Histoplasmosis in Animals

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Jacques Guillot, Christine Guérin, and René Chermette

Abstract

Histoplasma capsulatum is a dimorphic fungus that is widely distributed in the tropical or subtropical areas of the world and infects numerous mammalian hosts. The outcome of the disease depends on many factors including the immune status of the host, the inoculum size and the virulence of the isolate. The single species *H. capsulatum* is supposed to include three distinct subspecies which do not share exactly the geographical distribution and which are responsible for variable clinical signs in different animal species. *Histoplasma capsulatum* var. *capsulatum* may be found in many regions all over the world; it is responsible for pulmonary and systemic infections with small-sized yeast-form cells in humans and many animal species, including companion animals. *Histoplasma capsulatum* var. *duboisii* is reported in Western and Central Africa and develops as large-sized yeasts with lymphadenopathy and dissemination to the skin and bones in primates. *Histoplasma capsulatum* var. *farciminosum* develops in the skin and the subcutaneous lymphatic system. In horses, the disease is called epizootic lymphangitis. It has been eradicated from large areas of the world but

J. Guillot (✉)
Department of Parasitology, Mycology and Dermatology, EnvA, Ecole nationale vétérinaire d'Alfort, UPEC, Maisons-Alfort, France

Dynamyc Research Group, EnvA, Ecole nationale vétérinaire d'Alfort, UPEC, Maisons-Alfort, France
e-mail: jacques.guillot@vet-alfort.fr

C. Guérin
Galapagos company, Romainville, France
e-mail: guerinc.paris@free.fr

R. Chermette
Department of Parasitology, Mycology and Dermatology, Ecole nationale vétérinaire d'Alfort, Dynamyc Research Group, EnvA, UPEC, Maisons-Alfort, France
e-mail: rene.chermette@vet-alfort.fr

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is still a major cause of morbidity and mortality in various countries particularly in Africa. The condition has a serious effect on the health and welfare of severely affected animals.

5.1 Causative Agents

Like other dimorphic fungi, *Histoplasma* organisms are characterised by their temperature-dependent transition from a saprophytic mould phase to a parasitic yeast form in host tissues. The ability to convert from the mould to the yeast form is a prerequisite for virulence. In the tissues of mammalian hosts, *Histoplasma* yeasts are oval and small in size (2 × 4 μm) with a thin wall and a narrow-based budding process. They are extracellular or may be found inside host macrophages (Fig. 5.1). In culture or in environmental conditions, *Histoplasma* organisms form branched septate filaments (1–2 μm in diameter). From these filaments, two types of conidia can be produced: round- or pear-shaped micro-aleurioconidia (2 × 4 μm) and tuberculate and refringent wall macro-aleurioconidia (6 × 15 μm) (de Hoog et al. 2009).

Histoplasma organisms can be found in soils in temperate and subtropical areas, but some regions are recognised as areas of hyperendemicity. This is the case for midwestern and southern USA and regions along the rivers (Missouri, Ohio or Mississippi) (Kauffman 2009). Traditionally, the single species *H. capsulatum* comprises three distinct subspecies with variable geographical distribution, host preferences and associated clinical signs (de Hoog et al. 2009). *Histoplasma capsulatum* var. *capsulatum* may be found in many different regions all over the world. The subspecies *capsulatum* is responsible for pulmonary and systemic infections with small-sized yeastlike cells in the macrophages of many mammals, including humans. *Histoplasma capsulatum* var. *duboisii* is present in Western and Central Africa. It develops as large (6 × 15 μm) yeasts with a thick wall in tissues of primates. The subspecies *duboisii* is responsible for lymphadenopathy with a possible dissemination to the skin and bones. *Histoplasma capsulatum* var. *farciminosum*

