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REVIEW

# Canine and Feline Parasitology: Analogies, Differences, and Relevance for Human Health

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**SUMMARY** Cats and dogs are treated as family members by most pet owners. Therefore, a high quality of veterinary care and preventive medicine is imperative for

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animal health and welfare and for the protection of humans from zoonotic pathogens. There is a general perception of cats being treated as "small dogs," especially in the field of clinical parasitology. As a result, several important differences between the two animal species are not taken into proper consideration and are often overlooked. Dogs and cats are profoundly different under evolutionary, biological, ethological, behavioral, and immunological standpoints. These differences impact clinical features, diagnosis, and control of canine and feline parasites and transmission risk for humans. This review outlines the most common parasitoses and vector-borne diseases of dogs and cats, with a focus on major convergences and divergences, and discusses parasites that have (i) evolved based on different preys for dogs and cats, (ii) adapted due to different immunological or behavioral animal profiles, and (iii) developed more similarities than differences in canine and feline infections and associated diseases. Differences, similarities, and peculiarities of canine and feline parasitology are herein reviewed in three macrosections: (i) carnivorism, vegetarianism, anatomy, genetics, and parasites, (ii) evolutionary adaptation of nematodes, including veterinary reconsideration and zoonotic importance, and (iii) behavior and immune system driving ectoparasites and transmitted diseases. Emphasis is given to provide further steps toward a more accurate evaluation of canine and feline parasitology in a changing world in terms of public health relevance and One Health approach.

**KEYWORDS** dog, cat, parasitology, zoonosis, humans, immunology, behavior

## INTRODUCTION

Around 50% of people in developed countries live at least with one companion animal (1). To date, dogs and cats are at the top of the pet list, and this has relevant implications for their health and welfare and, at the same time, for zoonotic risks for owners and general public. Accordingly, in the last decades, new insights on canine and feline parasitology have come in the spotlight of scientific and medical attention (2, 3).

There is still a general perception that cats and dogs are biologically closely related and that cats may be treated as "small dogs." In the parasitology world, this is not the case, although many parasites and/or transmitted diseases have the same transmission patterns for canine and feline hosts. Dogs and cats are carnivorous and share biological (e.g., hunting and territorialism) and artificial (e.g., living in anthropized environments) traits, which may favor infections and infestations from the same sources. However, some parasites are species specific, while many others infect/infest both dogs and cats via similar and different transmission patterns. For many of them, evolutionary, biological, anatomical, immunological, and ethological differences (Fig. 1 and 2) are related to specific host reactions, pathogenesis, and clinical courses. This means that canine and feline infections/infestations with the same parasite/s may result in completely different epizootiological and clinical outcomes. At the same time, infections or infestations with the same parasites in either dogs or cats may pose completely different risks of exposure and diseases for people (3).

This article provides an overview of major canine and feline parasites and vector-borne diseases with cosmopolitan occurrence, with a focus on the potential impact on human health. The demarcation line between parasitological worlds of dogs and cats should be kept in mind by veterinarians in their daily practice and by physicians who must consider canine and feline parasites in their differential diagnosis. The focus of the article is directed toward the following: (i) ethologic aspects and host-parasite evolution, such as predator-prey relationships and their influence on the epidemiology of key parasitic zoonoses; (ii) species-specific behaviors limiting or favoring chances of infection with certain pathogens rather than others, as is the case of pica, coprophagy, and grooming; (iii) immunological aspects driving various and diverse susceptibility and clinical courses for significant diseases in cats and dogs; (iv) analogies and

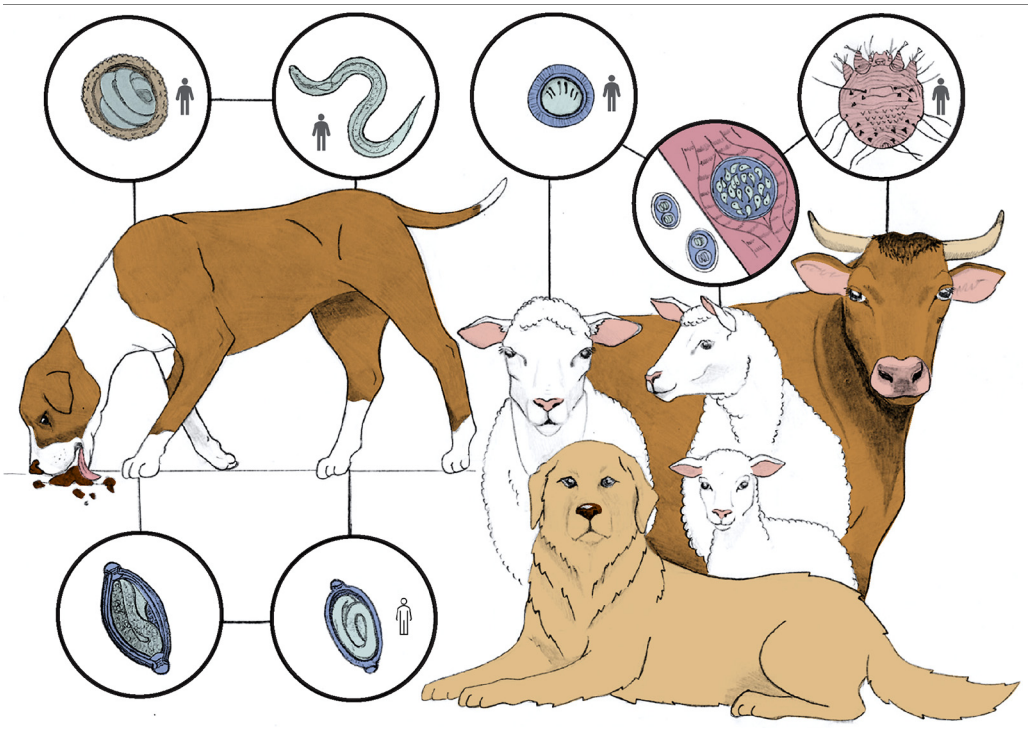

**FIG 1** Dogs are at more risk than cats to acquire infective stages of roundworms, hookworms, trichurids, and capillarids due to their tendency to ingest nonnutritive material (e.g., feces) from the soil. The close contact between dogs and farm animals influences the life cycle of *Echinococcus granulosus*, *Neospora caninum*, and *Sarcoptes scabiei*. Gray human figure, proven zoonotic potential; white human figure, uncertain zoonotic potential/few cases.

differences in dog and cat parasitoses in terms of clinical impact for pets and zoonotic potential. Accordingly, this article is organized into three macrosections, where parasitoses are grouped based on crucial factors influencing their biology and epidemiology. Zoonotic potential and clinical implications for humans are discussed for each parasite. In the first section, food sources, host intestine anatomy, and variations in parasite genetic profile are discussed in relation to major dog, cat, and human foodborne parasites. The second section describes the coevolution of parasites with their hosts, with the aim to interpret the differential significance of nematodes affecting dogs versus cats and their affiliation to humans. Finally, in the third section, the decisive role of animal behavior and divergences in their immune systems are perused to interpret the differences in arthropod species and frequency of infestations in dogs and cats; accordingly, the impact these discrepancies have in the occurrence of vector-borne diseases and related implications for human health are thoroughly examined.

## CARNIVORISM, VEGETARIANISM, ANATOMY, GENETICS, AND PARASITES

Numerous parasitoses are transmitted to vertebrates via the ingestion of food or water. Major foodborne parasitoses are herein discussed in relation to their transmission patterns. Insights on the parallelisms and diversities on the impacts they have in canine, feline, and human medicine are provided. Although predation is a main route of infection for certain feline parasites, these are discussed in the section dedicated to nematodes, as different factors are involved in their biology.

### *Toxoplasma* for Cats, *Neospora* for Dogs

**Toxoplasmosis and neosporosis in veterinary medicine.** The apicomplexan protozoans *Toxoplasma gondii* and *Neospora caninum* have many overlapping biological, epizootiological, and clinicopathological characteristics, with a life cycle relying on carnivorism. Nevertheless, they also show major differences: (i) definitive hosts of *T. gondii*

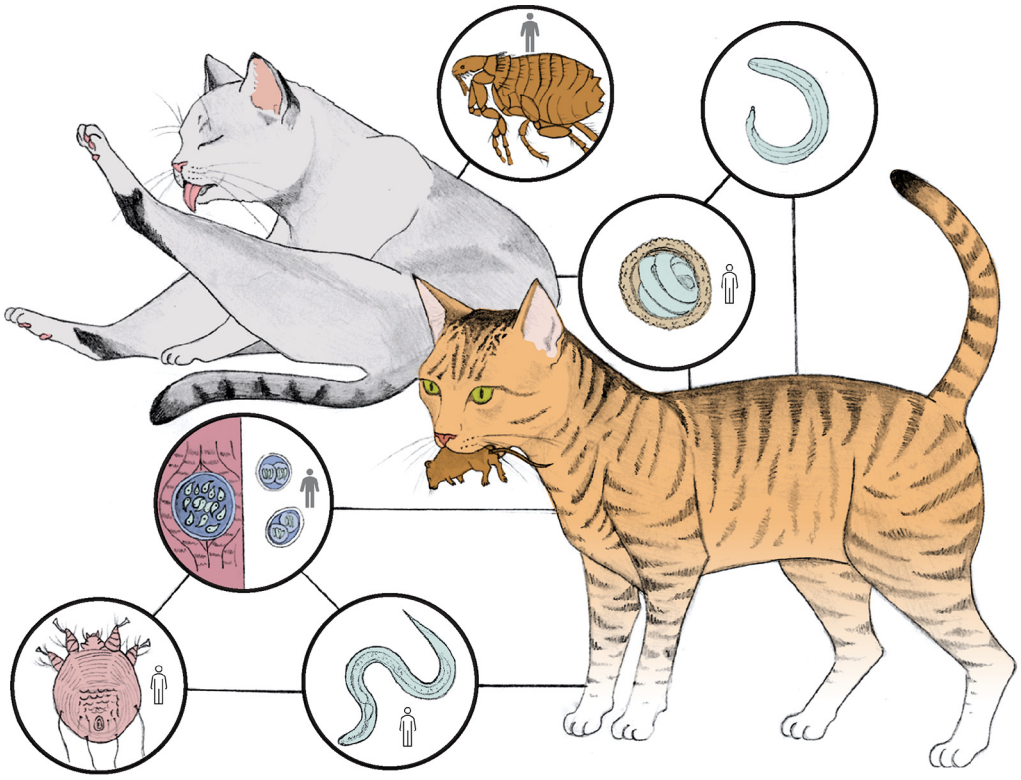

**FIG 2** Self-grooming reduces the entity of flea infestations in cats but enhances the chance of ingesting larvated eggs of roundworms. Predation is a main transmission route of feline parasites, such as roundworms, lungworms, *Toxoplasma gondii*, and hookworms. The strong feline predatory instinct has influences on host-parasite affiliations, as in the case of *Notoedres cati*. Gray human figure, proven zoonotic potential; white human figure, uncertain zoonotic potential/few cases.

are felids, while those of *N. caninum* are canids; (ii) *T. gondii* is a major abortive agent in small ruminants, while *N. caninum* causes abortion in cattle; and (iii) the former has a high zoonotic potential, while the latter has no impact on human health, albeit human seropositivity, particularly in immunocompromised individuals (4–7). Therefore, cats and dogs have very different roles as definitive hosts for these parasites in terms of both abortive relevance for livestock and public health (7).

Domestic and wild felids are the animals in which the enteroepithelial phase of *T. gondii* occurs, making them the only spreaders of the parasite in the environment through shedding of oocysts via their feces (4). Sporulated oocysts from the environment, tissue cysts in intermediate hosts, and transplacentally or lactogenically transmitted tachyzoites are the source of *T. gondii* infection for a plethora of vertebrates, including humans (7). Conversely, dogs and wild canids, as definitive hosts of *N. caninum* (8), are responsible for the infection of a significantly smaller range of vertebrates that, according to the current data, does not include humans (7, 9).

Toxoplasmosis has a key impact in veterinary medicine due to the abortions in sheep and goats and neurological disorders in other animals such as dogs and cats, while its role in causing abortion in cattle is minimal (10). On the other hand, *N. caninum* is a major abortion agent in cattle that is vertically transmitted from the dam to the calves and has a minor significance for other animals, except for dogs (7, 11). As a further difference, dogs are susceptible to *T. gondii* and may suffer from a systemic disease (12), while cats acquire neosporosis only experimentally (13).

Clinical feline toxoplasmosis is rare and more severe in congenital infections, while postnatal infections may develop to clinical disease in immunosuppressed cats, e.g., those affected by feline immunodeficiency virus (FIV) or feline leukemia virus (FeLV)

(14). Furthermore, a clinical disease due to reactivation of an older latent infection may occur in cats, when immunoregulators (e.g., cyclosporine but not glucocorticoids administered at the common anti-inflammatory doses) are administered to induce immunosuppression (14). Most clinical signs in cats involve the central nervous system and include anorexia, seizures, ataxia, hyperesthesia, uveitis, depression, fever, and dyspnea. Vertically infected kittens often die from severe pulmonary and hepatic diseases (14).

Clinical neosporosis in dogs may occur at any age after *in utero* or postnatal infection (15, 16). A discrimination between congenital and postnatal neosporosis is hard from a clinical point of view, especially in older dogs. Nevertheless, postnatal transmission is relatively rare, with a likelihood estimated at $<$3% for every year of life and mainly linked to access to raw meat or bovine fetal tissues (15, 17). Congenital infection is independent from the gestation age, and it is difficult to predict if puppies will be subclinically or clinically affected or will be born healthy, as this differs significantly within a litter. The percentage of seropositive puppies born from seropositive dams has been reported to vary from 3% to 54%, and only a few of those develop lesions and clinical signs (15). Furthermore, vertical transmission can occur across two generations (17). Congenital neosporosis usually manifests soon after birth as a progressive paraparesis, with gradual rigid hyperextension and atrophy of the hind legs, associated with infection of the spinal cord and skeletal muscles (16, 18). Incoordination and rear limb paralysis are common initial signs of clinical neosporosis, irrespective of the age of the dog, because of new infection or through reactivation of a latent infection, congenitally or postnatally acquired (19). Muscle atrophy, paralysis of the jaw, heart failure, and liver, spleen, kidney, and lung damage may also occur. The disease may further progress to encephalomyelitis and/or cerebellitis with tetraplegia, seizure-like signs due to triggering of epileptogenic foci, dysphagia, and dyspnea, common reasons for euthanasia of affected dogs if a fatal outcome does not occur before (18, 19). Cases of ulcerative dermatitis have also been reported in older or immunosuppressed animals (20).

**Key role of the immune system.** Lifelong protective immunity to toxoplasmosis develops after the first infection in cats and intermediate hosts, though long-living hosts, such as humans, may return seronegative (21). In accordance, in most cases, cats shed oocysts only after the first infection (22–25), and abortion or congenital transmission usually occurs only after the first maternal infection or after immunosuppression with parasite reactivation (26). On the contrary, the transplacental transmission of *N. caninum* takes place in consecutive pregnancies of both dogs and cattle (10). The duration of oocyst shedding by infected dogs and the chance of repeated oocyst elimination in subsequent infections is not clearly determined yet (10). Dogs shed no or few oocysts after being fed repeatedly with infectious material, and additionally, young dogs shed higher oocyst numbers than older dogs. There are cases in which dogs were still shedding oocysts at 4 months up to 2.5 years after initial diagnosis (10). In these cases, immunosuppression could play a role, but definitive conclusions on the oocyst elimination patterns in dogs with neosporosis are still lacking.

Although *T. gondii* and *N. caninum* are very closely related protozoa with similar genomes, the existing genetic differences are decisive in the interactions with their hosts. Rhoptry genes lead to distinct relationships with the host immune system, and the expansion of surface antigen genes of *N. caninum* are likely implicated in its narrow host preferences (7). Differences in genes which interplay with the host response are potentially associated with variations of pathogenicity in intermediate hosts, i.e., *T. gondii* being more pathogenic, and of transmission routes, i.e., mainly horizontal versus mainly vertical for *T. gondii* and *N. caninum*, respectively (11). The reasons behind these differences are attributed to *T. gondii* and *N. caninum* differentiation from a common ancestor, 28 million years ago, after the divergence of their respective definitive hosts, i.e., cat and dog (7, 11).

**Significant differences for humans.** Cats have been blamed for the impact of toxoplasmosis on public health for a long time, although humans do not become infected

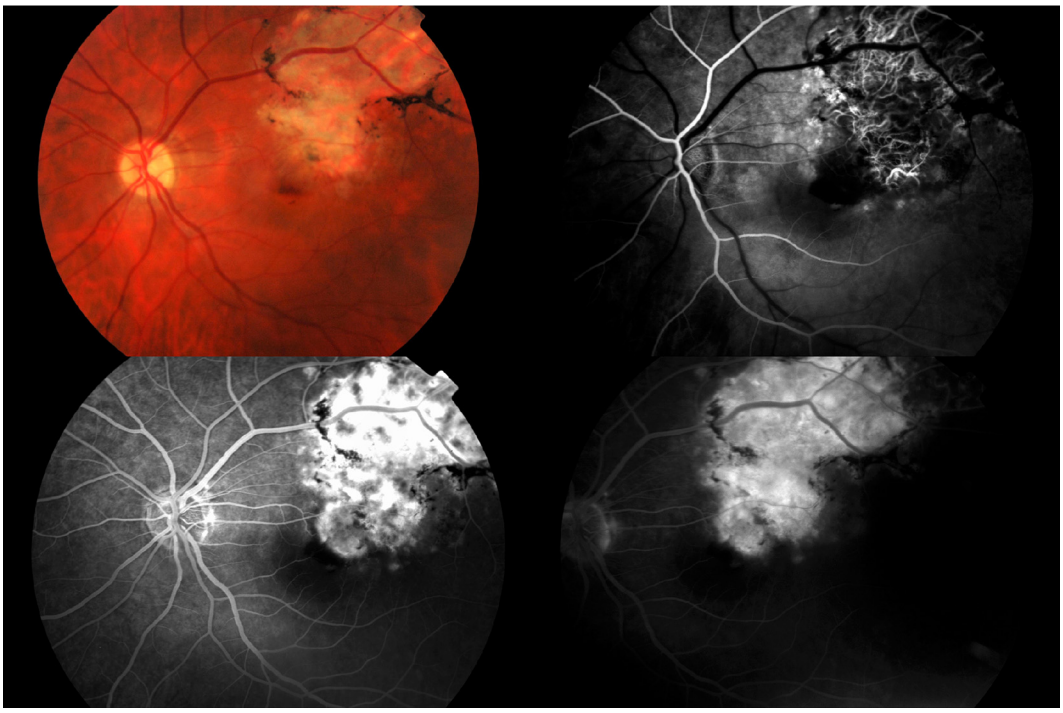

**FIG 3** Ocular toxoplasmosis in a human patient. Colored photography (top left) and fundus fluorescein angiography of the same eye fundus with visible lesions caused by *Toxoplasma gondii* (indicated by arrows). (Courtesy of Paris Tranos, ICO, FRCS; reproduced with permission.)

through direct contacts with cats. As spreaders of *T. gondii* oocysts in the environment, cats indirectly contribute to human infections when people ingest (i) raw and unwashed vegetables contaminated by sporulated oocysts (i.e., oocysts are not mature before 24 to 48 h after shedding), (ii) tissue cysts in raw or undercooked infected meat of intermediate hosts, and (iii) raw milk of ruminants, mainly sheep and goat, with recently acquired infection (27).

