Chapter 1
The Importance of *Rickettsiales* Infections

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1 Introduction

Bacteria of the order *Rickettsiales* are obligate intracellular parasites that infect a variety of hosts. The order *Rickettsiales* comprises the families: (1) *Rickettsiaceae*, with the genera *Rickettsia*, *Orientia*, *Occidentia*, "*Candidatus* (*Ca.*) Megaira", "*Ca.* Cryptoprodotis", "*Ca.* Arcanobacter", "*Ca.* Trichorickettsia", and "*Ca.* Gigarickettsia"; (2) *Anaplasmataceae*, with the genera *Anaplasma*, *Wolbachia*, *Ehrlichia*, *Neorickettsia*, *Aegyptianella*, "*Ca.* Neoehrlichia", "*Ca.* Xenohaliotis", and "*Ca.* Xenolissoclinum"; and (3) *Midichloriaceae* (Montagna et al. 2013; Szokoli et al. 2016a, b). All bacteria in the order *Rickettsiales* are Gram-negative Alphaproteobacteria. The *Rickettsiales* are widely regarded as being the closest relatives to mitochondria.

The common features of *Rickettsia* are their intracellular growth environment, their small genome sizes (1.1 Mb), and their low genomic G + C contents (29–33 %). The genus *Rickettsia* has an unusual arrangement of the rRNA genes. The 5S, 16S, and 23S rRNA genes are linked together in other bacteria, whereas in members of *Rickettsia* the 16S rRNA gene is separated from the 23S and 5S rRNA gene cluster and the 23S rRNA gene is preceded by a gene which codes for methionyl-tRNAf(Met) formyltransferase (Andersson et al. 1999).

The bite or inoculation of infectious fluids or feces from the ectoparasites such as fleas, lice, mites, and ticks are involved in the transmission of the pathogenic *Rickettsiales* including *Rickettsia*, *Orientia*, *Ehrlichia*, and *Anaplasma.* However, *Neorickettsia* are transmitted by ingestion of endoparasites (trematodes). *Neorickettsia*

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are vertically transmitted endosymbionts of parasitic flukes (Phylum: Platyhelminthes; Class: Trematoda; Subclass Digenea). Sennetsu fever, caused by *Neorickettsia sennetsu* is contracted by eating raw fish that are the vertebrate hosts of the flukes (Rikihisa et al. 2004; Dittrich et al. 2015); whereas, *Neorickettsia risticii* causes the Potomac horse fever. Notable exception in the order *Rickettsiales* is the *Wolbachia* that are maternally inherited intracellular bacterial symbionts that infect more than 60 % of all insect species (Moreira et al. 2009) and nematode (Taylor et al. 2005; Werren et al. 2008). Members of the family *Midichloriaceae* are also symbionts infecting insects, fish, and animals. *Candidatus* Midichloria mitochondrii is a bacterium that resides within animal mitochondria. They are localized both in the cytoplasm and in the intermembrane space of the mitochondria of ovarian cells of ticks (Sassera et al. 2006).

All age groups of humans and animals are at risk of infections by *Rickettsiales* especially in endemic areas. Both short- and long-term travelers are at risk for infection. Transmission is increased during outdoor activities in the spring and summer months when ticks, fleas, trematode-infected fish, and insects are most active. However, infection can occur throughout the year. Because of the 5- to 14-day incubation period for most rickettsial diseases, tourists may not necessarily experience symptoms during their trip, and onset may coincide with their return home or develop within a week after returning. Although the most commonly diagnosed rickettsial diseases in travelers are usually in the spotted fever or typhus groups, travelers may acquire a wide range of rickettsioses, including emerging and newly recognized species (Source: Centers for Disease Control and Prevention [CDC]).

2 Disease Caused by *Rickettsia*

The *Rickettsiaceae* are a family of obligate intracellular small Gram-negative coccobacilli which infect humans chiefly through insect vectors, mostly from animal hosts, but sometimes by transovarial transmission in the insects themselves (Cowan 2000). *Rickettsia* is the most prominent member of the family *Rickettsiaceae.* Rickettsioses are caused by obligate intracellular bacteria and include the typhus group and the spotted fever group of the genus *Rickettsia*. These zoonoses are among the oldest known vector-borne diseases (Parola et al. 2013). Currently, 29 *Rickettsia* species with validated and published names have been reported (http://www.bacterio.cict.fr/qr/rickettsia.html).

The most important species of *Rickettsia* includes:

R. prowazekii is the agent of epidemic typhus, transmitted by the human body louse (clothing), *Pediculus humanus* (but not by head lice) from active human cases or from healthy carriers or subclinical cases (Brill-Zinsser disease). The infectious agent in the feces of the body louse is usually inoculated by scratching of the site of the louse bite. Inhalation of an aerosol of dried louse feces in closed communities is sufficient to cause epidemics (Cowan 2000).

