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REVIEW

The threat of emerging and re-emerging pathogenic *Sporothrix* species

Anderson Messias Rodrigues · Paula Portella Della Terra · Isabella Dib Gremião · Sandro Antonio Pereira · Rosane Orofino-Costa · Zoilo Pires de Camargo

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Abstract Sporotrichosis is a neglected subcutaneous mycosis of humans and animals acquired by traumatic inoculation of soil and plant material (classical route) contaminated with infectious propagules of the pathogen or being bitten/scratched by infected cats (alternative route). Within a genus composed of 53 species displaying an essentially environmental core, there are only a few members which have considerable impacts on human or animal health. Infections are typically caused by *S. brasiliensis*, *S. schenckii* or *S. globosa*. Rare mammal pathogens include members of the *S. pallida* and *S. stenocereus* complexes. To illustrate the tremendous impact of emerging zoonotic sporotrichosis on public health, we discuss the main features of the expanding epidemics driven by *S. brasiliensis* in cats and humans. The cat entry in the transmission chain of sporotrichosis, causing epizooties (cat–cat) or zoonosis (cat–human), has contributed to the definition of new paradigms in *Sporothrix* transmission, reaching epidemic levels, making the disease a serious public health problem. Indeed, *S. brasiliensis* infection in humans and animals is likely to become even more important in the future, with projections of its expansion in biogeographic domains and host range, as well as greater virulence in mammals. Therefore, lessons from a long-standing outbreak in the state of Rio de Janeiro about the source and distribution of the etiological agents among outbreak areas can be used to create better control and prevention plans and increase awareness of sporotrichosis as a serious emerging zoonotic disease.

Keywords *Sporothrix* · Sporotrichosis · Emerging zoonoses · Control and prevention · Preparedness and biodefense · Pathogenicity · Virulence · *Sporothrix brasiliensis* · Neglected tropical diseases

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A. M. Rodrigues (✉) · P. P. Della Terra · Z. P. de Camargo
Laboratory of Emerging Fungal Pathogens, Cell Biology Division, Department of Microbiology, Immunology and Parasitology, Paulista School of Medicine, Federal University of São Paulo, São Paulo 04023-062, Brazil
e-mail: amrodrigues.amr@gmail.com

I. D. Gremião · S. A. Pereira
Laboratory of Clinical Research on Dermatozoonoses in Domestic Animals, Evandro Chagas National Institute of Infectious Diseases, Oswaldo Cruz Foundation (Fiocruz), Rio de Janeiro, RJ, Brazil

R. Orofino-Costa
Dermatology Department, Faculdade de Ciências Médicas, Universidade do Estado do Rio de Janeiro (FCM-UERJ), Rio de Janeiro, RJ, Brazil

The story behind the *Sporothrix* species pathogenic to mammals

Sporotrichosis is a fungal disease caused by the infection of *Sporothrix* spp. It usually affects the skin

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and mucous membranes, although other rare clinical forms may compromise joints, bones, central nervous system and lungs. The first clinical description of sporotrichosis was reported by Benjamin R. Schenck in 1898, proven by the isolation of the agent from finger injuries of a patient treated at John Hopkins Hospital in the USA (Fig. 1) [1]. Schenck carefully described the morphological features, development and results of inoculations of this microorganism. Such phenotypic features led Dr. Erwin F. Smith of the US Department of Agriculture in Washington to provisionally classify the agent in the genus *Sporotrichum* (Basidiomycota: Polyporales). In the original description of *Sporotrichum* by Johann Heinrich Friedrich Link in 1809 [2], 13 species were proposed in this genus, 11 of which were new and two of which had been described earlier by Christiaan Hendrik Persoon (1797) as *Dematium* [3], with *Sporotrichum badium* typifying the genus [MB164331] [2]. However, the classic features of sympodial conidiogenesis during the anamorphic state appear in other genera, such as *Hyalorhinocladiella* and *Pesotum*

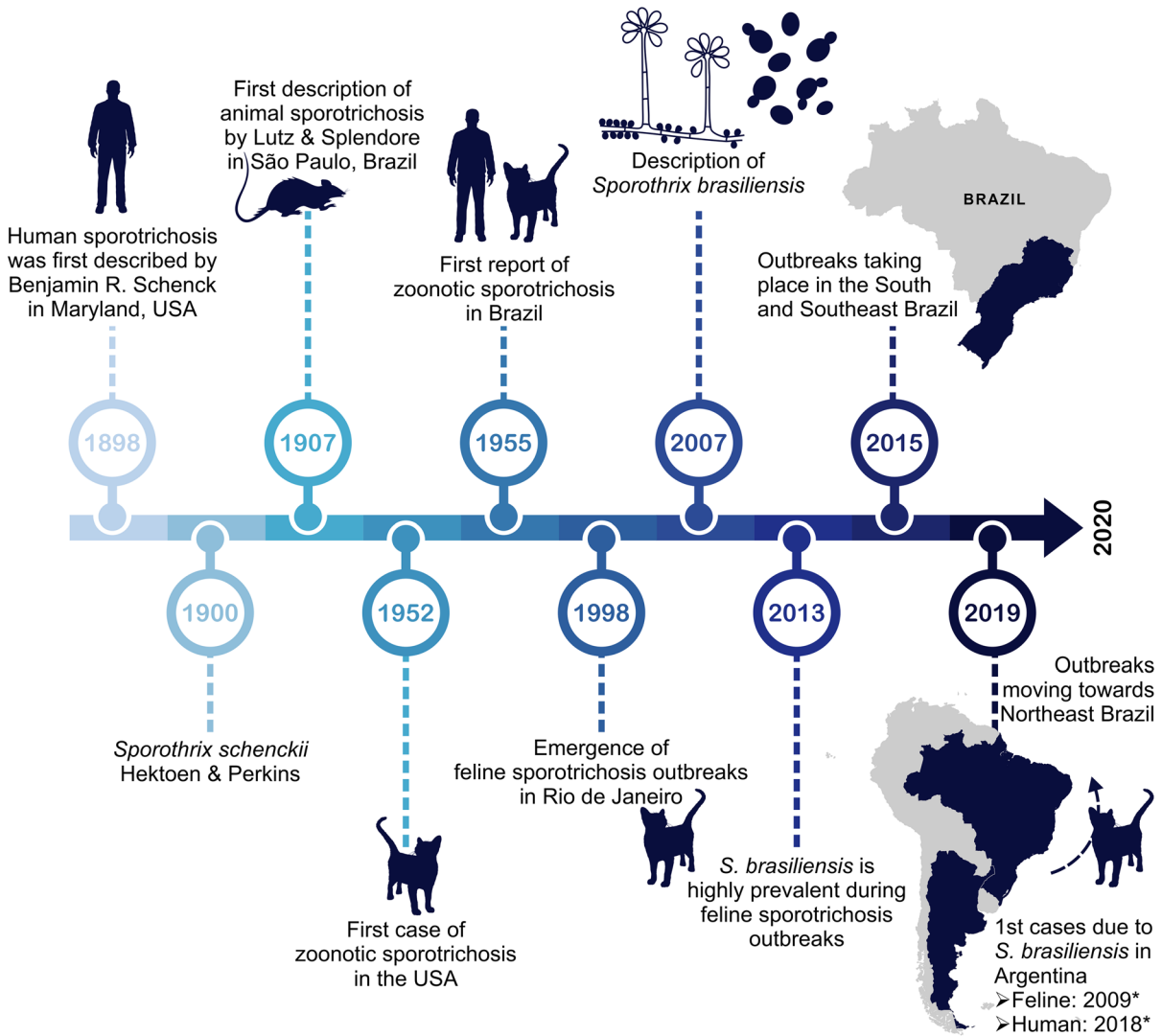

Fig. 1 Timeline of key groundbreaking events that contributed to the 120-year history of human and animal sporotrichosis. Despite a centenary disease, the emergence of *Sporothrix brasiliensis* as the main agent during feline sporotrichosis epizootic diseases and consequent zoonotic transmission in southern and southeastern Brazil has only been observed in recent decades (1998–2020)

(Ascomycota: Ophiostomatales). In 1885, Saccardo & Marchal described *Rhinocladium*, epitified by *Rhinocladium coprogenum* [MB208096] [4]. *Rhinocladium* was evidently coined to be analogous to *Sporotrichum*, but differed in having black spores. However, there is a marked overlap of phenotypic traits, making the taxonomy of these fungi an arduous task in the nineteenth century [5].

Two years after the isolation of the fungus by Schenck, Ludvig Hektoen & C. F. Perkins proposed the genus *Sporothrix* (Ascomycota: Ophiostomatales) in 1900 (Fig. 1). During this period, two human cases were described in Chicago [6]. In the subsequent years, *Sporothrix schenckii* and related species became the most important pathogens of the order Ophiostomatales [7]. In 1903, the fungus was first isolated in France and called *Sporotrichum beurmani* because it was considered different from the agent isolated by Schenck [8]. However, *Sporotrichum beurmani* was subsequently reclassified by Matruchot as *Sporotrichum schenckii* [9]. Although a few hundred human cases were described at the beginning of the last century in France by Beurmann and Gougerot [10], currently this mycosis is rare in that country and throughout Europe in general.

In Brazil, the disease was described for the first time in 1907 by Adolfo Lutz & Alfonso Splendore in rats (*Mus decumanus*) naturally infected in the sewer system of the city of São Paulo [11] (Fig. 1). Lutz & Splendore concluded that natural infection (rat–rat) is the result of bites through which the causative agent is introduced into the host tissues. This route was proven when the microorganism was isolated several times from the oral mucosa, and morphologically identical forms were found in the stomach mucosa [11]. Shortly thereafter, spontaneous sporotrichosis in horses was described in 1909, with findings of abscesses, which had been collected from the so-called cases of epizootic lymphangitis in Pennsylvania (USA) [12]. In the same year, Rispal and Dalous described a case of sporotrichosis following the bite of a horse [13]. The first reports of infected equines in Brazil date from 1934 [14–17]. Nevertheless, the first case reported in the literature of zoonotic-transmitted feline sporotrichosis (cat–human) occurred in New York in 1952 (Fig. 1) [18].

