Chapter

Epidemiology of Histoplasmosis

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Abstract

More prevalent than initially considered, histoplasmosis is primarily a non-contagious disease of the reticuloendothelial system, producing a broad spectrum of clinical manifestations, ranging from asymptomatic or self-limited infection, in immunocompetent patients to life-threatening, disseminated disease in immunocompromised ones. The causative agent is *H. capsulatum*, a thermally dimorphic, intracellular fungus, discovered in 1906, by the pathologist Samuel Darling, when examined tissues from a young man whose death was mistakenly attributed to miliary tuberculosis. Since then, histoplasmosis was described on six continents, with high and low endemicity areas. *H. capsulatum* is a soil-based fungus, commonly associated with river valleys in the temperate zone, and with the presence of bird and bat guano. Infection occurs when saprophytic spores are inhaled and change to the pathogenic yeast in the lungs, where *H. capsulatum* overcomes many obstacles to cause host injuries. Depending on geographic distribution, morphology, and clinical symptoms, three varieties have been historically recognized, two of them (*var. capsulatum* and *var. duboisii*) being pathogen to humans, and the third (*var. farciminosum*) has predominantly been described as an equine pathogen. In endemic areas, patients with AIDS or people who receive immunosuppressive therapies should be counseled to avoid high-risk activities; otherwise, precautionary measures should be taken.

Keywords: widely distributed, changing epidemiology, cellular immunity, occupational disease, global burden

1. Introduction

Fungi represent the second largest estimated species numbers after insects. Their kingdom comprises a huge variety of microorganisms, the newer estimates, based on data acquired from molecular methods, have predicted from 1.5 million fungal species, in some conservative estimates [1–4], to a spectacular 13.2 million, in others [5, 6], less than 150.000 species being merely cataloged to date [5–8]. For many years, it was believed that fungi were clinically insignificant, but the increased incidence of invasive fungal infections during the past 20 years has contradicted this hypothesis [9].

Compared to the enormous biomass of fungal species, the number of human pathogenic fungi is minuscule, but they exert a profound, global impact on human health. Billions of people are infected, [10] fungi causing more than a billion skin infections, more than 100 million mucosal infections, 10 million serious allergies [11], and more than 1.5 million deaths every year [4, 12]. Worldwide, mortality due to fungal infections exceeds that from breast cancer and malaria and is comparable

to that owing to tuberculosis and HIV, exerting a major threat to human health and, consequently, a huge burden to global healthcare budgets [11, 12].

In the past 15 years, in the world landscape, new species of fungi were yearly discovered at a rate varying from 2100 to 2600 species, most of them in Asia (41%) and Europe (23%), and a small part even in Antarctica (0.5%) (**Figure 1**) [8].

Also, the number of clinically relevant fungal species continued to grow, this fact being clearly demonstrated by their increasing number in the Atlas of Clinical Fungi, of which the first edition, in 1995, contained 320 species, while the fourth edition of the same book, published in 2020, counts more than 660 fungal species [13, 14].

Climate change will have an impact on the way we interact with our environment and, because fungi can easily adapt to these changes, the overall epidemiological picture of pathogens will also modify. This will likely expose us to varieties of fungi that humans and animals have never interacted with. Due to climate change, the diversity and number of soil microorganisms will undoubtedly change, as already seen with endemic fungi (**Figure 2**) and with the emergence of new fungal pathogens [4].

Furthermore, modern life-saving medical procedures and aggressive medical treatments may affect normal immune functions and, paradoxically, have given rise to large groups of people at risk for fungal infections. Patients at high risk include those with AIDS, those receiving immunosuppressive therapy, transplant recipients, and certain surgeries and those in intensive care settings [15, 16].

There is a growing body of evidence supporting the concern that climate change will affect the morbidity and mortality rates of infectious diseases, and that fungi will play an increasing role as primary or secondary pathogens [4].

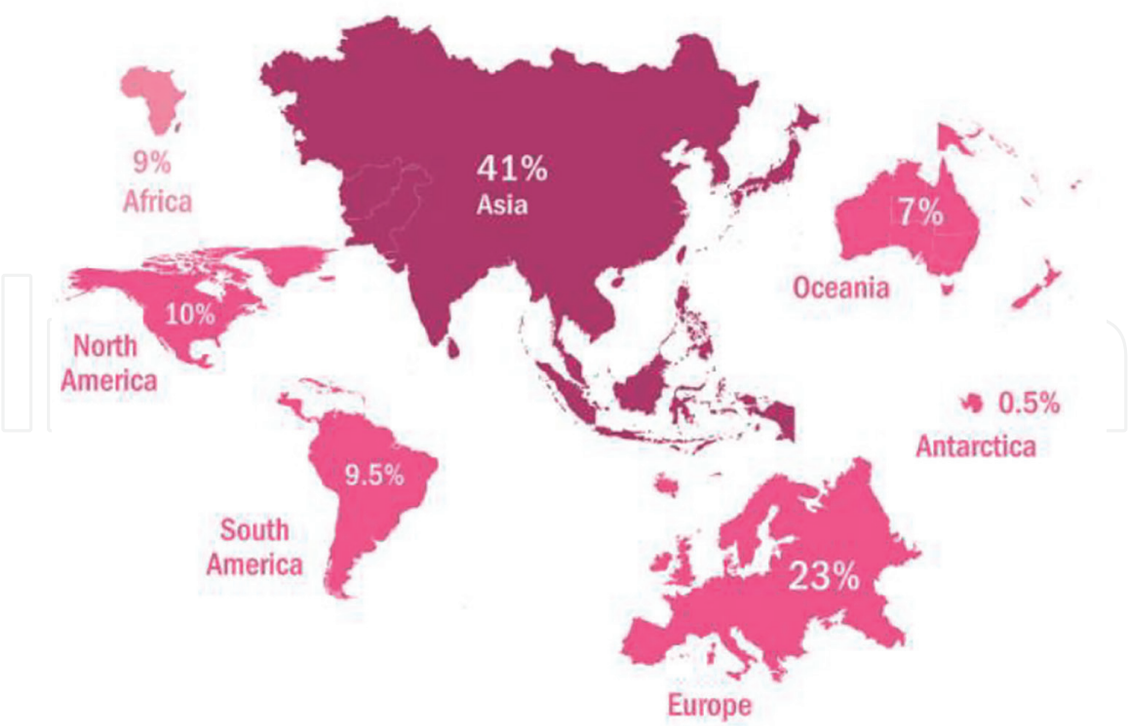

Figure 1.
Graphic map of the world's continents showing the uneven distribution of newly described species of fungi. The size of each continent is proportional to the global percentage of new species published from there and mainly reflects both the quantity of taxonomic expertise and the presence of undescribed species in those areas. Also, the map reflects the location of most research activity and taxonomic expertise. Artwork Creative Services/ RBG Kew. [8]. https://nph.onlinelibrary.wiley.com/doi/10.1002/ppp3.10148.

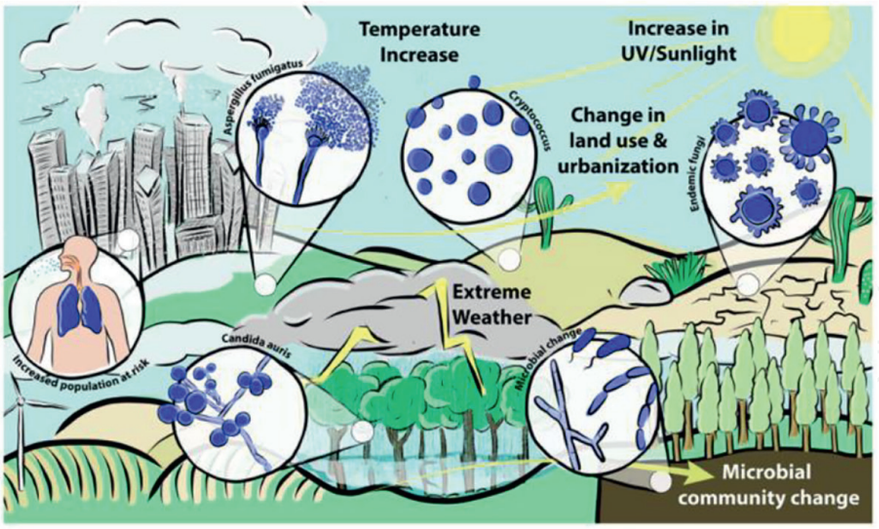

Figure 2.
Schematic overview of changes in the epidemiological landscape of fungal pathogens and associated changes in environmental parameters [4]. https://www.mdpi.com/2309-608X/7/5/367.

