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Review

Ticks and tick-borne diseases

Tiques et maladies vectorielles à tiques

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Abstract

Ticks are a major group of arthropod vectors, characterized by the diversity of pathogens they transmit, by their impact on human and animal health, and by their socioeconomic implication especially in countries of the Southern Hemisphere. In Europe, *Ixodes* is the most important tick due to its wide distribution in the ecosystems and the variety of transmitted pathogens, in particular *Borrelia* (responsible for Lyme borreliosis), but also the tick-borne encephalitis virus. Their increased presence in the environment since the beginning of the 20th century is undeniable, because of major modifications in the biodiversity caused by humans. Increasing the awareness of health professionals and the general population is required to achieve better control of these infections. Thus, “a better understanding of these tick-borne diseases for a better control” is a simple but effective approach, considering their ubiquity in the environment and their particular mode of pathogen transmission (long-lasting blood meal for hard ticks and delayed transmission for bacteria and parasites). Finally, these ectoparasites are problematic due to the potential allergic reactions and other damages caused by their saliva, in humans and animals.

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Keywords: Ticks; *Ixodes*; Tick-borne diseases; Lyme; Anthropization

Résumé

Les tiques représentent des acteurs majeurs dans les maladies à transmission vectorielle, tant par la diversité des agents infectieux transmis que par leur impact en santé humaine et animale, et leur impact socioéconomique surtout dans les pays de l'hémisphère sud. En Europe, les tiques *Ixodes* sont les vecteurs les plus importants sur le plan sanitaire, compte tenu de leur large répartition dans les écosystèmes et des différents agents infectieux transmis, parmi lesquels les bactéries du genre *Borrelia*, responsables de la borréliose de Lyme, et le virus de l'encéphalite à tique. L'augmentation de ces tiques dans l'environnement est indéniable depuis le début du XX^e siècle, du fait des modifications majeures apportées par l'homme sur la biodiversité. La sensibilisation du personnel médical et du grand public fait partie des actions essentielles pour mieux contrôler ces infections transmises par les tiques. « Mieux les connaître pour mieux s'en protéger » constitue donc une approche simple, mais efficace compte tenu de leur présence ubiquiste dans notre environnement et du mode particulier de transmission des agents infectieux qu'elles sont susceptibles d'héberger (repas sanguin long le plus souvent et délai de transmission variable pour les bactéries, virus et parasites). Enfin, en tant qu'ectoparasites, les tiques sont aussi susceptibles de provoquer des nuisances plus ou moins importantes par la composition spécifique de leur salive, tant chez l'homme que chez l'animal.

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Mots clés : Tiques ; *Ixodes* ; Maladies à tiques ; Lyme ; Anthropisation

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1. Ticks

Ticks are present worldwide and, depending on species, they may be observed in highly varied habitats, from the driest to the most humid. Ticks are acarines that may be distinguished from insects by the absence of segmented body and by their spherical form. A total of 900 species of ticks have been identified. They are mainly divided into two families: hard ticks or Ixodidae and soft ticks or Argasidae. A third family has been identified, i.e. Nuttalliellidae, but it is only made of one species: *Nuttalliella namaqua* [1]. This species is rarely observed and will thus not be referred to in the present article. A total of 193 species are part of the Argasidae family, mainly as two major genera: *Argas* and *Ornithodoros*. Almost 700 species are part of the Ixodidae family, and they are divided into seven genera. The main genera are: *Amblyomma*, *Dermacentor*, *Haemaphysalis*, *Hyalomma*, *Ixodes*, and *Rhipicephalus*. In France the most frequent genera are *Ixodes* (widely prevalent), *Dermacentor*, and *Rhipicephalus* for hard ticks, and the *Argas* genus for soft ticks (Fig. 1).

1.1. Tick morphology

Ticks are large acarines (several millimeters long) with a non-segmented body or idiosome (merged prosoma [or thorax] and opisthosoma [or abdomen]), four pairs of legs in nymphs and adults, and three pairs of legs in larvae. Hard ticks have a hard dorsal scutum covering one third of their body, except for males as their entire body is covered by the scutum. This is why male hard ticks ingest small quantities of blood or no blood at all. Soft ticks do not have any scutellum. Their tegument looks like crumpled leather. The feeding structure of hard ticks is located in front of the head; it is quite large for *Ixodes* ticks and smaller for other hard ticks. Soft ticks have a very small and barely visible feeding structure located on the underside of the body or sub-terminal part of their body.

1.2. The various stages of development

Ticks go through four development stages: eggs, larvae, nymphs, and male/female adults. Blood must be ingested

in-between each stage to induce molting. Ticks are thus hematophagous at all stages.

Female hard ticks drop off their vertebrate host after the blood meal, to lay thousands of eggs in the vegetation and die. *Ixodes* male ticks (Prostriata) do not feed, but they can be found on a host when they need to breed. Males of other hard ticks (Metastricata) can feed, but only very small quantities of blood (twice their weight). Most of these ticks feed on three different hosts and drop off on the ground between each stage to molt (three-host cycle, most ticks). For two-host cycles, larvae and nymphs stay on the same host and for one-host cycles, the whole life cycle of the tick occurs on one animal [2].

