Looking in apes as a source of human pathogens

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Because of the close genetic relatedness between apes and humans, apes are susceptible to many human infectious agents and can serve as carriers of these pathogens. Consequently, they present a serious health hazard to humans. Moreover, many emerging infectious diseases originate in wildlife and continue to threaten human populations, especially vector-borne diseases described in great apes, such as malaria and rickettsiosis. These wild primates may be permanent reservoirs and important sources of human pathogens. In this special issue, we report that apes, including chimpanzees (*Pan troglodytes*), bonobos (*Pan paniscus*), gorillas (*Gorilla gorilla* and *Gorilla beringei*), orangutans (*Pongo pygmaeus* and *Pongo abelii*), gibbons (*Hylobates* spp., *Hoolock* spp. and *Nomascus* spp) and siamangs (*Symphalangus syndactylus syndactylus* and *Symphalangus continentis*), have many bacterial, viral, fungal and parasitic species that are capable of infecting humans. Serious measures should be adopted in tropical forests and sub-tropical areas where habitat overlaps are frequent to survey and prevent infectious diseases from spreading from apes to people.

1. Introduction

It is well known that the majority of emerging infectious diseases are of zoonotic origin and are primarily caused by wildlife- or vector-borne pathogens [1]. The increased incidence of zoonoses highlights the critical need for real-time pathogen monitoring in wildlife animals, especially in at-risk regional "hotspots" where new emerging infectious diseases have been reported [1].

Apes (superfamily Hominoidea) include the lesser apes, known as gibbons and siamangs, that are represented by 4 genera (*Hoolock*, *Hylobates*, *Symphalangus* and *Nomascus*) and the great apes that also contain 4 genera (*Homo* (humans), *Pan* (chimpanzees and bonobos), *Gorilla* (gorillas) and *Pongo* (orangutans)) [2]. Because of their high genomic similarity and close evolutionary relationships to human beings, apes share many diseases with humans [3]. These shared infectious diseases may result from pathogens inherited from a common ancestor [4]. However, cross-species transmission between close relatives is also possible. Many factors can create opportunities for pathogen transmission between apes and humans, including their frequent contact during ecotourism, searching for food, research or simply sharing the same ecosystem (i.e., habitat overlap) [5]. The establishment of new infections in humans depends on both the pathogen and human biology (i.e., the capacity of pathogen to expand its host range and become a human pathogen) [5]. Ape pathogens most likely need very few changes, if any, to infect humans. Thus, the absence of appropriate and timely immune responses in the naive humans leads to the emergence and rapid spread of the infectious diseases [5].

Mathematical models showed that a high proportion of pathogens are shared between close relatives such as humans and apes [4–7]. Moreover, recent research has alerted the scientific communities to the emergence of human infections linked to African great apes [8]. Chimpanzees were found to be the natural reservoir of the pandemic and non-pandemic human immunodeficiency virus type 1 (HIV-1) [9], the causative agent of acquired immune deficiency syndrome (AIDS). Moreover, a new *Mycobacterium tuberculosis* strain was recovered from a wild chimpanzee [10], and gorillas were identified as the origin of the human malaria parasite *Plasmodium falciparum* [11]. *Rickettsia felis*, an emerging vector-borne pathogen that causes rickettsioses, was documented in the feces of many species of apes, including gorillas, chimpanzees and bonobos [12]. It is important to note that for AIDS and malaria, African great apes have much more variety of causative related pathogens than those in humans. This difference in pathogen variety suggests that either some specific ape pathogens have not yet been able to infect and spread widely throughout the human population or that cross-infection/adaptation of these species in human beings yet to occur [8].

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Unfortunately, the published data regarding pathogens of the apes that live in Asia remain quite poor. Large surveillance efforts in these ape populations are required to document the potential for zoonotic diseases from this continent to spread to humans.

Although the transmission of infectious diseases between apes and humans can occur in both directions, this review focuses on the importance of apes as carriers and possible source of infective organisms that have the potential to become human pathogens.