Sporotrichosis is a very common infection in Brazil [19]. In the 1920s, Aguiar Pupo [20] described 76 cases of human sporotrichosis referred to the Skin and Syphilis Service of Santa Casa de Misericordia Hospital in São Paulo, without feline involvement. The description of the first case of zoonotic sporotrichosis in Brazil (cat–human) should be attributed to Floriano de Almeida and colleagues [21] in the 1950s, when they described the high frequency of mycosis in São Paulo, probably related to weather conditions (Fig. 1). Among the alternative routes of transmission, they reported cat scratching and cavy, mouse and dog bites in a series of 344 cases, in which there was a predominance of sapronotic transmission, i.e., through trauma to plant thorns and straw. Interestingly, in the 1950s there was a predominance of human sporotrichosis in urban areas (93%), the preferential location of lesions being the upper limbs and face (85%), with a frequency of cutaneous and lymphatic forms and rarity of systemic and disseminated forms [21].

The period between the late 1950s and the early 1990s was marked by the low frequency of zoonotic transmission in southeastern Brazil [14, 22–24]. However, in the mid-1990s, cases of sporotrichosis began to emerge in cats in Rio de Janeiro, with the isolation of *S. schenckii s.l.* from the claws and oral cavity of infected animals [25], where human patients reported being scratched and/or bitten by cats in 68% of the cases [26]. Therefore, some 60 years after the first description of sporadic cases of zoonotic transmission in the 1950s [21], sporotrichosis has become a major public health problem in Brazil, threatening pet owners as well as veterinarians. Currently, it is well known that animal–animal and animal–human transmissions occur mainly due to scratching and biting by infected cats in urban areas, confirming the secular and pioneering findings of Lutz and Splendore [11], Pupo [20] and Almeida et al. [21]. Inter-human transmission is very rare, with only a few cases described in Brazil [20], China [27] and the USA [28].

After 122 years since the discovery of *Sporothrix* [1], it is now known that this is not a monotypic taxon, i.e., formed by a single species, but a diverse genus, with marked genetic and ecological diversity, which is reflected in the many different associations between organisms and their hosts or niches [19, 29]. As a result of extensive genetic, ecological and biological diversities, the taxonomy in *Sporothrix* is historically inconsistent. However, considerable improvements have been made in recent years, and currently *Sporothrix* (Ascomycota: Ophiostomatales) harbors 53 species described, compiled in Table 1. Such

Table 1 Legitimate names in the genus *Sporothrix* Hektoen et Perkins 1900 and their relationship to infection in mammals

Species	Group/clade	Pathogenicity to mammals[a]	Type strain[b]	MycoBank[c]	Year[d]	References
Sporothrix abietina (Marm. & Butin) Z.W. de Beer, T.A. Duong & M.J. Wingf.	*S. gossypina* complex	Not reported	CBS 125.89	MB817561	1990	[32, 33]
Sporothrix aemulophila T. Musvuugwa	*S. candida* complex	Not reported	CBS 140087	N/A	2015	[34]
Sporothrix africana G.J. Marais & M.J. Wingf.	*S. stenoceras* complex	Not reported	PREM 51893	MB466529	2001	[35]
Sporothrix aurorae (X.D. Zhou & M.J. Wingf.) Z.W. de Beer, T.A. Duong & M.J. Wingf.	*S. gossypina* complex	Not reported	CBS 118837	MB817562	2006	[33, 36]
Sporothrix bragantina (Pfenning & Oberw.) Z.W. de Beer, T.A. Duong & M.J. Wingf.	Group H	Not reported	CBS 474.91	MB817564	1993	[33, 37]
Sporothrix brasiliensis Marimon, Gené, Cano & Guarro	Pathogenic clade	Yes	CBS 120339	MB501166	2007	[38]
Sporothrix brunneoviolacea Madrid, Gené, Cano & Guarro	Group I	Not reported	CBS 124561	MB515559	2010	[39]
Sporothrix cabralii de Errasti & Z.W. de Beer	*S. candida* complex	Not reported	CIEFAP456	N/A	2016	[40]
Sporothrix candida (Kamgan et al.) Z.W. de Beer, T.A. Duong & M.J. Wingf.	*S. candida* complex	Not reported	CBS 129713	MB817565	2012	[33, 41]
Sporothrix cantabriensis (P. Romón et al.) Z.W. de Beer, T.A. Duong & M.J. Wingf.	*S. gossypina* complex	Not reported	CBS 136529	MB817566	2014	[9, 33]
Sporothrix chilensis A.M. Rodrigues, R.C. Choappa, G.F. Fernandes, G.S. de Hoog, Z.P. de Camargo	*S. pallida* complex	Yes, few cases	CBS 139891	MB811444	2015	[42]
Sporothrix curviconia de Hoog	Group G	Not reported	CBS 959.73	MB323929	1974	[43]
Sporothrix dentifunda (Aghayeva & M.J. Wingf.) Z.W. de Beer, T.A. Duong & M.J. Wingf.	*S. inflata* complex	Not reported	CBS 115790	MB817567	2005	[33, 44]
Sporothrix dimorphospora (Roxon & S.C. Jong) Madrid, Gené, Cano & Guarro	Group F	Not reported	CBS553.74	MB515560	2010	[39]
Sporothrix dombeyi Z.W. de Beer, T.A. Duong & M.J. Wingf.	Group I	Not reported	CBS 455.83	MB817568	1984	[33, 45]
Sporothrix epigloea (Guerrero) Z.W. de Beer, T.A. Duong & M.J. Wingf.	Group H	Not reported	CBS 573.63	MB817569	1971	[33, 46]
Sporothrix eucalyptigena (Barber & Crous) Z.W. de Beer, T.A. Duong & M.J. Wingf.	Group H	Not reported	CBS 139899	MB817570	2015	[33, 47]
Sporothrix eucastaneae (R.W. Davidson) Z.W. de Beer, T.A. Duong & M.J. Wingf.	*S. gossypina* complex	Not reported	CBS 424.77	MB817571	1978	[33, 48]
Sporothrix euskadiensis (P. Romon et al.) Z.W. de Beer, T.A. Duong & M.J. Wingf.	*S. gossypina* complex	Not reported	CBS 122138	MB817572	2014	[33, 49]
Sporothrix fumea (Kamgan et al.) Z.W. de Beer, T.A. Duong & M.J. Wingf.	Group I	Not reported	CBS 129712	MB817573	2012	[33, 41]
Sporothrix fusiformis (Aghayeva & M.J. Wingf.) Z.W. de Beer, T.A. Duong & M.J. Wingf.	*S. gossypina* complex	Not reported	CBS 112912	MB817574	2004	[33, 50]
Sporothrix gemella (Roets et al.) Z.W. de Beer, T.A. Duong & M.J. Wingf.	*S. pallida* complex	Not reported	CBS 121959	MB817575	2008	[33, 51]
Sporothrix globosa Marimon, Cano, Gené, Deanna A. Sutton, H. Kawas. & Guarro	Pathogenic clade	Yes	CBS 120340	MB501167	2007	[38]

Table 1 continued

Species	Group/clade	Pathogenicity to mammals[a]	Type strain[b]	MycoBank[c]	Year[d]	References
Sporothrix gossypina (R.W. Davidson) Z.W. de Beer, T.A. Duong & M.J. Wingf.	*S. gossypina* complex	Not reported	ATCC 18999	MB817576	1971	[33, 52]
Sporothrix guttuliformis de Hoog	*S. inflata* complex	Not reported	CBS 437.76	MB323934	1978	[53]
Sporothrix humicola de Meyer, Z.W. de Beer & M.J. Wingf.	*S. pallida* complex	Yes, single case	CBS 118129	MB511688	2008	[54]
Sporothrix inflata de Hoog	*S. inflata* complex	Not reported	CBS 239.68	MB323935	1974	[43]
Sporothrix itsvo Musvuugwa, L.L. Dreyer & F. Roets	*S. candida* complex	Not reported	CBS 141063	MB816106	2016	[55]
Sporothrix lunata (Aghayeva & M.J. Wingf.) Z.W. de Beer, T.A. Duong & M.J. Wingf.	*S. gossypina* complex	Not reported	CBS 112927	MB817577	2004	[33, 50]
Sporothrix luriei (Ajello & Kaplan) Marimon, Gené, Cano & Guarro	Pathogenic clade	Yes, few cases	CBS 937.72	MB536900	2008	[56, 57]
Sporothrix macroconidia H. Wang, Q. Lu & Z. Zhang	–	Not reported	CFCC 52628	MB828886	2019	[58]
Sporothrix mexicana Marimon, Gené, Cano & Guarro	*S. pallida* complex	Yes, few cases	CBS 120341	MB501168	2007	[38]
Sporothrix narcissi (Limber) Z.W. de Beer, T.A. Duong & M.J. Wingf.	*S. stenoceras* complex	Not reported	CBS 138.50	MB817578	1950	[33, 59]
Sporothrix nebularis (P. Romon et al.) Z.W. de Beer, T.A. Duong & M.J. Wingf.	Group G	Not reported	CBS 122135	MB817579	2014	[33, 49]
Sporothrix nigrograna (Masuya) Z.W. de Beer, T.A. Duong & M.J. Wingf.	Group G	Not reported	MAFF410943	MB817580	2004	[33, 60]
Sporothrix pallida (Tubaki) Matsushima T.	*S. pallida* complex	Yes, few cases	CBS 131.56	MB323939	1975	[61]
Sporothrix palmiculminata (Roets et al.) Z.W. de Beer, T.A. Duong & M.J. Wingf.	*S. pallida* complex	Not reported	CBS 119590	MB817581	2006	[33, 62]
Sporothrix phasma (Roets et al.) Z.W. de Beer, T.A. Duong & M.J. Wingf.	Group E	Not reported	CBS 119721	MB817582	2006	[33, 62]
Sporothrix polyporicola (Constant. & Ryman) Z.W. de Beer, T.A. Duong & M.J. Wingf.	Group F	Not reported	CBS 669.88	MB817583	1989	[33, 63]
Sporothrix prolifera (Kowalski & Butin) Z.W. de Beer, T.A. Duong & M.J. Wingf.	*S. gossypina* complex	Not reported	CBS 251.88	MB817584	1989	[33, 64]
Sporothrix protearum G.J. Marais & M.J. Wingf.	*S. stenoceras* complex	Not reported	#85068	MB436466	1997	[65]
Sporothrix protea-sedis (Roets et al.) Z.W. de Beer, T.A. Duong & M.J. Wingf.	*S. pallida* complex	Not reported	CBS 124910	MB817585	2010	[33, 62]
Sporothrix pseudoabietina H. Wang, Q. Lu & Z. Zhang	*S. gossypina* complex	Not reported	CFCC 52626	MB828887	2019	[58]
Sporothrix rapaneae Musvuugwa, L.L. Dreyer & F. Roets	*S. candida* complex	Not reported	CBS 141060	MB816107	2016	[55]
Sporothrix rossii Z.W. de Beer, T.A. Duong & M.J. Wingf.	*S. gossypina* complex	Not reported	CBS 116.78	MB817586	1971	[33, 52]
Sporothrix schenckii Hektoen & C.F. Perkins	Pathogenic clade	Yes	CBS 359.36	MB101184	1900	[6]
Sporothrix splendens G.J. Marais & M.J. Wingf.	*S. stenoceras* complex	Not reported	PREM 51079	MB359978	1994	[66]

