

Ticks (Ixodida)

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Ticks are well-known vectors of human and veterinary pathogens. They transmit a greater variety of infectious organisms than any other group of blood-sucking arthropods. Worldwide, they are the most important vectors in the veterinary field and are second only to mosquitoes in terms of their public health importance. Ticks transmit numerous protozoan, viral, bacterial (including rickettsial), and fungal pathogens. In humans, thousands of cases of tick-borne diseases caused by these agents occur annually, and the incidence of human disease is increasing globally. In addition, the bites of ticks can cause toxic reactions, allergic responses, and even fatal paralysis, while the wounds that they produce can create entry sites for secondary microbial infections and diminish the value of livestock by damaging their hides. Tick-borne diseases such as babesiosis, anaplasmosis, theileriosis, heartwater, and many others result in economic loss to those who raise livestock in many tropical and subtropical regions of the world. Although difficult to measure precisely, the global economic impact of ticks and tick-borne diseases is estimated to be in the multiple billions of dollars (U.S.) (Jongejan and Uilenberg, 2004). The study of ticks has contributed greatly to our ability to understand and control the spread of infectious diseases.

This chapter reviews the remarkable adaptations and behavior of ticks that facilitate their success as blood-feeding parasites and the diverse tick-host pathogen interactions that contribute to their role as vectors of human and animal disease agents. For more detailed information about the biology of ticks, the reader is referred to Sonenshine and Roe (Vol. 1, 2014). For detailed information on human tick-borne diseases, the reader is referred to Bowman and Nuttall (2008), Goodman et al. (2005), Sonenshine and Roe (Vol. 2, 2014), and Eisen et al. (2017). For more detailed information on veterinary tick-borne diseases, the reader should consult Uilenberg (1995), Jongejan and Uilenberg (2004), and Sonenshine and Roe (Vol. 2, 2014).

TAXONOMY

Ticks constitute the Suborder Ixodida, of the acarine Order Parasitiformes, and are exclusively parasitic. The Ixodida contain three extant families: the **Ixodidae**, **Argasidae**, and **Nuttalliellidae** (Table 27.1). The Ixodidae are subdivided

TABLE 27.1 Families and Genera of Ticks

Family	Subfamily (Subgroup)	Genera
Ixodidae	Ixodinae (Prostriata)	<i>Ixodes</i>
	Amblyomminae (Metastriata)	<i>Amblyomma</i>
	Bothriocrotoninae (Metastriata)	<i>Bothriocroton</i>
	Haemaphysalinae (Metastriata)	<i>Haemaphysalis</i>
	Hyalomminae (Metastriata)	<i>Hyalomma</i>
	Rhipicephalinae (Metastriata)	<i>Anomalohimalaya</i> , <i>Cosmioma</i> , <i>Dermacentor</i> , <i>Margaropus</i> , <i>Nosoma</i> , <i>Rhipicentor</i> , <i>Rhipicephalus</i>
Argasidae	Argasinae	<i>Argas</i>
	Ornithodorinae	<i>Ornithodoros</i> , <i>Carios</i>
	Otobinae	<i>Otobius</i>
Nuttalliellidae		<i>Nuttalliella</i>

After Horak et al. (2002); Murrell and Barker (2003).

into the Prostriata, represented by the single genus *Ixodes* with 244 species, and the Metastriata with 459 species, comprising the remaining 14 genera (Guglielmone et al., 2010, 2014). There are 707 recognized species in this family, representing about 78% of all tick species that have been described (Table 27.1). The Argasidae contain four genera and about 190 species (Guglielmone et al., 2010). The **Nuttalliellidae** is a monospecific family, represented by only one species, *Nuttalliella namaqua*.

Ixodidae, also known as the hard ticks, are grouped into the Prostriata and the Metastriata based on morphologic characters. Prostriate ticks have a prominent anal groove located anterior to the anus and extending to the posterior body margins. Metastriate ticks have a small slit-like anal groove that is located posterior to the anus and does not extend to the body margin (Table 27.1).

For additional information on taxonomy of the Ixodida, please review Filippova (1966, 1967), Roberts (1970), Keirans (1992), Klompen and Oliver (1993), Durden and Keirans (1996), Klompen et al. (2000), Murrell et al. (2000), Barker and Murrell (2008), Walker et al. (2000), Beati and Keirans (2001), Barker and Murrell (2002), Horak et al. (2002), and Guglielmone et al. (2014).

The following subsections provide descriptions of some of the more important tick genera and species of particular importance as vectors of human or domestic animal disease-causing agents.

Family Ixodidae (Hard Ticks)

Genus *Ixodes*

This is the largest tick genus, with an estimated 244 species. *Ixodes* species are known as the **Prostriata**, characterized by a distinctive anal groove that encircles the anus anteriorly. They also lack eyes and other light-sensitive organs on the dorsum. Males have sclerotized ventral plates, which are absent in males of other genera. The genus is worldwide in distribution, including Antarctica. Four species are particularly important as vectors of microbial agents to humans: the **blacklegged tick** (*Ixodes scapularis*) in eastern North America; the **castor bean tick**, or **sheep tick** (*I. ricinus*) in Europe and western Asia; the **taiga tick** (*I. persulcatus*) in northeastern Europe and northern Asia; and the **western blacklegged tick** (*I. pacificus*) in the far western United States. Other, non-human-biting *Ixodes* spp. serve as enzootic (maintenance) vectors of important tick-borne disease agents, such as *I. dentatus*, *I. affinis*, and *I. spinipalpis* in North America, and *I. ovatus* in northern Asia and Japan.

Genus *Dermacentor*

This is one of the more important genera of metastriate ticks, with 35 species. The basis capituli appears rectangular when viewed dorsally. A pair of medially directed spurs occurs on the first pair of coxae. The palps are short and thick, and the scutum is almost always ornamented. Most *Dermacentor* spp. are three-host ticks that feed on diverse mammals. Adults attack medium-sized or large mammals, whereas the immatures feed on small mammals and lagomorphs. *Dermacentor* species are found mostly in Europe, Asia, Africa, and North and Central America. In North America, important species are the **American dog tick** (*D. variabilis*), the **Rocky Mountain wood tick** (*D. andersoni*), the **Pacific Coast tick** (*D. occidentalis*), and the **winter tick** (*D. albipictus*). In Central and South America and some Caribbean islands, an important species is the **tropical horse tick**, *D. nitens* (designated previously as *Anocentor nitens*). In Europe, two important species are *D. reticulatus* and *D. marginatus*.

Genus *Rhipicephalus*

Ticks of the genus *Rhipicephalus* are recognized by the hexagonal shape of the basis capituli when viewed dorsally. Important species include the **brown dog tick** (*R. sanguineus*) and the **brown ear tick** (*R. appendiculatus*). *Rhipicephalus* ticks mainly parasitize mammals, and only rarely are they found as larvae or nymphs on birds and reptiles. Representative species are found throughout the world. *Rhipicephalus sanguineus* is cosmopolitan in distribution, although more recent studies have indicated that the complex has both temperate and tropical lineages, which may be later assigned to separate species. Among the more important are the five species of the subgenus *Boophilus*, formerly considered as a separate genus (Murrell and Barker, 2003). Subgenus *Boophilus* ticks are small and lack ornamentation. The basis capituli is short and broad, with rounded lateral margins. These ticks are one-host parasites of ungulates. Subgenus *Boophilus* ticks are found in most tropical and subtropical regions of the world. Important species include the **cattle tick** (*Rhipicephalus [B.] annulatus*) and the **tropical fever tick** or **southern cattle tick** (*Rhipicephalus [B.] microplus*). The genus *Rhipicephalus* contains 84 described species.

Genus *Haemaphysalis*

This is the second largest tick genus, which is recognized by the pronounced lateral projection of palpal segment 2 in most species (including all three North American species), which extends well beyond the basis capituli. These small

ticks lack eyes. *Haemaphysalis* spp. parasitize birds and mammals in most regions of the world. An important species is the rabbit tick *H. leporispalustris*, widespread throughout much of North America. Several species in the Old World are important pests and/or vectors of animal and human disease agents, such as *H. longicornis* in Asia and the Pacific region (including Australia), *H. punctata* in Europe, and *H. spinigera* in India. The genus contains about 167 species.

Genus *Hyalomma*

This is a relatively small genus of ~30 species of medium-sized to large Old World ticks. They are characterized by their elongated palps, which are at least twice as long as wide. The distinct eyes are located in sockets adjacent to the posterolateral edges of the scutum. *Hyalomma* ticks are unornamented. Most species live in xeric environments where they parasitize small and medium-sized wild mammals and livestock. Some species parasitize birds or reptiles. The distribution of *Hyalomma* spp. is limited to the Old World, primarily in arid or semiarid habitats. An important subspecies is *H. marginatum marginatum*, a vector of Crimean-Congo hemorrhagic fever (CCHF) virus. Other important species are *H. truncatum* in Africa, *H. asiaticum* in central Asia, and *H. detritum* in Asia and the Mediterranean basin. *Hyalomma detritum* is of major veterinary importance as a vector of the agent of bovine tropical theileriosis.

Genus *Amblyomma*

Adults of most species in this genus are medium or large in size. The palps are long with segment 2 at least twice as long as segment 3. The scutum is usually ornamented with varying-colored iridescent patterns. Eyes are present in most species (absent in species formerly assigned to *Aponomma*) but are not situated in sockets. Virtually all terrestrial vertebrate species serve as hosts, although amphibians are rarely attacked. The distribution is worldwide, primarily in humid tropical or subtropical regions. Examples of important species include: the **Gulf Coast tick** (*A. maculatum*) and **lone star tick** (*A. americanum*) in North America; the **tropical bont tick** (*A. variegatum*) in Africa and on some Caribbean islands; and the **bont tick** (*A. hebraeum*) in Africa. The genus contains about 130 species (including 20 species formerly assigned to the genus *Aponomma*, now in part, a synonym of *Amblyomma*).

The remaining genera of the Ixodidae contain relatively few species, none of which are known to be important in pathogen transmission. These include *Anomalohimalaya*, *Bothriocroton*, *Cosmiomma*, *Nosoma*, *Margaropus*, and *Rhipicentor*. A genus previously designated as *Anocentor*

was invalidated and its single species transferred to the genus *Dermacentor*. Similarly, the genus *Aponomma* is no longer considered valid and its species were transferred to the genus *Amblyomma* or to the new genus *Bothriocroton*.

Family Argasidae (Soft Ticks)

Genus *Argas*

Argas ticks have a flattened body margin, a lateral sutural line, and a leathery, folded cuticle. The many small integumental folds usually have a button-like appearance, each with a pit on its top. Most species parasitize bats or birds. The genus is worldwide in distribution, mostly in xeric environments or dry caves in otherwise humid environments. Examples of important species are the **fox tick** (*A. persicus*) and the **pigeon tick** (*A. reflexus*). About 57 species have been described.

Genus *Carios*

These ticks are similar to those of the genus *Argas*, but differ in the structure of their Haller's organ on the tarsus of the foreleg. In most *Carios* the setiform seta is replaced by a second serrate seta. The roof of Haller's organ in both subgenera is solid, lacking perforations. The host range includes mammals (mainly bats) and birds. Approximately 10 species formerly classified in the genus *Antricola*, now a synonym of *Carios* according to some authors, possess a tuberculated cuticle. The females have a distinctive, scooplike hypostome; the hypostome is vestigial in the males. The *Antricola* species are parasites of New World bats. Thus far, none has been implicated in the transmission of microbial disease agents. A species formerly classified in the genus *Nothoaspis*, now a synonym of *Carios* according to some authors, is similar to *Antricola*, but the anterior dorsal surface bears a smooth shield-like structure, the pseudoscutum. The current classification of the genus *Carios* is based on Horak et al. (2002) and Klompen and Oliver (1993). One important species is *Carios capensis*, found on seabirds. The bat tick, *Carios kelleyi*, has been implicated as a potential vector of rickettsiae and borreliae (Reeves et al., 2006). The genus contains approximately 87 species.

Genus *Ornithodoros*

Nymphs and adults have a leathery cuticle with innumerable tiny wrinkles and small protuberances (mammillae) and a rounded body margin; they lack a lateral, sutural line. Mammillae are smaller and more numerous than those found in *Argas*. The host range is diverse and includes reptiles, birds, and mammals. The genus is worldwide in distribution. Examples of important species include the **African tampan**

(*O. moubata*) and the **cave tick** (*O. tholozani*). In North America, several species (e.g., *O. hermsi*, etc.) are important as vectors of relapsing fever spirochetes to humans and animals. The genus contains about 38 species.

Genus *Otobius*

The integument of the nymphs is spinose, whereas that of the adults is granulated. There are just two nymphal instars. The adults do not feed, and the hypostome is vestigial. *Otobius* ticks are found in North America, Africa, and Asia, having been inadvertently introduced onto the latter two continents. The genus contains two species: the **spinose ear tick** (*O. megnini*) and *O. lagophilus*.

Family Nuttalliellidae

The only known species in this family, *Nuttalliella namaqua*, occurs in eastern and southern Africa. It shares features with both the Argasidae and the Ixodidae but also has several unique morphological traits. This tick has

ball-and-socket joints that articulate the leg segments, a small, dorsal pseudoscutum, and a highly wrinkled cuticle with numerous pits and elevated rosettes. While considered a generalist feeder, it has been collected from the nests of rock hyraxes and swallows in South Africa, Namibia and Tanzania (Mans et al., 2011; Latif et al., 2012). Although rare and of no known medical or veterinary importance, recent studies of the biology and ecology of this species have provided new insights into the evolution of ticks (Mans et al., 2011, 2012).

MORPHOLOGY

External Anatomy

The major external regions of ticks are the **capitulum** (gnathosoma), **idiosoma**, and the legs (Figs. 27.1–27.3). The capitulum (Figs. 2.3C, 27.3) consists of the **basis capituli**, which articulates with the body; the segmented **palps**, the **chelicerae**, and the toothed **hypostome**. The capitulum of ixodid ticks is located at the anterior end of

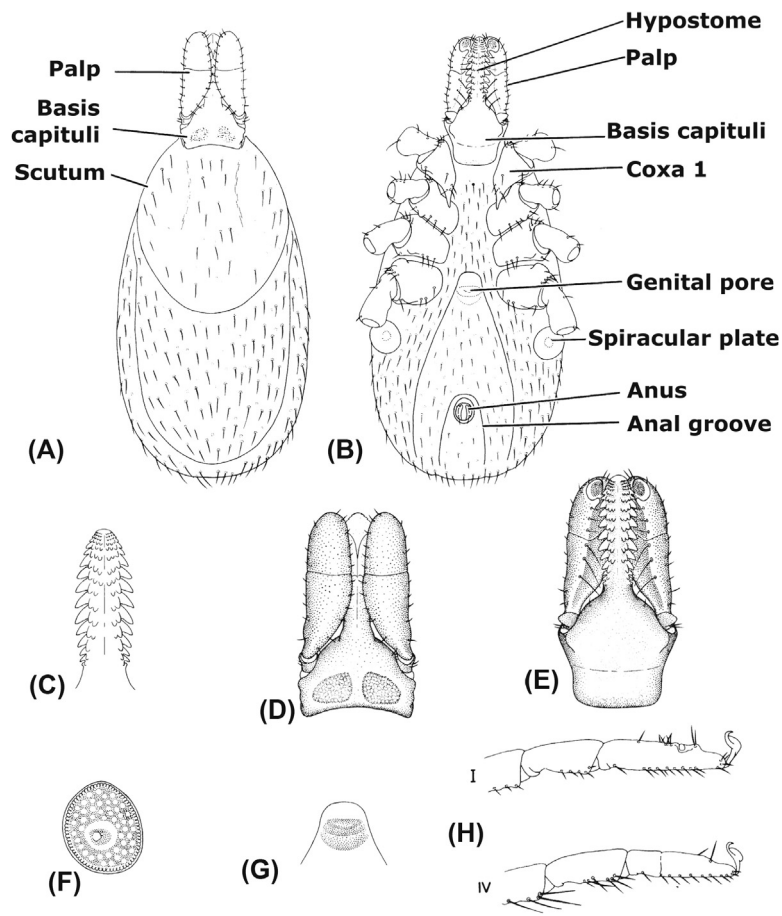


FIGURE 27.1 External morphology of representative female ixodid tick (*Ixodes pacificus*). (A) Dorsal view. (B) Ventral view. (C) Hypostome. (D) Capitulum, dorsal view. (E) Capitulum, ventral view. (F) Spiracular plate. (G) Genital pore. (H) Legs I and IV. Modified from Sonenshine (1991), with permission of Oxford University Press.

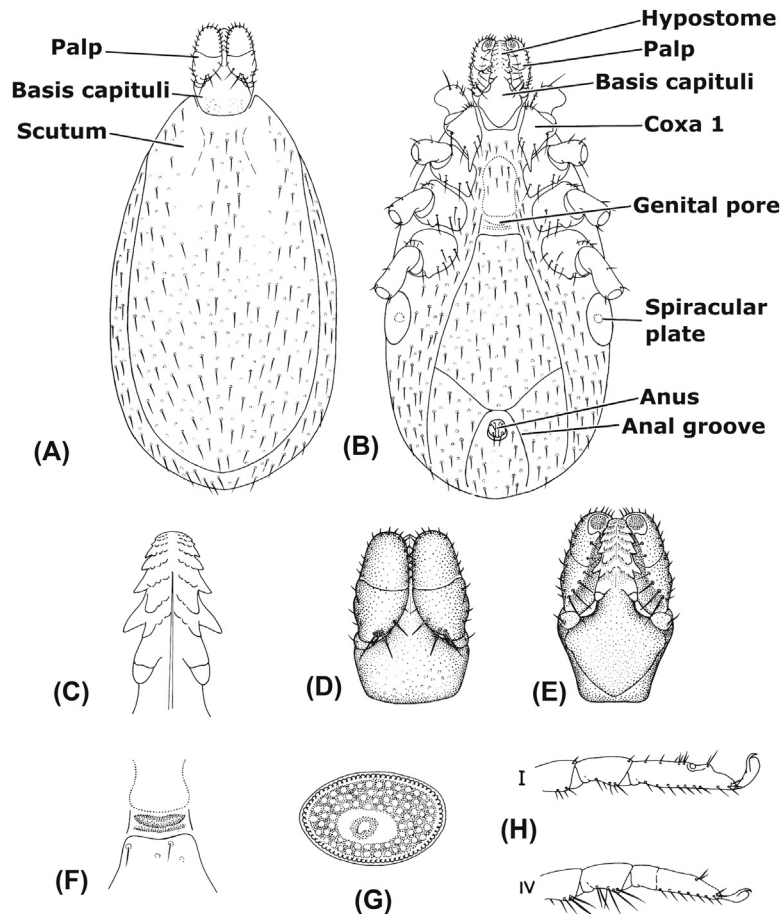


FIGURE 27.2 External morphology of representative male ixodid tick (*Ixodes pacificus*). (A) Dorsal view; (B) Ventral view; (C) Hypostome; (D) Capitulum, dorsal view; (E) Capitulum, ventral view; (F) Genital pore; (G) Spiracular plate; (H) Legs I and IV. Modified from Sonenshine (1991), with permission of Oxford University Press.

the body. Females bear paired clusters of pores, the **porose areas**, located dorsally on the **basis capituli**. The porose areas secrete antioxidants that inhibit degradation of the waxy compounds in the secretions of **Gené's organ**, which coat the eggs as they are laid. The **chelicerae** are located on the dorsal aspect of the capitulum. Their shafts, surrounded by spinose sheaths, lie between the palps and often extend even farther anteriorly than the palps. Each chelicera bears two digits distally. The larger, medial digit can be moved laterally; the smaller outer digit resides in a cavity of the medial digit and moves with it. Both digits have sharp denticles. The chelicerae are used to cut host tissues during attachment. The hypostome is a prominent, ventrally located structure that bears rows of recurved teeth on its ventral surface; teeth are absent in some nonfeeding males. A narrow food canal is located on the mid-dorsal surface. The palps consist of four distinct segments. In nymphs and adults of most ixodid species, the small terminal (fourth) segment is recessed in a cavity in segment 3 and bears numerous fine setae at its tip.

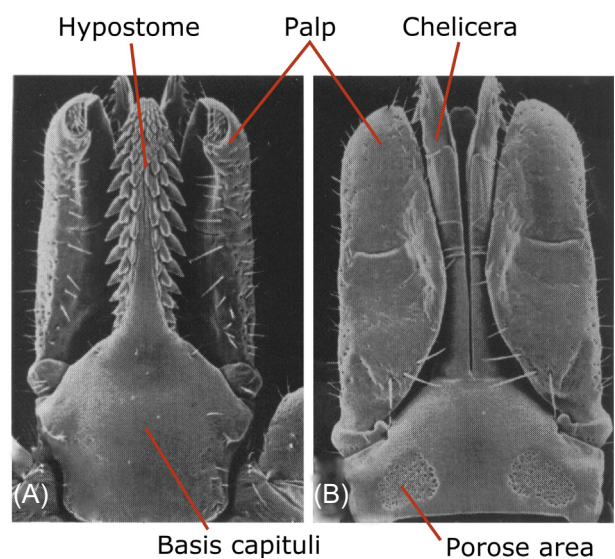


FIGURE 27.3 Capitulum of a representative ixodid tick (*Ixodes scapularis*), scanning electron micrographs. (A) Ventral view. (B) Dorsal view. Modified from Sonenshine (1991), with permission of Oxford University Press.

The capitulum of adult and nymphal argasids is similar. However, it is situated just below an anteriorly protruding body extension, or **hood**, and is not visible dorsally in nymphs or adults (Figs. 27.4 and 27.5). The four palpal segments are about equal in size. Small flaps, the cheeks, occur alongside the capitulum in many species and can be folded to cover the delicate mouthparts. In argasid larvae, the mouthparts protrude anteriorly, as in ixodids.

The body, exclusive of the capitulum, is the **idiosoma**. It is divided into two parts: the anterior podosoma that bears the legs and the genital pore, and the posterior opisthosoma, the region behind the coxae that bears the

spiracles and the anal aperture. The cuticle is relatively tough with sclerotized plates (sclerites) in certain locations. It serves as the site of muscle attachment and protects the animal from desiccation and injury. The cuticle bears numerous sensory setae as well as various pores representing the openings of dermal glands or sensilla.

The legs are jointed and articulate with the body via the **coxae**. Larvae are easily recognized by the presence of only three pairs of legs, whereas nymphs and adults have four pairs of legs. The structure of the legs is similar in the Ixodidae and Argasidae. Each leg is divided into six segments: the coxa, trochanter, femur, patella (=genu), tibia, and tarsus. The coxae are inserted ventrally and allow limited rotation in the anteroventral and dorsoventral planes. The other segments can be flexed, so that the legs can be either folded against the ventral body surface for protection or extended for walking. A pair of claws and a padlike pulvillus are present on each tarsus of most species. The pulvillus is absent in argasid nymphs and adults. An odor-detecting sensory apparatus, **Haller's organ** (Fig. 27.6), is evident on the dorsal surface of the tarsus of leg I in all stages. This organ consists of an anterior pit and a posterior capsule. Olfactory and mechanosensory, but not gustatory functions also have been associated with this organ (Nuss et al., 2016). The tick's Haller's organ uses novel molecular processes for chemosensation different from those found in insects. Haller's organ also functions as an infrared receptor (Mitchell et al., 2017). Variations in the structure of Haller's organ are useful for distinguishing genera and species.

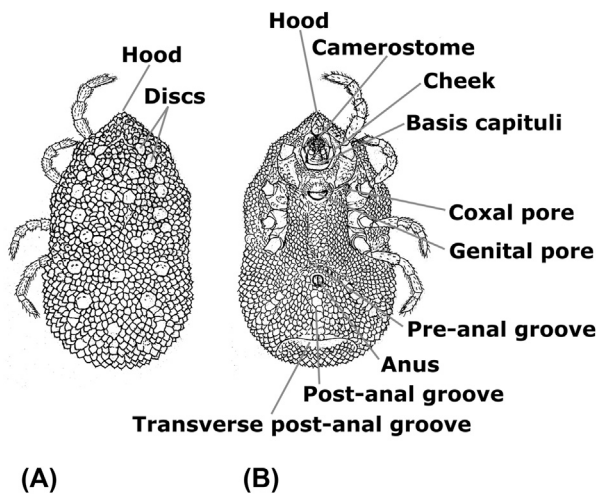


FIGURE 27.4 External morphology of a generalized argasid tick (*Ornithodoros*). (A) Dorsal view. (B) Ventral view.



FIGURE 27.5 A representative argasid tick (*Carios kelleyi*). (A) Female, dorsal view. (B) Female, ventral view. Courtesy of Jim Gathany, Centers for Disease Control and Prevention.

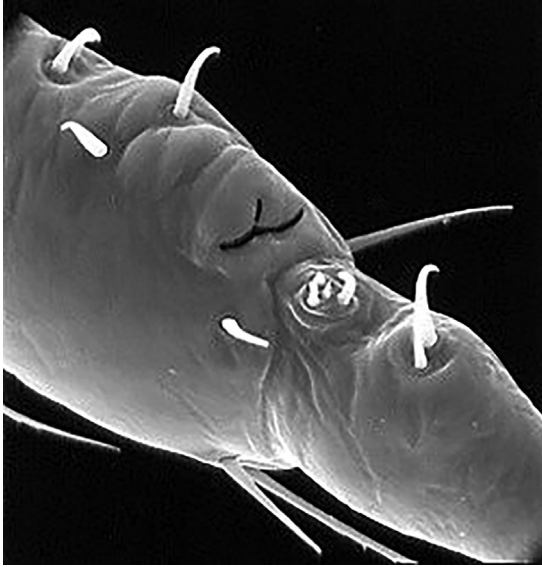


FIGURE 27.6 Haller's organ of the larval stage of *Amblyomma rotundatum*, a parasite of reptiles and amphibians in the Americas; scanning electron micrograph. Courtesy of the U.S. National Tick Collection, Georgia Southern University.

Ixodidae

Ixodid ticks, also called **hard ticks**, are illustrated in Figs. 27.1–27.3. Females have a hard cuticular plate or scutum on the anterior half of the dorsal body surface (Fig. 27.1A). In males, the scutum occupies virtually the entire dorsal surface (Fig. 27.2A). Elsewhere, the cuticle contains tiny surface folds, which give it a fingerprint-like appearance when viewed at high magnification. The body of the female posterior to the scutum expands enormously during feeding as new cuticle is synthesized to accommodate the bloodmeal. In males, however, the larger scutum limits expansion. The scutum bears setae and tiny pores termed **sensilla auriformia**. The latter are believed to serve as proprioceptive organs. When present, a simple eye occurs along each posterolateral margin of the scutum.

Immediately posterior to the scutum in the females are paired **foveal pores** (absent in *Ixodes*) from which a volatile sex pheromone, 2,6-dichlorophenol, is emitted. The dorsal body surface posterior to the scutum, the **alloscutum**, has innumerable fine folds. In females, a paired protrusible organ, Gené's organ, lies in the dorsal foramen between the scutum and the capitulum (capitular foramen). The ends of this organ protrude during oviposition and apply wax to each egg as it is deposited. In *Ixodes* males, hard sclerotized plates cover the ventral body surface (Fig. 27.2B). In females, the genital pore is a U- or V-shaped opening, with prominent marginal folds (Fig. 27.1G), but in males it is covered by a movable plate (Fig. 27.2F). Other ventral structures include: paired

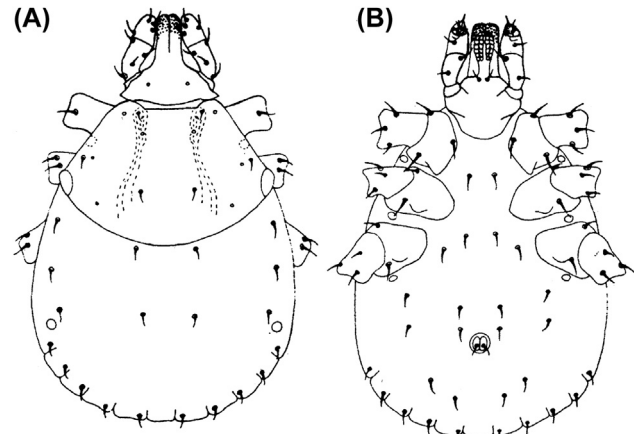


FIGURE 27.7 Larva of representative ixodid tick (*Dermacentor variabilis*), with legs beyond coxae and trochanters not shown. (A) Dorsal view. (B) Ventral view. From Clifford et al. (1961).

spiracular plates behind coxae IV in adults and nymphs (absent in larvae), each with a small ostium that opens to the respiratory system; and the anal aperture, located near the posterior margin. The entire body is covered by numerous setae and the porelike sensilla auriformia. Larvae possess few setae, although their number and relative placement provide valuable taxonomic characters for generic and subgeneric differentiation (Fig. 27.7).

Argasidae

The major external body features of argasid ticks, also known as **soft ticks**, are illustrated in Figs. 27.4 and 27.5. The body margins are rounded in most species. In *Argas*, however, they are flattened and covered by small marginal discs. Eyes, when present, occur on folds lateral to the coxae. A tiny coxal pore, the opening of the duct from the paired coxal glands, occurs bilaterally between the coxae of legs I and II. The spiracular plates, located between coxae III and IV, are relatively small and inconspicuous. In females, the genital pore appears as a horizontal slit surrounded by a prominent fold. In males, the pore is subtriangular or suboval, without a genital apron. There are no foveal pores.

Internal Anatomy

The internal organs of a typical tick are illustrated in Fig. 27.8. The organs are bathed in a circulating fluid, the hemolymph. The hemolymph is an aqueous medium rich in salts, amino acids, soluble proteins, and other dissolved substances. In addition, it contains several types of hemocytes, the most prominent of which are the plasmatocytes and granulocytes. These cells often function in phagocytosis of invading microbes, as well

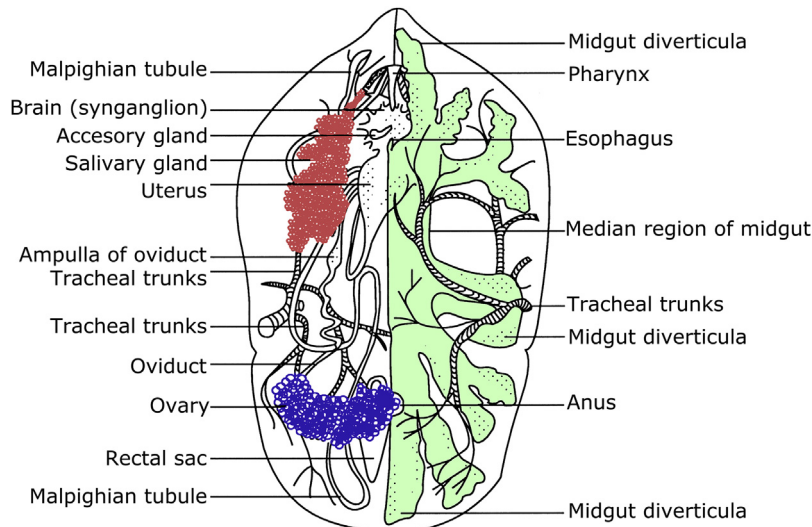


FIGURE 27.8 Internal anatomy of typical argasid tick, female; midgut shown on right side; midgut removed on left side to reveal underlying organs. Modified from Balashov (1972), with permission from Copyright Agency of Russia.

as other functions (Matsuo et al., 2009). Four major categories of cell types are generally recognized in tick hemolymph, namely, prohemocytes, nongranular plasmatocytes, granulocytes (type I and II), and spherulocytes (Borovickova and Hypša, 2005). A simple heart, situated mid-dorsally, filters and circulates this vital body fluid. Muscles extend from the dorsal and ventral cuticular surfaces to the inner surfaces of the coxae, chelicerae, and other structures.

The most prominent internal organ is the midgut, a large saclike structure with numerous lateral diverticula. The shape of the midgut depends on the state of engorgement. In unfed ticks, the diverticula are narrow, tubelike structures. In fed ticks, they enlarge and obscure most of the other organs as they fill with blood. Branches of the tracheal system ramify over the surfaces of the diverticula and surround the other internal organs. Ticks respire through these innumerable tiny air tubes, which open to the exterior via the paired spiracles.

Paired salivary glands are situated anterolaterally. These large glands, which resemble clusters of grapes, are connected via the salivary ducts to the mouthparts. Their salivary secretions empty into the salivarium located between the chelicerae and the hypostome. Tick saliva contains pharmacologically active compounds that facilitate attachment and suppress host inflammatory responses. The salivary glands eliminate excess water from the bloodmeal. In ixodid ticks, most water in the bloodmeal is extracted by specialized salivary-gland cells and excreted into the host as the tick feeds.

Other prominent internal structures are the reproductive organs. In males, these include the testes, the tubular vasa deferentia, the seminal vesicle, and the ejaculatory duct that

is connected to the genital pore. The ejaculatory duct is obscured by the large, multilobed accessory gland that secretes the components of the spermatophore. In females, the reproductive organs include the ovary, paired oviducts, uterus, vagina, and the seminal receptacle. The ovary is small and inconspicuous in unfed ticks but expands enormously during feeding and especially after mating. In gravid females, the ovary is distended with large, amber-colored eggs.

In argasid and ixodid ticks, excretion is accomplished by the **Malpighian tubules**, a pair of long, coiled structures that empty into the rectal sac. Nitrogenous wastes are excreted in the form of guanine. In argasid ticks, paired **coxal glands** adjacent to the coxae of leg I extract excess water and salts accumulated during feeding and excrete this watery waste via the coxal pores. Each gland consists of a membranous sac that serves as a filtration chamber and a coiled tubule that selectively reabsorbs small, soluble molecules and ions. Relapsing fever spirochetes may be transmitted to vertebrate hosts via the **coxal fluid** of infected ticks.

The central nervous system in ticks is fused to form the **synganglion**, located anteroventrally above the genital pore. The synganglion, which regulates the function of the structures described above, is the fused central nervous system. Large pedal nerves extend from the synganglion to the legs; smaller nerves innervate the palps, chelicerae, cuticular sensilla, and the internal organs. Transcriptomes of the synganglion of different tick species have described expression of neuropeptides, neuropeptide receptors, and neurotransmitter receptors and their roles in regulating their physiological processes (Bissinger et al., 2011; Sonenshine et al., 2014; Egekwu et al., 2016). Remarkably, almost all

of these molecules occur in the synganglia of the different tick species examined, including ixodid and an argasid tick species. However, statistically significant differences were observed in gene expression of genes that regulate patterns of blood-feeding, water elimination, pharyngeal pump action, cuticle synthesis, and reproductive activity; differences that help explain the major differences in feeding, development, and reproduction between ixodid and argasid ticks.

