

Parasitic, fungal and prion zoonoses: an expanding universe of candidates for human disease

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Abstract

Zoonotic infections have emerged as a burden for millions of people in recent years, owing to re-emerging or novel pathogens often causing outbreaks in the developing world in the presence of inadequate public health infrastructure. Among zoonotic infections, those caused by parasitic pathogens are the ones that affect millions of humans worldwide, who are also at risk of developing chronic disease. The present review discusses the global effect of protozoan pathogens such as *Leishmania* sp., *Trypanosoma* sp., and *Toxoplasma* sp., as well as helminthic pathogens such as *Echinococcus* sp., *Fasciola* sp., and *Trichinella* sp. The zoonotic aspects of agents that are not essentially zoonotic are also discussed. The review further focuses on the zoonotic dynamics of fungal pathogens and prion diseases as observed in recent years, in an evolving environment in which novel patient target groups have developed for agents that were previously considered to be obscure or of minimal significance.

Keywords: Emerging infections, fungi, parasites, prion, review, zoonoses

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Zoonotic infections are defined as diseases that can be transmitted from vertebrate animals to humans and vice versa, a definition that encompasses different means of transmission: vector-borne, waterborne, foodborne, through direct contact, or with the animal host serving as a pathogen reservoir that allows for infestation of the human environment, e.g. soil in cases of infections that could be subclassified as sapro-zoonoses [1].

The recent recognition of the so-called neglected tropical diseases [2] has shed light on 13 infections of major morbidity burden, localized predominantly in the developing world: the majority of these infections are zoonotic, either in essence or technically, and the vast majority of them are parasitic in nature. However, beyond these infections, there are numerous other zoonotic protozoan, helminthic and fungal pathogens that directly or indirectly bridge human and animal pathology, or, depending on the agent, human pathology and animal vector ecology. A 2001 effort by Taylor *et al.* [3] to list all potentially zoonotic agents concluded that the majority of human pathogens are zoonotic. The particular pathogen list included numerous obscure agents for which demonstration of infectivity for humans or zoonotic background might be marginal;

however, the list included an extensive array of significant infectious diseases, a list that is likely to expand in the future as novel human immunocompromised populations are affected. Moreover, the recognition of the potential of bovine spongiform encephalopathy (BSE) to cause human disease added another category to the list of zoonoses, that of prion diseases. Although prions cannot strictly be considered to be infectious agents, as they are not pathogens as such, BSE possesses all the typical characteristics of a zoonotic infection. The present review focuses on parasitic, fungal and prion zoonoses, discusses the true zoonotic nature of the clinically significant ones among them and their correlations, and focuses on the enormous burden of disease that they cause, both in the developing world and in the world in general.

Zoonotic Parasites

Table I shows clinically significant zoonotic protozoan infections. The majority of helminthic species are technically zoonotic, excluding *Taenia solium* and *Taenia saginata*, *Brugia* spp. (although *Brugia malayi* may possess a significant zoonotic

TABLE 1. Clinically significant protozoan zoonoses

Pathogen	Comments
<i>Babesia</i> sp.	Babesiosis is possibly under-recognized, owing to misdiagnosis as malaria in certain areas with limited diagnostic facilities
<i>Balantidium coli</i>	High seroprevalence, related to pigs, in certain endemic areas, such as the Philippines, the Western Pacific (location of a recent outbreak), and Latin America. However, it induces minor disease [5]
<i>Blastocystis hominis</i>	Of unknown prevalence, as asymptomatic carriage may be included; however, the zoonotic impact on human disease transmission unknown. The theory of correlation with irritable bowel syndrome adds further importance to the pathogen [6]
<i>Cryptosporidium parvum</i>	Limited, but demonstrated, zoonotic aspects of human infection [7]. The absence of further subtyping of isolates implicated in certain outbreaks precludes evaluation of the extent of zoonotic transmission, although certain of these outbreaks have a definite correlation with improper practices of cattle farming [8]
<i>Giardia lamblia</i>	Limited, but existing, zoonotic (compared to human) contamination as source of human infection [7,8]
<i>Leishmania</i> spp.	The WHO estimates that 1.5 million cases of cutaneous leishmaniasis and 500 000 of visceral leishmaniasis occur annually. The majority (almost 90%) of visceral leishmaniasis cases are observed in Bangladesh, India, Nepal, Brazil, and Sudan; the latter, as of November 2010, is the location of a massive outbreak [9]
<i>Plasmodium knowlesi</i>	Possibly the commonest cause of malaria in Southeast Asia, Malaysia in particular, transmitted partly from macaques to humans [10]
<i>Toxoplasma gondii</i>	Re-emerging because of the disease caused in HIV patients and expanding recognition of consequences in pregnancy. Seroprevalence and disease burden are related to numerous socio-economic/religious factors [11]
<i>Trypanosoma brucei</i>	<i>Trypanosoma brucei rhodesiense</i> is the zoonotic agent, although accounting for a small percentage of the African trypanosomiasis burden, located in Tanzania, Uganda, Malawi, and Zambia; elimination efforts have been less successful than for <i>T. brucei gambiense</i> [12]
<i>Trypanosoma cruzi</i>	The zoonotic, sylvatic or domestic, parameter of human transmission is disproportionate to the enormous burden of disease, in terms of sheer numbers of infected persons, chronic sequelae and mortality, and importation to the USA and Europe through immigration

