Medical Mycology November 2011, **49**, 785–798

informa
healthcare

Review Article

Epidemiology of endemic systemic fungal infections in Latin America

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Although endemic mycoses are a frequent health problem in Latin American countries, clinical and epidemiological data remain scarce and fragmentary. These mycoses have a significant impact on public health, and early diagnosis and appropriate treatment remain important. The target population for endemic disease in Latin America is mostly represented by low-income rural workers with limited access to a public or private health system. Unfortunately, diagnostic tools are not widely available in medical centers in Latin America; consequently, by the time patients are diagnosed with fungal infection, many are already severely ill. Among immunocompromised patients, endemic mycoses usually behave as opportunistic infections causing disseminated rather than localized disease. This paper reviews the epidemiology of the most clinically significant endemic mycoses in Latin America: paracoccidioidomycosis, histoplasmosis, and coccidioidomycosis. The burdens of disease, typically affected populations, and clinical outcomes also are discussed.

Keywords Latin America, endemic mycoses, paracoccidioidomycosis, histoplasmosis, coccidioidomycosis

Introduction

The rich diversity of Latin American biomass and climates provides a similarly rich range of habitats for different microorganisms, including pathogenic fungi. Additionally, the countries within this region have a large population of rural workers who are primarily engaged in agricultural activities and are exposed to diverse fungal habitats in soil [1]. They are, therefore, at increased risk for inhaling infectious conidia or from fungal inoculation by transcutaneous trauma.

Received 19 August 2010; Received in final revised form 3 March 2011; Accepted 29 March 2011

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DOI: 10.3109/13693786.2011.577821

Endemic mycoses are frequently found throughout Latin America, where they have an important impact on public health. These mycoses include histoplasmosis (caused in Latin America by two of the eight groups of *Histoplasma capsulatum* clades; the A and B clades [2]), paracoccidioidomycosis (PCM; *Paracoccididoides brasiliensis*), and coccidioidomycosis (CM; *Coccidioides immitis* and *C. posadasii*).

Despite the substantial number of patients with endemic mycoses in this region, clinical and epidemiological data remain scarce and fragmentary. Information is often reported in case studies, which frequently focus on exceptional rather than typical clinical situations and are often written in Spanish or Portuguese. The objective of this article is to review the epidemiology of the most clinically significant systemic endemic mycoses in Latin America, providing a critical evaluation of the burden of the disease, populations that are typically affected, and

clinical outcomes. Although clinical presentation of these mycoses is not the focus of this article, it is a factor attending physicians should be aware of.

Methods

We identified and reviewed published articles on PCM, histoplasmosis, and CM using the complete Scientific Electronic Library Online (SciELO) and MEDLINE databases up to May 2010. Articles were reviewed irrespective of date and language of publication. Articles were retrieved using the following key words: fungal infection, mycosis, endemic mycosis, paracoccidioidomycosis, histoplasmosis, and coccidioidomycosis. Each of these search terms was combined with the following: Latin America, South America, Central America, Mexico, Brazil, and Argentina.

An additional search was performed on MEDLINE and SciELO from 1975 to 2010 with the following search terms: 'skin test survey' plus paracocciodioidomycosis, coccidioidomycosis, histoplasmosis, spherulin, paracoccidioidin, or histoplasmin. Surveys in non-Latin American countries or in animals were removed.

The reference lists of major English-, Spanish-, and Portuguese-language reviews dealing with fungal infections or endemic mycoses also were examined to ascertain that no relevant references had been missed during our initial literature searches.

In the course of our analysis, we made exhaustive efforts to collect all available information on the following topics: geographical distribution of the fungal infections of interest, incidence and prevalence rates, susceptible populations, mortality rates, and sequelae.

Results

Paracoccidioidomycosis

PCM, previously identified as South American blastomycosis, is an endemic systemic fungal infection caused by the thermally dimorphic fungus *Paracoccidioides brasiliensis* [3,4]. Recently, the use of molecular methods showed that *P. brasiliensis* is not a single species but rather a species complex comprising at least three cryptic species: S1 (present in Brazil, Argentina, Paraguay, Peru, and Venezuela); PS2 (*P. lutzii*; from Brazil and Venezuela); and PS3 (restricted to Colombia) [5]. The clinical impact of this genotypic diversity has not been evaluated.

While histoplasmosis is the most prevalent systemic mycosis in Central American countries [6], PCM is predominantly found in South America [7–9]. Approximately 80% of PCM cases in Latin America have been reported in Brazil, primarily in the states of São Paulo, Paraná, Rio Grande do Sul, Goiás, Rio de Janeiro, and Rondonia [10,11]. Cases also have been reported in Venezuela, Colombia, Ecuador, and Argentina [10,12]. No cases have been reported in Chile, Surinam, Nicaragua, or Belize [3]. With the exception of one case each in Trinidad, Granada, and Guadeloupe, the Caribbean Islands appear free of this mycosis [13]. Nonautochthonous cases have been reported outside endemic areas but only in patients who have lived in or visited Latin America [3,14]. Figure 1 shows the geographical distribution of PCM in Latin America [15].

