



## Review Article

# Fungal infections in animals: a patchwork of different situations

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## Abstract

The importance of fungal infections in both human and animals has increased over the last decades. This article represents an overview of the different categories of fungal

infections that can be encountered in animals originating from environmental sources without transmission to humans. In addition, the endemic infections with indirect transmission from the environment, the zoophilic fungal pathogens with near-direct transmission, the zoonotic fungi that can be directly transmitted from animals to humans, mycotoxicoses and antifungal resistance in animals will also be discussed. Opportunistic mycoses are responsible for a wide range of diseases from localized infections to fatal disseminated diseases, such as aspergillosis, mucormycosis, candidiasis, cryptococcosis and infections caused by melanized fungi. The amphibian fungal disease chytridiomycosis and the Bat White-nose syndrome are due to obligatory fungal pathogens. Zoonotic agents are naturally transmitted from vertebrate animals to humans and vice versa. The list of zoonotic fungal agents is limited but some species, like *Microsporium canis* and *Sporothrix brasiliensis* from cats, have a strong public health impact. Mycotoxins are defined as the chemicals of fungal origin being toxic for warm-blooded vertebrates. Intoxications by aflatoxins and ochratoxins represent a threat for both human and animal health. Resistance to antifungals can occur in different animal species that receive these drugs, although the true epidemiology of resistance in animals is unknown, and options to treat infections caused by resistant infections are limited.

**Key words:** Opportunistic fungi, pathogenic fungi, zoophilic fungi, zoonoses, mycotoxicoses, antifungal resistance, mycoses in animals, veterinary mycology.

## Introduction

The ISHAM Veterinary Mycology Working Group (ISHAM-VMWG) has been established in 2010 by a group of experts to support all scientific aspects that deals with mycology and veterinary sciences, including: diagnosis and identification of fungal pathogens of veterinary importance, pathophysiology and immunology of fungal diseases in animals, epidemiology, prevention, control and eradication of animal mycoses, mycotoxins and mycotoxicosis in animals, standardization of animal model, and development of alternatives. The first general meeting of ISHAM-VMWG was held in June 2012 during the 18th congress of ISHAM in Berlin, Germany. There was a great opportunity to share expertise, recent activities, and also discuss future plans among members. Attendees were scientists and veterinarians from all over the world. The membership has been open to any with a scientific interest in fungi affecting animal species, understanding a veterinary disease problem, development of animal models of human fungal disease. Since then, ISHAM VMWG was highly involved in international educational activities. The international veterinary mycology course is a 5 days' educational event under the umbrella of ISHAM. The course is organized every two to three years and the next one will be hold in June 2018 in Amsterdam, The Netherlands. ISHAM-VMWG published several scientific articles in the peer-reviewed journals. Attempts are also under way to complete a textbook on emerging and epidemic fungal infection by the end of 2017 and the Atlas of Veterinary Pathogenic Fungi by 2020.

Fungi are relatively uncommon causes of disease in healthy and immunocompetent humans and nonhuman vertebrates, even though hosts are constantly exposed to infectious propagules.<sup>1,2</sup> However, an increasing number of recalcitrant fungal diseases in animals have occurred over the last two decades, originating from opportunistic and pathogenic fungi.<sup>2</sup>

Opportunistic fungi have a preferred habitat independent from the living host and cause infection after accidentally penetration of intact skin barriers, or when immunologic defects or other debilitating conditions exist in the host.<sup>3</sup> In contrast, pathogens are defined as having advantage of the vertebrate host; in obligatory pathogens the host is indispensable to complete their life-cycle and for nutrient acquisition, growth, niche establishment, and reproduction.<sup>4</sup> Zoonoses are infections that can be naturally transmitted between vertebrate animals and humans.<sup>5</sup> From a global perspective, zoonotic infections have been recognized for many centuries, and account for the majority of emerging and reemerging infectious diseases, worldwide.<sup>6</sup>

The present article only highlights a selected list of infections caused by environmental fungi that can be encountered in animals, as well as zoonotic fungi that can be transmitted from animals to humans. Another area of veterinary significance is the presence of mycotoxins in animal feed, and the eventual risks of mycotoxicoses. In addition, the development and epidemiology of antifungal resistance in animals will also be discussed.

## Opportunistic fungal infections with no transmission

### Aspergillosis

Aspergillosis in animals covers a wide range of diseases from localized conditions to fatal disseminated infections, as well as allergic reactions caused by fungi belonging to the genus *Aspergillus*.<sup>7,8</sup> The numerous members of this genus are saprobic filamentous fungi commonly found in soil, decaying vegetation, and on seeds and grains, with an occasional potential to infect living animal hosts including insects, birds, and mammals.<sup>9,10</sup>

Although there are more than 300 known species in the genus, animal aspergilloses are mainly caused by *A. fumigatus*, and only rarely by a few other species.<sup>9,10</sup> Modern classification of *Aspergillus* species is by polyphasic taxonomy and has led to the distinction of 22 distinct sections, of which *Aspergillus*, *Fumigati*, *Circumdati*, *Terrei*, *Nidulantes*, *Ornati*, *Warcupi*, *Candidi*, *Restricti*, *Usti*, *Flavipedes*, and *Versicolores* contain clinically relevant species.<sup>11</sup>

In animals, aspergillosis is primarily a respiratory infection that may become generalized; however, tissue predilection is variable between species. Similar to infections in humans, animals exhibiting inability to produce a normal immune response are at higher risk of infection. Aspergillosis may also occur in healthy animals under environmental stress and other immune-compromising conditions.<sup>12,13</sup>

In invertebrates, *A. sydowii* causes a recently recognized, large epizootic affecting sea fan corals (*Gorgonia* species),<sup>14</sup> first documented in 1995 near Saba the Bahamas and subsequently spreading throughout the Caribbean basin, including in the Florida Keys.<sup>15,16</sup> *Aspergillus* species are also known to infect honeybee (*Apis mellifera*) brood, causing stonebrood disease over all larval stages.<sup>17,18</sup> *Aspergillus* species with the ability to produce mycotoxins such as *A. flavus*, *A. fumigatus*, and *A. niger* have been suggested to be the primary cause of this disease.<sup>19</sup> In reptiles, *Aspergillus* species such as *A. fumigatus*, *A. niger* and *A. terreus* have been isolated from both cutaneous and disseminated infections,<sup>20</sup> mainly promoted by immune-compromising conditions, such as husbandry deficiencies or inappropriate temperatures, humidity, or poor enclosure hygiene.<sup>21</sup> Avian aspergillosis is predominantly a disease of the respiratory tract, but all organs can be involved, leading to a variety of acute or chronic manifestations.<sup>22,23</sup> All avian species should probably be considered as susceptible. *Aspergillus fumigatus* has been involved in significant common-source sapronotic die-offs of domestic and free-ranging wild birds.<sup>24</sup> Economic significance of aspergillosis is most readily apparent in poultry production, where disease occurs late in the growing cycle.<sup>25</sup>

Sinonasal, bronchopulmonary, and disseminated infections are major forms of aspergillosis in dogs and cats.<sup>26–28</sup> In dogs, a breed or gender predisposition can be recognized.<sup>29</sup> Aspergillosis also has been also reported in cats stressed by underlying disease (such as feline Immunodeficiency Virus and Feline Leukemia Virus) or immunosuppression.<sup>30–32</sup> *Aspergillus felis* has been the most frequently reported etiologic agent of sinoorbital aspergillosis in cats, followed by cryptic species of the section *Fumigati*, including *A. udagawae* and *A. viridinutans*.<sup>32,33</sup> In ruminants, *Aspergillus* species, particularly *A. fumigatus*, are known worldwide to cause mycotic pneumonia, gastroenteritis, mastitis, placentitis, and abortions.<sup>34</sup> *Aspergillus* species also cause guttural pouch infections, keratomycosis and pneumonia in horses.<sup>35–39</sup> In marine mammals, aspergillosis can be primary or secondary to any chronic infection, physiologic stress, or immunosuppression.<sup>40</sup> Aspergillosis may also occur in various non-human primate species, particularly in immunocompromised hosts.<sup>41</sup>

### Mucormycosis

Mucormycosis is a saprobic opportunistic infection caused by fungi in the order *Mucorales* in the former class Zygomycetes.<sup>42</sup> Within the order, the most often identified species belong to the genera *Rhizopus*, *Mucor*, *Rhizomucor*, *Lichtheimia* (formerly *Absidia*), *Apophysomyces*, *Cunninghamella*, and *Saksenaea*. The natural habitat for the *Mucorales* is soil, and they are typically isolated from decaying organic material. The fungi are often also found in indoor and outdoor air, in food stuffs, and in dust.<sup>42</sup> Mucormycosis in animals (both domesticized and wild, and in mammalian and non-mammalian) and humans are similar with respect to epidemiology, portal of entry, localization, and formation of lesions.<sup>43–54</sup>

