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# Epidemiological Aspects of Sporotrichosis Epidemic in Brazil

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**Abstract** Generally, in Brazil, the transmission of sporotrichosis is by traumatic inoculation of fungi with the handling of organic matter. However, since the late 1990s, sporotrichosis in the great metropolitan area of Rio de Janeiro has become an urban endemic/epidemic zoonotic phenomenon, with transmission from infected cats to humans. Middle-aged housewives are the most affected population, particularly from deprived social strata. With the consolidation of the epidemic, vulnerable groups have been affected and the most striking group is people with HIV infection because of the superimposed burdens of both infections. Other states in Brazil have also presented zoonotic cases, however, with smaller dimensions. *Sporothrix brasiliensis* is the primary species involved in this hyperendemic. We believe that the combination of susceptible hosts, a virulent infecting species, and the absence of an effective public health structure are some of the possible associated factors that resulted in this catastrophe.

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**Keywords** Brazil · Rio de Janeiro · Epidemiology · Transmission · Zoonosis · Cat · Hyperendemic · Soil · Sporotrichosis · Urban area · HIV infection · HIV/AIDS epidemic · Opportunistic infection · Notifiable disease · Deprived social strata · Pet · Molecular epidemiology · *Sporothrix schenckii* · *S. schenckii* complex · *S. brasiliensis* · *S. globosa* · *S. mexicana* · T3B fingerprinting · Calmodulin gene · MALDI-TOF MS

## Introduction

Brazil is a country of continental dimensions. The southeast and south regions are more urbanized, populated, and developed than the other regions, which have their own geographical features. The northern region has an extensive exuberant tropical forest. The northeast has a drier climate, and the midwest has tropical savannas and plateaus.

Lutz and Splendore first reported sporotrichosis in Brazil in 1907. They identified the first case of naturally infected animals in rats [1]. Terra and Rabelo (1912) described the first case of sporotrichosis in Rio de Janeiro, and since that report, isolated cases have been reported in different regions of the country [2]. Naturally acquired feline sporotrichosis was only reported in Brazil in 1956 [3]. Because sporotrichosis is not a reportable disease in Brazil, there is little information on the incidence of this disease, and the known data are from case reports, the majority of which were from the southeast and southern regions (Fig. 1). However, this parameter may reflect the development of medical resources in these regions because favorable conditions exist for the growth of *Sporothrix* and the acquisition of infection in the whole country. In different case series, classical transmission of sporotrichosis by traumatic inoculation of fungi occurs with the handling of organic matter. The majority of cases are observed among adult men in contact with soil as

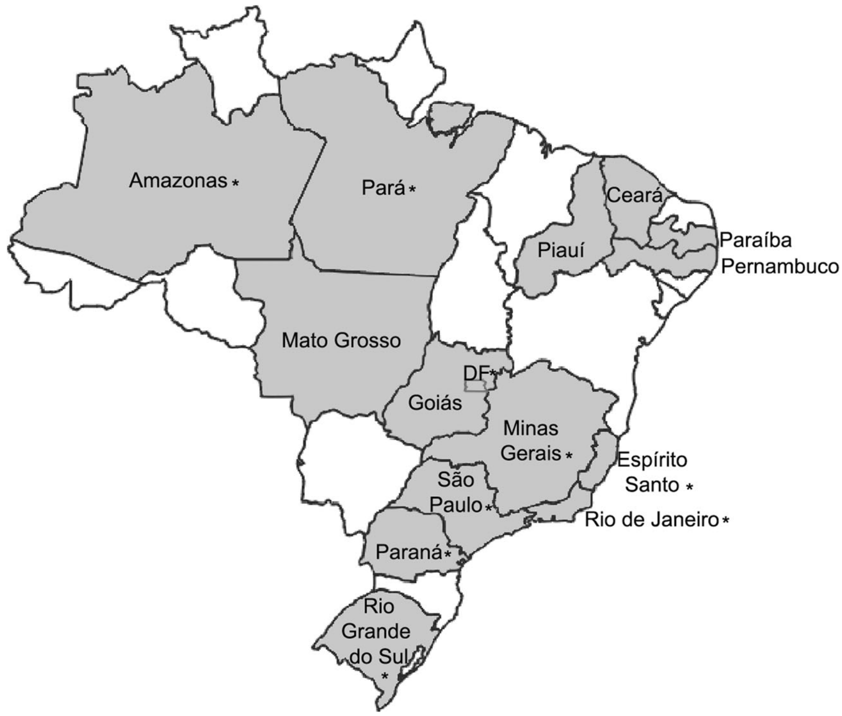


**Fig. 1** Map of Brazil indicating the Brazilian states in which epidemiological studies of sporotrichosis have been conducted. Molecular epidemiology studies of *Sporothrix* spp. strains have been performed in states depicted in *gray*, and those marked with *asterisks* have human and/or animal cases of sporotrichosis reported in the literature

