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Review

Fleas and flea-borne diseases

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SUMMARY

Flea-borne infections are emerging or re-emerging throughout the world, and their incidence is on the rise. Furthermore, their distribution and that of their vectors is shifting and expanding. This publication reviews general flea biology and the distribution of the flea-borne diseases of public health importance throughout the world, their principal flea vectors, and the extent of their public health burden. Such an overall review is necessary to understand the importance of this group of infections and the resources that must be allocated to their control by public health authorities to ensure their timely diagnosis and treatment.

Introduction

The past decades have seen a dramatic change in the geographic and host ranges of many vector-borne pathogens, and their diseases. This process is often driven by climate change and the destruction of wild habitats. Fleas, as hosts for a wide range of largely understudied pathogens (except *Yersinia pestis*), are no exception, and flea-borne diseases may re-emerge in epidemic form. Examples of this are the changing ecology of murine typhus,[1] the finding of *Rickettsia spp* in new hosts,[2] and the finding of fleas on new hosts or in geographical areas previously unreported in the literature.[3] Therefore, it is timely to provide a concise review of flea biology, synanthropic fleas, and flea-borne diseases, presenting updated evidence on their evolutionary history, emergence, and re-emergence.

Fleas and their biology

Fleas (Insecta, Siphonaptera) are small, laterally flattened, wingless, and highly specialized insects. Fleas are of great importance as vectors of pathogens in many parts of the world. Both adult males and females are obligate hematophagous ectoparasites of mammals and birds. About 2574 species belonging to 16 families and 238 genera have been described, but only a minority is synanthropic, that is they live in close association with humans (Table 1).[4,5]

Morphology

Adult fleas are strongly sclerotized, and ca. 2–10 mm in length. They have thin, flattened bodies and backward-directed spines on their legs and bodies that facilitate forward movement through fur, hair, or feathers and prevent them from being easily dislodged (Figure 1). Compound eyes are absent. Antennae are short, situated in lateral grooves, and are erectable in males, allowing the support of the female during copulation. Fleas have three thoracic segments, each sustaining a pair of legs. They have strongly developed hind legs that permit them to jump up to 150 times their own body length.[6,7] This behavior is possible due to resilin, an elastomeric protein, which is compressed during the flexion of the coxa in the metathorax, and then rapidly relaxed. Larval morphology is inconspicuous, and newly hatched flea larvae are slender, white, segmented, and worm-like. They are sparsely covered with short hairs and are 1–2 mm in length (first instar) or 4–5 mm length (second instar). Some have an egg-tooth, which is used to cut their way out of the egg.[8] Flea eggs are pearly white, oval with rounded ends, and approximately 0.5 mm long.[7]

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Table 1
Siphonaptera families (from Lewis 1999, 1993 4,5)

Family	Distribution (region)	Genera	Species	Major host
Ancistropsyllidae	Oriental	1	3	Ungulates
Ceratophyllidae	Cosmopolitan but predominantly Holarctic	44	403	Primarily rodents, occasionally viverrids, mustelids, birds, and a single species on an insectivore (Siberian mole)
Chimaeropsyllidae	Ethiopian	8	26	Rodents, insectivores, elephant shrews
Coptopsyllidae	Palearctic	1	19	Rodents (gerbils and their allies)
Ctenophthalmidae	Primarily Holarctic, some in southern hemisphere	42	548	Rodents, occasionally pikas, insectivores (shrews and moles), marsupials, and a single species on mustelids
Hystrichopsyllidae	Nearctic, Palearctic, Neotropical, Australian	6	36	Rodents, insectivores
Ischnopsyllidae	Cosmopolitan	20	122	Bats
Leptopsyllidae	Palearctic, Nearctic, Oriental, a few species in Australian or Ethiopian regions (Madagascar)	29	230	Rodents, lagomorphs (hares, rabbits, pikas), insectivores, and rarely elephant shrews and foxes
Malacopsyllidae	Neotropical	2	2	Edentales (armadillos)
Pulicidae (includes tungid flea)	Cosmopolitan	27	182	Very broad host range, including carnivores, ungulates, bats, edentales (armadillos), and occasionally birds (*Cariama spp*).
Pygiopsyllidae	Ethiopian, Oriental Australian, and one Neotropical genus	37	166	Rodents, marsupials, insectivores, and occasionally monotremes, birds, or tree shrews
Rhopalopsyllidae	Neotropical, southern Nearctic, Oceanic	10	122	Primarily rodents, some on oceanic seabirds
Stephanocircidae	Primarily Neotropical, two Australian species	9	51	Rodents, a few species on marsupials
Vermipsyllidae	Holarctic	3	39	Carnivores and ungulates
Xiphiopsyllidae	Ethiopian	1	8	Rodents

Life cycle

As holometabolous insects, fleas complete a cycle from egg to adult through several larval stages and a pupal stage. The completion of the entire life cycle from egg to adult emergence varies significantly among species, and details are mostly known from synanthropic flea species. *Xenopsylla cheopis* for instance takes between nine and 15 days for its full development, but may take much longer depending on conditions.[9]

Egg

Once on a host, adult fleas take a blood meal and mate. Generally, a blood meal is required to complete ovary development in female fleas.[10] The female then begins laying eggs in the fur or the surroundings of the host. Thus, flea eggs may be deposited in all those places to which domestic animals have access. Female life time fecundity varies among species, and depending on ecological parameters. Some species only produce a low number of eggs (e.g., *X. cheopis* (rat flea)), whereas others are rather prolific (e.g., *Tunga penetrans* (chigoe flea)).[11–13] Eggs may hatch in one to 10 days, depending on temperature and humidity.[8] Due to their spherical or oval shape, they roll into cracks and crevices on the floor or in or near nests and bedding.