The fungus has been isolated only sporadically from the environment; the disease has a long period of latency and no outbreaks have been reported [16]. Consequently, its true ecological niche remains unclear [8]. Most available data on the habitat of this pathogen suggest that the fungus is a soil saprophyte, where it appears to be most prevalent in regions with acidic soil [17]. Cases of PCM are seen mostly in regions with significant rainfall, abundant forests, waterways, and temperature variation limited to 17–24°C [18]. In a large series of Colombian cases, several independent ecological variables were found to be significant: altitude from 1,000–1,499 m above sea level, yearly rainfall from 2,000–2,999 mm, and the presence of humid forests and coffee/tobacco crops [19]. Simoes *et al*. [20]

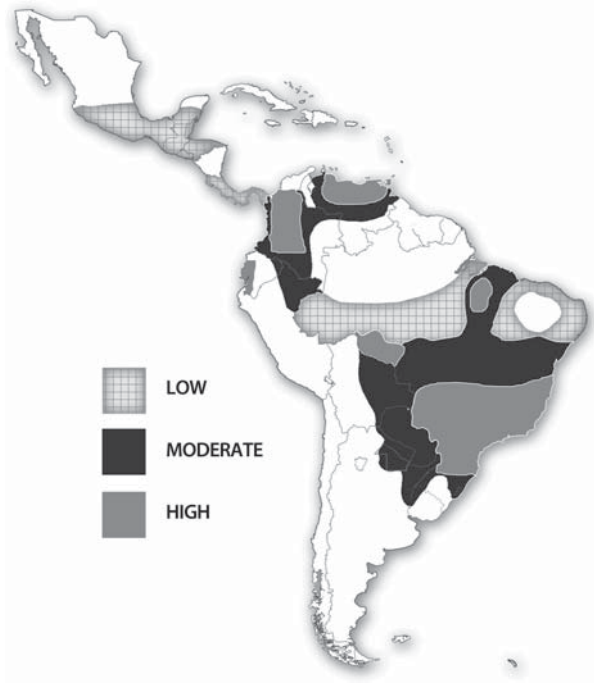

Fig. 1 Map showing the distribution of paracoccidioidomycosis in Latin America. Reprinted from Springer. In Kauffman C, Mandell G. *Atlas of Fungal Infections*. 2nd edition; Philadelphia, Pennsylvania, 2007. Paracoccidioidomycosis. Colombo AL, Queiroz-Telles F. Figure 4-1; © 2007 with kind permission from Springer Science + Business Media BV [163].

explored climatic influences on PCM by establishing ecologic correlates related to distribution of this infection in a hyperendemic area in southeastern Brazil. It was found that certain types of soils plus high annual precipitation rates (1,500 mm and 1,600 mm) were significantly associated with prevalence density [20]. Barrozo *et al*. further analyzed the records of 91 acute/subacute patients in whom infection was calculated to have occurred 1–2 years previously and found that absolute air humidity, soil water storage, and Southern Oscillation Index enhanced human infection [21].

PCM is observed as a natural infection mostly in humans; however, sporadic infections have been reported in wild and domestic animals, particularly in the nine-band armadillo (*Dasypus novemcinctus*) [16–22]. Both humans and animals are thought to acquire PCM by inhalation [17]. *P. brasiliensis* usually causes a benign and transient pulmonary infection that may progress to an acute form or more frequently (>90%) reactivate later as a chronic and insidious disease [10,14,23].

Approximately 10 million people in Latin America are infected with *P. brasiliensis*, of whom only about 1–2% will develop PCM [24]. The infection is usually acquired during the first two decades of life (peak incidence between 10 and 20 years of age); clinical manifestations are uncommon in this age group and generally occur in a small percentage of individuals by reactivation of a latent infection [25].

Several investigators have indicated that PCM is more prevalent among rural workers engaged in intensive agriculture, particularly in coffee, cotton, and tobacco plantations [1,19]. However, this epidemiological scenario may change according to new agricultural practices. The significant increase in sugar cane plantations in the southwest region of Brazil may result in a decrease in the incidence of PCM; growing sugar cane is usually associated with heavy pesticide use (including antifungal azole derivatives) and plant burning, which may significantly elevate the soil temperature. The combination of these agricultural practices may affect several soil microorganisms, including *P. brasiliensis* [1].

In a case-control study conducted in an endemic PCM area in Brazil, the risk of developing PCM was 14-fold greater in smokers than nonsmokers and 3.6-fold greater among individuals with an alcohol intake of 50 g/day compared with those with lesser or no alcohol intake [26]. The chronic form of the disease is mostly documented among male rural workers aged 30–60 years from endemic areas [3]. Women appear to be protected from the disease but not infection, probably due to estrogen suppression of the mycelial-to-yeast transformation and its accompanying influence on immune functions [3,10,17,27,28]. Although cell-mediated immunity plays a major role in the defenses against *P. brasiliensis*, the disease is not prevalent among patients with AIDS or others with severe T-cell mediated immunodeficiency (e.g., cancer patients and organ transplantation recipients) [3]. Retrospective chart reviews at Brazilian university hospitals have identified few patients with comorbid PCM and HIV/AIDS infection; rates of coinfection range from 0.8–1.5% [29–32]. However, a study of 3,583 deaths due to systemic mycoses in AIDS patients in Brazil from 1996–2006 reported that PCM was the most frequently reported cause of death (~51% of all deaths due to systemic mycoses) [33].

Table 1 presents the results of the literature search for epidemiological skin test surveys for *Paracoccidioides* in Latin America [34–60]. A 1998 summary of 58 epidemiological surveys of paracoccidioidin test in Brazil reported a wide variation in the percentage of individuals testing positive for infection, ranging from 2.0% among children in a Rio de Janeiro slum to 82.0% in Cachoeira do Sul, Rio Grande do Sul [61]. In the Bolívar state in southern Venezuela, PCM is an endemic disease with one to seven cases diagnosed each year [34]. The rate of *P. brasiliensis* infection as determined through paracoccidioidin skin testing was 13.2% in rural (Monte Ralo) and 19.7% in urban (Upata) areas [34,35].

