Endemic fungal infections in the Asia-Pacific region

A. CHAKRABARTI* & M. A. SLAVIN†

*Department of Medical Microbiology, Postgraduate Institute of Medical Education & Research, Chandigarh, India, and
†Department of Infectious Diseases, Peter MacCallum Cancer Centre, East Melbourne, Victoria, Australia

Endemic mycoses are important fungal infections in their respective habitats. In the Asia-Pacific region, an accurate epidemiological picture of endemic mycoses is elusive; few epidemiological surveys have been performed, and limited laboratory facilities and experience with fungal infections have further hampered recognition of infection. However, pockets of endemics do indeed exist, and endemic fungal infections can have a significant impact on public health. This article reviews the most common endemic mycoses in the Asia-Pacific region: histoplasmosis, penicilliosis, and sporotrichosis. Blastomycosis, which has been infrequently reported within the region, is also briefly discussed. Certain areas of the Asia-Pacific region are endemic for histoplasmosis; however, the ecologic niche for this infection remains unclear. Penicilliosis is restricted to Southeast and Eastern Asia, whereas sporotrichosis is encountered in tropical areas of the Asia-Pacific region linked to environmental reservoirs distinct from those seen in the Western world. Before the advent of acquired immune deficiency syndrome (AIDS), histoplasmosis and penicilliosis were only occasionally reported; however, the incidence of both mycoses has increased with the rise in the incidence of AIDS. Comprehensive studies are needed to fully assess the areas of endemcity and the impact of endemic mycoses in the Asia-Pacific region.

Keywords Asia, Pacific, endemic mycoses, histoplasmosis, penicilliosis, sporotrichosis

Introduction

Endemic mycoses are a group of diseases caused by diverse fungi that share common characteristics. These fungi occupy a specific etiologic niche in the environment, are dimorphic in nature (yeast or spherule form in tissue and mycelial form in the environment), and are able to produce infection in healthy hosts.

Endemic mycoses are a frequent problem in the Asia-Pacific region and have an important impact on public health. In spite of this, clinical and epidemiological data for this region are limited. The most common endemic mycoses in the Asia-Pacific region are histoplasmosis, caused by Histoplasma capsulatum; penicilliosis, caused by Penicillium marneffei; and sporotrichosis, caused by Sporothrix schenckii.

This article reviews the epidemiology of histoplasmosis, penicilliosis, and sporotrichosis in the Asia-Pacific region. Blastomycosis, which has been infrequently reported in some countries within the region, is also briefly discussed. Unlike Latin American countries, autochthonous (i.e., indigenous) coccidioidomycosis and paracoccidioidomycosis are not reported in the Asia-Pacific region, except as imported mycoses, and are therefore not discussed here.

Methods

We identified and reviewed papers on histoplasmosis, penicilliosis, sporotrichosis, and blastomycosis using the PubMed®/MEDLINE® databases up to May 2010, irrespective of date and language of publication. Papers
were retrieved using the following key words: fungal infection, mycosis/mycoses, endemic mycosis/mycoses, histoplasmosis, penicilliosis, sporotrichosis, and blastomycosis. Each of these search terms was combined with the following: Asia or Pacific, as well as individual country names India, China, Thailand, Australia, or New Zealand. The countries included in the references selected are those defined by the United Nations as being in Eastern Asia, Southern Asia, Southeastern Asia, or Oceania [1]. Papers on management or antifungal susceptibility were not included.

**Histoplasmosis**

Histoplasmosis-causing *H. capsulatum*, was originally classified into three varieties: *H. capsulatum* var. *capsulatum*, *H. capsulatum* var. *duboisii*, and *H. capsulatum* var. *farciminosum*. Subsequently, combined data analysis of partial sequences of four protein encoding genes of 46 *H. capsulatum* isolates identified at least six distinct clades within this species [2]. The analysis found five clades of *H. capsulatum* var *capsulatum*: (i) class 1 North American; (ii) class 2 North American; (iii) Central American; (iv) South American group A; (v) South American group B; and one clade for *H. capsulatum* var *duboisii*. *H. capsulatum* var *farciminosum* was found within the South American *H. capsulatum* var *capsulatum* group A clade [2]. *H. capsulatum* var *duboisii* infection is restricted to Africa [3]; only one imported case of histoplasmosis due to *H. capsulatum* var *duboisii* has been reported in the Asia-Pacific region (Japan), and it was from the cerebrospinal fluid of a female Ugandan patient infected with human immunodeficiency virus (HIV) [4]. In contrast, histoplasmosis due to *H. capsulatum* var *capsulatum* is reported in many countries of the Asia-Pacific region. However, no data are available about the clades of *H. capsulatum* causing human disease from this region. Although previously considered rare, the incidence of histoplasmosis is expected to increase significantly in this region with the rise in the number of patients with acquired immune deficiency syndrome (AIDS) [5-9].