Figure 1. Morphology of the cat flea *Ctenocephalides felis*; male (top) and female (bottom).

Larvae

Larvae lack legs or eyes or other conspicuous morphological characteristics, but possess biting mouthparts. They pass through three stages (instars) of varying duration, depending on the availability of food, relative humidity, and other environmental factors.[13] Larvae are free moving and survive by feeding on organic debris found in their environment. Some are also known to feed on flea feces, which may be essential for successful development.[8] Since larvae are negatively phototactic (avoid light) and positively geotropic (prefer to move downward as a response to gravity),[14] they are found deep in carpet fibers, mattresses or couch stuffing materials, and organic debris (branches, leaves, etc.). They accumulate in areas where the animal spends a great amount of time (e.g., pet resting areas).

Pupae

The ovoid, whitish, and loosely spun pupal cocoon is sticky, and quickly becomes coated with debris, which helps to camouflage it. Some fleas may spin multiple cocoons (e.g. *Xenopsylla sp*).[15] If the pre-emerged adult does not receive the proper stimulus to emerge, it can remain dormant in the cocoon for several weeks and in rare conditions as long as one year, until a suitable host arrives (diapause).[13] This stage can extend the lifespan of the flea, and is troublesome from a control standpoint. Other fleas may not require any stimulus for emergence.[16]

Adult (imago)

Once the flea emerges from the cocoon, it immediately seeks a host to find a blood meal. Depending on species, adult fleas may prefer the hosts habitat ('nest' fleas), or the host itself ('body' fleas). Newly emerged fleas are attracted by various stimuli produced by these hosts. The known cues to host-finding in fleas are body heat, movement, and exhaled carbon dioxide.[15] If the flea does not find a host, it can survive for some time, depending on species, humidity, and temperature.[15] Once fed, fleas usually survive less time if

subsequently starved, than an unfed flea. Adults make up only about 5% of a flea population.[8,13,16,17]

Taxonomy, phylogeny, and evolution

The majority of characteristics used for the morphological identification of flea species are based on the shape and structure of their extraordinarily complex genitalia, and the presence and distribution of setae, spines, and ctenidia on the body.[18,19] Identification requires an extensive knowledge of flea morphology. New molecular data have explored phylogenetic relationships at the ordinal, familial, and generic level. Whiting and colleagues showed that the order Siphonaptera is monophyletic, and most closely related to Boreidae (snow fleas, Mecoptera).[19] Their recent analyses based on four genes show that many extant families are paraphyletic and thus warrant a reorganization of taxonomy.[20] In the context of flea host specificity and fleas as vectors, taxonomy and phylogenies play important roles as scaffolding for further knowledge acquirement regarding vector–flea and flea–host co-evolutionary patterns. Furthermore, better resolved scenarios of flea evolution allow for a deeper understanding of adaptation to certain ecological parameters, which may ultimately affect vector efficiency, and thus influence the rate of human infection.

Host specificity

Host specificity is important from the standpoint of transmission of disease agents. In general, hosts that are taxonomically related or are similar in their ecologies are likely to share flea species, and thus have the potential of hosting similar pathogens. Fleas are rarely specific at the host species level, but some clades of fleas associate with a particular host group at higher ordinal levels. Generally, mammals that have vast home ranges and do not inhabit dens for rearing their young, almost always lack fleas of their own, whereas hosts (mammals or birds) with dens or nests exhibit a more specific flea fauna. Recent studies[20] have shown that fleas likely emerged with mammals and speciated with rodents, which still have the most speciose extant fauna (74%). Only 8% of fleas are known from insectivores, 5% each from marsupials and bats, whereas 6% of the total diversity is ornithophilic (Figure 2).

Fleas as vectors

Fleas are mainly vessel feeders, thus damaging blood vessels directly. Another, more concerning effect of this dietary preference is that fleas themselves are hosts to pathogens, and thus provide a natural avenue for pathogen dispersal. The two commonly known

