



## *Sporothrix brasiliensis* infecting cats in northeastern Brazil: New emerging areas in Paraíba state

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**ABSTRACT:** Sporotrichosis is a subcutaneous mycosis caused by fungus of the *Sporothrix* complex, and in Brazil the main species reported is *Sporothrix brasiliensis*, of which the diseased cat is the transmitter. Although, its occurrence has increased in the state of Paraíba, Brazil, since 2016, data on the disease in this state are limited. Therefore, this research aimed to identify molecularly isolates of *Sporothrix* spp. from domestic cats from cities in Paraíba, and in this way to expand the understanding of the disease in the state. Thirty-nine samples were analyzed, obtained from skin lesions of domestic felines, from the following cities in Paraíba: João Pessoa, Pilões, Patos, Areia, Bananeiras and Guarabira. Cytological analysis was performed to screen the samples, followed by fungal culture, and the molecular characterization of the isolates was performed, using the species-specific Polymerase Chain Reaction (PCR) or partial sequencing of the calmodulin gene. All isolates were identified as *S. brasiliensis*. The sequencing showed 100% similarity to the *S. brasiliensis* CBS 120339 strain. In view of this, it is concluded that in the study areas the species involved in cases of feline sporotrichosis is *S. brasiliensis*, its presence in Paraíba demonstrated the spread of the agent in regions distant from the epicenters in Brazil, alerting to the possible occurrence of zoonotic outbreaks similar to those found in the South and Southeast regions of the country. In addition, it highlights the emerging role of felines in the transmission of sporotrichosis in new endemic areas of Brazil.

**Key words:** sporotrichosis, geographic expansion, cats, molecular identification.

## *Sporothrix brasiliensis* infectando felinos no nordeste do Brasil: novas áreas emergentes no estado da Paraíba

**RESUMO:** A esporotricose é uma micose subcutânea causada por fungos do complexo *Sporothrix*, e no Brasil a principal espécie relatada é *Sporothrix brasiliensis* da qual o transmissor é o gato doente. Embora sua ocorrência tenha aumentado no estado da Paraíba, Brasil, desde 2016, os dados sobre a doença neste estado são limitados. Diante disso, esta pesquisa teve por objetivo identificar, molecularmente, isolados de *Sporothrix* spp. procedentes de felinos domésticos de cidades da Paraíba, e dessa maneira expandir a compreensão da enfermidade no estado. Foram analisadas 39 amostras, obtidas de lesões cutâneas de felinos domésticos, oriundas das seguintes cidades paraibanas: João Pessoa, Pilões, Patos, Areia, Bananeiras e Guarabira. Realizou-se análise citológica, para triagem das amostras, a seguir cultura fúngica, e posteriormente a caracterização molecular dos isolados, utilizando a Reação em Cadeia da Polimerase (PCR), espécie-específica ou sequenciamento parcial do gene calmodulina. Todos os isolados foram identificados molecularmente como *S. brasiliensis*. O sequenciamento demonstrou 100% de similaridade com a cepa *S. brasiliensis* CBS 120339. Contudo, conclui-se que nas áreas do estudo a espécie envolvida em casos de esporotricose felina é *S. brasiliensis*, sua presença na Paraíba demonstra a disseminação do agente em regiões distantes dos epicentros no Brasil, alertando para a possível ocorrência de surtos zoonóticos, semelhantes aos encontrados nas regiões Sul e Sudeste do país. Além disso, destaca o papel emergente dos felinos na transmissão da esporotricose em novas áreas endêmicas do Brasil.

**Palavras-chave:** esporotricose, expansão geográfica, gatos, identificação molecular.

## INTRODUCTION

Sporotrichosis is a mycosis of worldwide importance for public health, caused by dimorphic fungi of the genus *Sporothrix* (ZHANG et al., 2015).

This genus includes species of medical importance such as *S. schenckii* sensu stricto, *S. brasiliensis*, *S. globosa*, and *S. luriei*, which constitute the so-called pathogenic clade (RODRIGUES et al., 2020). Moreover, *S. mexicana*, *S. chilensis*, and *S. pallida*

may accidentally infect humans and animals, thus having the potential to impact the health of immunosuppressed populations (DIAS et al., 2011; MORRISON et al., 2013; RODRIGUES et al., 2016; THOMSON et al., 2019).

