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Review

The ecology of ticks and epidemiology of tick-borne viral diseases

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ABSTRACT

A number of tick-borne diseases of humans have increased in incidence and geographic range over the past few decades, and there is concern that they will pose an even greater threat to public health in future. Although global warming is often cited as the underlying mechanism favoring the spread of tick-borne diseases, climate is just one of many factors that determine which tick species are found in a given geographic region, their population density, the likelihood that they will be infected with microbes pathogenic for humans and the frequency of tick–human contact. This article provides basic information needed for microbiologists to understand the many factors that affect the geographic range and population density of ticks and the risk of human exposure to infected ticks. It first briefly summarizes the life cycle and basic ecology of ticks and how ticks and vertebrate hosts interact, then reviews current understanding of the role of climate, sociodemographic factors, agricultural development and changes in human behavior that affect the incidence of tick-borne diseases. These concepts are then illustrated in specific discussions of tick-borne encephalitis and Crimean-Congo hemorrhagic fever.

Contents

1. Introduction

Ticks are obligate parasites that transmit a multitude of pathogens to animals and humans. Interest in human tick-transmitted pathogens has experienced an upsurge in the past few decades. Routine application of tools for the detection of fragments of foreign DNA or RNA in ticks, together with a high degree of interest in the quantification of disease risk for humans, has led to a marked increase in the number of reports on the eco-epidemiology of tick-borne diseases. The discovery of formerly unknown

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mechanisms of pathogen transmission, such as the non-viremic (co-feeding) transmission of TBE virus (TBEV) (Labuda et al., 1993a,b), and the emergence or re-emergence of certain tick-borne diseases, such as the ongoing epidemic of Crimean-Congo hemorrhagic fever in Turkey have also created a wealth of research interest (Gale et al., 2010). A further surge of interest in ticks and tick-borne pathogens has been inspired by recent claims about the impact of forecasted climate change on the spatial distribution of ticks and associated pathogens (Brownstein et al., 2003; Ostfeld et al., 2005; Ogden et al., 2008a,b; Jaenson et al., 2009). However, this research has been fraught with difficulty from the outset because of insufficient knowledge about the nature of the tick-pathogens associations (Randolph, 2009; Medlock et al., 2013). An adequate understanding of how the climate shapes the transmission cycles of tick-transmitted disease agents awaits a more rigorous analysis that is often limited by lack of data (Eisen, 2008).

Much attention has been devoted to account for the expected modifications of the dynamics of tick-transmitted pathogens, as driven only by environmental factors (reviewed by Patz et al., 2003). It is however believed that the drivers of changes in the epidemiology of tick-transmitted pathogens are likely dependent on socio-demographic factors, agricultural development (or abandonment), deforestation, and the extent to which humans contact the interface of the ecosystem of the disease (Patz et al., 2003). This introduces a high degree of uncertainty when we attempt to capture such local or regional patterns of risk of pathogen transmission. Areas where tick-transmitted pathogens circulate are very focal. This is why the term "foci of transmission" apply precisely to such spatial distribution of tick-transmitted pathogens. These foci are not only defined by the microclimate conditions, but by the presence and abundance of key reservoir hosts, necessary for the maintenance of the pathogens in the field. Since the faunal composition of hosts has a focal nature (Randolph, 2009) it may affects the dynamics of the pathogens at the local scale, because both the effects on the survival of ticks and the presence of key reservoirs hosts. It is thus important to determine the impact of the composition of the community of hosts on the chain of transmission of the pathogen, and not only the environmental factors.

This article aims to provide information on the associations among climate, tick-transmitted pathogens, faunal composition of hosts, pathogens and human activities, and how they may interact. It is divided in six parts. In the first, we examine the basic points of the biology and the ecology of ticks, with a focus on the relationships of ticks with climate and hosts. The second section examines the relationships between ticks and hosts, defining some important terms in research on these relationships. The third is devoted to reviewing the factors that regulate the abundance of tick populations, with a special focus on climate, the composition of the community of hosts, and the features of the landscape. The fourth part is devoted to examining two examples of tick-transmitted viruses, tick-borne encephalitis (TBE) and Crimean-Congo hemorrhagic fever (CCHF), to illustrate potential regulatory factors operating on their dynamics. The fifth section is devoted to briefly review developments in modeling the distribution and the seasonal dynamics of ticks, in an attempt to capture the environmental niche of ticks and their transmitted pathogens. The concluding section outlines principal research needs in the field.

2. Basic tick biology and ecology

Ticks are divided into two large families, the Argasidae and the Ixodidae, with a total of about 850 species (Guglielmone et al., 2010). The former are commonly known as "soft ticks" and the latter as "hard ticks". The two families have a different life cycle. This review focus on Ixodidae, not because argasid ticks are less important, but because of the large body of research conducted on Ixodidae in the last decades.

All ticks are obligate temporary parasites of vertebrate animals and are characterized by a complex developmental cycle. Fig. 1 shows a diagram of the typical life cycle of an ixodid tick. The life cycle typically includes the larva (hatching from the egg, Fig. 1A), that, after feeding (Fig. 1B), drops to the ground and molts to the nymph. The nymphal stage finds a suitable host (Fig. 1C), feeding again and returning to the ground for a further molt. The resulting adult will find a third host, feed again and mate, and the females will lay eggs (Fig. 1D). The engorged adult female lays thousands of eggs, which are left among the decaying vegetation at protected sites where a high relative humidity will ensure their survival. At each blood meal, ticks thus can become integrated into the epidemiological chain of pathogen transmission, by means of the so-called transstadial (stage-to-stage, also called horizontal) or transovarial (female-to-egg, also called vertical) passages. For a tick-transmitted pathogen to persist in the environment, it must be acquired from an infected host, passed into the next active stage of the tick, and then successfully transmitted into a new host (Kahl et al., 2002). This complicates the dynamics of a pathogen in the field, which depend upon both the survival and activity rates of the tick and the composition of the community of hosts (Estrada-Peña et al., 2013b).

Ticks therefore feed once in each active stage and ingest massive amounts of blood, which provides the energy necessary for molting or oviposition. Ticks commonly mate while on their host, but some species may mate in vegetation, while questing for a host. Most species have evolved a life cycle involving three different hosts (as illustrated in Fig. 1) but a few have evolved a life cycle involving only two hosts. In the two-host scheme, both larvae and nymphs feed on the same host, without dropping to the ground to molt. Every species of medical interest has a two- or three-host life cycle pattern, as explained. A few species, which are mainly parasites of wild ungulates and livestock, have evolved a one-host life cycle, in which each stage feeds, molts and mates on the same host.

Some ticks have evolved so-called "nidicolous behavior," so that they are commonly parasites of nesting birds or carnivores that build burrows. Fed stages of the species that have evolved such a survival strategy drop from the host within the nest or burrow, increasing their chances of survival, because they have a shelter in a protected environment. After the molt, the active stages feed on the vertebrates occupying the burrow.

The timing and total duration of the life cycle are highly variable. Some species may complete the three stages of their life cycle in one year, while others, mainly those inhabiting cold climates, may expend up to three or four years to accomplish the complete development from egg to engorged female. The temperature regulates the development of the off-host stages of the life cycle. The total life span of a tick depends on the reserves of energy obtained in the previous blood meal, and how these reserves are exhausted as a consequence of stress by the climate.

Ticks may use different groups of hosts for each active stage. It is common for immatures (larvae and nymphs) to feed upon small animals, such as rodents and birds, while adults may commonly feed upon large carnivores and ungulates. However, this is not a rule for every species of ticks. Some species may be highly specific for a particular type of host. The absence of such key host(s) in a particular area may prevent the occurrence of ticks that specifically feed on it. Some of these hosts also play an essential role in maintaining and transmitting pathogens, such that a given pathogen might not exist in an area if such key reservoir hosts are not present. For example, some small forest mammals are the reservoirs of a flavivirus causing tick-borne encephalitis (TBE) in humans (Süss, 2008). If these reservoirs are not present in an area, the tick may feed on other hosts, but the pathogen will not circulate. Most importantly in this context, ticks rely on the movements of their

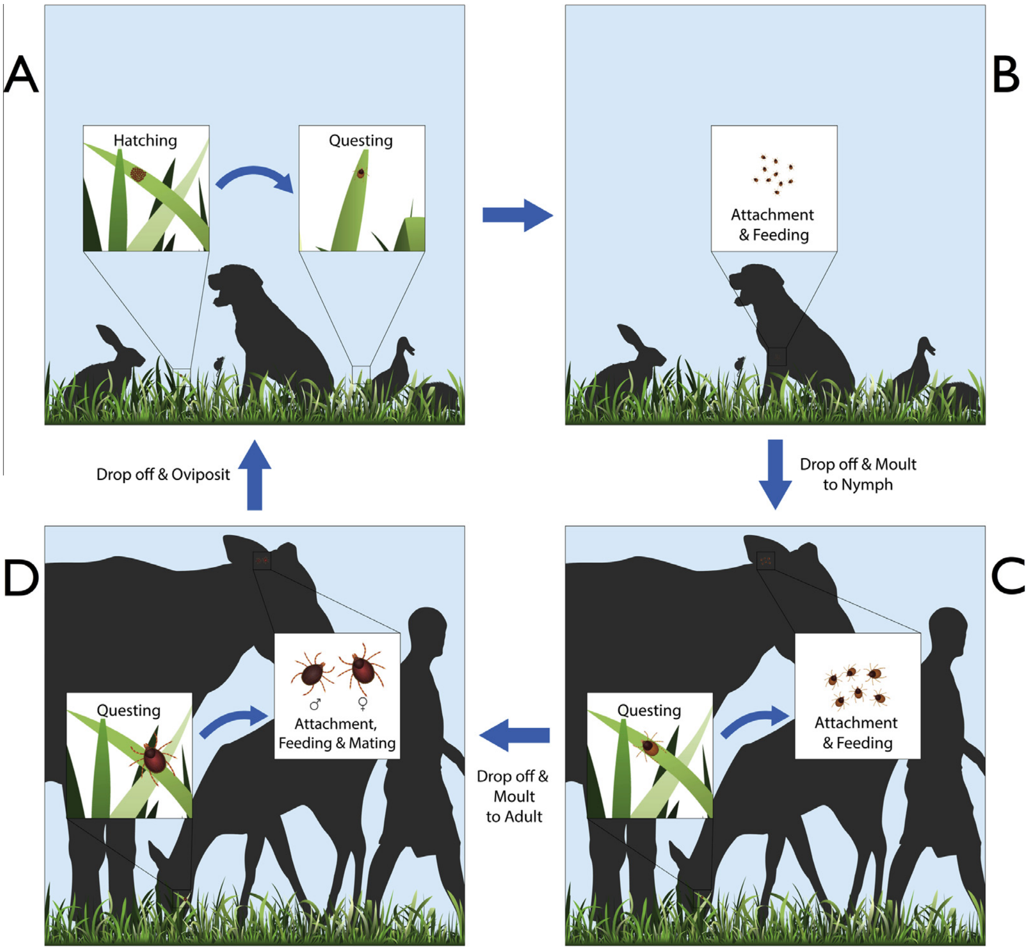

Fig. 1. Idealized life cycle of an ixodid tick with three hosts, showing the three stages (larva, nymph and adult). The eggs incubate in ground litter (A), protected against stressful environmental conditions (e.g. water losses). When the larvae hatch, they climb to the vegetation, questing for a host (A → B). Larvae feed on such hosts (B), and when engorged, drop off to the ground and molt to nymphs (B → C). The nymphs quest for a second host, feed, and perform a second molt off the host (C → D). The resulting adults attach to a third host, feed and mate, and the females drop off for egg laying on the ground. Image courtesy of Alexander J. MacAuley, University of Texas Medical Branch, Galveston, TX, USA.

hosts to gain new territories, because they do not fly. Geographic barriers that prevent the movements of animals thus impose constraints to the dispersal of ticks.

Once on the host, ticks actively search for a favorable place for feeding. They then probe the skin and insert their mouthparts. The first step in feeding is the secretion of a substance that solidifies in contact with the skin of the hosts. It contributes to the fixing of the tick, and is called “cement”. A few hours after the tick becomes attached to the host’s skin, a complex sequence of events starts, mainly originated in the salivary glands of the tick. The feeding tick begins a series of peristaltic movements that inoculate the saliva through the mouthparts into a so-called “feeding cavity”. At the same time, a dramatic series of changes occur in the salivary glands, whose cells are deeply transformed, adapting its physiology and pharmacological secretive properties to the new “active” status. The inoculation of several dozen pharmacologically active compounds (Nuttall and Labuda, 2004, 2008) contributes to the sustained flow of blood into the feeding cavity, to the lysis of the cells in the surroundings of the feeding place, and to evade the immune response. Transmission of the pathogen is likely to start approximately 24 h after the commencement of feeding, but some may be inoculated sooner.

Feeding ticks concentrate the blood meal by removing the excess of water. This helps to accommodate the large blood intake (several milliliters) in the relatively small body of the engorging tick. Immature stages (larvae and nymphs) commonly feed for 3–6 days, while adults may feed for as long as two weeks. Digestion of the blood may start during the very first hours after the beginning of feeding, and it usually lasts for several weeks or even months. While digestion is taking place, the pathogens acquired from the hosts cross throughout the gut wall, incorporate into the hemolymph circulation of the tick, and invade the cells of the body tissues. After the molt is complete, the tick takes some days for the complete hardening of its cuticle and then actively quest for a new host (Estrada-Peña et al., 2013b).

Both the microclimate (e.g. the climate at the lower layers of vegetation) and the abundance and availability of hosts shape the seasonality and abundance of ticks during the course of the year, a feature known as “phenology”. Throughout this paper, we will use this term to refer to tick life cycle events and how these are influenced by seasonal and inter-annual variations in weather. Each tick stage prevails at definite times of the year according to the specific combinations of climate and seasonal changes in host abundance. In the process of finding and feeding upon a host, ticks must quest in the vegetation. Questing is the process in the life cycle in which active stages search for a host (Estrada-Peña et al., 2013b). It is the beginning of a period of activity in which the ticks gain a vantage point on the vegetation and seek a host. The duration and the intensity of these periods of questing, and even the simultaneous questing of different stages of the same species of tick, have deep implications for the epidemiology of tick-transmitted pathogens (Nuttall and Labuda, 1994). The restriction of the questing activity of ticks to a defined period in the temperate regions of the world is a consequence of the seasonality of the climate and the regional events of weather. The contact rates between host and ticks are regulated by principles resembling mass-action laws in chemistry: the more abundant ticks and hosts are, the more frequent contacts are, and questing ticks find a host in less time. A higher host density may reduce the time to find a suitable host, thus reducing mortality of the ticks (Barnard, 1991).

Empirical studies confirm that the developmental and questing activity of ticks are regulated by the climate (Lees and Milne, 1951; Gray, 2008; Perret et al., 2000, 2003, 2004; Randolph et al., 2002; Estrada-Peña and Venzal, 2007; Daniels et al., 1996; Lindsay et al., 1999; Ogden et al., 2006). There are two key processes in the life cycle of any species of tick: development of the molting stage (or the oviposited eggs) and periods of questing activity. The temperature regulates the development rates and the mortality depends on the losses of water, which are regulated by the relative humidity and the air saturation deficit. During the winter, low temperature prevents fast development, which progresses slowly until the rise of temperatures in the spring. Large numbers of active ticks appear in the vegetation in the spring in temperate regions as a consequence of the synchronous development of molting ticks driven by the rise of temperature after the winter. The regulatory effects of either temperature or water availability are not the same in every geographical domain. In cold climates, temperature will probably play the most significant role in the regulation of phenology (together with the photoperiod – see below), while in dry regions, water availability becomes a key variable.

The second central process in the tick life cycle, which also has a direct impact on the ability to transmit pathogens, is the period of questing for a host. It is necessary to understand how ticks become active and the factors responsible for their patterns of activity, before further explaining the effects of the weather on the general circulation of pathogens. Most ticks remain inactive in the lowest layers of vegetation until they begin to quest, a process that is triggered by specific combinations of climate and photoperiod, which is the ratio of hours of light and darkness in a day (Belozerov, 1982). Photoperiod may act on the molting stages, activating or delaying molting until more favorable conditions are available, or on the questing stages, activating or delaying the onset of activity. This is believed to ensure the success of the population by finding a host, feeding and entering into the molting period before the onset of winter, and to stop any further activity until the beginning of the next spring. Although photoperiod has been largely ignored when investigating the regulation of the seasonality of ticks, this factor alone may deeply affect the epidemiology of tick-transmitted viruses (Estrada-Peña et al., 2013a).

During questing, ticks may lose water that they normally regain by descending at intervals to the litter zone where they may reabsorb water vapor from the atmosphere (Lees, 1946; Lees and Milne, 1951; Rudolph and Knülle, 1974; Kahl and Alidousti, 1997). When they are hydrated, they ascend to the vegetation. The seasonal activity of ticks is thus characterized by several cycles of ascending and descending movements in the vegetation, regulated by temperature and losses of water. The energy reserves of the tick, plus its ability to retain water, together with the water content of the air and the temperature, are therefore the factors regulating the questing and survival of ticks in the field.

In conclusion, temperature plays a central role in the regulation of the tick life cycle. However, mortality rates are related to the water content of the air: if the relative humidity drops below some species-specific limit, below which ticks are not able to absorb water from the atmosphere, the saturation deficit can take control of the regulation of such mortality rates.

3. Maintenance and transmission of pathogens among ticks and hosts

After a blood meal, pathogens remain in the gut contents with the ingested blood. Each pathogen has different mechanisms of passing through the gut membrane. Laboratory studies have demonstrated that some pathogens might enter the gut cell by expressing molecules that enable the recognition of specific receptors in the cell membrane. This might be the case of *Anaplasma* spp., which express the MSP1a protein, an adhesin that is believed to binds to specific portions of tick gut cells (de la Fuente et al., 2001). In the case of the spirochaetes of the complex *Borrelia burgdorferi* s.l., OspA, OspB, and OspD are expressed by *B. burgdorferi* residing in the gut of unfed ticks, suggesting they promote the spirochete persistence in ticks between blood meals (Schwan et al., 1995). OspA promotes the attachment of *B. burgdorferi* to the tick protein TROSPA, present on tick gut epithelial cells (Pal et al., 2004). OspB also has an essential role in the adherence of *B. burgdorferi* to the tick gut (Neelakanta et al., 2007). During transmission to the mammalian host, when the infected tick begins to feed and the spirochetes in the midgut begin to multiply rapidly, most spirochetes cease expressing OspA on their surfaces. Simultaneous with the disappearance of OspA, the spirochete population in the midgut begins to express an OspC and migrate to the salivary gland of the tick. Upregulation of OspC begins during the first day of feeding and peaks 48 h after attachment (Schwan and Piesman, 2000).

Tick-transmitted viruses employ other mechanisms of dispersion. The TBE virus is internalized into gut cells by endosomes that ticks produce to digest ingested blood. After viruses are internalized into cells via endocytic pathways, they must escape from the endosome to the cytosol. Enveloped viruses, like TBEV, utilize membrane fusion to cross the membrane barrier and reach the cytoplasm (Mudhakir and Harashima, 2009). In this particular example, the virus used the class II fusion protein that dissociates in the low pH of the tick gut cell to mediate fusion with the endosomal membrane and release into the cytoplasm (Mudhakir and Harashima, 2009). The receptors and mode of entry of CCHFV into tick cells are currently unknown (Simon et al., 2009).

Two events in the tick life cycle are of epidemiological significance in the maintenance of transmitted pathogens. Because ticks feed once at each stage, the pathogen must to be able to persist in each new stage after molt, to pass into a new cohort of vertebrates by means of an infective bite. This is called trans-stadial passage (i.e. from stage to stage). It involves the acquisition of a pathogen by a tick while feeding on an infective reservoir host, the subsequent molt to the next active stage of the tick, and the further persistence of the pathogen in the newly molted tick. Another key feature in the life cycle of some tick-transmitted pathogens is trans-ovarial (vertical) passage, i.e. the persistence of a pathogen acquired by a tick and transferred to the cohort of eggs by the engorged female. This is commonly regarded as a way of massive dissemination of the pathogen throughout the next generation of ticks and to a naive generation of hosts. Both mechanisms of persistence of pathogens depend on the rates at which they are passed onto the next stage of the tick, which is regulated by species-specific mechanisms (Hartemink et al., 2008). In the case of tick-transmitted viruses, transmission rates from the infected engorged females to eggs are negligible (see Section 5).

The role of ticks and their hosts in the maintenance and transmission of pathogens cannot be determined solely by field studies, which commonly report only the detection of a sequence of nucleic acid in a number of specimens of ticks. Complementary laboratory studies should be designed to capture the essentials of the role played by each element of the system. These laboratory tests would confirm the hypotheses built upon field studies. To qualify as a true vector of a pathogen, the tick must (i) feed on infectious vertebrates (ii) acquire the pathogen during the blood meal (iii) maintain the pathogen through one or more trans-stadial molts and (iv) transmit the pathogen to previously unexposed hosts while feeding again (Kahl et al., 2002). Assigning vector status to a tick, based solely on the detection of nucleic acids, or reservoir status to a host species, based solely on serologic studies, is not acceptable. Detection of nucleic acids of pathogens in a tick or host indicates that it possesses carrier status (see below for definitions), and detection of antibodies in host serum merely indicates that an animal has been exposed to the pathogen. Whether or not pathogen transmission takes place from tick to host or from host to tick must be addressed experimentally in the laboratory.

