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RESEARCH ARTICLE

BE AWARE OF THE ARTHROPOD-BORNE DISEASE: RICKETTSIOSIS, PLAGUE, BARTONELLOSIS, AND RELAPSING FEVER BORRELIOSIS

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ABSTRACT

Victims of arthropod-borne diseases may be unaware of the source or circumstances of infection. Symptoms are often vague, initially, and characteristic lesions at the bite site or rashes may be lacking. This review aims to enhance the awareness and recognition of currently relevant diseases borne by hemophagous ectoparasitical arthropods, namely, fleas (endemic typhus and flea-borne spotted fever, plague, cat-scratch disease), human body lice (epidemic typhus, trench fever, louse-borne relapsing fever), and soft ticks (tick-borne relapsing fever). Each disease is described according to five criteria, which are important in disease identification and preventive awareness: Pathogen, vector, incubation period, symptoms, and region.

INTRODUCTION

"Neglected bacterial zoonoses" have been highlighted recently (1-5). Potentially indistinct clinically, such as flea-borne rickettsioses, louse- and tick-borne relapsing fever borreliosis, and leptospirosis, they may be confused with well-recognized infectious diseases, especially when barred laboratory confirmation (3). In the USA, flea-borne rickettsiosis causes infections in certain foci (6,7); endemic typhus (or "murine typhus") *(Rickettsia typhi)* is nonspecific at presentation and often unsuspected by clinicians (6). Moreover, in industrialized nations, the homeless contract "historical" louse-borne trench fever *(Bartonella quintana)* (1,8), while showing a significantly high seroprevalence of epidemic typhus *(Rickettsia prowazekii)* and relapsing fever *(Borrelia recurrentis)*, both louse-borne (8). The latter disease enters Europe with African refugees since 2015 (2). Flea-borne plague *(Yersinia pestis)* remains a serious threat in endemic sylvatic areas worldwide, though endemicity has been overcome in Europe (9). This schematized review on arthropod-borne infectious diseases aims to facilitate their recognition, thus awareness of disease care and prevention. Information is given on pathogens and their reservoirs, vectors, incubation periods, symptoms, and regions affected. The section on vectors includes "atypical" arthropods found naturally infected, though not proven as competent vectors, in order to alert to this potential threat. The diseases presented, caused by gram-negative and spirochetal bacteria, are treated with antibiotics.

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ARTHROPOD-BORNE INFECTIOUS DISEASES

Transmission: Victims may lack preventive awareness, and detrimental exposure to hemophagous arthropod vectors may be unnoticed, delaying diagnosis and treatment (5,6). Fleas transmit *Y. pestis* by regurgitation when feeding on a host, though also via their feces, which is the normal route of infectious contamination by fleas, such as of bite wounds (10). Conjunctival inoculation of infected flea feces may occur (11). A louse bite is not infectious. Louse feces, described as powdery (12), infect wounds or mucosa, are often aerosolized; crushing lice poses risks (12-14). Louse-borne *B. recurrentis* forces through intact human skin and mucosa (12). Notably, any "atypical" arthropod found infected but unconfirmed as a competent vector could transmit a pathogen on being crushed. As an example, crushing of *B. recurrentis*-infected bedbugs, *Cimex lectularius*, was concluded to have spread infection in an orphanage in China (15). Soft ticks (Argasidae), genus *Ornithodoros*, transmit relapsing fever borreliae other than *B. recurrentis* via saliva on feeding or via coxal fluid, the latter route not involving *O. hermsi* (5,15) and other American *Ornithodoros* vectors (15). Hard ticks (Ixodidae), via saliva, transmit the neurotropic *Borrelia miyamotoi*, which causes a relapsing fever-like illness (4,5). In argasids and ixodids, salivary ingredients include anti-hemostatic and anti-inflammatory molecules activating at the bite site (5). Pathogens, in some arthropod genera, pass transovarially to progeny, including *R. typhi* (6), *Rickettsia felis* (7) (fleas); *B. miyamotoi* (16) (ixodids); borreliae (argasids) (4,5,15), e.g., in the vectors *Ornithodoros turicata* and *Ornithodoros moubata*, scarcely in *O. hermsi* (15).