Soft ticks have several nymphal stages (between two and eight); ticks feed on blood in-between each nymphal stage. Both males and females feed, and females lay a few hundred eggs after each blood meal. A blood meal lasts approximately 15 to 30 minutes, except for larvae as they can feed for up to several days [2]. This is why soft ticks are very rarely observed on patients, but rather in their habitats.

1.3. The blood meal

Ticks are all strictly hematophagous. Looking for hosts to feed on is therefore essential for their survival. They have developed a highly complex detection system (sensory bristles, pedipalps, Haller's organ on front legs) to detect hosts, mainly wild animals. Humans are accidental hosts. Ticks end up biting humans when they visit the tick's habitat. Conversely, mosquitoes come into the human habitat. These differences are associated with highly different prevention and vector control measures, which will be addressed later on. The blood meal is long in hard ticks, i.e. between 3 and 10 hours depending on the development stage, and tick bites rather occur during the day. Female adults may ingest blood amounts equivalent to up to 100 times their weight. However, later-stage soft ticks (nymphs and adults) only feed for a few minutes and bites rather occur at night.

1.4. Tick bite and saliva

The tick bite mechanism is particularly sophisticated. After finding a warm and humid spot on the skin, ticks pierce the



Fig. 1. Various genera of ticks. From left to right: dorsal side of ticks with *I. ricinus*, *Dermacentor*, and *Rhipicephalus* hard ticks and *A. reflexus* soft tick. For *I. ricinus*, feeding structures are particularly large and for *A. reflexus*, they cannot be seen as they are located on the stomach. (Photo credit: JM. Bérenger – Vitrome, IHU Méditerranée Infection – Marseille).

Différents genres de tiques. De gauche à droite : tiques en face dorsale avec tiques dures *I. ricinus*, *Dermacentor* et *Rhipicephalus*, tique molle *A. reflexus*. Note pour *I. ricinus*, les pièces piqueuses particulièrement grandes et pour *A. reflexus* les pièces piqueuses non visibles, car présentes sur la face ventrale. (Crédit photo : JM. Bérenger – Vitrome, IHU méditerranée infection – Marseille).

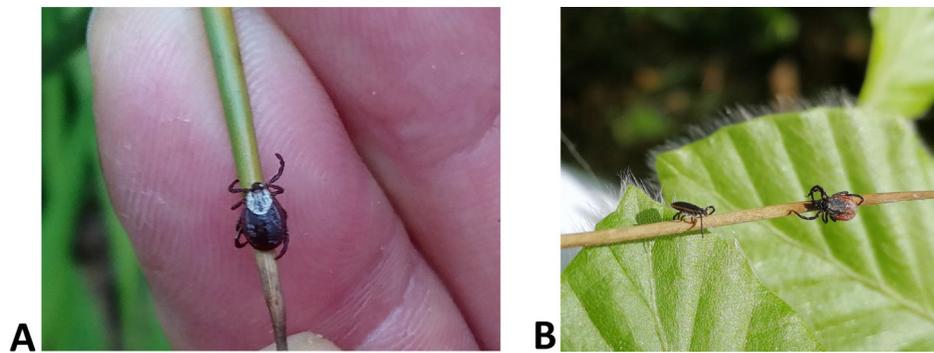


Fig. 2. Questing ticks. A. *D. reticulatus* female tick. B. *I. ricinus* female tick. (Photo credit: N. Boulanger).
Tiques à l'affût. A. Femelle de *D. reticulatus*. B. Femelle d'*I. ricinus*. (Crédit photo : N. Boulanger).

epidermis with their sharp blades (chelicerales) and settle with their denticulated harpoon (hypostome). Ticks then secrete a cement-like substance that keeps them firmly attached to the skin and prevents premature dropping off. An inoculation compartment is formed around the feeding structures, followed by an hemorrhage. The role of tick saliva has extensively been studied and most involved molecules have been identified, mainly in hard ticks because of the long duration of their blood meals. Saliva has a pharmacological action on the host (coagulation and pain inhibition, etc.) but it also inhibits the host's local immune responses through immunosuppressive properties targeting various skin cells [3]. Tick saliva may cause allergic reactions in some hosts, either by inducing an immediate reaction at the bite site – that should be distinguished from erythema migrans observed with Lyme borreliosis – or leading to ascending paralysis mainly observed with *Ixodes* tick saliva [4]. More than 70% of tick bites in adults occur on the legs [5].

Saliva of *Argas* soft ticks is also known to induce an anaphylactic shock in susceptible individuals [6]. Cross allergy to red meat, tick saliva, and an anti-cancer drug (cetuximab) has recently been reported in Australia, the United States, and Europe. This cross allergy is associated with a reaction to galactose- α [7].

2. Ticks of medical interest in France

Various works on ticks were initiated by French entomologists, such as Gilot, Beaucournu, Guigen, and Perez to only name a few [8,9]. Studies thus started to be performed well before the 2016 French national plan on Lyme disease [10].

Approximately 40 species of ticks are currently identified in France. The present article only focuses on the most frequent in humans and on those that may pose public health problems. Considering the major environmental changes made by humans since the start of the 20th century, *Ixodes* ticks now live in anthropogenic forest ecosystems where ticks' favorite wild animals proliferate. All ecosystems are affected, even those located in urban and suburban areas where *Ixodes* ticks may be found [11,12].