Prevalence and geographic distribution vary among *Sporothrix* species, reflecting the interaction among host species, pathogens, and environmental conditions (ZHOU et al., 2014). *S. brasiliensis* is highly prevalent in South America and was considered restricted to Brazil (RODRIGUES et al., 2014; GREMIÃO et al., 2017), but it has also been recently reported in Argentina, Paraguay and England (GARCÍA DUARTE et al., 2017; CÓRDOBA et al., 2018; RACHMAN et al., 2022). In contrast, *S. schenckii sensu stricto* is widely distributed in the Americas, Africa, and to a lesser extent, in Asia and Europe (ZHANG et al., 2015). *S. globosa* is frequently reported in Asia, especially in China, and it has also been reported in Europe (MOUSSA et al., 2017). Finally, *S. luriei* has been reported in Brazil, India, Africa, and Italy (AJELLO & KAPLAN, 1969; ALBERICI et al., 1989; PADHYE et al., 1992; OLIVEIRA et al., 2011).

*Sporothrix* spp. have been isolated from cats, dogs, armadillos, and aquatic animals; however, studies on disease outbreaks in Brazil indicate the existence of an epizootic sporotrichosis in the feline population (RODRIGUES et al., 2016), in addition, sick cats are the main transmitters of zoonotic sporotrichosis (GREMIÃO et al., 2017), and transmission involving cats has been increasingly reported (RODRIGUES et al., 2020). The metropolitan region of Rio de Janeiro is hyperendemic for zoonotic sporotrichosis, especially by *S. brasiliensis* (GREMIÃO et al., 2017). Moreover, a molecular analysis of *Sporothrix* strains from the nearby states of Minas Gerais, São Paulo, Rio Grande do Sul, and Paraná indicated a high prevalence of *S. brasiliensis* among cats with sporotrichosis, which shows how the disease has spread across the country (RODRIGUES et al., 2020).

In the state of Paraíba, feline sporotrichosis was first reported by NUNES et al. (2011) in a cat from the municipality of Itaporanga, in the state's backwoods. However, many aspects of human and animal sporotrichosis still need to be clarified in the state. Therefore, this study performed the molecular identification of *Sporothrix* spp. isolated from clinical cases of feline sporotrichosis from different locations in Paraíba, Brazil.

This study was conducted between June 2018 and November 2020, and 39 samples were

collected from domestic cats from the following cities in Paraíba: João Pessoa (n=29), Pilões (n=4), Patos (n=3), Areia (n=1), Bananeiras (n=1), and Guarabira (n=1). The samples were obtained by rubbing a sterile swab on the surface of skin lesions of cats with suspected sporotrichosis. Initially, a cytopathological analysis was performed, and those samples that were positive in this screening test were sent for mycological analysis, the isolates were initially processed at the Preventive Veterinary Medicine Laboratory of the Agricultural Sciences Center of the Federal University of Paraíba. Each sample was cultured on Sabouraud dextrose agar with chloramphenicol and incubated at 25 °C, and its growth observed daily for 15 days. After fungal growth, slide cultures were prepared to observe fungal micromorphological aspects. Samples with *Sporothrix*-compatible morphology were then inoculated into 1.5-ml Eppendorf tubes containing Sabouraud dextrose agar culture medium with chloramphenicol, and maintained at 25 °C for 7 days. After growth, they were stored at 4–8 °C until further shipping to the Evandro Chagas National Institute of Infectious Diseases, Rio de Janeiro, Brazil, where the isolates were molecularly characterized.