Human toxoplasmosis is very common worldwide, and it is estimated that one-third of the global population is seropositive (28, 29). The infection in immunocompetent individuals usually remains asymptomatic, though acute toxoplasmosis can manifest with fever, malaise, lymphadenopathy, hepatosplenomegaly, and ocular involvement (Fig. 3) (30, 31). Rarely, a severe disseminated disease, including hepatitis, pneumonitis, myocarditis, myositis, and encephalitis, may occur in immunocompetent patients (32). In immunocompromised and immunodeficient people, e.g., AIDS patients or transplant recipients, toxoplasmosis has severe and potentially deadly health consequences, including necrotizing encephalitis, commonly due to reactivation of a latent infection in the brain (Fig. 4), and disseminated pulmonary lesions (30, 33). Cerebral toxoplasmosis is the most frequent opportunistic illness in people infected with HIV (30). Another major implication of human toxoplasmosis is the infection of a fetus that may occur when a woman acquires the infection for the first time while pregnant or closely before conceiving. The impact in congenital infections depends on the gestational age. During the first trimester of pregnancy, the probability of a fetal infection is low (around 10% to 15%), and abortion is the typical result, while later in pregnancy, the chances of fetus infection rise (up to ~70%), but the consequences diminish in severity (34, 35). Congenital toxoplasmosis may lead to severe and fatal damage to the central nervous system (e.g., cerebral calcifications, micro- or macrocephaly, bulging fontanelle, seizures, abnormal muscle tone, and mental retardation), eyes (e.g., retinochoroiditis), and auditory function, though there are also infants born without any symptoms (35, 36). Nevertheless, symptoms may appear later in life (months to many years after birth) and usually include chorioretinitis and neurological disfunctions (37). It has

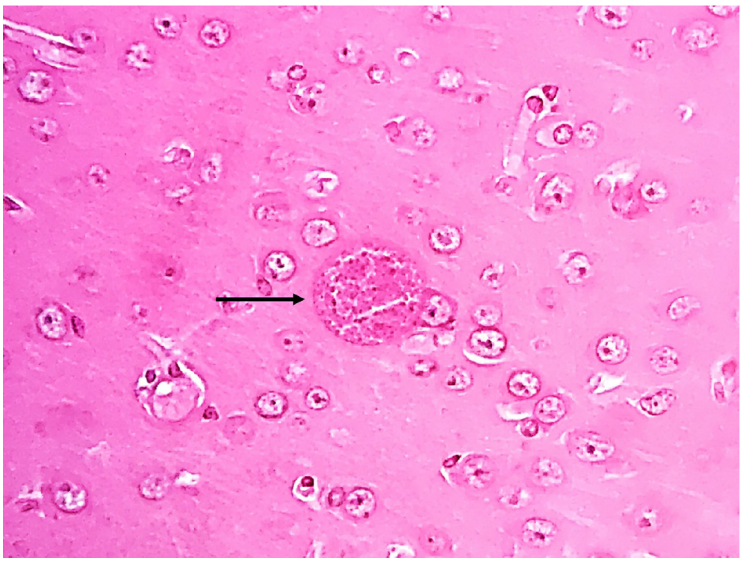

**FIG 4** *Toxoplasma gondii* bradyzoites (arrow) in human brain. (Courtesy of Simona Gabrielli, Dipartimento di Sanità Pubblica e Malattie Infettive, Università La Sapienza, Rome, Italy; reproduced with permission.)

also been suggested that congenital toxoplasmosis may be involved in behavioral disorders and psychosis (38).

To date, *N. caninum* has no proven zoonotic relevance, and its impact in human pregnancy is nil or at least unknown, as viable *N. caninum* forms have never been isolated from people thus far (9). Nevertheless, the serological evidence of human exposure and the ability of the parasite to cause fetal lesions in experimentally infected nonhuman primates and to infect human cells *in vitro* should spur further studies of any possible importance of human exposure to *N. caninum* (6, 9).

At the end, the diverse evolution of *T. gondii* and *N. caninum* from their common ancestor resulted in the adaptation to different hosts and in different zoonotic roles (7). Definitive hosts of both protozoa become infected mainly by consuming suitable preys for their species, i.e., rodents and birds for felids and cattle for canids, but only *T. gondii* displays zoonotic potential. Given the impact on public health, prevention of toxoplasmosis is mandatory, especially in immunocompromised individuals and during pregnancy. Preventive measures include consumption of adequately cooked meat, thorough washing of fruits and vegetables when consumed raw, safe raw meat handling, and basic principles of personal hygiene (e.g., hand washing after contact with soil or cat feces).

### *Echinococcus*: Evolutionary and Adaptation Notes

**Epizootiological and epidemiological roles of dogs and cats.** *Echinococcus granulosus sensu lato* and *Echinococcus multilocularis* tapeworms infect carnivores (definitive hosts), in which adult worms develop in the small intestine (39, 40). Carnivores become infected when they ingest the larvae (cystic forms) from the viscera of the intermediate hosts (41). Herbivores and omnivores, e.g., sheep, cattle, goats, pigs, and humans, serve as intermediate hosts and become infected by ingesting *Echinococcus* eggs shed in the feces of infected carnivores. Intermediate hosts harbor the larval forms, i.e., the hydatid and alveolar cysts for *E. granulosus sensu lato* and *E. multilocularis*, respectively, in the liver, lungs, and other organs and tissues. Very rarely, carnivores may harbor the cysts, which normally develop only in the intermediate hosts (41), while human cystic (CE) and alveolar (AE) echinococcoses have a great impact on public health.

Dogs and other canids are primary definitive host of various *Echinococcus* species, including *E. granulosus sensu lato*, which conversely does not reach adulthood in cats

(40, 41). Adult *E. multilocularis* may infect dogs and cats, although felines present varied susceptibilities and uncertain roles in transmission patterns in enzootic areas for *E. multilocularis* (40, 42, 43). Of the *E. granulosus sensu lato* group that may infect dogs, *E. granulosus sensu stricto* plays the most important zoonotic role, while the impact on human health of *Echinococcus vogeli*, *Echinococcus ortleppi*, and *Echinococcus canadensis* is minor and that of *Echinococcus equinus* is nonexistent (44). Felidae of Central and South America and lions of Africa are the proper definitive hosts of *Echinococcus oligarthrus* and *Echinococcus felidis*, respectively (45).

The involvement of dogs and cats in the epidemiology of zoonotic echinococcosis is reversed compared to that of *T. gondii* and *N. caninum* (see "*Toxoplasma* for Cats, *Neospora* for Dogs"), as dogs shed infectious *Echinococcus* eggs into the environment, while cats have only an unclear role for one single zoonotic species, i.e., *E. multilocularis*.

**Anatomy, biochemistry, and evolution.** The reasons why cats are suitable definitive hosts of *E. multilocularis* but not of *E. granulosus sensu lato* are unknown. The eligibility of a definitive host for *Echinococcus* species depends on the size of Lieberkuhn crypts (intestinal glands between the villi, covered with epithelium), which allow adult worms to attach to the intestinal mucosa (46), but no prominent differences exist between dogs and cats (15.8 and 17.5 $\mu$m, respectively) but rather between them and red foxes (4.8 $\mu$m) (43). The space needed for *E. granulosus sensu lato* to establish in the intestine is bigger than that for *E. multilocularis*, and this may explain why red foxes are suitable hosts for *E. multilocularis* and not for *E. granulosus sensu lato* (47, 48). Further data are necessary to understand if crypt characteristics or other anatomical features drive differences in the susceptibility of dogs and cats to adult *Echinococcus*.

Differences in bile compositions between dogs and cats could be the reason why the latter animals are unsuitable hosts for adult *E. granulosus sensu lato* (49), because host bile composition is decisive for the establishment and development of *Echinococcus*. As a result, intermediate hosts do not acquire the intestinal infection via the ingestion of the cysts, and definitive hosts do not develop the larval forms by digesting eggs, with only scattered exceptions, as described below (41, 50, 51).

The adaptation of *E. granulosus sensu lato* and *E. multilocularis* to dogs and cats as definitive hosts, rather, depends on the predator-prey associations and the animal species serving as intermediate hosts. Those of *E. granulosus sensu lato* are large mammals (e.g., sheep, cattle, and pigs), while those of *E. multilocularis* are small rodents such as muskrats, voles, and mice (43, 52, 53). The main intermediate hosts of *E. granulosus sensu lato* can be preyed by dogs but not by cats, while those of *E. multilocularis* can be preyed by both. Thus, the ability of *E. multilocularis* to develop in cats is a factual evolutionary response to its adaptation to rodents as intermediate hosts.

**Animals and people: a different clinical impact.** The presence of adult *Echinococcus* spp. in the intestines of dogs and cats is generally considered minimally pathogenic, and heavy infections do not cause apparent clinical signs even though the parasites penetrate deep between the intestinal villi (54). In the rare cases when cysts of *E. granulosus* and *E. multilocularis* establish in dogs and cats, the health impact in these animals may be severe. In fact, the development of larval *E. granulosus* may result in excessive numbers of hydatids that fill up all the peritoneal space, causing life-threatening and intense dilatation of the abdomen, ascites, and organ dysfunction (50, 51). Alveolar echinococcosis in dogs is described in highly enzootic areas, i.e., central Europe and North America (55, 56), with the typical lesions, mainly in the liver but also in the lungs and other organs (57). The disease is progressive and fatal if left untreated (58). The alveolar cysts of *E. multilocularis* are even rarer in cats (56).

Humans are considered dead-end hosts for *Echinococcus* spp., as they are normally outside the prey range of definitive hosts (45). Human CE has a worldwide distribution, with higher rates in South America, Eastern Europe, Southern and Eastern Mediterranean, the Middle East, some sub-Saharan countries, and Western China, where free-ranging livestock farming is spread in rural and suburban areas (45, 59). Genotypes G1 to G3 (sheep/buffalo strains) of *E. granulosus sensu stricto* cause most

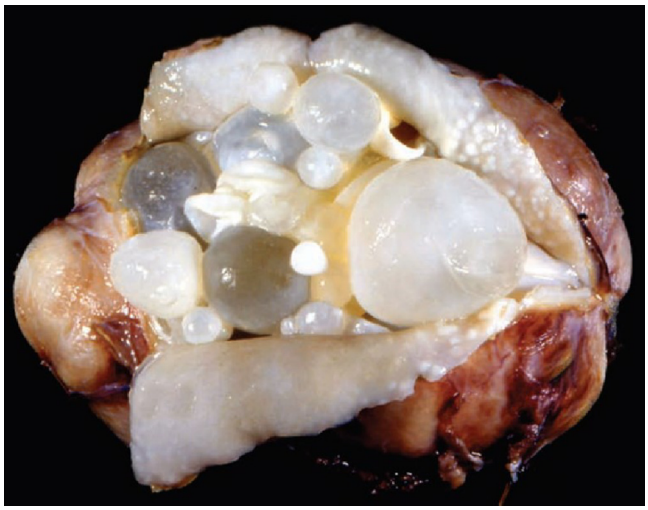

**FIG 5** Human cystic echinococcosis, large cyst with internal daughter cysts. (Courtesy of Giuseppe Cringoli, University of Naples, Italy; reproduced with permission.)

human CE cases worldwide, in which cysts develop primarily in the liver (Fig. 5) and lungs and are often fertile (53, 60). The spreading of CE in many parts of the world is due to the high infectivity of *E. granulosus sensu stricto* compared to that of other *Echinococcus* species (53). Even though CE may be subclinical and the presence of a cyst(s) is incidentally revealed during imaging examination performed for other reasons (Fig. 6), symptoms associated with the localization of the cysts and the involved organ(s) are occasionally severe, potentially fatal, and include upper abdominal discomfort, distress, cholestasis, dyspnea or coughing, neurological disorders, and pathological fractures (40, 54, 59). The prevalence of human CE increases with age, causing a lifelong health issue for infected people and involving significant medical and social cost. CE is the most geographically distributed *Echinococcus* infection though underreported both in humans and animals (60, 61).

Human AE displays significant epidemiological and clinical differences compared to those of CE. As a result of the narrow intermediate host adaptability of *E. multilocularis*,

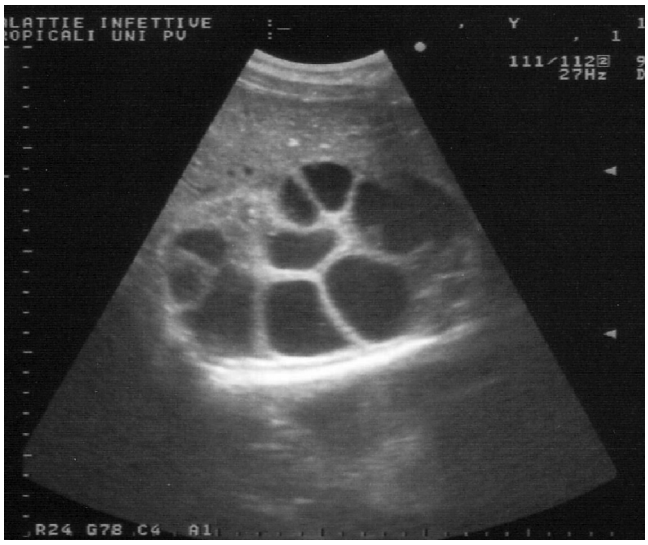


**FIG 6** Hepatic ultrasonography in a human patient with cystic echinococcosis, presence of multiple hydatids in the liver. (Courtesy of Enrico Brunetti, Department of Clinical, Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Pavia, Italy; reproduced with permission.)

this metacestodosis is relatively rare in humans, even where it is prevalent in animals (45). It occurs mostly in Northern and Central Europe, Asia, and North America, with evidence of expansion in Eastern and Western Europe (59, 62). AE is one of the most pathogenic parasitic zoonoses in temperate and arctic regions of the Northern Hemisphere (63) and develops slowly, with the first symptoms appearing the earliest approximately 1 year up to decades after infection in immunocompetent patients, or faster in immunodeficient individuals (64, 65). It is an aggressive and often deadly disease that displays neoplasmatic characteristics (65). The liver is the primary organ affected by larval *E. multilocularis*, but the infection may threaten other organs due to metastatic dissemination and/or infiltration of neighboring sites (64).

CE is one of the few parasitoses for which organized control or eradication efforts were successfully implemented in some insular areas, but in continental areas, the decrease of cases is considered a more realistic goal to set (60, 66, 67), and additional control strategies, e.g., livestock vaccination, could be also considered, especially because diagnostic hindrances prevent reliable large-scale diagnosis in dogs (60, 67, 68). Unfortunately, similar control measures for *E. multilocularis* are unrealistic due to its sylvatic life cycle.

In any case, as a contaminated environment is the primary source of *Echinococcus* species infection, prevention on a case-by-case level is achievable by avoiding the inadvertent ingestion of eggs by applying basic hygiene measures, e.g., washing fruits and vegetables, drinking only sanitized water, and washing hands after contact with soil or other potentially contaminated materials. These simple measures are particularly important in areas where *Echinococcus* spp. are prevalent, e.g., rural territories shared by sheep and dogs and forested environments with foxes and rodents living in sympatry. This is also true if one considers the description of human cases caused by the neotropical species *Echinococcus oligarthrus* and *Echinococcus vogeli*, maintained by small felids and canids preying on rodent intermediate hosts (69), and by the big-felid-related *Echinococcus felidis* having large mammals (e.g., hippopotamuses) as intermediate hosts (70).

### Protozoa Contaminating Water, Soil, and Vegetables

***Giardia*, *Cryptosporidium*, and *Blastocystis*.** *Giardia duodenalis* (syn*., Giardia intestinalis* and *Giardia lamblia*), *Cryptosporidium* spp., and *Blastocystis* spp. are protozoa with a direct life cycle playing a major role in diarrheal diseases of animals and humans (71, 72). Dogs and cats may be infected by these zoonotic parasites, though their involvement as an indirect source of human infections is not fully unraveled yet. The infection occurs via ingestion of parasite cysts (*Giardia* spp. or *Blastocystis* spp.) or oocysts (*Cryptosporidium* spp.), shed in the feces of infected individuals into the environment (72–74).

Eight genotypic assemblages (A to H) are currently recognized within the species *G. duodenalis* (75). Most of them infect more than one species, and some have zoonotic potential. Dogs usually harbor assemblages C and D, and cats harbor assemblage F. Both may also be infected by assemblages A and B, which have the widest geographic distribution and are primarily found in humans (75–77). In general, dogs are more frequently parasitized by zoonotic assemblages (i.e., assemblages A and B) than cats (76, 78).

Among the various *Cryptosporidium* species and genotypes, dogs and cats are predominantly infected by *Cryptosporidium canis* and *Cryptosporidium felis*, respectively, while *Cryptosporidium hominis* infects humans (79). In some cases, *Cryptosporidium parvum* and *Cryptosporidium muris*, which are the species of animal origin most frequently infecting people, have occasionally been identified in dogs and cats (79).

The traditional names of *Blastocystis* species initially used were based on the host from which the isolate originated, e.g., *Blastocystis hominis* from humans or *Blastocystis ratti* from rodents. They have recently been abandoned because of the high genetic diversity of the parasite (80, 81). Host specificity as well as pathogenic potential of the isolates is associated with variations in the small-subunit (SSU) rRNA gene. To date, 22 valid *Blastocystis* subtypes (STs) have been identified on this basis (80), but no valid

species has been characterized yet. In humans, 10 subtypes (ST1 to ST9 and ST12) have been identified. Of these, only ST9 is exclusively found in humans, while the rest may be considered zoonotic (81). Most (90%) human isolates belong to ST1 to ST4; of these, the subtypes ST3 and ST1 are also found in dogs, and ST4, a mainly rodent subtype, is also found in cats (72, 74, 81).