The opportunistic pathogenic members of the *Mucorales* are ubiquitous within the domesticated environment of animals and in indoor habitats, but infection almost invariably is established only when the normal balance between animal and the agent is disturbed.<sup>43</sup> In line with other opportunistic fungal infections in animals, for example, candidiasis and aspergillosis, predisposing factors are not related to the animal species but to the infected animal *per se*.<sup>43–54</sup> General predisposing factors favoring mucormycosis in humans also apply for animals, that is, infections are seen in hosts that are immunocompromised or otherwise debilitated due to metabolic disorders. However, overwhelming exposure to mucoralean fungi or disturbance of the bacterial microbiota in the forestomach may cause infection in otherwise healthy animals.<sup>55</sup> Two examples in cattle are of interest, that is, mucormycotic ruminitis and lymphadenitis. The rumen of ruminants is anaerobic, but the ruminal wall

represents an aerobic-anaerobic interface, which therefore is colonized by microaerobic bacteria.<sup>43</sup> Antibiotic treatment will destroy this normal micro-aerobic bacterial flora, facilitating infection by *Mucorales*. Mucormycotic ruminitis is therefore a well-known sequel to intensive antibiotic treatment of cattle.<sup>52</sup> Heavy exposure to *Mucorales* fungi through contaminated food stuffs is a cause of infection of intestinal lymph nodes. Notably, lesions of mucormycotic lymphadenitis are macroscopically indistinguishable from bovine tuberculosis.<sup>56</sup>

Ruminant mucormycosis may also be respiratory, occur in other parts of the gastrointestinal tract, or systemically.<sup>51,53</sup> Due to the frequently observed angioinvasion of *Mucorales*, hematogenous spread to multiple organs is often reported. In pregnant cows, the fungus frequently spreads to the placenta, although *Aspergillus fumigatus* is the predominant course of bovine mycotic placentitis and abortion.<sup>57</sup>

In horses, mucormycotic lesions have been reported in different organs, especially in the respiratory system and gastrointestinal tract, and may lead to systemic spread to multiple organs.<sup>48</sup> Moreover, cases of localized skin infection have also been described.<sup>47</sup> Mucormycosis in pigs is uncommon, again especially affecting lungs, gastrointestinal tract and lymph nodes.<sup>58</sup> In dogs and cats some cases of mucormycosis have been described as a cause of, for example, enteritis or systemic spread.<sup>59</sup> Few, scattered reports are available on the occurrence of mucormycosis in different kinds of avian species. Especially the respiratory organs and gastrointestinal tract are often involved.<sup>60–63</sup> Cases in wild living animals have been described, for example, in dolphin, bison, and seal.<sup>64,65</sup>

## Candidiasis

The genus *Candida* is currently being reclassified along phylogenetic lines. In its classical sense, it comprises over 200 species of which 15 have been isolated from infections in humans and animals.<sup>66,67</sup> Most prominent as causes of disease are *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei*.<sup>68–73</sup> These species are also frequently found as part of the microbiota of healthy humans and animals<sup>74–78</sup> and are thus considered as commensal and facultatively pathogenic. While *C. albicans* and *C. glabrata* appear to occur only in association with warm-blooded hosts, other infectious *Candida* species are also known from the environment. Infections are usually caused by strains that commensally precolonized the host rather than by vertical or longitudinal transfer,<sup>79,80</sup> and the zoonotic potential can thus be considered to be low. Although *C. albicans* is the most virulent *Candida* species, others might be more promi-

nent in specific animals depending on the site of infection (Table 1).

Candidiasis can be superficial, affecting the skin, mucosal membranes of the gastrointestinal and urogenital tract. Dissemination of the fungus can lead to candidemia or localized infection of internal organs. In contrast to humans, epidemiological data and systematic analysis of risk factors are lacking for veterinary candidiasis. Animal candidiasis is mentioned in veterinary textbooks as occasionally affecting domestic animals.<sup>81–83</sup> Given the fact that the general factors contributing to candidiasis are not host-specific, it seems likely that the general risk factors described for human patients are also applicable to veterinary medicine.<sup>84,85</sup> Cutaneous candidiasis is rather frequent in dogs, usually in association with atopy, other immune diseases, immunosuppressive disorders, or medical treatment leading to immunosuppression<sup>86–94</sup> and clinically resembles *Malassezia* infections. It can also occur in birds, especially in chicken, but rarely in other species. Mucosal oral and gastrointestinal candidiasis occurs most commonly in birds, where it is the prevalent form of candidiasis. It is referred to as thrush or sour crop, characterized by white-grayish lesions, often accompanied by hyperkeratosis.<sup>95–97</sup> Similar disorders have been described in horses, cattle, dogs, cats, and pigs, usually associated with young age, antibiotic use, or immunosuppression.<sup>81,98–100</sup> Lesions in mammalian hosts are often invasive and ulcerative. Systemic *Candida* infection is usually rare in dogs and cats. However, surgery and trauma, for example, by foreign bodies, can lead to introduction of *Candida* into deeper tissue or the peritoneal cavity, leading to granuloma formation or peritonitis, which has been described in cats and dogs.<sup>101–105</sup> Candidiasis of the urinary tract likewise occurs in dogs and cats, manifesting as candiduria and cystitis, usually in association with antibiotic treatment due to previous bacterial infections, or other underlying diabetes mellitus.<sup>106–113</sup> Environmental *Candida* species, such as *C. parapsilosis*, *C. tropicalis*, and *C. guilliermondii*, can cause abortion in horses and cattle,<sup>114–118</sup> and *Candida* mastitis is a well-described sequel of intramammary antibiosis in dairy cattle.<sup>119–135</sup> Disseminated candidiasis has been reported in dogs, cats, sheep, calves, horses, ferrets, and alpacas (Table 1). The symptoms of this disease are often unspecific, and may lead to myocarditis, endocarditis or endophthalmitis. Of note, eye infections in horses have rather frequently been reported in the absence of disseminated disease.

Although candidiasis is a rare infection in animals, it is an important differential diagnosis to bacterial infections, and candidiasis can also occur secondary to bacterial infections. It should be considered as a possible option especially when hosts do not respond to antibiotic treatment.

**Table 1.** Selected case reports of candidiasis in animals. *Candida* spp.: species not determined or several species.

Host species	<i>Candida</i> species	Types of infection	Predisposing factors		
Birds	<i>Candida</i> spp.	Oral and gastrointestinal candidiasis (pigeons, parrots, Galliformes, Passeriformes, raptors)	None; concomitant infections by other pathogens; immunosuppression		
	<i>C. albicans</i>				
	<i>C. krusei</i>				
	<i>C. albicans</i>	Pulmonary candidiasis (sun conure, raptors)	–		
	<i>C. albicans</i>	Cutaneous candidiasis (Passeriformes, chicken)	–		
Dogs	<i>C. albicans</i>	Myocarditis (canary)	–		
	<i>C. guilliermondii</i>	Joint infection	Leishmaniasis and intra-articular corticosteroid injections		
	<i>C. albicans</i> , <i>C. glabrata</i>	Peritonitis	Intestinal surgery, corticosteroids		
	<i>C. albicans</i> , <i>C. guilliermondii</i> , <i>C. parapsilosis</i> , <i>C. tropicalis</i>	Dermatitis, incl. otitis externa	Atopia and other autoimmune diseases, immunosuppressive disorders and drugs, other infections		
	<i>C. albicans</i> , <i>C. parapsilosis</i> , <i>C. tropicalis</i>	Urinary tract (candiduria, cystitis)	Diabetes mellitus, lower urinary tract diseases incl. bacterial infections and antibiotic treatment, neoplasia		
	<i>C. albicans</i> , <i>Candida</i> spp.	Disseminated candidiasis (incl. endophthalmitis, pericarditis, spondylitis)	Intestinal surgery, immunosuppression, neoplasia, catheterization		
	<i>C. albicans</i> <i>Candida</i> spp.	keratitis pneumonia	– Concurrent bacterial pneumonia and aspergillosis		
Cats	<i>C. parapsilosis</i> <i>C. albicans</i>	Granulomatous rhinitis Urinary tract	Corticosteroid treatment Diabetes mellitus, lower urinary tract diseases incl. bacterial infections and antibiotic treatment, neoplasia		
	<i>Candida</i> spp. <i>C. albicans</i> <i>Candida</i> spp.	(candiduria, cystitis) Intestinal granuloma Disseminated candidiasis (incl. ocular involvement)	Suspected trauma by foreign body Diabetes mellitus, immunosuppression		
	<i>C. albicans</i>	Pyothorax	–		
	Ruminants	Cattle	<i>C. albicans</i> , <i>C. catenulata</i> , <i>C. guilliermondii</i> , <i>C. kefyr</i> , <i>C. krusei</i> , <i>C. maltosa</i> , <i>C. rugosa</i> and others	Mastitis	Intramammary antibiotic treatment, environmental contamination, milking hygiene
			<i>C. parapsilosis</i> , <i>C. tropicalis</i>	Abortion	–
<i>Candida</i> spp. <i>C. albicans</i>			Otitis externa Gastrointestinal infection	– Antibiotics, concurrent gastrointestinal mucormycosis	
Alpacas, lamas, guanaco		<i>C. glabrata</i> <i>C. albicans</i> <i>Candida</i> spp. <i>C. krusei</i>	Disseminated candidiasis Bronchopneumonia	Antibiotics, young age	
		<i>C. albicans</i>	Disseminated candidiasis	Immunosuppression suspected	
Camel Sheep	<i>Candida</i> spp. <i>C. albicans</i>	Dermatitis			
	<i>Candida</i> spp.	Disseminated candidiasis			
Horses	<i>Candida</i> spp. <i>Candida</i> spp. <i>C. parapsilosis</i> <i>C. albicans</i> <i>Candida</i> spp. <i>Candida</i> spp. <i>C. guilliermondii</i> <i>C. pseudotropicalis</i>	Keratitis Arthritis Endocarditis Systemic candidiasis Oral candidiasis Gastroesophageal candidiasis Abortion	Birth hypoxia, sepsis Young age and immunodeficiency Young age		
	Pigs	<i>C. albicans</i>	Mucocutaneous candidiasis	Possibly immunosuppression due to viral infection (porcine circovirus 2)	