2. Apes as a reservoir and source of human pathogenic bacteria

Although bacterial and rickettsial diseases represent more than half of the emerging infectious diseases worldwide [1], the literature contains few reports regarding the pathogenic bacteria of apes and no report of transmission to human beings. Enteric bacterial agents such as *Salmonella* spp., *Shigella* spp., *Campylobacter* spp. and *Escherichia coli* can be carried by many species of gorillas [13,14]. Feces of infected animals are the most likely primary sources of these bacteria. Nizeyi et al. reported that the prevalence of isolation for *Campylobacter* spp., *Salmonella* spp., and *Shigella* spp. in mountain gorillas (*Gorilla gorilla beringei*) from Uganda is 19%, 13%, and 6%, respectively, without enteric illness in any observed gorillas [13]. *Salmonella* species and *Shigella* spp. (*Shigella sonnei*, *Shigella boydii*, and *Shigella flexneri*) were isolated principally from subadult and adult gorillas [13]. However, the prevalence of these enteropathogens may have been underestimated due to the low sensitivity of the classical methods used for their detection. The molecular survey conducted recently by Whittier et al. on *G. beringei* using real-time PCR confirmed that the prevalence of *Campylobacter* spp. can reach 85% in mountain gorilla populations [15].

Respiratory bacterial agents have also been recovered in wild great apes (chimpanzees and gorillas) [16–18]. Three bacteria including *Pasteurella multocida*, *Streptococcus pneumoniae* and *Klebsiella pneumoniae,* which are also infectious to humans, have been detected in apes that died from pneumonia. Molecular characterization of these strains indicated the presence of pathogenicity factors such as type 4 fimbriae and superoxide dismutases in *P. multocida* and pneumolysin in *S. pneumonia* that could explain their potential virulence relevance [16,17]. However, in most cases, a viral upper respiratory tract infection by metapneumovirus predisposed these great apes to bacterial infections [16–18].

Several emerging bacteria have been characterized and found to be infective in wild great apes; these bacteria include *Bacillus anthracis* [19] and *M. tuberculosis* [10]. First, two outbreaks of anthrax caused by a variant of *B. anthracis* "*B. cereus* var. *anthracis*" killed at least 6 chimpanzees in Côte d'Ivoire and 3 chimpanzees and one gorilla in Cameroon [19]. Moreover, a recently case of a wild chimpanzee infected with *M. tuberculosis* has been documented in Côte d'Ivoire [10]. The phylogenomic analyses demonstrated that this strain belongs to a new lineage of the *M. tuberculosis* complex, but it is more closely related to lineage 6 that has been described in humans and is known as *Mycobacterium africanum* (West Africa 2) [10].

Finally, *R. felis*, a fastidious intracellular pathogen transmitted to human by ectoparasites and the bites of infected mosquitoes, has also been detected in gorilla, chimpanzee and bonobo feces using molecular methods [12]. In the aforementioned study, the feces of 11% of apes living in the wild (a total of 1028 samples tested) were found to be positive for *R. felis* and *R. felis*-like organisms, thus indicating the importance of apes as potential host or reservoir for this emerging rickettsial bacterium in sub-Saharan Africa where its infection is a common public health problem [12].