an occupational hazard [4, 5]. Few outbreaks of feline zoonotic sporotrichosis have been reported in São Paulo before the 1990s, with case reports in cats, their owners, and the veterinarians [6, 7]. In Rio Grande do Sul State, the hunting of armadillos is a mechanism of both environmental and zoonotic transmission to humans [8]. Epidemiological survey studies with the sporotrichin skin test detected subclinical infection in approximately one third of individuals tested from both rural and urban areas. The positive reactions were primarily in older people who had contact with soil and/or plants [9, 10].

## The Zoonotic Epidemic

Around the world, over the years, different outbreaks of sporotrichosis were reported, like the largest one in the 1940s in the gold mines in South Africa [11]; the cases related to the exposure to contaminated sphagnum moss on the pine trees in the USA [12]; and the contact with contaminated hay in the USA in the 1990s [13] and in western Australia in the 2000s [14]. Other countries present high regional endemic levels of sporotrichosis, like Peru [15], India [16], Mexico [17], Japan [18], and China [19], but none have the zoonotic transmission as the keystone for the maintenance of the endemic levels. Argentina and Uruguay, on the border with Brazil [20, 21], and Malaysia [22] may be exceptions, with cases mainly related to the contact with armadillos and cats, respectively.

Since the late 1990s, sporotrichosis in the great metropolitan area of Rio de Janeiro, southeast Brazil, has become an urban endemic/epidemic zoonotic phenomenon, with transmission from infected cats (Fig. 2) to humans (Fig. 3) [23, 24, 25•, 26•]. This high prevalence of cases has created a sporotrichosis belt in this region [25•]. Middle-aged housewives, followed by retired people and students, are the most affected population, particularly from deprived social strata [24]. The predominant route of infection involves inoculation through the skin by bites and scratches from cats with sporotrichosis, although in some cases, the cats are apparently healthy or there is no recognized trauma [23, 24]. The number of cases has continuously increased for more than 17 years, surpassing 5000 cases on record at the Evandro Chagas National Institute of Infectious Diseases (INI), a Reference Unit in Rio de Janeiro.

With the consolidation of the epidemic, vulnerable groups have been affected. The elderly, pregnant women, and children have presented with important clinical manifestations or a serious dilemma when treating this mycosis [27•, 28, 29]. However, the most striking group is people with HIV infection because of the superimposed burdens of both infections. A greater than proportional increase in patients with sporotrichosis co-infected with HIV has been documented. Recently, we assessed 48 patients co-infected by *Sporothrix* spp. and HIV and 3570 patients with sporotrichosis over time in one of the largest isolated or associated cohorts. The sociodemographic characteristics of the co-infected group were mainly young males, which may reflect the dynamics of the HIV/AIDS epidemic in Brazil. A predominance of non-white patients (70.8 %) and a low education level was also present in this group, indicating a more disadvantaged group for the sporotrichosis scenario. It is remarkable that approximately half of the patients were simultaneously diagnosed with the two infections due to the presence of opportunistic

