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Ticks and tick-borne diseases: a One Health perspective

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Tick-borne diseases are common occurrences in both the medical and veterinary clinical settings. In addition to the constraints related to their diagnosis and clinical management, the control and prevention of these diseases is often difficult, because it requires the disruption of a complex transmission chain, involving vertebrate hosts and ticks, which interact in a constantly changing environment. We provide a contemporary review of representative tick-borne diseases of humans and discuss aspects linked to their medical relevance worldwide. Finally, we emphasize the importance of a One Health approach to tick-borne diseases, calling physicians and veterinarians to unify their efforts in the management of these diseases, several of which are zoonoses.

Vector-borne diseases on the rise

Ticks were the first arthropods to be established as vectors of pathogens and currently they are recognized, along with mosquitoes, as the main arthropod vectors of disease agents to humans and domestic animals globally [1,2]. Moreover, the incidence of tick-borne diseases (TBDs) is increasing worldwide [3–5]. For instance, more than 250 000 human cases of Lyme borreliosis were reported from 2000 to 2010 in the United States (see http://www.cdc.gov/lyme/stats/chartstables/reportedcases_statelocality.html), and the disease is also increasing in Europe, where over 50 000 cases are reported each year in humans [5]. Hence, the need for a comprehensive approach towards a better management of these diseases is evident. In this article, we provide a contemporary review on some of the most important TBDs of humans. In particular, we discuss the general aspects of these diseases and present a list of tick species found on humans around the world, highlighting their relevance in terms of pathogen transmission. Finally, we emphasize the importance of a One Health approach (see Glossary) to TBDs, calling physicians and veterinarians to better unify their efforts in the management of these zoonoses.

The expanding world of tick-borne diseases

The spectrum of TBDs affecting domestic animals and humans has increased in recent years; many important zoonotic TBDs, such as anaplasmosis, babesiosis, ehrlichiosis, and Lyme borreliosis are increasingly gaining more attention from physicians and veterinarians. With the development of molecular biology, new species, strains, or genetic variants of microorganisms are being detected in ticks worldwide [6,7], and the list of potential tick-borne pathogens continues to increase [8–11]. Some of these agents, such as *Rickettsia slovaca*, *Rickettsia parkeri*, and *Rickettsia massiliae*, were identified in ticks, decades before these were associated with human diseases [12]. Other tick-borne pathogens, including many flaviviruses (e.g., Omsk hemorrhagic fever virus, Powassan encephalitis virus, and Kyasanur forest disease virus) have been implicated in human disease in new geographical regions (Table 1) [5,13]. Despite the enormous contribution of molecular biology to the discovery of new species or strains of tick-borne pathogens, genetic data must be interpreted with caution. For instance, the evaluation of partial 16S rRNA gene sequences amplified from the castor bean tick *Ixodes ricinus* revealed a plethora of *Rickettsia* sequences,

Glossary

Amplifying host: a host in which the level of pathogen can become high enough that a vector (e.g., a tick) that feeds on it will probably become infectious.
Anamnesis: the complete history recalled and recounted by a human patient.
Anaplasmosis: a tick-borne disease caused by rickettsiae of the genus *Anaplasma*.
Anthropophilic: from Greek *anthropos* (human) and *philein* (to like); usually said of parasites that prefer human beings to animals.
Babesiosis: a tick-borne disease caused by protozoa of the genus *Babesia*.
Control measures: actions or measures (e.g., elimination of reservoirs and vectors) adopted to restrain or reduce the prevalence of individual disease.
Ehrlichiosis: a tick-borne disease caused by rickettsiae of the genus *Ehrlichia*.
Entomopathogenic fungus: a fungus that can act as a parasite of insects, killing or seriously disabling them.
Hard ticks: hard ticks (family Ixodidae) are so-called because they have a dorsal scutum in all developmental stages (larva, nymph, and adults).
Lyme borreliosis: a tick-borne disease caused by bacteria of the genus *Borrelia*.
One Health approach: an interdisciplinary approach for combating threats (e.g., tick-borne diseases) to the health of animals, humans, and the environment they share on Earth.
Petechiae: a small purplish spot on skin or mucous membrane.
Preventive measures: actions or measures (e.g., vaccination, use of repellents) adopted to reduce the incidence of a disease or infection.
Reservoir host: an individual or a population of animals that is chronically infected with the causative agent of a disease and can act as a source of further infection.
Sentinel animal: an animal that may be used as an indicator of the presence of a pathogen.
Soft ticks: soft ticks (family Argasidae) are so-called because they lack a dorsal scutum in the nymphal and adult stages; larvae may present a dorsal plate, which is of taxonomic relevance.
Transmission time: time frame occurring from the initiation of feeding by an arthropod vector and the inoculation of an infectious agent in the host. It may vary widely according to vectors and pathogens.
Vector competence: the intrinsic ability of a vector to become infected with, to replicate, and to transmit a pathogen to receptive hosts.