Table 1 continued

Species	Group/clade	Pathogenicity to mammals[a]	Type strain[b]	MycoBank[c]	Year[d]	References
Sporothrix stenoceras (Robak) Z.W. de Beer, T.A. Duong & M.J. Wingf.	*S. stenoceras* complex	Yes, few cases	CBS 237.32	MB817587	1932	[33, 67]
Sporothrix stylites de Mey., Z.W. de Beer & M.J. Wingf.	*S. pallida* complex	Not reported	CBS 118848	MB511687	2008	[54]
Sporothrix thermara (J.A. van der Linde et al.) Z.W. de Beer, T.A. Duong & M.J. Wingf.	Group H	Not reported	CBS 139747	MB817619	2016	[33, 68]
Sporothrix uta Musvuugwa, L.L. Dreyer & F. Roets	*S. gossypina* complex	Not reported	CBS 141069	MB816108	2016	[55]
Sporothrix variecibatus Roets, Z.W. de Beer & Crous	*S. gossypina* complex	Not reported	CBS 121961	MB511457	2008	[51]
Sporothrix zambiensis (Roets et al.) Z.W. de Beer, T.A. Duong & M.J. Wingf.	*S. stenoceras* complex	Not reported	CBS 124912	MB817588	2010	[33, 69]

[a]Pathogenicity to the warm-blooded host (including humans and small vertebrates) based on published data

[b]Type strain or reference sample used for species description

[c]MycoBank: Online database available at http://www.mycobank.org/, documenting mycological naming novelties (new names and combinations)

[d]Year of publication of the species

[e]Bibliographic reference of the taxon, including legitimate combination

improvement was only possible with the use of phylogenetic studies that demonstrated the species boundaries in *Sporothrix*, enabling characterizing the classic agent *S. schenckii* sensu stricto and related species including *S. brasiliensis*, *S. globosa* and *S. luriei* [30, 31].

For a long time, the medically relevant *Sporothrix* were classified as a "species complex," called the *S. schenckii* complex [38, 70–74]. Nevertheless, with the progress of knowledge of the biology of *Sporothrix* species, the denomination of a species complex is no longer appropriate [75]. de Hoog et al. [76] define a species complex as a monophyletic clade of species with equivalent clinical relevance. Therefore, developments in basic and clinical research into the system *Sporothrix* sporotrichosis reveal significant differences among pathogenic *Sporothrix* spp., which include morphological [77], physiological [78], genetic [79], epidemiological [80] and virulence [81, 82] traits, as well as varying susceptibility to antifungals [83, 84], among other aspects, favoring the recognition of distinct species rather than a complex of cryptic species.

There is currently a suggestion to adopt the term "clinical clade" or "pathogenic clade" to refer to *S. brasiliensis*, *S. schenckii*, *S. globosa* and *S. luriei*, which are often isolated from human and animal cases [33, 85]. The remaining *Sporothrix* are nested in an "environmental clade," where they are often associated with substrates that vary from the soil and decomposing organic matter to insects and plants (Fig. 2). Indeed, these environmental species are rare agents of infections in mammals and are distributed in different clades, such as the *S. pallida* complex (e.g., *S. chilensis*, *S. mexicana*, *S. humicola* and *S. pallida*) [42, 74, 86–89] and the *S. stenoceras* complex [90] (Table 1). The advances achieved following the new taxonomic classification in *Sporothrix* are fascinating. The main ones are covered in the next topics.

What is known about *Sporothrix*'s ecological niche?

Sordariomycetes is the largest class of Ascomycota after the Dothideomycetes [91]. Most fungi in the Sordariomycetes are terrestrial, while some can be found in aquatic habitats. They are plant, arthropod and mammalian pathogens and have been isolated as endophytes from various plants [92]. Ophiostomatales (Benny and Kimbrough [93]) is an order in the Sordariomycetes and includes genera such as *Sporothrix*, *Ophiostoma*, *Hyalorhinocladiella*, *Grosmannia*,

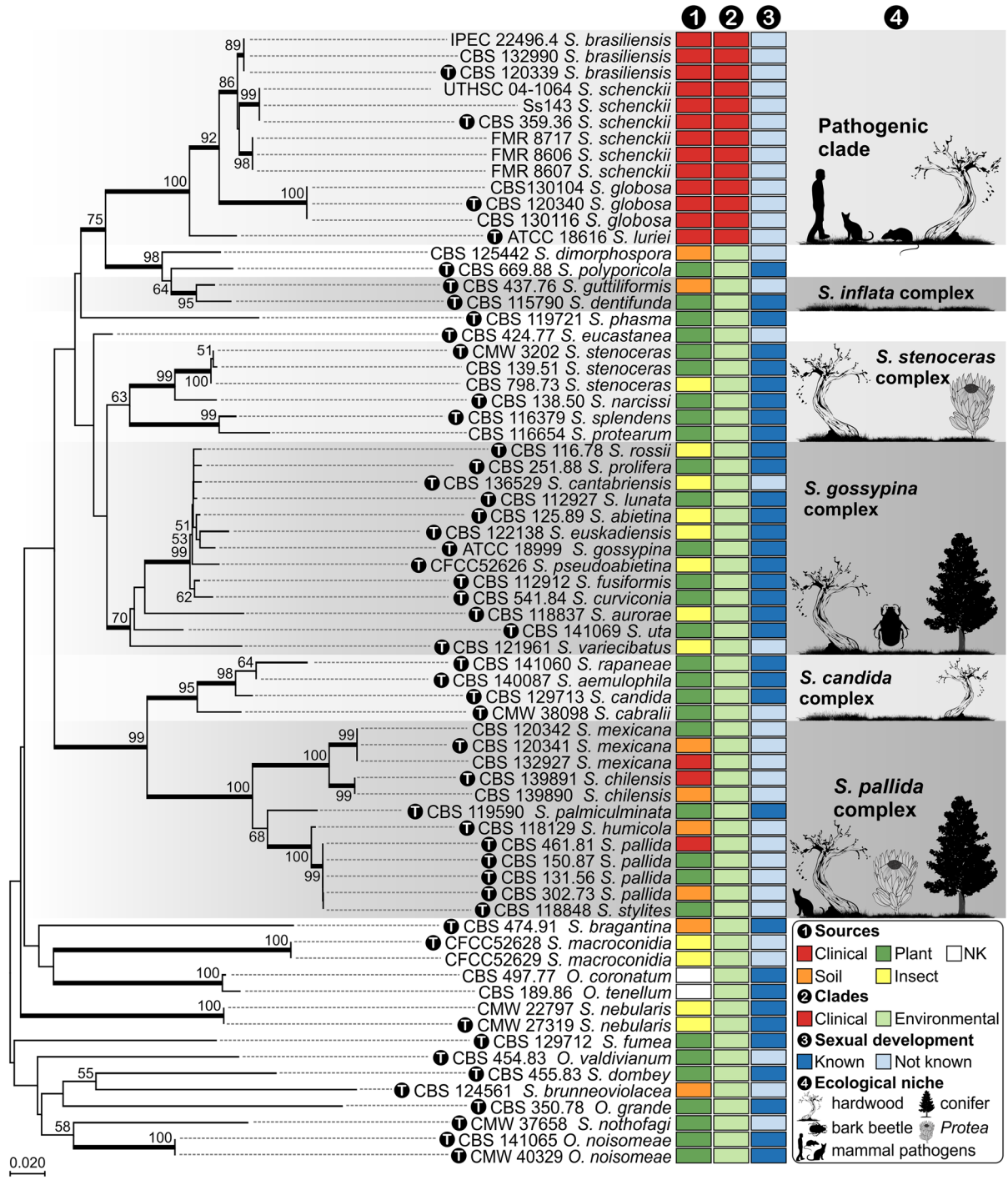

Fig. 2 Phylogenetic relationships between members of clinical and environmental relevance in *Sporothrix*, based on calmodulin sequences (exon 3–5). Origin (clinic, plants, soil, insects, etc.), genetic clades/species complexes, sexual development and ecological niche in *Sporothrix* and related species are presented

Ceratocystiopsis, *Leptographium*, *Pesotum*, *Raffaelea*, *Graphilbum*, among others. *Sporothrix* comprises a diversity of saprophytic organisms that are widely distributed in nature (Fig. 2). In this scenario, many ascomycetes within Ophiostomatales are considered to be phytopathogenic agents (e.g., *Ophiostoma ulmi*,

the agent of Dutch elm disease), producing a variety of diseases related to the vascular wilting of their hosts [94]. However, despite this close relationship with plant pathogens, there is no supporting evidence that *S. schenckii* and species in the clinical clade are phytopathogens. Another interesting ecological aspect established among the Ophiostomatales is the relationship between fungi and beetles (Coleoptera: Scolytinae). Such relationships in *Sporothrix* include commensalism, mutualism and parasitism and can be found in all parts of the world [75]. Definitely, beetles are an important form of dispersal of environmental *Sporothrix* and *Ophiostoma* species [49, 95]. However, we cannot be extrapolated to agents of infections in mammals [75]. Consequently, little is known about the ecology of medically relevant *Sporothrix*, which makes it difficult to anticipate and improve the public health response to future outbreaks.

Within a genus displaying an essentially environmental core, only a few species have emerged in recent years with the ability to infect warm-blooded hosts. Historically, several articles described the isolation of *Sporothrix* spp. (*S. schenckii s.l.*) from environmental sources, making a link between the fungi isolated in nature and the agents isolated from human lesions. However, in these same scenarios, it is not uncommon to find reports of a lack of pathogenicity of environmental strains, limited fungal growth at high temperatures (35–40 °C), or even no thermal dimorphism [39, 96–100]. Altogether, this information suggests that these historical environmental isolates belong to the environmental clade (e.g., *S. pallida*, *S. stenoceras*, *S. inflata*, *S. humicola*, etc.) (Fig. 2). Therefore, it is fundamental to use molecular diagnostic tools to correctly identify environmental-borne isolates of *Sporothrix* [100].

