

Hospital morbidity due to paracoccidioidomycosis in Brazil (1998–2006)

Ziadir Francisco Coutinho, Bodo Wanke, Claudia Travassos, Rosely Magalhães Oliveira, Diego Ricardo Xavier and Carlos E. A. Coimbra Jr.

Fundação Oswaldo Cruz, Rio de Janeiro, Brazil

Abstract

OBJECTIVE To analyse hospital morbidity records due to paracoccidioidomycosis in Brazil, including its nationwide distribution in time and space, as well as key epidemiological and sociodemographic characteristics.

METHODS Descriptive analysis of hospital morbidity records due to paracoccidioidomycosis covering the period January 1998 to December 2006. Hospital records were obtained from the Hospital Information System of the Brazilian Unified Health System (SIH/SUS).

RESULTS There were 6732 hospitalisations (82% male) due to paracoccidioidomycosis in the period, representing 4.3 per 1.0 million inhabitants. Admissions due to this mycosis were recorded in 27% of the 5560 Brazilian municipalities, covering 35% of the country. Ten municipalities concentrated 52% of all admissions. The temporal distribution of admissions for paracoccidioidomycosis showed a slight increase. The geographical analysis showed two distinct patterns of the disease: (i) traditional areas of southern and south-eastern regions, covering 60% of admissions, and (ii) a second pattern in northern Brazil revealed a transverse band of higher concentration with about 27% of admissions, particularly along the southern border of the Amazon region.

CONCLUSION This first nationwide analysis of hospitalisation due to paracoccidioidomycosis in Brazil shows that it is the most prevalent systemic mycosis in Brazil. Despite its importance, there are major deficits in its proper registry, diagnostics and treatment. The particular epidemiological and medical challenges of paracoccidioidomycosis will not be met while the disease continues to be perceived as an isolated infectious entity restricted to a few faraway regions of the globe.

keywords paracoccidioidomycosis, mycosis, hospitalisation, morbidity, health services, tropical neglected diseases

Introduction

Paracoccidioidomycosis is a systemic mycosis caused by *Paracoccidioides brasiliensis*, occurring from Southern Mexico to Northern Argentina [1]. This disease constitutes a major challenge due to its numerous clinical presentations that needs careful differential diagnosis, mainly from pulmonary tuberculosis, as approximately 14% of patients with paracoccidioidomycosis may be co-infected with *Mycobacterium tuberculosis* [2–4].

Knowledge of the epidemiology of paracoccidioidomycosis remains fragmented as most population-based surveys carried out in endemic regions are limited to intradermal testing with paracoccidioidin [5–7]. The non-existence of morbidity records in all endemic countries further renders it impossible to calculate paracoccidioidomycosis prevalence or incidence.

Notwithstanding its ‘epidemiological invisibility’, paracoccidioidomycosis is a serious cause of disease and death and especially affects rural young men. Treatment usually begins late, when the disease has already spread to several organs. Depending on the affected organ, scars and other sequels can incapacitate patients for life, forcing young subjects into early retirement, with socio-economic consequences. In Brazil, paracoccidioidomycosis represents the eighth most frequent cause of death due to chronic or recurrent infectious and parasitic diseases and presents the highest mortality rate among the systemic mycoses [1, 8].

The objective of this paper is to contribute to the epidemiology of paracoccidioidomycosis in Brazil by analysing hospital admission records from the Hospital Information System of the Brazilian Health System (SIH-SUS).

Methodology

A descriptive study of hospital admissions due to paracoccidioidomycosis in Brazil was carried out between January 1998 and December 2006. The data source consisted of Standard Hospital Admission Authorization Forms (AIH – *Autorização de Internação Hospitalar*) provided by DATASUS, as of July 2007. This is an open access health and mortality information system maintained by the Brazilian Ministry of Health (available at <http://www2.datasus.gov.br/DATASUS/index.php>). Of a total of 104 971 228 hospitalisations recorded in the period, those in which the primary diagnosis was paracoccidioidomycosis (ICD-10: B41) and blastomycosis were selected (ICD-10: B40).