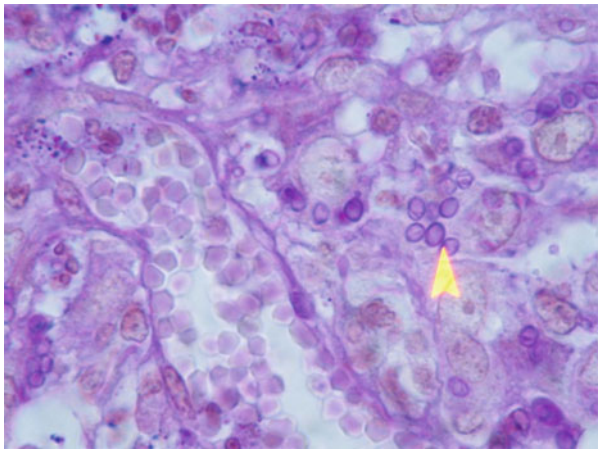

Fig. 5.1 Photomicrograph of subcutaneous tissue in a cat. Large numbers of *Histoplasma capsulatum* organisms filling the cytoplasm of macrophages are visible (arrow). Periodic acid stain (courtesy from Georges Plassiart, Metz, France)

can be found in many countries from Africa, Asia and South America. This subspecies infects the skin and the subcutaneous lymphatic system of horses, donkeys and mules. It has also been recovered from humans, dogs, cats and badgers. Using multilocus sequence typing (MLST), Kasuga et al. (2003) divided the species *H. capsulatum* into the following eight geographically separate groups: North American-1, North American-2, Latin American (=A), Latin American (=B), Australian, Netherlands (of Indonesian origin), Eurasian and African. The subspecies *farciminosum* was composed of three phylogenetic groups, supporting the hypothesis that this taxon is a collection of strains from different clades rather than a true phylogenetic species. Many strains from Europe and Asia were supposed to represent a single clone because they shared the same alleles at all four investigated loci. As no resolution of the branching order of the clades could be obtained, Kasuga et al. (2003) suggested that *H. capsulatum* radiated rapidly over a short period, most probably 3–13 million years ago.

Isolates of *H. capsulatum* were classified in two chemotypes according to the composition of the cell wall (Reiss et al. 1977). Chemotype I includes isolates without polysaccharide α-(1,3)-glucan in their cell wall. All isolates from this chemotype belong to the North American-2 clade defined by Kasuga et al. (2003). Isolates from other *H. capsulatum* clades are corresponding to chemotype II. Their cell wall contains α-(1,3)-glucan, which might be required for virulence and immune evasion. However isolates from chemotype I are recovered from lesions despite the absence of α-(1,3)-glucan (Rappleye et al. 2007).

5.2 Epidemiology of Histoplasmosis

The main historical facts and pioneering events that contributed to our knowledge on epidemiology of human and animal histoplasmosis are summarised in Fig. 5.2. A large diversity of domestic and wild mammals can be infected by *H. capsulatum* (Chermette and Guillot 2010): non-human primates, equids (including horses, donkeys and mules), cattle, dromedaries, rabbits (Brandoa et al. 2014), hedgehogs (Snider et al. 2008), pigs, dogs, cats, other carnivores such as grey (*Urocyon cinereoargenteus*) and red foxes (*Vulpes vulpes*), brown bears (*Ursus arctos*), raccoons (*Procyon lotor*), striped (*Mephitis mephitis*) and spotted (*Spilogale putorius*) skunks, European badgers (*Meles meles*) and sea otters (*Enhydra lutris*) (Morita et al. 2001). Spontaneous or experimentally induced histoplasmosis has also been reported in various species of rodents among which common (*Mus musculus*) and white-footed mice (*Peromyscus leucopus*); black (*Rattus rattus*), grey (*Rattus norvegicus*) and spiny rats (*Proechimys semispinosus*); and opossums of the genera *Didelphis* and *Philander*. *Histoplasma* organisms have also been isolated from many different species of bats whose guano is considered the best substrate for the proliferation and survival of the filamentous form of the subspecies *capsulatum*.

