This study, however, did not include the significant population diagnosed in hospitals. Previous surveys conducted in university hospitals in Rio de Janeiro showed higher levels of primary MDR-TB, of 4.5% and 3.6%.[14,15]

The present prospective survey on drug resistance was carried out in six teaching, tertiary and TB reference hospitals in Rio de Janeiro State, Brazil.

PATIENTS AND METHODS

Setting

Six hospitals in Rio de Janeiro metropolitan region were included in the study: a general teaching hospital, Hospital Universitário Clementino Fraga Filho (HUCFF); two state TB reference hospitals, Hospital Estadual Santa Maria (HESM) and Instituto Estadual de Doenças do Tórax Ary Parreiras (IEDTAP); two general hospitals, Hospital Municipal Raphael de Paula e Sousa (HMRPS) and Hospital dos Servidores do Estado (HSE); and one reference centre for research on infectious disease, the Instituto de Pesquisa Evandro Chagas (IPEC). The six hospitals together register around 1000 TB cases per year, accounting for approximately 46% of all cases reported from hospital settings in Rio de Janeiro State over a 1-year period. Routine infection control measures were already in place only in HUCFF and IPEC. The hospitals were included as a convenience sample, selected by their ability to conduct all the tests required by the study.

Patient eligibility and registration

All TB patients registered in a period of 12 consecutive months between 2004 and 2006 in both inpatient and out-patient units were included in the study. Only patients with identified *Mycobacterium tuberculosis*, who had undergone DST, had given informed consent and could be interviewed by previously trained staff were included. The standardised questionnaire included socio-demographic, epidemiological and clinical data (Table 1). We excluded patients with conflicting DST results and used a combination of smear microscopy and culture for the initial diagnosis. Löwenstein-Jensen (LJ) culture medium onto which the specimen was inoculated after decontamination with sodium hydroxide (2–4%) was used, as recommended elsewhere.[17]

Complementary data were also gathered on all patients registered in each hospital in the Rio de Janeiro TB notification database, the Disease Surveillance System (Sistema de Informação de Agravos de Notificação–SINAN).

Definitions

Resistance among previously treated TB cases was defined as presence of resistant *M. tuberculosis* isolates in patients who, in response to direct questioning, declared having received previous anti-tuberculosis treatment for $\geqslant$1 month.

Resistance among non-previously treated TB cases was defined as presence of resistant *M. tuberculosis* isolates in patients who, in response to direct questioning, denied having received previous anti-tuberculosis treatment for as much as 1 month.

MDR-TB was defined as an *M. tuberculosis* isolate resistant to at least isoniazid (INH) and rifampicin (RMP). DR-TB was defined as an *M. tuberculosis* isolate resistant to at least one drug investigated, including INH or RMP.

Laboratory tests

Clinical samples of all patients eligible for anti-tuberculosis treatment were collected and DST of *M. tuberculosis* strains was performed by the proportion method using LJ medium.

Resistance was expressed as the percentage of colonies that grew on recommended critical concentrations of the drugs tested (i.e., 0.2 mg/l for INH, 2 mg/l for ethambutol (EMB), 4 mg/l for dihydrostreptomycin sulfate (streptomycin, SM) and 40 mg/l for RMP.

The criterion for drug resistance was growth of $\geqslant$1% of the bacterial population on media containing the critical concentration of each drug. The results of the tests were recorded on standardised forms, in accordance with proposed guidelines.[18,19]

All laboratories enrolled in the study were checked for quality control and staff training. Clinical investigators were blinded to DST results, and laboratory technicians were blinded to chest radiograph results and clinical predictors. At the final stage of the study, we submitted 8% of randomised strains (20 susceptible and 33 resistant) for quality control in certified regional laboratories (IPEC and HUCFF).

Table 1 Bivariate analysis for resistance to at least one drug (DR- and MDR-TB) in the total population