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Table 1. Causative agents, vectors, and distribution of representative tick-borne diseases of humans

Diseases	Pathogens	Proven or putative vectors[a]	Distribution	Refs
African tick bite fever	*Rickettsia africae*	*Amblyomma hebraeum, A. variegatum*	Africa, West Indies	[1,5]
Human granulocytic anaplasmosis	*Anaplasma phagocytophilum*	*Haemaphysalis concinna, H. punctata, Ixodes ricinus, I. pacificus, I. scapularis, Rhipicephalus bursa*	Europe, North America	[1,5]
Human monocytic ehrlichiosis	*Ehrlichia chaffeensis*	*Amblyomma americanum*	North America	[1,5]
Lyme borreliosis	*Borrelia burgdorferi* sensu lato	*Ixodes hexagonus, I. pacificus, I. persulcatus, I. ricinus, I. scapularis*	Asia, Europe, North America	[1,5]
Mediterranean spotted fever	*Rickettsia conorii*	*Rhipicephalus sanguineus, R. turanicus*	Africa, Asia, Europe	[1,5,18]
Q fever	*Coxiella burnetii*	Many species of different genera	Africa, Asia, Australia, Europe, North America	[1,5]
Relapsing fever	*Borrelia* spp.	*Ornithodoros* spp.	Africa, Asia, Europe, North America	[1,5,66]
Rocky Mountain spotted fever	*Rickettsia rickettsii*	*Amblyomma americanum, A. aureolatum, A. cajennense, Dermacentor andersoni, D. variabilis, R. sanguineus*	North, South and Central America	[1,5,36,67]
Tularemia	*Francisella tularensis*	Many species of different genera	Asia, Europe, North America	[1,5,64,68,69]
Babesiosis	*Babesia divergens, B. microti*	*Ixodes ricinus, I. scapularis*	Europe, North America	[1,5]
Colorado tick fever	Coltivirus	*Dermacentor andersoni*	Western North America	[1,5]
Crimean–Congo hemorrhagic fever	Naiovirus	*Amblyomma variegatum, H. punctata, Hyalomma anatolicum, H. marginatum, H. truncatum, R. bursa*	Africa, Asia, Europe	[1,5]
Kyasanur forest disease	Flavivirus	*Haemaphysalis spinigera, H. turturis*	Indian subcontinent	[1,5]
Louping ill	Flavivirus	*Ixodes ricinus*	Western Europe	[70]
Omsk hemorrhagic fever	Flavivirus	*Dermacentor marginatus, D. reticulatus, I. persulcatus*	Asia	[5]
Powassan encephalitis	Flavivirus	*Dermacentor andersoni, Haemaphysalis longicornis, I. cookei, I. scapularis*	Asia, North America	[13,70]
Tick-borne encephalitis	Flavivirus	*Ixodes persulcatus, I. ricinus, H. concinna, H. punctata*	Asia, Europe	[5,70]

[a]The list of potential vectors may actually be longer.

including the first report of *Rickettsia australis* in Europe [14]. However, a meticulous analysis of these data revealed that 16S rRNA sequences of *Rickettsia helvetica* were most likely misinterpreted as *R. australis* [15].

Ticks and wildlife are the main reservoirs of tick-borne pathogens of medical and veterinary concern. Nonetheless, the expanding spectrum of tick-borne pathogens affecting domestic animals and humans will require new studies on the epidemiology, diagnosis, and ecology of these newly recognized diseases. For example, *R. massiliae*, a bacterium firstly isolated from brown dog ticks (*Rhipicephalus sanguineus*) in France, has been implicated in human cases of spotted fever in Europe and South America [16,17]. A laboratory study also suggested the potential of the tick *Rhipicephalus turanicus* in the transmission of *R. massiliae* [18]. In a human case recently diagnosed in Argentina, the patient exhibited no antibodies against *Rickettsia conorii*, and the definitive diagnosis of infection by *R. massiliae* was achieved by amplification and sequencing of bacterial DNA from a skin sample. Importantly, this patient was successfully treated with doxycycline [17], which is the drug of choice for the treatment of tick-borne rickettsioses [19].

Wildlife may serve as reservoirs or amplifying hosts of several human pathogens; the vast majority of TDBs are from wildlife reservoirs [2,4,5]. However, tick-borne pathogens traditionally associated with disease in domestic animals may also eventually emerge as human pathogens.

For example, human babesiosis caused by *Babesia divergens* has been known in Europe for a long time as a zoonosis from cattle [2]. More recently, *Ehrlichia canis* has been implicated in a few human cases from Venezuela [20], and a new strain of *E. canis* has been detected in dogs from Peru [21]. Serologic evidence of ehrlichial infection in humans has been reported in South America [22], but molecular data on *Ehrlichia* species infecting humans in this region is limited [20,23].

Tick infestation: human-biting tick species

Ticks constitute a diverse group with at least 898 recognized species, distributed among three families: Argasidae (194 spp.), Ixodidae (703 spp.), and Nuttalliellidae (1 sp.) [24–26]. They parasitize a wide range of animals, including humans, which are accidental hosts for several tick species (Table 2), such as the lone star tick *Amblyomma americanum*, *I. ricinus*, and *R. sanguineus* [27,28]. Human behavior (e.g., sitting on logs, gathering wood, sitting against trees, and walking) might increase the risk of exposure to ticks [29]. For instance, people visiting forested areas might be exposed to hard ticks whereas people entering tick-infested caves and burrows might be exposed to soft ticks (Figure 1) [27].