Flea-Borne Disease: Fleas, recognized by jumping behavior (distance of ≥30 cm), suck mammalian and avian blood. Eggs are deposited near the host, such as on pads used by pets. In humans, the bite produces a punctate hemorrhagic lesion, usually with a surrounding wheal and itching. A central itching papule may develop in 12-24 hours due to a delayed-type immunological skin reaction. Probing the skin area, fleas may cause clusters of lesions (10). As noted in 1994 in India, plague broke out when scores of rats perished and their infected fleas sought nearby humans as hosts. Travelers to such regions were recommended to use insect repellents, avoid the handling of dead or sick animals, which are infectious themselves, and take prophylactic antibiotics (17). The flea-borne bacteria and diseases presented are: *Rickettsia, R. typhi* (endemic typhus), *R. felis* (flea-borne spotted fever); *Yersinia, Y. pestis* (plague); *Bartonella, B. henselae* (cat-scratch disease).

Endemic Typhus and Flea-Borne Spotted Fever

Pathogen: The coccobacilli *R. typhi* and *R. felis,* genus *Rickettsia* (Rickettsiaceae), are the inciting agents. Among rickettsiae, *R. typhi* is classified in the typhus group, *R. felis* in the diverse spotted fever group (3). *R. felis* has antigenic and genetic resemblance with both groups. Globally, rats *(Rattus rattus, Rattus norvegicus)* are principal reservoirs for *R. typhi* though in USA foci are superseded by opossums *(Didelphis marsupialis),* which also harbor *R. felis* (6,7), and by (implicated) domestic cats (6,7,18). Moreover, cats are indicated as reservoir hosts for *R. felis,* adding to the flea-borne rickettsial disease burden (7,18). Within blood vessels, rickettsiae multiply in endothelial cells, triggering widespread vasculitis with heightened vascular permeability. Vital organs may be affected (12).

Vector: The rat flea, *Xenopsylla cheopis*, transmits *R. typhi*. The cat flea, *Ctenocephalides felis,* prevalent on opossums and cats, transmits *R. typhi* and *R. felis* in certain suburban regions of southern California and Texas (6,7,18). *R. felis,* as cause of human rickettsiosis, may be under-recognized in the USA (18), where, beyond these *R. typhi* foci, *R. felis*-infected *C. felis* infests wildlife (as opossums, bobcat) and other animals, e.g., dogs (7) and feral cats (18). *C. felis* living on domestic dogs and cats also carries *R. felis* in Ethiopia (19) and other countries, being considered the primary domestic flea (18-20). It parasitizes raccoons, rats (21). While *C. felis* is the principal vector of *R. felis*, even having *R. felis*-infected salivary glands, other carriers exist, including chigger and mesostigmata mites (Asia) (20); fleas, e.g., *Ctenocephalides canis* (19,20), *Pulex irritans* (7,19), *X. cheopis;* and ticks, e.g., *Rhipicephalus sanguineus, Haemaphysalis flava, Ixodes ovatus,* and *Carios (=Ornithodoros) capensis* (20).

Incubation period: Days: 7-14 *(R. typhi)* (6).

Symptoms: *R. typhi* infection, though often self-limiting, may be severe (22). Fever, lasting 3-7 days, headache, and arthralgia occur. A non-pruritic centrifugal rash affects ~50% of cases, appearing, on average, ~1 week from onset of fever (6). In serious illness, it has appeared during the second week (22). It lasts 1-4 days, is macular, maculopapular (6), or petechial, and may involve palms and soles (22). In Texas, from 1985 to 2015, 11 deaths traced or ascribed to *R. typhi* were reported (patient median age of 62 years). Six patients had mentioned animal exposure (cats, dogs, opossums), and 3 had confirmed also fleas. The case fatality, 0.4%, contrasted with the USA pre-antibiotic 4.6%. Symptoms included: Temperature range of 37.2-40.3°C at presentation, pneumonia, pneumoedema, encephalopathy, meningitis, hepatitis, acute kidney injury, and thrombocytopenia (22). Endocarditis, splenic rupture, and hemiparesis may occur. Neurological complications, with fever, stiff neck, headache, may arise 10-21 days from initial onset of febrile illness (6). *R. felis* causes an inoculation eschar (mimicking tick-borne rickettsiosis), fever, headache, rash; also vomiting, diarrhea, myalgia, conjunctivitis, photophobia, and, at times, local lymphadenopathy (21). Neurological signs may appear. Pneumonia and subacute meningitis have occurred, also acute polyneuropathy-like symptoms. The rash, commonly maculopapular, and eschar may be lacking, though dark skin may mask the rash (20). *R. typhi* is considered more morbific, typically, than *R. felis* (22).

