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Seroprevalence of Histoplasmosis in Somali, Burmese, and Hmong Refugees Residing in Thailand and Kenya

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Abstract

Histoplasmosis is known to be endemic to the Midwestern United States, but cases have been reported throughout much of the world. Somali, Hmong, and Burmese (ethnically Karen) persons make up some of the largest refugee populations coming the United States in recent years. Yet, information about risk of *Histoplasma capsulatum* infection amongst these populations is limited. This study used the CDC Migrant Serum Bank to test ~100 samples from each of Somali, Burmese, and Hmong U.S.-bound refugees. Samples were tested by enzyme immunoassay for *Histoplasma capsulatum* IgG. Overall 1% (2/299) of refugee serum samples were positive for *H. capsulatum* IgG. One of 99 samples obtained from Hmong refugees was positive, and the other positive sample came from among 100 Burmese refugee samples. *H capsulatum* IgG positivity was detected at low levels in Hmong and Burmese refugees. No IgG positivity was detected among 100 Somali refugees.

Keywords

Histoplasma capsulatum; Seroepidemiologic studies; Refugee; Refugee health

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Compliance with Ethical Standards

Conflict of interest Authors Durkin and Wheat are employees of MiraVista Diagnostics. The other authors have no conflicts of interest to declare.

Human and Animal Participants Data obtained using samples from the CDC Migrant Serum Bank in this retrospective study was determined to not include human subjects, as defined under 45 CFR 46.102(f) and so IRB approval and informed consent were not required. The article does not contain any studies with human participants or animals performed by any of the authors.

Background

Histoplasmosis is the most common endemic mycoses in the United States [1]. While most infections are asymptomatic, a subset of those infected go on to develop pulmonary symptoms and dissemination may be fatal [1]. *Histoplasma capsulatum* infection is often thought of as a disease of the Ohio and Mississippi River valleys in the United States [2–4]. More recently, areas outside of North America such as parts of Central and South America, Africa, and Asia have been recognized as endemic to histoplasmosis [5–7]. In HIV cohorts in Latin America, histoplasmosis is increasingly reported and is now considered one of the most common opportunistic infections [8]. However, the global distribution of histoplasmosis is largely unknown.

We sought to obtain more information about histoplasmosis in refugee groups, specifically Burmese (Myanmar—ethnically Karen), Hmong (from Laos), and Somali refugees given the large numbers of persons from these groups that have come to the United States in recent years. From 1975 to 2014 over 1,300,000 refugees entered the United States from East Asia. Though 900,000 were from Vietnam, nearly half of the remainder came from Laos [9, 10]. From 2007 to 2015, nearly 150,000 refugees were admitted from Burma [11]. Prior to entering the United States, Burmese and Hmong refugees resided in refugee camps in Thailand [12]. The Hmong, whose camps were in northern and eastern Thailand, did not travel frequently to Laos (due to geography and the political situation) [12]. The Burmese, whose camps were on the border in western Thailand, had fairly frequent and fluid travel between western Thailand and Myanmar [12]. From 1975 to 2014 over 100,000 Somali refugees have come the United States [13], with over 52,000 coming from 2007 to 2015 [11, 13]. The Somali refugees who samples were tested in this study had spent a majority of their time in camps in northern and central Kenya.

There is only limited information available of histoplasmosis in the regions from which these populations came to the United States [14–20].

Refugees undergo a required medical exam prior to entering the United States. This examination includes testing for excludable communicable diseases (e.g. syphilis, tuberculosis, gonorrhea, and leprosy) that would preclude the refugee from entering the United States. The Centers for Disease Control and Prevention established the Migrant Serum Bank in 2002. The Migrant Serum Bank collects leftover unidentified serum samples from refugees who undergo this examination. The goal of the serum bank is to allow for greater understanding of emerging infections that affect migrant populations [21].

This study sought to provide information on exposure to, and potential risk of, exposure to *H capsulatum* in populations from Laos (Hmong), Myanmar (Burmese), and Somalia who had resided for prolonged periods in western, northern, and north-eastern Thailand and northern/central Kenya. To our knowledge none of these populations have had serological data published with reference to histoplasmosis, and none have had skin testing published in at least three decades [15, 17, 18, 20].