	Total (N = 595)	Drug-susceptible	DR-TB*			MDR-TB†		
			n‡	PR (95%CI)	P value	n	PR (95%CI)	P value
Age, years								
<40	296	249	46	Reference		19	Reference	
40–60	240	191	49	1.0 (0.9–1.1)	0.14	24	1.0 (0.9–1.1)	0.11
>60	59	52	7	0.9 (0.8–1.0)	0.46	1	0.9 (0.9–1.0)	0.15
Race								
Non-White§	393	322	71	1.1 (0.8 –1.7)	0.40	29	0.9 (0.5–1.8)	0.98
White	202	171	31			15		
Sex								
Male	409	339	70	0.9 (0.6–1.4)	0.97	32	1.2 (0.6–2.3)	0.55
Female	186	154	32			12		
Education, years								
<8	359	295	64	1.1 (0.8–1.7)	0.37	27	1.1 (0.6–2.2)	0.59
⩾8	220	187	33			14		
Marital status								
Unmarried	368	304	64	0.9 (0.9–1.0)	0.85	23	1.0 (0.9–1.0)	0.14
Married	220	183	37			21		
Dwelling with basic sanitation¶								
No	66	49	17	1.6 (1.0–2.6)	0.02	8	1.8 (0.9–3.8)	0.09
Yes	512	434	78			33		
Smoker								
Yes	356	290	66	1.2 (0.8–1.8)	0.25	28	1.2 (0.6–2.2)	0.50
No	234	199	35			15		
Alcohol abuse#								
Yes	148	112	36	1.6 (1.1–2.3)	0.009	19	2.2 (1.2–3.9)	0.004
No	440	374	66			25		
Drug use								
Yes	118	92	26	1.0 (0.9–1.1)	0.14	10	1.1 (0.5–2.3)	0.64
No	471	395	76			34		
Diagnosis in reference hospital								
Yes	213	152	61	2.6 (1.8–3.8)	0.00001	32	4.7 (2.5–9.0)	0.000001
No	382	341	41			12		
Health care worker								
Yes	52	41	11	1.2 (0.7–2.1)	0.44	6	1.6 (0.7–3.6)	0.24
No	538	447	91			38		
Household contact								
Yes	138	112	26	1.2 (0.7–1.8)	0.38	7	0.6 (0.2–1.4)	0.28
No	440	371	69			34		
Previous admission to TB hospital								
Yes	128	95	33	1.7 (1.2–2.5)	0.002	16	2.1 (1.1–3.8)	0.01
No	458	392	66			27		
Previous incarceration								
Yes	24	22	2	0.4 (0.1–1.7)	0.23	1	0.5 (0.1–3.8)	0.53
No	566	466	100			43		
Previous TB treatment								
Yes	156	112	44	2.1 (1.5–3.0)	0.00002	27	4.4 (2.4–7.8)	0.000001
No	435	378	57			17		
HIV status								
Positive	111	96	15	0.7 (0.4–1.2)	0.19	5	0.5 (0.2–1.3)	0.14
Negative	355	288	67			31		
Cough								
Yes	398	321	77	1.6 (1.0–2.4)	0.02	34	1.6 (0.8–3.2)	0.14
No	192	169	23			10		
Chest X-ray with cavitation								
Yes	292	221	71	2.2 (1.3–3.6)	0.0005	36	3.8 (1.5–9.6)	0.001
No	157	140	17			5		
Fever								
Yes	409	350	59	0.6 (0.4–0.9)	0.01	25	0.5 (0.3–1.0)	0.05
No	179	138	41			19		
Dyspnoea								
Yes	323	272	51	0.8 (0.5–1.2)	0.38	21	0.7 (0.4–1.3)	0.31
No	265	216	49			23		

* Resistance to at least one drug.
† All MDR-TB subjects are included in the drug-resistant group.
‡ Full data were not available for all subjects.
§ Black and mixed patients (no Asians).
¶ Water supply and sewers.
# CAGE criteria.[16]
DR = drug-resistant; MDR-TB = multidrug-resistant tuberculosis; PR = prevalence ratio; CI = confidence interval; HIV = human immunodeficiency virus.

Table 2 Bivariate analysis for resistance to at least one drug (DR- and MDR-TB) in patients without previous tuberculosis treatment