## Cryptococcosis

The genus *Cryptococcus* (teleomorph *Filobasidiella*) comprises basidiomycetous yeast species, most of which are environmental saprophytes that do not cause infections in human or animal.<sup>136</sup> The pathogenic agents of cryptococcosis are classified into two species, *C. neoformans* and *C. gattii*.<sup>137</sup> The species *C. neoformans* comprises two varieties, *C. neoformans* var. *grubii* and *C. neoformans* var. *neoformans*. The species *C. neoformans* consists of the VNI-VNIV and VNB molecular genotypes, comprising var. *grubii* (serotype A or VNI, VNII, and VNB strains), var. *neoformans* (serotype D or VN IV strains), and serotype AD strains (VNIII), which represents hybrids of the two varieties.<sup>138</sup> The species *C. gattii* is subdivided into two serotypes (B and C), and four molecular types VGI, VGII, VGIII, and VGIV varying in virulence, geographic distribution, and possibly susceptibility to antimycotic drugs.<sup>136,139</sup> Diseases caused by other *Cryptococcus* species, such as *Cryptococcus laurentii* and *Cryptococcus albidus*, have been reported infrequently and generally in immunocompromised hosts.<sup>140</sup>

The two species differ ecologically: *C. neoformans* was isolated primarily from bird droppings,<sup>141</sup> whereas *C. gattii* was associated with trees, primarily *Eucalyptus* species, initially in Australia,<sup>142,143</sup> where the importance of koalas feeding on these trees in perpetuating the yeast's persistence in the environment was suggested.<sup>144</sup> Subsequently, infections with *C. gattii* were reported in other regions as well.<sup>145</sup> In addition, differences are found in the population at risk: while *C. neoformans* infects primarily immune-compromised patients, *C. gattii* may affect people with intact immune systems.<sup>146</sup> A large outbreak of human and animal *C. gattii* infections that started in 2000 in Vancouver island have been seen during the following years. Molecular analysis of the isolates showed, however, that more than one type was involved.<sup>147</sup> Of note, identical genotypes were isolated from humans and animals including marine mammals and in the affected environment.<sup>147</sup>

*Cryptococcus neoformans* infections have been reported in a large variety of animals from lower invertebrates such as soil dwelling amoebae, nematodes, cockroaches, and mites, to higher mammals.<sup>145</sup> Cats are the most frequently infected animals with the involvement of the upper and/or lower respiratory tract, subcutaneous granulomata, and disseminated infections. Dogs may present with similar symptoms but central nervous system (CNS) involvement is more common.<sup>148</sup> Moreover, cryptococcosis has been reported causing mastitis in dairy animals<sup>149</sup> and respiratory infections in horses.<sup>150</sup>

*Cryptococcus gattii* was isolated from different animal species, including cats, dogs, marine mammals, ferrets, and

llamas in the regions affected by the outbreak that started in Vancouver Island and subsequently spread to the Pacific Northwest regions of the United States.<sup>151</sup> The upper respiratory tract infections and subcutaneous masses were the most frequent primary lesions, but in several cases the CNS, lymphatic tissue, lungs, oral cavity, and eyes were affected.<sup>152</sup> Among pets, a higher number of CNS involvement in dogs was found, whereas subcutaneous masses were shown more frequently in cats.<sup>153</sup> CNS involvement was associated with higher mortality rates. In addition, gastrointestinal infections in dogs have been reported.<sup>146</sup> Moreover, a disseminated canine infection with *C. neoformans* var. *grubii* was reported.<sup>153</sup> Surveys have shown that incidence of cryptococcosis does not increase in environment contaminated with bird dropping, including immunocompromised patients.<sup>154,155</sup> Nevertheless, molecular analysis indicated in some cases that human and environmental isolates were identical.<sup>156,157</sup>

About eight decades ago, Sangiorgi described the presence of *Cryptococcus* in the large mononuclear cells of liver and spleen of a rat (*Rattus norvegicus*).<sup>158</sup> Further, during their investigation about histoplasmosis, Emmons et al., in 1947 isolated *Cryptococcus* from mice and rats.<sup>159</sup> After a long gap, naturally acquired cryptococcosis was again reported, but this time in the greater bandicoot rat (*Bandicota indica*).<sup>160</sup> Pathological lesions were observed only in liver and lungs but other organs like kidneys, spleen, and brain were found positive for *Cryptococcus neoformans* var. *grubii*. Singh et al. also isolated *C. n. grubii* from animal's burrow and surrounding bamboo debris,<sup>160</sup> thus suggesting *B. indica* as a sentinel animal, which potentially amplified the pathogen in the environment.

Recently, a case cluster of cryptococcosis has been observed in a synanthropic Southeastern Asian murid (*Mus musculus castaneus*).<sup>161</sup> Unlike bandicoot rats, no lesions were recorded in any organ of the animals, however, *C. n. var. grubii* was recovered from cultures of tissue homogenates of brain, lungs, liver, and kidneys. The habitat soil and fresh feces of the animals were also positive for the fungus. It is interesting to note that, despite the presence of *Cryptococcus* in the central vein, neither liver nor any other organ exhibited pathological signs. Since the pathogen passes through the animal host without affecting it and all isolates recovered from *M. musculus* were weakly pathogenic to experimental mice, which define the status of *M. musculus* as passenger host for *C. n. var. grubii* in a more appropriate manner. It is noteworthy that in most of the cases, *Cryptococcus* yeasts have been isolated from apparently healthy rodents.

Of note, household rodents are nuisance animals and may serve as a continuous source of infection for humans

and their pets. On one hand, rodents especially rats and mice have expanded their geographic range dramatically and also have significantly extended the territory of harbored pathogens,<sup>162</sup> but on the other hand, they may play a role to prevent human cases acting as sentinel for the presence of *Cryptococcus* in the environment.<sup>163</sup> On the basis of degree of interaction between host and harbored pathogens, rodents may be termed as natural reservoirs, alternate hosts, sentinel animals, carriers, and passenger hosts.

### Infections due to melanized fungi

Several members of melanized fungi have been reported sporadically as causative agents of severe phaeohyphomycoses, chromoblastomycosis, and mycetoma in human and animals.<sup>164,165</sup> However, the potential pathogenicity of infections in crustaceans, captive and farmed fish, amphibians, aquarium animals, and other cold-blooded vertebrates has increasingly been recognized<sup>166–169</sup> (Table 2). In contrast, reports of infections in warm-blooded animals are relatively scant.<sup>170–172</sup> It has been hypothesized that cold blooded animals are more accessible to these fungi by their naked, wet skin, while other vertebrates are protected by fur or feathers.<sup>173</sup> In line with this suggestion, the only non-human vertebrate infections by *Chaetothyriales* are cases of encephalitis in cats and dogs, where the portal of entry is via inhalation and the texture of the skin is irrelevant.<sup>164</sup>

In vertebrates, two basic types of (sub)cutaneous infection are associated with black fungi: (i) those with yeast cells or hyphal elements in tissue leading to necrosis (phaeohyphomycosis)<sup>164</sup>; and (ii) those with muriform cells in tissue leading to host tissue proliferation (chromoblastomycosis).<sup>174</sup> The main types of systemic infections are disseminated—osteotropic or neurotropic—or single-organ; the main organs affected are lungs and brain. In cold-blooded animals such a classification is less apparent; most infections can be regarded as disseminated, while muriform cells have been reported in amphibians.<sup>175,176</sup>

