

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

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### 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).<sup>1,2</sup> 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.<sup>2</sup>

The modern era of TB control has also been characterised by serious nosocomial events.<sup>3–5</sup> 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.<sup>1,6,7</sup>

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%,<sup>8,9</sup> 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%.<sup>10,11</sup>

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

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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,<sup>2</sup> few comprehensive reports of well-conducted drug resistance studies of in-patients 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.<sup>12</sup> 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.<sup>13</sup>

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%.<sup>14,15</sup>

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 in-patient 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.<sup>17</sup>

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  $\geq 1$  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  $\geq 1\%$  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.<sup>18,19</sup>

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<br>(N = 595) | Drug-<br>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.<sup>16</sup>

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<br>(N = 433) | Drug-<br>susceptible | DR-TB*         |               |         | MDR-TB <sup>†</sup> |                |         |
|---|--------------------|----------------------|----------------|---------------|---------|---------------------|----------------|---------|
|   |                    |                      | n <sup>‡</sup> | 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 <sup>§</sup>                      | 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 <sup>¶</sup> |                    |                      |                |               |         |                     |                |         |
| 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 <sup>#</sup>                  |                    |                      |                |               |         |                     |                |         |
| 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.

<sup>†</sup>All MDR subjects are included in the drug-resistant group.<sup>‡</sup>Full data were not available for all subjects.<sup>§</sup>Black and mixed patients (no Asians).<sup>¶</sup>Water supply and sewers.<sup>#</sup>CAGE criteria.<sup>16</sup>

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<br>(N = 156) | Drug-<br>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.<sup>16</sup>

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  $\chi^2$  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.<sup>20</sup> Variables used in the multivariate model are listed in Tables 1, 2 and 3. A *P* value  $\leq 0.2$  was used to select variables for inclusion in the multivariate regression analysis. A forward stepwise elimination procedure was performed using *P*  $\leq 0.05$  as a criterion for inclusion in the model. For the analysis of trends in resistance prevalence, the Cuzick non-parametric test was applied.<sup>21</sup> 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).<sup>13</sup> 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,<sup>16</sup> 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

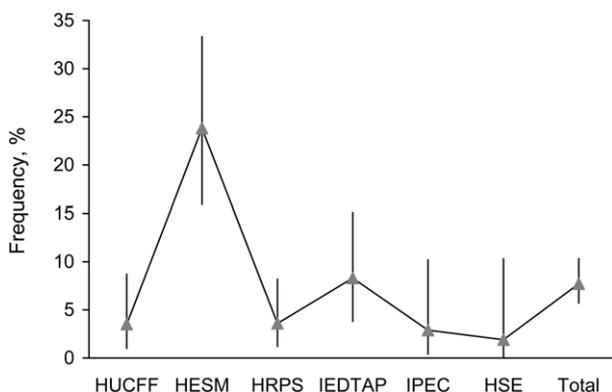
The results of quality control gave an accuracy for INH and RMP DST of 96.2%, for SM 92.5% and for EMB 96.1% (data not shown).

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<br>( <i>n</i> = 433)<br><i>n</i> (%) | Previously treated<br>( <i>n</i> = 156)<br><i>n</i> (%) | Overall<br>( <i>N</i> = 595)*<br><i>n</i> (%) |
|--|---|---|---|
| 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).

## DISCUSSION

The strengths of this study conducted in a developing country include 1) the large number of TB cases

**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.

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<sup>22</sup> and similar to that reported in other hospitals in Brazil, in Rio de Janeiro<sup>14,15</sup> and in Salvador/Bahia.<sup>23</sup> 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%,<sup>24–27</sup> and to data gathered from the National Drug Resistance Survey in Peru and Guatemala, which ranged from 3.0% to 5.3%.<sup>2</sup>

DR-TB surveys at hospitals seem to reflect the TB control in the regions where the institutions are located.<sup>28</sup> 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.<sup>23,24</sup> 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,<sup>8,15,26,27,29</sup> 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.<sup>30</sup>

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).<sup>11</sup>

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%.<sup>27</sup> 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.<sup>31</sup>

Although SM is no longer used in first-line regimens, SM resistance has been described in a series of hospital surveillance surveys.<sup>15,24,26,27</sup> 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,<sup>32,33</sup> and is an association frequently reported by hospital drug surveys.<sup>29,34,35</sup> 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,<sup>27,36</sup> 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 ( $P \leq 0.01$ ) 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.<sup>37</sup>

