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Factors associated to relapse of leprosy in Mato Grosso, Central-Western Brazil

ABSTRACT

OBJECTIVE: To analyze factors associated with relapse of leprosy.

METHODS: Retrospective case-control study including 159 patients older than 15 diagnosed with leprosy attending reference centers for leprosy in five municipalities in the state of Mato Grosso, central-western Brazil. Cases (n=53) were patients with relapsed leprosy diagnosed from 2005 to 2007 who were compared with controls (n=106) matching for gender and operational classification who were considered cured after treatment in 2005. Data was obtained from the local Notifiable Diseases Database, medical records and interviews. For the analyses conditional logistic regression and hierarchical approaches were used.

RESULTS: After adjustment, the following factors were associated with relapse of leprosy: living in rental housing (OR = 4.1; 95%CI: 1.43;12.04); living in houses constructed of wood and mud (OR = 3.2; 95%CI: 1.16;8.76); living with dwellings with more than five people (OR = 2.1; 95%CI: 1.03;4.36); alcohol use disorder (OR = 2.8; 95%CI: 1.17;6.79); irregular treatment (OR = 3.8; 95%CI: 1.44;10.02); lack of knowledge about the disease/treatment (OR = 2.6; 95%CI: 1.09;6.13); use of public transportation to get to the clinic (OR = 5.5; 95%CI: 2.36;12.63); clinical form of the disease (OR = 7.1; 95%CI: 2.48;20.52), and treatment regimen (OR = 3.7; 95%CI: 1.49;9.11).

CONCLUSIONS: The predictive factors of relapse are associated with housing conditions, living habits, organization of health services, clinical forms of leprosy and treatment regimen. Health services should educate patients on the disease as well as ensure consistent treatment.

DESCRIPTORS: Leprosy, prevention & control. Recurrence. Leprostatic Agents, supply & distribution. Socioeconomic Factors. Case-Control Studies.

INTRODUCTION

The introduction of multidrug therapy (MDT) for leprosy control marked the decline of leprosy cases in Brazil in recent years.^a However, endemic leprosy has remained a major health concern.^b The emergence of drug resistance among other factors is associated with relapse of leprosy.^{15,c}

There were reported 16,063 relapsed cases of leprosy worldwide from 2004 to

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^a World Health Organization. Global strategy for further reducing the leprosy burden and sustaining leprosy control activities (Plan period: 2006-2010). Geneva; 2005.

^b World Health Organization. Global leprosy situation. *Wkly Epidemiol Rec.* 2010;85(35):337-48.

^c World Health Organization. Guidelines for global surveillance of drug resistance in leprosy 2009. http://www.searo.who.int/LinkFiles/Situation_1-Guidelines_GSDRL_GLP-09.pdf

2009. There were 1,483 relapsed cases in Brazil in 2009, corresponding to 3.9% of new cases diagnosed during 2009. Relapsed cases of leprosy are not included in the indicator of incidence, i.e., new case detection rate but they affect the prevalence of the disease.^b

According to World Health Organization (WHO),²² the estimated risk of relapse after the implementation of MDT is 1.1% for paucibacillary (PB) cases and 0.8% for multibacillary (MB) cases in nine years following treatment. Relapse rates are between 3% and 17% with 2 to 15 years for relapse.^{4,8,9,21}

There are major differences in the relapse rates among Brazilian regions such as the Brazilian legal Amazon border.^d The state of Mato Grosso, central-western Brazil, accounted for 6% to 20% of relapsed cases between 2004 and 2006.⁶

Studies on factors associated with relapsed leprosy are relatively scant in Brazil and most have focused on clinical/laboratory and treatment factors overlooking socioeconomic aspects and those related to health services. They have pointed out the following determinant factors: household contacts,^{10,24} persistence of bacillus (bacterial index [BI] $\geq 2+$),^{4,9,10,24} interval between initial treatment and relapse, clinical form of leprosy, duration/type of MDT and drug reaction events.^{4,8,10,21,24}

The present study aimed to describe factors associated with relapse of leprosy.

METHODS

This is a retrospective case-control study including 159 patients older than 15 diagnosed with leprosy attending reference centers for leprosy in five municipalities (Cáceres, Cuiabá, Diamantino, Rondonópolis e Várzea Grande) in the state of Mato Grosso, central-western Brazil.