Inhalation is supposed to be the primary mode of entry of *H. capsulatum* var. *capsulatum*. Animals that are immunocompromised or were subjected to a large dose of infectious fungal elements are at a greater risk to develop infection with dissemination. Infection is caused by the inhalation of propagules from the saprobic

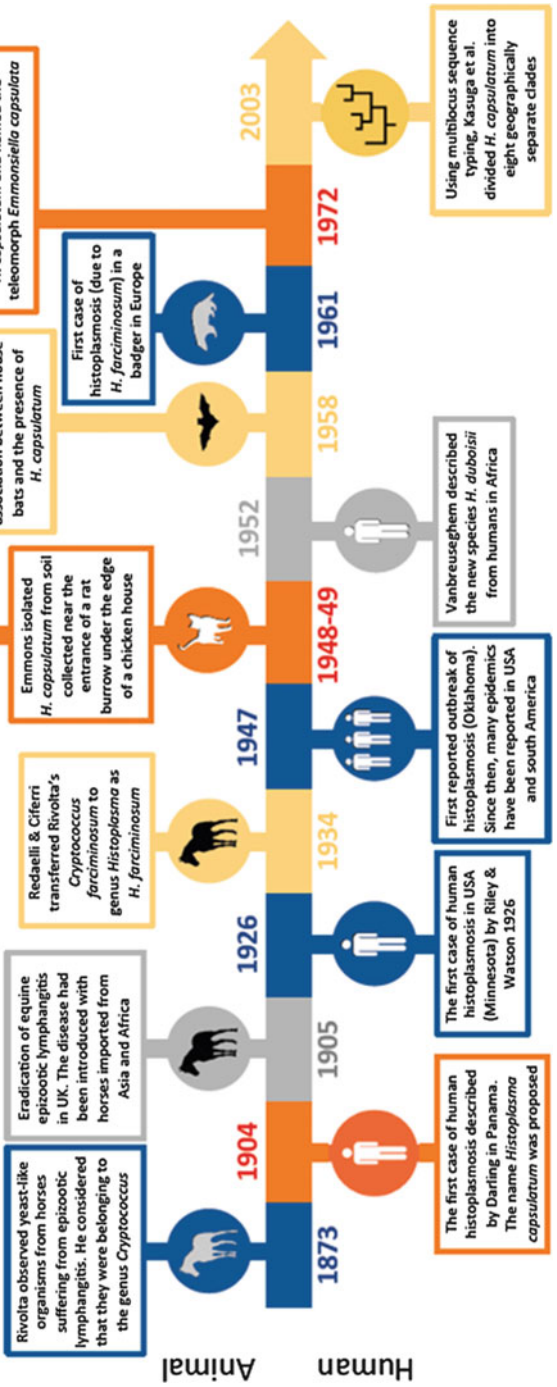

Fig. 5.2 Chronological order of the main facts and pioneering events that contributed to the epidemiological studies on human and animal histoplasmosis

filamentous phase. This phase develops in special habitats, particularly on bat guano that has accumulated in confined spaces such as caves. A second possible mode of entry by ingestion of infective material has been suggested. This could account for cases of primary gastrointestinal histoplasmosis in dogs and cats (Brömel and Sykes 2005; Stark 1982). A moderate climate with constant humidity seems to be the most appropriate combination for the development and survival of *Histoplasma*. In companion animals, infection due to *H. capsulatum* var. *capsulatum* is most frequently observed in endemic/enzootic regions of the Mississippi and Ohio River valleys in North America (Brömel and Sykes 2005; Sykes and Guillot 2015). Cases were also reported from South America (Forjaz and Fischman 1985), Italy (Mantovani et al. 1968; Reginato et al. 2014), Greece (Mavropoulou et al. 2010), Japan (Murata et al. 2007; Ueda et al. 2003) and Australia (Mackie et al. 1997). Recently, cases of feline histoplasmosis were reported in Colorado, California, New Mexico and Texas, locations that were traditionally considered as non-enzootic (Balajee et al. 2013). A massive *H. capsulatum* infection in juvenile raccoons from northern California was reported by Clothier et al. (2014). In 2005, an infected northern sea otter (*Enhydra lutris kenyoni*) was found on Kodiak Island, Alaska (Burek-Huntington et al. 2014). Histological examination revealed the presence of *Histoplasma* yeasts and the subspecies *capsulatum* could be identified by direct sequencing. The authors suggested that the sea otter was contaminated by migratory birds or through aerosol transmission.

