Drug resistance profile of *Mycobacterium tuberculosis* in the state of Mato Grosso do Sul, Brazil, 2000-2006*

Perfil de resistência de *Mycobacterium tuberculosis* no estado de Mato Grosso do Sul, 2000-2006

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Abstract

Objective: To determine the drug resistance profile of *Mycobacterium tuberculosis* in the state of Mato Grosso do Sul, Brazil, between 2000 and 2006. **Methods:** Descriptive study of reported tuberculosis cases in the Brazilian Case Registry Database. We included only those cases in which *M. tuberculosis* culture was positive and sensitivity to drugs (rifampicin, isoniazid, streptomycin and ethambutol) was tested. Löwenstein-Jensen and Ogawa-Kudoh solid media were used for cultures, as was an automated liquid medium system. Sensitivity tests were based on the proportion method. **Results:** Among the 783 cases evaluated, males predominated (69.7%), as did patients in the 20-49 year age bracket (70%), a diagnosis of pulmonary tuberculosis (94.4%) and positive HIV serology (8.6%); 645 (82.4%) were new cases, and 138 (17.6%) had previously been treated. Resistance to at least one drug was found in 143 cases (18.3%). The primary resistance (PR) rate was, respectively, 8.1%, 1.6%, 2.8% and 12.4%, for monoresistance, multidrug resistance (MDR), other patterns of resistance and resistance to at least one drug, whereas the acquired resistance (AR) rate was 14.5%, 20.3%, 10.9% and 45.7%, respectively, and the combined resistance (CR) rate was 9.2%, 4.9%, 4.2% and 18.3%, respectively. In PR, streptomycin was the most common drug, whereas isoniazid was the most common in AR and CR (7.2% and 3.7%, respectively). **Conclusions:** These high levels of resistance undermine the efforts for tuberculosis control in Mato Grosso do Sul. Acquired MDR was 12.7 times more common than was primary MDR, demonstrating that the previous use of drug therapy is an indicator of resistance. These levels reflect the poor quality of the health care provided to these patients, showing the importance of using the directly observed treatment, short course strategy, as well as the need to perform cultures and sensitivity tests for the early diagnosis of drug resistance.

Keywords: Tuberculosis; Drug resistance, multiple; *Mycobacterium tuberculosis*.

Resumo

Objetivo: Determinar o perfil de resistência a drogas de *Mycobacterium tuberculosis* no estado de Mato Grosso do Sul no período entre 2000 e 2006. **Métodos:** Estudo descritivo de casos notificados de tuberculose no Sistema de Informação de Agravos de Notificação, com cultura positiva para *M. tuberculosis* e testes de sensibilidade a rifampicina, isoniazida, estreptomicina e etambutol. Para as culturas, utilizaram-se os meios sólidos Löwenstein-Jensen e Ogawa-Kudoh, assim como um sistema automatizado com meio líquido; para os testes de sensibilidade, o método das proporções. **Resultados:** De 783 casos, 69,7% eram de pacientes masculinos, na faixa etária de 20-49 anos (70%), com forma pulmonar (94,4%) e sorologia positiva para HIV (8,6%); 645 (82,4%) eram casos novos, e 138 (17,6%) eram casos tratados. Identificou-se qualquer resistência em 143 casos (18,3%). A taxa de resistência primária (RP) foi, respectivamente, 8,1%, 1,6%, 2,8% e 12,4%, para monorresistência, multirresistência (MR), outros padrões de associação de drogas e qualquer resistência, ao passo que a taxa de resistência adquirida (RA) foi, respectivamente, 14,5%, 20,3%, 10,9% e 45,7%, e a taxa de resistência combinada (RC) foi, respectivamente, 9,2%, 4,9%, 4,2% e 18,3%. A estreptomicina foi a droga mais comum na RP (3,4%), e a isoniazida foi a mais comum na RA e RC (7,2% e 3,7%, respectivamente). **Conclusões:** Os níveis de resistência são elevados, prejudicando o controle da tuberculose em Mato Grosso do Sul. A MR adquirida, 12,7 vezes superior à MR primária, evidencia o uso prévio de medicamentos como indicativo de resistência. Os níveis refletem a fragilidade da atenção ao doente, mostrando a importância do tratamento diretamente observado, assim como das culturas e testes de sensibilidade para o diagnóstico precoce da resistência.