Most cases of human parasitism are related to hard ticks (Table 2). However, cases of infestation by soft ticks have been sporadically reported and may lead to severe medical conditions in bitten persons. For instance, many *Ornithodoros* spp. have been implicated in the epidemiology of TBDs (e.g., relapsing fever) affecting humans [27,30]. Similarly, the pigeon tick *Argas reflexus* is a known cause of IgE-mediated anaphylaxis in human patients [31]. Ticks of the genus *Ornithodoros* are recognized to cause local lesions and systemic illness generally referred to as tick toxicosis. A recent case of toxicosis was diagnosed in a Brazilian dog bitten by the *mouro* tick *Ornithodoros brasiliensis* [32]. The animal presented disseminated skin rash, pruritus, mucosal hyperemia, lethargy, and fever but was negative for tick-borne pathogens. A new soft tick species was recently discovered in a bat cave in Brazil and found to be highly anthropophilic [33]. One of the researchers responsible for the species description was accidentally bitten by a female tick, and an intense inflammatory response was recorded 24–48 h after the tick bite, with intense swelling, redness, heat, and pain. Probably, the inflammatory response was induced by the tick saliva [33].

Tick species found on humans vary from region to region [27,28]. In South America, approximately 30 tick species have been found on humans [28,34]. Most cases of human infestation recorded in this region are related to *Amblyomma* ticks [28,34], which are frequently associated with wildlife [35]. Some of these *Amblyomma* species (e.g., yellow dog tick *Amblyomma aureolatum*, the Cayenne tick *Amblyomma cajennense*, and *Amblyomma triste*) have been implicated as vectors of rickettsiae, such as *R. rickettsii* and *R. parkeri* [4,36]. Until recently, human parasitism by *R. sanguineus* was considered rare in South America [28,37]. However, a recent study carried out in northern Brazil reported several cases of human parasitism by this tick [34], which may suggest a high level of environmental infestation [37,38].

Recent studies have shown that the actual diversity of ticks potentially infesting humans is greater than previously believed. For instance, a study carried out in a single Turkish province revealed the occurrence of 24 tick species on humans, although only 800 of the 5999 ticks collected were identified to species level [39]. Similarly, 26 tick species were identified among the 2528 ticks collected from humans in several districts of Amasya, another province in Turkey, where Crimean–Congo hemorrhagic fever is endemic [40]. The medical significance of the parasitism by some of these tick species is unknown, but any case of human infestation by ticks should be regarded as of clinical significance. Ticks should be preserved for identification, which in turn might provide physicians and veterinarians with information about the potential health risks their patients may be exposed to.

Ticks may live in many types of environments. For instance, most bat-associated soft tick species are typically found in caves [26], whereas ticks of wild terrestrial mammals are commonly found in forested areas [41]. Domestic animals (e.g., cattle and dogs) may carry ticks infected by pathogens and also represent a risk to humans [42]. All these aspects of tick ecology should be considered before planning any control strategy against ticks and TBDs.

Tick-borne disease control: the need for a One Health approach

The integrative thinking on human and animal health comes from ancient times, but it was in the 20th century that the American epidemiologist C.W. Schwabe comprehensively revisited the concept of 'One Medicine' (commonly referred to as 'One Health'), proposing to unify human and veterinary medicine against zoonotic diseases, including rabies [43]. More recently, the role of companion animals and the vector-borne diseases they share with humans have been conceptualized with a One Health approach [2,44].

Similarly to other vector-borne diseases (e.g., malaria, leishmaniasis), TBDs may be difficult to control due to their complex epidemiology that may involve different tick vectors and animal hosts. Veterinarians and physicians have long dealt with TBDs in their daily routine, following parallel, but often non-convergent pathways. It is now clear that an integrated approach is required for the control of TBDs, particularly for those of zoonotic concern. It is necessary to unify the animal and human branches of medicine towards a better management of this important group of diseases, filling the gaps of communication between physicians and veterinarians to accelerate diagnosis, to expedite treatment decisions and the implementation of preventive measures.

The One Health approach: the principle

The principle of the One Health approach for the management of TBDs is to increase the level of communication between physicians and veterinarians dealing with patients with past or present history of tick bites, particularly those with unexplained febrile illness in areas where TBDs are endemic (Figure 2). Specific procedures regarding patients' management (e.g., referral to a reference hospital or treatment center) should respect the organization and infrastructure of local healthcare systems and

Table 2. Ticks frequently found attached to humans and animals and their main associated pathogens[a]