R. typhi (murine typhus) is the causal agent of endemic typhus, is carried by the rat flea *Xenopsylla cheopis*, and typically infects man in markets, grain stores, breweries, and garbage depots (Cowan 2000). It is often a mild illness, but can become more aggressive in refugee camps. Endemic typhus is highly treatable with antibiotics. Most people recover fully, but death may occur in the elderly, severely disabled or patients with a depressed immune system. The most effective antibiotics include tetracycline and chloramphenicol.

R. rickettsii is the agent of Rocky Mountain spotted fever. The pathogen is transmitted to humans by the bite of infected tick species. In the United States, these include the American dog tick (*Dermacentor variabilis*), Rocky Mountain wood tick (*Dermacentor andersoni*), and brown dog tick (*Rhipicephalus sanguineus*). Typical symptoms include fever, headache, abdominal pain, vomiting, and muscle pain. A rash may also develop, but is often absent in the first few days, and in some patients, never develops. Rocky Mountain spotted fever can be a severe or even fatal illness if not treated in the first few days of symptoms. Doxycycline is the first-line treatment for adults and children of all ages, and is most effective if started before the fifth day of symptoms (Source: CDC).

R. conorii is responsible for the disease Boutonneuse fever, Mediterranean spotted fever, Israeli tick typhus, Astrakhan spotted fever, Kenya tick typhus, Indian tick typhus, or other names that designate the locality of occurrence while having distinct clinical features. The pathogen is transmitted by the brown dog tick *Rhipicephalus sanguineus*.

R. africae is the causative agent of African tick-bite fever, is transmitted by *Amblyomma hebraeum* and *A. variegatum* ticks. African tick-bite fever is a neglected disease that has been mainly detected in tourists who are bitten by ticks while traveling in disease-endemic areas.

R. akari is the causative agent of rickettsialpox. Rickettsialpox is a cosmopolitan, mite-borne, spotted fever rickettsiosis. The disease is characterized by a primary eschar, fever, and a papulovesicular rash. Rickettsialpox was first identified in New York City in 1946 (Paddock et al. 2006). The arthropod vector of *R. akari* includes the house mouse mite (*Liponyssoides sanguineus*), and the principal rodent host, the house mouse (*Mus musculus*), brown rat (*Rattus norvegicus*), and reed vole (*Microtus fortis pelliceus*).

3 Disease Caused by *Orientia*

Orientia tsutsugamushi is the causative organism of scrub typhus. Scrub typhus is transmitted by infected mites [(trombiculid mite larvae) (*Leptotrombidium* spp.), commonly called chiggers] encountered in high grass and brush, is endemic in northeastern Japan, southeast Asia, the western Pacific Islands, eastern Australia, China, and parts of south-central Russia, India, and Sri Lanka. An estimated one billion people in the endemic area are at risk for scrub typhus and an estimated one million new cases occur annually. Most travel-acquired cases of scrub typhus occur during

visits to rural areas in endemic countries for activities such as camping, hiking, or rafting, but urban cases have also been described. Scrub typhus is an acute febrile illness characterized by fever, rash, and eschar, and often leads to severe clinical complications such as interstitial pneumonia, acute renal failure, meningoencephalitis, gastrointestinal bleeding, and multi-organ failure. Mortality rates for scrub typhus range from <1 to 50 % depending upon proper antibiotic treatment, health status of the patient, and virulence of the infected strain of *O. tsutsugamushi* encountered. Scrub typhus can be effectively treated with antibiotics including doxycycline, chloramphenicol, and azithromycin. However, re-infection is common due to the wide variety of antigenically distinct serotypes (Min et al. 2014). As yet there are no vaccines to protect against *Orientia* (Kelly et al. 2009).

4 Disease Caused by *Ehrlichia*

Ehrlichiosis is the general name used to describe several bacterial diseases that affect animals and humans. Human ehrlichiosis is a disease caused by at least three different ehrlichial species in the United States: *Ehrlichia chaffeensis*, *Ehrlichia ewingii,* and *Ehrlichia muris*-like (EML). Ehrlichiae are transmitted to humans by the bite of an infected tick. The lone star tick (*Amblyomma americanum*) is the primary vector of both *Ehrlichia chaffeensis* and *Ehrlichia ewingii* in the United States. Typical symptoms include fever, headache, fatigue, and muscle aches. Usually, these symptoms occur within 1–2 weeks following a tick bite. Ehrlichiosis is diagnosed based on symptoms, clinical presentation, and later confirmed with specialized laboratory tests. The first-line treatment for adults and children of all ages is doxycycline (Source: CDC; Rikihisa 1991; Paddock and Childs 2003; Rikihisa 2010).