The interactions between the elements of any tick–host–pathogen system are thus key features to understand pathogen prevalence in questing ticks. The evaluation of such interactions is a necessary preliminary step in risk assessment, and it is therefore necessary to summarize the framework of relevant terminology proposed by Kahl et al. (2002) that was constructed to address major pitfalls in the research of the relationships among ticks, hosts and pathogens. We have included such a framework in Fig. 2.

When hosts are fed on by infected vector ticks (Fig. 2A), they may be exposed to the pathogen, and may then become either *carriers* or *non-carriers* (Fig. 2B). As the term implies, carrier hosts are those carrying the pathogen. However, a carrier host is not necessarily infective to ticks and therefore the terms non-reservoir and reservoir must be used to define infectivity status (Fig. 2C). The former are incapable of transmitting the infection to uninfected ticks. *Reservoir capacity* of the hosts describes the absolute contribution made by a particular reservoir host species to the natural prevalence of infection by a given pathogen within a certain site. Such reservoir capacity may be different at different sites, because of the faunal composition of the community of hosts and their relative contribution to the epidemiological events in the transmission of the pathogen. *Host infectivity* denotes the efficiency with which the host transmits the infection to ticks feeding on it.

Reservoir capacity is dependent upon the infectivity of the host for feeding ticks and the duration of the infective period (Mather et al., 1989; Mannelli et al., 2003; Randolph and Craine, 1995; Kahl et al., 2002), which is highly variable for the different tick-transmitted pathogens, from a few days to months. By feeding on reservoir hosts, ticks are exposed to pathogens (Fig. 2D) and they may become either *non-carrier* or *carrier ticks*. The former are unable to acquire the pathogen, even if they feed on viremic hosts, and they therefore have no importance in the epidemiology of such pathogens. Carrier ticks may be *vectors* or non-vectors after feeding on infected reservoirs.

The above definitions imply that the relationships among ticks, hosts and pathogens are quantitative instead of being simply qualitative. The first is the *vector capacity*, which quantitatively defines the potential of the tick to transmit a pathogen. The second is called the *vector competence*, which only defines the adequacy of the tick to be a vector of a pathogen. This means that such relationships have wide ranges of variability even if necessary contacts between competent tick vectors and reservoir hosts are produced on regular spatial and temporal scales. The rules governing the transmission of a pathogen may be even more complex if several species of reservoirs and ticks overlap in the same territory, each with different abilities to carry and transmit the pathogen, that may or may not overlap their periods of activity, be present at different densities, or have different sensitivity to the actions of the environmental or biotic factors. We will further elaborate on these concepts in Section 4.2.

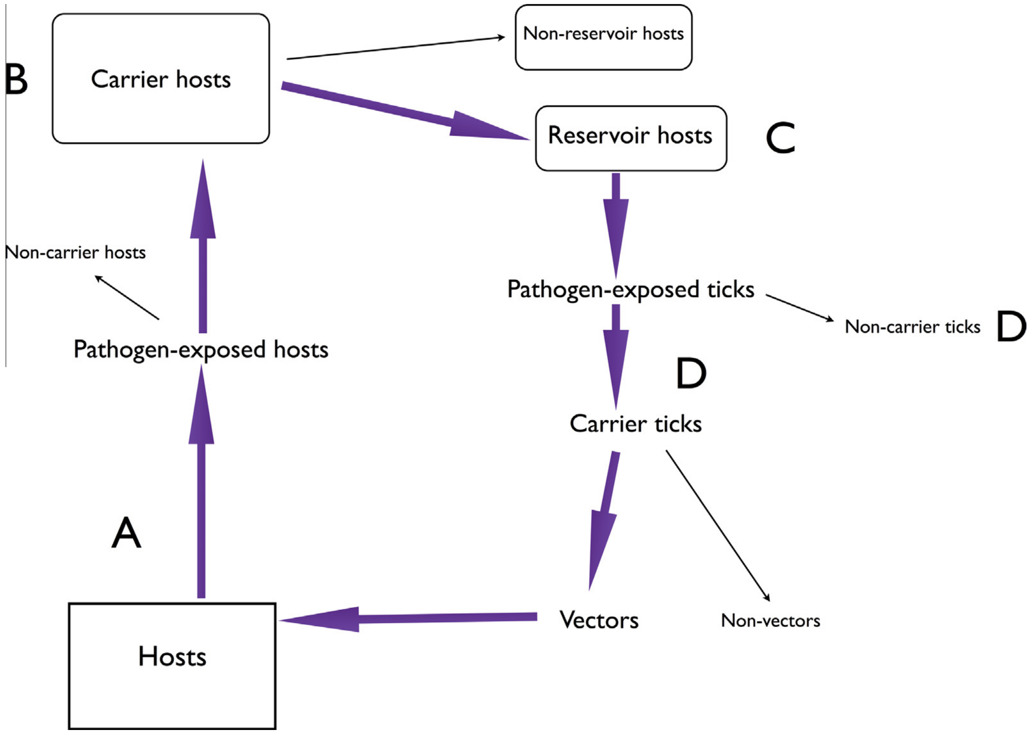

Fig. 2. The chain of events in the interface of ticks, hosts, and pathogens, indicating the standard denominations of relationships between ticks and hosts. Hosts (A) are exposed to pathogens, and then become either carrier hosts (B), if there is no further pathogen transmission, or reservoir hosts (C), if the pathogen is transmitted to feeding ticks. The detection of a pathogen in a vertebrate is therefore insufficient to determine if it is a carrier or a reservoir host. Ticks that feed on reservoir hosts may become carrier ticks (D), if there is no further pathogen transmission, or vectors, if they are capable of transmitting the pathogen to new hosts. The detection of a pathogen in a tick is therefore insufficient to determine if it is a carrier or a vector. The chart has been developed from concepts by Kahl et al. (2002), and is partially modified from Estrada-Peña et al. (2013a).

4. Factors affecting the abundance of tick populations

4.1. Weather and microclimate

The microclimate in the layers of vegetation populated by ticks is an important factor regulating the abundance of their population. The weather also regulates the periods of the year when ticks are active (Belozerov, 1982). It therefore exerts some not yet totally quantified effects on the mortality and developmental rates of the population of ticks, but also on the phenological component of the cycle, e.g. activating a cohort of questing ticks earlier or later in the year. To understand how climate may affect the seasonal activity and the survival of ticks, a reliable recording of the weather is needed. Ticks are responsive only to the microclimate, e.g. the temperature and the water contents recorded between the litter and the height where the ticks quest. These data are commonly recorded with programmable microloggers. Attempts to relate field observations of the activity or physiology of ticks and the weather recorded at climate stations placed two meters above the ground will probably produce unreliable correlations, because these two series of weather records do not always correlate. Some evidence may be obtained from standard climate stations, but their limitations must be assumed before interpreting the observed correlations.

It is important to collect ticks from the vegetation to have an estimate of their density (e.g. the abundance per unit area) and to correlate with the weather features. The common procedure for collection of questing ticks is to drag a piece of fabric, such as flannelette or blanket, across the vegetation surface or over the leaf litter. These can either be large pieces of fabric dragged behind the operator, or more commonly are relatively small pieces ($1\ m^2$) mounted on poles and brushed over the vegetation, a procedure known as "flagging." Ticks adhering to the fabric are collected at varying intervals, but it should be kept in mind that prolonged dragging distances result in a loss of ticks. Sampling must be conducted over patches of homogeneous vegetation, but a stratified approach may be adopted to obtain a reliable representation of questing ticks in a given area (Estrada-Peña et al., 2013b).

Vegetation cover affects the efficiency of the flagging or dragging method and heterogeneously modifies the microclimate at the level where the ticks quest, thereby affecting their behavior and their observed abundance (Tälleklint-Eisen and Lane, 2000). It also affects the abundance of hosts, and this may influence the perceived abundance of ticks, at the scale of small patches of vegetation. Tick abundance may vary significantly by aspect (exposure, such as south-facing) in hilly or mountainous areas (Lane et al., 1985).

In the summer in temperate areas, long periods of high temperatures (together with a high desiccating power of the air) may promote a rise of the mortality rates of molting or questing stages. Long winters or abnormally low minimum winter temperatures may induce high mortalities in the population of ticks overwintering in the ground. However, it is well known that long periods of snow covering the ground may confer a protective effect, by isolating ticks overwintering in the ground from very low temperatures. It has been reported that the milder winter periods recorded in the past decades in northern Europe, northern United States, and southern Canada, have promoted the spread of at least two tick species to northern latitudes, namely *Ixodes scapularis* and *Amblyomma americanum* (Childs and Paddock, 2003). The tick *Ixodes ricinus* has been reported to spread north in Sweden (Lindgren et al., 2000; Lindgren and Jaenson, 2006; Eisen, 2008), Norway (Skarpaas et al., 2006), Finland (Jääskeläinen et al., 2006), as well as in Germany (Hemmer et al., 2005; Süss, 2008). Nearly all these data were collected along the fringes of tick distribution and do not apply to core distribution areas.

At least in the case of Sweden, it is known that spread into northern latitudes is produced not only because winter temperatures, which impose restrictions to colonization in the northern range of the tick, are becoming warmer, but also because some species of wild animals that feed the adults of the tick are becoming more abundant in these territories (Jaenson et al., 2012a). Such large hosts provide a blood meal for literally hundreds of tick females on the same animal. In southern Canada and the northern United States, the driver of the northern spread of *I. scapularis* seems to be warmer temperatures in winter. Migratory birds fly from the United States to Canada and they carry immature stages of the tick. A warmer climate facilitates the colonization of these areas in Canada by the moving ticks that otherwise are unable to survive under such cold conditions (Ogden et al., 2008a).

Short-term changes in regional weather may also promote variations in the seasonal pattern of tick populations. For example, mild temperatures in autumn and winter could affect the development rates of the ticks, and the newly molted stages might quest in the vegetation a few days before the "historical" period of activity in the region. In the same sense, if winter temperatures are high enough to promote questing behavior, ticks may quest out of the periods when they were recorded. This was reported for the unusually warm winter of the year 2006 in Germany, where adult *I. ricinus* were collected while questing throughout the winter, a period when they are not commonly active (Dautel et al., 2008; Gray, 2008; Gray et al., 2009).

In any case, the effects of the weather on the observed seasonality of ticks in the field are not yet well understood, because of the many uncertainties operating at the smallest scale. Several studies have addressed the quantification of the effects of different combinations of temperature and relative humidity on each of the processes for several species of ticks, expressing such effects as equations describing a physiological response (i.e. Corson et al., 2004; Mount et al., 1997; Randolph et al., 2002; Estrada-Peña, 2002). However, we do not yet know how the long-term trend of a variable (e.g. the yearly averaged temperature) would impact the complete life cycle of ticks in the field and their ability to persist in the field as permanent populations (e.g. populations that have a growth rate greater than 1). As far as we are aware, no studies have been devoted to capture the phenotypic plasticity of ticks under a range of temperature and water availability. Phenotypic plasticity applies to the ability of an organism to adapt to change its phenotype in response to changes in the environment (Price et al., 2003). For example, ticks could adapt and persist into warmer or drier conditions if the abiotic variables have a sustained trend towards such a range of values, probably by modifications of the external layer of cuticular hydrocarbons that protect the tick from water losses (Estrada-Peña et al., 1996). These aspects have not yet been addressed.

4.2. The importance of hosts for ticks and pathogens

Besides the influence of the weather on the tick life cycle, two parameters are also essential: the composition and the abundance of the host communities. They have deep implications for the circulation of tick-transmitted pathogens, because the relative abundance of potential reservoir hosts may produce large variations in the prevalence of such pathogens (reviewed by Dobson et al., 2006). An important consequence is that the risk to humans of a tick-transmitted pathogen is proportional to the density of infected vectors, which not only depends on climate, but also on the density of infected reservoir hosts. The risk is therefore related to the total abundance of ticks, to the densities of reservoirs and the rates of the pathogen on them. For persistence of some pathogens in the

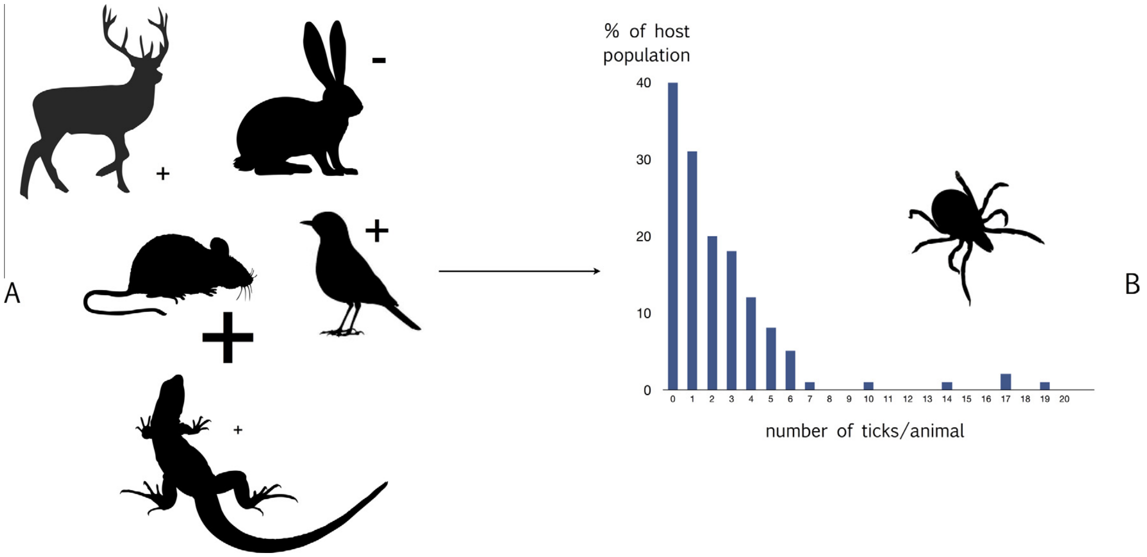

Fig. 3. The hypothetical relationships of ticks and their hosts in the field, which are of particular importance in the epidemiology of tick-transmitted pathogens. Ticks may or may not be randomly distributed on definite animal species, or have preferences to feed upon specific groups of hosts (A: denoted by a variable size of the + sign). Such preferences are further modulated by the distribution of ticks *on* members of the host population, following a negative binomial distribution, in which most host animals carry few ticks, and a few of them carry large numbers (B).

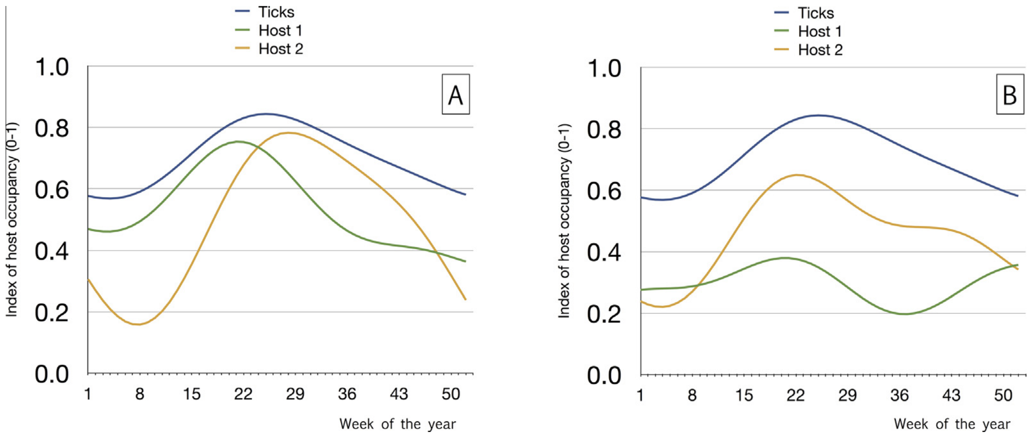

Fig. 4. Hypothetical figures of the abundance of ticks and the size of the host population under field conditions, showing different degrees of synchronicity, which affect the parasitic rates and thence the prevalence rates of ticks with pathogens. In A, the population of ticks shows a maximum of abundance around the middle of the year, and coincides with the maximum activity of two different species of hosts. The ticks will have high contact rates with abundant populations of hosts, and the parasites will become "diluted" over the hosts. This would hypothetically decrease the prevalence rate of pathogens in ticks. In B, ticks have the same pattern of activity, but the populations of hosts are either lower or have a different seasonal distribution. This would concentrate the population of ticks on hosts, that, if reservoirs of a pathogen, could transmit it to the majority of ticks, resulting in a high prevalence rate of such pathogen.

field, a seasonal synchronicity among the questing stages of vectors and the abundance of reservoir hosts is also necessary (Randolph and Rogers, 2000).

Figs. 3–5 illustrate some basic concepts of the interactions among ticks and their hosts. Questing ticks access the population of hosts by simple laws similar to those of mass-action in chemistry: the greater the density of available hosts, the higher the probability that a tick will find a host (Mount et al., 1997; Corson et al., 2004; Dobson et al., 2011). However, ticks may have preferences towards groups of hosts. Thus, the relative abundance of each host may deeply influence the transmission of a pathogen in the ecosystem (Fig. 3A), because only one or a few species of hosts may act as reservoirs of the pathogen (Kahl et al., 2002). Furthermore, ticks are distributed on hosts according to a negative binomial distribution (Anderson and Gordon, 1982; May, 1978; Poulin, 1993), a special kind of aggregated distribution in which most hosts have only a few ticks, while a few carry large numbers (Fig. 3B). This is also of importance in regulating the prevalence of a pathogen in its vectors, because most ticks tend to concentrate on a few hosts, which may, or may not, be reservoirs of the pathogen. However, one of the most important concepts regarding the regulation of tick-transmitted pathogens is the synchronicity among the populations of both ticks and reservoir hosts (Fig. 4). If the two populations have a synchronized life cycle, the abundance of ticks will parallel the abundance of hosts, and ticks will spread over a large number of hosts (Fig. 4A). In the first case, the copious questing ticks may become diluted over a large population of hosts. In another hypothetical scenario (Fig. 4B), the seasonal activity pattern of ticks and hosts is not synchronized, so that maximum tick activity coincides with low host abundance, concentrating most ticks on a few hosts (Kitron, 1998).

As mentioned, climate may deeply affect the questing activity of ticks. It has been also demonstrated that weather determines the height at which ticks quest in the vegetation (Randolph and

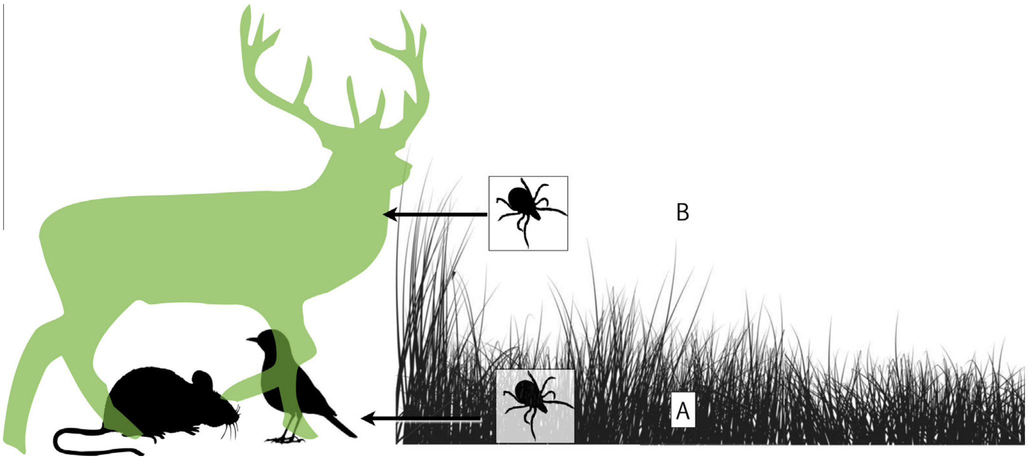

Fig. 5. Illustrations showing the different height at which ticks quest, as affected by the available water in the air. In situations of low relative humidity, ticks must limit their movements to the lower strata of vegetation (A). They are therefore in closer contact with small hosts that may be reservoirs of viruses. However, under conditions of high availability of water in the air, ticks quest higher in the vegetation, out of the reach of small animals, and concentrating greater numbers on large vertebrates (B). These larger hosts may feed large populations of ticks, therefore increasing their numbers, but they are not commonly reservoirs of the virus.

Storey, 1999), that in turn affects the parasitism rates of different hosts. In situations of low relative humidity, ticks must limit their movements to the lower strata of vegetation to minimize loss of water (Fig. 5A). They are therefore in closer contact with small hosts that are reservoirs of viruses. However, under conditions of high availability of water in the air, ticks quest higher in the vegetation (Fig. 5A), where they are out of the reach of small animals, and concentrating higher numbers on large vertebrates, like ungulates, that are usually not reservoirs of tick-transmitted pathogens. This is of potential importance in those transmission cycles in which rodents and/or birds are major reservoirs of tick-borne pathogens. The weather, the type of vegetation and human activities, disturbing the dominant vegetation, may modify or add further uncertainty to such a finely tuned synchronicity among hosts and ticks, resulting in a variable pattern of parasitic rates on hosts.