	Total (N = 433)	Drug-susceptible	DR-TB*			MDR-TB†		
			n‡	PR (95%CI)	P value	n	PR (95%CI)	P value
Age, years								
<40	237	207	30	Reference		10	Reference	
40–60	158	135	23	1.1 (0.6–1.9)	0.59	7	1.1 (0.4–2.7)	0.89
>60	38	34	4	0.8 (0.3–2.2)	0.71	0	0.0 (0.0–0.0)	0.99
Race								
Non-White§	283	243	40	1.2 (0.7–2.1)	0.41	11	0.9 (0.3–2.5)	0.50
White	150	133	17			6		
Sex								
Male	285	247	38	1.0 (0.6–1.7)	0.88	15	3.8 (0.9–16.8)	0.04
Female	148	129	19			2		
Education, years								
<8	262	225	37	1.1 (0.7–1.9)	0.55	9	0.7 (0.2–1.7)	0.46
⩾8	165	145	20			8		
Marital status								
Unmarried	159	139	20	0.9 (0.5–1.5)	0.72	8	1.5 (0.5–3.8)	0.38
Married	269	232	37			9		
Dwelling with basic sanitation¶								
No	48	37	11	1.9 (1.1–3.5)	0.02	3	1.8 (0.5–6.1)	0.33
Yes	378	334	44			13		
Smoker								
Yes	244	213	31	0.9 (0.5–1.5)	0.83	8	0.7 (0.2–2.0)	0.58
No	187	162	25			8		
Alcohol abuse#								
Yes	98	80	18	1.5 (0.9–2.6)	0.08	7	2.3 (0.9–6.1)	0.06
No	333	294	39			10		
Drug use								
Yes	82	68	14	1.3 (0.7–2.4)	0.24	3	0.9 (0.2–3.1)	0.88
No	350	307	43			14		
Diagnosis in reference hospital								
Yes	126	101	25	1.9 (1.1–3.1)	0.008	10	3.4 (1.3–8.9)	0.05
No	307	275	32			7		
Health care worker								
Yes	35	30	5	1.1 (0.4–2.5)	0.83	2	1.5 (0.3–6.3)	0.56
No	398	346	52			15		
Household contact								
Yes	93	79	14	1.2 (0.6–2.1)	0.47	1	0.2 (0.0–1.6)	0.10
No	334	293	41			16		
Previous admission to TB hospital								
Yes	18	17	1	0.4 (0.1–2.8)	0.32	0	0	0.38
No	414	358	56			17		
Previous incarceration								
Yes	83	72	11	1.0 (0.5–1.9)	0.88	3	0.9 (0.2–3.5)	0.98
No	245	214	31			9		
Previous TB treatment								
Yes	272	232	40	1.4 (0.8–2.5)	0.16	11	1.1 (0.4–2.8)	0.88
No	159	143	16			6		
HIV status								
Positive	187	153	34	1.7 (0.9–3.2)	0.06	15	4.6 (1.1–19.9)	0.02
Negative	116	104	12			2		
Cough								
Yes	307	268	39	0.7 (0.4–1.3)	0.36	11	0.7 (0.2–1.9)	0.54
No	124	105	19			6		
Chest X-ray with cavitation								
Yes	230	196	34	1.3 (0.8–2.2)	0.24	11	1.5 (0.6–4.2)	0.34
No	200	178	22			6		

*Resistance to at least one drug.
†All MDR subjects are included in the drug-resistant group.
‡Full data were not available for all subjects.
§Black and mixed patients (no Asians).
¶Water supply and sewers.
#CAGE criteria.[16]
DR = drug-resistant; MDR-TB = multidrug-resistant tuberculosis; PR = prevalence ratio; CI = confidence interval; HIV = human immunodeficiency virus.

Table 3 Bivariate analysis for resistance to at least one drug (DR- and MDR-TB) in previously treated patients related

	Total (N = 156)	Drug-susceptible	DR-TB*			MDR-TB†		
			n‡	PR (95%CI)	P value	n	PR (95%CI)	P value
Age, years								
<40	73	55	18	Reference		11	Reference	
40–60	69	46	23	1.3 (0.8–2.2)	0.26	15	1.4 (0.7–3.0)	0.27
>60	14	11	3	0.8 (0.3–2.5)	0.80	1	0.5 (0.1–3.5)	0.48
Race								
Non-White§	105	75	30	1.0 (0.6–1.7)	0.41	11	0.9 (0.3–2.5)	0.95
White	51	37	14			6		
Sex								
Male	119	88	31	0.7 (0.4–1.2)	0.88	15	3.8 (0.9–16.8)	0.04
Female	37	24	13			2		
Education, years								
<8	95	68	27	1.1 (0.6–2.1)	0.55	9	0.7 (0.2–1.7)	0.46
⩾8	54	41	13			8		
Marital status								
Unmarried	59	42	17	1.0 (0.6–1.7)	0.72	8	1.5 (0.5–3.8)	0.38
Married	96	69	27			9		
Dwelling with basic sanitation¶								
No	132	99	33	1.3 (0.6–2.7)	0.02	3	1.8 (0.5–6.1)	0.33
Yes	17	11	6			13		
Smoker								
Yes	108	74	34	1.4 (0.7–2.6)	0.83	8	0.7 (0.2–2.0)	0.58
No	46	36	10			8		
Alcohol abuse#								
Yes	50	32	18	1.4 (0.8–2.3)	0.08	7	2.3 (0.9–6.1)	0.06
No	103	77	26			10		
Drug use								
Yes	36	24	12	1.2 (0.7–2.1)	0.24	3	0.9 (0.2–3.1)	0.88
No	118	86	32			14		
Diagnosis in reference hospital								
Yes	84	49	35	3.3 (1.7–6.4)	0.008	10	3.4 (1.3–8.9)	0.005
No	72	63	9			7		
Health care worker								
Yes	17	11	6	1.27 (0.6–2.5)	0.83	2	1.5 (0.3–6.3)	0.56
No	137	99	38			15		
Household contact								
Yes	45	33	12	0.9 (0.5–1.7)	0.47	1	0.2 (0.0–1.6)	0.10
No	104	76	28			16		
Previous admission to TB hospital								
Yes	50	27	23	2.3 (1.4–3.8)	0.96	5	1.8 (0.6–5.1)	0.21
No	103	83	20			12		
Previous incarceration								
Yes	6	5	1	0.5 (0.1–3.4)	0.32	0	0	0.38
No	148	105	43			17		
HIV status								
Positive	28	24	4	0.4 (0.1–1.1)	0.88	3	0.9 (0.2–3.5)	0.98
Negative	107	72	35			9		
Cough								
Yes	123	86	37	1.3 (0.6–2.7)	0.16	11	1.1 (0.4–2.8)	0.88
No	32	25	7			6		
Chest X-ray with cavitation								
Yes	103	67	36	2.7 (1.1–6.6)	0.06	15	4.6 (1.1–19.9)	0.02
No	40	35	5			2		
Fever								
Yes	99	77	22	0.5 (0.3–0.9)	0.36	11	0.7 (0.2–1.9)	0.54
No	55	33	22			6		
Dyspnoea								
Yes	91	74	17	0.4 (0.2–0.7)	0.24	11	1.5 (0.6–4.2)	0.34
No	64	37	27			6		

