

## Rhinosporidiosis in the Americas: A Systematic Review of Native Cases

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**Abstract.** Rhinosporidiosis is a chronic mucosal infection caused by *Rhinosporidium seeberi*, an aquatic protistan parasite. It presents as nasal or ocular polypoidal or vascularized masses. It is endemic in tropical and subtropical areas, especially in South Asia; *R. seeberi*'s endemicity in the Americas is often overlooked. The objective of this study was to describe the demographic and clinical characteristics of patients with rhinosporidiosis in the Americas, its management, and patient outcomes. This study is a systematic review of cases of human rhinosporidiosis in the Americas reported in the literature from 1896 to February 28, 2019. This review screened 1,994 reports, of which 115 were eligible for further analysis. The selected reports described 286 cases of human rhinosporidiosis between 1896 and 2019. Cases were diagnosed in Brazil (32.2%), Colombia (24.4%), Paraguay (12.6%), and the United States (11.9%). The majority of the cases (91%) occurred in geographic areas with altitudes < 1,000 m above sea level and in areas with median temperatures  $\geq 25^{\circ}\text{C}$  (67.3%). Most of the patients presented nasal (65%) and ocular involvement (35%). Surgical treatment was provided for 99.6% of patients, but 19.8% of them recurred. This review describes the under-recognized geographic distribution and clinical presentation of rhinosporidiosis in the Americas and highlights clinical differences to cases in Asia, specifically in reference to a higher prevalence of ocular disease and higher relapse rates.

### INTRODUCTION

Rhinosporidiosis is a chronic mucosal infection caused by *Rhinosporidium seeberi*. It is a pathogen with debated taxonomy because neither culture methods nor animal models are available. It had been classified as a sporozoan and as a fungus; however, it has been reclassified under a new clade of aquatic protistan parasites, Ichthyosporidia (Mesomycetozoa), through molecular methods.<sup>1–6</sup> The presumed natural habitat of *R. seeberi* is stagnant water, and infection probably occurs through transepithelial penetration. The most common clinical presentation is that of polypoidal or vascularized masses, especially in the nasal cavity (70–75%) and in the eye (10–18%).<sup>7–9</sup> Rare locations include the genitourinary tract, anal canal, lung, liver, spleen, bone, and brain.<sup>7,10–13</sup> Documentation of mature sporangia and endospores in tissue biopsy is the gold standard for diagnosis. Surgical resection is the treatment of choice; anecdotally, dapsone has been used to prevent recurrences.<sup>1,11,12,14</sup>

The disease has an almost universal distribution; cases have been reported in all continents except Australia. It is endemic in tropical and subtropical areas. Most cases are reported in South Asia, especially India and Sri Lanka (88%), followed by South America and Africa.<sup>2,7,9–11</sup> Although the disease was first described in Argentina more than a century ago, adequate environmental conditions for transmission are present throughout the Americas, and endemic areas in Paraguay and Brazil have been reported, the endemicity of *R. seeberi* in the Americas is still underrecognized.<sup>10,15–18</sup> Characterization of this disease in the continent has been limited due to a paucity of reports, often published in low-impact journals.

The objective of this review was to describe the demographic and clinical characteristics of patients with rhinosporidiosis in the Americas, its management, and patient outcomes.

### MATERIALS AND METHODS

**Eligibility criteria.** All the studies that described human cases of rhinosporidiosis in the Americas were included. Studies describing cases of rhinosporidiosis in animals or continents other than America were excluded.

**Search strategy.** A search of the Lilacs, PubMed, and Google Scholar databases was performed from 1896 to February 28, 2019, with the following search terms: (“*Rhinosporidium*” [MeSH Terms] OR “rhinosporidiosis” [MeSH Terms] OR “rhinosporidium” [All Fields] OR “*Rhinosporidium seeberi*” [All Fields] OR “rhinosporidiosis” [All Fields] OR “rhinosporidiosis” [DeCS]). The search limit was species (“Humans”). The search was performed without language restrictions. A manual search for references cited in the reviewed articles was performed. Authors of articles with incomplete information were contacted.