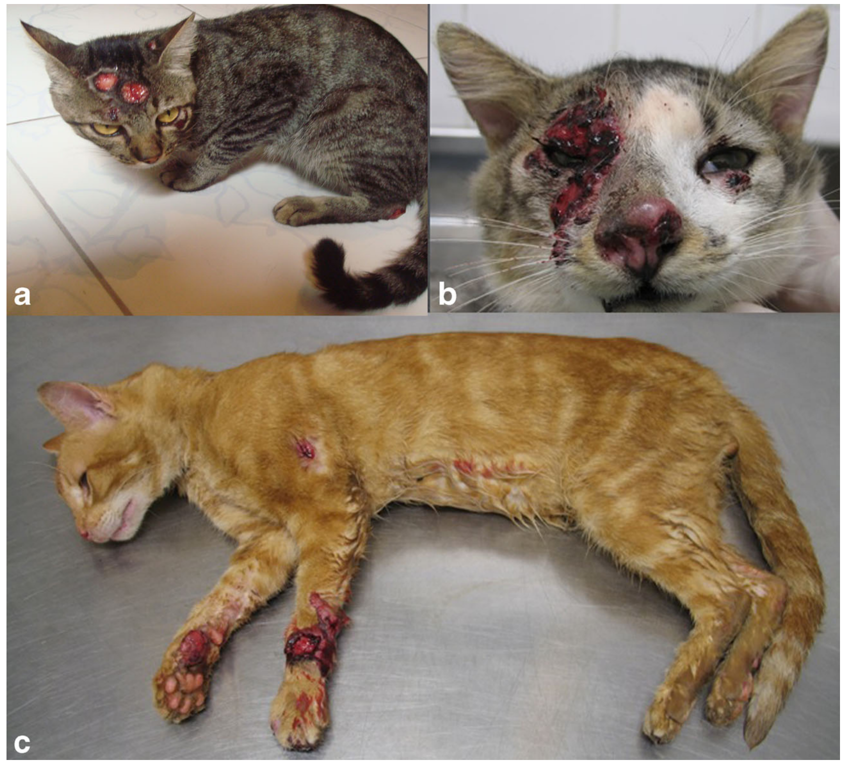


**Fig. 2** Feline sporotrichosis. **a** Lesions on the head and posterior left limb*. **b** Mucocutaneous lesions on the face**. **c** Disseminated cutaneous lesions**. (Images:*courtesy of Hildebrando Montenegro and Elisabete Aparecida da Silva—Centro de Controle de Zoonoses de São Paulo (COVISA/SMS/PMSP), São Paulo, SP, Brazil; **Courtesy of Dr. Sandro Antonio Pereira and Dr. Isabella Dib Ferreira Gremião—Laboratório de Pesquisa Clínica em Dermatozoonoses em Animais Domésticos—Lapclin-Dermzoo/INI/Fiocruz, Rio de Janeiro, RJ, Brazil.)

sporotrichosis or other HIV-related conditions and entered into HIV care relatively late, which denotes a worse prognosis. Furthermore, HIV infection aggravates sporotrichosis, with a higher incidence of severe disseminated cases and a greater number of hospitalizations and deaths. Today, sporotrichosis, irrespective of HIV infection, is an important cause of hospitalization and mortality at our institute. In 2008, sporotrichosis was the primary mycosis associated with HIV infection in our institute,

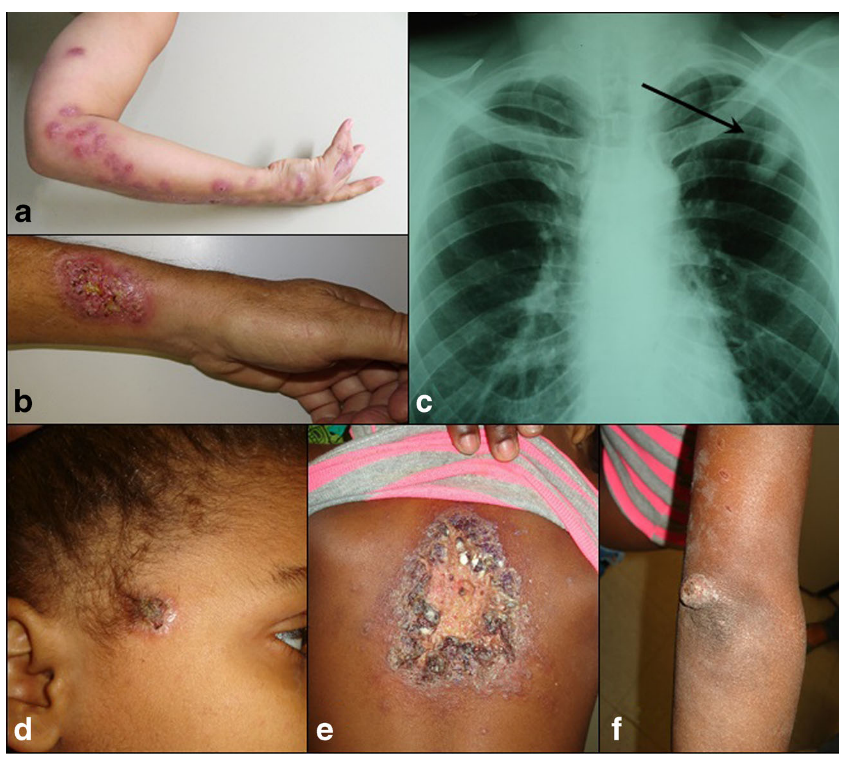


**Fig. 3** Clinical forms of human sporotrichosis. **a** Lymphocutaneous on the superior limb—commonest presentation. **b** Fixed cutaneous on the superior limb. **c** Pulmonary extracutaneous (the *arrow* shows a cavitation in the apex of the left lung)—extremely rare form. **d**–**f** Disseminated cutaneous (face, trunk, and superior limb of a girl)

supplanting the classical opportunistic mycoses associated with AIDS, cryptococcosis, and histoplasmosis [26•, 27–30].

