THROUGH A GLASS, DARKLY:
THE GLOBAL INCIDENCE OF TICK-BORNE DISEASES

Christopher D. Paddock, M.D., M.P.H.T.M., and Sam R. Telford III, Sc.D.

Draft background paper written to stimulate discussion
for the Institute of Medicine Committee on Lyme Disease and Other Tick-Borne
Diseases: The State of the Science
workshop entitled:
"Critical Needs and Gaps in Understanding Prevention, Amelioration, and Resolution of
Lyme and Other Tick-Borne Diseases: The Short-Term and Long-Term Outcomes"
Washington, D. C., October 11-12, 2010

The responsibility for the content of this article rests with the author(s) and does not
necessarily represent the views of the Institute of Medicine or its committees and
convening bodies.
INTRODUCTION

Several events that occurred during the final decades of the 20th Century, and at the cusp of the 21st Century, suggest that increases in the scope and magnitude of tick-borne infections have occurred worldwide. These include recent national and regional epidemics of historically recognized diseases, including tick-borne encephalitis (TBE) in Central and Eastern Europe, Kyasanur forest disease (KFD) in Karnataka state in India, Crimean-Congo hemorrhagic fever (CCHF) in northern Turkey and the southwestern regions of the Russian Federation, and Rocky Mountain spotted fever (RMSF) in Arizona and Baja California (Randolph, 2008; Pattnaik, 2006; Maltezou et al., 2010; McQuiston et al., 2010; Bustamente Moreno and Pon Méndez, 2010a ). Globally, the recognized number of distinct and epidemiologically important diseases transmitted by ticks has increased considerably during the last 30 years. By example, > 10 newly recognized spotted fever rickettsioses have been identified since 1984 (Raoult et al., 1996; Parola et al., 2005; Paddock et al 2008; Shapiro et al., 2010). In the United States, only 2 tickborne diseases, RMSF and tularemia, were nationally notifiable in 1990; by 1998, this list included 3 newly recognized infections: Lyme disease, human granulocytic ehrlichiosis [anaplasmosis] (Anaplasma phagocytophilum infection), and human monocytic ehrlichiosis Ehrlichia chaffeensis infection), each of which has increased steadily in average annual incidence. Lyme disease is now the most commonly reported vector-borne illness in the United States, with the number of reported cases increasing 101% (from 9,908 to 19,931) during 1992-2006. (Bacon et al., 2008). During 2000-2008, the annual reported incidence of RMSF in the United States also increased dramatically, from 1.7 to 9.4 cases per million persons (Figure 1), representing the steepest rise to the highest rate ever recorded (Openshaw et al., 2010). From 2000-2007, the incidence of infections caused by A. phagocytophilum and E. chaffeensis also increased linearly,
from 0.80 to 3.0, and 1.4 to 3.0, cases per million population, respectively (Dahlgren et al, in press).

Against this background of rapidly expanding pathogen recognition and escalating incidence have been concerns about the accuracy of case counts that form the basis for these statistics (Mantke et al., 2008; Raoult and Parola, 2008; Paddock, 2009). Many of these agents were catapulted into the realm of human recognition by extraordinary advances in molecular technology; however, epidemiologic tools for capturing cases and calculating incidence have not undergone similar transformative changes and paradoxically, the discoveries of new pathogens made possible by contemporary diagnostic methods have cast suspicion on certain aspects of the distribution, frequency, and clinical heterogeneity, of some older, historically recognized, tick-borne diseases. In essence, the pace of pathogen discovery has eclipsed fundamental epidemiologic knowledge of many of the diseases caused these agents.

Incidence rates of tick-borne infections pale in comparison with those of many other arthropod-borne diseases, including malaria, dengue, Chagas’ disease, onchocerciasis, and leishmaniasis. Only Lyme disease, with tens of thousands of new cases each year, distributed across several continents, can be considered as prevalent across a wide distribution (Table 1); however, Lyme disease is still less common, by an order of magnitude, than leishmaniasis, represented by 1 million new cases a year among a population at risk of 350 million persons (Anonymous, 1994). Nonetheless, in some regions of the world, such as Europe, tick-borne diseases are the most widespread and medically important of all vector-borne infectious diseases (Randolph, 2010). In addition, some tick-borne diseases are associated with high case-fatality rates or long-term morbidity, and frequently generate considerable fear among the population.
who reside in areas where these pathogens are endemic; in this context, public health concerns may far exceed actual disease burden. By example, the average annual incidence of Brazilian spotted fever in São Paulo State, Brazil, during 2000-2008 ranged from 0.2 to 1.1 cases per million population, comprising only 285 total cases; however, 89 of these resulted in death, for an average case-fatality rate of 31% (www.cve.saude.sp.gov.br/htm/zoo/fm_i8503.htm) Other tick-borne diseases, including CCHF and KFD, are associated with high case-fatality rates that rival or exceed those of many of the most severe infectious diseases (Hoogstraal, 1979; Swanepoel et al., 1987; Pattnaik, 2006).