It is also necessary to state in this context that some pathogens are transmitted to humans by relatively well-known species of ticks, which have been more thoroughly investigated because of their obvious importance to public health. An example is the *I. ricinus* complex of species, involved in the transmission of the bacterium *B. burgdorferi* s.l. in wide regions (Kurtenbach et al., 2006). This is also the case of ticks for the genus *Hyalomma*, on which researchers have focused much attention because its involvement in the transmission of CCHF (reviewed by Hoogstraal, 1979; Bente et al., 2013). However, some species of ticks may be associated with the maintenance of "cryptic" cycles of transmission of pathogens among reservoir hosts, without direct involvement in transmission to humans, which perpetuates the transmission of the pathogen in the ecosystem (Telford et al., 1996). This is the case for *Ixodes dentatus* and *Ixodes cookie* in USA, as vectors of *B. burgdorferi* s.l. among their wild hosts. It is also the case for *Ixodes hexagonus* in Europe, which is a good vector of *B. burgdorferi* s.s. in the laboratory (Gern et al., 1991); the suspected role of the Palearctic *Ixodes frontalis* (a parasite of birds) in supporting a cycle of transmission among their hosts, a hypothesis that has been never empirically confirmed (Estrada-Peña et al., 1995); or the possible role of *Ixodes trianguliceps*, a parasite of rodents in the Palearctic, in enhancing the transmission of *Anaplasma phagocytophilum* (Bown et al., 2006). These ticks involved in cryptic cycles may contribute to sustaining active foci of pathogen(s) in an ecosystem, without noticeable clinical cases in humans, because there is no vector linking the reservoir hosts to humans.

Two consequences may be derived from ecosystems in which a pathogen circulates in this type of hidden cycle. Let's first consider that only the species of tick involved in the transmission of pathogens among wild vertebrate hosts exists in the ecosystem. In this case, the pathogen will remain unnoticed until a tick that links it to humans is introduced. However, it is possible (and probably is the most common case) that several species of ticks use the same host resources, but at different prevalence rates. Some ticks are "restricted" to the circulation of the pathogen among wild reservoirs, because they do not bite humans. Other(s) may redirect the pathogen to humans, even feeding simultaneously on the same infected reservoirs. Two species of ticks with different capacity of transmission of a pathogen may coincide on the same host, which may have a different immune response to each species of ticks. This is expected to influence the rates of transmission of such pathogen to humans, but this is a point that has not yet been confirmed for viral diseases affecting humans.

In conclusion, the abundance and seasonality of hosts, variability of tick abundance and regional weather all interact to produce a changing epidemiological landscape. It must be realized that the parasitic rates between ticks and hosts, the vector capacity for some pathogens, or the composition of host communities are basically local or regional processes. Therefore, the uncertainty may be high: the empirical rules obtained for mechanisms operating in a community of hosts, ticks and pathogens in a region, may be difficult to apply to other areas which have different communities of ticks or hosts. In large ecosystems, there is unlikely to be a single driver of the transmission rates of the pathogen among ticks and hosts.

4.3. Land use and habitat fragmentation

It has long been evident that patterns of land use could have an important influence on the risk of tick bites to humans (Burgdorfer, 1975; Gray et al., 2009; Vanwambeke et al., 2010). A territory may have a greater risk of transmission of pathogens, either because it is more visited by humans, or because larger populations of ticks and reservoirs of the pathogen are established in it.

Humans use the land in different ways, and may have a higher tendency to visit some particular sites (e.g. because of their interest for tourism) or exploit and work lands that may be near areas with high densities of ticks and reservoir hosts. For example, the forest stands of the northeastern United States have considerable populations of vertebrates supporting large numbers of ticks and the circulation of tick-transmitted pathogens, like *Borrelia* spp. Human populations at risk are therefore those sharing the habitat with infected vectors, commonly found at the ecotone (the transition zone) between the forest and grass areas (i.e. Kitron, 1998). Furthermore, the "attractiveness" of a landscape for humans could encourage a larger number of visitors to enjoy activities in the wild, and such areas would be among those with the highest risk of transmission of pathogens to humans. Areas that support human activities such as agriculture or leisure involve a greater risk of transmission of tick-borne pathogens, not because ticks are more abundant, but because there is more tick–human contact.

Habitat fragmentation is the emergence of spatial discontinuities (fragmentation) in the preferred environment of an organism. Habitat fragmentation can be caused by slow natural processes that alter the physical environment (Sahney et al., 2010) or by human activity such as land conversion, which can alter the environment much faster. Habitat fragmentation has an effect on the modulation of the abundance of ticks and their hosts, and thence on the transmission rates of pathogens. For example, large patches of forest may become fragmented because of urbanization and agricultural activities, leaving several smaller patches of forest immersed in a matrix of other habitat classes. The area of the patch is the primary determinant of the number of species and the abundance of animals (Rosenzweig, 1995). It has been demonstrated that the tick *I. ricinus* is less abundant in unconnected patches, probably because they are scarcely visited by vertebrate hosts (Estrada-Peña, 2002, 2003). This may have importance in the patterns of transmission of pathogens, because hosts have different responses to the fragmented habitat, theoretically resulting in changes in species composition according to the spatial configuration of the habitat (Ostfeld and Keesing, 2000; Ostfeld, 2009).

A further concept is the so-called "dilution effect" (Ostfeld et al., 2001), about which much debate still continues (Huang et al., 2013; Wood and Lafferty, 2012). Increased community diversity leads to decreased transmission risk for any particular host species (Ostfeld et al., 2001). Although not universal, dilution occurs because species of hosts added as diversity increases are often either low-quality hosts, or non-host species, and can disrupt transmission of the parasite in a range of ways. Alternatively, in some cases new species in a community may be suitable hosts for existing parasites, having positive impacts on their dynamics, creating a 'spillback' effect on the original hosts, which suffer from higher infection rates as a consequence. Krasnov et al. (2007) provided empirical evidence of such dilution effects on the characteristics of a population of ticks. Under conditions of high biodiversity, ticks could have a large array of hosts to feed upon, therefore minimizing the risk of transmission. Describing the connections and interaction patterns between the host, vector and pathogen has proven useful in elucidating key properties of these systems.

Habitat fragmentation is not universally responsible for the dilution effect, but may impact diversity rates at the scale of the landscape patch. The fragmentation of large patches of habitat commonly produces several, variable-sized patches, containing different communities of vertebrate hosts. The size of each patch and the distance between two patches regulate the exchange of vertebrates (Rosenzweig, 1995). Therefore, near and large patches will allow for an exchange of vertebrates (and their ticks) as well as a dilution of the prevalence rates of tick-transmitted pathogens. However, small patches commonly support a low biodiversity of vertebrate species, and are poorly connected with other patches. If the competent reservoir host remains isolated in such unconnected patches, the lack of exchange of both ticks and hosts with nearby patches will fuel a self-amplified loop of pathogen prevalence in the ticks and hosts. There are, however, several contradictory results in studies devoted to understand the dilution effect, and most probably a unifying perspective is necessary in this hypothesis (Ogden and Tsao, 2009; Randolph et al., 2012; Wood and Lafferty, 2012), which looks promising as a general framework to explain the processes behind tick–host–pathogen relationships.

In summary, trends of climate may obviously promote changes in the habitat, but large effects resulting from human activities are much faster and may not be directly linked to the climate. Such activities are known to have a deep impact on the transformation of biotopes that may or may not operate on infection rates of ticks with pathogens. These changes and their effects have only been addressed in a few studies (e.g. Walsh, 2013).

5. Tick-transmitted diseases: a tale of two viruses

5.1. Tick-borne encephalitis

Over the past decades, TBE has become a growing public health concern in Europe and Asia. It the most important viral tick-borne disease in Europe, and it is also important in the Far East and in other parts of Asia. Adequate reviews of the topic exist (i.e. Donoso et al., 2008; Süss, 2008, 2011) as well as comprehensive analyses of the human incidence rates in several zones of eastern Europe (Randolph, 2008, 2010; Sumilo et al., 2007, 2008) and a view of the evolution of cases in Europe (available online at http://ecdc.europa.eu/en/healthtopics/tick_borne_diseases/tick_borne_encephalitis/country-profiles/Pages/country-profiles.aspx).

TBEV is one of the best examples of the complex distribution of a tick-transmitted pathogen. Risk areas for TBEV have a patchy pattern: the virus is found only in a subset of sites where the tick vector (*I. ricinus* or *Ixodes persulcatus*) and the main known reservoirs (small forest mammals) are present. The concurrent existence of both vector and reservoirs does not necessarily support the existence of foci of circulation of the pathogen. It is thus necessary to resolve some basic premises to evaluate the risk for humans: where TBEV occurs, where vectors might potentially circulate the pathogen, and where TBEV cases have as a consequence been registered.

Competent vertebrate reservoirs of TBEV are small forest mammals, especially rodents and insectivores (*Apodemus flavicollis*, *Apodemus sylvaticus*, *Myodes glareolus*, *Myodes rufocanus*, *Microtus agrestis*, *Sciurus vulgaris*, *Talpa europaea*, *Sorex araneus*, *Erinaceus concolor*), as well as goats, sheep and rarely cattle. These animals are reservoirs without development of clinical symptoms. The role of some forest passerines and other birds as hosts of TBEV has not yet been fully elucidated. The main vectors are ticks of the genus *Ixodes* (*I. ricinus* in the western Palearctic and *I. persulcatus* from western Russia to Japan). There are two basic modes of human infection with TBEV: by the bite of an infective tick, or by consumption of infected unpasteurized goat milk or other unpasteurized dairy products (summarized by Estrada-Peña et al., 2014). Fig. 6 includes the known geographical range of the different TBEV subtypes in the Palearctic. The strains in the western range are transmitted by *I. ricinus*. The range of TBEV in Russia east to Japan overlaps with the recorded distribution of the tick *I. persulcatus*, suggesting that ecological conditions supporting transmission to humans exist almost everywhere the vector is present. Fig. 7 shows a higher detail of the patchy distribution of the western subtype of TBEV in Europe. Fig. 8 shows the known distribution of *I. ricinus*, the only recognized tick vector of TBEV in the western Palearctic, as reported for the administrative regions, to compare the distributions of the virus and the vector. Fig. 9 shows the updated distribution of this tick, built the compilation of its records with coordinate pairs. Data in both Figs. 8 and 9 should be considered complementary and are intended to compare with the patchy distribution of TBEV as shown in Fig. 7.

TBEV circulates in a series of interactions between the pathogen, ticks and reservoirs, and is able to persist in a given habitat over long periods of time (Nuttall, 1999). The occurrence of vector

Fig. 6. Geographic range of the European, Siberian and Far-eastern subtypes of the tick-borne encephalitis virus, as isolated from ticks, vertebrate hosts and human cases. The map shows the known range of the different viral subtypes.

ticks and suitable vertebrates on which they can become infected is crucial for virus existence in a given area (Fig. 10). The following mechanisms of virus transmission between ticks occur:

(i) feeding/co-feeding (Labuda et al., 1993a,b);
(ii) (vertical transmission (Dobler et al., 2011); and perhaps
(iii) (sexual transmission (Stefanoff et al., 2012).

The co-feeding transmission mechanism for TBEV has been summarized by Randolph (2011). In most vector-borne pathogens, the underlying biological concept is that an infected vector delivers an inoculum of the pathogen to a susceptible host during the blood meal. If this host is receptive and also transmission-competent, this inoculum developed into a systemic infection as the pathogens spread to many parts of the body, from where vectors could subsequently acquire infections as they fed (Randolph, 2011). Co-feeding transmission, however, involves the presence of two different stages of a tick (i.e. larvae and nymphs) feeding in near proximity on the same host. In the case of TBEV, infected nymphs can transmit the virus to co-feeding larvae, even in the absence of a systemic infection of the host. Coincident aggregated distributions of larvae and nymphs among their rodent hosts increase the number of larvae co-feeding with any infected nymph, and so augment the potential amplification of infection prevalence in ticks (Randolph, 2011).

In the laboratory, co-feeding transmission is especially effective, and the virus can be transmitted through this mechanism from a feeding vector tick to co-feeding ticks even on immune hosts, in the absence of a systemic infection of the host (Labuda et al., 1993a). Studies have shown that tick saliva contains factors that modulate host inflammatory, coagulation and immune responses to improve blood feeding and pathogen transmission (Jones et al., 1989; Alekseev et al., 1991; Labuda et al., 1993a; Nuttall and Labuda, 2008; Randolph, 2009). Inoculation of salivary gland extracts and TBEV into laboratory animals resulted in enhanced transmission from hosts to nymphal ticks, compared to pathogen inoculation alone (Labuda et al., 1993b). SAT helped to explain the mechanism behind the observation of TBEV transmission between co-feeding ticks in the absence of a systemic infection (Labuda et al., 1993a,b; Randolph, 2009). Results from laboratory experiences show that this way of transmission may infect high percentages of larvae co-feeding with infected nymphs (Randolph, 2011). Based on laboratory findings and field data, the co-feeding route should be enough to maintain the foci of TBE in the field (Randolph, 2011). However, such co-feeding transmission route has not been so far demonstrated in the field (Dobler, pers. comm.).

Co-feeding transmission imposes constraints, because it requires co-feeding by at least two tick stages in synchrony in their seasonal activity (Randolph and Rogers, 2000) to produce the transmission from nymphs to larvae. Because ticks feed once and then molt into the next stage, it is necessary that two different stages of the tick feed simultaneously on the host, in close proximity on its body surface. In short, the seasonal activity of both stages of the tick must be synchronized. Thus, infected nymphs feeding on hosts together with and in near proximity of uninfected larvae will infect the latter while taking a blood meal without a systemic infection. If tick co-feeding is the main mechanism supporting foci of TBEV in the field, climate requirements must support the phenology ensuring its persistence. As tick phenology is reset each year by winter conditions (Randolph et al., 2002), the critical stages (larvae and nymphs for TBEV) may emerge from winter diapause more or less in synchrony in the spring, depending on whether temperatures rise sufficiently rapidly to cross the threshold for larval activity (ca. 10 °C mean daily maximum) soon after the threshold for nymphal activity (ca. 7 °C mean daily maximum) (Randolph and Sumilo, 2007). The variability of thermal conditions associated with seasonal synchrony between tick stages has been identified as the key determinant of the focal distribution of TBEV across Europe allowing predicted risk of TBEV to be mapped (Randolph, 2000).

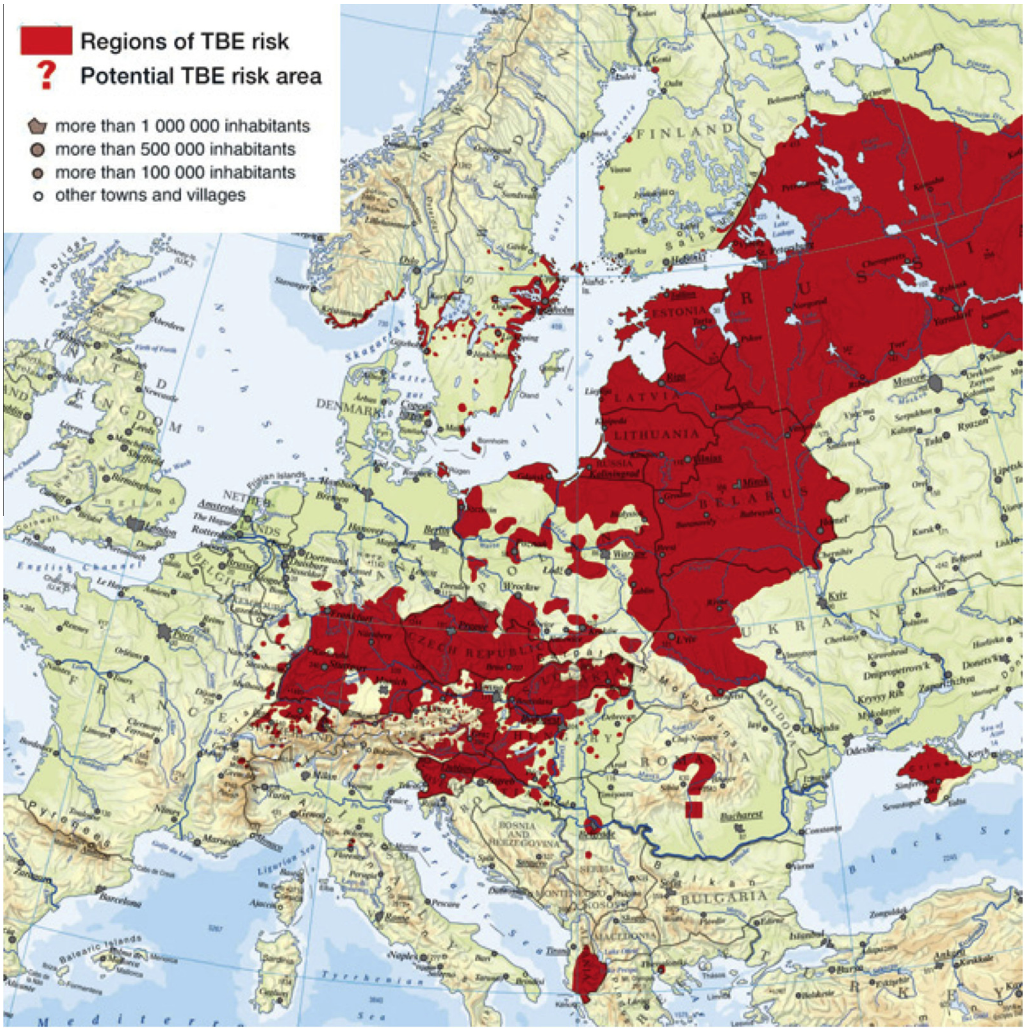

Fig. 7. Geographic range of the European subtypes of the tick-borne encephalitis virus (adapted from Barrett et al., 2008). The map indicates areas where human infections have occurred.

However, some studies point to other mechanisms of transmission to support the existence of TBEV foci (i.e. Danielová et al., 2002; Knap and Avšič-Županc, 2013), most probably because no long-term studies have been performed testing how climate actually impacts transmission rates of TBEV.

Altogether, this information suggests that climate may exert control of natural cycles of TBEV transmission and delineate both their intensity (in terms of tick prevalence rates) and their geographic distribution. According to the prevalent hypothesis outlined above, the weather at the beginning of spring may exert a regulatory effect on the synchrony of active immature ticks, conditioning the necessary coexistence of nymphs and larvae on the same hosts. Because of the short time of feeding for both larvae and nymphs, small changes in the temperature during that period may promote a lack of synchronicity of a few days, enough to prevent "backward" transmission of the virus. The extreme fragility of TBEV foci would therefore be driven primarily by small changes in spring temperatures. The system seems to be very local in nature.

Even though adequate combinations of environmental features driving the phenology and abundance of ticks and their reservoirs can explain the maintenance of TBEV foci, an understanding of the processes governing the introduction of the virus into new territories remains elusive. As noted, ticks move only while feeding on hosts, so that the movements of hosts carrying infected ticks should explain the introduction of infected ticks into new territories (Randolph, 1998). Simulations have been carried out to evaluate the requirements for dispersal of TBEV and the probability of producing a secondary focus by spreading ticks (e.g. Rosà et al., 2003). Such an approach has provided evidence of a requirement for an initially large number of infected ticks invading the new territory to produce a permanent secondary infection without extinction. Large ungulates could in theory provide such a means of transportation, because they may carry hundreds of ticks. However, these animals are commonly hosts for adult ticks, not for immatures, and the probability of transmission of virus from engorged females (the dispersing stage feeding on large ungulates) to larval progeny (the new generation colonizing the invaded territory) is low (Jaenson et al., 2012a). It therefore seems plausible that mammalian hosts for adult ticks are not primarily responsible for the spread of TBEV to new foci.

A hypothetical second option is the movement of infected ticks by birds, either in local or migratory flights. Birds are well known hosts for immature ticks, and their involvement in the dispersion of other tick-transmitted pathogens by carrying infected ticks, such as Lyme borreliosis, has been well established (e.g. Hasle et al., 2009; Ogden et al., 2008a; Poupon et al., 2006). The local flights of birds commonly cover several kilometers a day, so that this could hypothetically be an adequate means of transportation for infected ticks. However, birds are not reservoirs of TBEV and the vertical route of infection is reported to be of very low efficiency.