LIFE HISTORY

The life cycle includes four stages: the egg, larva, nymph, and adult. Ixodid ticks have only one nymphal instar, whereas argasid ticks have two or more nymphal instars. All ticks feed on blood during some or all stages in their life cycle; therefore, they are obligate ectoparasites. Larvae attack hosts, feed, detach, and develop in sheltered microenvironments where they molt to nymphs. Nymphs seek hosts, feed, drop, and molt to adults (except in argasid ticks, which molt into later nymphal instars). Adult ticks seek hosts, feed, and, in the case of engorged ixodid females, drop off to lay their eggs (Fig. 27.9).

In contrast to most other hematophagous arthropods, ticks can be remarkably long-lived. Many can survive for one or more years without feeding. Their life cycles vary greatly, with the greatest differences evident between the Ixodidae and Argasidae.

Ixodid Life Cycles

Immature and adult ticks each take a bloodmeal, except for the nonfeeding males of some species (especially members of the genus *Ixodes*). Following contact with the host, a tick uses its chelicerae to puncture the skin and its hypostome to

securely anchor itself. In many species, attachment is known to be reinforced by secretion of cementing substances with the saliva into and around the wound site. Females feed only once. Following mating, females ingest blood rapidly (24–48 h) and swell enormously. Replete, mated females drop from their hosts, find a sheltered location, and subsequently oviposit hundreds to thousands of eggs (Fig. 27.9). For *D. variabilis*, the average egg production is 5,400. For *Hyalomma impeltatum*, the reported average is nearly 10,700 eggs per female. The greatest number ever recorded was produced by an *Amblyomma nuttalli* female that produced close to 23,000 eggs. The eggs are deposited in a single, continual mass over many days or weeks. The female dies on completion of egg laying.

Males swell only slightly during feeding. They usually remain on their hosts, feed repeatedly, and inseminate several females. Mating typically occurs on the host. Certain species of *Ixodes*, however, mate on their hosts, in nests, or in vegetation. Many *Ixodes* males have vestigial hypostomes, and these species invariably mate off the host. Except for *Ixodes* species, males and females require a bloodmeal to stimulate oogenesis and spermatogenesis. More than 90% of the life cycle is spent off the host. Molting usually occurs in some sheltered microhabitat such as soil and leaf litter, or in host nests. After molting, nymphal and adult ticks must seek another host and feed. When host seeking and feeding occur in all three parasitic stages, the pattern is termed a **three-host life cycle** (Fig. 27.10). This is characteristic of more than 90% of ixodid species.

In tropical climates with frequent rainfall, developmental times are relatively short, and several generations may occur each year. In regions with alternating dry and rainy seasons, the life cycle is longer because ticks cease host seeking during the driest period. In colder temperate or subarctic regions, development is slower, and ticks commonly undergo diapause during the coldest months. As a result, the life cycle may take two or more years. An example of a diapausing species is *Dermacentor variabilis*. Larvae feed on mice or other small mammals, mostly in spring. Fed larvae drop off and molt to nymphs that again attack small mammals. Fed nymphs drop off and molt within a few weeks. If the adults feed and reproduce in the same year, the entire life cycle can be completed within several months. Thus, under favorable conditions in nature, the typical three-host life cycle can be completed in less than 1 year. However, adverse environmental conditions can prolong the life cycle to 2 or more years. The life cycle of *Ixodes ricinus* may require up to 4 years in the northern parts of its range in Europe



FIGURE 27.9 Lone star tick (*Amblyomma americanum*), female, that has just finished depositing an egg mass of about 4,000 eggs. Photograph by Gary R. Mullen.

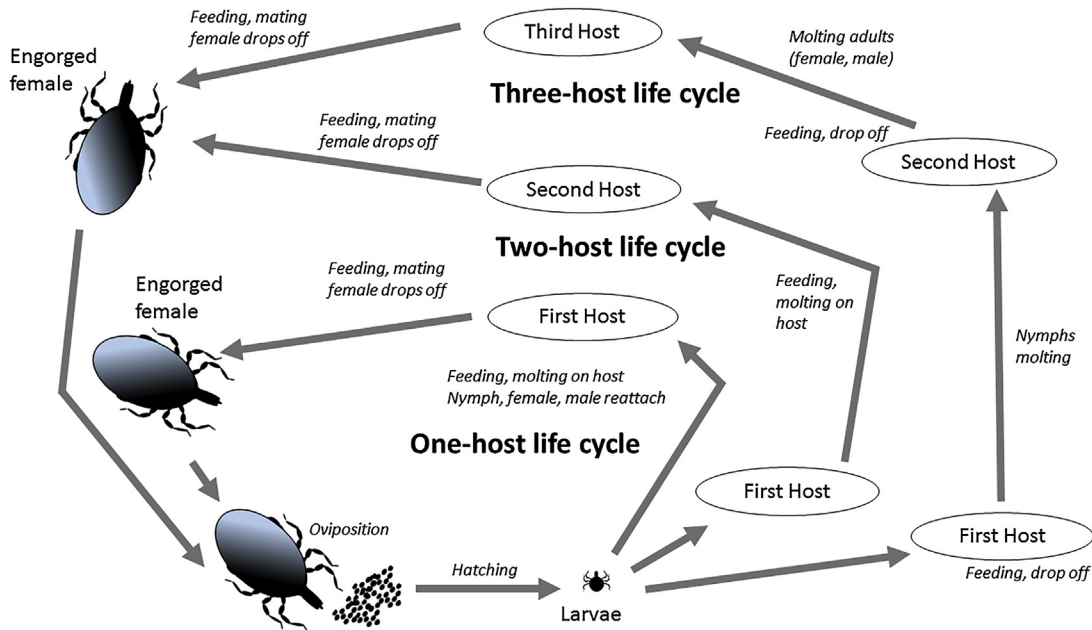


FIGURE 27.10 Three basic life cycles of ixodid ticks: (1) one-host ticks (inner circle) in which the larva, nymph, and adult all attach to, and develop on, a single host (e.g., *Rhipicephalus (Boophilus) annulatus*). (2) Two-host ticks (middle circle) in which larva and nymph feed on one host and the adult attaches and feeds on a second host (e.g., *Hyalomma dromedarii*). (3) Three-host ticks (outer circle) in which larva, nymph, and adult each parasitize a different host (typical of most ixodid ticks). Most argasid ticks have a multihost life cycle involving more than three hosts; with several nymphal instars, each potentially feeding on a different host. Courtesy of W. L. Nicholson.

(Hoogstraal, 1985). In Ireland, the life cycle takes 3 years, with each stage requiring approximately 1 year before developing to the next (Gray, 1991).

A few ixodid species exhibit a **two-host** or **one-host life cycle** (Fig. 27.10). For example, in the two-host camel tick (*Hyalomma dromedarii*), fed larvae molt on their hosts, and the unfed nymphs reattach soon after emergence. Following engorgement, the nymphs drop off the host, molt, and feed again as adults on a second host. In the one-host cattle tick *R. (B.) annulatus*, and in other species of the subgenus *Boophilus*, all stages feed and molt on the same host. Mating also occurs on this host. Replete, fertilized females drop off the host and oviposit in soil.

Argasid Life Cycles

In contrast to the ixodids, most argasids have two or more nymphal instars in their life cycle, each of which must consume a bloodmeal. This pattern is termed the multihost life cycle. Molting occurs off the host in cracks, crevices, or beneath debris in or near the nest. Argasid females take repeated small bloodmeals and lay small batches of eggs (Fig. 27.11), typically fewer than 500 eggs/batch after each feeding. These are termed multiple gonotrophic cycles, and as many as six gonotrophic cycles have been



FIGURE 27.11 Argasid tick (*Ornithodoros turicata*), female, depositing small batches of eggs. Photograph by Jerry F. Butler.

reported in some species. The interval between feedings is typically several months. Mating usually occurs off the host. Because of the multiple nymphal instars that may number six or even seven in some species, argasid ticks often live for many years. In addition, these ticks are highly resistant to starvation, which can extend their longevity even further. In some species that feed on migratory bats or birds, diapause serves to delay oviposition or development during the periods when hosts are absent.

The larvae of most *Ornithodoros* and *Carios* spp. that parasitize bats and birds remain attached to their hosts for many days, just as do ixodid ticks. Following the larval bloodmeal, they molt twice without additional feeding. Thereafter, the life cycle is similar to the typical argasid pattern. Another species with an unusual life cycle is *Otobius megnini*. This tick exhibits a high degree of host and body-site predilection specificity that regulates its feeding and development. Females do not feed and are autogenous (i.e., oviposit without feeding).

BEHAVIOR AND ECOLOGY

Feeding behavior, even on preferred hosts, is not a uniform process. Blood-feeding begins soon after contact and acceptance of recognition features that determine that the animal is a suitable host. In ixodids, a tick may crawl about the host for several hours in search of a suitable feeding site. Once a site has been selected, the tick cuts into the skin with its cheliceral digits and inserts its hypostome to initiate the attachment process. Shortly after they attach, most ixodid ticks secrete cement during the first 1–2 days to secure themselves at the wound site. Subsequently, the tick begins salivating into the developing hematoma and sucking blood; salivating and blood sucking alternate, often for extended periods of time for each process. The feeding lesion enlarges as the tick injects anticoagulant and antihemostatic compounds into the wound; recruitment of host leucocytes to the wound site also contributes to tissue lysis and fluid influx around the tick's mouthparts. Successful blood feeding depends upon the secretion of an extensive array of antihemostatic, anti-inflammatory, and immunomodulatory proteins and lipids in the tick saliva so as to suppress the host's ability to reject the feeding tick. Of particular importance in tick saliva are antagonists of the intrinsic pathway factor X (Xa) and factor V (Va), which converts prothrombin to thrombin. Thrombin in turn converts plasma fibrinogen to fibrin and clots the blood. Tick saliva blocks blood coagulation by inhibiting factor Xa. In addition, many species also secrete proteins that inhibit thrombin directly or inhibit the conversion of prothrombin to thrombin by inhibiting factor V. Other salivary proteins prevent platelet aggregation, also important for blood coagulation, and proteins that bind, antagonize, or degrade important host mediators of pain, itching, and inflammation, particularly the host's histamine, serotonin, and bradykinin. Nevertheless, ticks feeding on the same host (i.e., tick-sensitized individuals) often encounter significant resistance and are unable to engorge, drop off, or even die, a phenomenon known as acquired resistance to tick bite (Wikel, 2014). Our knowledge of the tick's ability to antagonize the

host's hemostatic mechanisms is still incomplete (Ribeiro et al., 2017), but more information has become available with new advances using next-generation sequencing, genomics, proteomics, and metabolomics of tick salivary glands (e.g., Ribeiro et al., 2006; Kazimírová and Štibrániová, 2013; Chmelař et al., 2016).

Digestion of the bloodmeal takes place in the midgut. Erythrocytes and other blood cells are lysed soon after ingestion. Hemoglobin from lysed cells binds to receptors on the midgut epithelial cells and is incorporated by a process known as receptor-mediated endocytosis into tiny vacuoles in the digestive cells (Coons et al., 1986). The vacuoles fuse with lysosomes, forming specialized phagolysosomes, wherein hydrolytic enzymes released into these acidic vacuoles carry out digestion of the hemoglobin (Gough and Kemp, 1995; Mendiola et al., 1996). Subsequently, a cascade of proteolytic enzymes digest the hemoglobin, liberating dipeptides and free amino acids for transport out of the cell and into the hemolymph (Horn et al., 2009). Most of the heme released following hemoglobin digestion is detoxified to hematin, which accumulates in specialized "hemosomes" (Lara et al., 2003), while the amino acids liberated from the globin moieties are passed into the hemolymph. The latter provides the primary nourishment derived from the tick's bloodmeal. Although some other proteins, various lipids, and carbohydrates are also digested, most proteins ingested with the bloodmeal remain in the midgut lumen.

Ixodid ticks feed gradually prior to mating because first they must create new cuticle to accommodate the massive bloodmeal. Typical attachment periods range from as few as 2 days for larvae to as long as 13 days for females. When feeding is completed, the weight of blood and other fluids consumed ranges from 11 to 17 times the tick's prefeeding body weight in ixodid larvae and from 60 to 120 times the tick's prefeeding body weight in ixodid females. Measurements of blood volume consumed range from 0.7 mL to as high 8.9 mL per female in some ixodid species. Nymphal and adult argasid ticks attach for only brief periods. This can be as little as 35–70 min for adults. These ticks do not secrete cement during attachment; instead, they attach solely with the mouthparts, especially the hypostome. Argasid ticks swell to the extent that their cuticles can stretch. New cuticle is not secreted during feeding as it is in ixodid ticks.

In ticks, mating can occur either during feeding or off the host. In the metastriate Ixodidae, mating occurs while the adults are attached and feeding. Unfed adults are sexually immature and require a bloodmeal to stimulate gametogenesis. Mating is usually regulated by sex pheromones and follows a complex, hierarchical pattern

of responses. Feeding females secrete a volatile **sex-attractant** pheromone, usually **2,6-dichlorophenol**, that excites males feeding nearby on the same host. The males detach and seek the females that they recognize by means of the mounting sex pheromone (a mixture of cholesteryl esters) on the female's body surface. The male climbs onto the dorsum of the female, then moves to her ventral surface and searches for her gonopore. Once a male locates the gonopore, he probes the opening with his chelicerae. Spermatophores, containing spermatozoa, are produced in the large accessory gland of the sexually mature male during the mating process. At this time, the spermatophore emerges from the male's genital pore, whereupon the male seizes it with his mouthparts and inserts it into the female's vulva. Copulation is essential to initiate rapid engorgement by the blood-feeding females. In most ixodid ticks, the attached females do not fully engorge unless inseminated by a conspecific male, and the ovary remains in the nonvitellogenic state; however, parthenogenesis is known to occur in some species. Full engorgement by the female leads to a remarkable sequence of molecular and physiological changes that result in vitellogenin production, ovarian development, and oviposition (Lomas et al., 1997; Mitchell et al., 2007; Thompson et al., 2005, 2007).

In prostriate Ixodidae and in argasid ticks, the adults become sexually mature soon after the nymphal molt. These ticks usually mate in the nests or in vegetation, although ticks of some prostriate species also may mate on the host. There is evidence that mating in argasid ticks is regulated by one or more sex pheromones, although no specific compounds have been identified to date.

A preovipositional period of up to several weeks precedes egg laying in ixodid ticks. During oviposition, the cuticle of the vulva softens and evaginates as the eggs pass through it, thereby serving as an ovipositor. The emerging eggs are waxed by secretions from **Gené's organ**. The process of oviposition continues for several weeks. Typically, about 50%–60% of the female's body weight at the time of drop-off is converted to eggs. The number of eggs deposited is directly proportional to the size of the engorged female. At the completion of oviposition, the spent female dies. Thus, there is only a single gonotrophic cycle among ixodids. In the Argasidae, however, mated females commence oviposition soon after feeding, but deposit small clutches containing only a few hundred eggs. Following oviposition, the females remain active and seek hosts again. These ticks feed and lay eggs after each meal; they do not need to mate again. The number of gonotrophic cycles varies but rarely exceeds six.

Most tick species live in forests, savannahs, second-growth areas of scrub and brush, and grassy meadows.

Others remain buried in sand or sandy soils, under stones, in crevices, or in the litter, duff, and rotting vegetation at the floor of woods and grasslands. In contrast, almost all argasids and some ixodids, especially males and immatures of several species of the genus *Ixodes*, are **nidicolous**. They live in the nests, burrows, caves, or other shelters used by their hosts.

Non-nidicolous ticks are active during certain periods of the year when climatic conditions favor development and reproduction. During such periods they engage in host-seeking behavior. In temperate and subpolar regions, seasonal activity is regulated by ambient temperature, changing photoperiod, and incident solar energy. In tropical regions, where day length or temperature varies only slightly throughout the year, tick activity is often controlled by the transition from the dry to the rainy season. Host-seeking ticks exhibit at least two strategies for locating potential targets for their bloodmeals. Ambush ticks climb onto weeds, grasses, bushes, or other leafy vegetation to wait for passing hosts. When stimulated by the presence of a host, they extend their forelegs anterolaterally in what is called **questing behavior** (shown in Fig. 27.12A) and quickly grasp the hair, feathers, or clothing of a passing host. Hunter ticks emerge from their refuges in the soil, sand, or duff when excited by host odors and run rapidly across the ground to attack hosts.

After contacting a potential vertebrate host, the tick must perceive appropriate host-recognition cues that enable it to determine whether to attach and feed, or to drop off and resume host-seeking. Odors, radiant heat, visual images, or vibrations stimulate the tick and enable it to recognize its prospective host. Odors are probably the most important stimuli. Electrophysiological studies have shown that larvae of *Rhipicephalus (B.) microplus* respond to odors from extracts of cattle skin but not to dry air. Human breath also elicits a response but not as vigorously as that caused by cattle extracts. Among the more important attractants emitted by hosts are carbon dioxide in animal breath, and ammonia in urine and other animal wastes. Other odors that attract ticks are butyric acid and lactic acid, which occur commonly in sweat and other body fluids. Acetone and 1-octen-3-ol have also been shown to attract ticks (Carr et al., 2013). Little is known about the molecular biology of chemoreception in ticks. Using next-generation sequencing and comparative transcriptomics, Carr et al. (2017) found that the chemosensory function of the tick Haller's organ is olfactory but not gustatory. The olfactory mechanism is different from insects, lacking odorant binding peptides, and apparently using an olfactory G protein-coupled receptor (GPCR) signal cascade unique to the Haller's organ for odor detection and the terminator protein β -arrestin to terminate



FIGURE 27.12 The brown dog tick (*Rhipicephalus sanguineus*). (A) Female, dorsal view. (B) Male dorsal view. Photograph courtesy of Centers for Disease Control and Prevention.

neuronal responses (Carr et al., 2017). Small increases in radiant heat excite ticks and act synergistically with host odors. Visual cues may be important, especially in certain hunter ticks that can discriminate dark shapes against the bright background of the sky. Host-seeking ticks of many species respond to shadows, resulting in extension of their legs to facilitate contact. Remarkably, the Haller's organ of ixodid ticks can also function as an infrared detector (Mitchell et al., 2017) enabling the ticks to respond to distant warm-blooded hosts, especially at night.

Other stimuli that elicit questing behavior include vibrations, sound, and tactile cues. Vibrating the grass stems on which ticks are perched can elicit questing behavior almost immediately. *Rhipicephalus (B.) microplus* larvae respond to sounds in the 80–800 Hz range, typical of the frequencies produced by feeding cattle, whereas the sounds produced by barking dogs reportedly attract *Rhipicephalus sanguineus* (Waladde and Rice, 1982). Tactile stimuli perceived when ticks contact their hosts, in combination with short-range attractants such as heat and odor, help to determine the selection of suitable feeding sites. Ticks will not attach to a host unless the appropriate stimuli are received in a particular sequence.

The timing of drop-off from the host offers important ecological advantages. For non-nidicolous ticks, such drop-off rhythms are synchronized with host behavioral patterns. This tends to disperse fed ticks in optimal habitats where they can develop and reproduce. Photoperiod

appears to be the dominant exogenous factor affecting drop-off patterns. The daily light:dark cycle induces a regular rhythm of feeding and dropping off. This effect, termed **photoperiodic entrainment** is partially reversible. In a series of elegant experiments with *H. leporispalustris*, the existence of an endogenous drop-off rhythm entrained by the scotophase or dark period was shown. The rhythm was affected only partially by changing the photoperiodic regime and was maintained even when hosts were held in constant darkness. Detachment may occur while the hosts are inactive in their nests or burrows or, alternatively, it may be coordinated with the period of maximum host activity. In *D. variabilis*, fed larvae and nymphs drop soon after night begins. In contrast, immatures of *H. leporispalustris* drop off during daylight hours when their lagomorph hosts are confined in their burrows or warrens.

Ticks exhibit varying degrees of host specificity. More than 85% of argasid and ixodid ticks exhibit relatively strict host specificity. However, the evolutionary significance of this phenomenon is uncertain. Others have debated that most of the existing tick-host-association patterns may be explained as artifacts of biogeography and ecological specificity as well as incomplete sampling (McCoy et al., 2013). Regardless of how host specificity evolved, it is clear many species are specialists. Examples include certain species of argasids (e.g., some *Carios* spp.) that infest only bats, and the ixodids *Dermacentor*

albipictus, *R. (B.) annulatus*, and *R. (B.) microplus* that feed only on large ruminants. Many of the nidicolous ticks are highly host-specific. Examples include *Ixodes marxi* that feeds almost exclusively on squirrels, *Amblyomma tuberculatum* that, in most stages and primarily as adults, parasitizes the gopher tortoise, and *Argas arboreus* that attacks herons.

At the opposite extreme are ticks that are opportunistic species with catholic feeding habits. Examples include *Ixodes ricinus* and *I. scapularis*. Larvae and nymphs of these species feed readily on lizards, birds, small mammals, and larger hosts like sheep and humans. Adults feed on larger mammals, especially ungulates, and also attack humans. More than 300 species of vertebrates have been recorded as hosts for *I. ricinus*, and more than 120 have been recorded for *I. scapularis*.

Host specificity is influenced by evolutionary history, ecological and physiologic factors, and the ability of the ticks to avoid host rejection. Many species belonging to the less specialized and phylogenetically primitive genus *Amblyomma* and all species of the former *Aponomma* (now included in *Amblyomma* or *Bothriocroton*) feed on reptiles or primitive mammals. Ticks adapted to a specific habitat type (e.g., grassland) encounter only those vertebrates adapted to the same habitat. Questing height also is important. Ticks questing on or near the ground are exposed mostly to small animals, while those questing higher in the vegetation are more likely to encounter larger animals.

The extent to which different hosts are used depends on host behavior and opportunities for contact, such as foraging range, time of day and time spent foraging, habitats visited, and other factors. White-footed mice, which forage extensively on the ground, acquire numerous *I. scapularis* immatures, whereas flying squirrels, which spend much less time on the ground, are rarely infested. A similar relationship exists among migratory birds. In the United States, ground-feeding birds that forage in habitats shared with cottontail rabbits are heavily infested with immatures of the rabbit tick *H. leporispalustris*. Birds that forage above ground in bushes or trees rarely encounter these ticks. Acceptance of a vertebrate animal also is dependent on physiological factors and the ability of the ticks to recognize it as a host.

Host utilization may be influenced by the ability of ticks to evade or suppress host homeostatic systems and avoid rejection. This was first reported in a landmark paper by Trager (1939), who noted that the feeding success of *D. variabilis* on guinea pigs declined with frequent re-exposures. The guinea pig is a South American rodent and an unnatural host for this North American tick. When fed on its natural hosts (e.g., white-footed mice), *D. variabilis* experiences little if any rejection when feeding on tick-naïve hosts, but increasing rejection may

occur when ticks attempt to feed on tick-sensitized hosts (Krause et al., 2009). Similarly, *I. scapularis* saliva contains pharmacologically active compounds that suppress host mediators of edema and inflammation such as anaphylatoxins, bradykinin, and other kinins, but lacks compounds to suppress histamine. Because histamine-induced edema does not occur in the white-footed mouse, this does not deter tick feeding on this host. However, recent research indicates that white-footed mice do develop a strong, granulomatous inflammation in response to repeated tick challenge by *I. scapularis*, but the dermal architecture is largely unaffected, allowing the ticks to remain attached (Anderson et al., 2017). However, histamine-containing basophils are very abundant in guinea pigs, and cutaneous basophil hypersensitivity develops rapidly even after a single feeding by these ticks (Ribeiro, 1989). *Ixodes scapularis* saliva also contains an enzyme that destroys complement, thereby facilitating the survival of pathogens such as *Borrelia burgdorferi* ingested during blood-feeding (Valenzuela et al., 2000).

Ticks occur in many terrestrial habitats ranging from cool, arboreal northern forests to hot, arid deserts. Each species, however, has become adapted to specific types of habitats where generally it is found in greater abundance. Typical habitat associations of non-nidicolous ixodid ticks include forests, meadows and other clearings, grasslands, savannahs, and semi-desert or desert areas. At one end of the spectrum are species that have very limited resistance to desiccation and occur in cool, moist forests (e.g., *I. scapularis* and *I. ricinus*). In the middle are the many species that can survive at least brief periods of desiccation during host seeking or development (e.g., *Dermacentor variabilis*, *Amblyomma maculatum*, and *A. americanum*). At the other end of the spectrum are the desiccation-tolerant species adapted to survive in arid steppes, semi-deserts, and other xeric environments (e.g., *Hyalomma asiaticum* and *Ornithodoros savignyi*).

Water balance is a critical determinant of a tick's ability to survive while waiting for hosts, sometimes requiring weeks or months. When they begin to desiccate, they retreat to more sheltered, humid microenvironments such as the rotting vegetation in a meadow or damp leaf litter on the forest floor. They secrete a hygroscopic salivary secretion onto their mouthparts that collects atmospheric water (direct sorption). After repeated cycles of secretion and drinking the condensed water, the rehydrated ticks are able to resume host-seeking. Some ticks are able to remain in the questing position for many days without rehydration, while others must return to their humid microenvironments each day.

Ixodes scapularis is an example of a tick with very limited desiccation tolerance. Consequently, it is most abundant in dense, humid, forest habitat or in dense shrub-

dominant habitats adjacent to large rivers, bays, or the Atlantic Ocean. Another desiccation-intolerant species is *Ixodes ricinus*. This tick is widespread in the British Isles, Continental Europe, and western Asia, where it frequents woodlands, damp meadows, pastures, and ecotones.

Dermacentor variabilis is an example of a species exhibiting greater tolerance to desiccation. It flourishes in the ecotone between secondary growth deciduous forests and lush, grassy meadows, as well as along secondary roads and trails in forested habitats. The dense ecotonal vegetation provides shade, increased moisture, protection from intense solar radiation, and food plants that support the tick's mammalian hosts. This type of environment is ideal for the immature stages of *D. variabilis*. Adults, with their greater resistance to desiccation and greater mobility, venture further afield to quest in sunlit meadows or along roads and trails.

The camel tick, *Hyalomma dromedarii*, is an example of a desiccation-tolerant species. This desert tick is common in the steppes and semi-desert habitats in large areas of North Africa and the Middle East. Larvae and nymphs generally live in rodent burrows. Adults bury themselves in sand and duff near their hosts, especially around caravansaries and similar locations where camels and other livestock are kept.

Nidicolous ticks living in or near the nests of their hosts are adapted to highly specialized environments. Normally the temperature and relative humidity in a burrow, cave, or similar type of shelter are more uniform throughout the year than in the external macroenvironment. The higher relative humidity in such microenvironments is due in part to the presence of hosts, their wastes, and plant materials used to construct or line their nests. Nidicolous ticks exhibit behavioral patterns that restrict their distribution to these sheltered locations. They avoid bright sunlight and low humidity, the type of conditions prevalent at the entrances of burrows or caves. Confined within these cryptic, restricted locations, nidicolous ticks become active when hosts are present. However, when hosts are absent, they may wait for up to several years for hosts to return or until they die of starvation.

Seasonal activity refers to the period of the year when ticks actively seek hosts. For example, *D. variabilis* larvae emerge from winter **diapause** in spring to feed on small mammals, especially mice and voles. Activity accelerates rapidly as increasing numbers of larvae emerge from overwintering sites to attack hosts, culminating in the seasonal peak within a few weeks. Thereafter, activity continues unabated, with larval abundance declining as more individuals find hosts, desiccate, or die of starvation. Nymphal and adult ticks also feed during the warm spring and early summer months. In the southern parts of its range, overwintering *D. variabilis* adults emerge early and soon overlap with those that develop from nymphs fed in the

spring. Thus, the seasonal peak for adults occurs in early summer. As a result, most females oviposit in July and August, and the newly hatched larvae enter diapause as day length diminishes. In the southeastern United States, the entire life cycle is completed in 1 year. Occasionally, a small secondary peak of *D. variabilis* larval activity occurs in the fall. In the northern part of its range, however, tick activity is delayed due to cooler spring temperatures and shorter day lengths. As a result, although larvae and nymphs feed in the late spring and summer, adults emerge too late in the summer to commence questing activity. These adults undergo diapause and emerge the following spring. This pattern of feeding and diapause results in a 2-year life cycle.

Ixodes scapularis also exhibits distinct seasonal activity periods. In the northern part of its range, larval activity does not occur until middle or late summer and the nymphs that molt from the fed larvae diapause until the following spring. Nymphs that feed in the spring molt in summer, but the young adults delay host-seeking until fall. This pattern results in a 2-year life cycle. In the southernmost part of its range, *I. scapularis* activity occurs earlier in the year. These southern populations may complete their life cycle in just 1 year.

A few tick species are active during the cooler months of the year, especially fall and winter. Larvae of the winter tick (*Dermacentor albipictus*), a 1-host tick that feeds on horses, deer, elk, moose, and other large ungulates, commence host-seeking activity in late summer or early fall. Larvae and nymphs feed and molt on the same hosts and the resulting adults reattach, feed, and mate. Replete females drop off the host and oviposit in the soil. In the northern-most parts of its range, adults usually do not appear until late winter, with peak occurrence in April. Subsequent oviposition and hatching occur in late spring. At this time, larvae undergo diapause, presumably in response to increasing daylight, and do not commence host seeking until after an extended period of declining photoperiod. Development proceeds faster farther south. On stanchioned bovines at Kerrville, Texas, in the southern United States, the entire process of feeding, molting, and production of engorged females is completed in 21–36 days. Engorged females that drop off their hosts in winter do not oviposit until the following spring.

In tropical regions, where day length is nearly uniform throughout the year and where there is no prolonged dry season, the seasonal activity of many tick species (e.g., *Rhipicephalus appendiculatus*) is often influenced by the distribution of rainfall. Farther from the equator, particularly in colder regions in southern Africa, *R. appendiculatus* diapauses during the dry season.

In contrast, most argasid ticks do not exhibit patterns of seasonal activity. This is especially true for ticks infesting

the nests or burrows of nonmigratory hosts such as rodents and carnivores. However, nidicolous ticks that parasitize migratory birds and bats tend to delay oviposition so that hatching occurs at about the time the hosts return.

Diapause is an important behavior that enables ticks to survive adverse environmental conditions and conserve energy until conditions improve. Diapausing ticks become inactive, reduce their metabolic rates, and do not feed on hosts even when given the opportunity. Newly emerged larvae, freshly molted nymphs, and adults of many species enter diapause before seeking hosts, particularly if they emerge during periods of declining photoperiod. This is termed host-seeking diapause. Diapause enables *D. variabilis* larvae and adults to survive the cold winters that occur throughout most of the tick's range. It also determines the length of the life cycle, 1 year in the south but 2 years in the northern part of its range. Diapause delays activity of *I. scapularis* nymphs at more northern latitudes so that they do not commence host seeking until spring or early summer. It also may delay adult activity that usually begins in fall, often several months after molting (Gray et al., 2016).

Another type of diapause is morphogenetic diapause, in which development or oviposition is delayed. In *Dermacentor marginatus*, oviposition rather than hatching is delayed. Thus, females that feed in spring or early summer lay eggs immediately, but those that feed in late summer or early fall oviposit the following spring. A remarkable example of morphogenetic diapause occurs in certain argasid ticks that inhabit the nests of birds or the roosts of bats. Females of the bat tick *Carios kelleyi* (Fig. 27.5) oviposit immediately after feeding in spring. However, those that feed in fall delay oviposition until the following spring. Because the bats migrate to cold caves or caverns far from the tick's normal habitats, this ovipositional delay avoids the risk that larvae will emerge at a time when no hosts are available.

TICK SPECIES OF MEDICAL-VETERINARY IMPORTANCE

The following ticks are important as household pests, species that transmit disease agents to humans, and species that are injurious to livestock or transmit disease agents to animals. The more important tick-borne diseases of humans and other animals are listed in Tables 27.2 and 27.3.

The **brown dog tick** (*Rhipicephalus sanguineus*) exists currently as a complex of species (Fig. 27.12) and is a common household pest throughout most of the world (Nava et al., 2014). The primary host for all life stages is the domestic dog, which can become heavily infested. However, in many areas bordering the Mediterranean Sea, western Asia, and Africa, this tick also feeds readily on a

wide range of wildlife (especially small mammals) and also attacks humans. Recent work has demonstrated tropical and temperate lineages that may exhibit biological differences. It often infests kennels, houses, and peridomestic areas, especially when dogs are kept indoors, which can produce considerable distress when the owners encounter thousands of these ticks. Seasonal activity peaks in summer, although activity peaks can occur throughout the year when ticks inhabit heated homes. This species is the primary vector of *Rickettsia conorii*, which causes **Mediterranean spotted fever** or **Boutonneuse fever** in many Mediterranean countries. It has been implicated as the vector for *Rickettsia rickettsii* in the southwestern United States, Mexico, and parts of Central and South America. In dogs and some other animals, this tick is a vector of the agents of cyclic thrombocytopenia (*Anaplasma platys*), canine ehrlichiosis (*Ehrlichia canis*), canine hepatozoonosis (*Hepatozoon canis*), and canine babesiosis (*Babesia vogeli* and a small *B. gibsoni*-like species).

The **brown ear tick** (*Rhipicephalus appendiculatus*) and related species are major pests of livestock in eastern, central, and southern Africa. Hosts include most domestic ruminants and many wildlife species, to which it attaches predominantly in and around the ears. It is the vector of the agent of **East Coast fever**, a protozoan disease that afflicts ruminant livestock within its range. Many other species of *Rhipicephalus* are important livestock pests and vectors of pathogens (e.g., *R. bursa* is a vector of the agents of equine, bovine, and small ruminant babesiosis and bovine and ovine anaplasmosis in the Mediterranean area). *Rhipicephalus evertsi* and *R. turanicus* are two other species injurious to livestock.

The genus *Haemaphysalis* contains numerous species that attack mammals and birds. In North America, an important species is the widespread **rabbit tick** (*H. leporispalustris*). Larvae and nymphs attack ground-feeding birds as well as lagomorphs, while adults feed only on lagomorphs. Larvae and nymphs are active in the late summer and fall, while adults feed in the spring. This species contributes to the maintenance of **Rocky Mountain spotted fever** (*Rickettsia rickettsii* infection) among wildlife. In India, an important species of this genus is *H. spinigera* that occurs in dense forest habitat. Larvae feed on small mammals and ground-feeding birds, but nymphs and adults attack larger animals, including monkeys, cattle, and even humans. Larvae are active during October and November, nymphs from November to June, and adults mostly in July and August. This tick species is the principal vector of the virus that causes **Kyasanur Forest disease**.