**Different parasites: similar epizootiology and clinical manifestations.** More similarities than discrepancies are evident in terms of prevalence and involvement in zoonotic transmission patterns for giardiosis and cryptosporidiosis in dogs and cats, although these are very different parasites (82). Puppies and kittens are more often infected than adults, probably because young animals are naive and less immunocompetent, and both animal species have been reported to shed *Giardia* cysts more frequently than *Cryptosporidium* oocysts (83–85). This is due to the narrow host range of *Cryptosporidium*, i.e., dogs and cats are infected mainly by *C. canis* and *C. felis,* respectively, and less frequently by other species such as *C. parvum* (74, 86). Conversely, the host range of *G. duodenalis* is broader, as dogs, and less often cats, may also share genotypes usually infecting other animals (87). Strains of varied pathogenicity have been identified for both parasites (88), and they cause infections that may remain subclinical or manifest with gastrointestinal signs such as acute or chronic diarrhea, abdominal pain, nausea, vomiting, and weight loss (76, 88). For instance, *Giardia* cysts may be found in feces of both healthy and symptomatic (diarrheic) animals at similar percentages (85). Other than age and strain involved, clinical presentation of giardiosis is also influenced by genetic predisposition, coinfections, gut microbiota, nutritional status, stress, and immunosuppression (89). Analogously, dogs are often subclinically infected with *Cryptosporidium*, but when signs are present, they manifest as an acute small-bowel diarrhea (83). Diarrhea is more common in cats, especially kittens, than in dogs, and the oocyst shedding may persist for months, with recurrent clinical signs. Factors that are associated with the infection are weaning or other environmental stress and nutritional deficiencies, while coinfection with the immunosuppressive feline leukemia virus does not seem to predispose them to cryptosporidiosis (90).

The clinical impact of *Blastocystis* species infection in animals has not been thoroughly investigated. The infection remains subclinical in most infected dogs and cats (81, 91), though there are reports of diarrheal episodes (92). Shelter dogs and cats, due to their living conditions and scarce hygiene, seem to be more at risk of harboring and shedding *Blastocystis* spp. than owned pets (91, 93).

**Human diseases and pet involvement.** The extent of zoonotic transmission of *Giardia* and *Cryptosporidium* from dogs or cats to humans and vice versa is still unclear (78), although companion animals and people may share different species/genotypes. In general, dogs and cats are considered to play a limited role as a source of giardiosis to humans (94, 95). The human infection is caused by assemblages A and B, which are also considered two separate species (*G. duodenalis* and *Giardia enterica*, respectively), and are isolated from dogs and cats only occasionally (75, 76, 78). However, controversial results have been generated by molecular characterization of assemblages infecting dogs, cats, and humans living in the same communities. In some cases, animals and humans share the same *Giardia* isolates (96), while in others, the genotypes are different (94, 95). Three different subassemblages are described within assemblage A: subassemblage AI is most commonly found in animals, including cats, while subassemblages AII and AIII are found mostly in humans and wild ruminants, respectively (78). Moreover, assemblages more commonly affecting dogs and cats, i.e., C-D and F, respectively, have been reported in humans only seldom (97). Further large-scale surveys are still necessary to ultimately ascertain the extent of the zoonotic transmission of *Giardia* spp., as the mere detection of the same assemblages in companion animals and humans does not prove a cross-transmission (82). Human infection occurs via the ingestion of cysts contaminating fruits, vegetables, or water, and those infected can either be asymptomatic or present with diarrhea, epigastric pain, nausea, and vomiting 1 to 2 weeks postinfection (78). This acute phase usually lasts for 1 to 3 weeks but, in some cases, may persist

longer. Self-limiting infections are also frequently observed, and chronic infections are also possible (78). In rare cases, postinfection implications include irritable bowel and chronic fatigue syndromes and extraintestinal complications such as cognitive dysfunction, ocular impairment, arthritis, and myopathy (78). However, the exact correlation of these clinical sequelae with giardiosis needs further investigation.

Human cryptosporidiosis is more common in developing countries, due to inadequate nutrition, hygiene measures, and water quality. Most human infections are caused by *C. hominis* and *C. parvum*, while *C. canis* and *C. felis* and other species of animal origin are relatively rare and account for ~4% of all cryptosporidiosis cases in developing countries (74, 79, 98, 99). People become infected by ingesting oocysts contaminating fruits and vegetables, water, and soil. The difference in virulence of various genotypes and some factors such as age, general health and immunocompetence, and prior exposure to the parasite determine the clinical presentation (90). The main symptom is diarrhea, varying from watery and continuous to scant and intermittent, and rarely containing blood. Other observed symptoms include fever, loss of appetite, nausea, vomiting, and malaise, while in some rare cases, hepatitis, pancreatitis, reactive arthritis, and respiratory implications have been reported (90).

Companion animals have recently been considered more frequently involved in the transmission of zoonotic *Blastocystis* than in the epidemiology of human giardiosis and cryptosporidiosis (74), despite data supporting that cross-infections by *Blastocystis* between dogs, cats, and their owners is uncommon (100). *Blastocystis* strains ST1 to ST9 and ST12 are zoonotic, while ST3 has been classified as primarily anthroponotic and is the most common subtype in humans (74). Human infection by *Blastocystis* spp. occurs by the ingestion of the cystic form of the parasite from the environment (contaminated soil, surfaces, food, and water), and accordingly, close contact with infected animals (e.g., shelter personnel and owners of infected pets) is hypothesized to be sometimes a risk factor (101). The infection in humans has a worldwide distribution and is one of the most frequently detected in epidemiological surveys, i.e., both in symptomatic and healthy individuals (93). Nonetheless, the pathogenic role of *Blastocystis* spp. in both animals and humans is still controversial (102, 103), as the parasite is sometimes considered an agent of extraintestinal and gastrointestinal disorders (abdominal pain, vomiting, urticaria, diarrhea, and irritable bowel syndrome), while other authors include it in the healthy gut flora (72, 80, 93). It is suggested that only some subtypes may be pathogenic to humans, though ST3 is present in both symptomatic and asymptomatic individuals (81). *In vitro* and *in vivo* assays have identified specific virulence factors associated with the disruption of the intestinal barrier (81). For example, ST7 uses hydrolases that cause damage in host tissues. Nevertheless, numerous other studies have not identified any distinct differences in the STs isolated from symptomatic versus those from asymptomatic cases. At the same time, gut microbiota may also be decisive for the pathogenicity of *Blastocystis* (81). To date, molecular identification and correlation with clinical manifestation have not ultimately clarified the relation of *Blastocystis* with clinical symptoms in humans (81); thus, further investigations are warranted to draw any final conclusions.

Overall, the variety of assemblages, genotypes, and subtypes of these protozoa render their epidemiological tracking complicated. However, the current data show a relatively limited and even debated zoonotic transmission of *Giardia* spp. and *Cryptosporidium* spp. from dogs and cats and, conversely, a possibly greater potential of *Blastocystis* spp. to share genotypes between dogs, cats, and humans. Regardless, these protozoa are of utmost importance for immunocompromised patients as opportunistic pathogens implicated in severe and potentially life-threatening diarrheal syndromes (104). The direct life cycle of these parasites makes prevention of human infection relatively simple by the application of the sanitary measures discussed above for *Echinococcus* spp.

## EVOLUTIONARY ADAPTATION OF NEMATODES: VETERINARY RECONSIDERATION AND ZOONOTIC IMPORTANCE

This section explores the multifaceted world of parasitic nematodes affecting dogs

and cats, with a focus on their various transmission patterns and coevolution adaptation mechanisms within their hosts. Variability and complexity of evolutionary strategies of the several nematodes harbored by canines and felines are discussed in this section of the article, with veterinary and public health perspectives.

## Roundworms and Hookworms: Masters of Transmission

**Biology and transmission patterns.** Nematodes of veterinary and public health significance may inhabit the small intestines of dogs and cats. The roundworm *Toxocara canis* and the hookworm *Ancylostoma caninum* infect dogs, and the corresponding parasites *Toxocara cati* and *Ancylostoma tubaeforme* infect cats. Others, like the less distributed ascarid *Toxascaris leonina* and the ancylostomatid *Uncinaria stenocephala* infect dogs and, less frequently, cats (105, 106). In some geographies, dogs (but no cats) may also harbor the raccoon roundworm *Baylisascaris procyonis* (107), and both dogs and cats can be parasitized by the tropical hookworms *Ancylostoma ceylanicum* and *Ancylostoma braziliense* (105).

As a result of their multiple and highly adapted ways of transmission, the roundworms *T. canis* and *T. cati* are the most widespread helminths of pets, while hookworms are more prevalent in dogs than in cats. Roundworms are acquired via various routes, e.g., ingestion of infective larvae in eggs or paratenic hosts and transplacental or lactogenic transmission to the fetus or offspring. The fecal-oral route is more important in dogs, as they ingest infectious ascarid eggs from the environment (Fig. 1) more often than cats (108, 109). *Toxocara* spp. are also transmitted via paratenic hosts, and this is particularly important for *T. cati*, due to the feline predatory instinct. It is occasional that dogs and cats become infected with roundworms by preying and ingesting infective eggs when self-grooming, respectively, (Fig. 2) (106, 110–112).

Vertical transmission plays a key role in *T. canis* life cycle. Bitches are a primary source of infection for puppies, via the reactivation of arrested somatic larvae and the subsequent transplacental and lactogenic infection of the offspring (106). Conversely, prenatal infections with *T. cati* do not occur, while the lactogenic transmission takes place only when a queen acquires the nematode at late pregnancy, as cats are not as permissive as dogs for somatic larval arrest and reactivation (113). The reasons for these biological differences among roundworms likely rely on immunity mechanisms. Murine models have shown that a predominant T helper type 2 (Th2) response occurs after or in concomitance with a downmodulation of T helper type 1 (Th1) response during chronic *T. canis* infection with somatic larvae (114). Thus, the commonly Th1-oriented immune responses of cats (115) may impair the establishment of somatic larvae. These features could also explain why cats, in contrast to dogs and a range of other vertebrates, have never been reported to have larva migrans syndromes by *B. procyonis* (116, 117).

The infection of dogs with *B. procyonis* occurs after the ingestion of larvated eggs from the environment or by ingesting infective larvae in rodent paratenic hosts (117, 118). Indeed, the role that dogs play in the biology and epizootiology of *B. procyonis* is unusual, as they act as both definitive (i.e., develop patent intestinal infections) and paratenic (i.e., suffer clinical larva migrans) hosts (119, 120). It is also singular that dogs are the only nonprocyonid animal species infected by *B. procyonis*, and this is of importance, as people may inadvertently ingest eggs which have become infectious in the environment. Cats do not develop intestinal infections or suffer larva migrans syndromes caused by this parasite, and similarly, no other carnivore is permissive for *B. procyonis*. The reasons are hard to determine, and this biological feature seems a parasitological paradox, considering that a common source of infection is represented by paratenic hosts that are preyed by cats, coyotes, and foxes and that these carnivores live in sympatry with raccoons in many areas enzootic for *B. procyonis* (118). A low level of adaptation of this parasite to nonprocyonid hosts due to a recent host-switching event spurred by a rise of raccoon populations and simultaneous conurbation could be at the basis of the occasional occurrence of this roundworm in dog populations (118). It is unknown if *B. procyonis* will adapt also to cats in the future and if, as other

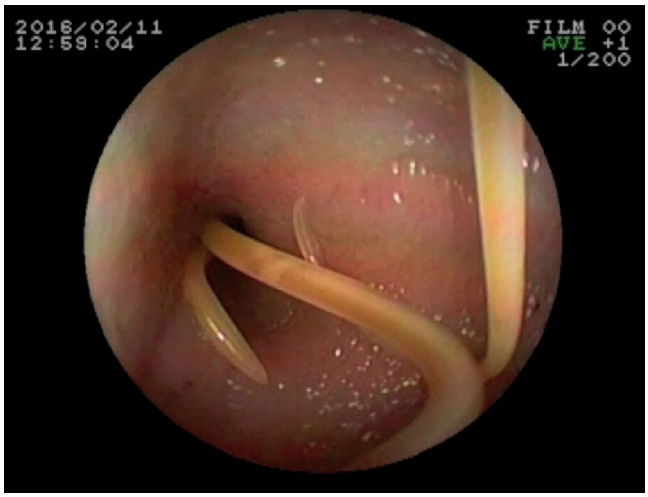


**FIG 7** Endoscopic visualization of *Toxocara cati* in a cat. (Courtesy of Enrico Bottero; reproduced with permission.)

ascarids (e.g., *T. leonina*), it will infect wildlife and domestic dogs and cats in areas of sympatry.

The predation of paratenic hosts could result in the infection of pets by ancylostomatid hookworms, but the primary sources of infection are third stage larvae (L3) in the environment that invade the definitive host by skin penetration or ingestion (106, 121). In most geographic areas, the prevalence of hookworms in dogs is higher than in cats (122–124). While *A. caninum* is transmitted vertically via lactation, cats (as in the case of *T. cati*) are not permissive to the establishment of somatic larvae of *A. tubaeforme*. Moreover, *A. tubaeforme* and *U. stenocephala* are not as successful as *A. caninum* in percutaneous infections (106, 112), and this reduces the infection chances for cats. Dogs are at higher risk than cats of acquiring hookworms from the soil (Fig. 1). This is important considering that the main transmission route of *U. stenocephala* is fecal-oral, as L3 survive in the environment for months, even at low temperatures (125). Conversely, *A. caninum* and *A. tubaeforme* L3 are less resistant and survive only a few weeks in the environment (105). This explains why *U. stenocephala* is more common in dogs than in cats and also more frequent than *A. caninum* in dogs in certain areas (126, 127). The tropical species *A. ceylanicum* and *A. braziliense* are very similar species in terms of biology, epizootiology, geographic distribution, and transmission patterns. Their life cycles are similar when animals ingest L3, while *A. braziliense* has a quicker development when larvae invade the skin (128).

**Danger for dog and cat small bowels.** Roundworms live free in the lumen of the small intestine, eating the nutrients they need from its content (Fig. 7). Mild infections are usually subclinical, while clinical signs are evident during larval migration and intestinal infections of moderate or high parasitic load. Migration of larval worms causes pneumonia, cough, nasal discharge, and pulmonary edema, which can potentially be fatal in puppies after a heavy transplacental infection (112). Adult worms induce enteritis characterized by vomiting, diarrhea, ascites, anorexia, emaciation, poor coat, nasal discharge, dysbacteriosis, and pot belly in both dogs and cats. Heavily infected animals may present episodes of vomitus and/or diarrhea with worms expelled spontaneously (Fig. 8). Heavy infections may lead to the death of puppies and kittens due to intestinal obstruction or occlusion, duodenum dilatation, peritonitis, rupture of the intestine, penetration into the peritoneal cavity, hemorrhage, or bile and pancreatic duct blockage (106).

Hookworms are considered among the most pathogenic nematodes parasitizing dogs and cats, as they may cause severe intestinal damage resulting in a fatal outcome, depending on different factors, including the species involved (e.g., *A. braziliense* and

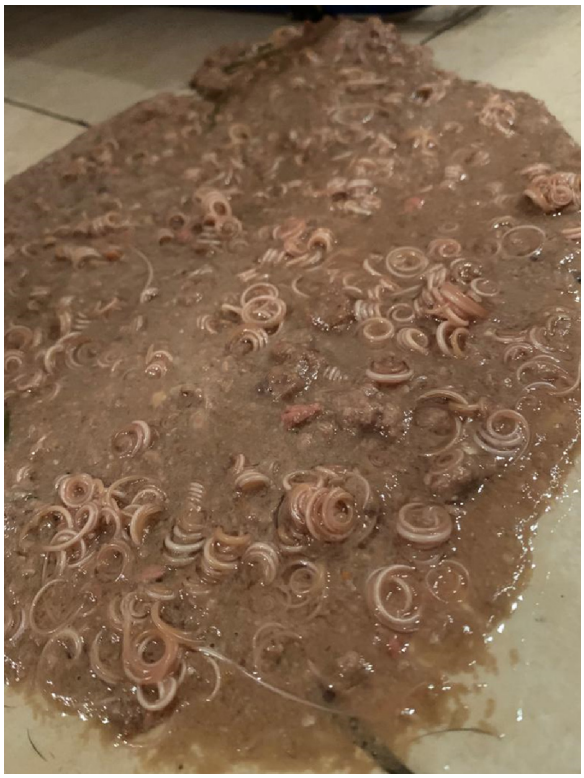

**FIG 8** Adult *Toxocara canis* in the vomitus of a massively infected dog. (Courtesy of Eleonora Grillotti, Ambulatorio Veterinario Reate, Rieti, Italy; reproduced with permission.)

*U. stenocephala* are mildly pathogenic, while *A. caninum* causes important exsanguination) (106, 129). Both immature and adult worms bite the gut mucosa and continuously suck blood, causing clinical signs and high death rate, especially in puppies and kittens that have a limited ability to compensate for blood loss (106, 129). Animals may suffer enteritis, hemorrhagic diarrhea, iron deficiency anemia, weight loss to cachexia, reduced growth, circulatory collapse, lethargy, and lack of stamina (106, 112).

**Danger for the human body.** *Toxocara canis* is traditionally acknowledged as a globally distributed major zoonotic parasite, while the role of *T. cati* in human infections requires further investigations, as it may have been erroneously underestimated for a long time (106, 130). Recent surveys indicate that *Toxocara* species eggs are found more commonly in sandpits rather than the soil of parks and that *T. cati* is the most common roundworm in urban areas (131, 132).

Humans can suffer larva migrans syndromes when they inadvertently ingest *Toxocara* infective eggs from the soil or infective larvae in paratenic hosts. After infection, the larvae wander throughout the body via the bloodstream and settle in tissues and organs, where they do not reach adulthood but cause local reactions and lesions. Though some infections are asymptomatic, two major syndromes may occur, i.e., visceral larva migrans (VLM) and ocular larva migrans (OLM). The former involves mainly the liver and lungs (and sometimes the brain, causing cerebral larva migrans), while the latter involves the eyes and optic nerve (130). Severe symptoms are frequent in children, particularly toddlers, affected by VLM, which is characterized by signs that vary according to the localization of the larvae, e.g., pneumonitis, myocarditis, necrotic hepatitis, meningoencephalitis, seizures, and neuropsychiatric signs (133–136). Clinical signs of OLM are also often serious and range from impaired vision to glaucoma, detachment of the macula, and total loss of sight (136). Unfortunately, many cases of OLM may resemble a retinoblastoma, and erroneous diagnoses cause unnecessary eye enucleations (110). Other minor syndromes exist, e.g., long-term exposures to

migrating larvae in some anatomical sites may cause nonspecific respiratory, neurological, and behavioral signs (137–139) or more specific skin diseases (136, 140). Cases of adult *T. cati* passing from the anus or the mouth of children have been published, but these events have been attributed to ingesting worms from vomitus or feces of an infected cat (141, 142). *Toxocara leonina* is not considered zoonotic, although old records have posed some suspicions on its ability to cause infections in humans, albeit never ultimately confirmed (106).