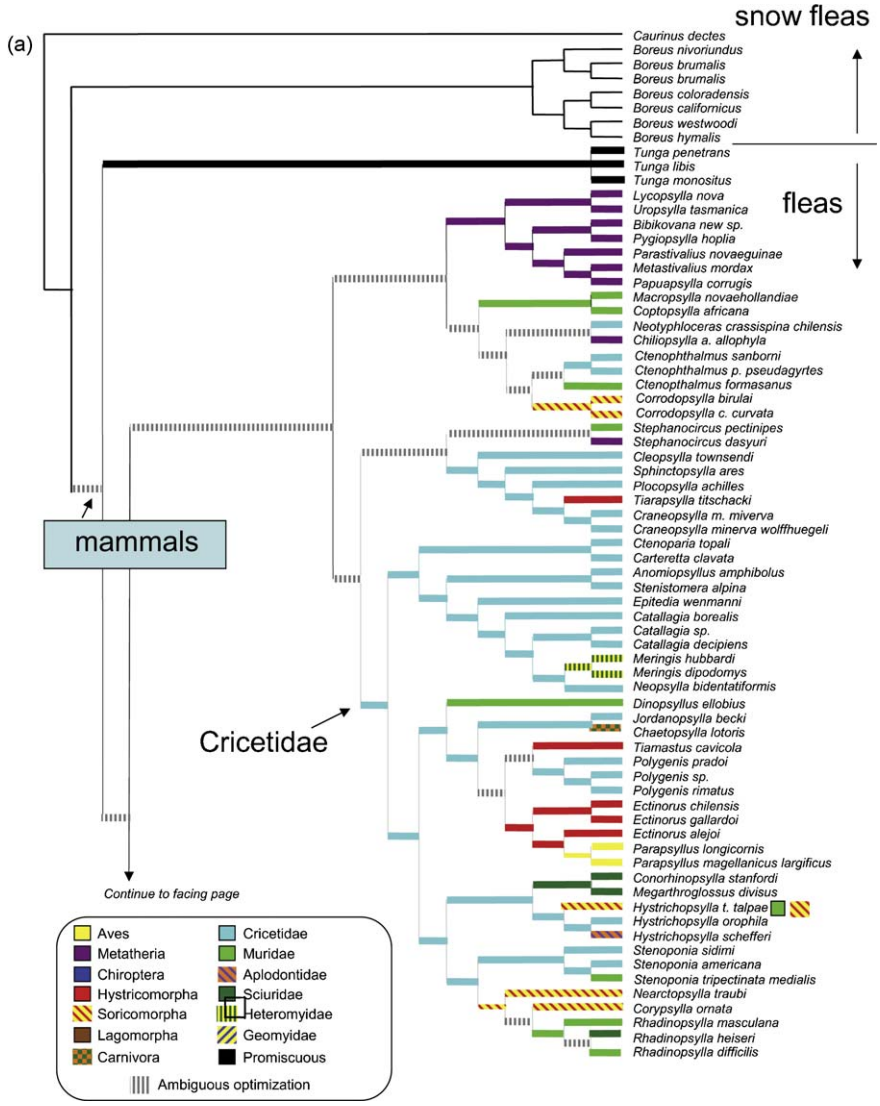

Figure 2. Phylogenetic relationships among fleas based upon four molecular loci. This topology has host association data mapped on the topology, as described in Vashenok[10].

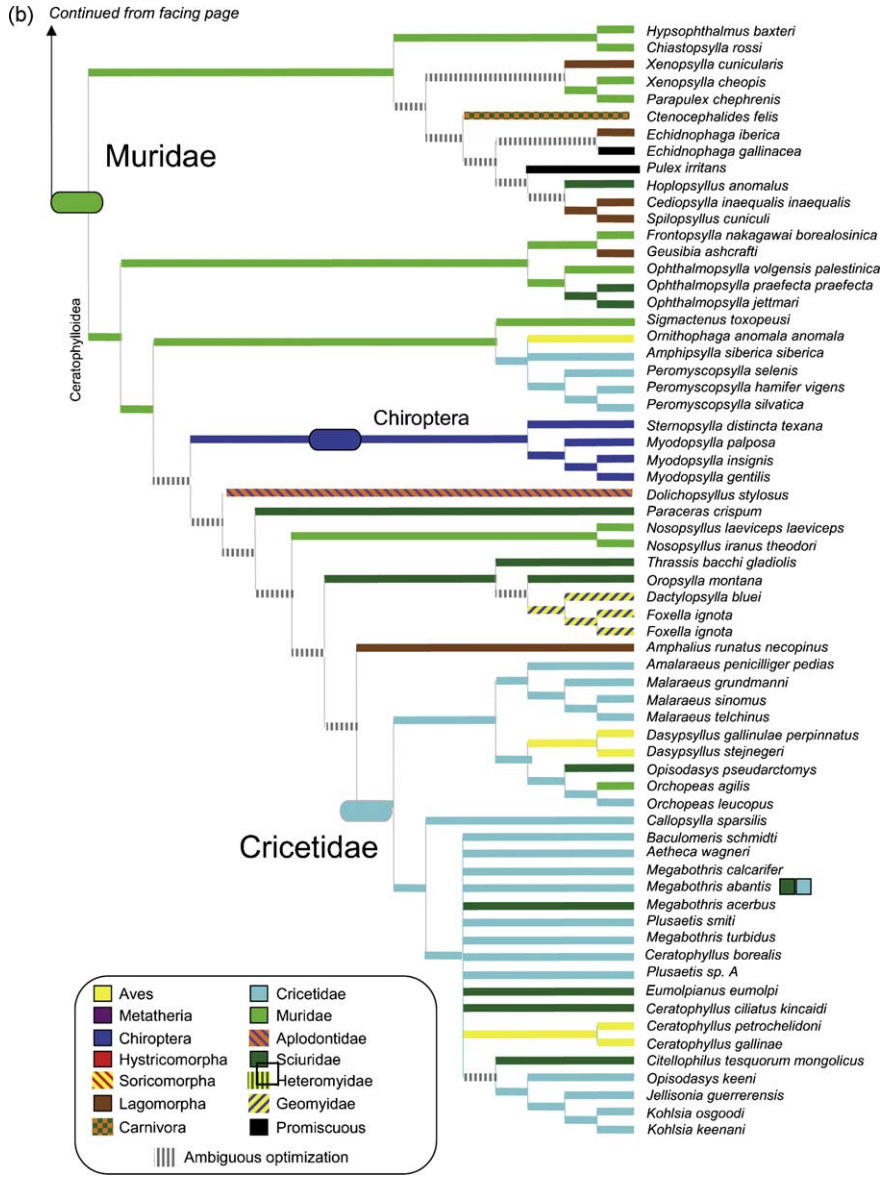

Fig. 2. (*Continued*).

ways of pathogen transmission by fleas are by oral route through regurgitation of blood meals, or by fecal route, by contaminated fecal pellets. Specific examples of this will be given in the following sections.