**TABLE 1** Estimated global incidence and distribution of major tick-transmitted infections.

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common (&gt;10,000 new cases each year)</td>
<td>Lyme disease – Holarctic (Bacon et al. 2008)</td>
</tr>
<tr>
<td>Common (1000-10,000 new cases each year)</td>
<td>Tick-borne encephalitis – Holarctic (<a href="http://www.isw-tbe.info/upload/medialibrary/12th_ISW-TBE_Newsletter.pdf">www.isw-tbe.info/upload/medialibrary/12th_ISW-TBE_Newsletter.pdf</a>)</td>
</tr>
<tr>
<td></td>
<td>Tick-borne relapsing fever – tropical Africa; western United States (Felsenfeld, 1971; Trape et al., 1996; Vial et al., 2006)</td>
</tr>
<tr>
<td></td>
<td>Tick-borne spotted fever group rickettioses – global (Ravery et al. 2008; Openshaw et al., 2010)</td>
</tr>
<tr>
<td></td>
<td>Ehrlichiosis and anaplasmosis – global (Demma et al., 2005b)</td>
</tr>
<tr>
<td></td>
<td>Masters’ disease – eastern, central, and south-central United States (CDC, 1990)</td>
</tr>
<tr>
<td>Moderately common (100-1,000 new cases each year)</td>
<td>Colorado tick fever and other coltivirus infections – western United States; central Europe (<a href="http://www.cdphe.state.co.us/dc/zoonosis/tick/Colorado_tick_diseases.pdf">http://www.cdphe.state.co.us/dc/zoonosis/tick/Colorado_tick_diseases.pdf</a>)</td>
</tr>
<tr>
<td></td>
<td>Babesiosis – northeastern United States; Europe (Telford et al., in press)</td>
</tr>
<tr>
<td></td>
<td>Omsk hemorrhagic fever – eastern Russia and Siberia (Lvov, 1988)</td>
</tr>
<tr>
<td></td>
<td>Tick-borne tularemia – eastern and central United States; central Europe; Russian Federation (CDC, 2002)</td>
</tr>
<tr>
<td></td>
<td>Kyasanur forest disease – Karnataka and adjacent states in India; Saudi Arabia (Dandawate et al., 1994; Pattnaik, 2006)</td>
</tr>
<tr>
<td>Rare (sporadic cases)</td>
<td>Powassan/deer tick virus – Canada; northeastern and north central United States (Ebel, 2010)</td>
</tr>
</tbody>
</table>

This discussion compares perceived and actual burden of tick-borne infections suggested by existing surveillance data, evaluates some of the strengths and limitations of current systems that measure incidence, and suggests several approaches for improving the accuracy of incidence determinations for these diseases. While tick-borne infections also pose important veterinary health problems around the world, this synopsis focuses on the occurrence of these diseases in human populations. Although this discussion also incorporates some information that is anecdotal, inferred, or derived from non-controlled circumstances, we hope that a contemporary
synthesis of all observations may serve as a guide for subsequent epidemiologic approaches to this remarkably diverse and important collection of zoonotic diseases.

**CASE COUNTS, REPORTING, AND INCIDENCE OF TICK-BORNE DISEASES**

Are the global rises in incidence reflective of true events or greater levels of reporting? Simplistically, increased reporting is indeed responsible for these trends; however, this question is somewhat circular, because incidence statistics are obtained through reported cases of disease. Incidence rates are dependent directly on the size of the population at risk during a specific interval of time and the number of identified cases of disease; however, from most of the scientific literature, it is difficult to determine whether a change in incidence reflects increased transmission, better reporting, or a change in the denominator. Case counts of the same disease may vary dramatically by the year or region because of ecologic, climatologic, or social variables or by changes in reporting practices. Ideally, surveillance systems for tick-borne diseases accurately identify rises or declines of the disease in question; however, any of a number of variables may change over time, including case definitions, confirmatory assays, or the appearance or emigration of cognizant and enthusiastic clinicians who actively search for cases and pursue confirmatory diagnostic tests.