From a clinical point of view, *B. procyonis* is probably the most harmful zoonotic ascarid. This is a key parasite of the domestic animal-wildlife interface, especially in regions of North America where it causes intestinal infection in raccoons and may also parasitize dogs (107, 143). The relocation of raccoon populations from their native regions to Europe has introduced this zoonotic agent in new areas, and consequently, *B. procyonis* is now present in Central and Northern Europe (144–147). The proximity of raccoons to humans and pet populations is a key health risk, because eggs of *B. procyonis* survive and retain their infectivity for years, being a source of infection for wildlife, paratenic hosts, and dogs (148). Dogs infected by *B. procyonis* may be more dangerous than raccoons, because they defecate indiscriminately while raccoons have "latrines," i.e., defined areas for defecation (149). Accordingly, the results of a recent study where *Baylisascaris* species eggs were recorded in the feces of domestic dogs in various regions of the United States are of high public health concern (120). In fact, infected dogs may spread *B. procyonis* ova into the environment, where they can become infectious and then inadvertently swallowed by human beings, as happens for *Toxocara*. Though the ability of *B. procyonis* to develop in the intestines of dogs is undisputed, the real infection rate could be overestimated, as some dogs have spurious infections, i.e., they shed *Baylisascaris* eggs due to ingestion of raccoon feces (120). Dogs are more prone to pica and coprophagy than cats (108, 109), and this adds another reason why cats do not have any role in the transmission pattern of this harmful parasite. Notwithstanding, the factual role of dogs in causing human larval syndromes by *B. procyonis* is unknown. Cases of OLM by *B. procyonis* from South America have been attributed to animals other than raccoons, including dogs (150). As with other animal roundworms, humans become infected with *B. procyonis* by inadvertently ingesting larvated eggs. The larvae cause a deadly neural larva migrans (NLM) syndrome but may also induce OLM, VLM, a diffuse unilateral neuroretinitis, and covert infections. The number of described human cases of NLM caused by *B. procyonis* is relatively low, but its pathogenicity renders the control of infection in populations of domestic animals fundamental, given that this parasite causes permanent and life-threatening cerebral damage (151). Importantly, *B. procyonis* is difficult to recognize in dogs, as this infection is unexpected. Roundworm eggs are usually not subjected to thorough microscopic analysis, which would allow the discrimination between *Toxocara* spp. and *B. procyonis*. In fact, *Toxocara* spp. and *Baylisascaris* spp. present microscopic similarities (Fig. 9) requiring an experienced operator to discriminate them (117).

Dogs and cats act as dissimilar sources of hookworm infections for people, because animal ancylostomatids have various degrees of zoonotic potential and different geographical distributions. Humans suffer when L3 present in the soil enters the skin and causes cutaneous lesions ranging from local irritation to a cutaneous larva migrans (CLM) syndrome. In some cases, animal hookworms induce ocular or neurological signs and intestinal diseases.

The U.S. CDC states CLM to be a "zoonotic infection with hookworm species that do not use humans as a definitive host, the most common being *Ancylostoma braziliense* and *Ancylostoma caninum*" and that it "has been associated with *Ancylostoma caninum*, *Ancylostoma braziliense*, and *Uncinaria stenocephala*, which are all hookworms of dogs and cats."

However, the role of animal hookworms in causing human diseases was questioned already a decade ago (105, 106). It is established that *A. braziliense* is the agent of CLM in humans, causing typical dermatitis with cutaneous serpiginous tracks (Fig. 10). In general, the geographic distribution of CLM overlaps that of *A. braziliense* (152, 153),

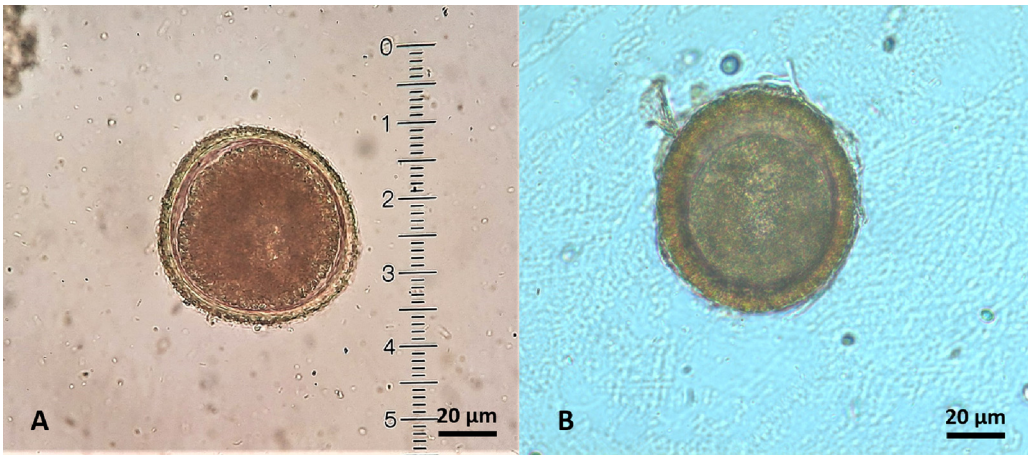


**FIG 9** Microscopic similarity between *Toxocara* (left) and *Baylisascaris* (right) eggs.

and the disease is endemic in (sub)tropical regions of the Southern Hemisphere, being absent in areas where this hookworm does not occur. Nonetheless, recent literature analyses have described cases of presumed CLM in Europe (105, 154–156) based on clinical presentations and epidemiological considerations, while unequivocal identification of the causative agent was not provided. Thus, the factual roles of *A. caninum*, *A. tubaeforme*, and *U. stenocephala* as agents of cutaneous lesions and CLM are still unclear. The ability of *A. tubaeforme* and *U. stenocephala* to infect humans is questionable, because they have a negligible ability to penetrate human skin (105, 106), while *A. caninum* is proven to cause local lesions (e.g., papular/pustular eruptions) rather than serpiginous tracks typical of CLM (157–159). Other conditions occasionally attributed to *A. caninum* are myositis, unilateral subacute neuroretinitis, and eosinophilic en-

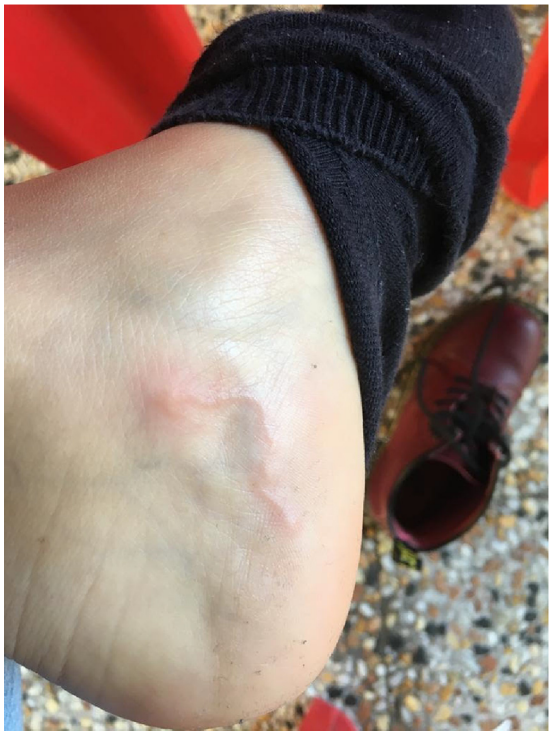

**FIG 10** Serpiginous tracks caused by cutaneous larva migrans in a human patient. (Courtesy of Flavia Stangherlin; reproduced with permission.)

teritis (160–163). A recent case of CLM in Ecuador was attributed to *A. caninum*, based on the presence of hookworm-infected dogs in the areas where the patients lived, though, again, no identification of the causative agent in the human skin was performed (164). Although infections by adult *A. caninum* have been described (165), *A. ceylanicum* is the key animal hookworm that can mature in the human bowel and cause patent infections, though it may also cause an OLM-like syndrome (166). Dogs and cats are reservoirs of *A. ceylanicum* for human infection, especially where this nematode is enzootic, i.e., in rural areas of Southern and Pacific Asia, where it is the second most common hookworm in people (167, 168).

Overall, larvated eggs of ascarids are of major epizootiological and epidemiological importance, especially due to (i) their resistance in the soil even under harsh conditions, (ii) the huge numbers of elements shed by infected animals, and (iii) their global geographical spread (106). In wide regions of North America, and in some Europe territories, dogs shedding *B. procyonis* eggs due to spurious or real infection are a potential source of a deadly disease for people (107). Regarding ancylostomatids, both dogs and cats may contaminate the environment, causing human CLM (*A. braziliense*) and intestinal infections (*A. ceylanicum*) in subtropical and tropical regions (105, 166). In the Northern Hemisphere, dogs infected with *A. caninum* are the source of soil contamination and thus of human infection, resulting in clinical conditions caused by migrating larvae. Nonetheless, the apparent rise of autochthonous CLM in Europe and a possible current and/or future spreading of *A. braziliense* in warmer areas of Europe deserve further investigations, as it has been hypothesized that global warming could foster the spread of tropical hookworms in areas of the Northern Hemisphere where they are not endemic (154).

### Trichuridae and Capillariidae: Still Incomplete Knowledge

**Current data and missing information.** The whipworm *Trichuris vulpis* inhabits the colons and ceca of dogs worldwide, while felid whipworms are extremely rare and poorly studied. Also, the taxonomical status of felid *Trichuris* is controversial: two species, i.e., *Trichuris serrata* and *Trichuris campanula*, have been reported from cats, but incomplete descriptions and the presence of overlapping features have led to the hypothesis that they belong to a single species named *Trichuris felis* (110, 169–171). *Capillaria aerophila* infects trachea and bronchi of cats and dogs (172) and may infect humans as well (173), while the closely related *Capillaria boehmi* (syn. *Eucoleus boehmi*) has a narrow host range and no zoonotic potential (174, 175).

While many aspects of the clinical role of *Trichuris* spp. and *Capillaria* spp. in animals have been recently investigated, their current impact on human health is still far from being clarified.

**Clinical impact in dogs and cats.** The rarity of whipworms in cats may be attributed to the absence of paratenic hosts in the *Trichuris* life cycle that, instead, play a crucial role in the transmission of other intestinal nematodes to cats (see "Roundworms and Hookworms: Masters of Transmission" above). To date, cats infected by whipworms have been reported only in Australia and in tropical and subtropical areas of North and South America (170, 171, 176–178). This geographical distribution overlaps that of the human whipworm *Trichuris trichiura*, which occurs mainly in regions with a warm and humid climate (179). Whipworms have a direct life cycle, with the embryonated egg being the infective stage (110, 169). Experiments have shown that the embryonation of trichurid eggs is temperature dependent, and although no data are available on the embryogenesis of cat whipworms, it is likely that their eggs share similar biological features with *T. trichiura*, which optimally develops and rapidly becomes infective at high temperatures (128). In contrast, *T. vulpis* eggs can survive in the soil even under harsh conditions and in cold climates and contaminate the ground all over the world (169, 180). Given the positive influence of temperature on trichurid egg maturation, global warming could permit the spread of the feline species *T. felis* to new areas (171, 178). Therefore, a careful morphological evaluation (and eventually, molecular confirmation) should always be performed in the presence of barrel-shaped or lemon-like eggs

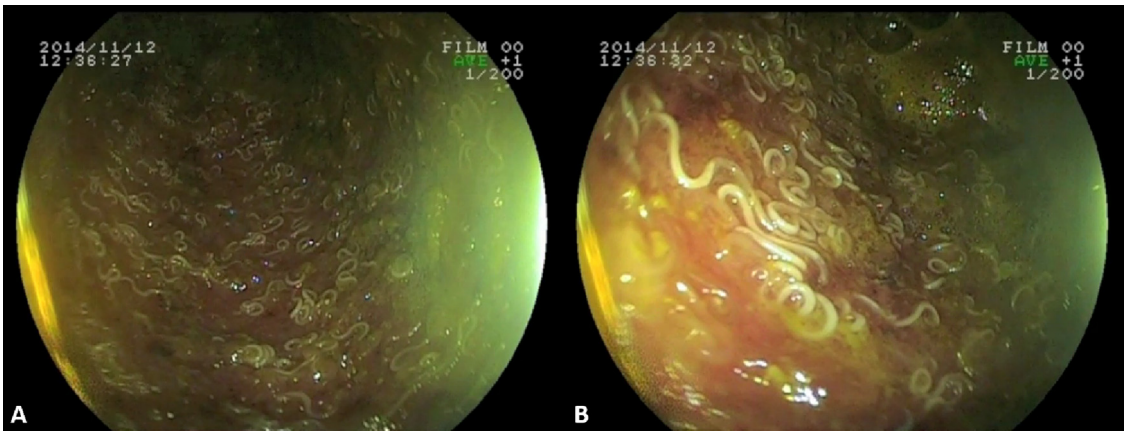


**FIG 11** Endoscopic visualization of *Trichuris vulpis* infection. (Courtesy of Enrico Bottero; reproduced with permission).

retrieved by fecal examination of cats. Further studies are also warranted in order to clarify the clinical impact of feline trichurosis.

Once ingested, embryonated eggs of *Trichuris* spp. hatch in the large intestine. Differences in terms of specific bacterium-induced hatching patterns have been demonstrated *in vitro* for *Trichuris muris* and *Trichuris suis* eggs (181). This close interaction between *Trichuris* species eggs and the animal microbiota can be explained by the coevolution process between the parasite and the host and is suggested to result in a host-specific hatching stimulus (181, 182). Considering that dogs and cats have different microbiota (183, 184), it can be argued that the different prevalences of whipworms in dogs and cats are related to different levels of coevolution between the parasites and the host microbiota.

The lungworm species *C. aerophila* lacks host specificity and infects a wide range of wild animals, such as felids, canids, mustelids, and humans (185–188). Conversely, the closely related *C. boehmi* lives beneath the epithelium of nasal cavities and sinuses of dogs and wild canids, but it has never been recorded in cats or humans (174, 189–191). The reasons for these differences in terms of host specificity, though these are very closely related nematodes, have never been investigated and are unknown.

Whipworm in dogs may lead either to subclinical infections or to acute or chronic enteritis (Fig. 11) (169). Common clinical signs are reduced growth rate, bouts of watery or hemorrhagic diarrhea alternating with periods of normal stools, weight loss, lethargy, dehydration, anemia, hyponatremia, and hyperkalemia (110, 169, 180, 192, 193). Sometimes, anemia and dehydration may lead to a fatal outcome (169). Conversely, whipworm infection in cats is described as a disease with a low clinical importance (177, 194), and typhlitis has been reported only recently (178).

Respiratory capillariases are often subclinical, though adult worms induce lesions in airways, leading to respiratory signs in both dogs and cats (172, 195–198). Chronic cough, tracheal hypersensitivity, bronchovesicular sounds, nasal discharge, sneezing, wheezing, and dyspnea have been described in animals infected by *C. aerophila* (195, 199, 200). High parasitic burden, mixed infections with other lungworms, and immunodeficiency may lead to life-threatening bronchopneumonia and respiratory failure (172, 195). Clinical signs of nasal capillariasis can be unapparent, but sneezing, reverse sneezing, nasal discharge, epistaxis, gagging, and impairment of the scenting ability are often recorded (197, 198, 201, 202). Neurological disorders due to ectopic localization or migration of *C. boehmi* are occasionally a cause of meningoencephalitis and cerebral granulomas (191, 203).

**Zoonotic infections: what is the real hazard?** Human trichurosis is caused by the host specific species *T. trichiura*. Although *T. trichiura* DNA has been isolated from feces of dogs and cats (204, 205), to date, there is no scientifically sound evidence of its ability to infect these animals. Eggs or DNA passed in feces do not necessarily correspond

to infection of the host but rather could indicate a passive transit through the host gut ("pseudoparasitism"). This phenomenon is a common event, e.g., eggs of the feline roundworm *T. cati* have been found with high prevalence in dog feces (206, 207). Thus, the presence *T. trichiura* eggs in canine and feline stool samples can be the result of coprophagy or of egg ingestion from the environment via contaminated food or water. Therefore, cross-transmission of *T. trichiura* between humans, dogs, and cats is excluded. Anyway, as dogs are more prone than cats to coprophagy and to ingest soil material (108, 206), studies investigating their role as mechanical transmitters of *T. trichiura* (and for other soil-transmitted parasites such as the human roundworm *Ascaris lumbricoides*) eggs in sympatric settings would be important from an epidemiological point of view.

The transmission of *T. trichiura* in humans occurs via ingestion of embryonated eggs through food or soil contaminated with human feces (208). The highest prevalence of the infection is recorded in developing tropical and subtropical regions, where standards of hygiene are poor and the warm and humid climate is favorable for the development of the eggs (208). Human infection is characterized by gastrointestinal symptoms such as abdominal pain, painful passage of stools, mucus discharge, diarrhea, and chronic anemia in heavy infections (209, 210). Children may develop the so-called "massive infantile trichuriasis," a severe disease associated with malnutrition, iron deficiency anemia, chronic mucoid diarrhea, rectal bleeding, rectal prolapse, and finger clubbing (211–213). The disease contributes to chronic, long-term nutritional morbidity, and it is incriminated as a cause of cognitive impairment (208, 214).

Two whipworms of animals have been incriminated to have a zoonotic ability, *T. vulpis* and the pig whipworm *Trichuris suis*. While *T. suis* may indeed infect people (215), ultimate evidence is yet to be generated for *T. vulpis*. Reports of human infections by *T. vulpis* exist in the medical literature, but its zoonotic potential is questionable because of the lack of sufficient morphological and molecular validation. This nematode has been identified in a few human clinical cases based on the size of eggs shed by allegedly infected people (216–218). Though eggs of *T. vulpis* and *T. trichiura* have different sizes, it has been proven that *T. trichiura* occasionally produces large eggs resembling those of *T. vulpis* (219). Worms identified as *T. vulpis* were also found in feces of infected children (220, 221). Nevertheless, in these cases, morphological descriptions were lacking, and findings were not molecularly confirmed. Recent surveys have confirmed that *T. vulpis* DNA can be isolated from human feces (204, 205, 222), but the ability of the parasite to establish in the human bowel was not proved, and the possibility that the eggs were ingested from the environment was not excluded (204, 205, 222). To date, ultimate evidence of human patent intestinal infections by *T. vulpis* (e.g., endoscopic visualization of adult parasites in the large intestine followed by microscopic and genetic identification of the worms) has not been published. Two cases of VLM caused by *T. vulpis* were described 40 years ago in Japan based on immunological methods (223). However, parasite larvae were not found in the tissues, and again, findings were later considered uncertain (169, 224). In another case, histological and immunological methods were applied to diagnose a presumptive VLM caused by *T. vulpis*, but an unequivocal identification of the parasite was not provided because of the morphological similarity between *T. vulpis* and other *Trichuris* spp. in histological sections and because other *Trichuris* species (e.g., *T. trichiura* or *T. suis*) antigens were not included in the immunodiagnosis (225).

Clinical signs in presumptive cases of human infection by *T. vulpis* are poorly described, with no definitive evidence of the ability of this parasite to cause compatible intestinal symptoms. As an example, chronic diarrhea, abdominal pain, and vomiting have been reported in a woman from the United States diagnosed with a patent mixed infection by *T. vulpis* and *T. trichiura* only based on egg size (218). Furthermore, clinical signs were unreported when *T. vulpis* DNA was detected in human feces (204, 205, 222).