Region: Hot seasons facilitate flea propagation, hence *R. typhi* disease. Cases occur worldwide, such as in Africa, the Mediterranean, Far East, Hawaii, tropical and subtropical coastal urban areas and ports (6), in the USA mainly in central and south-central Texas and southern California (Los Angeles and Orange counties) (7). *R. felis* infections, more common in hot countries, arise worldwide (21), e.g., in Mexico, Brazil, Tunisia, Egypt, Israel, Thailand, South Korea, Laos, France, Sweden, Germany, Spain (20), and Texas (USA) (7,20,22). In Senegal and Kenya, *R. felis* was found cause of unexplained fever (20). *R. felis* circulates in Riverside County (southern California) (18), in *R. typhi* foci in southern regions of California and Texas (6,7), and in other USA states (7).

Plague

Pathogen: The coccobacillus *Y. pestis,* genus *Yersinia* (Yersiniaceae), is the inciting agent. Rapidly advancing in hosts, it replicates intracellularly, resisting phagocytosis, and later extracellularly with resistance to complement-mediated lysis; dissemination to internal organs, such as the lung, may occur (23,24). Feeding fleas, especially *Xenopsylla,* regurgitate *Y. pestis,* which multiplies in the flea's proventriculus causing blockage. Flea feces are infective for up to 3 years (10). Permanent rodent reservoirs tend to exist in semiarid, not hot, desert areas. In North America, reservoirs are found mainly in the Southwest (USA) and Pacific coastal regions. Worldwide, certain mice, voles, and gerbils are implicated as enzootic hosts, e.g., *Peromyscus* species, *Microtus californicus,* and *Meriones meridianus,* respectively (23). Epizootic hosts readily die, releasing fleas or infecting humans directly (sylvatic plague), e.g., rabbits, ground squirrels (including susliks), rock squirrels, mice, voles, rats, chipmunks, marmots (including tarabagans), gerbils, and prairie dogs. Unlike other carnivores, domestic cats develop systemic illness. They are implicated in having sparked primary pneumonic plague in humans (23). Respiratory droplets cause this form of plague, such as in a primary pneumonic plague epidemic (17,23). Undercooked ingested meats transmit plague (21).

Vector: Fleas of the genus *Xenopsylla* are important, mainly *X. cheopis* (moderately warm, moist climates), also *X. brasiliensis* (South America, Africa, India), *X. astia* (Southeast Asia, Indonesia), *X. vexabilis* (Pacific islands). Flea vectors also include *Oropsylla montanus* (most important vector in the USA, parasitizing squirrels); *Oropsylla silantiewi*, *Ctenophilus tesquorum*, *Rhadinopsylla ventricosa* (species in the former

USSR); *Nosopsyllus fasciatus* (cool, temperate climates) (23). Infected "atypical" arthropods are ticks (23); body lice, *Pediculus humanus corporis* (8,25) (Clades A, D); and head lice, *Pediculus humanus capitis* (Clade A) (25).

Incubation period: Days: 2-6 (bubonic form); 1-3 (pneumonic form) (23).

Symptoms: Fleabites, rarely causing a lesion, or wound contamination with infected matter are routes of contracting bubonic plague (40-60% case fatality without antibiotics). Fever, chills, headache, and, often, gastrointestinal complaints (diarrhea, vomiting) occur. Tender regional buboes, typically inguinal or femoral, develop, as *Y. pestis* spreads from the inoculation site. Bacteremia occurs frequently. Pneumonia, septicemia, or meningitis may be secondary manifestations (23). In primary pneumonic plague, inhaled *Y. pestis* rapidly multiplies in lung, particularly in alveoli, while suppressing host immunity. Once symptoms appear (fever, headache, nausea, vomiting, cough with bloody sputum), victims promptly die from necrotizing pulmonary hyperinflammation (case fatality up to 50% with antibiotics) (24). Primary septicemic plague (fever, chills, headache, gastrointestinal complaints, abdominal pain) causes sepsis without lymphadenopathy (23), from direct inoculation of *Y. pestis* into the bloodstream, and may, like bubonic plague, produce secondary pneumonia via dissemination (24). Separate clinical manifestations of plague include meningitis (primary) and pharyngitis (21).

Region: Europe, struck by 3 pandemics and reporting plague until 1950, has no known sylvatic reservoirs today. Globally, *Y. pestis* strains from the first 2 pandemics are considered extinct (9). Endemicity persists in Africa, Asia, and the Americas, including the western USA (21,23). In recent decades, countries experiencing outbreaks included the Democratic Republic of the Congo (DRC), Madagascar, Zambia (24), Algeria, and Libya (9). Countries with natural foci and spillover include Brazil, Peru, Bolivia, Ecuador; Tanzania, Uganda (9,21), Kenya, southern neighboring countries of Zambia; Kazakhstan, Mongolia, India, China, Thailand, Vietnam, and Indonesia (21). In DRC, *Y. pestis*-infected head and body lice were found (25).