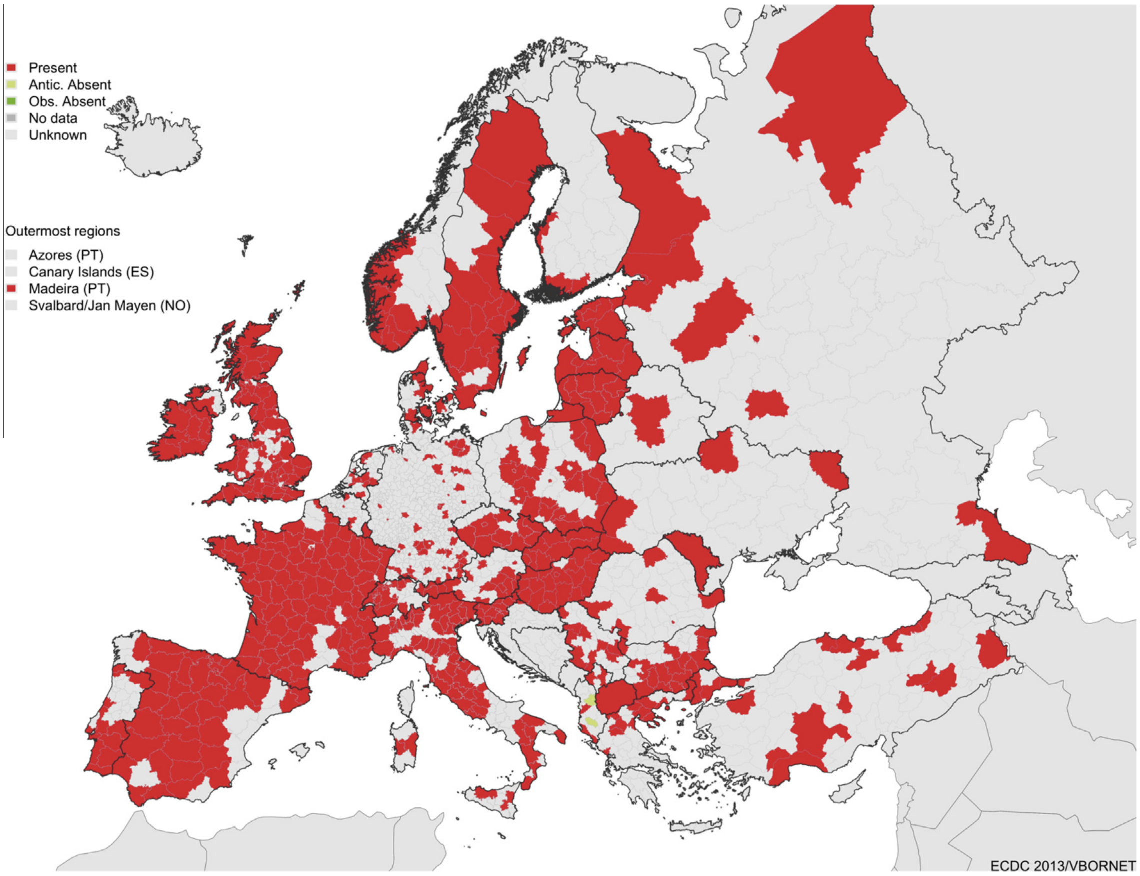

Fig. 8. Distribution of *I. ricinus* according to information from the administrative divisions in the continent, as collected, examined and summarized by the VBornet network, supported by the European Center for Disease Control. Only reliable reports published in the scientific literature are included in the map. Data are available at http://ecdc.europa.eu/en/activities/diseaseprogrammes/emerging_and_vector_borne_diseases/Pages/VBORNET-maps-tick-species.aspx (last update, April, 2013).

Therefore, larvae of ticks carried and transported by birds are expected to be uninfected while disseminating. Birds can also disseminate nymphs, already infected as larvae by feeding on rodents in the focus of origin. Once such infected nymphs gain the new territory, they would molt to adults, therefore breaking the transmission cycle of TBEV in the newly gained patch or territory. Following the previous chain of logical reasoning, birds should not be effective means of transportation of TBEV to new foci. However, these hypotheses have been not yet confirmed in the field.

The most plausible option seems to be the dissemination of infected ticks by the short and continuous movements of rodents, which will sustain a "continuum" of ticks, infected by TBEV at low prevalence rates, along territories where the tick and the reservoir co-exist. The emergence of foci of TBEV could be determined by changes in climate variables that drive the amplification of foci (Materna et al., 2008), sudden changes in composition of the host community (Stjernberg et al., 2008), or drastic increases in the abundance of ticks through increases in hosts for adults (Jaenson et al., 2012b). The high variability of the composition and relative densities of the community of reservoirs, its phenology, and the different prevalence rates of ticks on different hosts could explain the variable nature of TBEV foci. An adequate combination of environmental determinants would keep virus transmission active and self-amplified in a newly invaded area, or it could become extinct through several consecutive cycles of inadequate environmental conditions, driving it to disappear. Such combinations of isolated foci constitute the epidemiological landscape of TBEV: a patchy distribution of active foci (detected by the occurrence of human cases) that may or may not be "active" during a longer or shorter period, and that may become "reactivated" after several years of epidemiological silence, as passively surveyed by the number of human cases.

Weather has been considered the main driver of changes in the distribution of foci of TBEV in Europe by some authors. It has been reported that *I. ricinus* and TBEV now reach higher altitudes in the mountains of the southern Czech Republic, in a consistent pattern after the year 2000, than reported for the years 1970–1980 (Daniel et al., 2004, 2008; Danielová et al., 2006; Materna et al., 2008). This pattern is claimed to be independent of the abundance of hosts above a threshold, and to be purely driven by the trend of climate. A similar pattern of spread in latitude has been reported for southern and central Sweden, where the tick vector has been recorded at more northern latitudes in recent years, together with an increase in the number of TBEV cases (Jaenson et al., 2012a). The spreading of populations of roe deer into far northern Sweden because of changes in land use is a factor that, together with the climate, would support larger populations of *I. ricinus* (Jaenson et al., 2012b).

Most current claims about the spread of TBEV in Europe are based on the examination of series of clinical cases. However, such series are not a direct mirror of the "activity" of TBEV foci, and the mechanisms regulating an upsurge of the disease are far too complex to permit direct conclusions. This is why it has been proposed to check active foci by direct examination by PCR of ticks collected in the field (Gäumann et al., 2010). It has been speculated that changes in host abundance, social habitats, economic fluctuations, environmental changes, and to a lesser extent climate changes have all played a role in the increased incidence of TBEV in recent

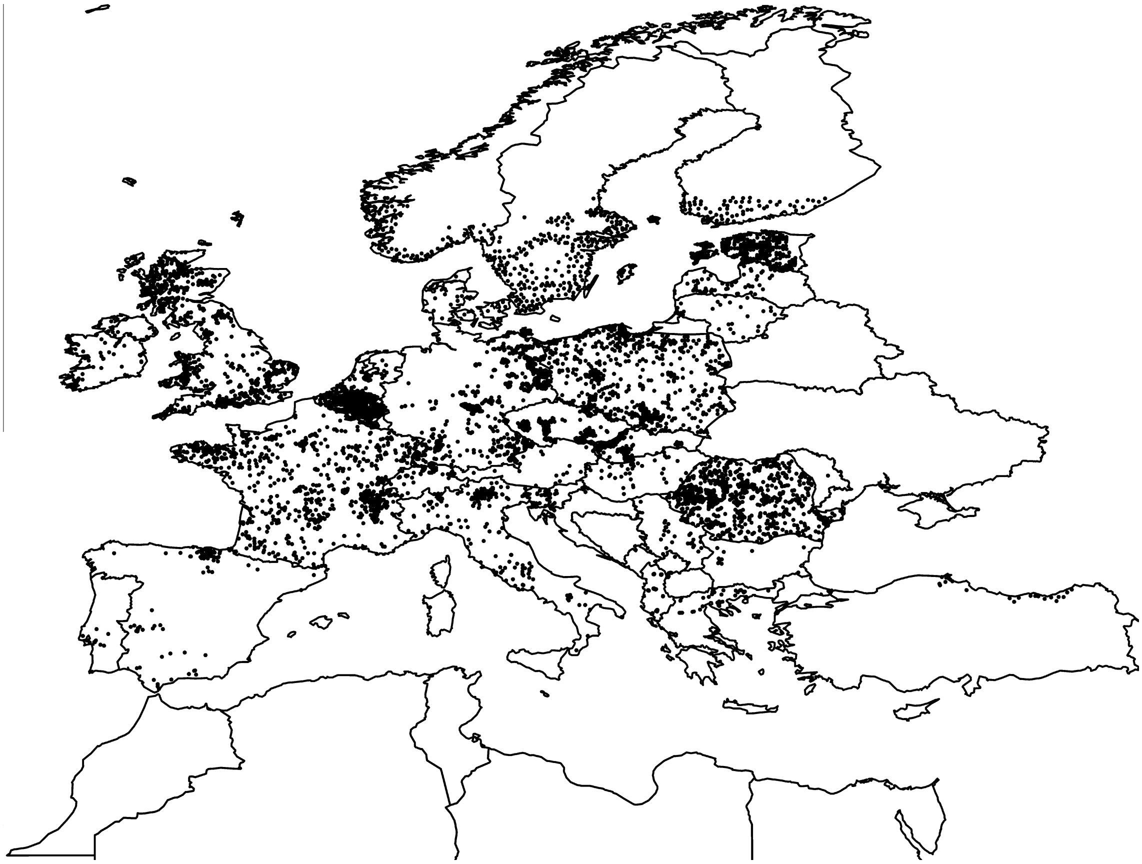

Fig. 9. Distribution of *I. ricinus*, mapped as points according to the coordinates of the site of collection. This differs from map in Fig. 8 in which actual coordinates of collections, instead of the complete administrative divisions, are included as "positive" to the tick, allowing a finer mapping of the tick's range. It is observed that the distribution of *I. ricinus* in western Palearctic is larger than the distribution of TBEV. Map originally published by Estrada-Peña et al. (2013a,b,c,d).

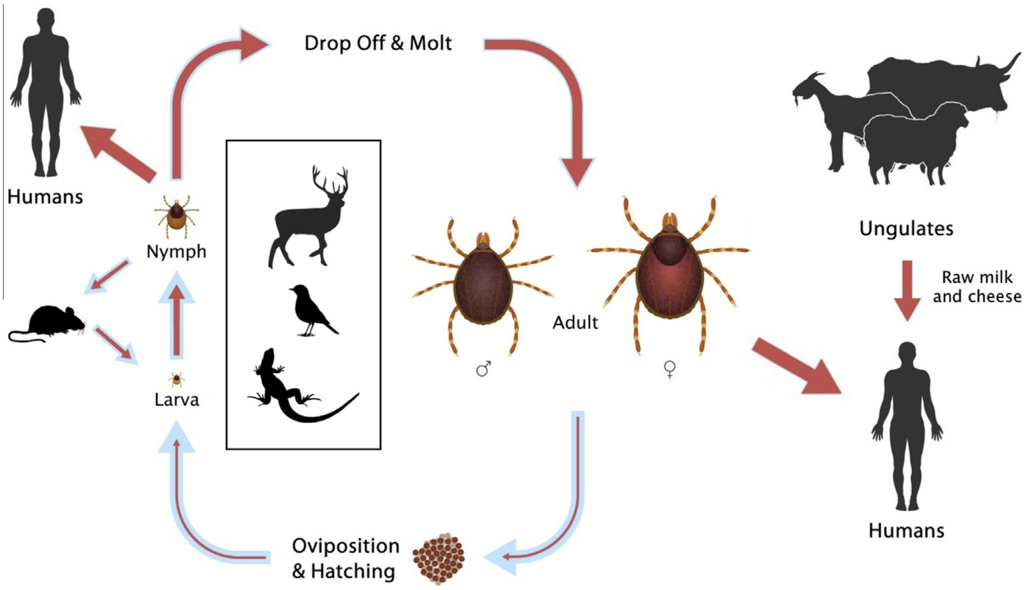

Fig. 10. Schematic cycle of transmission of the tick-borne encephalitis flavivirus. It shows the importance of some species of rodents on which the larva and nymph may feed together, that may produce a back-transmission of the virus from the infected nymphs to the co-feeding larvae, without systemic circulation of the virus in the host. The large hosts for adults are necessary only for the completion of the life cycle of the tick, but have been not reported as important in the transmission of the virus in the nature. The course of the tick life cycle is indicated by blue arrows. The possible transmission of the virus between ticks and mammals or directly between ticks is marked by red arrows. Figure prepared with material originally created by Alex McAuley.

years (Lindgren and Gustafson, 2001; Sumilo et al., 2006, 2007, 2008; Zeman and Beneš, 2004). In any case, it is difficult to correlate series of human clinical cases against raw weather features, because weather has several collateral effects, affecting not only the tick life cycle, but also the habits of humans. This has been demonstrated in a series of data for TBEV cases in the countries of the Baltic Sea (Sumilo et al., 2007) and the Czech Republic (Zeman and Beneš, 2004), which have been summarized by Randolph and Sumilo (2007), with a focus on outdoor activities reportedly accounting for most of the upsurge of cases in Eastern Europe.

It has however been questioned whether changes in social habits and land use can be applied to regional foci of TBEV in parts of eastern Europe, and whether they alone can explain the complete picture (Süss, 2008). Thus, although the political turn-around and resulting socioeconomic changes in the behavioral pattern of exposed populations in the former Eastern Bloc at the beginning of the 1990s certainly were a significant influence factor, that does not explain the increase in the number of TBEV cases since the 1990s in Italy, Hungary, Finland and Germany. Although the TBEV incidence in risk areas of Germany has shown the same trend as in the Baltic States, the political turn-around only took place in the eastern part of the country, where TBEV incidence is very low compared to southern Germany (Süss, 2008).

In conclusion, the evaluation of factors that potentially drive the evolution of foci of TBEV speculate about an effect of weather on short-term changes of these foci, together with the presence of reservoir hosts infecting immature ticks and large hosts for feeding adult females. The repercussions of weather may disturb or enhance the transmission of the virus in areas where the main tick vectors exist, but there is a high uncertainty regarding how foci are evolving. This complexity makes a linear response to climate change unlikely, so that an exclusive focus on climate change might result in the neglect of social phenomena (Randolph, 2008). We do not know the long-term effects of subtle alterations of the prevailing weather on the (re)emergence of TBEV foci, other than the expected spread of the tick vector towards northern latitudes and higher altitudes. In some places, such spread is also linked to large populations of the main ungulate hosts, supporting an increase in the density of newly established tick populations. Nevertheless, we still do not know how the virus may invade new territories and produce permanent foci of active transmission. There is a need for basic research regarding the faunal composition of host communities, and how the densities of reservoirs may affect the evolution of active foci of the virus.

5.2. Crimean-Congo hemorrhagic fever

Crimean-Congo hemorrhagic fever (CCHF) is a serious tick-transmitted human disease that has the largest known distribution of any other tick-transmitted virus (Ergonul and Whitehouse, 2007; Bente et al., 2013; Fig. 11). Since the first outbreak of CCHF was described in the Crimean peninsula in 1945, clinical cases have been reported in Africa, Asia, and Europe (Balkans and Russia). The CCHF virus (CCHFV) is known to circulate in large areas of the Mediterranean region, Africa and Asia, with foci as far north as latitude 50°. Since 2000, however, the incidence and geographic range of confirmed CCHF cases have markedly increased, with the disease being reported for the first time in Turkey, Iran, India, Greece, the Republic of Georgia, and some Balkan countries. Remarkably, even though the first cases of CCHF in Turkey were identified in 2002 following several decades of serological evidence (Vorou, 2009), more than 6300 cases have been diagnosed in the ensuing 10 years. A large increase has also occurred in Iran since the first human infection was recognized in 1999 (Chinikar et al., 2010; Keshtkar-Jahromi et al., 2013).

In an expert consultation organized in 2008 by the European Center for Disease Control after the re-emergence of CCHF in Greece, a short-term priority was recognized to be “endemic regions in countries with CCHFV in southeastern Europe should be further mapped on national and international levels, and the degree of CCHFV risk in all countries should be estimated” (Maltezou et al., 2010). Interest in the disease grew after the large increase in cases in Turkey and new viral isolates were reported in areas near Turkey such as the Balkans and Russia (Ergonul and Whitehouse, 2007) or southwestern Spain (Estrada-Peña et al., 2012a). Studies have focused on outlining the probable routes for virus introduction into Western Europe from the original foci of the disease (Gale et al., 2010) and assessing its endemic potential.

The virus is transmitted to mammals and humans through the bite of hard ticks, mainly of the genus *Hyalomma* (Hoogstraal, 1979). Humans may also become infected through direct contact with the blood or tissues of infected humans or livestock (Hoogstraal, 1979; Bente et al., 2013). The principal species implicated in transmitting CCHFV in Eurasia are *Hyalomma marginatum*, *Hyalomma turanicum*, *Hyalomma anatolicum* and *Hyalomma scupense*. However, laboratory studies on the transmission abilities of these ticks are scarce, mainly because the inherent difficulties in such studies, because the pathogen is a Biosafety Level 4 organism (Gargili et al., 2013). Some other tick species from the genera *Dermacentor*, *Amblyomma*, *Rhipicephalus* and *Haemaphysalis*, have been found to harbor CCHFV in the field or have been artificially infected in the laboratory, but there is little evidence of their involvement in natural transmission or maintenance of foci (Watts et al., 1988). All reports about natural transmission by way of an infected vector have involved ticks of the genus *Hyalomma* (Watts et al., 1988). It would appear that *Hyalomma* ticks or their hosts are also necessary for the maintenance of active foci of the virus in the field, even during periods of silent activity. This is of importance because mammal hosts infected with the virus develop a low-level, short-term viremia. Birds, which are also common hosts for the immature *Hyalomma* ticks, seem to be refractory to the infection.

Hoogstraal (1979) compiled information about the research of the areas of active transmission of CCHFV in Crimea, after initial recognition of the virus, and summarized the epidemiological background in the region. Some of the features common to the different epizootics that have been recorded in Crimea and Astrakhan Oblast are a war devastation of the rural countryside steppe that resulted in the explosion of population of hares, which are important hosts for the immatures of *H. marginatum*. Severe winters commonly mark the end of epizootic waves, most probably because the death of high numbers of ticks as a consequence of unusually long periods of low temperature. Thus, the favorable climatological, faunal, and ecological nature of the Volga floodplain and delta areas of Astrakhan Oblast, together with the environmental changes wrought by a major socioeconomic drive, were interrelated in the development of epizootic CCHFV (Hoogstraal, 1979). However, only the winter climate reduced the virus flow from an epidemic to an endemic rate.

This early research on CCHFV in the Crimean peninsula has parallels with the current situation in Turkey, where thousands of cases have been reported every year since 2002 (see below). The abandonment of rural areas, and the growth of brush that may serve as a shelter for animals acting as hosts for immature ticks, has been hypothesized to raise the density of infected ticks. However, no statistically significant differences have been recorded between the temperature in winter before and after the onset of the epidemic (Estrada-Peña et al., 2007).

The tick genus *Hyalomma* is widespread in different ecological areas of the Palearctic and Afrotropical regions. Larvae and nymphs commonly feed on the same hosts, which are many species of

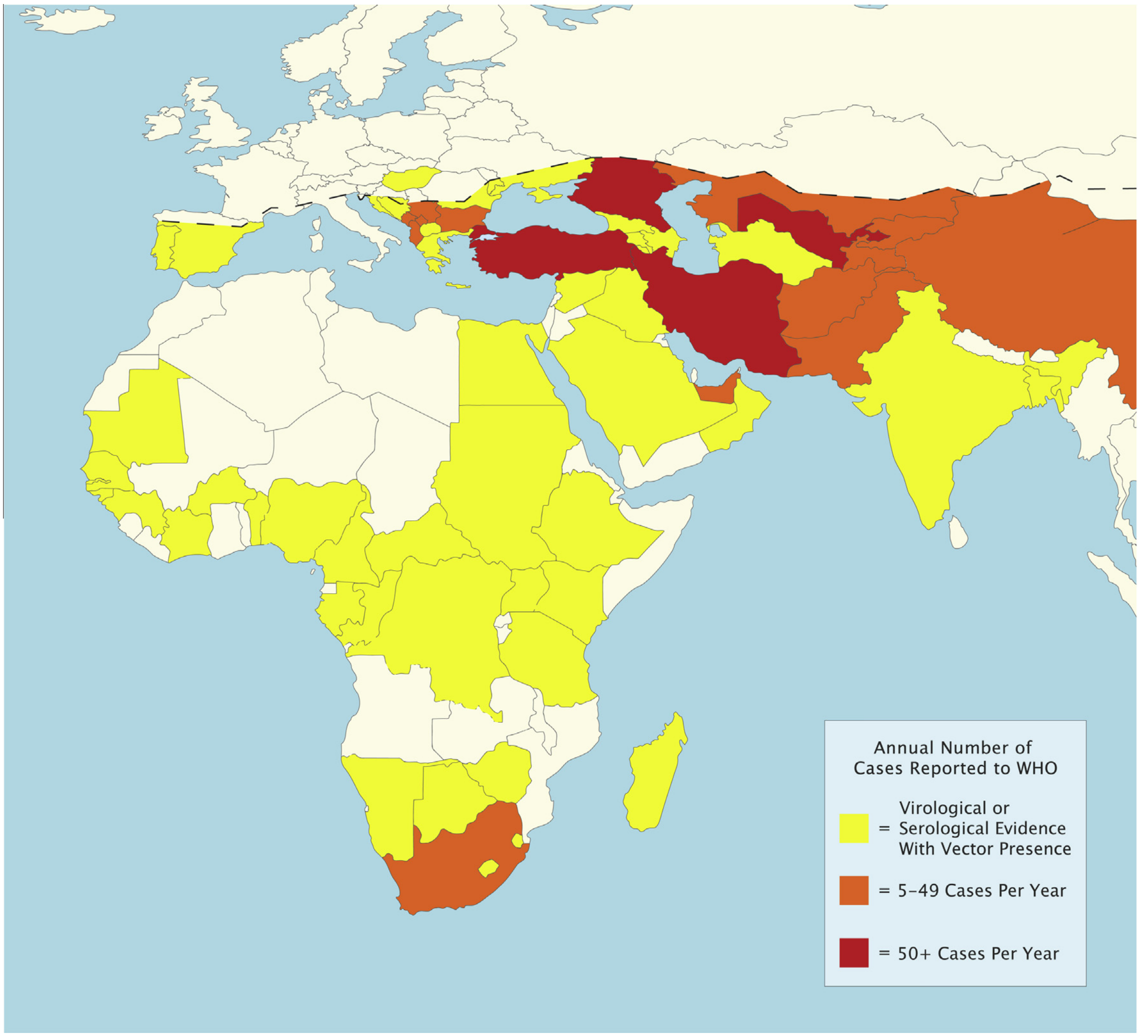

Fig. 11. Recorded distribution of CCHFV, modified from the information provided by the World Health Organization (map accessed at http://www.who.int/csr/disease/crimean_congoHF/en/). The map only shows countries where clinical cases have been reported or serological tests have identified positive samples. The black line in Europe marks the northern limit of the reported distribution of permanent populations of the tick, although isolated records have been reported northern to that line. Figure originally published by Bente et al. (2013).

small mammals and birds. It is thus a two-host tick, although it may behave as a three-host tick under some conditions (Hoogstraal, 1979). An additional characteristics of *Hyalomma* ticks is that they have evolved an "ambush" strategy to find a host. While most species of ticks passively quest for a host in the vegetation, species of the genus *Hyalomma* are able to walk several dozens or even hundreds of meters (Balashov, 1972) to actively contact the detected host. This is presumed to be a strategy that evolved in ticks inhabiting dry or desert environments, where the chance of passively contacting a host is low (Hoogstraal, 1979). With such active walking, unfed ticks may have a greater probability of finding a host.