On the other hand, *C. aerophila* is a zoonotic parasite, although thus far, only a limited number of human cases have been published (186, 226–231). Fifteen different

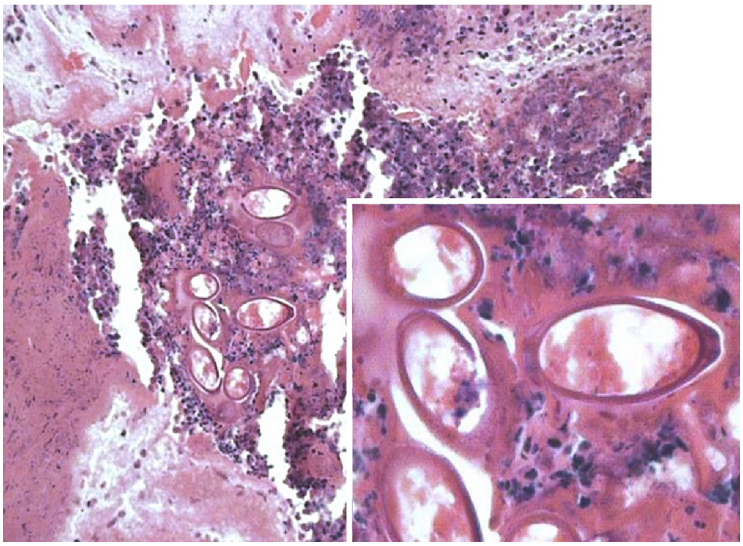

**FIG 12** Bronchial biopsy sample from a human patient. Capillarid eggs (square magnification) surrounded by necrotic tissue and eosinophilic infiltration. (Courtesy of Dušan Lalošević, Faculty of Medicine, University of Novi Sad, Serbia; reproduced with permission.)

haplotypes of *C. aerophila* have been molecularly characterized from dogs, cats, and wildlife, but possible differences in their zoonotic roles have never been investigated (187). Transmission patterns in humans are also unknown, although the inadvertent ingestion of embryonated eggs is the most likely way of infection for people. Clinical symptoms include coughing, mucoid or blood-tinged expectorates, fever, dyspnea, fatigue, and eosinophilia (186, 228–230). Bronchial carcinoma-like lesions (Fig. 12) have also been described in the last published case of human infection by *C. aerophila* (186). However, pulmonary capillariasis in humans is still neglected, and the infection could be underdiagnosed because the symptoms overlap those of a plethora of other respiratory diseases (172).

At the end, these nematodes pose a minor hazard for human health. The actual role of *T. vulpis* as a cause of zoonosis must be further clarified and should be evaluated cautiously, keeping in mind that *T. vulpis* DNA in human feces has been detected in rural areas, where eggs of *T. trichiura* are found in canine stool samples, advocating for accidental parasite element ingestion from a highly contaminated environment (204, 205). Accordingly, patterns of transmission of *C. aerophila* in areas where foxes, i.e., the natural reservoir of these parasites, are sympatric with dogs and cats need further investigation. Furthermore, the knowledge about the epidemiological role of dogs and cats in human pulmonary capillariasis and the impact of this infection on human health is still scant.

### Heartworms and Lungworms: To Be or Not To Be (Infected)?

**Terminology and classification.** The use of the traditional terms "heartworm" and "lungworm" for cardiopulmonary nematodes of dogs and cats is confounding. The most-known extraintestinal nematode of companion animals is *Dirofilaria immitis*, transmitted by the bite of infected mosquitoes. This nematode is commonly called "canine heartworm," although it inhabits the pulmonary arteries and is found in the right heart chambers only under some circumstances (232). The localization in the pulmonary vessels determines the nature of canine heartworm disease or dirofilariasis, which is, paradoxically, a primarily pulmonary disease that involves the heart only in later stages (233). This parasite is a major threat for dog health due to its pathogenic potential and its spread to many European and U.S. areas, which occurred by the 2000s (233). *Angiostrongylus vasorum*, classically known as the "French heartworm," is transmitted with the ingestion of intermediate (terrestrial gastropod) or paratenic hosts. It lives in the pulmonary arteries of

dogs, though commonly referred to as a "lungworm" (234, 235). The nematodes that parasitize the airways of dogs and/or cats (i.e., true lungworms) are the metastrongyloid *Filaroides/Oslerus* spp., *Aelurostrongylus abstrusus*, *Troglostrongylus brevior*, and *Crenosoma vulpis*, all acquired by the ingestion of intermediate (terrestrial gastropods) or paratenic (small vertebrates) hosts, and the capillarids *C. aerophila* and *C. boehmi*, having a direct life cycle with terrestrial invertebrates acting as facultative intermediate hosts (172, 236, 237). These nematodes have a null to minor zoonotic potential, as humans can be accidentally infected only by *D. immitis* and *C. aerophila* (232, 238). However, people can be parasitized by two closely related metastrongyloids affecting rodents, i.e., *Angiostrongylus cantonensis* and *Angiostrongylus costaricensis* (239, 240).

**Nematodes, arteries, and macrophages.** Nematodes inhabiting the blood vessels infect mainly dogs, while cats are typically parasitized by worms living in the airways. Accordingly, *Dirofilaria* and *Angiostrongylus* are of major importance in dogs and of less concern in cats, and lung infections by *A. abstrusus* and *T. brevior* are of utmost interest in feline medicine (241, 242). An opposite situation occurs in dogs, because the infections by worms of airways, i.e., *Capillaria* spp. and *C. vulpis*, have low prevalence and minor clinical importance compared to those of *D. immitis* and *A. vasorum* (243).

Helminths are excellent manipulators of host immune system and powerful tolerance inducers (244, 245), and they have evolved so to downregulate the immune response of different cell populations in tissues and host environments. A key example is given by *D. immitis* (246), which causes a typical chronic illness in dogs, while in cats, it is the agent of an unpredictable disease, ranging from subclinical to acute events and sudden death (233, 247). The unsuitability of cats as hosts of *D. immitis* is associated with feline heartworm-associated respiratory disease (HARD), an acute eosinophilic response caused by the arrival and early death of immature *D. immitis* in the pulmonary vessels (248). Although HARD may pass unnoticed in many cases, cats develop severe lung lesions and display signs similar to those of asthma or allergic bronchitis (247, 249). This eosinophilic reaction derives from the activation of pulmonary intravascular macrophages (PIMs) (250), i.e., specialized phagocytes that permanently reside in the pulmonary capillaries of cats (246). In some cats, despite the initial HARD phase, adult *D. immitis* establishes and produces molecules that downregulate PIMs, ensuring parasite tolerance (247). The death of adult *D. immitis* interrupts the anti-inflammatory effect of parasite secretions, thus setting the background for severe lung lesions, thromboembolism, and sudden death (246, 247, 251). This is a mechanism that does not occur in dogs, because PIMs are absent from their pulmonary vessels (246). Thus, the arrival of *D. immitis* L5 in the pulmonary arteries of dogs is followed by adult development, leading to a classical chronic infection (233).

Being unsuitable hosts for *D. immitis*, patent dirofilariasis is rare in cats (247), in which, similarly, there are no records of patent angiostrongyliasis, as only immature *Angiostrongylus chabaudi* and *A. vasorum* have been described (242, 252–254). A relatively narrow host range of *A. vasorum* and its primary affiliation to canids (255) may explain the inability to complete its life cycle in domestic cats. Likewise, the closely related *A. chabaudi*, whose natural host is the European wildcat (*Felis silvestris*) (256–259), has a specific adaptation to wildcats, likely due to downregulatory mechanisms which do not occur in domestic cats. It is plausible that wildcats have PIMs, as they are very closely related to *Felis catus*. Therefore, the host-parasite coevolution has likely led to PIM downregulation induced by *A. chabaudi* in the natural host in parallel with the downregulation of pulmonary alveolar macrophages (PAMs), as observed for *A. vasorum* in dogs (260). In fact, a downregulatory mechanism has been developed by adult *A. vasorum* toward canine PAMs as a survival strategy (260). Active PAMs would normally produce a more intense eosinophilic response toward *A. vasorum* first stage larvae (L1) that hatch and penetrate alveoli and would result in more severe lung damage with destruction of the larvae (260).

From an evolutionary standpoint, *D. immitis* has adapted to cats to a greater extent than *A. chabaudi*, due to (i) the wide distribution and high density of domestic and

wild canids acting as definitive hosts of *D. immitis* and (ii) the transmission via active vectors which may bite both canids and felids (233). Conversely, *A. chabaudi* is not actively transmitted by vectors, and the natural reservoir is elusive and lives mainly in forests and remote wild habitats, thus resulting in a low parasitic pressure on domestic cats.

**Animals, airways, macrophages, and age.** The cat lungworm *A. abstrusus* inhabits the terminal bronchioles, alveolar ducts, and alveoli of cats worldwide (241, 261). However, no similar parasites exist in canids. This lungworm is closely related to *A. vasorum* with which it has overlapping life cycles but different sites of parasitism. While larval *A. vasorum* stops inside the vessels and reaches adulthood in dogs (262), *A. abstrusus* perforates them to reach the lung parenchyma (263). Both *A. abstrusus* and *A. vasorum* belong to the Angiostrongylidae family and have a monophyletic relationship within the Carnivora order (264, 265). Therefore, after the divergence of cats and dogs from a common ancestor (264), *A. abstrusus* could have evolved differently from *A. vasorum* (and *A. chabaudi*) to escape PIM activity and take refuge inside the lungs (265). The immune response of cats is mostly directed toward *A. abstrusus* eggs and larvae rather than adult worms, as also happens in dog angiostrongyliasis, where inflammatory infiltration is triggered around *A. vasorum* larvae (265, 266). This suggests a downregulating action elicited by adult angiostrongylids and further supports the existence of similar mechanisms induced by *A. chabaudi* in its definitive host. Analogously, other mammals possessing constitutive PIMs, i.e., cattle, horses, pigs, sheep, goats, pigs, reindeer, and rabbits (246, 267), are not commonly parasitized by nematodes in pulmonary vessels but rather by those inhabiting the airways (128), and the majority of *Angiostrongylus* spp. inhabiting pulmonary vessels are adapted to animals lacking PIMs, i.e., dogs, rodents, and mustelids (268, 269).

Nematodes inhabiting lung parenchyma and airways of canids (i.e., *Oslerus osleri*, *Filaroides hirthi*, and *Filaroides milksi*) are extremely rare (174). These filaroids have a direct life cycle, which seems a less successful transmission strategy, as the lack of intermediate and/or paratenic hosts reduces considerably their transmission patterns compared to those of other respiratory parasites (174).

The importance of the crenosomatid *C. vulpis* in canine medicine is limited compared to that of the crenosomatid *T. brevior* in cats. While the latter seriously threatens the lives of cats, especially kittens (261, 270), *C. vulpis* usually infects dogs aged $>$1 year, and its pathogenicity is limited (174, 271, 272). Conversely, feline troglostrongylosis is of main concern, as *T. brevior* is vertically transmitted and causes irreversible pulmonary hypertension, airways occlusions, and death (261, 270, 273). Although *C. vulpis* and *T. brevior* are closely related, a vertical route of infection has been described only for the latter (273). This biological difference could be attributed to the dissimilar reproductive features of their natural reservoirs, i.e., the red fox for *C. vulpis* and the European wildcat for *T. brevior* (172, 274). European wildcats are scarcely prolific, and *T. brevior* may have adapted to vertical transmission to amplify its dissemination (275). This strategy is not necessary for *C. vulpis*, as foxes are prolific and ubiquitous (276). The broader host range of *C. vulpis* (277) further supports the lack of necessity for this parasite to develop additional transmission routes. It is worth noting that, similarly to *A. chabaudi*, *T. brevior* is a typical parasite of European wildcats. Nevertheless, troglostrongylosis is of primary concern in domestic cats while angiostrongyliasis has nil relevance (242, 261, 270). This confirms further the affiliation of nematodes living in the airways of domestic cats versus those living in blood vessels.

***Dirofilaria* in humans: a matter of geography.** Humans are not definitive hosts of nematodes living in heart, pulmonary vessels, or lung parenchyma and airways.

In areas where *D. immitis* is enzootic, humans may be bitten by infected mosquitoes; thus, immature or mature *D. immitis* is sporadically found in the pulmonary arteries of humans (232, 278, 279). Nevertheless, variable clinical consequences associated with pulmonary dirofilariasis and clinical manifestations related to noncardiopulmonary localizations are described (278). Human infections differ significantly from canine heartworm

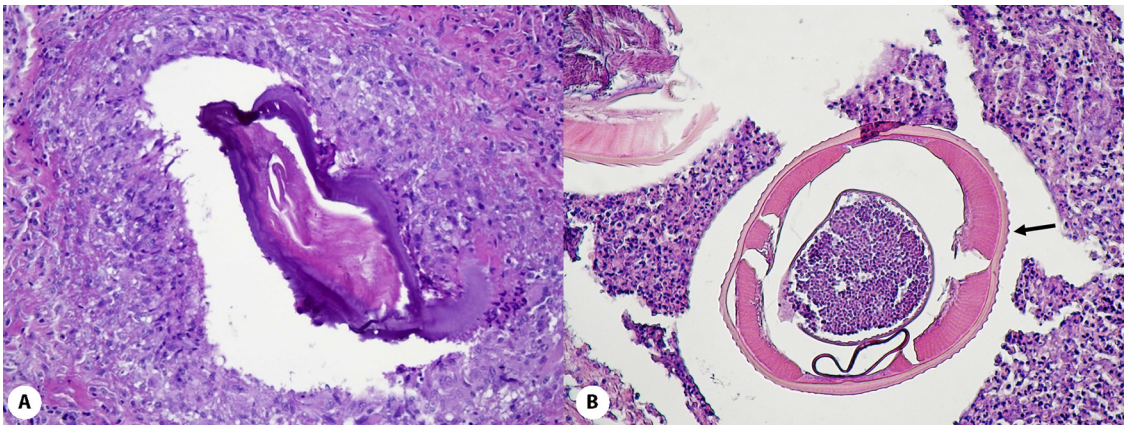


**FIG 13** (A) Histologic section from a mammary nodule of a human patient containing an adult *Dirofilaria repens* (Courtesy of Elisabetta Scoccia; reproduced with permission.) (B) *Dirofilaria repens* cross-section from an eye nodule of a human patient. The longitudinal ridges of the cuticle (arrow) are a morphological characteristic of the species.

disease, as the main outcome is the development of pulmonary nodules because of inflammatory responses induced by the dead parasite, incorporated into a granuloma that is visible as a "coin lesion" at X-ray imaging and computed tomography (232, 278). Coin lesions can be asymptomatic, but respiratory and nonspecific signs may occur, the most frequent being chest pain, cough, fever, malaise, and hemoptysis (278).

A possible correlation between *D. immitis* and the occurrence of allergic conditions in humans living in highly enzootic areas has been supposed (280), but the methodology applied (e.g., collection of data by questionnaire, unknown medical history of dog owners, and IgE detection in humans irrespectively of dog ownership) renders any conclusion indefinite, and sound large-scale surveys are necessary to corroborate this faint hypothesis.

Human infections by *D. immitis* are more frequent in the Americas and in Asia than in Europe (279, 281, 282), where people are most often infected by the subcutaneous *Dirofilaria repens*. This is interesting from an epidemiological standpoint, because *D. repens* infects humans more frequently even where *D. immitis* is more prevalent (282). Around a decade ago, the lower occurrence of *D. immitis* in European people was attributed to a possible existence of separate genotypes with various levels of pathogenicity on the different continents (282). Since then, no studies have been conducted to investigate this hypothesis in more depth, and it cannot be excluded that *D. immitis* infections in humans are overlooked in Europe due to (i) diagnostic hindrances inherent to detection and interpretation of lung lesions, (ii) asymptomatic infections, and (iii) scant awareness. Further studies are advocated to assess if new reports are due to a factual spreading or to undiagnosed cases in the past.

Sporadic noncardiopulmonary localizations, associated with corresponding lesions and diseases, have been described for *D. immitis* in different anatomical areas, mainly subcutaneous or cavitary (283–285). However, these localizations are more often recorded for *D. repens* (Fig. 13), which has clearly a higher zoonotic potential than *D. immitis* and is a public health concern in Europe (286).

Human infections with microfilaremia are described for *D. repens* but not for *D. immitis* (287, 288). This difference can be due to the different localization of these filariids. While human pulmonary arteries are a hostile environment for the development of adult *D. immitis*, the same is not true for the subcutis, probably because it is less exposed to the activity of phagocytes. Accordingly, PIMs can determine the unsuitability of humans to *D. immitis*, limiting the establishment of adult nematodes in pulmonary arteries, as described for cats. Although PIMs exist in humans (289), it is still not clear if they are permanently present (290) or if they have a role in the pathogenesis of coin lesions and/or in preventing patent infections.

**Zoonotic angiostrongyliasis.** To date, no human infections caused by canid or felid *Angiostrongylus* species have been described. Humans can, however, be parasitized by zoonotic *Angiostrongylus* species affecting rodents, i.e., *A. cantonensis* and *A. costaricensis* when ingesting infectious L3 on contaminated vegetables or in intermediate (snails and slugs) or paratenic (amphibians, reptiles, shrimps, and crabs for *A. cantonensis*) hosts (239, 240, 291, 292).

*Angiostrongylus cantonensis* is the primary cause of human eosinophilic meningitis worldwide and is endemic in South-Pacific areas, South-East Asia, and the Hawaiian Islands and is described also in Texas and Louisiana (United States), Egypt, Brazil, the Canary Islands, Japan, and South Africa (292–295). Records of neuroangiostrongyliasis due to *A. cantonensis* in Europe derive mainly from travelers that had visited regions of endemicity, though a recent autochthonous case has been described in France (240, 296, 297). Damages to the human brain caused by *A. cantonensis*, due to intense inflammatory reaction triggered by L3 migration and followed by parasite death, are often irreversible and life threatening (292, 298). Although a patent infection has never been described in humans, it has been recently hypothesized that *A. cantonensis* is able to reach human lungs more frequently than thought, especially in the case of massive infection (299).

*Angiostrongylus costaricensis* is spread particularly in South America and the Caribbean (239) and recorded also in the United States (291), where both autochthonous and imported human infections have been diagnosed (300–302). Human cases described in Europe derive from people that traveled to areas of endemicity (303, 304), and to the best of the authors' knowledge, autochthonous infections have never been reported. This nematode causes massive eosinophilic infiltrations in the intestinal wall and mesenteric vasculitis (239). Some cases are acute and manifest as an appendicitis-like disease requiring urgent laparotomy/laparoscopy, with unpredictable prognosis (239).

Despite evidence that dogs may be patently infected by *A. costaricensis* under experimental and natural conditions (305, 306), companion animals have no factual involvement in human angiostrongyliasis. Human neural and abdominal angiostrongyliases are neglected foodborne diseases caused by the consumption of traditional raw-fish dishes, contaminated vegetables, or unsanitized well water in areas of endemicity (307–309). Their epidemiology mostly relies on behavior and hygiene conditions of people living in areas where rodents are infected in high prevalence.