* Resistance to at least one drug.
† All MDR subjects are included in the drug-resistant group.
‡ Full data were not available for all subjects.
§ Black and mixed patients (no Asians).
¶ Water supply and sewers.
# CAGE criteria.[16]
DR = drug-resistant; MDR-TB = multidrug-resistant tuberculosis; PR = prevalence ratio; CI = confidence interval; HIV = human immunodeficiency virus.

Patients were tested for HIV by the enzyme-linked immunosorbent assay and Western blot or immunofluorescence as a confirmatory test.

Ethics

The study was approved by the Hospital Universitário Clementino Fraga Filho Ethics Research Committee (central level of this multicentre study) and by each hospital ethics committee.

Data analysis

Comparisons were performed of variables associated with susceptible population with DR and with MDR associated results. In the bivariate analysis, the prevalence of resistance was analysed using the χ^2 test for categorical variables and the Mann-Whitney test for continuous variables. Associations between putative predictive factors and outcomes were expressed as prevalence ratios (PRs) and their respective 95% confidence intervals (95%CIs). Multivariate analysis was performed by Poisson regression with robust variance to all cases and subgroups according to history of previous treatment.[20] Variables used in the multivariate model are listed in Tables 1, 2 and 3. A P value $\leqslant 0.2$ was used to select variables for inclusion in the multivariate regression analysis. A forward stepwise elimination procedure was performed using $P \leqslant 0.05$ as a criterion for inclusion in the model. For the analysis of trends in resistance prevalence, the Cuzick non-parametric test was applied.[21] Data were analysed using STATA 9.0 software (StataCorp, College Station, TX, USA).

RESULTS

During the study period, of 1319 TB cases considered eligible and reported to SINAN by the six hospitals, 696 (52.7%) had bacteriological confirmation available from the moment of diagnosis. Of these, 30 (4.3%) did not undergo DST, 71 (14.1%) could not be interviewed or did not provide informed consent, and a final 595 (85.5%) were included in the study. Of the 595 TB patients included, 156 (26.2%) reported previous TB treatment, 433 (73.8%) had no previous treatment, and this information could not be obtained due to clinical conditions for six individuals. In the final analysis, the following numbers of patients were included from each hospital: HUCFF ($n = 126$), HESM ($n = 99$), HRPS ($n = 139$), IEDTAP ($n = 114$), IPEC ($n = 74$), and HSE ($n = 43$).

Patient characteristics

Patient characteristics and the results of bivariate analysis are shown in Tables 1, 2 and 3. The general patient characteristics (Table 1) were typical of TB patients in resource-limited countries, including those described in the Brazilian national information system (SINAN).[13] There were twice as many male as female patients. The median age was 40 years (interquartile range 35–50). Only one patient was aged <15 years, had not been previously treated and was susceptible to all drugs; 393 (66%) patients were non-White, 111 (18.7%) were seropositive for HIV, 148 (24.9%) were categorised as alcoholic according to the CAGE criteria,[16] and respectively 356 (59.8%) and 118 (19.8%) mentioned smoking and intravenous drug habits. Comparison of patients with and without DST results (group of excluded patients) showed no statistically significant differences in the variables (data not shown).