Systemic phaeohyphomycosis occurs mainly in healthy and in debilitated vertebrates. Infections in crustaceans, captive and farmed fish, amphibians, aquarium animals, and other cold-blooded vertebrates have regularly been reported.<sup>164</sup> Susceptibility to infection may enhance due to transportation to adjacent basins, stress under aquarium conditions, environmental pollution, or environmental changes. Mesophilic and oligotrophic, waterborne *Exophiala* species commonly occur in low-nutrient drinking water, aquaria and fish nurseries<sup>173</sup> and may cause massive death upon stress of the animals. *Exophiala psychrophila* caused high mortality in farmed Atlantic salmon smolt (*Salmo salar*).<sup>177</sup> *Exophiala pisciphila* was associated with epizootics in cold-blooded vertebrates<sup>178</sup> and infections

in coastal smooth dogfish (*Mustelus canis*)<sup>179</sup> and marine potbelly seahorses (*Hippocampus abdominalis*). *Exophiala aquamarina* repeatedly caused disseminated infections in several species of fish.<sup>180</sup> *Exophiala equina*, originally isolated from limb infection in a horse<sup>181</sup>; however, it has been reported from disseminated infection in a Galapagos giant tortoise (*Geochelone nigra*).<sup>182</sup> The related species *E. cancerae*<sup>173,177</sup> was isolated from tissue of moribund mangrove crabs (*Ucides cordatus*) with Lethargic crab disease (LCD), causing extensive epizootic mortality along the Brazilian coast.<sup>168</sup> Occasional coinfection by another black yeast-like fungus, *Fonsecaea brasiliensis* has been described.<sup>183</sup>

Chromoblastomycosis has been mainly associated with humans.<sup>174</sup> However, several cases of subcutaneous infections have been reported in toads,<sup>184</sup> although the presence of typical muriform cells in the tissues were lacking<sup>174</sup>. Older reports of muriform cells in cold-blooded animals<sup>175,185</sup> need confirmation of the etiologic agent.

Members of the order *Pleosporales* have rarely been reported from animals. In the *Venturiales*, *Verruconis gallopava* has repeatedly been described from brain infections in birds. In the literature *Capnodiales* are represented by *Cladosporium* as reported agent of animal disease, but because of frequent occurrence of this genus as environmental contaminants such cases need additional molecular tests for credibility; none of the animal cases ascribed to *Cladosporium* has been proven by sequencing.<sup>164</sup>

## Endemic infections with indirect transmission from the environment

### Coccidioidomycosis

There are two distinct cryptic species within the genus *Coccidioides* (Ascomycota, Pezizomycotina, Eurotiomycetes, Onygenales, Onygenaceae): *Coccidioides immitis* and *C. posadasii*.<sup>186</sup> Both species are dimorphic fungi with an environmental saprotrophic phase and a host-associated parasitic phase. By definition, dimorphic fungi are defined by their temperature-dependent transition from a saprophytic mold to a parasitic yeast form upon transition into a mammalian host. Both *Coccidioides* species cause the disease coccidioidomycosis also referred to as San Joaquin Valley fever, valley fever, desert rheumatism, or “cocci/coccy.” Although a broad diversity of animals is susceptible to infection by *Coccidioides* species, severe or disseminated disease is mainly reported in pet dogs.<sup>187</sup>

### Histoplasmosis

*Histoplasma capsulatum* is a dimorphic fungus widely distributed in the tropical or subtropical areas of the world

**Table 2.** Diseases caused by black-yeasts and their filamentous relatives in animals.

Host species	Fungal species	Type of infection	
Class Eurotiomycetes, Order Chaetothyriales, Family Herpotrichiellaceae			
Invertebrates	Mussel shells ( <i>Bathymodiolus brevior</i> )	<i>Capronia moravica</i>	Disseminated infection
	Mangrove land crab ( <i>Ucides cordatus</i> )	<i>Exophiala cancerae</i>	Primary disseminated infection
	Earthworms ( <i>Octolasion tyrtaeus</i> )	<i>Exophiala jeanselmei</i>	Late embryonic stages of the earthworm naturally infected presenting healthy-appearing and necrotic eggs
	Worms ( <i>Eisenia foetida</i> )	<i>Exophiala jeanselmei</i>	cocoon albumen naturally infected with healthy-appearing and necrotic eggs
	Mangrove land crab ( <i>Ucides cordatus</i> )	<i>Fonsecaea brasiliensis</i>	Secondary disseminated infection
Amphibians	Toads, wild and captive frogs ( <i>Hyla caerulea</i> , <i>H. septentrionalis</i> , <i>Pternobylaf odiens</i> , <i>Phyllobates rinitatis</i> , <i>Rhacophorus</i> spp.)	<i>Fonsecaea pedrosoi</i> , <i>Fonsecaea</i> spp., <i>Rhinocladiella</i> spp., <i>Phialophora</i> spp.	Skin lesion and disseminated infection with neurological disorders and multifocal dermatitis; pigmented hyphae invaded multiple organs with mild cell necrosis and minimal inflammatory cell response
	Marine toad ( <i>Bufo marinus</i> ), Spadefoot toad ( <i>Scaphiopus holbrookii</i> )	<i>Fonsecaea</i> spp. <i>Phialophora</i> spp.	Phaeohyphomycosis: skin lesion and disseminated infection
	Frog ( <i>Bufo japonicus formosus</i> ) False tomato frogs ( <i>Dyscophus guineti</i> )	<i>Veronaea botryosa</i>	Disseminated infection
Reptiles	Galapagos tortoise ( <i>Geochelone nigra</i> )	<i>Exophiala equina</i>	Hematogenous dissemination
	Turtle	<i>Exophiala jeanselmei</i>	Disseminated infection
Fishes	Seadragons ( <i>Phyllopteryx taeniolatus</i> )	<i>Exophiala angulospora</i>	Disseminated infection
	Fish (Atlantic salmon; Channel catfish; smooth dogfish), Seahorse	<i>Exophiala pisciphila</i>	Disseminated infection
	Fish (Cutthroat trout Atlantic salmon)	<i>Exophiala salmonis</i>	Disseminated infection
	Fish (Siberian sturgeon: <i>Acipenser baerii</i> , <i>A. transmontanus</i> )	<i>Veronaea botryosa</i>	Disseminated infection
Mammals	Dog, leopard, alpaca	<i>Cladophialophora bantiana</i>	Skin lesion to disseminated infection
	Cat	<i>Cladophialophora bantiana</i> , <i>Exophiala attenuata</i> , <i>Exophiala spinifera</i> , <i>Fonsecaea multimorphosa</i> , <i>Phialophora verrucosa</i>	Skin lesion Skin lesion Phaeohyphomycosis Brain disseminated infection
	Horse	<i>Cladophialophora bantiana</i> , <i>Exophiala equina</i>	Phaeohyphomycosis with presence of skin ulcerative lesion
Class Eurotiomycetes, Order Venturiales, family Symptoventuriaceae			
Birds	Turkey, Chicken, gray-winged Trumpete, quail, owl	<i>Verruconis gallopava</i>	Encephalitis
Amphibians	Toad	<i>Ochroconis humicola</i>	Skin lesion
Reptiles	Tortoise	<i>Ochroconis humicola</i>	Cutaneous lesions
Fishes	Coho salmon, Atlantic salmon, rainbow trout, scorpion fish, walking catfish	<i>Ochroconis humicola</i>	Disseminated infection
	Fish ( <i>Chinook salmon</i> )	<i>Ochroconis tshawytschae</i>	Disseminated infection
Mammals	Cat	<i>Ochroconis gallopava</i>	Disseminated infection
Class Dothideomycetes, Order Capnodiales, family Davidiellaceae			
Mammals	Cat, dog, sheep	<i>Cladosporium</i> spp.	Disseminated infection
Class Dothideomycetes, Order Pleosporales, family Pleosporaceae			
Mammals	Cat, dog, horse	<i>Alternaria alternata</i>	Skin lesion

and infects numerous mammalian hosts. The population of *H. capsulatum* include three distinct subspecies determined by geographical distribution and clinical signs.<sup>188</sup> *Histoplasma capsulatum* var. *capsulatum* has a global dis-

tribution, causing pulmonary and systemic infections in a diversity of mammals, including humans. *Histoplasma capsulatum* var. *duboisii* is endemic/enzootic in western and central Africa, which causes lymphadenopathy, and

dissemination to the skin and bones, mainly in humans and other primates. *Histoplasma capsulatum* var. *farciminosum* affects the skin and the subcutaneous lymphatic system in equids (horses, donkeys, and mules) but has also been recovered from humans, dogs, cats, and badgers. Disease outcome is variable and depends on the immune status of the host, inoculum size, and the virulence of the isolate.<sup>189</sup>

### Paracoccidioidomycosis

Paracoccidioidomycosis is an endemic/enzootic mycosis acquired by airborne inhalation of infective conidia of *Paracoccidioides* spp. present in the environment.<sup>190,191</sup> The disease is caused by *Paracoccidioides brasiliensis* and *P. lutzii*, which are dimorphic fungi belonging to the Ajellomycetaceae.<sup>192</sup> Paracoccidioidomycosis is the major systemic mycosis in Latin American countries and ranks eighth among causes of human death from infectious and parasitic diseases in Brazil.<sup>193,194</sup> Naturally acquired Paracoccidioidomycosis has been reported in dogs<sup>194–195</sup> and armadillos.<sup>197</sup>