From 1984 to 1994, the incidence of PCM in Colombia fluctuated between 0.5 and 2.2 cases per million inhabitants [19]. *P. brasiliensis* infection rates, as determined by paracoccidioidin skin testing of up to 65%, were reported in three communities where cases of acute PCM had been found; contact with bats was associated with high infection rates [36]. The environmental characteristics associated with the highest incidence rate ratios (IRRs) in 940 patients who developed PCM were an altitude of 1,000–1,499 m above sea level (IRR = 6.37), annual rainfall of 200–300 cm (IRR = 2.15), presence of humid forests (IRR = 1.79), and coffee and tobacco crops (IRR = 3.59) [19]. From 1989 to 1998, the Corporación para Investigaciones Biológicas and the Laboratorio de Salud Pública diagnosed 76 PCM cases, of which two occurred in HIV-infected individuals [62]. Both of these individuals were severely immunosuppressed at the time of diagnosis. In one case, the diagnosis of PCM preceded the AIDS diagnosis; in the other case, the diagnoses were made simultaneously.

PCM also is endemic in the northeastern and northwestern parts of Argentina [37]; epidemiological surveillance through paracoccidioidin skin testing has been performed in northeastern and northwestern subregions of the country [37–39,63]. In 2000 to 2001, PCM was the most frequently diagnosed mycosis in patients suspected of having a systemic mycosis (47 of 965 patients in 25 medical centers from 12 provinces and Buenos Aires) [64].

PCM is a disseminated process involving many different organs and tissues, particularly the lungs, skin, upper

Table 1 Results of epidemiological *Paracoccidioides*, *Histoplasma*, and *Coccidioides* skin test surveys in Latin America published between 1975 and 2010.

Reference	Region/State, Country	Population	Patients, *n*	Percentage positive
Lima *et al*. 1975 [40]	Piaui, Brazil	Residents aged 0–≥50 years	177	6.2 PCD 14.7 HSM
Veronesi *et al*. 1975 [41]	Sao Paulo, Brazil	Median age 20 years	170	12.0 PCD 25.3 HSM
Fava Netto *et al*. 1976 [99]	Sao Paulo, Brazil	PCM patients	100	24.0 HSM
Netto *et al*. 1976 [42]	Sao Paulo, Brazil	Aged 9–60 years	79	10.1 PCD 8.9 HSM
Moraes & Almeida 1976 [100]	Matto Grosso, Brazil	Residents aged 0–≥50 years	95	63.1 HSM
Campos & Fava Netto 1978 [43]	Sao Paulo, Brazil	Residents aged 0–60 years	160	35 PCD 25 HSM
Lacaz *et al*. 1978 [146]	Sao Paulo, Brazil	Hospital patients aged >11 years	347	0.3 CD*
Lacaz *et al*. 1978 [147]	Sao Paulo, Brazil	Aged 11–80 years	393	0.25 CD*
Mok & Netto 1978 [44]	Amazonas, Brazil	Long-term residents aged >11–80 years	495	4.8 PCD 42.3 HSM
de Andrade *et al*. 1984 [45]	Bahia, Brazil	Aged 3 months–73 years	177	5.6 PCD
Bagatin 1986 [46]	Sao Paulo, Brazil	Workers and patients aged 15–30 years	226	49.6 PCD
Guedes *et al*. 1986 [47]	Amazonas, Brazil	Residents aged 30–80 years	109	4.6 PCD 12.8 HSM
Hay *et al*. 1987 [48]	Georgetown, Guyana	Hospital patients and laboratory workers aged 9–71 years	49	67.3 PCD (30.6% in those with negative HSM tests)
Pereira 1988 [49]	Goiás, Brazil	Residents aged 0–≥60 years	966	19.5 PCD
da Costa *et al*. 1989 [50]	Paraíba, Brazil	Residents aged ≥2 years	1,957	19.5–57.4 PCD 18.5–31.5 HSM
de Martin & de López 1989 [51]	Panama City, Panama	Children aged 2–15 years	110	12.7 PCD
Fredrich 1989 [148]	Tijuana, Mexico	Aged 9–57 years	1,128	10.0 CD†
Diógenes *et al*. 1990 [52]	Ceará, Brazil	Residents aged ≥5 years	138	32.1 PCD 61.5 HSM
Santos & Pedrosa 1990 [53]	Alagoas, Brazil	Aged 2–71 years	107	11.2 PCD 14.0 HSM
Suárez Hernández *et al*. 1992 [101]	Ciego de Avila, Cuba	Poultry farm workers Other workers	392 265	28.8 HSM 13.2 HSM
van Gelderen de Komaid *et al*. 1992 [38]	Tucumán, Argentina	Aged 3–110 years	224	0.9 PCD 53.6 HSM
Cadavid & Restrepo 1993 [36]	Antioquia, Colombia	Long-term residents aged >11 years	54	45 PCD
Coimbra *et al*. 1994 [54]	Rondônia/Mato Grasso, Brazil	Attempted to test all members 3 different tribes aged >1 year	552	6.4–43.8 PCD 5.8–80.5 HSM
van Gelderen de Komaid *et al*. 1995 [37]	Tucumán, Argentina	Aged 0–90 years	229	1.7–9.2 PCD 21.3–48.3 HSM
Mangiaterra *et al*. 1996 [55]	Chaco, Argentina	Children aged 2–15 years	344	1.6 PCD 9.2 HSM
Rodrigues & Resende 1996 [56]	Minas Gerais, Brazil	Adult male mining workers	417	13.4 PCD 17.5 HSM
Padua y Gabriel *et al*. 1999 [149]	Coahuila, Mexico	Aged 8–98 years	1,653	40.2 CD
van Gelderen de Komaid *et al*. 1999 [39]	Tucumán, Argentina	Aged 6–86 years	287	0–10.2 PCD 22.4–38.1 HSM
Kalmar *et al*. 2004 [57]	Mato Grosso, Brazil	Children aged 7–18 years	282	4.6 PCD‡
Cermeño *et al*. 2005 [35]	Bolívar, Venezuela	Aged 6 months–65 years	193 204	19.7 PCD 34.0 HSM
Cermeño *et al*. 2004 [34]	Bolívar, Venezuela	Aged 6 months–65 years	173 175	13.2 PCD 42.7 HSM
Fornajeiro *et al*. 2005 [58]	Paraná, Brazil	Aged 18–61 years	118	43 PCD‡
Gascón *et al*. 2005 [102]	Various	Spanish travelers to Latin America	342	20.2 HSM
Zembrzuski *et al*. 2005 [59]	Rio Grande do Sul, Brazil	Male soldiers aged 17–19 years	354	39–82 PCD 48–89 HSM
Cermeño *et al*. 2009 [60]	Bolívar, Venezuela	Aged 6 months–65 years	275 275	10.2 PCD 7.6 HSM