5 Disease Caused by *Anaplasma*

Anaplasmosis is a tick-borne disease caused by the bacterium *Anaplasma phagocytophilum.* It was previously known as human granulocytic ehrlichiosis (HGE) and has recently been renamed as human granulocytic anaplasmosis (HGA). Anaplasmosis is transmitted to humans by tick bites primarily from the black-legged tick (*Ixodes scapularis*) and the western black-legged tick (*Ixodes pacificus*). Of the four distinct phases in the tick life-cycle (egg, larvae, nymph, adult), nymphal and adult ticks are most frequently associated with transmission of anaplasmosis to humans. The mammalian reservoir for *A. phagocytophilum* infection within the United States includes white-footed mice (*Peromyscus leucopus*), raccoons (*Procyon lotor*), gray squirrels (*Sciurus carolinensis*), gray foxes (*Urocyon cinereoargenteus*), and redwood chipmunks. Typical symptoms of the disease include fever, headache, chills, muscle aches, hematological abnormalities, including leucopenia and thrombocytopenia; and increased serum aminotransferase liver enzyme

activity, which suggests mild to moderate liver injury. Usually, these symptoms occur within 1–2 weeks of a tick bite. Anaplasmosis is initially diagnosed based on symptoms and clinical presentation, and later confirmed by the use of specialized laboratory tests. The first-line treatment for adults and children of all ages is doxycycline (Rikihisa 2003, 2010, 2011).

6 Disease Caused by *Neorickettsia*

Neorickettsia sp. are found in various species of trematodes (flukes) (endoparasites of vertebrates and invertebrates). When humans ingest metacercaria stage of infected trematodes encysting in the fish, *Neorickettsia sennetsu* is transmitted to humans causing sennetsu fever (Rikihisa et al. 2005; Dittrich et al. 2015). Whereas, when dogs ingest the metacercaria stage of infected trematodes encysting in the fish, *Neorickettsia helminthoeca* is transmitted to dogs causing salmon poisoning disease (Headley et al. 2011). When horses ingest metacercaria stage of infected trematodes encysting in the aquatic insects (mayflies, caddisflies), *Neorickettsia risticii* is transmitted to horses and cause Potomac horse fever. The first line of treatment is the antibiotic doxycycline (humans and dogs) and oxytetracycline (horses) (Gibson et al. 2005; Rikihisa 2006; Lin et al. 2009).

7 Significance of *Wolbachia*

Wolbachia are intracellular bacteria that are found in arthropods and nematodes. *Wolbachia* is the most renowned insect symbiont, due to its ability to manipulate insect reproduction and to interfere with major human pathogens thus providing new avenues for pest control (Bourtzis et al. 2014). These alphaproteobacteria endosymbionts are transmitted vertically through host eggs and alter host biology in diverse ways, including the induction of reproductive manipulations, such as feminization, parthenogenesis, male killing, and sperm–egg incompatibility. They can also move horizontally across species boundaries, resulting in a widespread and global distribution in diverse invertebrate hosts (Werren et al. 2008). Mosquitoes are responsible for the transmission of arboviruses including Dengue, Chikungunya, and Zika viruses. Recent studies demonstrate that *Wolbachia pipientis* could be used to control mosquito (*Aedes aegypti*) population (Iturbe-Ormaetxe et al. 2011), thereby controlling dengue and chikungunya infection (Moreira et al. 2009; Hoffmann et al. 2011; Walker et al. 2011; Bull and Turelli 2013; Aliota et al. 2016). *Aedes aegypti*-harboring *Wolbachia* are highly resistant to infection with two strains of Zika virus. *Wolbachia*-harboring mosquitoes displayed lower viral prevalence and intensity and decreased disseminated infection and, critically, did not carry infectious virus in the saliva, suggesting that viral transmission was blocked (Dutra et al. 2016).

Commercial enterprises have come up with several strategies to control Zika virus. One of the strategies involves rearing mosquitoes infected with a particular strain of *Wolbachia* and releasing the males into the environment. When these male mosquitoes mate with wild females that do not carry the same strain of *Wolbachia*, the resulting fertilized eggs do not hatch as the paternal chromosomes are not properly developed. As infected male mosquitoes continue to be released to breed with wild partners, the pest population dwindles (Waltz 2016). It is clearly not understood how *Wolbachia* inhibits viruses in mosquitoes; though it is thought that *Wolbachia* produce a cellular lipid environment that is antagonistic to viral replication (Molloy et al. 2016).

Though *Wolbachia* causes negative effects in arthropods, a *Wolbachia* strain associated with the bedbug *Cimex lectularius*, designated as *w*Cle, was shown to be essential for normal growth and reproduction of the blood-sucking insect host via provisioning of B vitamins (Hosokawa et al. 2010). *Wolbachia* has also been described from nematode hosts such as those responsible for onchocerciasis (river blindness), lymphatic filariasis (elephantiasis), and dirofilariasis (heartworm), where the symbiotic interaction has features of mutualism. Wolbachial symbiont is essential for the life of some of nematode species, as such antibiotic against *Wolbachia* can be used as anti-filarial drug treatment (Taylor et al. 2013).