## BEHAVIORS AND THE IMMUNE SYSTEM DRIVING ECTOPARASITES AND TRANSMITTED DISEASES

In general, dog and cat ectoparasitoses are considered similar, despite key differences, originating from biological, behavioral, and immunological drivers, between canine and feline external parasites. This variability also has an impact on diseases transmitted via bites from infected vectors. Hence, the occurrence of infestations and transmitted diseases is different in dogs and cats, which have distinct epidemiological roles for vector-borne diseases affecting pets and humans. This section discusses the main ectoparasitoses and vector-borne diseases of dog and cats, with insights on their relevance to human health.

### Adaptive Mites and Consequences for Pets and People

**Burrowing mites are not for everyone.** The burrowing mite *Sarcoptes scabiei* commonly infests dogs and other mammals, including humans, but very rarely cats (310, 311). Conversely, cats have their "own" burrowing mite, i.e., *Notoedres cati* (312). Sarcoptic and notoedric mange are severe infestations of dogs and cats, and they can be life threatening, especially when the skin lesions are large and multiple. At the same time, human scabies is a parasitosis of major relevance, while human infestation by *N. cati* has null importance.

The evolution of *S. scabiei* explains why cats are an exception for sarcoptic mange. In fact, this mite originated from an ancestor parasitizing hominids and then coevolved with humans, who have then transmitted it to animals as they have tamed them as a

result of a parasitic spillover (313, 314). Dogs were among the first domesticated animals (313), while the domestication of cats began between 5,000 to 25,000 years later, and it is considered still ongoing (315). This time lapse could have influenced the adaptation of *S. scabiei* and the transmission from humans to domesticated and wild animals (313, 314). The adaptability of *S. scabiei* and the interbreeding of different strains have then originated different varieties that are taxonomically classified on the basis of host origin (314, 316, 317). A variant associated with felids has never been described.

The host range of these mites derives from a predator-prey affiliation. Dogs are more used to physical contact with humans and animals of other species (e.g., shepherd dogs in contact with farm animals) (Fig. 1), and this was probably essential in the origin of the epizootiology and epidemiology of sarcoptic mange (313). Most felids are instead solitary animals, with tactile contacts mostly limited to mating and preying (264, 318). While *S. scabiei* has a broad host spectrum (313, 314), the host range of *Notoedres* mites is restricted to small and medium-size felids, bats, rodents, lagomorphs, civets, coatis, and small Indian mongooses, with only few exceptions (312). Cats prey (Fig. 2) on small animals such as rodents, squirrels, and bats. Medium-size felids, such as lynxes, are commonly infected by both *N. cati* and *S. scabiei*, as they prey on both animals harboring both mites, e.g., rodents or foxes and roe deer, respectively (319–321). Accordingly, big felids, e.g., lions, are more frequently infested by *S. scabiei*, which is widely present in the wild mammals they hunt (322–325).

The mite-predator-prey affiliation has been evidenced also in experimental settings that have proved the inability of *S. scabiei* var. *canis* to infect mice, rats, and Guinea pigs, while it can infect rabbits and then reinfect other dogs (326, 327). This confirms the influence of the predator-prey relationship in the evolution of *S. scabiei* and *N. cati*, as rabbits can be infected by both mites and can be preyed on by both cats and dogs (328).

Clinical aspects provide additional evidence of these dynamics. The typical anatomical localizations of skin lesions caused by *S. scabiei* and *N. cati* reflect physical contacts that occur during hunting, scavenging, and/or social behaviors. For instance, small felids come in contact with their preys mainly with head and forelimbs, i.e., the anatomical districts most often affected by notoedric mange lesions (312, 329). Larger felids, conversely, often prey on big animals with which they come in contact with the whole body (330), justifying why sarcoptic mange is often generalized (329).

Canid rubbing and scent rolling with the whole body on strong-smelling material, e.g., carcasses, further increase the chance of generalized sarcoptic mange (329, 330). In fact, *S. scabiei* can survive off-host and on dead hosts for hours to days (328), and the transmission with direct contact of dogs with carrions is highly probable. This off-host survival is another key difference that could have contributed to the broader host spectrum of *S. scabiei* than that of *N. cati*, as the latter is unable to survive in the environment (331). However, the strict host affiliations of these mites are not always "dogmatic." It should be kept in mind that they are adaptive ectoparasites and that *S. scabiei* varieties and *N. cati* can sporadically infect cats and dogs, respectively (310, 332).

**Scabies in humans: debunking the mite.** Around 300 million people worldwide suffer from scabies annually, regardless of socioeconomic level and geographies, although overcrowding, poor hygiene, malnutrition, homelessness, and reduced access to health care are main predisposing factors and the reason why scabies is the most common skin disease in developing countries (333–335).

The clinical disease in humans is caused by variants of *S. scabiei* from domestic and wild animals and by its proper variant *S. scabiei* var. *hominis* (326, 336–338). Among animal-acquired cases of scabies in humans, those derived from contact with infected dogs and the associated *S. scabiei* var. *canis* are predominant (326, 337). Only exceptional cases of human infection with *N. cati* have been documented (312, 339).

The clinical course of human scabies acquired by animal varieties is different from that of scabies caused by *S. scabiei* var. *hominis*, as it is mild and self-limiting and not

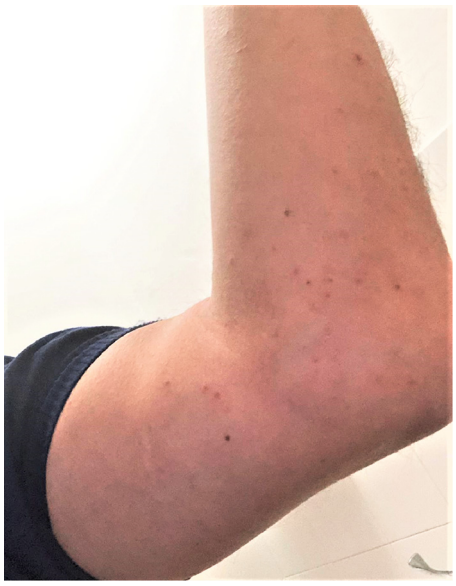

**FIG 14** Erythematous papular lesions in human scabies.

human-to-human transmitted (317, 340, 341). More specifically, dog-derived human scabies is a transient disease and less severe than the disease acquired by infested people (341). In dog-acquired scabies (and in rare cases of cat-derived notoedric infestation), clinical signs start with itchy papular, vesicular, or erythematous lesions, predominantly on the trunk, forearms, and thighs and in contact areas (312, 340, 341). Typical burrows are absent, because *S. scabiei* var. *canis* does not reproduce on human skin (340, 341).

Scabies caused by *S. scabiei* var. *hominis* typically has an incubation period of 3 to 6 weeks in primary infestations and only 1 to 3 days in occasional reinfestations (334). Humans become infected with prolonged skin-to-skin contact and, more rarely, through fomites (317, 335). Pruritus is not present in the early infection, as female mites release immune-modulating substances when they burrow into the skin (335), but then a shift in the immune response occurs and clinical signs appear (328, 342). Scabies in immunocompetent patients is characterized by intense pruritus (that worsens at night and with a rise in temperature) and erythematous papular eruptions (Fig. 14) on the periumbilical area, waist, genitals, breasts, buttocks, armpits, fingers, and interdigital spaces. These are typical lesions that do not occur with the infection caused by the canine strain (317, 340). Burrows appear as ~5-mm brownish-grayish thin lines and are practically pathognomonic, though their visualization is often impaired by excoriations and/or secondary infections (317). Immunocompromised and genetically predisposed individuals that become infected with *S. scabiei* var. *hominis* develop crusted scabies ("Norwegian scabies"), i.e., a form caused by the massive proliferation of mites (317, 334, 335). Infested immunocompromised people are highly contagious and manifest generalized fissured, erythematous, and crusted plaques with a verrucous aspect and mild or no itching (317). If untreated, crusted scabies can be life-threatening due to secondary bacterial infections (317, 342). Current research on human scabies is focusing on the host immune response, and recent data suggest that immunodiagnosis, vaccines, and immunotherapy can greatly improve long-term control strategies (328, 342). This is particularly true not only for human-derived mange but also for the transmission occurring from animals, although of less clinical relevance. Given the high adaptive abilities of these mites, particular attention should be given to parasites shared between domestic and wild animals. Outbreaks of scabies may be more frequent in the future due to increased presence of wild reservoirs, such

**TABLE 1** Occurrence of major vector-borne pathogens in cats and dogs worldwide

| Pathogen | Occurrence[a] | | Reference(s) |
|---|---|---|---|
| | Dog | Cat | |
| Tick-borne pathogens | | | |
| *Rickettsia conorii* | +++ | + | 501, 502 |
| *Rickettsia rickettsii* | +++ | + | 503, 504 |
| *Ehrlichia* | +++ | + | 505, 506, 507 |
| *Anaplasma* | +++ | + | 501, 507, 508 |
| *Babesia* | +++ | + | 387, 509 |
| *Borrelia* | +++ | + | 349 |
| *Hepatozoon* | +++ | ++ | 354, 510, 511 |
| *Cytauxzoon* | − | ++ | 512, 513 |
| Flea-borne pathogens | | | |
| *Rickettsia felis* | + | + | 507, 514 |
| *Rickettsia typhi* | + | + | 447, 507 |
| *Bartonella* | + | +++ | 357 |
| Other | | | |
| *Leishmania* | +++ | + | 468, 507, 515, 516 |

[a]−, absent; +, infrequent; ++, frequent; +++, very frequent.

as foxes, in domestic and peridomestic environments, with subsequent increased chances of contact with pets and other domestic animals (314, 338). For instance, an outbreak of scabies of fox origin has been documented on a farm in Switzerland, where foxes have transmitted mites to the animals of the farm (pigs, goats, dogs, horses, and oxen) that then passed the infestation to humans (338).

These events suggest that the high adaptability of *S. scabiei* requires higher standards of monitoring and control in both wild reservoirs and domestic animals, with the aim to reduce further adaptations of *S. scabiei* variants to humans.

### Ticks and Fleas: Dog or Cat Lovers and the Risks Humans Bear

**Impacts of immune system, inbreeding, and behavior.** Ticks and fleas are the most common ectoparasites of dogs and cats. They cause direct harm to animals but, more importantly, are agents of vector-borne diseases (VBDs) of veterinary and medical importance. Dogs are more frequently affected by ticks, whereas cats are affected more by fleas. As a consequence, dogs are prevalently infected by tick-borne pathogens (TBPs), while cats mainly act as reservoirs of flea-borne pathogens (FBPs) (Table 1) (115, 343–347).

Various hypotheses have been proposed for the minor susceptibility of cats to VBDs compared to that of dogs (Table 1), including differences in immune responses and species behaviors. Indeed, the immune response of cats to certain pathogens is predominantly cell mediated and confers natural resistance, in contrast to the prevailing humoral immune response of dogs (115). It is also proposed that genetic decline due to inbreeding in dogs has caused relatively higher probabilities of antigen presentation and restricted major histocompatibility complex types (115). Such genetic basis of higher susceptibility to VBDs (115) is supported by the predisposition of certain dog breeds to leishmaniosis and Lyme disease (348, 349) and by the evidence of predisposition of some cat breeds to hemoprotozoa (350).

The differences in TBP and FBP prevalences in dogs and cats are also due to their behavior dissimilarities. Grooming is a key behavior characteristic impacting tick and flea presence on animals. Self-grooming in cats (i.e., ~8% of their nonsleeping time, ~4% of their entire life) (351) serves as a preventative mechanism against ectoparasites (Fig. 1), especially ticks (351, 352). As, in most cases, ticks must be attached for a while before transmitting pathogens, cats that promptly remove ticks by self-grooming are rarely infected by TBPs (115, 353). Hepatozoonosis is an exception, as it is one of the most frequent feline VBDs in certain areas (354), acquired by tick ingestion facilitated by self-grooming (355, 356).

Moreover, immunity and animal behaviors have an impact on the epidemiology of zoonotic diseases transmitted by fleas, and accordingly, cats and dogs have different

roles (i.e., active infectors versus passive carriers) in the epizootiology/epidemiology of flea-borne diseases (FBDs), especially bartonelloses and rickettsioses (357, 358). Although animals acquire fleas mainly from an infested environment, social behaviors of cats (e.g., affiliative rubbing and bunting) favor a direct host-to-host transmission of fleas, especially in colonies (359, 360). Direct flea transmission between dogs is less frequent, because tactile communication among dogs is short lasting and only complementary to postural or olfactory signals (361, 362). Similarly, territorial fights between cats commonly favor the transmission of important FBPs, i.e., *Bartonella* spp., *Rickettsia felis*, and *Rickettsia typhi*. In fact, these bacteria are transmitted with the inoculation of contaminated flea feces in skin wounds (363, 364).

**Tick-borne diseases: common in dogs, less common in cats.** TBPs are common in dogs worldwide, and especially, the Anaplasmataceae *Ehrlichia* and *Anaplasma* have a >50% prevalence in some areas of Europe and the Americas (365–367). *Ehrlichia canis* and *Ehrlichia chaffeensis* infect mononuclear cells, causing monocytic ehrlichiosis (366), while *Ehrlichia ewingii* has tropism to granulocytes and causes granulocytic ehrlichiosis (368). *Anaplasma phagocytophilum* and *Anaplasma platys* infect granulocytes and platelets, causing granulocytic and thrombocytotropic anaplasmosis, respectively (366, 367).

Clinical features of ehrlichiosis and anaplasmosis are well known in dogs (366). Monocytic and granulocytic ehrlichiosis in dogs may either be subclinical or entail a course with fever, anorexia, lethargy, lymphadenopathy, hemorrhagic diathesis, epistaxis, and thrombocytopenia (366). Canine granulocytic and thrombocytotropic anaplasmosis can also be subclinical or cause clinical signs similar to those present in canine ehrlichiosis, although often self-limiting (366, 367).

Occasional clinical feline anaplasmosis and ehrlichiosis have been described with nonspecific signs similar to those recorded in dogs (358, 369, 370). Nevertheless, the pathogenic role of *Ehrlichia* and *Anaplasma* is less clearly defined in cats than in dogs (358). The infrequent diagnosis of these diseases in cats may be related to a number of factors, e.g., an unknown pathogenicity of TBPs in these animals, a successful immune response, or a factual lower prevalence of these pathogens due to the faster removal of ticks by cats.

Most dogs seropositive for *Borrelia* spp. do not display evident signs, although lameness, arthritis, fever, glomerulonephritis proteinuria, hyperazotemia, peripheral edema, and body cavity effusions have been described (349, 371). Conversely, to date, there is no evidence of clinical signs associated with *Borrelia* infection in cats, albeit reports of seroconversion (349).

*Rickettsia rickettsii* causes Rocky Mountain spotted fever (RMSF), a potentially fatal disease of dogs living in the Americas (372, 373). Infected dogs often suffer lethargy, anorexia, fever, lymphadenomegaly, and ocular and neurological signs (373, 374). In Europe, *Rickettsia conorii* causes Mediterranean spotted fever (MSF) (375). Although clinical disease is very rare, dogs infected with *R. conorii* may suffer from a febrile illness with myalgia, lameness, thrombocytopenia, and hypoalbuminemia (375). Tick-borne rickettsioses in cats are extremely poorly studied, and at present, clinical RMSF or MSF has never been documented, although cats can be seropositive (376, 377).

The pathogeneses of ehrlichiosis, anaplasmosis, and borreliosis mostly rely on the formation of immune complexes (349, 378, 379); thus, the predominantly cell-mediated response in cats (115) may render clinical infections less frequent than in dogs. This peculiarity has also influenced, with all likelihood, the lower occurrence of clinical infection by *Rickettsia* spp. in cats, as it has been demonstrated that the pathogenesis and severity of these microorganisms depend on the efficiency of their intracellular destruction after the infection.

Babesiosis is also a TBD with higher relevance in dogs than in cats. Different *Babesia* species cause clinical babesiosis in dogs, depending on the geographical area, e.g., *Babesia rossi* in Africa and Asia, *Babesia canis* in Europe, *Babesia vulpes* in the United States and Europe, *Babesia conradae* in the United States, and *Babesia vogeli* and *Babesia gibsoni* throughout the continents (380–385). Large *Babesia* species *B. rossi*, *B.*

*canis*, and *B. vogeli* are thought to be more pathogenic than the small-sized species (*B. gibsoni*, *B. conradae*, and *B. vulpes*), causing subclinical infections or fever, splenomegaly, thrombocytopenia, hemolytic anemia, icterus, hematuria, bilirubinuria, and hemoglobinuria (383). *Babesia rossi* is the most pathogenic large species in dogs, followed by *B. canis* that causes an acute moderate-to-severe illness and by *B. vogeli*, whose infections can be acute or chronic and are usually mild to moderate (383). Hemolytic anemia is the main clinical sign regardless of the species involved (383). *Babesia rossi* and *B. canis* can cause severe and hyperacute disease leading to shock and multiorgan dysfunction (386). Of the small-sized *Babesia*, *B. gibsoni* may occasionally cause a relevant disease in dogs (383).

The few feline-related species, *Babesia felis*, *Babesia leo*, and *Babesia cati*, have a limited distribution, i.e., in Africa (*B. felis* and *B. leo*) and Asia (*B. cati*), and only a partially known clinical impact (387). The scant clinical reports indicate that infected cats may develop pyrexia, lethargy, anemia, and icterus (387, 388). Very rarely, other *Babesia* species, e.g., *B. canis*, *B. gibsoni*, *B. vogeli*, *B. vulpes*, *Babesia microti*, and *Babesia lohae* have been detected in domestic cats, but they are currently not considered of importance in feline veterinary medicine (387). Possible reasons why *Babesia* has a limited distribution in cats could be figured out with a comparison of the biology of developmental stages in the vertebrate host with those of *Cytauxzoon* spp. This hemoprotozoan is the most important feline TBP, although many aspects (identity and epizootiology of species, vectoral role of ticks, pathogenesis, and therapy) are yet to be clarified (370, 389, 390). Despite the apparently limited distribution, feline cytauxzoonosis due to *Cytauxzoon felis* is a life-threatening disease in cats in North America, characterized by fever, lethargy, dyspnea, vomiting, icterus, and death in most infected cats within a week (390), while different, yet undefined, species circulate in Europe, where they cause milder diseases (391–393).

There are no known *Cytauxzoon* species infecting dogs. A possible explanation could rely on the different life cycle of these Piroplasmida inside the vertebrate host and subsequent different interactions with the immune systems of dogs and cats. Namely, while *Babesia* spp. are exclusively intraerythrocytic in vertebrate hosts, the life cycle of *C. felis* includes a tissue stage in the acute phase, with schizogony occurring in macrophages, followed by the infection of red blood cells by merozoites (394, 395). It is known that T lymphocytes, natural killer (NK) cells, and macrophages play crucial roles in the resistance to *Babesia* spp., whose parasitic stages are highly exposed to cell-mediated immune factors (396). Also, the subsequent complement activation and opsonization trigger the destruction of the parasite (396). Therefore, the majority of *Babesia* spp. are unable to establish in cats due to their marked cell-mediated immune response in addition to the subsequent efficacious production of antibodies (396). Differently, *C. felis* hides inside macrophages, and its ability to elude the cellular mechanisms of antigen presentation favors infection and disease progression (397). Cats develop a protective immunity against *C. felis* only if they survive the tissue phase, which can lead to death within 3 weeks from the infection (395).