Descritores: Tuberculose; Resistência a múltiplos medicamentos; *Mycobacterium tuberculosis*.

Introduction

Although tuberculosis is a severe infectious disease, practically all new cases are curable, as long as the principles of chemotherapy are observed. The appropriate drug combination, the correct dosage, the use of the drugs for a sufficient amount of time and adherence to treatment are the means of avoiding bacterial persistence and the development of drug resistance.[1] Until the 1980s, the number of cases of the disease was decreasing worldwide. The resurgence of the disease in the 1990s was due to structural and demographic factors, as well as to HIV infection.[2-4]

Drug resistance is caused by the amplification, induced by humans, of the natural phenomenon of spontaneous mutations in the *Mycobacterium tuberculosis* bacillus.[5] The selection of mutants is facilitated by the rapid multiplication of the bacilli (on the order of 10^8 to 10^9) within pulmonary cavities, due to the high local concentration of oxygen and to the protection of these microorganisms by thick walls, which impede the presence of the drugs at appropriate inhibitory concentrations.[6] Inappropriate treatment create a favorable environment for the development of multidrug-resistant tuberculosis (MDR-TB).[1]

In Brazil, a multidrug resistant bacillus is defined as a bacillus that presents in vitro resistance to the rifampicin-isoniazid combination and to one other drug from any of the standard regimens. The international criterion, which was adopted in the present study, defines multidrug resistance as in vitro resistance to the rifampin-isoniazid combination.[1,7]

The increase in the frequency of strains of *M. tuberculosis* resistant to drugs seen in the USA and Europe in HIV-positive individuals has once again drawn the attention of the international scientific community.[8] Publications on these epidemics have led the World Health Organization (WHO) to show their support and declare tuberculosis a global emergency, implementing, in 1994, the Global Project on Anti-Tuberculosis Drug Resistance Surveillance, in order to determine the prevalence of primary and acquired MDR-TB combined,[7] which allowed the identification of six "hot spots".

According to a study carried out by the WHO, the prevalence of primary MDR-TB in Brazil was 0.9% during the 1994-1997 period, and the prevalence of primary and acquired MDR-TB during that same period was 1.3%, lower than the world average of 2.2%, which led to Brazil being excluded from the list of "hot spots".[7] However, a study conducted by Becerra et al.,[9] in which the indicators of the Global Project on Anti-Tuberculosis Drug Resistance Surveillance were added to the estimated annual absolute number of expected cases of MDR-TB and to the estimated annual incidence of MDR-TB per 100,000 population, showed Brazil to be a region in which intervention was needed in order to contain the spread of MDR-TB.[9]

Drug resistance is a growing problem nearly everywhere in the world.[10] The WHO Fourth Global Report on Anti-tuberculosis Drug Resistance in the World, which includes data related to the 2002-2007 period, revealed that Central and Western Europe rank highest regarding the proportions of resistance to at least one drug and multidrug resistance, and that Africa and the Americas follow.[11]

The determination of initial drug resistance is complicated by the lack of sensitivity tests in the diagnosed cases, which increases the possibility of inappropriate treatment and therefore increases the period of dissemination of multidrug resistant bacilli in the community.[1,12,13]

Although cultures to detect *M. tuberculosis* and tests of sensitivity to drugs have been performed at the *Laboratório Central de Saúde Pública do Mato Grosso do Sul* (LACEN-MS, Mato Grosso do Sul State Central Laboratory of Public Health) since 1995, the resistance rates are unknown. The purpose of the present study was to determine, based on routine laboratory tests performed at the LACEN-MS, the drug resistance profile of *M. tuberculosis* strains among the reported cases of tuberculosis in the state of Mato Grosso do Sul, Brazil, between 2000 and 2006, as one means of evaluating the effectiveness of the Tuberculosis Control Program in the state.