Methods

At the time of study, 15,616 sera of adults ≥19 years of age were available for Somali, Burmese, and Hmong refugees in the Migrant Serum Bank (stored at −70 °C). Of the total available sera, 100 samples for each population were randomly selected from all available samples from each location using SAS version 9.3 (Cary, NC). The samples included were collected from June 2003 through August 2007.

Specimens were shipped to MiraVista Laboratories (Indianapolis, IN). At MiraVista, enzyme immunoassays (EIA) were performed for anti-*Histoplasma capsulatum* IgG against serum [22, 23]. Microplates were coated with a proprietary MVista *Histoplasma* antigen and the procedure was completed as previously described [22, 23]. Results were expressed by comparison to a standard curve as EIA units. Reproducibility was investigated by duplicate testing, and positive and negative controls performed as expected. Results were considered positive if ≥10, indeterminate if 8–9.99, and negative if <8 units. This assay has been used in prior studies and using this cutoff shown to have 87.5% sensitivity and 95% specificity in acute pulmonary histoplasmosis [22, 23].

Statistical analysis was performed using SPSS version 22 (IBM Corporation, Armonk, NY). Percent IgG positivity by EIA was summarized using frequency for each sample group.

Results

We tested 299 serum samples from 100 Burmese, 100 Somali, and 99 Hmong refugees for Histoplasma seropositivity (Fig. 1). The sample from one Hmong refugee was not received for testing. Available demographic information of the refugees and location prior to immigration are described in Table 1. Overall, 2 (0.67%) of 299 samples were positive for anti-*Histoplasma* IgG. An additional two sera were indeterminate (i.e. 8–9.9 units). Thus, overall, 4 (1.4%) of 299 samples were positive or indeterminate, and 295 (98.66%) of 299 were seronegative. Figure 2 shows a scatter plot of all samples with cutoffs for positivity and indeterminate values.

Table 2 shows sample outcome by population group. Of 99 Hmong, one (1%) was seropositive, none were indeterminate, and 98 were seronegative. Among 100 Burmese, one (1%) was seropositive, two (2%) indeterminate, and 97 seronegative. Among 100 Somalis, all 100 were seronegative.

Discussion

We found only a 1% rate of anti-*H capsulatum* IgG positivity by EIA among Burmese and Hmong refugees who had immigrated to the United States. The positivity rate was zero among the Somali refugee population. This suggests that recent histoplasmosis exposure is rare amongst these populations.

There is one case report of histoplasmosis in a Laotian person living in Australia [16], another in a Burmese male who had been living in Taiwan [14], and multiple cases in Thailand where refugees resided prior to immigration to the United States [20]. Skin test

studies in the 1950s in Myanmar found wide ranging skin test positivity (8–86%), though positivity was relatively low (4–5%) in northern and northeastern Thailand where refugee camps were located [15, 20]. No skin testing studies have been published from Laos. *H. capsulatum* DNA has also been detected in soil surveys in Thailand [24, 25].

Our testing was performed using IgG detection rather than skin testing but found much lower rates overall. However, one should note that the 95% confidence intervals found in our study would be similar to the lower range of the skin testing studies [15, 20]. Further, there are extremely wide ranges in the skin testing studies lending some degree of uncertainty. Additionally while histoplasmin skin testing is positive for life in 90% of exposed individuals; IgG positivity likely only persists for several years, possibly for a shorter duration than the time subjects spent in refugee camps [23, 26]. As an example of the effect of duration of antibody persistence relative to that of skin testing, Richer and colleagues included 50 subjects from Miami/Dade County where histoplasmin skin test positivity is 2.8% and found no positive samples for IgG anti-*Histoplama* IgG antibodies [23]. Among 50 subjects in Indianapolis where skin test positivity is 55.1%, only 3 of 116 serum samples for anti-*Histoplama* IgG antibodies [23]. This may indicate that one's antibody response waning over time allows for low seropositivity in a region as compared to skin test positivity.