The absence of *Cytauxzoon* in dogs could also depend on its tropism for macrophages and, specifically, for PIMs that are absent in dogs (246, 395, 398). Indeed, one of the main characteristics of feline cytauxzoonosis is the presence of giant PIMs containing schizonts in the endothelium of the lungs (399). As mentioned above, PIMs are the first immunological barrier in cats; thus, it can be argued that their presence could be pivotal for the development of *C. felis*. This is corroborated by successful experimental infections of sheep with *C. felis*, which constitutively have PIMs (290, 400).

Hepatozoonosis has high prevalence rates in both dogs and cats (354, 401). The agents of dog hepatozoonosis are *Hepatozoon canis* with a global distribution and *Hepatozoon americanum* in the Americas (402). *Hepatozoon canis* infection may be subclinical or life threatening depending on the parasite load, associated with nonspecific clinical signs, including fever, lymphadenopathy, and pale mucous membranes (402). Instead, *H. americanum* causes more severe signs such as muscular atrophy and

**TABLE 2** Summary of laboratory and anatomopathological alterations associated with zoonotic *Bartonella* species infections in cats, dogs, and humans

| *Bartonella* species | Primary reservoir | Vector | Sign or alteration type | Description[a] | | | Reference(s) |
|---|---|---|---|---|---|---|---|
| | | | | Cats | Dogs | Humans | |
| *Bartonella clarridgeiae* | Cats | Fleas (*Ctenocephalides felis*), ticks[b] | Clinical signs | CA, asymptomatic or fever, neurologic dysfunction, lymphadenomegaly, reproductive failure;<br>NC, blindness | CR, fever, weakness, depression, anisocoria, tachypnoea, pale mucous membranes, bradycardia | CA, asymptomatic or fever, headache, malaise, lymphadenomegaly;<br>NC, papules | 357, 438–440, 517, 518 |
| | | | Laboratory alterations | CA, anaemia, eosinophilia | CR, neutrophilia, thrombocytopenia | | 517, 518 |
| | | | Clinical-pathological alterations | CA, splenomegaly, cholangitis, myocarditis, interstitial nephritis;<br>NC, lymph node hyperplasia[c], neuritis, hepatitis[c] | NC, endocarditis, lymphocytic hepatitis | CA, endocarditis, lymphadenopathy | 357, 438, 439, 517–519 |
| *Bartonella elizabethae* | Rats | Fleas (*Xenopsylla cheopis*) | Clinical signs | | NC, lethargy, weight loss. CR, decreased appetite, vomiting, pale mucous membranes | NC, headache, lethargy, muscle pain, conjunctival suffusion;<br>CR, fever, malaise, weakness lymphadenomegaly[c] | 413, 440, 520–523 |
| | | | Laboratory alterations | | NC, anaemia;<br>CR, neutrophilia, monocytosis, eosinophilia, azotaemia | NC, anemia | 440, 520, 522 |
| | | | Clinical-pathological alterations | | | NC, endocarditis, neuroretinitis;<br>CR, bacillary angiomatosis | 413, 523, 524 |
| *Bartonella henselae* | Cats | Fleas, ticks[b] | Clinical signs | CA, asymptomatic or fever, lethargy, lymphadenomegaly, neurological signs, reproductive failure;<br>NC, stomatitis | CA, asymptomatic;<br>NC, fever, epistaxis, lymphadenomegaly;<br>CR, anorexia[c], lethargy[c], oral ulcerations[c], nasal discharge[c], neurological signs, weight loss | CA, fever, malaise, development of papules and pustules after a cat scratch, headache, anorexia, lymphadenomegaly, erythema, arthralgia;<br>NC, neurological signs, cutaneous petechiae, purpura | 357, 416, 438, 517, 520, 522, 523 |
| | | | Laboratory alterations | CA, anemia, eosinophilia, hyperglobulinemia;<br>NC, thrombocytopenia | NC, eosinophilia, hyperglobulinemia, hyperinsulinemic hypoglycemia syndrome, monoclonal gammopathy, thrombocytopenia/thrombocytosis;<br>CR, lymphopenia, neutrophilia, monocytosis | NC, monoclonal and biclonal gammopathy, hemolytic anemia, thrombocytopenia | 357, 438, 517, 520, 522 |
| | | | Clinical-pathological alterations | CA, splenomegaly, cholangitis, interstitial nephritis, endocarditis, myocarditis, uveitis;<br>NC, diaphragmatic myositis, hepatitis, conjunctivitis, keratitis, corneal ulcers, urinary tract infection, systemic reactive angioendotheliomatosis | NC, endocarditis, panniculitis, polyarthritis, bacillary peliosis, granulomatous hepatitis, peliosis hepatis, granulomatous lymphadenitis, vasculitis and/or thrombosis, hemangiopericytoma | CA, lymphadenitis, meningitis, encephalitis, pulmonary nodules, bacillary angiomatosis, uveitis, granulomatous hepatis, bacillary peliosis, epithelioid haemangioendothelioma, arthritis;<br>NC, myositis, glomerulonephritis, pneumonia, pleuritis, paronychia, osteomyelitis, polyarthritis, periodontitis, hepatosplenomegaly, nodules in the head of the pancreas, pseudotumoral lesions involving the mammary glands, the liver, and the spleen, endocarditis, myocarditis, Parinaud oculoglandular syndrome, focal retinal phlebitis, | 357, 413, 416, 438, 517, 520, 525 |

(Continued on next page)

**TABLE 2** (Continued)

| *Bartonella* species | Primary reservoir | Vector | Sign or alteration type | Description[a] | | | Reference(s) |
|---|---|---|---|---|---|---|---|
| | | | | Cats | Dogs | Humans | |
| | | | | | | neuroretinitis, optical nerve neovascularization and/or granuloma, retinal artery vein occlusions, aneurysm, vasculitis, thrombosis | |
| *Bartonella koehlerae* | Cats | Fleas | Clinical signs | CA, asymptomatic | CR, fever, anorexia, joint pain, weight loss, polyuria, polydipsia, arrhythmia, tachycardia, collapse[c] | CR, headache, joint and muscle pain, shortness of breath, hallucinations, depression, sensory neuropathy, anxiety, peripheral visual deficit | 438, 440, 442, 526 |
| | | | Laboratory alterations | | NC, hyperinsulinemic hypoglycemia syndrome; CR, neutrophilia, thrombocytopenia, hypoalbuminemia, azotemia, proteinuria | | 357, 526 |
| | | | Clinical-pathological alterations | CA, endocarditis, myocarditis; CR, systemic reactive angioendotheliomatosis[c] | NC, endocarditis splenic disease; CR, renal infarction, glomerulonephritis, bronchopneumonia | CA, endocarditis; CR, epithelioid haemangioendothelioma[c] | 357, 438, 440, 525–528 |
| *Bartonella quintana* | Humans | Lice (*Pediculus humanus corporis*), fleas, bed bugs, ticks[b] | Clinical signs | CA, asymptomatic | CA, asymptomatic | CA, asymptomatic or fever, lymphadenopathy, headache, shin pain, dizziness, rash, nausea, vomiting, weight loss, myalgia, bone pain, maculopapular rash | 357, 416, 438, 523, 529, 530 |
| | | | Laboratory alterations | | | NC, thrombocytopenia | 522 |
| | | | Clinical-pathological alterations | | NC, endocarditis | CA, bacillary angiomatosis, lymphadenitis, splenomegaly, endocarditis, septicaemia, uveitis, neuroretinitis | 357, 438, 523, 529 |
| *Bartonella rochalimae* | Canids | Fleas[b], ticks[b] | Clinical signs | CA, asymptomatic | CA, asymptomatic; CR, fever, epistaxis, weight loss, heart murmur, coughing, increased respiratory effort, lameness, haematochezia, seizures | CR, fever, myalgia, nausea, headache, insomnia, macular rash | 357, 415, 531 |
| | | | Laboratory alterations | | NC, anaemia, thrombocytopenia, leukocytosis with neutrophilia or eosinophilia; CR, hypo/hyperglobulinemia | CR, anemia, neutrophilia | 415, 531 |
| | | | Clinical-pathological alterations | | NC, endocarditis; CR, polyarthropathy | CR, splenomegaly | 357, 415, 531 |
| *Bartonella vinsonii* subsp. *berkhoffii* | Dogs, coyotes, foxes | Fleas[b], ticks[b] | Clinical signs | CA, asymptomatic; NC, lameness | CA, asymptomatic or fever, intermittent lameness; NC, epistaxis arrhythmias, syncope, sudden death; CR, anorexia[c], lethargy[c], oral ulcerations[c], nasal discharge[c], weight loss[c], respiratory distress | NC, neurological disorders, muscle weakness, muscle pain, arrhythmias; CR, lack of coordination, memory loss headaches, insomnia, weight loss | 357, 414, 416, 517, 522 |
| | | | Laboratory alterations | | NC, anaemia, thrombocytopenia; CR, thrombocytosis[c], lymphopenia[c], eosinophilia[c] | NC, anemia, thrombocytopenia | 357, 416, 517, 522 |

(Continued on next page)

**TABLE 2** (Continued)

| *Bartonella* species | Primary reservoir | Vector | Sign or alteration type | Description[a] | | | Reference(s) |
|---|---|---|---|---|---|---|---|
| | | | | Cats | Dogs | Humans | |
| | | | Clinical-pathological alterations | NC, osteomyelitis, endocardial fibrosis complex endomyocarditis, polyarthritis, systemic reactive angioendotheliomatosis | CA, lymphadenitis, endocarditis, myocarditis, granulomatous rhinitis;<br>NC, uveitis, choroiditis, splenomegaly, polyarthritis, bacillary angiomatosis, chorioretinitis, meningoencephalitis, hemangiosarcoma;<br>CR, cutaneous hemangiopericytoma, peliosis hepatis | CA, endocarditis;<br>NA, myocarditis, arthritis, chorioretinitis, meningoencephalitis, hemangiopericytoma;<br>CR, epithelioid haemangioendothelioma | 357, 413, 416, 438, 517, 522, 523, 525 |

[a]CA, confirmed association with the pathogen; NC, no confirmed association with the pathogen; CR, case report.
[b]Not confirmed.
[c]Clinical aspects observed in mixed infections with different *Bartonella* species.

lameness due to myositis and, frequently, a fatal outcome in the absence of treatment (402). In cats, hepatozoonosis is due to the cosmopolitan *Hepatozoon felis*, causing subclinical or mild infections with nonspecific signs, although severe cases have been described, and to *Hepatozoon silvestris*, found only in Europe, with little known clinical impact, but a fatal case due to severe myocarditis was described in a cat in Switzerland (354, 403, 404).

In general, TBDs are not as common in cats as in dogs, but recent evidence suggest that feline infections may spread and gain importance in the near future. For instance, high rates of tick infestations in the United States are recorded in indoor cats, and in the United Kingdom, cats are more frequently presented to veterinarians with ticks than dogs, especially with *Ixodes ricinus* that may infest cats earlier in the year than that for dogs (405–407). Many factors are incriminated for the increasing prevalence of ticks and TBDs in cats, such as the rising global prevalence of ticks due to climate change, the limited use of ectoparasiticides and repellents on this species (408–410), and the development of acaricide resistance in common ticks (411, 412).

**Flea-borne diseases: a feline issue.** The most important FBPs in pets are bacteria of the genus *Bartonella*, i.e., Gram-negative organisms that cause infections with significant zoonotic potential. Various species belonging to this genus have different roles in causing diseases in companion animals and humans, but in general, FBDs are more relevant from a public health rather than a veterinary point of view, as previously discussed. The most important zoonotic *Bartonella* species isolated from domestic dogs and cats (Table 2) are *Bartonella henselae*, *Bartonella clarridgeiae*, and *Bartonella koehlerae*, followed by *Bartonella bovis* (formerly *Bartonella weissi*), *Bartonella quintana*, and *Bartonella vinsonii* subsp. *berkhoffii* (413, 414). Cats are unsuitable reservoirs for *B. quintana*, *B. vinsonii* subsp. *berkhoffii*, and *B. bovis*, and their role in the transmission patterns of the zoonotic species *B. rochalimae* is uncertain (2, 415). Cats are considered the reservoir for most of the zoonotic *Bartonella* species, except for *B. vinsonii* subsp. *berkhoffii*, for which dogs display prolonged bacteremia, acting as reservoirs for human infection (357).

Although both dogs and cats can suffer from clinical bartonellosis, there is evidence that cats are more often subclinical carriers, while dogs develop severe signs and diseases, including endocarditis, myocarditis, granulomatous hepatitis, lymphadenitis, meningoencephalitis, rhinitis, bacillary angiomatosis, peliosis hepatis, immune-mediated hemolytic anemia, polyarthritis, and uveitis (357, 416, 417). Interestingly, the canine *B. vinsonii* subsp. *berkhoffii* is an exception, causing severe clinical alterations such as osteomyelitis and endomyocarditis in cats (357, 417).

Among other FBPs, *Rickettsia felis* and/or *Rickettsia typhi* has never been definitively proved to cause disease in dogs or cats, although both species can seroconvert (358).

Overall, the apparent "natural resistance" of cats to clinical illness due to arthropod-borne infections and their higher predisposition to flea infestations could have influenced the evolution of FBPs. This has probably led to the selection of cats as reservoir species for a higher number of microorganisms transmitted by fleas than that for dogs.

Fleas are also the intermediate host of the dog- and cat-affiliated parasite *Dipylidium caninum*, a cestode with limited pathogenic potential in these animals, although diarrhea, emesis, retarded growth rate, and poor general condition have been reported (418).

**Clinical TBDs and FBDs in humans.** From a public health perspective, spotted fever group (SFG) rickettsiae and *Borrelia* spp. are the most relevant TBPs. The widely distributed brown dog tick *Rhipicephalus sanguineus* is the vector of *R. conorii*, the agent of MSF, which presents as a flu-like febrile disease, potentially life threatening when patients develop vasculitis and multiorgan failure (419, 420). RMSF caused by *R. rickettsii*, transmitted by different tick species, is among the most lethal infectious diseases in the Americas, characterized by nonspecific clinical signs, e.g., fever, headache, muscular pain, nausea, vomiting, and loss of appetite, which render a clinical diagnosis challenging and often lead to fatal multiorgan failure (421–423). Patients who recover from

severe RMSF may develop permanent disabilities, such as blindness, cognitive deficits, ataxia, and hemiparesis (421). Though questioned for a long time, the role of dogs as source of *R. conorii* for ticks, and indirectly for humans, is now acknowledged (424). Dogs are now considered epidemiological sentinels of MSF, though cats may also seroconvert (377).

Lyme disease, caused primarily by the spirochete *B. burgdorferi sensu stricto* in North America and by *B. burgdorferi sensu stricto*, *Borrelia afzelii*, or *Borrelia garinii* in Europe, is the most common tick-borne zoonosis in the Northern Hemisphere (425). This is an emerging public health threat due to its increasing global occurrence and severe clinical manifestation that involves the skin (i.e., erythema migrans, borrelial lymphocytoma, acrodermatitis chronica atrophicans), nervous system (i.e., neuroborreliosis with lymphocytic meningitis, cranial neuritis, or radiculoneuritis), joints (arthritis), and rarely the heart (carditis) (425–427).

Despite the major relevance for dogs, ehrlichiosis and anaplasmosis are of less importance for people. Human monocytic ehrlichiosis may present as a flu-like disease, though the factual pathogenic role of *E. canis* must be further elucidated (428, 429). Anaplasmoses usually vary from asymptomatic to mildly symptomatic, though a potentially fatal illness may occur in the case of organ failure and opportunistic infections (429, 430).

The role of canine and feline *Babesia* species in causing disease to immunocompetent and immunocompromised people is still unknown. Most cases of human babesiosis are due to *B. microti* (affecting rodents) in North America or *Babesia divergens* (affecting cattle) in Europe (431). Other species such as *Babesia duncani* (whose vector and reservoir hosts are unknown) and *Babesia venatorum* (affecting cervids) are rarely detected in people (431). Human babesiosis varies from asymptomatic to severe and lethal in immunocompromised individuals (431, 432).

To date, there are no reports of human hepatozoonosis, apart from a single old record of *Hepatozoon* gamonts in the white blood cells of a patient suffering from anemia and icterus (433). Thus, at present, hepatozoonosis is not a concern for public health.

Among FBPs, the most important zoonotic *Bartonella* is *B. henselae*, the causative agent of cat scratch disease (CSD), or cat-scratch fever. Fleas acquire the microorganisms through bloodmeal during bacteremia and shed them in their feces. The bacteria can be then transmitted to other animals and humans by inoculation of infectious flea feces in an open wound (357). While infected cats may directly transmit *B. henselae* to humans, dogs are epidemiological sentinels that usually do not transmit the disease to people (357). Human CSD is a febrile flu-like disease causing regional lymphadenopathy that can last for several months and cause important inflammations, e.g., encephalitis, retinitis, and endocarditis, with life-threatening implications, such as systemic angioproliferative lesions, in immunocompromised patients (434, 435). Cats are often coinfected by *B. henselae* and *B. clarridgeiae* (436, 437). The role of *B. clarridgeiae* in human health has been questioned for a long time, though some data suggest that it might be pathogenic and associated with fever, headache, malaise, and lymphadenomegaly (438–440). *Bartonella koehlerae* has been isolated from a kitten whose owner developed a CSD-like condition (441), and it has been also considered responsible for various symptoms in humans, ranging from nonspecific illnesses to neuromuscular disorders (416, 442). However, its zoonotic role requires more investigations, as some clinical scenarios have been recorded in people coinfected by *B. vinsonii* subsp. *berkhoffii* genotype II (416). The latter is the most frequent genotype in canids and humans and is highly pathogenic, causing endocarditis, arthritis, and neurological disorders even in immunocompetent people. To date, *B. vinsonii* subsp. *berkhoffii* DNA has been detected in both fleas and ticks, and its primary vector species remain to be ultimately defined (443, 444).

Human infection by *R. felis* and *R. typhi* occurs via flea feces and bites (364, 445), and high prevalence in cats has been associated with local outbreaks in humans (446,

447). Infected dogs favor the circulation of these pathogens, increasing the risk for people to come in contact with infected fleas (447, 448). The cat flea *C. felis* transmits *R. felis*, the worldwide distributed agent of "cat flea typhus" or "flea-borne spotted fever," although the vectorial role of other arthropods cannot be excluded (364, 449). For instance, *R. felis* DNA was recently found in different wild-caught species of mosquitoes in the United States (450), and it has been experimentally transmitted by *Anopheles gambiae* to rodents (451). The peridomestic cycle of *R. typhi*, i.e., the causative agent of murine typhus (MT), involves cats, dogs, other animals, and their fleas (447). Cats can be asymptomatic carriers of *R. typhi*, and an association between infected cats and cases of murine typhus in people has been reported several times (446, 447, 452).