### Blastomycosis

Blastomycosis is a serious fungal disease of dogs, humans, and occasionally other mammals such as cats and horses caused by geographically restricted, thermally dimorphic fungus *Blastomyces dermatitidis*.<sup>198,199</sup> Blastomycosis is mainly common in dogs residing in or visiting enzootic areas.<sup>200</sup> The incidence of blastomycosis in dogs is 8–10 times that of humans,<sup>201</sup> presumably related to time spent outdoors, proximity to soil, and activities, such as digging, that may result in soil disturbances and increase conidial exposure. Most affected dogs are immunocompetent.<sup>202</sup>

## Infections due to zoophilic pathogens with near-direct transmission

### Chytridiomycosis

The amphibian fungal disease chytridiomycosis is a major infectious disease responsible for amphibian decline and one of the greatest fungal threats to frog and salamander (urodele amphibians) biodiversity.<sup>203</sup> This lethal skin disease is caused by members of the genus *Batrachochytrium*, chytridiomycetes belonging to the order *Rhizophydiales*. The first known etiologic agent of amphibian chytridiomycosis, *B. dendrobatidis* (*Bd*), was identified in 1998 and today causes disease in a wide variety of amphibian species across the three orders, that is, frogs and toads (*Anura*), salamandrines and newts (*Urodela*), and caecilians (*Gymnophiona*).<sup>204,205</sup> *Bd* has caused the rapid decline or

extinction of an estimated 200 amphibian species,<sup>206</sup> which is probably even an underestimation due to the cryptic behavior of many amphibians and the lack of monitoring.<sup>207</sup> The worldwide emergence of chytridiomycosis is mostly likely due to the rapid worldwide transmission of the virulent lineage ‘*Bd* Global Panzootic Lineage’ (*Bd*GPL).<sup>208</sup> *Bd*GPL has caused declines in Australia, Mesoamerica, North America, and Southern Europe. Determinants of host susceptibility, *Bd* strain virulence<sup>208</sup> and a conducive environment,<sup>209</sup> underpin pronounced differences in the outcome of exposure to *Bd*, which ranges from mass die-offs and population crashes over erratic or even lack of any observed mortality and host-pathogen coexistence.<sup>210</sup> Some host species are refractory to infection.<sup>211</sup>

A second chytrid species, *B. salamandrivorans* (*Bsal*) has recently emerged and has been causing mass mortality in fire salamandrines (*Salamandra salamandra*) in Belgium, the Netherlands, and Germany. This fungus is pathogenic for most western Palearctic salamandrine and newt taxa and is considered a major threat to the region’s biodiversity.<sup>212,213</sup> Salamandrines can be resistant (no infection, no disease), tolerant (infection in absence of disease), moderately susceptible (infection resulting in clinical disease with possibility of subsequent recovery), or highly susceptible (infection resulting in lethal disease). Infection experiments demonstrated that frogs and toads are not susceptible to *Bsal* but can act as infectious carriers.<sup>214</sup> *Bsal* is believed to have originated from Asia where it appears to be endemically present.<sup>212,215</sup>

For both (non-zoonotic) species the global trade in amphibians is considered a potent force in spreading novel virulent lineages into naive host populations. Long distance spread is most likely to have occurred due to movement of infected amphibians, particularly through the pet trade but also via accidental movement in the frog meat industry (although the latter is likely significant for ranaviruses, since most frog products are frozen).<sup>216</sup> The listing of *Bd* as an internationally notifiable disease by the OIE, with the aim to improve trade safety, represents the first disease that is listed solely because of a biodiversity concern. Although rigorous quarantine and surveillance protocols are, for example, in place for most livestock diseases, improved standards are needed for wildlife.<sup>217</sup>

Counteracting the impact of chytridiomycosis on amphibian populations remains a major challenge.<sup>218</sup> *Bsal* mitigation is further complicated by the production of encysted spores that remain infective for a long time and are resistant to predation.<sup>214</sup> Although immunization,<sup>219</sup> disinfection,<sup>220</sup> and the use of biocontrol with, for example, probiotics or predatory microorganisms,<sup>221,222</sup> may offer some perspectives for *in situ* mitigation, captive assurance

colonies of threatened amphibians currently offer the sole effective, be it last resort solution to prevent amphibian extinction due to chytrid infections.

### Bat white-nose syndrome

*Pseudogymnoascus destructans* (*Pd*) (formerly known as *Geomyces destructans*<sup>223,224</sup>) is the causative agent of white-nose syndrome of hibernating bats in Northeastern America.<sup>225,226</sup> Since its detection in 2006, it caused the worst mass mortality known in mammals with millions of dead bats. Formerly abundant bat species are now regionally extinct.<sup>227</sup>

The psychrophilic fungus *Pd* finds an ideal substrate in the skin of hibernating bats overwintering in cool and moist cavernous hibernacula, as they lower their body temperature to ambient temperature of 12–15°C. As the fungus ceases to grow at temperatures above 20°C,<sup>224</sup> *Pd* will neither be able to infect bats that are active in summer, nor other mammals or humans. The fungal growth mostly remains restricted to the outer skin, but in contrast to dermatophytes the fungus may invade deep into the dermis,<sup>228</sup> leading to severe erosive to ulcerative lesions, particularly on the wing membranes. Macroscopically, aerial hyphae appear as white powdery patches around muzzle and on wing membranes, but the histological diagnostic hallmark—mandatory for the confirmation of the disease—are cup-like epidermal erosions filled with fungal hyphae or their full thickness invasion of the wing membrane.<sup>228</sup> Microscopic evidence of disease are the distinctly asymmetrically curved conidia. In North America *Pd* infection is associated with aberrant hibernation behavior and a distinct increase in arousals from torpor bouts, a physiologic state lasting up to 15 days during which bats reduce metabolic activity and immune response to a minimum as well as lowering their body temperature to ambient degrees. The premature consumption of the stored energy by frequent activity phases is one of the presumed causes of death. Additionally, it is thought that the skin damages could result in a life-threatening imbalance in homeostasis leading to mortality.<sup>229,230</sup>

Since its discovery, *Pd* is spreading in a radial fashion from the index cave in New York State throughout the North American continent. Last year, *Pd* appeared across the Rocky Mountain barrier as the first hibernacula in Washington State tested positive for the fungus.<sup>231</sup> However, all isolates obtained from various affected American hibernacula show a genetic relationship of a single clonal genotype, highlighting that *Pd* seems a novel pathogen introduced into a naïve host population.<sup>232</sup> Currently, eight bat species are confirmed with *Pd* lesions in North America, and an additional six bat species at least carry the fungus.

Meanwhile, hibernating bats of 17 species from various parts of Europe were shown to carry the fungus with similar clinical appearance, but neither changes in hibernation behavior nor associated mortality have ever been found.<sup>233</sup> The reasons for these intercontinental differences are not clear, but European bats seem to resist the impact of the infection to a certain degree. Recent investigations in the phylogenetic relationships of *Pd* strains used microsatellites to reveal not only long time diversification of European fungus strains but also found Eurasia as the likely source of origin for the *Pd* clone occurring in North America.<sup>234</sup> Fungal conidia can easily be harvested from affected bats as well as from hibernacula walls,<sup>233</sup> and the accidental transport of *Pd* from Europe via contaminated gear or clothing is the favored hypothesis for the emergence of *Pd* in North America. However, the main transmission of fungal spores seems to be bat-to-bat contacts and *Pd* infection will remain an ongoing threat for hibernating North American bats. As long as the fungus can spread further to unaffected populations, it will result in sinister consequences for biodiversity and the ecological and economical services provided by bats to mankind.<sup>235</sup>

### Zoonotic outbreaks with direct animal to human transmission

According to the official definition from the World Health Organization, zoonoses are diseases and infections that are naturally transmitted between vertebrate animals and humans (and *vice versa*). Among transmissible fungal pathogens, a few species should be considered as zoonotic (Table 3).