Cat-Scratch Disease

Pathogen: The coccobacillus *B. henselae,* genus *Bartonella* (Bartonellaceae), causes a cyclic intraerythrocytic bacteremia in mammals, such as rats, cats, dogs, and horses. It invades immature and mature human erythrocytes and infects other cells (endothelial cells, pericytes, macrophages). In anemia of unknown cause, *B. henselae* is a possible agent (26). Cats are the main reservoir (1).

Vector: Of the genus *Ctenocephalides,* the species *C. felis* transmits between cats. Its feces contaminate the cats' claws and mouth; bleeding gums of cats release infectious blood. A cat scratch or bite transmits *B. henselae* to humans, often children (11). *C. felis* can also parasitize humans, posing a general threat when infected with a pathogen (20). Infected "atypical" arthropods include ticks, e.g., *Dermacentor reticulatus* (27,28), *Ixodes scapularis* (1), *Ixodes ricinus* (1,28), *Ixodes pacificus* (29), and *Ixodes persulcatus* (27). A role for ticks in *B. henselae* transmission has been discussed (1,29). *Aedes* mosquitoes (27), the woodlouse hunter spider, and the woodlouse are carriers (1). As detected in *B. henselae*-infected ticks, co-infection with agents of Lyme borreliosis exists, such as with *Borrelia burgdorferi* in *I. scapularis* and *I. ricinus* (1) and with *Borrelia afzelii* in *I. ricinus* (28).

Incubation period: Days: 7-14 (30).

Symptoms: Local lesions develop within 3-30 days post-inoculation in most patients. One or more 3-5 mm red-brown papules appear. Over a period of 1-3 weeks, they may become vesicular, papular crusted. Regional lymphadenopathy tends to occur 1-3 weeks from infection (11). It usually lasts 2-8 weeks; the lymph nodes may suppurate. Aches, anorexia, and malaise occur in 75% of patients, low-grade fever in 9%. The disease is often self-limiting. Some patients' manifestations include: Prolonged fever (children); arthritis; hepatosplenomegaly; encephalopathy, attacking 1-6 weeks after onset of lymphadenopathy, with confusion, severe headache (30); Parinaud's oculoglandular syndrome (granulomatous unilateral conjunctivitis with regional preauricular lymphadenopathy), affecting ~5-10% of patients, presumably caused by conjunctival inoculation of infectious flea feces (11). Rare manifestations include pneumonia, pleural effusion, osteomyelitis (31), transverse myelitis, transient hemiplegia, endocarditis (patients with previous valvulopathy), and neuroretinitis (11). In HIV-infected and also immunocompetent patients, a separate manifestation may develop, namely a vascular disease caused by proliferating infected endothelial cells (bacillary angiomatosis, also from *B. quintana*), with heavy bleeding of cutaneous lesions when stabbed, possibly involving other organs, e.g., lymph nodes, spleen. In HIV-infection, the associated hepatic peliosis may occur (12).

Region: Cat-scratch disease occurs worldwide, in northern temperate zones mostly during the second half of the year (30,31), thought as due to seasonal cat breeding and acquisition of kittens (31). In cats, seroprevalence of *B. henselae* is highest in warm or humid climates, where also the incidence of cat flea infestation is increased (11); e.g., in the warm to temperate climate of Bishoftu, Ethiopia, domestic cats carry *C. felis* infected, also co-infected, with *B. henselae* and *R. felis* (19).

Louse-Borne Disease: The human body louse lives in clothing, seeking skin to feed. Eggs are deposited in fabric folds and, for warmth, preferably close to the host's skin. The hatched young feed immediately. Lice typically feed 5 times daily (12). Regular changing and washing of infested clothes and beddings are critical measures in delousing and prevention (32). Fabrics should be washed at 52°C for 30 minutes (2). History of seeing lice in clothing, washing clothes after 2 days or less often, and washing beddings once a month or less often were independently associated with symptomatic illness (trench fever, epidemic typhus) in a crowded male youth rehabilitation center in western Rwanda (32). At the bite site, a red spot forms from an injected vasodilator and disappears in 1-2 hours without itching or swelling (33). An allergic reaction to inoculated proteins, which include an anesthetic and an anticoagulant, arises within 3-4 weeks from initial bites and may trigger pruritus; bites now are detectable. Secondary infections may occur. Frequently bitten skin areas may darken (vagabond's disease) (12). The 3 louse-transmitted pathogens involve humans as single or important reservoir, causing relapses, bacteremia, and proliferating during civil unrest, cold

weather, and crowded, unhygienic conditions (12): *Rickettsia*, *R. prowazekii* (epidemic typhus); *Bartonella*, *B. quintana* (trench fever); *Borrelia*, *B. recurrentis* (relapsing fever). Other causative borreliae are argasid-borne and ixodid-borne (5) (see under Tick-Borne Disease).