Cases (n = 53) were patients with relapsed leprosy diagnosed from 2005 to 2007 who were compared with controls (n=106) who were considered cured after treatment in 2005. The controls were matched by gender and operational classification to minimize or eliminate the confounding effect due to the predominance of relapse among MB and male cases.⁶ The criteria for the diagnosis of relapses in leprosy were based on the Brazilian Ministry of Health protocols^e and included new lesions and/or exacerbations of previous lesions, new neurological lesions with inadequate response after treatment with corticosteroids and/or thalidomide and

bacteriological and/or histopathological test results consistent with active forms in patients who were considered cured following treatment.

Data from the local Notifiable Diseases Database (SINAN/MT) were used to identify subjects in medical records of health facilities and contact them for an interview. These data included: reporting municipality and facility; date of reporting; date of diagnosis; patient's municipality of residence; patient name; gender; age; entry type; clinical form, operational and therapeutic regimen; degree of disability assessed at diagnosis; date of treatment start and end; and type of cure.

Information on demographic characteristics (age and education), clinical/laboratory features and treatment (clinical form, treatment regimen, frequency of treatment, number, type and site of lesions, nerve thickening, reactive state, side effects, physical disability, BI, skin biopsy and logarithmic index of biopsies) was obtained from medical records, disability assessment forms and reporting forms.

Interviews were carried out to collect information on socioeconomic and epidemiological factors (individual and family monthly income in minimum wages, occupation status, housing status, types of home construction materials, sewage system, garbage collection, number of people living in the dwelling, type of household contact, comorbidities/concurrent conditions and hospitalization); habits (smoking and alcohol use), organization of health services (home visits, guidance, drug availability at the facility, type of transportation to get to the health facility) and variables related to skin color/ethnicity.

BI and skin biopsies were performed at reference laboratories in the state of Mato Grosso and at the Instituto Lauro de Souza Lima, in Bauru, Southeastern Brazil, which is a national reference center. Housing conditions and ethnicity were defined based on the *Instituto Brasileiro de Geografia e Estatística* (IBGE –Brazilian Institute of Geography and Statistics criteria.^f Skin color/ethnicity (white, black, Asian, mixed and native) was self-reported and categorized into mixed (mulatto, mestizo and mixed) and non-mixed (white, black, Asian and native).¹³ The CAGE questionnaire¹⁴ (C: cut-down; A: annoyed; G: guilty; E eye-opener) was used to evaluate alcohol use. The cutoff for the test was two or more positive answers. Patient guidance was defined as two or more information provided on pathogenicity, mode of transmission, treatment and warning signs of disease severity. Regular or irregular treatment was

^d Ministério da Saúde. Casos confirmados notificados no Sistema de Informação de Agravos de Notificação - Sinan Net/hanseníase 2008. [citado 2008 jun]. Disponível em: <http://dtr2004.saude.gov.br/sinanweb/>

^e Ministério da Saúde. Secretaria de Vigilância em Saúde. Portaria Conjunta Nº 125, de 26 de março de 2009. Define ações de controle da hanseníase. *Diário Oficial da União*. 27 mar 2009; Seção 1:73.

^f Instituto Brasileiro de Geografia e Estatística. Pesquisa Nacional de Amostra por Domicílios - PNAD 2008. Questionário de pesquisa [citado 2008 abril]. Disponível em: <http://www.ibge.gov.br/home/estatistica/populacao/trabalhoerendimento/pnad2008/questpnad2008.pdf>

assessed through information on medical records on the duration of supervised monthly doses following the WHO/MDT regimen (PB cases: six doses within nine months; and MB: 12 doses within 18 months and 24 doses within 36 months). Clinical and treatment criteria were defined according to leprosy control activities.⁹

Eligibility criteria included: (i) cases: individuals older than 15 diagnosed with relapsed leprosy living in the study municipalities and recorded in the SINAN/MT database between 2005 and 2007 ($n = 82$). Of them, 17 were excluded due to transfer, diagnostic error, treatment dropout and/or death. Of 65 (79.3%) records, 12 were not located for interview, totaling 53 cases included in the study; (ii) control group: individuals older than 15 living in the municipalities where the cases originated and considered cured in 2005 and who did not relapse until December 31, 2008, completing a three-year interval following treatment. A total of 983 individuals who were considered cured and were recorded as “new case” in the SINAN/MT in 2005 were included. Of these, those who were transferred ($n = 251$) and double entered ($n = 6$) were excluded, resulting in 106 controls (2:1).

