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MINIREVIEW

Considerations about the Geographic Distribution of *Histoplasma* Species

Maria Lucia Taylor,[a] María del Rocío Reyes-Montes,[a] Daniel A. Estrada-Bárcenas,[b] Rosely M. Zancopé-Oliveira,[c] Gabriela Rodríguez-Arellanes,[a] José Antonio Ramírez[a]

[a]Unidad de Micología, Departamento de Microbiología y Parasitología, Facultad de Medicina, Universidad Nacional Autónoma de México (UNAM), Mexico City, Mexico
[b]Coleccion Nacional de Cepas Microbianas y Cultivos Celulares, Centro de Investigación y de Estudios Avanzados, Instituto Politécnico Nacional (CINVESTAV, IPN), Mexico City, Mexico
[c]Laboratório de Micología, Instituto Nacional de Infectología Evandro Chagas, Fundação Oswaldo Cruz (FIOCRUZ), Rio de Janeiro, Brazil

ABSTRACT Histoplasmosis is a mycotic infection principally affecting pulmonary tissue; sometimes, histoplasmosis can progress into a systemic disease. This infection involves immunocompetent and immunosuppressed human and other mammalian hosts, depending on particular circumstances. Histoplasmosis infection has been documented worldwide. The infection is acquired by inhaling infective mycelial propagules of the dimorphic fungus *Histoplasma capsulatum*. New reports of clinical cases of histoplasmosis in extreme latitudes could be related to human social adaptations and climate changes in the world, which are creating new favorable environments for this fungus and for bats, its major natural reservoirs and dispersers. *Histoplasma* has been isolated from most continents, and it is considered a complex of cryptic species, consisting of various groups of isolates that differ genetically and correlate with a particular geographic distribution. Based on updated studies, *Histoplasma* taxonomy is adjusting to new genetic data. Here, we have suggested that *Histoplasma* has at least 14 phylogenetic species distributed worldwide and new genotypes that could be under deliberation. *Histoplasma*'s geographic radiation began in South America millions of years ago when the continents were joined and the climate was favorable. For fungal spreading, the role of bats and some birds is crucial, although other natural factors could also participate.

KEYWORDS *Histoplasma* spp., worldwide distribution, climate changes, bats, spreading, *Histoplasma capsulatum*

Systemic mycosis histoplasmosis evolves primarily as a respiratory infection with pulmonary involvement, acquired by inhalation of infective propagules of its causative agent, the dimorphic fungus *Histoplasma capsulatum* (1). *H. capsulatum* must be considered a primary pathogen due to its ability to cause disease in immunocompetent hosts. Sometimes, this fungus can act as an opportunistic microorganism, occasionally causing severe infection in immunosuppressed individuals (1). It is important to highlight that *H. capsulatum* does not colonize the upper and lower respiratory tracts of the host and that its presence in host tissues is always indicative of an active or latent infection process, usually associated with tissue modification and damage. *H. capsulatum* does not fulfill the parameters necessary to be considered a colonizing and a commensal microorganism, according to the Casadevall and Pirofski (2) criteria. *H. capsulatum* does not belong to the normal microbiota of the respiratory tract, nor is the respiratory epithelium an appropriate site to make commensalism for this type of respiratory pathogen. In addition, this pathogen does not need a colonization stage to increase the amount of its infective propagules, as do certain colonizing microorganisms.

Histoplasmosis is not contagious, and airborne transmission by nasal secretions has never been reported. Overall, this fungal infection is autolimited by the innate immune response of the host. Sometimes, depending on the condition of host innate defenses,

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Address correspondence to Maria Lucia Taylor, emello@unam.mx.
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the adaptive immune response is required to provide adequate protection by avoiding the development of the infection and promoting fast elimination of the fungus (3). Under this circumstance, adaptive immunity can be useful for detecting immunological evidence of past infections through a delayed hypersensitive reaction (positive histoplasmin skin test). In most cases, depending on the size of the inhaled inoculum, the virulence and the phylogenetic species of the fungal strain (*Histoplasma* genotypes), and the immune conditions of the host exposed to fungal propagules, clinical manifestations can progress from mild to severe forms of the disease with or without granulomatous reaction, and they can even lead to a fatal outcome (4).