Europe is usually considered non-endemic/enzootic for *H. capsulatum.* However, in a review about humans with histoplasmosis in Europe over a 5-year period (from January 1995 to December 1999), Ashbee et al. (2008) identified eight patients (from Germany, Italy and Turkey) who had never travelled abroad and hence may correspond to autochthonous cases. Histoplasmosis has also been reported in wild and domestic animals in Europe. Several investigations demonstrated that *H. capsulatum* may be responsible for cutaneous lesions in Eurasian badgers (*Meles meles*) in Switzerland (Burgisser et al. 1961), Denmark (Jensen et al. 1992), Germany (Grosse et al. 1997; Eisenberg et al. 2013) and Austria (Bauder et al. 2001). Infection was limited to the skin and subcutaneous lymph nodes. The badger's habitat and its rummaging and omnivorous mode of life are potential predisposing factors to infectious diseases, including tuberculosis and histoplasmosis. Recently, *H. capsulatum* var. *capsulatum* DNA was detected from the lungs of a bat (*Nyctalus noctula*) trapped in France (González-González et al. 2013). Disseminated histoplasmosis was described in a cat in Greece (Mavropoulou et al. 2010) and in dogs in Italy (Mantovani et al. 1968; Reginato et al. 2014).

The subspecies *farciminosum* was epidemiologically investigated between January 2003 and June 2004 in 19,082 carthorses in Ethiopia (Ameni 2006). A mean prevalence of 18.8% was reported. The highest prevalence (39%) was observed in the Mojo region. The prevalence of infection was associated with average annual temperatures rather than mean annual rainfall. Statistically significant association was also observed between the altitude and the prevalence of infection: histoplasmosis was more frequently reported in humid and hot regions with an altitude from 1500 to 2300 m (Ameni 2006). Equine histoplasmosis has been reported from China, India, Indonesia, Iraq, Israel, Japan, Pakistan and Syria. In Africa, cases are reported in many countries: Algeria, Angola, Cameroon, Chad,

Egypt, Ethiopia, Ghana, Morocco, Nigeria, Togo, Tunisia, Senegal and Sudan (Guérin 2010). Official disease distribution maps from OIE (Office International des Epizooties) indicate that equine histoplasmosis in Africa is restricted to Ethiopia, Senegal and South Africa (OIE WAHID Maps 2005). The disease is also reported from South and Central America (Al-Ani 1999). Compared to major equine epizootic diseases, infection due the subspecies *farciminosum* is not frequently diagnosed. The confusion with other infectious diseases may probably account for this situation.

Infections limited to the skin were also reported in cats residing in Switzerland (Fischer et al. 2013) and in eastern France (Fantini et al. 2014). In these cases, histopathological examination revealed the presence of microorganisms consistent with *Histoplasma* (Fig. 5.1), and the subspecies *farciminosum* was identified by PCR and MLST approach directly from the tissues (Guillot et al. 2015).

Inoculation is considered the primary mode of entry of *H. capsulatum* var. *farciminosum*, probably mostly by contamination of cutaneous wounds in horses (Guérin 2010). Nevertheless experimental transmission of the disease by subcutaneous or intradermal inoculation of pus containing *H. capsulatum* var. *farciminosum* yeasts gave inconstant results. Some cases of direct transmission between infected and healthy wounded animals or after mating have been suspected (Al-Ani and Al Delaimi 1986). The subspecies *farciminosum* has also been isolated from the digestive tract of hematophagous flies (Gabal and Hennager 1983). Ameni and Terefe (2004) indicated that there was a significant association between histoplasmosis and the presence of ticks in mules. Seasonal changes may have a significant effect upon direct transmission efficiency, as rain increases mud projections on wounds, delays healing processes and increases the risk of infection in horses (Guérin et al. 1992). Telluric contamination of exposed and vulnerable body areas such as limbs, eyes or nostrils could explain the main localisations of primary lesions.

5.3 Infections Due to *Histoplasma capsulatum* var. *capsulatum*

Histoplasmosis due to *H. capsulatum* var. *capsulatum* has a wide range of clinical manifestations, presenting as mild respiratory distress, acute respiratory infection or life-threatening disseminated disease. The outcome is variable according to the inoculum size and the strain virulence. Once inhaled, *Histoplasma* propagules convert to yeasts in the lungs. A granulomatous inflammatory response occurs that consists primarily of macrophages, variable numbers of lymphocytes and sometimes fibrosis. Some animals control the initial infection but remain latently infected with small numbers of yeast cells. Subsequent immune suppression can lead to reactivation of infection years later. As a consequence, the incubation period may range from 2 to 3 weeks to several years. *Histoplasma* organisms may be found in pulmonary lymph nodes, in reticuloendothelial organs (liver, spleen and bone marrow), in the skin, in the central nervous system and in the small and/or large intestinal tract.