Although the geographic distribution of *S. brasiliensis*, *S. schenckii*, *S. globosa* and *S. luriei* has been extensively studied based on clinical cases, these species have rarely been isolated from nature, probably due to their low concentration in environmental samples [101, 102]. In nutrient-rich culture media, the fast-growing fungi of some ascomycetes that dominate soil diversity and richness globally, such as *Alternaria*, *Aureobasidium*, *Cladosporium*, *Penicillium*, *Fusarium*, *Chaetomium*, *Acremonium* and *Curvularia* [103, 104], grow faster than most *Sporothrix* spp. Therefore, the use of selective culture media (e.g., Sabouraud agar with chloramphenicol and cycloheximide) would help to overcome this problem.

Ramírez-Soto et al. [101] described that *Sporothrix* spp. were isolated from soil from different regions or provinces of 16 countries. Most environmental isolates were identified as *S. schenckii*, while *S. pallida*, *S. brasiliensis*, *S. globosa* and *S. mexicana* were rare. Pathogenic *Sporothrix* species are estimated to grow in soil with a wide temperature range (6.6–28.8 °C) and wide relative humidity range (37.5–99.0%), but are also associated with a variety of plants, flowers, decaying wood and cane leaves, potentially facilitating their establishment and proliferation in the environment [101].

Therefore, the ecology of the pathogenic clade remains a puzzle to be solved. Robust ecological studies that demonstrate factors related to density, diversity, seasonal fluctuation and distribution of *Sporothrix* of medical relevance in the environment are lacking [102]. Molecular identification will be crucial to distinguish among *S. brasiliensis*, *S. schenckii*, *S. globosa* and other environmental *Sporothrix* species, especially those embedded in the *S. pallida* and *S. stenoceras* complexes commonly found in soil and decaying organic matter (Fig. 2).

The geography of *Sporothrix* and sporotrichosis

Sporotrichosis is a mycosis with wide geographic distribution. However, the incidence of the disease varies widely from country to country, mostly based on the observation of case reports [105]. Just as its incidence fluctuates in the host population, the etiological agent involved varies according to the geographic region (Fig. 3). Historically, the largest human outbreak with an environmental source occurred between 1938 and 1949 at a gold mine in Witwatersrand, South Africa, where more than 3000 cases were documented in Bantu natives who were infected with *Sporothrix* propagules [106–108]. Currently, case reports on the African continent still refer to sapronotic transmission of the disease in humans [109–114], with sporadic cases of infection in animals [115].

A recent outbreak of lymphocutaneous sporotrichosis in a South African gold mine revealed *S. schenckii s. str.* as the main etiological agent, and *S. mexicana* was recovered from environmental samples

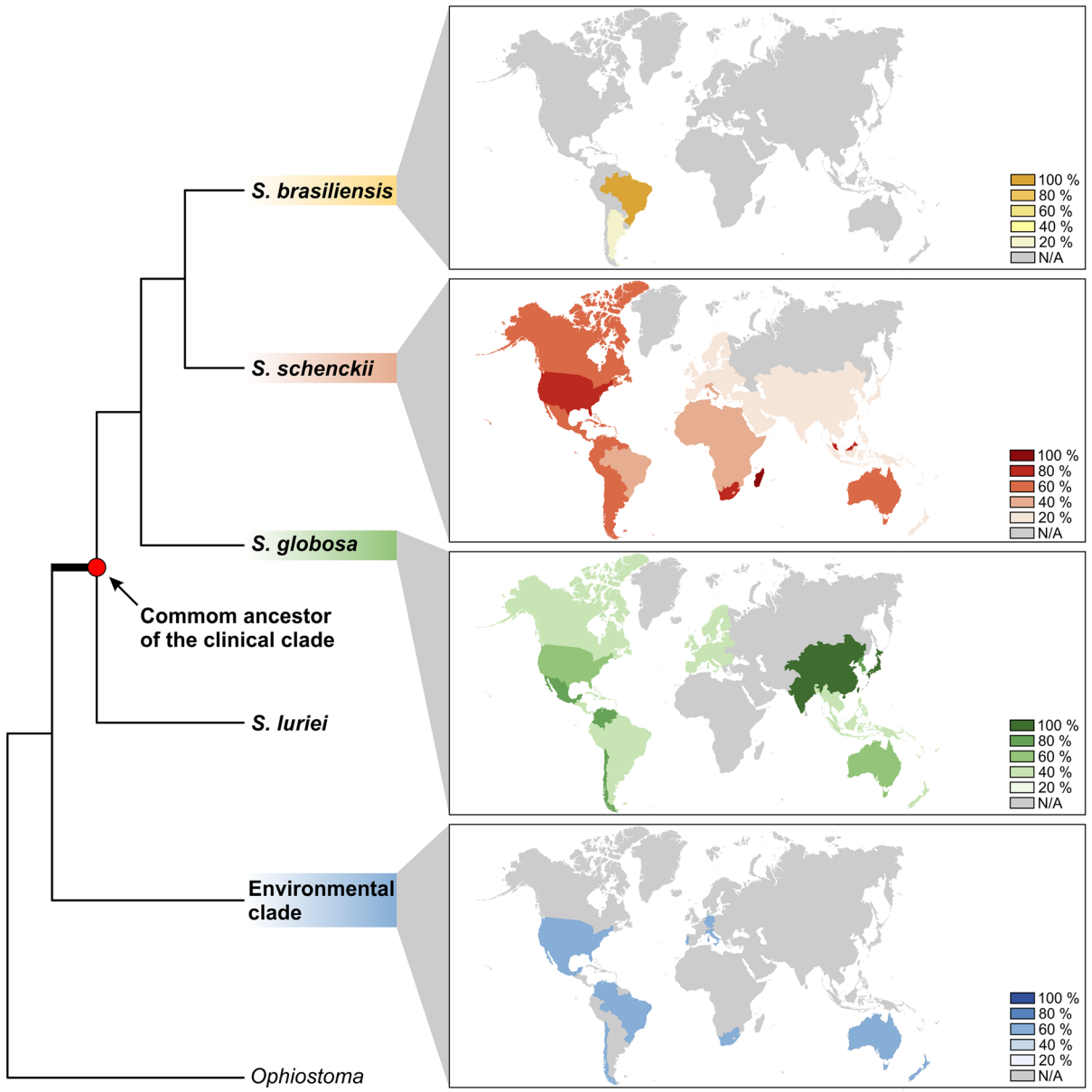

Fig. 3 Recent global distribution of *Sporothrix* species poses a substantial risk to public health. Note that the different species have a very particular geographic distribution, being *S. brasiliensis* a fungus restricted to the South and Southeast of Brazil until mid-2010. On the other hand, *S. globosa* is an emerging species in Asia, although it is found less frequently in other parts of the world such as the Americas and Europe. The survey is based mainly on a data series published in the literature [38, 74, 80, 105, 109, 129, 131, 133, 141, 142, 146, 147, 149, 151, 158, 167, 180, 195]

(Fig. 3) [109]. Outside the main transmission area in South Africa, sporadic cases have been reported in Madagascar [116], Zimbabwe [117], Nigeria [118] and Sudan [119]. Surprisingly, the HIV/AIDS epidemic in South Africa does not appear to be associated with a concomitant increase in sporotrichosis cases, which remain infrequent [120, 121]. However, reports in Africa at the beginning of the twentieth century [106, 107] were fundamental for understanding the factors underpinning fungal transmission, characterizing sporotrichosis as an occupational disease.

In Asia, sporotrichosis is a common subcutaneous infection in Japan, China, India and Malaysia. In Japan, sporotrichosis was very common between the 1940s and 1980s, with a significant decrease thereafter [122]. It has been reported throughout India, with high prevalence in the northern sub-Himalayan region, the northeastern states and certain areas of southern Karnataka [97, 123–125]. Sporotrichosis due to *S. globosa* is also common throughout China, with high prevalence in the northeast, especially in Jilin [126–128]. There is a higher incidence of cases during winter, possibly associated with contamination of the home environment with plant material (wood, branches, sticks) used for cooking as well as for heating. It is interesting to note that in these areas, the agent is widely distributed in nature and is recovered from environmental samples such as cornstalks, dead branches, rotten wood, sludge, soil and tree bark, with a success rate of isolation of around 10% [129]. Therefore, in Asia the main route of transmission is the traumatic inoculation of plant material containing *S. globosa* propagules [85].

Australia has sporadic human cases of sporotrichosis (usually caused by *S. schenckii*, *S. globosa* or *S. mexicana*), which have been reported in the last three decades, especially in the eastern and western parts of the country (Fig. 3) [130, 131]. The first case of feline sporotrichosis in Australia was reported in 1983 by Mackay et al. [132], although animal manifestation seems to be rare in the country. Recently, an atypical case caused by *S. pallida* was described in cats [133].

In the USA, human sporotrichosis due to *S. schenckii s. str.* also has an important occupational aspect, affecting mainly gardeners and farmers (Fig. 3). The largest outbreak occurred in 1988 involving 84 patients in 15 states who were exposed to the fungus present in Wisconsin-grown *Sphagnum* moss used for the packaging of evergreen tree seedlings [134, 135]. An estimated 1471 sporotrichosis-associated hospitalizations occurred in the USA between 2000 and 2013 and were associated with HIV/AIDS, immune-mediated inflammatory diseases and chronic obstructive pulmonary disease [136].

The geographical distribution of *Sporothrix* species is wide, and in most areas > 80% of cases are caused by a single predominant molecular species, such as in Asia: *S. globosa* (99.3%); Australia and South Africa: *S. schenckii* (94%); southeastern South America: *S. brasiliensis* (88%); and western South and Central America and North America: *S. schenckii* (89%) [129].

Sporotrichosis is the most common subcutaneous mycosis in Latin America [137], with areas of high endemicity in Brazil, Colombia [138], Peru [139, 140] and Venezuela [141]. However, recent epidemics occurring in Brazil are peculiar, especially in the South and Southeast regions, with the potential for zoonotic transmission of *S. brasiliensis*, nearly always related to cats as the main source of fungal infection for humans, dogs and other cats [142]. It is difficult to estimate the real magnitude of the epidemic. Since 2011, the notification is mandatory in the state of Rio de Janeiro, but not in the other Brazilian states with rare punctual exceptions at regional and municipal levels [143–147]. Efforts have been made in recent years by the General Office to Coordinate Communicable Diseases (Ministry of Health), including education of the population about the main aspects of the disease [148].