H. marginatum is presumed to be the most prominent vector of the virus to humans in a large region extending from the Balkans in Europe to Pakistan and Afghanistan in the Middle East (Ergonul and Whitehouse, 2007). The immature stages of *H. marginatum* infest birds and medium-sized mammals, and these hosts can transmit the virus to feeding immatures (Zeller et al., 1994a,b). Large ungulates serve as hosts for the adults transmitting the virus to the feeding females (Nalca and Whitehouse, 2007; Wilson et al., 1991; Zeller et al., 1997). Tick females contribute to the infection by vertical transmission of the virus to the eggs. Feeding on infected hosts or through non-systemic (co-feeding) transmission of the virus might also infect ticks (Gordon et al., 1993, see Fig. 12). Phylogenetic analysis has also revealed evidence of genome re-assortment and recombination during co-infection of a single host, indicating the potential for the future emergence of novel variants (Chamberlain et al., 2005; Hewson et al., 2004). Important epidemiological information about the species of ticks involved in the transmission and the prevalence of CCHFV has been published (e.g. Wilson et al., 1990, 1991; Chapman et al. 1991; Zeller et al., 1994a,b, 1997).

Recent reports of an increased incidence of CCHFV have stimulated speculation about the presumed effects of climate on the historical geographic range of *H. marginatum* in the Palearctic region (Maltezou and Papa, 2010; Purnak et al., 2007) and the probable spread of the pathogen. The main concern relates to the spread of the presumed main vector vector, *H. marginatum*, from the Mediterranean basin into northern European latitudes (Estrada-Peña et al., 2012b). It has been reported that tick larvae molt into nymphs while attached to a host, lengthening the duration of attachment (12–26 days) and thus enabling the passive transport of immature *Hyalomma* ticks by migrating birds over long distances (Hoogstraal et al., 1961). Every year, millions of passerine birds arrive in Europe from Africa, parasitized by ticks that serve as vectors of CCHFV, which is known to exist in large areas of Africa.

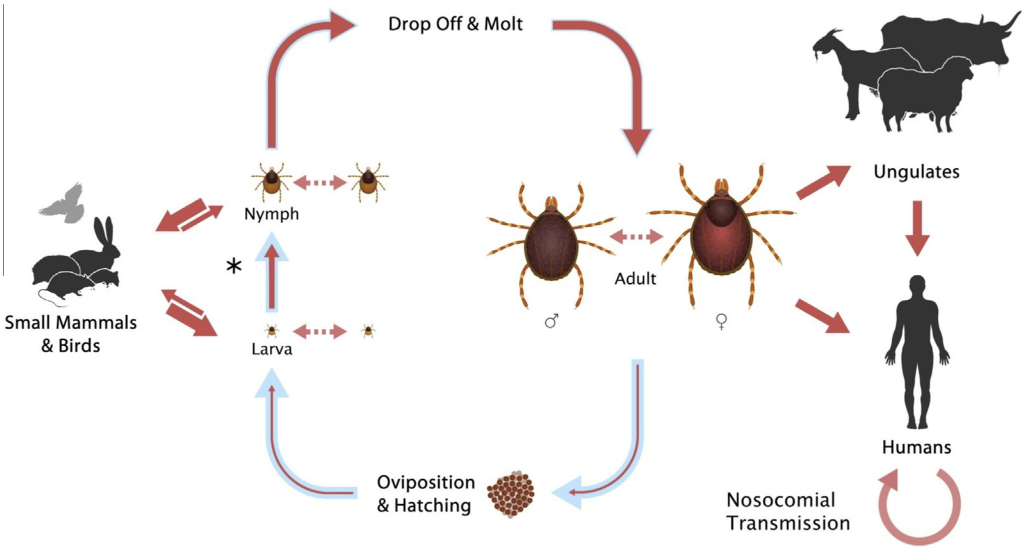

Fig. 12. Schematic cycle of transmission of CCHFV by ticks of the genus *Hyalomma*. Image originally published by Bente et al. (2013). The course of the tick life cycle is indicated by blue arrows. Larvae find a small animal host for their blood meal, and, depending on the tick species the larvae either remain attached to their host following engorgement and molt in place (two-host ticks) or fall off and molt (three-host ticks); this transition is marked by an asterisk. The nymphs then either continue to feed on the animal on which they molted (two-host ticks) or attach to a new small animal (three-host ticks). Adult ticks find a large animal to feed. The engorged females drop off and find a suitable location for ovipositing. The possible transmission of the virus between ticks and mammals or directly between ticks is marked by solid red or dashed arrows, respectively. For each form of virus transfer, the thickness of the red arrow indicates the efficiency of transmission. Infection of humans can occur through the bite of an infected tick or through exposure to the body fluids of a viremic animal or CCHF patient. Figure originally published by Bente et al. (2013).

However, there is no evidence that birds fed upon by CCHFV-infected ticks become viremic. Hoogstraal (1979) cited a number of Russian reports of the recovery of infected ticks from a variety of bird species, but noted that birds were apparently not hosts for viral replication.

With the exception of ostriches, there is no evidence that birds are hosts for the replication of CCHFV (Shepherd et al., 1987). This conclusion was supported by the only two subsequent studies, as researchers were unable to detect antibodies to CCHFV in 37 different species of wild birds in South Africa (Shepherd et al., 1987). However, many competent tick vectors of CCHFV feed on birds during their larval and nymph stages, and could potentially be carried great distances. As an example, an adult male *Hyalomma rufipes* tick was identified on a horse during a survey in the Netherlands (Nijhof et al., 2007). As the horse had not been imported, it was concluded that the tick was introduced as a nymph by a migratory bird from Africa. Similarly, immature *H. rufipes* have been recovered from birds as far north as Norway (Hasle et al., 2009), and adults of this species were found feeding on cattle in Hungary (Hornok and Horváth, 2012). *H. rufipes* is endemic in many regions of Africa. However, the species is not known to have permanent populations in Europe, because it is an Afrotropical tick (Estrada-Peña and Venzal, 2007). Published data (Bosch et al., 2012) have suggested that the timing of spring migratory birds from Africa to Europe would overlap with adequate conditions for the molting of *Hyalomma* immatures when arriving in wide areas of the Mediterranean basin with current climate conditions. A recent analysis concluded that the establishment of new enzootic foci of CCHF outside of southwestern Europe is very unlikely in the foreseeable future (Hoek et al., 2012). However, these arguments conflict with the unpredictability of the epidemic in Turkey.

How the climate could affect the flight of migratory birds, how attached ticks might enter central Europe at higher rates, or how many infected ticks may spread over the European continent each year are key variables that have not been empirically addressed. A recent modeling framework evaluated the impact of the different variables affecting the transmission rates of CCHFV and the effects of a warmer climate on rates of tick development (Estrada-Peña et al., 2013c). The study concluded that, other than small changes resulting from an increased abundance of ticks because of more permissive weather, major impacts on the circulation of CCHFV should only be expected after a hypothetical higher availability of infected domestic ungulates, which commonly feed large numbers of adult females and would increase the efficiency of vertical passage. An engorged female *Hyalomma* may lay around 10,000 eggs, therefore amplifying the transmission potential. Even if vertical transmission has a relatively low efficiency, the effects of such high potential for the spread of CCHFV should not be disregarded. Such situations, involving the international livestock market near or within areas where CCHFV naturally circulates, together with a tendency towards milder winters, are being observed in some areas of Europe, with a consequent risk for (re-)emerging virus foci (Estrada-Peña et al., 2013c). It is also necessary to state the role of wild ungulates in the feeding of adult *Hyalomma* (Ruiz-Fons et al., 2006), which could greatly contribute to the dissemination of infected ticks. Such studies have not yet been empirically addressed.

Climate change is the current ubiquitous explanation for the increased incidence of CCHF (i.e. Gunaydin et al., 2010; Maltezou and Papa, 2010; Uyar et al., 2011; Vescio et al., 2012). However, an assessment of the effects of climate on the incidence of the disease in Turkey found little evidence of the involvement of climate in the distribution of the disease (Estrada-Peña et al., 2010). The recent epidemic began with some isolated cases in Tokat province (Gözalan et al., 2004). The human health authorities soon realized that more clinical cases were being reported from neighboring sites, then later over a large territory in the country. It was however noticed that the area where clinical cases were reported was within the expected distribution of the tick *H. marginatum* in the country, (Estrada-Peña et al., 2007). This was considered as evidence of some special conditions that could exist “within” the range colonized by the tick that could reinforce transmission, to switch the foci from silent to active. The comparative analysis of incidence rates and regional weather, including monthly values of several climate variables as captured by remote sensing (therefore referred to the conditions on the Earth’s surface at the available resolution), concluded that the climate was not different in sites with active foci of CCHFV, compared to sites where *H. marginatum* is also common, but human cases have not been reported (Estrada-Peña et al., 2010).

In Turkey, the highest incidence of human cases of CCHFV showed a strong correlation with the presence of particular land use categories, especially small and highly mosaic agricultural localities (Estrada-Peña et al., 2007). This was consistent with the most common reported transmission mechanism, the bite of an infected tick, and with hypothetically increased densities of ticks in fragmented sites, which in turn provide an environment for greater human exposure. However, land use is not the only factor operating on active foci of CCHFV. At least in the case of Turkey, the progressive abandonment of farm lands has lead to the proliferation of dense brush that promotes colonization by hosts of immature *Hyalomma* ticks, such as hares and ground-feeding birds. This empirical verification must, however, be paralleled with a similar abundance of hosts for the adults, which fuel the cycle of vertical transmission of virus by infected females. Furthermore, there is evidence that a fragmented landscape, not necessarily of agricultural lands, with many small patches existing within a matrix of unsuitable tick habitat, may lead to isolated populations of both ticks and hosts, producing an amplification cycle in which ticks feed on infected hosts (Estrada-Peña et al., 2010). For CCHFV eco-epidemiology, the degree of habitat patchiness contributes to increase the contact rates among viremic hosts, humans and ticks, and also leads to the occurrence of isolated amplification foci, with a higher human exposure to ticks (Estrada-Peña et al., 2010). As with other ticks, the vectors of CCHFV require a vertebrate host to move across significant distances, and because host populations are relatively isolated in such fragmented landscapes, there are few local movements of hosts. The ongoing epidemic in Turkey cannot be explained by the "invasion" of a new highly pathogenic strain of the virus over the territory (Bente et al., 2013). The epidemic situation in Turkey should be observed under a multivariate perspective, in which probably the climate has the smallest effect. The progressive abandonment of agricultural lands, the growth of dense layers of vegetation adequate for the survival of both the ticks and the main hosts of the immatures, the further fragmentation of the habitat leading to self-amplified foci of viral circulation, and the greatest contact rates of humans with foci of the virus are all enough reasons as to account for the rise in the reporting of cases.

The probability for CCHFV to be supported by ticks other than the well-known vector *H. marginatum* in cryptic cycles should not be disregarded. The opportunity for such a vector-switch might occur if ticks of more than one species feed on the same viremic host, or if infected and uninfected ticks of two different species take blood meals in close proximity (Bente et al., 2013). Such transmission between tick species presumably occurs in areas such as Turkey, where CCHFV circulates widely and more than one competent vector is present. Our current knowledge about the existence of such cryptic cycles of transmission is uncertain in part because of misinterpreted reports about the detection of viral RNA in ticks that have presumably fed on viremic hosts (i.e. Albayrak et al., 2010; Bursali et al., 2011; Gunes et al., 2011; Tekin et al., 2012; Telmadarraiy et al., 2010; Yesilbag et al., 2012). These reports assumed that the viral RNA detected in the tick is a proof of its role as a vector, ignoring the fact that a hematophagous arthropod will contain remnants of pathogens present in the host's blood (Kahl et al., 2002).

Other than the importance of regional weather driving an increased fitness of ticks in foci of CCHFV, and the existence of peculiar characteristics of the landscape favoring either the circulation of the virus or contact of infected ticks with humans, the most important factors affecting foci of CCHFV are the hosts for ticks. Other than the vertebrates supporting efficient transmission of the virus, an increased abundance of hosts will likely fuel the abundance of ticks. A higher density of hosts such as hares and birds for immature stages may obviously increase abundance of immature ticks. However, such increase in hosts feeding immature stages must be paralleled with similar changes in either wild ungulates or livestock that must support the feeding adults. These gaps in our knowledge of the epidemiology of CCHFV limit our capacity to build an adequate scenario aimed at evaluating the impact of a changing background on transmission rates of CCHFV. All these aspects warrant further evaluation of the multifaceted epidemiology of CCHFV in endemic regions, not only to understand the factors driving the actual foci, but also to extrapolate the conditions that could potentially shape silent or active foci in new areas.

Several scenarios are of concern regarding the possible spread of CCHFV to new foci or the re-emergence of former ones. Hypotheses about these scenarios must be approached from the perspective of the combined actions of climate, the movements of large ungulates, increased habitat fragmentation and abandonment of agricultural areas. The first concern is the impact that a warmer, drier climate may have on the distribution range of *Hyalomma* in Europe, where they already occupy a climate niche consisting of warm, dry environments (Estrada-Peña et al., 2013c; Gray et al., 2009). The second is the presumed spread of active foci of the virus into the Mediterranean basin, or the entry of infected ticks from Africa to Europe. We however do not know if CCHFV currently colonizes the range occupied by its main tick vector, *H. marginatum*, across the Mediterranean region. Therefore, considering the widespread distribution of the virus, wherever its tick vectors exist, the hypothesis that CCHFV is already present throughout the Mediterranean region has sound probabilities. Nevertheless, the virus has never been actively surveyed in questing ticks in such a wide range, and has currently been reported only from the western and eastern parts of the Mediterranean basin (data summarized by Bente et al., 2013).

Other than the uncertainties in our knowledge of the epidemiology of foci of CCHFV (like the involvement of different vectors, the transmission rates between ticks and vertebrates, or the existence of cryptic cycles), it is currently unknown if the range of the virus in the Mediterranean basin coincides with the distribution of *Hyalomma* ticks, e.g. if the virus exists everywhere adequate ticks and vertebrate infective hosts exist. Therefore we can only guess how the behavior of these presumed foci could be. The first identification of CCHFV in southwestern Europe (Estrada-Peña et al., 2012a) has since been corroborated by additional detections in newly collected *H. lusitanicum* ticks in the same area while feeding on *Cervus elaphus*. However, active surveys of the virus in questing ticks from neighboring regions of the focus of original detection, separated by not more than 300 km. and with a similar vertebrate fauna, have been negative. Nevertheless, the absence of human cases is the rule in the western Mediterranean, and seems to be intuitively contrary to a situation in which the pathogen is widespread. Such an absence of cases could be supported in a scenario of epidemic silence, considering a very low rate of contact between humans and tick vectors. A sudden and disproportionate rise in the density of infected ticks could potentially alter the equilibrium in such a system, increasing the contact rate and hypothetically driving it to an epidemic situation.

If the range of CCHFV coincides with the distribution of its main tick vector in the Mediterranean basin, the high density of large ungulates could boost the density of the vector. If CCHFV is present only in isolated pockets in the Mediterranean region, then the movements of large ungulates (livestock trade and wild ungulate movements) could introduce the virus into territories not yet colonized. Such movements of animals could also introduce potentially infected vertebrates into areas where large populations of tick vectors already exist, thus spreading the virus into the resident tick population. However, we do not know if the presumed absence of human cases in the western Mediterranean is the result of the absence of CCHFV, the circulation of a non-pathogenic viral strain, differences in human behavior allowing different contact rates with infected ticks, or is caused by some hypothetical properties of local virus strains that result in lower abilities to replicate in the vector or lower transmission rates from infective hosts to vectors.

In conclusion, foci of CCHFV have been active since its discovery in the year 1945. It is well known that, as for other tick-transmitted diseases, there are cycles of higher or lower incidence, that must result from fluctuations in weather and, most importantly, from changes in host availability and subsequent amplification of tick populations. It is known that mild winters will improve the suitability of an area for ticks, probably resulting in a rise of active ticks the following spring. However, the impact of the weather on disease incidence and the prevalence of the virus in ticks are insufficient to account for the dramatic differences observed in areas of the Mediterranean basin. Conditions where ungulates sustain a large population of ticks commonly derive from problems in management, associating poor control of ticks, the concentration of large flocks in natural pasture areas and large increases in the abundance of wild ungulates. Such poor management offers opportunities for ticks, which remain unnoticed until such suitable background produces an explosive population increase in a short time.

Lessons learned from previous epidemic episodes suggest that an adequate environment for ticks and the presence of large numbers of hosts are a dangerous situation that may lead to the epidemic activity of silent foci. We have not yet characterized several parameters affecting the transmission of CCHFV from cattle to feeding ticks, such as the duration of viremia, transmission efficiency to ticks and conditions necessary for adequate replication of the virus and for vertical passage. We also have not yet established the epidemiological conditions behind the silent periods between epidemic situations, because the main source of data to explore the trends of CCHFV is passive surveillance of human cases and, in some instances, serological studies in animals. However, conclusions are that new CCHFV foci may be rare, and that the resurgence of unnoticed foci is the result of a slow accumulation of conditions driving the abundance of hosts that amplify the vector population and transmission to humans. Clinical cases are evident only after the tick–human contact rate exceeds a threshold of transmission. Greater habitat fragmentation, the effects of abandoned lands on the host population, by promoting bush growth and thence a better host habitat, and the introduction of infected ticks by cattle movements might be the major reasons behind the changes observed in active foci. A coordinated active survey to detect the virus in questing ticks seems to be the most reliable method of tracking its presence and prevalence rates in vectors.

6. Modeling the climate niche of ticks and pathogens

There is increased interest in the preparation of maps delineating areas where a risk of ticks or tick-transmitted pathogens could be expected. Even with the acknowledged limitations that restrict our ability to capture the complete set of factors that shape the distribution of ticks, efforts are being made to produce regional maps showing a probability for ticks to persist as permanent populations (i.e. Leighton et al., 2012; Ogden et al., 2008b). However, without reliable information about the abundance and range of critical species of hosts (see above), it is not possible to obtain high-resolution maps applied to tick-transmitted pathogens.

Such estimations of the effects of the weather on the distribution, phenology or spread of ticks and pathogens are commonly based on:

(i) Evaluation of the "climate niche" of the ticks and the building of so-called correlative models (e.g. Estrada-Peña, 1998, 1999) and
(ii) The development of process-driven models that aim to capture the complete tick life cycle, based on equations directed to explain each process (development and mortality rates, questing activity, etc.) in separate "boxes" (e.g. Randolph et al., 2002; Dobson et al., 2011; Estrada-Peña et al., 2011a,b; Estrada-Peña and Estrada-Sánchez, 2014).

The first approach is intended to obtain information about the variables driving the distribution of an organism, while the second attempts to describe every single process of its life cycle, obtained in the laboratory or from controlled field studies, modeling observations about its fitness under different conditions. We will briefly explain in this chapter the conceptual background of both approaches and point to some procedural gaps in the application of these concepts. A complete explanation of the many methodological, statistical and biological abstractions of the environmental niche is outside the purpose of this paper; the reader is referred to the conceptual review by Halvorsen (2012).

6.1. Correlative models

Correlative models are based on the idea that populations of living organisms are constrained to a "portion" of the available environmental conditions (Peterson, 2006). Such a "niche" is defined in terms of non-interactive, abiotic variables such as temperature, precipitation, and vapor pressure as the intersection of environmental values at which populations have a variable fitness, but always a positive growth. Thus, within these climate envelopes, species may vary in abundance along environmental gradients that together correspond to optimal and less optimal conditions. This concept assumes that the weather is the most important factor that drive the tick's life cycle in the field, and that niches can be reconstructed by relating data on occurrence of the tick with sets summarizing climate, topographic, edaphic (e.g. soil-derived features), and other "abiotic" or "ecological" variables, commonly known as covariates. Correlative models are based on the information extracted from the known distribution of the target organism (Austin et al., 2006). A presence record suggests that, at some stage, individuals of that species were able to develop, survive to the adult stage and successfully reproduce in that location. Spatial conditions, such as climate, are also geo-referenced to that site, and are then inferred to be within the tolerance range of that species. This trains the coefficients of the model such that other sites with similar conditions are weighted in favor of a prediction of presence, ultimately defining a space of suitable environmental conditions. As far as we are aware, an approach including also the distribution and density of hosts, as a limiting factor for tick persistence (the "biotic" part of the niche of the ticks) has not yet been addressed.