**Incidence and Regional Context**

Incidence statistics of tick-borne infections, when interpreted flatly as national rates, characteristically lose impact and meaning. These zoonoses are influenced profoundly by a complex mixture of predictable and unpredictable factors that include landscape, climate, wildlife hosts, and tick distributions that coalesce to create regional pockets of intensified risk (Pavlovsky, 1966); in this context, incidence rates for these diseases assume far greater impact when viewed regionally. Because of marked differences in population sizes across regions, it is axiomatic that high incidence does necessarily equate to a large number of reported cases. By example, sparsely populated Cameron County, Pennsylvania, reported only 14 cases of Lyme disease during 2002-2006; however, the county’s average annual incidence rate was greater than the incidence of the more populous Windham County, Connecticut, where approximately 18 × as many cases were reported during the same interval (Bacon et al., 2008). Nantucket County in Massachusetts, reported 151 cases of Lyme disease during 1992-2006, representing only 0.061% of 248,074 total reports received by CDC during this interval; however, it ranked highest in incidence of all U.S. counties during 1992-2001, and third during 2002-2006, with rates of 361 to 755 per 100,000 population (Figure 2a). By comparison, the average annual rate of Lyme disease in the entire state of Massachusetts was 14.5 per 100,000 population during the same study period (Bacon et al., 2008).

During 1989-2000, Portugal reported the highest country-wide incidence of Mediterranean spotted fever (MSF) in the Mediterranean basin (9.8 per 100,000 persons); however, the regional incidence in this small country ranged markedly, from 3.1 per 100,000 in Lisboa and Vale do Teja, to 31 per 100,000 in the nearby region of Alentejo (de Sousa et al., 2003). During 2000-2007, 11,531 cases of RMSF were reported from 46 states and the District of Colombia; however, approximately two-thirds of these cases originated from only 5 states (Arkansas, Missouri, North Carolina, Oklahoma, and Tennessee), where the incidence ranged from 20.3 to 52.6 per million persons (Figure 2b). By comparison, the national incidence of
RMSF during the study period was 4.9 per million (Openshaw et al., 2010). These statistics are magnified further when foci of infected ticks overlap rural or undeveloped regions with relatively low population density. During 2003-2009, 88 cases of RMSF were reported from 3 Apache Indian communities in Eastern Arizona that resulted in an average annual incidence of 437 /million persons for this 5,000 square mile region, more than 62 times greater than the national average (McQuiston et al., 2010). In some circumstances, regional variation develops when cultural, racial or socioeconomic homogeneity exists among the population at risk. By example, the incidence of RMSF among American Indians has risen dramatically (Figure 3), when compared with other racial groups in the United States: during 2001-2005, the average annual incidence among American Indians was 16.8 per 1,000,000 population, compared with rates of 4.2 and 2.6 among white and black racial groups, respectively (Holman et al., 2009).

**Trends in frequency and distribution**

Dramatic shifts in numbers of reported cases of tick-borne diseases over time and space are well-recognized; indeed, such shifts are epidemiologic hallmarks of many of these infections. National or regional trends are best characterized by surveillance systems with sufficient maturity and camber to accommodate for input that might otherwise immediately confound interpretation. The incidence of TBE in the Czech Republic has exhibited at least 4 cycles of rising and declining incidence since 1971, with the greatest upsurge occurring during 1990-1995, when the incidence climbed steadily from approximately 1.7 to 7.2 /100,000 persons (Kriz et al., 2004). Similar increases were witnessed in several other eastern European countries during this same interval (Figure 4) (Šumilo et al., 2007; Randolph, 2008) and more recently, has extended across several countries of Western Europe, including Italy, Germany, and Switzerland, where the incidence of TBE in 2006 exceeded average levels for the previous decade by as much as 183% (Zimmerman, 2005; Randolph et al., 2008; Rizzoli et al., 2009).