The records for blastomycosis were considered equivalent to paracoccidioidomycosis because, even though the designation ‘South American blastomycosis’ was officially substituted by ‘paracoccidioidomycosis’ in 1971 [9], Brazilian physicians continue to use these terms interchangeably. Hospital admissions for other diseases that constitute common differential diagnoses related to paracoccidioidomycosis, namely tuberculosis (A15-19), bronchial and lung cancer (C34), coccidioidomycosis (B38), histoplasmosis (B39) and cryptococcosis (B45), were also analysed. Classification and codification of diseases followed the World Health Organization’s 10th edition of the International Classification of Diseases and Related Health Problems – ICD [10].

Coefficients of hospital admissions were calculated on the basis of the resident population in municipalities, according to the 1991 and 2000 Brazilian Demographic Censuses and the 1996 Counting and Intercensus Projection (2009), available at DATASUS (<http://www2.datasus.gov.br/DATASUS/index.php>).

Hospital admissions were analysed according to their frequency by place of patient residence and place of occurrence and their temporal and spatial distribution. Information about the displacement of patients for hospitalisation was spatially represented. The following patient characteristics were considered: age (<1 year, 1–4 years, 5–14, 15–49, >50 years), sex, primary diagnosis, secondary diagnosis and hospital death. The proportional morbidity from infectious and parasitic diseases and non-infectious diseases related to causes of differential diagnoses listed above was also calculated.

Coefficients of hospital admissions for paracoccidioidomycosis per one million inhabitants were estimated (average number of hospital admissions or deaths with diagnosis of paracoccidioidomycosis for the period between 1998 and 2006/average population for the same period per one million inhabitants), and the hospital

death rate from paracoccidioidomycosis per 100 hospital admissions (number of deaths from paracoccidioidomycosis/number of hospital admissions of patients with diagnosis of paracoccidioidomycosis per 100 hospital admissions). To test the variation through time in the distribution of the monthly frequency of hospital admissions at the national and regional levels, linear correlation was used and straight-line linear regression was estimated. A 95% reliability interval was adopted.

The study was approved by the Ethics Research Committee of the Brazilian National School of Public Health.

Results

A total of 6732 hospital admissions for paracoccidioidomycosis were registered in Brazil between January 1998 and December 2006 with an annual average of 748 admissions. The admission rate for paracoccidioidomycosis was 4.3 admissions per one million inhabitants, and cases were reported in all 26 states. According to place of residence, the South region accounted for the highest rate of hospital admissions for paracoccidioidomycosis (6.9) and the North-east the lowest (2.8). The South admitted 8% of all cases in the country (Table 1 and Figure 1). There were 334 hospital deaths among patients with paracoccidioidomycosis during the study period, representing a hospital death rate of 5%, which was highest in the South (7%) (Table 1).

Table 2 shows the distributions of patients according to sex and age. Men accounted for 82% of all hospital admissions. Ages ranged from 5 days to 99 years (average = 44 years; median = 45 years). Patients ≥ 15 years represented 92% of all admissions and 84% were men. There were 13 683 hospital admissions with main diagnosis of systemic mycosis: 6732 (49%) of them had diagnoses of paracoccidioidomycosis, followed by cryptococcosis with 4055 (30%) and coccidioidomycosis with 2582 (19%).