3. Apes as a reservoir and source of human pathogenic viruses

There have been various studies demonstrating that apes, especially African great apes, constitute a potential reservoir and source of numerous human pathogenic viruses [20] (Fig. 1). Most species of apes, if not all, can carry retroviruses (family *Retroviridae*) including simian immunodeficiency viruses (SIVs), simian T-cell lymphotropic viruses (STLVs) and simian foamy viruses (SFVs). Thus, considerable research has been conducted to understand the prevalence, genetic diversity, geographic distribution and transmission of these viruses in ape populations [21,22]. It is now well established that the human immunodeficiency viruses HIV-1 groups M and N are very closely related to SIVcpzPtt of chimpanzees (*Pan troglodytes troglodytes*) and thus are of chimpanzee origin, while HIV-1 group P is of western gorilla (*Gorilla gorilla gorilla*) origin [22]. Despite numerous interspecies transfers of the retrovirus from apes to human, only HIV-1 group M originated from chimpanzees in Cameroon and subsequently spread worldwide to become responsible for the pandemic form of AIDS in humans [9,21,22]. Currently, no evidence has been found of SIV infections in Asian apes (orangutans and gibbons) [23]. In contrast to SIVs that are present principally in African gorillas and chimpanzees, STLVs are also retroviruses but are widely distributed among African and Asian apes including gorillas, chimpanzees, orangutans and gibbons [23,24]. In the early 2000s, a serological survey followed by molecular confirmation indicated that a wild-caught gorilla and a wild-caught chimpanzee were infected with STLV-1 strains that were closely related to HTLV-1 strains present in human inhabitants of the same region (south Cameroon); this suggests the possible transmission of STLV-1 to humans from African apes [24]. More recently, phylogenetic studies confirmed this conclusion and showed that STLVs cluster according to geographical origin rather than by host species, leading to the hypothesis that many interspecies transmissions have occurred between primates, including those from apes to humans [21,23].

Ebola virus belongs to the *Filoviridae* family and is a highly virulent virus of humans and nonhuman primates that causes severe hemorrhagic fever and death within few days. This virus has been responsible for outbreaks in several countries of Sub-Saharan Africa, such as the Democratic Republic of Congo, Gabon, Sudan, Ivory Coast, Uganda and, most recently, Guinea [25,26]. Although bats are considered the natural hosts of filoviruses, Ebola virus transmission to humans appear to be linked to direct contact with live or dead apes. Hunters that come into contact with the infected gorilla and chimpanzee carcasses are especially at risk of contracting the disease [25]. Recent surveillance of Asian apes in Indonesia for filoviruses showed that 18.4% of healthy orangutans (*Pongo pygmaeus*) are seropositive for the Ebola virus. This high seroprevalence in asymptomatic orangutans suggests that this ape may serve as carrier or host and thus could present a potential risk for humans living in this region of Asia [27].

The hepatitis B virus (family *Hepadnaviridae*) has also been characterized in apes from both Africa and Asia at high frequencies comparable to those obtained from humans in endemic zones [28]. The presence of cross-species transmission and/or recombination between human and ape hepatitis B virus variants [28] and the close genomic similarity of human and ape hepatitis B viruses [29] calls for extensive phylogenetic investigations to understand the diversity, the evolution and the worldwide spread of this virus.

Other pathogenic viruses, including adenoviruses [30] (family *Adenoviridae*), *Lymphocryptovirus* [31] and cytomegaloviruses [32] (family *Herpesviridae*), metapneumoviruses [16-18] (family *Paramyxoviridae*), polyomaviruses [33] (family *Polyomaviridae*) and enteroviruses [34] (family *Picornaviridae*), are not exclusively