Cases of human sporotrichosis occur in 25 of the 26 Brazilian states (Fig. 4a), representing the main endemic areas and clinical forms of the disease [74, 80, 83, 85, 147, 149, 150]. In this context, we highlight the southern and southeastern regions of Brazil, which have a very high incidence of human cases, directly linked to the epizooties of feline sporotrichosis [80, 151, 152]. However, sporotrichosis has been expanding rapidly toward the northeast in recent years (2015–2019). Sporadic cases have been diagnosed in the past in the northeastern region [153], nearly always without the cat participation in the transmission chain, thus involving classic sapronotic transmission, which seems to occur less frequently today. Reports of isolated cases are from the states of Rio Grande do Norte [154], Paraíba [155] and Pernambuco [156] (Fig. 4b).

Currently, *S. brasiliensis*, including cases of human and animal origin, occurs in nearly all Brazilian regions (Fig. 4). The first human cases of sporotrichosis by *S. brasiliensis* were described in the southern and southeastern regions [157], with Rio de Janeiro as the epicenter [38]. Molecular analyses based on rDNA and protein coding loci (e.g., calmodulin, β-tubulin, elongation factor 1α) support the monophyly of this agent [38, 158]. To date, only Argentina has reported the occurrence of *S. brasiliensis* in humans and cats outside Brazil [159, 160].

During epizooties in cats, there is a high prevalence of *S. brasiliensis* as an etiological agent [80, 161]. Consequently, in these areas zoonotic transmission favors the high frequency of *S. brasiliensis* among humans. *Sporothrix brasiliensis* has important virulence attributes, being the most virulent species in murine models such as BALB/c [81, 162], C57BL/6 [163] and OF-1 mice [82]. This exacerbated virulence in mice is also observed in the human host, and *S. brasiliensis* is associated with atypical [157, 164, 165] and more severe forms of the disease, including disseminated cutaneous infection in immunocompetent hosts and systemic disease [165, 166].

Sporothrix brasiliensis, *S. schenckii* and *S. globosa* occur in sympatry in Brazil. Compared to *S. brasiliensis*, *S. schenckii s. str.* has a higher genetic diversity and a homogeneous distribution throughout Brazil, with the occurrence of several genetic clusters [85, 149]. Brazilian isolates of *S. schenckii* mostly come from cases of human sporotrichosis and are the prevalent etiological agent in areas free of feline sporotrichosis outbreaks. In Brazil, there is a low incidence of cases of human sporotrichosis caused by *S. globosa* or *S. mexicana* (Fig. 3) [74, 149, 167, 168].

Feline sporotrichosis leads to zoonotic transmission

Domestic animals are susceptible to various fungal diseases that can be directly transmitted to humans. However, these diseases are often overlooked by health authorities [169]. Among emerging pathogens, approximately 75% are zoonotic, and in general zoonotic pathogens are twice as likely to be associated with emerging diseases than non-zoonotic pathogens [170]. Because domestic animals have close contact with their owners, they play an important role in the emergence of human infections. This situation is aggravated in underdeveloped countries, where sanitary conditions and public health infrastructure are inadequate [169, 171].

Cats are the animal most affected by sporotrichosis, and skin ulcers are the main clinical signs observed [151]. Feline sporotrichosis has a wide spectrum of clinical manifestations, ranging from a single skin

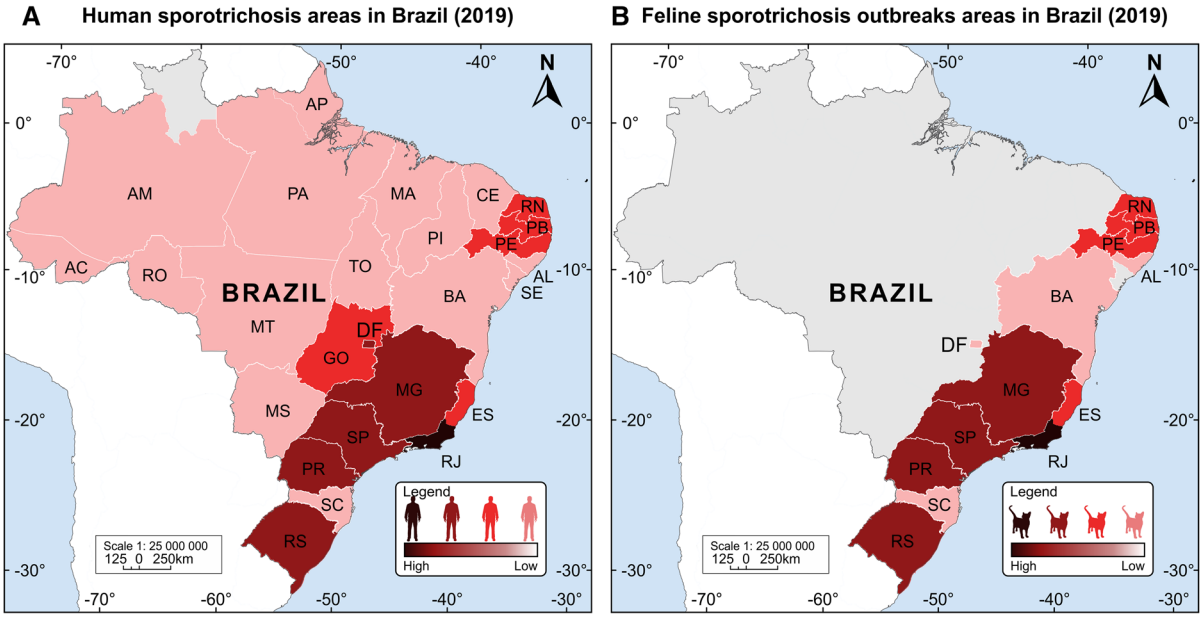

Fig. 4 Expansion of human and feline sporotrichosis in recent years. **a** Cases of human sporotrichosis have been reported in 25 of 26 Brazilian states, with significant differences in their frequency. **b** In recent decades (1998–2019), Brazil has recorded the largest epizootic feline sporotrichosis with the consequent zoonotic transmission in Rio de Janeiro, with thousands of cases documented in the literature. Currently, the zoonotic sporotrichosis driven by *S. brasiliensis* is expanding rapidly, toward Northeast Brazil. The map was drawn based on case reports available on the literature [74, 80, 105, 129, 142, 146, 147, 149, 151, 158, 180]

lesion to fatal disseminated systemic forms [143, 172, 173]. In cats, systemic involvement and respiratory signs are frequent, which can lead to severe forms that are difficult to treat and may lead to death [174]. Such involvement in cats seems to be unrelated to the immunodeficiency determined by coinfection with feline retroviruses [151].

Skin lesions in cats contain a high number of yeasts (i.e., high fungal load), so these animals have a high zoonotic potential for *Sporothrix* transmission, which demonstrates the importance of this animal species in the epidemiological chain of sporotrichosis [144, 145, 175]. The cat–cat, cat–dog or cat–human contact patterns involving scratches and bites also contribute to the occurrence of epizootics or zoonotic transmission, respectively [80]. Factors such as cats' entry into the chain of transmission of sporotrichosis, associated with the emergence of *S. brasiliensis* during epizootic events, contribute to making this mycosis a major zoonosis nowadays.

The thermal resistance exhibited by *S. brasiliensis* may be an important mechanism of adaptation to cats (body temperature $\sim$ 39 °C) and can partially explain the success of infection of this species over other etiological agents [80], such as *S. globosa*, which is more sensitive to temperatures above 35 °C. However, the emergence of sporotrichosis by *S. brasiliensis* may be a result of multifactorial events, including: (1) the evolution of *Sporothrix* over time (e.g., mutability and natural selection); (2) high virulence of *S. brasiliensis* to the warm-blooded vertebrate hosts; (3) recent introduction of *S. brasiliensis* into a naïve host population (e.g., lack of natural resistance); (4) behavioral aspects of cats (e.g., licking, scratching, etc.); and (5) human practices (e.g., population growth; rural to urban migration; poverty; ecological changes due to land use; increased numbers of cats as pets; use of cats as a means of rodent control, etc.). It is unlikely that the above events act alone during the emergence of sporotrichosis. The combination of delayed diagnosis and delayed treatment of diseased cats, the abandonment of healthy/sick cats in streets, the inappropriate disposal of infected cat carcasses (often buried in yards or left on wasteland), coupled with the absence of public policies for containment of the disease, has made transmission reach epidemic proportions [171, 176].

Understanding the nature of agent persistence and spread are important determinants that influence the emergence of *S. brasiliensis*. Indeed, *S. brasiliensis* meets these basic criteria, since it was introduced/established in a naïve/vulnerable host population of cats and the fungus has the ability to spread from host to host, causing large epizooties, increasing its incidence in the population [151, 173, 177, 178]. This is easily observed in epidemiological studies, which have shown that *S. brasiliensis* is dependent on the feline host for its emergence in southern and southeastern Brazil [80, 149]. The increase in the number of cases in cats is usually followed by an increase in the number of human cases, which poses a serious public health problem.

Major epizootic outbreaks of feline sporotrichosis have been reported in the states of Rio de Janeiro, São Paulo and Rio Grande do Sul [172, 179, 180]. The outbreaks occurring in Rio de Janeiro began in the second half of the 1990s, with an abrupt and continuous increase from 1998. From 1991 to 2015, 4517 human cases were recorded by Oswaldo Cruz Foundation (Fiocruz) in Rio de Janeiro [146]. At the same institution, between 1998 and 2014, 244 dogs were diagnosed [142], while 4916 cats were diagnosed through 2017. In Rio Grande do Sul, from 1958 to 1987, 311 cases of sporotrichosis were observed in humans [181] and between 1967 and 2002, 304 more cases were confirmed in the southern region [181]. Currently, in southern Brazil, massive zoonotic transmission has also been detected [80, 149, 181–184], with characteristics similar to the ongoing epidemic in Rio de Janeiro (Fig. 4b).

Feline sporotrichosis caused by *S. brasiliensis* has been described in all the states in the southeastern region of Brazil, mainly in Rio de Janeiro [80, 161, 185, 186], São Paulo [180], Minas Gerais [80] and Espírito Santo [187, 188]. It is believed that these epidemiological patterns are mostly due to the proximity of these states to the epizootic region of Rio de Janeiro and the possibility of cats' migration from the endemic area to these adjacent regions with their owners [161]. Cases of sporotrichosis in cats have also been documented in other regions, such as Mato Grosso [189], Santa Catarina [190], Distrito Federal [191] and Paraná [80].