2.1. *Ixodes ricinus*

I. ricinus ticks are the most prevalent ticks in France, except around the Mediterranean basin as the climate is too dry. *I. ricinus* ticks are also observed in central Corsica because of a humid and continental climate. In continental climates, diapause is observed in *I. ricinus* ticks during winter and they are usually active from March to October depending on climatic conditions. In oceanic climates, *I. ricinus* ticks are active almost all year round. Most ticks wait for their host, in a position known as “questing”, on the tips of grasses and leaves (Fig. 2). Highly susceptible to desiccation, *Ixodes* ticks drop off the host on a regular basis to rehydrate on the ground. They are able to climb, up to one-meter high, and to come down on vegetation. They, however, never fall from trees. *Ixodes* ticks are ubiquitous and can feed from more than 300 hosts: small and large mammals, reptiles, birds (Fig. 1) [13].

2.2. *Dermacentor reticulatus* and *D. marginatus*

Adult *D. reticulatus* and *D. marginatus* ticks are mainly found on humans, and nymphs and larvae are found in animals' hutches. They have short feeding structures and their cuticle is marbled (Fig. 1). *D. marginatus* ticks are particularly prevalent around the Mediterranean basin. They are thermophilic ticks, commonly found in open areas such as clearings, but also in forests. *D. reticulatus* ticks are more frequently observed in continental climates. They are commonly found on dogs and sheep ungulates. They can also be found on humans, most often with bites on the scalp [14]. Adult-stage ticks are also questing ticks, just like *Ixodes* ticks (Fig. 2).

2.3. *Rhipicephalus sanguineus*

This species of ticks is mainly observed in dogs (Fig. 1). They are endophilic ticks found in doghouses, kennels, outside walls of houses or even inside houses. These ticks can bite humans at all stages. They have short feeding structures. *R. sanguineus* is mainly prevalent in warm weather regions with mild winters [14].

Table 1
Main human infectious diseases transmitted by ticks.
Principales pathologies infectieuses humaines transmises par les tiques.

Diseases	Infectious agents	Vector ticks	Hosts acting as reservoirs	Geographical distribution
<i>Virus (arbovirus)</i>				
Tick-borne encephalitis	<i>Flavivirus</i>	<i>I. ricinus</i> ; <i>I. persulcatus</i>	Wild mammals, vectors	Asia, Europe
Crimean-Congo hemorrhagic fever http://www.who.int/mediacentre/factsheets/fs208/en/	<i>Nairovirus</i>	<i>Hyalomma marginatum</i>	Wild mammals, vectors	Europe, Asia, Africa
<i>Bacteria</i>				
Q fever or coxiellosis	<i>Coxiella burnetii</i>	<i>Rhipicephalus</i> spp. <i>Dermacentor</i> spp.	Mammals	Worldwide
Lyme borreliosis	<i>B. burgdorferi</i> sensu lato	<i>Ixodes</i> spp.	Small mammals, birds, reptiles	Northern Hemisphere
Borreliosis/tick-borne recurrent fever	<i>Borrelia</i> spp.	<i>Ornithodoros</i> spp; <i>Ixodes</i> spp.	Rodents	Europe, Northern America, tropical and subtropical regions
Mediterranean spotted fever	<i>Rickettsia conorii</i>	<i>R. sanguineus</i>	Dogs	Africa, Asia, Europe
Tick-borne African fever	<i>Rickettsia africae</i>	<i>Amblyomma</i> spp.	Mammals	Sub-Saharan Africa
Tick-borne lymphadenopathy (TIBOLA)	<i>Rickettsia slovaca</i> , <i>R. raoultii</i> , <i>R. rioja</i>	<i>Dermacentor</i> spp.	Sheep, deer	Europe
Tularemia	<i>F. tularensis</i>	Various genera of ticks	Jackrabbits, rabbits, rodents	Worldwide
Human granulocytic anaplasmosis	<i>A. phagocytophilum</i>	<i>I. ricinus</i> ; <i>I. pacificus</i> ; <i>I. scapularis</i>	Numerous mammals	Europe, Northern America, Russia
<i>Parasites</i>				
Babesiosis	<i>Babesia divergens</i> , <i>B. microti</i> , <i>B. venatorum</i>	<i>I. ricinus</i>	Bovines, rodents, deer	Europe

2.4. *Argas reflexus*

A. reflexus ticks usually feed on pigeons (Fig. 1). They can bite humans when their usual host is not available. In that case, they leave the pigeons' nest and come into houses where they bite humans at night during short blood meals. In urban areas they are most commonly found in attic flats, close to pigeons; in rural areas houses close to dovecotes are affected [8]. *A. reflexus* bites may be responsible for major allergic reactions to their saliva, that may even trigger an anaphylactic shock. These ticks have never been proven responsible for the transmission of infectious agents to humans.