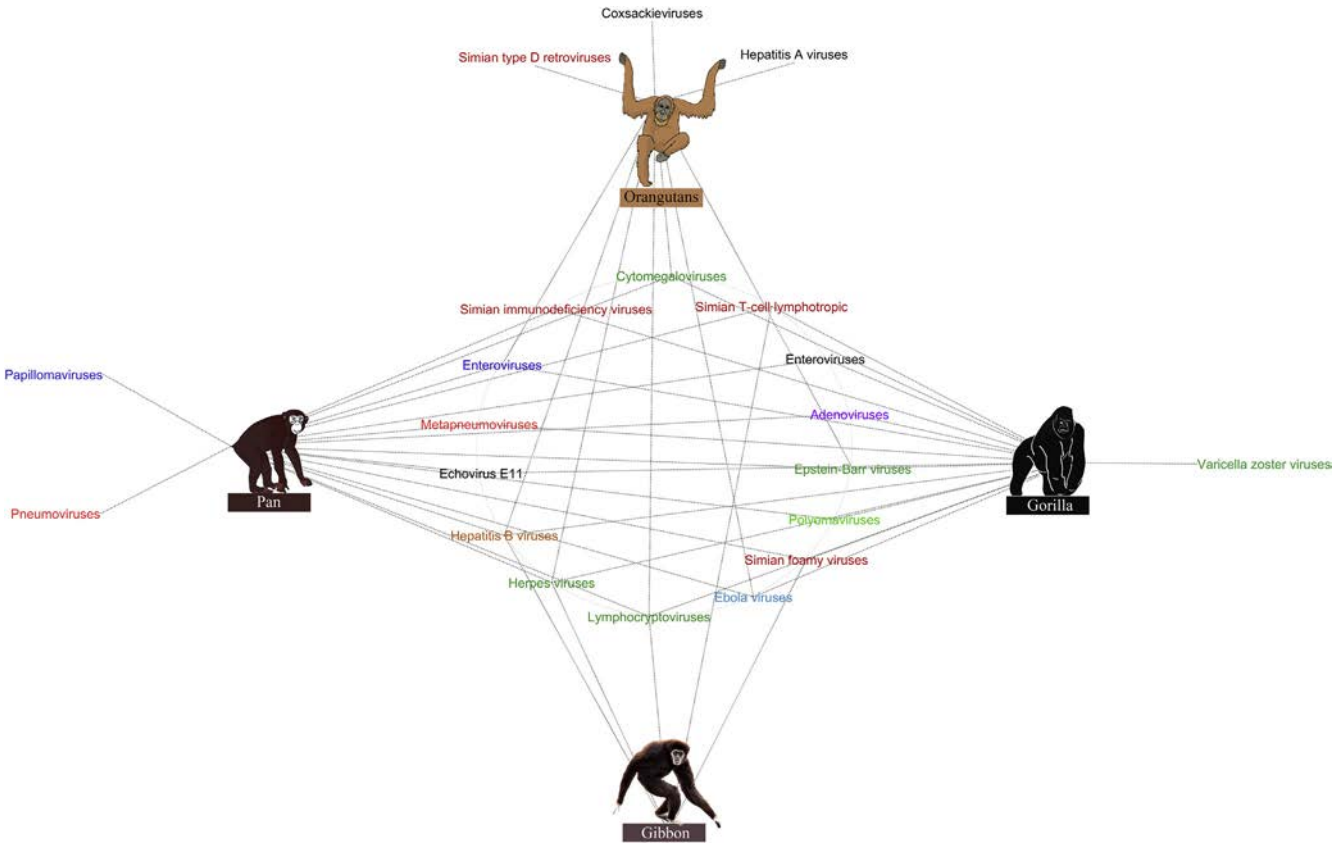

Fig. 1. Apes (chimpanzees, gibbons, gorillas and orangutans) serving as viral reservoirs. Viral genera and species are distributed into the following nine families: *Retroviridae* (dark red), *Herpesviridae* (green), *Hepadnaviridae* (orange), *Adenoviridae* (purple), *Papillomaviridae* (blue), *Filoviridae* (light blue), *Picornaviridae* (black), *Paramyxoviridae* (red) and *Polyomaviridae* (light green). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

human-specific and have also been detected in apes. Moreover, based on phylogenetic analyses, some of these viruses variants found in apes are remarkably closely related to human viruses, indicating the zoonotic potential of primate viruses to spread horizontally into the local human populations [30–34].

4. Apes as a reservoir and source of human parasites

Parasitological studies from different free-ranging and captive apes have revealed a multitude of parasite species ranging from single-celled protozoa to multicellular helminths [35] (Fig. 2). The high load of these parasites in the various ape hosts may render these animals potential zoonotic reservoirs that could be responsible for an emerging parasitic zoonosis [20].