Methods

Cases of tuberculosis were selected from among those reported between January of 2000 and December of 2006 and included in the *Sistema de Informação de Agravos de Notificação* (SINAN, Brazilian Case Registry Database). There were a total of 6,810 reported cases, 5,845 of which were new cases and 963 of which had previously been treated. Of

Table 1 – Annual distribution of the cases of tuberculosis registered in the Case Registry Database, according to the history of treatment for tuberculosis, Mato Grosso do Sul, 2000-2006.

Profile/year	2000		2001		2002		2003		2004		2005		2006		Total	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
New cases	30	81.1	36	80.0	56	69.1	80	81.6	114	78.1	175	85.4	154	90.1	645	82.4
Treated cases	7	18.9	9	20.0	25	30.9	18	18.4	32	21.9	30	14.6	17	9.9	138	17.6
Total	37	100.0	45	100.0	81	100.0	98	100.0	146	100.0	205	100.0	171	100.0	783	100.0

those 6,810 cases, 783 (all of which occurred in individuals who resided in the state of Mato Grosso do Sul) had presented positive cultures for *M. Tuberculosis* and had been submitted to sensitivity tests, performed using samples of sputum, cerebrospinal fluid, secretion, urine, blood, etc. Solid media (Löwenstein-Jensen and Ogawa-Kudoh) were used for cultures, as was an automated liquid medium system (BACTEC MGIT 960/BD; Becton Dickinson, Sparks, MD, USA). Tests of sensitivity to rifampicin, isoniazid, ethambutol and streptomycin were based on the proportion method[6] and were conducted under the supervision of the Adolfo Lutz Institute of São Paulo.

Cases diagnosed as being attributable to nontuberculous mycobacteria were excluded, as were those occurring in individuals who did not reside in the state of Mato Grosso do Sul.

The cases were classified considering the history of previous treatment and the duration of the tuberculosis treatment. New cases were defined as those that were registered in the SINAN under the categories "new case" or "does not know" and those in which the culture material had been collected before patients had completed 30 days of treatment, as well as those for which there was no record in the SINAN database within the last 5 years. Treated cases were defined as those registered in the SINAN under the categories "readmission after treatment noncompliance" or "recurrence", as well as those cases receiving treatment for tuberculosis for at least 30 days, regardless of the initial operational classification.

For the evaluation of drug resistance, the cases were classified, according to the WHO criteria, as drug-resistant tuberculosis (resistant to one or more drugs) and MDR-TB (resistant to at least the rifampicin-isoniazid combination). Primary resistance (PR) was defined as resistance to one or more drugs in patients who had received tuberculosis treatment for less than 30 days. Acquired resistance (AR) was defined as resistance to one or more drugs developed after at least 30 days of tuberculosis treatment. Combined resistance (CR) refers to all cases presenting drug resistance, regardless of the treatment history.

The cases were also evaluated regarding the HIV serology data in the SINAN, tested cases being defined as those in which the result was definitively positive or negative.

In order to tabulate and analyze the results, the program Microsoft Excel, version 7.0, was used.

The present study was approved by the Research Ethics Committee of the Federal University of Mato Grosso do Sul (Protocol no. 1.347).

Results

Among the 783 cases of tuberculosis studied, males predominated (69.7%) and the difference between genders was statistically significant (p < 0.01). Regarding the age group distribution, 70% of the cases were in the 20-49 year age bracket, 94.4% of which had been diagnosed with pulmonary tuberculosis. There were 456 cases (58.2%) for which HIV serology data
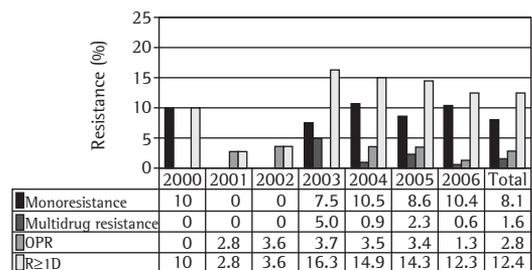