A hierarchical approach and conditional logistic regression with regression coefficients in terms of logarithmic odds ratio were used.²³ Three hierarchical levels including distal, intermediate and proximal level factors were analyzed (Figure). The distal level included socioeconomic variables; the intermediate level was divided into I (demographic and lifestyle factors) and II (factors related to health service organization). This approach allowed measuring the contribution of each hierarchical

level and minimizing underestimation of risk effects. The first (distal) level was overdeterminant. The set of variables in this level was analyzed independently from those of other levels and included the adjustments of variables at other subsequent levels when they were statistically significant ($p < 0.05$), in the same order used for other levels. Variables remained in the final model when adjustments were appropriate (Figure). The modeling process included the variables selected in the crude analysis at a 5% significance level. The logistic regression analysis was conducted following the proposed plan for hierarchical approach.

Data were double entered using EpiInfo version 3.2.1 and all statistical analyses were conducted using SPSS 15.0.

The study followed ethical principles and was approved by Research Ethics Committee at Hospital Universitário Júlio Muller (protocol no. 321, April 2007).

RESULTS

Of 159 cases and controls, 33.3% were cases and 66.7% controls. The following variables were significantly associated with relapse of leprosy in the univariate analysis: living in rental housing; living in houses constructed of wood and mud; living with more than five people (distal level determinants) (Table 1); mixed skin color, alcohol use disorder, irregular MDT, no guidance on the disease/treatment, and use of buses for transportation to get to the health facility (intermediate levels I and II) (Table 2); clinical form and treatment regimen (proximal level) (Table 3).

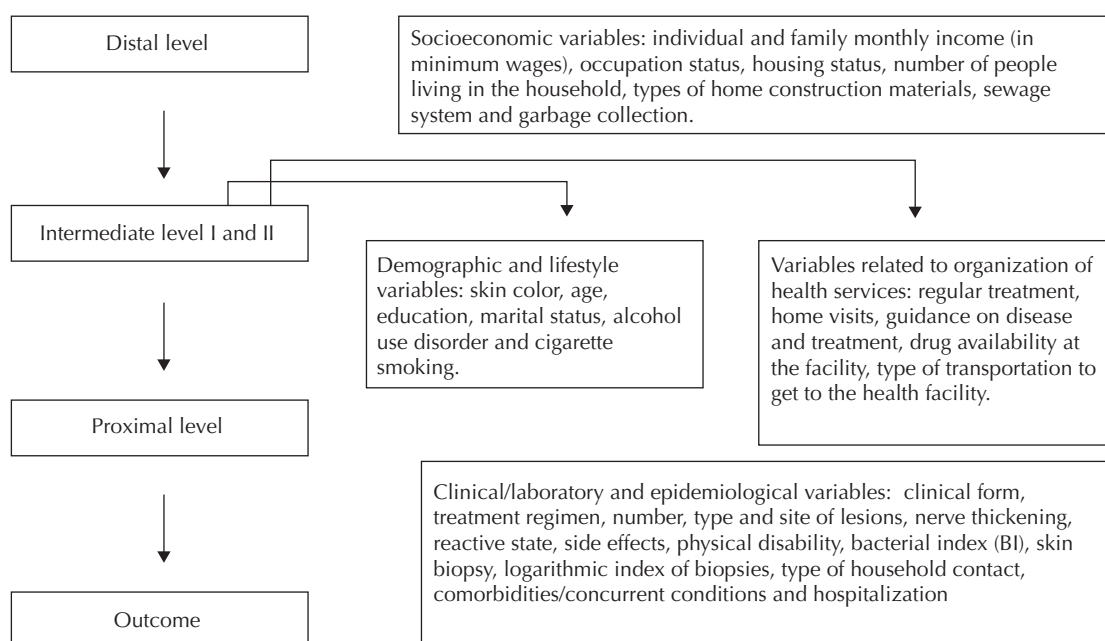


Figure. Hierarchical approach to relapse in leprosy.

Table 1. Distribution of relapse cases according to the results of distal level variables in the bivariate analysis. State of Mato Grosso, Central-Western Brazil, 2009.