Since July 2013, because of the hyperendemic status and the serious health issue of sporotrichosis in Rio de Janeiro, the disease became notifiable in the state. The several following considerations for this poverty scenario are important: the zoonotic potential from cats to humans; their natural behavior of circulating in the neighborhood, often getting involved in fights with other animals, leads to the spread of the mycosis; the proliferation of cats in squares and vacant lots, forming numerous colonies without any sanitary control in Rio de Janeiro; the lack of infrastructure for their treatment; and the improper treatment of sick or dead cats by their current/former owners in the majority of cases [23, 24, 25•, 26•, 27•, 28, 29, 30•, 31].

States neighboring Rio de Janeiro have also presented zoonotic cases since 2010, although these cases may be underreported due to the lack of notification in the rest of the country. This spread was expected as a characteristic of the epidemic, involving an easily carried pet. Although there are no indexed publications regarding official human cases to date, there appears to be an increase in the number of cases correlated to contact with sick cats in the São Paulo great metropolitan region and inner municipalities of the state. After work promoted by the State Health Secretariat to actively identify both feline and human cases of the disease on a home-by-home basis, Silva and collaborators reported 11 humans affected in 2011 and 2012 [32]. In a recent study in the metropolitan area of São Paulo, 163 cases of feline sporotrichosis were reported from 2011 through 2013 [33•]. A study from Bauru, a city more than 300 km from the city of São Paulo, reported 25 human patients treated of sporotrichosis from 2003 to 2013, ten of whom were related to previous contact with sick cats [34]. In the metropolitan area of Vitória, Espírito Santo State, in the southeast, there was a report of a family outbreak of sporotrichosis [35, 36•]. In Juiz de Fora, in Minas Gerais State, there were also cases of the disease related to sick cats (personal report from Dr. Marcelino Martins). In the mid-western part of the country, in Brasília, the federal district of Brazil, there was a report of another family outbreak involving three people, likely related to their undiagnosed cat, which died with several ulcerated cutaneous lesions [37]. In the most southern state of Brazil, Rio Grande do Sul, two cities have concentrated human cases correlated to zoonotic transmission [38]. In Pelotas, Madrid et al. [39] reported 15 domestic cats and 3 humans, 2 pet owners, and 1 veterinary clinic attendant, diagnosed with sporotrichosis between 2002 and 2006. In Rio Grande, although no human cases have officially been reported yet, 64 felines were confirmed with sporotrichosis from June 2010 through June 2013, based on a study at the Federal University of Rio Grande [40].

## Molecular Epidemiology

During the last decade, the advances of molecular techniques and improved *Sporothrix* genetic information brought about a new approach for the epidemiology of sporotrichosis in Brazil, molecular epidemiology. The use of molecular tools allowed for the typing of *Sporothrix* strains from 14 states and the Brazilian Federal District [27•, 28, 29, 30•, 31, 32, 33•, 34, 35, 36•, 37–41], indicating that sporotrichosis in Brazil is more widespread than previously thought (Fig. 1).

For over a century, *Sporothrix schenckii* was considered to be an ascomycetous dimorphic organism (Ascomycota, Pyrenomycetes, Ophiostomatales, Ophiostomataceae) and was recognized as the sole agent of sporotrichosis [42]. Previous studies using mitochondrial DNA (mtDNA) analysis reported heterogeneity profiles in *S. schenckii* strains [43, 44]. Several molecular studies using different methodologies, such as restriction fragment length polymorphism (RFLP) from different gene targets, random amplified polymorphic DNA (RAPD) [43, 45, 46], DNA sequencing of the internal transcriber spacer (ITS) regions of the ribosomal RNA (rRNA) [46, 47], PCR targeting of the DNA topoisomerase II gene [48], amplified fragment length polymorphism (AFLP) [49], and M13 PCR fingerprinting [47] have shown that *S. schenckii* isolated from distinct geographic regions of the world present with different genetic characteristics, supporting the hypothesis that they do not belong to the same species.