Early reports of histoplasmosis came from Australia in 1948 [10] and India in 1954 [11]. By 1970, 16 culturally confirmed cases had been diagnosed from seven Asian countries [12]. Another 48 cases were reported from Southeast Asia in 1972 [13]. In spite of such early recognition of the disease, the true prevalence of histoplasmosis in its various clinical forms in the Asia-Pacific region is still poorly documented because of lack of awareness of fungal diseases and poor laboratory facilities in most of this region. Nevertheless, it still appears that pockets of endemcity do exist throughout this region. For example, most of the 37 cases of histoplasmosis reported in India until 1972 were from eastern India [5]. In addition, the reporting of histoplasmosis cases from other geographic locations of this region corroborates the theory of pocket distribution of the disease [6-9,14]. Although areas of infection are probably widespread, more accurate disease recognition will depend on better awareness, expertise, and diagnostic facilities rather than only on regional reports of preponderance of the disease. In 2005, a single center in southern India reported 19 cases of histoplasmosis, illustrating that awareness and diagnosis are essential to identify the disease [15].

Histoplasmosis endemicity can be evaluated by population-based use of a histoplasmin skin test. This was aptly demonstrated when a major endemic area of histoplasmosis was identified in the northeastern and midwestern United States (US) by testing the skin of US military recruits, which revealed a skin-test positivity rate of 80–90% in the population tested [16]. The overall rate of histoplasmin skin-test positivity of the world population, however, is 5–14%; the rate is 5% in the general population and 14% in medical students and hospitalized patients [17]. Attempts have been made to determine whether histoplasmosis is endemic in certain areas of the Asia-Pacific region; however, an overall endemicity study has not been performed [5,7,8,18,19]. One study from Malaysia reported a 3% histoplasmin skin-test positivity rate in a group of children who were schooled near a cave from which *H. capsulatum* had been isolated [18]. Studies carried out in northern India between 1952 and 1979 reported skin-test positivity rates ranging from 0–12.3% [5]. A systematic study in China reported a histoplasmin skin-test positivity rate of 19%; in which the positivity rate was higher in Hunan and Jiangsu provinces (southeast China) than in the Xinjiang Autonomous region (northeast China) [8]. The same study also reported that the skin-test positivity rate was significantly higher in hospitalized patients than in healthy volunteers in the same geographic region (26% versus 9%; *P* < 0.01) and that, among all patients, those with pulmonary tuberculosis and lung cancer had the highest positivity rate (each approximately 33%) [8]. A study from Sichuan Province in China reported that up to 35% of students from southern Sichuan Province (southeast China, bordering Tibet) were positive for histoplasmin, whereas only 6% tested positive in the northern part of the same province [20]. A histoplasmin skin-test positivity rate of 17% has also been reported in east-central China [21]. In a study from the Philippines, 26% of long-term residents showed histoplasmin positivity [19].

All of these studies demonstrate that certain areas of the Asia-Pacific region are endemic for histoplasmosis. There has been very little work conducted to isolate *H. capsulatum* from soil or other environmental sources in the Asia-Pacific region; hence the ecologic niche for this region.
in a 61-year-old American man with Hodgkin’s disease who had toured Southeast Asia [43]. From 1974 to 1988, only 20 cases of penicilliosis were reported [39]. Since then, the disease has been frequently detected in patients with AIDS who live in or travel to endemic areas in Southeast Asia [42]. The disease is highly prevalent and, after tuberculosis and cryptococcosis, is the third most common opportunistic infection in patients with AIDS in Chiang Mai province, the largest province in northern Thailand [37]. By 1995, the number of patients with AIDS with penicilliosis in Bangkok and northern Thailand increased to more than 1300 [44]. In contrast, the disease has a relatively low prevalence in southern Thailand, even though there is a large population of patients with AIDS in this area [45]. There has been only one report of penicilliosis in both Australia and Japan [46,47]. Consistent with other reports, the Australian patient was a Burmese immigrant with advanced HIV infection [46].