3. Tick-borne diseases

Ticks are the most important vectors of vector-borne diseases in terms of human and animal health [15]; they come first before mosquitoes which are in first position in terms of human health with malaria, dengue, etc. Ticks are responsible for the transmission of many infectious agents: bacteria (*Borrelia*, *Anaplasma*, etc.), viruses (tick-borne encephalitis), and even parasites (*Babesia*, *Theileria*) (Table 1). Pathologies associated with these infectious agents are mostly zoonoses for which humans are accidental hosts and represent a dead-end for the infectious agent. The host acquires the infectious agent in tick-infested habitats. Transmission usually occurs

through hematophagous bites, but also through exposure to bodily fluids infected with tularemia or through blood transfusions for *Babesia* spp., etc. [16]. The pathogen may persist for a long time in ticks because it can be transmitted from stage to stage (transstadial transmission), from females to eggs (vertical transmission), and/or from tick to tick via the host (horizontal transmission) depending on the pathogen. The co-feeding phenomenon allows some infectious agents, for instance the tick-borne encephalitis virus and bacteria responsible for Lyme disease, to be transmitted from an infected tick to a healthy tick at the site of the bite on an animal, in the absence of viremia or bacteremia in the host [17].

Although ticks may host various microorganisms (symbiotes and pathogens) that can be detected via their DNA, their presence in ticks is not necessarily associated with an infectious risk for humans. This is explained by several reasons: DNA detection may not necessarily mean that a living pathogen is present on the vector arthropod. And, even with a living infectious pathogen, the vector arthropod does not necessarily have the ability to transmit this pathogen [18]. For ticks infected with bacteria or parasites, the infectious agent is not immediately transmitted as bacteria and parasites have to mature and/or migrate towards salivary glands before being transmitted to the vertebrate hosts. This process may take 24 hours [19].

Ticks have been identified for thousands of years [20], and tick-associated pathogens have been observed for a long time



Fig. 3. Erythema migrans associated with Lyme borreliosis. A. Typical presentation. B. Atypical presentation. C. Inflammatory reaction to the tick bite, probably associated with saliva. (Photo credit: C. Lenormand, clinique dermatologique, Strasbourg, and N. Boulanger).

Érythème migrant lors d'une borréliose de Lyme. A. Typique. B. Non typique. C. Réaction inflammatoire à la piqûre de tique, probablement associée à la salive. (Crédit photo : C. Lenormand, clinique dermatologique, Strasbourg et N. Boulanger).

as well, although most medical descriptions date from the 20th century. One may, however, note that humans have had a major impact on the ecosystems of ticks. Forest culture – both deforestation and reforestation – has an impact on tick populations, just like changes in wildlife (disappearance of species, introduction of new species, proliferation of species attracting ticks, etc.) [21]. Climate change has an impact on ticks: they are now observed in northern regions of the world (Canada, Nordic countries) and at higher altitudes (above 1,500 m), but they may also be less frequent in southern regions depending on their adaptive capacity. Better awareness of vector-borne diseases from health professionals and the general population, and improved direct diagnostic methods (mainly molecular biopsy, i.e. PCR, or culture) are associated with better management of patients and affected animals.

Although *Ixodes* ticks – prevalent in France – are likely to host various microorganisms, the risk of transmitting the infectious agent to humans following a tick bite is inferior to 3% according to a recent Dutch study [22]. Even when the infectious pathogen is transmitted to humans, all transmissions are not necessarily associated with clinical disease, as reported by a recent French study investigating the seroprevalence of seven pathogens (*Borrelia burgdorferi* sensu lato, *Francisella tularensis*, tick-borne encephalitis virus, *Anaplasma phagocytophilum*, *Babesia* spp., and *Bartonella henselae*) in forestry workers [23].

3.1. Bacterial infections

Borrelia spp. Bacteria of the *Borrelia* genus are spiral-shaped extracellular spirochetes belonging to *Spirochaetales* and to the *Spirochaetaceae* family. The *Borrelia* genus is divided into two groups:

- *Borrelia* responsible for Lyme borreliosis, only transmitted by hard ticks of the *Ixodes* genus, and;
- *Borrelia* responsible for relapsing fever, mainly transmitted by soft ticks (*Ornithodoros* and *Argas*), except for body lice for *B. recurrentis* or hard ticks of the *B. miyamotoi* group [24].

Both of these groups have recently been reclassified as “*Borrelia*” and “*Borrelia*” genera, respectively, within the new *Borreliaceae* family [25]; however, for the sake of clarity, we use the former term “*Borrelia*” in the present article.

Lyme borreliosis. Bacteria responsible for Lyme disease belong to the *B. burgdorferi* sensu lato (sl) group, with 21 species

identified. Lyme disease is the most prevalent vector-borne disease in the Northern Hemisphere. The vector is *I. scapularis* on the eastern coast of the United States and *I. pacificus* on the western coast. The main vectors in Europe are *I. ricinus*, and *I. persulcatus* in eastern Europe and Asia. The most pathogenic species for humans in Northern America is *B. burgdorferi* sensu stricto (ss), although other species of the complex are active in this region. In Europe, five species are observed in human pathologies: three are frequently observed (*B. burgdorferi* ss, *B. garinii*, *B. afzelii*) and two are only rarely observed (*B. spielmanii* and *B. bavariensis*) [24]. The animal reservoir is highly varied, with rodents (*B. afzelii* and *B. bavariensis*) and birds (*B. garinii* and *B. valaisiana*) [26], due to specificities related to the host’s immune system [27]. The immune system of incompetent hosts, such as deer, is able to kill *Borrelia*. However, these incompetent hosts contribute to maintaining large populations of ticks in the environment as they are the preferential hosts of adult ticks.