Tick-transmitted pathogens may have a climate niche that may be linked to the niche of the species of tick(s) that act as vector(s). For instance, the phylogenetic arrangement of the genetic variants of flaviviruses, which are transmitted by arthropods, coincides with features of the climate (Gaunt et al., 2001; Randolph and Rogers, 2002), suggesting that specific genetic virus variants evolved under precise weather conditions. This reflects an effect of at least some of the abiotic variables on the evolution of the flaviviruses, or, most probably, on the evolution of the arthropods that transmit these viruses. For example, the etiological agent of Lyme borreliosis, *B. burgdorferi* s.l., is mainly found in areas where the most important tick vectors, the species in the complex *I. ricinus*, are prevalent (Kurtenbach et al., 2006). However, climate is not the only predictor of the distribution of these pathogens because the prevalence rates of pathogens in ticks are strongly dependent upon the availability of reservoir hosts. Most pathogens transmitted by ticks are thus restricted to sites where adequate reservoir hosts exist, and therefore their distribution is not driven only by the abiotic conditions of the territory, although these can indirectly affect the presence and abundance of the reservoir(s). A correlative model built to explain the distribution and prevalence rates of *B. burgdorferi* s.l. in ticks in Europe showed that climate is a surrogate for the population cycles of the reservoirs and vectors, but the predictive uncertainty at the local scale was very high (Estrada-Peña et al., 2011b). The link of the pathogens with the weather may be complex and difficult to disentangle from other indirect effects. The construction of a correlative model to explain prevalence rates of tick-transmitted pathogens should account for other variables affecting demographic rates and seasonality of both ticks and hosts, as well as a detailed description of the effects of relative densities of the community of hosts on the transmission rates of the pathogen. As stated by Eisen (2008) we still lack an empirical knowledge for several of these effects and actions, for which fieldwork is still necessary.

In any case, the purposes of the correlative models are:

(i) to infer the variables driving the observed distribution and capture the abiotic niche of the tick (i.e. the environmental covariates that are responsible for its observed range);
(ii) to project such inference into the geographic space, so as to outline the areas which have similar abiotic niches to the observed distribution; and
(iii) to project these conclusions under new combinations of environmental variables (i.e. future climate scenarios) to detail possible new areas of available habitat under such future conditions.

The tendency in modeling of health-threatening arthropods is the production of a map, developed from points (ii) and (iii) above, together with a measure of the "fitness" of the organism in the geographical space (Pearson and Dawson, 2003; Kearney, 2006). Such an index is not a probability of the presence of the tick, but the similarity of the environmental variables in a point of the map, compared with the set of data used to train the model (Heikkinen et al., 2006). The projections of such models onto different geographical or environmental backgrounds will therefore only reflect the similarity of the abiotic niche, not a probability of colonization. Failure to acknowledge this basic postulate of correlative models may produce spurious conclusions when examining the resulting maps, projected from the captured niche.

The building of correlative models may be distorted by erroneous assumptions or procedural gaps at any of these steps, resulting in unreliable conclusions that decrease the trustworthiness of the model. The most common methodological gaps are:

(i) the use of a partial set of records of the known distribution of the target organism (Jiménez-Valverde et al., 2012).
(ii) the selection of an unreliable set of explanatory variables that do not account for factors actually operating on the distribution of the target species (Kearney, 2006); and
(iii) the projection of the model into new scenarios of environmental covariates (.e.g. future climate scenarios) without checking the new relations among the covariates, which may largely interfere with the projections of the model (Williams and Jackson, 2007).

Implicit in the concepts of correlative modeling is that many of the ecological processes and interactions that lead to successful persistence at a site are statistically associated with the chosen environmental covariates. It is therefore necessary to build the model based on the most complete and updated distribution of the organism, or else some portions of the niche will be under-represented in the model. This is called "representativeness" in the geographical and environmental spaces (Halvorsen, 2012), meaning that every potential observation unit in the study area and each interval in the environmental covariates have the same probability of being sampled. This representativeness is relevant for model calibration. Thus, the subjective use of a partial set of records of the organism to be modeled will produce unreliable inferences about its niche. Most importantly in this context, the statistical tools that evaluate the reliability of the model are blind to these gaps, because there is a negative relationship between the predictive abilities of the model and the relative occurrence (Lobo et al., 2008). This effect derives from the negative association between the extent of the area occupied by the species, in relation to the total extent of the studied area (the relative occurrence area), and the discrimination capacity. The performance of a poorly fit model can be improved simply by increasing the area of the geographic background (Jiménez-Valverde et al., 2008, 2012). This is why models for restricted species usually yield higher discrimination values than those for widespread species, and why the use of a partial set of occurrences yields inaccurately high estimates of a model's performance.

A particularly important point in correlative modeling is the appropriate choice of the explanatory covariates (Kearney, 2006). There is a tendency to make an automatic selection of the best covariates by the modeling algorithm, without further checking their ecological significance – a point that has been mentioned by Randolph (2002) and Heikkinen et al. (2006), among others. Such "blind selection" of environmental covariates will construct statistically reliable models, but ecologically non-significant associations; such models will therefore produce unreliable results when projected onto different geographical or environmental backgrounds.

Additional potential drawbacks in correlative modeling of the distribution of ticks include issues derived from the structure of the data and the environmental covariates, which may inflate the reliability of the model, such as autocorrelation (Legendre, 1993) and colinearity (Storch et al., 2003). These issues have been addressed by Estrada-Peña et al. (2013d) who performed a comparison of the statistical errors associated with the use of interpolated climate datasets, compared with remotely sensed information, which was almost free of systematic errors inflating models. A third source of potential inflation of the results of correlative modeling is the utilization of variables that are correlated with others, such as altitude and temperature. A model fitted with environmental covariates that are correlated will always yield a higher statistical significance, but will provide an unreliable explanation of the observed distribution.

Correlative models may be an important source of data in assessing some factors determining the distribution of ticks or tick-transmitted pathogens. However, extreme care must be observed in producing ecologically sound models, without spurious information that only contributes to inflating their statistical reliability, but not their biological significance.

6.2. Process-driven models

Another approach to understanding the effects of climate on ticks and their transmitted pathogens is the building of process-driven models (i.e. Mount et al., 1997; Ogden et al., 2005; Dobson et al., 2011; Estrada-Peña and Estrada-Sánchez, 2014). These models aim to describe every "process" (e.g. egg development, density-dependent mortality, etc.) of the tick life cycle with equations that define the response of the tick to given combinations of variables, such as temperature and humidity. Process-driven models capture the physiology of the tick. While correlative models assume that a record of presence results from a balance of the physiological processes of the tick, resulting in a positive population outcome, process-driven models address each process separately, and are therefore versatile tools to evaluate the impact of climate on the complete life cycle. Process-driven models are commonly built upon observations of the life cycle carried out under laboratory or controlled experiences under field conditions. Because of their inherent difficulties, these observations are made on a limited number of tick populations, and might not completely reflect the total range of plasticity of the species.

Process-driven models are the only way to capture the importance of each environmental covariate for any tick stage, as well as the time of year at which they operate. It is necessary to recall that ticks are impacted not only by average and extreme values of the weather, but also by a specific combination of weather values at a precise moment of the year. This is the factor that defines tick phenology (Randolph, 2002), and process-driven models are oriented towards its capture. The projection of process-driven models on the geographical space, a procedure that is increasingly being used in the prediction of the habitat for mosquitoes (i.e. Kearney, 2006), has not been yet totally addressed for ticks, but Ogden et al. (2008a,b) have evaluated the impact of climate trends on the northern spread of the tick *I. scapularis* in southern Canada using such kind of modeling approach. Similarly, Estrada-Peña and Estrada-Sánchez (2014) have developed a process-driven model for *I. ricinus*, in which the importance of each process for the growth of the population and how it is impacted by the weather are specifically addressed. It is therefore a direct evaluation of how the physiological adaptability of the tick could affect its fitness under different combinations of temperature and humidity.

7. Priorities for future research: a set of questions and how to answer them

We foresee several priorities for research on ticks and tick-transmitted pathogens. First, there is a need for a better understanding of the relationships of ticks with the environment (e.g. the vegetation) and the microclimate. Such a background is necessary to build reliable maps of the distribution of the most important species of ticks, together with the predicted exposure of humans to these arthropods at several scales of resolution. While predictions of habitat suitability for ticks at the continental scale are informative, it is also necessary to capture the fine relationships of ticks with microclimate, and how host availability may contribute to modulating the responses of ticks to prevailing weather features.

The first necessary step is the recording and mining of the features of microclimate and the community of hosts that impact the life cycle of ticks. It is necessary to abandon dependence on large-area analyses, which establish general associations of weather alone with the perceived abundance of ticks. Ticks have complex life cycles that depend on both microclimate and the community of hosts. They have a large number of survival strategies to manage the changing effects of weather and host availability. It will be necessary to identify the molecular factors that regulate the response of the tick to temperature, photoperiod, and moisture, to draw solid conclusions regarding the regulation of the tick life cycle, and thence its fitness along a gradient of environmental conditions.

The distribution of tick-transmitted pathogens depends less on climate and more on the community of hosts and human actions on the landscape. We do not know the relative contribution of each species of host and the impact of livestock on the epidemiological events driving the emergence of foci of tick-transmitted pathogens. In the two disease systems reviewed in this paper, TBE and CCHF, a complete understanding of how the composition of the community of hosts drives the distribution and spread of active or silent foci is still lacking. General rules should ideally be obtained from field and laboratory studies, such as the duration of viremia in hosts in comparison to the time of attachment of ticks, or the potential of a single host to infect feeding ticks. There is not yet a complete and validated theory about how and why foci of TBE or CCHF evolve in time and expand or retreat in space, under different conditions of weather, vector and host species composition and densities.

The current procedure of evaluating the presence and activity of foci of tick-transmitted viruses is based, for most parts of their range, on passive surveys of human cases. Although these surveys have a perceptible interest, they cannot reliably measure the biological features governing these foci. Serological surveys in domestic and wild animals must be combined with the detection of viral nucleic acid in both ticks and hosts, to establish the species of reservoirs that circulate the pathogen in the field, which species of ticks are involved in the transmission, and how the circulation of the pathogen is correlated with rates of antibody positivity in vertebrates. Field surveys should ideally be combined with laboratory studies aimed at addressing the capacity of ticks to transmit the pathogen – a feature that may be obscured by the complexities and logistic problems of field studies. This is obviously a major task that should ideally be addressed by coordinated groups.

We do not expect prominent advances in the field of tick-transmitted viruses until long-duration studies are carried out under a gradient of climate conditions and an array of composition of host communities. Preliminary conclusions, based only on statistical associations of series of human clinical cases, could introduce noise into our understanding of the dynamics of tick-transmitted viruses. The real risk for humans must be measured by the exposure of people to infected ticks, not as a series of clinical cases recorded over a large region. These data have an obvious informative value, but cannot be used to draw conclusions on the impact of changes of natural factors on foci of tick-transmitted pathogens. Decision-makers should abandon such overly simplified approaches, and adopt an approach based on active and combined surveys of ticks, pathogens and hosts, to capture the complex behavior of systems of tick-transmitted pathogens in nature.

Knowledge of ticks and tick-borne viruses will accumulate from coordinated surveys that aim to collect ticks questing and feeding on livestock and wild hosts at intervals not longer than 10 days, so as to capture adequately their seasonality. These active surveys should ideally be correlated with weather data recorded by micro-loggers placed at different heights over the surface of the ground, to monitor adequately the conditions of temperature and water availability and they modulate the behavior of ticks and hosts. Several ecosystems with different host communities and tick rates on hosts should ideally be sampled, to adequately address the importance of each species of host. These field surveys should ideally continue for several years. Laboratory studies using tick colonies and, if possible, the same species of hosts recorded in the field, should complement these empirical data. Laboratory studies should ideally address the transmission rates of viruses to ticks, to capture the relative contribution of each species of host to the circulation of the virus. Last, but not least, molecular studies will be needed to address the interactions of viruses, ticks and hosts and the mechanisms used by the viruses to disseminate into the salivary gland of the tick. These studies, when applied to an ecosystem, will ideally provide an adequate framework to predict the risk of tick-borne viral diseases for humans.

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References

Albayrak, H., Ozan, E., Kurt, M., 2010. Molecular detection of Crimean-Congo haemorrhagic fever virus (CCHFV) but not West Nile Virus (WNV) in hard ticks from Provinces in Northern Turkey. Zoonoses Public Health 57, e156–e160.

Alekseev, A.N., Chunikhin, S.P., Rukhkyan, M.Y., Stefutkina, L.F., 1991. Possible role of Ixodidae salivary gland substrate as an adjuvant enhancing arbovirus transmission. Med. Parazitol. (Mosk) 1, 28–31.

Anderson, R.M., Gordon, D.M., 1982. Processes influencing the distribution of parasite numbers within host populations with special emphasis on parasite-induced host mortalities. Parasitology 85 (02), 373–398.

Austin, M.P., Belbin, L., Meyers, J.A., Doherty, M.D., Luoto, M., 2006. Evaluation of statistical models used for predicting plant species distributions: role of artificial data and theory. Ecol. Model. 199 (2), 197–216.

Balashov, Y.S., 1972. "Bloodsucking ticks (Ixodoidea) – vectors of diseases of man and animals", in Miscellaneous Publications of the Entomological Society of America. [Cairo: Medical Zoology Department, U.S. Naval Medical Research Unit Number Three (NAMRU-3)], pp. 161–376.

Barnard, D.R., 1991. Mechanisms of host–tick contact with special reference to *Amblyomma americanum* (Acari: Ixodidae) in beef cattle forage areas. J. Med. Entomol. 28, 557–564.

Barrett P.N., Plotkin S.A., Orenstein W.A., 2008. Tick-borne encephalitis virus vaccine. In: Plotkin, S.A., Orenstein, W.A. (Eds.), Vaccines. Saunders & Elsevier, Philadelphie, pp: 84-88.

Belozerov, V.N., 1982. Diapause and biological rhythms in ticks. In: Obenchain, F.D., Galun, R. (Eds.), Physiology of Ticks. Pergamon Press, Oxford, U.K., pp. 469–500.

Bente, D.A., Forrester, N.L., Watts, D.M., McAuley, A.J., Whitehouse, C.A., Bray, M., 2013. Crimean-Congo hemorrhagic fever: history, epidemiology, pathogenesis, clinical syndrome and genetic diversity. Antiviral Res. 100 (1), 159–189.

Bosch, J., Muñoz, M.J., Martínez, M., de la Torre, A., Estrada-Peña, A., 2012. Vector-borne pathogen spread through ticks on migratory birds: a probabilistic spatial risk model for South-Western Europe. Transbound. Emerg. Dis. 60, 403–415.

Bown, K.J., Begon, M., Bennett, M., Birtles, R.J., Burthe, S., Lambin, X., Ogden, N.H., 2006. Sympatric *Ixodes trianguliceps* and *Ixodes ricinus* ticks feeding on field voles (*Microtus agrestis*): potential for increased risk of *Anaplasma phagocytophilum* in the United Kingdom? Vector Borne Zoonotic Dis. 6, 404–410.

Brownstein, J.S., Holford, T.R., Fish, D., 2003. A climate-based model predicts the spatial distribution of the Lyme disease vector *Ixodes scapularis* in the United States. Environ. Health Perspect. 111 (9), 1152.

Burgdorfer, W., 1975. A review of Rocky Mountain spotted fever (tick-borne typhus), its agent, and its tick vectors in the United States. J. Med. Entomol. 12 (3), 269–278.

Bursali, A., Tekin, S., Keskin, A., Ekici, M., Dundar, E., 2011. Species diversity of ixodid ticks feeding on humans in Amasya, Turkey: seasonal abundance and presence of Crimean-Congo hemorrhagic fever virus. J. Med. Entomol. 48, 85–93.

Chamberlain, J., Cook, N., Lloyd, G., Mioulet, V., Tolley, H., Hewson, R., 2005. Co-evolutionary patterns of variation in small and large RNA segments of Crimean-Congo hemorrhagic fever virus. J. Gen. Virol. 86, 3337–3341.

Chapman, L.E., Wilson, M.L., Hall, D.B., 1991. Risk factors for Crimean-Congo hemorrhagic fever in rural northern Senegal. J. Infect. Dis. 164, 686–692.

Childs, J.E., Paddock, C.D., 2003. The ascendancy of *Amblyomma americanum* as a vector of pathogens affecting humans in the United States. Annu. Rev. Entomol. 48, 307–337.

Chinikar, S., Ghiasi, S.M., Hewson, R., Moradi, M., Haeri, A., 2010. Crimean-Congo hemorrhagic fever in Iran and neighboring countries. J. Clin. Virol. 47, 110–114.

Corson, M.S., Teel, P.D., Grant, W.E., 2004. Microclimate influence in a physiological model of cattle-fever tick (*Boophilus* spp.) population dynamics. Ecol. Model. 180, 487–514.

Daniel, M., Danielová, V., Kříž, B., Kott, I., 2004. An attempt to elucidate the increased incidence of tick-borne encephalitis and its spread to higher altitudes in the Czech Republic. Int. J. Med. Microbiol. 293 (Suppl.), 55–62.

Daniel, M., Kříž, B., Danielová, V., Beneš, Č., 2008. Sudden increase in tick-borne encephalitis cases in the Czech Republic, 2006. Int. J. Med. Microbiol. 298, 81–87.

Danielová, V., Holubová, J., Pejcoch, M., Daniel, M., 2002. Potential significance of transovarial transmission in the circulation of tick-borne encephalitis virus. Folia Parasitol. 49, 323–325.

Danielová, V., Rudenko, N., Daniel, M., Holubová, J., Materna, J., Golovchenko, M., Schwarzová, L., 2006. Extension of the *Ixodes ricinus* ticks and agents of tick-borne diseases to mountain areas in the Czech Republic. Int. J. Med. Microbiol. 296 (S1), 48–53.

Daniels, T.J., Falco, R.C., Curran, K.L., Fish, D., 1996. Timing of *Ixodes scapularis* (Acari: Ixodidae) oviposition and larval activity in southern New York. J. Med. Entomol. 33, 140–147.

Dautel, H., Dippel, C., Kämmer, D., Werkhausen, A., Kahl, O., 2008. Winter activity of *Ixodes ricinus* in a Berlin forest. Int. J. Med. Microbiol. 298, 50–54.

de la Fuente, J., Garcia-Garcia, J.C., Blouin, E.F., Rodríguez, S.D., García, M.A., Kocan, K.M., 2001. Evolution and function of tandem repeats in the major surface protein 1a of the ehrlichial pathogen *Anaplasma marginale*. Anim. Health Res. Rev. 2 (02), 163–174.

Dobler, G., Hufert, F., Pfeffer, M., Essbauer, S., 2011. Tick-borne encephalitis: from microfocus to human disease. In: Progress in Parasitology. Springer, Berlin, Heidelberg, pp. 323–331.

Dobson, A., Cattadori, I., Holt, R.D., Ostfeld, R.S., Keesing, F., Krichbaum, K., Hudson, P.J., 2006. Sacred cows and sympathetic squirrels: the importance of biological diversity to human health. PLoS Med. 3 (6), e231.

Dobson, A.D., Finnie, T.J., Randolph, S.E., 2011. A modified matrix model to describe the seasonal population ecology of the European tick *Ixodes ricinus*. J. Appl. Ecol. 48, 1017–1028.

Donoso, M.O., Schädler, R., Niedrig, M., 2008. A survey on cases of tick-borne encephalitis in European countries. Euro Surveil. 13 (17).

Eisen, L., 2008. Climate change and tick-borne diseases: a research field in need of long-term empirical field studies. Int. J. Med. Entomol. 298, 12–18.

Ergonul, O., Whitehouse, C.A., 2007. Introduction. In: Ergonul, Whitehouse (Eds.), Crimean-Congo Hemorrhagic Fever. A Global Perspective. Springer, The Netherlands, pp. 3–13.

Estrada-Peña, A., Oteo, J.A., Estrada-Pena, R., Gortazar, C., Osacar, J.J., Moreno, J.A., Castella, J., 1995. *Borrelia burgdorferi* sensu lato in ticks (Acari: Ixodidae) from two different foci in Spain. Exp. Appl. Acarol. 19 (3), 173–180.

Estrada-Peña, A., Gray, J.S., Kahl, O., 1996. Variability in cuticular hydrocarbons and phenotypic discrimination of *Ixodes ricinus* populations (Acarina: Ixodidae) from Europe. Exp. Appl. Acarol. 20 (8), 457–466.

Estrada-Peña, A., 1998. Geostatistics and remote sensing as predictive tools of tick distribution: a cokriging system to estimate *Ixodes scapularis* (Acari: Ixodidae) habitat suitability in the United States and Canada from advanced very high resolution radiometer satellite imagery. J. Med. Entomol. 35, 989–995.

Estrada-Peña, A., 1999. Geostatistics as predictive tools to estimate *Ixodes ricinus* (Acari: Ixodidae) habitat suitability in the western Palearctic from AVHRR satellite imagery. Exp. Appl. Acarol. 23, 337–349.

Estrada-Peña, A., 2002. Understanding the relationships between landscape connectivity and abundance of *Ixodes ricinus* ticks. Exp. Appl. Acarol. 28 (1–4), 239–248.

Estrada-Peña, A., 2003. The relationships between habitat topology, critical scales of connectivity and tick abundance *Ixodes ricinus* in a heterogeneous landscape in northern Spain. Ecography 26 (5), 661–671.

Estrada-Peña, A., Venzal, J.M., 2007. Climate niches of tick species in the Mediterranean region: modelling of occurrence data, distributional constraints, and impact of climate change. J. Med. Entomol. 44, 1130–1138.

Estrada-Peña, A., Vatansever, Z., Gargili, A., Aktas, M., Uzun, R., Ergonul, O., Jongejan, F., 2007. Modeling the spatial distribution of Crimean-Congo hemorrhagic fever outbreaks in Turkey. Vector Borne Zoonotic Dis. 7, 667–678.