Histoplasmosis infection in humans and other mammals has been reported on all continents (1), with the exception of Antarctica. The disease is predominant in American and African regions (5), where the infection is considered endemic. In recent years, human histoplasmosis cases have increased in areas of nonendemicity, as reported by Patel et al. (6). The epidemic form of histoplasmosis, usually associated with outbreaks, is described mainly in Latin American countries, where there is a close relationship between high risks of infection and human occupational and tourist activities (7, 8).

In the past, histoplasmosis was reported in tropical and subtropical regions of the world between latitudes 45°N and 35°S; however, autochthonous outbreaks in extreme latitudes, such as 54°N in AB, Canada (9) and 38°S in Argentinian Patagonia (10), suggest the major spreading of *H. capsulatum* in the environment. An increased number of histoplasmosis outbreaks and their reports at extreme latitudes may be attributed to environmental changes in the fungal ecological niche, as well as to behavioral changes of its natural reservoirs and dispersers, which undoubtedly supports a wider geographical distribution of *H. capsulatum*. This phenomenon could be associated with climate change and human social modifications, perhaps in adjustment to new economic conditions, influencing *Histoplasma* distribution. With regard to the role of climate change in the geographic expansion of *Histoplasma*, Kasuga et al. (11, 12) suggested that since a million years ago, *Histoplasma* spread from cold to temperate regions. This is compatible with the optimal conditions for its survival in the environment (saprobic stage) and in infected wild hosts (parasitic stage).

Histoplasma capsulatum is an ascomycete with a haploid anamorph asexual stage and a temporary and diploid teleomorph sexual stage, known as *Ajellomyces capsulatus*. *H. capsulatum* displays thermally regulated dimorphism, although other conditions can stimulate its morphogenesis. This fungus does not require an infectious life cycle for its maintenance in nature (13). However, the nonvirulent mycelial infective morphotype, which is organized with hyphae and conidia, aerosolizes mainly small hyphal fragments and microconidia that may be easily inhaled by mammalian hosts, creating an infectious life cycle (see Fig. 1). The nonvirulent characteristic of the mycelial morphotype was elegantly demonstrated in the past by Medoff (14), using an inhibitor of the fungal dimorphic transition. To cause progressive infection and disease in the host, a morphotype transition from the nonvirulent (mycelium) to the virulent (yeast) morphotype of *H. capsulatum* is essential (15). Therefore, once in the host compartment or in special culture medium at 37°C, the fungus activates its thermodimorphic process and converts to the yeast morphotype, which displays a multiplicity of virulence factors, enabling successful infection and producing pulmonary or disseminated diseases. *H. capsulatum* yeast is a facultative intracellular parasite that can survive and replicate within macrophages and other phagocytes. The yeast morphotype has developed efficient strategies to circumvent the intracellular antimicrobial activities of host cells (16).

CURRENT PHYLOGEOGRAPHY OF *HISTOPLASMA* SPECIES BASED ON GENETIC DIVERSITY ANALYSES

Among dimorphic fungi, the *Histoplasma* genus is presumed to be one of the most widely spread in the world. Studies conducted by Vincent et al. (17), Spitzer et al. (18), and Keath et al. (19) showed that *H. capsulatum* consists of various groups of isolates that differ genetically and correlate with particular geographic distributions. Six classes (genotypes) were described. First, according to Vincent et al. (17), the fungus was classified into