Tick families and species	Associated pathogens	Refs
Argasidae (soft ticks)		
Argas monolakensis	Mono Lake virus	[1]
Argas reflexus	*Aegyptianella pullorum*[b]	[1]
Ornithodoros asperus	*Borrelia caucasica*	[1]
Ornithodoros capensis	SOLV	[27]
Ornithodoros coriaceus	*Borrelia coraciae*	[27]
Ornithodoros erraticus	*B. crocidurae*, *Borrelia hispanica*, ASFV[b]	[1,27,70]
Ornithodoros hermsi	*Borrelia hermsi*	[1]
Ornithodoros maritimus	SOLV	[27]
Ornithodoros moubata	ASFV[b], *Borrelia duttonii*	[1,70]
Ornithodoros sonrai	*B. crocidurae*	[66]
Ornithodoros tartakovskyi	*Borrelia tatyschewii*	[1]
Ornithodoros tholozani	*Borrelia persica*	[1]
Ornithodoros turicata	*Borrelia turicatae*	[1]
Ornithodoros savignyi	AHFV[b]	[30]
Ixodidae (hard ticks)		
Amblyomma americanum	*Borrelia lonestari*, *Ehrlichia chaffeensis*, *Francisella tularensis*, *Rickettsia parkeri*, *Rickettsia rickettsii*	[1,27,67,71,72]
Amblyomma aureolatum	*R. rickettsii*	[36]
Amblyomma cajennense	*Candidatus* 'R. amblyommii'[b], *Rickettsia honei*, *R. rickettsii*	[1,36,73]
Amblyomma coelebs	*Candidatus* 'R. amblyommii'[b]	[36]
Amblyomma hebraeum	*Ehrlichia ruminantium*[a], *Rickettsia africae*, *Theileria mutans*[b]	[1]
Amblyomma maculatum	*E. ruminantium*[b], *Hepatozoon americanum*[b], *R. parkeri*	[1,36]
Amblyomma neumanni	*Candidatus* 'R. amblyommii'[b]	[36]
Amblyomma ovale	*Hepatozoon canis*[b]	[74]
Amblyomma triste	*R. parkeri*	[36]
Amblyomma variegatum	*E. ruminantium*[b], *R. africae*, *T. mutans*[b], THOV, BHAV, CCHFV	[1,27,70,75]
Dermacentor andersoni	*Anaplasma marginale*[b], *F. tularensis*, *R. rickettsii*, CTFV, POWV	[1,68]
Dermacentor auratus	*Rickettsia sibirica*	[73]
Dermacentor marginatus	*Babesia canis*[b], *Coxiella burnetii*, *F. tularensis*, *R. sibirica*, *Rickettsia slovaka*, BHAV, OHFV	[1,68,70,73,75]
Dermacentor nuttalli	*R. sibirica*	[1]
Dermacentor reticulatus	*A. marginale*[b], *Babesia caballi*[b], *B. canis*[b], *C. burnetii*, *F. tularensis*, *Rickettsia helvetica*, *R. sibirica*, *R. slovaka*, OHFV	[1,68,70,73,76,77]
Dermacentor silvarum	*Rickettsia heilongjiangensis*, *R. sibirica*	[73]
Dermacentor variabilis	*A. marginale*[b], *F. tularensis*, *R. rickettsii*	[1,27]
Haemaphysalis concinna	*Anaplasma phagocytophilum*, *F. tularensis*, *R. sibirica*, TBEV	[1,69,78]
Haemaphysalis flava	*Rickettsia japonica*	[1]
Haemaphysalis longicornis	*Babesia gibsoni*[b], *Babesia ovata*[b], *Theileria buffeli*[b], *R. japonica*, POWV	[1,13]
Haemaphysalis punctata	*A. phagocytophilum*, *Babesia major*[b], *Babesia motasi*[b], *C. burnetii*, *T. buffeli*, BHAV, CCHFV, TBEV	[1,27,70,75,78]
Haemaphysalis spinigera	KFDV	[1,70]
Haemaphysalis turturis	KFDV	[1]
Hyalomma anatolicum	*Theileria annulata*[b], *Theileria lestoquardi*[b], CCHFV	[1,70]
Hyalomma asiaticum	*T. annulata*[b], *R. sibirica* subsp. *mongolitimonae*, BHAV	[1,73,75]
Hyalomma marginatum	*Rickettsia aeschlimannii*, *T. annulata*[b], BHAV, CCHFV	[1,70,75]
Hyalomma truncatum	*R. sibirica* subsp. *mongolitimonae*, BHAV, CCHFV	[1,73,75]
Ixodes cookei	POWV	[1]
Ixodes hexagonus	*Borrelia burgdorferi* sensu lato	[1]
Ixodes holocyclus	*Rickettsia australis*	[1]
Ixodes ovatus	*R. japonica*	[1]
Ixodes pacificus	*A. phagocytophilum*, *B. burgdorferi* s.l.	[1]
Ixodes persulcatus	*B. burgdorferi* s.l., OHFV, TBEV	[1,70]
Ixodes ricinus	*A. phagocytophilum*, *Babesia divergens*, *B. microti*, *B. burgdorferi* s.l., *F. tularensis*, *R. helvetica*, LIV, TBEV	[1,64,70]
Ixodes scapularis	*A. phagocytophilum*, *B. microti*, *B. burgdorferi* s.l., POWV	[1,70]
Rhipicephalus bursa	*A. marginale*[b], *Anaplasma ovis*[b], *A. phagocytophilum*, *Babesia bigemina*[b], *Babesia ovis*[b], BHAV, CCHFV	[1,70,75,78]
Rhipicephalus microplus	*A. marginale*[b], *B. bigemina*[b], *B. bovis*, *Theileria equi*[b]	[1]

Table 2 (*Continued*)

Tick families and species	Associated pathogens	Refs
Rhipicephalus sanguineus	*Babesia vogeli*[b], *Ehrlichia canis, H. canis*[b], *Rickettsia conorii, Rickettsia massiliae, R. rickettsii*	[1,12,27,38]
Rhipicephalus turanicus	*R. conorii, R. massiliae*	[27]

[a]Only the most representative tick species are included and the list of associated pathogens may actually be longer; for example, many of these ticks have been found carrying genetic material of *Rickettsia* species or strains of unknown pathogenicity [73].