**Criteria for case selection.** The first investigators (PS, ZN, ACA) performed the literature search, eliminated duplicate articles, and reviewed the titles and abstracts against the predefined eligibility criteria. Full-text articles were obtained from the databases, main authors, universities, and scientific organizations. Full-text articles were reviewed by four investigators (PS, ZN, CJJ, and ACA); any discrepancy was resolved by consensus between the authors.

**Data extraction and analysis.** Information about sex, age, lesion location, type of lesion, type of treatment, outcome, risk factors, and place of residence of each patient was registered in a Microsoft Office Excel database. Geolocation with the ArcGIS Online program was performed for cases that described the place of residence.

**Ethics.** This was a retrospective study, based on previously published articles. Approval by the investigation ethics committee was not required.

### RESULTS

A total of 1,994 articles were screened; these included 874 articles in the Google Scholar database, 504 in the PubMed database, and 613 in the Lilacs database. Screening by title and abstract resulted in the exclusion of 314 articles referring

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to animals, 1,538 articles of cases from continents other than America, and 10 articles that were not case reports. The full-text versions of 19 eligible articles were not available and were not included in the final analysis. Ultimately, 115 articles were selected for final analysis, describing 286 cases of rhinosporidiosis (Figure 1; Supplemental materials). Of these 286 cases, 156 had reported residence data for geolocation. One of the reports was a case series that presented compiled data rather than individual patient information.

The selected reports described 286 rhinosporidiosis human cases between 1896 and 2019 in the Americas. Cases were diagnosed in Brazil (92 cases, 32.2%), Colombia (64 cases, 24.4%), Paraguay (36 cases, 12.6%), United States (34 cases, 11.9%), Venezuela (18 cases, 6.3%), and Argentina (13 cases, 4.5%) (Table 1). Geolocation for these cases is depicted in Figure 2. For the geographic areas involved, the median altitude above sea level was 134 m (interquartile range [IQR]: 30–357.5), the median annual precipitation was 1,356 mm (IQR: 1,011–1,891), and the median average annual temperature was 25.9°C (IQR: 20.2–27.4). City of origin was available for 156 patients; 91% (142) of cases occurred in geographic areas with altitudes < 1,000 m above sea level and 67.3% (105) in regions with median temperatures  $\geq 25^\circ\text{C}$ .

Most patients were male ( $N = 220$ ; 77.7%), with a median age of 15 years (IQR: 11–24.8) (Table 2). Risk factors were described for 33 patients; the most common one was exposure to free-flowing or stagnant water. Lesions were located in the nasal area in 65% ( $N = 186$ ) of patients and in the ocular area in 35% ( $N = 100$ ) of patients. These lesions were described as polypoid in 156 patients (68.7%), tumoral in 39 patients (17.2%), and papillomatous in 21 patients (9.3%).

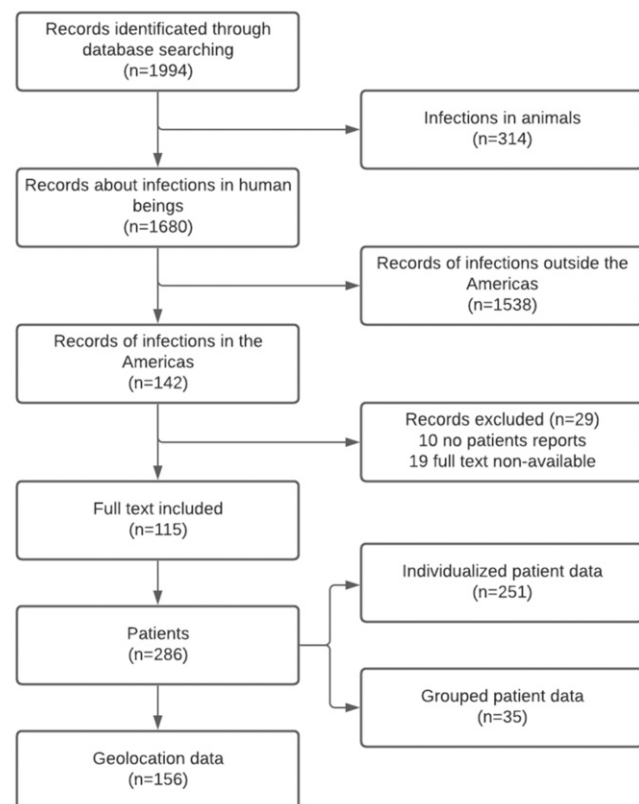


FIGURE 1. Flow diagram of database search.