Important synanthropic fleas

There is no flea specific to humans, and only a fraction of all fleas come into contact with humans on a regular basis. Many fleas, however, associate with domesticated animals, and may thus have an economic, rather than direct effect on humans and their health. Although *Pulex irritans* is frequently called the human flea, recent works in Africa have described an abundance of human-associated fleas (*P. irritans*, *Ctenocephalides felis*, and *X. cheopis*) in human dwellings in plague-endemic regions of Africa.[21,22]

Brief descriptions of the most common synanthropic species are provided in the following text.

Pulex irritans (human flea)

This flea has a nearly cosmopolitan distribution. It is mistakenly called the human flea, because it attacks a wide variety of mammals, including guinea pigs, domestic dogs,[23] cats,[24] rats,[25] and goats.[26] Infestations can reach tremendous levels, particularly when farmers share their dwellings with their livestock, or hold these animals in corrals or buildings adjacent to their homes.

Ctenocephalides felis felis (cat flea) and Ctenocephalides canis (dog flea)

The cat flea is extremely common on cats and dogs in many temperate and tropical regions, but it also infests opossums,[27] raccoons,[27] and rats.[28] It represents the great majority of fleas in human homes. The dog flea is closely related to the cat flea and is very similar to it in appearance and biology. Despite its name it is actually less common on dogs than cat fleas.

Xenopsylla cheopis (oriental rat flea)

Various species of *Xenopsylla* are found throughout Africa and central and southern Asia, coinciding with the distribution of gerbils or rats. *X. cheopis* is common in many tropical and warm temperate environments around the world, although it probably arose in north-eastern Africa. This flea is the primary vector of *Y.*

pestis – the agent of plague,[29] and is involved in the transmission of murine (endemic) typhus[30] and parasitic helminths.[31] Recently, *Bartonella spp* have also been detected.[32]

Nosopsyllus fasciatus (northern rat flea)

The northern rat flea is common on commensal rats in temperate regions, especially *Rattus norvegicus*.[33] It spends more time in the host's nest than the oriental rat flea (*X. cheopis*) and is very likely to occur on rats with underground burrows. *N. fasciatus* occasionally infests other mammals, including mice,[34] voles,[35] ground squirrels, carnivores,[36] and occasionally humans.[34] Although considered to be a relatively poor vector of plague,[33] it has been implicated in the maintenance and transmission of *Salmonella enteriditis*,[37] *Francisella tularensis*,[38] and *Trypanosoma lewisi*,[39] a blood protozoan of rats.

Echidnophaga gallinacea (sticktight flea)

This small, angular-headed species is widely distributed in tropical and semitropical environments.[40] It belongs to a group of fleas called sticktights, because of the females' habit of using their serrated mouthparts to anchor themselves to their hosts. They then begin feeding while waiting for a male to copulate. Once a female begins feeding, she remains attached for many days. Eggs are deposited in the host's nest or in the ulcers caused by heavy infestations of these fleas. These fleas are by no means restricted to fowl, and also infest a wide variety of mammals, including dogs,[23] cats,[41] rabbits,[42] rodents,[28] and birds.[40]

Tunga penetrans (sand flea, jigger, chigoe)

T. penetrans is a small flea, and exhibits the unique traits of female neosomy, tachygenesis, and burrowing. Neosomy is radical intrastadial metamorphosis, characterized by cuticular growth in unsclerotized parts of the abdomen, without correlated molting. In endemic areas, fleas inhabit sandy beaches and soil, and it is commonly found in human dwellings.[43–45] The primary hosts are cows,[46] pigs,[47] and dogs,[48] but may also be humans.[48] Due to its poor jumping ability, the most common location for bites is the foot. The female flea first burrows its head into the skin until reaching the dermis with its capillary supply. In this position the flea feeds on blood and breathes air through the last pair of its abdominal stomata.[44] The volume of the fertilized sand flea increases by a factor of approximately 2000, reaching the size of a pea.[45] It remains as a 'foreign body' in the skin for a period of up to three weeks, during which time it matures, releases eggs, and eventually dies.

