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Epidemiological aspects of travel-related systemic endemic mycoses: a GeoSentinel analysis, 1997–2017

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Abstract

Background: International travel has increased in the past few decades, placing more travellers at risk of acquiring systemic endemic mycoses. There are limited published data on systemic endemic mycoses among international travellers. We report epidemiological characteristics of non-migrant, international travellers who acquired systemic endemic mycoses during travel.

Methods: We analysed records of non-migrant international travellers with a confirmed diagnosis of histoplasmosis, coccidioidomycosis, paracoccidioidomycosis, blastomycosis or talaromycosis reported from 1997 through 2017 to GeoSentinel, a global surveillance network now consisting of 70 travel or tropical medicine centres in 31 countries.

Results: Sixty-nine records met the inclusion criteria. Histoplasmosis was most frequently reported; the 51 travellers with histoplasmosis had the lowest median age (30 years; range: 8–85) and shortest median duration of travel

(12 days; range: 5–154). Coccidioidomycosis was reported in 14 travellers; travellers with coccidioidomycosis were older (median 62 years; range: 22–78) and had the longest median number of days between return from travel and presentation to a GeoSentinel site (55 days; range: 17–273). Almost all travellers with coccidioidomycosis were exposed in the USA. Other systemic endemic mycoses were less frequently reported, including blastomycosis (three travellers) and talaromycosis (one traveller).

Conclusions: Although relatively rare, systemic endemic mycoses should be considered as potential travel-related infections in non-migrant international travellers. Epidemiological exposures should be used to guide diagnostic evaluations and treatment.

Key words: Systemic endemic mycoses, GeoSentinel, traveller

Introduction

Systemic endemic mycoses are a group of fungal infections, including histoplasmosis, coccidioidomycosis, paracoccidioidomycosis, blastomycosis and talaromycosis, that share several characteristics. These fungi are dimorphic, have the potential to cause systemic infection, are found in the environment (particularly in soil) and are transmitted by inhalation of fungal spores or through the skin.[1] Some of these diseases may occur worldwide, while others occur in distinct geographical regions.

Histoplasmosis is the most common systemic endemic mycosis and has the largest geographic distribution, including North America, Central America, South America, Africa, Asia and Oceania. Some autochthonous cases have been described in Europe.[2] The prevalence may vary considerably within a country; for example, in the USA, most patients are exposed in the South and Midwest, particularly in the Ohio and Mississippi River valleys.[3] Paracoccidioidomycosis is primarily found in tropical and subtropical regions of Central and South America, particularly in Brazil, where it is considered a major public health issue in some regions.[4] Talaromycosis, caused by the fungus *Talaromyces marneffei* (formerly *Penicillium marneffei*), is endemic in Southeast Asia (particularly Thailand, Vietnam, Laos and southern China). Patients with human immunodeficiency virus (HIV) infection are at highest risk; it has a high case fatality rate of 11–21% depending on immune status and treatment.[5]

Coccidioidomycosis is found in warm and dry climates, including some states in the southwest USA.[6] The incidence in the USA increased in recent years with an estimated 150 000 new infections.[7,8] In some endemic regions of Central and South America, coccidioidomycosis leads to a large number of hospital admissions (e.g. Brazil's hospital admissions reached 7.1 per 100 000 inhabitants in 2011).[9] Blastomycosis is also found in temperate climates and has been reported mainly from North America, with sporadic cases reported from China, India, the Middle East, Africa and Central and South America.[10–12]

These fungi are endemic in popular tourist destinations.[13] International tourist arrivals have increased in the past few decades from 278 million globally in 1980 to 1.2 billion in 2016 and are expected to reach 1.8 billion by 2030.[13] In 2016, after France (82.6 million international tourist arrivals), the USA and Spain were the second most popular international tourism destinations, with 75.6 million international tourist arrivals each. Asia and the Pacific (Oceania) had the strongest growth of all tourist destinations in 2016 compared to 2015 (9% and 308.4 million tourist arrivals), while Central and South America had increases of 5 and 7%, with 10.7 and 32.8 million international tourist arrivals, respectively.[14]

The number of non-migrant international travellers who acquire systemic endemic mycoses remains unclear. Current evidence is based predominantly upon case series and outbreak investigations. Comprehensive data assessing the frequency of systemic endemic mycoses among international travellers are lacking. The aim of this analysis was to describe epidemiologic characteristics among non-migrant international travellers who acquired systemic endemic mycoses during travel and were reported to GeoSentinel.