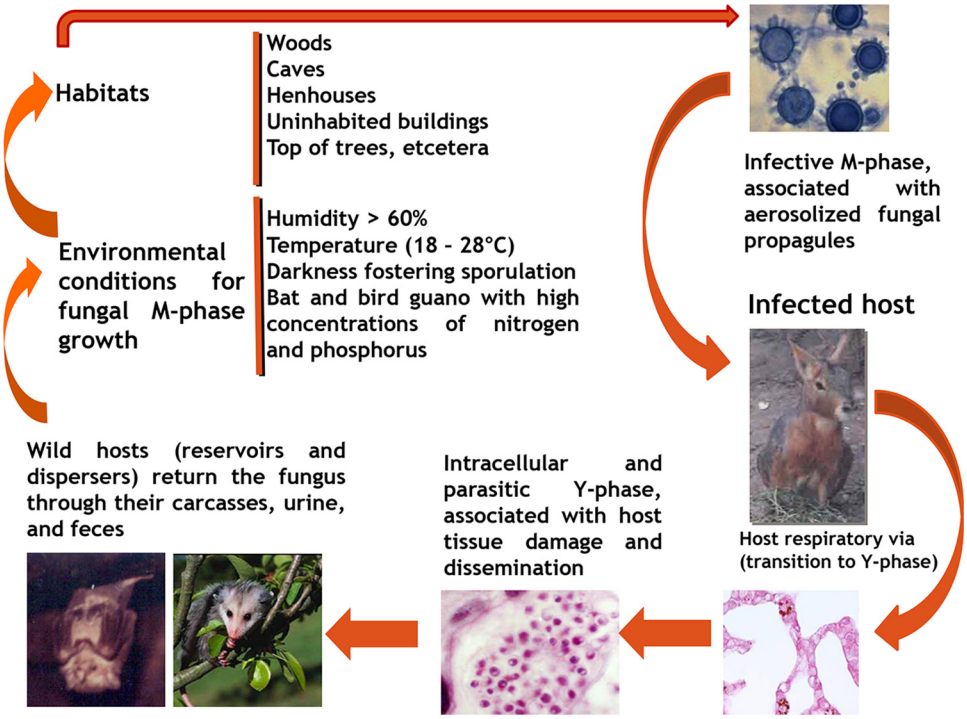

FIG 1 Representation of the *H. capsulatum* life cycle according to natural and host environments. (Photographs of tissue samples are courtesy of A. Pérez-Torres, used with permission; photos of infective M-phase and wild hosts are from the archive of Maria Lucia Taylor's research laboratory.)

the following three classes: classes 1 and 2 were formed by some strains from the United States, and class 3 grouped a limited number of *H. capsulatum* strains from Central (Panama) and South America (Colombia). Subsequently, Spitzer et al. (18) incorporated class 4 into this previous genotyping classification, considering an *H. capsulatum* isolated in the soil from Florida, USA. Then, Keath et al. (19) identified other two genotypes (classes 5 and 6). Class 5, with four subclasses, 5a to 5d, comprised isolates from AIDS patients from Puerto Rico and isolates from Panama. Class 6, described by Keath et al. (19), was recognized in a DNA sample obtained from an AIDS-histoplasmosis patient from Panama.

Nowadays, *Histoplasma* is considered a complex of cryptic species (11, 12, 20–22). An innovative phylogeographic study of *H. capsulatum* developed by Kasuga et al. (12) recorded seven phylogenetic species: North American class 1 (NAm 1), North American class 2 (NAm 2), Latin American group A (LAm A), Latin American group B (LAm B), Australian, Netherlands, and African clades. Due to low support values in phylogenetic reconstruction analyses, an 8th *H. capsulatum* clade, the Eurasian clade, had not been considered a phylogenetic species by Kasuga et al. (12), and to date, its precise classification remains uncertain.

Originally, based on its geographic distribution and clinical manifestations, *H. capsulatum* was classified into the following three varieties: *H. capsulatum* var. *capsulatum*, which is extensively distributed, *H. capsulatum* var. *duboisii*, found in Africa, and *H. capsulatum* var. *farciminosum*, reported mainly in Asia as a horse pathogen. Fungal isolates from this preliminary classification were reclassified into different phylogenetic species in the pioneering proposal of Kasuga et al. (12), changing the outdated original classification. Thus, *H. capsulatum* var. *capsulatum* was placed in all phylogenetic species, *H. capsulatum* var. *duboisii* belongs to African phylogenetic species, and *H. capsulatum* var. *farciminosum* is found in NAm 2, African phylogenetic species, and, particularly, the Eurasian clade.

Kasuga's classification incorporates precise concepts that are very important for the taxonomy of *Histoplasma*, and this classification has been used to identify this fungus until now and to implement new taxonomic studies. Additional information has improved this classification, and according to Teixeira et al. (20), *H. capsulatum* has increased to 11 the number of