Ape parasites can be transmitted to humans through vector-mediated transmission (usually arthropods) via fecal-oral transmission or through direct or prolonged contact with apes [20]. Although little published data has demonstrated the direct transmission of parasites from apes to human, a number of zoonotic diseases have been reported, providing evidence of shared susceptibility of both apes and human to same pathogens [36]. The transmission of these pathogens among primates in the wild may have negative consequences for public health and wildlife conservation management programs [37].

4.1. Apes as reservoir for human parasitic protozoa

Regarding unicellular eukaryotic organisms, apes exhibit several blood/tissue and intestinal protozoa that can cause diseases of concern for human beings (Fig. 2). Members of the blood and tissue apicomplexan parasites of the genus *Plasmodium* have been described in gorillas, chimpanzees and bonobos [11,38–41]. Indeed, very recent data provided definitive evidence that the most virulent human malaria parasite (*P. falciparum*) originated from gorillas [11]. In addition to the occurrence of *Plasmodium* species that cause malaria (*P. falciparum*, *Plasmodium vivax*, *Plasmodium malariae*, *Plasmodium ovale*) in a wide range of apes, other members of the genus *Plasmodium* have also been reported to cause natural infections in apes (Fig. 2).

Furthermore, kinetoplastid protozoans, such as species of *Trypanosoma*, have been reported in gorillas, chimpanzees and orangutans [42,43], and the first natural infection cases of the hemoflagellate protozoan *Trypanosoma cruzi*, the causative agent of human Chagas disease, have been reported in chimpanzees and gibbons [44,45]. Although the transmission of this parasite requires a blood-sucking triatomine insect, direct transmission could also occur among the infected captive animals and their zookeepers [45].

The free-living amoeba *Balamuthia mandrillaris,* the etiological agent of human granulomatous amoebic encephalitis, has been identified in brain tissue from both gorillas and gibbons [46]. Although *B. mandrillaris* is regarded as an emergent threat to humans, the transmission of this pathogen from apes to human is rarely recorded. However, close contact between humans and infected non-human primates might increase the risk of transmission [46].

The gastrointestinal walls of apes are colonized by parasitic protozoan, and fecal-based studies of wild populations of gorillas, chimpanzees and orangutans revealed the presence of certain intestinal human parasites such as *Entamoeba histolytica* [6], *Giardia*