Epidemic Typhus

Pathogen: The coccobacillus *R. prowazekii*, genus *Rickettsia* (Rickettsiaceae), is classified in the typhus group of rickettsiae. It survives in louse feces for up to 100 days. Its multiplication in the louse's midgut epithelial cells causes rupture of the gut and escape of blood. The louse turns red and soon dies ("red louse disease") (12). *Glaucomys volans*, the southern flying squirrel, with its ectoparasites, is the zoonotic reservoir (USA) (8,12,14,34).

Vector: The body louse, *P. h. corporis*, genus *Pediculus*, is the vector. "Atypical" carriers include *P. h. capitis* (35) and ticks of the genera *Hyalomma* (Africa) (14) and *Amblyomma* (Mexico) (14,22); the *Amblyomma* species reaches into southern Texas (22).

Incubation period: Days: 10-14 (12).

Symptoms: Malaise and vague symptoms are noted before high fever, severe headache, and myalgia occur; chills, arthralgia, and anorexia are other early complaints (12). Untreated, the fever typically abates after 2 weeks (14). A macular rash appears, on average, on illness day 5, first axillary, then thoracic, affecting extremities, and becoming petechial (36). It is not noted consistently (32,36) and may be nearly unrecognizable in dark-skinned persons (12). In October 1998, a 65-year-old male, who had returned to France from Msila, a town in east-central Algeria, where he had endured pruritus and scratching, presented with mild confusion, fever of 40°C, relative bradycardia, myalgia, nausea, vomiting, diarrhea, splenomegaly, and scattered thoracic maculae. After 2 days, semicoma, bilateral interstitial pneumonia, purpuric rash, severe thrombocytopenia, and apparent disseminated intravascular coagulation and acute renal failure were observed. He recovered with antibiotic treatment (36) (10-30% case fatality without antibiotics (12)). Jaundice, myocarditis, and seizures may occur (12). Epidemic typhus may resemble typhoid fever in the early phase of illness (36). Infection, by an unknown mechanism, may become dormant even after clinical cure and later arouse recrudescent typhus (Brill-Zinsser disease) (12,14,34), with louse-driven epidemic potential (12).

Region: Highlands are threatened, located in the Andes region (Peru), in the Himalayas, and in central and eastern Africa (14), e.g., Burundi (8,12), Rwanda (32). Affected regions or populations also include Algeria (36) (Msila is part of Algerian highlands, the Hautes Plaines); the eastern USA (sylvatic epidemic typhus) (14,34); Mexico (14); Central America; China (12,14) in Southeast (14); rural Russia (8); homeless persons showing seroprevalence of *R. prowazekii* in Marseille, France (8), and Houston, USA (8,22). Migrants in southeastern Turkey bear *R. prowazekii*-infected head lice (35).

Trench Fever

Pathogen: The coccobacillus *B. quintana*, genus *Bartonella* (Bartonellaceae), has a tropism for endothelial cells (12) and invades human erythrocytes and erythroblasts of bone marrow (37). In louse feces, it survives for up to 1 year (12). Asian macaques, cats, and dogs are zoonotic reservoir hosts (1).

Vector: Of the genus *Pediculus*, *P. h. corporis* is the vector, with discovered *Y. pestis* co-infection in DRC (25). "Atypical" arthropods found infected include *P. h. capitis* (1,8,25,35,38); the flea *C. felis* (1,8,21); the ticks *I. pacificus* (29), *I. persulcatus*, and *D. reticulatus* (27); bedbugs *(C. lectularius)* (1); and *Aedes* mosquitoes (27).

Incubation period: Days: 15-25 (12).