Molecular analysis was performed on 39 samples. For this, the samples were cultured in potato dextrose agar (PDA) medium, incubated at 30 °C for seven days, and total DNA extraction was performed from colonies of *Sporothrix* spp., in the filamentous phase, from which fungal cells were collected and macerated, after freezing with liquid nitrogen. Cell lysis was performed with TBE buffer (1M Tris pH 8, 50mM EDTA, 20% sucrose), and DNA precipitation with 100% ethanol and 3M sodium acetate (MUNIZ et al., 2010). The isolates were identified using species-specific polymerase chain reaction (PCR) primers for *S. brasiliensis*, *S. schenckii*, and *S. globosa* (RODRIGUES et al., 2015). The six isolates for which species-specific PCR amplification failed were identified using partial sequencing of the calmodulin gene (CAL), following MARIMON et al. (2007). Automated sequencing was performed using the platform at Fundação Oswaldo Cruz (PDTIS/FIOCRUZ, Brazil). Sequences of DNA strands were generated and edited using Sequencher ver. 4.9 software package (Genes Codes Corporation, USA), followed by alignment using MEGA version 4.0.2. The sequences herein obtained were compared with *Sporothrix* sequences from NCBI GenBank using the Basic Local Alignment Search Tool (BLAST). All phylogenetic analyses were performed using maximum likelihood in MEGA (version 6.0; <http://www.megasoftware.net/>). Calmodulin sequences

from the following strains were included in the alignment: *S. brasiliensis* CBS 120339, *S. schenckii* FMR 8604, *S. globosa* FMR 8600, *S. luriei* CBS 937.72, *S. pallida* CBS 302.73, *S. mexicana* FMR 9108, and *S. chilensis* Ss470. The calmodulin sequence of *Grossmannia serpens* CBS 141.36 was used as an outgroup. Tree significance was evaluated using the bootstrap confidence test with 1,000 repetitions (FELSENSTEIN, 1985). All sequences from isolates included in the genotypic analysis were deposited in GenBank under the accession numbers MZ261813, MZ261814, MZ261815, MZ261816, MZ261817, and MZ261818.

The sporotrichosis diagnosis of the 39 cats included in the present study was molecularly confirmed as *S. brasiliensis*. Table 1 shows the city of origin, identified species and molecular technique used in each *Sporothrix* isolate from domestic cats in the state of Paraíba. Its geographic distribution and the number of samples identified by municipality are shown in figure 1.

The phylogenetic tree of the CAL locus obtained using maximum likelihood revealed three distinct and major clades. All six *Sporothrix* isolates from Paraíba were grouped into the *S. brasiliensis* clade (confidence level of 98%). Moreover, the analysis using BLAST showed a 100% similarity to the *S. brasiliensis* CBS 120339 strain.

The first recorded case of *Sporothrix* infection in animals was reported in Brazil in 1907 (LUTZ & SPLENDORE, 1907). Until 1990, only isolated cases, small outbreaks, and case series were recorded in the country (BARROS et al., 2001). From the late 1990s, the route of transmission of the disease, which was predominantly classical sapronotic, changed significantly to the alternative route involving animal-to-animal and zoonotic transmissions. This led to an alarming increase in cases of sporotrichosis in cats in the city of Rio de Janeiro, which is the epicenter of the disease in Brazil, with a record of 6,060 cases in cats between 1907 and 2020 (RABELLO et al., 2022). Since then, feline sporotrichosis epizootic, whose center of origin is Rio de Janeiro (DE CARVALHO et al., 2021), has spread geographically, and affected many neighboring states, such as Minas Gerais, São Paulo, Espírito Santo, Rio Grande do Sul and also states at great distances, in the northeast region as reported in the present study (RODRIGUES et al., 2020) where *S. brasiliensis* was detected in clinical isolates from cats in the state of Paraíba, demonstrating the geographic spread of the species responsible for the sporotrichosis epizootic in Brazil.

Epidemiological studies have reported the presence of *S. brasiliensis* species in humans in the northeastern region of Brazil since 1997 (RODRIGUES et al., 2014). However, studies on those species that cause feline sporotrichosis in the northeastern region have not yet been published. In this study, *S. brasiliensis* was molecularly detected for the first time in clinical isolates from cats in the northeastern region of Brazil, specifically in the state of Paraíba.