Overall, the temporal distribution of hospital admissions for paracoccidioidomycosis in the country showed a slight increase over the period, but this trend was not statistically significant ($r = 0.148$; P value = 0.126). However, the temporal frequency distribution by region was statistically significant at the 5% level. The number of hospital admissions presented a trend towards lower levels in the South-east and North-east regions, as showed by their negative linear correlation coefficients between the number of hospital admissions for paracoccidioidomycosis per month ($r = -0.262$; P value = 0.006 and $r = -0.309$; P value = 0.001, respectively). On the contrary, in the Central-West, North and South regions, the monthly distribution of hospital admissions for

Table 1 Frequency distribution of hospitalisations due to paracoccidioidomycosis, annual mean, hospitalisation rate, hospital deaths and mortality according to geographic regions and states of residence, Brazil (1998–2006)

Region/State of residence	Total	Annual mean	Hospitalisation rate	Hospital death	Hospital mortality
North	735	82	6.1	31	4.2
Rondônia	256	28	20	14	5.5
Acre	88	10	16.5	6	6.8
Amazonas	6	1	0.2	0	0
Roraima	12	1	3.9	2	16.7
Pará	286	32	4.9	7	2.4
Amapá	1	0	0.2	0	0
Tocantins	86	10	7.9	2	2.3
North-east	687	76	1.6	19	2.8
Maranhão	359	40	6.9	9	2.5
Piauí	136	15	5.2	5	3.7
Ceará	57	6	0.8	1	1.8
Rio Grande do Norte	5	1	0.2	0	0
Paraíba	15	2	0.5	1	6.7
Pernambuco	8	1	0.1	0	0
Alagoas	7	1	0.3	1	14.3
Sergipe	4	0	0.2	0	0
Bahia	96	11	0.8	2	2.1
South-east	3823	425	5.7	206	5.4
Minas Gerais	911	101	5.5	50	5.5
Espírito Santo	116	13	4	9	7.8
Rio de Janeiro	873	97	6.6	41	4.7
São Paulo	1923	214	5.6	106	5.5
South	554	62	2.4	38	6.9
Paraná	280	31	3.2	21	7.5
Santa Catarina	187	21	3.8	8	4.3
Rio Grande do Sul	87	10	0.9	9	10.3
Central-West	907	101	8.3	39	4.3
Mato Grosso do Sul	76	8	3.9	5	6.6
Mato Grosso	625	69	26.7	15	2.4
Goiás	160	18	3.4	15	9.4
Distrito Federal	46	5	2.4	4	8.7
Unknown	26	3	0	0	0
Total	6732	748	4.3	334	5

paracoccidioidomycosis, which accounts for 32% of the total, showed an upward trend, with a positive linear correlation coefficient ($r = 0.450$; P value = 0.000, $r = 0.304$; P value = 0.001 and $r = 0.593$; P value = 0.000, respectively).

Information about patient's flow from place of residence to place of hospitalisation was obtained for 99.61% cases. Of the total number of admissions, 89% (5981) occurred in the patient's own state of residence. Curiously, one particular state in the North-east – Piauí – accounted for 73% of the hospital admissions in this region.

Only 27% of the total 5560 municipalities in Brazil had residents hospitalised for paracoccidioidomycosis, and these admissions took place in hospitals located in 512 municipalities (9.1%) (Figure 2). Ten municipalities

absorbed 23% of the total 1480 hospital admissions for paracoccidioidomycosis: South-east [São Paulo (370 cases), Rio de Janeiro (212), Belo Horizonte (117), Ribeirão Preto (87), Campinas (57), Petrópolis (48), Barra Mansa (47), Duque de Caxias (46) and Nova Iguaçu (40)], Center-West [Cáceres (194), Alta Floresta (50) and Brasília (46)], North [Rio Branco (63) and Porto Velho (55)] and North-east [Teresina (48)] (Figure 2).