To infect and cause disease in healthy humans, true pathogenic fungi should meet four basic criteria: (i) growth at elevated human body temperatures, (ii) bypassing around or penetrating through surface host barriers, (iii) secretion of lytic enzymes for acquiring nutrients from the host tissues, and (iv) evasion or resistance to the host's immune defense systems. The fungi that infect previous healthy humans represent a small group, many more invasive fungal infections now occurring in patients with underlying serious illnesses [15, 17].

The severity and outcome of infection is determined by both the extent of the exposure to the organism and by the immune status of the patient [18].

Therefore, with the expansion of the susceptible population and the increase in the frequency of mycotic infections, the mortality due to invasive mycoses was estimated at one and a half million deaths annually [12, 18].

Histoplasmosis is the most prevalent cause of fungal respiratory infections and has a vast spectrum of clinical manifestations, ranging from a self-limited, acute, influenza-like illness to a progressive disseminated life-threatening infection [19, 20].

2. Historical milestones for *H. capsulatum* and histoplasmosis

The first description of the disease was made in December 1905 by the pathologist Samuel Taylor Darling, when examining smears of tissues and bone marrow from a young carpenter from Martinique, whose death was mistakenly attributed to acute miliary tuberculosis. Darling found an enormous number of small, oval, and round bodies, located in alveolar epithelial cells and in the plasma of the spleen and rib marrow, which he attributed to a parasite resembling to be closely related to Leishmania. He proposed the name *H. capsulatum*, because of the similarity of its halo with a capsule [21].

Only a few years later, in 1912, Henrique da Rocha Lima, inferring the mycotic nature of this pathogen, offered a correct depiction of the microorganism and recognized *H. capsulatum* as a fungus [22].

The first case diagnosed in humans with an acute disseminated form of histoplasmosis was that of a 6-year-old child who died in 1932 [23].

De Monbreun cultivated and described the fungus from blood cultures taken 2 days before death and from the spleen at autopsy, in 1934. Also, in 1939, a culture of *H. capsulatum* was isolated by the same De Monbreun from a case occurring in a dog. He noticed that primary isolated colonies contained both mycelial and yeast phases from the fungus and was able to convert the mycelial phase to the yeast-like one by inoculating susceptible animals. Ciferri and Radaelli managed to convert a strain of *H. capsulatum* to the yeast form by cultural methods, growing it on blood agar at 37°C [22].

In 1941, Zarafonetis and Lindberg prepared histoplasmin, which is a filtrate of a culture of *H. capsulatum*, in the mycelial phase [24]. On the African continent, histoplasmosis was first reported in 1942 by Duncan [25].

Four decades after it was first described, histoplasmosis was considered a rare, acute, and lethal disease, based on reported cases in the medical literature. Starting with 1945, this belief was contradicted by several investigators, arguing that, in fact, fatal cases were the exception rather than the rule, the infection occurring in certain areas of the USA, in an asymptomatic or benign form, rarely recognized clinically by physicians and being misdiagnosed as tuberculosis [26].

In 1945, Christie and Peterson were the first using histoplasmin in an epidemiological survey, which clearly demonstrated the correlation between pulmonary calcifications and histoplasmin sensitivity in tuberculin-negative persons [27].

Also in 1945, Palmer confirmed the existence of subclinical cases of histoplasmosis, which reacted positively to the histoplasmin skin test [28]. Only 1 year later, the same Palmer demonstrated that the highest frequency of histoplasmin reactors was discovered in the same area of the USA, where clinical cases of histoplasmosis had been repeatedly diagnosed [28].

Furcolow demonstrated in 1949 the development of asymptomatic, benign, pulmonary infiltrations, indistinguishable from tuberculosis, in a group of tuberculin-negative, histoplasmin-positive persons, using a series of chest radiographs over a three-year period [29].

In 1949, Emmons isolated macroconidia of *H. capsulatum* from soil samples, by examining saline suspension by direct microscopy and demonstrated that the fungus goes through a developmental saprophytic cycle in soil [30].

A first description as a new variant of Histoplasma was made by Vanbreuseghem in 1952, and, in honor of Professor Albert Dubois, who provided the isolates, the fungus was named *H. capsulatum* var. duboisii [31].

In 1969, Edwards and colleagues published the first map of histoplasmin skin reactivity in the USA, illustrating the endemicity of the disease primarily in the Ohio and Mississippi River valleys [32].

Kwon-Chung, in 1972, reported the observation of sexual reproduction of *H. capsulatum* [33] and, only a few months later, he stated that Emmonsiella capsulata is the teleomorph or sexual stage, resulting from the sexual compatibility + and – mating types of *H. capsulatum* (asexual stage or anamorph) [34].

In 2003, Hwang and his colleagues conducted the first large genomic study, which identified and compared genes that exhibit phase-specific patterns of expression in *H. capsulatum*, providing a more complete description of both the yeast and mycelial phases of the fungus [35].

Using the multilocus sequence typing (MLST) method, in 2003, Kasuga performed the first analysis across the global distribution of the Histoplasma species. He found intermixed isolates from the three variants of Histoplasma in multiple phylogenetic clades and refined the classification of the fungus by identifying eight phylogenetic clades of *H. capsulatum* [36].

In 2014, it was documented and reported transplacental transmission of *H. capsulatum* in a series of patients [37].

For the first time in the medical literature, cases of mixed infection with different mating types of Histoplasma were described in two patients living with HIV in 2019, in an endemic area of Brazil [38].

In 2022, *H. capsulatum* was first detected by molecular techniques in the soil and penguin excreta collected from the Antarctic Peninsula [39].

To guide research, development, and more robust public health actions, in October 2022 WHO developed the first fungal priority pathogens list (WHO FPPL) which included Histoplasma spp. in the high-priority group [40].

3. The epidemiologic triad of histoplasmosis

Like other infectious diseases, histoplasmosis results from the complex interaction between the pathogen and the susceptible host in a favorable environment that supports the transmission of the agent from the source to that host.

3.1 Agent

Histoplasmosis is a worldwide distributed non-contagious fungal infection caused by *H. capsulatum*.

3.1.1 Characteristics of H. capsulatum

H. capsulatum is a thermally dimorphic, primary systemic, and endemic fungal pathogen. *Thermal dimorphism* implies the existence of the pathogen in two different forms, depending on the temperatures. *H. capsulatum* presents itself, either in a hyaline mold in the environment or in the laboratory at 25–35°C, or in an intracellular budding yeast form in mammalian tissues or when grown on enriched medium in the laboratory at 37°C [41]. Thermal dimorphism is not restricted to the fungus morphology, but also implies the shift between the saprophytic, avirulent mycelial form, and the parasitic, pathogenic yeast form [42].

The fungus is characterized as a *primary pathogen* because of its ability to cause infection both in previous healthy individuals and immunocompromised hosts and *systemic* for its tendency to involve deep viscera after dissemination from the lungs [17, 41].

In 95% of immunocompetent individuals, the infection with *H. capsulatum* evolves usually benign and asymptomatic. Histoplasmosis is life-threatening particularly in immunocompromised patients, clinical manifestations, and the prognosis of the disease depending on the size inoculum and virulence of the infecting strain [17]. Since the beginning of HIV pandemic in 1980s, histoplasmosis has also been considered an AIDS-defining illness starting with 1987 [43–45].

H. capsulatum is also known as an *endemic* fungus, its natural habitat being delimitated to specific geographic regions and infection is acquired by inhalation of the spores from that specific environment or geographic area. Endemic areas for histoplasmosis include Mid-western and South-eastern parts of the United States (especially Ohio, Mississippi, and Missouri river valleys), Central and South America, sub-Saharan Africa, Eastern Asia, and Australia [46].

In the kingdom of fungi, *H. capsulatum* specie belongs to the phylum Ascomycota, family Onygenaceae [47, 48].

In fact, *H. capsulatum* is the asexual (anamorph) state of the fungus, which has a heterothallic form, designated Ajellomyces capsulatus or Emmonsiella capsulata (teleomorph or sexual state). The last is the perfect state of the fungus, being capable of producing sexual spores. When encountered and combined onto a sporulating medium, mating types (+) and (−) produce fruiting bodies containing asci. Although the mating type ratio in soil is 1:1, in isolates from patients the (−) mating type is found two to seven times more frequently than the opposite mating type [34, 49–52].