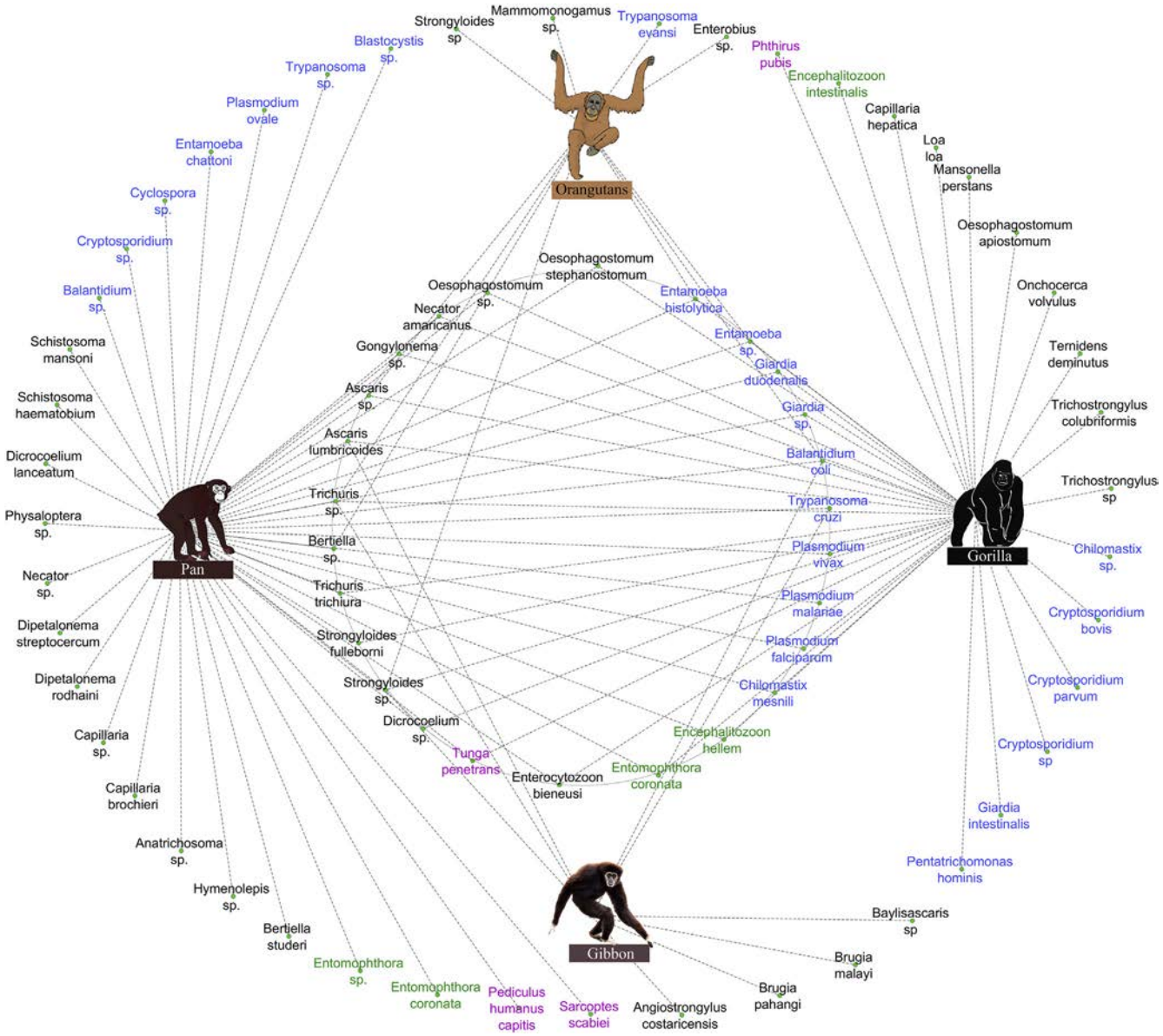

Fig. 2. Parasitic reservoir of apes (chimpanzees, gibbons, gorillas and orangutans). Helminths (black), Protozoa (blue), Fungi (green) and Arthropods (pink). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

duodenalis [6,47] and *Cryptosporidium* species [48] in the guts of these animals. Moreover, common human subtypes of *Blastocystis* sp. that are often associated with chronic infections have also been identified in the digestive tracts of both captive and free-living apes including gorillas, chimpanzees, bonobos, gibbons and orangutans [49]. Furthermore, the ciliated parasite *Balantidium coli* that cause human balantidiasis has also been detected in the stools of a wide range of gorilla, chimpanzee and orangutan populations [6]. The major source of infection with these enteric parasites is through the fecal-oral route [50]. Although there is less opportunity for the feces of wild apes to contaminate human water supplies, transmission is still possible, especially for people who are involved in caring for captive apes [51].

4.2. Apes as a reservoir of human helminths

Coprological studies revealed the presence of a variety of intestinal nematodes among gorilla, chimpanzee and orangutan populations (Fig. 2). For example, the common human enteric round worm *Ascaris lumbricoides*, the whipworm *Trichuris trichiura* and species of the pinworm *Enterobius* have been found in the gastrointestinal tracts of almost all of the great apes [6]. In addition, species of *Oesophagostomum* and *Strongyloides*, nematodes that cause oesophagostomosis and strongyloidiasis, respectively, have also been detected in the guts of African great apes [6,52]. Some reports described human infections with species of *Oesophagostomum* in northern Togo and Ghana, particularly in regions where apes live in close proximity to humans [53]. The digestive tracts of apes such as gorillas and chimpanzees can also be infected with the zoonotic parasite for *Necator americanus*, the hookworm that causes human hookworm. Molecular evidence revealed the possibility of cross-infection with *Necator* hookworms in humans and great apes that co-exist in the same area [54].