Discussion

Paracoccidioidomycosis is a major neglected mycosis in Brazil, having been diagnosed in 27% of the country's 5560 municipalities. Its disease burden can be inferred by the fact that it comprises 50% of hospital admissions due to all systemic mycoses. The prevalence of this disease

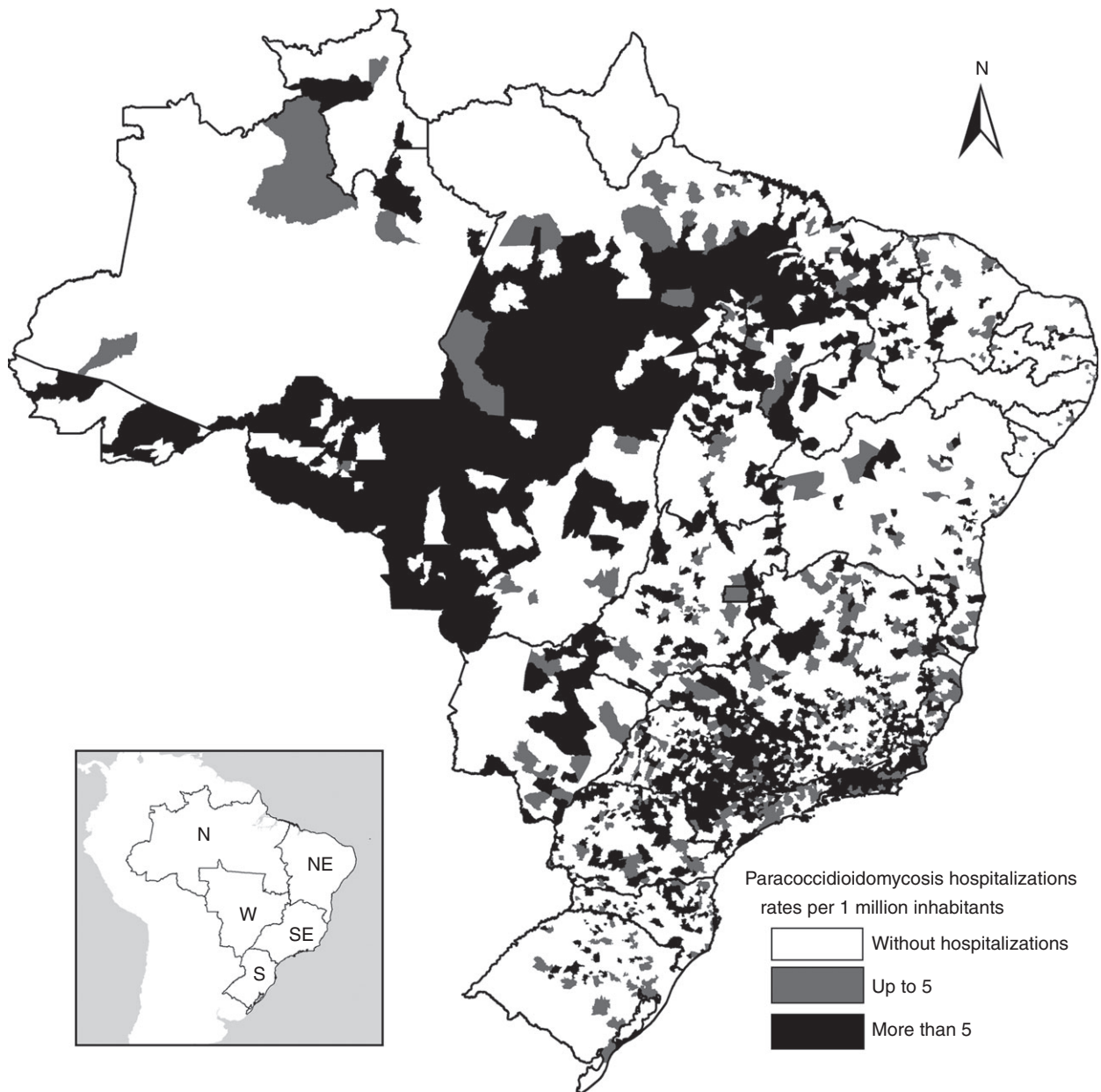


Figure 1 Distribution map of paracoccidioidomycosis hospitalisation rates per 1 million inhabitants according to state and municipality of residence, Brazil, 1998–2006.

over other systemic mycoses is also reflected in mortality statistics, as it is the main cause of death among all mycoses in the country [8, 11].