The most frequent clinical manifestation in humans is a typical cutaneous inflammation, i.e. erythema migrans (centrifugal inflammatory lesion of at least 5 cm) (Fig. 3). In the absence of antibiotic therapy, the lesion may progress to an early disseminated stage, and then to a late disseminated stage with cardiac, joint, neurological, or cutaneous involvement depending on the infectious agent [24].

The diagnosis is based on an Elisa assay. Any positive result should then be confirmed by Western blot [28]. The antibiotic therapy duration is two to four weeks, depending on molecules [29]. The likelihood of persisting clinical manifestations increases with diagnostic delays. However, one cannot talk about “chronic Lyme disease” because living bacteria can no longer be detected [30]. However, immunity against Lyme borreliosis is non-protective. A patient may thus be recurrently infected if frequently exposed to tick bites. The rate of *Borrelia*-infested ticks in France is usually around 10% to 20%. Species mainly observed in ticks and humans are *B. afzelii* and *B. garinii* [31].

Tick-borne relapsing fever. Soft ticks such as *Ornithodoros* usually transmit these *Borrelia* species. More recently described in human pathology, *B. miyamotoi* is transmitted by hard ticks of the *I. ricinus* complex [32]. Although present in Europe, this species seems to be mainly pathogenic for immunodeficient people [33,34].

A total of 22 species have been validated in this *Borrelia* group. They are observed in tropical areas (Africa mainly), but

also in the United States [35]. The main symptoms of the infection are successive peaks of fever or “relapsing” fever due to changes in bacterial surface antigens. Such changes enable them to temporarily escape the host’s immune system. Tick-borne relapsing fever is under-diagnosed in tropical regions because of the differential diagnosis of malaria. Diagnosis is based on May-Grünwald Giemsa staining of blood smears because, unlike Lyme borreliosis, bacteremia is high during a fever peak ($10^5 - 10^7$ bacteria/mL).

Rickettsioses. Rickettsioses are transmitted by various arthropods, including ticks. The *Rickettsia* genus includes small intracellular Gram-negative bacteria. *Rickettsia* spp. associated with ticks are observed worldwide and the distribution area of each species is similar to that of its vector [36]. These bacteria interact with endothelial cells, thus increasing vascular permeability which is responsible for clinical manifestations [37]. A total of 25 pathogenic species have been identified, divided into three groups: typhus group (mainly transmitted by lice and fleas), spotted fever group, and a transitional group. Twenty of the 21 species of the spotted fever group are transmitted by ticks, acting both as the vector and main reservoir. Four main species are observed in France:

- *R. conorii*, responsible for Mediterranean spotted fever, is transmitted by *R. sanguineus* in the south of France, although also present in Europe, Asia, and Africa. After a one-week incubation period, acute fever onset is observed with headaches, arthralgia, and muscular pain. A black spot is observed at the bite site, followed by a rash after three to five days of fever (mainly on extremities). Severe cases have been reported with multiple organ dysfunction syndrome, mainly in Portugal [38];
- *R. slovaca*, *R. raoultii* (and *R. rioja*) are responsible for TIBOLA (tick-borne lymphadenopathy) or SENLAT (scalp eschar and neck lymphadenopathy) or DEBONEL (*Dermacentor*-borne necrosis erythema lymphadenopathy). They are transmitted by the *Dermacentor* tick. This is currently the most frequent rickettsiosis in Europe. After approximately a week of incubation (1 to 15 days), cervical adenopathy and black spots – most often on the scalp – are observed; fever is not always present;
- *R. helvetica*, first described in 1993 in Switzerland and seemingly less pathogenic, is transmitted by *I. ricinus* [38]. Pathogenicity varies by patient.

Treatment is based on doxycycline or azithromycin.

Imported from Africa, *R. africae* is observed in France; it is transmitted by *Amblyomma variegatum*.

Human granulocytic anaplasmosis. The Anaplasmataceae family (*Rickettsiales* order) includes strictly intracellular bacteria of the *Anaplasma* and *Ehrlichia* genera, which are transmitted by ticks [39].

Human monocytotropic ehrlichiosis is caused by *Ehrlichia chaffeensis*. This species was first identified in humans in the 1990s and is only present in the United States. Its main reservoirs are white-tailed deer and its vector is the *Amblyomma americanum* tick.

Among species of the *Anaplasma* genus, *A. phagocytophilum* – responsible for human granulocytic anaplasmosis (HGA) – is the most important from a clinical standpoint [40]. *A. phagocytophilum* invades white cells (neutrophils, monocytes, and macrophages) and is usually found in vacuole as a morula. HGA has first been reported in 1994 on the eastern coast of the United States [41]. HGA is prevalent in temperate regions as it has been reported in both animals and humans in Europe, Asia, the United States, and Australia. Bacterial prevalence rates vary by country and by tick species, with rates between <1% and 20% for *I. ricinus* in Western Europe and between 1.7% and 16.7% for *I. persulcatus* in Eastern Europe [42]. In France, 1–2% of ticks are infected and human infections are mainly observed in Eastern France [31]. Differences in *Anaplasma* ecotypes could be responsible for prevalence disparities in humans. After one to three weeks of incubation following an infected tick bite, disease onset presents as fever and is frequently associated with chills, faintness, or generalized musculoskeletal pain with headaches and myalgia. Biological results usually show increased transaminase level, increased C-reactive protein level, and cytopenia (thrombopenia, neutropenia). The diagnosis of anaplasmosis is based on bacterial DNA detection on whole blood PCR. It can also be based on the detection of increased antibody levels after a four-week period. HGA treatment is based on doxycycline [43].