HIV, human immunodeficiency virus.

reservoir), *Onchocerca volvulus* and *Trichuris trichiura* (although both are defined as zoonotic in the Taylor list [3]), and *Wuchereria* spp. Among the numerous remaining helminths, however, some have only marginally zoonotic life cycles, and others cause human disease of limited significance. *Dracunculus medinensis*, causing dracunculiasis, is an example of the former: its potential zoonotic reservoir has not been persuasively demonstrated [4], and the successful eradication campaign without any pure zoonotic-related interventions argues against the characterization of the disease as zoonotic. *Enterobius* sp. is another example; pets can serve as egg carriers, facilitating human-to-human transmission, although they are not actually infected themselves. The commonest helminthic infection worldwide, schistosomiasis, cannot be considered to be a true zoonosis, as snails, which constitute the natural helminth reservoir, are invertebrates, and the participation of vertebrates, excluding humans, in the life cycle of *Schistosoma* spp. is non-existent or of extremely limited significance (for *Schistosoma mansoni* and *Schistosoma malayensis*). Other helminths that exhibit a strict localized profile, e.g. *Oesophagostomum* sp. which are of importance only in certain African regions (Ghana and Togo), are also excluded from Table 2. The remaining species of helminths that are clinically significant for humans on a broad basis, and are truly zoonotic in nature, are summarized in Table 2.

Zoonotic Fungi

Table 3 summarizes clinically important zoonotic fungi. It does not include agents that are only theoretically zoonotic, e.g. *Blastomyces dermatitidis*, which could in theory be transmitted to humans by pet dogs, but for which the role

and extent of such a means of transmission have not been demonstrated. The same applies to *Pneumocystis jirovecii*: although it has been recognized to cause a respiratory syndrome in numerous animal species, transmission from one species to another is not considered to be feasible [47].

Prion Zoonoses

The BSE outbreak and the disease induced in humans, variant Creutzfeldt–Jakob disease, represent a typical zoonotic story, despite the cause not being a living organism, a pathogen as such, but a prion. Since 1996, 218 human cases have been recognized, the majority of them (171) in the UK [48], and one cannot rule out further detection of cases in the future, taking into account the protracted ‘incubation period’ observed in Creutzfeldt–Jakob disease. The lessons learned from the BSE/variant Creutzfeldt–Jakob disease outbreak are numerous, at all levels, extending to the huge financial burden imposed.

In summary, the increasing recognition of novel parasitic and fungal pathogens, the increase of immunocompromised human populations that are theoretical targets for unconventional pathogens and the increasing interaction of humans with their environment (the consequences of which are covered in detail elsewhere in this issue) are expected to expand the list of zoonotic parasites and fungi. However, the burden of disease is already enormous, and remains disproportionate to the scientific and public health attention paid to it. A brief look at Tables 1–3 demonstrates that many of the included species have a geographical distribution that primarily affects the developing world. The identification of other neglected ‘neglected diseases’ should be a priority for global public health initiatives, taking into account the effect