Similar to what has been reported previously, most cases of paracoccidioidomycosis were diagnosed among men (82% of the total), thus reinforcing the idea that, for biological or behavioural reasons, men are more susceptible to

this mycosis than women [12]. It is possible that under certain occupational conditions, like farming, men are more exposed to inhaling soil dust particles at work, thus increasing the risk of paracoccidioidomycosis infection and disease [3, 12]. The lower frequency of the disease observed in women may also be due to a protective effect of estrogens, as it has been shown by various authors [13].

Table 2 Absolute, age-specific and accumulated frequency distribution of hospitalisations due to paracoccidioidomycosis, according to five age groups, by sex, Brazil (1998–2006)

Age groups	Male		Female		Total		Accumulated frequency
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	
<01 years	15	45.00	18	55	33	0.49	0.49
01–04 years	39	49.00	40	51	79	1.20	1.66
05–14 years	244	60.00	161	40	405	6.00	7.68
15–49 years	2923	81.00	670	19	3593	53.40	61.05
≥50 years	2283	87.00	339	13	2622	39.00	100.00
Total	5504	82.00	1228	18	6732	100	100.00

Paracoccidioidomycosis was less frequently reported in subjects <15 years. Less than 10% of hospital admissions in the period occurred in this age group, with no observable difference between sexes, thus agreeing with previous studies that show that it is only when age progresses over 15 years that men tend to predominate in morbidity and mortality statistics [2, 8, 14, 15].

The analysis of patient flow reveals important deficiencies in the Brazilian network of hospitals capable of diagnosing and treating paracoccidioidomycosis. For instance, 30% of all patients living in the North region had to go elsewhere in search of treatment. The low number of hospital admissions in the North and North-east regions might be explained by difficult access to its services on the part of the rural population and/or due to low quality of the services available. Teresina, the capital of the state of Piauí, represents the major attraction centre of hospital admission for this mycosis in Brazil, as it receives patients from several neighbouring states, especially Maranhão, Pará, Tocantins and Piauí (Figure 2).

The overall 5% hospital death rate due to paracoccidioidomycosis shown in this study is unacceptably high for a disease whose proper diagnosis and treatment can be achieved with minimal technological investment. Regional analysis has shown even higher hospital mortality rates, surpassing 8% of admitted patients [3, 15].

It should be taken into account that tuberculosis persists as the most frequent respiratory disease that requires differential diagnoses with paracoccidioidomycosis among all hospitalised patients because both diseases present similar signs (X-ray images) and symptoms. In Brazil, up to 15% of patients with paracoccidioidomycosis may also have tuberculosis [3, 16, 17]. Mistaken diagnosis is common, thus placing patients' lives at risk by prescribing the wrong set of drugs and by delaying proper treatment [18].

Adding to the challenges involved in the proper diagnoses and reporting of paracoccidioidomycosis in Brazil, other systemic fungal diseases such as cryptococcosis, as

well as lung and bronchial cancer, must be investigated, not only for their clinical and radiologic similarities, but also because these diseases may occur simultaneously [16–18].

An unexpected result of this study was the excessive number of hospitalisation records reported as coccidioidomycosis in the period, totalling 2582 cases. Even more surprising was the fact that a major proportion of these cases was reported from hospitals completely outside the restricted endemic area where this disease is known to occur. Coccidioidomycosis has been diagnosed sporadically in arid zones in North-eastern Brazil, and only a handful of clinical cases were thoroughly investigated [19, 20]. Although we did not have access to complete patient records, we believe that such an inflated total results from the misclassification of disease names and codes at hospital statistics services.

Confusion in the nomenclature of paracoccidioidomycosis and other systemic mycosis by Brazilian practitioners and hospital registers is also evident in the continued use of the inadequate term 'South American blastomycosis', as we have noted in this analysis, even though it was officially abandoned in the 1970s. This introduces errors in national morbidity and mortality information systems, since as we observed in this study, 51% of paracoccidioidomycosis cases were reported as 'blastomycosis', a disease that occurs predominantly in North America [21], or as 'South American blastomycosis', a term that is not even listed in current editions of the International Classification of Diseases nor in any other health information system available in Brazil.