CD, coccidioidin; HSM, histoplasmin; PCD, paracoccidioidin.
*Coccidioidomycosis tested using spherulin.
†Coccidioidomycosis tested using coccidioidin and spherulin.
‡Paracoccidioidomycosis tested using 43-kD glycoprotein (gp43).

gastrointestinal tract, lymph nodes, adrenal glands, and central nervous system (CNS), as well as other organs [11,12,14,65–67]. Recent studies suggest that the natural course of PCM consists of two different clinical stages: the first stage is characterized by the presence of mucosal lesions plus alveolar-interstitial infiltrates; the second stage by skin lesions plus the existence of lung fibrosis [68]. The former would correspond to disease of shorter duration, and the latter to a longer evolution.

PCM-related sequelae are frequently underestimated and mortality rates may be high. In Brazil, several retrospective studies of PCM-related outcomes have been published [66,69–71]. In a retrospective analysis of 3,181 PCM deaths throughout the country during 1980–1995, PCM was found to be associated with the highest mortality rate among systemic mycoses with a mean annual mortality rate of 1.45 per million inhabitants [69]. In another analysis of 551 deaths due to PCM throughout Paraná State from 1980–1998, the mean annual mortality rate was 3.48 per million inhabitants [70]. In Campo Grande, Mato Grosso do Sul from 1980–1999, 422 adults and children had PCM; 30.3% had long-term sequelae and 7.6% died [71]. Additionally, from 1981–2001, 6.3% of 63 children aged 2–15 years from Campinas, São Paulo state, with PCM had long-term sequelae and 9.5% died [66]. In a Colombian report published in 1996, a series of 57 cases of systemic mycoses in children were reported; four had PCM [72].

In a study of 47 PCM patients treated with itraconazole, more than 50% had lung fibrosis at the end of treatment [73]; unfortunately, the high percentage of smokers among PCM patients (>93%) can hinder lung function studies [12]. In another clinical trial involving 53 patients in Brazil, voriconazole showed equivalent results to itraconazole in the treatment of PCM patients but with more toxic effects [74].

A prospective study of adrenal function in 22 patients with PCM reported that three patients (14%) had clinical signs of Addison disease and five patients (23%) exhibited an abnormally low cortisol response [75]. After 6 months of treatment with ketoconazole eight of 18 subjects (44%) had adrenal insufficiency (including four of five previously subnormal responders) [75]. A small study of three patients with PCM and adrenal insufficiency, however, reported that adrenal function was fully recovered in all three patients after treatment with ketoconazole or sulfonamides [67]. A prospective, controlled study in 38 patients with PCM reported that 14% of patients with disseminated disease had subnormal cortisol responses, lower than previously estimated [76]. The authors recommended that evaluation of adrenocortical function should be routinely performed in all patients with confirmed PCM as early detection of adrenal failure would avoid further damage to the glands [76]. In Colombia, Onate *et al*. found 2.9% of 207 PCM patients with adrenal insufficiency; all improved after specific therapy consisting of itraconazole, prednisolone, and fluorocortisone [77].

Histoplasmosis

The pathogens causing histoplasmosis are distributed in eight different *Histoplasma capsulatum* clades (one to four clades found in the Americas and the remaining clades found in Africa, Europe, Eurasia, and other continents) [2,6,78].

A recent phylogenetic analysis suggested that dispersion of *H. capsulatum* worldwide began between 3 and 13 million years ago in Latin America [2]. *H. capsulatum* is found primarily in microfoci, especially in soil containing large amounts of bird excreta or bat guano [6,79–82]. Soil analyses have shown that *H. capsulatum* does not grow at pH levels less than 5 or greater than 10 or at temperatures greater than 40°C [82]. Air currents can carry the conidia for miles, exposing individuals who have no direct contact with contaminated sites [82,83]. Infection with *H. capsulatum* develops when microconidia or small hyphal elements are inhaled and convert to yeasts in the lungs, or when organisms in previous quiescent foci of infection are reactivated during immunosuppression [81].