Methods

Data source

GeoSentinel is a global clinician-based sentinel surveillance system of travel-related illness among international travellers and migrants, established in 1995 as a collaboration between the Centres for Disease Control and Prevention (CDC) and the International Society of Travel Medicine.[15] It currently consists of 70 specialized travel and tropical medicine clinical sites in 31 countries, mostly affiliated with academic medical centres (www.istm.org/geosentinel). All sites have experienced diagnosing and treating patients with travel-related infectious diseases and used the best reference diagnostic methods available in their country. Clinicians determine the final diagnosis coding in GeoSentinel from a list of standard diagnostic codes. GeoSentinel has five systemic endemic fungal infection diagnosis codes: histoplasmosis, coccidioidomycosis, blastomycosis, paracoccidioidomycosis and talaromycosis.

Clinicians may also use the diagnosis code 'other' to input other systemic endemic fungal diagnoses. Upon review of the 'other' diagnosis code, the only other systemic endemic fungal infection identified in the database was talaromycosis. GeoSentinel's data collection protocol has been reviewed by CDC's National Center for Emerging and Zoonotic Infectious Diseases and is classified as public health surveillance and not human subject research. For sites located in countries where national regulations required it, additional ethics clearance was obtained.

Inclusion and exclusion criteria

GeoSentinel records were included if they met the following case definition: 'a confirmed case of histoplasmosis, coccidioidomycosis, blastomycosis, paracoccidioidomycosis or talaromycosis in a

non-migrant international traveller for which there was a recorded region of exposure, and without the possibility of exposure to the diagnosed mycosis where the traveller resides'. Travellers from an endemic area who had a definitive exposure while abroad in an outbreak setting were included. Regions of exposure were determined using modified United Nations Children's Fund country groupings described elsewhere.[16] A 'confirmed' case of histoplasmosis, coccidioidomycosis, blastomycosis, paracoccidioidomycosis or talaromycosis was defined as 'a compatible clinical history in addition to a positive finding from at least one of the following tests: microscopy, culture, histopathology, nucleic acid or other antigen test or seroconversion or rising serology titre'.

Cryptococcosis was not included; *Cryptococcus neoformans* is not commonly considered an endemic mycosis, and GeoSentinel does not provide species data to include *Cryptococcus gattii*. Furthermore, *C. neoformans* is widely distributed making it difficult to ascertain the country of exposure.

Data extraction

Data were extracted on traveller demographic characteristics (sex, age, country of residence), trip details (e.g. duration, travel reason, previous travel), clinical information (date of presentation, time to presentation, inpatient or outpatient status, whether there was a pre-travel consultation with a health care provider, syndrome at presentation, other diagnoses and comorbid conditions) and area of acquisition (region or country of exposure). Duration of travel was reported among those who visited one destination country only. Information on specific symptoms was not available, and clinical treatment and outcomes are not routinely reported.

Statistical analysis

Data were managed using Microsoft Access (Redmond, Washington, USA). All analyses were descriptive and frequencies were performed using SAS version 9.4 (Cary, NC, USA).

Results

Records meeting the case definition

From 1997 through 2017, 69 records met the case definition. The most frequently reported endemic mycosis was histoplasmosis (51; 74%), followed by coccidioidomycosis (14; 20%), blastomycosis (3; 4%) (Table 1) and talaromycosis (1; 2%). There were no patient records in the database with a diagnosis of paracoccidioidomycosis.

Histoplasmosis

Travellers with histoplasmosis (n = 51) had a median age of 30 (range: 8–85) (Table 1). More than 80% of travellers with histoplasmosis travelled for tourism (25; 49%) or education (17; 33%). Histoplasmosis was most frequently acquired in Central America or Mexico (34; 69%) [including Nicaragua (14), Guatemala (6), Costa Rica (5), Mexico (3), Belize (3) and Honduras (2); one traveller acquired histoplasmosis in Central America, but the specific country of exposure could not be ascertained]. Histoplasmosis was also acquired in South America (9; 19%) [Ecuador (three travellers), Brazil (two travellers), Peru (two travellers), Bolivia (one traveller) and Guyana (one traveller)]. The median duration of travel was 12 days (range: 5–154); the median number of days between returning from travel and presenting to a GeoSentinel site was 16 days (range: 1–137). Forty-seven per cent of travellers with histoplasmosis were hospitalized. Only three travellers (6%) were reported to have HIV/acquired immune deficiency syndrome (AIDS).

Coccidioidomycosis

Travellers with coccidioidomycosis (n = 14) were older than those with other systemic endemic mycoses [median age: 62 years (range 22–78 years)] (Table 1). The most frequent reasons for travel were tourism (10; 72%) and business (3; 21%). Almost all travellers with coccidioidomycosis (13 of 14; 93%) were infected in the USA; one traveller acquired the infection in Mexico. The median number of days between return from travel and presentation to a GeoSentinel site was the longest of the endemic mycoses in this analysis (55 days; range: 17–273). Four (29%) travellers were hospitalized. One traveller was reported to have an immune-compromising condition (insulin-dependent diabetes mellitus). Another traveller was reported to have been taking an immunosuppressing or immunomodulating agent within 3 months prior to the clinic visit.