A possible limitation of this study lies in the fact that the analysis was limited to admission records available through the Hospital Information System (SIH) of the Brazilian public health system (SUS). It is well known that the system has incomplete coverage throughout the country. Moreover, classification errors of disease categories may occur due to a number of reasons that could not be controlled in this analysis. Notwithstanding, various

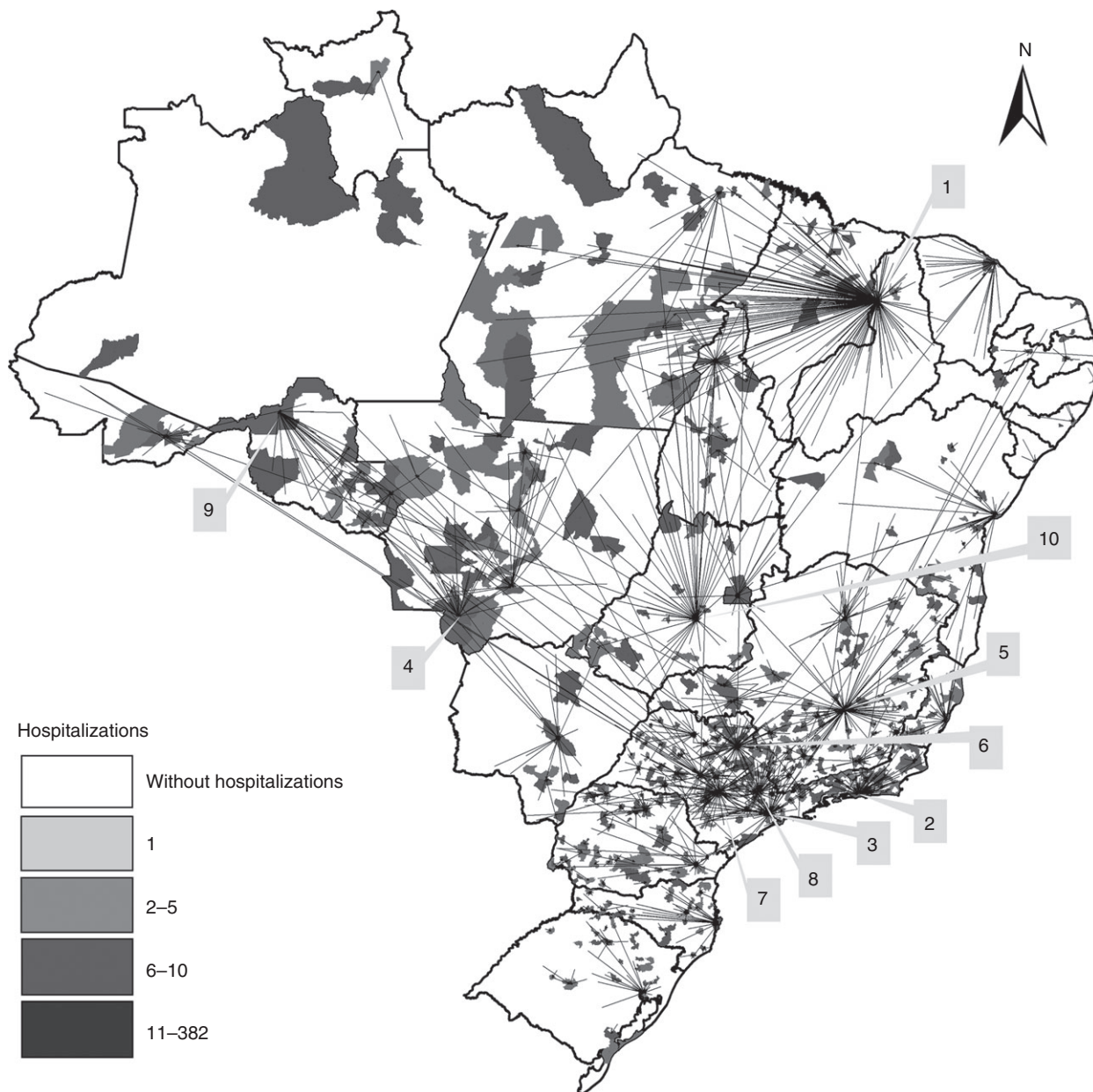


Figure 2 Distribution map of paracoccidioidomycosis hospitalisation flow according to municipality of residence, Brazil, 1998–2006.

authors have shown that, despite its limitations, the system presents internal consistency and can be used in epidemiologic analysis [22, 23]. An inherent limitation of the study is related to the impossibility of estimating either prevalence or incidence rates of paracoccidioidomycosis in the overall population. By only looking at hospitalised cases, the analysis is limited to a relatively small proportion of all cases, as most patients are

handled at outpatient clinics. Notwithstanding, we are confident that our study sheds important light on the epidemiology of an often ignored tropical neglected disease.

Cases of paracoccidioidomycosis outside its known geographic area in tropical and subtropical Latin America have increased in recent years, due primarily to migration to Europe and North America [24, 25]. In addition, travellers returning from endemic regions in

Latin America are increasingly being later diagnosed with the disease in their home countries [26, 27]. Even though cases of this mycosis are increasingly frequent in non-endemic areas, the timely diagnosis and treatment of paracoccidioidomycosis continues being hampered by the lack of experience on the part of medical personnel and limited laboratory resources to carry out adequate serologic and microscopic examinations. Surprisingly, in many endemic countries, including Brazil, patients are also faced with a similar conundrum. The differential diagnosis of individuals presenting chronic respiratory symptoms and a pulmonary infiltrate should include malignancy, tuberculosis, *Pneumocystis* pneumonia, sarcoidosis and other infectious causes. It is only when this complex set of diagnostic procedures are incorporated into hospital routines and physicians perform differential diagnosis on all suspect patients, particularly those coming from endemic areas, that the time span between correct diagnosis and prompt treatment of paracoccidioidomycosis will shorten.