Histoplasmosis occurs most commonly in North and Central America, but it also is found in South America and in many diverse areas of the world, including parts of Asia and Africa [6,10]. There is a large spectrum of clinical forms of histoplasmosis, and its clinical presentation is strongly influenced by the extent of exposure of patients to *H. capsulatum* propagules, age, immunological status of the patient, and the presence of chronic pulmonary disease previous to fungal infection [6,82,83].

The large majority of patients exposed to *H. capsulatum* (>99%) remain asymptomatic or develop only mild symptoms that are never recognized as being due to histoplasmosis [6]. Acute pulmonary histoplasmosis may affect individuals whose occupational or recreational activities cause them to disrupt soil or accumulated guano in endemic areas and are exposed to large amounts of fungal propagules. Individuals who develop chronic cavitary histoplasmosis generally have an underlying pulmonary disorder [6,84]. Disseminated disease usually occurs in the immunocompromised host; particularly during infancy, HIV infection, hematologic malignancy, solid organ transplantation, hematopoietic stem cell transplantation, treatment with corticosteroids or tumor necrosis factor antagonists, or congenital T-cell deficiency [6]. In contrast, chronic progressive disseminated histoplasmosis occurs mostly in older adults who are not overtly immunosuppressed [6,85]. The symptoms of disseminated histoplasmosis include

fever, malaise, anorexia, and weight loss [6]. Disseminated histoplasmosis can involve every organ system; patients may have obvious systemic infection with widespread dissemination or focal disease in a single organ [6]. Involvement is common in the reticuloendothelial system, skin, gastrointestinal tract, gut, adrenal gland, and CNS [6].

Since 1987 more than 90% of HIV-infected persons with histoplasmosis have disseminated disease with AIDS being considered as a defining illness [10,82,86]. The mycosis is the first manifestation of AIDS in 50–75% of HIV-positive patients, and patients with CD4 counts of less than 150 cells/μl are at highest risk [6,10,81]. Overall, disseminated histoplasmosis has been reported to occur in approximately 2–5% of patients with AIDS who live in endemic areas [10,81,86]. Since the late 1990s, the prevalence of disseminated histoplasmosis has declined in HIV-positive populations with access to highly active antiretroviral therapy (HAART), but it remains high in populations without access to or failing to comply with HAART regimens [6,87–89].

Mortality rates due to disseminated disease are high; a study of 30 AIDS patients with disseminated histoplasmosis reported a mortality rate of 37% in patients who did not receive HAART compared with zero in patients receiving HAART [90]. Similarly, a retrospective study of 61 patients with disseminated histoplasmosis reported a mortality rate of 31% in immunocompromised patients and 17% in immunocompetent patients [91].

Long-term sequelae are common in histoplasmosis. A retrospective 17-year study of histoplasmosis patients reported the following: broncholithiasis and fibrosing mediastinitis, with the latter being a manifestation of a hyperreactive host stage; recurrent pneumonia and hemoptysis as a result of cavitation [92]. Respiratory insufficiency also is common in patients with disseminated disease [89,93]. Adrenal insufficiency and failure has been frequently reported among patients with disseminated histoplasmosis [94–97]. The results of a long-term study of 54 patients with disseminated histoplasmosis in the 1970s reported that approximately 50% developed adrenal insufficiency, which was the most common cause of death [94]. CNS histoplasmosis, including chronic meningitis, often accompanies progressive disseminated histoplasmosis, especially in infants [83,98]. CNS histoplasmosis may not be diagnosed in a timely fashion and rates of treatment failure and relapse are high [83,98]. Table 1 shows histoplasmin skin test survey results from various Latin American countries and regions [34,35,37–39,41–43,52–56,59,60,99–102].

In different parts of Mexico, histoplasmin skin test surveys have revealed a prevalence of infection ranging from 5–50%, whereas the estimated incidence of histoplasmosis has ranged from 0.1–0.29 cases per 100,000 [10]. Between 1953 and 1997, 102 outbreaks of histoplasmosis (including a total of 1,444 cases) were reported to the Instituto Nacional de Diagnóstico y Referencia Epidemiológica in Mexico City [10]. From 1988–1994, 1,065 cases from several outbreaks were reported to the Dirección General de Epidemiología [10]. Most cases occurred in the central and southeastern parts of Mexico (Veracruz, Oaxaca, Campeche, Colima, and Tabasco States) [10]. Figure 2 shows the geographical distribution of histoplasmosis in Latin America [103].

According to histoplasmin reactivity studies, the prevalence of *H. capsulatum* infection in endemic areas in Panama may be as high as 50% [89]. From 1997–2003 at the Arnulfo Arias Madrid Hospital in Panama City, 7.65% of patients with HIV infection had culture-positive *H. capsulatum* [89]. Of 104 patients, only 14 (13.5%) for whom detailed records were available were receiving antiretroviral therapy at the onset of histoplasmosis symptoms; 5.8% of patients had a relapse and 12.5% died [89].

In the Bolívar state of Venezuela, the rate of histoplasmin reactivity in a rural area was determined to be 42.7% (2004) [34], whereas the rate was 34% (2005) in the city of Upata [35]. In patients with AIDS, histoplasmosis was documented in 29 of 66 (44%) autopsies performed

Fig. 2 Map showing the distribution of histoplasmosis in Latin America. Adapted with permission from Guimarães AJ, Nosanchuk JD, & Zancopé-Oliveira RM, 2006 [164]. Distribution in Mexico and Central America reproduced with permission from WB Saunders Company. This figure was published in *Medical Mycology*. Rippon JW. Histoplasmosis (*Histoplasmosis capsulati*). © WB Saunders Company: 1988 [103]. Additional information added from epidemiological skin test surveys reported in Table 1.

in one study [104]. In another Venezuelan study, of 158 cases of histoplasmosis seen between 2000 and 2005, most (85%) patients had a known risk factor: AIDS (34%); malignant disease (13%); contact with bats or poultry (12%); or aged less than 2 years (10%) or more than 65 years (7%) [105].