Estrada-Peña, A., Vatansever, Z., Gargili, A., Ergönul, Ö., 2010. The trend towards habitat fragmentation is the key factor driving the spread of Crimean-Congo haemorrhagic fever. Epidemiol. Infect. 138, 1194–1203.

Estrada-Peña, A., Martínez Avilés, M., Muñoz Reoyo, M.J., 2011a. A population model to describe the distribution and seasonal dynamics of the tick *Hyalomma marginatum* in the Mediterranean Basin. Transbound. Emerg. Dis. 58, 213–223.

Estrada-Peña, A., Ortega, C., Sánchez, N., DeSimone, L., Sudre, B., Suk, J.E., Semenza, J.C., 2011b. Correlation of *Borrelia burgdorferi* sensu lato prevalence in questing *Ixodes ricinus* ticks with specific abiotic traits in the western Palearctic. Appl. Environ. Microbiol. 77 (11), 3838–3845.

Estrada-Peña, A., Palomar, A.M., Santibáñez, P., Sánchez, N., Habela, M.A., Portillo, A., Oteo, J.A., 2012a. Crimean-Congo hemorrhagic fever virus in ticks, southwestern Europe, 2010. Emerg. Infect. Dis. 18, 179.

Estrada-Peña, A., Jameson, L., Medlock, J., Vatansever, Z., Tishkova, F., 2012b. Unraveling the ecological complexities of tick-associated Crimean-Congo hemorrhagic fever virus transmission: a gap analysis for the Western palearctic. Vector Borne Zoonotic Dis. 12, 743–752.

Estrada-Peña, A., Gray, J.S., Kahl, O., Lane, R.S., Nidhoj, A., 2013a. Research on the ecology of ticks and tick-borne pathogens-methodological principles and caveats. Front. Cell. Infect. Microbiol. 3, 29.

Estrada-Peña, A., Ruiz-Fons, F., Acevedo, P., Gortazar, C., la Fuente, J., 2013b. Factors driving the circulation and possible expansion of Crimean-Congo haemorrhagic fever virus in the western Palearctic. J. Appl. Microbiol. 114, 278–286.

Estrada-Peña, A., Estrada-Sánchez, A., Estrada-Sánchez, D., de la Fuente, J., 2013c. Assessing the effects of variables and background selection on the capture of the tick climate niche. Int. J. Health Geogr. 12 (1), 43.

Estrada-Peña, A., Farkas, R., Jaenson, T.G., Koenen, F., Madder, M., Pascucci, I., Jongejan, F., 2013d. Association of environmental traits with the geographic ranges of ticks (Acari: Ixodidae) of medical and veterinary importance in the western Palearctic. A digital data set. Exp. Appl. Acarol. 59 (3), 351–366.

Estrada-Peña, A., Estrada-Sánchez, D., 2014. Deconstructing *Ixodes ricinus*: a partial matrix model allowing mapping of tick development, mortality and activity rates. Med. Vet. Entomol. 28, 35–49.

Estrada-Peña, A., Hubálek, Z., Rudolf, I., 2014. Tick-transmitted viruses and climate change. In: Singh, S.K. (Ed.), Viral Infections and Global Change. Wiley Blackwell, pp. 573–594.

Gale, P., Estrada-Peña, A., Martinez, M., Ulrich, R.G., Wilson, A., Capelli, G., Fooks, A.R., 2010. The feasibility of developing a risk assessment for the impact of climate change on the emergence of Crimean-Congo haemorrhagic fever in livestock in Europe: a review. J. Appl. Microbiol. 108 (6), 1859–1870.

Gargili, A., Saravanan, T., Bente, D., 2013. Influence of laboratory animal hosts on the life cycle of *Hyalomma marginatum* and implications for an in vivo transmission model for Crimean-Congo hemorrhagic fever virus. Front. Cell. Infect. Microbiol. 3.

Gäumann, R., Mühlemann, K., Strasser, M., Beuret, C.M., 2010. High-throughput procedure for tick surveys of tick-borne encephalitis virus and its application in a national surveillance study in Switzerland. Appl. Environ. Microbiol. 76 (13), 4241–4249.

Gaunt, M.W., Sall, A.A., de Lamballerie, X., Falconar, A.K., Dzhivanian, T.I., Gould, E.A., 2001. Phylogenetic relationships of flaviviruses correlate with their epidemiology, disease association and biogeography. J. Gen. Virol. 82, 1867–1876.

Gern, L., Toutoungi, L.N., Hu, C.M., Aeschlimann, A., 1991. *Ixodes* (*Pholeoixodes*) *hexagonus*, an efficient vector of *Borrelia burgdorferi* in the laboratory. Med. Vet. Entomol. 5 (4), 431–435.

Gordon, S.W., Linthicum, K.J., Moulton, J.R., 1993. Transmission of Crimean-Congo hemorrhagic fever virus in two species of *Hyalomma* ticks from infected adults to cofeeding immature forms. Am. J. Trop. Med. Hyg. 48, 576–580.

Gözalan, A., Akin, L., Rolain, J.M., Tapar, F.S., Oncül, O., Yoshikura, H., Esen, B., 2004. Epidemiological evaluation of a possible outbreak in and nearby Tokat province. Mikrobiyol. Bül. 38 (1–2), 33.

Gray, J.S., 2008. *Ixodes ricinus* seasonal activity: implications of global warming indicated by revisiting tick and weather data. Int. J. Med. Microbiol. 298, 19–24.

Gray, J.S., Dautel, H., Estrada-Peña, A., Kahl, O., Lindgren, E., 2009. Effects of climate change on ticks and tick-borne diseases in Europe. Interdiscip. Perspect. Infect. Dis. 12, 10. http://dx.doi.org/10.1155/2009/593232. Article ID 593232.

Guglielmone, A.A., Robbins, R.G., Apanaskevich, D.A., Petney, T.N., Estrada-Peña, A., Horak, I.G., Barker, S.C., 2010. The Argasidae, Ixodidae and Nuttalliellidae (Acari: Ixodida) of the world: a list of valid species names. Zootaxa 2528, 1–28.

Gunaydin, N.S., Aydin, K., Yilmaz, G., Caylan, R., Koksal, I., 2010. Crimean-Congo hemorrhagic fever cases in Eastern Black Sea Region of Turkey: demographic, geographic, climatic, and clinical characteristics. Turk. J. Med. Sci. 40, 829–834.

Gunes, T., Poyraz, O., Vatansever, Z., 2011. Crimean-Congo hemorrhagic fever virus in ticks collected from humans, livestock, and picnic sites in the hyperendemic region of Turkey. Vector Borne Zoonotic Dis. 11 (10), 1411–1416.

Halvorsen, R., 2012. A gradient analytic perspective on distribution modeling. Sommerfeltia 35, 1–165.

Hartemink, N.A., Randolph, S.E., Davis, S.A., Heesterbeek, J.A.P., 2008. The basic reproduction number for complex disease systems: defining R0 for tick-borne infections. Am. Nat. 171 (6), 743–754.

Hasle, G., Bjune, G., Edvardsen, E., Jakobsen, C., Linnehol, B., Røer, J.E., Leinaas, H.P., 2009. Transport of ticks by migratory passerine birds to Norway. J. Parasitol. 95 (6), 1342–1351.

Heikkinen, R.K., Luoto, M., Araújo, M.B., Virkkala, R., Thuiller, W., Sykes, M.T., 2006. Methods and uncertainties in bioclimatic envelope modelling under climate change. Prog. Phys. Geogr. 30 (6), 751–777.

Hemmer, C., Littmann, M., Löbermann, M., Lafrenz, M., Böttcher, T., Reisinger, E.C., 2005. Tickborne meningoencephalitis, first case after 19 years in northeastern Germany. Emerg. Infect. Dis. 11, 633–634.

Hewson, R., Gmyl, A., Gmyl, L., Smirnova, S.E., Karganova, G., Jamil, B., Hasan, R., Chamberlain, J., Clegg, C., 2004. Evidence of segment reassortment in Crimean-Congo haemorrhagic fever virus. J. Gen. Virol. 85, 3059–3070.

Hoek, M., Fischer, E., van den Hengel, R., Backer, J., de Koeijer, A. (2012). Workshop on a Risk Assessment of Crimean Congo Haemorrhagic Fever in Western Europe. Report number: 12/CVI0361 Lelystad, the Netherlands 23–24 May 2012.

Hoogstraal, H., 1979. The epidemiology of tick-borne Crimean-Congo hemorrhagic fever in Asia, Europe, and Africa. J. Med. Entomol. 15 (4), 307–417.

Hoogstraal, H., Kaiser, M.N., Traylor, M.A., Gaber, S., Guindy, E., 1961. Ticks (Ixodidea) on birds migrating from Africa to Europe and Asia. Bull. World Health Organ. 24, 197–212.

Hornok, S., Horváth, G., 2012. First report of adult *Hyalomma marginatum rufipes* (vector of Crimean-Congo haemorrhagic fever virus) on cattle under a continental climate in Hungary. Parasit. Vectors 5, 170.

Huang, Z.Y., de Boer, W.F., van Langevelde, F., Olson, V., Blackburn, T.M., Prins, H.H., 2013. Species' life-history traits explain interspecific variation in reservoir competence. A possible mechanism underlying the dilution effect. PLoS One 8 (1), e54341.

Jääskeläinen, A.E., Tikkakoski, T., Uzcategui, N.Y., Vaheri, A., Vapalahti, O., 2006. Siberian subtype tickborne encephalitis virus, Finland. Emerg. Infect. Dis. 12, 1568–1571.

Jaenson, T.G., Eisen, L., Comstedt, P., Mejlon, H.A., Lindgren, E., Bergström, S., Olsen, B., 2009. Risk indicators for the tick *Ixodes ricinus* and *Borrelia burgdorferi* sensu lato in Sweden. Med. Vet. Entomol. 23 (3), 226–237.

Jaenson, T.G., Hjertqvist, M., Bergström, T., Lundkvist, Å., 2012a. Why is tick-borne encephalitis increasing? A review of the key factors causing the increasing. Parasit. Vectors 5, 184.

Jaenson, T.G., Jaenson, D.G., Eisen, L., Petersson, E., Lindgren, E., 2012b. Changes in the geographical distribution and abundance of the tick *Ixodes ricinus* during the past 30 years in Sweden. Parasit. Vectors 5 (8).

Jiménez-Valverde, A., Lobo, J.M., Hortal, J., 2008. Not as good as they seem: the importance of concepts in species distribution modelling. Divers. Distrib. 14, 885–890.

Jiménez-Valverde, A., Acevedo, P., Barbosa, A.M., Lobo, J.M., Real, R., 2012. Discrimination capacity in species distribution models depends on the representativeness of the environmental domain. Glob. Ecol. Biogeogr. 22, 508–516.

Jones, L.D., Hodgson, E., Nuttall, P.A., 1989. Enhancement of virus transmission by tick salivary glands. J. Gen. Virol. 70, 1895–1898.

Kahl, O., Alidousti, I., 1997. Bodies of liquid water as a source of water gain for *Ixodes ricinus* ticks (Acari: Ixodidae). Exp. Appl. Acarol. 21, 731–746.

Kahl, O., Gern, L., Eisen, L., Lane, R.S., 2002. Ecological research on *Borrelia burgdorferi* sensu lato: terminology and some methodological pitfalls. In: Gray, J.S., Kahl, O., Lane, R.S., Stanek, G. (Eds.), Lyme Borreliosis: Biology, Epidemiology and Control. CABI Publishing, New York, pp. 29–46.

Kearney, M., 2006. Habitat, environment and niche: what are we modelling? Oikos 115 (1), 186–191.

Keshtkar-Jahromi, M., Sajadi, M.M., Ansari, H., Mardani, M., Holakouie-Naieni, K., 2013. Crimean-Congo hemorrhagic fever in Iran. Antiviral Res. 100 (1), 20–28.

Kitron, U., 1998. Landscape ecology and epidemiology of vector-borne diseases: tools for spatial analysis. J. Med. Entomol. 35 (4), 435–445.

Knap, N., Avšič-Županc, T., 2013. Correlation of TBE incidence with Red Deer and Roe Deer abundance in Slovenia. PLoS One 8 (6), e66380.

Krasnov, B.R., Stanko, M., Morand, S., 2007. Host community structure and infestation by ixodid ticks: repeatability, dilution effect and ecological specialization. Oecologia 154 (1), 185–194.

Kurtenbach, K., Hanincová, K., Tsao, J.I., Margos, G., Fish, D., Ogden, N.H., 2006. Fundamental processes in the evolutionary ecology of Lyme borreliosis. Nat. Rev. Microbiol. 4 (9), 660–669.

Labuda, M., Jones, L.D., Williams, T., Nuttall, P.A., 1993a. Enhancement of tick-borne encephalitis virus transmission by tick salivary gland extracts. Med. Vet. Entomol. 7, 193–196.

Labuda, M., Jones, L.D., Williams, T., Danielova, V., Nuttall, P.A., 1993b. Efficient transmission of tick-borne encephalitis virus between cofeeding ticks. J. Med. Entomol. 30, 295–299.

Lane, R.S., Anderson, J.R., Yaninek, J.S., Burgdorfer, W., 1985. Diurnal host seeking of adult Pacific Coast ticks, *Dermacentor occidentalis* (Acari: Ixodidae), in relation to vegetational type, meteorological factors, and rickettsial infection rates in California, USA. J. Med. Entomol. 22, 558–571.

Lees, A.D., 1946. The water balance in *Ixodes ricinus* L. and certain other species of ticks. Parasitology 37, 1–20.

Lees, A.D., Milne, A., 1951. The seasonal and diurnal activities of individual sheep ticks (*Ixodes ricinus* L.). Parasitology 41, 189–208.

Legendre, P., 1993. Spatial autocorrelation: trouble or new paradigm? Ecology 74, 1659–1673.

Leighton, P.A., Koffi, J.K., Pelcat, Y., Lindsay, L.R., Ogden, N.H., 2012. Predicting the speed of tick invasion: an empirical model of range expansion for the Lyme disease vector *Ixodes scapularis* in Canada. J. Appl. Ecol. 49 (2), 457–464.

Lindgren, E., Gustafson, R., 2001. Tick-borne encephalitis in Sweden and climate change. Lancet 358, 16–18.

Lindgren, E., Jaenson, T.G.T., 2006. Lyme borreliosis in Europe: influences of climate and climate change, epidemiology, ecology and adaptation measures. Publications of the Regional WHO Office for Europe, EUR/04/5046250.

Lindgren, E., Tälleklint, L., Polfeldt, T., 2000. Impact of climatic change on the northern latitude limit and population density of the disease-transmitting European tick *Ixodes ricinus*. Environ. Health Perspect. 108, 119–123.

Lindsay, L.R., Mathison, S.W., Barker, I.K., Mcewen, S.A., Gillespie, T.J., Surgeoner, G.A., 1999. Microclimate and habitat in relation to *Ixodes scapularis* (Acari: Ixodidae) populations on Long Point, Ontario, Canada. J. Med. Entomol. 36, 255–262.

Lobo, J.M., Jiménez-Valverde, A., Real, R., 2008. AUC: a misleading measure of the performance of predictive distribution models. Glob. Ecol. Biogeogr. 17, 145–151.

Maltezou, H.C., Papa, A., 2010. Crimean-Congo hemorrhagic fever: risk for emergence of new endemic foci in Europe? Travel Med. Infect. Dis. 8 (3), 139–143.

Maltezou, H.C., Andonova, L., Andraghetti, R., Bouloy, M., Ergonul, O., Jongejan, F., Kalvatchev, N., Nichol, S., Niedrig, M., Platonov, A., Thomson, G., Leitmeyer, K., Zeller, H., 2010. Crimean-Congo hemorrhagic fever in Europe: current situation calls for preparedness. Euro Surveil. 15, 10, pii=19504.

Mannelli, A., Boggiatto, G., Grego, E., Cinco, M., Murgia, R., Stefanelli, S., De Meneghi, D., Rosati, S., 2003. Acarological risk of exposure to agents of tick-borne zoonoses in the first recognized Italian focus of Lyme borreliosis. Epidemiol. Infect. 131, 1139–1147.

Materna, J., Daniel, M., Metelka, L., Harcarik, J., 2008. The vertical distribution, density and the development of the tick *Ixodes ricinus* in mountain areas influenced by climate change (The Krkonose Mts., Czech Republic). Int. J. Med. Microbiol. 298 (S1), 25–37.

Mather, T.N., Wilson, M.L., Moore, S.I., Riberio, J.M.C., Spielman, A., 1989. Comparing the relative potential of rodents as reservoirs of the Lyme disease spirochete (*Borrelia burgdorferi*). Am. J. Epidemiol. 130, 143–150.

May, R.M., 1978. Host–parasitoid systems in patchy environments: a phenomenological model. J. Anim. Ecol., 833–844.

Medlock, J.M., Hansford, K.M., Bormane, A., Derdakova, M., Estrada-Peña, A., George, J.C., Van Bortel, W., 2013. Driving forces for changes in geographical distribution of *Ixodes ricinus* ticks in Europe. Parasit. Vectors 6, 1–11.

Mount, G.A., Haile, D.G., Daniels, E., 1997. Simulation of blacklegged tick (Acari: Ixodidae) population dynamics and transmission of *Borrelia burgdorferi*. J. Med. Entomol. 34 (4), 461–484.

Mudhakir, D., Harashima, H., 2009. Learning from the viral journey: how to enter cells and how to overcome intracellular barriers to reach the nucleus. AAPS J. 11, 65–77.

Nalca, A., Whitehouse, C.A., 2007. Crimean-Congo hemorrhagic fever virus infection among animals. In: Ergonil, O., Whitehouse, C.A. (Eds.), Crimean-Congo Hemorrhagic Fever a Global Perspective. Springer, Dordrecht, the Netherlands, pp. 155–165.

Neelakanta, G., Li, X., Pal, U., Liu, X., Beck, D.S., DePonte, K., Fish, D., Kantor, F.S., Fikrig, E., 2007. Outer surface protein B is critical for *Borrelia burgdorferi* adherence and survival within Ixodes ticks. PLoS Pathog. 3, e33.

Nijhof, A.M., Bodaan, C., Postigo, M., Nieuwenhuijs, H., Opsteegh, M., Franssen, L., Jebbink, F., Jongejan, F., 2007. Ticks and associated pathogens collected from domestic animals in the Netherlands. Vector Borne Zoonotic Dis. 7, 585–595.

Nuttall, P.A., 1999. Pathogen–tick–host interactions: *Borrelia burgdorferi* and TBE virus. Zentralbl. Bakteriol. 289, 492–505.

Nuttall, P.A., Labuda, M., 1994. Tick-borne encephalitis subgroup. In: Sonenshine, D.E., Mather, T.N. (Eds.), Ecological Dynamics of Tick-borne Zoonoses. Oxford University Press, New York, pp. 351–391.

Nuttall, P.A., Labuda, M., 2004. Tick–host interactions: saliva-activated transmission. Parasitology 129, S177.

Nuttall, P.A., Labuda, M., 2008. Saliva-assisted transmission of tick-borne pathogens. In: Bowman, A.S., Nuttall, P.A. (Eds.), Ticks: Biology, Disease and Control. Cambridge University Press, Cambridge, pp. 205–219.

Ogden, N.H., Barker, I.K., Beauchamp, G., Brazeau, S., Charron, D.F., Maarouf, A., Lindsay, L.R., 2006. Investigation of ground level and remote-sensed data for habitat classification and prediction of survival of *Ixodes scapularis* in habitats of southeastern Canada. J. Med. Entomol. 43 (2), 403–414.

Ogden, N.H., Lindsay, L.R., Hanincová, K., Barker, I.K., Bigras-Poulin, M., Charron, D.F., Thompson, R.A., 2008a. Role of migratory birds in introduction and range expansion of *Ixodes scapularis* ticks and of *Borrelia burgdorferi* and *Anaplasma phagocytophilum* in Canada. Appl. Environ. Microbiol. 74 (6), 1780–1790.

Ogden, N.H., St-Onge, L., Barker, I.K., Brazeau, S., Bigras-Poulin, M., Charron, D.F., Francis, C.M., Heagy, A., Lindsay, L.R., Maarouf, A., Michel, P., Milord, F., O'Callaghan, C.J., Trudel, L., Thompson, R.A., 2008b. Risk maps for range expansion of the Lyme disease vector, *Ixodes scapularis*, in Canada now and with climate change. Int. J. Health Geogr. 7, 24.

Ogden, N.H., Tsao, J.I., 2009. Biodiversity and Lyme disease: dilution or amplification? Epidemics 1 (3), 196–206.

Ogden, N.H., Bigras-Poulin, M., O'callaghan, C.J., Barker, I.K., Lindsay, L.R., Maarouf, A., Charron, D., 2005. A dynamic population model to investigate effects of climate on geographic range and seasonality of the tick *Ixodes scapularis*. Int. J. Parasitol. 35 (4), 375–389.

Ostfeld, R.S., 2009. Biodiversity loss and the rise of zoonotic pathogens. Clin. Microbiol. Infect. 15 (s1), 40–43.

Ostfeld, R.S., Keesing, F., 2000. Biodiversity and disease risk: the case of Lyme disease. Conserv. Biol. 14 (3), 722–728.

Ostfeld, R.S., Schauber, E.M., Canham, C.D., Keesing, F., Jones, C.G., Wolff, J.O., 2001. Effects of acorn production and mouse abundance on abundance and *Borrelia burgdorferi* infection prevalence of nymphal *Ixodes scapularis* ticks. Vector Borne Zoonotic Dis. 1 (1), 55–63.