TABLE 2. Clinically significant zoonotic helminths

Pathogen	Comments
<i>Ancylostoma</i> spp.	Cutaneous larva migrans (<i>Ancylostoma brasiliense</i>) remains the commonest skin infection acquired in the tropics; however, autochthonous cases are increasingly being reported from western Europe. <i>Necator americanus</i> , the other cause of the syndrome, is only technically zoonotic. <i>Ancylostoma caninum</i> has caused localized outbreaks of eosinophilic enteritis. <i>Ancylostoma ceylanicum</i> , causing a minority of ancylostomiasis cases, is zoonotic, in contrast to <i>Ancylostoma duodenale</i>
<i>Angiostrongylus</i> spp.	Principally <i>Angiostrongylus cantonensis</i> in Southeast Asia and the Pacific. Also emerging in the Caribbean [13] as the commonest cause of eosinophilic meningitis
<i>Anisakis</i> spp.	Increasingly reported, apart from Japan, from western Europe, possibly owing to the emerging trend of raw fish consumption. Increasingly recognized as a cause of chronic urticaria [14]
<i>Clonorchis sinensis</i> and <i>Opisthorchis</i> spp.	<i>Clonorchis sinensis</i> is endemic in China, Korea, Taiwan, and Vietnam, <i>Opisthorchis viverrini</i> in Southeast Asia, and <i>Opisthorchis felineus</i> in the former Soviet Union republics, including Russia [15]: the estimated burden of human cases is 35 million, 10 million (8 million in Thailand and 2 million in Laos), and 1.2 million, respectively. Emerging because of the increasing dietary dependence on marine sources, owing to either survival or 'fashion' needs [16]; the latter may predispose to outbreaks in non-endemic areas [17]
<i>Diphyllobothrium</i> spp.	<i>Diphyllobothrium latum</i> is the commonest species implicated worldwide, and <i>Diphyllobothrium nihonkaiense</i> is prevalent in Japan and eastern Russia (recognized as <i>Diphyllobothrium klebanovskii</i>). In Europe, the incidence is decreasing in the Baltic and Scandinavian, previously endemic, regions, but the disease has emerged in sub-Alpine central Europe [18]. Can be recognized in non-endemic areas as a result of fish importation
<i>Dirofilaria</i> spp.	<i>Dirofilaria immitis</i> is an extremely rare cause of human disease in the USA. On the other hand, <i>Dirofilaria repens</i> is prevalent in Mediterranean countries and has been expanding northwards, being observed increasingly in central Europe: this has been correlated with climate change leading to warmer summers, which are ideal for <i>D. repens</i> [19]. Morbidity, on the other hand, is far from significant, typically in the form of a solitary subcutaneous nodule
<i>Echinococcus</i> spp.	Cystic echinococcosis (<i>Echinococcus granulosus</i>) remains a major zoonotic issue, particularly in Central Asia, South America, North Africa (and probably sub-Saharan Africa), directly related to inadequate public health practices [20]. The incidence of the disease in southern European countries, however, seems to have been significantly lower in recent years [21]. The extended period needed for disease recognition complicates accurate statistical evaluation of incidence trends and the global burden of disease. For 2008, 639 cases of disease caused by <i>E. granulosus</i> were confirmed in the European Union (EU), the majority arising in Bulgaria, Spain, and Germany [22]. Alveolar echinococcosis (<i>Echinococcus multilocularis</i>) is an emerging zoonosis in central Europe, with significant mortality [23] and the need for costly therapeutic interventions. Fifty cases were confirmed in the EU in 2008, in Germany, Lithuania, France, and Poland [22]. Rural regions in China remain hyperendemic, with an estimate exceeding 16 000 annual cases
<i>Fasciola</i> spp.	Hyperendemic areas worldwide with distinct eco-epidemiologic characteristics [24]. European (France, Spain, and Portugal), Caribbean (Cuba in particular), South American (Peru, Ecuador, Chile, and Bolivia), and Near/Middle East (Egypt, Iran) zones of endemicity have been recognized. The estimated number of human infections exceeds 2.4 million [15]
<i>Fasciolopsis buski</i>	Fasciolopsiasis is endemic in India, China, and Southeast Asia. The estimated burden of disease exceeds 1 million cases [15]. The most important of the intestinal flukes, although <i>Metagonimus</i> spp. are more prevalent in the Far East
<i>Gnathostoma</i> spp.	Gnathostomiasis remains rare in humans, even in endemic areas such as Southeast/East Asia and Latin America, owing to the difficulty that the pathogen has in invading humans (only late-third stage larvae are capable of this). However, it is increasingly being reported as a travel-related disease, owing to the recent trend of raw/undercooked food digestion [25]
<i>Paragonimus</i> spp.	Predominantly <i>Paragonimus westermani</i> . There are estimated to be more than 20 million cases worldwide [15] with widespread distribution in Asian, African and Latin American foci
<i>Thelazia</i> spp.	<i>Thelazia callipaeda</i> is the commonest cause of thelaziasis, a superficial eye parasitosis that may be under-recognized but endemic in Southeast/East Asia [26]
<i>Toxocara</i> sp.	More than 1 million people are exposed to or infected with <i>Toxocara</i> sp. in the USA, the prevalence being particularly high in inner-city populations of lower socio-economic status [27]. Varying seroprevalence has been reported worldwide [28]
<i>Trichinella</i> spp.	Worldwide prevalence varies and is associated with particular meat-consumption habits (dog meat in China; horse meat in France). An exhaustive review of country-by-country trichinellosis statistics has been published recently by Pozio [29]. For 2008, 670 trichinellosis cases were recorded in the EU, the majority associated with consumption of undercooked/raw bear meat or uninspected pork products [22]; the vast majority of these cases were reported from Romania, and have been directly correlated with the change in political regime [30]. The increased incidence of trichinellosis in the EU observed from 2006 onwards is a direct consequence of the burden of trichinellosis in Romania. In the USA, trichinellosis remains a disease predominantly related to raw/undercooked bear meat consumption, a habit of certain communities: of the 39 cases reported in 2008 [31], 30 arose from such an outbreak