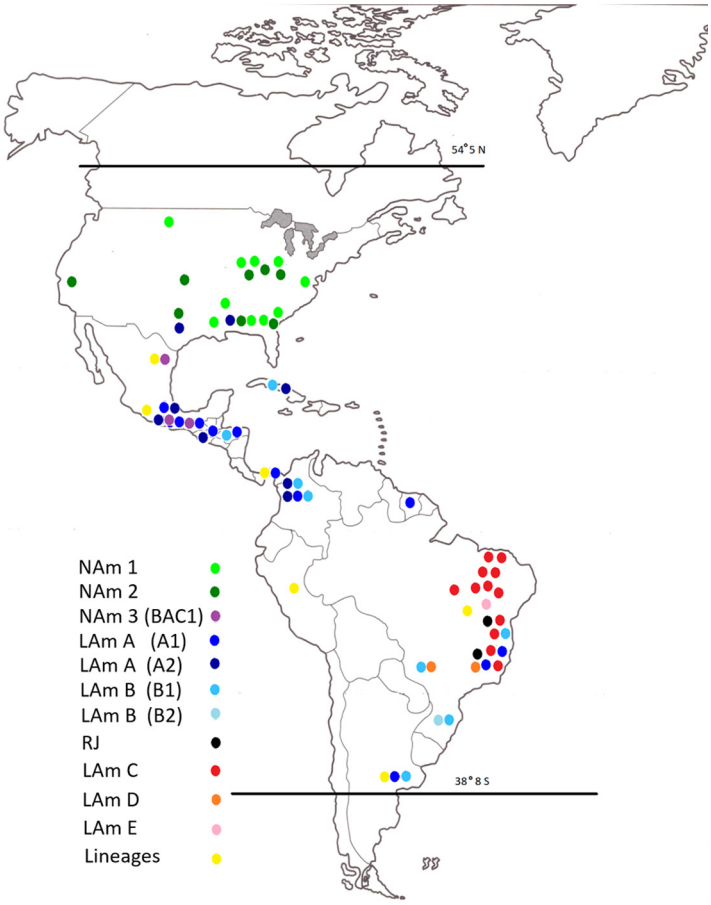

FIG 2 Distribution of the *H. capsulatum* genotypes on the American continent based on their current phylogeographic findings. Data were obtained from Kasuga et al. (12), Teixeira et al. (20), Damasceno et al. (25), Rodrigues et al. (26), and Vite-Garín et al. (22) classifications.

phylogenetic species distributed worldwide (Australian, African, Netherlands, LAm A1, LAm A2, LAm B1, LAm B2, NAm 1, NAm 2, Rio de Janeiro named RJ, and a bat-associated species-specific clade denominated BAC1). A subsequent report (22) proposed replacing the BAC1 clade described by Teixeira et al. (20) by the NAm 3 phylogenetic species, which is a sister group of the NAm 2 clade. This proposal is sustained by six new isolates of *H. capsulatum* cultured from infected tissues of different migratory *Tadarida brasiliensis* (Chiroptera: Molossidae) bats.

Overall, the appearance of new genotypes in existing organisms is probably due to different selective pressures, forcing them to rapidly adapt to several changes in environmental conditions (23, 24). In addition, the advent of more robust and accurate approaches has allowed for easier detection of subtle changes in the fungal genome.

The presence of new genotypes in the *Histoplasma* complex has been documented in some Brazilian geographic regions (25, 26). Damasceno et al. (25) suggested the existence of two cryptic species of *H. capsulatum* in the northeastern region of Brazil (Ceará state), which have been named populations Northeast BR1 and BR2. Subsequently, Rodrigues et al. (26) described a new phylogenetic species called LAm C, emphasizing the low genetic diversity of this particular *H. capsulatum* population found in the Ceará state of Brazil. Thus, it is reasonable to speculate that the fungal populations described by Damasceno et al. (25) and Rodrigues et al. (26) from the Brazilian northeastern region share similar *H. capsulatum* genotypes by their respective fungal isolates. Rodrigues et al. (26) also proposed new lineages and two other groups with high genetic diversity (LAm D and LAm E) in southeastern Brazil.

According to the above-mentioned authors, at present, it is possible to consider 11 clades of *Histoplasma* distributed in the Americas, highlighting the most genetically diverse in Latin American countries (see Fig. 2).

TABLE 1 Similarity of the *H. capsulatum* phylogenetic groups according to different reports

	Number of isolates[a] analyzed per phylogenetic species in reference:			
Phylogenetic species	**Kasuga et al. (12)**	**Teixeira et al. (20)**	**Rodrigues et al. (26)**	**Vite-Garín et al. (22)**
NAm 1	4	12	17	4
NAm 2	16	22	74	16
NAm 3	1 (EH-315)	3 (BAC1)	4 (Group II)	7 (Nam 3)
LAm A1	NC	30	NC	9

[a]The total number of *H. capsulatum* isolates analyzed through phylogenetic reconstruction per researcher group is indicated as follows: 137 by Kasuga et al. (12), 234 by Teixeira et al. (20), 474 by Rodrigues et al. (26), and 176 by Vite-Garín et al. (22). Isolates information was retrieved from different databases. NC, not considered.