All cat samples analyzed in this study were identified as belonging to the *S. brasiliensis* species, and this supports the hypothesis that this species is predominant in the feline sporotrichosis epizootic in Paraíba, as it occurs in other Brazilian states. Public health authorities in the state were alerted because feline *S. brasiliensis* caused a public health emergency of international interest in the southern and southeastern regions of Brazil due to the potential for zoonotic transmission (RODRIGUES et al., 2016; GREMIÃO et al., 2020). Moreover, *S. brasiliensis* is considered the most virulent species of *Sporothrix* in animals and humans (ARRILLAGA-MONCRIEFF et al. 2009; RODRIGUES et al., 2016). In cats, it often causes worrisome conditions with multiple skin lesions and frequent infestation of the nasal mucosa along with respiratory signs (GREMIÃO et al., 2014). In humans, it is often associated with rare and more severe forms of the disease, especially in immunocompromised patients (OROFINO-COSTA et al., 2013). In a study on experimental infection in a mouse model, *S. brasiliensis* was the only species that caused death when the inoculum was low; furthermore, compared to *S. schenckii sensu stricto* and *S. globosa* (ARRILLAGA-MONCRIEFF et al., 2009), it had a greater capacity for tissue dissemination and massive infiltration of fungal cells in the tissues studied, and compared to *S. schenckii sensu stricto*, it caused more severe disease in mice (BATISTA-DUHARTE et al., 2018).

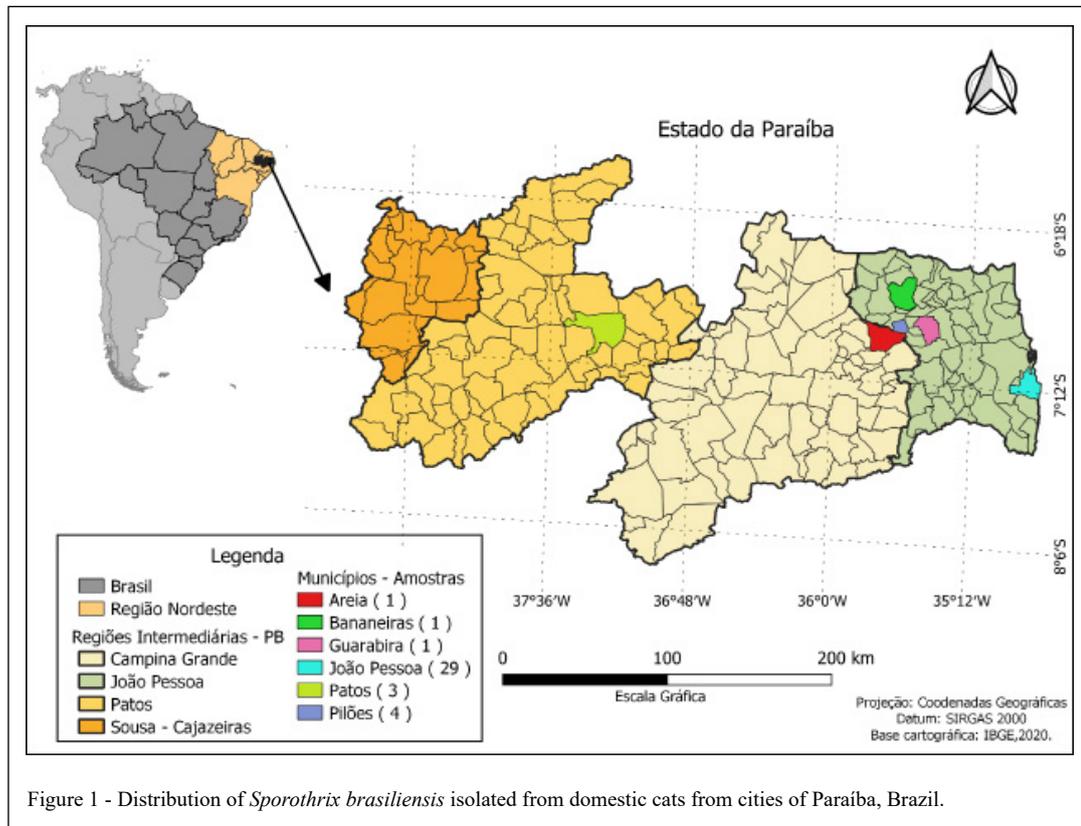
In this research, *S. brasiliensis* was detected in João Pessoa, the capital of Paraíba, and in cities in the interior of the state, which shows the spread of the pathogen in three different intermediate regions with different vegetation and climatic conditions, namely João Pessoa, Campina Grande and Patos. This finding should alert the public of the possible alarming spread of the disease in the interior of the state.