It is worth noting that the traditional view of the geographic distribution of so-called tropical diseases must be reconsidered. For decades, we learned from major medical textbooks that the transmission area of paracoccidioidomycosis was restricted to the south and south-east regions of Brazil, with a few incursions towards the North-east. These same texts also taught young physicians that coccidioidomycosis was restricted to North America. Currently, cases of paracoccidioidomycosis in Amazonian patients are exploding [8, 28], and as more research is performed, more cases of coccidioidomycosis are found in North-eastern Brazil [20]. These are only two examples of how misleading the medical literature has been over decades, particularly with regard to endemic mycoses, what is probably still being reflected in the little attention that fungi diseases receive on the part of physicians, laboratories and research grant agencies.

Latin America is particularly affected by tropical neglected infectious diseases, and paracoccidioidomycosis is part of this list (see [29]). This continental region is characterised by extreme social and ecological diversity that is subject to rapid changes and transformations. Massive migration is no longer an exclusive south-north phenomenon, but intraregional migration is a growing issue. Given this scenario, Latin America has become a hotspot for the emergence and spread of neglected infectious diseases, both inside and outside the region. It is our understanding that the particular challenges involved in the diagnosis and treatment of paracoccidioidomycosis will not be met while the disease continues being perceived as an isolated infectious entity restricted to a few faraway regions of the globe.

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Corresponding Author Ziadir Francisco Coutinho, Escola Nacional de Saúde Pública, Fundação Oswaldo Cruz, Leopoldo Bulhões 1480, Rio de Janeiro, RJ 21041-210, Brazil. E-mail: ziadir@centroin.com.br