Instead, based on information about *H. capsulatum* cryptic speciation, Sepúlveda et al. (21) suggested other improvements to *H. capsulatum* classification using a robust phylogenomic methodology. These authors renamed four geographical clusters from the American continent previously identified by Kasuga et al. (12), describing them as species of the *Histoplasma* genus: *H. capsulatum sensu stricto* Darling 1906 from Panama (previously lineage H81), *Histoplasma mississippiense* sp. nov. (known as NAm 1) and *Histoplasma ohiense* sp. nov. (known as NAm 2) from the United States, and *Histoplasma suramericanum* sp. nov. (known as LAm A) considering some isolates from Colombia. Recently, Almeida-Silva et al. (27) analyzed the phylogenomic and population structure data of clinical and environmental *Histoplasma* isolates from Brazil and suggested that *H. suramericanum* has at least two populations in South America. They highlighted the southern population of *H. suramericanum* supported by fungal isolates from the phylogenetic species RJ, which is endemic to Rio de Janeiro. Thus, these new records make it necessary to demand more extensive and accurate evidences to reach the most adequate taxonomy for *Histoplasma* and to better understand the ancestral history of this fungal genus.

Consistent with the information published by Kasuga et al. (12), Teixeira et al. (20), Rodrigues et al. (26), and Vite-Garín et al. (22), which shared similarities in the phylogenetic reconstruction results of *H. capsulatum*, we assumed that this fungus has at least 14 phylogenetic groups (Table 1) and four lone lineages (Table 2), which undoubtedly supports the high diversity of the *Histoplasma* genus around the world.

AN OVERVIEW OF HISTOPLASMOSIS AND THE SPREADING OF *HISTOPLASMA* IN THE WORLD

Based on clinical cases and histoplasmin skin test reports, histoplasmosis is found to be distributed more extensively throughout the world than we previously thought. Epidemiological evidence of this mycosis, obtained from autochthonous clinical cases, has been found in Asia, Africa, Australia, and North, Central, and South America (1, 28). The presence of *H. capsulatum* in Europe was initially associated with imported clinical cases in tourists and immigrants with or without immunosuppression conditions. However, positive histoplasmin skin tests reported in human populations in Italy (1, 29), the description of fungal infections in the different tissues of two badgers (30) and a hedgehog (31) in northern Germany, and evidence of the fungal presence in an infected bat captured in France (32) all support the existence of new ecological niches with favorable environments for *H. capsulatum* growth and spread in Europe.

Histoplasma capsulatum has been isolated from naturally infected wild or captive animals, human patients, or its ecological niches worldwide (12, 33–36). Kasuga et al. (12) studied

TABLE 2 *H. capsulatum* lone lineages that are in agreement with different reports[a]

	Number of isolates[a] analyzed per phylogenetic species in reference:			
Lineages	**Kasuga et al. (12)**	**Teixeira et al. (20)**	**Rodrigues et al. (26)**	**Vite-Garín et al. (22)**
H81/H82/H83	3	3 (Panama)	3	3
H140	2	2 (H140)	3 (140)	2
H153	1	1	1	2 (153/EH-696P)
H167	1	1	1	1

[a]Additional lone lineages have also been proposed by the authors mentioned above.

fungal isolates from different sources, including human clinical cases, collected in 25 countries from five continents, confirming the important natural distribution of this pathogen.