#### *Microsporium canis* from cats

Cats are becoming increasingly popular as pet and companion animals. Tens of thousands of European crossbred cats are abandoned each year and can be adopted for almost free from animal shelters. It is also fashionable to purchase expensive purebred cats from breeding units. In both cases, animals are acquired from communities and may be affected, visibly or not, by diseases that are transmissible to humans. Dermatophytosis caused by *Microsporium canis* is probably the most prevalent zoonosis that may occur in such situations.<sup>236</sup> In shelters, rapid turnover of cats of unknown status, promiscuity, and economic constraints for healthcare increase risks of contagion. In breeding units, *M. canis* is commonly enzootic, and appropriate antifungal treatments are either absent or incomplete. Asymptomatic carriage is frequent, cats being infected without obvious clinical signs.<sup>237</sup>

**Table 3.** Main fungal species responsible for zoonoses.

Fungal species	Distribution	Main reservoirs of fungal pathogens	Mode of transmission to humans	Human disease
<b>Zoophilic dermatophytes</b>				
<i>Microsporium canis</i>	Worldwide	Cats, dogs, rabbits	Direct contact with arthroconidia (formed on the skin of infected animals)	Dermatophytosis (tinea corporis or capitis)
<i>Trichophyton mentagrophytes</i>	Worldwide	Rodents, rabbits		
<i>Trichophyton benhamiae</i>	Worldwide	Rodents (Guinea-pigs for the <i>lutea</i> variety)		
<i>Trichophyton verrucosum</i>	Worldwide	Cattle		
<i>Nannizzia (Microsporium) persicolor</i>	Worldwide	Rodents, soil		
<i>Trichophyton erinacei</i>	Worldwide	Hedgehogs		
<b>Microsporidia</b>				
<i>Encephalitozoon cuniculi</i>	Worldwide	Rabbits	Ingestion of fungal spores (shed in the urine of rabbits)	Encephalitozoonosis (neurological signs, systemic disease)
<i>Encephalitozoon hellem</i>	Worldwide	Birds (Psittacidae)	Inhalation of fungal spores? Ocular contact	Encephalitozoonosis (respiratory signs, systemic disease)
<i>Encephalitozoon intestinalis</i>	Worldwide	Cattle, goats, pigs...	Ingestion of fungal spores (shed in the feces of infected animals)	Encephalitozoonosis (digestive signs, systemic disease)
<i>Enterocytozoon bieneusi</i> (many genotypes)	Worldwide	Many mammals	Ingestion of fungal spores (shed in the feces of infected animals)	Encephalitozoonosis (digestive or respiratory signs)
<b>Dimorphic fungi</b>				
<i>Histoplasma capsulatum capsulatum</i>	Worldwide	Soil, bats	Inhalation of fungal spores	Histoplasmosis
<i>Sporothrix schenckii</i>	Worldwide (but more frequent in tropical countries)	Soil, different mammals	Traumatic inoculation of contaminated soil, plants, and organic matter into skin or mucosa	Sporotrichosis
<i>Sporothrix brasiliensis</i>	Brazil	Cats	Scratches or bites from infected cats	

Cats may be sold while still receiving antifungal, so that they are still infected and contagious for congeners and humans at the time of purchase. *Microsporium canis* infection in cats may be highly polymorphic. This interferes with diagnosis and treatment of feline dermatophytosis.<sup>238</sup> Efficient vaccines against feline dermatophytosis are currently unavailable, partly due to a lack of knowledge on virulence factors. The keratinolytic secreted proteases were thought to be the most likely factors of dermatophyte's pathogenicity, due to peculiar ability of dermatophytes to use hard keratin *in vivo* as a growth substrate.<sup>239</sup> The enzymes were therefore purified from culture supernatants produced *in vitro* in media enriched by keratin. Subsequent characterization at the gene level and com-

plete sequencing of several dermatophyte genomes revealed several exo- and endoproteases, some of them belonging to large, expanded gene families.<sup>240</sup> These virulence genes are candidates for the development of vaccines. As an example, an *M. canis* 31.5 kDa keratinolytic protease, later called Sub3, was highly expressed by the fungus grown *in vitro* in the presence of feline keratin and *in vivo* in naturally infected cats,<sup>241</sup> and experimentally infected guinea pigs.<sup>242</sup>

Using RNA silencing,<sup>243</sup> and a sophisticated model of *in vitro* reconstructed feline epidermis,<sup>244</sup> and *ex vivo* models of human or animal epidermis, Sub3 was shown to contribute to the adherence of *M. canis* to host tissue. However, Sub3 is not required for the invasion of keratinized

structures *in vivo*.<sup>245</sup> Putative virulence factors involved in tissue invasion remain to be identified. This could be achieved by comparing *in vivo* and *in vitro* transcriptomes and secretomes, as used for *Trichophyton rubrum* and *T. benhamiae*.<sup>246,247</sup> The importance of newly discovered putative virulence factors could be tested by manipulation of dermatophyte genomes by gene knock-outs,<sup>248</sup> combined with pertinent animal models of dermatophytosis.<sup>249</sup>

### Infection due to *Sporothrix brasiliensis* from cats

Recent improvements in the taxonomy of *Sporothrix* led to the recognition of a clinically relevant clade comprising four dimorphic species *S. brasiliensis*, *S. schenckii*, *S. globosa*, and *S. luriei*, remote from environmental clades that included *S. chilensis*, *S. pallida*, and *S. mexicana* causing occasional infections.<sup>250,251</sup> Species from clinical clade show different virulence profiles, antifungal susceptibilities and geographical distributions.<sup>252</sup>

The classical route of transmission for humans and animals involves trauma with soil and plant materials. However, epidemics driven by *S. brasiliensis* usually occur as a result of animal-animal or animal-human transmission in an alternative route.<sup>253</sup> Remarkably, the largest epizootic due to *S. brasiliensis* among felines that lead to massive zoonotic transmission has been reported in the South and Southeast regions of Brazil since the 1990 s.<sup>254</sup> Initially, in Rio de Janeiro state during 1998–2003, 497 humans and 1056 cats were diagnosed with positive culture. Among these humans, 67.4% related scratch or bite from cats with sporotrichosis; 68% were women with mean age of 39 years old.<sup>255</sup> From 2005 to 2011, the total number of cats assisted at the national institute of infectology, Oswaldo Cruz foundation (IPEC/FIOCRUZ) was 2301. The median age of affected cats was 2 years old, and the median time between the observation of the lesions and to take to veterinary assistance was 8 weeks.<sup>256</sup> The most recent surveys indicate that about 244 dogs and 4703 cats were diagnosed through 2015 at IPEC/FIOCRUZ, characterizing the state of Rio de Janeiro as hyperendemic for feline sporotrichosis.<sup>254</sup>

Feline sporotrichosis has also been reported in São Paulo and Rio Grande do Sul states, with a distribution of 190 and 129 cats, respectively.<sup>257,258</sup> However, the number of affected cats may be underestimated, since sporotrichosis is not a notifiable disease. To understand the epidemic scenario caused by *S. brasiliensis* it is necessary to consider some aspects of the host-pathogen-environment interplay, such as the high susceptibility of cats to the fungal species; the high virulence of *S. brasiliensis* circulating during epidemics associated to a recent introduction of the pathogen in an urban feline population. Some characteristics of cat's behavior may be also taken into account, such as toileting

**Table 4.** The most common fungal species producing mycotoxins.

Mycotoxin	Fungal species
Aflatoxins	<i>Aspergillus flavus</i> , <i>A. parasiticus</i> , <i>A. nomius</i> , <i>A. argenticus</i> , etc.
Ochratoxin A	<i>Penicillium verrucosum</i> , <i>P. nordicum</i> , <i>A. ochraceus</i> , <i>A. carbonarius</i> , <i>A. niger</i> , <i>A. sclerotiumniger</i>
Deoxynivalenol	<i>Fusarium graminearum</i> , <i>F. culmorum</i> , <i>F. sporotrichioides</i> , <i>F. poae</i> , <i>F. tricinctum</i>
T-2 toxin	<i>F. sporotrichioides</i> , <i>F. poae</i>
Diacetoxyscirpenol	<i>F. graminearum</i> , <i>F. semitectum</i> , <i>F. tricinctum</i> , <i>F. oxysporum</i> , etc.
Nivalenol	<i>Fusarium nivale</i> , <i>F. poae</i>
Zearalenone	<i>Fusarium graminearum</i> , <i>F. culmorum</i>
Fumonisin B1	<i>Fusarium proliferatum</i> , <i>F. verticillioides</i> (syn. <i>F. moniliforme</i> ), <i>A. niger</i> , <i>A. carbonarius</i>

habits in contact with soil, sharpening the nails in environment, behavior during mating, and territorial disputes that frequently leads to scratches or bites spreading the fungus to other hosts.<sup>259,260</sup>

### Mycotoxins and mycotoxicoses

Mycotoxins are defined as the chemicals of fungal origin being toxic for (warm-blooded) vertebrates.<sup>261,262</sup> Mycotoxins are secondary metabolites produced during consecutive enzyme reactions via several biochemically simple intermediary products from the primary metabolism of acetates, mevalonates, malonite, and some amino acids.<sup>263</sup>

The contamination of foods and animal feeds with mycotoxins is a worldwide problem, and formation of mycotoxins by many important phytopathogenic and food spoilage fungi is undoubtedly one of the most significant risk factors to mammalian health.<sup>264</sup> Mycotoxins are categorized by fungal species, structure, and (or) mode of action. As shown in Table 4, a single species of fungi may produce one or several mycotoxins and individual mycotoxins may be produced by different fungal species.<sup>265,266</sup> Aflatoxins, ochratoxins, trichothecenes, zearalenone, fumonisins, tremorgenic toxins, and ergot alkaloids are main mycotoxins of public health and agro-economic importance.