Symptoms: The first fever period may last 2-4 days. Acute-onset high fever, headache, dizziness, and typical shin pains occur (8). The headache, frontal and retro-orbital, is severe. Conjunctival congestion and splenomegaly may be noted. Several relapses tend to occur, periodically, every 4-8 days, usually every 5 days, and milder with each attack (<1% case fatality without antibiotics) (12). *In vitro*, the erythrocytes, in which *B. quintana* multiplies, disintegrate after 5 days, releasing the pathogens (39). Louse-borne relapsing fever is differentiated by jaundice and bleeding (2), which occur also in argasid-borne relapsing fever (15). In 2002, in summer, a 54-year-old alcoholic homeless male of Marseille, France, exhibited typical symptoms that resolved spontaneously after 72 hours: Fever of 40°C, chills; headache; loss of balance and falling down from both severe shin pain (a pulling sensation) and dizziness. Five days later, he had similar symptoms for 2 days. *B. quintana* was detected in up to 1.5% of his erythrocytes and, on day 31, in erythroblasts, thereby apparently escaping host immune response and finding niches enabling chronic bacteremia (37). Other disease presentations include meningoencephalitis (rare) (12); chronic lymphadenopathy; bacillary angiomatosis, mostly in HIV-infection; among the homeless, chronic bacteremia or indolent endocarditis. Usually culture-negative, the endocarditis is potentially fatal if diagnosed late (8).

Region: Important affected regions and populations are the rural Peruvian Andes; central and eastern Africa, e.g., Burundi (8), Rwanda (32), DRC (25), Ethiopia (38); homeless persons, such as in Colombia, Algeria (1), Europe, the USA (1,8,12), and Russia (12). *B. quintana*-infected head lice, a potential threat, parasitize Nepalese slum children (8) and migrants in southeastern Turkey (35). Inhabitants of Ethiopia (38) and DRC (25) have infected head and body lice.

Louse-Borne Relapsing Fever

Pathogen: The spirochete *B. recurrentis*, genus *Borrelia* (Spirochaetaceae), is capable of cyclic antigenic variation, thereby avoiding host immunity and causing the relapses (3,12). This variation is present also in argasid-borne borreliae (5,40), e.g., in *B. hermsii*, *B. turicatae*, and also in ixodid-borne *B. miyamotoi* (5). The louse's hemolymph is infected on day 5 post-feeding, its feces on day 14; thereafter, feces may not be consistently infected (13). An animal reservoir is not known. Mild or asymptomatic human infection appears to ensure the pathogen's continuity between epidemics. Lice do not transmit to progeny and are not considered a reservoir (2).

Vector: Of the genus *Pediculus*, the vector is *P. h. corporis*. Head lice (2,38), first found infected in 2011 (38), and bedbugs *(C. lectularius)* (15) are "atypical" carriers. Co-infection with *B. quintana* occurred in body lice (38).

Incubation period: Days: 2-15, usually 5-8 (15).

Symptoms: The disease is considered as malaria-like (2,15,41,42), also when occurring in the tick-borne form (41,42). The first attack lasts, on average, 5-7 days. The first afrebile interval may last 5-9 days (15). A range of 3-27 days is noted for intervals in general (12). The attack is marked by acute-onset fever, chills, flushed face, severe occipital or occipitofrontal headache (frontal in malaria), and myalgia, especially of calves. Nausea, vomiting, backache, and nuchal rigidity may occur (15). The fever range is 39.5-40°C; the pulse rate is elevated. Patients experience joint pain and abdominal pain (12). A rash may appear at the attack's end, with rose-colored spots. These may last a few hours or up to 2 days and, in severe cases, become petechial. The rash spreads from the neck and shoulders to the thoracic sides and inner sides of the thighs and arms. Respiratory symptoms, splenomegaly, hepatomegaly, and jaundice may develop. Sweating begins late, early in malaria (15). In the untreated, a crisis ends the attack (12). It lasts ~1-2 hours, in reaction to disintegrating borreliae, and includes potentially severe hemodynamics uncharacteristic for malaria: Rapid defervescence with hypotension, sweats, possibly leading to shock. Convulsions or myocardial failure may occur (15); thirst is present (12). Antibiotic treatment triggers a similar crisis (Jarisch-Herxheimer reaction) (12), with initial rigors and temperature increase (12,40). Also the rate of respiration and pulse rises. A drop in temperature and blood pressure follows, though high cardiac output remains. Lactic acid levels in blood increase (15). The reaction, starting within 2 hours of antibiotic treatment, usually lasts less than 4 hours and is potentially fatal (40), demanding careful administering of antibiotics and monitoring (3,40). No relapses may occur or several, progressively milder, shorter. The disease commonly lasts up to 2 weeks (15) (case fatality of 10-40%, with antibiotics 2-4% (12)). Manifestations include myocarditis; perisplenitis; hemorrhagic, necrotizing hepatitis (2); encephalitis or other neurological involvement; abortion; anemia; hemorrhages with thrombocytopenia. Bleeding may be nasal (common), subarachnoid, cerebral, retinal, respiratory, gastrointestinal, urinary, from splenic rupture (12), and subconjunctival; cerebral hemorrhage is a common cause of death (2). Though observed, the neurological (2) and neuropsychiatric symptoms (15) are noted as more common in the tick-borne form.