In recent years, with the advent of molecular tools, the presence of *H. capsulatum* in humans and wild hosts has revealed a possible fungal spreading process over distant geographical regions. As already stated, the presence of *H. capsulatum* in the environment from France was demonstrated by González-González et al. (32), who studied samples from bats captured in two different regions of this country. They analyzed lung DNA samples from several bat specimens, using nested PCR amplification of the *H. capsulatum* Hcp100-specific marker; they found Hcp100-amplification in only one sample from a *Nyctalus noctula* (Chiroptera: Vespertilionidae) bat. The neighbor-joining analysis of the Hcp100 sequence obtained from the lung DNA of *N. noctula* revealed a high similarity with the sequence of the G217B *H. capsulatum* strain from Louisiana, USA. Different migratory routes of *N. noctula* have been reported in Northern, Central, and Eastern Europe (37), increasing the likelihood that *N. noctula* has acquired the fungus from other regions during its migration, in accordance with its role in fungal spreading in new environments. Recently, da Silva et al. (38), using the same molecular approach, investigated natural infection by *H. capsulatum* in bats from the Amazonian Forest region that have suffered climate and anthropogenic disturbances. They also studied bats captured in urban areas from Pará state in Brazil, which also belongs to the Amazonian region. They found two infected frugivorous bats, *Carollia perspicillata* and *Vampyriscus bidens* (Chiroptera: Phyllostomidae), out of 100 bats captured. Because Pará constantly suffers environmental disturbances resulting from deforestation for land use, it is possible to hypothesize that these disturbances may create conditions favoring *H. capsulatum* infection in susceptible human and mammalian hosts. Surprisingly, in both papers reported here, the infection rate in wild bats was very low, possibly explained by the recent infection events associated with fungal spreading in these areas that are only now suffering modifications in their fungal natural habitats. It is important to highlight that although the infection rate in these flying mammal hosts is occasionally low, their role as *H. capsulatum* dispersers is more important than the role of terrestrial mammal hosts since bats are able to cross long distances. This ability of bats is one of the probable reasons that *H. capsulatum* is so widespread, in contrast to other systemic pathogenic fungi, such as *Coccidioides* spp. and *Paracoccidioides* spp., whose dispersion is associated mainly with terrestrial mammal reservoirs and whose evolutionary history with bats is probably very recent, which agrees with the scarce reports of these fungal isolations in bats (39, 40).

The spread of *Histoplasma* over several countries on different continents could have occurred a long time ago, involving natural alterations or environmental changes related to human and other mammalian behaviors. According to Kasuga et al. (12), *Histoplasma* began its geographic radiation mainly in South America 3.2 to 13 million years ago, in the Pliocene and Miocene, when the continents were already merged and the global climate was warmer than it is today. Hence, as a result of this radiation, some clades have remained unlimited, such as LAm A in South America, which is widely distributed and the most genetically diverse. This high diversity could be due to fungal sexual reproduction events in the environment, which are responsible for the recombining population structures reported for this clade. Other clades were delimited into template geographic areas, where the fungal population presented less genetic diversity, probably due to asexual reproduction, generating clonal population structures, as in the case of LAm B and NAm 1 *Histoplasma* clades.

According to Rodrigues et al. (26), the high genetic diversity found in several isolates from Brazil, together with the presence of divergent cryptic species, suggests the role of bat and bird species in fungal spreading around the Brazilian territory and that this country could be the epicenter of *Histoplasma* dispersion in South America, which agrees with the *Histoplasma* geographic radiation proposed by Kasuga et al. (12).

In addition to the role of bats, other natural environmental factors, such as winds, tropical torments (storms, hurricanes), and, interestingly, the airstreams in bat caves, could contribute to spreading out airborne fungal mycelial spores. Birds are undoubtedly another natural disperser of fungal spores, causing fungal dispersion mainly over short distances, but birds are not considered genuine reservoirs of *H. capsulatum*. To date, there are only random

data confirming bird infection with *H. capsulatum*, such as the report by Quist et al. (41) of a coinfection with histoplasmosis and candidiasis in an *Eclectus roratus* parrot (Psittaciformes: Psittaculidae). It is well known that *H. capsulatum* grows favorably in soil containing guano from several species of bat and avian (mainly hens, chickens, and other birds), which have a high content of micronutrients. In different countries, guano from hens, chickens, or bats is manufactured as organic fertilizer, which is associated with a high risk of infection by *Histoplasma* aerosolized infective propagules (42–44).