3.1.2 Classifications and mycology of H. capsulatum

H. capsulatum was historically classified, according to geographic distribution, morphology, host-association, and clinical manifestations, into three varieties: (i) *H. capsulatum var. capsulatum*, responsible for classic histoplasmosis, causing pulmonary and disseminated infection worldwide; (ii) *H. capsulatum var. duboisii*, causing predominantly skin and bone lesions, mostly in the African continent; and (iii) *H. capsulatum var. farciminosum*, predominantly responsible for epizootic lymphangitis in equines. Morphologically, the two variants of *H. capsulatum* pathogenic for humans, cultured at 25°C, are macroscopically and microscopically indistinguishable. Growth is obtained on blood agar, chocolate agar, or Sabouraud's agar. Macroscopically, the mold is slowly growing as white (A type) or tan to brown (B type) colonies, usually in 2 to 6 weeks. The A type grows faster, is nonpigmented, and loses its ability to produce spores when subcultured. Also, yeast cells produced from the A type are less virulent in mice than those obtained from B type [49]. Microscopic evaluation of the mold reveals the mycelium, with septate, hyaline hyphae producing two types of conidia (**Figure 3**) Macroconidia are large (8–15 μm in diameter), spherical, thick-walled bodies formed on short, hyaline conidiospores. Their surface is decorated with spike-like or finger-like projections, hence the name tuberculate macroconidia, which represents the typical microscopic structure for presumptive diagnostic. Microconidia are small (2–4 μm in diameter), smooth-walled, oval to pyriform bodies, sessile or attached on short stalks, at right angles, on the sides of the hyphae. These conidia are considered infectious forms due to the small size that allows them to penetrate up to the level of the alveoli.

When cultured at 37°C on enriched media (such BHIA—brain heart infusion agar containing blood), both *H. capsulatum* var. capsulatum and *H. capsulatum* var. duboisii develop smooth, creamy, moist, and yeast-like colonies. Initially, the colony

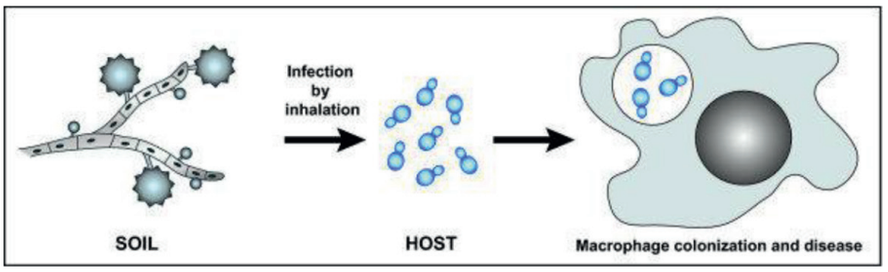

Figure 3.
H. capsulatum grows in the soil as a saprophytic mold (left). After inhalation, triggered by the temperature of the mammalian host, converts to the pathogenic yeast form (center) capable of intracellular replication within host macrophages (right) [53]. https://bmcmicrobiol.biomedcentral.com/articles/10.1186/1471-2180-11-216.

appears white or cream-colored and becomes gray with age. Microscopically, there are differences in yeast-like colonies between the two varieties of Histoplasma. Numerous round to oval budding, uninucleate yeast-like cells are revealed, small (2–4 μm) and thin-walled for *H. capsulatum* var. capsulatum, and large (8–15 μm) and thick-walled for *H. capsulatum* var. duboisii. The yeast cell reproduces by polar budding, resulting in the characteristic narrow bridge appearance (**Figure 3**) between the mother cell and the daughter cell [48, 49, 54].

The cultures of *H. capsulatum* are associated with high individual risk and require Class II Biological Safety (BSCII) precautions [49].

Between 1986 and 1992, Vincent, Spitzer, Keath, and their colleagues performed genetic studies by comparing soil, human or veterinary isolates and finally classified *H. capsulatum* into six genotypes or classes, correlated with a peculiar geographic distribution [55–57].

Using DNA sequence variations of protein-coding genes of isolates from six continents, in 2003, Kasuga and colleagues defined eight phylogenetic clades grouped in seven phylogenetic species, as follows: (i) North American class 1 clade (NAm 1); (ii) North American class 2 clade (NAm 2); (iii) Latin American group A clade (LAm A); (iv) Latin American group B clade (LAm B); (v) Australian clade; (vi) Netherlands (Indonesian?) clade; (vii) Eurasian clade—harboring isolates from China, India, Thailand, Egypt, and England; (viii) African clade. Each clade represents a genetically isolated specie, with only one exception, the Eurasian clade, which originated from LAm A specie. Thus, the original classification of Histoplasma became obsolete, *H. capsulatum* var. capsulatum being found in all phylogenetic species, *H. capsulatum* var. duboisii belonging to African phylogenetic species, and *H. capsulatum* var. farciminosum being placed in NAm 2 and African phylogenetic species and, mainly, in the Eurasian clade [36].

The studies carried out by Teixeira and colleagues refined this classification, and the number of phylogenetic species was increased to 11. He split LAm A and LAm B phylogenetic species into LAm A1 and LAm A2, respectively LAm B1 and LAm B2. Also, he added to the classification two new phylogenetic species, Rio de Janeiro—RJ, and a bat-associated clade—BAC1 (from Mexico), the last one being renamed NAm 3 for his similarities with NAm 2 [58].

In 2019, another improvement in phylogenetic classification of histoplasma was made due to Damasceno's et al. research on HIV-positive patient isolates from the northeastern part of Brazil. Two new monophyletic species were added to the previous classification of *H. capsulatum*, named Northeast BR 1 and Northeast BR 2 [45].

Using whole-genome data, Sepúlveda advanced a more robust analysis, dividing 30 isolates into 5 independently evolving lineages, which he considered separate phylogenetic species. He proposed another classification of the genus Histoplasma as follows: *H. capsulatum* sensu stricto (referring to the Panamanian lineage—H81), *H. mississippiense* (formerly known as NAm 1), *H. ohiense* (formerly known as NAm 2), *H. suramericanum* (formerly known as LAm A), and African clade [59].

Depending on the chemical differences of the wall, the yeast form of *H. capsulatum* is classified as chemotype I, when the α-(1,3)-glucan layer is absent and the fibers are entirely β-linked or chemotype II, when the wall contains a mixture of an α and β-(1,3)-glucans [60].

Chemotype I appears to be more virulent, being accountable for most infections in immunocompetent individuals in North America. Additionally, in mouse models, same chemotype causes more severe forms of disease than chemotype II [61].

3.1.3 Life cycle of H. capsulatum

The life cycle of the fungus does not necessarily require the yeast-phase transition and infection of a mammalian host. Rather, human infections are believed to be accidental, the resulting systemic mycoses being an unfortunate consequence of the fungus ability to adapt during its evolution as a species when encounter the hostile environment of the human body [61–63].

In the soil, the mold form of *H. capsulatum* may reproduce by either sexual or asexual process. In sexual reproduction, the haploid nuclei of two opposite mating types, if encountered, fuse to form a diploid nucleus, which then divides by meiosis and produces ascospores. The mycelia are also able to asexually reproduce by mitotic division, the process being known as conidiation. As a result of conidiation is the production of vegetative budding spores: macroconidia and microconidia. These conidia can germinate in the soil and further, depending on temperature, can adopt either the mold or the yeast form [64]. When the soil is disrupted, conidia and fragments of hyphal mycelia become aerosolized and are inhaled by a susceptible host. Once entered the lungs of the host, triggered by the warmer body temperature, these infectious propagules germinate within distal bronchioles and pulmonary alveoli and convert to budding yeast. The yeast is phagocytized by immune cells and reaches the regional lymph nodes, from where it can spread to other parts of the body through the bloodstream (**Figure 4**) [48, 62, 64].