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.<sup>13</sup>

## 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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## References

- Basu S, Andrews J R, Poolman E M, et al. Prevention of nosocomial transmission of extensively drug-resistant tuberculosis in rural South African district hospitals: an epidemiological modelling study. *Lancet* 2007; 370: 1500–1507.
- World Health Organization. Anti-tuberculosis drug resistance in the world. 4th global report. The WHO/International Union Against Tuberculosis and Lung Disease Global Project on Anti-tuberculosis Drug Resistance Surveillance 2002–2007. WHO/HTM/TB/2008.394. Geneva, Switzerland: WHO, 2008.
- Beck-Sagué C, Dooley S W, Hutton M D, et al. Hospital outbreak of multidrug-resistant *Mycobacterium tuberculosis* infections. Factors in transmission to staff and HIV-infected patients. *JAMA* 1992; 268: 1280–1286.
- Busillo C P, Lessnau K D, Sanjana V, et al. Multidrug-resistant *Mycobacterium tuberculosis* in patients with human immunodeficiency virus infection. *Chest* 1992; 102: 797–801.
- McGowan J E Jr, Blumberg H M. Community as a source of infection: inner-city tuberculosis in the USA. *J Hosp Infect* 1995; 30 (Suppl 1): S282–S295.
- Breathnach A S, de Ruiter A, Holdsworth G M, et al. An outbreak of multidrug-resistant tuberculosis in a London teaching hospital. *J Hosp Infect* 1998; 39: 111–117.
- Herrera D, Cano R, Godoy P, et al. Multidrug-resistant tuberculosis outbreak on a HIV ward—Madrid, Spain, 1991–1995. *MMWR* 1996; 45: 330–333.
- Miralles Martín P, Moreno Guillén S, Parras Vázquez F, et al. Drug-resistant tuberculosis at a general hospital. *Rev Clin Esp* 1996; 196: 21–23.
- Robert J, Trystram D, Truffot-Pernot C, Cambau E, Jarlier V, Grosset J. Twenty-five years of tuberculosis in a French university hospital: a laboratory perspective. *Int J Tuberc Lung Dis* 2000; 4: 504–512.
- Mendoza M T, Gonzaga A J, Roa C, et al. Nature of drug resistance and predictors of multidrug-resistant tuberculosis among patients seen at the Philippine General Hospital, Manila, Philippines. *Int J Tuberc Lung Dis* 1997; 1: 59–63.
- Ignatova A, Dubiley S, Stepanshina V, Shemyakin I. Predominance of multi-drug-resistant LAM and Beijing family strains among *Mycobacterium tuberculosis* isolates recovered from prison inmates in Tula Region, Russia. *J Medical Microbiol* 2006; 55: 1413–1418.
- World Health Organization. WHO report 2006. Global tuberculosis control: surveillance, planning, financing. WHO/HTM/TB/2006.362. Geneva, Switzerland: WHO, 2006.
- Ministério da Saúde, Brasil. Tuberculose: casos confirmados notificados no Sistema de Informação de Agravos de Notificação (Sinan). Brasília, Brazil: Ministério da Saúde, 2004. <http://dtr2004.saude.gov.br/sinanweb/tabnet/dh?sinan/tuberculose/bases/tuberbr.def> Accessed January 2008. [Portuguese]
- Fandinho F, Kritski A, Hofer C, et al. Drug resistance patterns among hospitalized tuberculosis patients in Rio de Janeiro, Brazil, 1993–1994. *Mem Inst Oswaldo Cruz* 1999; 94: 543–547.
- Brito R C, Gounder C, Lima D B, et al. Resistência aos medicamentos anti-tuberculose de cepas de *Mycobacterium tuberculosis* isoladas de pacientes atendidos em hospital geral de referência para tratamento de AIDS no Rio de Janeiro. *J Bras Pneumol* 2004; 30: 335–342. [Portuguese]
- Mayfield D, McLeod G, Hall P. The CAGE questionnaire: validation of new alcoholism screening instrument. *Am J Psychiatry* 1974; 131: 1121–1123.
- Akhtar M, Bretzel G, Boulahbal F, et al. Sputum examination for tuberculosis for direct microscopy in low-income countries. In: Management of tuberculosis. A guide for low-income countries. 5th ed. Paris, France: International Union Against Tuberculosis and Lung Disease, 2000.
- Canetti G, Froman S, Grosset J, et al. Mycobacteria: laboratory methods for testing drug sensitivity and resistance. *Bull World Health Organ* 1963; 29: 14.
- Aziz M A, Laszlo A, Raviglione M, Rieder H, Espinal M, Wright A. Guidelines for surveillance of drug resistance in tuberculosis. 2nd ed. Geneva, Switzerland: WHO, 2003.
- Barros A J, Hirakata V N. Alternatives for logistic regression in cross-sectional studies: an empirical comparison of models that directly estimate the prevalence ratio. *BMC Med Res Methodol* 2003; 3: 21.
- Cuzick J. A Wilcoxon-type test for trend. *Stat Med* 1985; 4: 87–89.
- Braga J U, Barreto A M W, Hijjar M A. Inquérito epidemiológico da resistência às drogas usadas no tratamento da tuberculose no Brasil 1995–97, IERDTB. Parte III: Principais resultados. *Bol Pneumol Sanit* 2003; 11: 6. [Portuguese]
- Matos E D, Lemos A C, Bittencourt C, et al. Anti-tuberculosis drug resistance in strains of *Mycobacterium tuberculosis* isolated from patients in a tertiary hospital in Bahia. *Braz J Infect Dis* 2007; 11: 331–338.
- Harrow E M, Rangel J M, Arriega M, et al. Epidemiology and clinical consequences of drug-resistant tuberculosis in Guatemalan Hospital. *Chest* 1998; 113: 1452–1458.