Other systemic endemic mycoses

Three travellers with blastomycosis were reported. Two travellers with blastomycosis were tourists, and one had visited friends and relatives. They acquired their infections in Mexico, China and Thailand.

One traveller with a prior solid organ transplant was reported to have acquired talaromycosis. This individual travelled to China for planned medical care.

Discussion

This analysis describes systemic endemic mycoses among international travellers presenting to GeoSentinel sites. The most frequently reported endemic mycosis was histoplasmosis. Although histoplasmosis is found worldwide, rates are much higher in the western hemisphere, but the global burden of histoplasmosis among international travellers remains unclear.[17] A Spanish study reported that 69 (20%) of 342 travellers had a positive histoplasmin skin test 1 month after travelling to Latin America; 13 (19%) were ultimately diagnosed with histoplasmosis.[18] However, reports of histoplasmosis in non-migrant international travellers are limited despite the relatively high incidence in some endemic regions and increasing global volume of travel.[18–23]

In our analysis, almost all travellers with histoplasmosis were exposed in the Americas. Most previously reported travel-associated histoplasmosis infections were acquired in Central and South America and associated with visits to bat-infested caves,[18,20] construction renovations or demolition activities.[21] Only two travel-associated outbreaks have been reported recently from outside the Americas—one in Uganda and the other in Malaysia.[22,23] Travellers with histoplasmosis in our analysis had the lowest median age, and one-third were students

Table 1. Characteristics of returned travellers with systemic endemic mycoses reported to GeoSentinel, January 1997 to December 2017[a]

Characteristic	Histoplasmosis ($n = 51$)	Coccidioidomycosis ($n = 14$)	Blastomycosis ($n = 3$)
Median age, years (range)	30 (8–85)[b]	62 (22–78)	48 (31–56)
Sex, *n* (%)			
• Female	20 (39%)	4 (29%)	1 (33%)
Pretravel consultation, *n* (%)			
• Yes	9 (18%)	2 (14%)	2 (67%)
• No	14 (27%)	6 (43%)	1 (33%)
• Unknown	28 (55%)	6 (43%)	0
Reasons for travel, *n* (%)			
• Business	2 (4%)	3 (21%)	0
• Education/student	17 (33%)	0	0
• Military	0	1 (7%)	0
• Missionary/volunteer/researcher/aid work	3 (6%)	0	0
• Tourism	25 (49%)	10 (72%)	2 (67%)
• Visiting friends and relatives	4 (8%)	0	1 (33%)
Region of exposure			
• Caribbean	2 (4%)	0	0
• Central America	34 (66%)	1 (7%)	1 (33%)
• North America	0	13 (93%)	0
• North East Asia	0	0	1 (33%)
• South America	11 (22%)	0	0
• Southeast Asia	1 (2%)	0	1 (33%)
• Sub-Saharan Africa	3 (6%)	0	0
Median duration of travel, days (range)[c,d]	12 (5–154)	43 (23–821)	8
Median days between return and presenting to a GeoSentinel site (range)[e]	16 (1–137)	55 (17–273)	5
Hospitalized	24 (47%)	4 (29%)	0
Co-morbid conditions			
• None known to exist	46 (90%)	12 (86%)	3 (100%)
• HIV/AIDS	3 (6%)	0	0
• Others	2 (4%)[f]	2 (14%)[g]	0

[a]Data on the one traveller with talaromycosis is not presented in the table.
[b]Data for two travellers missing.
[c]Among those who travelled to one destination country only ($n = 44$).
[d]Data for 14 travellers missing [histoplasmosis ($n = 6$), coccidioidomycosis ($n = 5$), blastomycosis ($n = 2$)].
[e]Data for 15 travellers missing [histoplasmosis ($n = 7$), coccidioidomycosis ($n = 5$), blastomycosis ($n = 2$)].
[f]Immunosuppressing/immunomodulating agents [currently or within 3 months of clinic visit ($n = 1$)], «other» immunocompromising condition ($n = 1$).
[g]Immunosuppressing/immunomodulating agents [currently or within 3 months of clinic visit ($n = 1$)], insulin-dependent diabetes mellitus ($n = 1$).

travelling for education. These findings are in part influenced by an outbreak of histoplasmosis among 14 otherwise healthy community college students who travelled to Nicaragua from the USA in 2001 and entered a cave with bats.[24] The infection rate among travellers in this outbreak was 100%. Twelve travellers developed symptoms, including fever, cough, night sweats, myalgia, chills, loss of appetite and headache, and all travellers had an abnormal chest X-ray; almost half were hospitalized, but none died.[24] The mortality of hospitalized histoplasmosis patients is 2–9% depending on age and immune status;[25,26] typically, elderly or immune-compromised patients are at higher risk of developing severe disease.[26,27] The largest known outbreak of histoplasmosis among travellers was reported among college students from the USA after returning from Acapulco, Mexico, in 2001.[28] These findings highlight the importance of histoplasmosis as a potentially severe travel-related disease, even among travellers who are not immune-compromised who may be exposed to a high infectious dose.[24]