8 Prevention of *Rickettsiales* Diseases

As yet there are no vaccines for any diseases caused by the bacteria of the order *Rickettsiales*. Antibiotics are not recommended for prophylaxis of rickettsial diseases. Travelers are instructed to minimize exposure to infectious arthropods during travel (including lice, fleas, ticks, mites) and animal reservoirs (particularly dogs) when traveling in endemic areas. The proper use of insect or tick repellents, self-examination after visits to vector-infested areas, and wearing protective clothing are ways to reduce risk (Source: CDC).

9 Taxonomy

The order *Rickettsiales* are obligatory intracellular Gram-negative bacteria belong to the group alphaproteobacteria. The order *Rickettsiales* consists of the family *Rickettsiaceae* and the family *Anaplasmataceae*. The family *Rickettsiaceae* contains the genus *Rickettsia* and the genus *Orientia*. The family *Rickettsiaceae* are short rods or coccobacilli but the family *Anaplasmataceae* are small pleomorphic cocci. The rickettsiae-causing diseases in humans belong to the families *Rickettsiaceae* and *Anaplasmataceae*. The family *Rickettsiaceae* include two genera. The genus *Rickettsia* comprises the highly related typhus group (TG)

and spotted fever group (SFG) and the genetically heterogeneous species *Orientia tsutsugamushi* that includes several serovars. The family *Anaplasmataceae* is currently comprised of seven established genera and *Candidatus* genera: *Ehrlichia, Anaplasma, Aegyptianella, Neorickettsia, Wolbachia*, "*Candidatus* Neoehrlichia", and "*Candidatus* Xenohaliotis".

10 Epidemiology

The rickettsiae are endemic worldwide. Rickettsiae are known or thought to be associated with invertebrates (arthropods and trematodes). The invertebrates are also the vectors that transmit the rickettsiae in human and other vertebrates. Humans are accidental hosts to the rickettsiae, except for epidemic typhus and recrudescent typhus or Brill-Zinsser disease. Some species of the rickettsiae within a biogroup appear to be confined to certain geographic areas of the world. These species acquire some biologic, pathogenic, and genetic characteristics within their respective area that make them different enough from each other within a biogroup to be classified as a new species, e.g., the SFG *Rickettsia japonica* is confined to Japan, and *Rickettsia rickettsii* appears to be limited to the Western Hemisphere. *Rickettsia felis*, a newly isolated *Rickettsia* that causes an endemic typhus-like syndrome, has at present only been isolated in the Western hemisphere. *Rickettsia conorii* is primarily found in the Mediterranean basin and Africa, and *O. tsutsugamushi* is found in Southeast Asia and Japan. In contrast, other species are ubiquitously found in various geographic areas of the world and appear to be biologically, genetically, and pathologically similar or nearly identical. Examples are *Rickettsia typhi*, which causes endemic typhus. Epidemic typhus caused by *Rickettsia prowazekii* was worldwide in the past. However, at present it appears to be confined to foci in areas of Africa, areas of the former Soviet Union, and South America. Sennetsu fever caused by *N. sennetsu*, which was thought to be limited to Asia and Japan, has now been reported in other geographic regions. In the United States, human monocytic ehrlichiosis (HME) is caused by *Ehrlichia chaffeensis*. In addition, a granulocytic anaplasmosis, which is caused by *A. phagocytophilum,* and was initially reported in equines, ruminants, and canines, is now found in humans (HGA). *Ehrlichia ewingii,* once thought to infect only dogs, has recently discovered to cause human granulocytic ehrlichiosis (Human ewingii ehrlichiosis). In the United States, RMSF, both types of endemic typhus caused by *R. typhi* or *R. felis*, HME and HGA are the most prevalent diseases. Most cases occur between May and September. Between May and September, environmental conditions are optimal for tick activity and human outdoor activities peak. However, a few cases have also been diagnosed during the winter months. Therefore, rickettsial diseases cannot be considered strictly seasonal. In the United States, most of the RMSF cases are east of the Rockies, with Oklahoma and the Carolinas leading the states. Ninety percent of endemic typhus cases in the United States are detected in the Southwest, especially in southern Texas, and in the West in southern California. A

few endemic typhus cases have been reported from Virginia, North Carolina, Oklahoma, and California. Classic louse borne epidemic typhus is not known to occur in the United States. However, a rickettsial organism closely resembling *R. prowazekii* was isolated from a flying squirrel (Hechemy et al. 2006).

11 Pathobiology

The intracellular sites of growth are different in members of the order *Rickettsiales*. Members of the SFG rickettsiae, e.g., *R. rickettsii*, grow in the cytoplasm and sometimes in the nucleus. In contrast, members of the TG, e.g., *R. typhi*, and the scrub typhus grow in the cytoplasm. Members of the family *Anaplasmataceae* replicate in the membrane-bound compartment that does not fuse with lysosomes. The replication site for *E. chaffeensis* within the cell is the early endosome, and those of *A. phagocytophilum* is early autophagosomes (Rikihisa 2011, 2015).