Ostfeld, R.S., Glass, G.E., Keesing, F., 2005. Spatial epidemiology: an emerging (or re-emerging) discipline. Trends Ecol. Evol. 20 (6), 328–336.

Pal, U., Li, X., Wang, T., Montgomery, R.R., Ramamoorthi, N., Desilva, A.M., Bao, F., Yang, X., Pypaert, M., Pradhan, D., Kantor, F.S., Telford, S., Anderson, J.F., Fikrig, E., 2004. TROSPA, an *Ixodes scapularis* receptor for *Borrelia burgdorferi*. Cell 119, 457–468.

Patz, J.A., Githeko, A.K., McCarty, J.P., Hussein, S., Confalonieri, U., De Wet, N. 2003. Climate change and infectious diseases. in: Climate Change and Human Health: Risks and Responses. World Health Organization, Geneva, pp. 103–137. Available at: <http://www.who.int/globalchange/publications/cchhbook/en/>.

Pearson, R.G., Dawson, T.P., 2003. Predicting the impacts of climate change on the distribution of species: are bioclimate envelope models useful? Glob. Ecol. Biogeogr. 12, 361–371.

Perret, J.L., Guerin, P.M., Diehl, P.A., Vlimant, M., Gern, L., 2003. Darkness induces mobility, and saturation deficit limits questing duration, in the tick *Ixodes ricinus*. J. Exp. Biol. 206, 1809–1815.

Perret, J.L., Guigoz, E., Rais, O., Gern, L., 2000. Influence of saturation deficit and temperature on *Ixodes ricinus* tick questing activity in a Lyme borreliosis-endemic area (Switzerland). Parasitol. Res. 86, 554–557.

Perret, J.L., Rais, O., Gern, L., 2004. Influence of climate on the proportion of *Ixodes ricinus* nymphs and adults questing in a tick population. J. Med. Entomol. 41, 361–365.

Peterson, A.T., 2006. Ecologic niche modeling and spatial patterns of disease transmission. Emerg. Infect. Dis. 12 (12), 1822.

Poulin, R., 1993. The disparity between observed and uniform distributions: a new look at parasite aggregation. Int. J. Parasitol. 23 (7), 937–944.

Poupon, M.A., Lommano, E., Humair, P.F., Douet, V., Rais, O., Schaad, M., Gern, L., 2006. Prevalence of *Borrelia burgdorferi* sensu lato in ticks collected from migratory birds in Switzerland. Appl. Environ. Microbiol. 72 (1), 976–979.

Price, Trevor.D., Qvarnström, Anna., Irwin, Darren.E., 2003. The role of phenotypic plasticity in driving genetic evolution. Proc. R. Soc. Lond. B Biol. Sci. 270 (1523), 1433–1440.

Purnak, T., Selvi, N.A., Altundag, K., 2007. Global warming may increase the incidence and geographic range of Crimean-Congo hemorrhagic fever. Med. Hypotheses 68 (4), 924–925.

Randolph, S.E., 1998. Ticks are not insects: consequences of contrasting vector biology for transmission potential. Parasitol. Today 14 (5), 186–192.

Randolph, S.E., 2000. Ticks and tick-borne disease systems in space and from space. Adv. Parasitol. 47, 217–243.

Randolph, S.E., 2002. Quantitative ecology of ticks as a basis for transmission models of tick-borne pathogens. Vector Borne Zoonotic Dis. 2, 209–215.

Randolph, S.E., 2008. Tick-borne encephalitis incidence in Central and Eastern Europe: consequences of political transition. Microbes Infect. 10 (3), 209–216.

Randolph, S.E., 2009. Tick-borne disease systems emerge from the shadows: the beauty lies in molecular detail, the message in epidemiology. Parasitology 136, 1403–1413.

Randolph, S.E., 2010. To what extent has climate change contributed to the recent epidemiology of tick-borne diseases? Vet. Parasitol. 167 (2), 92–94.

Randolph, S.E., 2011. Transmission of tick-borne pathogens between co-feeding ticks: Milan Labuda's enduring paradigm. Ticks Tick Borne Dis. 2, 179–182.

Randolph, S.E., Craine, N.G., 1995. General framework for comparative quantitative studies on transmission of tick-borne diseases using Lyme borreliosis in Europe as an example. J. Med. Entomol. 32, 765–777.

Randolph, S.E., Rogers, D.J., 2000. Fragile transmission cycles of tick-borne encephalitis virus may be disrupted by predicted climate change. Proc. R. Soc. Lond. B Biol. Sci. 267 (1454), 1741–1744.

Randolph, S.E., Rogers, D.J., 2002. Remotely sensed correlates of phylogeny: tick-borne flaviviruses. Exp. Appl. Acarol. 28 (1–4), 231–237.

Randolph, S.E., Storey, K., 1999. Impact of microclimate on immature tick-rodent host interactions (Acari: Ixodidae): implications for parasite transmission. J. Med. Entomol. 36 (6), 741–748.

Randolph, S.E., Sumilo, D., 2007. Tick-borne encephalitis in Europe: dynamics of changing risk. In: Takken, W., Knols, B.G.J. (Eds.), Emerging Pests and Vector-borne Disease in Europe. Wageningen Academic Publishers, Wageningen, pp. 187–206.

Randolph, S.E., Green, R.M., Hoodless, A.N., Peacey, M.F., 2002. An empirical quantitative framework for the seasonal population dynamics of the tick *Ixodes ricinus*. Int. J. Parasitol. 32, 979–989.

Randolph, S.E., Dobson, A.D.M., Allan, B.F., Dutra, H.P., Goessling, L.S., Barnett, K., Mitchell, C.E., 2012. Pangloss revisited: a critique of the dilution effect and the biodiversity-buffers-disease paradigm. Parasitology 139 (7), 847.

Ruiz-Fons, F., Fernández-de-Mera, I.G., Acevedo, P., Höfle, U., Vicente, J., de la Fuente, J., Gortazár, C., 2006. Ixodid ticks parasitizing Iberian red deer (*Cervus elaphus hispanicus*) and European wild boar (*Sus scrofa*) from Spain: geographical and temporal distribution. Vet. Parasitol. 140 (1), 133–142.

Rosà, R., Pugliese, A., Norman, R., Hudson, P.J., 2003. Thresholds for disease persistence in models for tick-borne infections including non-viraemic transmission, extended feeding and tick aggregation. J. Theor. Biol. 224 (3), 359–376.

Rosenzweig, Michael.L., 1995. Species Diversity in Space and Time. Cambridge University Press, Cambridge.

Rudolph, D., Knülle, W., 1974. Site and mechanism of water vapour uptake from the atmosphere in ixodid ticks. Nature 249, 84–85.

Sahney, S., Benton, M.J., Falcon-Lang, H.J., 2010. Rainforest collapse triggered Pennsylvanian tetrapod diversification in Euramerica. Geology 38 (12), 1079–1082.

Schwan, T.G., Piesman, J., 2000. Temporal changes in outer surface proteins A and C of the Lyme disease-associated spirochete, *Borrelia burgdorferi*, during the chain of infection in ticks and mice. J. Clin. Microbiol. 38, 382–388.

Schwan, T.G., Piesman, J., Golde, W.T., Dolan, M.C., Rosa, P.A., 1995. Induction of an outer surface protein on *Borrelia burgdorferi* during tick feeding. Proc. Natl. Acad. Sci. U.S.A. 92, 2909–2913.

Shepherd, A.J., Swanepoel, R., Leman, P.A., Shepherd, S.P., 1987. Field and laboratory investigation of Crimean-Congo haemorrhagic fever virus (Nairovirus, family Bunyaviridae) infection in birds. Trans. R. Soc. Trop. Med. Hyg. 81, 1004–1007.

Simon, M., Johansson, C., Mirazimi, A., 2009. Crimean-Congo hemorrhagic fever virus entry and replication is clathrin-, pH-and cholesterol-dependent. J. Gen. Virol. 90 (1), 210–215.

Skarpaas, T., Golovljova, I., Vene, S., Ljøstad, U., Sjursen, H., Plyusnin, A., Lundkvist, Å., 2006. Tick-borne encephalitis virus, Norway and Denmark. Emerg. Infect. Dis. 12, 1136–1138.

Stefanoff, P., Rosinska, M., Samuels, S., White, D.J., Morse, D.L., Randolph, S.E., 2012. A national case-control study identifies human socio-economic status and activities as risk factors for tick-borne encephalitis in poland. PloS one 7 (9), e45511.

Stjernberg, L., Holmkvist, K., Berglund, J., 2008. A newly detected tick-borne encephalitis (TBE) focus in south-east Sweden: a follow-up study of TBE virus (TBEV) seroprevalence. Scand. J. Infect. Dis. 40 (1), 4–10.

Storch, D., Konvicka, M., Benes, J., Martinková, J., Gaston, K.J., 2003. Distribution patterns in butterflies and birds of the Czech Republic: separating effects of habitat and geographical position. J. Biogeogr. 30, 1195–1205.

Sumilo, D., Bormane, A., Asokliene, L., Lucenko, I., Vasilenko, V., Randolph, S., 2006. Tick-borne encephalitis in the Baltic States: identifying risk factors in space and time. Int. J. Med. Microbiol. 296, 76–79.

Sumilo, D., Asokliene, L., Bormane, A., Vasilenko, V., Golovljova, I., Randolph, S.E., 2007. Climate change cannot explain the upsurge of tick-borne encephalitis in the Baltics. PLoS One 2 (6), e500.

Sumilo, D., Bormane, A., Asokliene, L., Vasilenko, V., Golovljova, I., Avsic-Zupanc, T., Randolph, S.E., 2008. Socio-economic factors in the differential upsurge of tick-borne encephalitis in central and Eastern Europe. Rev. Med. Virol. 18 (2), 81–95.

Süss, J., 2008. Tick-borne encephalitis in Europe and beyond – the epidemiological situation as of 2007. Euro Surveil. 13, 1–8.

Süss, J., 2011. Tick-borne encephalitis 2010: epidemiology, risk areas, and virus strains in Europa and Asia – an overview. Ticks Tick Borne Dis. 2, 2–15.

Tälleklint-Eisen, L., Lane, R.S., 2000. Spatial and temporal variation in the density of *Ixodes pacificus* (Acari: Ixodidae) nymphs. Environ. Entomol. 29, 272–280.

Tekin, S., Bursali, A., Mutluay, N., Keskin, A., Dundar, E., 2012. Crimean-Congo hemorrhagic fever virus in various ixodid tick species from a highly endemic area. Vet. Parasitol. 186 (3), 546–552.

Telford, S.R., Dawson, J.E., Katavolos, P., Warner, C.K., Kolbert, C.P., Persing, D.H., 1996. Perpetuation of the agent of human granulocytic ehrlichiosis in a deer tick-rodent cycle. Proc. Natl. Acad. Sci. 93 (12), 6209–6214.

Telmadarraiy, Z., Ghiasi, S.M., Moradi, M., Vatandoost, H., Eshraghian, M.R., Faghihi, F., Chinikar, S., 2010. A survey of Crimean-Congo haemorrhagic fever in livestock and ticks in Ardabil Province, Iran during 2004–2005. Scand. J. Infect. Dis. 42 (2), 137–141.

Uyar, Y., Christova, I., Papa, A., 2011. Current situation of Crimean Congo hemorrhagic fever (CCHF) in Anatolia and Balkan Peninsula. Turk Hijyen ve Deneysel Biyoloji Dergisi 68, 139–151.

Vanwambeke, S.O., Sumilo, D., Bormane, A., Lambin, E.F., Randolph, S.E., 2010. Landscape predictors of tick-borne encephalitis in Latvia: land cover, land use, and land ownership. Vector Borne Zoonotic Dis. 10 (5), 497–506.

Vescio, F.M., Busani, L., Mughini-Gras, L., Khoury, C., Avellis, L., Taseva, E., Christova, I., 2012. Environmental correlates of Crimean-congo haemorrhagic fever incidence in Bulgaria. BMC Public Health 12 (1), 1116.

Vorou, R.M., 2009. Crimean-Congo hemorrhagic fever in southeastern Europe. Int. J. Infect. Dis. 13, 659–662.

Walsh, M.G., 2013. The relevance of forest fragmentation on the incidence of human babesiosis: investigating the landscape epidemiology of an emerging tick-borne disease. Vector Borne Zoonotic Dis. 13 (4), 250–255.

Watts, D., Ksiazek, T., Linthicum, K., Hoogstraal, H., 1988. Crimean Congo hemorrhagic fever. The Arboviruses: Epidemiology and Ecology, vol. 2. TPM, Boca Raton, FL, pp. 177–222.

Williams, J.W., Jackson, S.T., 2007. Novel climates, no-analog communities, and ecological surprises. Front. Ecol. Environ. 5 (9), 475–482.

Wilson, M.L., González, J.P., Le Guenno, B., Cornet, J.P., Guillaud, M., Calvo, M.A., Digoutte, J.P., Camicas, J.L., 1990. Epidemiology of Crimean-Congo hemorrhagic fever in Senegal: temporal and spatial patterns. Arch. Virol. 1, 323–340.

Wilson, M., Gonzalez, J., Cornet, J., Camicas, J., 1991. Transmission of Crimean-Congo haemorrhagic fever virus from experimentally infected sheep to *Hyalomma truncatum* ticks. Res. Virol. 142, 395–404.

Wood, C.L., Lafferty, K.D., 2012. Biodiversity and disease a synthesis of ecological perspectives on Lyme disease transmission. Trends Ecol. Evol. 28, 239–247.

Yesilbag, K., Aydin, L., Dincer, E., Alpay, G., Girisgin, A.O., Tuncer, P., Ozkul, A., 2012. Tick survey and detection of Crimean-Congo hemorrhagic fever virus in tick species from a non-endemic area, South Marmara region, Turkey. Exp. Appl. Acarol., 1–9.

Zeller, H.G., Cornet, J.P., Camicas, J.L., 1994a. Experimental transmission of Crimean-Congo hemorrhagic fever virus by West African wild ground-feeding birds to *Hyalomma marginatum* rufipes ticks. Am. J. Trop. Med. Hyg. 50, 676–681.

Zeller, H.G., Cornet, J.P., Camicas, J.L., 1994b. Crimean-Congo haemorrhagic fever virus infection in birds: field investigations in Senegal. Res. Virol. 145, 105–109.

Zeller, H.G., Cornet, J.P., Diop, A., Camicas, J.L., 1997. Crimean-Congo hemorrhagic fever in ticks (Acari: Ixodidae) and ruminants: field observations of an epizootic in Bandia, Senegal (1989–1992). J. Med. Entomol. 34, 511–516.

Zeman, P., Beneš, C., 2004. A tick-borne encephalitis ceiling in Central Europe has moved upwards during the last 30 years: possible impact of global warming? Int. J. Med. Microbiol. 293 (Suppl.), 48–54.

Glossary

Carrier host: A carrier host is a vertebrate that is infected by a pathogen, as detected by serologic testing or by finding the nucleic acids of the pathogen in the tissues or blood of the host. This status does not automatically mean that the vertebrate will be able to transmit the infection to feeding ticks. Hosts that transmit infection are designated "reservoirs."

Carrier tick: A tick may be a carrier of a pathogen (e.g. nucleic acid of the pathogen may be detected in its tissues), but this status does not necessarily confer the ability to transmit the pathogen to a vertebrate. Ticks that transmit infection are designated "vectors."

Co-feeding infection: Co-feeding is a means of transmission of a pathogen among ticks feeding simultaneously and in close proximity on the same host. It requires co-feeding by at least two tick stages in synchrony in their seasonal activity to produce a "backward transmission" from e.g. infected nymphs to uninfected larvae. Co-feeding transmission is of special interest at least for the amplification of foci of tick-borne encephalitis virus (TBEV), and it does not require that the host is viremic. It is also called "non-systemic" transmission.

Ecotone: In ecology, the ecotone is the "frontier" between two categories of vegetation. In studies of ticks and tick-borne pathogens, the ecotone between forest and grassland is of particular importance, because small mammals and birds concentrate there, looking for shelter and food. Because these vertebrates are among the most important reservoirs for pathogens and ticks, such an ecotone tends to concentrate hazardous numbers of infected ticks.

Emergence or re-emergence (of a focus of tick-transmitted pathogens): A focus is said to be emerging when it is new, i.e. no animal or human infections were noticed before its appearance. A focus is re-emerging when, after a period of epidemiological silence, new clinical cases or animal infections are detected associated with the site. The definition implies that active surveys are carried out in the site to examine the number of clinical cases per time unit.

Environmental factors: In ecology, these are sets of variables (like temperature or precipitation) that affect the fitness of an organism in its habitat. The environmental factors are alternatively called the abiotic niche, because they explicitly disregard the biotic interactions of the organism with other species or populations. However, interspecific interactions among animal hosts and ticks may structure communities, and such effects are probably particularly frequent and more important than the environmental factors in pathogens transmitted by ticks.

Feeding cavity: The lesion in the host at which ticks feed. Having cut through the epidermis and into the layers of the dermis, the tick begins feeding and salivating into the expanding hematoma below the mouthparts. The feeding lesion expands as a result of anticoagulant and antihemostatic activity of the salivary compounds injected into the wound.

Habitat fragmentation (patchiness): Discontinuities (fragmentation) in the preferred environment for an organism, producing fragmentation of the populations. It may be a natural process, but can also be produced by human actions, such as the conversion of wild areas to farmland, road building or the expansion of towns. In the epidemiology of tick-transmitted pathogens, habitat fragmentation is important, because it may increase the circulation of pathogens in "closed" populations of reservoirs and ticks, fuelling a self-amplified loop, in which the prevalence rate of the pathogen in ticks may be high.

Host infectivity: The efficiency with which the host transmits an infection to ticks feeding on it.

Mass-action laws: A concept commonly used in chemistry, stating that the rate of a chemical reaction is directly proportional to the molecular concentrations of the reacting substances. The term has been applied to demographic processes, meaning that the densities of interplaying partners, such as hosts and ticks, have an important role in determining the probability of contact.

Nidicolous (endophilous) behavior: A way of life registered for some species of ticks, in which they stay in a protected shelter, such as a burrow or a nest that has been created by a small vertebrate host. Ticks that observe such nidicolous behavior are less stressed by environmental conditions that regulate mortality rates. These species are relatively independent of external conditions that could potentially cause a high mortality of the population, i.e. low water availability or cold temperatures. The opposite term is non-nidicolous (exophilous), referring to species of ticks that stand and quest for a host in the layer of vegetation above the ground.

Phenology: The study of periodic plant and animal life cycle events and how they are influenced by seasonal and inter-annual variations in climate, as well as habitat factors. Phenology has been principally concerned with the dates of first occurrence of biological events in their annual cycle. Examples for ticks include the date of egg hatching, the recruitment of active stages or the time when adults accumulate on hosts. In the scientific literature on ticks, the term is used more generally to indicate the time frame for any seasonal biological phenomena, including the dates of last activity before becoming dormant (e.g., ticks may be active from April to September).

Photoperiod: The number of hours of light and darkness in a day. It is known that the variable photoperiod in regions far from the equator is responsible for the regulation of the tick life cycle, and that the photoperiod determines the development and questing of ticks more than the temperature. It seems that photoperiod acts as a regulatory mechanism that allows a large plasticity in the life cycle of ticks, but many details of that regulation are still unknown.

Reservoir capacity (of hosts): The absolute contribution made by a particular reservoir host species to the natural prevalence of infection by a given pathogen within a certain site. Such capacity may be different at different sites, because of the faunal composition of the community of hosts, and their relative contribution to the epidemiological events in the transmission of the pathogen.

Reservoir host: A vertebrate that is able to become infected by a pathogen after a tick bite, and is able to transmit the pathogen to naïve feeding ticks. The homologous term for ticks is "vector."

Saturation deficit: An index of humidity typically characterized by the difference between the saturation vapour pressure and the actual vapour pressure in the air. The index has the particular utility of being proportional to the evaporation capability of the air. It is a term of general use in arthropods because has a direct relationship with their water losses, as an expression of their tolerance to desiccation.

Synchronous development: This term refers to the development of different cohorts of ticks. All ticks that fed in late summer and early autumn will interrupt the molting process in the winter, because low temperatures "restarts" the conditions of molting. All ticks in different cohorts have their molts synchronized, so that only one cohort of molting ticks exists. This is why there is a synchronous development, and almost all ticks begin to quest simultaneously in the next spring.

Trans-stadial passage: A process in which a pathogen is passed into the next active stage of a tick, alternatively called horizontal passage. When a tick feeds on an infected reservoir and acquires the pathogen, it disseminates in the tick tissues. After feeding, ticks must moult, and, in some cases, the pathogen will be passed to the next stage in the life cycle, after the molt. This condition is required for a tick to be considered a vector of a pathogen. Trans-stadial passage cannot be called "transmission," because there is no transmission to a different individual, but to the same one after feeding and molt.

Trans-ovarial passage: A process in which a pathogen is passed into the eggs and the hatching larvae after a female tick has fed upon an infected host, alternatively called vertical passage. After feeding, the engorged female lay thousands of eggs, and, in some cases, the pathogen will be passed to them. Each pathogen has specific rates of trans-ovarial passage and they may deeply affect the dynamics of tick-transmitted pathogens in the landscape.

Vector: A tick (or other organism) that becomes infected by a pathogen after feeding on a reservoir, is able to pass the pathogen to the next stage of its life cycle after molting, and is able to transmit the pathogen while feeding on a new host. The homologous term for vertebrates is "reservoir."