Diagnosis of penicilliosis is sometimes difficult, especially in areas like southern China where histoplasmosis is also endemic, because both diseases cause fever, weight loss, cough, anemia, lymphadenopathy, and hepatosplenomegaly [31,42]. Nevertheless, skin lesions appear to be more common in individuals with penicilliosis (60–85%) than in those with histoplasmosis (approximately 44% in two studies from Brazil) [48,49]. Cutaneous lesions related to penicilliosis frequently occur on the face, upper trunk, and extremities, and may consist of necrotic or generalized papules or nodules, some with central umbilication [39,42,50]. Lesions are papulonecrotic and may resemble the lesions of molluscum contagiosum [39,50]. However, in a retrospective review of cases from Hong Kong, only 28% patients with penicilliosis had skin lesions [41]. In a Thai hospital where the medical records of patients with histoplasmosis and penicilliosis were compared, no statistically significant difference was observed in the number of skin lesions between the two groups, although as expected, the number of patients with skin lesions was higher in the group with penicilliosis (53%) than in the group with histoplasmosis (38%) [31]. Laboratory findings were similar between the two groups except for hyperbilirubinemia, which was significantly more common in the penicilliosis group ($P = 0.02$) [31]. Clinical and laboratory characteristics of penicilliosis have been compared between HIV-positive and HIV-negative patients. Patients with HIV infection have been shown to have a higher incidence of fungemia, higher antigen titer as assessed by $P.$ marneffei-specific mannoprotein Mp1p enzyme-linked immunosorbent assay, and lower serum antibody levels than HIV-negative patients [51].

$P.$ marneffei was first isolated from the liver of the bamboo rat ($Rhizomys sinensis$) in Vietnam [52]. Since then, many studies have established that four species of bamboo

**Penicilliosis**

Penicilliosis caused by $P.$ marneffei, the only dimorphic species among >200 species of Penicillium, is an endemic disease found only in Southeast and Eastern Asia, including Thailand, northeast India, China, Hong Kong, Laos, Cambodia, Malaysia, Myanmar, Vietnam, and Taiwan [37-42]. Identification of the disease is relatively recent; the first natural infection in a human was reported in 1973.
rats (*R. marneffei*), *R. pruinatus*, *R. sumatrensis*, and the reddish-brown subspecies of *Cannomys badius*) in Southeast Asia may act as enzootic reservoirs for this fungus [42,53-57]. However, since bamboo rats live in remote, mountainous areas or in the jungle and have limited contact with people, the infection of humans from contact with bamboo rats is not likely [42,53]. Although some people eat bamboo rats, this would not spread the infection to humans. Bamboo rats may simply be another natural host of *P. marneffei* infection. Instead, a common environmental source of infection may exist through which spores may be inhaled or ingested to cause disease in both rats and humans [58]. Nevertheless, although the fungus has been isolated from soil samples collected from burrows of *R. pruinatus* and *R. sumatrensis*, [56,58], many attempts to isolate the fungus from other environmental sources have not been successful and definitive identification of the environmental reservoir for this fungus is not yet available. A case-control study of HIV-positive patients conducted in northern Thailand could not establish bamboo rats as a reservoir of infection for humans [59]. However, younger age (16–30 years compared with ≥31 years) and agricultural occupation were found to be independently associated with an increased risk for infection in humans [59]. The investigators further postulated that patients with a recent history of occupational or other exposure to soil, especially during the rainy season, may have provided favorable conditions for the fungus to sporulate in soil and create aerosols of spores.

Many molecular methods have been used in an attempt to type *P. marneffei* strains, including restriction fragment length polymorphism (RFLP), random amplified polymorphic DNA (RAPD), fingerprinting using repeat primer (GACA), and the phage M13 core sequence, and multilocus microsatellite typing (MLMT) [60-64]. The MLMT method has been found to be reproducible and discriminating [63,64]. Using 19 unique microsatellite types, strains could be divided into two geographically separated clades: ‘eastern clades,’ which contained isolates from mainland China, Hong Kong, Indonesia, and Vietnam; and ‘western clades,’ which contained isolates from Thailand and India [63]. Further studies are required to more firmly establish the epidemiology of *P. marneffei* infection.