	2000	2001	2002	2003	2004	2005	2006	Total
Monoresistance	10	0	0	7.5	10.5	8.6	10.4	8.1
Multidrug resistance	0	0	0	5.0	0.9	2.3	0.6	1.6
OPR	0	2.8	3.6	3.7	3.5	3.4	1.3	2.8
R≥1D	10	2.8	3.6	16.3	14.9	14.3	12.3	12.4

Figure 1 – Annual distribution of primary resistance of *Mycobacterium tuberculosis* according to the type of resistance—monoresistance, multidrug resistance, other patterns of resistance (OPR) and resistance to at least one drug (R ≥ 1D)—Mato Grosso do Sul, 2000-2006.

Table 2 – Annual distribution of the proportions of primary resistance, acquired resistance and combined resistance, by drug, Mato Grosso do Sul, 2000-2006.

Types of resistance	Year							Mean	95% CI
	2000	2001	2002	2003	2004	2005	2006		
Primary resistance									
Isoniazid	10.0	-	-	2.5	1.8	2.3	5.2	2.9	2.33-3.47
Rifampicin	-	-	-	-	-	-	-	-	0
Streptomycin	-	-	-	3.7	6.1	2.9	4.5	3.4	2.14-4.66
Ethambutol	-	-	-	1.2	2.6	3.4	0.6	1.7	0.80-2.60
Acquired resistance									
Isoniazid	-	11.1	12.0	11.1	6.3	3.3	5.9	7.2	5.39-9.01
Rifampicin	14.3	11.1	-	-	-	3.3	-	2.2	1.18-3.22
Streptomycin	-	11.1	-	-	3.1	6.7	5.9	3.6	2.44-4.76
Ethambutol	-	-	-	-	-	6.7	-	1.4	0.58-2.22
Combined resistance									
Isoniazid	8.1	2.2	3.7	4.1	2.7	2.4	5.3	3.7	2.38-5.02
Rifampicin	2.7	2.2	-	-	-	0.5	-	0.4	0.0-0.84
Streptomycin	-	2.2	-	3.1	5.5	3.4	4.7	3.4	2.14-4.66
Ethambutol	-	-	-	1.0	2.5	3.9	0.6	1.7	0.80-2.60

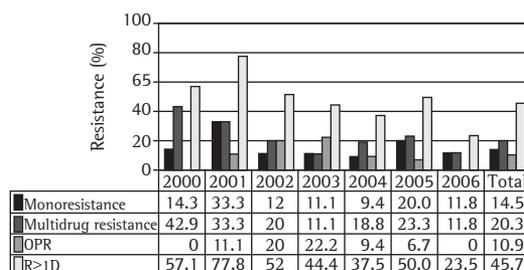were available, and the results were negative in 67 (8.6%).

Of the 783 cases, 645 (82.4%) were classified as new cases and 138 (17.6%) were classified as treated cases. In most of the years studied, the proportion of new cases was higher than 80%. However, in 2002 and in 2004 the proportion of new cases was approximately 70%. The 138 cases that had previously been treated corresponded to 30.9% of the cases investigated in 2002 and to 9.9% of the cases investigated in 2006, and this rate remained below 15% in the last 2 years of the study period (Table 1). Resistance to at least one drug was observed in 143 (18.3%) cases. Of those 143 cases, 140 (97.9%) were diagnosed based on the examination of sputum samples or bronchoalveolar lavage fluid.

The four types of PR—monoresistance, multidrug resistance, other patterns of resistance and resistance to at least one drug—are shown in Figure 1. The rifampicin-isoniazid combination and the rifampicin-isoniazid-streptomycin combination accounted for most of the cases of multidrug resistance. The isoniazid-streptomycin combination accounted for most of the cases of other patterns of resistance.

In 5 of the 7 years studied (Table 2), we observed primary monoresistance to streptomycin (mean, 3.4%), isoniazid (mean, 2.9%) and ethambutol (mean, 1.7%).