In the United States, the annual incidence of RMSF has undergone 3 major shifts (Figure 5) since national surveillance for this disease was initiated in 1920 (Childs and Paddock, 2003; Openshaw et al., 2010). Standardized national surveillance for Lyme disease has existed since 1991. While average annual incidence rates for the United States increased steadily during 1992-2006 (Figure 1), at least 88% of all U.S. cases reported in any given year, and 229,782 (92.6%) of the 248,074 cases reported cumulatively during this interval, originated consistently from the 10 states in which Lyme disease is highly endemic (Bacon et al., 2008). During the mid-1970s through the early 1980s, increases in the case numbers of reported spotted fever group rickettsioses were documented in several countries bordering the Mediterranean Sea, including Israel, Italy, and Spain (Piras et al., 1982; Segura and Font, 1982; Otero et al., 1982; Gross et al., 1982; Mansueto et al. 1986). Approximately 30 cases of MSF were reported in Italy each year during 1962-1973; however, during the next 6 years, the number of cases identified rose dramatically, to >800 annually by 1979 (Scaffidi, 1981). In the area of the Vallés Occidental near Barcelona, Spain, the incidence of MSF, per 100,000 persons, rose from 3.28 cases in 1979 to 19.05 cases in 1984 (Espejo Arenas et al., 1986). During the mid 1980s through the early 1990s, <20 cases of Japanese spotted fever were reported annually; during the subsequent 15 years, reports climbed steadily to 129 cases in 2009 (Anonymous, 1999; Anonymous, 2006; Anonymous, 2010).
FIGURE 2 Average annual incidence, by county of residence, of reported cases of Lyme disease, 1992-2008 (a) and Rocky Mountain spotted fever, 2000-2007 (b), in the United States. (Bacon et al., 2008; Openshaw et al., 2010).
Drivers of incidence

Unfortunately, the reasons suggested for major periods of increased or diminished incidence of tick-borne diseases have, with few exceptions, been difficult to investigate and even more difficult to corroborate. These infections have circulated dynamically in nature for many thousands of years, and biological equilibria among the pathogen, tick, and vertebrate hosts parasitized by the tick or infected by the pathogen characteristically exist in the absence of humans. Nonetheless, the emergence and flux of tick-borne diseases can most often be traced to specific human activities and behaviours that create disequilibrium in these cycles and position greater numbers of persons into disrupted ecosystems. Outbreaks of tick-borne disease are often linked to ecologic and social upheavals, resulting directly from human influence, that create circumstances advantageous for large numbers of ticks and reservoir hosts. During World War II, following the occupation of Crimea by Axis forces, there was abandonment of agricultural lands and diminished hunting of European hares *Lepus europaeus* because of combat activities. When Soviet troops reoccupied the Crimean steppes in 1944, pastures and farms had become overgrown by weeds, and hares had become extremely abundant and were heavily infected with *Hyalomma* ticks. The combination of these factors is believed to have contributed to an epidemic.
of CCHF among military personnel during 1944-1945, involving especially signalmen and surveyors, who frequented brushy areas (Hoogstraal, 1979).

More recently, a careful analysis of climatic and vegetation features with georeferenced cases of CCHF in Turkey during 2003-2008 identified a recent expansion of extensively fragmented habitats in the Anatolia region as the most important factor for the CCHF epidemic in this region. This process resulted from the loss of mature forests to farming activities, and the reversion of farms to dense undergrowth and subsequent to second growth forest with the emigration of persons from rural to urban areas (Estrada-Peña, et al. 2010). In a similar manner, whole-scale clearing of primary old-growth forests by inhabitants the northeastern United States in the late 18th and early 19th Centuries, followed by the abandonment of farms during the westward expansion of the late 19th Century, and subsequent deciduous successional growth that provided ideal habitats for white-tailed deer (*Odocoileus virginianus*) and deer ticks (*Ixodes scapularis* (*dammini*)), fueled the emergence of Lyme disease in the second half of the 20th Century (Spielman et al., 1985). In Italy, changes in forest management practices during the last several decades of the 20th Century resulted in a greater percentage of coppice cover (small areas of broad-leaved forest harvested regularly for firewood) to high-stand forests, improving habitat suitability for small reservoir hosts of *Ixodes ricinus* ticks and is believed to have contributed in part to the steadily increasing incidence of TBE observed in 17 northern alpine provinces since the early 1990s (Rizzoli et al., 2009).
Environmental disturbance is a frequent trigger for outbreaks of tick-borne infection. The most extensively studied example, Lyme disease in the northeastern United States, resulted from reforestation, increased deer density, and increased development and use of forested sites by humans (Spielman et al., 1985). It is likely that the deer tick vector and its microbial guild survived in relict sites during and after glaciation and through Colonial times (Telford et al., 1993; Hoen et al., 2009). Infestations of the deer tick were first recognized from the terminal moraine areas of southern New England and Long Island as well as northwest Wisconsin; these were also the sites where the first cases of Lyme disease or babesiosis were identified in the United States (Spielman et al., 1985; Scrimenti, 1970; Western et al., 1970). In the mid-1980s, the northernmost established infestation in the Northeast was in Ipswich, Massachusetts (Lastavica et al., 1989). Within a decade, the distribution of the deer tick expanded on a north-south axis to the Bar Harbor region in Maine southward to the coastal peninsula of Delaware, Maryland, and Virginia (Rand et al., 1998). Infestation of migratory birds (Battaly et al. 1993; Ginsberg 1993) by deer tick larvae and nymphs served as the primary mode of introduction. Transport of adult ticks by deer along major waterways also contributed to a rapid spread, particularly in the Hudson River Valley (Chen et al., 2005).