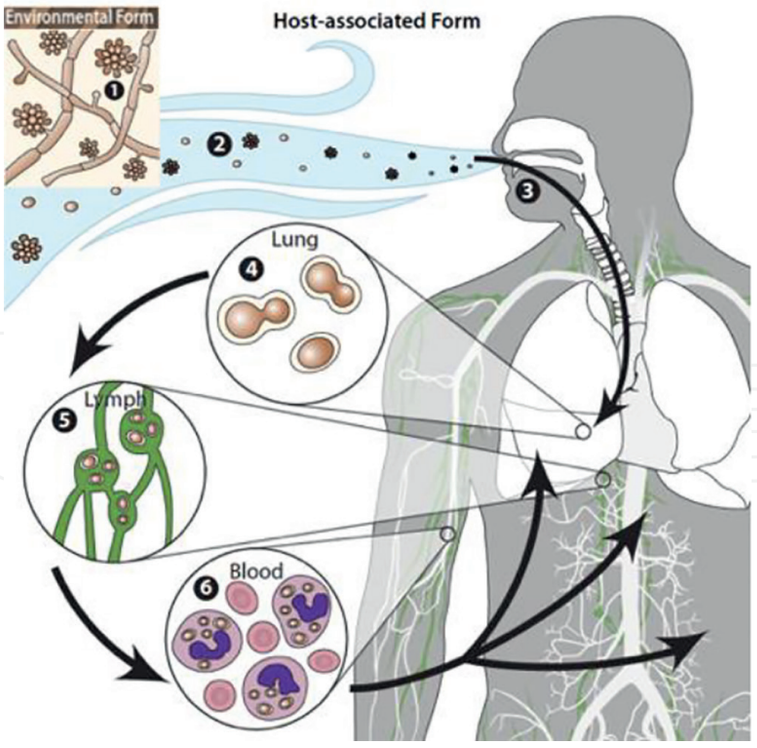

Figure 4.
Life cycle of H. capsulatum. The environmental form of H. capsulatum is a mold (1) with aerial hyphae, producing saprophytic spores (2) which are aerosolized and inhaled by the susceptible host (3). In the lungs (4), their transformation into the parasitic form of yeast takes place and, consequently, their dissemination through the lymphatic system (5) and then through the blood (6) to other organs. https://www.cdc.gov/fungal/diseases/histoplasmosis/causes.html

3.2 Host

The incubation period of the disease is not known with certainty [65], but some authors suggest an interval between 3 to 21 days [46, 66].

The extent and severity of the clinical picture of the disease are determined by the amount of conidia inhaled, the effectiveness of the host's cell-mediated immunity and the virulence of the infective strain of Histoplasma [48, 62, 67].

In most immunocompetent individuals, the infection is mildly symptomatic or even asymptomatic. About 95–99% of the primary infections in endemic areas have never been diagnosed as being histoplasmosis. However, acute severe pneumonia and chronic progressive pulmonary histoplasmosis can also occur in a healthy person if many conidia are inhaled. In individuals with impaired cell-mediated immunity, even a small inoculum or a previously considered avirulent strain can cause life-threatening to fatal disease [41, 48, 54, 62, 67, 68]. *H. capsulatum* primary infection can remain in a latent, quiescent state, without any symptoms, even for decades, and can reactivate if the host's immunosuppression occurs [48, 49, 68].

Patients at high risk for reactivating latent infection and developing disseminated histoplasmosis are those chronically receiving corticosteroids or chemotherapy, those receiving anti-cytokine therapies (tumor necrosis factor alpha or gamma interferons antagonists), individuals who have received solid organ transplantation, and patients with advanced HIV infection [63, 67]. Additional risk factors for histoplasmosis include smoking [69], COPD [70], extreme ages (infants younger than 2 years old, elderly older than 50 years old) [71], and genetics deficiencies (IFN-γ receptor 1 deficiency or histocompatibility complex haplotypes) [72, 73].

Histoplasmosis is reported among wild animals (rodents, marsupials, sloths, spotted skunks, opossums, baboons) and domestic animals such as cats, dogs, and horses [52, 65].

Some animal reservoirs could be used as sentinels in epidemiological surveillance of the disease in a defined territory, due to potentially wider environmental exposures and limited travel [74].

3.3 Environment

3.3.1 Natural habitat

The existence of *H. capsulatum* has been reported on all continents, including recently in Antarctica [39].

Although, in the past, histoplasmosis was reported in tropical and subtropical areas between latitudes 45°N and 35°S, autochthonous cases have been reported, in recent decades, in both Canada and Patagonia, demonstrating a geographical dispersion at extreme latitudes of *H. capsulatum*. The wide geographic spread of the fungus may be the result of behavioral changes in its natural reservoirs and dispersers as well as climatic changes in its natural habitat [75].

The natural habitat for *H. capsulatum* is soil enriched with bat guano or bird droppings, which favors the growth of its mycelial phase. Once contaminated, the fungus persists for many years in the soil under black bird roosts and chicken farms, even after the birds no longer stay in the area [15, 49]. Numerous other species of birds were strongly associated with *H. capsulatum* habitats: grackles, pigeons, starlings, and oil birds [76].

The fungus prefers the dark areas where temperatures are 22–29°C, near watercourses with humidity above 60%, and with porous, slightly acidic soil, high in nitrogen, and phosphorus elements [45, 68]. These conditions allow this geophilic-saprotrophic fungus to absorb the required nutrients from organic matter in soil and to unimpeded proliferate in the environment [47, 62]. Conidia of *H. capsulatum* were also isolated from air and water specimens [76].

3.3.2 Transmission routes

Typically, the portal of entry of *H. capsulatum* is the lung and the main transmission mode is indirect, through the inhalation of airborne infectious propagules from the environment. However, few cases of histoplasmosis have been attributed to indoor transmission of Histoplasma spores through building air handling systems or cleaning air ducts [77], through inhaling contaminated cocaine [78] and aerosolized conidia produced by composed organic fertilizers [79].

The infection is not contagious, airborne transmission by nasal secretions or direct host-to-host transmission of the fungus have never been established [61, 64, 75, 80]. Although exceptional, the vertical transmission route has been reported in newborns of mothers who manifested the disease in the last trimester of pregnancy, while receiving anti-TNF therapy or in the setting of HIV infection [80].

Also, donor-to-recipient fungal transmission through an infected allograft has been clearly documented [81, 82]. The incidence is rare (1 case per 1000 person-years) most infections occurring within 1–2 years after transplantation [83].

The transcutaneous route of transmission has also been suggested, especially in *H. capsulatum* var. duboisii, but the evidence is sparse, supported in some studies by the appearance of lesions at acupuncture needle pricks after mud baths and tattoos [65, 67, 84], or by sharing needles with an infected patient [85].

3.3.3 Risk factors for epidemiological process

Bats play a more important role than terrestrial mammal hosts in dispersion and transmission of the infection because of their ability to cross long distances and to spread the mycelia. The infected bats are also natural reservoirs of *H. capsulatum*, returning the fungus to the environment through their urine, feces, and carcasses. Although immune to disease, starlings and black birds contribute to the spreading of spores on their feathers, beaks, claws, and feet over short distances and, on the other hand, favor the mycelial growth in the soil through their droppings rich in nitrogen and phosphorus [48, 49, 75]. Wind, storms, airstreams in bat caves, and other natural environmental phenomenon are promoting factors for the epidemiological process. Poorly protected water supply basins or wells can be contaminated by water from sanitary and storm sewers that have washed away the soil, manure, dust, and decayed wood harboring *H. capsulatum* [86].

Studies performed to investigate the longevity of *H. capsulatum* in composed organic fertilizers obtained from hens and chicken manure demonstrated that some of them are associated with an important risk of infection by fungal-aerosolized conidia [75, 79].

Invasion and deforestation of the natural habitats of bats and birds and accelerated urbanization by disrupting the environment by excavation and construction are significant risk factors for producing air-borne conidiospores of *H. capsulatum*, and consequently infections [46, 75]. Once predominant in rural areas, histoplasmosis

became more prevalent in urban areas and was classified as an occupational and recreational disease. Builders, constructors, housekeepers, farmers, gardeners, tree cutters, hunters, speleologists, archeologists, and microbiology laboratory workers are at increased risk of acquiring occupational histoplasmosis. Outdoor recreational activities such as traveling in endemic areas, cave exploration, bird and bat watching, golf and tennis courses, and visiting amusement parks could be at risk of acquiring the fungus [45, 66, 79].

Histoplasmosis appears to affect all age groups from 13 months to 70 years [65], with a predominance of cases in men (2:1 male-to-female ratio), which might be related to outdoor occupational exposure [87].

3.3.4 Forms of manifestation of the epidemiological process

An "*endemic* disease" is, by definition, one "occurring frequently in a particular region or population." Histoplasmosis occurs, with low or greater endemicity, in some known areas, more frequently in some populations (e.g., up to 25% of people living with HIV in hyper-endemic areas develop manifest histoplasmosis) [88]. In certain locations from Americas, and parts of Asia and of Africa, skintest surveys indicate that more than half of the population acquired histoplasmosis early in life [89].