In Europe, *H. punctata* may transmit mild forms of the agents of bovine babesiosis (*B. major*) and theileriosis (*T. buffeli* and *T. orientalis*) or babesiosis of small ruminants (*B. motasi*). *Haemaphysalis longicornis* infests

TABLE 27.2 Representative Tick-Borne Diseases of Public Health Importance and Associated Characteristics (All Tick-Borne Diseases Have Not Been Included)

Disease	Causative Agent	Primary Tick Vector Species	Animal Host(s) Beyond Humans
Human babesiosis	<i>B. microti</i> ,	<i>Ixodes scapularis</i>	Rodents, cattle
	<i>B. divergens</i>	<i>Ixodes ricinus</i>	
	<i>B. duncani</i> (WA1, CA5)	Unknown	
	" <i>B. ventorum</i> " (EU-1)	<i>Ixodes ricinus</i>	
Tick-borne encephalitis	<i>Flavivirus</i> ^a	<i>I. ricinus</i> , <i>I. persulcatus</i>	Rodents, insectivores, carnivores, etc.
Kyasanur Forest disease	<i>Flavivirus</i> ^a	<i>Haemaphysalis spinigera</i>	Monkeys, small mammals, carnivores, birds, cattle
Powassan encephalitis	<i>Flavivirus</i> ^a	<i>Ixodes</i> , <i>Dermacentor</i> , and <i>Haemaphysalis</i> spp.	Rodents, hares, carnivores
Colorado tick fever	<i>Coltivirus</i> ^b	<i>Dermacentor andersoni</i>	Rodents, carnivores, domestic animals
Heartland virus	<i>Phlebovirus</i> ^c	<i>Amblyomma americanum</i>	Possibly raccoons and deer
Severe fever with thrombocytopenia syndrome virus	<i>Phlebovirus</i> ^c	<i>Haemaphysalis longicornis</i>	Goats, wild animals
Bourbon virus	<i>Thogotovirus</i> ^d	<i>Amblyomma americanum</i>	Deer, raccoons
Crimean- Congo hemorrhagic fever	<i>Nairovirus</i> ^c	<i>Hyalomma m. marginatum</i> , <i>H. m. rufipes</i> , others	Hares, hedgehogs, small mammals
Rocky Mountain spotted fever	<i>Rickettsia rickettsii</i>	<i>Dermacentor variabilis</i> , <i>D. andersoni</i> , <i>A. cajennense</i> , <i>Rhipicephalus sanguineus</i> , others	Small mammals, carnivores, dogs, rabbits, others
Boutonneuse fever ^e	<i>Rickettsia conorii</i>	<i>R. sanguineus</i> , <i>D. marginatus</i> , <i>D. reticulatus</i> , others	Small mammals, hedgehogs, dogs
African tick-bite fever	<i>Rickettsia africae</i>	<i>Amblyomma</i> spp.	Mammals, including humans
<i>Rickettsia parkeri</i> rickettsiosis	<i>Rickettsia parkeri</i>	<i>Amblyomma maculatum</i> group ticks	Cotton rats and others, cotton mice, dogs
Pacific Coast fever	" <i>Rickettsia philipii</i> " (364D)	<i>Dermacentor occidentalis</i>	Unknown, likely rodents
Human ehrlichiosis	<i>Ehrlichia chaffeensis</i>	<i>Amblyomma americanum</i> ,	Deer, dogs
Human ehrlichiosis	<i>Ehrlichia ewingii</i>	<i>Amblyomma americanum</i>	Dogs, deer
Ehrlichiosis	<i>Ehrlichia muris eauclairensis</i>	<i>Ixodes scapularis</i>	<i>Peromyscus leucopus</i> , dogs
Human anaplasmosis	<i>Anaplasma phagocytophilum</i>	<i>Ixodes scapularis</i> , <i>I. pacificus</i> , <i>I. ricinus</i> , <i>I. persulcatus</i>	Rodents, deer, dogs
Human anaplasmosis	<i>Anaplasma platys</i>	<i>Rhipicephalus sanguineus</i>	Dogs
Human anaplasmosis	" <i>Anaplasma capra</i> "	<i>Ixodes persulcatus</i>	Goats, sheep
Human anaplasmosis	<i>Anaplasma ovis</i>	<i>Rhipicephalus</i> spp., <i>Dermacentor</i> spp.	Sheep
Neoehrlichiosis	<i>Neoehrlichia mikurensis</i>	<i>Ixodes ricinus</i> , <i>I. persucatus</i>	Rodents, canines, badger, fox
Q fever	<i>Coxiella burnetii</i>	Many tick species	Large domestic livestock
Lyme disease	<i>Borrelia burgdorferi</i> , <i>B. afzelii</i> , <i>B. garinii</i> , <i>B. bissettii</i>	<i>Ixodes scapularis</i> , <i>I. ricinus</i> , <i>I. pacificus</i> , <i>I. persulcatus</i> , others	Mammals, birds

Continued

TABLE 27.2 Representative Tick-Borne Diseases of Public Health Importance and Associated Characteristics (All Tick-Borne Diseases Have Not Been Included)—cont'd

Disease	Causative Agent	Primary Tick Vector Species	Animal Host(s) Beyond Humans
Tick-borne relapsing fever	<i>Borrelia</i> spp.	<i>Ornithodoros</i> spp.	Various mammals
Tularemia	<i>Francisella tularensis</i>	<i>Haemaphysalis leporispalustris</i> , others	Lagomorphs, rodents, carnivores
Tick paralysis	Tick proteins	<i>I. holocyclus</i> , <i>I. rubicundus</i> , <i>D. variabilis</i> , <i>D. andersoni</i> ,	Cattle, sheep, dogs, other mammals, birds, others
Tick-bite allergies	Tick proteins	<i>Argas reflexus</i> , <i>Ornithodoros coriaceus</i> , <i>Ixodes pacificus</i> , etc.	Humans

^aFamily *Flaviviridae*.^bFamily *Reoviridae*.^cFamily *Bunyaviridae*.^dFamily *Orthomyxoviridae*.^eAlso known as *Mediterranean spotted fever*.

cattle and other large mammals in eastern Asia and the Pacific area, and was recently discovered in the United States (New Jersey and at least eight other states). This tick transmits the agent of bovine babesiosis (*B. ovata*) and a more pathogenic version of *T. buffeli*/*T. orientalis* in eastern Asia. Ticks of the *H. leachi* group are vectors of the agent of a severe canine babesiosis (*B. rossi*) in Africa.

The **American dog tick** (*Dermacentor variabilis*) (Fig. 27.13) is a major pest of people and domestic animals throughout much of the eastern and southcentral United States as well as some areas of southeastern Canada. Tick populations generally decline west of the Mississippi River basin, although *D. variabilis* may be locally abundant in some parts of the Midwestern and far western United States. Larvae and nymphs feed on small mammals and birds, but adults attack dogs, other medium-sized mammals, livestock, and humans. Larvae and nymphs are active in late winter and spring, while adults are most abundant in late spring and early summer. This species is the major vector of *R. rickettsii*, the agent of **Rocky Mountain spotted fever**, in the eastern United States. It also transmits the agents of **tularemia** (*Francisella tularensis*) and **anaplasmosis** (*Anaplasma marginale*) and can cause tick paralysis in dogs and humans. In western North America, the closely related **Rocky Mountain wood tick** (*Dermacentor andersoni*) (Fig. 27.14) is an important pest attacking humans, livestock, and wildlife. Adults and nymphs of this tick attack almost any medium-sized or large mammal, whereas larvae feed on small mammals. Adults and nymphs are active in late spring and early summer, while larvae are most abundant in the summer. *Dermacentor andersoni* is the primary vector of *R. rickettsii* and **Colorado tick fever**

virus in this region. It also transmits *Anaplasma marginale*, which causes **anaplasmosis** in domestic ruminants. In the Pacific Northwest, *D. andersoni* is an important cause of **tick paralysis**.

The **Pacific Coast tick**, *Dermacentor occidentalis*, has been associated with spotted fever group rickettsiosis in northern California. A rickettsial species, 364D, provisionally designated "*Rickettsia philipi*" found in these ticks, was shown to be the cause of a febrile illness with eschar formation at the bite site (Padgett et al., 2016).

Dermacentor spp. are also important in Eurasia. *Dermacentor reticulatus* is the main vector of the agents of European canine babesiosis (*Babesia canis*) and equine babesiosis (*B. caballi*); it can also transmit the agent of bovine anaplasmosis. *Dermacentor marginatus* is also an important pest of sheep and may be involved in the epidemiology of Q fever.

Dermacentor nitens (until recently, placed in a separate genus, *Anocentor*), the tropical horse tick, is an important pest of livestock in tropical Central and South America and parts of the Caribbean. It typically infests the ears and is a vector of the agent of equine babesiosis/therileriosis (*Theileria equi* or *B. caballi*).

The **blacklegged tick** (*Ixodes scapularis*) (Fig. 27.15A) is widespread throughout large areas of the eastern, southcentral, and midwestern United States. The species appears to be divided into northern and southern clades, which differ genetically and in behavior. The immature stages usually feed on small mammals, lizards, and birds, while adults are most common on white-tailed deer. All stages of the northern clade of *I. scapularis* will bite humans. Nymphal ticks, the stage most likely to transmit **Lyme disease** spirochetes to people, are active in late spring and early summer. Adults are active in the fall and

TABLE 27.3 Representative Tick-Borne Diseases of Veterinary Importance

Disease	Causative Agent	Primary Tick Vector Species	Affected Host(s)
Bovine babesiosis	<i>Babesia bigemina</i> <i>B. bovis</i>	<i>R. (Boophilus) annulatus</i> <i>R. (B.) microplus</i> , others	Cattle
Canine babesiosis	<i>B. canis</i> , <i>B. rossi</i> , <i>B. vogeli</i> , <i>B. gibsoni</i>	<i>R. sanguineus</i> , <i>Haemaphysalis leachi</i>	Domestic dogs
East Coast fever	<i>Theileria parva</i>	<i>Rhipicephalus appendiculatus</i>	Cattle, Cape buffalo
Tropical theileriosis	<i>T. annulata</i>	<i>Hyalomma</i> spp.	Cattle, water buffalo
Malignant theileriosis	<i>T. lestoquardi</i>	<i>Hyalomma anatolicum</i> , other tick species	Sheep
Feline cytauxzoonosis	<i>Cytauxzoon felis</i>	<i>Amblyomma americanum</i> , <i>Dermacentor variabilis</i>	Domestic and wild cats
Louping ill	<i>Flavivirus</i>	<i>Ixodes ricinus</i>	Sheep, grouse, others
African swine fever	<i>Iridovirus</i>	<i>Ornithodoros porcinus</i> , <i>Ornithodoros erraticus</i>	Domestic and wild pigs, warthogs
Tick-borne fever	<i>Anaplasma phagocytophilum</i>	<i>I. ricinus</i> , <i>I. scapularis</i> , <i>I. pacificus</i> , <i>I. persulcatus</i>	Domestic and wild ruminants, horses, dogs, humans
Canine ehrlichiosis	<i>Ehrlichia canis</i> <i>E. ewingii</i> <i>E. chaffeensis</i>	<i>R. sanguineus</i> , <i>I. ricinus</i> <i>A. americanum</i> , others	Dogs
	<i>E. muris eauclairensis</i>	<i>Ixodes scapularis</i>	Dogs
Heartwater	<i>Ehrlichia ruminantium</i>	<i>Amblyomma hebraeum</i> , <i>A. variegatum</i> , <i>Rhipicephalus (B.) microplus</i>	Ruminants
Bovine ehrlichiosis	<i>Ehrlichia minasensis</i> (<i>Ehrlichia</i> sp. UFMG-EV)	<i>Rhipicephalus (B.) microplus</i>	Cattle
Anaplasmosis	<i>Anaplasma marginale</i> , <i>A. centrale</i> , <i>A. ovis</i>	<i>Dermacentor</i> spp., <i>R. (Boophilus)</i> spp., <i>Hyalomma</i> spp., <i>Rhipicephalus</i> spp.	Cattle, sheep, other ruminants
Borrelioses	<i>Borrelia burgdorferi</i>	<i>Ixodes scapularis</i> , <i>I. ricinus</i> <i>I. pacificus</i> , <i>I. persulcatus</i>	Dogs, cats, cattle, horses, others
Avian spirochetosis	<i>Borrelia anserina</i>	<i>Argas persicus</i>	Turkeys, chickens, other birds
Epizootic bovine abortion	<i>Pajaroellobacter abortibovis</i>	<i>Ornithodoros coriaceus</i>	Cattle, deer
Tularemia	<i>Francisella tularensis</i>	<i>D. andersoni</i> , <i>A. americanum</i> , <i>D. variabilis</i> , others	Sheep, horses, rabbits, game birds
Q fever	<i>Coxiella burnetii</i>	Many tick spp.	Most domestic animals
Tick paralysis	Tick proteins	<i>Ixodes brunneus</i> , <i>I. rubicundus</i> , <i>Rhipicephalus evertsi</i> , <i>D. andersoni</i> <i>D. variabilis</i> , <i>Argas walkerae</i>	Ruminants, other mammals, dogs, wild birds, chickens,
Tick toxicoses	Tick proteins	<i>Ornithodoros savigny</i> , <i>O. lahorensis</i> , <i>A. persicus</i>	Cattle, sheep, birds
Sweating sickness	Tick proteins	<i>Hyalomma truncatum</i>	Cattle, sheep, other ruminants, dogs



FIGURE 27.13 The American dog tick (*Dermacentor variabilis*): (A) female, dorsal view, and (B) male dorsal view. Photograph courtesy of Centers for Disease Control and Prevention.



FIGURE 27.14 The Rocky Mountain wood tick (*Dermacentor andersoni*): (A) female, dorsal view, and (B) male dorsal view. Photograph courtesy of Centers for Disease Control and Prevention.

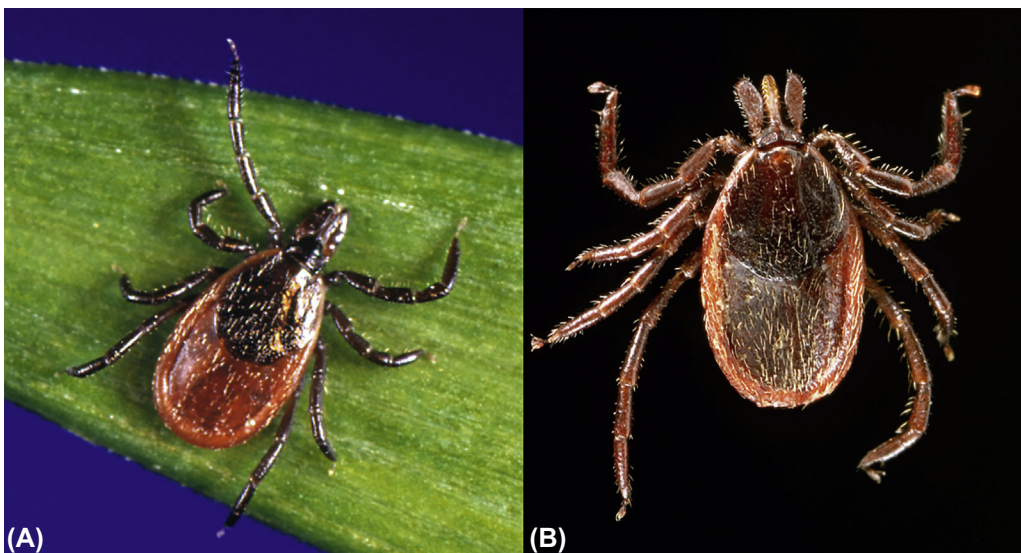


FIGURE 27.15 Important *Ixodes* ticks: (A) the blacklegged tick, *Ixodes scapularis*, female, dorsal view, and (B) the western blacklegged tick, *Ixodes pacificus*, female dorsal view. Photograph courtesy of Centers for Disease Control and Prevention.

early spring (and winter in southern latitudes). Larvae are most abundant in the summer. *Ixodes scapularis* is the primary vector of the Lyme disease spirochete *Borrelia burgdorferi*, and of *B. miyamotoi*, *B. mayonii*, the protozoan *Babesia microti* that causes **human babesiosis**, and *Anaplasma phagocytophilum*, the agent of **human granulocytic anaplasmosis**. More recently, it has been shown to be an important vector of **Powassan virus** (Flaviviridae), sometimes reported as deer tick virus, which causes a severe and occasionally fatal severe encephalitis in humans (Hernance and Thangamani, 2017). It is the only tick recorded to be infected with *Ehrlichia muris euclairensis*, an emerging cause of human ehrlichiosis in the upper midwestern United States (Johnson et al., 2015; Karpathy et al., 2016).

There is increasing evidence that *I. scapularis* in the United States consists of at least two genetic populations, which may account for the significant differences in behaviors. It has long been noted that northern populations of *I. scapularis* feed on rodents, particularly white-footed mice, from which they obtain their *B. burgdorferi* infections. Larval and nymphal *I. scapularis* in the southern United States are mainly found on lizards and are not usually encountered through routine methods used to collect northern *I. scapularis*. While it is common to encounter northern nymphs actively seeking hosts on leaves and twigs above the litter surface, host-seeking nymphs in southern *Ixodes scapularis* populations remain below the leaf litter surface and are rarely encountered during their most active seasons. These behavioral differences potentially result in decreased *I. scapularis* collections using flagging or dragging in southern areas, decreased tick contact with humans, and fewer cases of *I. scapularis*-associated diseases. The **western blacklegged tick**, *Ixodes pacificus* (Fig. 27.15B), is an important vector for *B. burgdorferi* in the western United States. The infection prevalence is generally lower than that seen in *I. scapularis*. Adult *I. pacificus* are primarily active in fall and winter.

In Europe, the **castor bean tick**, or **sheep tick** (*I. ricinus*), is a major pest of livestock and humans. This tick ranges from Ireland, Britain, and Scandinavia across continental Europe to Iran and southward to the Mediterranean Sea. In Britain and Ireland, it is commonly found in overgrown sheep pastures that contain dense mats of moist, rotting vegetation ideal for tick development and survival. On the European continent, *I. ricinus* abounds in mixed hardwood-pine forests and shrubs but rarely in grassy meadows. Larvae and nymphs attack mostly small mammals, insectivores, birds, and lizards. Adults are found most commonly on sheep, other domestic ruminants, and deer. However, this tick may attack virtually any vertebrate, including humans. Seasonal activity varies greatly in different regions throughout the tick's range. *Ixodes ricinus*

transmits the agents of **Lyme disease**, which, in Europe, include *Borrelia burgdorferi*, *B. garinii*, and *B. afzelii*. In addition, *I. ricinus* is the major vector of the virus which causes **tick-borne encephalitis**, and of *Anaplasma phagocytophilum*. In Ireland, Britain, and some other areas of western Europe, *I. ricinus* also transmits the virus, which causes **louping ill** in sheep, and the bacterium, *Staphylococcus aureus*, which causes **tick pyemia** in sheep. It is also a vector of an agent of human babesiosis and is of importance to livestock as the vector of *B. divergens*, which causes bovine babesiosis. Further east it is replaced by the aggressive **taiga tick**, *Ixodes persulcatus*, another major vector of human pathogens.

In Australia, an important species is the **Australian paralysis tick** (*Ixodes holocyclus*). This tick is found along the eastern coast of Queensland and Victoria provinces. It feeds on most wild mammals, domestic animals, and humans. *Ixodes holocyclus* is notorious as the cause of **tick paralysis** in Australia. In contrast to other diseases caused by an infectious microbe, tick paralysis is caused by a proteinaceous material, **holocyclotoxin** in the case of *I. holocyclus*, secreted in the tick's saliva. Even the bite of a single tick may be sufficient to cause a fatal paralysis.

Many species of *Hyalomma* are vectors of *Theileria annulata*, the agent of bovine tropical theileriosis, a major disease of cattle and domestic buffalo in much of Asia, including the Middle East, the Mediterranean basin, parts of southern Europe, and some parts of northern sub-Saharan Africa. The agent of theileriosis virulent to small ruminants, *Theileria recondita*, is also transmitted by *Hyalomma* spp. Important vectors include *H. detritum*, *H. anatolicum*, *H. asiaticum*, and *H. lusitanicum*. In the Mediterranean basin and parts of the former Soviet Union (the Crimea and adjacent areas of the former USSR), an important tick is *Hyalomma marginatum marginatum*. Larvae and nymphs attack hares, hedgehogs, and birds. Adults attack larger mammals, including domestic ruminants and humans. This tick is one of the most important vectors of **Crimean-Congo hemorrhagic fever virus**. In the adult stage, *Hyalomma* spp. infest particularly the perianal area, the perineum, or the tail switch, where they escape visual detection.

The **lone star tick** (*Amblyomma americanum*) (Fig. 27.16) is one of the most notorious tick pest species in the United States. It is found along the Atlantic coast from New York to Florida and west into Texas and Oklahoma. *Amblyomma americanum* larvae, nymphs, and adults readily attack humans and companion animals, as well as livestock and wildlife. Virtually any mammal or ground-feeding bird may be infested. It is often abundant in areas with large populations of deer, which serve as the primary hosts for the adult ticks. In the southeastern United States, nymphs and adults emerge from their winter diapause and commence host-seeking activity in late spring. Larvae generally appear in late summer. Seasonal



FIGURE 27.16 The lone star tick (*Amblyomma americanum*): (left to right) female, dorsal view; male dorsal view; nymph, dorsal view; and larva, dorsal view. Photograph courtesy of Centers for Disease Control and Prevention.

activity may be delayed farther north. *Amblyomma americanum* has been implicated as a vector of the agents that cause **human ehrlichiosis**, that is, *Ehrlichia chaffeensis* and *E. ewingii*, as well as tulararemia (*Francisella tularensis*), *R. rickettsii*, and an endosymbiotic spotted fever group rickettsial species, *R. amblyommatis* (previously “*Candidatus R. amblyommii*”).

Another important species in the United States is the **Gulf Coast tick** (*Amblyomma maculatum*) (Fig. 27.17), which is found in the southeastern and southcentral United States and Central America. Larvae and nymphs attack a wide range of birds and small mammals, but adults feed largely on ruminants. These ticks feed mainly on the head and ears. *Amblyomma maculatum* can cause severe injury to the skin of cattle and other livestock, often rendering the hides useless from the bites of these

ticks or from secondary infections and predisposing to screwworm and severe dermatophilosis. It is an efficient experimental vector of *Ehrlichia ruminantium* that causes heartwater, a major African disease of ruminants, which has been imported into the Caribbean area. *Amblyomma maculatum* group ticks transmit *Rickettsia parkeri* to humans in the eastern and in the southwestern United States (Allerdice et al., 2017).

In Africa, the **bont tick** (*Amblyomma hebraeum*) (Fig. 27.18) and the **tropical bont tick** (*A. variegatum*) attack livestock as well as wild ruminants. In addition, *A. variegatum* larvae and nymphs will parasitize ground-feeding birds, including herons and other migratory birds, and small mammals. *Amblyomma hebraeum* is restricted to southern Africa, but *A. variegatum* ranges throughout most of sub-Saharan Africa, Madagascar and several islands in

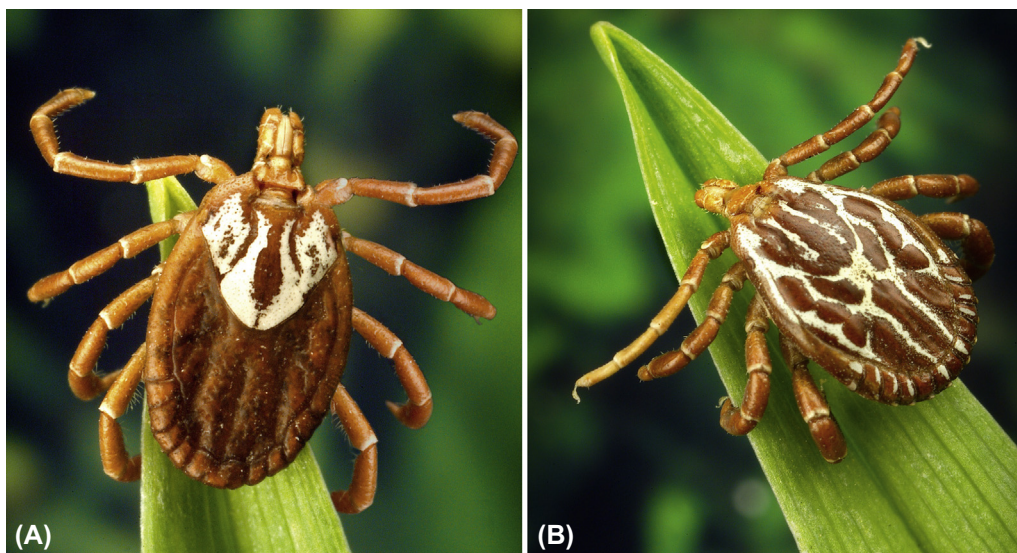


FIGURE 27.17 The Gulf Coast tick (*Amblyomma maculatum*): (A) female, dorsal view, and (B) male dorsal view. Photograph courtesy of James Gathany, Centers for Disease Control and Prevention.



FIGURE 27.18 The bont tick (*Amblyomma hebraeum*): (A) female, dorsal view, and (B) male dorsal view. Photograph courtesy of Centers for Disease Control and Prevention.

the Caribbean. These ticks are the major vectors of *Ehrlichia* (formerly *Cowdria*) *ruminantium*, which causes **heartwater** in ruminants, whereas *A. variegatum* is associated with severe forms of ruminant **dermatophilosis** (see later). They are also vectors of *Rickettsia africae*, the causative agent of an African human disease, which has been inadvertently introduced into the Caribbean.

Arguably the most important livestock tick on a global scale is the one-host **southern cattle fever tick**, *Rhipicephalus* (*Boophilus*) *microplus*. This species, and other members of the subgenus *Boophilus*, can cause large infestations in cattle and other ungulates (Fig. 27.19). The southern cattle fever tick originated in southern Asia but is now also established in Australia, the Pacific area, Mexico, Central and tropical South America, the Antilles, Madagascar, and large parts of eastern and southern Africa, where it has replaced the indigenous tick *Rhipicephalus* (*B.*) *decoloratus*. When present in large numbers, it may

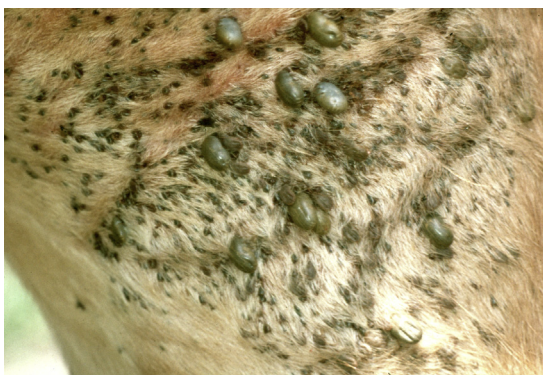


FIGURE 27.19 White-tailed deer heavily infested with ticks, *Rhipicephalus* (*Boophilus*) sp. Courtesy of U.S. Department of Agriculture, Animal Research Service, Kerrville, TX.

cause retarded growth and weight loss. It is even more important as the main vector of *Babesia bovis* and *B. bigemina*, agents of bovine babesiosis, and of *Anaplasma marginale*, which causes anaplasmosis. Other important species are *R. decoloratus* (although it is not a vector of *Babesia bovis*), present in much of sub-Saharan Africa, and *Rhipicephalus* (*B.*) *geigy*, which has replaced it in West Africa. Another species of major importance is the **cattle fever tick**, *Rhipicephalus* (*B.*) *annulatus*, ranging throughout large areas of North and sub-Saharan Africa north of the equator, parts of southern Europe and western Asia, and parts of North America, Central America, and South America. Only intensive surveillance has prevented its reintroduction, as well as that of *R. microplus*, into the United States from tick-infested herds in Mexico. *Rhipicephalus* (*B.*) *annulatus* is active throughout the year in the tropics. This one-host tick feeds almost exclusively on cattle, but it also infests white-tailed and other species of deer. It is a major pest of cattle, causing reduced weight gains and milk production in heavily infested animals. It is best known for its role in the transmission of the protozoan *Babesia bigemina*, which causes **Texas cattle fever**, and as a vector of *B. bovis* and *Anaplasma marginale*.

Among the Argasidae, the **fowl tick** (*Argas persicus*) and related *Argas* spp. are important parasites of poultry in the Old World. All life stages feed on these birds. Populations of this tick can reach enormous numbers in poultry barns and can cause high mortality due to exsanguination. This tick is the vector of the rickettsia *Aegyptianella pullorum* that causes **fowl disease** in domestic fowl. In the Mediterranean region, it is a vector of *Borrelia anserina*, the agent of **fowl spirochetosis**, an important poultry disease. In the New World, a complex of three species (*A. radiatus*, *A. sanchezi*, and *A. miniatus*) supplements the introduced and now established (yet rare)

A. persicus. The Old World diseases are also now known in the New World.

The genus *Ornithodoros* includes several species that live in animal burrows and poorly maintained homes or shelters, where they hide in cracks and crevices of walls, ceilings, and attics. In the western United States, *O. hermsi* often infests mountain cabins and other dwellings. Although rodents that infest dwellings are the principal hosts of *O. hermsi*, humans may be attacked when they enter such dwellings if rodents have been killed or driven out. This tick is notorious as a vector of the **relapsing fever** spirochete *Borrelia hermsii*.

In eastern and southern Africa, the human-biting **African tampan** (*Ornithodoros moubata*) and related species, such as *O. porcinus*, coexist with people and animals in mud huts where the tick hides in the walls. These species are the major vectors of the **relapsing fever** spirochete *Borrelia duttoni*. *Ornithodoros porcinus* may be involved in maintaining the virus of **African swine fever**, cycling between warthogs and ticks. The virus becomes directly contagious when it spreads to domestic pigs, and has subsequently been temporarily introduced to other continents. African swine fever is of major international importance. It has been difficult to eradicate from Spain and Portugal, where it has become established in a local species, *Ornithodoros erraticus*. *Ornithodoros porcinus* also occurs on Madagascar. Another species, *O. sonrai*, is thought to be implicated in the epidemiology of African swine fever in West Africa.

Ornithodoros savignyi is a major pest of camels, other domestic animals, and humans in the drier parts of Africa and southern Asia. Although it is not known to transmit pathogenic organisms, it often occurs in large numbers in the sand of sites where animals and humans congregate (e.g., resting sites, wells, etc.) and may be responsible for loss of blood and bites, which remain painful and itching for long periods.

Another important argasid in western North America is the **spinose ear tick** (*Otobius megnini*). It has become established in India, Madagascar, Kenya, and Turkey. It frequently infests livestock, especially cattle and horses, and most domestic ruminants. *Otobius megnini* also attacks wild ruminants, especially deer, antelope, mountain sheep, and may even bite humans. The larvae and second-stage nymphs feed, whereas the adults do not. This tick feeds in the ears, causing injury to the auditory canal (the nymphs are covered with spines) and secondary infections.

In the central and eastern United States, the bat tick *Carios kelleyi* (Fig. 27.5) has been shown to feed occasionally on human blood and to attack people in bat-infested houses. An erythematous skin rash, presumably due to a reaction to the bite, may occur (Gill et al., 2004).

PUBLIC HEALTH IMPORTANCE

Ticks are of public health significance mainly because of the zoonotic animal disease agents transmitted by them, which include an increasing array of bacterial, viral, and protozoan disease agents (Harwood and James, 1979; Sonenshine, 1993; Goodman et al., 2005). They also are important because their attachments can cause various kinds of dermatoses or skin disorders, such as inflammation, pain, and swelling. Rarely, they invade the auditory canal producing a condition known as **otoacariasis**. Certain species of ticks may cause a flaccid, ascending and sometimes fatal paralysis known as **tick paralysis**. Individuals bitten repeatedly by some ticks may develop allergic or even anaphylactic reactions (Van Wye et al., 1991).

Among the biological factors that contribute to the high vector potential of ticks are their persistent blood-sucking habit, longevity, high reproductive potential, relative freedom from natural enemies, and highly sclerotized bodies that protect them from environmental stresses. Further, the slow feeding behavior of ixodid ticks permits wide dispersal and increases their likelihood of acquiring pathogens during attachment to a host. **Transstadial passage** of microbial disease agents from larva to nymph or nymph to adult commonly occurs in vector ticks; transovarial transmission of many agents occurs in some ticks; and both phenomena contribute to the maintenance and spread of certain tick-borne agents.

Several other biological attributes of ticks also enhance their vector potential. First, pharmacologically active substances present in the saliva of ticks may promote feeding success and aid transmission of microbial agents. For example, the saliva of *I. scapularis* has antiedema, anti-hemostatic, and immunosuppressive properties. Second, ticks imbibe large quantities of blood during each feeding period. Indeed, certain species may increase their body weight by 100-fold or more. This is actually an underestimate of the amount ingested because feeding ticks concentrate the bloodmeal by secreting copious amounts of host-derived fluid back into the host. Third, ticks take multiple bloodmeals during their lifetimes. Those individuals that attain adulthood and that successfully feed as adults feed three (ixodids) or more (argasids) times.

It should be noted that ticks are far more efficient than insects in maintaining microbial agents in their bodies. In ticks, most internal tissues change gradually during development and transstadial survival of pathogens occurs frequently. In holometabolous insects, however, the extensive internal changes that occur during molting seem to have a harmful effect on most microorganisms that cause human disease.

As reviewed by Lane (1994) and Nuttall and Labuda (1994), ticks transmit microbes via several routes,

including salivary secretions (e.g., Lyme disease spirochete, Colorado tick fever virus, the agent of heartwater, and spotted fever group rickettsiae), coxal fluids (certain species of relapsing fever spirochetes), regurgitation (e.g., possibly the spirochetes that cause Lyme disease), and feces (Q fever organisms). A novel type of transmission, **saliva-activated transmission**, occurs in the case of some tick-borne arboviruses (Jones et al., 1992). In this model, one or more proteins secreted in tick saliva potentiate virus transmission. Moreover, this phenomenon seems to be the mechanism underlying “**nonviremic transmission**,” whereby arboviruses are transmitted from infected to uninfected ticks feeding simultaneously on a vertebrate host having no or very low levels of viremia (Nuttall and Jones, 1991; Nuttall and Labuda, 1994). Transmission between co-feeding infected and uninfected ticks, which also has been demonstrated for the Lyme disease spirochete, *Borrelia burgdorferi*, is important epidemiologically for two reasons (Randolph et al., 1996). First, some vertebrates that do not develop systemic infections still can serve as competent hosts for infecting vector ticks, and, second, it adds yet another transmission route for certain tick-borne pathogens. Although some tick-borne agents may be transmitted via two routes (e.g., transmission of certain relapsing fever spirochetes via coxal fluid secretions and by saliva), only one route is usually significant.

The more important tick-borne diseases of public health concern are summarized in [Table 27.2](#). The causative agent, clinical manifestations, ecology, and epidemiology of each of these diseases are discussed next.