Recently, an outbreak of feline sporotrichosis was observed in the metropolitan area of Recife, state of Pernambuco [192]. In the state of Alagoas, the first case of zoonotic transmission was described, associated with a cat [193]. Epidemiological studies indicate

the presence of *S. brasiliensis* in the northeastern region among humans since 1997 (e.g., isolates Ss43 and Ss44), reported by Rodrigues et al. [149]. Studies to identify the species causing feline sporotrichosis in the northeastern region have not yet been published, but we believe that *S. brasiliensis* may be the predominant species (Fig. 4b).

We draw attention to the interesting case of the state of São Paulo, where in the mid-1950s, 344 cases of sporotrichosis were reported by Almeida et al. [21], since when only basal levels of transmission have been described, almost always unrelated to feline transmission. Since 2008, the São Paulo Zoonosis Control Center (CCZ-SP) has been conducting epidemiological surveillance among cats, in which few cases of feline sporotrichosis were reported until December 2010 [15]. Since 2011, the number of cases has been growing drastically in the city of São Paulo and its metropolitan region (e.g., Guarulhos and Diadema), reaching hundreds of cases [180].

Zoonotic transmission by *S. brasiliensis* is nonexistent in areas outside Brazil [142], except for scarce cases in Argentina [159, 160]. On the other hand, zoonotic transmission involving *S. schenckii* has been described in Brazil, USA, Mexico, Panama, Argentina, India and Malaysia [142, 194]. In 2015, Kano et al. [195] reported an interesting outbreak of sporotrichosis in Malaysia due to zoonotic transmission by cats, and *S. schenckii s. str.* was the main etiological agent. The examples discussed above show the emergence of *S. brasiliensis* as a threat to human and animal health.

The impact of classic and alternative routes of *Sporothrix* infection

According to the basic concepts of virulence and pathogenicity [196], all agents inserted in the clinical clade (i.e., *S. brasiliensis*, *S. schenckii*, *S. globosa*) as well as some members of the environmental clade (e.g., *S. chilensis*, *S. mexicana*, *S. pallida* and *S. stenoceras*) are able to cause disease in humans and animals. However, it is important to note that the host damage in human and animal sporotrichosis changes according to multifactorial variables such as inoculum size, direct action of the pathogen and host immune response capacity [81, 197]. Therefore, the impact of classic and alternative routes considers a combination of factors composed of: (1) the transmitted cell morphotype (i.e., conidia or yeast); (2) the inoculum size; and (3) the etiological agent responsible for the infection.

We define the classic route as the direct contamination of the host through penetrating wounds by plant material containing fungal propagules present in the environment (e.g., soil, decaying wood, *Sphagnum* moss, vegetation and organic debris). This route has a strong occupational character, since it mainly affects people whose professional or recreational activity includes gardening, farming, floriculture, etc. In this sapronotic route, the occurrence of the disease has already been described in humans, dogs, cats, horses, cattle, camels, dolphins, goats, birds, pigs, rats, armadillos and other animals [198, 199].

The alternative route involves direct contamination of the host by scratches or bites of animals (e.g., rats, cats, dogs, etc.) and may occur as zoonosis (e.g., cat–human) or horizontal animal transmission (e.g., cat–cat, cat–dog, mouse–cat). The zoonotic transmission has an occupational factor, especially for veterinarians, their assistants and other professionals dealing directly with diseased animals. In addition, animal owners are another group highly exposed to *Sporothrix* infection. However, it is important to note that in endemic areas, more people are at risk of acquiring zoonotic sporotrichosis due to the proximity between humans and cats. The cat population in Brazilian households was estimated at 22.1 million, representing approximately 1.9 cats per household [200]. Data from the Brazilian Institute of Geography and Statistics (IBGE) indicate growth in the number of households with pet cats ($\sim$ 11.5 million household units), with the northern and northeastern regions having the highest proportions of cats (22.7% and 23.6%, respectively) [200]. The feline sporotrichosis epidemic is heading toward the Brazilian Northeast, where *S. brasiliensis* will find a dense population of susceptible hosts, mainly in Pernambuco, Alagoas and Rio Grande do Norte [156, 192, 193].

The high fungal load present in cat skin lesions is one of the main factors responsible for the success of horizontal animal transmission and *Sporothrix* zoonotic transmission. Inoculum size also directly influences the fungal burden in experimental sporotrichosis, since larger inocula favor the spread of the fungus to organs such as the spleen and lungs. *Sporothrix* propagules can be found in the oral cavity

and nasal cavity as well as in the claws of cats with or without clinical signs, facilitating transmission by biting and scratching. However, it seems that healthy cats play a minor role in *Sporothrix* transmission [185], as there is a low frequency of fungal isolation from the oral cavity and/or claws of healthy cats that were in contact with infected cats [144, 173, 201].

It is interesting that *S. brasiliensis* has already been detected in cats' feces by fungal isolation in culture [180] or by the use of molecular tools such as PCR [150]. Other infected animals, such as mice and dogs, can also transmit *Sporothrix* [21, 202]. However, the low fungal load observed in canine cutaneous lesions seems to be a limiting factor for successful transmission compared to transmission from cats.

The cell morphotype transmitted in sporotrichosis varies according to the transmission route. In the classic route, the morphotypes propagated are those found in the environment at a temperature of 25–30 °C, such as hyphae fragments and conidia. In the alternative route, the infecting morphotypes are generated at the body temperature of the warm-blooded vertebrate host (∼ 37–39 °C), thus favoring the spread of yeasts. In experimental sporotrichosis, when mice are challenged with conidia or yeasts, the latter appear to have advantages in inducing disease in vivo [81, 203].

As a third and important factor of this triad, the etiological agent is important in the development of sporotrichosis. In a model of disseminated sporotrichosis, Arrillaga–Moncrieff et al. [82] used OF-1 mice and compared virulence in different *Sporothrix* species, observing significant differences in virulence between environmental and clinical isolates, as well as differences among the main agents found in the clinical clade, suggesting that the lesion mechanisms may be species-specific. Based on the same experimental conditions (i.e., inoculum, host, immune system, environment), *S. brasiliensis* and *S. schenckii* are the most virulent agents, followed by *S. globosa* and *S. luriei*.

Fernandes et al. [81] used BALB/c mice to develop a murine model of systemic sporotrichosis and to test the virulence profile among *S. schenckii* isolates, from different geographic regions of Brazil and different clinical origins. The great variation of virulence observed among *S. schenckii* isolates was associated with protein secretion, immunogenicity and genetic diversity [81]. It is now known that the inoculation route (i.e., subcutaneous or intravenous) also plays an important role in the development of experimental sporotrichosis. Della Terra and collaborators [162] mimicked zoonotic transmission in a murine model and demonstrated that different isolates of *S. brasiliensis*, an admittedly clonal species, may have different virulence profiles, which raises questions about the existence of cryptic diversity in *S. brasiliensis*, an issue that deserves further investigation.

Compared to the alternative route, the classic route of infection could be considered less effective, causing cases of sporotrichosis in specific groups of patients belonging to certain occupational groups. However, there are also reports of large outbreaks by the classic route, especially in France (early twentieth century), the USA, South Africa and China, indicating that very specific ecological conditions (e.g., temperature, humidity, soil, vegetation) promote the fungus expansion in decaying plant material [129]. The alternative route involving feline transmission through scratching and biting is highly effective, manifested as epizooties or as zoonosis, placing a greater number of hosts at risk of sporotrichosis [19, 29, 75, 85].

Therefore, different transmission routes have different impacts and require different public policies to contain outbreaks. In the classic route, the use of appropriate tools for the manipulation of plant material as well as the removal of foci in nature is necessary to contain the outbreak. At the other extreme, where horizontal animal transmission (via cat–cat) and zoonotic *Sporothrix* transmission prevail (via cat–human), containment measures should be directed toward educational campaigns for cat owners in endemic areas, castration of cats in outbreak areas and implementation of appropriate antifungal treatment [19, 29, 75, 85, 187].

Human sporotrichosis and the emergence of atypical cases

Sporotrichosis is classically considered to be a subcutaneous mycosis caused by *S. schenckii* and related species that usually involves subcutaneous tissue with lymph node involvement and less frequently affects mucosa, bones, joints, muscles and central nervous system. In humans, the incubation period varies from several days to three months and most infections

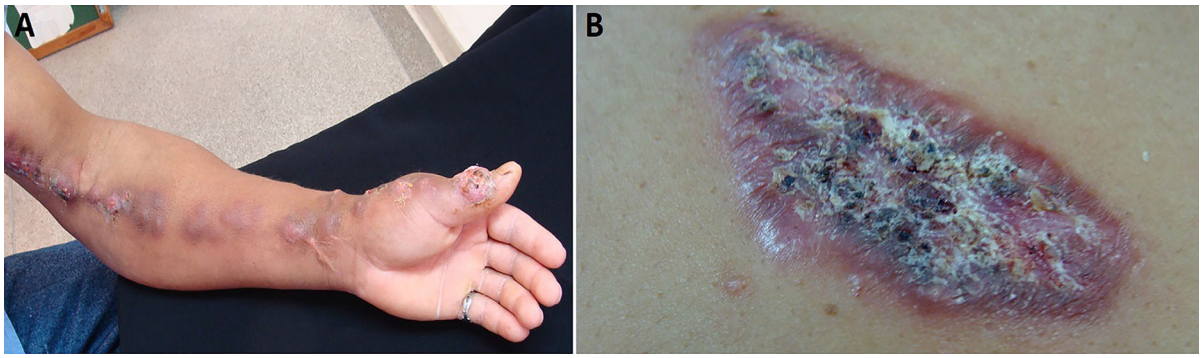

Fig. 5 Clinical aspects of cutaneous sporotrichosis. **a** Nodular ulcerative lesion in the thumb, followed by nodular and/or ulcerative lesions in the regional lymphatics (lymphocutaneous form). **b** Unique ulcerated and crusted skin lesion (fixed form)

become apparent within approximately 1–3 weeks [204].

Human sporotrichosis has several clinical manifestations. Currently, the classification adopted is based on the review published by Orofino–Costa et al. [166]. Most cases are lymphocutaneous (75–90%), which together with the fixed cutaneous form of the disease constitute more than 95% of sporotrichosis occurrences.

Lymphocutaneous sporotrichosis is characterized by the presence of small nodules, following the path along the regional lymphatic system, which ulcerate and fistulize (Fig. 5a). It is usually preceded by a well-defined episode of inoculation or cutaneous trauma, whose preferred location is the limbs [205]. Microbiological differential diagnosis includes a variety of skin pathogens and their appendages [206]. Fixed cutaneous sporotrichosis is characterized by the presence of a single localized lesion that can appear anywhere on the skin, usually as an ulcerated, verrucous or papular lesion (Fig. 5b). The fixed cutaneous form of sporotrichosis can be a challenge for clinical diagnosis, mimicking a number of other dermatological diseases such as lupus erythematosus, sarcoidosis, paracoccidioidomycosis, chromomycosis, tuberculosis and cutaneous leishmaniasis [105, 166].