Except for *Wolbachia* and "*Candidatus* Xenohaliotis", members of the family *Anaplasmataceae* infect cells of hematopoietic and bone marrow origin of mammals or birds. Generally wild animals are reservoirs of these bacterial infection and humans and domestic mammals or birds are infected by the bite of ticks infected with *Ehrlichia* or *Anaplasma* sp., or by ingestion of trematodes infected with *Neorickettsia*. *Wolbachia* is so far known to infect only invertebrate cells. However, it can be found in the blood stream of humans when released from filarial worms infesting the vertebrates. Among *Ehrlichia* species, so far *E. chaffeensis*, *E. ewingii*, and *E. canis* have been isolated and/or detected in the blood specimens from humans. In the genus *Anaplasma*, *A. phagocytophilum* and *A. platys*, and in the genus *Neorickettsia*, *N. sennetsu* are the species so far documented in humans.

No exotoxin has been reported to explain the pathogenic properties of the *Rickettsiaceae* and *Anaplasmataceae*. The diseases caused by the rickettsias are systemic illnesses exhibiting protean manifestations. The hallmark of the various diseases caused by the SFG and TG rickettsiae is the maculopapular rash; however, it is not found in every case. In SFG rickettsiae, it begins on the wrists and ankles and extends throughout the body. In scrub typhus and Mediterranean spotted fever (MSF), an eschar may develop at the site of the insect bite. In TG rickettsiae, the rash is usually centrally distributed on the trunk and rarely involves the palms and soles. The internal lesions caused by the pathogen are a vasculitis localized in the endothelium and smooth muscle. Vascular permeability is increased, causing various degrees of hemorrhage, tissue edema, and peripheral circulatory failure. The extent of the internal vascular lesions is related to the degree of pathogenicity of a given species, e.g., in scrub typhus, vascular damage is not usually as severe as that seen in RMSF (Hechemy et al. 2006).

Human ehrlichiosis and anaplasmosis also exhibits nonspecific protean manifestations (Rikihisa 2010, 2015), which are similar to those observed in patients

with RMSF. However, most patients do not have a rash. The onset of illness is abrupt. Symptoms include fever, chill, headache, myalgia, anorexia, nausea or vomiting, and weight loss. Thrombocytopenia, leucopenia, and liver enzyme abnormality are often reported. A meningitis syndrome or an encephalitis or encephalopathy syndrome may occur with HME, and *E. chaffeensis* may be detected in the cerebrospinal fluid. Fatal seronegative infection has been reported in HIV patients, and secondary infections due to *Anaplasma*-induced immunosuppression may lead to severe diseases and death. The patients also lack remarkable lesions such as cell lysis, tissue necrosis, abscess formation, or severe inflammatory reactions. The monocyte and granulocyte are the primary target cells for monocytic ehrlichiosis and granulocytic anaplasmosis/ehrlichiosis, respectively.

12 Vectors of *Rickettsiales*

12.1 Tick Vectors

The bacteria of the order *Rickettsiales* are usually spread to people through the bites of ticks, mites, fleas, or lice that previously fed on an infected animal. Organisms can be transmitted by bites from these ectoparasites or by the inoculation of infectious fluids or feces from the ectoparasites into the skin. Inhaling or inoculating conjunctiva with infectious material may also cause infection for some of these organisms. Tick-transmitted rickettsial diseases, such as ehrlichiosis and spotted fever rickettsiosis, are significant sources of morbidity and mortality (Source: CDC).

Ticks are members of the phylum Arthropoda, subphylum Chelicerata, class Arachnida, and subclass Acari (Keirans and Durden 2005). The tick family includes: *Ixodidae* (hard ticks), and *Argasidae* (soft ticks). These two groups differ in their anatomy, behavior, and life cycle (Bogitsh et al. 2005). The Ixodidae are called hard ticks because of their hard dorsal shield (scutum) and they attach to their host for prolonged periods. The hard ticks (Figs. 1.1 and 1.2) exhibit sexual dimorphism and are more commonly encountered by animals and people than soft ticks. The Argasid ticks are known as soft ticks, feed secretively for brief periods and are rarely seen (Fig. 1.3). Soft ticks are known to progress through several (2–7) instars in the nymphal stage prior to molting to the adult reproductive phase; the number of nymphal stages is dependent on species, host availability, and climatic and/or environmental factors. There is little difference in appearance between male and female soft ticks. Tick hosts include mammals, birds, amphibians, and reptiles (Keirans and Durden 2005). Ticks are usually active during summer months and the geographic range and distribution of ticks has increased due to climate change (Ogden et al. 2005).