Region: Recently, mainly Ethiopia, its neighboring regions in the Horn of Africa, and Sudan have been affected (2,41). The rural Peruvian Andes are involved (2,8). Homeless persons (Marseille, France) show seroprevalence of *B. recurrrentis* (8). Pygmies in the Republic of Congo bear *B. recurrrentis*-infected head lice (2), and relapsing fever patients in the highlands of Ethiopia have infected head and body lice (38).

Tick-Borne Disease: Ticks transmit several types of pathogens, such as bacteria, viruses, and protozoans. The bite may cause acute and chronic skin lesions (10); e.g., in argasids, local necrosis from *Ornithodoros brasiliensis* (4), local irritation, edema, followed by formation of subcutaneous nodules lasting months, from *O. turicata* (10), or, in relapsing fever, an argasid-caused eschar, rarely seen in North America (40). In humans, ixodids (nymphs, adults) attach and feed for several days (10,16). The larvae, nymphs, and adults of most normally present ixodids feed only once, followed, in adult females, by deposition of eggs and death (10). Argasid adult females feed several times and deposit eggs after each blood meal. Ixodids have 1 nymphal stage. Argasids, with a longer life cycle, may pass through 6 or more; and feeding, during the life cycle, may last from a few minutes to a few hours, generally 5-60 minutes and occurring at night (5). *Ornithodoros* species, transmitting relapsing fever borreliae, parasitize larger mammals, birds, but usually rodent species, which are reservoirs of infection, e.g., for *B. hermsii*, chipmunks *(Tamias)*, pine squirrels *(Tamiasciurus)*, deer mice *(Peromyscus)*, and woodrats *(Neotoma)*. As indicated, wild canids maintain *B. hermsii* and *B. turicatae*. The ticks infest animal burrows, nests, caves, dens, including reptile dens, e.g., gopher tortoise dens in Florida, which contain *O. turicata* (4). Dwellings sheltering ticks in earth floors and walls (sub-Saharan Africa) (42) and rodent-infested mountain cabins (western USA) (40) permit human infection. Next to argasid-borne relapsing fever borreliae, the newly emerged ixodid-borne pathogen *B. miyamotoi* is presented.

Tick-Borne Relapsing Fever

Pathogen and Vector: The pathogens, genus *Borrelia* (Spirochaetaceae), and their region-specific vectors (genus *Ornithodoros*) include:

B. hermsii, western USA, southern British Columbia (Canada) *(O. hermsi)* (4);

B. parkeri, western USA (4,5); western Canada *(O. parkeri)* (15);

B. turicatae, British Columbia (Canada) (5); western/southwestern USA to Florida (excluding Louisiana, Mississippi, Alabama) (4) and to parts of Kansas (10); Mexico (4,5); historical records for Central and South America *(O. turicata)* (4,15);

B. mazzottii, Mexico, Guatemala *(O. tajale)* (4,5,15);

B. venezuelensis, Panama, Venezuela, Colombia, Ecuador, Paraguay *(O. rudis)* (5); vector presence in Peru (10);

B. brasiliensis, Brazil (*O. brasiliensis)* (4,5,15), specifically in highlands of southern Brazil (4);

B. crocidurae, western and northern Africa *(O. sonrai)* (5);

B. duttonii, central, eastern, and southern Africa, Madagascar (*O. moubata* complex) (5);

B. hispanica, Maghreb, Iberia, Greece, Cyprus *(O. erraticus, O. marocanus)* (5);

B. persica, Egypt, Middle East, central Asia, India *(O. tholozani)* (5,15); e.g., *B. persica* circulates in Israel, Palestinian territories, Iran, Uzbekistan, Tajikistan (41);

B. microti, Iran *(O. erraticus)* (5,15);

B. caucasica, Caucasus (Georgia, Azerbaijan, Armenia) *(O. verrucosus)* (5,15).

B. miyamotoi is transmitted by *I. scapularis* and *I. pacificus* (North America), *I. ricinus* (Europe), and *I. persulcatus* (Asia) (5,16), by nymphal *I. scapularis* within 24 hours of attachment (16). Small rodents, such as *Apodemus* species, *Peromyscus leucopus, Myodes glareolus*, and birds are indicated as reservoir hosts (5).

Incubation period: Days: In argasid-borne infection, 4-18 (4) and, for USA infections, an estimated 7-14 (range of 2-29) (15); in *B. miyamotoi* disease, ~14 (5).