Variables	Cases		Controls		Total		Crude OR	95%CI	p-value
	n	%	n	%	n	%			
Housing status									
Owned	39	73.6	88	83.0	127	79.9	1		
Rented	10	18.9	07	6.6	17	10.7	3.22	1.14;9.09	0.026
Borrowed	04	7.5	11	10.4	15	9.4	0.82	0.25;2.74	0.748
Type of construction materials									
Masonry	42	79.2	98	92.5	140	88.1	1		
Wood/mud	11	20.8	8	7.5	19	11.9	3.21	1.20;8.55	0.019
Number of people living in the household									
<5	29	54.7	76	71.7	105	66.0	1		
≥5	24	45.3	30	28.3	54	34.0	2.10	1.06;4.17	0.034

The following variables were not associated with relapse: individual and family monthly income, occupation status and sewage system (distal level); age, education, marital status, smoking and number of cigarettes smoked (intermediate level I); home visits (intermediate level II); number, type and site of leprosy lesions, nerve thickening; reactive state, side effects, degree of disability at diagnosis, bacterial index, logarithmic index of biopsies, skin biopsy, type and household contacts of leprosy cases, comorbidities/

concurrent conditions, types of comorbidities, and hospitalization (proximal level).

The final model including factors associated with leprosy relapse is shown in Table 4. Those living in rental housing were 4.1 times more likely to relapse than those living in their own home/borrowed homes (95%CI 1.43;12.04). Those living in homes constructed of wood and mud were 3.2 times more likely to relapse than those living homes constructed of masonry (95%CI 1.16;8.76); and relapse was 2.1 times more likely

Table 2. Distribution of relapse cases according to the results of intermediate level I and II variables in the bivariate analysis. State of Mato Grosso, Central-Western Brazil, 2009.

Variables	Cases		Controls		Total		Crude OR	95%CI	p-value
	n	%	n	%	n	%			
Intermediate level I									
Skin color									
Non-mixed ^a	27	50.9	35	33.0	62	39.0	1	0.24; 0.93	0.030
Mixed	26	49.1	71	67.0	97	61.0	0.47		
Alcohol use disorder									
Positive CAGE	17	32.1	15	14.2	32	20.1	2.83	1.28; 6.27	0.010
Negative CAGE	36	67.9	91	85.8	127	79.9	1		
Intermediate level II									
Regular treatment									
Yes	38	71.7	96	90.6	134	84.3	1		
No	15	28.3	10	9.4	25	15.7	3.79	1.57; 9.17	0.003
Guidance									
Yes	33	62.3	88	83.0	121	76.1	1		
No	20	37.7	18	17.0	38	23.9	2.96	1.40; 6.28	0.005
Type of transportation									
On foot	12	22.6	51	48.1	63	39.6	1		
Bus	24	45.3	17	16.0	41	25.8	4.33	2.05; 9.17	< 0.000
Bicycle	10	18.9	16	15.1	26	16.4	0.76	0.32; 1.82	0.545
Car/motobike	07	13.2	22	20.8	29	18.2	1.72	0.68; 4.33	0.249

^a Non-mixed = combined category: white (n=33), black (n=27), Asian (n=2), native (n= zero).

Table 3. Distribution of relapse cases according to the results of proximal level variables in the bivariate analysis. State of Mato Grosso, Central-Western Brazil, 2009.

Variables	Case		Control		Total		Crude OR	95%CI	p-value
	n	%	n	%	n	%			
Clinical form ^a									
Indeterminate	07	18.4	05	4.8	12	8.4	01	1	
Tuberculoid	11	29.0	18	17.3	29	20.4	0.44	0.11;1.72	0.236
Borderline	06	15.8	57	54.8	63	44.4	0.07	0.02;0.31	< 0.000
Lepromatous	14	36.8	24	23.1	38	26.8	0.42	0.11;1.56	0.195
Clinical form									
Borderline	6	15.8	57	54.8	63	44.4	1		
Other ^b	32	84.2	47	45.2	79	55.6	6.47	2.49;16.78	< 0.000
Treatment regimen ^c									
MDT – 12 doses	13	30.2	69	65.1	82	55.0	01	1	
MDT – 24 doses	15	34.9	15	14.1	30	20.2	5.31	2.10;13.44	< 0.000
MDT – 6 doses	15	34.9	22	20.8	37	24.8	3.62	1.49;8.76	< 0.004

^a Clinical forms not classified: cases (n=15), controls (n=2)

^b Other = combined category: indeterminate, tuberculoid, lepromatous

^c Other treatment regimen: cases (n=10).