Clinical signs of histoplasmosis in cats and dogs are commonly non-specific, such as weight loss, inappetence, weakness, dehydration and fever (Brömel and Sykes 2005). *Histoplasma capsulatum* was first reported as a pathogen in a cat in 1949. In a

review of 571 cats with deep mycotic infections in the USA, histoplasmosis was with 16.7% the second most commonly reported fungal disease after cryptococcosis (46.1%) (Davies and Troy 1996). Approximately 40% of infected cats have respiratory signs such as dyspnoea and tachypnoea and to a lesser extent cough and nasal discharge. Respiratory signs may be absent in some animals with dissemination of *Histoplasma* to non-pulmonary sites. Thoracic radiographs usually reveal diffuse, linear, nodular or miliary interstitial patterns, but mixed interstitial-alveolar-bronchial patterns and an absence of abnormal findings have also been reported. Ocular signs (chorioretinitis, retinal detachment, optic neuritis, anterior uveitis or panophthalmitis) occur quite frequently (in more or less one-quarter of cats). In dogs, chronic diarrhoea (often with hematochezia or melena) and wasting (pale mucous membranes, weight loss and weakness) are frequently observed. Other clinical signs include cutaneous nodules, joint pain, lesions on the tongue, myosis, splenomegaly and ocular signs (such as anterior uveitis, chorioretinitis, optic neuritis and retinal detachment) (Brömel and Sykes 2005).

Systemic histoplasmosis with intermittent cough, dyspnoea, lymphadenopathy, hyperthermia, anorexia, weight loss and diarrhoea has been described, mostly in horses (Rezabek et al. 1993), more rarely in cattle (Morgado et al. 1976) and the dromedary (Chandel and Khere 1994). Occasionally, *H. capsulatum* var. *capsulatum* is also responsible for abortion in mares with lesions of placentitis and invasion of the foetus; perinatal death of foals, usually due to severe granulomatous pneumonia (Saunders et al. 1983); or ocular mycosis with keratitis in horses (Richter et al. 2003).

5.4 Infections Due to *Histoplasma capsulatum* var. *duboisii*

Infections due to *H. capsulatum* var. *duboisii* have been reported in baboons originating from West Africa after transfer to other locations (Gugnani and Muotoe-Okafor 1997). Secondary infections of the skin, subcutaneous tissues and the lymph nodes in the form of small papules and ulcerative granulomas have been reported in absence of involvement of the lungs and internal viscera. The subspecies *duboisii* has not been isolated from livestock but is recognised in humans and in some wild mammals including bats (*Nycteris hispida*, *Tadarida pumila*), baboons (*Papio cynocephalus*) and aardvarks (*Orycteropus afer*), which could be markers of endemic foci (Chermette and Guillot 2010). The virulence of *H. capsulatum* var. *duboisii* seems to be lower than that of *H. capsulatum* var. *capsulatum*, which is consistent with the tendency of the variety *duboisii* to form mainly localised cutaneous and subcutaneous infections (Rippon 1988).

5.5 Infections Due to *Histoplasma capsulatum* var. *farciminosum*

Following traumatic inoculation, the development of the subspecies *farciminosum* is usually responsible for nodular cutaneous lesions. In the skin, the fungus induces an inflammatory lesion containing granulocytes, macrophages and multinucleated giant cells. A fibrous and oedematous peripheral reaction further surrounds the nodule. An abscess progressively develops and starts to discharge yellow pus containing yeasts, macrophages and granulocytes. Finally, a granulation tissue appears and an ulcer with inverted borders is formed. Infected leucocytes or yeasts are able to spread the infection via lymphatic vessels to adjacent tissues. Bacterial superinfection may occur.