Tables 1, 2 and 3 show all of the variables investigated among all (Table 1), previously treated (Table 2) and non-previously treated subjects (Table 3). The Tables also show the distribution in susceptible, DR and MDR populations as well as the result of a bivariate analysis comparing DR and MDR subjects with drug-susceptible subjects.

Drug susceptibility

The results of quality control gave an accuracy for INH and RMP DST of 96.2%, for SM 92.5% and for EMB 96.1% (data not shown).

The distribution of resistance is shown in Table 4. The overall rate of resistance to at least one drug was high, with 102 cases (17.1%, 95%CI 14.3–20.5). Resistance rates were particularly high for INH ($n = 75$, 12.8%, vs. RMP $n = 50$, 8.4% and SM $n = 39$, 7.0%). Primary resistance to RMP was observed in 19 cases (4.3%). MDR-TB was present in 44 patients overall (7.4%, 95%CI 5.5–9.9), and in 27 previously treated patients (17.3%, 95%CI, 11.7–24.2). Among the 433 patients who denied receiving previous

Table 4 Drug resistance profile in 595 samples obtained from patients who attended the six study hospitals

	Not previously treated (n =433) n (%)	Previously treated (n =156) n (%)	Overall (N =595)* n (%)
Susceptible	376 (86.8)	112 (71.8)	493 (82.9)
DR	57 (13.1)	44 (28.2)	102 (17.1)
MDR	17 (3.9)	27 (17.3)	44 (7.4)
Number of drugs to which patients were resistant			
1	31 (7.1)	9 (5.8)	41 (6.9)
2	16 (3.7)	19 (12.2)	35 (5.9)
3	5 (1.2)	11 (7.1)	16 (2.7)
4	4 (0.9)	1 (0.6)	5 (0.8)
Resistance to each drug			
INH	38 (9.0)	37 (23.8)	75 (12.8)
RMP	19 (4.3)	31 (19.9)	50 (8.4)
EMB	5 (1.2)	13 (8.3)	18 (3.2)
SM	22 (5.6)	16 (10.3)	39 (7.0)
Monoresistance			
INH	15 (3.4)	2 (1.3)	17 (2.8)
RMP	1 (0.2)	2 (1.3)	3 (0.5)
EMB	0	0	0
SM	14 (3.2)	3 (1.9)	18 (3.0)

*Information on previous treatment not available for six patients.
DR = drug-resistant; MDR = multidrug-resistant; INH = isoniazid; RMP = rifampicin; EMB = ethambutol; SM = streptomycin.

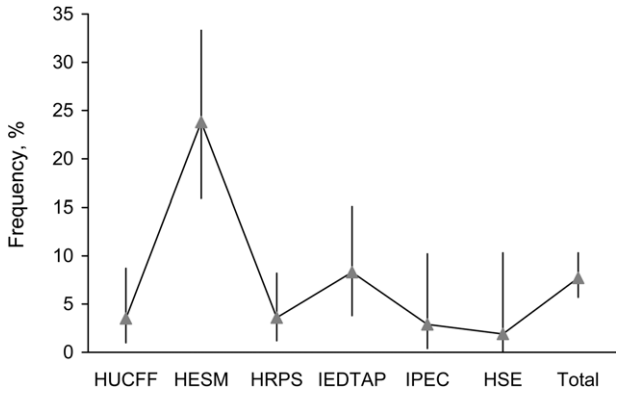

Figure Frequency and confidence intervals of MDR-TB for each hospital enrolled in the study. HUCFF = general teaching hospital; HESM = state reference TB hospital; HRPS = general hospital; IEDTAP = state reference TB hospital; IPEC = infectious disease reference hospital; HSE = general hospital; MDR-TB = multidrug-resistant tuberculosis.

anti-tuberculosis treatment, 57 (13.1%, 95%CI 10.2–16.8) were resistant to at least one drug and 17 (3.9%, 95%CI 2.4–6.3) to at least RMP and INH (MDR-TB; Table 4).

MDR rates varied considerably among hospitals (Figure), and were highest in the TB reference hospitals HESM (22/99, 22.2%, 95%CI 14.5–31.7) and IEDTAP (10/114, 8.8%, 95%CI 4.3–15.5).

In the final model of multivariate analysis of the general study population, we observed that independent factors previous treatment (PR 1.6, 95%CI 1.1–2.4), TB diagnosis in a TB reference hospital (PR 1.6, 95%CI 1.0–2.6) and fever (PR 0.5, 95%CI 0.3–0.8) were associated with DR-TB; and that previous treatment (PR 2.6; 95%CI 1.3–1.5) and TB diagnosis in a TB reference hospital (PR 3.3, 95%CI 1.5–7.2) were associated with MDR-TB (Tables 5 and 6).