- 25 Lin J, Sattar A N, Puckree T. An alarming rate of drug-resistant tuberculosis at Ngwelezane Hospital in northern KwaZulu Natal, South Africa. *Int J Tuberc Lung Dis* 2004; 8: 568–573.
- 26 Yang Z H, Rendon A, Flores A, et al. A clinic-based molecular epidemiologic study of tuberculosis in Monterrey, Mexico. *Int J Tuberc Lung Dis* 2001; 5: 313–320.
- 27 Mendoza M T, Gonzaga A J, Roa C, et al. Nature of drug resistance and predictors of multidrug-resistant tuberculosis among patients seen at the Philippine General Hospital, Manila, Philippines. *Int J Tuberc Lung Dis* 1997; 1: 59–63.
- 28 McGowan J E Jr. Nosocomial tuberculosis: new progress in control and prevention. *Clin Infect Dis* 1995; 21: 489–505.
- 29 Gomes C, Rovaris D B, Severino J L, Gruner M F. Perfil de resistência de '*M. tuberculosis*' isolados de pacientes portadores do HIV/AIDS atendidos em um hospital de referência. *J Pneumologia* 2000; 26: 25–29. [Spanish]
- 30 Enarson D A. Limitations of drug resistance surveillance. Conference on Global Lung Health and the 1997 Annual Meeting of the International Union Against Tuberculosis and Lung Disease, Paris, France. *Int J Tuberc Lung Dis* 1997; 1 (Suppl 1): S18 (abstract).
- 31 Laszlo A, Urbanczik R, Bretzel G, Rüsck-Gerdes S, Feldmann K. Ethambutol sensitivity test. *Int J Tuberc Lung Dis* 2003; 7: 603–605.
- 32 Canetti G. The J. Burns Amberson Lecture: present aspects of bacterial resistance in tuberculosis. *Am Rev Respir Dis* 1965; 92: 687–703.
- 33 Yew W W, Chau C H. Drug-resistant tuberculosis in the 1990s. *Eur Respir J* 1995; 8: 1184–1192.
- 34 Sharma S K, Turaga K K, Balamurugan A, et al. Clinical and genetic risk factors for the development of multidrug-resistant tuberculosis in non-HIV infected patients at a tertiary care centre in India: a case-control study. *Infect Genet Evol* 2003; 3: 183–188.
- 35 Harrow E M, Rangel J M, Arriega J M, et al. Epidemiology and clinical consequences of drug-resistant tuberculosis in a Guatemalan hospital. *Chest* 1998; 113: 1452–1458.
- 36 Dam T, Isa M, Bose M. Drug-sensitivity profile of clinical *Mycobacterium tuberculosis* isolates—a retrospective study from a chest-disease institute in India. *J Med Microbiol* 2005; 54: 269–271.
- 37 Wells C D, Cegielski J P, Nelson L J, et al. HIV infection and multidrug-resistant tuberculosis: the perfect storm. *J Infect Dis* 2007; 196 (Suppl 1): S86–S107.

## R É S U M É

**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 as-

socié 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.

## R E S U M E N

**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 aso-

ciado 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.