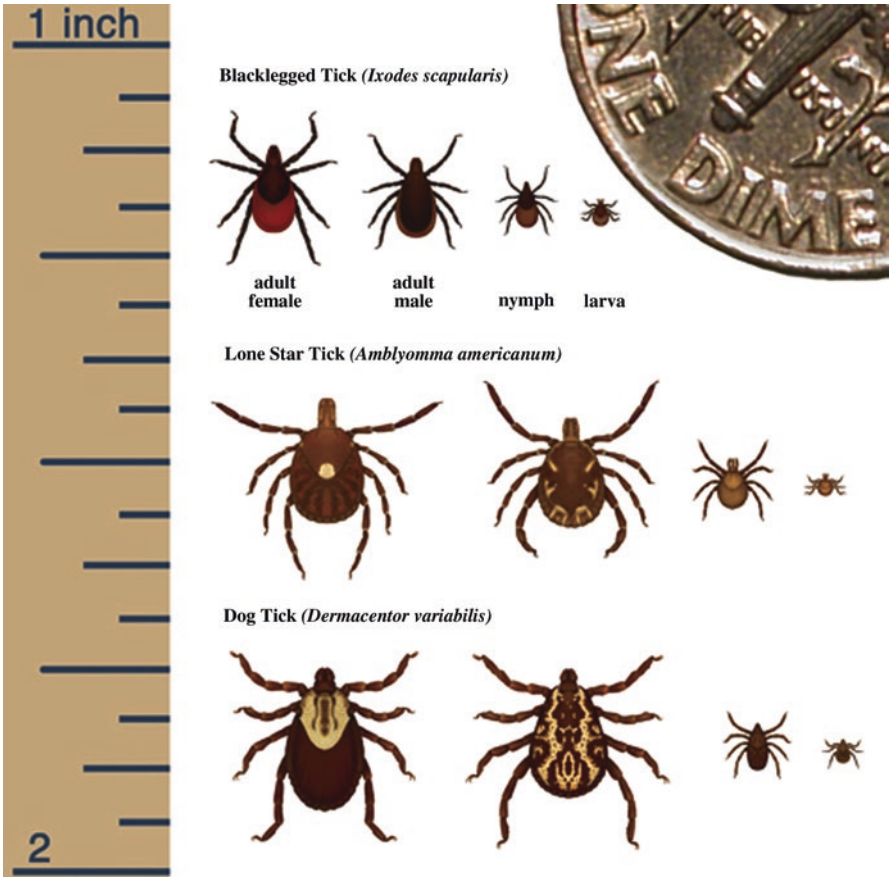

Fig. 1.1 Relative sizes of several ticks at different life stages. Credit: Centers for Disease Control and Prevention

Fig. 1.2 Female blacklegged (deer tick), *Ixodes scapularis* with its abdomen engorged with a host blood meal. Credit: CDC/Dr. Gary Alpert—Urban Pests—Integrated Pest Management (IPM)

Fig. 1.3 Dorsal view of the "soft tick" *Carios kelleyi* (Bat Tick). Credit: CDC/Jim Gathany/William L. Nicholson

12.2 Tick Feeding

Hard ticks parasitize vertebrate hosts for several days or more, and they must attach firmly enough to their host's skin to remain in place in spite of mechanical perturbations associated with various activities, including grooming of the host. The three main structures of ticks involved in feeding and providing a transmission pathway for microbes include the salivary glands, ventral hypostome, and the chelicerae. One of the important functions of the salivary glands relates to attachment. They excrete a proteinaceous cement that helps secure the hypostome of the tick so it is more secure in the body of its host (Anderson and Magnarelli 2008). It also excretes compounds that prevent clotting by slowing platelet aggregation and helps the tick evade the immune system by preventing neutrophil aggregation and T-cell response (Ribeiro 1989). These glands also help regulate water balance in ticks (Bowman and Nuttall 2008). The paired salivary glands are important not only to the function of feeding, but they are also involved in the transfer of microbial pathogens into the host.

The ventral hypostome is a plate armed ventrally with rows of spine-like denticles. At the center of the fixed ventral hypostome is a deep groove that functions to channel blood flow from the host to the tick's mouth and also to channel saliva from the tick's mouth to the host. They function to set the organism firmly in the skin for those ticks that do not secrete cement from their salivary glands (Richter et al. 2013). The chelicerae are paired shafts that have bundles of hook-like structures on their ends. They function to dig into the skin of the host and then pry the skin open so that the hypostome can enter and the feeding process can begin (Richter et al. 2013). They are the mobile component of the feeding apparatus. An overview of tick feeding and pathogen transmission mechanism is shown in Fig. 1.4.