Considering that birds move around in this contaminated soil, the fungus could be dispersed by air through their feathers over their surroundings and other diverse environments. Among the birds more frequently associated with *H. capsulatum* dispersion, we usually found starlings and black birds. Curiously, in Central and South America, *Steatornis caripensis* (Caprimulgiformes: Steatornithidae), called oilbirds or "guácharos," which is known to be a cave-dwelling bird, is also related to fungal dispersion. Another factor that could be involved in the spreading of *H. capsulatum* is the fungal interactions with different organisms of the microbiota that belong to bat guano and share the same ecological niche, such as the biological association between the fungus and mites present in bat guano (45). Mites consume organic components and microorganisms of the bat guano as part of their food web. Based on the findings reported by Estrada-Bárcenas et al. (45), *Sancassania sphaerogaster* (Acari: Acaridae) mites collected from the same microhabitat of *H. capsulatum* were able to eat *H. capsulatum* growing under laboratory conditions. In addition to this mycophagous activity, *S. sphaerogaster* mites also showed fungal phoresy when they were in contact with *H. capsulatum* cultures, suggesting that a short-range dispersion of the fungus may occur under natural conditions (45).

THE HISTORY BETWEEN BATS AND *H. CAPSULATUM*: THEIR RELATIONSHIP WITH THE GLOBAL GEOGRAPHICAL CHANGES

Since Kunz (33) compiled bat species, from which the fungus was isolated between 1970 and 1981, there has been an increasing number of bat species from which *H. capsulatum* has been isolated, particularly in America.

Bats are geographically dispersed and act as natural hosts for many pathogens, including fungi. Climate changes can influence the geographic distribution and abundance of bat species. Accelerated urbanization, deforestation, and invasion of their natural habitats have increased the risk of zoonotic diseases (46).

Infected bats are considered the main reservoir and disperser of *H. capsulatum*, which grows in their guano, which is rich in nitrogen, phosphorous, and other micronutrient contents (47–49). In most cases, the fungus is returned to environments through the carcasses, urine, and feces of infected bats, thus renewing the fungal load of other bat shelters (see Fig. 1). The role of bat feces in fungal dispersion is dubious because negative fungal isolation in repetitive assays was always found in bat fecal samples collected through the intestinal lavage of 208 bats analyzed, although *H. capsulatum* isolates were indeed recovered by culture of intestine tissue samples from seven bats. Histopathologic studies revealed a few alterations in the mucous membrane of the intestine without any inflammatory reactions (40). Likewise, no evidence of severe inflammatory reactions in the liver and spleen tissue sections of several bats was observed. However, cultures of *H. capsulatum* were obtained from these organs, which suggested the presence of dissemination processes in these infected specimens (47). However, according to Tesh and Schneidau (50), *H. capsulatum* was cultured from the fecal samples of experimentally infected *T. brasiliensis* bats, and the existence of yeasts in the kidneys of the infected bats suggests that bats and other mammal hosts could eliminate the fungus in their urine.

The size of bat populations may be related to anthropogenic activities, but the course of bats' symptomatic diseases must be considered another factor responsible for the decrease in their population. A significant percentage of *T. brasiliensis* bats captured in either Mexico or Argentina were infected with *H. capsulatum*, as demonstrated by González-González et al. (51). Certainly, a high population density of *T. brasiliensis* in their shelters increases the risk of infection, resulting in an increased percentage of *H. capsulatum* infections in their colonies.

The physical conditions of bat shelters could also increase the risk of infection for humans and bats, as has been documented by Taylor et al. (47). Thus, the colonial behavior of cave-dwelling bats and their high fidelity to the shelters along their migratory route, in the case of migratory bats, are important factors for explaining the dynamics of *H. capsulatum* dispersion in nature.

The interplay between *H. capsulatum* and bats could involve modifications in the physiology of wild hosts and their self-protective mechanisms against this type of microorganism. Possibly both geographic and climate changes, producing different selective pressures, have influenced the interactions between distinct organisms that share the same ecological niche, consequently giving them a common evolutionary history. The interaction between *H. capsulatum* and bats may have occurred since the Late Pliocene, considering the dated fossil of *Tadarida* sp. reported by Morgan and Ridgway (52). In particular, the interaction between *H. capsulatum* and *T. brasiliensis* could have taken place in the Late Pleistocene, in agreement with the first fossil report of this bat species by Morgan (53).