Symptoms: Compared to the louse-borne form, argasid-borne disease can be more prolonged; the initial attack is usually shorter and may last 3-5 days, but the intervals between relapses can be longer. Untreated illness may last from 3 weeks to 7 months. On average, 3-5 relapses occur, the first

arising after an interval of 7 days, usually, or after 3-40 days. Each relapse lasts a few hours or up to 4 days (15). Infection from *B. hermsii, B. persica,* and *B. caucasica* may be severe (15) but may be mild from *B. hispanica* and *B. crocidurae* (15,41). *B. caucasica* causes 10-15 relapses within 3 months; *B. turicatae* and *B. crucidurae* cause few or no relapses (15).

Symptoms from *B. duttonii* include fever, headache, tachycardia, arthralgia, myalgia, hepatosplenomegaly, and conjunctivitis; orange-colored urine may be noted (41). In Tanzania, *B. duttonii* has caused a high perinatal mortality, 436/1,000 births (3,41), and children aged below 5 years are also highly threatened (3). In northwestern Morocco, *B. hispanica* has produced 20.5% of unexplained fevers in a cohort of patients seen in 2005 and 2006. Symptoms included chills (88%), myalgia (61%), and gastrointestinal complaints, e.g., vomiting, diarrhea (54%). Patients (15%) reported ≥1 relapse. Tick bites were not mentioned (43). A 60-year-old male contracted relapsing fever, apparently in a squirrel-invaded campground in the Bear Valley region of Idaho (northwestern USA). Headache occurred, with fever reaching 40.6°C and ending with shaking chills after 3 days. Relapsing 13 days later, the fever lasted 2 days, peaking at 39.4°C, with blurred vision (iritis diagnosed) and diffuse abdominal pain. Fever, 39.7°C, headache, and visual complaints reasserted ~8 days later, with tachycardia and hypertension. Antibiotic treatment was initiated (40). Cutaneous manifestations in 2 cases were: An Afghan sheepherder sleeping in caves or under tents contracted *B. persica.* On admission (in 1948), he displayed some abdominal roseolae, with flushed face and fever of 42°C. *B. turicatae* infected a Texas boy, who had played in woods near his home. Dry flushed face with fever of ~40.1°C was noted on admission (in 1958). A papular eruption developed on day 3 on flexor surfaces of arms, spreading distally, but overcome after 6-7 hours. The patients also exhibited conjunctivitis and injected conjunctivae, respectively (15). Manifestations include iridocyclitis, such as from *B. hispanica,* lasting 2-3 weeks (15), though potentially causing permanent visual impairment (40); altered sensorium; facial palsy and radiculopathy, more common after the first relapse; meningitis or meningoencephalitis with sequelae, e.g., residual hemiplegia or aphasia. Myocarditis, diffuse bleeding, coma or stupor, and hepatic dysfunction are high-risk states. Children and pregnant women often endure serious disease, yet treated patients rarely die (40). *B. miyamotoi* disease, noted as similar to human anaplasmosis, causes an influenzalike syndrome (fever, chills, headache, arthralgia, myalgia, malaise, and, possibly, ≥1 relapse). Meningoencephalitis, with cerebrospinal fluid pleocytosis, has developed acutely or, in immunocompromised patients, slowly (5).

Region: Africa, the Middle East, central Asia, Spain, the Americas are affected (42). Disease cases in Mediterranean countries and North Africa are rare (43). In Africa, *B. duttonii* infection is concentrated in DRC, Uganda, Tanzania (41); *B. hispanica* infection in Morocco, especially in North (41,43). *B. crocidurae* infection is geographically distributed over a region encompassing Egypt, Libya, Tunisia, Algeria, Mali, Mauritania, Senegal, Gambia (41), and southern Morocco (43). In the USA, most cases occur in western mountainous states (Cascade, Sierra Nevada, San Bernardino, and Rocky Mountain ranges) (40). The disease burden is considered unknown or underreported in the Americas (4). *B. miyamotoi* affects North America, Europe, Asia (5,16), having 3 genotypes (American, European, Siberian). The latter infects both *I. persulcatus* and *I. ricinus* in a sympatric region of Estonia (5).

Conclusion

An arthropod-borne disease is recognized by its symptoms, but also by the circumstances of infection. In the medical literature, the presentation of individual case histories, of which some were recounted in this review, is important, as it clarifies the progression of a disease; moreover, it describes or indicates the circumstances of infection, thereby building associations with enzootic, epizootic, or urban epidemic sources and the pertaining arthropod vectors and their pathogens.

Declarations

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Abbreviation

DRC: Democratic Republic of the Congo

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