TABLE 1

Demographic characteristics of patients with rhinosporidiosis in the Americas

Characteristic	Patients ( $N = 286$ ), $n$ (%)
Country	
Brazil	92 (32.2)
Colombia	64 (22.4)
Paraguay	36 (12.6)
United States	34 (11.9)
Venezuela	18 (6.3)
Argentina	13 (4.5)
Mexico	9 (3.1)
Chile	5 (1.7)
Ecuador	4 (1.4)
Cuba	4 (1.4)
Canada	2 (0.7)
Panama	2 (0.7)
Bolivia	1 (0.3)
Costa Rica	1 (0.3)
French Guyana	1 (0.3)
Average temperature ( $^\circ\text{C}$ ), median (IQR)	25.9 (20.2–27.4)
Temperature, $^\circ\text{C}$ ( $N = 105$ )	
< 15	10 (9.5)
15–17.9	8 (7.6)
18–23.9	20 (19)
$\geq 24$	67 (63.8)
Altitude (a.a.s.l.), median (IQR)	134 (30–357.5)
Altitude (a.a.s.l.)	
0–900	93 (88.6)
901–1,700	5 (4.8)
1,701–2,500	2 (1.9)
> 2,500	5 (4.8)
Annual precipitation (mm), median (IQR)	1,356 (1,011–1,891)
< 750	11 (10.5)
750–1,249	30 (28.6)
150–1,749	36 (34.3)
$\geq 1,750$	28 (26.7)

a.a.s.l. = altitude above sea level; IQR = interquartile range.

Only two patients with ocular rhinosporidiosis presented with staphyloma.<sup>19,20</sup> Surgical treatment alone was provided for 236 patients (99.6%), 24 (10.3%) patients underwent cauterization in addition to surgical treatment, and seven (3.1%) patients received medications in addition to surgical treatment. Disease recurrence was documented in 26 of 131 cases (19.8%) for whom follow-up information was available. Of these 26 patients, one had HIV infection, and four had two or more documented episodes of recurrence. Of the 16 patients treated with surgical resection and cauterization for whom follow-up information was available, three (18.8%) had recurrent disease.

## DISCUSSION

Although *R. seeberi* is a pathogen with an almost universal distribution, its associated disease, rhinosporidiosis, has been greatly overlooked in endemic areas of the Americas.<sup>11,16,17</sup> It is renowned as an Asiatic disease and is characterized as endemic in Paraguay and Brazil only by a few authors.<sup>10,15–18</sup> In this systematic review, we identified 115 articles describing 286 cases of rhinosporidiosis in the Americas.

The countries with most of the reported cases were Brazil (32.2%), Colombia (22.4%), Paraguay (12.6%), and the United States (11.9%). The relative frequency of cases in these geographic areas is not surprising because most of the reported cases occur in ecosystems found throughout these countries: arid areas (precipitation < 200 mm) or tropical areas (average temperature > 24°C, altitude 0–1,000 m above sea