Flea-borne diseases

Despite continued efforts, we still lack much knowledge regarding the vector function of wild fleas, thus potentially missing an important piece of information. The most severe infection spread by fleas is plague, caused by *Y. pestis*.[49] Fleas are also known as vectors of murine typhus (endemic typhus, *Rickettsia typhi*), and play a role in the transmission of rural epidemic typhus (*Rickettsia prowazekii*) in the USA.[50] In recent years, the flea-borne spotted fever agent *Rickettsia felis* has emerged and can be found throughout the world.[51] Fleas have also been proven to harbor and sometimes transmit *Bartonella spp*, including *Bartonella henselae*, the agent of cat-scratch disease (CSD).[52,53]

Additionally, fleas are hosting helminths: *Dipylidium caninum* and *Hymenolepis diminuta*, respectively parasites of carnivores and rats.[54] Finally, in tropical areas, tungiasis caused by *T. penetrans* is a human disease directly linked to the parasitism of humans by fleas.[55] However, to many of the general population, the insidious attacks by fleas on people and domestic animals causing irritation, blood loss, and severe discomfort are equally important as disease threat.

Flea bites

The skin reaction to bites is of the delayed type. The lesion initially is a punctuate hemorrhagic area representing the site of probing by the insect. Lesions may occur in clusters, as the flea explores the skin surface, frequently re-probing. There is usually formation of a wheal around each bite, reaching its peak in 5 to 30 min. Pruritus (itching) is almost always present. In most cases there is a transition to a hardened papillar lesion within 12–24 h. In sensitized individuals the reaction appears faster, persisting for a week or more. The intense itching is often the reason people consult a physician rather than come to a clinic.[56]

Tungiasis (Tunga penetrans)

Infestation with this flea is usually limited to the feet, in the periungual region, but penetration can occur in any part of the body.[55,57–59] Within 24 h after penetration by the female flea, the site becomes irritated and painful. Erythema and edema develop around the lesion. The female needs eight to 12 days to reach maturity. During this process, its abdomen enlarges considerably and eventually reaches a diameter of 1 cm containing up to 200 ova.[60–62] The inevitable pruritus causes the host to scratch the lesion, which in turn helps to expel the eggs. Fleas can live in their host for several weeks.[61] After all eggs have been released, the flea dies.[61] Thereafter, the lesion desiccates in situ and eventually the remains of the ectoparasite are expelled. A small scar is left which, if it is limited to the epidermis, disappears over time. Without appropriate treatment however, secondary infections are common.[58,62] Various pathogenic bacteria have been isolated from tungiasis lesions: *Clostridium tetani*,[63] *Streptococcus pyogenes*, pathogenic *Staphylococcus aureus*, *Klebsiella aerogenes*, *Enterobacter agglomerans*, *Escherichia coli* and other Enterobacteriaceae. In areas with low vaccination coverage, tetanus is a common complication in children,[64,65] and immediate vaccination for patients is recommended. Sepsis, lymphedema, gangrene, and loss of toenails have been described.[55,64,66] Severe infestation with hundreds of jigger fleas can produce honeycomb-like lesions.[59]

The diagnosis of tungiasis is usually made by macroscopic inspection, where the embedded gravid female abdomen can be seen as a white patch with a black dot in its center. Frequently, a few eggs stick to the skin near the lesion, a finding that is pathognomonic for the infection.

The differential diagnosis of tungiasis includes myiasis, verruca vulgaris, ingrown toe nail, acute paronychia, mycotic granuloma, malignant melanoma, and arthropod bites.[67]

The first line of therapy is the mechanical extraction of the flea from the infected host. Removal is not always easy and may be painful for the patient. It can be accomplished using a sterile needle after cleaning the area with an antiseptic solution. This should be followed by irrigation with sterile saline and application of a topical antibiotic. The procedure bears the risk of bursting the flea, and inevitably leading to an exaggeration of the inflammatory response. An alternative is the enucleation of the cavity by curettage or punch biopsy.[66] Oral antibiotics may be indicated if a secondary infection develops. Prognosis is excellent as long as proper sterile methods are followed during extraction.

Although the treatment of infested lesions with topical ivermectin or metrifonate has appeared significantly more effective than placebo on the seventh day of therapy, all drugs

in this study failed to kill the ectoparasite in the early phase of its penetration.[68] Other therapeutic agents reported in the literature include topical chlorophenotane, clofenotane, 4% formaldehyde solution, chloroform, turpentine and 20% salicylated vaseline,[67] and oral thiabendazole.

Plague

Plague, caused by *Y. pestis* is a zoonotic disease primarily affecting rodents, but that can affect human beings. Small outbreaks continue to occur throughout the world; around 2000 cases are reported annually.[69] Plague has recently been recognized as a re-emerging disease and remains a serious problem for international public health, especially in Africa.[49,70,71] If used by the aerosol route of exposure as a bioterrorism agent, it could cause mass casualties.[69] *Y. pestis* has been the cause of three recorded pandemics.[72–76] At present, its circulation has been detected within populations of more than 200 species of wild rodents inhabiting natural plague foci on all continents, except for Europe, Australia, and Antarctica (Figure 3). The persistence of zoonotic foci is worrying, since persons living in these areas remain in close contact with rodents and fleas.