TABLE 3. Clinically significant zoonotic fungi

Pathogen	Comments
<i>Basidiobolus ranarum</i>	A rare cause of zygomycosis, and an indirect zoonosis, as amphibians, for which it is a commensal, participate in its life cycle. Usually reported in isolated cases, more than 300 of which exist in the literature [32]. <i>Conidiobolus</i> spp. are also rare causes of zygomycosis with zoonotic potential, as they can be isolated from reptiles, although not in the tropical African regions where human disease is observed [32]
<i>Cryptococcus neoformans</i>	Direct transmission from birds to humans is increasingly being demonstrated [33,34]; a zoonotic cycle (environmental disposition through bird excreta) is definitely implicated in transmission to humans [35]
<i>Histoplasma capsulatum</i>	As for <i>Cryptococcus neoformans</i> , the role of bird and bat excreta in sustaining <i>Histoplasma capsulatum</i> in the environment, leading to human infection, indicates a zoonotic parameter
<i>Mallasezia</i> spp.	<i>Mallasezia pachydermatis</i> outbreaks in nursery schools and immunocompromised populations have demonstrated the role that pet dogs can play as reservoir of the pathogen [36], which is transmitted to patients at risk through healthcare worker-pet owner carriage [37]
<i>Microsporium</i> spp.	Cats (and to a lesser degree dogs) constitute the main <i>Microsporium canis</i> reservoir facilitating transmission to humans [38,39], and potentially serious manifestations in immunocompromised individuals [40]
<i>Paracoccidioides brasiliensis</i>	Has not been demonstrated persuasively as zoonotic, but: (i) it has been demonstrated in wildlife (armadillos and monkeys) and domestic animals; (ii) the habitat of the pathogen remains elusive [41]; (iii) armadillo and human isolates may be common [42]; and (iv) the epidemiology of the disease indicates a rural predilection, consistent with most zoonotic infections [43]. Endemic in certain areas of Brazil, with an annual incidence in the range $0.3-3 \times 10^5$ [43]
<i>Penicillium marneffei</i>	Bamboo rats constitute the natural reservoir for spread of the pathogen; penicilliosis is the third commonest opportunistic human immunodeficiency virus-related infection in Southeast Asian populations, with thousands of cases being reported from Thailand in particular [44]
<i>Sporothrix schenckii</i>	Although zoonotic transmission to humans is not the predominant mode of human sporotrichosis development, it has been increasingly recognized, not only in professionals in contact with infected animals, but also in pet owners and particularly in childhood [45]
<i>Trichophyton</i> spp.	A zoonotic origin has been persuasively demonstrated for at least <i>Trichophyton mentagrophytes</i> [46]

of zoonoses on non-medical, socio-economic aspects of human life.

Transparency Declaration

The author declares no conflicts of interest.

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