[b]Unknown pathogenicity for humans, although there might be evidence suggesting that some of these microorganisms are pathogenic.Abbreviations: AHFV, Alkhurma hemorrhagic fever virus; ASFV, African swine fever virus; BHAV, Bhanja virus; CCHFV; Crimean–Congo hemorrhagic fever virus; CTFV; Colorado tick fever virus; KFDV; Kyasanur forest disease virus; LIV; Louping ill virus; OHFV; Omsk hemorrhagic fever virus; POWV; Powassan encephalitis virus; SOLV; Soldado virus; TBEV; tick-borne encephalitis virus; THOV; Thogoto virus.

follow the recommendations and rules of local public health authorities. The core principle is to increase the communication and exchange of information between physicians and veterinarians concerning all aspects of TBDs at local, regional, and national levels.

Wildlife and domestic animals and their associated ticks might be involved in the epidemiology of TBDs affecting humans. For instance, dog ticks (e.g., *R. sanguineus*, the American dog tick *Dermacentor variabilis*) are proven vectors of the spotted fever group rickettsiae [1]. Even if dogs might not necessarily be the main reservoirs or amplifying hosts of *R. conorii* and *R. rickettsii*, they might carry ticks infected by these pathogens to human dwellings, and both veterinarians and physicians should keep this in mind. When a dog brings an infected tick into a household, the direct risk of pathogen transmission to humans is minimal; once attached to a dog, ticks will hardly ever detach and move to another host. Indeed, whereas some ticks may move from a host to another during active feeding [3], larvae, nymphs, and females of hard ticks typically take a single blood meal. Nonetheless, the introduction of infected larvae and nymphs into a house could result in human infestations and tick-borne pathogen transmission by the next developmental stages after molting in the house, especially in case of ticks with fast development times. Moreover, the introduction of engorged females may cause the establishment of an in-house population of *R. sanguineus*, for example, which is well adapted to live in human dwellings.

Veterinarians and physicians are hardly ever knowledgeable about tick identification and should seek experts' opinions whenever needed for their clinical practice. A veterinarian dealing with a dog infested by ticks such as *D. variabilis* and *R. sanguineus* should not only prescribe a

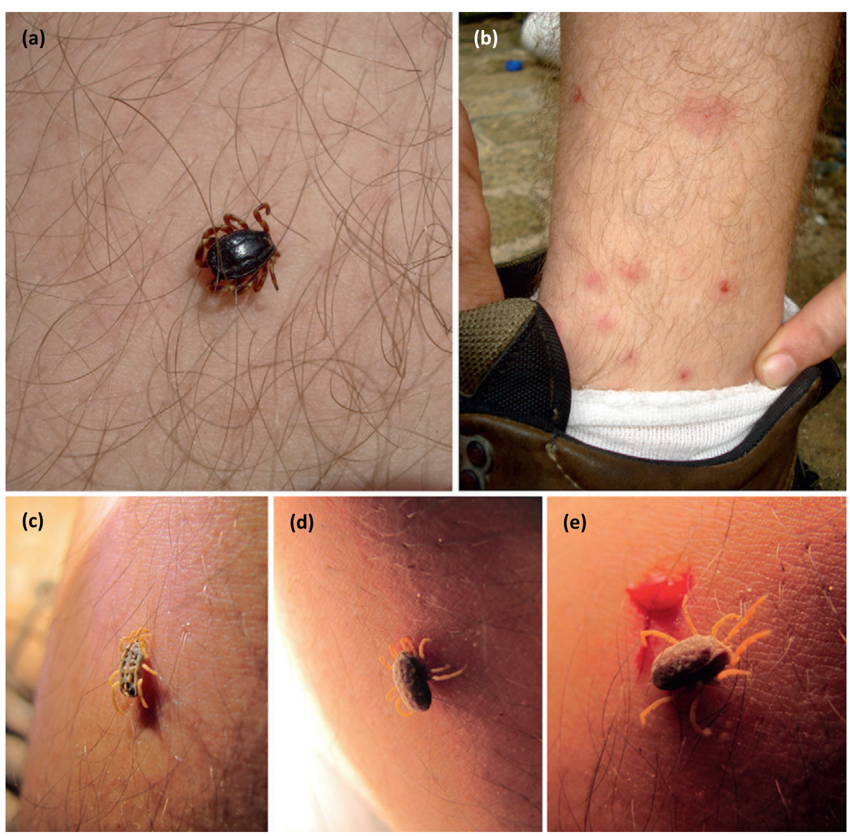

Figure 1. Tick infestation on humans. **(a)** *Hyalomma marginatum* male feeding on a man after working in a wooded area in southern Italy. **(b)** Skin reactions 24 h after being bitten by *Amblyomma* sp. larvae in a forest in northeastern Brazil. **(c, d, e)** *Ornithodoros* sp. feeding on a man after entering into a cave in northeastern Brazil.