While no clinical cases have been documented in cats or dogs infected by *R. felis* or *R. typhi*, the human disease may be relevant and severe. The diseases are clinically similar, characterized by nonspecific signs, such as fever, headache, chills, myalgia, malaise, and maculopapular rash (364, 453). Although *R. felis* can induce neurological, gastrointestinal, and respiratory signs, fatal cases have never been reported, while more severe health implications and death have been reported for *R. typhi* (364, 454, 455).

In the last years, two new flea-borne rickettsiae, defined as *Rickettsia felis*-like organisms (RFLOs), i.e., *Rickettsia asembonensis* and "*Candidatus* Rickettsia senegalensis" have been described, but information on their biology, primary hosts, vectors, and pathogenic and zoonotic potential is still meagre (423, 456). *Rickettsia asembonensis*, detected in a healthy dog in South Africa, has been considered zoonotic after reports of patients from Peru suffering from acute febrile illness (457) and a patient from Malaysia displaying fever, myalgia, arthralgia, conjunctival effusion, and petechiae (456). Thus, the attention toward these emerging RFLOs should be kept high.

The cosmopolitan zoonotic flea-borne tapeworm *D. caninum* is transmitted to humans by inadvertent ingestion of an infected flea. Children are at higher risk of infection with this cestode, due to their playing habits and close contact with pets (418, 458). Despite the high frequency of *D. caninum* in dogs and cats, human dipylidiasis is rarely reported. On the other hand, its real prevalence is most probably underestimated due to the lack of evident symptoms and a possible misdiagnosis with the pinworm *Enterobius vermicularis*, due to inappropriate and scarce anamnestic/diagnostic investigations (459). Human dipylidiasis can cause insomnia, epigastric pain, abdominal distension, constipation, urticaria, and intestinal obstruction (459). It was only recently shown that different genotypes occur in dogs and cats (460, 461), and further studies are required to investigate any biological, epidemiological, pathogenic, and zoonotic differences between these genotypes.

The control of ticks and fleas in companion animals with the appropriate use of ectoparasiticides and repellents is of utmost importance to protect the health and welfare of dogs and cats and for a reliable control of major diseases which can be transmitted to humans. TBDs and FBDs are a challenging issue in human medicine also, because the clinical scenario is extremely nonspecific, with signs and laboratory alterations which overlap each other (Table 3) and those of other illnesses, thus rendering a timely diagnosis difficult and demanding.

### *Leishmania infantum*: All for One, One for All

**General knowledge.** Dogs are the primary reservoir of *Leishmania infantum* (syn. *Leishmania chagasi*), i.e., the agent of a widely distributed and life-threatening zoonotic disease, transmitted by hematophagous female phlebotomine sandflies, i.e., *Phlebotomus* spp. in the Old World and *Lutzomyia* spp. in the Americas. Nonvectorial transmissions (e.g., transplacental and from bite wounds) have been described in some cases for dogs, but these mechanisms play a marginal role in the epizootiology of the infection (462, 463). Cats, on the other hand, display a natural immunological resistance to this parasite and, in enzootic areas, are less prevalently infected than dogs (464–468). Other species of *Leishmania* are only rarely isolated from both animal species (469–471). Visceral and, less frequently, cutaneous, mucocutaneous, and mucosal leishmanioses are the clinical forms

**TABLE 3** Clinical signs and laboratory alterations caused in humans by zoonotic vector-borne pathogens infecting dogs and/or cats

| Clinical sign or finding[p] | Presence or absence of vector-borne pathogen[a] | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Rc*[b] | *Rr*[c] | *Rf*[d] | *Rt*[e] | *Bb*[f] | *Aph*[g] | *Apl*[h,i] | *Ech*[j] | *Ee*[j] | *Eca*[k,i] | *Bc*[l] | *Be*[l] | *Bh*[l] | *Bk*[l] | *Bq*[l] | *Br*[l] | *Bv*[l] |
| Clinical signs | | | | | | | | | | | | | | | | | |
| Fever | + | + | + | + | + | + | + | + | + | + | + | + | + | | + | + | − |
| Headache | + | + | + | + | + | + | + | + | + | + | + | − | + | + | + | − | + |
| Lymphadenomegaly | + | + | + | + | + | + | − | + | + | − | + | + | + | − | + | − | − |
| Gastrointestinal | + | + | + | + | + | + | + | + | + | + | − | − | + | − | + | + | + |
| Myalgia and/or arthralgia | + | + | + | + | + | + | + | + | + | + | − | − | + | + | + | + | + |
| Cardiovascular | + | + | − | + | + | + | − | + | + | − | + | + | + | + | + | − | + |
| Neurological | + | + | + | + | + | + | + | + | + | − | − | − | + | + | + | + | + |
| Respiratory | − | + | + | + | + | + | − | + | + | − | − | − | + | + | − | − | − |
| Cutaneous | + | + | + | + | + | + | − | + | + | + | + | − | + | − | + | − | − |
| Ocular | + | + | − | + | + | + | − | − | − | − | − | + | + | + | + | − | − |
| Laboratory findings | | | | | | | | | | | | | | | | | |
| Anemia | − | − | − | + | + | + | + | + | + | + | − | − | + | − | − | + | + |
| Leukocytosis | + | + | + | + | + | + | − | + | + | − | − | − | − | − | + | − | − |
| Leukopenia | + | + | − | + | + | + | + | + | + | + | − | − | − | − | − | − | − |
| Thrombocytosis | + | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − | − |
| Thrombocytopenia | + | + | + | + | + | + | − | + | + | + | − | − | + | − | + | − | + |
| Gammopathy | − | − | − | − | − | − | − | − | − | − | − | − | + | − | − | − | − |
| >AST[m] | + | + | + | + | − | + | − | + | + | − | − | − | − | − | − | − | − |
| >ALT[n] | + | + | + | + | + | + | − | + | + | − | − | − | − | − | − | − | − |
| >ALP[o] | − | + | − | + | + | + | − | + | + | − | − | − | − | − | − | − | − |
| >Bilirubin | − | + | + | + | + | − | − | + | + | − | − | − | − | − | − | − | − |
| Erythrocyturia | + | − | − | + | − | − | − | − | − | − | − | − | − | − | − | − | − |
| Proteinuria | + | + | − | + | − | − | − | − | − | − | − | − | − | − | − | − | − |
| Hypoalbuminemia | − | + | − | + | − | − | − | − | − | − | − | − | − | − | − | − | − |

[a]Clinical sign or laboratory alteration reported (+) or not reported (−) in the course of human infection. *Rc*, *Rickettsia conorii*; *Rr*, *Rickettsia rickettsii*; *Rf*, *Rickettsia felis*; *Rt*, *Rickettsia typhi*; *Bb*, *Borrelia burgdorferi sensu lato*; *Aph*, *Anaplasma phagocytophilum*; *Apl*, *Anaplasma platys*; *Ech*, *Ehrlichia chaffeensis*; *Ee*, *Ehrlichia ewingii*; *Eca*, *Ehrlichia canis*; *Bc*, *Bartonella clarridgeiae*; *Be*, *Bartonella elizabethae*; *Bh*, *Bartonella henselae*; *Bk*, *Bartonella koehlerae*; *Bq*, *Bartonella quintana*; *Br*, *Bartonella rochalimae*; *Bv*, *Bartonella vinsonii* subsp. *berkhoffii*.
[b]420, 532, 533.
[c]421, 422, 534–538.
[d]364, 539, 540.
[e]364, 455, 541–545.
[f]538, 546.
[g]422, 429, 534, 547.
[h]548.
[i]Infection rarely reported in humans.
[j]429, 534, 538, 549.
[k]550.
[l]357, 413, 415–417, 438–440, 443, 444, 517–524, 526, 528, 529, 531, 551, 552.
[m]AST, aspartate transaminase.
[n]ALT, alanine aminotransferase.
[o]ALP, alkaline phosphatase.
[p]>, increased amount.

of *L. infantum* infection in humans, which is endemic in the areas of the world where canine leishmaniosis (CanL) is enzootic, i.e., in 50 countries in Europe, Africa, Asia, and the Americas (472–474).

**Dogs and cats: same parasite, different susceptibilities.** CanL is a well-studied, typically chronic disease displaying a wide range of clinical signs that involve practically all organs and systems due to its immunological nature (475). Infected dogs may present lymph node enlargement, splenomegaly, cutaneous and mucocutaneous lesions (e.g., ulcers, hyperkeratosis, alopecia, onychogryphosis), ocular lesions (e.g., conjunctivitis, blepharitis, scleritis, uveitis, panophthalmia, glaucoma), poor body condition, localized or generalized amyotrophy, polyarthritis, and myositis (473). On the other hand, feline leishmaniosis (FeL) is less extensively studied, and there is evidence that impaired immunocompetence is a predisposing factor of the disease (463). As coexisting pathological conditions or/and infections are common in cats that develop FeL, misidentification of clinical signs may occur and render an unequivocal appraisal of the disease difficult. Nevertheless, parasite-associated

lesions have been described in many organs and tissues of cats, e.g., skin, eyes, mucosae, liver, kidneys, lymph nodes, spleen, and bone marrow (463).

The clinical course of leishmaniosis in dogs depends on the dichotomic immune response to the infection, i.e., in sick dogs, the humoral response (Th2 type, with release of cytokines and interleukins, promoting downregulation of cellular immune response, high level of antibodies, and infection establishment) predominates the cell-mediated response (Th1 type, characterized by a series of cell and cytokine activations, resulting in phagocyte-based parasite elimination) and vice versa (466, 476). The natural immunity of cats to leishmaniosis relies on their inherently predominant Th1 immune response, with protective production of gamma interferon (IFN-γ) (115, 466), which may explain why cats rarely develop overt disease. Furthermore, antibodies against *L. infantum* in cats may have a protective role, in contrast to the adverse effects of the humoral response in dogs (477). This difference is also indicated by the frequent PCR negativity for protozoan DNA of cats with high antibody titers (470). The unspecific clinical signs of FeL may leave the disease off the differential diagnosis list, as it is considered rare, unlikely, and of minor concern compared to CanL. However, recent studies showed that cats are at high risk of exposure to sandfly bites and that records of clinical FeL are increasing (463, 464, 478).

In many enzootic regions, leishmaniosis occurs in higher prevalence in rural than in urban environments due to the biology of their vectors (479). Phlebotomine sandflies do not have a strict host preference (480, 481), but cats are not among their preferred hosts (482, 483). The progressive urbanization of many rural areas may, however, lead to the establishment of an urban life cycle involving cats due to the limited availability of other hosts (484, 485). In these cases, cats, as a proven source of infection to sandflies, may play a significant role in the epizootiology and epidemiology of leishmaniosis (484). Cats often remain unprotected against ectoparasites because of the general underestimation of VBD risk in these animals and because of the limited use of repellents on cats, due to the toxicity of most veterinary products containing pyrethroids (408, 463). This could lead to cats becoming one of the few available hosts for sandflies (486), as, at the same time, repellents are widely used in dogs in enzootic areas.

**Visceral leishmaniosis in humans: neglected and life threatening.** *Leishmania infantum* is less adapted to humans than other *Leishmania* species, e.g., *Leishmania donovani* and *Leishmania tropica*, of which humans are the reservoir host (487). Dogs are considered the main source for human infection by *L. infantum*, via infected phlebotomine vectors, albeit other animal species are important reservoirs of the parasite (488). For example, in a sudden outbreak of visceral leishmaniosis (VL) in Madrid in 2009 to 2012, hares living in the parks of the city were found infected in high prevalence and incriminated for the rise in human cases, because at the same time, the prevalence of infection in the dog population was stable (489, 490).

Nonvectorial transmission in humans includes blood transfusion, organ transplantation, needle sharing in drug users, and congenital infection (491). The infection often remains subclinical, especially in immunocompetent adults (492, 493). Children below 2 years of age and immunocompromised individuals (e.g., HIV and immunosuppressant-treated patients) are more prone to develop the disease (473). However, there are several cases reported in otherwise healthy adult humans (493). The most common form of disease caused by *L. infantum* in humans is visceral leishmaniosis (VL), characterized by fever, hepatosplenomegaly, anemia, leukopenia, fatigue, weight loss, and, often, a fatal outcome in untreated cases (492, 493). Less frequent clinical types of the infection are a cutaneous form (cutaneous leishmaniosis [CL]), displaying lesions on the exposed parts of the body, including erythematous nodules (Fig. 15), histiocyte and lymphocyte infiltration, and shallow ulcers and papules, leaving lifelong scars (494, 495), a form localized especially at the nasal mucocutaneous limits (474), and a mucosal form with painless ulcers, granulomas, and tumor-like masses in the nose, mouth, and larynx (472).

Although *L. infantum* is the most important and widespread zoonotic *Leishmania* species, causing VL and CL in Asia, Europe (mainly Mediterranean Basin), South

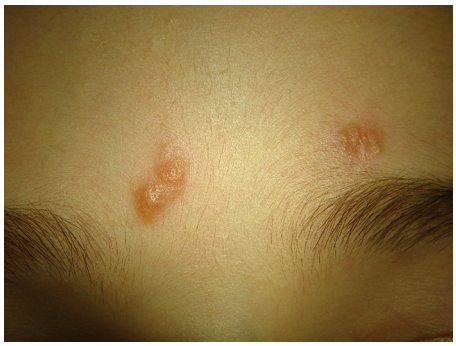

**FIG 15** Cutaneous nodules and ulcers caused by *Leishmania infantum* in a human patient (courtesy of Luigi Gradoni, Unit of Vector-Borne Diseases, Department of Infectious Diseases, Istituto Superiore di Sanità, Rome, Italy; reproduced with permission.)

America, and Africa, dogs can act as reservoir for other species, e.g., *Leishmania braziliensis*, *Leishmania panamensis*, and *Leishmania peruviana*, causing CL in humans in Southern and Central America (493).

Other than zoonotic leishmanioses involving dogs, cats, and other animals (e.g., rodents as reservoirs of CL, including species *Leishmania major*), humans can suffer from disease caused by two species of *Leishmania* with anthroponotic cycles, namely, *Leishmania donovani* and *Leishmania tropica*, both causing VL and CL (493). Humans are reservoir hosts for *L. donovani* and *L. tropica*; both species can cause clinical diseases in dogs, which may act as reservoir of *L. donovani* in certain areas (471, 496–498). Therefore, dogs may amplify the circulation of *L. donovani* and enhance transmission chances to humans. This is of great relevance given that VL due to this species is potentially fatal if not treated (493).

Overall, cases of both animal and human leishmanioses are increasing worldwide due to a series of anthropogenic causes. As examples, deforestation and urbanization have caused a rise of the incidence of leishmaniosis in peridomestic and urban environments, and wars or socioeconomic instability spur mass movements of people, fostering emergence and reemergence of leishmaniosis in given areas (493). These factors have led to an increase of imported cases of human leishmaniosis and/or to the risk of introduction of "new" species in previously free areas, as in the case of *L. tropica* in Italy (499). From this point of view, the prevention of the establishment of highly pathogenic species, such as *L. donovani*, in areas where they are not endemic is pivotal.

Awareness of epizootiological and epidemiological aspects of leishmaniosis is growing, and the guard should be kept high. Zoonotic VL is a severe and potentially lethal disease in humans, and prevention measures, e.g., use of repellents and application of prevention measures in dogs (e.g., repellents and vaccination), are of great importance, as VL remains one of the top parasitic diseases with outbreak and mortality potential. Accordingly, specialized health institutes, such as the WHO, have provided official recommendations for the management of human infections, for the control of sandflies and reservoirs, and for correct environmental management in a One Health perspective (https://www.euro.who.int/en/publications/abstracts/manual-on-case-management-and-surveillance-of-the-leishmaniases-in-the-who-european-region-2017).

## CONCLUSIONS

A network of immune functions, species-specific behaviors, and intrinsic and extrinsic biological features influences the host range of canine and feline parasites and accounts for different, host-dependent disease development and hazard for public health.

A predominantly Th1-oriented response of cats renders them less permissive to nematode hypobiotic stages, with implications for fetal and neonatal infections by intestinal parasites. Also, it has a great impact on the clinical and epidemiological

significance of VBDs, including the differential impacts of TBDs and leishmaniosis in dogs and cats.

Animal behaviors may prevent or increase the risk of infection by different parasites. Feline grooming reduces the occurrence of tick infestations and most TBDs in cats but enhances possibilities of other infections such as hepatozoonosis and dipylidiasis. Geophagia, pica, and coprophagia put many dogs at risk to be infected by parasites which are transmitted via the fecal-oral route, i.e., intestinal protozoa and nematodes, many with a zoonotic significance.

Cats and dogs show important differences in the physiology of their cardio-respiratory system. The presence/absence of PIMs is herein suggested as potentially responsible for both (i) the different heartworm/lungworm species infecting dogs and cats, and (ii) the diverse outcomes of *D. immitis* and *Angiostrongylus* infections. As HARD in cats is often misdiagnosed as asthma or allergic bronchitis, it would be worthwhile investigating if this is also the case in *Angiostrongylus* species infection in these animals.

The evolutionary pressure on parasites to adapt to the most available predator-prey relationship optimizes their biological features (45). Sarcoptic and notoedric mange, echinococcosis, toxoplasmosis, and neosporosis are key examples of the great impact of such dynamics on the epizootiology and epidemiology of parasitic diseases. Predation is the main route for feline infection with roundworms, hookworms, and lungworms, while dogs are at more risk of acquiring such parasites due to their tendency to ingest material from the soil (Fig. 1 and 2).

It seems that while some canine extraintestinal nematodes are able to infect and/or cause disease in cats (e.g., *D. immitis* and *C. aerophila*) (174, 254, 500), nematodes of cats have not been found thus far infecting dogs, not even under experimental conditions. In the future, this parasitological knowledge may be altered, as cats often live in urban settings where they are progressively subjected to a "dog-like" lifestyle with a decreased predatory hunting aptitude. Over time, there could be the possibility for a change in terms of coevolution of feline parasites toward canine hosts, and the next generations of parasitologists could face redrawn canine and feline parasitology.

The factual role of many parasites and VBDs in causing different diseases in dogs and cats, and the various roles they have in causing human pathologies, is too often underappreciated, mismanaged, or underdiagnosed by both veterinarians and physicians. Veterinary professionals are of key importance in implementing the control of parasites of veterinary and zoonotic concern to safeguard the health and welfare of pets and people and in educating the public and owners of companion animals. At the same time, a close cooperation with the medical community is pivotal for effective surveillance of zoonotic parasites and VBDs of dogs and cats. Veterinarians and physicians must keep their guard up against zoonotic dog and cat parasitoses and constantly provide advice and improve the knowledge of owners, with a special focus on those humans who are at higher risk of disease. In fact, the major goal of the "One Health" concept is based on the tight tie between the human health operators, vet practitioners, and the public.

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