among those living with five or more people (95%CI 1.03;4.36). Individuals of mixed skin color were 60% less likely to relapse compared with those of non-mixed skin color [adjOR = 0.4 (95%CI 0.19;0.84)]. Even after adjustment alcohol use disorder was a major predictor of relapse. Those who had a positive CAGE test were 2.8 times more likely to relapse than those who tested negative (95%CI 1.17;6.79). Relapse was 3.8 times more likely among those who had irregular than those who had regular treatment (95%CI 1.44;10.2). No guidance on disease and treatment increased by 2.6 times the odds of relapse (95%CI 1.09;6.13). Using bus transportation to get to the health facility was strongly associated with the outcome even after adjustment [adjOR = 5.5 (95%CI 2.36;12.63)]. As for clinical form, those classified as other (indeterminate / tuberculoid / lepromatous leprosy) were 7.1 times more likely to relapse compared to borderline forms (95%CI 2.48;20.52). Regarding treatment regimen, relapse in those categorized as other (MDT, 6 and 24 doses) was 3.7 times higher than in those receiving a treatment regimen of 12 doses (95%CI 1.49;9.11).

DISCUSSION

Living in rental housing, in houses constructed of wood and mud and with more than five people and use of public transportation to get to the health facility were factors associated with relapse in leprosy. Relapse was more likely in individuals with alcohol use disorder, treatment noncompliance, and who did not receive any guidance on the disease and treatment. The clinical form

of leprosy (indeterminate / tuberculoid / lepromatous) and treatment regimen (MDT / 6 and 24 doses) were also associated with relapse.

Mixed skin color was a protective factor for relapse even after adjustment. The majority of the population of Mato Grosso (54.6%) is of mixed skin color,⁸ and it is estimated that 80%–95% of the individuals exposed to the bacillus have natural resistance to leprosy. This finding supports the hypothesis of genetic influence on leprosy.¹⁶ This protective association could be explained by cellular immune response to the bacilli and its genetic influence. The potential association between skin color/ethnicity and socioeconomic factors was assessed. However, the variable ethnicity remained associated with relapse after adjusting for covariates at the same level and variables at the distal level.

Alcohol abuse that was identified as a predictive factor for relapse may be explained by the effect of alcohol on the metabolism of certain drugs, mainly antibiotics, affecting their absorption; tissue- and organ-specific effects of alcohol; increased susceptibility to infections; and treatment noncompliance.^{3,11}

Individuals living in rental housing constructed of wood/mud were more likely to relapse. The relationship between unfavorable socioeconomic conditions and higher risk of leprosy has been investigated in other studies.^{1,2} Unfavorable socioeconomic conditions, poor living conditions and immune response to *Mycobacterium leprae* are all factors that could favor relapse of leprosy.

⁸ Instituto Brasileiro de Geografia e Estatística. Contagem da população 2007: população recenseada e estimada, segundo os municípios de Mato Grosso. Rio de Janeiro; 2007.

Table 4. Risk factors for relapse in leprosy after adjustment. State of Mato Grosso, Central-Western Brazil, 2009.

Model	Crude OR	Adjusted OR	95%CI (adjusted OR)	p-value
Distal level				
Housing status ^a				
Owned/borrowed	1	1		
Rented	3.22	4.15	1.43;12.04	0.009
Type of construction materials ^a				
Masonry	1	1		
Wood/mud	3.21	3.18	1.16;8.76	0.025
Number of people living in the household ^a				
<5	1	1		
≥5	2.10	2.13	1.03;4.36	0.043
Intermediate level I				
Skin color ^b				
Non-mixed ^c	1	1		
Mixed	0.47	0.40	0.19;0.84	0.015
Alcohol use disorder ^b				
Positive CAGE	1	1		
Negative CAGE	2.83	2.82	1.17;6.79	0.021
Intermediate level II				
Regular treatment ^d				
Yes	1	1		
No	3.79	3.80	1.44;10.02	0.007
Guidance ^d				
Yes	1	1		
No	2.96	2.58	1.09;6.13	0.032
Transportation ^d				
On foot, bicycle, car/motorbike	1	1		
Bus	4.33	5.46	2.36;12.63	< 0.000
Proximal level				
Clinical form ^e				
Borderline	1	1		
Indeterminate/tuberculoid/lepomatous	6.47	7.13	2.48;20.52	< 0.000
Treatment regimen ^f				
MDT – 12 doses	1	1		
MDT – 6 and 24 doses	4.30	3.69	1.49;9.11	0.005

^a Adjusted for number of people living in the household and type of construction materials

^b Adjusted for the variable at the same level and all other variables in the distal level

^c Non-mixed = combined category (white, black, Asian and native)

^d Adjusted for all variables in the intermediate level II, skin color and type of construction materials

^e Adjusted for type of transportation, guidance and skin color

^f Adjusted for guidance, regular treatment, type of transportation, skin color and type of construction materials.