Among non-previously treated individuals, the following factors were independently associated with DR-TB: diagnosis in a TB reference hospital (PR 1.8, 95%CI 1.1–3.0) and lack of basic sanitation at home (PR 1.1, 95%CI 1.0–1.3). Diagnosis performed in TB reference hospital was the single factor independently associated with MDR-TB (PR 3.3, 95%CI 1.2–8.7; Tables 5 and 6).

In previously treated individuals, the following factors were independently associated with DR-TB: diagnosis in a TB reference hospital (PR 2.2, 95%CI 1.1–4.3), previous admission to a TB reference hospital (PR 1.6, 95%CI 1.0–2.6) and dyspnoea as a protective factor (PR 0.4, 95%CI 0.2–0.7). Variables independently associated with MDR-TB were diagnosis in a TB reference hospital (PR 3.6, 95% CI 1.5–8.7), male sex (PR 2.3, 95%CI 1.2–4.4) and dyspnoea (PR 0.3, 95%CI 0.1–0.7) as a protective factor (Tables 5 and 6).

Table 5 Multivariate adjusted prevalence ratios and 95%CIs for the association between DR-TB and selected variables

	Multivariate DR	
	PR (95%CI)	*P* value
Total patients		
Previously treated TB	1.6 (1.1–2.4)	0.01
TB reference hospital	1.6 (1.0–2.6)	0.02
Fever	0.5 (0.3–0.8)	0.004
Previously treated TB		
TB reference hospital	2.2 (1.1–4.3)	0.01
Previous admission to hospital in <2 years	1.6 (1.0–2.6)	0.04
Dyspnoea	0.4 (0.2–0.7)	0.005
Not previously treated for TB		
TB reference hospital	1.8 (1.1–3.0)	0.01
Lack of basic sanitation at home	1.1 (1.0–1.3)	0.04

CI = confidence interval; DR = resistance to at least one drug; PR = prevalence ratio; TB = tuberculosis.

Table 6 Multivariate adjusted prevalence ratios and their 95%CIs for the association between MDR-TB and selected variables

	Multivariate	
	PR (95%CI)	*P* value
Total patients		
Previously treated for TB	2.6 (1.3–5.0)	0.003
TB reference hospital	3.3 (1.5–7.2)	0.002
Previously treated for TB		
TB reference hospital	3.6 (1.5–8.7)	0.003
Male sex	2.3 (1.2–4.4)	0.006
Dyspnoea	0.3 (0.1–0.7)	0.004
Not previously treated for TB		
TB reference hospital	3.3 (1.2–8.7)	0.01

CI = confidence interval; MDR-TB = multidrug-resistant tuberculosis; PR = prevalence ratio.

DISCUSSION

The strengths of this study conducted in a developing country include 1) the large number of TB cases managed in six hospitals in a metropolitan area with a high burden of TB and HIV; 2) comparisons of HIV status, history of previous anti-tuberculosis treatment and other socio-demographic variables; 3) the prospective study design, ensuring a more complete clinical, laboratory and radiographic picture; and 4) the proficiency of the laboratories included.

With poor DOTS coverage, MDR-TB remains an important challenge for TB control in Rio de Janeiro State. We observed a high prevalence of previous anti-tuberculosis treatment, HIV infection, alcoholism and intravenous drug use, confirming the epidemiological data reported by Rio de Janeiro State's TB Control Programme. Patient characteristics were typical of TB in resource-limited countries. Overall, we found a prevalence rate of primary drug resistance higher than described previously in a Brazilian national survey[22] and similar to that reported in other hospitals in Brazil, in Rio de Janeiro[14,15] and in Salvador/Bahia.[23] These results are also similar to the few studies carried out in hospitals in developing nations, where primary MDR-TB ranged from 2.6% to 8%,[24–27] and to data gathered from the National Drug Resistance Survey in Peru and Guatemala, which ranged from 3.0% to 5.3%.[2]

DR-TB surveys at hospitals seem to reflect the TB control in the regions where the institutions are located.[28] In metropolitan regions with a high TB burden, TB control programmes have neglected the TB burden in hospital settings, where there is usually a lack of TB infection control and a higher case fatality rate due to diagnostic delays and the presence of comorbidities.[23,24] We must consider that this kind of resistance survey, which included only patients from hospital settings, is already biased. In a country such as Brazil, where TB treatment is decentralised to primary care settings, hospital TB populations tend to be composed of patients with more complex clinical features, including HIV, other comorbidities and more severe disease presentation.