Morbidity in humans is noted, as a rule, when rodent epizootics are spreading, and is a consequence of mainly flea bites, but also direct contact with infected animal tissues, the consumption of insufficiently cooked meat products, or the inhalation of aerosolized respiratory excreta of animals or patients with the pneumonic form of infection.[69,77–79]

[4,5] While only a small number (over 31) of these are proven vectors of plague, any flea species may be biologically capable of transmission under the appropriate conditions.[81] Important flea vectors include *X. cheopis* (nearly worldwide in moderate climates), *Xenopsylla brasiliensis* (Africa, India, and South America), *Xenopsylla astia* (Indonesia and Southeast Asia), *Xenopsylla vexabilis* (Pacific islands), and *N. fasciatus* (nearly worldwide in cool, temperate climates). *Oropsylla montanus* is the most important flea vector in the USA.[82] In the former USSR, *Ctenophilus tesquorum*, *Oropsylla silantiewi*, *Rhadinopsylla ventricosa*, as well as species of *Xenopsylla*, *Nosopsyllus*, *Neopsylla*, and *Citellophilus*, are considered important plague vectors.[83] The human fleas (*P. irritans*) may play an important role in spreading plague by human-to-human transmission.[49] In northwest Uganda, which has had recent plague outbreaks, cat fleas (*C. felis*) have been reported as the most common fleas in the home environment, which is suspected to be a major exposure site for human plague in this country. In the past, *C. felis* has been viewed as only a nuisance biting insect because limited laboratory studies have suggested that it is incapable of transmitting *Y. pestis* or is an inefficient vector.[22]

While infection can occur by direct contact or ingestion, these routes do not normally play a role in the maintenance of *Y. pestis* in animal reservoirs. Fleas acquire *Y. pestis* from an infected blood meal. Infection in the flea is restricted to the alimentary canal, and is not transmitted transovarially. Consequently, maintenance of plague in nature is entirely dependent upon cyclic transmission between fleas and mammals.[49]

Plague can have several clinical manifestations; bubonic plague is the most common. Other manifestations include septicemic plague without bubo, pneumonic plague (primary or secondary to bacteremia), meningitis, and pharyngitis.[79] Following an incubation period of two to five days, plague has a sudden onset of fever, chills, headache, malaise, myalgia, and nausea. Pneumonic plague is rapidly fatal if untreated. For further details we refer the reader to a major review on plague.[79]

All patients suspected of having bubonic plague should be placed in isolation until two days after starting antibiotic treatment to prevent the potential spread of the disease should the patient develop secondary plague pneumonia.[79,80]

The antibiotics and regimes used to treat *Y. pestis* infections and as prophylactic measures have been recently reviewed [81].

Rickettsial diseases

Rickettsia are obligate intracellular Gram-negative bacteria associated with arthropods including ticks, mites, body lice, and fleas.[84]

Murine typhus (Rickettsia typhi)

Murine typhus is a worldwide zoonosis, and also known as flea-borne, rat, urban and endemic typhus.[85] The etiologic agent, *R. typhi* (formerly *Rickettsia mooseri*) is transferred from a rodent reservoir by an arthropod (often *X. cheopis*) to humans.[85] Many recent reports stress this as a re-emerging disease, which spreads through travelers returning from endemic regions.[86]

R. typhi infects endothelial cells in mammalian hosts and midgut epithelial cells in the flea host. It is passed in the flea's feces, and transmission to humans is by fecal contamination.[1] The complete genome of *R. typhi* was reported in 2004.[87]

Incubation periods range from six to 14 days. Many of its symptoms are shared with other infectious diseases, and thus cases may be overlooked without a laboratory confirmed diagno-

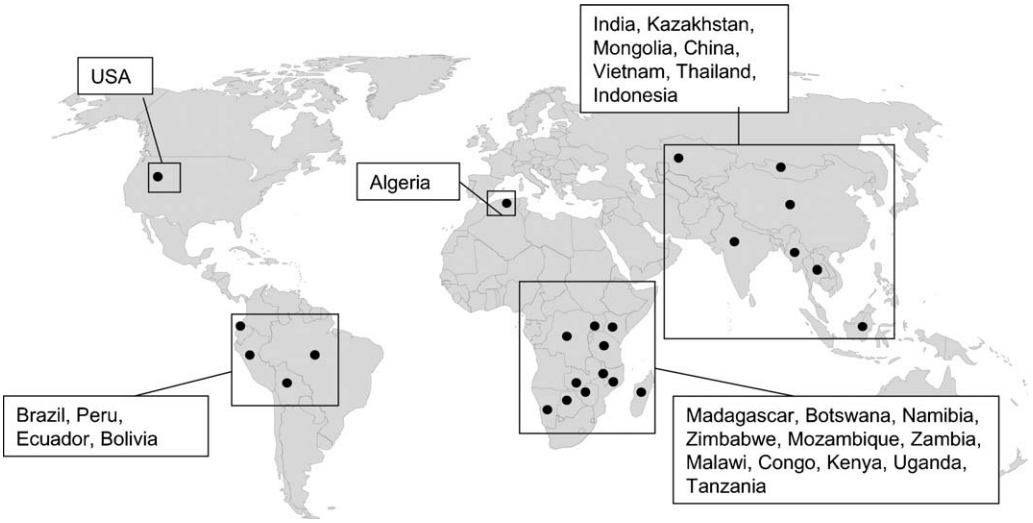

Figure 3. Geographical location of the plague worldwide, 1989–2003 (Source World Health Organization).