The *epidemic* form of histoplasmosis is usually associated with outbreaks. An outbreak is defined as involving at least two cases, usually originating from the same known source [77].

Outbreaks of histoplasmosis are closely related to exposure, especially of immunocompetent individuals, to a large amount of aerosolized conidia of *H. capsulatum* during occupational activities that disturb vegetation and soil, containing bird or bat droppings, or during recreational trips to abandoned archeological sites or bat caves [45, 90, 91]. Although most infections are not outbreak-associated [91], individuals acquiring histoplasmosis during an outbreak may experience more intense exposures and thus potentially develop more severe disease than persons sporadically infected [90]. Due to high dose exposure during outbreaks, attack rates have been estimated at 50–100% [92].

During outbreaks and in high-risk groups, the incidence of cases is higher than 100 per 100,000 inhabitants [52]. The epidemic form of manifestation of the epidemiological process is mainly described in some Latin American countries, but numerous reports also described outbreaks of histoplasmosis in the US and Canada prior to the 1980s [77]. In recent years, this type of exposure affects more people due to the shift of outbreaks from rural to urban areas [4].

Sporadic or isolated cases are related to passive exposure during normal daily activities, are usually diagnosed outside areas recognized as endemic, and cannot be associated with a specific situation or known source of infection [48, 74]. Estimative data suggest that only 1% of sporadic infections are symptomatic [92].

Histoplasmosis occurs infrequently in persons living in non-endemic areas, but increasingly imported cases are recognized and diagnosed in immigrants or after traveling in endemic locations, especially in individuals with impaired cellular immunity [89].

3.3.5 Distribution and burden of the disease

Histoplasmosis has a wide distribution around the globe, being reported on all continents excepting Antarctica.

The real burden of the disease seems to be underestimated because it is frequently misdiagnosed as tuberculosis [52], community-acquired pneumonia or other acute lower respiratory tract infections [93], and underdiagnosed due to poor availability of diagnostic tests [94]. In addition, the incidence of the disease is poorly described even in areas known to be endemic, since histoplasmosis is not a nationally notifiable condition by the clinicians, even in the USA [93]. However, recent global estimates found almost 500,000 cases of histoplasmosis and approximately 100,000 cases of disseminated histoplasmosis occurring annually [12].

Although exposure to *H. capsulatum* was initially thought to be limited to the traditional area described by the well-known Edwards' map, with the onset of the HIV pandemic in 1980s and the emergence of new cases outside this area, this theory has been challenged [69].

Consequently, an increasing number of reported cases, both from areas previously known and from areas not known to be endemic, disclosed a wider geographic distribution of the fungus than historically described (**Figure 5**) [69, 94].

According to Global Action for Fungal Infections (Gaffi), the case fatality rate of disseminated histoplasmosis is 15–30%, if timely treated, and more than 80,000 deaths with this diagnostic were estimated annually [95].

Since 1987, the disseminated form of histoplasmosis is considered an AIDS-defining event [96]. In people living with HIV (PLHIV) in endemic areas, the annual incidence of progressive disseminated histoplasmosis (PDH) is about 5%, with mortality rates remaining high, even with the availability of antiretroviral therapy (ART) [97].

In hyper-endemic areas up to 25% of PLHIV develop clinical histoplasmosis [88] and an estimated 20% will develop PDH, with fatal prognosis without timely diagnostic and therapy [97]. The annual incidence of the disease was estimated from 0.1 to 100 cases per 100,000 inhabitants, with the lowest rates described in temperate territories and the highest in tropical areas [52]. The incidence varies within continents and territories, histoplasmosis being known to be highly endemic in central and eastern areas of North America (in the Ohio and Mississippi River Valleys), Central and South America, and parts of sub-Saharan Africa [46, 62, 63]. The disease is also endemic in patchy regions of Southeast Asia and Australia [98, 99] and sporadically

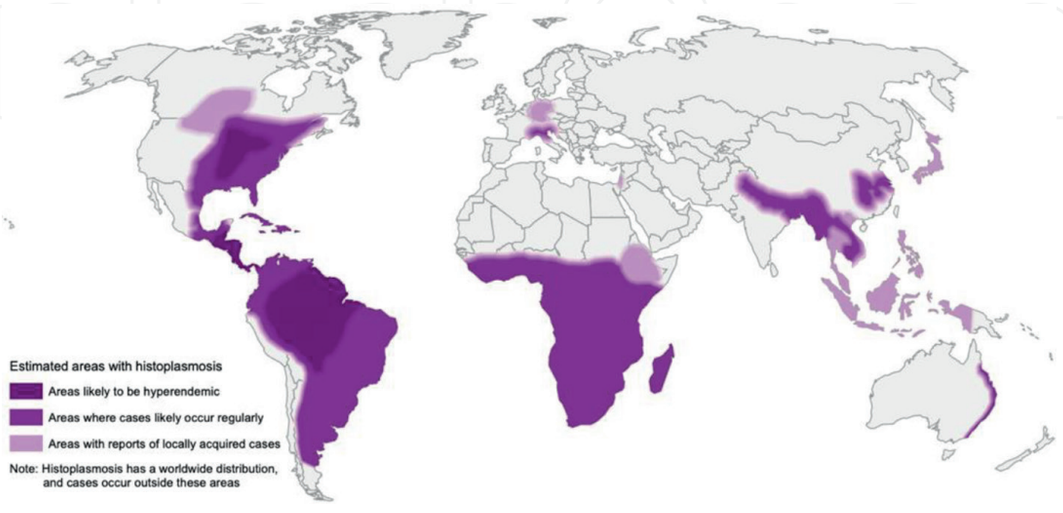

Figure 5.
World map estimating regions most likely to have histoplasmosis based on literature review (2020) [94]. https://link.springer.com/article/10.1007/s11046-020-00431-2.

reported in the remained continents, except Antarctica. Recently, the fungus has been detected in soil and penguin droppings even in the Antarctic peninsula [39].

The geographic distribution of *H. capsulatum* in the North America remains still unclear and requires further investigations [100].

In highly endemic areas around the US river valleys, population skin delayed type hypersensitivity to histoplasmin is around 90%, meaning that residents of these areas were exposed to the primary infection at some point in their lifetime [16, 69].

In most of them the infection is inapparent, asymptomatic and only less than 1% of them will develop the disease [101].

Extrapolating these figures to the entire population, nearly 50 million Americans are latently infected with *H. capsulatum* [16]. Epidemiological reports and studies have shown many cases of histoplasmosis diagnosed in humans or animals outside historically recognized endemic areas. The distribution of these cases extends beyond the originally defined boundaries of the US river valleys [43, 94], encompassing states in the north (Minnesota, Wisconsin, Michigan), northeast (New York), and west (California, Arizona, Idaho, and Montana) [74].

However, the real picture of Histoplasma geographic distribution, potential exposure, and relevant host factors is still incomplete in the USA, histoplasmosis not being part of the diseases with mandatory national notification, being voluntary reported only in 13 states. These states do not necessarily include the relevant ones where histoplasmosis has traditionally been diagnosed. A recent CDC report summarizes 2019 US surveillance data on histoplasmosis and confirmed that Histoplasma causes substantial illness in the USA, with the high rates of hospitalization and death. Reported data rely on the national case definition established in 2017 by the Council of State and Territory Epidemiologists (CSTE), which classifies histoplasmosis cases as confirmed or probable based on laboratory, and clinical and epidemiological criteria. The findings showed that the overall incidence of histoplasmosis was 1.8 cases per 100,000 population, 54% of patients were hospitalized, and 5% died. Three northeastern states were accountable for 65% of the cases: Minnesota (19%) with an incidence rate of 3.8, and Michigan (20%) and Illinois (26%) with a rate of 3.2 each [93]. Using county-level data on histoplasmosis cases reported between 2011 and 2014 in 12 states (covering the eastern half of the USA), a recent estimate from 2022 supports the hypothesis of a shift in the presence of *H. capsulatum* toward the northeastern and central states around the Great Lakes and the Atlantic coast [100].

In a retrospective study performed between 2002 and 2017 in PLHIV in the USA, the overall mortality rate proved to be 37% with an early mortality of 14.8% and late mortality of 22.2%, with no statistically significant difference in survival in those treated with HAART [102].