Other recent examples of range expansions of medically important tick species include the establishment of *Amblyomma americanum* (a vector of *E. chaffeensis* and *Ehrlichia ewingii*) in the northeastern United States (Paddock and Yabsley, 2007) *Amblyomma maculatum* (a vector of *Rickettsia parkeri*) throughout Arkansas (Trout et al., 2010), *I. scapularis* across the lower peninsula of Michigan (Hamer et al., 2010), and *Dermacentor reticularis* (a vector of *Rickettsia raoultii*) in western Germany and the Netherlands (Dautel et al., 2006; Nijhof et al., 2007).
Conversely, loss of host species or habitat may reduce the abundance of a historically dominant tick species. From a tick surveillance program in Ohio during 1984-1989, *D. variabilis* ticks accounted for 13,351 (97%) of 13,764 ticks submitted to the Vector-Borne Disease Unit of the Ohio Department of Health by the general public, physicians, and local health departments from every county in the state; fewer than 1% of the ticks submitted during this period were *A. americanum* (Pretzman et al., 1990). However, during 1994-1999, only 3,841 (62%) of 6,234 of the submitted ticks were *D. variabilis*, with 1351 (22%) now comprising *A. americanum* (Scott Odee, Richard Gary, pers. comm.). From 1978-1981, 1,342 adult *D. variabilis* ticks were collected in Panola Mountain State Park, Georgia, during a mark-and-release survey of ticks (Newhouse, 1983); however, *D. variabilis* was only rarely encountered when extensive tick surveys were conducted at this same park approximately 20 years later (M. Levin, pers comm.). The causes of these apparent shifts remain speculative; however, a hypothesis to explore is the effect of periodic scarcity of keystone hosts for *D. variabilis*, i.e., skunks and raccoons, from repeated rabies epizootics in certain areas of the eastern United States (Anthony et al., 1990; Guerra et al., 2003).

### Changes in Vertebrate Host Abundance and Distribution

The anthropogenic nature of tick-borne infections is considerable and sustained human activities that deplete or amplify the vertebrate host populations can manifest as surges of disease incidence in human populations. In Brazil, the capybara *Hydrochoerus hydrochaeris* is an important host species to the tick *Amblyomma cajennense*, a vector of RMSF, and an effective amplifying host for *R. rickettsii* (Souza et al., 2009). The resurgence of RMSF in many areas of São Paulo State in Brazil during 1998-2007 coincides with explosive increases in the numbers of capybara, and a broadening distribution of these rodents into urban areas of this region (Verdade and Ferraz, 2006). Collectively, these data suggest that dramatic increases in the numbers of RMSF in São Paulo State (www.cve.saude.sp.gov.br/htm/zoo/fm_i8503.htm) and other areas of southeastern Brazil may be linked closely to a rapidly expanding population of a tick and pathogen host species that is well adapted to anthropogenic habitats (Labruna et al., 2004; Angerami et al., 2006).