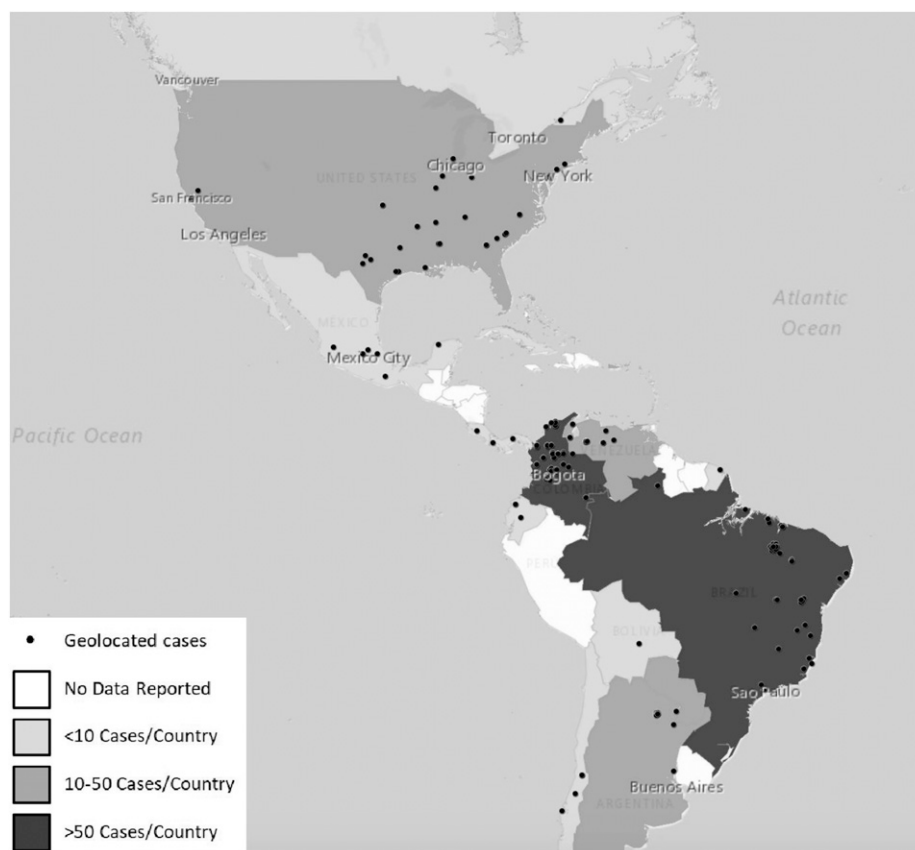


FIGURE 2. Geolocation of the reported cases of rhinosporidiosis in the Americas. This figure appears in color at [www.ajtmh.org](http://www.ajtmh.org).

level, and annual precipitation of 1,750–2,000 mm).<sup>3,11,18,20</sup> However, although 91% of cases did occur at low altitudes (< 1,000 m above sea level, median altitude of 134 m above sea level), only 67.3% of the cases occurred in geographic areas with median temperatures  $\geq 25^{\circ}\text{C}$ .

Based on circumstantial data, the presumed natural habitat of *R. seeberi* is stagnant or ground waters.<sup>3,11,12</sup> More convincing evidence of this association comes from an outbreak in Serbia, where 17 patients bathed during a holiday in the same lake and developed rhinosporidiosis.<sup>21</sup> In this review, 72.7% of the cases for whom this information was available reported exposure to free-flowing or stagnant water. Reports of rhinosporidiosis in dry areas of Sri Lanka suggest *R. seeberi* can survive in these types of environments and be infective.<sup>9,11,22</sup> The presumed mode of infection is the contact of a disrupted epithelial layer with water or dust containing *R. seeberi*. Similar to what is reported in India, most of the cases in this review lived in cities with rivers or lakes in the vicinity, where people usually bathe.<sup>8,9,11</sup>

Similar patients with rhinosporidiosis from other geographic areas, patients in the Americas are young (median age 15 years) and predominantly male.<sup>8,9,23</sup> Nasal compromise is the most frequent clinical presentation reported in both Asian cohorts and in the Americas.<sup>1,3,9,12</sup> Patients with nasal involvement usually present with a slow disease course of nasal obstruction, tumor-like masses, or bleeding.<sup>3,12,14</sup> With the exception of predominant ocular involvement reported in an outbreak in Serbia and in Sri Lanka where the main exposure was to water bodies,<sup>9,21</sup> ocular involvement is reported only for 10–18% of the cases in geographic areas outside of the

Americas; in contrast, 35% of patients in the Americas present with ocular involvement.<sup>7–9,12</sup> The relatively high incidence of ocular disease in the Americas could be related to the transmission mechanism with direct ocular inoculation (in dusty areas or direct contact with river water), as proposed by some authors, or to the pathogenicity of *R. seeberi* species in the Americas.<sup>9,24</sup> Patients with ocular involvement usually present with tumor-like masses or polyps affecting the conjunctiva and lacrimal sac. Patients complain of a foreign body sensation, ocular irritation, and tearing. Rare complications are visual impairment and staphyloma, which occurs due to scleral thinning and herniation of the intraocular content.<sup>7,8,20</sup> In this series only two cases of staphyloma were reported.<sup>19,20</sup>