In the USA, there are estimated 25,000 cases of life-threatening Histoplasma infections [18] and over 5000 histoplasmosis-related hospitalizations annually [70, 87]. Between 2001 and 2012, the proportion of histoplasmosis-related hospitalizations in people with diabetes, transplanted or receiving biologic agents had increased, while in people living with HIV/ AIDS had decreased from 21.5% to 17.3%. The mean length of histoplasmosis-associated hospitalizations is almost double compared with that non-histoplasmosis related. In 2012, the total burden for histoplasmosis-related hospitalizations was estimated at $371 million [70].

In Canada, histoplasmosis is considered endemic in the regions adjacent to the St. Lawrence River and the Great Lakes, especially Quebec and Ontario. A northward expansion of the disease has been observed, evidenced by a continued

increase (0.05 to 0.25 per 100,000 people) in confirmed cases of histoplasmosis in Alberta between 1990 and 2015 [43, 94, 103].

Histoplasmosis is endemic in Central and South America [94], excepting the western part of the two continents (west Mexico and Peru, and most of Chile) [43]. Histoplasmin skin test sensitivity average is 32% in the general population of Latin America [94]. High-endemicity areas are Guatemala, Brazil, Venezuela, Ecuador, Uruguay, Paraguay, and Argentina [16].

The variability of histoplasmin test results is high in the states of Latin America, with rates of nearly 90% in Guatemala, some areas of Mexico [69] and Southeastern Brazil, 63% in Midwestern Brazil [16], 42% in Trinidad and Tobago and Venezuela, and 37% in Costa Rica and Nicaragua [94].

Histoplasmosis is an increasing challenge for the Latin American population, especially the disseminated form of the disease occurring in HIV-positive patients [68]. In PLHIV histoplasmosis is as widespread as tuberculosis [94]. Some studies estimate more than 15,000 new histoplasmosis cases occurring annually [104] and up to 30% mortality rate [105].

In a large prospective cohort study, conducted in Guatemala between 2005 and 2009, which enrolled HIV-positive patients with suspected histoplasmosis, crude mortality in patients with histoplasmosis was 43.6 versus 30.8% among no-histoplasmosis patients. Also, early mortality rate was 24.8% among histoplasmosis cases, statistically significantly higher than non-histoplasmosis ones (9.3%). Coinfection with *Mycobacterium tuberculosis* was found in 9.9% of patients [106], data which is similar with other findings from some Latin America countries where mycobacterial coinfection was reported in 8% (in French Guiana) to 15% (Panama) of HIV+ patients with Histoplasma infection [107].

Interestingly, patients infected with Histoplasma alone had lower survival rates than those coinfected with Histoplasma and *M. tuberculosis* [106].

A robust study of more than 58% of the newly diagnosed HIV patients, reported by the national HIV program during 2017–2018, in Guatemala found that histoplasmosis was the most common opportunistic infection, with an overall incidence of 7.9%, varying from 1.1 to 19.7% in patients with CD4 cell counts higher than 350 cells/mm^3 and lower than 50 cells/mm^3, respectively. Of all patients enrolled, 18.1% had opportunistic infections, of which 36.4% was histoplasmosis. In those with two underlying opportunistic infections, histoplasmosis was frequently associated with cryptococcal disease and tuberculosis in 35.5 and 32.3% of cases, respectively. Mortality rates in disseminated histoplasmosis were significantly statistical higher than in non-disseminated cases (32.7 versus 13.3%) [108].

A screening program for histoplasmosis in HIV-positive patients in Guatemala showed an increasing trend in the number of newly diagnosed cases of histoplasmosis, with the annual incidence rising from 6.5% in 2017 to 8.8% in 2019. As a result of early diagnosis and rapid initiation of treatment, 180-day mortality rates showed an annual downward trend, from 32.8% in 2017 to 21.2% in 2019, underscoring the importance of implementing screening programs in endemic areas and populations at risk for decreasing mortality [109].

In a cohort of HIV-infected patients from French Guiana followed between 2010 and 2019, disseminated histoplasmosis was the most common opportunistic infection with an early case fatality rate of 3.9 within 1 month of diagnosis. It is important to emphasize that the analysis of the evolution of histoplasmosis cases showed that as diagnosis rates improved and, consequently due to treatment, the huge early fatality rate (40%) from 1992 to 1997 decreased more than 10 times in this cohort, leading to better outcomes in most patients with disseminated form of disease [110].

A systematic review of 3530 published cases of disease and isolates of *H. capsulatum* from environmental and animal sources between 1939 and 2018 in Brazil showed that histoplasmosis is endemic throughout Brazil, especially in Northeastern, Central-Western Southeastern, and Southern areas. Disseminated histoplasmosis was the prevalent form of disease, described in more than 80% of reported cases in Brazil. The main underlying condition was HIV infection, found in 97.2% of patients with immunosuppression. Coinfection with *M. tuberculosis* was found in 10.37% patients, these findings being like those found in Guatemala and other Latin American countries. Mortality rate was 33.1% [111]. The north-eastern state of Brazil, the estate of Ceará, is a highly endemic area of histoplasmosis, with many disseminated histoplasmosis cases in people living with HIV, being considered the area with the highest mortality rate due to histoplasmosis (33–42%) [45, 112].

Genetic diversity among isolates and sexual reproduction of *H. capsulatum* in Brazilian population support the hypothesis that Brazil is the center of origin of Histoplasma spp. in Latin America, most likely with the contribution of migratory birds and bats [52].

On African continent, despite the significant number of people living with HIV, histoplasmosis remains an underdiagnosed and neglected disease. The lack of skin tests surveys necessary to develop a much more detailed geographic understanding of the distribution of the disease has impeded the clear delimitation of areas of hyperendemicity.

An exhaustive review on histoplasmosis cases reported from 32 African countries between 1952 and 2017, performed by Oladele and her colleagues, reveals a comprehensive picture of the disease distribution across the continent. Both varieties of *H. capsulatum* coexist in the African territory, *H. capsulatum* var. capsulatum (Hcc) being found predominantly in Southern and Northern Africa and *H. capsulatum* var. duboisii (Hcd) being prevalent in the West, Central, and East of the continent. Moreover, Hcc is found mostly in HIV-positive adults, while Hcd is reported especially in immunocompetent children [113]. Although less common in the African AIDS patients, Hcd is more likely to produce the disseminated form of the disease [94, 113] with a case fatality rate around 23% [65].

The disease is more prevalent in Western Africa (especially Nigeria), Southern Africa (South Africa and Zimbabwe), and Central-Eastern countries (Congo, Uganda) with a nonuniform distribution of isolated cases in many other states across the continent [94, 113].

Of the total number of cases reported in Africa, Nigeria accounts for more than a quarter (26.4%), all exclusively involving Hcd and, with an overwhelming majority (96.7%), in HIV-negative patients [113]. Interestingly, Nigeria has high variable rate in the histoplasmin reactivity test between rural (35%) and urban areas (4.4%) [94, 113].

Hcc was the exclusive causative microorganism, affecting almost equally the HIV-positive and the negative population in South Africa, which had 13% of the cases of histoplasmosis in Africa. In Zimbabwe, the percentage of cases was 12% of mainland cases, diagnosed exclusively in HIV-positive patients, all but one caused by Hcc [113].

The prognosis of disseminated histoplasmosis in Africa is poor, fatality rates varying between 23% for *H. capsulatum* var. duboisii and 50% for *H. capsulatum* var. capsulatum infections [84, 114, 115].

Within Asia, histoplasmosis is endemic in China, especially along the Yangtze River [116], Thailand, South Korea, and India [17].

A study of hospitalized patients and healthy residents in China found overall values of histoplasmin reactivity of 9.0%, with higher values in Jiangsu province (15.1%) [117].

In Sichuan Province, histoplasmin test positivity was found between 21.8% in healthy adults and 28.6% in hospitalized TB patients [118].

A review of 300 cases of histoplasmosis recorded in China between 1990 and 2011 found three quarters of cases in southeastern territory, along the Yangtze River. More than 85% were patients with disseminated histoplasmosis, most of them with underlying immunocompromising conditions such as HIV infection, diabetes, and liver disease [116].

A study of 4211 lifelong residents of Thailand found uneven distribution in the 8 regions studied, with histoplasmin sensitivity ranging from rates of 4.8% in the north and northeast to 34.4% in the south and center, which are among the highest reported in Asia. Due to the endemicity of Talaromyces marneffei in the region, the hypothesis of overestimation of the sensitivity to histoplasmin through cross-reactivity with this fungal antigen was issued [119].