Human Babesiosis

Human babesiosis is an emerging disease caused by several species of protozoans in the genus *Babesia*. This genus also contains species of major veterinary importance, as do the related protozoan genera *Cytauxzoon* and *Theileria*. Species in all three genera belong to the family Babesiidae, order Piroplasmorida, and phylum Apicomplexa. They are often referred to as **piroplasms** because they possess pear-shaped, intraerythrocytic merozoites in the vertebrate host. *Babesia* spp. resemble malarial parasites (*Plasmodium* spp.) and other blood-infecting protozoans, especially in regard to their developmental cycles. More information about these important parasites can be found in Schetters and Brown (2006), Suarez and Noh (2011), Beugnet and Moreau (2015), and Solano-Gallego and Sainz (2016). Wilson and Chowning in 1908 were the first to incriminate babesial parasites as a probable cause of human infection among patients with Rocky Mountain spotted fever in the western United States. However, the first definitive case of babesiosis was not described until 1957 in a splenectomized Yugoslavian

cattle farmer who died of a babesial infection following an 8-day illness. In the United States, the disease was initially recognized in a California resident in 1968. To date, less than 100 cases of human babesiosis have been reported from Europe, while cases in the United States have reached over 1,700 cases annually. Sporadic cases occur elsewhere. In the United States, human babesiosis occurs principally along the Eastern Seaboard, especially on Nantucket Island, Massachusetts, and Long Island, New York, where the etiologic agent is *Babesia microti*. Other endemic foci of *B. microti* occur in Connecticut, Minnesota, and Wisconsin. The incidence appears to be increasing in Wisconsin, where 72% of the 32 cases reported from 1996 to 2005 occurred in 2004–2005. In the far-western United States, *Babesia duncani* has been identified in nine patients since 1991 (Conrad et al., 2006). Besides the index case, four of the patients previously had their spleen removed (one died), and two each were blood donors or blood recipients. This piroplasm, formerly designated as the WA1-type *Babesia* in the literature, lies in a distinct clade separable from *Babesia sensu stricto*, *B. microti*, and *Theileria* spp.

At least 70% of the cases in Europe are associated with the cattle piroplasm *B. divergens* (Genchi, 2007). Intriguingly, *Babesia* parasites similar to, but not identical with, *B. divergens* have been detected in three splenic men in Missouri (1992), Kentucky (2001), and Washington State (2002) (Herwaldt et al., 2004). Serosurveys suggest that a low percentage of Europeans ($\leq 3.4\%$) from several countries may be infected with *B. microti*, particularly individuals who engage in higher-risk outdoor activities like forestry. A newer *Babesia* species, *Babesia* sp. EU1, first described in 2003 based on isolates obtained from two splenic men in Austria and Italy, is an emerging zoonosis (Herwaldt et al., 2003). Phylogenetically, this organism is most closely related to *B. odocoilei*, a parasite of white-tailed deer in North America.

In humans, *Babesia* spp. may produce a malarial-like disease without the periodicity that often accompanies the human malarias. Following an incubation period of 1–4 weeks, the clinical course varies according to the etiologic agent and ranges from subclinical infection to a severe disease with sudden onset. Splenectomized persons infected with either *B. divergens* or *B. microti*, or elderly persons infected with *B. microti*, tend to develop severe or sometimes fatal illnesses. Signs and symptoms at onset include fever, chills, profuse sweating, headache, and generalized muscle aches. Joint pain, nausea, vomiting, and prostration may occur. Parasitemia and the resultant clinical course may persist for several months with severe anemia, jaundice, and hemoglobinuria. In many individuals, however, babesiosis is a mild, self-limited disease that requires only supportive therapy. Clindamycin and quinine in combination are the current drugs of choice, but azithromycin and atovaquone in combination are equally

effective in treating babesiosis patients with fewer adverse effects.

With few exceptions, *Babesia* species develop entirely within circulating red blood cells. Sporozoites are introduced via the saliva of a *Babesia*-infected tick during feeding. Once they gain entry into the bloodstream, most parasites develop asexually within red blood cells. Occasionally, *Babesia* invade lymphocytes, and only subsequent generations develop in the erythrocytes. Within the host cell, the parasites develop into **trophozoites** termed **meronts**, which multiply asexually by binary fission to produce **merozoites**. Some of the merozoites escape from the disintegrating host cells to invade other erythrocytes and continue the cycle. Other merozoites develop into gametocytes called **piroplasms** after entering previously uninfected erythrocytes. The gametocytes remain in an arrested state of development until they are ingested by a feeding tick.

When *Babesia*-infected blood is ingested by ticks, the gametocytes commence development, but the asexual stages are destroyed. The gametocytes escape from the dying host cells and transform into gamete-forming cells called gamonts, which develop structures (rays and spines) that are subsequently used to penetrate cells. Following gametic fusion, the resulting zygotes invade the tick's digestive epithelium, develop into motile **kinetes**, and migrate to other internal organs. Some *Babesia* spp., such as *B. divergens* and *Babesia* sp. EU1, invade the female tick's ovaries and are transmitted transovarially to the next generation, whereas others (e.g., *B. microti*) are not passed via the eggs. Instead, immature ticks are infected while feeding on a parasitemic host; the parasites invade the salivary glands, multiply, and are passed transstadially to the next stage.

In the northeastern and upper midwestern United States, *B. microti* is maintained in a transmission cycle involving the blacklegged tick (*I. scapularis*) and the white-footed mouse (*Peromyscus leucopus*). Meadow voles (*Microtus pennsylvanicus*) also are efficient reservoir hosts. Most people who acquire the infection are bitten by nymphal ticks. In the far-western United States the primary tick vector(s) and reservoir host(s) of *B. duncani* have not been identified, but the close similarity of babesial isolates from mule deer with *B. duncani* isolates from humans suggests that large ungulates might serve as reservoirs. In Europe, *I. ricinus* is the primary vector of both *B. divergens* and *Babesia* sp. EU1, whereas *Ixodes trianguliceps* transmits *B. microti* among small mammals (Randolph, 1991, 1994, 1995). The apparent paucity of human *B. microti* infections in Europe may be attributable to the fact that *I. trianguliceps* is a nidicolous tick that seldom attaches to people.

Babesia spp. may be transmitted via two other routes besides tick-feeding: blood transfusion and transplacentally. More than 50 cases of transfusion-associated *B. microti* infections have been reported in North America, and 10 cases of neonatal babesiosis have been published. *Babesia* ranks second only to *Plasmodium* among blood transfusion-acquired parasitic infections. Estimates of the percentages of *Babesia*-infected blood products in certain endemic settings in the United States (e.g., Connecticut, Massachusetts) range between 0.17% and 3.7%.

Tick-Borne Encephalitis Complex

Tick-borne encephalitis complex (TBE) is one of at least 12 related, but distinguishable, serotypes of tick-borne flaviviruses (Family Flaviviridae) that constitute the **TBE complex**. It includes such viruses as **Louping ill**, **Kyasanur Forest disease**, **Omsk hemorrhagic fever**, and **Powassan encephalitis**. Each of these viruses produces a clinically distinctive disease.

First described as **Russian spring-summer encephalitis** (RSSE) in 1932 from the far-eastern region of the former Soviet Union, TBE was recognized after World War II in central Europe, where it was termed central-European encephalitis (CEE). RSSE and CEE are now considered to represent a single entity, TBE, which has been classified into three subtypes (European, Siberian, and far-eastern) that vary in virulence for humans. In 2007, a novel variant of the far-eastern subtype was isolated from the brain of a 15-year-old boy in Primorsky District, Russia, who succumbed to the infection. Grard et al. (2007) proposed that TBE viruses be divided into four types: Western, Eastern, Turkish sheep, and Louping ill.

TBE is endemic in nearly 30 areas of Europe and northern Asian countries, and the incidence is estimated to be as high as 14,000 cases per year, with about 11,000 of them occurring in Russia. However, the number of risk areas across Europe and parts of Asia have increased (Petri et al., 2010). Few arthropod-borne zoonotic agents have received as much scientific scrutiny. In Russia, for instance, researchers published approximately 5,000–6,000 articles and 40–50 monographs on various aspects of TBE during the first 60 years following its discovery (Korenberg and Kovalevskii, 1999). In that regard, it has been estimated that 20,000–30,000 autonomous natural foci, ranging in size from a few square kilometers to several hundred kilometers, exist in Russia.

Illness in humans is accompanied by high, often biphasic, fever and headache, followed soon afterward by inflammation of the brain (encephalitis) and meninges (meningitis). Some patients develop muscle weakness or paralysis, especially in the right shoulder muscles.

Case-fatality rates average about 1%–2% for European strains, 20%–60% for far-eastern strains, and rarely exceed 6%–8% for Siberian strains (Charrel et al., 2004). Although Siberian strains are less lethal than far-eastern strains, they nevertheless tend to cause chronic or prolonged infections.

Fortunately, there are several highly effective, safe, and well-tolerated vaccines commercially available against TBE viruses in Europe and Russia (Petri et al., 2010). The two highly purified, formalin-inactivated, whole-virus vaccines developed in Europe have an overall efficacy of 99% when used in accordance with the recommended vaccination schedule. Notwithstanding, the number of reported cases of TBE increased an astounding 400% in Europe between 1974 and 2003 due to the complex interaction of ecological, economic, social, political, and climatic factors (Kunze et al., 2007). A notable exception has been Austria, which has experienced a dramatic decline in clinical cases as a result of increased vaccination coverage, from approximately 6% in 1980 to 88% of the entire population in 2006. The widespread use of vaccines in Austria from 2000 to 2006 is estimated to have prevented approximately 2,800 cases and 20 deaths from TBE (Heinz et al., 2007). In stark contrast, vaccination coverage in TBE-endemic countries bordering Austria is meager: 11% in the Czech Republic and 13% each in Germany and Switzerland.

Climatic changes may contribute to the geographic expansion or resurgence of some vector-borne diseases. They alone, however, cannot explain the recent upsurge in the incidence of TBE or the pronounced spatiotemporal heterogeneity of the virus in Central Europe and the Baltic Region (Rogers and Randolph, 2006; Randolph and Sumilo, 2007). Anthropogenic impacts on the landscape have allowed tick populations to expand and multiply; changes in human behavior may have resulted in a greater degree of contact with virus-laden ticks; and migrating birds can disperse TBE virus-infected *I. ricinus* ticks (Randolph, 2001; Waldenström et al., 2007). In Estonia, Latvia, and Lithuania, environmental changes resulting from political upheaval and socioeconomic transitional factors following the end of Soviet rule that presumably elevated human contact with infected ticks have been posited to play an important role in the increased incidence of TBE. Among Latvians, harvesting mushrooms and berries, or working in forests has been associated with unemployment, lower incomes, increased forest visitation, and a higher than average risk of being tick-bitten the previous year (Randolph and Sumilo, 2007). Weather conditions also may influence the frequency of forest visits and therefore the degree of tick exposure in this region.

The primary vectors of TBE viruses are *Ixodes ricinus* (European subtype) and *I. persulcatus* (Siberian and

far-eastern subtypes). Other tick species that have been found infected naturally (*Ixodes arboricola*, *I. hexagonus*, *I. trianguliceps*) may amplify viral infection. Although most mammals are susceptible to TBE virus, rodents, especially the bank vole (*Clethrionomys glareolus*), field mice (*Apodemus* spp.), and insectivores are the chief reservoir hosts. Viral amplification and enzootic maintenance occur by means of the seasonally synchronized co-feeding of virus-infected nymphs and large numbers of uninfected larvae during brief periods (2–3 days) of nonviremic infectivity within primary vertebrate hosts (Randolph et al., 1999; Randolph and Sumilo, 2007). Thus, transstadially infected nymphs transmit the virus horizontally to uninfected larvae, which molt up to a year later to produce infected nymphs. This nonviremic route of transmission between co-feeding ticks can even occur in rodents that are immune to TBE virus (Labuda et al., 1997). The principal environmental driver for synchronizing the springtime feeding of larvae and nymphs in TBE foci initially was thought to be a rapid rate of cooling in autumn, corrected for mid-summer maximum temperatures (Randolph et al., 2000). More recent evidence suggests that the rate of spring warming, corrected by January minimum temperatures, is more important in synchronizing larval and nymphal feeding activities than is the rate of autumnal cooling (Randolph and Sumilio, 2007).

Kyasanur Forest disease (Family Flaviviridae, Genus *Flavivirus*) was identified in 1957 from a sick monkey in Kyasanur Forest in Karnataka state, India (Holbrook, 2012). The virus is transmitted by ixodid ticks, especially *Haemaphysalis spinigera*. Once infected, the tick remains infected for life and can transmit the virus both transstadially and transovarially. Mammalian hosts for the tick and virus are rodents, shrews, and monkeys. Infection may cause epizootics with high fatality rates in primates. Exposure to sick or dead animals may also be a risk factor for human infection; person-to-person transmission is not known to occur. After an incubation period of 3–8 days, chills, fever, and headache occur. Severe muscle pain, gastrointestinal distress, vomiting, and bleeding may occur 3–4 days after initial symptoms. Patients may recover after one to weeks of illness, but a subset of patients may have additional fever, severe headache, mental disturbances, tremors, and vision deficits. The estimated case-fatality rate ranges from 3% to 5%. The disease is found in southern India, with about 500 cases per year. More recently, cases have been identified from additional states in the south, west, and east of the country. Similar viruses have been discovered in Saudi Arabia (Alkhurma hemorrhagic fever virus) and China (Nanjianyin virus).

Powassan virus, named after the town in Ontario, Canada, where it was originally isolated from a 5-year-old boy who succumbed to the infection, is a *Flavivirus* (family

Flaviviridae) related to TBE viruses. It was first recognized in scattered localities in the United States, Canada, and in eastern parts of the former Soviet Union. The virus causes a disease known as **Powassan encephalitis** that is characterized in its acute stage by encephalitis, severe headache, and fever. Nausea, labored breathing, and neurologic disorders, including partial paralysis, occur frequently. As many as 50% of recovered patients may suffer permanent nerve damage due to neuronal loss and necrosis and more severe infections can have a case-fatality rate of about 10%. Thirty-one cases were reported from the northeastern United States and Canada from 1958 to July 2001, and incidence has been increasing to approximately 1.9 cases per year between 1999 and 2007 (Ebel, 2010). Cases also have been recorded in Russia (Charrel et al., 2004).

Tick vectors of Powassan virus belong to the genera *Ixodes*, *Dermacentor*, and *Haemaphysalis*. In the United States, isolates of the virus have been obtained from *Ixodes cookei* and *Ixodes marxi* in the east and *Dermacentor andersoni* and *Ixodes spinipalpis* in the west. *Ixodes cookei* feeds on various wild and domestic animals and (rarely) on humans. Marmots (woodchucks) are important hosts of *I. cookei* and are excellent reservoirs of the virus. Similarly, the snowshoe hare amplifies populations of vector ticks and the virus. The virus has been isolated twice from naturally infected foxes, a red squirrel, a white-footed mouse, and a spotted skunk, but the reservoir competence of these species remains to be determined. Antibodies to the virus have been detected in 38 wild and five domestic mammalian

species. *Dermacentor andersoni* is the most important vector in the western United States and Canada. In the former Soviet Union, the virus has been isolated from *Haemaphysalis neumanni*, *I. persulcatus*, and *Dermacentor silvarum* and from mosquitoes. *Apodemus* spp. mice and *Microtus* spp. voles are the primary vertebrate hosts in the Eastern Hemisphere (Charrel et al., 2004).

In the northeastern United States, a genotype of Powassan virus (known as lineage II) identified during the 1990s is also called **deer tick virus** (DTV). This lineage is maintained in white-footed mice in the northeastern and upper midwestern United States and is transmitted by *Ixodes scapularis*. In the laboratory, 90% of *I. scapularis* larvae acquired DTV from needle-inoculated mice; the efficiency of transstadial passage was 22%; and the resultant nymphs transmitted the infection to naïve mice after having been attached for as few as 15 min. Clinical disease in humans attributable to DTV was reported in 2001. Clinical features included fever, fatigue, double vision, and weakness, with progressive neurological involvement. Two deaths have been reported in the literature (Ebel, 2010).

Colorado Tick Fever

Colorado tick fever (CTF) is caused by a *Coltivirus* in the family Reoviridae (Fig. 27.20A). Coltiviruses were formerly divided into two subgroups, A and B, based on their genetic relatedness. North American and European

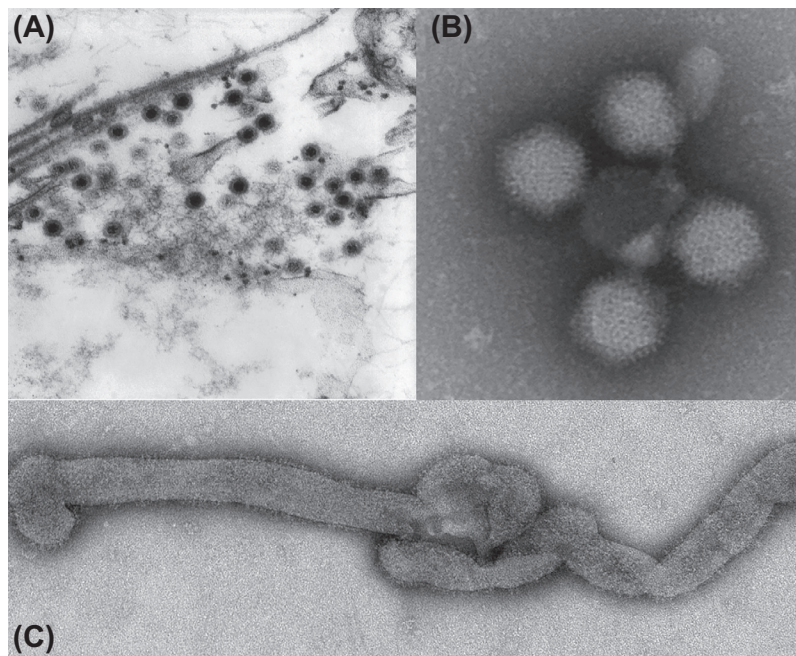


FIGURE 27.20 Electron micrographs of some tick-borne viruses: (A) Colorado tick fever virus, genus *Coltivirus*; (B) Heartland virus, genus *Phlebovirus*; and (C) Bourbon virus, genus *Thogotovirus*. Courtesy of Centers for Disease Control and Prevention.

species were placed in subgroup A, and Asian species in subgroup B (Marfin and Campbell, 2005). In 2000, researchers proposed that subgroup B coltivirus were sufficiently distinct to warrant inclusion in a separate genus, *Seadornavirus*. Subgroup A coltivirus currently comprise four antigenically related viruses: CTF virus in western North America; Salmon River virus in Idaho, USA; **Eyach virus** in the Czech Republic, France, and Germany; and “California hare coltivirus” in the United States (Attoui et al., 2005). The latter virus was isolated first from a western gray squirrel in 1965, and a similar if not identical virus was isolated 11 years later from a black-tailed jack rabbit (Lane et al., 1982). Notably, these isolates originated in either northwestern or westcentral California, far outside the distributional ranges of the primary mammalian hosts of CTF virus and of the Rocky Mountain wood tick (*Dermacentor andersoni*), the primary bridge vector to humans. Furthermore, this virus is the only one of the subgroup A coltivirus that has not been associated definitively with human illness.

Symptoms of CTF usually appear within 4 days (range, 1–14 days) following the attachment of an infected tick. The disease is characterized by a biphasic fever, chills, headache, generalized musculoskeletal aches, and malaise. Some patients experience eye pain, intolerance of light, chills, sore throat, and nausea. The virus develops in most internal organs and may spread to the brain or bone marrow. Although CTF sometimes is depicted as a mild febrile illness, acutely ill patients usually are bedridden, and as many as 14% require hospitalization (Marfin and Campbell, 2005). Convalescence may be prolonged, with some patients taking several weeks to recover. Case-fatality rates are very low, usually less than 0.2%, and all reported deaths have involved children. Early in the course of disease, CTF may be mistaken for Rocky Mountain spotted fever because up to 12% of CTF patients develop a maculopapular or petechial rash.

In endemic regions, people engaged in outdoor activities in mountainous or highland areas from about 4,000 ft to over 10,000 ft (1,219–3,048 m) are at risk of exposure to virus-infected ticks. In Rocky Mountain National Park, Colorado (USA), natural foci occur on south-facing slopes covered with open stands of pine and shrubs on dry, rocky surfaces. Cases are reported from March to November, but most occur in the spring and early summer when adult and nymphal ticks are active. The distribution of CTF approximates that of *D. andersoni* in western North America. The virus has been isolated from ticks, humans, or both from parts of the United States and Canada. In the United States, 476 (61%) of 777 cases reported to 12 state health departments between 1987 and 2001 were contracted in Colorado, with Utah (n = 122) and Montana

(n = 106) ranking second and third (Marfin and Campbell, 2005). Risk factors for the disease include being male, 10–49 years of age, and occupational or recreational exposure at higher elevations (1,200–3,000 m) in the Rocky Mountains or other endemic mountainous areas of the western United States. Transfusion-associated CTF has been reported.

CTF virus is passed efficiently from stage-to-stage in *D. andersoni* ticks, but transovarial passage does not occur. Therefore, the virus is maintained horizontally as host-seeking nymphs, previously infected while feeding as larvae on viremic hosts, attach to and infect susceptible small mammalian hosts. The virus has been isolated from *D. albipictus*, *D. occidentalis*, *D. parumapertus*, *Haemaphysalis leporispalustris*, *Ixodes sculptus*, *I. spinipalpis*, and *Otobius lagophilus*. Larvae and nymphs of *D. andersoni* feed on small mammals, especially ground squirrels, mice, and rabbits. Nymphs, which quest higher in vegetation than larvae, also attack larger mammals such as small carnivores and occasionally humans. Important hosts of the immatures include golden-mantled ground squirrels, deer mice, bushy-tailed woodrats, chipmunks, and rabbits. Adults parasitize larger mammals, such as porcupines, elk, deer, antelope, carnivores, and humans. Competent reservoir hosts include the golden-mantled ground squirrel, least chipmunk, deer mouse, bushy-tailed woodrat, and porcupine. Viremia in amplifying hosts may persist for weeks or months, and possibly even longer in hibernating mammals. In the latter case, overwintering hosts may serve as a source of infection for uninfected immature ticks the following spring (Marfin and Campbell, 2005).

Eyach virus, which was isolated for the first time from *I. ricinus* ticks in Germany in 1976, is antigenically related to, but distinct from, CTF virus (Charrel et al., 2004). Additional strains of the virus were isolated from *I. ricinus* and *I. ventralloi* ticks in France in 1981. Serologic surveys demonstrated that Eyach virus occasionally infects people in France and the former Czechoslovakia and may cause encephalitis and polyradiculoneuritis in some patients. The transmission cycle has not been defined, but the primary reservoir is believed to be the European rabbit (Charrel et al., 2004).

Crimean-Congo Hemorrhagic Fever

Crimean-Congo hemorrhagic fever (CCHF) is caused by a negative-stranded RNA virus in the genus *Nairovirus*, Family Bunyaviridae (Bente et al., 2013; ICTV, 2017). The disease was first identified in 1944 and later in 1969, as the two locations led to the hyphenated geographical name. *Hyalomma* spp., especially *H. marginatum*, serve as

reservoirs and vectors for the CCHF virus. Ticks maintain the virus transstadially and transovarially. Additional ixodid tick species within the genera *Amblyomma*, *Dermacentor*, *Haemaphysalis*, *Ixodes*, and *Rhipicephalus* have been found infected naturally or experimentally, but *Hyalomma* spp. ticks are the main vectors to humans. Domestic livestock can serve as amplifying hosts, while hares and hedgehogs may serve as wildlife hosts for immature ticks. Interestingly, there is no evidence that the virus causes illness in non-human animals. The disease is found in about 30 countries in eastern and southern Europe, the Mediterranean region, China, central Asia, the Middle East, India, and Africa. More recently, large numbers of cases have been reported from Turkey. People at risk include livestock workers, animal handlers, and slaughterhouse workers, and case reporting has increased. Healthcare workers in endemic areas can also become infected through contact with body fluids. Clinical illness includes headache, high fever, back pain, joint pain, stomach pain and vomiting. Changes in mood and sensory perception may be seen in more severe cases. Petechiae in the palate, severe bruising, uncontrolled bleeding and nosebleed may begin on about the fourth day of illness and last for up to 2 weeks. Case fatality rates of 9%–50% have been observed in hospitalized patients. Treatment is mainly supportive, although ribavirin may provide additional benefit.

Severe Fever and Thrombocytopenia Syndrome Virus

Severe fever and thrombocytopenia syndrome virus (SFTSV) was first identified as a cause of severe illness and death in China in 2007 (Mansfield et al., 2017). The virus is a member of the genus *Phlebovirus*, Family Bunyaviridae (ICTV, 2017). Isolation of the virus from patients confirmed the etiology in patients and additional cases began to accumulate. Clinical signs include fever, vomiting, diarrhea, thrombocytopenia, leukopenia, and multiple organ failure. The case-fatality of SFTSV infections has been estimated to be 6%–30% (Liu et al., 2014). Since its first recognition, the disease has been identified in other provinces of China, Japan, and South Korea. Ecological studies have shown that *Haemaphysalis longicornis* is the primary vector, with infection rates of 2%–5%. Goats, cattle, dogs, pigs, and chickens are naturally exposed to the virus, but goats and other livestock may be important amplifying hosts contributing to human epidemiology. Many wildlife species have shown serological evidence of exposure, and certain rodents have been found to be infected.

Heartland Virus

Heartland virus was first isolated from two male patients in northwestern Missouri (McMullan et al., 2010). This virus is also in the genus *Phlebovirus*, Family Bunyaviridae (Fig. 27.20B). They had been bitten by lone star ticks, *Amblyomma americanum*, from which the virus was subsequently isolated (Savage et al., 2013, 2017). Fever, headache, fatigue, and mental stupor were seen in both patients. Both men recovered with supportive care, as have other people shown to be infected by laboratory testing. Three patients (from Oklahoma, Tennessee, and Georgia) died. The virus has been found in a low number of nymphal and in lower numbers of adult *A. americanum* ticks. Raccoons and white-tailed deer are suspected amplifying hosts based on serology (Bosco-Lauth et al., 2015; Riemersma and Komar, 2015). The virus is the first phlebovirus identified from the Western Hemisphere and is most closely related to SFTSV. Additional epidemiologic investigations are needed to better characterize the clinical spectrum of disease.

Bourbon Virus Disease

During laboratory studies of the Heartland virus, plaque neutralization assays showed abnormal plaques from patients suspected of having Heartland viral disease (Kosoy et al., 2015). Subsequent genetic characterization identified a new virus, designated Bourbon virus (from the locality of Bourbon Co., Kansas, USA). This virus belongs to the genus *Thogotovirus* in the family Othromyxoviridae (Fig. 27.20C). Unfortunately, the index case patient died of the infection. Studies are underway to determine the prevalence of this new disease, but it appears to be uncommon. In 2017, a death in eastern Missouri was confirmed to be a consequence of Bourbon virus. The virus has been identified from *A. americanum* ticks collected in another part of Missouri, so the full range of this virus is still to be determined (Savage et al., 2017).

Rocky Mountain Spotted Fever

This disease was first recognized in the Bitterroot Valley of western Montana in 1872. Rocky Mountain spotted fever (RMSF) is widely distributed throughout most of the United States and, to a lesser extent, in Canada and Central and South America. In the United States, the disease was recognized only in the West until the 1930s when cases were detected for the first time in the east. Since 1985, about 600–800 cases of RMSF have been reported yearly with an annual national incidence ranging from 0.24 to 0.32 per 100,000 population. Most cases now occur east of the

Mississippi River in the southcentral and southeastern states, especially along the Atlantic coast (Fig. 27.21). Cases tend to occur in foci in rural areas and suburban communities near major population centers. In the southeastern states, the seasonal peak of reported cases typically occurs in July, coincident with, or shortly after, the period of peak abundance of adult *D. variabilis*. In the northeastern states, the peak is usually in May or early June, although a bimodal pattern may occur in this region.

RMSF is caused by a rickettsia of the spotted fever group, *Rickettsia rickettsii*, an intracellular bacterium that multiplies freely in the cytoplasm and occasionally in the nuclei of host cells. It can cause a severe disease of the circulatory system with significant mortality in untreated or inappropriately treated cases. Rickettsiae multiply in the endothelial linings of capillaries, smooth muscle of arterioles, and in other blood vessels (Fig. 27.22B). After an incubation period of about 7 days, patients develop fever, intense headaches, joint pain, muscle aches, nausea, and other symptoms. While dermatologic features may not appear until later in the disease course, a characteristic **maculopapular rash** (Fig. 27.22A) occurs in most patients several days after onset of symptoms. It consists of many tiny, pink or reddish spots, some of which may coalesce.

The rash first appears on the hands and feet, gradually spreads to cover the entire body, and may persist for a week or longer. This particular pattern of progression is an important clinical feature of RMSF and helps to distinguish it from rashes produced by other vector-borne disease agents, such as epidemic typhus and allergic reactions. However, the extent of the rash indicates further progression of the disease and increasing severity. Severe cases may culminate in delirium or coma. Death can occur at any time during the acute clinical phase as a result of renal failure, clotting within blood vessels, shock, or encephalitis. Currently, 2%–5% of RMSF patients in the United States may die despite the availability of effective antibiotic therapy. Even treated patients may die, primarily due to delayed or inappropriate treatment.

Rickettsia rickettsii is transmitted by the bite of ixodid ticks. In the United States and Canada, *D. variabilis* (Fig. 27.13) and *D. andersoni* (Fig. 27.14) are the primary vectors. The elegant, pioneering work of **Dr. Howard T. Ricketts** at the turn of the 20th century elucidated the role of *D. andersoni* and its vertebrate hosts in the transmission cycle of *R. rickettsii*. Ricketts detected the agent in wild-caught ticks, and demonstrated experimentally that *D. andersoni* could transmit it to susceptible laboratory and

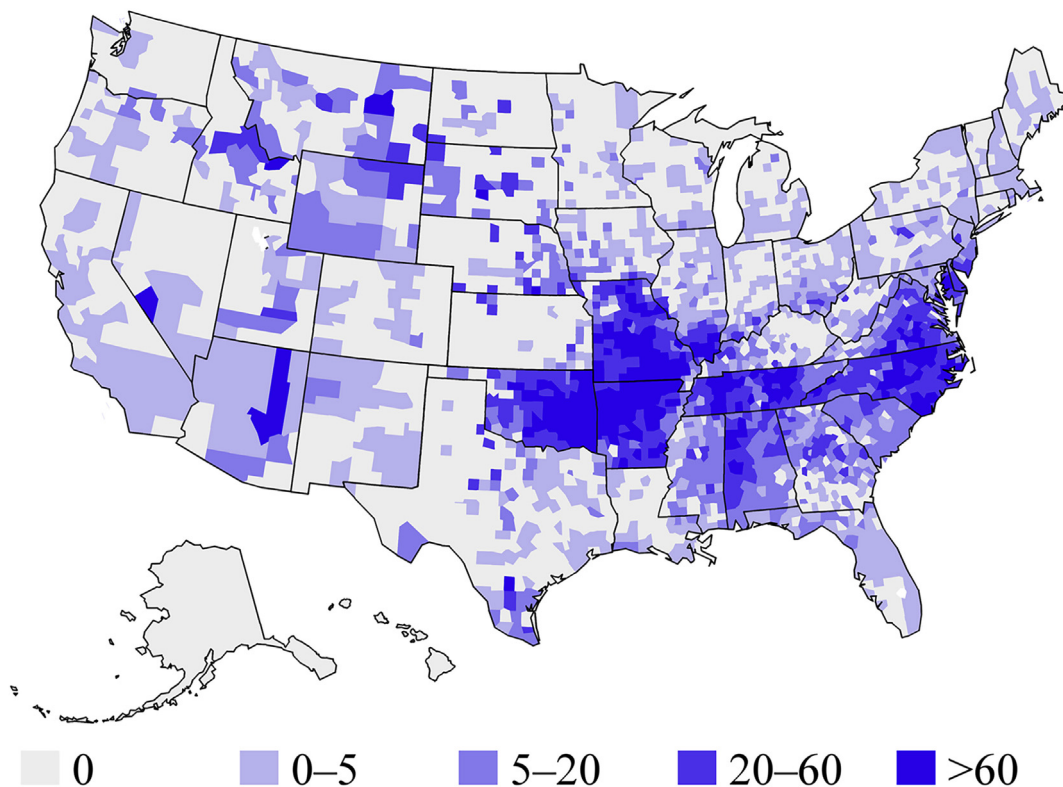


FIGURE 27.21 Reported incidence rate of spotted fever rickettsiosis, by county—United States, 2000–2013. *Per 1,000,000 persons per year. Courtesy Rickettsial Zoonoses Branch, Centers for Disease Control and Prevention.

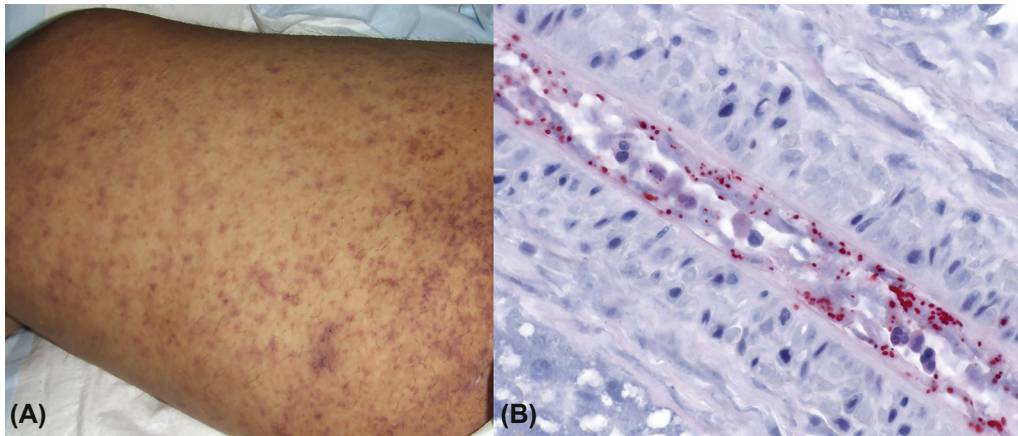


FIGURE 27.22 Rocky Mountain spotted fever (RMSF): (A) maculopapular rash with central petechiae associated with RMSF and (B) *Rickettsia rickettsii*, stained red by immunohistochemistry, in blood vessel endothelial cells. Courtesy of Christopher D. Paddock, Centers for Disease Control and Prevention.

wild rodents by the bite. Further, he showed that *R. rickettsii* is passed transstadially and transmitted transovarially within populations of ticks. His contributions laid the foundation for subsequent studies of tick-borne zoonotic agents in the United States and abroad.

Dermacentor variabilis is abundant throughout eastern North America, but it has a much more limited distribution in the West where it is not known to transmit *R. rickettsii*. In contrast, *D. andersoni* is restricted to western North America. The immature stages of both tick species feed on rodents and other small mammals, while the adults attack larger mammals, including people.