Mycotoxins cause intoxications in both animals and humans, resulting in severe diseases called acute or chronic mycotoxicoses,<sup>267</sup> depending on species and susceptibility of the host. It is also believed that with a mycosis, mycotoxins produced by the invading fungi can suppress immunity, therefore increasing the infectivity of the fungus.<sup>268</sup> Acute mycotoxicoses have a rapid onset and an obvious toxic response, while the most frequent type of mycotoxicoses occurs after the long-lasting exposure of an

**Table 5.** General toxic effects of the most common mycotoxins.

Toxicity	Mycotoxins
Dermatotoxic	Trichothecenes, verrucarins, sporidesmins
Estrogenic	Zearalenone
Genotoxic	Aflatoxins, sterigmatocystin, ochratoxin A, zearalenone, patulin, trichothecenes
Hematotoxic	Aflatoxins, ochratoxin A, zearalenone, trichothecenes
Hepatotoxic	Aflatoxins, ochratoxins, rubratoxins, sterigmatocystin etc.
Immunotoxic	Aflatoxins, ochratoxin A, trichothecenes, patulin
Nephrotoxic	Ochratoxin A
Neurotoxic	Fumonisin, penitrem A, fumitremorgens
Gastrotoxic	Trichothecenes

animal/human to low dosages of the toxin(s).<sup>269</sup> The negative effects of mycotoxins on various animals have been extensively described in the literature (Table 5). In poultry farms, contaminated feeds with aflatoxins to broilers causes negative metabolic responses and enzyme activity resulting reduced body weight gain, and tissue necrosis.<sup>270</sup> In dogs, ingestion of a variety of mouldy foods, including grains, walnuts, almonds, and peanuts, as well as nonspecific garbage, has been associated with tremorgenic mycotoxicosis. Dogs are more commonly affected than other species of domestic animals, probably because of their tendency to scavenge; intoxication of several dogs within the same household has also been reported. The most common sources of tremorgenic mycotoxins are fungi of the genus *Penicillium*.<sup>271</sup> Ruminants such as cattle, sheep, goats, and deer are generally resistant to the direct adverse effects of mycotoxins, which appear to be due to capability of rumen's microbiota to degrade mycotoxins.<sup>272</sup> However, bovine production (milk, beef, or wool), reproduction, and growth can be altered when ruminants consume mycotoxin-contaminated feed for extended periods of time.<sup>273</sup> Negative effects of the mycotoxins have been also documented on the pig's reproductive function.<sup>274</sup>

From the public health perspectives, mycotoxins are considered as endogenous contaminants, that is, formed directly in the matrix by toxic mycobiota. The mycotoxins of most concern from a food safety perspective include the aflatoxins (B1, B2, G1, G2, and M1), ochratoxin A, patulin, and toxins produced by *Fusarium* moulds, including fumonisins (B1, B2, and B3), trichothecenes (principally nivalenol, deoxynivalenol, T-2 and HT-2 toxin) and zearalenone. If edible animals are fed by mouldy materials containing certain mycotoxins, those are either converted into other toxic substances or are accumulating in their products (milk, eggs) or directly in the viscera, muscles dedicated

for human consumption.<sup>9</sup> Given the frequent consumption of milk and dairy products particularly by infants, mycotoxins are an issue of considerable importance to public health.<sup>265</sup> Aflatoxins and ochratoxins are the most toxic products and have been shown to be genotoxic, that is, can damage DNA and cause cancer in animal species. By their structure, aflatoxins are difuranocoumarol lactons, recently known in about 20 derivatives. Aflatoxins B1, B2, G1, and G2 are the most frequent one, with the toxicity decreasing in the row AFB1 > AFG1 > AFB2 > AFG2. AFB1 is the most potential proven human carcinogen (IARC class I) of biological origin, and its metabolite AFM1 proved the same toxicity, with hepatocells being the target structures of the action.<sup>265</sup> Ochratoxins are polyketid derivatives of dihydroisocoumarin including ochratoxin A (OTA, the most toxic), B, C (ethylester OTA), and D. The sources include barley, ray, oat, wheat, rice, maize, beer, coffee, tea, wine/ raisins, spices, and porcine products (meat, viscera) and other meat and meat products of nonruminant animals exposed to feedstuffs contaminated with this type of mycotoxin. Ruminants such as cows and sheep are generally resistant to the effects of ochratoxin A due to hydrolysis to the nontoxic metabolites by protozoa in the reticulorumen sac before absorption into the blood.<sup>275</sup> Importantly, OTA in urine was found to be a better indicator of OTA consumption than OTA in plasma. Low blood serum/plasma concentrations of OTA have been reported for healthy persons in many countries.<sup>276</sup>

The European Food Safety Authority (EFSA) has carried out risk assessments on certain mycotoxins in animal feed that are considered to pose a potential risk to human or animal health including aflatoxin B1, deoxynivalenol, zearalenone, ochratoxin A, fumonisins, and T-2 and HT-2. Each of the recommendations has been used as a basis for the current legislative controls on these mycotoxins. The maximum permitted levels (MPLs) for substances that are present in, or on, animal feed that pose a potential danger to animal or human health or to the environment, or could adversely affect livestock production are summarized in Table 6.

### Antifungal resistance in animals with fungal infections

Many of the antifungal agents that are used in humans are also used in animals for the treatment of invasive fungal infections. These can include the polyenes (e.g., amphotericin B and nystatin), the azoles, including both the imidazoles and triazoles, the allylamines (e.g., terbinafine), and the echinocandins. Table 7 summarizes the uses of various antifungals that have proved successfully in various animal species.

**Table 6.** The European Food Safety Authority (EFSA) maximum permitted levels for six mycotoxins in animal feed that are considered to pose a potential risk to human or animal health (Directive 2003/100/EC, amending Directive 2002/3 and Recommendation 2006/576/EC).

	Products intended for animal feed	Maximum content in mg/kg (ppm) relative to a feedingstuff with a moisture content of 12%
<b>Aflatoxin B1</b>	All feed materials	0.02
	Complete feedingstuffs for cattle, sheep and goats with the exception of:	0.02
	- complete feedingstuffs for dairy animals	0.005
	- complete feedingstuffs for calves and lambs	0.01
	Complete feedingstuffs for pigs and poultry (except young animals)	0.02
	Other complete feedingstuffs	0.01
	Complementary feedingstuffs for cattle, sheep and goats (except complementary feedingstuffs for dairy animals, calves and lambs)	0.02
	Complementary feedingstuffs for pigs and poultry (except young animals)	0.02
	Other complementary feedingstuffs	0.005
<b>Deoxynivalenol</b>	Feed materials	
	- cereals and cereal products with the exception of maize by-products	8
	- maize by-products	12
	Complementary and complete feedingstuffs with the exception of:	5
	- complementary and complete feedingstuffs for pigs	0.9
- complementary and complete feedingstuffs for calves (< 4 months), lambs and kids	2	
<b>Zearalenone</b>	Feed materials	
	- cereals and cereal products with the exception of maize by-products	2
	- maize by-products	3
	Complementary and complete feedingstuffs	
	- complementary and complete feedingstuffs for piglets and gilts (young sows)	0.1
	- complementary and complete feedingstuffs for sows and fattening pigs	0.25
- complementary and complete feedingstuffs for calves, dairy cattle, sheep (including lambs) and goats (including kids)	0.5	
<b>Ochratoxin A</b>	Feed materials	
	- cereals and cereal products	0.25
	Complementary and complete feedingstuffs	
	- complementary and complete feedingstuffs for pigs	0.05
- complementary and complete feedingstuffs for poultry	0.1	
<b>Fumonisin B1 and B2</b>	Feed materials	
	- maize and maize products	60
	Complementary and complete feedingstuffs for:	
	- pigs, horses (Equidae), rabbits and pet animals	5
	- fish	10
- poultry, calves (<4 months), lambs and kids	20	
<b>T-2 and HT-2</b>	Compound feed for cats	0.05

### Mechanisms of antifungal resistance

Resistance to antifungal drugs can occur through various mechanisms. These can include: (1) nonsynonymous point mutations within the gene encoding the target enzyme leading to alterations in the amino acid sequence, (2) increased expression of the target enzyme through increased tran-

scription of the gene encoding it, (3) decreased concentrations of the drug within the fungal cells due to drug efflux, (4) changes in the biosynthetic pathway resulting in reduced production of the target of the antifungal drugs. For the azoles, each of these mechanisms have been associated with reduced susceptibility in *Candida albicans*, and several are

**Table 7.** Recommended indications of antifungals in veterinary practice. Adapted from reference no. 309 with the permission of authors.