The four types of AR, the same as the types of PR, are described in Figure 2. The rifampicin-isoniazid combination, together with the rifampicin-isoniazid-streptomycin combination, accounted for 71.4% of the cases of multidrug resistance. There was a progressive increase in the cases of other patterns of resistance until 2003, followed by a decrease in these cases and finally by the absence of cases of other patterns of resistance in 2006. The isoniazid-streptomycin-ethambutol combination accounted for most of the AR cases.

Acquired monoresistance to isoniazid, rifampicin or streptomycin (Table 2) was higher than 10% in the first 4 years of the study period, decreasing by approximately 50% in the follo-

	2000	2001	2002	2003	2004	2005	2006	Total
Monoresistance	14.3	33.3	12	11.1	9.4	20.0	11.8	14.5
Multidrug resistance	42.9	33.3	20	11.1	18.8	23.3	11.8	20.3
OPR	0	11.1	20	22.2	9.4	6.7	0	10.9
R≥1D	57.1	77.8	52	44.4	37.5	50.0	23.5	45.7

Figure 2 – Annual distribution of acquired resistance of *Mycobacterium tuberculosis* according to the type of resistance—monoresistance, multidrug resistance, other patterns of resistance (OPR) and resistance to at least one drug (R ≥1D)—Mato Grosso do Sul, 2000-2006.
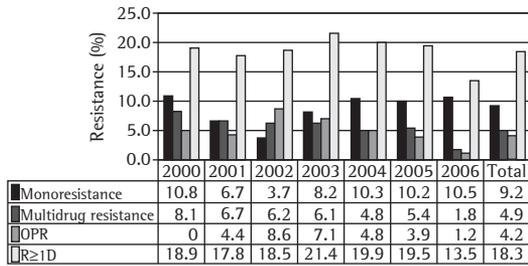
	2000	2001	2002	2003	2004	2005	2006	Total
Monoresistance	10.8	6.7	3.7	8.2	10.3	10.2	10.5	9.2
Multidrug resistance	8.1	6.7	6.2	6.1	4.8	5.4	1.8	4.9
OPR	0	4.4	8.6	7.1	4.8	3.9	1.2	4.2
R≥1D	18.9	17.8	18.5	21.4	19.9	19.5	13.5	18.3

Figure 3 – Annual distribution of combined resistance of *Mycobacterium tuberculosis* according to the type of resistance—monoresistance, multidrug resistance, other patterns of resistance (OPR) and resistance to at least one drug (R ≥ 1D)—Mato Grosso do Sul, 2000-2006.

wing years. The mean rates of monoresistance were 1.4% for ethambutol, 2.2% for rifampicin, 3.6% for streptomycin and 7.2% for isoniazid.

The four types of CR, the same as those of PR and AR, are shown in Figure 3. The rifampicin-isoniazid combination and the rifampicin-isoniazid-streptomycin combination together accounted for 73.8% of the cases of multidrug resistance. The isoniazid-streptomycin combination accounted for 57.6% of the cases of other patterns of resistance.

Rifampicin accounted for the lowest proportions of combined monoresistance whereas isoniazid accounted for the highest proportions, the latter decreasing over the course of the period under study, albeit still observed in each of the years studied (Table 2).

Discussion

The demand for laboratory tests began to increase in 2002, due to the implementation of tuberculosis control measures in 26 cities, which increased the number of individuals with respiratory symptoms examined and led to the intensified investigation of resistance among new cases.

The occurrence of PR to one or more drugs used in the treatment for tuberculosis, since the beginning of treatment, can be caused by a natural mechanism, resulting from genetic mutations, and can be present even before exposure to the drugs.[14] In the present study, resistance to rifampicin was not observed among the cases of PR to drugs used in isolation, which is different from what has been observed worldwide, where rifampicin ranks third among the drugs causing

PR. Even in Central and Western Europe, where the rate of resistance is lower, resistance to rifampicin is 1.1%.[11] Different patterns of resistance can be related to tuberculosis/HIV coinfection, HIV infection being central to the risk of developing active tuberculosis, either by endogenous reactivation or exogenous infection,[15] the precise impact of which remains undetermined.[1] In the present study, the highest rate of resistance was to streptomycin, a finding that is similar to that observed worldwide.[11] Since streptomycin is not used in new cases,[16] this finding probably indicates that, in Brazil, there has been endogenous reactivation of strains that emerged before the 1980s.