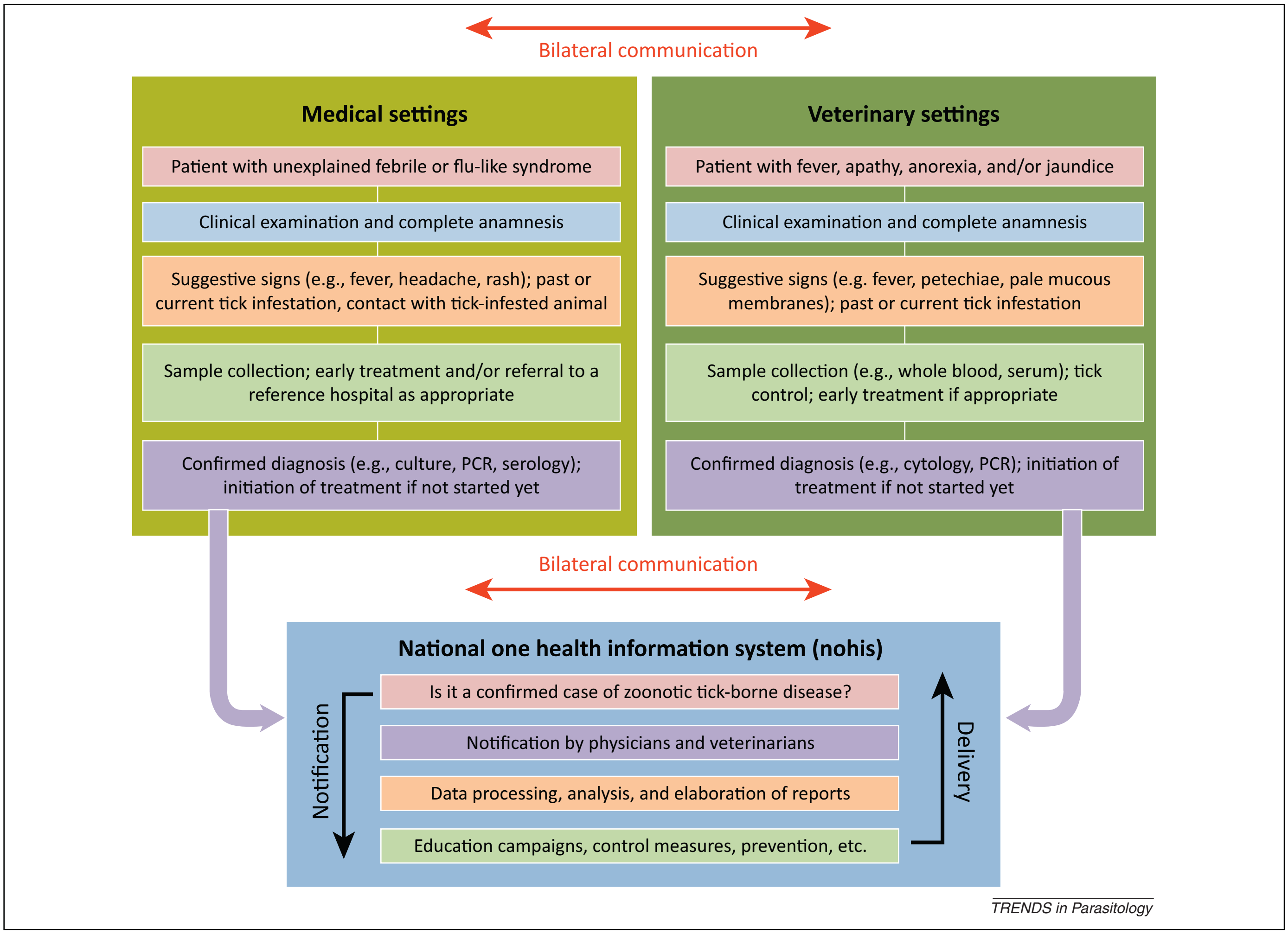

Figure 2. Suggested One Health approach for tick-borne diseases.

product to kill the ticks on the animal but also inform the owner about the potential risks for his patient's health and the health of the persons living with the dog. Once informed, the owner will be aware of the risks and immediately seek medical assistance if any sign such as fever, headache, or rash is observed. Conversely, if a physician is dealing with a patient infested by ticks, he should ask his patient about the presence of tick-infested animals and advise him to seek the help of a veterinarian. Education of human patients and pet owners might be pivotal to control certain TBDs, because reducing the risk of tick infestation on pets might diminish the probability of bringing infected ticks into the house; as said, these ticks could eventually drop off, molt, and subsequently enter into contact with people living in that house.

Another theoretical situation could be a physician dealing with a patient with confirmed or suspected Rocky Mountain spotted fever. In any case, the physician should start the treatment as soon as possible [4] and investigate the possible origin of infection. If the patient has a tick bite history, a detailed anamnesis might be helpful to assess where/when the patient got the tick. As an example, a higher level of infestation by *R. sanguineus* was detected on dogs and in the environment in eastern Arizona, during an outbreak of Rocky Mountain spotted fever [38]. If the presence of a tick-infested dog is confirmed, the patient should be advised to contact a veterinarian to seek information about how to control the tick infestation on the dog and eventually in the environment. One may argue that this is an obvious procedure in medical practice, but it is not. The daily routines of medical physicians and veterinarians are most often disconnected. The lack of a comprehensive view of the problem might have severe consequences, considering that diseases such as Rocky Mountain spotted fever can be fatal [38] if not properly managed. Although patients with suspected TBD might not always recall a history of tick bite, most of them will easily remember and report a possible contact with tick-infested animals, which indirectly may suggest a potential past tick exposure. When collecting information about tick bite history, the physicians should also ask their patients about past or current contact with tick-infested animals and, eventually, contact the veterinarian to seek additional data. The bilateral information exchange might be vital to increase awareness and to expedite a treatment decision for both humans and animals. In developing regions, where the access to veterinary services for pet owners (or even to healthcare for humans) may be limited, the establishment of a One Health initiative against tick and TBDs may be challenging.