In Thailand, histoplasmosis is reportable to the Ministry of Public Health, and between 1984 and 2010, a total of 1253 cases were documented among exclusively patients living with HIV in this country [120].

In Myanmar, a study of histoplasmin skin test sensitivity in prisoners and their families showed rates ranging from 8.4 to 27.1% [98, 121].

Cases of histoplasmosis have also been reported in other Southeast Asian countries, where histoplasmin reactivity ranges from 2.7–63.6% in Indonesia, 11.8% in Malaysia, 33.7% in Vietnam, and 6.4–26% in the Philippines, supporting the hypothesis of the endemicity of histoplasmosis in these areas [94, 98].

Histoplasma has been known to be present in India for many years since it was first reported to be present in the soil of Gangetic Plain in 1975 [122]. Most cases of histoplasmosis were reported in north-eastern areas, especially West Bengal and Assam states, crossed by the Ganges, Yamuna, and Brahmaputra Rivers. Yet, it is very likely that the number of cases is underestimated, due to misdiagnosis as tuberculosis or leishmaniasis [123, 124]. The histoplasmin test positivity rate reported in a study between 1950 and 1970 was 12.3% in northern India [125].

In a retrospective analysis of cases published between 2001 and 2015, it was found that most of them were reported in the north-eastern part of India, six times more frequently in men than in women, and were associated with agricultural activity. Patients with underlying immunocompromising conditions were around 33% of cases, of which HIV infection was the main cause of immunosuppression. The mortality rate was 27.5% in immunosuppressed versus 10% in immunocompetent patients with histoplasmosis [124].

In Japan, histoplasmosis is rarely reported, and most diagnosed cases are considered imported from endemic areas [44]. A study on 187 bat guano samples collected from 67 bat-inhabited caves in Japan was unable to detect *H. capsulatum*, by either method [126].

Isolated and scattered cases of locally acquired histoplasmosis have been reported since 1948 in all Australian states except Tasmania. Endemic areas are Queensland and northern New South Wales, regions traversed by the long Dumaresq and Macintyre rivers. In a report of cases and literature review of cases in Australia, 41% of disseminated form was found in HIV infected patients. The prognosis of patients with disseminated disease was poor, this form being associated with a 30% recurrence rate and a 37% mortality rate [99].

Europe is a non-endemic area for histoplasmosis, and the disease is rarely reported and is considered a predominantly imported disease. The majority of cases are linked to travel in endemic areas or immigration [127].

In a review of 118 cases of histoplasmosis diagnosed in Europe between 1995 and 1999, more than 93% of patients had a history of migration or travel to a known endemic area. The remaining 6.8% were considered autochthonous European cases, and these patients having no travel history outside their country of origin (Italy, Turkey, and Germany). Notably in this survey, cases of disseminated histoplasmosis were diagnosed among elderly residents of the United Kingdom who fought in India and Myanmar during World War II and who had not left their country of origin for over 50 years after returning from the war. Out of 8 non-imported cases, Italy was the country with the most cases diagnosed as autochthonous [128]. This is consistent with the isolation of *H. capsulatum* in the soil [129] and dogs [130] in the Po Valley area in Italy and with the histoplasmin positivity rate of 1.2% in the population of this area. Few sporadic cases of autochthonous histoplasmosis have also been described in Spain [131].

A more recent systematic review of histoplasmosis cases in the literature identified 223 patients diagnosed between 2005 and 2020 in 17 European countries and Israel. Only eight cases were classified as autochthonous (four in Italy, two in Spain, one in Ireland, and one in Israel), the remaining majority of 96.4% being imported, especially from Latin America and Sub-Saharan Africa. More than 64% of imported cases of histoplasmosis were diagnosed in 3 European countries: Spain (36.7%), France (19.5%), and Italy (7.9%). The other countries reporting the remaining cases of imported histoplasmosis were the Netherland, Germany, Switzerland, United Kingdom, Poland, Austria, Slovenia, Portugal, Greece, Ireland, Sweden, Belgium, Finland, Denmark, and Israel. Most of the cases were recorded in HIV-infected patients (over 51.1%), in whom progressive disseminated histoplasmosis was the most common form of clinical presentation (89.47%). The patients with other immunocompromising diseases were 12.5%, histoplasmosis manifesting in its disseminated form in 57.1% of these cases. In a smaller percentage (6.2%), the picture of progressive disseminated histoplasmosis was also encountered in immunocompetent individuals. The worst outcome of histoplasmosis (32% mortality rate) was registered in patients with other than HIV underlying immunocompromised conditions, while in patients living with HIV infection the mortality rate was 24.3% [132].

In conclusion, doctors from non-endemic areas must consider in certain cases the differential diagnosis with histoplasmosis in immunosuppressed patients and especially in those with HIV infection, because early diagnosis and rapid institution of therapy improve the outcome of the disease and patient's survival [97].

4. Pathogenesis

In most cases, the onset of infection occurs *via* inhalation of airborne microconidia or mycelial fragments of *H. capsulatum* [133]. The portal of entry are the lungs, the fungus bypassing the innate defenses of the host (muco-ciliary clearance, nasal and pharyngeal mucus, and pulmonary surfactant) and reaching the terminal bronchioles and pulmonary alveoli [54].

Shortly after it was inhaled, triggered by the body temperature, it undergoes the dimorphic switching to the budding yeast form within hours and is deposited in macrophages [64].

It may happen that the conidia enter the alveolar macrophages and become yeast there, or the transition occurs first and then the yeast enters the macrophages.

Fungus internalization into the macrophages is determined by a couple of specific immune evasive mechanisms: i.) Histoplasma maximizes macrophages recognition through heat shock protein 60 kDa (HSP60), which mediates the fungal detection and binding by the CD18 integrin family of receptors, on the surface of the macrophages [62, 64]. ii.) Concomitantly, *H. capsulatum* minimizes detection of immunostimulatory β-glucans by Dectin-1 receptors of dendritic cells both by synthetizing an α-(1,3)-glucan layer covering its β-glucans upper layer and by secreting endoglucanase, which enzymatically removes the remained uncovered, still exposed β-glucans. Once internalized, *H. capsulatum* resides in the phagosome compartment without fusing with the lysosome, displaying several pathogenic mechanisms, and thus blocking normal phagosome maturation process in macrophages One of these mechanisms consists in alkalinization of the phagosome and phagolysosome, maintaining the pH between 6.0 and 6.5, which both inhibit the normal function of lysosomal hydrolases and maximize iron acquisition from the host transferrin. Other required strategies for growing and proliferation within nutrient-depleted phagosome compartment are the following: expressing antioxidant enzymes (superoxide dismutase 3 Sod3 and catalase B CatB) that eliminate reactive oxygen intermediates [63, 134], expressing enzymes involved in gluconeogenesis for providing energy and glucans, using amino acids as carbon, nitrogen, and sulfur sources, acquisition of essential vitamins, and trace metals (iron, zinc, and copper) [134].

Thereby, macrophages are not only ineffective in neutralizing *H. capsulatum* yeast but, on the contrary, serve the pathogen by creating a hospitable intracellular niche, in which it can unabatedly multiply and survive [62]. The intracellular deposition and proliferation of the fungus varies, depending on the yeast elements and the host cells; at some point, the multiplied yeast cells destroy the macrophage and are ingested both by new other alveolar macrophages and by other phagocytic cells recruited at the site of infection [135].

During the next 2 weeks after inhalation, when specific immunity develops [136], macrophages also act as vehicles, initially in spreading the fungus to hilar and mediastinal lymph nodes and later in hematogenous dissemination of infection to multiple organs [137].

Besides the macrophages, which are the main host cells for *H. capsulatum* [64], other host defense cells, including dendritic cells and neutrophils, are recruited at the locus of infection and interact with the fungus [62].

By releasing their azurophilic granule contents, neutrophils can inhibit *H. capsulatum* growth. In the case of a small inoculum, it has been hypothesized that this fungistatic activity of neutrophils could be sufficient to cleanse the host, without triggering the subsequent mechanisms of the adaptive immune response [138].

Dendritic cells engulf some yeast cells, *via* fibronectin receptors, and are capable to kill them, thus releasing nucleic acids of the destroyed yeasts, and recovering presentable antigens [62].