Though we found low rates of positivity, our study represents an important update in the literature for these populations. Histoplasmosis is endemic in the central United States. Yet, it is often not recognized that histoplasmosis is present in much of the world as well [5]. The most recent skin testing studies referenced above were from the 1980s, however, some were from the 1950s and 1960s. Factors influencing the distribution are incompletely understood but proximity to rivers, moderate temperatures and soil bird and/or bat guano content seem to play a role [1, 7]. Given these factors and ongoing climate change, in addition to increased use of immune suppressive medications, it's likely that our understanding of the distribution of *Histoplasma* endemicity will continue to change.

The present study has limitations. The anonymized samples limit the demographic and other sample specific information. In addition, the refugees included in this study originated from specific areas, typically refugee camps and so conditions and exposures may be more specific to these geographic locations than their locations of origin (Fig.1). Finally, one needs to consider that it is well established that *H. capsulatum* antigen testing is known to cross react with *Penicillium* (*Talaromyces*) *marneffei* antigen [27]. It isn't clear whether histoplasmin skin test positivity could have been caused by cross-reaction in individuals who were exposed to *P. marneffei* [28]. However, this would be another possible explanation for higher skin testing positivity rates than the EIA positivity rates we found. One may also posit that the low rates found in our study could be more consistent with the relatively rare clinical rate of reporting in these areas.

No Somalis were seropositive for anti-*Histoplasma* IgG antibodies. As with the Burmese and Hmong populations, similar limitations should be considered although cross-reaction with *P. marneffei* is extremely unlikely given the geographic distribution of this fungus. Skin testing in Somalia found 0.3–25.7% positivity in two studies from the 1970s and 1980s [17, 18]. Both studies found higher rates in Southern Somalia in populations with proximity to

the Jubba River [17, 18]. There have been published case reports of histoplasmosis in Kenya near the Tana, Kilundu, and Athi-Galan-Sabaki, Rivers [19]. While none of the cases were near the Kakuma refugee camp hosting Somalis, the case in Machakos, near the Athi-Galan-Sabaki River is about 80 km from Nairobi. Our study doesn't provide additional evidence of *H capsulatum* infection in these locations.

In conclusion, we found low levels of seropositivity for *H. capsulatum* IgG obtained by EIA among Hmong and Burmese refugee populations who have since entered the United States and had been residing in Thailand. In addition, seroprevalence in 100 Somali refugees residing in Kenya tested was zero. Clinicians caring for these populations can be reassured that clinical histoplasmosis would be unusual in newly arrived refugees from these areas, and if observed after arrival to the United States would more likely have been acquired locally. Clinicians should keep in mind that without prior exposure, these populations might be at higher risk for histoplasmosis. In addition, these data may suggest that histoplasmosis exposure in Laos, Myanmar and Kenya may be limited though further study in this area is needed.

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References

1. Wheat LJ, Azar MM, Bahr NC, Spec A, Relich RF, Hage C. Histoplasmosis. Infect Dis Clin North Am. 2016; 30(1):207–27. [PubMed: 26897068]
2. Kuzma JF. Histoplasmosis—the pathologic and clinical findings. Dis Chest. 1947; 13(4):338–44. [PubMed: 20251852]
3. Christie A. Histoplasmosis and pulmonary calcification—geographic distribution. Am J Trop Med Hyg. 1951; 31(6):742–52. [PubMed: 14894759]
4. Edwards LB, Acquaviva FA, Livesay VT, Cross FW, Palmer CE. An atlas of sensitivity to tuberculin, PPD-B, and histoplasmin in the United States. Am Rev Respir Dis. 1969; 99(4):Suppl: 1–132.
5. Bahr NC, Antinori S, Wheat LJ, Sarosi GA. Histoplasmosis infections worldwide: thinking outside of the Ohio River valley. Curr Trop Med Rep. 2015; 2(2):70–80. [PubMed: 26279969]
6. Wheat LJ, Freifeld AG, Kleiman MB, Baddley JW, McKinsey DS, Loyd JE, et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. Clin Infect. 2007; 45(7):807–25.
7. Hage CA, Azar MM, Bahr N, Loyd J, Wheat LJ. Histoplasmosis: up-to-date evidence-based approach to diagnosis and management. Semin Respir Crit Care Med. 2015; 36(5):729–45. [PubMed: 26398539]
8. Neglected Histoplasmosis in Latin America Group. Disseminated histoplasmosis in Central and South America, the invisible elephant: the lethal blind spot of international health organizations. AIDS. 2016; 30(2):167–70. [PubMed: 26684816]
9. Bureau of Population, Refugees, and Migration. Refugee Admissions Program for East Asia 2014 https://www.state.gov/j/prm/releases/onepagers/228693.htm