To a lesser extent, systemic manifestations occur, usually related to patients with some immune system deficit [123, 157, 205, 207]. Advanced age, alcoholism, diabetes mellitus, Cushing syndrome, prolonged corticosteroid therapy or immunosuppressive drugs, AIDS, nephropathies, among others, are predisposing conditions for systemic disease. Systemic sporotrichosis with multiple organ or system involvement is a common manifestation in AIDS patients [207, 208].

The manifestation of the different clinical forms of sporotrichosis depends on the balance between the different virulence factors related to the characteristics of the pathogens, as well as the amount and type of inoculum (i.e., conidia or yeast) or the immune state of the host [81]. With the emergence of *S. brasiliensis*, some unusual clinical manifestations of sporotrichosis have become more frequent, such as disseminated or more aggressive infection in immunocompetent and immunosuppressed individuals [157, 208], ocular manifestations [164, 209, 210], hypersensitivity reactions [165], among other atypical forms [165].

Improving early diagnosis is the key to tackle sporotrichosis

Direct research of the etiological agent in human injury, despite the progress of mycological techniques, is still an insecure method due to the scarcity of fungal elements in human lesions. On the other hand, the high fungal load present in the exudate of cat skin lesions favors the direct research of the etiological agent in the lesions of these animals. The reference standard method for the diagnosis of human and feline sporotrichosis in the laboratory is still the cultivation of the material collected from the tissue and exudates for fungal isolation, a method with high sensitivity for both cases, especially if the material is pus from the lesions, although negative cultures do not invalidate the diagnosis of sporotrichosis. Clinical and laboratory diagnosis of sporotrichosis in endemic areas is efficient [211].

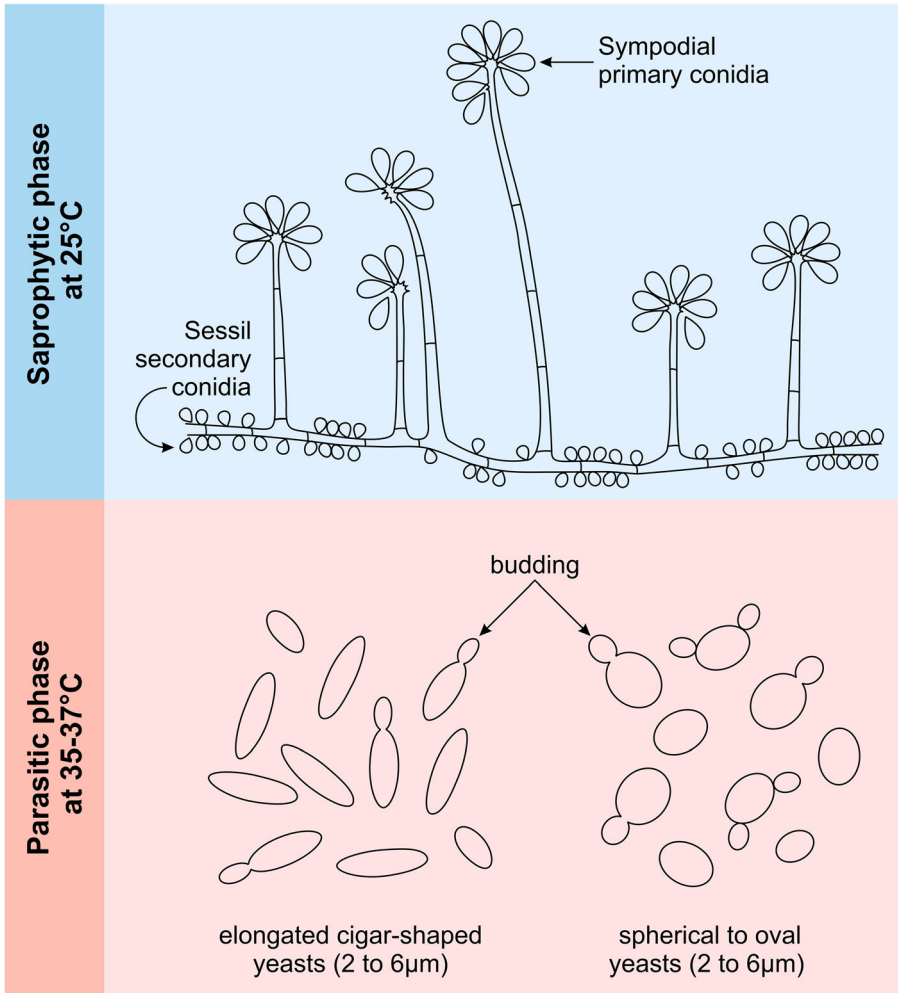

Fig. 6 Morphology of the saprophytic (25 °C) and parasitic (35–37 °C) phase of *Sporothrix*. During growth at 25 °C, *Sporothrix* develops septate hyaline hyphae with erect conidiophores. Two types of conidia are produced: thin-walled hyaline conidia (primary or sympodial conidia) or thick-walled, dark brown conidia (secondary or sessile conidia). The pathogenic phase is characterized by oval or spherical yeasts (2–6 µm), sometimes elongated in a cigar shape

Initial isolation should be done by planting clinical material on SDA and Mycosel Agar at room temperature (25 °C). Colonies are usually visible within 5–15 days, but some may take up to 4 weeks to appear [29, 75]. *Sporothrix* is a thermodimorphic fungus, so the colony isolated at room temperature should then be subcultured on blood agar or BHI followed by incubation between 35 and 37 °C to revert to the yeast phase.

Sporothrix colonies at 25 °C are initially small and creamy and may turn brown, dark gray or almost black within two weeks. Occasionally, some isolates may have poor tolerance at temperatures above 35 °C, especially *S. globosa*. Micromorphological characteristics are important for the generic characterization of *Sporothrix* of clinical interest in the diagnostic laboratory. *Sporothrix* presents delicate hyaline septate hyphae (∼ 1–2 µm wide) with two types of conidia: thin-walled hyaline conidia (also known as primary or sympodial conidia) or thick-walled, dark brown conidia (also known as secondary conidia or sessile conidia). Hyaline conidia are usually oval to elliptical and are arranged in a flowerlike arrangement (daisy bouquet) at the end of the conidiophores. Sessile conidia emerge from undifferentiated hyphae and can be found in different forms such as pyriform and ovoid to spherical (Fig. 6). There is a large morphological overlap in *Sporothrix*, and

speciation based on these traits alone is not recommended [74, 141, 212].

Demonstration of dimorphism helps confirm the identity of the *Sporothrix* included in the clinical clade (i.e., *S. brasiliensis*, *S. schenckii*, *S. globosa* and *S. luriei*), since *Ophiostoma*, *Pesotum* and *Rhinocladiella* can produce unicellular conidia similar to primary conidia of *Sporothrix* spp. Yeast colonies are initially creamy to gray-yellow in color and soft after 5 days of incubation at high temperatures. Microscopically, these colonies are composed of single- or multiple-budding round or oval cigar-shaped cells, similar to those seen in infected cat smears (Fig. 6) [29, 75].

Alternative methods for direct mycological diagnosis in feline sporotrichosis include histopathology, cytopathological examination and immunohistochemistry, with reported sensitivities of 91.3%, 87.0% and 88.6%, respectively [213]. Histopathological examination of the sporotrichosis skin lesion reveals a mixed granulomatous and pyogenic inflammatory process, which can suggest the diagnosis. Characteristic structures that can be seen in tissues include rounded, oval or cigar-shaped yeasts, sometimes surrounded by eosinophilic material, constituting the asteroid body. Examination of exudate from skin lesions of *Sporothrix*-infected cats often reveals numerous round, oval or cigar-shaped yeasts within macrophages and neutrophils or in the extracellular environment [213]. These structures measure 3–5 µm in diameter and 5–9 µm in length and are surrounded by a clear halo. Recently, Gonsales et al. reported the high sensitivity (97.5%) of using cell block cytology (imprint) as an efficient and rapid tool for diagnosing sporotrichosis in cats, particularly during epidemics [214].

Serology has been greatly improved in recent years and is highly sensitive for the detection of circulating antibodies (specifically IgG) against *Sporothrix* antigens [215]. Serology can be an auxiliary tool, especially as serological screening for the diagnosis of clinical forms that resemble other cutaneous diseases such as leishmaniasis or others, when access to the parasitized material is difficult, as well as for cure monitoring. Several antigenic preparations, which range from crude to purified fractions, are used in serological diagnosis. Most cases require only one serum sample, and it is possible to make a presumptive diagnosis of recent or active infection, in addition to serological follow-up. Therefore, serology plays a fundamental role in understanding the prevalence and transmission of this fungus in endemic areas and can also guide the treatment of the disease [166].

Other techniques can be used as alternatives in serological diagnosis, such as immunoblot [216–218], immunofluorescence [219], latex agglutination [220], among others. However, none of the serological tests mentioned above can differentiate the various etiological agents *Sporothrix* spp., since there is a large antigenic overlap of *S. brasiliensis*, *S. schenckii* and *S. globosa* [211, 215].

A good diagnostic technique combines characteristics such as ease of application, speed, accuracy, high sensitivity and low cost [221]. In sporotrichosis, there is growing demand for new molecular diagnostic methods to correctly identify pathogenic species. Correct identification down to species level (e.g., *S. brasiliensis*) requires molecular characterization of the agent. DNA sequencing associated with phylogenetic analysis is the standard reference method for recognition of the 53 *Sporothrix* species, including those of clinical interest (Fig. 7). Major targets used for molecular identification include calmodulin [38], β-tubulin [31], EF-1α [80], ITS1/ITS2 + 5.8s [158], among others. The ribosomal operon is a good barcoding marker, facilitating routine laboratory routine (Fig. 7a). However, in some cases, especially for species included in the *S. pallida* complex, additional markers such as β-tubulin need to be used (Fig. 7b). Calmodulin is an excellent marker for identification as well as it works as an initial step for exploring genetic diversity and population structure in *Sporothrix* (Fig. 2).