**Sporotrichosis**

Sporotrichosis is a subacute or chronic subcutaneous, granulomatous mycosis caused by intradermal inoculation of the dimorphic soil saprophyte *S. schenckii* via minor local trauma [65,66]. Sporotrichosis is commonly encountered in many areas of the Asia-Pacific region [67-72]. It is believed that the ecologic factors that promote the growth and viability of *S. schenckii* are a mean temperature between 26 and 27°C, humidity of 92–100% [73], and the presence of plant material such as sphagnum moss, decaying vegetation, soil, and hay [65]. Sporotrichosis has been reported under a wide range of climatic and geographic conditions in India, Japan, and Australia [67-72,74]; however, sporotrichosis is rarely reported in Thailand, Vietnam, or Indonesia, which have similar climatic conditions [75].

No population-based study is available that reports the exact prevalence of sporotrichosis in the Asia-Pacific region. However, an exploratory population-based study showed that it is possible to use sporotrichin antigen to determine the prevalence of sporotrichosis [69]. Through a skin-test survey of 275 subjects in Himachal Pradesh State, India, using sporotrichin and peptido-rhamnomanan antigen prepared from *S. schenckii*, it was shown that the proportion of the population who were skin-test positive in case villages (as defined by ≥2 confirmed cases of sporotrichosis per village) ranged from 23–40%, compared with 6.5–7.6% in control villages where no sporotrichosis case was detected [69]. Analysis by age and occupation showed higher skin-test positivity rates in older age groups and in those engaged in horticulture, nursery work, gardening, woodwork, and farming. The average temperature of case villages was found to be 15.5–23.6°C with a diurnal humidity range of 56–58% [69].

Outbreaks of sporotrichosis in the Asia-Pacific region are often linked to contact with contaminated hay [71,76]. In a study from India that evaluated different environmental sources such as thorns, corn stalks, sphagnum moss, grass blades, and soil samples collected from areas close to the homes of individuals with sporotrichosis for the presence of *S. schenckii*, the fungus was isolated only from soil and corn stalks [77]. This study suggests that hay, corn stalks, and soil are possible sources of *S. schenckii* in the Asia-Pacific region, rather than the source of sphagnum moss commonly reported in the Western world [82]. However, the reservoir of infection in the Asia-Pacific region has not yet been systematically identified and these data would be important for the implementation of preventive strategies. Sporotrichosis has been reported in animals such as cats, nine-banded armadillos, horses, and donkeys; however, it is unclear whether animals are a reservoir for human infection [65]. In a unique case, feline transmission of lymphocutaneous sporotrichosis to a human, however, has been encountered in India [78].

Reports from Latin America show that sporotrichosis is more common in males than in females [65], and it has been postulated that women may be inherently resistant to sporotrichosis [79]. In contrast, reports from India and Japan show the opposite pattern [67,70,80-83], and in Australia, sporotrichosis has been reported with nearly equal frequency in both sexes [76]. The contrasting picture in the Asia-Pacific region may reflect differences in
gender-related outdoor activities, where women also participate in horticulture or farming. Although rare, cases of familial sporotrichosis have also been reported in the Asia-Pacific region [76,84].

Sporotrichosis may occur in one of four clinical forms: lymphocutaneous, fixed cutaneous, multifocal (disseminated) cutaneous, and extracutaneous [66]. Sporotrichosis is usually distributed unilaterally, but bilaterally distributed sporotrichosis is occasionally reported in the Asia-Pacific region [85]. After reviewing reports from Japan of more than 3500 sporotrichosis cases, 16 cases of bilateral distribution were identified [85]. Most of the sporotrichosis cases reported in the Asia-Pacific region are either lymphocutaneous or fixed cutaneous, although multifocal cutaneous and extracutaneous forms of the disease have also been observed on rare occasions [86,87]. Multifocal cutaneous sporotrichosis may develop in patients with immunosuppression or when a topical steroid is misused, as was reported in one case in Japan [86]. S. schenckii may very rarely cause disseminated systemic (extracutaneous) disease. A rare case of fatal pulmonary (extracutaneous) sporotrichosis, caused by S. schenckii var. luri, has also been reported from the northwestern region of India [98].