In Colombia, a study conducted by the Corporación para Investigaciones Biológicas in Medellín compared clinical characteristics of patients with disseminated histoplasmosis (including 30 who had AIDS and 22 who were not coinfected with HIV) [90]. Compared with patients without HIV infection, patients with AIDS were more likely to have skin lesions ($P = 0.001$), anemia, leukopenia, and an elevated erythrocyte sedimentation rate ($P = 0.001$) and were less likely to respond to the antifungals used ($P = 0.012$) [90]. HAART significantly improved the response to antifungal therapy for histoplasmosis ($P = 0.030$) and was associated with lower treatment failures or death ($P = 0.03$) [90]. Another Colombian report described the clinical presentation of disseminated histoplasmosis in seven malnourished children in whom treatment with itraconazole produced favorable responses [106].

According to a 2006 publication, 26 outbreaks of histoplasmosis involving 184 patients had been reported in Brazil since 1958, with the number of cases per outbreak ranging from 2–13 [107]. A 1998 summary of 88 epidemiological surveys of histoplasmin sensitivity reported positive rates ranging from 2.60% in Salvador, Bahia, to 93.20% in Ilha do Governador, Rio de Janeiro [61]. Disseminated histoplasmosis was the AIDS-defining condition in 52.6% of HIV-infected patients in a 1992–2005 case series published in 2007 from the city of Uberaba, Minas Gerais [87]. When patients with comorbid histoplasmosis and AIDS in Brazil and the United States were compared, those in Brazil were far more likely to have skin lesions (66% vs 1–7%) and gastrointestinal findings (24% vs 2–8%), and had a higher death rate (39% vs 5–13%), which may have been linked to genetic differences in *H. capsulatum* species in Latin America versus the United States [108]. High rates of cutaneous involvement (~44%) have been reported in other Brazilian studies [87,109]. A recent Brazilian study reported that mucocutaneous manifestations of histoplasmosis were caused by two specific strains of *H. capsulatum* and that unique pathogenic characteristics of these Latin American species may explain the increased dermatotropism compared with other countries [110].

Epidemiological surveillance studies using histoplasmin skin testing have documented *H. capsulatum* infection rates between 22.4% and 53.6% in the province of Tucumán in northwestern Argentina [37,39]. Cases of acute pulmonary histoplasmosis also have been reported in Ecuador [111], Costa Rica [112], and Nicaragua [113]; and disseminated histoplasmosis has been reported in Costa Rica [114], Peru [115], and Guatemala [116]. Histoplasmosis has not been found endogenously in Chile [111].

The Centers for Disease Control in the United States have published guidelines to protect workers at risk from histoplasmosis. The guidelines include suggestions to communicate health risks to workers in endemic areas; to control aerosolized dust when removing bat or bird manure from a building or during construction, excavation, and demolition; and to wear personal protective equipment [117].

Coccidioidomycosis

CM was first discovered in Argentina in 1892 [118]. CM is caused by the genus *Coccidioides*, a dimorphic fungi with a filamentous form during the saprophytic phase and a yeastlike form during the parasitic phase [119]. Two geographically distinct species exist: *C. immitis* (found in California) and *C. posadasii* (found in Arizona, Texas, Mexico, Central America, and South America) [120]. Genetic analysis suggests that *Coccidioides* was carried south from North America in mammals between 9,000 and 140,000 years ago [121]. Figure 3 shows the geographical distribution of CM in Latin America [122–124].

Coccidioides spp. are endemic primarily in regions with an elevation of less than 4,500 ft (~1,372 m), an arid climate (yearly rainfall 10–50 cm), extremely hot summers, mild winters, and alkaline, sandy, silty soil [119,122,125]. The incidence of CM is strongly influenced by seasonal precipitation, severity of wind and dust storms, continued influx of susceptible hosts (new residents or tourists) into endemic regions, and disruption and aerosolization of desert surface by construction, wildfires, and earthquakes [119]. Infection usually occurs during the dry season [122], and epidemics are caused by favorable climatic and other environmental factors, not by the emergence of more virulent strains [126,127]. Arthroconidia are released into the air by soil disruption and wind, and infection occurs by inhalation into the lungs or, on rare occasions, after percutaneous implantation into tissue [119].

Populations at risk for CM include those who participate in outdoor activities. Outbreaks of CM have occurred in connection with military maneuvers, construction work, earthquakes, landslides, and armadillo-hunting expeditions [119,122,128–130]. Men are more likely than women to be infected and to experience disseminated disease [122,131]. Although CM affects all age groups, the overall incidence increases with age; extremes of age are associated with increased risk of chronic pulmonary disease and dissemination [122,132].