12.3 Tick Life Cycle and Behavior

Ticks are present all over the world (Keirans and Durden 2005). However, they are most diverse in tropical and sub-tropical climates (Anderson and Magnarelli 2008). There is clear distinction in the ecology of the two major tick groups. The hard ticks

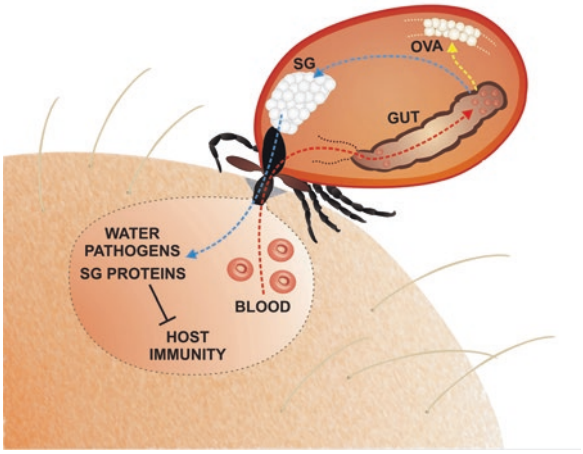

Fig. 1.4 An overview of tick feeding and pathogen transmission mechanism. The pathogen transmission is tightly linked with physiology of blood feeding and tick innate immunity. Ingested blood meal is accumulated in the midgut content. Hemoglobin and other proteins are taken up by the tick midgut cells and digested intracellularly in the digestive vesicles. Liberated amino acids and other compounds are transported to the peripheral tissues and ovaries, supplying mainly egg development. The blood meal is concentrated by reabsorption of excessive water, which is spitted back into the wound by the action of salivary glands. Tick saliva contains a great variety of anticoagulant, immunomodulatory, and anti-inflammatory molecules that facilitate pathogen acquisition and transmission (Credit: Hajdušek et al. 2013)

(*Ixodidae*) spend most of their life on host organisms feeding on blood; whereas, the soft ticks (*Argasidae*) only feed on host blood at night, and spend most of their day hiding in stable microclimate nesting sites (Bogitsh et al. 2005). The important characteristics of these nesting sites include low light and stable microclimates (wind, temperature, humidity). They also must have a high probability of host contact (Anderson and Magnarelli 2008).

During development, the tick goes through four life stages: egg, six-legged larva, eight-legged nymph, and adult. After hatching from the eggs, ticks must eat blood at every stage to survive. Ticks can take up to 3 years to complete their full life cycle, and most will die because they do not find a host for their next feeding. In ticks from *Ixodidae*, this is usually a three host process where they feed and then molt to move onto the next stage (Anderson and Magnarelli 2008). Some species are two-host or even one-host ticks where they feed and molt on the same host. This is generally because the tick lives in an area where host organisms are sparsely distributed (Anderson and Magnarelli 2008; CDC [http://www.cdc.gov/ticks/life_cycle_and_hosts.html]).

Ticks find their hosts by detecting animals' breath and body odors, or by sensing body heat, moisture, and vibrations. Some species can even recognize a shadow. In addition, ticks pick a place to wait by identifying well-used paths. Then they wait for a host, resting on the tips of grasses and shrubs. Ticks cannot fly or jump, but many tick species wait in a position known as "questing" (Fig. 1.5). While questing,

Fig. 1.5 A deer tick (blacklegged tick), *Ixodes scapularis* questing on a blade of grass. Image credit: CDC

ticks hold onto leaves and grass by their third and fourth pair of legs. They hold the first pair of legs outstretched, waiting to climb onto the host. When a host brushes the spot where a tick is waiting, it quickly climbs aboard. Some ticks will attach quickly and others will wander, looking for places like the ear, or other areas where the skin is thinner (Source: CDC).

The vast majority of ticks do not commonly use humans as their host organism. Only 33 of the 878 known species of ticks are known to commonly feed on people (Anderson and Magnarelli 2008), and only 222 of the 878 known species have been documented to feed on humans at all (Anderson and Magnarelli 2008). The difference between these two numbers is somewhat attributed to people coming into close proximity with the main host of that species of tick. The tick *Argas monolakensis* has been found to readily feed on humans despite the main host being *Larus californicus Lawrence*, the California gull (Schwan et al. 1992). Thus, a Tick may feed on humans even though that is not its main host. This is also observed in many other species such as *Rhinicephalus sanguineus* (brown dog Tick) and *Ixodes scapularis* (deer tick) (Dantas-Torres et al. 2006; Kilpatrick et al. 2014).

To remove a tick

1. Use fine-tipped tweezers to grasp the tick as close to the skin's surface as possible.
2. Pull upward with steady, even pressure. Do not twist or jerk the tick; this can cause the mouth-parts to break off and remain in the skin. If this happens, remove the mouth-parts with tweezers. If you are unable to remove the mouth easily with clean tweezers, leave it alone and let the skin heal.
3. After removing the tick, thoroughly clean the bite area and your hands with rubbing alcohol, an iodine scrub, or soap and water.
4. Dispose of a live tick by submersing it in alcohol, placing it in a sealed bag/container, wrapping it tightly in tape, or flushing it down the toilet. Never crush a tick with your fingers (Source: CDC).

12.4 *Other* Rickettsiales *Vectors*

Ticks are not the only vectors for transmission of bacteria of the order *Rickettsiales*. Other closely related ectoparasites such as lice and mites have been known to transmit rickettsial diseases, but ticks have a greater contribution to human infection than either of these.