Antifungal agent	Animal species	Indications	
Systemic	Amphotericin B	Birds	Aspergillosis, Candidiasis
		Dogs	Aspergillosis, Cryptococcosis, Blastomycosis, Histoplasmosis, Coccidioidomycosis, Mucormycosis
		Cats	Aspergillosis, Cryptococcosis, Blastomycosis, Histoplasmosis, Coccidioidomycosis, Mucormycosis
		Horses	Aspergillosis, Candidiasis, Histoplasmosis, Coccidioidomycosis, Sporotrichosis, Mucormycosis
	Nystatin	Birds	Candidiasis of the gastrointestinal tract
	Terbinafine	Dogs	Cryptococcosis, Sporotrichosis, Dermatophytosis and <i>Malassezia</i> dermatitis
		Cats	Cryptococcosis, Sporotrichosis, Dermatophytosis
	Ketoconazole	Birds	Aspergillosis, Candidiasis
		Dogs	Blastomycosis, Histoplasmosis, Cryptococcosis, Coccidioidomycosis, Sporotrichosis, <i>Malassezia</i> dermatitis and Dermatophytosis
		Cats	Blastomycosis, Histoplasmosis, Cryptococcosis, Coccidioidomycosis, Sporotrichosis, Dermatophytosis
	Parconazole	Birds (guinea fowl)	Candidiasis (trush)
	Fluconazole	Birds	Candidiasis
		Dogs	Cryptococcosis, Blastomycosis, Aspergillosis (nasal)
		Cats	Aspergillosis (CNS infection), Cryptococcosis, Blastomycosis, Coccidioidomycosis
	Itraconazole	Birds	Aspergillosis, Candidiasis
		Dogs	Aspergillosis, Blastomycosis, Histoplasmosis, Cryptococcosis, Coccidioidomycosis, Sporotrichosis, Dermatophytosis and <i>Malassezia</i> dermatitis
		Cats	Dermatophytosis
			Aspergillosis, Sporotrichosis, Cryptococcosis, Blastomycosis, Histoplasmosis, Phaeohiphomycosis
		Horses	Aspergillosis, Coccidioidomycosis, Mycotic keratitis, Dermatophytosis
	Voriconazole	Rodents, rabbits and fur animals	Dermatophytosis
		Birds	Aspergillosis
		Dogs	Aspergillosis, Scedosporiosis
		Cats	Aspergillosis
		Horses	Aspergillosis (systemic), <i>Aspergillus</i> keratitis
		Dogs	Aspergillosis, Mucormycosis
	Posaconazole	Cats	Aspergillosis, Mucormycosis
Cats		Cryptococcosis	
Flucytosine	Dogs	Dermatophytosis	
	Cats	Dermatophytosis	
	Horses	Dermatophytosis, Sporotrichosis	
	Ruminants	Dermatophytosis	
	Rodents, rabbits and fur animals	Dermatophytosis	
Griseofulvin	Dogs	Dermatophytosis	
	Cats	Dermatophytosis	
Topical	Clotrimazole	Birds (Raptors)	Aspergillosis
		Dogs	Aspergillosis, Dermatophytosis and <i>Malassezia</i> dermatitis
		Cats	Aspergillosis, Dermatophytosis
		Rodents, rabbits and fur animals	Dermatophytosis
	Miconazole	Birds	Aspergillosis
		Dogs	<i>Malassezia</i> dermatitis
		Cats	Dermatophytosis, <i>Malassezia</i> dermatitis
		Rodents, rabbits and fur animals	Dermatophytosis
	Enilconazole	Birds	Aspergillosis
		Dogs	Disinfection ( <i>Aspergillus</i> and other pathogenic fungi)
			Dermatophytosis, <i>Malassezia</i> dermatitis
		Cats	Aspergillosis
			Dermatophytosis, <i>Malassezia</i> dermatitis
		Horses	Aspergillosis
		Ruminants	Dermatophytosis
	Rodents, rabbits and fur animals	Disinfection (dermatophytes and other pathogenic fungi)	
Natamycin	Horses	Dermatophytosis	
	Ruminants	Dermatophytosis	
Thiabendazole	Birds	Disinfection	
	Horses	Dermatophytosis	
	Ruminants	Dermatophytosis	
	Rodents, rabbits and fur animals	Dermatophytosis	

associated with resistance in other *Candida* species. Alterations in the target enzyme (lanosterol 14- $\alpha$ -demethylase) due to point mutations in the encoding gene *ERG11* leads to decreased susceptibilities to the azoles.<sup>277–289</sup> Overexpression of the *CDR1*, *CDR2*, and *MDR1* genes that encode for efflux pumps leads to azole resistance.<sup>290,291</sup> Azole resistance has also been documented in *A. fumigatus* and is due to point mutations within the *CYP51A* gene that encodes the enzyme responsible for converting lanosterol to ergosterol.<sup>292–294</sup> In isolates with environmental exposure to the azoles tandem repeats in the promoter region along with along with point mutations in the gene (e.g., TR<sub>34</sub>/L98H and TR<sub>46</sub>/Y121F/T289A) have been found and cause increased expression of *CYP51A*.<sup>295</sup>

### Reports of antifungal resistance in different animal species

Several studies have analyzed fungal isolates from different animals for resistance to antimycotic agents, and many of them reported surprisingly high levels of azole resistance in yeasts. In a retrospective study, Beltaire et al. analyzed fungal strains isolated from equine uteri collected between 1999 and 2011 and showed resistance rates of 19% and 2% for itraconazole and fluconazole, respectively.<sup>296</sup> Cordeiro et al. investigated 59 *C. tropicalis* isolates predominantly derived from healthy animals and found resistance to fluconazole and/or itraconazole in 50%, whereas all isolates were susceptible to caspofungin and amphotericin B.<sup>297</sup> Using the same microbroth dilution assay, Brilhante et al. analyzed *Candida* isolates from the nasolacrimal duct of healthy horses and found that 40% of the *C. tropicalis* isolates were resistant to fluconazole and itraconazole.<sup>298</sup> The same group found high rates of fluconazole and itraconazole resistance also for *Candida* isolates from rheas and cockatiels,<sup>299,300</sup> and efflux pumps were a major resistance mechanism.<sup>301</sup> Using a commercial kit covering eleven commonly used agents, Lord et al. tested 144 *Candida*, *Cryptococcus*, *Rhodotorula*, and *Trichosporon* isolates from bird feces for antifungal resistance.<sup>302</sup> They reported that 45.8% of the strains were resistant to at least four of the 11 drugs, and 18.1% were resistant to all antifungals tested. A recent study found similar resistant levels for 111 *C. glabrata* isolates from the feces of sea gulls and 79 *C. glabrata* isolates from human patients, while other have reported only moderate azole resistance in *Candida* strains isolated from raptors.<sup>303,304</sup> These studies indicate that resistance to certain azoles is a common phenomenon in pathogenic yeasts isolated from some animals. Strikingly, the azole resistance rates of *C. albicans* and *C. tropicalis* isolated from healthy animals are higher than those reported in some studies in

humans.<sup>305,306</sup> This indicates that the elevated resistance levels found in animals may not simply reflect a natural resistance of the respective species. However, differences in the methodology and breakpoints used, as well as the limited number of isolates included in several animal studies make a direct comparison of data obtained for animal and human isolates difficult.

Azole resistance has also been described for *Aspergillus*,<sup>292</sup> but up to now reports of resistant strains derived from animals are sparse. Acquisition of azole resistance can occur under prolonged therapy. Clinically, invasive infections caused by azole-resistant *A. fumigatus* are challenging to treat due to the lack of therapeutic options. In humans, lipid formulations of amphotericin B can be used, and 5-flucytosine has also been recommended to be added to other therapies in patients with central nervous system infections caused by resistant isolates.<sup>307</sup> However, both antifungals have limitations, including toxicities, which may prohibit their long-term use in both humans and animals. Depending on the mechanism of resistance, higher doses of certain triazoles may be attempted, and there is a recent report of the successful treatment of invasive aspergillosis caused by an *A. fumigatus* isolate harboring a TR<sub>46</sub>/Y121F/T289A mutation in a bottlenose dolphin with high dose posaconazole.<sup>308</sup> Here, the oral solution of posaconazole was incorporated into gelatin capsules and administered with a goal of achieving trough concentrations of >3 mg/l, which was achieved after prolonged administration and resulted in clinical improvement.

Fungi that cause disease in humans can also cause serious infections in different animal species, associated with significant morbidity and mortality. Examples of invasive mycoses in animals include infections caused by non-transmissible opportunistic fungi (aspergillosis, mucormycosis, candidiasis, cryptococcosis, and infections caused by melanized fungi, endemic environmental pathogens (coccidioidomycosis, histoplasmosis, paracoccidioidomycosis, and blastomycosis), zoophilic fungal pathogens (chytridiomycosis and Bat White-nose syndrome). The list of zoonotic fungal agents (transmissible mycoses) is limited, however some of species (like *Microsporium canis* and *Sporothrix brasiliensis* from cats) have a strong public health impact. The fungal secondary metabolites 'mycotoxins' have been associated with severe toxic effects to vertebrates. Mycotoxins are also a major concern for public health. Majority of antifungal agents including the polyenes, the azoles, and the echinocandins that are used in humans are also used in animals for the treatment of fungal infections. Similarly, many limitations also occur in some animal species, including variable pharmacokinetics, adverse effects, drug interactions, and antifungal resistance.

## Declaration of interest

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