Rocky Mountain spotted fever in dogs and their owners: a lesson from Mississippi

Dogs are susceptible to *R. rickettsii* and may die from that infection. Concurrent cases of Rocky Mountain spotted fever in dogs and their owners have been reported in the United States [45,46]. An example concerning the importance of adopting a One Health strategy while dealing with TBDs comes from Mississippi [46]. A farm dog was referred to a local veterinarian because of a possible seizure. The dog presented petechiae of the gums and sclera, pale mucous membranes, rectal temperature of 38.5°C, and was unable to stand. Various medications, including doxycycline, were administered, but the dog succumbed the same day with suspected ehrlichiosis. Eight days later, another dog owned by the same farmer died as well. Two weeks later the dogs' owner was examined at a hospital emergency room with a 2-day history of severe headache, fever, nausea, vomiting, severe back pain, and an inability to walk unassisted. The clinical picture led to a misdiagnosis of lower back sprains and acute cystitis–urinary tract infection. Treatment with several drugs, including trimethoprim–sulfamethoxazole, was initiated, and the patient's condition worsened, resulting in her death 3 days later, caused by Rocky Mountain spotted fever [46]. Then, the veterinarian examined two other sick dogs present on the premises where the deceased patient lived and promptly initiated treatment with doxycycline; both dogs recovered. One of them had a high level of anti-*R. rickettsii* antibodies, which is not confirmatory but suggests that these dogs were suffering from Rocky Mountain spotted fever. This case report exemplified how physicians could benefit from information generated by veterinarians and vice versa. Unfortunately, the lack of initial suspicion of Rocky Mountain spotted fever fatally resulted in unfavorable outcomes for the farmer and some of her dogs.

Tick control and TBD prevention: current practices

The control of ticks is largely based on the use of chemicals on animals and in the environment (Box 1). Several active ingredients with killing and/or repellent effects are commercially available for use on companion animals and livestock. These active ingredients might be prescribed in different formulations, such as sprays, soaps, shampoos, powders, impregnated collars, dip solutions, pour-on, and spot-on applications. Products commonly used to control ticks on companion animals are often formulated as spot-on applications, impregnated collars, and sprays [47], whereas pour-on and dip solutions are frequently used to control ticks infesting livestock [48]. Moreover, new strategies for the control of tick on wildlife (e.g., white-tailed deer) have also been developed and studies indicate that they might be useful in reducing the level of environmental infestation by some tick species (e.g., *A. americanum* and the blacklegged tick *Ixodes scapularis*), thus contributing to the control of certain TBDs, such as Lyme borreliosis [49].

Alternative tick control strategies have been proposed, including use of anti-tick vaccines and of biological control agents, such as entomopathogenic fungi [50,51]. Indeed, non-chemical approaches might be rather useful in some situations, particularly to reduce the level of environmental infestation. For example, pasture management and rotational grazing can help to reduce the level of tick infestation on livestock [48], although these approaches are not always feasible due to land availability constraints and lack of compliance by farmers.

Box 1. Tick control and tick-borne disease prevention

- The control of ticks is generally based on the use of acaricides on animals and in the environment. These products are made up of different active ingredients, alone or in combination [47]. Tick control programs should also include integrated, non-chemical strategies.
- Non-chemical strategies have been used (e.g., rotational grazing for the control of the one-host cattle tick *Rhipicephalus microplus*), although they might not be feasible in some areas due to shortages of grazing land and lack of compliance by farmers [48].
- New alternative control measures have been investigated, including the use of entomopathogenic fungi and anti-tick vaccines, usually in association with acaricidal treatments [48,50].
- People should avoid tick-infested environments. For people visiting or working in these areas, the use of tick repellents is advised. Tick repellents include *N*,*N*-diethyl-3-methylbenzamide (DEET), permethrin and picaridin. They can be applied directly on the skin (e.g., DEET, picaridin) or on clothing, shoes, bed nets, and camping gear (e.g., DEET, permethrin, picaridin) [52].
- People visiting tick-infested areas should check themselves and their children to remove any attached tick immediately, to reduce the risk of tick-borne pathogen transmission [4]. Bathing or showering and thorough physical inspection soon after exposure to a tick habitat is also recommended to eliminate unattached ticks and localize attached ones.
- Because the transmission of some tick-borne pathogens during blood feeding is not immediate [56], the use of compounds with antifeeding or fast-killing effects can help to prevent pathogen transmission. Some commercially available products can prevent dogs from becoming infected by tick-borne pathogens [79,80].
- TBDs in humans may eventually be prevented by vaccination [5]. Some vaccines are also available for veterinary use [53–55].

Heavy tick infestations on humans are less common; usually patients are presented with one or a few ticks attached [28,34,37]. The treatment of choice for tick infestation on humans is the prompt removal of attached ticks using a curved forceps or fine point tweezers [4,5]. Ticks have barbed mouthparts and secrete a cement-like substance with saliva that allows them to firmly attach to the skin of the host. Care should be exercised to avoid crushing the tick's body, so as to prevent the contact of potentially infectious tick fluids with skin. It is important to wash the bite wound area with antibacterial soap and water after tick removal, and the disinfection of bite wounds with ordinary antiseptics is also recommended [4]. Furthermore, patients should be advised to seek medical attention if skin rash or flu-like symptoms are recorded some days or weeks after tick removal.

The best preventive measure against TBDs is to stay away from ticks. For obvious reasons, this is not feasible for individuals who live in or visit tick-infested environments. In this case, the use of protective clothing should be advised as well as the use of tick repellents (Box 1), which might be available for use on clothing and/or skin [52].