These immune responses combined with dendritic cells production of proinflammatory TNF, IL-6, IL-12, and type I interferons (IFN-I) stimulate activation of $CD4^+$ lymphocytes [62, 139]. Once activated, this specific adaptive immune response can either clear the infection or cause the formation of epithelioid granulomas [54], with later evolution toward fibrosis and calcification, mimicking tuberculosis [97].

Like Mycoplasma tuberculosis, *H. capsulatum* could remain dormant, in a quiescent state in this fibrotic tissue, even for decades, and reactivate when cell-mediated immunity is impaired by other diseases or immunosuppressive therapies [54, 68, 97].

Additionally, in situations where T helper lymphocytes are low or even absent, as might be found in severely immunosuppressed patients, dendritic cells can activate $CD8^+$ cells, by cross-presenting them *H. capsulatum* antigen acquired from apoptotic macrophages [140]. In these cases, the granuloma formation is almost absent, the proliferation of macrophages occurring in the tissues, and the patients tend to develop progressive, disseminated form of disease [97].

Although humoral immunity has an unclear role in the pathogenesis of histoplasmosis, depletion of B cells has nevertheless been shown to increase the severity of histoplasmosis, while experimental treatments with monoclonal antibodies to *H. capsulatum* surface antigens have been beneficial in disease evolution in mice [16].

In conclusion, T lymphocytes and phagocytes are essential cellular elements of *H. capsulatum* pathogenesis, the outcome of infection being orchestrated by the dynamics between innate and adaptive host responses and yeast virulence factors [61, 141].

5. Prevention and prophylaxis

5.1 Non-pharmacologic strategies for prevention

People with occupations or hobbies that involve outdoor activities associated with soil aerosolization and exposure to guano for birds or bats, agricultural and forestry workers, fishermen or hunters, and people employed in construction have a 5–10 times higher risk than from the general population [66].

To reduce the risk of illness in immunosuppressed patients living in areas endemic for histoplasmosis, the CDC recommends protective measures: avoid disturbing soil contaminated with chicken or bird guano or cleaning chicken coops, demolishing, remodeling, renovate or cleaning buildings, exploring caves, tunnels, or old archeological sites.

To minimize the risk of infection with *H. capsulatum* at the workplace, concrete measures are needed that can be identified by applying the control hierarchy framework used by health and safety at work specialists. Thus, the following measures are required:

- preventing the accumulation of bird or bat droppings and excluding bats or birds from a building by sealing all entry and exit points, installing lights in daytime roost areas, building bat houses near former roosts, using of visual and auditory deterrents, the periodic application of non-toxic chemical substances to repel birds, and the installation of mechanical anti-bird roosting systems;

- controlling dust generation and aerosolized dust by spraying the dry material with water, adding a surfactant or wetting agent to the water, using an industrial vacuum cleaner with a filter to collect the contaminated material, using bulldozers that have air-conditioned cabs and HEPA filtration, covering the bed of trucks carrying dirt or debris from a construction site, and washing the trucks before leaving the construction site;

- disinfecting potentially contaminated material using formaldehyde is no longer recommended because it causes a variety of health problems and there are no approved products registered specifically as soil disinfectants or as being effective against Histoplasma;

- administrative controls by publication of health risk warnings displayed in areas known or suspected to be contaminated with Histoplasma and by training workers on potential workplace hazards and associated safety practices, procedures, and safeguards;

- wearing personal protective equipment (PPE) to protect employees from Histoplasma contamination by using respirators equipped with filters or masks, safety glasses, disposable protective clothing, and covering shoes or boots.

The hierarchy of controls can also be used to prevent worker exposure to *H. capsulatum* in laboratory environments by: knowledge of the laboratory safety manual, training of laboratory personnel, medical supervision, through aseptic microbiological practices, handling of clinical and culture samples in a biosafety level (BSL)-3 laboratory and a laminar flow Biological Safety Cabinet (BSC) with wearing appropriate PPE, packing or taping closed culture plates, not performing slide cultures, and testing with molecular and proteomic approaches.

Including systematic collection of occupational information as part of histoplasmosis surveillance could facilitate the identification of future workplace-associated outbreaks and the identification of specific risk factors that require further evaluation [66].

5.2 Specific prevention

To date, there is no immunization option available to prevent or treat any fungal infection. Although there have been numerous attempts to develop a potential vaccine against histoplasmosis, these candidates have only been tested on murine models. Various strategies have been used in the search for an effective vaccine for histoplasmosis. The active immunization approaches used in the research consisted of administration of recombinant heat shock protein rHsp60 or only the small protein fragment F3 of rHsp60, the surface protein H antigen, or auto-transplantation into a murine model of dendritic cells, primed *in vitro*, with apoptotic macrophages obtained by phagocytizing *H. capsulatum* yeast, inactivated by heat.

Research studies based on passive immunization methods have focused on the administration of monoclonal antibodies (mAbs Ig.M against histone 2B, mAbs Ig.G against rHsp60) or therapeutic pan-anti-fungal antibodies.

Immune system modulation strategies targeting the programmed cell death receptor-1 (PD-1) and its ligand (PD-L) have suggested that selective blockade of the PD-1/PD-L pathway may play a key therapeutic role in fungal immunity, not only for histoplasmosis but also for other mycoses [142].

The latest research in this field, approaching revolutionary methods of reverse vaccinology, comparative genomics, and molecular docking, have identified some candidate targets to produce both vaccines and new drugs against *H. capsulatum*. The most promising candidate vaccine target appears to be beta-1,3-glucanosyl transferase, the enzyme involved in the elongation of beta-(1-3)-glucans in the fungal cell wall, but further *in vivo* research is needed to test its efficacy and safety [143].

Recently, the WHO has released the fungal priority pathogen list (FPPL) to strengthen the global response against fungal infections. The FPPL highlights the need for actions, interventions, and strategies that focus on three main areas: surveillance, research and development, and public health actions [40].

5.3 Prophylaxis

Prophylactic use of antifungal drugs has been studied only in persons with HIV infection [48]. A placebo-controlled trial showed that primary prophylaxis with itraconazole capsules prevents histoplasmosis in patients living with HIV infection, and even a survival benefit was not demonstrated [144].

Prophylaxis of histoplasmosis with 200 mg daily of itraconazole should be considered only in patients with HIV infection with CD4 cell counts <150 cells/ mm^3, in highly endemic areas in which the incidence of the disease is higher than 10 cases per 100 patient-years (A-I evidence-based recommendation).

In other immunosuppressed patients, daily prophylaxis with itraconazole may be appropriate, in specific circumstances (C-III). There are no data on the role and appropriate duration for prophylaxis in a patient who is receiving immunosuppressive therapy for organ transplantation, malignancy, or chronic inflammatory disease and who, concomitantly, exhibits radiographic or serologic evidence of past histoplasmosis [19]. On the other hand, the risk for histoplasmosis appears to be low in patients receiving immunosuppressive therapy for solid organ or bone marrow transplantation, with an estimated incidence less than 1%, even in endemic areas [145]. For patients receiving therapy with TNF antagonists, there is a risk for developing the disseminated form of the disease, histoplasmosis being considered the most common fungal infection associated with this treatment [146]. History of active histoplasmosis in the last 2 years could be considered a benchmark for initiating prophylaxis with itraconazole during immunosuppression. Also, patients who have finished treatment for histoplasmosis and who are about to receive a transplant or to start new immunosuppressive therapies should be tested for the levels of urinary histoplasma antigen before the intervention and then every 2 or 3 months after. An increase in urinary antigen levels indicates the need for further investigation for active histoplasmosis, but a consistent elevation of the urinary histoplasma antigen level should prompt empirically initiation of antifungal therapy, in the context of ongoing immunosuppression [19].

Transplacental transmission of *H. capsulatum* to the fetus [146] could be prevented by administering antifungal therapy before delivery, but there are no evidence-based guidelines for the management of the vertical mode of transmission. Histopathological examination of the placenta for granuloma and for other organisms resembling *H. capsulatum* should be performed [19].

6. Conclusion

Histoplasma infections are more widespread than traditionally appreciated, mainly due to misdiagnosis in some regions or diagnostic and therapeutic deficiencies in others. Expanding surveillance and case reporting would provide a more accurate picture for a better understanding of the geographic distribution of histoplasmosis. The disease remains an important factor in morbidity and mortality in many parts of the world.

Conflict of interest

The authors declare no conflict of interest.

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