10. Migration Policy Institute. Countries of birth for US immigrants, 1960–Present 2016 http://www.migrationpolicy.org/programs/data-hub/charts/immigrants-countries-birth-over-time?width=1000&height=850&iframe=true
11. US Department of State. Refugee Admissions Statistics 2016 https://www.state.gov/j/prm/releases/statistics/
12. Lee D. Personal communication to authors. 2016
13. Bureau of Population, Refugees, and Migration. Refugee Admissions Program for Africa 2014 https://www.state.gov/j/prm/releases/onepagers/228692.htm
14. Hung MN, Sun HY, Hsueh PR, Hung CC, Chang SC. Meningitis due to *Histoplasma capsulatum* and *Mycobacterium tuberculosis* in a returned traveler with acquired immunodeficiency syndrome. J Formos Med Assoc. 2005; 104(11):860–3. [PubMed: 16496069]
15. Jayanetra P, Prajaktam R, Satapathayawong B, Atichartrakarn V, Thianprasit M, Waropastrakul C, Poopaibul K, Kanjanasthiti P. The magnitude of the public health problem posed by the mycoses. Part II: the lack of information. J Infect Dis Antimicrob Agents. 1987; 4:175–84.
16. Jordan AS, Chavada R, Nagendra V, McNeil HP, Kociuba K, Gibson KA. A budding surprise from the joint. Med J Aust. 2013; 199(10):700–1. [PubMed: 24237103]
17. Maresca B, Ali AI, Kobayashi GS, Sacco M. Incidence of histoplasmin skin test reactivity in Somalia: an epidemiological study. Mycopathologia. 1987; 98(2):77–81. [PubMed: 3600740]
18. Nuti M, Tarabini GC, Adorisio E, Zardi O. Histoplasmosis diffusion in Somalia: study of skin-test and serological survey. Biochem Exp Biol. 1979; 15(2):111–7. [PubMed: 555667]
19. Pamnani R, Rajab JA, Githang'a J, Kasmani R. Disseminated histoplasmosis diagnosed on bone marrow aspirate cytology: report of four cases. East Afr Med J. 2009; 86(12 Suppl):S102–5. [PubMed: 21591519]
20. Randhawa HS. Occurrence of histoplasmosis in Asia. Mycopathologia et mycologia applicata. 1970; 41(1):75–89. [PubMed: 4938836]
21. Posey DL, Blackburn BG, Weinberg M, Flagg EW, Ortega L, Wilson M, et al. High prevalence and presumptive treatment of schistosomiasis and strongyloidiasis among African refugees. Clin Infect Dis. 2007; 45(10):1310–5. [PubMed: 17968826]
22. Bahr NC, Sarosi GA, Meya DB, Bohjanen PR, Richer SM, Swartzentruber S, et al. Seroprevalence of histoplasmosis in Kampala, Uganda. Med Mycol. 2016; 54(3):295–300. [PubMed: 26527637]
23. Richer SM, Smedema ML, Durkin MM, Herman KM, Hage CA, Fuller D, et al. Improved diagnosis of acute pulmonary histoplasmosis by combining antigen and antibody detection. Clin Infect Dis. 2016; 62(7):896–902. [PubMed: 26797210]
24. Norkaew T, Ohno H, Sriburee P, Tanabe K, Tharavichitkul P, Takarn P, et al. Detection of environmental sources of *Histoplasma capsulatum* in Chiang Mai, Thailand, by nested PCR. Mycopathologia. 2013; 176(5–6):395–402. [PubMed: 24030846]
25. Wongprommek P, Chayakulkeeree M. Clinical characteristics of histoplasmosis in Siriraj hospital. J Med Assoc Thai. 2016; 99(3):257–61. [PubMed: 27276735]
26. Wheat J, French ML, Kohler RB, Zimmerman SE, Smith WR, Norton JA, et al. The diagnostic laboratory tests for histoplasmosis: analysis of experience in a large urban outbreak. Ann Intern Med. 1982; 97(5):680–5. [PubMed: 6814316]
27. Wheat J, Wheat H, Connolly P, Kleiman M, Supparatpinyo K, Nelson K, et al. Cross-reactivity in *Histoplasma capsulatum* variety capsulatum antigen assays of urine samples from patients with endemic mycoses. Clin Infect Dis. 1997; 24(6):1169–71. [PubMed: 9195077]
28. Mochi A, Edwards PQ. Geographical distribution of histoplasmosis and histoplasmin sensitivity. Bull World Health Organ. 1952; 5(3):259–91. [PubMed: 14935779]