In equids, the subspecies *farciminosum* is responsible for a debilitating disease called epizootic lymphangitis (Guérin 2010; Scantlebury and Reed 2009). The incubation period ranges from 1 and 7 months. The classical presentation is a superficial lymphangitis. Sometimes genital organs or bones are involved. Hyperthermia is rarely reported. The lesions are present on the skin and more rarely on the mucous membranes (lips, conjunctiva, nasal or respiratory epithelium). Five types of lesions have been described:

1. The initial lesion is a cutaneous ulcer with inverted borders and painful outline; thick, yellowish and sometimes bloody pus is produced, mostly observed on the limbs, thorax, chest, neck and head.
2. The cord is a congested or knotted rope lymph vessel (Fig. 5.3).
3. The spots are hemispheric nodules, 0.5–3 cm diameter, tough and painless, isolated or lined on a cord.
4. The tumours are located on lymph nodes, up to 5–30 cm diameter, and may turn into fistula.
5. The engorgements are due to a diffuse reaction within the conjunctive tissue and are observed around the lower limbs.

Fig. 5.3 Lesions of equine epizootic lymphangitis in Ethiopia. (Left) Ulcers and nodules; (right) cordlike lesions (courtesy from Christine Guérin)

Fig. 5.4 A lesion of feline histoplasmosis due to *Histoplasma capsulatum* var. *farciminosum* (Fischer et al. 2013)

Infected horses become restless because of the disturbance due to numerous flies attracted by cutaneous lesions. There is a progressive loss of appetite and condition as severity of the disease increases. Because of its debilitating nature and its high case fatality, some horse-owners in Ethiopia have started to refer to equine histoplasmosis as "horse AIDS" (Ameni 2006). In a study investigating the economics of the carthorse industry in Ethiopia, Aklilu and Zerfu (2010) reported that losses to the owner due to morbidity of a horse with histoplasmosis resulted in more than a 50% reduction in daily earnings.

Infection due to *H. capsulatum* var. *farciminosum* has been reported in animals other than equids. Histoplasmosis in four dogs diagnosed in Japan lacked pulmonary or gastrointestinal lesions and was characterised by multiple granulomatous or ulcerated lesions on the skin and in the mouth. The subspecies *farciminosum* was reported as the causative agent in these cases (Murata et al. 2007). In Europe, similar observations have been made in badgers in Germany (Eisenberg et al. 2013) but also in cats in Switzerland (Fischer et al. 2013) and eastern France (Fantini et al. 2014, Guillot et al. 2015) (Fig. 5.4).

5.6 Diagnosis of Histoplasmosis in Animals

A definitive diagnosis of histoplasmosis is made by cytologic or histopathologic identification of *Histoplasma* yeasts. The latter are typically observed within macrophages or, less frequently, free in pyogranulomatous exudates. *Histoplasma* yeasts are small (2 × 4 μm), oval or globose elements surrounded by a clear halo. Histopathological sections should be examined very carefully because the yeasts are small and quite difficult to visualise upon regular staining, like HE. Sometimes

Histoplasma yeasts stain poorly with PAS, making the silver staining GMS more valuable. Differential diagnosis includes other fungi (*Sporothrix* spp., *Blastomyces dermatitidis*, *Cryptococcus* spp.), which develop as yeasts in tissues, but also protozoa like *Leishmania* spp.

Culture is possible on Sabouraud dextrose agar without cycloheximide or on brain-heart infusion with blood. With an incubation temperature of 27–30 °C, *Histoplasma* fungi form whitish and slow-growing colonies. Incubation periods of 2–4 weeks may be required before growth is appreciated. Under these conditions, infective conidia (thick-walled, large, tuberculate macroconidia and small oval microconidia) are produced. Because these conidia may cause infection in laboratory personnel, the growth of the mycelial phase of *Histoplasma* poses a health hazard and should be performed in specialised laboratories with adapted levels of confinement.

PCR techniques have been developed for the diagnosis of human histoplasmosis (Muraosa et al. 2016). These techniques could also be applied in animals. Several serological techniques, including immunodiffusion and complement fixation tests, have been used to detect human antibodies to *H. capsulatum*, but serology does not seem to be a reliable diagnostic tool (Kauffman 2009). This also applies to dogs and cats. Serology for *H. capsulatum* antibodies in nine cases of canine disseminated histoplasmosis revealed a titer of 1:8 in one case (Mitchell and Stark 1980). Serology to detect antibodies against *H. capsulatum* was positive in only four out of nine feline cases (Davies and Troy 1996).