Travellers with coccidioidomycosis were older and had the longest median duration from the time of return from travel to presentation at a GeoSentinel site. The long time may reflect the indolent or subacute nature of coccidioidomycosis but also may be due to GeoSentinel sites' function as referral or specialty centres after preliminary evaluation by another physician or facility. Coccidioidomycosis outbreaks are often associated with occupational exposures (e.g. construction, field work, etc.), but may also be from environmental disruptions such as earthquakes or dust storms.[29] Although we identified only one traveller exposed in Mexico, many reports among travellers to Mexico engaging in missionary construction work have been reported.[30,31]

In this analysis, one traveller with blastomycosis acquired the infection in Mexico, while two others acquired the infection in Asia (Thailand and China). Few autochthonous cases from Asia have been published, possibly indicating a very low disease burden in this region.[10,11] No human blastomycosis infections have been published from Thailand. However, recently, cutaneous blastomycosis was detected in a Persian cat from Thailand (confirmed by histopathology and PCR from tissue samples).[32] We report here the first published travel-related blastomycosis

infection acquired in Thailand. Nevertheless, the risk of blastomycosis for travellers visiting Asia is likely low. Although we only report one traveller with talaromycosis, this disease represents a serious public health issue in Southeast Asia and should be considered in immune-compromised travellers returning from Southeast Asia.[5]

No traveller with paracoccidioidomycosis met our inclusion criteria. This may be because: (i) paracoccidioidomycosis usually occurs in rural areas that may be off the usual tourist routes, (ii) clinicians may not be testing for it, (iii) laboratories may not be able to test (if the best reference diagnostic methods are not available in their country, as is the case for the *Histoplasma* antigen test outside the USA) or (iv) the majority of travellers may remain asymptomatic and not seek medical care. Also, recent travel history may not indicate a risk of paracoccidioidomycosis (or other systemic endemic mycoses), because the exposure may have been months or even years prior.[4]

This analysis of GeoSentinel surveillance data has several limitations. GeoSentinel surveillance data are not population-based, so risks and rates cannot be determined. GeoSentinel does not routinely collect data on all traveller co-morbidities; therefore, this analysis likely underreports the number of travellers with each systemic endemic mycosis that may have an underlying immune-compromising condition. For example, over 90% of travellers with histoplasmosis in our study were presumed to be healthy individuals without any evidence of being immune-compromised; only three travellers were noted to have HIV/AIDS. Additionally, of those travellers with HIV/AIDS, T cell counts and viral loads were not available to assess the degree of immune-compromise. Similarly, death is not well recorded through GeoSentinel surveillance; data are collected from a single time point and may not capture a later death. Given the specialized nature of GeoSentinel sites as tropical or travel medicine referral centres, the data are not generalizable to all international travellers, and the median number of days between returning from travel and visiting a GeoSentinel site varies considerably. Furthermore, we are unable to quantify the number of travellers who may have had an exposure but remained asymptomatic or did not seek care at a GeoSentinel site. Furthermore, information on specific symptoms was not available, and clinical treatment and outcomes are not routinely reported. Despite the use of standard diagnosis codes, data coding and entry practices might vary by clinician and site (e.g. cases of systemic endemic mycoses may not have been entered into the database if a specific diagnostic code was not available). Furthermore, diagnostic testing information was not routinely collected; therefore, we are limited by our reliance on the reporting providers' clinical judgement and their interpretation of diagnostic test results.

In conclusion, systemic endemic mycoses should be considered in the differential diagnosis of non-migrant international travellers. Clinician knowledge of the geographic distributions and the modes of transmission of systemic endemic mycoses may improve personalized pre-travel consultation and help prevent infections in travellers who may be at increased risk of exposure or greater risk of infection if exposed. Clinicians should also be aware of the Infectious Disease Society of America's recommendations on systemic endemic mycoses, which can assist with both diagnostic and treatment recommendations.[33–36]

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Authors' contributions

Study design: H.J.F.S., R.J.S., K.M.A., T.R., S.J., C.L., D.H.H. Data collection: H.J.F.S., T.R., M.P.G., M.L., R.L.V., A.D., H.A., C.C.A., E.S., P.G., E.B., S.J., D.H.H. Analysis: H.J.F.S., R.J.S., K.M.A., D.H.H. Interpretation: H.J.F.S., R.J.S., K.M.A., T.R., M.P.G., M.L., R.L.V., A.D., H.A., C.C.A., E.S., P.G., E.B., S.J., C.L., D.H.H.

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