Molecular typing of S. schenckii by different methods has provided useful information about the epidemiology of sporotrichosis in the Asia-Pacific region [72,88-92]. RFLP of mitochondrial (mt) DNA has been used to classify S. schenckii into 30 mt DNA types clustered into two major groups (groups A and B) [72,88,90,92,93]. This typing scheme has identified local genetic homogeneity in the Asia-Pacific region but genetic variability in other regions. In one study, most isolates from South Africa and North, Central, and South America belonged to group A, whereas most isolates from Asia-Pacific belonged to group B [72]. The types that predominated in different Asia-Pacific countries were type 13 in Australia, types 4 and 5 in Japan, type 4 in China, types 5 and 20 in India, and type 4 in Thailand [72]. Further, mt-DNA typing is helpful in distinguishing morphologically similar S. schenckii-like strains into true S. schenckii isolates and non-S. schenckii isolates [89]. Based on RFLP analysis of ribosomal DNA (rDNA), S. schenckii can also be classified into four additional types (rDNA types I to IV), which supports the results of mt DNA analysis [94]. Most isolates from the Asia-Pacific region in this type of analysis belonged to type IV [72]. In a study using RAPD analysis of S. schenckii strains, isolates of different sporotrichosis clinical forms showed distinct genotypes [91]. Pulse field gel electrophoresis of Sfi I and Not I digested DNA from environmental and clinical isolates confirmed the link between contact with hay and increased incidence of sporotrichosis in Western Australia [92]. This study made a tremendous impact, in that the number of sporotrichosis cases has markedly declined since the introduction of the use of long-sleeved shirts and gloves as the recommended method of hay handling [92]. Recently, by molecular analysis of calmodulin gene sequences, it was observed that S. schenckii constitutes a complex number of phylogenetic species: S. brasiliensis, S. schenckii, S. globosa, S. mexicana, S. albus, and S. inflata [95]. The few Asian isolates analyzed from India and Japan demonstrated similarity to European isolates and were proposed to belong to the new species, S. globosa [95]. However, more studies are required to determine the clinical and epidemiological significance of these findings.

**Blastomycosis**

It is not clear whether blastomycosis is endemic in the Asia-Pacific region because very few autochthonous cases have been reported; these cases were isolated cases mostly from India where the fungus was isolated from pulmonary, cutaneous, and cerebral lesions [96-100]. Interestingly, the fungus has been isolated from the lung and liver of bats, Rhinopoma hardwickei hardwickei, captured in Delhi [101,102] but it is not known whether bats could be a reservoir for human infection. Blastomycosis has also been reported as an imported mycosis in this region [103].

**Conclusions**

It is difficult to obtain a complete and accurate epidemiological picture of endemic fungal infections in the Asia-Pacific region. Such infections are not notifiable diseases, and few epidemiological surveys have been completed. Lack of laboratory facilities and experience with fungal infections has further limited knowledge of the epidemiological landscape. In addition, much of the available data are in the form of case reports, which often focus on exceptional rather than typical presentations of the mycoses. However, it is clear that pockets of endemicity do exist and that endemic fungal infections can have a significant impact on public health. Further, some endemic mycoses also appear to demonstrate peculiarity in distribution and clinical pattern in the Asia-Pacific region when compared with the same infections in other parts of the world. Comprehensive studies are needed to fully assess the areas of endemicity and the impact of these mycoses in the Asia-Pacific region.

**Acknowledgements**

The authors acknowledge the help of Sheena Hunt, PhD, Susan Quiñones, PhD, and Denise Myers of ApotheCom for their encouragement in writing this review and their
help in collecting references and editing the manuscript (funded by Merck & Co., Inc.).

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References


© 2011 ISHAM, Medical Mycology, 49, 337–344
Asia-Pacific endemic mycoses


48 Mora DJ, dos Santos CTB, Silva-Vergara ML. Disseminated histoplasmosis in acquired immunodeficiency syndrome patients in Uberaba, MG, Brazil. Mycoses 2008; 51: 136–140.


This paper was first published online on Early Online on 26 January 2011.