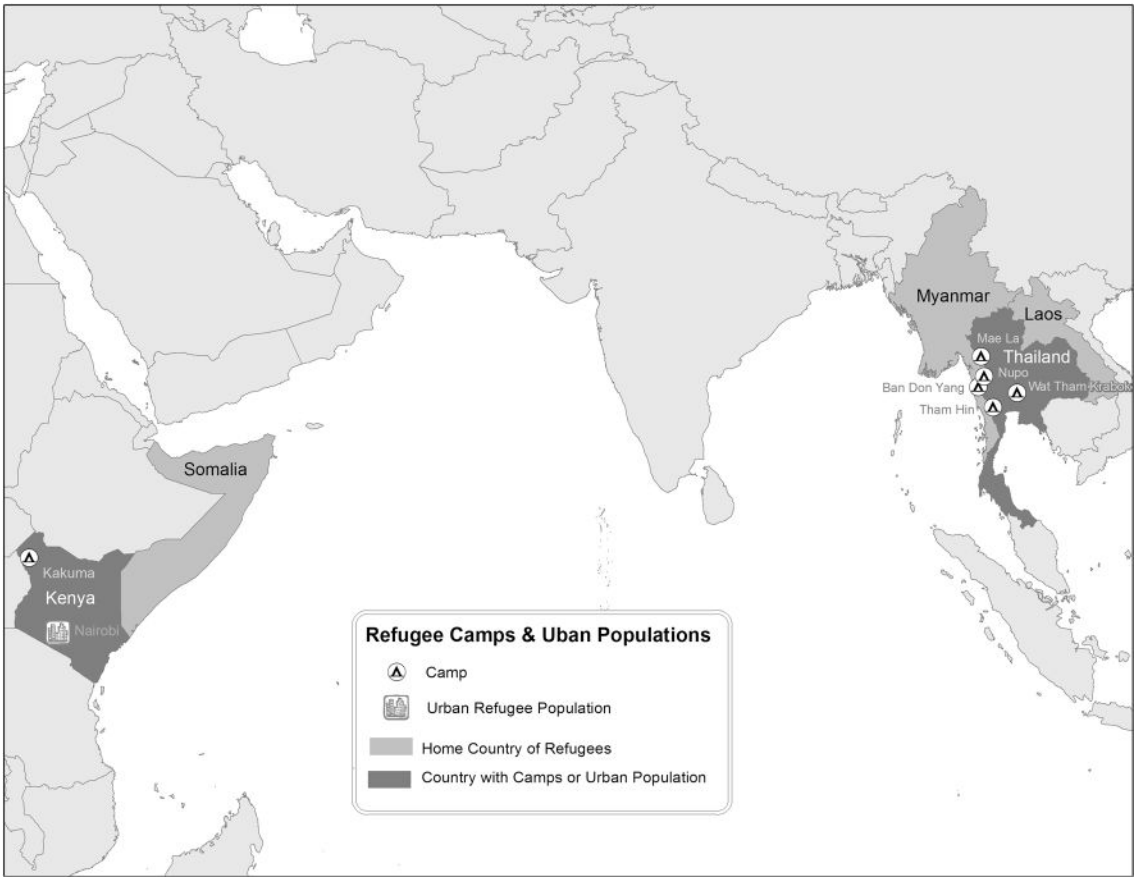

Fig. 1.