In addition to enteric nematodes, the great apes are also susceptible to a variety of filarial nematodes including *Onchocerca volvulus*, a nematode that causes human onchocerciasis in Africa

and has been observed in gorillas, *Dirofilaria immitis,* a nematode that is responsible for severe human heart problems and has been detected in orangutans, and *Loa loa,* the etiological agent of human loaiasis that has also been reported in gorillas and chimpanzees [55].

Little information regarding the diversity and transmission of cestodes and trematodes between humans and apes is available. The only cestode that is considered to be a potential zoonosis from apes is *Hymenolepsis nana*, for which chimpanzees might serve as reservoir host [56]. Regarding the parasitic trematodes, the blood flukes *Schistosoma mansoni* and *Schistosoma haematobium*, the causative agents of schistosomiasis, have been observed in chimpanzees [56,57].

4.3. Apes as reservoir for human pathogenic fungi

Little data exists concerning the occurrence and diversity of fungi in great apes. However, the primary zoonotic fungal diseases of concern for humans belong to group of microsporidia, and intracellular parasitic species belonging to the genera *Enterocytozoon* and *Encephalitozoon* have been reported in multiple species of apes [58], as shown in Fig. 2. The transmission mode of these intracellular parasites remains unclear, but it is thought that close contact between apes and humans increases the risk of transmission of these infectious diseases [58].

4.4. Apes as reservoir for arthropods causing human disease

In addition to their role as vectors of many severe parasitic diseases, arthropods such as fleas, lice, ticks, and mites also serve as intermediate biological hosts for a variety of infectious disease agents (Fig. 2). *Tunga penetrans* is a parasitic flea that cause human tungiasis and has been confirmed to use different primates as reservoirs [55]. *T. penetrans* has been observed infecting the skin of gorillas. The risk of transmission of this arthropod to humans increases in cases of direct contact, particularly in endemic areas [55].

The most prevalent sucking lice species that colonize humans are *Pthirus pubis* and *Pediculus humanus capitis*. These species have also been reported to be associated with apes, and evidence suggests that these parasites may be able to switch between human and ape hosts [55]. Interestingly, apes such as gorillas can also be parasitized by *Pthirus gorilla*, a louse that is phylogenetically a very close relative of the human parasite *P. pubis* and is regarded as a common pubic louse. It is assumed that our human ancestors contracted *P. gorilla* millions years ago by either living in close proximity to gorillas or using their bedding sites [59]. Finally, different species of mites belonging to the genus *Sarcoptes* have been documented to invade a wide range of ape hosts. The itch mite *Sarcoptes scabiei* is the causative agent of human *scabies* and has observed to also infest the skin of gorillas. The possibility of transmission of *S. scabiei* to humans increased when they came into close contact with infested animals [55].

5. Conclusion

The identification of natural or wild sources for pathogens is necessary to avoid the emergence or reemergence of infectious diseases. Apes, our closest relatives, deserve special attention because they constitute serious reservoir of many micro- and macro-pathogens for humans including viruses, bacteria, parasitic helminths and protozoans. Thus, people living close to or in direct contact with apes are at risk for inter-species transmission and infection. Non-invasive methods showed these potential interactions could be involved in many emerging infectious diseases such as HIV and malaria. However, many additional efforts are essential to detect anthropozoonoses from wild apes and to prevent transmission to humans. Future investigation of pathogens in Asian apes is required, and the large-scale monitoring of bacterial and fungal species in ape populations is needed to gain global insights into the emerging zoonotic events from wildlife.

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