In 2003, cases of RMSF were reported from southeastern Arizona, which had previously reported few cases. Subsequent investigation showed an annual human incidence 300 times that anywhere else in the United States. The brown dog tick (*Rhipicephalus sanguineus*) (Fig. 27.12) was implicated as the vector (Demma et al., 2005b). The nymphal stage was identified as the likely vector to humans. *Rickettsia rickettsii* infection rates in the ticks reached 10% at the home of a fatal case and was 4% overall. High numbers of ticks were documented in the peridomestic environment but were rarely found in dwellings. The tick numbers were associated with the lack of control measures and an excessive stray or free-roaming dog population in the affected communities. Since then, cases continue to be reported from Arizona (Drexler et al., 2017). By the 2000s, RMSF cases were reported from northern Mexico and now number hundreds of cases, with fatalities primarily in children (Alvarez-Hernandez et al., 2017). In retrospect, Parker and coworkers (1933) knew that this species had been shown to transmit this pathogen to humans in Mexico, and conducted studies to demonstrate that *R. sanguineus* is a very efficient vector in experimental infections. Other tick species that help to maintain *R. rickettsii* in nature include *H. leporispalustris*, which

feeds on birds and rabbits, and *Ixodes texanus*, which feeds on raccoons. The lone star tick, *A. americanum* (Fig. 27.16), has been found infected naturally at high rates with **spotted fever group rickettsiae**, *R. amblyommatis*, which were believed to be nonpathogenic for humans. However, recent studies have suggested that a mild illness may result from bites of this tick and that serologic evidence can develop after such bites. Although *A. americanum* is suspected as a vector of RMSF rickettsiae and is capable of laboratory transmission (Parker et al., 1933; Levin et al., 2017), especially in endemic areas outside the distribution of *D. variabilis*, it is not considered to be a primary vector of *R. rickettsii*. In Central America and South America, various species of *Amblyomma* (*A. cajennense*, *A. mixtum*, *A. sculptum*, *A. patinoi*, *A. aureolatus*, *A. tonelliae*, and *A. tenellum*) have been implicated as vectors of *R. rickettsii* or closely related rickettsiae.

Larval and nymphal ticks maintain the infection from year-to-year and infect susceptible rodents when the ticks emerge to feed in the spring. Infected ticks must remain attached for at least 10 h before transmission can occur; this is known as the **reactivation phenomenon**. The delay in transmission is due to the fact that *R. rickettsii* seems to be in an avirulent state in unfed ticks and the rickettsiae become virulent only after prolonged attachment of the tick to its host or following ingestion of blood by ticks.

Most humans who contract RMSF are infected by the bite of adult ticks in late spring or summer, although nymphs occasionally transmit the infection. Only about 1%–3% of adult *Dermacentor* ticks in most foci are infected with spotted fever group rickettsiae, a small proportion of which are *R. rickettsii*. As previously noted, *Rhipicephalus* may show much higher prevalences of specific *R. rickettsii* infection. Ticks can be assayed for evidence of rickettsial infection by examination of their

hemolymph using immunofluorescence assays (IFAs). However, precise estimates of tick-infection prevalences with *R. rickettsii* are complicated by the potential presence of nonpathogenic spotted fever group rickettsiae, such as *Rickettsia montanensis*, *R. bellii*, and *R. rhipicephali*. IFA tests that employ species-specific monoclonal antibodies can resolve these. However, polymerase chain reaction (PCR) assays and nucleotide sequencing have provided more reliable means for determining tick infection prevalences and have largely replaced other methods.

Culture isolations of *R. rickettsii* have been made from numerous small and medium-sized wild mammals. Species that have been implicated as natural reservoirs include meadow voles and deer mice. In these animals, there are few if any obvious signs of clinical disease during infection. Young dogs in certain areas may also serve as short-term reservoirs for the pathogen and contribute infected ticks to the environment.

The period when rickettsiae are present in the blood of reservoir hosts is usually brief, often less than a week. Ticks feeding on infected animals may acquire rickettsiae, which produce generalized infections in tick tissues. In western North America, people normally become infected when they enter tick-infested habitats while engaged in outdoor activities in rural areas. In eastern North America, humans acquire their infections both in rural and peridomestic settings because dogs, which are significant hosts of adult *D. variabilis*, carry infected ticks into the home environment. Dog ownership is often noted as a risk factor in human cases.

Boutonneuse Fever

Boutonneuse fever, also known as Indian tick typhus, Kenya tick typhus, Crimean tick typhus, Marseilles fever, Mediterranean spotted fever, and Mediterranean tick fever, shares many features with Rocky Mountain spotted fever. However, the causative agent, *Rickettsia conorii*, does not occur in the Americas. It has an extensive range in southern Africa, India, central Asia, the Middle East, Europe, and North Africa. Patients with Boutonneuse fever develop fever, chills, severe headaches, and a rash. In addition, a button-like (=boutonneuse) ulcer called an **eschar** or a **tache noir** usually forms at or near the site of tick attachment (Fig. 27.23). The disease is generally milder than Rocky Mountain spotted fever, and most patients recover without antibiotic treatment. However, strains vary in virulence, and one that occurs in Israel has caused severe illness and several deaths. In temperate regions, cases of Boutonneuse fever are most common in late spring and summer, coincident with the seasonal activity of the primary tick vectors.

Rickettsia conorii is transmitted by several species of ixodid ticks in six genera (*Amblyomma*, *Dermacentor*,

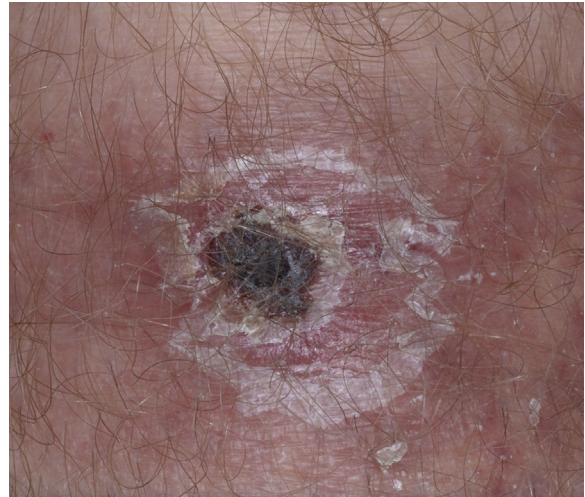


FIGURE 27.23 An eschar or tache noir lesion, may develop at the site of tick bite with infection by certain spotted fever group rickettsiae. Courtesy of Christopher D. Paddock, Centers for Disease Control and Prevention.

Haemaphysalis, *Hyalomma*, *Ixodes*, *Rhipicephalus*). In Europe, *Dermacentor reticulatus*, *D. marginatus*, and *I. ricinus* are important vectors. *Rhipicephalus sanguineus* is the principal vector in southern Europe, the Middle East, and North Africa, especially in countries bordering the Mediterranean Sea. Larvae and nymphs of *R. sanguineus* feed on small mammals, especially rodents and hedgehogs, whereas the adults feed mainly on larger mammals including humans. Lagomorphs, rodents, and possibly birds can serve as reservoir hosts. Dogs are susceptible to infection and transport vector ticks into and around human domiciles. Development of *R. conorii* within populations of ticks is similar to that of *R. rickettsii* in *D. andersoni* and *D. variabilis*.

Separate subspecies of *R. conorii* have been shown to cause human disease in Israel, Sicily, and Portugal (Israeli spotted fever) and areas surrounding the Caspian Sea and in Chad (Astrakhan spotted fever) (Parola et al., 2005).

Other Spotted Fever Group Rickettsiae

African tick bite fever (also called South African tick typhus) is caused by *R. africae*. The clinical features are similar to those of Boutonneuse fever, but multiple eschars are more likely with this infection. This species is responsible for much of the imported spotted fever group rickettsial infections from sub-Saharan Africa and has been identified as established in the French West Indies. The pathogen is transmitted by ticks of the genus *Amblyomma*.

Additional rickettsioses are summarized by Parola et al. (2005) and will not be discussed at length here. *Rickettsia sibirica* may cause Siberian spotted fever and certain subspecies may cause lymphangitis-associated rickettsiosis or

tick-borne lymphadenitis (also known as *Dermacentor*-borne necrosis—erythema—lymphadenopathy). *Rickettsia aeschlimannii* has infected patients in Morocco in South Africa, *R. massiliae* causes illness in Spain, Italy, Canary Islands, and Argentina, while *R. helvetica* has been identified in humans from France and Sweden.

Queensland tick typhus is caused by *R. australis* and is found along the eastern coast of Australia. *Rickettsia honei* is found on Flinders Island near Tasmania (Flinders Island spotted fever), Thailand, and elsewhere. **Japanese spotted fever** is caused by *R. japonica* in southwestern Japan.

***Rickettsia parkeri* rickettsiosis** (also called tidewater fever) is caused by *Rickettsia parkeri*. Although the organism had been identified over 60 years earlier, *R. parkeri* was first reported as a human infection in 2004 (Paddock, 2005). Human infection is characterized by clinical findings similar to, and possibly confused with, RMSF. However, an eschar at the bite site with a maculopapular rash provides evidence of possible *R. parkeri* infection. Cases of the infection have been confirmed in the eastern United States inland to Virginia and, with newly identified cases from the southwestern United States (Allerdice et al., 2017). Infection by *R. parkeri* is associated with bites of the Gulf Coast tick, *Amblyomma maculatum* (Fig. 27.17), in which field studies have demonstrated infection by the rickettsiae.

Pacific Coast tick fever, caused by a novel rickettsial organism (provisionally designated 364D and later as “*Rickettsia philipii*”), was first described from California patients in 2008. The disease is characterized by one or multiple eschars, fever, and headache. It is transmitted to humans by the tick *Dermacentor occidentalis*. Larval, nymphal, and adult ticks have been found infected in nature, but the roles of various wildlife hosts for the tick have not been determined (Padgett et al., 2016).

Human Ehrlichiosis

Ehrlichiae are obligate intracellular organisms in the Family Anaplasmataceae that invade the cells of the vertebrate hematopoietic system. Several species in the genus *Ehrlichia* are important to human and veterinary health and grow within cytoplasmic vacuoles of monocytes, granulocytes, lymphocytes, or platelets. On infection of a cell, the ehrlichiae divide by binary fission to form microcolonies, known as **morulae**; cells may contain one or many morulae (Fig. 27.24). Although they are not commonly detected in routine examination of stained peripheral blood smears, the presence of morulae is helpful in presumptive diagnosis. Specific PCR assays and cell culture provide useful diagnostic methods.

Human infection by Anaplasmataceae was first described in Japan in the 1950s. The etiologic agent,

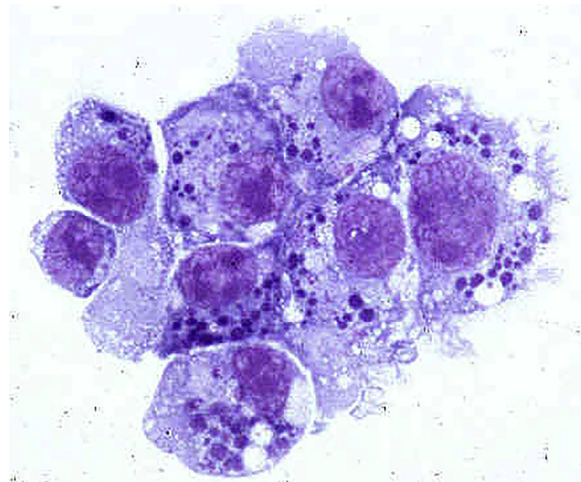


FIGURE 27.24 *Ehrlichia chaffeensis* growing as microcolonies, or morulae, in a cultured canine monocytic cell line (DH82), Wright–Giemsa stain. Courtesy of Rickettsial Zoonoses Branch, Centers for Disease Control and Prevention.

Neorickettsia sennetsu, is transmitted to humans by an unknown mechanism, but ingestion of infected fish parasites is suspected. In the United States, human ehrlichiosis was first recognized as a febrile illness following a tick bite. Investigations of the disease in different parts of the world have found multiple species causing human disease. These organisms were reclassified into the family Anaplasmataceae in 1999, so that currently members of three genera and one proposed genus are recognized as human pathogens.

Ehrlichia chaffeensis is primarily found in the southeastern and southcentral United States, although there is evidence of wider distribution of this or similar agents. This species primarily invades the monocytic leukocytes (Fig. 27.24). The disease, originally called **human monocytic ehrlichiosis**, manifests as an acute illness with high fever, severe headaches, aching muscles and joints, and other nonspecific signs and symptoms. A rash is not common but may occur in about 20%–30% of younger patients. The disease can be mild, although many patients may require hospitalization. Severe cases can occur and may result in death, especially in those with compromised immune systems. Many cases of *E. chaffeensis* infection have been reported since its recognition, with 4,613 cases during the period 2008–2012 (Nichols Heitman et al., 2016). The primary vector for *E. chaffeensis* is *Amblyomma americanum* (Paddock and Childs, 2003; Childs and Paddock, 2003). This tick species feeds readily on many animals, including white-tailed deer, which serve as a reservoir for the ehrlichiae and an important host for the tick. Other wild and domestic animals have been identified as potential reservoirs based on serologic, cultural, and molecular studies.

Ehrlichia ewingii was first detected in granulocytes of human patients from Missouri in 1999 (Buller et al., 1999). Since then, additional cases have been reported, primarily in immunocompromised patients (Nichols Heitman et al., 2016). The etiologic agent has been recorded from several southern states where it was known to be a cause of illness in dogs. Experimental and field studies have determined that *Amblyomma americanum* is the primary vector of this organism. The reservoir for the pathogen is not known, but the organism has been identified in white-tailed deer. Other reservoirs may include wild or domestic canines.

Recently, *E. muris euclairensis* (also known as the *Ehrlichia muris*-like agent), was detected in both people and dogs in the upper midwestern United States. The blacklegged tick, *I. scapularis*, was identified as the primary vector in experimentally infected and field-collected ticks. The organism has been detected in white-footed mice from endemic areas. More than 70 patients have been reported, and all resided in or traveled to Minnesota or Wisconsin (Johnson et al., 2015). Ticks removed from military personnel in other parts of the country have not been infected (Stromdahl et al., 2015). The main symptoms are fever and malaise, and successful treatment may be achieved with doxycycline.

Human Anaplasmosis

Human granulocytic anaplasmosis is caused by *Anaplasma phagocytophilum*, and this infection is widely distributed in temperate areas of North America, Europe, and Asia (Nicholson, 2018; Goodman et al., 2005). The pathogen resides in vacuoles in the cytoplasm of infected granulocytic cells (neutrophils and eosinophils) and replicates as microcolonies known as **morulae**. The number of cases reported in the United States has increased each year, with 8,896 cases reported in the period 2008–2012 (Dahlgren et al., 2015). The number of human cases in Europe or Asia has not been as high, but reports are increasing there as well.

Human disease manifests as fever, headache, chills, malaise, myalgia, and nausea in most patients. Vomiting, diarrhea, cough, arthralgia, and confusion are less common features of the infection. Rash is infrequently noted. Leukopenia, thrombocytopenia, and elevated hepatic enzymes may be found in clinical laboratory studies. Anaplasmosis cases reported to national surveillance systems have been increasing over the last several years. Severe complications are uncommon, but may be more frequent in elderly patients or patients with compromised immune systems. Complications due to delayed or inappropriate treatment may occur in patients coinfecting with other tick-borne pathogens. More than a third of

anaplasmosis patients require hospitalization, and <1% can die. These infections respond well to doxycycline treatment.

In the United States, the pathogen is transmitted to humans and domestic animals by the blacklegged tick *Ixodes scapularis* in the eastern and upper midwestern states and by *Ixodes pacificus* in northern California and other far western states. Local enzootic transmission is also known to occur among small mammals in certain areas by host-specific enzootic vectors (e.g., *Ixodes spinipalpis* among woodrats). In Europe, *Ixodes ricinus* serves as the primary tick vector, while *I. persulcatus* is the main vector in Asia. The pathogen is passed transstadially, but not transovarially in the ticks. A wide range of wildlife hosts in each geographic area provide blood-meals to the ticks and may serve as reservoirs for the bacteria. In the United States, *Peromyscus leucopus* mice, *P. maniculatus* mice, *Neotoma* spp. woodrats, and various squirrel species have been demonstrated as reservoirs, but the maintenance in nature may be more complex as multiple wildlife species have been found to be infected in various parts of the world (Nieto and Foley, 2008). Domestic animals may also be infected and show clinical signs. *Anaplasma phagocytophilum* infection in ruminants was known for many years as tick-borne fever in Europe.

Other *Anaplasma* spp. have been found to infect humans with similar clinical features in various geographic regions. Their impact on public health will require additional attention as limited epidemiological studies have been conducted. *Anaplasma platys* was described from febrile patients in Venezuela and in the United States and is likely transmitted by the brown dog tick. *Anaplasma ovis* has been found in Europe, Asia, Africa, and North America with human cases in Cyprus and Iran. *Rhipicephalus* and *Dermacentor* ticks that feed on ruminants appear to be the vectors. A new species, designated “*Anaplasma capra*,” has been recently identified in patients in China and has been associated with goats and sheep. The pathogen has been detected in *Ixodes persulcatus* ticks (Li et al., 2015). Further study will be needed to determine the full spectrum of illness and the eco-epidemiological features of these and other novel *Anaplasma* infections.

Human Neoehrlichiosis

Infection by the bacterial agent informally named “*Candidatus* Neoehrlichia mikurensis” is an emerging disease of humans in Europe and Asia (Silaghi et al., 2016). The pathogen represents a distinct taxon that has not yet been formally named, and thus was given a candidate designation. The organism appears to be widespread among certain species of small rodents in Europe and Asia. Voles have been found to be the most frequently

infected, and the vectors are *Ixodes ricinus* and *I. persulcatus* in endemic areas. Related pathogens have been identified in foxes and badgers in Europe and *I. holocyclus* ticks in Australia. Human cases have not been numerous, occur mainly in elderly adults, and are often associated with immune suppressive therapy or immunocompromised immune systems. Clinical features include fever, localized pain in joints or muscles, vascular and thromboembolic events, and transitory ischemic attacks. Leucocytosis with neutrophilia and anemia may be seen in laboratory studies. The infection responds to doxycycline treatment. In North America, the genus is represented by “*Candidatus Neoehrlichia lotoris*” found in raccoons, but no human cases have been identified, and the tick associate has not been determined.

Q Fever

First recognized among livestock handlers in Australia in 1935, Q fever is now known to occur on five other continents (Europe, Asia, Africa, North America, South America) and is probably worldwide in distribution. The etiologic agent, *Coxiella burnetii*, is a bacterium that develops in the phagolysosomes of the cytoplasm of susceptible cells. *Coxiella burnetii* can survive for months or years outside host cells under environmental conditions that are lethal to other bacteria. It can survive in dried tick feces, dried or frozen tissues, soil, and water.

After an incubation period of about 20 days, Q fever is characterized by sudden onset of fever, chills, sweats, diarrhea, sore throat, painful sensitivity to light, muscle pain, and headache. Fever may persist for 2 weeks and show a biphasic pattern. Fatigue, enlargement of the liver, and inflammation of the lungs, accompanied by a mild cough and chest pain, occur frequently. A rash is usually absent; when present, it appears on the trunk and shoulders. Q fever may become chronic, in which case it causes inflammation of the lining of the heart and its valves. The case-fatality rate is less than 1% in acute cases but may rise to 30% in chronic cases.

Transmission by ticks was first reported in 1938. Both argasid and ixodid ticks have been found infected naturally with *C. burnetii* or similar organisms. Subadult ticks infected while feeding on bacteremic hosts develop a generalized infection in their tissues. Following the transstadial molt, nymphs or adults transmit *C. burnetii* by bite, and females can pass the organism transovarially. Argasid ticks also can disseminate the organism via infectious coxal fluids. Notably, *C. burnetii* can survive in contaminated tick feces for as long as 6 years, which facilitates spread to humans and domestic animals. More recent work has questioned many of the historical associations of ticks with *C. burnetii* (Duron et al., 2015). *Coxiella*-like endosymbionts are widespread in many

species of ticks and may have been misidentified as pathogenic *C. burnetii*. Recent studies have shown that *Coxiella*-like symbionts may be found in all life stages of several species of *Amblyomma* ticks, densely colonizing the salivary glands and ovaries with a function of improving reproductive fitness (Machado-Ferreira et al., 2016). Further work will be needed to better understand the true role of ticks in natural cycles of *C. burnetii*.

Coxiella burnetii can be maintained in enzootic cycles involving domestic animals (e.g., sheep, cattle, goats), wildlife, and their associated ticks. A cycle exists among Australian kangaroos (*Macropus major* and *M. minor*), the marsupial bandicoot (*Isodon torosus*), and their associated host-specific ticks. Transmission to cattle and humans occurs when wild mammals also are parasitized by the nonspecific *Ixodes holocyclus*. In mammals, infection is usually asymptomatic, but abortions sometimes occur. Small mammals (e.g., *Apodemus*, *Microtus*, *Clethrionomys*, *Arvicola*, and *Pitymys* species) living in and around agricultural communities may link the domestic and sylvatic cycles. These animals develop high rickettsemias and shed the organism in their feces for weeks after becoming infected. Dogs, cats, birds, and reptiles also are susceptible to infection and may play a role in maintaining the infection in natural habitats. Although ticks are important in maintaining the pathogen horizontally and vertically in enzootic cycles, they rarely transmit *C. burnetii* to humans by bite. Instead, persons who handle infected animals or their products, or materials contaminated by tick feces, are at increased risk of acquiring *C. burnetii*. Tick excreta are an important source of infection because they are often highly contaminated and easily aerosolized. However, aerosols emanating from afterbirth membranes and associated fluids, blood, urine, feces, nasopharyngeal discharges, and milk containing high concentrations of the organism constitute the most common means for spreading the infection. As these materials dry, *C. burnetii* can be spread in aerosolized dust and debris present in animal stalls, barns, storerooms, and similar facilities. The most common site of Q fever epidemics is on farms or in farming communities, usually when domestic animals are being handled, such as during wool-shearing, lambing, calving, and slaughtering. Milk and milk products may be particularly important means of disseminating *C. burnetii* to humans; the organism may survive in contaminated milk and butter for up to 3 months.

Lyme Disease

Lyme disease, also known as Lyme borreliosis, erythema chronicum migrans, Bannwarth’s syndrome, and tick-borne meningopolyneuritis, is a tick-borne disease caused by spirochetes in the group of related species known as the

Borrelia burgdorferi sensu lato (s.l.) complex (Fig. 27.26). This expanding group now includes at least 23 named genospecies and many recognized “genotypes” that remain unnamed at the time of writing; at least four *B. burgdorferi* s.l. species are important pathogens for humans, including *Borrelia burgdorferi* sensu stricto (s.s.), *B. afzelii*, *B. garinii*, and *B. spielmanii*. Several other genospecies reportedly infect humans occasionally or rarely (e.g., *B. bissettii*, *B. lusitaniae*, *B. americana*, *B. andersonii*, *B. bissettii*, and *B. mayonii*) (Clark et al., 2013; Golovchenko et al., 2016; Pritt et al., 2016; Rudenko et al., 2016).

The genome of the B31-type strain of *B. burgdorferi* s.s. was sequenced in 1997. North American and European populations of *B. burgdorferi* s.s. reportedly belong to genetically distinct populations, and this genospecies may have originated in Europe instead of North America as proposed earlier (Margos et al., 2008). During the previous two decades, whole genome sequences have been determined for isolates of several others of the *B. burgdorferi* s.l. complex, including *B. afzelii*, *B. bissettii*, *B. garinii*, *B. chilensis*, *B. mayonii*, *B. miyamotoi*, *B. spielmanii*, and *B. valaisiana* (Casjens et al., 2011a; Casjens et al., 2011b; Schutzer et al., 2011; Schutzer et al., 2012).

Although the etiologic agent was not discovered until 1981 (Burgdorfer et al., 1982), human cases have been documented in the medical literature dating back to the early 19th century. First recognized in the United States as a new form of inflammatory arthritis in Old Lyme, Connecticut, during the mid-1970s (Steere et al., 1977), Lyme disease and related disorders have since been reported from most states in the United States, southern Canada, and many countries of Europe and Asia. Human cases of Lyme disease also have been reported from Africa, Australia, Mexico, and South America (including Uruguay, Argentina, and Chile).

Lyme disease is the most commonly reported vector-borne disease throughout the temperate regions of the Northern Hemisphere, including North America and Europe, where the various syndromes account for hundreds of thousands of new cases annually. Using data collected between 2005 and 2010, the U.S. Centers for Disease Control and Prevention (CDC) estimated an incidence of 106.6 cases per 100,000 persons and that approximately 329,000 (95% confidence interval 296,000–376,000 and about 10 times the number of cases reported) people in the United States develop Lyme disease annually (Nelson et al., 2015). In Europe, the highest frequencies of the disease occur in Central Europe and Scandinavian countries including Austria, Germany, Slovenia, and Sweden where the annual incidence has been estimated to be as high as 120 (Slovenia) to 130 (Austria) cases per 100,000 residents (Steere et al., 2005). Much work remains to determine the public or veterinary

health risks of *B. chilensis* in South America (Ivanova et al., 2014).

In the United States, Lyme disease is most prevalent in the northeastern states, especially in New York, Pennsylvania, New Jersey, and southern New England (Fig. 27.25); during 2008–2015 a total of 275,589 cases were reported to the CDC (Schwartz et al., 2017). Other major regional foci occur in the Upper Midwest, especially in Wisconsin and Minnesota, and in northern California. In the northeastern United States, people living in close proximity to forests, or in suburban communities having a mosaic patchwork of wooded areas and homes, have the highest risk of exposure to spirochete-infected ticks. White-tailed deer thrive in these habitats and, consequently, *I. scapularis* ticks abound. Moreover, infection rates in *I. scapularis* nymphs and adults are high. In one study in New York, 30% of nymphal and 50% of adult ticks were found to be infected with *B. burgdorferi*.

On the other hand, northern California cases are most likely to occur in semirural or rural settings where *I. pacificus* is abundant. However, infection prevalences in this tick (typically 1%–2% in adults, 2%–15% in nymphs) are generally much lower than they are in northeastern populations of *I. scapularis*, and the risk of infection to humans is correspondingly lower. Cases occur throughout the year, but most often are seen in spring and early summer when the nymphs reach peak densities. In contrast, *I. pacificus* adults are primarily active in fall and winter, when temperatures are cool and humidities are high.

In addition to greater awareness and increased tick-surveillance activities, several ecological and epidemiological factors have contributed to the current epidemic of Lyme disease in the northeastern United States and Europe. These include the occurrence of abundant, efficient tick vectors on both continents; the presence of numerous natural hosts for the immature and adult stages of the vectors; high rates of spirochetal infection in reservoir populations; anthropogenic changes (e.g., deforestation, reforestation, suburbanization) that favor an increased abundance of amplifying hosts and infected vector ticks; and close proximity of susceptible human populations to populations of tick vectors. Moreover, efficient transspecies transmission among the mammalian hosts of *B. burgdorferi*, a generalist micro-parasite, seems to have fueled the rapid epidemic spread of Lyme disease in the northeastern United States (Hanincová et al., 2006). In some European countries, the greater species diversity of *B. burgdorferi* s.l. spirochetes pathogenic for humans also may have contributed to the upsurge in reported cases as populations of *I. ricinus* expanded and increased in abundance.

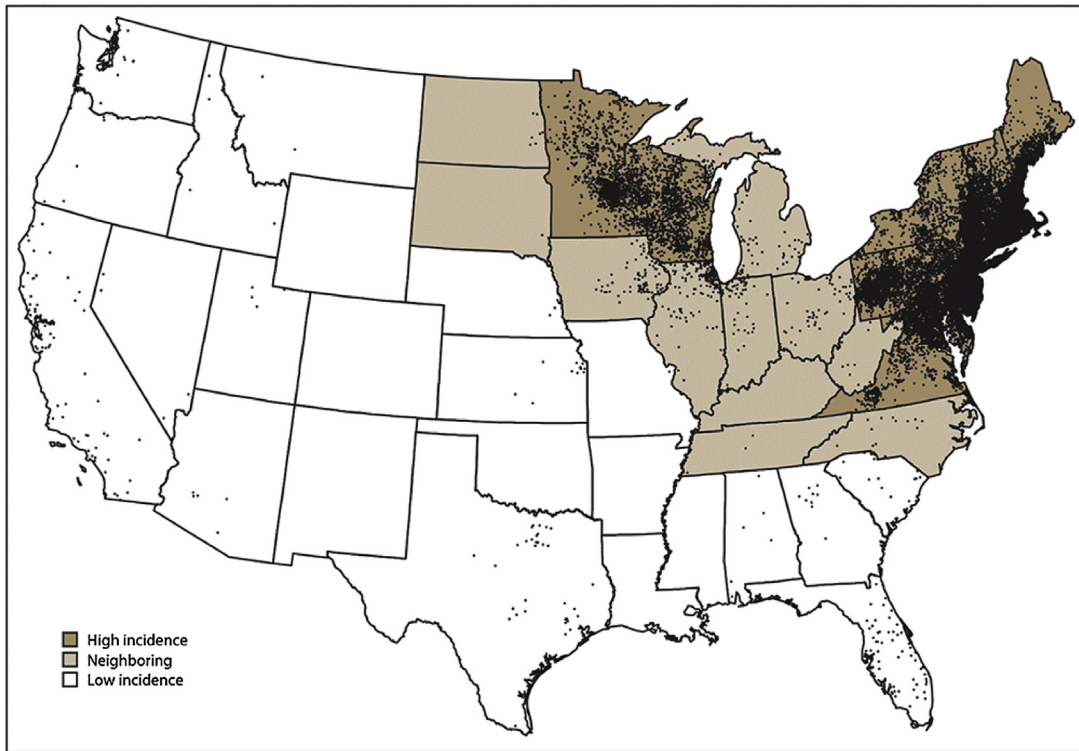


FIGURE 27.25 Lyme disease, mean annual number of confirmed cases by county of residence—United States, 2008–2015. Courtesy of Centers for Disease Control and Prevention.

When injected into humans by a feeding tick, borreliae multiply and disseminate in the skin. Gradually, they invade the bloodstream and may spread throughout the body, often localizing in the bursae of the large joints, in the central or peripheral nervous systems, and in the heart. Clinical signs and symptoms usually appear within 1–2 weeks (range, 3–32 days) following the bite of an infectious tick. Most cases occur during the late spring or summer, coincident with the seasonal activity of the nymphal stages of the primary vectors. *Ixodes persulcatus* is a notable exception; the adult female of this Eurasian tick seems to be the primary life stage that transmits spirochetes to humans (Piesman and Humair, 2012).

Early-stage Lyme disease is characterized by nonspecific (“flu-like”) symptoms and by an erythematous skin rash, erythema migrans (EM), which is present in 60%–80% of patients. Erythema migrans is a slowly expanding, usually circular or elliptical, but sometimes triangular- or irregularly shaped lesion that often exhibits bright red outer margins and partial central clearing (Fig. 27.26B). Most patients have one EM lesion at the site of tick attachment, but 25%–50% may develop multiple satellite lesions. The rash should not be confused with erythematous skin lesions that develop within minutes to a few hours, and tend to expand rapidly in size, after the attachment of an *Ixodes* tick. Such lesions

typically result from allergic hypersensitivity reactions following the injection of tick-salivary proteins (Steere et al., 2016). In the range of the lone star tick, a clinical entity known as southern tick-associated rash illness (STARI) is temporally linked to a bite by *Amblyomma americanum*. An erythema migrans-like skin lesion is the dominant sign, but the rash may be accompanied by mild systemic features such as myalgia, arthralgia, fatigue, fever, chills, and headache. The cause is not yet known, and serologic and molecular studies for borreliosis and rickettsiosis have not shown evidence for these infections. Recently, a new diagnostic approach using metabolic characterization has led to the ability to differentiate STARI from early Lyme disease with an accuracy of 85%–98% (Molens et al., 2017).

Untreated Lyme patients may manifest no further signs or symptoms of illness, or they may go on to develop late-stage Lyme disease within one to several months. Late manifestations, cardiac, neurologic, arthritic, or further dermatologic abnormalities may occur either alone (e.g., acrodermatitis chronica atrophicans, caused by *B. afzelii*) or in combination. Recently, several sudden fatal cases of Lyme carditis were reported (Muehlenbachs et al., 2016).

The following account of the remarkably diverse ecology of *B. burgdorferi* s.l. spirochetes is selective because of

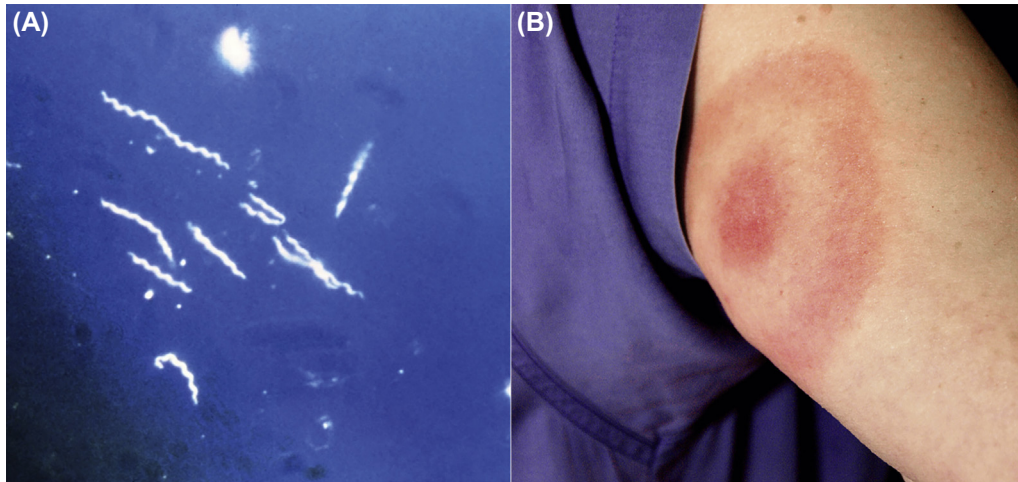


FIGURE 27.26 Lyme disease: (A) *Borrelia burgdorferi* spirochetes as seen under darkfield microscopy and (B) erythema migrans skin lesion on arm of patient, commonly seen in early stage of Lyme disease. Courtesy of Centers for Disease Control and Prevention.

space constraints. The interested reader is referred to pertinent chapters in Gray et al. (2002) and to Piesman and Humair (2011) for greater in-depth coverage of the voluminous literature regarding the ecology in different geographic regions.