Later, based on phenotypic and molecular aspects, it was proposed that *S. schenckii* is a complex of six distinct species, *Sporothrix brasiliensis*, *Sporothrix mexicana*, *Sporothrix globosa*, *S. schenckii sensu stricto*, *Sporothrix luriei*, and *Sporothrix pallida* [50–52]. In the last few years, all of the species of this complex were recognized as agents of sporotrichosis [27•, 28, 53–56]. Molecular studies concluded that β-tubulin gene sequence analysis is highly recommended for taxonomic studies of *Sporothrix* species isolated from the environment [50], and calmodulin gene sequence analysis is recommended for *Sporothrix* species of clinical origin [51]. To the best of our knowledge, all six species of this complex have been described in Brazil [55, 57]. However, human cases of sporotrichosis in our country were only caused by *S. brasiliensis*, *S. globosa*, *S. mexicana*, and *S. schenckii* [27•, 28, 29, 30•, 31, 32, 33•, 34, 35, 36•, 37–57].

Before the description of these species within the *Sporothrix schenckii* complex, the most common method for *Sporothrix* typing was mtDNA RFLPs [43]. This method is based on the digestion of the DNA isolated from *Sporothrix* mitochondria by the restriction enzyme *Hae*III. As of 2009, 32 different types of mtDNA were described for *S. schenckii sensu lato* strains worldwide [58]. However, few Brazilian strains were typed by this method. Three strains belonged to type 3 mtDNA and one strain to type 4 mtDNA. Notably, these groups are phylogenetically distinct from each other, such that type 3 mtDNA is within group A and type 4 is within group B [58]. Unfortunately, this study does not provide information about the Brazilian state from which these strains were isolated.

Two other molecular studies were performed without the classification of strains within the *S. schenckii* complex, all using strains from the epidemic zoonotic area of sporotrichosis in Rio de Janeiro. In the first study, the authors used ITS sequencing and M13 PCR fingerprint analysis for the molecular typing of 88 strains from 59 different human sporotrichosis cases and concluded that the strains from Rio de Janeiro originated from a common source and that different subtypes of *Sporothrix* were not related to different clinical presentations of the patients [47]. The second study used RAPD and M13 PCR fingerprinting in 19 human and 25 related cats from this endemic area, confirming the similarity between human and animal strains, indicating domestic cats as the vehicle for sporotrichosis dissemination in the Rio de Janeiro metropolitan area [59]. After the description of the *Sporothrix* complex, there have been no studies using molecular approaches correlating cat strains with the strains isolated from their owners or veterinarians, leaving a gap in this field. Therefore, the application of molecular tools for *Sporothrix* strain typing at the species level is of great importance for a better understanding of sporotrichosis epidemics.

After the description of the *Sporothrix* complex, several molecular tools that were previously applied for *S. schenckii sensu lato* strains were improved by research groups and used for the identification of species in this complex [60, 61]. The first study described a PCR-RFLP technique in which the calmodulin gene is cut with the restriction enzyme *Hha*I as an alternative approach for the identification of four species in this complex (*S. schenckii sensu stricto*, *S. brasiliensis*, *S. globosa*, and *S. luriei*). *S. mexicana* and *S. pallida* generated similar electrophoretic profiles being and were difficult to differentiate them using this technique [60]. Clinically relevant *Sporothrix* species can also be recognized by the ITS sequence analysis, and this study reported that an increased geographic sampling did not affect delimitation success in the clinical clade of the *S. schenckii* complex [61].

The two major species causing sporotrichosis in Brazil, *S. brasiliensis* and *S. schenckii*, have been studied using molecular methods and showed a different pattern of reproduction and spread in the epidemic areas of sporotrichosis in our country. Using comparative genomic approaches of the *MAT* loci in *Sporothrix* strains, *S. brasiliensis* showed an asexual profile of propagation because they originated from a single mating type. Moreover, calmodulin sequencing and variability of the intergenic region of the mitochondrial DNA between *COX2* and *ATP9* also support that *S. brasiliensis* is a clonal species. The same molecular studies, however, showed that *S. schenckii* is a recombinant species that likely undergoes sexual reproduction in nature, generating strains with a high degree of genetic variability, even within a restricted geographic region [41–61, 62•].