In addition, the finding reported by Taylor et al. (54), regarding the presence of a unique GACG$(GA)_{11}$GA haplotype of the (GA)n microsatellite in a highly specific cluster formed by nine *H. capsulatum* isolates cultured from *T. brasiliensis* tissue samples, advocates for a probable parallel evolution between *T. brasiliensis* and *H. capsulatum*. It is also interesting to mention that until now, the NAm 3 phylogenetic species of *H. capsulatum*, previously mentioned in this paper, and the fungal GACG$(GA)_{11}$GA haplotype have been associated with only naturally infected *T. brasiliensis* bats in Mexico. The latter suggests that these flying mammals are susceptible to particular genotypes of *H. capsulatum* and that this million-year-long host-parasite interaction has possibly evolved into a species-specific relationship.

NEW GENOTYPES OF *HISTOPLASMA* AND THEIR IMPACT IN THE HISTOPLASMOSIS CLINICAL MANIFESTATIONS

It has been difficult to determine how fungal genotypes impact histoplasmosis clinical course and manifestations. It will be suitable to accept that differences in virulence factors among *H. capsulatum* strains from different genotypes are the unique responsible cause. However, in the interplay between the fungus and the host, several host-associated factors could interfere with the outcome of histoplasmosis infection, such as sex, age, stress, nutritional conditions, risk of massive infective inoculum (depending on occupational and tourist activities), immunosuppression, and genetic predisposition to certain clinical manifestations of histoplasmosis (7, 8).

Regarding *H. capsulatum* genotypes versus clinical manifestations of histoplasmosis, data have been accumulated over time in distant geographical areas. The NAm 1 phylogenetic species has been isolated primarily from AIDS patients, in contrast to NAm 2 phylogenetic species, which can infect immunocompetent and immunosuppressive hosts (11). Clinical differences between AIDS-associated histoplasmosis patients from Brazil and those from the United States, in regard to *H. capsulatum* strains isolated from Latin America and North America, have been documented (55, 56), highlighting an increased dermatotropism in the Latin American *H. capsulatum* genotypes, which causes frequent skin and mucocutaneous clinical manifestations.

Interesting published data (25, 57) have recorded some compelling clinical cases of coinfection with different genotypes of *H. capsulatum* (Northeast BR1 and BR2) in the same AIDS-histoplasmosis patient, which also revealed differences in their mating types (MAT1-1 and MAT1-2). Although the consequences of this type of coinfection are unknown at present, it is possible to assume that this coinfection could interfere with the host immune response and pathogenesis of the disease.

At the experimental level, differences in the outcome of the disease and in the host tissue damage caused by distinct *H. capsulatum* genotypes were first reported by Durkin et al. (58), who infected mice intratracheally with sublethal doses of yeasts from Latin America (classes 5 and 6) and North America (class 2) fungal strains. They found that class 5 and 6 strains caused more tissue damage and fatal outcomes in mice than class 2 *H. capsulatum* strain.

Sepúlveda et al. (59), using *Histoplasma* strains representative of the NAm 1 and NAm 2 phylogenetic species as well as those from the Panama lineage to infect mice intranasally with low or high sublethal doses of *H. capsulatum* yeasts, showed that clinical manifestations (weight loss), pathogenesis (lung inflammatory infiltrate), host response (cytokines production), and disease resolution (fungal clearance) differed in these experimental histoplasmosis models, depending on the *H. capsulatum* inoculum size and the virulence of its phylogenetic group. Their results highlight the highest virulence of the lineage from Panama in mice exposed to a lower yeast inoculum, rather than NAm 1 and NAm 2 strains. Later, Jones et al. (60), studying the same conditions to generate murine histoplasmosis infection, suggested that yeasts of the NAm 2 strain of *Histoplasma* are found mostly within alveolar macrophages and produce progressive lung inflammation, contrasting with the *Histoplasma* lineage from Panama.

Finally, an original contribution by Sahaza et al. (4), using susceptible mice intranasally infected with mycelial infective propagules, showed clear differences in cytokines production during the course of murine histoplasmosis when two distinct *H. capsulatum* genotypes were used, underscoring how an LAm A strain from Mexico induced higher levels of pro- and anti-inflammatory cytokines in the lungs of infected mice than an NAm 2 strain from the United States.

CONCLUSIONS

Climate change can lead to *H. capsulatum* genotype selection so the fungus can adapt better to new environments. The geographical expansion of histoplasmosis can be attributed to environmental factors, be it "natural" or occasioned by humans. Natural factors are associated mainly with bird or bat involvement. Bats are considered the most significant dispersers for *H. capsulatum* worldwide. Dispersal through the air is another mechanism whereby this pathogen can be spread, usually over short geographical distances.

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