At least 40 species of ixodid ticks and two species of argasid tick have been found infected naturally with *B. burgdorferi* s.l. spirochetes. In most endemic foci, however, only a single member of the *Ixodes ricinus* complex serves as the primary vector to people. Thus, spirochetes are transmitted to humans by *I. scapularis* and *I. pacificus*, in eastern and western North America, respectively; by *I. ricinus* in Europe and western Asia; and by *I. persulcatus* in eastern Europe and Asia. Other *Ixodes* ticks that seldom or never attach to humans, and do (e.g., *I. jellisoni*) or do not belong to the *I. ricinus* complex (e.g., *I. spinipalpis* in the western United States; *I. dentatus* in the eastern United States; and *I. ovatus* in Japan), may serve as efficient enzootic (maintenance) vectors of *B. burgdorferi* s.l. Ticks in other genera rarely serve as vectors to people. For example, *A. americanum* in New Jersey and the southeastern United States has been implicated, even though several experimental studies have shown that it is an incompetent vector of certain isolates of *B. burgdorferi* (Feir et al., 1994; Clark et al., 2013; Rudenko et al., 2016).

The timing of feeding by different stages of a vector also may influence prevalence in vectors and hosts, as well as risks for people. Infective nymphal *I. scapularis*, infected with *B. burgdorferi* s.l. from feeding as larvae during the summer of the preceding year, feed on naïve mice during spring and ensure that reservoir hosts are available to infect the cohort of larvae that emerges from eggs during the summer. This reversal of the feeding phenology (nymphs feed during spring before larvae feed during

summer) amplifies the prevalence of infection in both the reservoir hosts and the vectors, therefore increasing the risk of transmission to people in the northeastern United States (Spielman et al., 1985).

In *Ixodes* spp. immatures, development of *B. burgdorferi* s.s. begins with ingestion of an infectious bloodmeal. *Borrelia burgdorferi* s.l. normally develop extracellularly by binary fission in the midgut diverticula of *Ixodes* spp. ticks, although spirochetes have been found occasionally in oocytes of the ovaries and in secretory cells of the salivary glands. Following the transstadial molt and resumption of tick feeding on another host, spirochetes escape from the midgut, enter the hemocoel, and migrate to the salivary glands (Zung et al., 1989). In some ticks, borreliae spread to other organs as well. Thus, spirochetes are maintained within populations of vector ticks by transstadial passage and by replenishment as noninfected ticks feed on infectious hosts. Transovarial transmission of *B. burgdorferi* s.l. has been documented in some of its primary vectors, but this mechanism appears to be inefficient for perpetuating and distributing most genospecies (e.g., *B. burgdorferi* s.l. by *I. pacificus* or *I. scapularis*).

The potential importance of the seasonal timing of vectors on epidemiologic patterns is illustrated by the classic 2-year transmission cycle involving *I. scapularis* in the northeastern and upper midwestern regions of the United States. In the colder, northern, regions, larval *I. scapularis* feed on reservoir hosts later in the summer than do nymphs of the prior year's cohort. This results in nymphs infected with borreliae feeding on, and infecting, naïve reservoir hosts; uninfected larvae then feed on those infected hosts and cycle amplifies in the tick populations increasing the risks to people in the region (Spielman et al., 1985; Lane, 1994; Piesman and Gray, 1994). Where winters are somewhat mild, the larvae feed simultaneously or

earlier in the season than do the nymphs and little or no amplification occurs by this ecological pattern of immature feeding. However, when ecological patterns seem simple, we should all look closer at the details. More recent accounts have shown the importance of simultaneous feeding activity and future studies focused on the importance of the timing of feeding may be warranted.

In addition to ticks, spirochetes have been detected in mosquitoes, deer flies, and horse flies in the northeastern United States and Europe, where anecdotal accounts suggest that some individuals may acquire spirochetal infections following the bites of blood-sucking insects. Although the overall role of insects in the ecology and epidemiology of *B. burgdorferi* s.l. appears to be minimal, and the finding of pathogens consumed in a bloodmeal should not be used to implicate a vector, further investigation may be warranted.

Wherever the ecology of *B. burgdorferi* s.l. has been studied intensively, typically one or more species of rodents or insectivores, and less often birds or lizards, have been implicated as primary reservoir hosts. Different genospecies may be associated with different vertebrates or even classes of vertebrates. Thus, *B. afzelii* and *B. burgdorferi* are associated predominantly with small mammals, *B. garinii* and *B. valaisiana* primarily with birds, and *B. lusitaniae* with lizards; however, *B. burgdorferi* and *B. garinii* parasitize some birds and small mammals, respectively.

The term reservoir, as used herein, pertains to those vertebrate host species that (1) are infected commonly with a particular borreliacidal genospecies, (2) maintain infections for prolonged periods, if not for life, (3) remain infectious for ticks that feed on them, and (4) are fed upon commonly by vector-competent ticks. However, each local nidus includes a different community of potential reservoir hosts, and it is the community ecology of hosts and vectors that determines the importance of each local host species in the ecological maintenance of pathogens, including *B. burgdorferi* s.l. Body size and natural history have been suggested to characterize reservoir hosts of *B. burgdorferi* s.l.; specifically small body size, populations that occur in high density, and a fast pace of life characterize reservoir competence (Ostfeld et al., 2014; Barbour et al., 2015).

In North America, competent reservoirs of *B. burgdorferi* s.l. include white-footed mice, eastern chipmunks, short-tailed shrews, and masked shrews in the Northeast and Upper Midwest, and western gray squirrels, dusky-footed woodrats, some species of chipmunks, and California kangaroo rats in the farwestern United States. In Europe, common shrews, bank voles, wood mice, yellow-necked field mice, edible and garden dormice, gray squirrels, red squirrels, hedgehogs, and hares exhibit varying degrees of reservoir competence for *B. burgdorferi*

s.l., and reservoirs of *B. garinii* include a variety of migratory birds (Piesman and Humair, 2011). In some geographic regions, a few species of birds (e.g., American robin and song sparrow in the United States; Eurasian blackbird) may play significant enzootiologic roles by providing populations of immature ticks with bloodmeals, by infecting vector ticks with *B. burgdorferi* s.l. and by transporting infected ticks considerable distances and thereby establishing new foci of infection. Conversely, some vertebrates that are excellent hosts of vector ticks, such as deer and certain lizards in North America, and roe deer in Europe, do not serve as reservoir hosts even though they may greatly increase the tick population. They help to reduce tick-infection prevalences and the risk of human exposure to spirochetes; this has been termed **zooprophylaxis**. Nonetheless, these and certain other vertebrate hosts are important tick-maintenance hosts that sustain local or regional tick abundance.

As an example, the western fence lizard is an important maintenance host of *I. pacificus* immatures in many biotopes in California. Its reservoir incompetence stems from the fact that it contains a heat-labile, spirochete-killing (borreliacidal) factor in its blood. This factor destroys spirochetes in the midgut diverticula of infected nymphs either while they feed, or soon after they have fed, on lizard blood, with the result that, after the transstadial molt, the adult ticks are devoid of spirochetes. Eliminating spirochetal infections from vector ticks like *I. pacificus* seems like it might reduce the force of transmission of a zoonotic agent to humans or other animals by reducing the prevalence in infected adult ticks, but the ecological impacts are complicated; even a zooprophylactic species, such as the western fence lizard, may increase the force of transmission by promoting larger tick populations (Swei et al., 2011).

The mechanism responsible for the borreliacidal activity in preimmune sera from the western fence lizard and the southern alligator lizard was demonstrated to reside in proteins comprising the alternative complement pathway (Lane and Quistad, 1998; Kuo et al., 2000). In Europe, complement-mediated borreliacidal effects observed for specific combinations of vertebrate-host serum and different genospecies of *B. burgdorferi* s.l. generally coincided with what was known about the reservoir potential of the mammalian and avian species evaluated (Kurtenbach et al., 1998, 2002).

To understand the role of lizards, birds, or mammals in the community ecology of *B. burgdorferi* s.l. and Lyme disease risk, each vertebrate species must be assessed separately under both field and laboratory conditions before biologically meaningful conclusions can be reached (e.g., (Mather et al., 1989; LoGiudice et al., 2003; Brisson et al., 2008), and then the numbers (or, if possible, the relative proportion) of ticks that feed on each host must be

determined in the field. In that regard, few lizards had been studied intensively enough with the exception of the western fence lizard in northern California. Findings stemming from the earlier studies collectively resulted in a belief that other lizards, in general, might be reservoir-incompetent hosts. However, although some lizards indeed are nonreservoir hosts, others are reservoir competent. In the southeastern United States, several lizards are hosts for *B. burgdorferi* s.l. and serve as a source of spirochete infection for ticks (Levin et al., 1996; Clark et al., 2005). Likewise, in several European countries (Germany, Italy, Slovakia) and in Tunisia, at least four species of lizards have been implicated as primary reservoir hosts of *B. lusitaniae* (Tijssse-Klasen et al., 2010; Ragagli et al., 2011).

The various *B. burgdorferi* s.l. genospecies are generalist pathogens that infect a range of hosts. Likewise, the ticks that transmit infections to humans, domestic animals and many wildlife species are generalist feeders. Although the tendency is to look for simple reservoirs for control purposes, the reservoirs and vectors of this group of pathogens is complex and managers need to know the local system of vectors and vertebrate hosts maintaining the pathogen in nature in order to manage the risks for people or domestic animals.

Tick-Borne Relapsing Fever and *Borrelia miyamotoi* Disease

Human cases of tick-borne relapsing fevers (TBRF), also known as tick-borne spirochetoses and endemic relapsing fevers, are caused by about 20 species of borreliae; and the list will likely continue to grow. Classically, all TBRFs were associated with one or a couple of different species of argasid tick in the genus *Ornithodoros*. More recently, a spirochete, *B. miyamotoi*, which is closely related to TBRF spirochetes from North America, and divergent from *B. burgdorferi* s.l., has been shown to be transmitted by the primary vectors of Lyme disease; resulting in the names “argasid-borne relapsing fevers” and hard tick-borne relapsing fever (or *B. miyamotoi* disease, BMD). *Borrelia miyamotoi* has been found to occur in from Russia, Europe, Japan, and the United States (Fish, 2013; Crowder et al., 2014; Telford et al., 2015; Khasnatinov et al., 2016; Iwabuchi et al., 2017).

Human cases of TBRF occur on five of the seven continents, and cycles include the associations of ticks and borreliae shown in [Table 27.4](#). Early descriptions confused TBRFs with louse-borne relapsing fever caused by *B. recurrentis*, and transmission by ticks was not recognized until the pioneering work of Dutton and Todd (1905) who detected spirochetes in *Ornithodoros moubata* from East Africa; and after Joseph Dutton died of

the disease in 1904 at the age of only 30 years (Köhler, 2006).

Onset of TBRF in humans is characterized by fever, chills, and a throbbing headache, usually without a pronounced rash or an ulcer at the bite site. Following the incubation period of approximately 1 week, an episode of fever usually lasts 3–5 days during which time spirochetes are present in the peripheral blood. The febrile period ends in a period of crisis involving very high fever (up to 106.7°F). Subsequent relapses of 3–5 days follow periods of 5–7 days during which spirochetes are difficult to find in the bloodstream. This alternating cycle of febrile and afebrile periods in untreated patients may be repeated two or more times, accounting for the epithets of relapsing fevers (Dworkin et al., 2008). Depending on the number of cycles, the illness may be extended for several weeks or longer and sometimes ends in death. Other signs or symptoms that occur often include muscle ache, joint pain, abdominal pain, nausea, vomiting, diarrhea, and a petechial rash on the trunk; acute respiratory distress has occurred and TBRF has been associated with neural disease. Although the full range of the pathology caused is beyond our scope, the pathophysiology appears to be related to mild disseminated intravascular coagulation and vascular microemboli that form around individual borreliae (Dworkin et al., 2008). This range of signs indicates that severe clinical conditions might occur more often than previously reported.

The epidemiology of TBRF in the United States, and the possibilities for reemergence of tick- and louse-borne relapsing-fever infections globally, have been reviewed recently (Dworkin et al., 2008; Trape et al., 2013; Forrester et al., 2015). Argasid borne borreliae show a high level of vector specificity, mostly with species in the genus *Ornithodoros*, which is in contrast to the specificity of most *B. burgdorferi* s.l. genospecies and of *B. miyamotoi* with their primary vectors.

In certain TBRF-endemic areas of Tanzania, the annual incidence of *B. duttonii* infection reportedly is 384 per 1,000 in infants (less than 1 year of age) and 163 per 1,000 in children (less than 5 years of age); the perinatal mortality rate is a staggering 436 per 1,000 (McConnell, 2003). Likewise, in Senegal, the average incidence of *B. crociduræ* infection in all age groups was 11 per 100 person-years from 1990 to 2003 (Vial et al., 2006). In marked contrast, the incidence of TBRF in endemic areas of developed countries (e.g., Israel, United States) is orders of magnitude lower (Sidi et al., 2005).

The relapsing nature of the disease is explained by the antigenic variability of the borreliae (Dworkin et al., 2008; Forrester et al., 2015; Lopez et al., 2016). Some spirochetes are able to alter their surface-protein composition, probably through transposition of the genes encoding them.

TABLE 27.4 Associations of Argasid-Borne Relapsing Fever Spirochetes, Their Vectors, Main Reservoir Group, and the General Geographic Areas Where the Diseases Occur

<i>Borrelia</i> sp.	<i>Ornithodoros</i> sp. Vectors	Reservoirs	Geographic Region
<i>B. baltazardii</i>	Unknown	Unknown	Iran
<i>B. brasiliensis</i>	<i>O. brasiliensis</i>	Unknown	Brazil
<i>B. caucasica</i>	<i>O. verrucosus</i>	Rodents	Caucasus Mountains to Iraq
<i>B. crocidurae</i>	<i>O. sonrai</i>	Rodents & insectivores	West and North Africa
<i>B. dipodilli</i>	<i>O. erraticus</i> ^a	Rodents	North Africa, East Africa, western Asia
<i>B. duttoni</i>	<i>O. moubata</i> ; <i>O. porcinus</i>	Humans Humans	Central Africa, Eastern Africa, and southern Africa Central Africa, Eastern Africa, and southern Africa
<i>B. graingeri</i>	<i>O. graingeri</i>	Rodents	Kenya
<i>B. hermsii</i>	<i>O. hermsi</i>	Rodents	Western USA and southwestern Canada
<i>B. hispanica</i>	<i>O. macrocanus</i> ; <i>O. occidentalis</i> ; <i>O. kairouanensis</i>	Rodents Probably rodents Probably rodents	Iberian Peninsula, Greece, Cyprus and North Africa Iberian Peninsula and North Africa Tunisia
<i>B. kalaharica</i>	Unknown	Unknown	Southwestern Africa
<i>B. latyschewii</i>	<i>O. tartakowskyi</i>	Reptiles & rodents	Central Asia, Iran, and Iraq
<i>B. mazzottii</i>	<i>O. talaje</i>	Rodents	Southern USA, Mexico, and Central America
<i>B. merionesi</i>	<i>O. costalis</i> ; <i>O. merionesi</i>	Rodents Rodents	North Africa North Africa
<i>B. microti</i>	<i>O. erraticus</i>	Rodents	Africa and Iran
<i>B. parkeri</i>	<i>O. parkeri</i>	Rodents	Western USA
<i>B. persica</i>	<i>O. tholozani</i>	Rodents	Middle East and Asia
<i>B. turicatae</i>	<i>O. turicata</i>	Rodents	USA and Mexico
<i>B. tillae</i>	<i>O. zumpti</i>	Rodents	Southern Africa
<i>B. neotropicales</i>	Unknown	Unknown	Central America
<i>B. venezuelensis</i>	<i>O. rudis</i>	Rodents	Central America and South America

^aThe *O. erraticus* complex of ticks in North and West Africa has been partially resolved (Trape et al., 2013), but further resolution is merited to define geographic distributions and clarify the taxonomy.

Consequently, new populations of spirochetes emerge in an infected host with each relapse and they multiply before the host can mount an effective antibody response against them. Crisis occurs as the spirochetes are controlled by the immune response, the infection is controlled (or death occurs) and a short period of respite occurs.

In their tick vectors, borreliae ingested with blood disseminate to the internal organs, including the salivary glands. Spirochetes are passed transstadially so that, once infected, ticks remain so for life; transovarial transmission has not been shown to be important in the epidemiology of relapsing fevers (Dworkin et al., 2008; Tabuchi et al., 2008). This, together with the long life-span of *Ornithodoros* ticks, and the resultant lag times in the transmission cycle, enhances the likelihood that relapsing fever spirochetes will persist in tick-infested habitats for prolonged periods. Transovarial transmission of relapsing-fever group

spirochetes has been demonstrated in *O. coriaceus*, *O. erraticus*, *O. hermsi*, *O. moubata*, *O. tartakowskyi*, *O. tholmani*, *O. turicata*, *O. sonrai*, and *O. verrucosus*, but not in *O. parkeri*, *O. rudis*, or *O. talaje* (Burgdorfer and Schwan, 1991; Dworkin et al., 2008; Tabuchi et al., 2008). Borreliae also invade the coxal glands of some *Ornithodoros* spp. and can be transmitted to hosts via coxal fluid excreted during or soon after the bloodmeal.

Rodents serve as the primary reservoir hosts of most borreliae transmitted by *Ornithodoros* ticks. Four notable exceptions are *B. anserina*, *B. coriaceae*, “*B. lonestari*”, and *B. duttoni*. In the United States “*B. lonestari*” was once thought to be the cause of southern tick-associated rash illness (STARI); the association of STARI and “*B. lonestari*” has been discounted. Columbian black-tailed deer have been implicated as reservoirs of *B. coriaceus* in California, and white-tailed deer as reservoirs of

ixodid-transmitted “*B. lonestari*” in the southern United States. *Borrelia anserina* is an important pathogen of chickens and other fowl but is not zoonotic.

The established dogma is that only humans serve as reservoirs of *B. duttoni*, the cause of East African tick-borne or endemic relapsing fever. Recent evidence, however, suggests that *B. duttoni* (or a related strain) is a zoonosis in central Tanzania (McCall et al., 2007). Domestic animals associated closely with households (i.e., tembe houses consisting of adobe walls, flat earthen roofs, and soil floors) in a TBRF endemic region were infected with borreliae that shared greatest homology with *B. duttonii*. Nearly half of 122 houses surveyed were infested with *O. moubata* s.l. ticks, and 11% of the chickens and 9% of the pigs tested were PCR positive. Also, a mark-release-recapture experiment revealed that about 3% of the recaptured ticks had moved from their release sites in pigpens into adjoining or nearby houses 7–25 days postrelease; whether this is generally true for *B. duttoni* or related to a specific strain of borreliae in Tanzania remains to be reported and more work is warranted.

Epidemiologically, TBRF is a highly focal disease; presumably as a result of the host specificity and natural history of the tick vectors. In the United States, most human cases are caused by *B. hermsii*, between 1990 and 2011, TBRF was reported mainly from 12 western states (Fig. 27.27) with 70% of the cases being reported from California, Colorado, and Washington (Forrester et al.,

2015); however, the most cases for a county ($n = 29$) came from Kootenai County, Idaho. Because this is not a reportable disease in the US, the numbers reported to authorities likely under-report the actual number of cases. The median elevation for the 10 counties with the most cases was 3,840 ft (range 1,178–7,562 ft) illustrating that TBRF occurs most commonly at mid-elevations where the vector, *O. hermsii* lives in rodent burrows in coniferous forests and feeds most commonly on rodents such as chipmunks, tree squirrels, and ground squirrels. Interestingly, *B. hermsii* has been isolated from a northern spotted owl that died from the infection (Thomas et al., 2002) suggesting that avian species might also be involved as part of the reservoir (Dworkin et al., 2008; Yabsley et al., 2012). In addition, to *B. hermsii*, *O. turicata* transmits *B. turicatae* in the southwestern US, Florida, Mexico, and Central America. This vector lives in limestone caves, animal burrows, and in peri-domestic structures where there are animals to feed upon (Dworkin et al., 2008). People generally become infected at night when they stay in structures or caves where the vectors occur.

Another vector of relapsing-fever spirochetes in western North America is *O. parkeri*, which typically occurs at lower elevations than *O. hermsii*. Although new isolates of *B. parkeri* were only recently obtained, cases have been identified from appropriate exposure to semi-arid, sagebrush, habitats, prairie dog burrows, and other rodent burrows, since 1934. This tick rarely infects humans because *O. parkeri* ticks inhabit the burrows of rodents

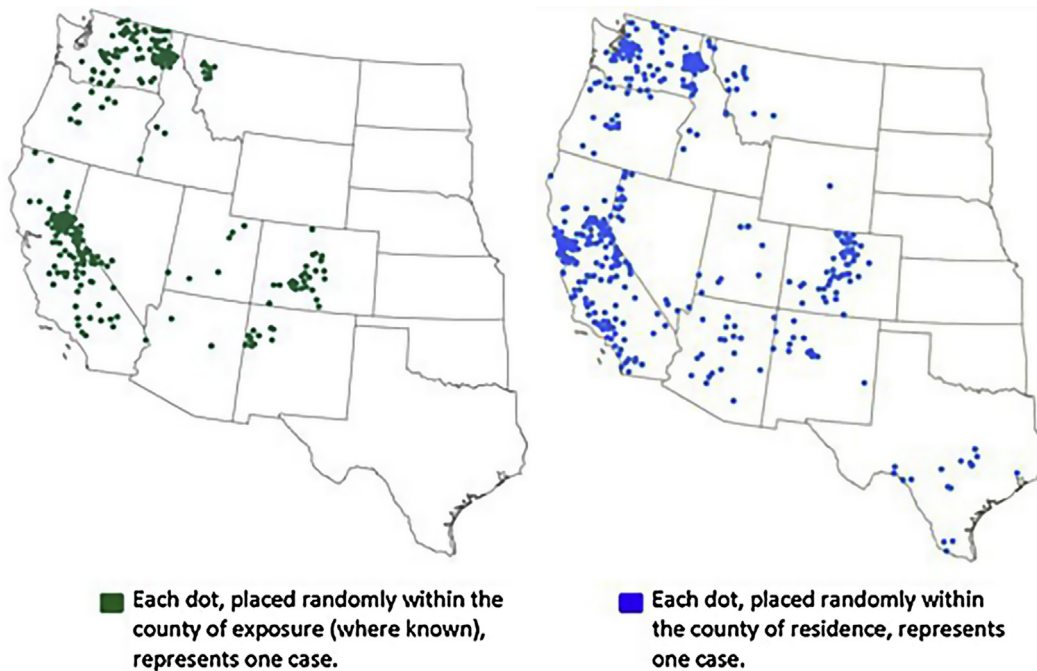


FIGURE 27.27 Human cases of tick-borne relapsing fever in the United States between 1990 and 2011. Courtesy of Centers for Disease Control and Prevention.

(e.g., California ground squirrels) and therefore have little opportunity to feed upon people.

Borrelia miyamotoi has been known since the 1990s (Fukunaga et al., 1995), but was only reported as a human pathogen in the US in 2013 (Branda and Rosenberg, 2013; Krause et al., 2015). The geographic range, like that of Lyme disease, includes the Holarctic region overlapping the distributions of the primary vectors *I. ricinus*, *I. persulcatus*, *I. pacificus*, and *I. scapularis*. It differs from other TBRFs because it is transmitted by a hard tick and because the signs are somewhat less pronounced (Telford et al., 2015). However, the organism clearly groups phylogenetically with the TBRF borreliae from North America (Barbour, 2014). The pathogen has been identified in a number of wildlife species and birds. High prevalences have been noted in wild turkeys collected in Tennessee.

One of the difficulties of studying TBRF has been related to the classification of the borreliae, for which taxonomy continues to be revised and expanded. As an example of taxonomic changes in the vector, the *O. erraticus*-complex used to be discussed as the “large variety” and the “small variety.” Trape and coworkers (Trape et al., 2013) recently described nine species that were once all discussed as *O. erraticus* in western Africa, northern Africa, and the Iberian Peninsula, and additional work is needed to resolve species relationships in Central Asia, the Middle East, and Eastern Europe. As noted by Estrada-Peña et al. (2010), there are about 190 species of argasid ticks, and the generic and subgeneric taxonomy is somewhat controversial for about 130 of those species. The potential for understanding the natural history, and therefore the potential for management, depends upon the assumption that we know what species we are studying or reporting. Only then can researchers evaluate the nuances of transmission cycles and accurately describe the risks.

Tularemia

Tularemia was first identified as a distinct clinical entity in Japan in 1837, where it was attributed to infected hares. It was first recognized in the western United States in 1911 by McCoy, who described it as “a plague-like disease of rodents.” The organism was detected in tissues of the California ground squirrel. In the United States, it has long been associated with hunters, who acquire the infection while skinning wild rabbits (hence the colloquial name, “**rabbit fever**”), and with persons who handle infected livestock, especially sheep. Tularemia is increasingly becoming more of a concern throughout Europe with over 15,000 cases recorded between 1997 and 2013 (Maurin and Gyuranecz, 2016). Workers in the former Soviet Union

recognized this disease among trappers handling European water voles (*Arvicola amphibius*) and established that it was caused by the same bacterium. For excellent overviews of tularemia, see Jellison (1974), Bell (1988), Eisen (2007), Foley and Neito (2010), Telford and Goethert (2011), Carvalho et al. (2014), Mani et al. (2016) and Maurin and Gyuranecz (2016).

The causative agent, *Francisella tularensis*, is a pleomorphic, gram-negative, aerobic bacterium. It exists in different forms termed biovars, which are strains having special biochemical or physiological properties. Two biovars of *F. tularensis* occur in North America; a highly virulent form associated with rabbits, cats, sheep, and ticks (type A, biovar *F. t. tularensis*), and an apparently waterborne, less virulent form associated with beavers, muskrats, and voles (type B, biovar *F. t. holarctica*). Biovar *F. t. tularensis* (Type A1 (virulent subtype in the central United States) and A2 (less virulent in the western United States)) is the most common and known from North America and recently Europe. This type is fatal in 5%–7% of untreated patients. Biovar *F. t. holarctica* (= *palaearctica*) occurs throughout the Northern Hemisphere and is rarely fatal to humans. A third biovar, *F. t. mediaasiatica*, is found in Central Asia, whereas a fourth biovar, *F. t. novicida*, exists in parts of the United States and possibly in Australia.

Francisella tularensis is transmitted by many blood-feeding arthropods other than ticks, including deer flies, mosquitoes, and fleas (Petersen et al., 2009). It is also transmitted by handling infected animals, inhalation of contaminated dust, drinking infected water, and eating insufficiently cooked, infected meat. Patients infected with *F. tularensis* experience fever, headache, and nausea, usually accompanied by development of an ulcerated lesion at the site of inoculation. Other clinical manifestations include enlargement of regional lymph nodes, pneumonia, and occasionally a rash. Although seven clinical types have been recognized, the ulceroglandular form accounts for about 80% of cases (Jellison, 1974). The pneumonic form is particularly prone to produce severe illness; if left untreated, it may persist for 2–3 months and become chronic thereafter.

Many species of ixodid ticks have been found infected naturally with *F. tularensis*. In North America alone, this agent has been detected in, or isolated from, at least 13 species of ixodids in four genera (one *Amblyomma* spp., five *Dermacentor* spp., two *Haemaphysalis* spp., and five *Ixodes* spp.). Ticks are considered by some workers to be reservoirs of *F. tularensis*, or at least part of a multi-host reservoir system, together with their primary vertebrate hosts. Transstadial passage of the agent occurs in susceptible ticks, but earlier claims that transovarial

transmission also occurs have not been confirmed. Ongoing studies on Martha's Vineyard, Massachusetts (USA) have demonstrated a wide diversity of *F. tularensis* genotypes in *D. variabilis*, suggesting long-standing enzootic transmission. All of the infected ticks harbored biovar *F. t. tularensis*, yet the infection rate was quite low (<1%) (Goethert et al., 2004). Recent studies have demonstrated that *A. americanum* and *D. variabilis* can both serve as bridge vectors for *F. tularensis* in the central United States and are most likely responsible for the tick-related cases observed in the region during the summer months (Mani et al., 2016).

Although tularemia is mainly an infection of wild lagomorphs and rodents, natural infections have been reported in numerous species of mammals (both domestic and wild) and birds. In the United States, a relatively high number of cases come from handling infected cats (bites, scratches, body fluids or tissues). In one study of 106 tularemia cases in Nebraska between 1998 and 2012, 48% of the cases were cat-associated (Larson et al., 2014). Fish, frogs, and toads have been found infected occasionally. Skunks and raccoons, both hosts of *D. variabilis*, have recently been identified as important sentinels for enzootic transmission in the eastern United States (Berrada et al., 2006).

Epizootics are spread mainly by water or ticks. Waterborne epizootics occur in western Siberia, where lakes and other fresh water habitats are contaminated by infected dead and dying muskrats and voles. Fur trappers and others who handled carcasses of infected water voles, muskrats, or water contaminated by them, have contracted the disease in large numbers. *Ixodes apronophorus* transmits *F. tularensis* among European water voles, furthering the spread of the disease along shorelines. Interestingly, recent studies have demonstrated that mosquito larvae can acquire *F. t. holarctica* from water and homogenates of 5 day old adult mosquitoes can infect mice (Bäckman et al., 2015).

In parts of North America, *F. tularensis* is acquired by hunters as they skin freshly killed rabbits. Lagomorphs were identified as the source of infection in over 80% of the cases of tularemia acquired in California between 1927 and 1951; of these, jackrabbits were implicated in 71% of the cases in which a distinction was made between jackrabbits and cottontail rabbits. On the other hand, ticks are much more significant than lagomorphs as a source of human infection in the south-central United States, especially in Arkansas and Missouri, where the lone star tick (*Amblyomma americanum*) is the primary vector (Mani et al., 2016). Since 1990, 41% of the tularemia cases in the United States have been reported from this region, with the cases involving *A. americanum* nymphs and adults and *Dermacentor variabilis* adults (Eisen, 2007).

Tick Paralysis

Tick paralysis is a host reaction to compounds secreted in the saliva of feeding ticks. This malady has been reported from North America, Europe, Asia, South Africa, and eastern Australia. It was first reported in Australia in 1824 by William Howell who described a tick “which buries itself in the flesh and would in the end destroy either man or beast if not removed in time” (cited in Harwood and James, 1979).

The affliction is characterized by a progressive, flaccid, ascending paralysis. In humans, it usually begins in the legs with muscle weakness and loss of motor coordination and sensation. Paralysis gradually extends to the trunk, with loss of coordination in the abdominal muscles, back muscles, and eventually the intercostal muscles of the chest. Paralysis of the latter may lead to death from respiratory failure. During advanced stages, the patient may be unable to sit up or move the arms and legs; chewing, swallowing, and speaking may become difficult. The condition progresses rapidly, and death may ensue within 24–48 h after onset of symptoms. In North America, the case-fatality rate is about 10% in the Pacific Northwest; most of those who die are children (Gregson, 1973). In Washington state alone, 33 cases were reported between 1946 and 1996, mostly in children less than 8 years old (Dworkin et al., 1999). In a 1-week period in May 2006, four cases of tick paralysis were reported from Colorado (CDC, 2006). In most North American cases, symptoms abate within hours following detection and removal of the attached tick or ticks, and recovery may be complete within 48 h. If paralysis has progressed too far, complete recovery may take up to 6 weeks. In contrast, paralysis induced by the Australian tick, *Ixodes holocyclus*, may worsen after tick removal, and full recovery may take up to several weeks (Grattan-Smith et al., 1997).

The nature of the toxin(s) causing tick paralysis has not been determined for most species of ticks that cause this condition. Intensive research on the salivary components of *I. holocyclus* has revealed the existence of a protein, named **holocyclotoxin**, which produces paralytic symptoms. A different salivary-gland protein has been implicated as the toxin in *D. andersoni* females.

Typically, only female ticks can induce tick paralysis. In southern Africa, however, nymphs of the **Karoo paralysis tick** (*Ixodes rubicundus*) can cause paralysis in laboratory rabbits, and larvae of the soft tick *Argas walkerae* produce a toxic protein that can paralyze chickens. Female ticks must be attached to the host for several days (usually 4–6) before they begin secreting the toxins. For excellent reviews of the mechanisms of pathology among the tick paralyses, see Gothe et al. (1999) and Mans et al. (2004).

Seventy-three species of ticks in 10 genera reportedly cause tick paralysis in humans, other mammals, and birds (Durden and Mans, 2016). Worldwide, the ticks of greatest concern for humans are *I. holocyclus*, *I. rubicundus*, *D. andersoni*, and *D. variabilis*. *Dermacentor andersoni* populations from various regions in Canada differ in their paralyzing ability. Apparently this is under genetic control, as selection can increase this ability in the laboratory (Lysyk and Majak, 2003).

Although reported from many regions in North America, tick paralysis in humans and domesticated animals has been documented most often from the Pacific Northwest in the United States and British Columbia in Canada. Cases in humans and other animals occur in spring and early summer, coincident with the activity period of adult *D. andersoni*. In the eastern United States, cases in dogs and humans are caused by *D. variabilis*, whereas in California this tick has been associated only with paralysis in dogs.

In contrast to paralysis produced by *Dermacentor* species or *I. holocyclus*, in which feeding by one female is sufficient to cause this condition, severity of the disease in South Africa is directly related to the number of attached *I. rubicundus*.

In England and France, human paralysis has been attributed infrequently to *I. hexagonus*. In California, several mild cases have been ascribed to *I. pacificus* prior to the 1950s, but these earlier observations were not well documented and no new cases in humans have been reported since then.

Tick-Bite Allergies

The bites of many species of ticks can cause host reactions other than paralysis. These range from minor, localized, inflammatory reactions that subside soon after tick removal to severe, systemic reactions involving skin rash, fever, nausea, vomiting, diarrhea, shock, and death. Severe toxic or allergic reactions may follow the bites of the soft ticks *Argas brumpti*, *A. reflexus*, *Ornithodoros coriaceus*, *O. moubata*, and *O. turicata*. In Europe, severe reactions and even loss of consciousness have occurred following attacks by the pigeon tick, *A. reflexus*, which infests buildings where pigeons roost. This tick is particularly prone to bite people if the birds have been driven away. In the far-western United States, reports that bites of the **pajaroello tick** (*O. coriaceus*) are more feared than those of rattlesnakes seem exaggerated, but severe allergic reactions have been documented (characterized by edema, pain, erythema, tissue necrosis, ulceration, and prolonged healing). Bites of the bat tick, *Carios kelleyi*, in Iowa induced large erythematous lesions in some individuals (Gill et al., 2004).

Attached *Ixodes pacificus* sometimes causes severe allergic reactions and, in rare cases, anaphylactic shock in persons previously sensitized to its bite (Van Wye et al., 1991). Likewise, individuals bitten by *I. holocyclus* may experience anaphylactic reactions involving tick-specific IgE.