Candidatus Neoehrlichia mikurensis. This species has been described in Japan and belongs to the Anaplasmataceae family [44]. However, several reports such as in the Netherlands with *I. ricinus* ticks feeding on deer [45] as well as in Italy [44], had already highlighted the presence of gene sequences in this bacterium. The main reservoir is made of rodents and the vector is *Ixodes* spp., among which the prevalence is 1%–20% depending on European regions. Although a few human cases of infection have been reported, *Candidatus Neoehrlichia mikurensis* is mainly considered an emerging pathogen [46]. The bacterium invades endothelial cells. This pathogen is responsible for atypical symptoms, mainly in immunodeficient patients: fever, sepsis, and weight loss [46,47]. Infections caused by this bacterium are treated with doxycycline.

Ticks are also likely to transmit other bacteria, but their role as vectors is less important as there are other more effective transmission modes: e.g., for bacteria of the *Coxiella*, *Bartonella*, *Francisella* (etc.) genera.

Q fever. *Coxiella burnetii* is a Gram-negative, obligate, intracellular bacterium, commonly found in animal and human monocytes and macrophages. This bacterium is responsible for Q fever, a worldwide zoonosis, and can infect numerous animal species [48]. Humans are contaminated through the respiratory route, when directly in contact with infected animals (mainly ruminants), or through the digestive route following consumption of dairy products or unpasteurized or poorly pasteurized derived dairy products. Ticks only play a secondary role in the transmission. Clinical manifestations of human Q fever are influenza-like illness (fever, headaches, arthralgia, myalgia), atypical pneumonia, or hepatitis. Severity is related to the potential onset of a chronic infection (mainly endocarditis).

Tularemia. *F. tularensis* is a Gram-negative intracellular bacterium. Its prevalence is low, but it is highly virulent and

contagious because of an easy dissemination and transmission via aerosols. *F. tularensis* is observed in various regions of the world, mainly in the Northern Hemisphere, and most often as sporadic cases [49]. It is mainly a zoonosis: the most receptive species are rodents and lagomorphs (hares). *Dermacentor* and *Ixodes* ticks can transmit tularemia. However, direct transmission is most frequent, with various transmission modes: direct contact with animals (scratches, bites, licks), ocular route, oral route (undercooked meat consumption), inhalation. The clinical presentation is highly varied and depends on the bacterial portal of entry. Disease onset is abrupt with an influenza-like illness. The ulceroglandular presentation is most frequent. Increased transmission of this bacterium by ticks has been reported in Switzerland in April 2018 by the Federal Office of Public Health [50].

Bartonellosis. Bacteria of the *Bartonella* genus are Gram-negative hemotrophic bacteria transmitted by arthropod vectors (sandflies – *B. bacilliformis*; body lice – *B. quintana*). A total of 13 species have been identified as potentially pathogenic for humans over the past 20 years: mainly *B. henselae* and *B. quintana*. Three species are commonly found on cats (*B. henselae*, *B. clarridgeiae*, *B. koehlerae*). However, ticks are believed to also transmit various *Bartonella* species, but the vector ability of *I. ricinus* has only been proven with *B. henselae* [51] and *B. birtlesii* [52]. Little human data is available to describe the role of ticks in *Bartonella* transmission.

3.2. Viral infections

Numerous viruses may be transmitted to humans and animals by ticks. Most of these viruses belong to three families of viruses transmitted by hard ticks: Bunyaviridae, Flaviviridae, and Reoviridae [53]. The most important tick-borne viral infection in humans are: tick-borne encephalitis virus (TBEV), endemic in Central and Eastern Europe; and Crimean-Congo hemorrhagic fever (CCHF) virus.

Tick-borne encephalitis. The tick-borne encephalitis virus (TBEV) is an RNA virus belonging to the *Flavivirus* genus. Ticks acquire the virus during blood meals on a vertebrate host at the viremic phase, and then transmit it to their host during the following meal. Ticks may also acquire the virus when co-feeding on non-viremic or poorly viremic vertebrate hosts [17]. Vertical transmission (from female animals to newborn animals) has been reported in vector ticks, although not frequent (<0.5%) [54]. TBEV infection is the most important neuroinvasive disease transmitted by ticks in Europe and Asia, with thousands of human cases per year. Three virus subtypes have been reported, with geographical distributions more or less correlated with the vector geographical distributions: European subtype transmitted by *I. ricinus* and *I. hexagonus* ticks, and Siberian and Far Eastern subtypes both transmitted by *I. persulcatus* [55].