Several arguments document the role of white-tailed deer in the emergence and expansion of Lyme disease, babesiosis, ehrlichiosis, and anaplasmosis (Piesman et al., 1979; Spielman et al., 1993; Paddock and Yabsley, 2007). These 4 diseases were identified and characterized during the last 3 decades of the 20th century, following a period of near-exponential growth of white-tailed deer populations in multiple regions of the eastern United States. At the end of the 19th Century, following several decades of overhunting and habitat loss, an estimated 300,000-500,000 deer existed in the United States. Intensive conservation efforts, coupled with expansive environmental changes that inadvertently provided ideal habitats for these animals to proliferate, caused an eruptive increase of the numbers of deer to approximately 18 million animals by 1992. Because these animals serve as keystone hosts for deer ticks and *A. americanum*, the extraordinary increase in range and numbers of white-tailed deer also contributed to increases in these vector tick populations. Because *O. virginianus* is also an important reservoir host for *E. chaffeensis* and *E. ewingii*, this remarkable increase in numbers also expanded considerably the reservoir pool of these pathogens (Paddock and Yabsley, 2007). In a similar manner, roe deer (*Capreolus capreolus*) were nearly extirpated from the Italian Alps by the end of World War II; however, changes in wildlife practices during the last 50 years enabled a dramatic rebound of this species, by as much as 2000% in some provinces. Because
rode deer are also considered crucial in maintaining and amplifying *I. ricinus* tick populations, an upsurge in deer density in northern Italy is likely to have contributed, in part, to the rapid and steady rise in TBE incidence witnessed in this same region since the early 1990s (Rizzoli et al., 2009).

Mediterranean spotted fever all but disappeared from the Côte Varoise of France during 1952-1966, a period that closely approximated the disappearance wild rabbits (*Oryctolagus cuniculus*) following an epizootic of myxomatosis along the Mediterranean coast. In 1967, a dramatic resurgence of MSF in the region occurred simultaneously with the recovery of the wild rabbit population, suggesting to some investigators that these two events were linked ecologically and epidemiologically (Le Gac et al., 1969). Disequilibrium among domesticated animals may create drastic changes as well. More than 90 cases of RMSF, including 11 deaths, have been reported from several small communities in the White Mountain area of eastern Arizona since 2003. This outbreak appears to be linked directly to enormous numbers of *R. rickettsii*-infected *R. sanguineus* ticks in the peridomestic environment that resulted from unchecked populations of stray and free-ranging dogs in the community (Demma et al., 2005; Nicholson et al., 2006). During the 1940s, investigators in Mexico reported a similar occurrence in states of Sonora, Coahuila, Durango, Nuevo León, and San Luis Potosí (Bustamente and Varela, 1947).

**Climate Change**

Direct effects of climate change on the incidence of tick-borne infections remain largely speculative; (Šumilo et al., 2007; Rizzoli et al. 2009; Randolph, 2009a; Randolph, 2010; Randolph et al., 2008). Many transmission models have been developed, but the lacuna in virtually all of these systems is a quantitative assessment of the “zoonotic bridge”, i.e, biological events that introduce the pathogen from the natural enzootic cycle into the realm of human health (Spielman and Rossignol, 1984). Risk factors for human exposure to vectors, and human-associated factors that modify this risk, including activity patterns and the use of personal protection, remain poorly studied. In addition, incidence data of sufficient duration and at the appropriate temporal and spatial scales are often not available to validate existing quantitative models. Accordingly, if we cannot accurately predict incidence for a site over a short interval of time, despite readily measured surveillance variables, then any long-term prediction for the results of climate change remain conjectural. Nonetheless, climate change has been implicated frequently as an important driver of incidence. The spread of tick-borne borreliosis in West Africa is possibly linked to a sub-Saharan drought that allowed the tick vector *Alectorobius sonrai*, to colonize new savannah areas (Trape et al., 1996). It has been suggested that warmer weather increases the frequency with which *R. sanguineus* will bite humans and thereby transmit its associated pathogens (Parola et al., 2008).

Of the tick-borne diseases, TBE perhaps has the best incidence data across a range of scales, as well as ecological data, that permit detailed examination for causality. For several years, rising incidence of TBE throughout central Europe was attributed by many investigators to climate change (http://www.ecologyandsociety.org/vol2/iss1/art5/) During the mid-1980s, the incidence of TBE in Sweden increased from 2 to 5 per 100,000 persons, and two opposing factors confounded epidemiologic analyses: an increase in roe deer density, to suggest a greater abundance of *I. ricinus* ticks and increased transmission, and the introduction of a TBE vaccine, suggesting greatly diminished risk. Even with confounding, a multiple regression analysis of
meteorological data and TBE incidence suggested that a milder winter in the previous year, concomitant with 2 consecutive mild spring and fall seasons, predicted increased incidence.