Mites (Fig. 1.6) are closely related to ticks. The Trombiculid mite (genus *Leptotrombidium)*, especially the larval stages (commonly called chigger) is the major vector involved in transmission of several rickettsial diseases. They are involved in infecting humans with pathogenic O*rientia tsutsugamushi* that causes Scrub Typhus (Yamashita et al. 1994). Transmission of *Orientia* to the rodent host or the human incidental host occurs during feeding chigger stage of mites. Vertical or transovarial transmission appears to be essential to the maintenance of the infection in nature; thus, the mite serves as both the vector and the reservoir. As the larval stage is the only parasitic stage of *O. tsutsugamushi*, to maintain disease transmission, it is necessary for *O. tsutsugamushi* to be transmitted transstadially through the nymph and adult stages and transovarially transmitted through the eggs to the progenies. The efficiency of transmission of *Orientia* by infected chiggers is important in determining how the disease is maintained in nature (Shin et al. 2014).

Louse (Fig. 1.7) infestation, called pediculosis, is very contagious and is easily transmitted by close body-to-body contact or contact with infested linen, brushes, or clothes, according to the species of louse. Pediculosis corporis, caused by body lice (*Pediculus humanus*), is a major public health concern. It is strongly associated with close body-to-body contact, and occurs only when clothes are not changed or washed regularly. These conditions are more prevalent in individuals living in crowded and unhygienic environments, such as refugee camps or shelters for the homeless. Body lice are known to transmit epidemic typhus, caused by *R. prowazekii*. The mortality rate of epidemic typhus varies from 0.7 to 60 % for untreated cases. Lice become infected with *R. prowazekii* when they feed on bacteremic individuals; however, lice die within 1 week after becoming infected. Humans with

Fig. 1.6 Photograph of a mite, a member of the Class *Arachnida*, Order *Acari*. Image credit: CDC

Fig. 1.7 Body lice live and lay eggs on clothing and only move to the skin to feed. Image credit: CDC

Fig. 1.8 The Oriental rat flea, *Xenopsylla cheopis.* Image credit: CDC

self-limiting infections that fail to clear the bacteria and exhibit bacterial persistence in adipose tissue endothelial cells constitute the main reservoir of *R. prowazekii*. Under stress, infection recrudescence can occur years after the primary infection, resulting in a relatively mild bacteremic illness called Brill–Zinsser disease (Badiaga and Brouqui 2012).

Flea-borne infections are emerging or re-emerging throughout the world, and their incidence is on the rise (Bitam et al. 2010). Fleas (Fig. 1.8) (class: Insecta, order: Siphonaptera) are small, laterally flattened, wingless, and highly specialized insects about 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. They have strongly developed hind legs that permit them to jump up to 150 times their own body length. 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. Fleas are involved in the transmission of *Rickettsia typhi* (causes murine typhus) and *Rickettsia felis* (causes cat flea typhus).

R. typhi is a member of the typhus group rickettsiae. The disease is characterized by headache, rash, and fever and occurs worldwide in a variety of environments. The oriental rat flea *Xenopsylla cheopis* is the main vector of *R. typhi.* The classic cycle of murine typhus involves rats (*Rattus norvegicus* and *R. rattus*) as reservoirs, and their fleas. However, other vertebrate hosts, such as house mice, shrews, opossums, skunks, and cats, which live in or enter rat-infested buildings and human habitations, may be involved in the epidemiology of murine typhus. Although *X. cheopis* is considered the major vector of murine typhus, natural infection with *R. typhi* has been reported in other flea species (Christou et al. 2010). *R. typhi* infects endothelial cells in mammalian hosts and mid-gut epithelial cells in the flea host. It is passed in the flea's feces, and transmission to humans is by fecal contamination (Bitam et al. 2010).

The cat flea (*Ctenocephalides felis*) serves as the primary vector and reservoir of *R. felis. R. felis* transmission is primarily vertical (transovarial and transstadial) within a flea population, rather than horizontal between fleas through a bloodmeal. Infection by *R. felis* has been attributed to flea saliva rather than feces (Giudice et al. 2014).

The distribution of vectors and associated pathogen transmission rates can be affected by changes in the ambient temperature and climate. Such climate changes will cause local vector populations to migrate to more favorable climates alongside vertebrate hosts and also alter the life cycle duration of vectors. Unchecked expansion of vectors would potentially adversely affect human health. There is a need to be vigilant in identifying both current and emerging vector-borne diseases in the environment. Influence of climate change on temperature levels may be far-reaching. Not only could it affect arthropod life cycles but also human activities as well. Use of the land in affected areas will be influenced and long-term activities such as farming and tourism will indirectly affect transmission of arthropod-borne diseases. Better understanding of endemic diseases will equip doctors, veterinarians, and public health officials with the information needed to prevent outbreaks and provide proper treatment (Abdad et al. 2011).

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