Alpha-Gal Allergy

A novel food allergy to α -1,3-galactose, a mammalian oligosaccharide, was recognized in the early 2000s and has been termed alpha-gal allergy (also known as alpha-1,3-galactose allergy or red meat allergy) (van Nunen, 2015). Patients treated with the oncologic drug cetuximab had reported hypersensitivity reactions found to be associated with elevated levels of IgE to alpha-gal molecules. Occurrence of increased alpha-gal IgE was greater than expected in non-oncologic patients in the southern United States. Later, it was noted that the distribution of patients with the reaction was similar to that of the lone star tick, *Amblyomma americanum*. Weeks to months after a bite by *A. americanum*, a hypersensitivity reaction might occur following ingestion of red meat from nonprimate mammals (primarily beef, lamb, or pork). As case reports and more structured studies were published, the reaction to ingestion of red meat following a known tick bite appeared to be both temporally associated and dose-dependent. IgE to the alpha-gal epitope develops after bites from the lone star tick. The food allergy manifests generally 3–6 h after ingestion of red meat in both adults and children. The clinical signs usually appear as gastrointestinal symptoms and hives, but can range from chronic urticaria to life-threatening anaphylaxis.

While most patients have been identified in the United States, the allergy has now been reported from multiple countries and associated with additional tick species in those regions (e.g., *Ixodes ricinus* in Europe, *Ixodes holocyclus* in Australia, *Haemaphysalis longicornis* in Asia, and *Amblyomma sculptum* in South America) (Araujo et al., 2016). The epitope has been identified in whole tick homogenates, midgut homogenates, and tick saliva. Patients with B-negative blood groups may be more susceptible (Hamsten et al., 2013). This tick-associated allergy is an emerging phenomenon and deserves further study as to what factors influence development of this atypical allergy and how the reactions might be prevented.

VETERINARY IMPORTANCE

Ticks are of veterinary concern mostly because of the many microbial disease agents they can transmit to livestock, companion animals, and wildlife. Ticks also are important because of the debilitating and sometimes fatal host reactions produced in domesticated livestock and companion

animals as a result of the feeding activities of certain species (e.g., tick toxicosis, tick paralysis). Moreover, livestock, as well as wildlife, may suffer from exsanguination, leading to anemia and death. In Oklahoma and Texas (USA), for example, significant mortality in white-tailed deer fawns has been associated with heavy infestations of *Amblyomma americanum*. Livestock breeds in tick-infested areas have been subjected to natural selection and are able to acquire immunity to infestation upon exposure to local tick species. Exotic livestock breeds from tick-free regions, have no such immunity when first imported and do not acquire a high degree of immunity on exposure.

Livestock and poultry that are heavily infested with ticks may experience economically significant reductions in body weight, milk or egg production, and general unthriftiness, and may on occasion even die of anemia when infested by large numbers of ticks. Some species routinely or incidentally invade the auditory canal of bovines or other mammals, a condition known as otocariasis, which may be accompanied by serious secondary bacterial infections. Tick bites, especially by species with a long hypostome (e.g., *Amblyomma*) may generate abscesses by secondary bacterial infection and cause the loss of one or more quarters of the udder. Other consequences can be lameness, due to ticks attached in the interdigital space and wounds that attract myiasis-producing flies, causing significant reduction in the value of the hide, fleece, or carcass.

The following section provides an overview of the major tick-borne diseases of veterinary importance.

Piroplasmoses

Piroplasmoses are protozoan diseases caused by *Babesia* (Family Babesiidae) (Fig. 27.28) and *Theileria* (Family Theileriidae, which also includes the genus *Cytauxzoon*). Parasites of both genera live and multiply in erythrocytes of the vertebrate host. The term itself refers to the developmental stage of the protozoan in the erythrocytes,

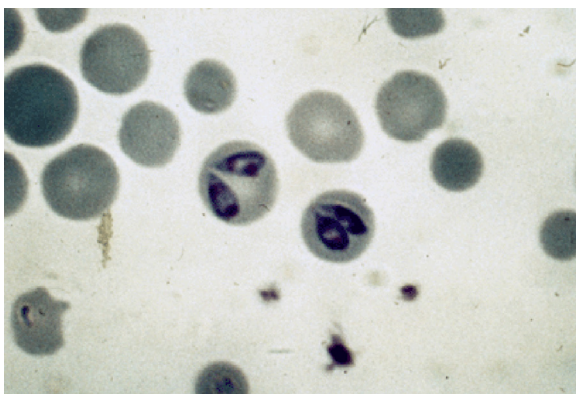


FIGURE 27.28 *Babesia* species in the blood of an infected animal. Courtesy of Gerrit Uilenberg.

i.e., “piroplasm,” literally meaning a pear-shaped structure. This is the stage infective to ticks. In ticks the parasite undergoes a sexual cycle with macro- and microgametes developing in the midgut and ending with infective sporozoites in the salivary glands.

Some piroplasm species were formerly classified as *Babesia*. However, after it was discovered that they undergo schizogony during development in vertebrate hosts and that they are not transmitted transovarially, they were moved to other genera (Uilenberg, 2006). Examples include *Babesia equi* and *B. microti*. *Babesia equi* is now classified as *Theileria equi* (Mehlhorn et al., 1986), whereas, based on phylogenetic studies using molecular comparisons, *B. microti* has been placed between the families Babesiidae and Theileriidae (Kjemtrup et al., 2006).

Babesia and *Theileria* species exhibit basic differences in their developmental biology and ability to be transmitted by infected ticks to their offspring. Whereas *Babesia* (sensu stricto) is transmitted both transstadially (i.e., from one developmental stage of the tick to the next) and transovarially (from mother to offspring via her eggs), *Theileria* is transmitted only transstadially. As a result, *Babesia* persists in infected ticks throughout their development as larvae, nymphs, and adults; unfed larvae of the next generation are already infected when they hatch from the eggs. In contrast, *Theileria* does not persist into the next generation. Unfed tick larvae are never infective. Nymphs and adults become infective only if they feed on an infected vertebrate host or if the tick was infected in its previous developmental stage.

There are also genus-specific differences between these piroplasms in their vertebrate hosts. *Babesia* develops and multiplies only in erythrocytes (Fig. 27.28), whereas *Theileria* develops and multiplies in both erythrocytes and lymphoid cells. The latter first undergoes multiplication (schizogony) in lymphocytes, producing macroschizonts (i.e., schizonts containing large nuclei, also known as Koch’s blue bodies), which appear a few days after the onset of symptoms. Later, as infected lymphocytes transform to lymphoblasts, microschizonts appear in the lymphoblasts. Merozoites released from the lymphoblasts then invade host erythrocytes. Piroplasms of both genera multiply in the erythrocytes by budding, with *Babesia* usually producing two daughter cells and *Theileria* usually four.

Babesioses

Infections of cattle by *Babesia* species is often severe, especially when involving *B. bovis* or *B. bigemina* (in tropical and subtropical regions) and *B. divergens* (in Europe and parts of North Africa). The severity depends on the susceptibility of the animal (natural resistance) and its

immune status (acquired resistance). Animals develop high temperatures, cease feeding, and become anaemic. One of the more characteristic and common symptoms is hemoglobinuria, causing the urine to become red or brownish, hence the name “redwater” for this disease. Icterus (jaundice) is often seen in severe cases. As babesiosis progresses, the animals become lethargic and eventually lapse into a coma and may die. Central nervous symptoms are often seen in infections by *B. bovis*. Considerable variation in severity has been noted in different geographical regions. This is attributed to differences in virulence among the parasites, as well as variation in the susceptibility of different cattle breeds. Nursing animals are protected by passive immunity acquired from antibodies in the colostrum of immune cows, resulting in young animals being more resistant than older ones. When all young animals in a population are infected, there is typically little or no clinical disease, particularly in local breeds. This situation is called **endemic stability**. Endemic stability may also occur in theilerial and ehrlichial infections.

The most important vectors of **bovine babesiosis** are *Rhipicephalus* (previously *Boophilus*) species especially *R. (B.) microplus* and *R. (B.) annulatus*. Although eradicated from the United States in the early decades of the 20th century, *R. annulatus* and *R. microplus* still occur in Mexico, and occasionally in extreme southern Texas near the Mexican border, and stringent controls are maintained to prevent their reintroduction. Moreover, white-tailed deer are hosts for *R. annulatus* and *R. microplus* and serve as a wild reservoir for these vector ticks and possibly the *Babesia* species. *Babesia divergens* is transmitted by the tick *Ixodes ricinus* in Europe and North Africa. In eastern, central, and southern Africa, *R. (B.) decoloratus* is an important vector (but only of *B. bigemina*), with *R. (B.) geigy* replacing it in West Africa. Domestic buffalo, or water buffalo, may also contract babesiosis, with *B. orientalis* having been described recently from buffalo in China.

Dogs are often victims of **canine babesiosis**, caused primarily by large (*B. canis*, *B. rossi*, and *B. vogeli*), and small (*B. gibsoni*, and *B. conradae*) forms. The brown dog tick (*Rhipicephalus sanguineus*) (Fig. 27.12) is a widespread vector, whereas, *Dermacentor reticulatus* is an important vector in Europe, and ticks of the *Haemaphysalis leachi* group are known to transmit agents of canine babesiosis in Africa.

Babesiosis also affects other animals, such as small ruminants and horses (*Babesia caballi*) (Schetters and Brown, 2006; Scoles and Ueti, 2015). In the latter case, this disease is of particular concern regarding the international movement and commerce of horses. Wild and domestic cats in southern Africa have been identified as infected with *B. felis*, *B. leo*, and *B. lengau* (Bosman et al., 2007, 2013).

The tick vectors of these pathogens are unknown. Wild mammals are commonly infected, usually with host-specific *Babesia* species.

Immunization against bovine babesiosis is carried out in some countries by injecting attenuated strains of the parasites, produced in donor cattle, with all the inherent risks associated with live vaccines. While tick control is emphasized, there also are commercially available inactivated vaccines against canine babesiosis, produced in blood cultures. Their efficacy, however, has not yet been well evaluated, while the existence of several species and/or strains further complicates their practical use.

Theilerioses

Theileria species infect a wide range of domestic and wild animals, particularly in the Old World. The more important agents of veterinary interest are *T. annulata* and *T. parva* in cattle, *T. equi* in horses, *T. lestoquardi* in sheep, and *Cytauxzoon felis* in domestic cats.

East Coast Fever (ECF) is a disease of cattle and domestic buffalo caused by *Theileria parva*. The disease, which has been known from East Africa since the 19th century, is widespread in eastern, central, and southern Africa. Movement of cattle has played a major role in the periodic outbreaks of ECF during the 20th century. Epizootics with high mortality tend to occur when very susceptible exotic breeds (e.g., taurine breeds, but even Asian zebu breeds) are introduced into areas endemic for *T. parva*. In endemic areas there may be a situation approaching endemic stability in local breeds.

An estimated 25 million cattle are at risk for acquiring ECF. Infected animals develop enlarged lymph glands and, after a few days, develop a high fever, become listless, and stop feeding. This may be followed by diarrhea and mucous discharges from the eyes and nose, and frequently by pulmonary signs, due to edema of the lungs. Mortality may exceed 90% in adult animals, but is usually much less in calves.

Theileria parva can also cause severe illness in some cattle, called **Corridor disease**. This results from transmission of the parasite from wild buffalo, the primary host of *T. parva*, to domestic cattle by ticks. It is believed that classical ECF has evolved from adaptation of the parasite to tick transmission between cattle. Water buffalo are also highly susceptible to ECF, but there are very few of them in endemic regions of Africa.

The primary vector of *T. parva* is *Rhipicephalus appendiculatus*, a tick whose geographical distribution coincides largely with that of ECF throughout much of eastern, central, and southern Africa. Corridor disease also occurs outside the known range of *R. appendiculatus* but within that of another competent vector, *Rhipicephalus zambeziensis*.

Another, somewhat milder disease of cattle is **tropical theileriosis**, caused by *Theileria annulata*. It is transmitted by several *Hyalomma* species (e.g., *H. anatolicum* in Eurasia) and affects both domestic cattle (*Bos* spp.) and the Asian domestic buffalo. Although clinical signs are similar, this disease differs from babesioses in the absence of hemoglobinuria and the less severe anemia that it causes in infected animals.

Tropical theileriosis is arguably of even greater importance than ECF because of its much wider distribution throughout North Africa, northern parts of sub-Saharan Africa, southern Europe, the Middle East, and elsewhere in central Asia, India, and China. In this regard the name of the disease is a misnomer because it also occurs in some temperate regions. Similarly, its other name, **Mediterranean theileriosis**, is misleading, as it occurs outside the Mediterranean basin. Other bovine-related theileriosis affecting large ruminants include *T. mutans* (Benign theileriosis), *T. taurotragi* (Benign African theileriosis), *T. velifera*, *T. orientalis* (oriental theileriosis), *T. buffeli*, *T. sinensis* and *T. sergenti*.

Immunization against tropical theileriosis and East Coast fever of cattle is used in some countries. In the case of tropical theileriosis, live attenuated, schizont-based vaccines, produced in lymphoblastoid cell cultures against *T. annulata*, have provided satisfactory results. However, similar vaccines for ECF have not proved effective. Instead, immunizations entail injection of live, fully virulent sporozoites obtained from ticks, followed by specific treatment to prevent clinical disease. Although homologous immunity is excellent, antigenic diversity complicates the results in the field.

Many other *Theileria* spp. cause infection, and often disease, in other livestock and wildlife in different regions of the world. Like *Babesia caballi*, *Theileria equi* is of significant concern to horse owners and a major obstacle to the international movement of horses (Scoles and Ueti, 2015; Wise et al., 2013). In small ruminants, particularly sheep, *Theileria lestoquardi* (**malignant theileriosis**) can be a serious problem, causing fatalities where it occurs in the Old World. Additionally, recent discoveries of new species of pathogenic *Theileria* in small ruminants (*T. luwenshuni* and *T. uilenbergi*) which cause cervine theileriosis, have been made in China.

Domestic cats are prone to suffer from a theilerial disease called **feline cytauxzoonosis**, caused by *Cytauxzoon felis*. It is closely related to *Theileria* and in the United States is often fatal in untreated or naive animals. While originally thought to be transmitted by *Dermacentor variabilis*, the primary vector is now considered to be *A. americanum*. The bobcat (*Lynx rufus*) and domestic cats may be the primary hosts of *C. felis*. The disease course is rapid, with onset of fever, lethargy, and anorexia after an incubation period of 5–20 days. Death often occurs within

a week of onset. Leukocytosis, hemolytic anemia, icterus, and elevated hepatic enzymes are often seen on laboratory studies. Other species of *Cytauxzoon* occur in wild cats (Felidae) in various parts of the world (Meinkoth and Kocan, 2005).

Louping Ill

Although known to sheep herders in Scotland for centuries, louping ill (LI) was not recognized as a separate clinical entity until 1913. Its viral etiology was not established until 1931. Louping ill virus causes an economically important disease of sheep and red grouse (a game bird) in England and Scotland. It also occasionally infects cattle, horses, pigs, and humans, often with severe or fatal consequences. The causative agent is a flavivirus that is antigenically similar to other members of the **Tick-borne encephalitis complex**, and the only member of the complex present in the British Isles. Similar diseases occur sporadically in a few other European and Scandinavian countries. The latter are caused by viruses distinguishable from LI virus by nucleotide sequencing. They have been named according to the country in which they were first recognized, such as Spanish sheep or goat encephalomyelitis and Turkish/Greek goat encephalomyelitis (Gritsun et al., 2003).

Infected sheep lose their appetites and become feverish. On about the fifth day after onset, the fever rises and the animals become uncoordinated and develop tremors. Seriously ill animals walk with an awkward, erratic, “louping” gait, hence the name of the disease. Many sheep die shortly after locomotor signs appear, but others develop a chronic condition that may persist for several weeks. Mortality in different breeds of sheep varies considerably, reaching 100% in some susceptible flocks. Recovered animals often show signs of permanent neurologic damage. Experimentally infected red grouse experience mortality rates of up to 78%.

Historically, the disease has been most prevalent in areas of unimproved pastures and moorlands where *Ixodes ricinus* is abundant. LI is passed transstadially in ticks but not transovarially. Field and laboratory studies suggest that the vector competence of *I. ricinus* for the virus is not high. In enzootic areas of northern Britain, for example, only 0.1%–0.4% of ticks are infected with the LI virus.

Although *I. ricinus* parasitizes many vertebrate hosts, tick populations inhabiting sheep rangeland are supported principally by this animal. Small mammals are not abundant on many upland sites grazed by sheep and, when present, tend to support low tick loads. This and other limited evidence suggest that small mammals are not infected with LI virus. Moreover, sheep exposed to LI virus develop high viremias and are infective to ticks for several days. Other vertebrates, both domestic and wild,

that may contribute to the maintenance of the virus are cattle, goats, mountain hares, and several species of ground-inhabiting birds, especially red grouse, willow grouse, and ptarmigan. These species serve as hosts for *I. ricinus* and occasionally develop viremias high enough to infect feeding ticks. Two other experimentally proven routes of transmission may amplify LI virus in natural foci: nonviremic transmission of the virus among co-feeding infected and uninfected ticks on mountain hares, and the ingestion of infected ticks by red grouse during their first season (Gilbert, 2016). It has been estimated from field observations that 73%–98% of viral infections in young-of-year red grouse might occur as a result of eating infected ticks.

African Swine Fever

This disease was first recognized in Kenya in 1921, as a catastrophic illness that killed 99% of infected pigs. Since then, sporadic epidemics of African swine fever have been reported from many African countries south of the Sahara, in Europe, and in the western hemisphere in Cuba, Haiti, the Dominican Republic, and Brazil.

The disease is caused by a large icosahedral DNA virus (family Iridoviridae) that attacks cells of the reticuloendothelial system, especially monocytes. The host range of the virus is limited to domestic pigs, European wild boars, warthogs, and bush pigs, all species of the family Suidae. In its acute form, animals develop fever about 3 days postinfection, the fever persists for three or 4 days, the temperature drops, and death ensues. In its subacute form, an irregular fever lasts for three or 4 weeks, whereupon the animals either recover or die. In its chronic form, animals may survive for long periods before succumbing to a secondary illness, most commonly pneumonia. Chronically infected animals usually experience stunted growth and emaciation, and serve as long-term reservoirs of the virus.

The primary vectors in Africa are *Ornithodoros* spp. of the *moubata* group, particularly *O. porcinus* (Jori et al., 2013). These ticks occur in eastern, central, and southern Africa. In these regions there is a sylvatic cycle between ticks and wild Suidae, particularly the warthog, in which the cases of infection show no symptoms. Once the infection has passed to domestic pigs, it spreads as a contagious disease and has been transported as such to various parts of the world. In north and west Africa, ticks in the *Ornithodoros erraticus* group are the primary vectors. These ticks spread to the Iberian Peninsula (Spain and Portugal) where ASFV became established in local *Ornithodoros erraticus* populations, which made eradication a difficult and lengthy affair. In West Africa, the tick *Ornithodoros sonrai*, also in the *O. erraticus* group, is suspected of playing a role in the persistence of the virus.

In the New World, *O. coriaceus*, *O. turicata*, and other *Ornithodoros* species have been demonstrated to be competent experimental vectors, raising concern about the potential establishment of African swine fever virus in North America. It is a porcine disease of major global importance, because of the high mortality it causes and the absence of a vaccine, despite numerous attempts to develop one.

Diseases Caused by Members of the Family Anaplasmataceae

The taxonomy of the Family Anaplasmataceae has been stable since 2001. The genera *Anaplasma*, *Ehrlichia* (including the former *Cowdria*), *Neorickettsia*, and *Wolbachia* have been united in the family Anaplasmataceae, to which the genus *Aegyptianella* has been added. The genus *Neoehrlichia* has also been proposed, but not formally described.

Ehrlichioses and Anaplasmoses

The diseases caused by members of the genera *Ehrlichia* and *Anaplasma* have long been known in veterinary medicine. These pathogens infect the leukocytes or platelets of livestock, companion animals, and wildlife. The ehrlichiae grow as distinct microcolonies, or **morulae**, within the cytoplasm of host cells (Fig. 27.24). The disease manifestations caused by these agents can range from asymptomatic to fatal.

Canine ehrlichiosis, due to *E. canis*, was first recognized in 1935. The cosmopolitan distribution of this pathogen corresponds with that of its primary vector, *Rhipicephalus sanguineus*. *Ehrlichia canis* occurs in mononuclear cells, but it is often difficult to find in blood smears. In the United States, serosurveys of civilian and military dogs have revealed that the disease is present in most states. Dogs infected with *E. canis* develop fever, conjunctivitis, and swelling of various tissues. The disease causes a reduction in the numbers of all blood cells (red, white, and platelets), and thus is also referred to as **canine tropical pancytopenia**. Infected animals stop eating, lose weight, and frequently appear depressed. Acute infection is often followed by a debilitating chronic phase, accompanied by anemia and sometimes hemorrhagic nasal bleeding. The German Shepherd breed is particularly susceptible to acute severe illness. These animals suffer from low white-blood-cell counts and damage to the lymph glands, bone marrow, and spleen. Animals with severe infection usually die without antibiotic treatment. In other breeds, particularly mongrels, the disease is often milder and ranges from asymptomatic to chronically symptomatic.

Transstadial transmission of *E. canis* occurs in *R. sanguineus*, and transstadially infected nymphal or

adult ticks can transmit *E. canis* to susceptible dogs. Transovarial transmission occurs rarely, if at all. Dogs apparently serve as the primary reservoir of *E. canis* because inapparent infections can persist for over 5 years, and the agent is continually present in chronically infected dogs.

Infection by *E. ewingii* causes a disease in dogs known as **canine granulocytic ehrlichiosis**. The pathogen grows within neutrophils of infected animals. The infection is usually mild and may manifest as polyarthritis. Dogs can maintain infections with this pathogen for over 2 years during which they can serve as reservoir hosts for the maintenance of the pathogen in local communities (Starkey et al., 2015). Although its actual distribution may be wider, *E. ewingii* is primarily found in the south-central and southern United States (Beall et al., 2012). White-tailed deer may serve as a natural wildlife reservoir. The agent is passed from *A. americanum* nymphs to adults, and transstadially infected adults can transmit the infection to susceptible dogs (Anziani et al., 1990). Naturally infected lone star ticks have been identified in North Carolina and elsewhere (Wolf et al., 2000). *Ehrlichia ewingii* is morphologically indistinguishable from *A. phagocytophilum* in blood smears, and molecular assays provide confirmation of infection. In the south-central and southeastern United States, dogs can also become infected with *E. chaffeensis*, the agent of human monocytotropic ehrlichiosis, when fed upon by an infected *A. americanum* tick. On its own, *E. chaffeensis* produces only a mild disease in dogs. However, coinfections with either *E. ewingii* or *E. canis* can produce more severe outcomes.

Recently, a new *Ehrlichia*, *E. muris eauclairensis*, was detected in both people and dogs in the upper midwestern United States. The blacklegged tick, *I. scapularis*, has been identified as the primary vector in experimental-infected and field-collected ticks. Little is known regarding the ecology or the effect of this pathogen on dogs except for one case in which the dog experienced fever, decreased appetite, lethargy, and recurrent vomiting (Hegarty et al., 2012).

Heartwater

Heartwater is an ehrlichial disease of large ungulates (livestock and game) caused by *Ehrlichia* (formerly *Cowdria*) *ruminantium* (Fig. 27.29). The disease occurs primarily in sub-Saharan Africa and neighboring islands (e.g., Madagascar, Reunion Island, Mauritius, the Comoros, and São Tomé). It has been inadvertently transported to the western hemisphere where it now occurs on several Caribbean islands. It is one of four most important tick-borne cattle diseases in tropical regions (babesioses, theilerioses, anaplasmosis, and heartwater).

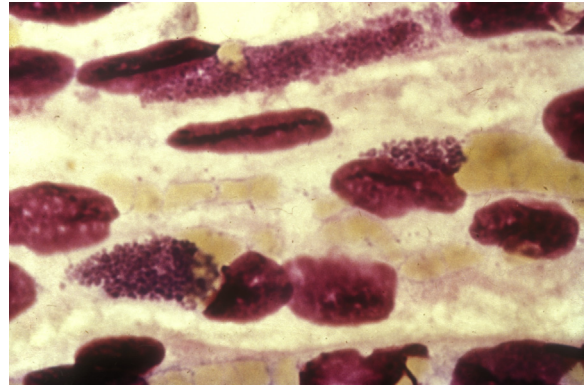


FIGURE 27.29 *Ehrlichia ruminantium* is seen as three masses of organisms in brain tissue of a goat that had died of heartwater. Courtesy of Gerrit Uilenberg.

Heartwater affects all domestic ruminants, especially cattle, sheep, and goats. Domestic buffaloes are also highly susceptible, but they are almost absent in endemic regions. As in several other tick-borne diseases, local breeds are much less susceptible than exotic ones, and endemic stability may occur, particularly in cattle. However, even local breeds of small ruminants may suffer considerable losses.

Infected animals develop fever, and after a few days, develop central nervous system signs. They may become disoriented, and show signs of motor disorder, especially abnormal walking, trembling, and muscle twitching. In addition, cattle may develop profuse diarrhea. As the illness progresses, they develop convulsions and die soon afterwards. Dead and dying animals commonly show a massive accumulation of fluids in the membrane surrounding the heart (pericardium) and edema in the lungs and other organs. Surviving animals become immune. Ruminants which appear healthy can actually be carrying *E. ruminantium* at low levels which can be infective to ticks for up to a year (Allsopp, 2010). Additionally, ticks in heartwater endemic areas have very low infection rates (1%–7%) which increases the difficulty of elimination of the pathogen once it is established in a particular region. Calves are protected by a short period of age-dependent tolerance, and possibly to some extent also by maternal antibodies transferred in milk. As a result, infected calves often develop only mild illness, or none at all. The disease is quite severe in exotic breeds of sheep and goats, with Angora goats being a most susceptible breed. Introduction of exotic livestock disrupts endemic stability and often leads to epidemics of the disease. Similarly, rapid resurgences of vector tick populations following drought also can lead to devastating epidemics. Moreover, endemic stability can be disrupted by excessive use of pesticides, which destroys the natural herd immunity that results from constant, low-level challenge by small numbers of infected ticks.

In ruminants, multiplication of *E. ruminantium* is observed in endothelial cells, which is easiest seen in the capillaries of brain-cortex smears (Fig. 27.29). However, its presence in circulating neutrophils in the blood has also been demonstrated.

The agent of heartwater is transmitted by at least 10 African species of *Amblyomma* ticks, most of which have indiscriminant feeding habits. In view of its enormous geographic range and adaptability to varying climatic conditions, the tropical bont tick, *A. variegatum* is the primary vector in most enzootic areas of Africa and the Caribbean. The bont tick, *Amblyomma hebraeum* (Fig. 27.18), which is found in subtropical southern Africa, is also an important vector. Other *Amblyomma* species are important locally as vectors to livestock and wild ungulates. *Ehrlichia ruminantium* is maintained transstadially within populations of ticks, in which there is multiplication in the gut and later in the salivary glands. The pathogen is transmitted by the bite of the tick. Ticks remain infected for long periods, possibly for life. Transovarial transmission has been reported but appears to be exceptional.

There is considerable strain diversity, which complicates the development of a reliable and safe vaccine. Immunization is currently carried out, particularly in South Africa, by inoculating blood from a sheep reacting to a well-characterized stock (i.e., Ball 3). The injection has to be carried out intravenously, and the animals have to be closely monitored in order to treat them in good time. The procedure is risky from several points of view and is labor-intensive and far from 100% effective.

In the 18th or 19th century, the tick *A. variegatum* and the causal agent of heartwater were introduced into the Caribbean region with cattle from West Africa. The tick is, or has been, present on several islands of the Lesser Antilles, whereas heartwater is known to occur on Guadeloupe, Marie-Galante, and Antigua. It is likely that the tick is spread from island to island by another African immigrant, the cattle egret. Because of the constant threat of invasion of more islands and particularly the American mainland, an eradication program has been set up, but lack of continuity in financing and international coordination has led to intermittent abandonment of this program (Pegram, 2006). Some islands have been freed from the tick, but the constant migration of cattle egrets can easily result in reinvasion. Invasion of the North American or South American mainlands would be disastrous for the livestock industry, not only because of heartwater, but even more so because *A. variegatum* is associated with severe dermatophilosis. Three American species of *Amblyomma* ticks are experimental vectors of heartwater, one of them, *A. maculatum*, being an efficient vector. Additionally, white-tailed deer are susceptible hosts and could serve as potential reservoirs should heartwater become introduced to North America.

For further information about heartwater, see the reviews by Camus et al. (1996), Mahan (2006), and Allsopp (2010, 2015).

Granulocytic Anaplasmosis

Anaplasma phagocytophilum is an important pathogen of livestock and domestic animals (including dogs and cats), and also a cause of human granulocytic ehrlichiosis, an important zoonosis. In Europe, *Ixodes ricinus* transmits this rickettsia, the causative agent of **tick-borne fever** (also called **pasture disease**) to sheep, cattle, and goats. Reduced milk production, and abortions can occur in infected animals. The organism infects granulocytes (neutrophils and eosinophils) and induces a marked immunosuppression that may predispose animals to secondary infections (such as pyaemia by *Staphylococcus aureus* in lambs) and reduce their antibody response to vaccination against other diseases. *Anaplasma phagocytophilum* also causes infection and febrile illness in horses in the United States and has also been found in Europe. In the USA it is transmitted by *Ixodes pacificus* and *I. scapularis*. It may also cause a mild illness in dogs, in which it is morphologically indistinguishable from *Ehrlichia ewingii*. *Anaplasma phagocytophilum* is passed transstadially, but not transovarially, in the tick vector. Further review of this topic can be found in Dugat et al. (2015).

Other Anaplasmoses

Anaplasma platys infects canine platelets, causing their numbers to fluctuate over time. While primarily considered a canine pathogen, variants have been identified as causing disease in cattle and humans. This infection is mild and is often diagnosed as **canine cyclic thrombocytopenia**. The tick vector(s) of this species have not been determined, although *Rhipicephalus sanguineus* is often found to be infected. This species has been identified in the southern United States, Greece, Taiwan, and Japan and other locations.

In many tropical and subtropical regions, cattle and domestic buffalo can be infected with *A. bovis*, which is usually benign, whereas more pathogenic congeneric parasites occur in Central and West Africa, and Brazil. Known vectors belong to the genera *Hyalomma*, *Rhipicephalus* and *Amblyomma*. *Anaplasma bovis* develops in mononuclear cells, as does the closely related *Ehrlichia ovina* in small ruminants. Many other *Anaplasma* spp. and *Ehrlichia* spp. have been described, and more are being discovered every year. One example is "*Anaplasma capra*" identified from goats in China. It has been found to infect humans, although the agent has not been fully characterized after isolation into pure culture. The pathogenic potential of these newly recognized taxa may not be fully known, and further study is needed.

Erythrocytic Anaplasmosis

This section is limited to “classical” anaplasmosis, caused by rickettsial agents residing in red blood cells. Anaplasmosis was first described in South Africa in 1910 by Max Theiler, who also identified and named the primary agent 1 year later. This parasite, *Anaplasma marginale*, and two related species, sometimes considered to be subspecies or variants of it, (*A. centrale* and *A. ovis*), infect red blood cells of cattle and sheep throughout much of the world. Other described species either are not recognized as separate taxa or have no standing in taxonomic nomenclature. Anaplasmosis is now considered one of the most important diseases of livestock. The causative agent, *Anaplasma marginale*, is a pleomorphic, coccoid rickettsia that occurs and multiplies in membrane-bound inclusions called colonies in the cytoplasm of infected erythrocytes.

Disease onset is abrupt following a lengthy incubation period of 2–6 weeks. Common clinical manifestations include fever of several days duration, labored breathing, loss of muscle tone in the rumen, constipation, and hemolytic anemia, often followed by jaundice (Fig. 27.30). Animals usually recover when infected with strains of mild virulence, whereas 30%–50% of those infected with highly virulent strains may die. Moreover, severity of disease and case-fatality rates increases with age. Cattle that recover from acute anaplasmosis maintain a persistent, low-level parasitemia that protects them from reinfection; however, they constitute a reservoir of infection in the herd.

Approximately 20 species of ixodid ticks serve as vectors of *Anaplasma* species. The main vectors in subtropical and tropical countries are *Rhipicephalus* (*Boophilus*) ticks: *R. (B.) microplus*, *R. (B.) annulatus*, *R. (B.) decoloratus*, and probably *R. (B.) geigy*. *Hyalomma*

spp. and other *Rhipicephalus* spp. also play an important role. In North America, the primary vectors are *Dermacentor* species: *D. andersoni*, *D. albipictus*, *D. occidentalis*, and *D. variabilis*. In Europe, *D. reticulatus* and possibly *D. marginatus* appear to play a role. Blood-sucking flies in the family Tabanidae (horse flies and deer flies), and other blood-sucking insects, have been implicated as mechanical vectors. Mechanical transmission can also occur during vaccination and dehorning campaigns, when the same needles, syringes, or other instruments are used on several animals.

Anaplasma marginale undergoes a complex developmental cycle in ticks involving five morphological forms (Kocan et al., 2010). Details of the life cycle have been elucidated in *D. andersoni* and are presumably representative of the parasite’s development in its other tick vectors. It has recently been shown that endosymbiont bacteria within the ticks may influence tick susceptibility for *A. marginale* infection (Gall et al., 2016). The genetic and morphologic characteristics of *Anaplasma* spp. and their development within ticks are similar to those of *Ehrlichia ruminantium* and other *Ehrlichia* spp. in their tick vectors. *Anaplasma marginale* is passed transstadially, but not transovarially, within ticks. *Dermacentor andersoni* females infected as nymphs begin transmitting the infection by the sixth day of feeding on a susceptible host, whereas male ticks that acquire infection as adults can transmit the pathogen within 24 h. Male ticks are of considerable importance as vectors because they feed repeatedly. They also readily transfer between hosts that are in close contact, and are therefore capable of transmitting *A. marginale* to multiple hosts. The transfer of ticks between individuals also explains why one-host ticks such as *Rhipicephalus* (*Boophilus*) spp. are vectors of *A. marginale*.

Cases occur frequently on farms located adjacent to tick-infested woodlands. In the eastern United States, the presence of white-tailed deer is considered a risk factor because this cervid is an important host of tick vectors. However, white-tailed deer are not competent reservoirs of *A. marginale* and therefore do not serve as a source of infection for noninfected ticks. In the western United States, mule deer are not only primary hosts but also competent reservoirs of *A. marginale*. Although national statistics are not available, prevalence rates of up to 20% are reported from states throughout the United States where tick vectors are present.