However, climate change alone does not adequately explain the remarkably rapid increase in the incidence of TBE across much of Europe during the last few decades, particularly in the Baltic States (Figure 4); the factors that influence changes in TBE transmission, and ultimately human risk, appear to be more numerous and complex. What is known is that the risk of TBE in humans is dependent on the frequency of exposure to bites by infected ticks, which is dependent on human behaviour and on various biotic and abiotic factors, including climate (Rizzoli et al., 2009). Starting in 1989, mean springtime temperatures increased across the Baltics; however, the change in TBE incidence among these counties was spatiotemporally heterogeneous and inconsistent with regional weather phenomena (Sumilo et al., 2007).

Simultaneously, a decline of collective farming in the post-communism Baltic States conceivably induced successional growth that promoted landscape changes, altering the fauna associated with *I. ricinus* ticks. In addition, berry picking, mushroom gathering, and other socioeconomically related food-seeking activities placing individuals in more frequent contact with tick-infested habitats are believed to have increased during this same period, as a result of economic changes associated with the fall of the Soviet Union. In this context, short-term climate changes that provided optimal growing conditions for mushrooms and berries in Baltic forests may indeed have been a driver for risk, but only in direct association with human behaviors that resulted in increased exposure to tick-infested habitats (Figure 6) (Randolph, 2008; Randolph et al., 2010).

**FIGURE 6** Hypothetical explanation for the usurge in cases of tick-borne encephalitis in Estonia, Latvia, and Lithuania, following the end of Soviet rule (Šumilo et al., 2007)
Changes in Funding and Scientific Interest

Scientific, medical, or veterinary interest in a particular pathogen, or changes in the epidemiologic programs or organizational frameworks used to survey for a particular disease, may have enormous impact on the recorded incidence. By example, only 27 cases of Powassan encephalitis were reported in North America during the 3 decades after its discovery in 1958; however, the introduction of West Nile virus to the continent in the late 1990s stimulated enhanced surveillance for arthropod-borne encephalitis by state and local health departments, and is believed to be the major factor in the recognition of 20 U.S. cases of this disease during 1999-2009, including identifications from 4 northeastern and upper Midwestern states that had never previously reported the disease (Hinten et al., 2008; Hoang Johnson et al., 2010).

Prior to the early 1980s, research in tick-borne infections focused largely on RMSF, TBE, and diseases associated directly with animal health, such as babesiosis and theileriosis. The emergence of Lyme disease in the northeastern United States during the late 1970s, particularly at sites where an affluent population lived or vacationed, stimulated a renaissance in tick biology and ecology that was driven, in part, by increased availability of state and federal funds for Lyme disease research. A single individual with interest in a specific disease, particularly one that is otherwise infrequently diagnosed and seldom reported, can have tremendous impact on the incidence of that disease. By example, no cases of MSF from Algeria were documented in the medical literature until 1clinician identified 93 cases during a 4-month interval in 2004 (Mouffok et al., 2006). Austria and Slovenia have among the highest reported rates of Lyme disease in Europe, with an average annual incidence of 135 and 206 per 100,000 population, respectively (Smith and Takkinen, 2006); however reporting in these countries is likely enhanced because of particularly energetic Lyme disease researchers who work in this region (Stanek and Strle, 2009). Conversely, it has been suggested that the precipitous drop in reported cases of RMSF witnessed in the United States during the 1950s might be attributable, in part, to the death in 1949 of R. R. Parker, who had been the driving force behind U.S. surveillance activities for this disease for more than 3 decades (Burgdorfer, 1975).

ACTIVE AND PASSIVE SURVEILLANCE

In the United States, surveillance data for tick-borne diseases are acquired voluntarily through separate but complementary reporting instruments that collectively comprise a national system of passive surveillance. The National Electronic Disease Surveillance System (NEDSS), (formerly the National Electronic Telecommunications System for Surveillance [NETSS]) represents the primary reporting instrument. Incidence statistics for all U.S. tick-borne diseases are calculated from electronically reported data; however, these systems acquire relatively limited supplemental information, so that detailed clinical data must be gathered by using other collection instruments, including an extended NEDSS record for Lyme disease, and a standardized case report form (CRF) for RMSF, ehrlichiosis, and anaplasmosis. State or local health departments are responsible for ensuring that cases reported to CDC through NEDSS meet the case definition for these diseases, while CRF data are generally screened at CDC for accuracy and consistency. Understandably, compliance with requests to physicians and state and local health department staff to provide supplemental data when reporting these diseases has been consistently problematic. By example, only 61% of Lyme disease cases reported to CDC during 1992-2006 contained data for reported signs and symptoms (Bacon et al., 2008). During
2000-2007, the number of CRFs submitted for RMSF was approximately 68% of the 11,531 cases reported through NETSS (Openshaw et al., 2010). In addition to CRFs not being submitted, those that are often lack requested information necessary to confirm the diagnosis approved by the Council of State and territorial Epidemiologists and CDC. Indeed, only 6% of RMSF CRF cases could be classified as confirmed during 2000-2007 (Openshaw et al., 2010). The non-submission of CRFs and the incompleteness of supplementary data collection suggest that a considerable percentage of cases tick-borne disease in the United States are unavailable for detailed analyses, including analysis of risk factors that determine severity (Childs and Paddock, 2002).