The proportion of monoresistance remained relatively stable throughout the study period; multidrug resistance was detected from 2003 onward; and other patterns of resistance were detected from 2001 onward, increasing until 2003, probably due to the intensified investigation of individuals with respiratory symptoms. The lower proportion of cases of resistance in the first years of the study period are due to the profile of the individuals investigated, since there was a predominance of patients who had previously been treated (in accordance with the recommendations of the Brazilian National Ministry of Health). From 2003 onward, the rates of multidrug resistance and other patterns of resistance decreased. These variations determined the behavior of the variations in the rates of resistance to at least one drug, which increased until 2003 and decreased in the 3 subsequent years, being 12.4% for the study period as a whole. These rates are lower than the worldwide average (17.0%) and close to that observed in Africa (11.4%).[11]

There were reports of primary multidrug resistance in the last 4 years of the study period, with rates in decline but higher than those found in Central and Western Europe (0.9%) and Africa (1.5%).[11] In the present study, the rates of primary multidrug resistance were higher than that found for Brazil in the last resistance survey (1.1%)[17] and that found at a referral center for infectious diseases in the State of Minas Gerais (0.3%).[18] However, in 2006, this rate was lower than the WHO estimate for Brazil for the same year (0.9%).[11]

The rates of PR to at least one drug were lower than the average of the rates found in

the world (17.0%) and the rates found in the Americas (14.9%), very close to those found in Canada and Honduras (12.0%), and higher than those found in Paraguay (10.0%) and Argentina (11.1%).[11]

Regarding AR to drugs used in isolation, isoniazid, rifampicin and streptomycin are of note, not only because, for each of those drugs, the rates of acquired monoresistance were higher than were the rates primary monoresistance but also because there was a reduction in the former over the last 3 years of the study period. The reduction in the rates of acquired monoresistance indicates greater adherence to treatment and greater attention to the sources of active tuberculosis. These proportions are lower than those found worldwide (resistance to isoniazid of 27.7%, resistance to rifampicin of 17.5%, and resistance to streptomycin higher than 20.0%). The proportions of resistance to rifampicin and streptomycin observed in the last years of our study period were lower than those reported for Central and Western Europe, which are regions presenting low rates of resistance.[3]

All of the types of AR were detected in most of the years evaluated in the present study. Acquired multidrug resistance was the highest but maintained a trend toward a decrease throughout the study period. There was a reduction in the proportions of acquired multidrug resistance (from approximately 40% to almost 12%), but the mean value observed for the study period (20.3%) was higher than that found in Africa, the Americas, Central and Western Europe and Asia.[11] The rates found in recent surveys of other Latin American countries were higher than those found in the present study: 26.5% for Guatemala (2002); 24.3% for Ecuador (2003); and 23.5% for Peru (2006).[11] The rates found in Mato Grosso do Sul were 5.8 times higher than was that found between 2000 and 2004 at a referral center for infectious diseases in the state of Minas Gerais (3.5%).[18] In the present study, the source of the test data was the entire public health care system. Therefore, the rates found for acquired multidrug resistance indicate the need to adopt urgent measures in order to correct failings in the health care system and tuberculosis control programs.[19-21]

Rates of the AR type other patterns of resistance were lower in the last 3 years of the study period than in 2002 and 2003, which shows the need for monitoring to confirm whether this reduction will be sustainable.