The pulse field gel electrophoresis (PFGE) technique was also useful in the study of polymorphisms in the *S. schenckii* complex at the chromosomal level. This molecular tool showed intra- and interspecies variations in the chromosome number and size of Brazilian *Sporothrix* strains. For instance, *S. schenckii* showed four to seven chromosomes, ranging in size from 2 to 7 Mb. Its sibling species, *S. brasiliensis*, however, presented five to seven chromosomes, varying from 2.9 to 7 Mb, but with few polymorphisms in the karyotype compared to *S. schenckii*. The other studied species, *S. mexicana* and *S. luriei*, presented four and six chromosomal bands in the PFGE, respectively [63].

Using a haplotype network approach based on the calmodulin and ITS sequences of 22 strains of *S. brasiliensis* and 39 strains of *S. schenckii*, it has been confirmed that the epidemic species *S. brasiliensis* has a low genetic diversity that is correlated to a small variability of in vitro antifungal susceptibility to itraconazole and posaconazole. By contrast, the *S. schenckii* strains were clustered into ten different haplotypes that correlates with the high variability for the minimal inhibitory concentrations to the most commonly drugs used for the treatment of sporotrichosis in Brazil [64].

Regarding feline sporotrichosis in Brazil, several studies are of particular interest. The first study identified feline *Sporothrix* strains at the molecular level and showed that *S. schenckii*, *S. brasiliensis*, and *S. pallida* are agents of sporotrichosis in cats from Rio Grande do Sul. Moreover, *S. luriei* was identified in a case of canine sporotrichosis in this same Brazilian state [55]. Another study, using 32 *Sporothrix* spp. strains from four Brazilian states, revealed a high prevalence of *S. brasiliensis* among cats [65]. This is similar to a previous report using RAPD and M13 fingerprinting [59], showing similar genotypes between feline and human strains of *Sporothrix*, thereby confirming that sporotrichosis in zoonotic areas is transmitted primarily by cats [59, 65]. Further studies revealed feline sporotrichosis cases due to *S. brasiliensis* in Espírito Santo State [36•] and São Paulo [33•]. In other countries, like Peru [66], the USA [67], and Malaysia [22], feline cases have also been reported and cat ownership has been a risk for developing sporotrichosis. Different from Brazil, the implicated species seems to be *S. schenckii sensu stricto*, according to some molecular reports from these regions.

Currently, there is still a gap in techniques that allow for the identification and typing of all species included in the *Sporothrix* complex. This gap was partially filled by some studies. A PCR fingerprinting using the universal primer T3B was reported by Oliveira and collaborators [68] to distinguish species of the *Sporothrix* complex. The T3B fingerprinting generated clearly distinct banding patterns, allowing for the correct identification of all 35 clinical isolates at the species level, the results of which were confirmed by partial CAL gene sequence analyses. Overall, there was a 100 % agreement between the species identification using both genotypic methodologies. These profiles also accurately distinguished the species that were misidentified by phenotypic analysis. The proposed identification technique is simple, reliable, more rapid, less expensive, and requires less technical expertise than sequencing. This methodology also supports *Sporothrix* typing because small variations within band patterns are observed within species, particularly *S. brasiliensis*. Furthermore, this methodology was also validated with environmental samples [69].

Matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) was used to establish a reference database for the identification of 70 environmental and clinical isolates of the *Sporothrix* complex. The MALDI-TOF MS of the strains *S. brasiliensis*, *S. globosa*, *S. mexicana*, *S. schenckii sensu stricto*, *S. luriei*, and *S. pallida* enabled the identification of all of the isolates at the species level, as confirmed by partial calmodulin gene sequence analyses [70•]. Moreover, dendrograms can be generated with the software, allowing for future epidemiologic studies.

## Conclusions

Zoonotic sporotrichosis is hyperendemic in urban Rio de Janeiro and is spreading to other neighbor and distant urban areas of Brazil. *S. brasiliensis* is the primary species involved in this hyperendemic. The molecular epidemiology of *Sporothrix* is critical for the description and understanding of these changes. In the dynamics of the infection, the combination of susceptible hosts, a virulent infecting species, and the absence of an effective public health structure are some of the possible associated factors that resulted in this catastrophe. It is of fundamental importance to continue studies on the ecoepidemiology and the clinical characteristics of sporotrichosis. For the control of a zoonosis, such as sporotrichosis in Brazil, there is a need to prioritize and continue health policies to achieve success.

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**Compliance with Ethics Guidelines**

**Conflict of Interest** The authors declare that they have no conflict of interest

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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