Approximately 60% of individuals who are exposed to the fungus remain asymptomatic [133]. Of the remaining

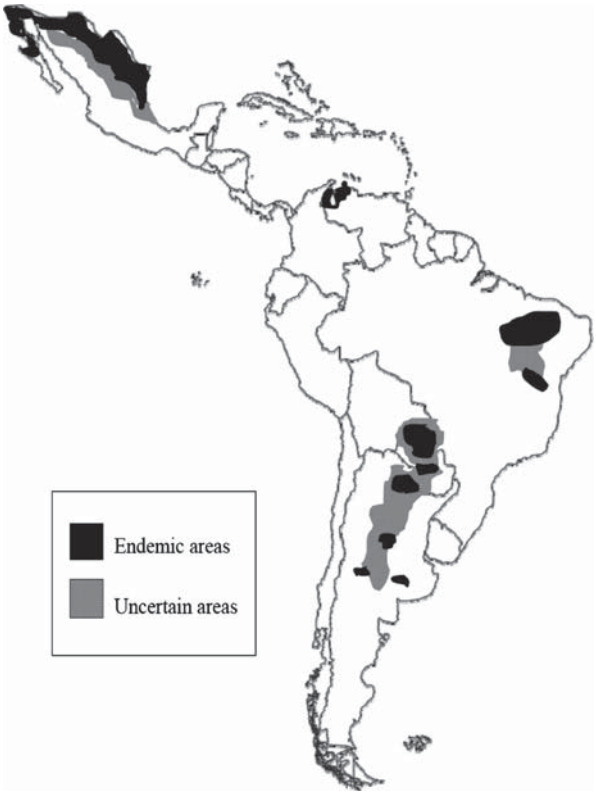

Fig. 3 Map showing the distribution of coccidioidomycosis in Latin America. Adapted with permission from Hector RF & Laniado-Laborin R, 2005 [123]. The information on endemic coccidioidomycosis in Northeast Brazil was taken from Cordeiro *et al*., 2010 [124]. The information on endemic coccidioidomycosis in Venezuela was taken from Laniado-Laborin, 2007 [122].

40% of patients with symptomatic disease, there are various manifestations ranging from a primary, benign, pulmonary infection (commonly known as 'valley fever') to a progressive pulmonary or extrapulmonary disease involving the skin, bones and/or joints, CNS, and other organ systems [123]. Most patients with primary disease recover spontaneously and retain lifelong protective immunity [123].

The main risk factors for disseminated CM include black or Asian (especially Filipino) ethnic backgrounds, the third trimester of pregnancy, and immunocompromise [119,122]. Other risk factors include conditions and medical treatments that affect T-cell function (i.e., HIV infection, cancer chemotherapy, and immunosuppression following hematopoietic stem cell transplantation or solid organ transplantation) [122]. Host genes, especially HLA class II and ABO blood group, may contribute to dissemination and severity of infection [119,134].

Disseminated CM may lead to substantial morbidity and mortality, although long-term follow-up data and mortality rates are limited [135]. Clinical manifestations of disseminated CM include acute or chronic progressive pneumonia, pulmonary nodules and cavities, extrapulmonary nonmeningeal disease, and meningitis [136]. Coccidioidal meningitis is the most lethal manifestation of CM infection [137]. Before the availability of amphotericin B, it was usually fatal [138]. More recently, patients have achieved remission after treatment with triazole antifungal agents [137].

CM is an opportunistic infection in persons infected with HIV [122,131]. Before the era of HAART, CM incidence was high among HIV-infected residents of endemic areas and was often fatal [139]. Typical presentations in HIV-infected individuals included diffuse pulmonary disease characterized by nodules and interstitial infiltrates; severe disseminated disease is prevalent, and meningitis is frequently observed [81,86,139]. Upon the onset of HAART use, the CM incidence dropped sharply among patients with HIV, but it is increasing again largely because of HAART noncompliance [139,140].

The incidence of CM also is increasing in many endemic areas [119,126]. The endemic regions for *Coccidioides* spp. are limited to the western hemisphere, mostly between the 40° North and South latitudes in Central and South America [122]. However, isolated CM cases have been reported outside endemic areas, presumably because of travel [122].

Mexico has the highest incidence of CM in Latin America. Although CM is not a reportable disease in Mexico and its actual incidence is unknown, available data suggest that its prevalence is increasing [122,141]. Most epidemiological studies have focused on the northern desert areas of Mexico, mainly in the states of Sonora, Coahuila, Nuevo León, and the Baja California peninsula [141–143]. Surveillance studies have reported infection rates ranging from 9.2% in Tijuana, Baja California (1985, coccidioidin test) to 93.0% in Matamoros, Coahuila (2005, ELISA) [141,144]. In 1994, the overall incidence of CM in Mexico was 1.3 cases per 100,000 inhabitants (2.6 in Nuevo León, 2.1 in Tamaulipas, 1.8 in Chihuahua, 1.2 in Baja California, and 0.7 in Sonora) [141]. A study that reviewed autopsy records between 1983 and 2000 from a hospital in Monterrey, Nuevo León, found that mortality due to CM was 0.67%, and conditions associated with CM-related death included pregnancy, chronic renal failure, and AIDS [145].

Table 1 presents the results of our literature search for epidemiological coccidioides skin test surveys in Latin America [146–149]. Venezuela is thought to have the second-highest incidence of CM in Latin America [150]. The states of Falcón, Lara, and Zulia are considered endemic areas on the basis of case reports and skin test surveys [122,150]. Epidemiological surveys in these areas have reported positive coccidioidin skin test responses of about 50% [122,150].