Large number of people living in the household was associated with relapse even after adjustment. Overcrowding is a determining factor for disease development.² But different health conditions may be associated with the spatial and social organization that determines the risk of disease in certain population groups.¹ Potential exogenous reinfection could be one explanation. Household contacts of leprosy cases were

investigated in this study and a similar distribution of cases and controls was found. Yet, the possibility of exogenous reinfection cannot be ruled out given the high rate of leprosy in the area studied.⁷

The higher risk of relapse found for MDT regimens of 6 doses compared with 12 doses suggests potential errors in the operational classification of disease in the initial treatment. The choice of treatment regimen

should be based on careful evaluation of leprosy cases which can ensure more accurate treatment and higher cure rates; however, a definite diagnosis without laboratory confirmation and/or negative results, especially in bacilliferous cases, can lead to misdiagnosis and subsequent disease reactivation.⁶ Short-term treatment with insufficient number of drugs to treat patients with low immune response can favor relapse.¹⁷ Alternatively serological tests can be used for the classification of PB and MB leprosy in the initial treatment and to confirm suspected relapse.¹² Greater risk of relapse was found among those individuals treated with MDT with a 24-dose regimen. This can be explained by disease severity possibly associated with bacterial persistence and specific immune response.^{4,8,9,16} MB cases treated with 24 doses have higher risk of relapse and are associated with borderline-lepromatous and lepromatous leprosy and high BI ($\geq 2+$) in initial treatment.^{4,8} The use of alternative drugs to replace the standard regimen for leprosy treatment should be considered.^{4,8,18} Antimicrobial combinations seem to be effective but minocycline plus rifampicin only have proven to eliminate all *M. leprae*; antimicrobial combinations that include rifampin and either ofloxacin, clarithromycin or minocycline can improve treatment effectiveness.^{4,8,18} However, these more severe cases should receive treatment in specialized centers.^c

The organization of health services is apparently the most important factor associated with relapse as it can be changed within the health system. The risk of relapse in individuals who had irregular treatment was almost four times as high as compared to those with regular treatment. Irregular treatment, which is seen as a form of noncompliance, may be related to the patient himself (not complying with prescribed treatment course, incorrect drug use and/or missing medical appointments) or to the organization of services (failure to schedule returns, lack of drugs at the facility, lack of direct supervision of drug treatment, and inadequate relationship between patients and providers).^{11,19} The risk of relapse for the group of individuals who did not receive any guidance on the disease and treatment was nearly three

times higher than that in those who reported receiving guidance. Sociocultural aspects such as knowledge, attitudes and practices about leprosy and access to information may affect treatment compliance.^{5,11,19} Ongoing patient education and community involvement including strategies to facilitate successful treatment can help the implementation of disease control actions. Successful relapse prevention requires taking responsibility, from political decision-making to health care quality.^e

The use of public transportation to get to the health facility proved an important predictor of relapse. In municipalities with specialized care centers, diagnosis and treatment of leprosy are still partially centralized, which may contribute to difficult access to treatment. Patients living close to health facilities have more access to services and thus show greater treatment compliance. This is corroborated by the fact that 48.1% of controls reported not requiring public transportation to get to the health facility, i.e., they lived within the catchment area. Home visits as a protective factor could explain this finding but they were evenly distributed between cases and controls. Decentralization and regionalization have been discussed as a strategy for hierarchization of health services and greater equity, suggesting that there is a need to implement regulatory mechanisms of health care.^h

A limitation of the present study is that controls could not be investigated prior to 2005. These individuals could not be interviewed for data collection due to intense population migration within the state of Mato Grosso, especially in the areas studied. Some of the controls included in the study could relapse in the future. However, the methodological approach of matching cases and controls minimized this effect.²⁰

In conclusion, the predictive factors for relapse in leprosy are associated with living conditions, living habits, organization of health services, clinical forms of disease and treatment regimens. To prevent relapse, health services should provide appropriate guidance to patients and ensure regular treatment.

^h Ministério da Saúde. Portaria nº 95, de 26 de janeiro de 2001. Norma operacional da assistência à saúde - NOAS-SUS 01/2001. *Diário Oficial Uniao*. 29 jan 2006; Seção 1:48.

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