This virus is present as more or less stable microclusters, defined based on autochthonous human cases and/or on its detection among field-collected ticks. Other animals may act as competent reservoirs: wild animals such as micromammals (field mice, voles), foxes, wild boars, deer [56], but also domestic

animals (goats, cows, sheep, and dogs) [57]. TBEV prevalence rates among *I. ricinus* ticks in Europe usually vary from 0.1% to 1.22% depending on countries, studied areas, and analyzed tick stages [58].

The human infection is seasonal, with a peak during spring and summer due to the activity of vector ticks. Another contamination mode has been reported, through the ingestion of raw dairy products (cheese, milk) from infected domestic animals [56].

The infection may be asymptomatic. Following incubation, the typical manifestation presents as an influenza-like illness. Following temporary improvement for a few days, meningitis symptoms may be inconsistently observed and may be associated with encephalitis signs in 50% of patients and with myelitis signs in less than 10% of patients. The case fatality is 0.5%–3% for the European and Siberian subtypes, but reaches 35% for the Far Eastern subtype [56]. An effective vaccine is available for this infection. A sharp increase in tick-borne encephalitis cases was reported in 2016 in Eastern France [59].

Crimean-Congo hemorrhagic fever. The disease was first characterized in the 1940s in the Crimea when a severe hemorrhagic fever epidemic sparked. The virus was then coined “Crimean-Congo hemorrhagic fever virus” (CCHFV), following isolation of the antigenically identical Congo virus in 1956. The virus belongs to the *Nairovirus* genus from the Bunyaviridae family. It is a large, enveloped, double-stranded DNA virus (group I).

CCHFV distribution reflects the geographical distribution of vector tick species, mainly those of the *Hyalomma* genus but also of the *Dermacentor* and *Rhipicephalus* genera. The virus is observed in Africa, Europe, and Western Asia, but it has never been reported in the New World. Little data is available on the virus prevalence among ticks, and results vary (0.7% to 33%) depending on the detection technique and on the tested tick species. The virus circulates via an enzootic cycle including a large panel of vertebrate hosts among which the virus is asymptomatic; only humans contract the disease. The main vertebrate hosts of the virus are hares, hedgehogs, rodents, and domestic species (bovine animals, sheep, caprines, horses, and pigs). Domestic hosts are considered viral enhancers: they are viremic for at least one week following contamination and develop specific antibodies targeting the virus that can be detected by serological testing.

Tick bite remains the main infectious route in humans. However, contacts with infected bodily fluids or tissues from viremic animals may lead to contaminations [60]. CCHF human infection is characterized by epidemic flares in summer, enabling cluster identification. This is an emerging infection. The clinical presentation is characterized by fever that may lead to a fatal hemorrhagic syndrome in 50% of cases. Two cases of CCHF were reported in 2016 in Spain following tick bites, including one death [54]. The prevalence of the virus among ticks is relatively low in Europe (Turkey is particularly affected though). The presence of *H. marginatum* vector has been confirmed in Camargue and in the area of Montpellier, France [54]. Migratory birds from Africa also play a role in the virus circulation [61].

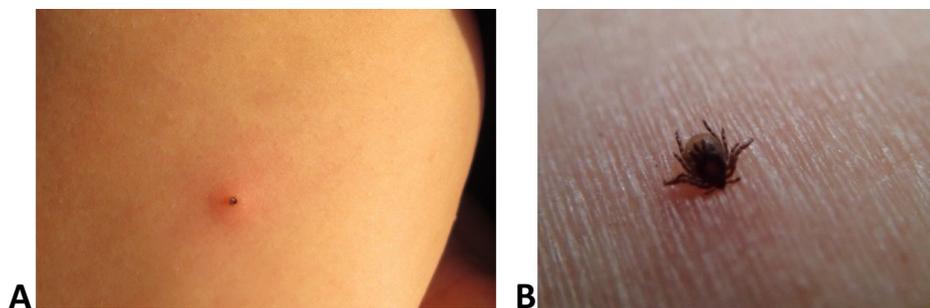


Fig. 4. Tick bites from *I. ricinus* (A) Larva and (B) Nymph. (Photo credit: N. Boulanger).
Piqûre de tique *I. ricinus* (A) Larve et (B) Nymphe. (Crédit photo : N. Boulanger).

3.3. Parasitic infections

Babesiosis or piroplasmosis. Ticks may transmit parasites (helminths and Apicomplexa protists); members of the *Babesia* genus are the most pathogenic for humans. *Babesia* sp. is highly similar to *Plasmodium* sp. (responsible for malaria), but sporozoites of *Babesia* sp. are present in the salivary glands of ticks and directly penetrate into red blood cells (no hepatic cycle).

More than 100 species have been characterized and classified as small or large *Babesia* spp. The most pathogenic species for humans are *B. microti* and *B. divergens*, and more recently *B. venatorum* (*Babesia* sp. EU1). *Ixodes* ticks are the vectors of these species. Transmission of the parasite at the sporozoite stage occurs only a few days after attaching to the host as they first need to mature inside salivary glands. Natural hosts of these species, acting as reservoirs, are rodents, bovine animals, and deer [62].