The prevention of TBDs can also be achieved by vaccination of individuals at risk, although only a few effective vaccines are currently available for the prevention of TBDs either in animals or in humans. Veterinarians are provided with vaccines against anaplasmosis, babesiosis, and Lyme borreliosis [53–55], but these vaccines are for species that only infect animals. A vaccine is commercially available for the prevention of tick-borne encephalitis in Europe and eastern Russia, although this has not been enough to reduce the global number of human cases of the disease [5,13]. A vaccine against Lyme borreliosis was approved in 1999 by the US Food and Drug Administration, but was withdrawn from the market in 2002 [5].

Because the transmission of certain tick-borne pathogens (e.g., *Borrelia burgdorferi*) is not immediate [5,56], the prompt removal of all attached ticks might greatly reduce the risk of infection and this should be strongly emphasized by physicians and veterinarians.

Concluding remarks

The risk of TBDs is increasing worldwide, and this situation seems to be driven by several interacting factors. Wildlife populations can naturally migrate, bringing ticks and tick-borne pathogens from one area to another [57]. Human travelers may also play a role in the translocation of wildlife species and in the introduction of exotic tick species into previously free areas [58,59], which may eventually carry relevant pathogens [57,58]. TBDs are increasingly being diagnosed in travelers returning from endemic areas [60], which might represent a diagnostic challenge for less-experienced physicians in non-endemic areas. Political scenarios may also influence the epidemiology of TBDs. For instance, the upsurge in tick-borne encephalitis in Central and Eastern Europe has been explained by several biotic and abiotic factors, including the political transition with the end of Soviet rule [61]. The risk of infection by tick-borne pathogens is strongly influenced by tick and host population dynamics. For example, it has been demonstrated in northwest Spain that the frequency of *R. conorii*-seropositive dogs increases during summer [62], which concurs with the period of highest activity of *R. sanguineus* [63].

Humans often become infected by tick-borne pathogens (e.g., *Anaplasma phagocytophilum*, *Babesia microti*, *B. burgdorferi* sensu lato, and *R. rickettsii*) by entering wooded areas infested by ticks that are usually parasitic on wildlife. There is also an increased risk of being inoculated with several agents at once from a single tick bite, as questing ticks may often be coinfected by several pathogens [3,64]. However, the actual risk of contracting TBDs by pet owners and farmers is uncertain. For instance, cattle are the main reservoirs of *B. divergens* [2], but the risk of acquiring *B. divergens* by farmers during daily work with animals has not yet been quantified. Similarly, *R. sanguineus* is reputed to be the main vector of *R. conorii* [27], but the role of dogs in the epidemiology of Mediterranean spotted fever is still poorly understood.

It is a fact that TBDs are on the rise and the unification of health professional efforts is vital to rectify this situation and to reduce their current burden in terms of morbidity and mortality. Attitude change and increased communication between physicians and veterinarians could play a pivotal role in this process, and it is evident that there is a need for a One Health approach towards a better management of TBDs. The diagnosis of TBDs is challenging [65], and information exchange from physicians to veterinarians and vice versa is beneficial for both sides, but mainly for patients. In this changing scenario of TBDs, continuous education is essential. Physicians and veterinarians must be aware of new discoveries and developments to improve their clinical practice. National and local conferences on One Health, where veterinarians and physicians could sit around the same table, should be promoted worldwide.

Because dogs and cats can act as sentinels for certain human diseases, veterinarians may play a decisive role by notifying public health authorities when appropriate and implementation of national integrated information systems (Figure 2), coupling animal and human disease data, would be valuable. Untreated animals (e.g., stray dogs and cats) could serve as sentinels: (i) for tick infestation pressure in the outside environment; (ii) for pathogen diversity in the tick population; and (iii) for the pathogen infection pressure, reflected by their incidence in the unprotected animal population. But again, it is imperative to emphasize that pet owners should be advised to keep their animals protected against ectoparasites.

Finally, researchers should endeavor to generate novel research-based information on traditional and emerging TBDs (Box 2), which should be translated into practice. Education is key to controlling TBDs, and beyond a shadow of doubt, public health decision makers, researchers, physicians, veterinarians, dog owners, farmers, travelers, etc., should be aware of TBDs and how they should be dealt with. The immediate removal of a tick from the skin of a patient might save a life; this is a small step for a physician, but significant action for the prevention of TBDs. This slogan should to be reinforced in practice.

Box 2. Outstanding questions on tick-borne diseases

- Epidemiology
  - Vector and host population dynamics and TBD spatiotemporal distribution
  - Climate change, human behavior, economics, and politics and TBD incidence
- Diagnosis and treatment
  - Rapid tests for tick-borne pathogen detection in humans and animals
  - Quantitative assays for the detection of tick-borne pathogens in ticks
  - New drugs for treatment of tick-borne protozoal infections
- Vector issues
  - Questing versus feeding ticks as indicators of pathogen transmission risk
  - Transmission times of pathogens during tick feeding
  - Vector competence of different tick species or strains for emerging pathogens
- Host issues
  - Role of wildlife as reservoirs or amplifying hosts of tick-borne pathogens
  - Livestock and companion animals as sentinels of TBDs
- Prevention and control
  - Prevention and control of TBDs in humans and domestic animals
  - Impact of dog tick control on the risk of tick-borne pathogen transmission in humans

Update

After this Review was written, a new species of argasid tick has recently been described from Australia, which brings the world tick fauna to 899 and the number of argasid species to 195 [81].

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