Feline sporotrichosis was first reported in Paraíba in 2011 (NUNES et al., 2011). It appeared insidiously in the following years, with an increase in the number of cases from 2016 onwards, given that there are epidemiological surveys and reports from

Table 1 - City of origin, identified species and molecular method used for each *Sporothrix* isolate (n=39) from domestic cats in Paraíba, Northeastern Brazil.

Isolates	City of origin	Species	Method	GenBank accession no. (CAL)
PB 2	Patos	<i>S. brasiliensis</i>	species-specific PCR	-
PB 6	João Pessoa	<i>S. brasiliensis</i>	species-specific PCR	-
PB 7	Pilões	<i>S. brasiliensis</i>	species-specific PCR	-
PB 8	Pilões	<i>S. brasiliensis</i>	species-specific PCR	-
PB 9	Patos	<i>S. brasiliensis</i>	species-specific PCR	-
PB 11	João Pessoa	<i>S. brasiliensis</i>	species-specific PCR	-
PB 12	João Pessoa	<i>S. brasiliensis</i>	CAL	MZ261813
PB 15	João Pessoa	<i>S. brasiliensis</i>	species-specific PCR	-
PB 16	João Pessoa	<i>S. brasiliensis</i>	species-specific PCR	-
PB 17	João Pessoa	<i>S. brasiliensis</i>	species-specific PCR	-
PB 18	João Pessoa	<i>S. brasiliensis</i>	species-specific PCR	-
PB 20	João Pessoa	<i>S. brasiliensis</i>	species-specific PCR	-
PB 21	João Pessoa	<i>S. brasiliensis</i>	species-specific PCR	-
PB 22	João Pessoa	<i>S. brasiliensis</i>	species-specific PCR	-
PB 23	João Pessoa	<i>S. brasiliensis</i>	species-specific PCR	-
PB 24	João Pessoa	<i>S. brasiliensis</i>	species-specific PCR	-
PB 26	João Pessoa	<i>S. brasiliensis</i>	species-specific PCR	-
PB 27	Areia	<i>S. brasiliensis</i>	species-specific PCR	-
PB 28	João Pessoa	<i>S. brasiliensis</i>	species-specific PCR	-
PB 29	João Pessoa	<i>S. brasiliensis</i>	CAL	MZ261814
PB 31	Pilões	<i>S. brasiliensis</i>	species-specific PCR	-
PB 32	João Pessoa	<i>S. brasiliensis</i>	species-specific PCR	-
PB 33	João Pessoa	<i>S. brasiliensis</i>	species-specific PCR	-
PB 34	João Pessoa	<i>S. brasiliensis</i>	CAL	MZ261815
PB 35	João Pessoa	<i>S. brasiliensis</i>	species-specific PCR	-
PB 38	Guarabira	<i>S. brasiliensis</i>	species-specific PCR	-
PB 39	João Pessoa	<i>S. brasiliensis</i>	species-specific PCR	-
PB 40	João Pessoa	<i>S. brasiliensis</i>	species-specific PCR	-
PB 41	João Pessoa	<i>S. brasiliensis</i>	species-specific PCR	-
PB 42	Pilões	<i>S. brasiliensis</i>	species-specific PCR	-
PB 45	João Pessoa	<i>S. brasiliensis</i>	species-specific PCR	-
PB 46	João Pessoa	<i>S. brasiliensis</i>	species-specific PCR	-
PB 47	João Pessoa	<i>S. brasiliensis</i>	species-specific PCR	-
PB 49	João Pessoa	<i>S. brasiliensis</i>	CAL	MZ261816
PB 50	João Pessoa	<i>S. brasiliensis</i>	CAL	MZ261817
PB 51	Patos	<i>S. brasiliensis</i>	species-specific PCR	-
PB 53	Bananeiras	<i>S. brasiliensis</i>	CAL	MZ261818
PB 54	João Pessoa	<i>S. brasiliensis</i>	species-specific PCR	-
PB 66	João Pessoa	<i>S. brasiliensis</i>	species-specific PCR	-
CBS 120339	Brazil	<i>S. brasiliensis</i>	CAL	AM116899
FMR 8604	Peru	<i>S. schenckii</i>	CAL	AM117429
FMR 8600	Spain	<i>S. globosa</i>	CAL	AM116908
CBS 937.72	South Africa	<i>S. luriei</i>	CAL	AM747302
CBS 302.73	United Kingdom	<i>S. pallida</i>	CAL	AM398396
FMR 9108	Mexico	<i>S. mexicana</i>	CAL	AM398393
Ss470	Chile	<i>S. chilensis</i>	CAL	KP711816
CBS 141.36	Italy	<i>Grosmanniaserpens</i>	CAL	JN135300