Map of countries of origin and refugee camp locations. This map presents the home countries (Somalia, Myanmar (Burma) and Laos) for persons from which the samples in this study came. Refugee camp locations in which these persons spent years prior to immigration to the United States are noted by markers in Kenya (Somali refugees), western Thailand (Burmese—ethnically Karen refugees), and southwestern Thailand (Hmong refugees). Map courtesy of Dr. C. Virginia Lee, Centers for Disease Control

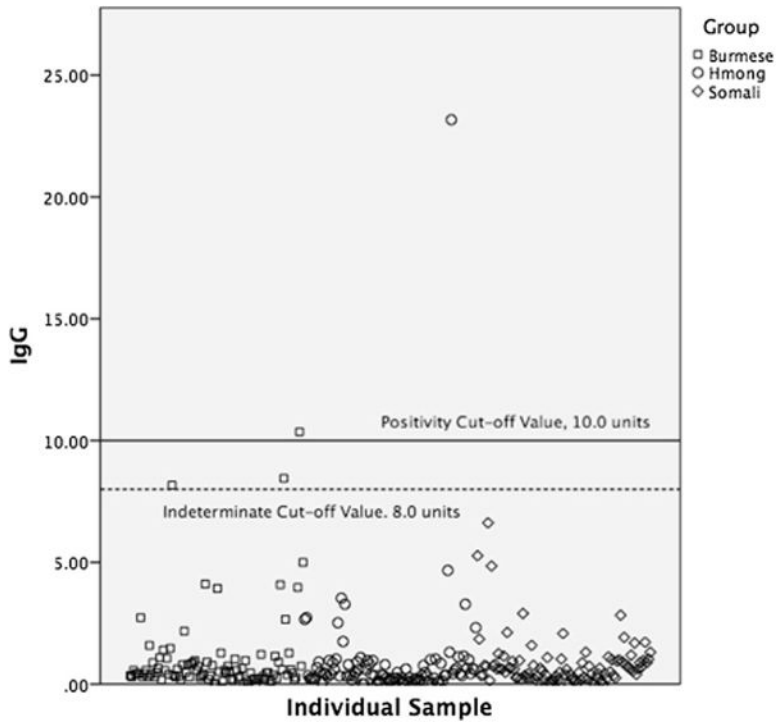

Fig. 2. Scatter plot

of serum *Histoplasma* Enzyme Immunoassay IgG results. The results of serum EIA *Histoplasma* IgG testing with the positive cutoff noted by a *solid horizontal line* at 10 units and a *dotted horizontal line* at 8 units marking indeterminate results

Table 1

Summary characteristics of test populations

Group	Camp location	Years sera collected	Number of specimens	Median age (IQR, years)	Percent female
Burmese (Karen)	Thailand *	2004–2007	100	33 (27–42)	42
Hmong	Thailand **	2004–2005	99	30 (25–46)	44
Somali (Bantu and other ethnicity)	Kenya ***	2003–2007	100	32 (24–50)	51

IQR interquartile range

* Thailand-Burma (Myanmar) border refugee camps: Ban Don Yang, Mae La, Nupo, and Tham Hin;

** Wat Tham Krabok;

*** Kakuma and Nairobi

Table 2

Serum *Histoplasma* enzyme immunoassay IgG results by group

Group	Total samples	Positive samples n (%, 95% CI)	Indeterminate samples n (%, 95% CI)
Hmong	99	1 (1.01, 0–2.96)	0 (0, N/A)
Burmese	100	1 (1, 0–2.95)	2 (2, 0–4.74)
Somali	100	0 (0, N/A)	0 (0, N/A)

N/A not applicable, 95% CI 95% confidence interval