In general, higher INH resistance rates have been described in drug resistance surveys in both industrialised and developing countries,[8,15,26,27,29] probably due to the wide use of the drug worldwide in first-line treatment regimens. We found INH resistance in 23.8% of previously treated patients and 9.0% of non-previously treated subjects. INH monoresistance may not be of clinical significance, as patients can be cured even in the presence of INH resistance.[30]

On the other hand, initial RMP resistance should be carefully monitored, as it may have serious repercussions on treatment efficacy. In our study, RMP resistance occurred in 50 strains (8.4%). A high incidence of initial RMP resistance was identified in a prison hospital in Tula, Russia (41% in non-previously treated cases and 88.9% in previously treated cases).[11]

Lower rates of primary EMB resistance were found in this study (1.2%). The Brazilian Ministry of Health advocates the use of EMB only in special situations, and not in the three-drug first-line regimen, which consists of RMP, INH and PZA. A higher rate of resistance to EMB has been described in hospital surveys in countries that use this drug more widely, such as the university hospital in the Philippines, where primary EMB resistance was 39%.[27] Furthermore, it is important to remember that even with the best laboratory practice the efficiency and reproducibility of DST for EMB using the proportion method are often poor, due to the narrow range between critical drug resistance concentrations and the minimum inhibitory concentrations of susceptible strains, confusion about the preparation of drug solutions and the choice of critical concentrations and resistance proportions in the proportion method.[31]

Although SM is no longer used in first-line regimens, SM resistance has been described in a series of hospital surveillance surveys.[15,24,26,27] These results may be related to the reactivation of latent *M. tuberculosis* infection; however, as molecular typing analysis was not performed in these studies, it was not possible to distinguish between old and new infection.

Previous exposure to anti-tuberculosis drugs has been identified as the main factor associated with drug resistance since the first use of drugs for TB treatment,[32,33] and is an association frequently reported by hospital drug surveys.[29,34,35] In our study, overall, previous treatment for TB appeared as an independent associated factor with both DR and MDR.

In TB reference hospitals where there is no TB infection control in place, the isolation of bacteria resistant to multiple antimicrobial agents, ranging from 5.3% to 12.0% of patients who denied undergoing previous TB treatment, is particularly disturbing. Such cases of primary drug resistance most likely result from the ongoing transmission of resistant strains. Molecular typing of these *M. tuberculosis* isolates is underway. Moreover, it should be noted that, given the 95%CIs of resistance found, other studies with larger samples would be more representative.

Drug resistance in TB reference hospitals reflects TB control in each reference region. Countries or regions with a high TB burden generally report higher levels of drug resistance in such hospitals,[27,36] while in regions with better TB control DR is low, even in reference hospitals, as reported from Hamburg, Germany, where an MDR-TB rate of 1.8% was found. We found that being a patient from a reference TB hospital was an independent factor ($P \leqslant 0.01$) associated with the occurrence of DR- and MDR-TB in general in both non-previously treated and previously treated populations. Although this suggests that nosocomial transmission occurred, our study did not collect the epidemiologic data that would be necessary to establish where transmission occurred, and community transmission is therefore also a possible explanation for the study findings. These findings highlight the particular attention these hospitals should receive, particularly with regard to biosafety measures, to avoid nosocomial TB transmission.

HESM alone had a significantly higher rate of DR and MDR. Although this hospital does not have ideal biosafety conditions in place, it does have an inpatient unit for MDR-TB; however, only three patients enrolled in this study attended the hospital with a prior diagnosis, and most MDR-TB cases were diagnosed after hospitalisation. Another important characteristic of the patients in this unit is that there were high rates of drug abuse, alcoholism, homelessness and other social problems, which may have contributed to higher rates of recent infection and irregular use of medication.

As the present study was prospective, using information gathered from interviews and medical records, the loss of information required in interview was very low (in almost all variables it was less than 5%). However, the study had limitations regarding laboratory access and chest X-ray results: HIV testing was not available for 44.9% of patients and chest X-ray results for 22%, as a result of the poor quality of the TB control activities and/or of routine clinical practice in some hospitals. In our study, we were not able to show an association of HIV infection and DR, as described in some series, although there is supporting

evidence to suggest that this association occurs and that it may be more closely related to environmental factors such as transmission in congregate settings rather than biological factors.[37]

The findings of fever as an independent factor associated with DR in the general population and dyspnoea as a protective factor associated with DR in previously treated patients are not easily explained and should be confirmed by other studies. Furthermore, the association of lack of basic sanitary conditions in the home could indicate social problems that can contribute to a higher risk of recent infection and poor living conditions, frequently related to TB and MDR-TB in Brazil.[13]

CONCLUSIONS

High levels of DR and MDR-TB were found in this hospital sample. The results suggest that the Rio de Janeiro State TB programme needs to include hospitals in their agenda. Although our study did not establish conclusively where transmission of drug-resistant strains occurred, hospitals should be recognised as a potential setting for the spread of resistant TB strains, and urgent measures to prevent nosocomial TB transmission should be taken by TB control programmes. Timely and systematic monitoring of the susceptibility of *M. tuberculosis* isolates to first-line drugs is essential. Such studies should also be repeated at other TB care facilities to confirm if these results can be generalised to the entire state and other regions in Brazil.