Antigen detection tests are now widely used for the diagnosis of human histoplasmosis. The tests are usually performed on urine specimens. In a retrospective study, Cook et al. (2012) compared the results of a urine antigen assay with standard diagnostic methods in cats with clinical signs of histoplasmosis. Antigenuria was detected in 17 out of 18 infected cats. The histofarcin skin test was developed by Soliman et al. (1985) for horses. This test proved to be a valuable tool in diagnosing epizootic lymphangitis in the field (Ameni et al. 2006). A delayed, intradermal, type IV hypersensitivity reaction indicates previous exposure to *Histoplasma*.

5.7 Control of Histoplasmosis in Animals

In dogs and cats infected by the subspecies *capsulatum* or *farciminosum*, the treatment of choice is oral itraconazole. The recommended dose is 10 mg/kg q 12–24 h for a minimum of 4–6 months. Treatment should be continued for at least 2 months after resolution of clinical signs (Brömel and Sykes 2005). In dogs, amphotericin B has been used successfully to treat local and disseminated histoplasmosis, but relapses are common.

In horses infected by the variety *farciminosum*, most of reported treatments date back to the beginning of the twentieth century. Some of them (iodide, mercuric, arsenic or imidazole-derived drugs) were efficient, but were always long, relatively expensive and toxic. In combination with surgical removal of the lesion or cauterisation, these treatments led to recovery within 4–6 weeks (Guérin 2010).

Amphotericin B is the listed drug of choice for the treatment of clinical cases of epizootic lymphangitis by the OIE (Anon 2004).

Elimination of the infection can be achieved by culling infected horses and application of strict hygiene practices to prevent spread of the organism. However, culling is hardly acceptable in highly endemic areas where the use of horse-drawn taxis and carts to generate an income is a means of survival for a significant number of families.

Boquet and Nègre developed a vaccine against epizootic lymphangitis obtained from a yeast culture inactivated by heat (cited by Curasson 1942). Subcutaneous injections every 7 days during 5 weeks proved to be efficient for the treatment of horses. More recently, a live attenuated vaccine was developed and tested in China. This vaccine was reported to protect 75.5% of horses inoculated, with immunity persisting for more than 2 years (Zhang et al. 1986). This vaccine is not commercially available, and there were some issues of adverse reactions that would need addressing (Scantlebury et al. 2015).

5.8 Public Health Considerations

The potential role of bats in spreading *H. capsulatum* var. *capsulatum* remains unclear. However, the high risk of natural bat infection with this fungus in caves has been well-documented. In a recent investigation in Mexico, lung samples from 122 bats were examined (Gonzalez-Gonzalez et al. 2014). A total of 98 samples revealed *Histoplasma* infection. Benedict and Mody (2016) provided an update on the epidemiologic features of 105 documented human outbreaks in the USA. The presence of bats (or bat droppings) was reported in 24 (23%) outbreaks and the presence of birds or bird droppings in 59 (56%). Birds most frequently involved were chickens (41% of bird-related outbreaks) and blackbirds (starlings, grackles), pigeons and gulls.

Transmission of *H. capsulatum* from companion animals to humans has never been reported. However, infected pets may be a sentinel for human exposure, and this is especially relevant if the animal resides with immunocompromised human beings. Concurrent infections of owners and companion animals were reported after exposure to the same environment or source of infective material (Dillon et al. 1982, Davies and Colbert 1990). A common-source environmental exposure was also suggested in a study evaluating the geographical specificity of *H. capsulatum* var. *capsulatum* isolates in Brazil (de Medeiros Muniz et al. 2001). Using the MLST typing technique, Balajee et al. (2013) demonstrated that isolates from feline and human cases were genetically distinct. However, the feline cases were from California, Colorado and Texas, whereas the human cases were from different regions (Missouri and Georgia). This result might indicate that the genetic differences were related to geographic distance rather than to host specificity.

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