Immunization against bovine anaplasmosis is complicated by the existence of antigenic diversity, particularly when inactivated vaccines are used. In several countries the related rickettsia *A. centrale* is injected as a live vaccine, obtained from donor cattle, and gives a satisfactory degree of protection against anaplasmosis caused by *A. marginale*.

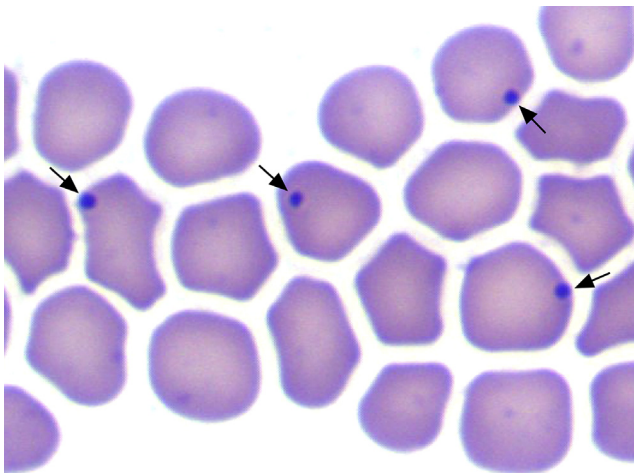


FIGURE 27.30 Blood smear showing *Anaplasma marginale* (arrows) in bovine red blood cells. (Photograph by Susan M. Noh, U. S. Department of Agriculture).

Borrelioses

Borrelioses are diseases of birds and mammals caused by spirochetes in the genus *Borrelia* (Fig. 27.31). Important tick-borne borrelioses include avian spirochetosis and Lyme disease. **Avian spirochetosis** is a highly fatal disease of turkeys, pheasants, geese, doves, chickens, and canaries in Europe, Africa, Siberia, Australia, Indonesia, India, and North, Central, and South America. It causes severe losses to the poultry industry in certain countries. Infected birds develop high fever, diarrhea, and become cyanotic. Birds that survive develop a long-lasting immunity. *Argas persicus*, and related ticks (subgenus *Persicargas*) transmit the etiologic agent, *B. anserina*, via infectious tick feces or by bite. *Borrelia anserina* is related to borreliae in the relapsing fever group. Transstadial passage and transovarial transmission occur, and ticks can remain infective for 6 months or longer.

Dogs, cats, cattle, horses, and possibly sheep can be infected with certain etiologic agents of **Lyme disease** (*Borrelia burgdorferi* s.l.). This disease, or related disorders, has been reported from numerous countries on five continents: Africa, Asia, Europe, North America, and South America. Earlier claims that *B. burgdorferi* is present in Australia have not been confirmed by recent field, sentinel, and laboratory studies. However, recent studies in various South American countries indicate the presence of Lyme-like illnesses (Baggio–Yoshinari syndrome in Brazil), some of which have been attributed to strains of *Borrelia* spp., including members of the *B. burgdorferi* sensu lato complex. Populations of domestic dogs living in areas highly endemic for *B. burgdorferi* can have seroprevalence rates as high as 90%, even though relatively few seropositive animals manifest overt clinical signs. Indeed, 25%–50% of apparently healthy dogs in some areas may have significant antibody titers to *B. burgdorferi*. In hyperendemic foci of the northeastern, northcentral and farwestern United States, the most commonly observed clinical manifestations among dogs

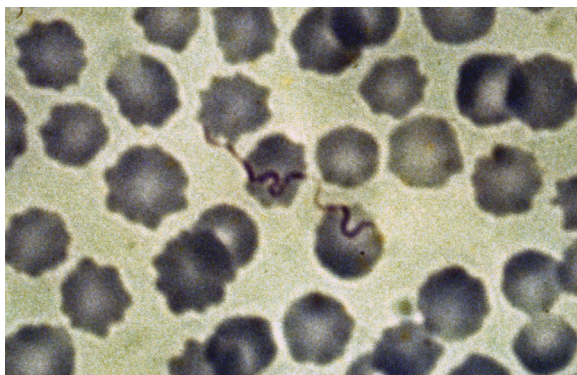


FIGURE 27.31 A *Borrelia* spirochete in the peripheral blood of an infected cow, Wright-Giemsa stain. Courtesy of Gerrit Uilenberg.

are lameness, inappetence, fever, and fatigue. Dysfunction of the central nervous system, heart block (secondary to myocarditis), and a renal syndrome have been associated with *B. burgdorferi* infection in some dogs.

Cats reportedly are exposed to *Ixodes scapularis* infected with *B. burgdorferi* and can develop elevated antibody titers to this spirochete; however, the clinical significance of these findings is unknown. In northern California (USA), outdoor cats living in rural or semirural settings occasionally are bitten by *I. pacificus* females but apparently at a frequency much lower than that of dogs.

Lyme disease has been reported in cattle and horses in the northeastern and upper midwestern United States. Antibodies against *B. burgdorferi* have been detected in serum or synovial fluid in cattle exhibiting lameness or arthritis, but a causal relationship between exposure to such spirochetes and clinical disease in bovines has not been established. In some areas of the United States and Europe, serological studies have recorded prevalence rates of up to 48% in horses living in areas with known exposure to *B. burgdorferi*-infected ticks. Although arthritis, edema, and dermatitis have been observed in some animals, clinical illness attributable to *B. burgdorferi* infection apparently is uncommon in horses.

Bovine borreliosis is a benign disease of cattle, sheep, and horses that occurs in Africa and Australia (Burgdorfer and Schwan, 1991). Infected animals experience one or two attacks of fever, loss of appetite, weight loss, anemia, and weakness. The causative agent, *Borrelia theileri*, is transmitted by *Rhipicephalus* spp. and possibly other genera of ixodid ticks. This borrelia, along with the lone star agent (“*B. lonestari*”) and *B. miyamotoi*, form a clade that is distinct from, but most closely related to, the relapsing fever group spirochetes. Recently, several relapsing fever bacteria, including *B. turicatae*, *B. hermsii*, and *B. persica*, have been reported as causing disease in dogs (Cutler et al., 2017).

Epizootic bovine abortion (EBA), also known as “foothill abortion,” is a major disease of rangeland cattle in the far-western United States, particularly California. Since its first recognition as a distinct clinical entity during the 1950s, various microorganisms have been evaluated or proposed as potential etiologic agents. Recently, a novel delta-proteobacterium (*Pajaroellobacter abortibovis*) identified in thymus tissue from EBA-affected fetuses and detected in wild-caught *O. coriaceus* ticks by PCR was implicated as the etiologic agent (King et al., 2005; Brooks et al., 2016).

Tularemia

Tularemia, caused by the bacterium *Francisella tularensis* subspp. *tularensis*, is primarily a disease of rodents and

lagomorphs (rabbits and hares) in the Northern Hemisphere. Although best known for its public health importance, *F. tularensis* also is a veterinary pathogen that can cause devastating epizootics in domestic sheep. Reliable reports of epizootics in North America date back to 1923 when serious losses occurred in eastern Montana and southern Idaho (Jellison, 1974). These outbreaks shared several features: animals were put on rangeland enzootic for *F. tularensis* in early spring, they grazed in sagebrush areas where *D. andersoni* ticks were abundant, and they became heavily infested with ticks. *Dermacentor andersoni* is considered the principal vector *F. tularensis* in the western United States. As many as 50% of a sheep herd may become sick, and 10% may die within a few days. Diseased animals that survive such outbreaks may lose weight and condition during their illnesses. Although sheep usually are quite resistant to infection with *F. tularensis*, reduced vitality of animals after a long winter, shortage of feed, exposure to early spring storms, and heavy infestations of ticks predispose flocks to epizootics. Over 14,000 cases of tularemia in sheep were recorded in the United States between 1923 and 1945. In contrast, only about 40 cases were reported in sheep in Canada by 1945. Although outbreaks continue to occur, case numbers have dropped considerably due to timely detection and effective control measures.

Epizootics of tularemia among sheep constitute a risk factor for humans. Jellison and Kohls (1955) presented records of 189 human cases of tularemia associated with the sheep industry in the United States. Of these, 66 cases occurred among sheep shearers. Other individuals found to be at particular risk were sheep owners, sheep herders, veterinarians, and spouses of sheep handlers.

Domestic cats appear to be more susceptible to *F. tularensis* subsp. *tularensis* than dogs. Infection occurs when a cat ingests an infected animal, the most common being rabbits. These infected cats, then, are able to transmit tularemia to their owners through bite, scratch, and contact of bodily fluids with the human's skin. In the central United States, feline tularemia cases peak between March and June and between September and November. These seasonal peaks may reflect what is actually happening in the definitive rabbit hosts and their relationship with tick vectors. The May/June peak coincides with the primary questing activity of *A. americanum*, which are important vectors. The September/November seasonal peak coincides with the activity cycles of two other potential tick vectors, *Haemaphysalis leporispalustris* and *I. scapularis*, both of which are known to feed on rabbits and reported with natural infections of *F. tularensis* (Mani et al., 2016). More research is needed to better understand the link between cats, rabbits, humans, and potential tick vectors.

Q Fever

Coxiella burnetii, the agent that causes Q fever, is widespread in populations of domestic livestock and wildlife. Infection in mammals other than humans, however, is typically benign. For that reason, this disease is discussed primarily in the section on public health importance. Nonetheless, *C. burnetii* is also a veterinary pathogen, which can induce abortion in pregnant cows and ewes. Goats are known reservoirs of *C. burnetii*, but recent research suggests their role in the natural maintenance of the disease is limited. It is interesting that the genotypes found in human endocarditis are associated with genotypes circulating in goats. Because infected animals excrete large numbers of *C. burnetii* in their waste and in birthing tissues and fluids, they pose a significant health risk for animal handlers. Infected ticks produce infectious feces that can contaminate the wool of sheep and become aerosolized when handled. However, for the general public, the danger of acquiring infection arises from inhalation of bacteria-laden dust as it becomes airborne. As noted earlier, *Coxiella*-like endosymbiotic bacteria are often found in ticks, but are not thought to infect animals.

Dermatophilosis

Dermatophilosis, also called **cutaneous streptothricosis**, is a skin disease of domestic and wild mammals, including occasional humans, and is caused by the bacterium *Dermatophilus congolensis*. It is especially economically important to cattle and sheep production. In sheep, the disease may be known as **lumpy wool**. The pathogen is transmitted from animal to animal by mobile zoospores. The infection is widespread, probably cosmopolitan, and normally benign. Transmission and the development of severe skin lesions (Fig. 27.32) following infection are favored by humidity and heat, and by the presence of certain *Amblyomma* spp., notably, the tropical bont tick



FIGURE 27.32 Senepol cattle on the Caribbean island of Nevis, affected by severe dermatophilosis. Courtesy of Gerrit Uilenberg.

A. variegatum. The role of this tick had long been suspected in Africa, and even earlier in the Caribbean region, where this African tick had been introduced.

The role of *A. variegatum* in this disease was experimentally confirmed by Walker and Lloyd (1993). Although *D. congolensis* is not introduced when the tick feeds, the saliva of attached *A. variegatum* adults influences the pathogenesis of dermatophilosis, causing severe dermatophilosis in ruminants when the tick is present. Dermatophilosis therefore is not a tick-borne disease but rather a tick-associated disease.

Host resistance to dermatophilosis varies significantly in different areas, with much higher resistance in local breeds than in exotic stock. The constant high humidity in the Antilles is particularly favorable for the transmission and development of dermatophilosis and also to the multiplication and survival of *A. variegatum*. The recent expansion of *A. variegatum* in Zimbabwe into the Highveld, the prime cattle production zone in the country, has challenged earlier notions of how arid conditions affect the spread of this disease. As a result of the significant reduction of tick control throughout the country, there are reports of herd infections rates up to 60%. While still associated with the rainy season, there are challenges for how to implement tick control in areas experiencing low resource challenges, particularly among exotic breeds.

Dermatophilosis is considered the most important cattle disease in some of the Caribbean islands, where it presents a greater concern than heartwater. In the 1980s, when cattle on many of the islands were newly exposed to *A. variegatum*, they were particularly susceptible to severe dermatophilosis (Fig. 27.32). On the island of Nevis, for example, losses of 75% of cattle to this disease were reported and farmers were forced to abandon their cattle-breeding operations (Hadrill et al., 1990). This is in contrast to the islands of Guadeloupe and Marie-Galante, where the tick was introduced from endemic areas of West Africa two or three centuries ago and “Creole” sheep became more resistant to infection. No vaccine is currently available, and the only prevention is intensive tick control. This poses a significant concern should *A. variegatum* be introduced to the American mainland.

Tick Paralysis

The first reports of tick paralysis in livestock originated in Australia in 1890 and in British Columbia, Canada, in 1912. This condition is most common in livestock and pets and causes injury or death to thousands of animals each year. Tick paralysis has been reported from many countries in North America, Europe, Asia, and Africa. There are at least 73 species of ticks that can cause paralysis; however, most studies have only focused on a relatively few (Mans et al., 2004; Durden and Mans, 2016).

In South Africa, the **Karoo paralysis tick** (*Ixodes rubicundus*) is thought to be responsible for annual losses of sheep and goats and a low percentage of game animals in some areas. Other animals affected include cattle and species of wild antelope. Induction of paralysis by *I. rubicundus* is directly related to the total number of ticks feeding on a host. Stock farmers regard tick paralysis as one of the most important problems affecting their operations. The disease occurs in hill rangeland or mountainous terrain covered with a “Karoo” type of vegetation, which is grassy areas interspersed with shrubs or trees. Although *I. rubicundus* parasitizes many wild mammals, only antelopes are known to develop paralysis.

Another tick that paralyzes sheep and goats in Africa, particularly in South Africa, although not as severely or as often as *I. rubicundus*, is *Rhipicephalus evertsi evertsi*. This tick has been recognized as a cause of tick paralysis since 1900. The induction, duration, and severity of the paralysis are related to the number of female ticks that have engorged to body weights of 15–21 mg. *Hyalomma* ticks have been implicated as causing paresis or paralysis of camels in the Sudan and Somalia.

In North America, three species of *Dermacentor* ticks cause paralysis in companion animals and livestock. In the eastern and western United States, *D. variabilis* is a common cause of tick paralysis in domestic dogs. In the Sierra Nevada foothills of northern California, for example, an average of six cases was seen in two veterinary practices during a 1-year investigation (Lane et al., 1984). Dogs were infested with a mean of 32 ticks; 98% were *D. variabilis* adults. Another tick from the same region, *D. occidentalis*, is responsible for occasional cases of tick paralysis in cattle, ponies, and deer, but not dogs.

The most important species of paralysis-inducing tick in North America is *D. andersoni*, which was responsible for paralyzing sheep and cattle in the Pacific Northwest (British Columbia, Washington, Idaho, and Montana. Individual outbreaks have involved up to 320 animals with cases occurring most frequently from April to June when adult *D. andersoni* activity is greatest.

In Australia, *Ixodes holocyclus* induces paralysis in dogs, cats, horses, and humans. This tick inhabits a narrow zone along the eastern coast of Queensland and Victoria. Drugs administered along with hyperimmune serum to dogs with advanced paralysis improve chances for full recovery. Among several drugs tested, phenoxybenzamine hydrochloride, an alpha-adrenergic-blocking agent, has been found to be most effective.

In Europe and Asia, tick paralysis is widely scattered. In Macedonia and Bulgaria, paralysis in sheep, goats, chickens and cattle has been attributed to *Haemaphysalis punctata*, and in Crete, the former Yugoslavia, and the former Soviet Union, livestock are sometimes paralyzed by

bites of *I. ricinus*. Recently, *R. sanguinius* has been linked with tick paralysis in dogs in Italy.

Birds are also susceptible to tick paralyzes. Larvae of *Argas walkerae* induce paralysis in chickens in South Africa. A toxic fraction isolated from replete larvae of this argasid tick consists of two proteins having “membranophilic” properties and molecular masses of 32 and 60 kDa; extracts containing these proteins induced paralysis in 1-day-old chicks. In the southeastern United States, a number of species of wild birds, especially passeriforms, are paralyzed by attached *Ixodes brunneus* females. Single adult ticks can render a bird incapacitated and can lead to death from exposure and predation.

General reviews of tick paralysis and tick toxicosis (see later) have been given by Gothe (1999), Mans et al. (2004), and Durden and Mans (2016).

Tick Toxicoses

Toxic reactions have been associated with the bites of certain species of ticks, notably, argasids. In Africa, cattle bitten by *Ornithodoros savignyi* may die of toxicosis in just 1 day. Sheep attacked by *O. lahorensis* in eastern Europe and in the southern region of the former Soviet Union may tremble, gnash their teeth, exude frothy saliva, experience paralysis, and sometimes perish. In Brazil, *Ornithodoros brasiliensis* has been broadly implicated in human and canine cases of tick toxicosis. In Europe, *Argas persicus* can cause leg weakness in ducks and geese; this condition resembles a true toxicosis and not a paralysis. A toxic illness that affects mainly calves in large areas of central, eastern, and southern Africa is known as **sweating sickness**. Wild hosts include eland, antelope, and zebra. The illness, which begins 4 or more days after *Hyalomma truncatum* tick attachment, is characterized by fever, loss of appetite, lacrimation, salivation, and an eczema-like skin disease but no paralysis. Approximately 75% of afflicted animals die. The active principal component is a salivary gland protein; this is present in females of only certain strains of this tick species. A similar disease has been reported in India and Sri Lanka.

Large numbers of *Rhipicephalus appendiculatus* (the brown ear tick) in southern Africa also have been suspected of causing tick toxicosis in cattle. This may be partly complicated by the transmission of the mildly pathogenic agent *Theileria taurotragi*.

PREVENTION AND CONTROL

Historically, control of ticks and tick-borne diseases almost always relied on pesticides to kill the ticks and o drugs to kill the infectious agents. The cattle tick *R. (B.) annulatus* was eradicated in the United States by dipping

cattle in pesticide solutions, thereby eliminating the deadly Texas cattle fever. Quarantine, pasture rotation, and elimination of deer also were used in the effort to eradicate this vector. It has been estimated that reintroduction of cattle ticks, *Rhipicephalus (B.)* spp., could cost the United States cattle industry more than US\$1 billion annually to achieve eradication again. Costs to the worldwide cattle industry were estimated in 1984 by the Food and Agriculture Organization of the United Nations at more than US\$7 billion. Damage to other livestock and valuable wildlife by ticks and tick-borne diseases is much more difficult to estimate. Losses due to human illnesses have never been calculated.

Treatment with acaricides still provides the most widely used means to control or prevent tick attacks. However, intensive use of acaricides has resulted in many populations of ticks resistant to the limited chemical tools currently available for use (Rodríguez-Vivas et al., 2018). Promising alternatives, such as **vaccines** or **pheromone-acaricidal treatments**, are being investigated. Two commercial recombinant vaccines have been available against the southern cattle tick, *R. (B.) microplus*, based on a so-called concealed antigen, which occurs in the tick gut but is not exposed to the host immune system during normal feeding. Research continues on multiple other antigens and other important tick species. These and other novel alternatives are discussed later. Integrated management of ticks using a combination of techniques and tools will provide the most sustainable means of reducing tick numbers.

Personal Protection

Personal protective measures are the most effective means for preventing tick bites in persons who enter tick-infested habitats. However, these practices are used less often than desired even in endemic areas (Butler et al., 2016). People at risk for tick bite should wear boots, socks, long trousers, and light-colored clothing. Trousers should be tucked into the boots, socks should be drawn over trousers, and the socks should be taped to form a tight seal. The clothing should be treated with a repellent or **acaricide**. It is now possible to obtain clothing permanently impregnated with permethrin that remains efficacious for the life of the garment, despite repeated washings (Faulde and Uedelhoven, 2006; Vaughn et al., 2014). A recent study showed that wearing protective clothing was 40% effective in preventing Lyme disease (Vasquez et al., 2008). Exposed skin also should be treated with repellents suitable for use on humans (Pages et al., 2014). Permethrin should not be applied to skin.

Each person should conduct daily self-examinations (“tick checks”) for ticks during and after exposure to tick-infested areas. Early removal of attached ticks is

important in minimizing the risk of contracting tick-borne diseases. Ticks should be removed by grasping the capitulum as close to the skin as possible with a pair of fine forceps and gently pulling the tick with a slow, steady force until its mouthparts release their hold. Turning or twisting the tick should be avoided to prevent the hypostome breaking off in the wound.

The most widely used personal protectant is the repellent DEET, usually available as a lotion or a spray. Applications should be repeated as per label instructions to maintain maximum protection, but should be applied cautiously on children to avoid adverse reactions that occasionally follow overuse. Newer formulations of DEET, picaridin, and some plant-based repellents will provide varying periods of protection and may have characteristics that are more desirable to the user (e.g., non-oily feel, rapid evaporation of the carrier, etc.).

Acaricides

Acaricides are chemicals used to kill ticks and mites. The term ixodicides is sometimes applied to acaricides used against ticks. Acaricides include arsenical preparations, chlorinated hydrocarbons (e.g., DDT and lindane), organophosphorus compounds (e.g., coumaphos), carbamates (e.g., carbaryl), formamidines (e.g., amitraz), pyrethroids (e.g., permethrin, flumethrin), formamidines (e.g., amitraz), macrocyclic lactones (e.g., ivermectin), phenylpyrazoles (e.g., fipronil), insect growth regulators (e.g., fluazuron), and isoxazolines (e.g., afoxalaner, fluralaner, sarolaner). The synthetic pyrethroids are among the safest and most effective pesticides and are now widely used for tick control. Fipronil is a moderately toxic broad-spectrum phenylpyrazole insecticide, widely used against ticks and other ectoparasites of pets. The introduction of the isoxazolines has provided a convenient oral dosing for pets with long-lasting efficacy.

One way to kill ticks on host animals is to dip livestock and pets in a pesticide bath. When used for cattle, this is termed a cattle dip. Dipping alone is not always effective. Often, ticks hidden in sheltered locations (e.g., between the toes, in the ears, or under the tail) are missed and survive to lay eggs and reestablish the pest population. This is valid for motorized spray-races (facilities where cattle are directed into a chute where pressurized spray is directed from various angles). For intensive tick control, dipping is therefore supplemented by applying an acaricidal cream (“tick-grease”) or spray to such sites. Acaricides can be delivered as sprays, using manual or motorized high-pressure sprayers to provide a mist that can reach every part of the animal’s body. They can also be delivered as **pour-ons** or **spot-ons**. These are topical formulations in which the acaricide is mixed with surfactants to spread the liquid over the animal’s hair coat. Finally, they may be

applied as **dusts**, in which acaricides are mixed with talc and deposited directly onto the animal’s fur. The familiar “flea powders” for pets, which are effective against ticks as well as fleas, and the dust bags used for treating cattle are examples of acaricidal dusts.

To achieve long-lasting efficacy, acaricides can be incorporated into plastic or other suitable matrices that provide a slow release of the toxicant over a period of weeks or months. **Plastic collars**, such as the familiar flea and tick collars, are widely used for control of ticks on cats and dogs. Newer collar products containing flumethrin for ticks and imidicloprid for fleas have been used to reduce ticks in rickettsial endemic areas (Drexler et al., 2014). Similarly, acaricide-impregnated plastic ear tags are widely used for control of ear-infesting ticks (e.g., Gulf Coast tick and spinose ear tick) on cattle and other large domestic animals. However, they are much less effective for control of ticks that attach around the groin, udder, and other parts of the hindquarters of these animals. **Systemic acaricides** offer another means of providing long-lasting and effective tick control. In this case, the toxicant is introduced into the host’s blood to kill ticks as they feed on the treated animals. Unfortunately, most acaricides are too toxic to administer to animals systemically. An exception is ivermectin, which can provide excellent control of certain ticks on cattle for 2–3 months.

Each application method has its advantages and disadvantages. Dips and spray-races are suitable for treating large numbers of animals. The efficacy of manual spraying depends on the person applying it and it can only be applied to a limited number of animals, whereas the application by pour-ons can be expensive. Dip sites where persistent arsenical and chlorinated hydrocarbon compounds may have been used for many years are often heavily contaminated and can represent a significant environmental hazard.

The development of **acaricide resistance** by ticks is a continuing concern. Ticks have been found to be resistant to arsenic, cyclodiene pesticides, other chlorinated hydrocarbons, organophosphorus insecticides, pyrethroids, and formamidines. Resistance may occur in one or more species in an area, while other species in the same locality remain acaricide-susceptible. Some strains of cattle ticks in Australia and elsewhere have been found to be resistant to most or all of the acaricides currently in use, including pyrethroids and amitraz. Resistance of cattle ticks to pyrethroids and organophosphorus compounds has also been found in Mexico and poses concerns regarding the possible reestablishment of these ticks into the United States. Continued research is necessary to discover and develop new pesticide products to overcome resistance to compounds already in use. Efforts to identify genetic markers of resistance and develop monitoring assays will provide tools to identify resistant populations so that

knowledge can be used to enhance other tick control strategies (Lees and Bowman, 2007; Miller et al., 2017).

Pheromone-Assisted Control

The difficulties and high cost of tick control on animals have stimulated interest in alternatives to the conventional methods described above. Such alternatives help to reduce the use of acaricides. Research with tick pheromones suggests that combinations of pheromones and acaricides can be significantly more effective for controlling ticks than the acaricide alone, because ticks are unlikely to develop resistance to their own pheromones (Carr and Roe, 2016). A pheromone-acaricide combination applied to a single spot-on cattle can be effective in killing the Gulf Coast tick. Another promising device is the “tick decoy” in which the sex pheromone 2,6-dichlorophenol and an acaricide are impregnated into plastic beads on the surface of which “mounting” sex pheromone is applied. Male ticks are attracted to decoys on the animal’s hair coat and killed. This also disrupts mating activity, so that any surviving females cannot lay viable eggs. For the livestock-parasitizing bont ticks *Amblyomma hebraeum* and *A. variegatum*, a tail-tag decoy was developed that uses a mixture of tick-specific phenols to attract ticks to specific sites on cattle and kill them when they attach nearby. Field trials with tail-tags have demonstrated promising efficacy for up to 3 months (Norval et al., 1996; Kelly et al., 2014).

Passive Treatment

Another way to apply acaricides to animals is by means of self-treating devices. Animals seeking food or nesting materials visit these devices and acquire an acaricide, spreading it over their fur and skin to kill ticks. An example is biodegradable cardboard tubes containing a permethrin-impregnated cotton balls. Mice collect the cotton for nesting material, thereby spreading the pesticide among nest mates. Such tubes have been effective in reducing populations of *Ixodes scapularis* and the occurrence of Lyme disease in some localities, especially in residential communities; however, they have not been effective in other situations. Bait boxes containing the acaricide fipronil were found to be effective in killing *I. scapularis* nymphs and larvae on small mammals, reducing these stages by as much as 68% and 84%, respectively, and the infection rate of white-footed mice with *B. burgdorferi* by as much as 53%. Subsequently, the abundance of *I. scapularis* adults in the targeted area was reduced by 77%. Tick infection with *Anaplasma phagocytophilum* was also significantly reduced (Dolan et al., 2004). A commercialized version of the bait box has

found to eliminate up to 97% of *I. scapularis* on rodents (Schultze et al., 2017).

Another example is the **self-treating applicator** for controlling blacklegged ticks (*I. scapularis*) on white-tailed deer (Sonenshine et al., 1996). Animals become coated with oil containing an acaricide as they remove food from the applicator. A similar technique was used in Zimbabwe for treating wild ungulates (Duncan and Monks, 1992). Perhaps the most effective example of this strategy is the “four-poster” self-applicating device for treating white-tailed deer against ticks. Deer attracted to corn or other food bait in the device acquire acaricide from cloth-covered rollers. Field studies showed up to 80% and 99.5% efficacy in controlling *I. scapularis* and *A. americanum* nymphs, respectively (Carroll et al., 2002).

Hormone-Assisted Control

Hormones and insect growth regulators (IGRs) such as methoprene also have been used to disrupt tick development in laboratory experiments. Analogues or mimics of ecdysteroids are effective in killing ticks by delaying their development, disrupting oviposition, or killing the larvae when they hatch from eggs deposited by treated females. However, these compounds do not appear to be uniformly effective against all types of ticks.

BIOLOGICAL CONTROL

The use of biological control has been successful with ticks. Fungal and nematode pathogens have been effective within particular environmental conditions. Predators have also been investigated, but their role is generally considered augmentive and is not likely to significantly reduce tick numbers.

In a recent study, integrated use of broadcast application of the fungus *Metarhizium anisopliae*, fipronil-based bait stations to treat rodents, and reduction of deer was able to significantly reduce questing tick nymphs in the study area (Williams et al., 2018). Such combination of approaches will lead to better and more sustainable control.

Vaccines

Anti-tick vaccines have been used successfully. In Australia, a commercial recombinant antigen vaccine has been developed for the control of the southern cattle tick *R. (B.) microplus*, based on a so-called concealed antigen (Bm86) in cells of the tick gut. A similar recombinant vaccine, based on the same antigen, has been developed in Cuba. Recent reports suggest that the recombinant Bm86 can reduce tick fecundity by as much as 90%. Although it is possible that antigen-resistant strains of cattle ticks may

appear, large-scale vaccination of cattle herds with these recombinant vaccines offers a promising alternative or supplement to acaricides. The vaccines are active not only against *R. (B.) microplus*, but also against related species.

Research on many other antigens and other tick species is in progress (de la Fuentes and Contreras, 2015). Of special interest is the development of novel combinations using RNAi (see Chapter 28) to silence subolesin and a tick-protective antigen, Rs86 (similar to Bm86); the synergistic effect of silencing both genes causes a much greater reduction of tick feeding and oviposition than targeting either one alone (de la Fuente et al., 2006). Another promising vaccine targets tick-cement protein, disrupting attachment success, as well as midgut injury and the tick's ability to transmit pathogens (Labuda et al., 2006). More recently, peptide vaccines produced to the tick ribosomal protein P0 have shown 90% efficacy against *Rhipicephalus sanguineus* when fed upon immunized rabbits (Rodríguez-Mallon et al., 2012). This same vaccine showed 96% efficacy against *R. (B.) microplus* (Rodríguez-Mallon et al., 2015).

Management

Management practices provide another means of reducing tick numbers. Zero-grazing (i.e., keeping animals confined in stables) minimizes exposure to ticks. Acaricides can be applied directly to vegetation. However, because ticks commonly occur in microhabitats covered by vegetation, leaf litter, soil, and other natural materials, or in the nests, burrows, and other cavities used by their hosts, they often do not come in direct contact with these toxicants. Therefore, to be effective, the acaricides must reach the ticks as vapors or by contact when the ticks move about while seeking hosts. Public opposition to treatment of natural habitats with pesticides has made it unpopular to use this form of tick control except for the most compelling reasons. In recent years, acaricidal treatment of natural areas has been limited largely to military bases or selected recreational areas. Alternatives include habitat modifications such as burning or clearing vegetation or host removal (e.g., removal of deer by hunting and deer-exclusion fences). Burning or clearing vegetation removes the dense cover under which ticks shelter, thereby reducing ground-level humidity as well as exposing them to intense ultraviolet radiation and heat. Such changes can make the habitat unsuitable for tick survival. In field trials in southwestern Georgia, regular prescribed burning was found to significantly reduce tick populations and may also reduce exposure to tick-borne pathogens (Gleim et al., 2017).

Integrated Tick Management

Integrated management of ticks provides the most sustainable and effective means of reducing ticks in the residential environment (Stafford, 2007). Integrated control of ticks also can include the timing of acaricide treatments (e.g., when most engorged females of a particular species drop from their host); livestock management practices such as rotational grazing; cattle-breed resistance, selected use of acaricides, and pathogens and predators of ticks.

Monitoring

Tick surveys often are conducted to determine whether tick control is warranted and, if so, when it should be implemented. The most common method for sampling ticks is the use of a **flag** or **drag cloth** pulled or dragged through the vegetation. Ticks collected on the cloth are counted as the number of a given species per unit of distance dragged (e.g., 100 m) or the number collected per hour of dragging. Although absolute measures of tick population densities cannot be obtained in this manner, the relative abundance of ticks in different areas sampled can be determined. Tick species collected can provide an indication of potential risks of tick-borne diseases in a given area. There are biases to each method of tick monitoring, so the results must be carefully interpreted.

An alternative to dragging is the use of **carbon dioxide traps**. Carbon dioxide gas from a block of dry ice or from a compressed-gas cylinder is the tick attractant. Ticks adhering to or crawling around the trap are counted after a few to several hours of operation. When more reliable estimates of tick abundance are required, a mark-and-recapture method can be used. Using this method, the numbers of marked ticks recaptured from a previous sample are compared with the number of unmarked ticks to obtain an estimate of the entire tick population in the area studied.

For tick-infested cattle, horses, mules, and other livestock, a time-tested method is the **scratching technique**, whereby livestock inspectors pass their hands over different regions of the animal's body to detect attached ticks. A similar technique is used in combination with visual inspection to examine wild animals. For example, investigators can be assigned to deer check stations during hunting season to count all ticks on hunter-killed animals. Another technique for sampling ticks is to trap small and medium-sized wild animals and hold them over trays filled with water or alcohol to catch fed ticks as they detach.

Eradication

In a few cases, tick eradication may be practicable. An example is the Cattle Tick Fever Eradication Program that was initiated in the southern United States in 1907. This program led to the eradication of *R. (B.) annulatus*, *R. (B.) microplus*, and Texas cattle fever from the United States by 1960. However, reinvasion from Mexico continues to be a constant threat, because of illegal movement of livestock across the United States–Mexico border and uncontrollable wild hosts. Tick utilization of native wildlife and exotic hoofstock is a growing concern (Perez de Leon et al., 2012). Attempts to eradicate *R. (B.) microplus* in other areas (U.S. Virgin Islands, Argentina, Uruguay, Australia, and Papua New Guinea) have been unsuccessful, despite reductions of more than 99% of the tick populations in some localities. Acaricide resistance, as well as reinvasion by ticks and their rapid repopulation of areas in the eradication zone, are major contributing factors.

An attempt to eradicate *Amblyomma variegatum*, a vector of the agent of heartwater and associated with bovine dermatophilosis, from islands in the Caribbean has been successful on some islands (Eddy, 2002; Pegram et al., 2004). However, it has not achieved its overall purpose, which was to eradicate the tick from the Western Hemisphere. Although the lack of international collaboration, political will, and funding have been contributing factors, there are also technical reasons that have prevented successful eradication of this tick on some of the islands where it is well established. The tick continues to be a major threat to the American mainland and the Greater Antilles.

Occasionally eradication has been achieved in the case of exotic species that were recognized soon after their introduction to a new area. An example includes the eradication of the African species *R. evertsi* soon after it was introduced into a wild-animal compound in Florida. Eradication is easiest if exotic species are identified as soon as possible after their introduction. This was addressed following the discovery of *Amblyomma marmoratum* and *A. sparsum*, both vectors of heartwater, on nine different premises in Florida (Burridge et al., 2000).

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