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RÉSUMÉ

CONTEXTE : Enquête sur la résistance aux médicaments antituberculeux dans six hôpitaux à Rio de Janeiro, Brésil.

OBJECTIF : Estimer le taux de résistance à l'égard d'au moins un médicament (DR) et celui de la multirésistance (MDR) et identifier les facteurs qui y sont associés.

SCHÉMA : Enquête transversale au cours d'une période d'un an dans chaque hôpital entre 2004 et 2006. Les hôpitaux ont été inclus sous forme d'échantillon de convenance.

RÉSULTATS : Parmi 55 patients investigués, 156 (26,2%) avaient bénéficié antérieurement de traitements antituberculeux ; 433 (72,8%) n'avaient pas été traités antérieurement et chez 6 (1,0%) aucune information n'était disponible. Parmi les individus non traités antérieurement, il y a eu 17 cas de MDR (3,9% ; IC95% 2,4–6,3) et après analyse multivariée, le seul facteur indépendamment associé avec la TB-MDR a été le diagnostic de TB dans un hôpital de référence (ratio de prévalence [PR] 3,3 ; IC95% 1,2–8,7). Parmi ces individus antérieurement traités, la MDR a concerné 27 (1,3% ; IC95% 11,7–24,2) et a été en association indépendante avec les facteurs suivants : le diagnostic dans un hôpital de référence TB (PR 3,6 ; IC95% 1,5–8,7) ; le sexe masculin (PR 2,3 ; IC95% 1,2–4,4) ; et la dyspnée (PR 0,3 ; IC95% 0,1–0,7).

CONCLUSION : Les niveaux de DR et de TB-MDR se sont avérés élevés. La méthodologie de cette étude ne nous a pas permis de déterminer les contributions relatives de la transmission communautaire et nosocomiale, et d'autres études sont nécessaires. Néanmoins, l'hôpital doit être considéré comme un contexte potentiel de transmission des souches résistantes de TB et il est urgent d'améliorer les politiques d'évitement de la transmission nosocomiale de la TB.

RESUMEN

MARCO DE REFERENCIA: Encuestas sobre tuberculosis farmacorresistente en seis hospitales de Río de Janeiro, en Brasil.

OBJETIVO: Estimar la frecuencia de tuberculosis multidrogorresistente (TB-MDR) y de resistencia como mínimo a un medicamento antituberculoso y determinar los factores asociados.

MÉTODO: Se llevó a cabo un estudio transversal durante un período de un año en cada hospital, entre el 2004 y el 2006. Los hospitales se incluyeron mediante un muestreo de conveniencia.

RESULTADOS: De 595 pacientes, 156 (26,2%) habían recibido previamente tratamiento antituberculoso; 433 (72,8%) no tenían antecedente de tratamiento y no se obtuvo información en 6 pacientes (1,0%). En los pacientes sin antecedente de tratamiento antituberculoso, se diagnosticó TB-MDR 17 casos (3,9%; IC95% 2,4–6,3) y en el análisis multifactorial el único factor asociado independientemente con la MDR fue el diagnóstico en el hospital de referencia de TB (cociente de prevalencia [PR] 3,3; IC95% 1,2–8,7). En los pacientes con antecedente de tratamiento previo se observó MDR en 27 casos (17,3%; IC95% 11,7–24,2), la cual se asoció independientemente con: el diagnóstico en el hospital de referencia (CP 3,6; IC95% 1,5–8,7); el sexo masculino (PR 2,3; IC95% 1,2–4,4); y la disnea (PR 0,3; IC95% 0,1–0,7).

CONCLUSIÓN: Se encontraron altos niveles de TB farmacorresistente y TB-MDR. El diseño de este estudio no ha permitido determinar las contribuciones relativas de la transmisión comunitaria y nosocomial, y otros estudios son necesarios para establecerlas. Sin embargo, es importante reconocer el hospital como un posible entorno de transmisión de las cepas de TB resistente y es urgente mejorar las políticas encaminadas a evitar esta transmisión.