Human babesiosis cases are rare but severe; they are mainly observed in immunodeficient individuals (40% case fatality). Two *B. divergens* infection cases have been reported in immunocompetent patients in 2009 in Eastern France [63]. Humans and animals may also be contaminated via blood transfusions [40]. The clinical presentation depends on the host's immune status and on the involved *Babesia* species. The main symptoms of human babesiosis are fever, jaundice, anemia, and hemoglobinuria. Treatment in humans depends on the patient's immune system: combination of atovaquone and azithromycin in immunocompetent patients, and clindamycin and quinine for severe cases [62].

4. Prevention

4.1. Individual-based prevention

Physical prevention. Larva and nymph bites from *Ixodes* ticks are the most difficult to detect because of their small size (Fig. 4). Primary prevention against ticks is mainly based on simple measures such as wearing long and bright clothes (Fig. 5), tucking one's trousers inside socks, wearing a cap for children to avoid bites on the scalp – although it should be noted that ticks do not fall from trees. People should also check their body for ticks after being outdoors in infested areas: any warm and humid body parts, skin folds, belly button, genitals, ears, and scalp.

Skin repellents. Primary prevention against ticks may also rely on the use of skin repellents [64]. Data update is currently underway on the effectiveness of skin repellents against tick bites [65,66]. Specificities for the use of these skin repellents are updated every year in the monthly epidemiological report (French acronym BEH) published by the French national agency for public health (Santé publique France) [67].

Repellents do not kill ticks; they only repel them, preventing them from biting humans or animals. The choice of repellent depends on various factors, including the individual's status (age, pregnant woman), and on the intention for use. For all repellents, attention should be paid to the nature and proportion of active ingredients, to the duration of action, and to the maximum daily applications. The pharmaceutical form also plays an important role in the repellent activity.



Fig. 5. Bright clothes are an excellent individual-based primary prevention measure as adult ticks (A) or nymph (B) of *I. ricinus* can be easily spotted. Tick removers are highly effective for removing ticks (C). (Photo credit: N. Boulanger).

Les vêtements clairs constituent un excellent moyen de prévention primaire individuelle, car ils permettent de repérer facilement une tique adulte (A) ou une nymphe (B) d'*I. ricinus*. Le tire-tique est très efficace pour l'extraction des tiques (C). (Crédit photo : N. Boulanger).

Current repellents are based on external application molecules (on skin or clothes). Four molecules are known to be effective against tick bites:

- PMD (P-menthane-3, 8-diol), *Corymbia citriodora* eucalyptus extract;
- DEET (diethyltoluamide) has been largely used for several decades and is the reference molecule. However, it is known to impair synthetic fibers (rayon, spandex, vinyl, etc.) and plastic materials (glasses, watch strap);
- IR35/35[®] (N-butyl, N-acetyl-3-ethylaminopropionate);
- KBR 3023 or picaridin (piperidine-1-carboxylic acid).

Other natural products are being studied, such as 2-undecanone (BioUD[®]) derived from tomatoes, decanoic acid (ContraZek[®]) derived from coconut or palm kernel, geraniol, Margosa extract or margosa (Neem), and lavender extract. The other essential oils are usually not recommended or very rarely recommended as they are highly volatile. Their repellent effect is limited to 20 minutes to one hour. Some components of these essential oils are skin irritants (citral, farnesol, trans-2-hexenal) or carcinogenic (eugenol) [68].

Repellent-treated clothing. Repellent-treated clothing is an alternative to skin repellents. Permethrin is widely used. It may be applied as a spray (on the external side of clothes in a ventilated area, and must be left to dry), with a 6-week effectiveness. Cloth immersion in a permethrin bath is more effective. The repellent effect lasts six months and resists to several washings.

Other individual-based protection measures. Following a tick bite, mechanical extraction of the tick is the best effective method and must be performed as rapidly as possible to avoid any potential transmission of pathogens [64]. Tick removers are particularly useful and should be recommended (Fig. 5). However, using products such as oil, ether, or nail polish to facilitate the tick removal is useless. No study has demonstrated the effectiveness of such products.

4.2. Collective measures

Environmental treatment of at-risk housing areas may be performed, and mainly consists of getting rid of falling leaves and of mowing lawns. Green areas are more and more frequent in urban areas, and may represent targeted ecosystems [11]. Building up fences around housing areas helps keep deer at bay, as they are the main carriers of adult ticks [69].

5. Conclusion and perspectives

Vector-borne diseases transmitted by ticks have been on the rise worldwide since the start of the 20th century because of increased human activities with an impact on forest ecosystems, wild life animals, and domestic animals. In the Northern Hemisphere, human diseases such as Lyme borreliosis are the most prevalent. However, in southern countries vector-borne veterinary diseases have an impact on socioeconomic issues, due to invasive ticks which are disease vectors for livestock. Most of

these tick-borne diseases are zoonotic diseases, and the interaction between hosts-vectors-pathogens is still poorly understood for most of them. Tick and tick-borne disease research has been neglected compared with mosquito-borne diseases (malaria, dengue, Zika, etc.). It must be developed to further knowledge on tick circulation and persistence in the environment, infectious agent transmission and persistence among vectors and vertebrate hosts to develop effective multidisciplinary control measures (tick control, diagnosis, vaccine).

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Disclosure of interest

The authors declare that they have no competing interest.

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