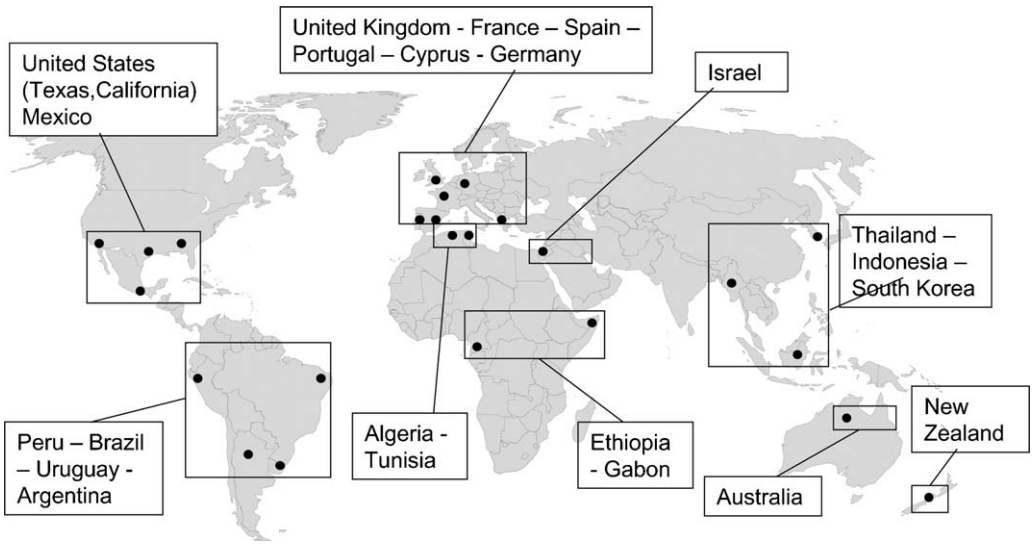

Figure 4. Geographical distribution of *Rickettsia felis* detected in fleas, and reported cases of flea spotted fever rickettsioses.

sis. The most common clinical manifestations are high fever, severe headache, chills, myalgia, weakness, and nausea.[88] The pathognomonic rash is described as macular (49%), maculopapular (29%), papular (14%), petechial (6%), and morbiliform (3%), usually centrally distributed on the trunk, but also found on the extremities.[89] Physicians practicing in or near *R. typhi*-endemic areas need to consider murine typhus in the differential diagnosis of a febrile illness without a clear source of infection.

Patients respond rapidly to treatment with tetracycline, doxycycline, or fluoroquinolone. Untreated patients show signs for two to three weeks and a significant number are hospitalized, with up to 10% requiring intensive care.[90]

Flea-borne spotted fever (Rickettsia felis)

This emerging rickettsiosis is caused by a member of the spotted fever group of *Rickettsia spp*. It was probably first detected in cat fleas, *C. felis*, in 1918, but is in fact hosted by a variety of fleas.[51] Although few confirmed human cases have been described, this infection occurs worldwide; the geographical distribution is summarized in Figure 4. There is controversy regarding the culture of *R. felis*; the first isolate grown at 37 °C has been lost[91] and the conditions of culture did not allow the reproduction of this work. *R. felis* has been propagated reproducibly only at temperatures below 35 °C.[92] The genome of *R. felis* has been sequenced and comprises one or two plasmids.[93,94] More cases have been described in hot countries. Infected people may develop severe clinical signs, commonly involving fever, headache, and rash. Other signs include marked fatigue, myalgia, photophobia, conjunctivitis, abdominal pain, vomiting, and diarrhea, as well as solitary, black crusted skin lesions, muscle pain, local lymphadenopathy (in some cases), and a characteristic inoculation eschar at the site of the flea bite.[51,92] Thus it may be misdiagnosed as the similar tick-borne rickettsiosis.

Patients have been successfully treated with doxycycline.[95] In vitro studies have shown *R. felis* is sensitive to doxycycline, rifampin, thiamphenicol, and fluoroquinolones.[96]

Bartonelloses

The genus *Bartonella* contains aerobic, fastidious, Gram-negative bacilli (Proteobacteria, alpha-2 subgroup).[97] Currently, 23 *Bartonella* species are recognized and associated with mammalian hosts, and 11 species have been implicated in human disease.[98] The role of fleas as competent vectors of *Bartonella spp* has been poorly studied. Current known records are summarized in Table 2, and pathogens are introduced in the following text.

Bartonella henselae

This pathogen is associated with the extremely common, worldwide zoonotic CSD. Transmission mainly occurs directly by a cat scratch and possibly via a cat bite or possibly the cat flea, *C. felis*.

The initial lesion consists of a papule, pustule, or vesicle that develops at one week, and enlarged lymph nodes at two to three

Table 2
Bartonella species detected in fleas worldwide

Flea	Bartonella	Disease in humans	Known geographical distribution region of Bartonella [Ref.]
Ctenocephalides felis	*B. henselae, B. clarridgeiae, B. quintana, B. koehlerae*	CSD, BA, BAC, END	France 106, Japan, New Zealand, Thailand, UK, USA
Ctenocephalides canis	*B. henselae*	CSD, BA	Japan
Pulex irritans /Pulex simulans	*B. quintana, Bartonella sp*	BAC, END	Gabon, Peru 107
Xenopsylla cheopis	*B. elizabethae, B. tribocorum*	END	Algeria, Egypt 28
Leptopsylla segnis	*Bartonella sp, B. elizabethae*	END	Algeria, Egypt 28
Nosopsyllus fasciatus	*Bartonella sp*	Unknown	Thailand
Oropsylla hirsuta	*Bartonella sp*	Unknown	USA (Colorado)
Archeopsylla erinacei	*B. clarridgeiae, B. elizabethae*	END	Algeria unpublished data
Pulex sp	*B. rochalimae*		Peru
Ornithophaga sp	*Bartonella sp, B. elizabethae*	END	Portugal
Stenoponia tripectinata	*Bartonella sp*	END	Portugal
Ctenophthalmus nobilis	*B. taylorii, B. grahamii*	END	England
Ctenophthalmus lushniensis	*B. clarridgeiae*	END	China