In the Americas, 99.6% of cases were treated by surgical resection, which is the gold standard for treatment.<sup>9,20</sup> Despite surgical management, recurrence was reported for 19.8% of the cases with available follow-up information. This number is in sharp contrast with a 2–5.8% relapse rate reported for patients in Asia, with the exception of one case series in Sri Lanka that reported a recurrence rate of 37% and up to 100% for patients with disseminated disease.<sup>1,7,9–11,13,23</sup> Recurrences may be related to incomplete surgical excision of the lesion by its base; thus, some authors have proposed adding cauterization of the wound to surgical resection to prevent relapse.<sup>20</sup> However, our study showed that cauterization after surgery did not improve relapse rates (18.8%).<sup>10,25</sup> Other possible causes for the high relapse rate are re-exposure to the pathogen, underlying host factors, or higher virulence of the pathogen specific to the Americas species. In the

TABLE 2

Clinical characteristics, treatment, and outcome of patients with rhinosporidiosis in the Americas

Variable	Patients (N = 286) n (%)
Sex (N = 283)	
Male	220 (77.7)
Age (years), median (IQR)	15 (11–24.8)
< 10	35 (17.2)
10–19	97 (47.5)
20–30	37 (18.1)
> 30	35 (17.2)
Risk factor (N = 33)	
Free flowing or stagnant water (wells, rivers, and dams)	24 (72.7)
Horses, cows, and dogs	10 (30.3)
Goats	1 (3)
Cotton picking	1 (3)
Lesion localization	
Nasal	186 (65)
Nasal	184 (64.3)
Nasopharynx	2 (0.7)
Ocular	100 (35)
Conjunctival	90 (31.5)
Palpebral	6 (2.1)
Ocular	3 (1.0)
Lacrimal	1 (0.3)
Type of lesion (N = 227)	
Polypoid	156 (68.7)
Tumoral	39 (17.2)
Papillomatous	21 (9.3)
Granulomatous	4 (1.8)
Flat	4 (1.8)
Hemangiomas like	1 (0.4)
Carcinomatous like	1 (0.4)
Verrucous like	1 (0.4)
Medical treatment (N = 234)	
No	228 (97.4)
Dapsone	2 (0.9)
Antibiotic	2 (0.9)
Diamino diphenyl sulfone	2 (0.9)
Itraconazole	1 (0.4)
Surgical treatment (N = 237)	236 (99.6)
Cauterization (N = 234)	24 (10.3)
Cryotherapy (N = 234)	2 (0.9)
Outcome (N = 131)	
No relapse	105 (80.2)
Relapse	26 (19.8)

Americas, most patients had short follow-up periods of 6 months to a year; only in a few cases the follow-up period extended for up to 8 years.<sup>10,19,20,26–34</sup> The follow-up period in Asian cases is usually only 6–18 months. The Sri Lanka cohort reports a high recurrence rate but does not specify the follow-up period, which may have been longer.<sup>8,9,13,23,25,35–38</sup>

This study has some limitations. The main limitation of this study was its reliance on published data, which probably represent just a fraction of the total number of cases in an area due to under-reporting. Moreover, the reported cases in the literature probably depict unusual cases, which may represent a bias toward a higher incidence of ocular compromise and high relapse rates. Finally, some articles were not available for review or had incomplete information.

In conclusion, this review highlights the neglected endemicity of *R. seeberi* in the Americas, especially in low-altitude areas in South America (< 1,000 m above sea level). The clinical presentation is similar to the one reported in Asia, with a higher prevalence of ocular involvement and higher relapse rates. The generalized unawareness of this disease's local

endemicity may translate to a lack of recognition of its clinical presentation and missed opportunities for diagnosis and treatment. Thus, educating the medical community about where this disease presents, as well as on its early recognition and treatment, is of critical importance.

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