Independent DNA sequencing methods are also useful in the diagnosis of sporotrichosis. Some methods are useful for generic *Sporothrix* identification, such as conventional PCR [222], nested PCR [223] and real-time PCR [224]. Molecular techniques capable of differentiating *S. brasiliensis*, *S. schenckii*, *S. globosa* and *S. luriei* employ pure culture extracted DNA and include PCR-RFLP (HhaI enzyme *CAL*-RFLP) [225], species-specific PCR [150], rolling circle amplification (RCA) [226], real-time PCR [227] and T3B RAPD [228].

Matrix-assisted laser desorption ionization–time-of-flight mass spectrometry (MALDI-ToF MS) for rapid and specific fungal identification was first introduced in many developed countries [229] and has recently emerged around the globe as a promising

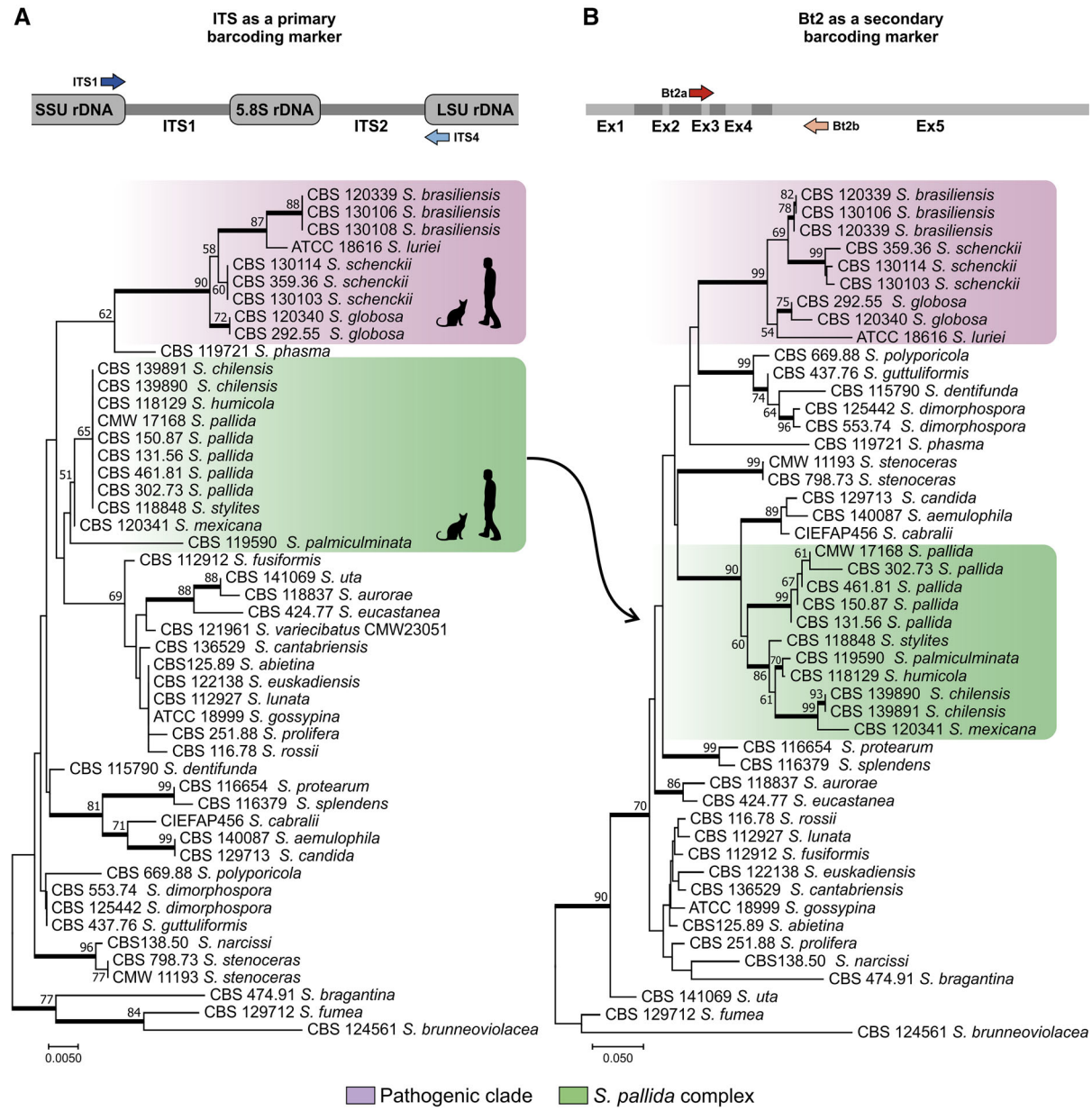

Fig. 7 Molecular identification of sporotrichosis agents can be performed using the ITS region as a barcoding marker. Members of the *S. pallida* complex will require the use of accessory markers to increase the identification power. **a** Phylogenetic relationships between members of clinical and environmental relevance in *Sporothrix*, based on rDNA sequences (IT1 + 5.8 s + ITS2). **b** Phylogenetic relationships based on β-tubulin sequences. Analysis method: neighbor-joining (model: T93 + G). The numbers near the branches refer to the resampling percentages (1000 bootstraps). Sequences were retrieved from Genbank and were previously published [33, 42, 149]

method that is progressively replacing phenotypic identification methods [230]. MALDI-ToF has the advantage of identifying *Sporothrix* directly from colonies grown in culture dishes within minutes, with considerable material and labor savings. The reliability and accuracy of MALDI-ToF in identifying clinically relevant *Sporothrix* have been demonstrated by Oliveira et al. [231] and are comparable to the molecular methods currently in use for the identification of *Sporothrix* spp.

Therapy

The therapy used for the treatment of sporotrichosis is diverse and depends on the severity of the disease, the type and extent of lesions, the patient's immune status and the etiological agent. In emerging countries, potassium iodide is a low-cost drug that has been successfully used to treat the cutaneous or lymphocutaneous forms of human sporotrichosis in immunocompetent individuals [164, 232] and in some feline cases, associated or not with itraconazole [233–235]. Clinical studies prove the effectiveness of this drug using lower dosages that considerably reduce adverse reactions reported by patients or animal owners [166, 233, 235]. Potassium iodide is also recommended for the treatment of cat cases refractory to itraconazole (in those presenting nasal mucosal lesions and respiratory signs) [235]. The precise mechanism by which potassium iodide acts is still unknown [236], although Brilhante et al. [237] recently reported the efficacy of this drug in inhibiting biofilm formation of *Sporothrix* cells, grown in the planktonic state and mature biofilms in both filamentous and yeast forms. Itraconazole is the drug of choice for treatment in humans (100–200 mg/day orally) and cats (8.3–27.7 mg/kg/day) [151, 166, 238], but other azoles (e.g., posaconazole) as well as other antifungal classes, such as allylamine (terbinafine) and polyene (amphotericin B), may be employed depending on the clinical factors and condition of the patient's immune system. The disseminated disease is more difficult to treat than cutaneous sporotrichosis and requires long-term treatment, and amphotericin B is usually indicated, followed by oral itraconazole therapy. To prevent relapse, long-term therapy may be necessary for patients with immunosuppressive conditions [239].

Due to the detection of resistance in some clinical isolates of *S. brasiliensis* [83], in addition to the therapeutic failure of human and feline treatment with conventional drugs [217, 240], there is a need to introduce alternative therapies to increase treatment possibilities. In recent years, research has shown that a variety of natural compounds, synthetics and crude extracts have in vitro antifungal effect against *Sporothrix* spp., which include terpinen-4-ol and farnesol [241], miltefosine [242, 243], pentamidine [244], TCAN26 (a structural analogue of miltefosine) [245], H3 (a 24-sterol methyltransferase inhibitor) [245], clotrimazole [246], β-dihydrofuran naphthoquinone isomers (naphthoquinone) [247], coumarin derivatives [248], as well as extracts of piperaceae (*Piper abutiloides*) [249], marjoram (*Origanum majorana* L.) and rosemary (*Rosmarinus officinalis* L.) [250, 251]. Many of the above compounds show synergism with itraconazole as well as significant antifungal activity against itraconazole resistant isolates. However, studies with appropriate animal models should be performed to evaluate the effectiveness and safety of alternative therapeutic regimens [29].

Molecular identification of *Sporothrix* species associated with in vitro susceptibility testing is important to aid in treatment choice and management. *Sporothrix brasiliensis* shows lower MICs and generally responds well to antifungal drugs in most clinical cases, whereas *S. mexicana* shows higher MICs and is tolerant in vitro to the action of the main commercially available antifungals for the treatment of sporotrichosis [83, 252]. The effectiveness of posaconazole and amphotericin B against *S. brasiliensis* and *S. schenckii* has been demonstrated by in vivo studies using murine models of infection and treatment [253–256]. A moderate efficacy of voriconazole against *S. schenckii* infection has been reported in murine sporotrichosis, whereas in animals infected with *S. brasiliensis* the drug did not work [254].

Thermotherapy and cryotherapy are occasionally used in humans (for example, in pregnant women with localized disease or in very thick verrucous lesions) and in cats, alone or in combination with antifungals [257–260]. The success of thermotherapy has been demonstrated in a feline case with localized lesion [151]. In this technique, the skin temperature in the lesion area is increased to 42–43 °C twice a day with a hot water bag, infrared source or other methods [257].

Perspectives

Further knowledge is needed of the epidemiology and transmission dynamics of *Sporothrix*. The epidemiology of sporotrichosis is no longer the same after the improvements made to the taxonomic classification system. In addition, the use of more refined molecular techniques has changed the secular view of an occupational disease associated with plant and soil management. New molecular technologies have emerged in recent years with the power to reveal the

entire genome of a microbe at a low cost. These will help track *S. brasiliensis* during outbreaks as well as reveal the factors underpinning *S. brasiliensis* emergence in mammals.

The *Sporothrix* sporotrichosis system is moving toward the era of comparative and functional genomics, which will allow exploring new horizons in molecular epidemiology, ecology, diagnosis and pathogen–host relationship. The alternative route broke a paradigm in a disease in which classic transmission was unaltered for over a century. We must anticipate the emergence of *Sporothrix* outbreaks based on the lessons taken from recent episodes. Ecological studies are desirable because there is uncertainty about the *Sporothrix* reservoirs in the environment. Human sporotrichosis and feline sporotrichosis are treatable diseases. However, prompt and accurate diagnosis is important for early institution of antifungal treatment, which in the case of cats can disrupt the chain of transmission of the fungus to humans and other animals. It is essential to communicate better with the public. Public awareness and education about responsible animal keeping and the main aspects of transmission in endemic areas are important tools to contain future outbreaks and to limit the expanding frontiers of this emerging and re-emerging disease.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

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