Regarding AR to at least one type of drug, the proportion found was higher than the worldwide average (35.0%) and than that found for the Americas (28.1%) but close to that found for Asia and the Western Pacific.[11] In addition, this proportion was higher than that found in recent surveys of other countries: 43.8% in Ecuador (2003) and 41.7% in Peru (2006).[11] Despite the reduction of over 50% in the last year of our study period, the rates of AR to at least one drug were over twice as high as those recorded in the last Brazilian national survey (21.0%)[17] and those found in São Paulo at a referral center for the treatment of MDR-TB in the 1990s.[19] They were, however, lower than those found in Guatemala (54.8% in 2002) and in the Dominican Republic (52.1% in 2005).[11]

The rates for CR caused by a drug used in isolation were lower than the average rates found in the world (proportion of resistance to isoniazid, rifampicin, streptomycin and ethambutol of 13.3%, 6.3%, 12.6% and 3.9%, respectively).[11]

The mean rate of combined multidrug resistance found in the present study (4.9%) was lower than the worldwide average (5.3%). It was, however, higher than the rates found in Africa (2.2%), in Central and Western Europe (1.5%) and in the Americas (4.0%). It was also higher than that estimated by the WHO for Brazil (1.4%) and for Latin America (3.5%), although it was close to that found for Argentina in 2005 (4.4%).[11] In addition, it was higher than the rate found for Brazil in the last national survey (2.2%)[17] and the rate found for the state of Espírito Santo (0.87%)[20]; however, it was lower than the rate found for the state of Rio de Janeiro (10.6%).[22]

In the present study, the mean rate for CR to at least one drug was 18.3% (range, 13.5-21.4%). This rate is lower than the worldwide rate, but higher than those observed in the Mediterranean, Central and Western Europe, the Americas and Africa.[11] Recent studies carried out at various health care facilities in Brazil, using exclusively respiratory samples, indicated that there were great variations in the rates of resistance: 12.6% for the city of São Vicente (in the state of São Paulo); 19.17% for the state of Minas Gerais; 21.3% for the community of Complexo

de Manguinhos (in the state of Rio de Janeiro); and 24.9% for the state of Ceará.[14,18,22,23]

The present study allowed the determination of the rates of resistance in the state of Mato Grosso do Sul. We underscore that the highest rate of PR was to streptomycin (3.4%) and that there was no PR to rifampicin. The highest rates of AR were to isoniazid (7.2%) and ethambutol (1.4%), whereas the highest rates of CR were to isoniazid (3.7%) and rifampicin (0.4%).

The mean rate of PR to at least one drug was 12.4%, monoresistance presenting the highest proportion (8.1%), followed by other patterns of resistance (2.8%) and multidrug resistance (1.6%). The mean rate of AR to at least one drug was 45.7%, multidrug resistance presenting the highest proportion (20.3%), followed by monoresistance (14.5%) and other patterns of resistance (10.9%). The mean rate of CR to at least one drug was 18.3%, monoresistance presenting the highest proportion (9.2%), followed by multidrug resistance (4.9%) and other patterns of resistance (4.2%).

The present study also allowed the identification of the behavior of the resistance rates over the years, showing initially increasing rates of PR that decreased in the last years of the study period. This behavior might be related to the intensified investigation of new cases and the reduction in the number of sources (resistant cases of the disease) within the community. In most cases of PR, resistance was identified because of the initiative of the LACEN-MS to perform cultures and carry out sensitivity tests in all suspect materials. This measure favored the adjustment to the treatment regimens, the reduction in treatment duration and the reduction in the risk of treatment failure, as well as contributing to the reduction in the rates of resistance over the study period.

The rates of AR, principally multidrug resistance, decreased over the study period, acquired multidrug resistance decreasing by over 70% when compared with PR and with the mean rates for the study period. Acquired multidrug resistance was 12.7 times more common than was primary multidrug resistance, demonstrating that the previous use of drug therapy is associated with resistance.

In conclusion, the rates of resistance found in our study were high, reflecting a lack of proper attention given to the sick patient, the poor application of the directly observed treatment strategy and the inappropriate use of short-course treatment regimens. It is necessary to monitor these rates in order to properly control tuberculosis in the state of Mato Grosso do Sul. For the early diagnosis of drug resistance and its correct management, we recommend more frequent use of culture tests and sensitivity tests.

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