CSD, cat scratch diseases; BA, bacillary angiomatosis; BAC, bacteremia; END, endocarditis.

weeks, after a cat bite or scratch, usually on the arm.[99] Although the initial lesion heals uneventfully, regional lymphadenopathy (pathognomonic) develops one week later and persists for two weeks to three months before resolving spontaneously.

In 75% of patients the adenopathy occurs with mild systemic symptoms including fever, malaise, fatigue, headache, anorexia, weight loss, and emesis that usually resolves within two weeks. Enlarged lymph nodes can be tender, and up to 20% of these nodes suppurate. Most cases are self-limiting with the adenopathy resolving spontaneously in two to four months. In immunocompromised patients (e.g., the HIV-positive), bacillary angiomatosis may occur. This is a potentially fatal pseudoneoplasic vascular proliferative disease that might mimic Kaposi sarcoma. Additionally, it may cause an acute onset of febrile illness in HIV-positive patients, with arthralgia, myalgia, headaches, and lymphadenopathy or hepatosplenic involvement.[100] Endocarditis due to *B. henselae* occurs most often in patients with pre-existing valvulopathies who have contact with cats and their fleas.[101] The mortality rate is high (25%) and most patients require valve replacement surgery.

In vitro, *B. henselae* is susceptible to most antibiotics, although only aminoglycosides are bactericidal.[102] Most cases of CSD, however, respond very poorly to antimicrobial therapy and the disease generally resolves spontaneously within four months.[103] There is an unresolved debate as to whether patients with complicated CSD benefit from antibiotics,[104] although most HIV-positive patients respond well.[104] In patients with suppurative lymph nodes, needle aspiration is an appropriate treatment.

Bartonella quintana

These infections have recently re-emerged, predominantly among the homeless populations in cities in both Europe and the USA.[105] The pathogen has been detected in cat fleas[106] and in *P. irritans*,[107] although its main vector is the body louse. *B. quintana* has been identified in the dental pulp of domestic cats.[108] After the louse bite or after scratching and inoculating louse feces, the incubation period varies between 15 and 25 days.

Asymptomatic infections to severe illness have been reported, but the classical clinical symptoms correspond to an acute febrile illness, often accompanied by severe headache and pain in the long bones of the legs. Although trench fever may result in prolonged disability, no fatalities have been recorded. In a few cases, the illness becomes chronic with nervous manifestations, fever, anemia, weight loss, and also causes bacillary angiomatosis.

Bacteremia and endocarditis should be suspected in homeless, chronic alcoholic patients with culture-negative endocarditis, as well as in patients regularly exposed to flea bites.[30]

Effective antibiotic therapy for suspected trench fever should include an aminoglycoside (gentamicin) for at least 14 days, in association with ceftriaxone and/or doxycycline for six weeks.

General prevention of flea-borne infections

Flea control is typically undertaken for two reasons, first to reduce the risks of disease transmission and second to address a pest problem or economic losses associated with parasitization of domestic animals by fleas. The strategies used for each situation are often different, and the best results are achieved when the biology and behavior of the host are taken into account.[109]

Typically, flea control involves using insecticidal dusts to treat runways, burrows, and pet bedding. In emergencies, liquid spray formulations of insecticides can be applied to runways and burrow entrances. Flea eggs can be reduced by regular vacuuming of carpets and pet bedding areas. Contact with vectors can be minimized by eliminating rodents in the household. In the case of domestic animal or pet infestations, veterinary advice should be sought.[110]

Conclusions

Flea-borne organisms are widely distributed throughout the world in endemic disease foci, where components of the enzootic cycle are present. However, flea-borne diseases could re-emerge in epidemic form because of changes in vector–host ecology due to environmental and human behavior modifications. While local environmental changes are frequent, global climate change may influence parameters of flea development, distribution, and disease transmission on a much larger scale. For many fleas, temperature and humidity are crucial for development and survival. The warmer temperatures predicted through most climate change scenarios could lead to an increased expansion of flea vectors into the northern hemispheres.[109] Furthermore, our myopic concentration on synanthropic vectors often leads us to forget about the vast number of flea species associated with wild animals. Climate change, and our continued encroachment on natural areas, may provide new lines of transmission for a largely unknown pathogen population of wild fleas.

The incidence of flea-borne diseases and tick-borne diseases in the world is much greater than is generally recognized by physicians and health authorities. As a result, diagnosis and treatment are often delayed by health care professionals who are unaware of the presence of these infections and thus do not take them into consideration when attempting to determine the cause of a patient's illness. In the absence of major and dramatic outbreaks, health authorities often fail to allocate adequate funding to the surveillance and control of this group of diseases. It is important that those engaged in all aspects of public health surveillance are aware of the distribution and epidemiology of this group of diseases and are able to prepare for their control when necessary.

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