PCR specific-primers: (Sbra-F and Sbra-R; Ssch-F and Ssch-R, Sglo-F and Sglo-R). CAL: Partial sequencing of the calmodulin gene.



veterinarians and animal protectors on the growing casuistry of feline sporotrichosis, which reached epizootic proportions only in recent years in the state (FRANÇA et al., 2022). This is comparable to the evolution of the disease in Rio de Janeiro (the epicenter of the disease in Brazil), where the disease was insidious until the late 1990s, after which its morbidity increased significantly (RABELLO et al, 2022). This fact, combined with the presence of genotypic *S. brasiliensis* CBS 120339 in Paraíba, which was also found in human isolates from Rio de Janeiro, warns of the possible occurrence of zoonotic outbreaks of similar proportions to those in the southeast and south of the country.

In 2018, it became mandatory to report human cases of sporotrichosis in Paraíba, due to the sudden increase in the number of cases (PARAÍBA, 2018; FRANÇA et al., 2022). According to the epidemiological bulletin of the Paraíba Health Department, 536 reports were registered between 2018 and July 2021, of which 314 were confirmed as cases of the disease (MEDEIROS, 2021). Considering that the spread of human sporotrichosis caused by *S.*

*brasiliensis* transmitted by cats also occurs in the northeastern region (DE OLIVEIRA BENTO et al., 2021), the data published in this study highlight the role of cats as possible transmitters of *S. brasiliensis* in Paraíba.

Breaking the zoonotic chain of sporotrichosis transmission in Brazil is a major challenge posed by this disease (BARROS et al., 2010). Considering the epidemiological profile, measures that prevent cat-to-cat and cat-to-human transmission of *S. brasiliensis* have a significant impact on the control of this public health problem in Paraíba. Recommended actions include increasing the number of zoonoses surveillance centers (Unidades de Vigilância em Zoonoses - UVZ) in the state, since only two of the 223 cities in Paraíba - João Pessoa and Campina Grande - have a UVZ; free availability of drugs for the treatment of animal diseases, as is already the case for the human population in the state in addition to diagnosis, castration, euthanasia when necessary, and cremation of dead animals, in UVZs; awareness campaigns regarding the disease for the population throughout the state; containment

of the abandonment of sick animals through increased control and punishment by relevant public agencies; implementation of a reporting system for cases of animal sporotrichosis for the purpose of epidemiological surveillance of the disease; in addition to biosecurity measures to minimize the risk of transmission of pathogens to currently unaffected neighboring cities. In the long term, intervening in the spread of this animal disease will have a positive impact on the state's public health system and protect highly vulnerable animal and human populations.

It can be concluded that in the study areas, the species involved in cases of feline sporotrichosis is *S. brasiliensis*. The data also demonstrated the spread of the pathogen to a new area of distribution in the northeastern region of Brazil, which is far from the epicenters of the country. Our study also warns of the occurrence of zoonotic outbreaks in Paraíba, which are similar to those recorded in the Southeast and South regions. Finally, the spread of the disease to cities in the interior of the state has been demonstrated, as well as the emerging role of cats as potential transmitters of *S. brasiliensis* in new endemic areas.

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## AUTHORS' CONTRIBUTIONS

All authors contributed equally to the study's design and its conduct, as well as the preparation of this article, which all authors also revised and approved.

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## BIOETHICS AND BIOSECURITY COMMITTEE APPROVAL

This study was approved by the Animal Ethics Committee (CEUA) of the Universidade Federal da Paraíba under protocol 091/2017.

## DECLARATION OF CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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