A 12-year epidemiological study of CM in Ceará, Northeast Brazil, published in 2010 reported 19 cases of CM, all among male patients aged 13–43 years, all but one of whom had been armadillo hunting [124]. In 1999, a report described 11 confirmed and three possible autochthonous cases of CM in the northeast region of Brazil (states of Bahia, Ceará, Piauí, and Maranhão) [130]. *Coccidioides* has been isolated in Brazil from armadillo tissues, soil from armadillo burrows, and dogs [122,130,151]. A 1979 case report described a 35-year-old male native of Piauí who had extensive lung involvement, including pulmonary nodules [152]. A minor outbreak of CM occurred in Piauí in 1991 in three human males and eight dogs after digging an armadillo out of its burrow and consuming it. Three dogs died, an 11-year-old boy recovered spontaneously after 2 weeks, and two adult males who developed severe pneumonia with bilateral infiltrates recovered after treatment with amphotericin B [130]. Until 1965, only 27 cases of CM had been reported in Argentina [153]. In 1999, a study from Muñiz Hospital, Buenos Aires, reported eight cases of chronic CM (five pulmonary and three disseminated) [154]. Smoking (three cases) and alcoholism (two cases) appeared to be predisposing factors [154].

In 1979, the first case of CM was reported in northwest Nicaragua in an 8-year-old girl who had extensive pulmonary and cutaneous disease [155]. CM also is endemic in certain regions of Guatemala, Honduras, Bolivia, and Paraguay [122,150]. In Colombia, CM is a rare disorder with only three isolated case reports. A large skin-testing survey conducted in the arid zones of the northern departments of La Guajira and Magdalena reported a low percentage of positive coccidioidin reactors, indicating that a real endemic area does not appear to exist in Colombia [156,157].

Discussion

It is difficult to obtain a complete and accurate epidemiological picture of endemic fungal infections in Latin America, partly because such infections are not considered reportable diseases in this region. Although many epidemiological surveys have been completed, they have often focused on microregions rather than on entire regions or countries. Considerable information is available for Brazil, Argentina, Colombia, Venezuela, and Mexico, but very little information is available for other Latin American countries (i.e., Bolivia, Paraguay, Uruguay, Ecuador, and most nations from Central America). In addition, much information on mycoses in Latin America has been reported as case studies, which by their nature report on exceptional clinical situations rather than more typical presentations; hence, case reports have not been a focus in this review. Despite the previously mentioned limitations, it is clear that endemic mycoses are important concerns in Latin America, as they affect hundreds of thousands of people. Although such mycoses occur primarily in specific geographic areas and there are strong variations of incidence rates within regions, these infections can be found in almost all of Latin America, with the exception of Chile (Table 1).

The percentage of infected subjects, as determined by skin test surveys, ranged from 0.9–82% for PCM (median rate of approximately 12%); 5.8–80.5% for histoplasmosis (median rate of approximately 22%); and 0.3–40% for CM (results from four surveys) (Table 1).

Endemic fungi have been reported to have a propensity for causing disseminated infection in patients with impaired T-cell immunity, such as those with cancer (lymphoma and solid organ cancer), those receiving high doses of corticosteroids, solid organ transplant recipients and especially AIDS patients. Among immunocompromised patients, endemic mycoses usually behave as opportunistic infections causing disseminated disease rather than pulmonary or localized mycosis typically found in immunocompetent patients [158–161].

In Latin America, PCM appears to be responsible for the highest burden of disease compared with CM and histoplasmosis, but histoplasmosis is most commonly found among patients with AIDS, solid organ transplantation, and other diseases associated with impaired T cells [6]. It is not clear why PCM is infrequent among immunocompromised patients, but it has been suggested that prophylaxis with trimethoprim and sulfamethoxazole against *Pneumocystis* also prevents infection due to *P. brasiliensis* [29].

The target population for endemic disease in Latin America is mostly represented by rural workers with low incomes and limited access to a public or private health system. It is well established that the definitive diagnosis of endemic mycosis is based on the microscopic visualization of fungal elements usually documented in biopsy samples of any infected organ, scrapings of superficial lesions, or in sputum, abscess, and lymph nodes aspirates. Serologic tests also provide prompt results although their sensitivity and specificity may vary substantially depending on the kind of assay and antigen preparations used, as well as the clinical presentation of the mycosis and the presence of comorbidities. Unfortunately, most diagnostic tools for endemic mycosis are not routinely used in most medical centers in Latin America due to cost and lack of human resources trained in medical mycology. Consequently, by the time most patients are diagnosed with fungal infection, they are already severely ill with multiple organs compromised by the disease [3,162].

In conclusion, judging by the reported sequelae and mortality rates associated with systemic endemic mycoses addressed in this paper, it is clear that there is a need to incorporate new strategies into the health care system for

early diagnosis and prevention of such conditions in endemic areas. Evaluation of systemic endemic mycosis should be warranted in patients from endemic regions who have respiratory symptoms, oral or cutaneous lesions, and Addison syndrome. To enable this strategy, local health authorities in Latin America should make basic diagnostic screening tests available in all medical centers located in endemic areas.

Acknowledgment

The authors would like to thank Sheena Hunt, PhD, in association with ApotheCom, for providing editorial assistance for the authors' original work, which was funded by Schering-Plough, now Merck & Co., Inc., Whitehouse Station, New Jersey, USA.

Declaration of interest: Dr Colombo has received educational and research grants from United Medical, Merck, and Pfizer, and is a consultant for Merck and Pfizer. Dr Tobón has served as a speaker for Janssen and Merck. Dr Restrepo has no affiliation with and has received no grants from pharmaceutical companies. Dr Queiroz-Telles has received research grants from Astellas, Janssen, Merck, and Pfizer; is a consultant for Pfizer, Merck, and Astellas; and has served as a speaker for Pfizer. Dr Nucci has received research grants from Merck and Pfizer and served as a speaker and consultant for Merck, Pfizer, and Astellas.

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This paper was first published online on Early Online on 9 May 2011.

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