Case Definitions

Establishing an accurate and specific case definition that couples well-defined clinical characteristics with specific laboratory confirmation is fundamentally important in all forms of surveillance and provides the foundation from which subsequent epidemiologic parameters are derived. The absence of standardized case definitions for tick-borne diseases that cross regional or national borders remains a crucial problem in the accumulation of broad scale incidence data for many of these infections. Despite a system of mandatory reporting for TBE in Poland since 1970, no standardized case classification for this disease existed until 2005, creating a mix of confirmed, probable, or possible cases that were defined by clinical or laboratory criteria that differed among the county’s multiple provinces. When a national working group created a uniform case definition and retrospectively evaluated data from 1999-2002, they determined that only 25% of cases reported during this interval had sufficient laboratory testing to be classified as confirmed (Stefanoff et al., 2005).

Case definitions are not immutable, and as clinical knowledge about a particular disease expands and evolves, the case definition may be remodeled to include clinical or laboratory data specific to the disease. Because so many tick-borne infections are relatively new to science and medicine, it is not surprising that case definitions and surveillance systems for several of these diseases have required years or decades of refinement (Table 2). In this context, incidence statistics, particularly early in the evolution of these systems, should be interpreted cautiously, and comparisons of data from year-to-year, or even decade-to-decade, may be misleading. While passive surveillance requires a reasonably high level of stability to maintain its effectiveness, it must also remain malleable, and responsive to new information gained about a particular disease. By example, the nationally notifiable disease category of “Rocky Mountain spotted fever” was modified in 2010 to a less specific, but more inclusive and more accurate designation of “Spotted fever rickettsiosis, including Rocky Mountain spotted fever”, to adjust to recent data identifying causes of spotted fever group rickettsioses in the United States other than \textit{R. rickettsii} (Council of State and Territorial Epidemiologists, 2009a).

<table>
<thead>
<tr>
<th>Disease (year of first case definition)</th>
<th>Year of change(s) in case definition</th>
<th>Change(s)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lyme disease (1990)</td>
<td>1996</td>
<td>Recommendation of 2-tiered approach for serologic confirmation</td>
<td>CDC 1996a</td>
</tr>
<tr>
<td></td>
<td>2008</td>
<td>Inclusion of western blot testing as a single confirmatory assay; addition of probable and suspect categories to case classification</td>
<td>CDC, 2008a</td>
</tr>
<tr>
<td>Ehrlichiosis (1996)</td>
<td>2000</td>
<td>Inclusion of <em>Ehrlichia ewingii</em> as an agent of ehrlichiosis; distinction between laboratory assays for <em>Ehrlichia chaffeensis</em> and <em>Ehrlichia phagocytophila</em> (<em>Anaplasma phagocytophilum</em>); formation of new reporting category, ehrlichiosis/anaplasmosis, human, undetermined.</td>
<td>CDC, 2000</td>
</tr>
<tr>
<td></td>
<td>2008</td>
<td>Nomenclature change from human monocytic ehrlichiosis to <em>E. chaffeensis</em> infection; from ehrlichiosis (unspecified, or other agent) to <em>E. ewingii</em> infection; from human granulocytic ehrlichiosis to <em>Anaplasma phagocytophilum</em> infection; inclusion of ELISA format as laboratory criterion for diagnosis of probable infection.</td>
<td>CSTE 2009a</td>
</tr>
<tr>
<td>Rocky Mountain spotted fever (1990)</td>
<td>1996</td>
<td>Inclusion of PCR testing for laboratory confirmation; single titer of greater than or equal to 64 defined as laboratory criterion for a probable case.</td>
<td>CDC, 1996b</td>
</tr>
<tr>
<td></td>
<td>2004</td>
<td>Inclusion of ELISA format as laboratory criterion for diagnosis of confirmed or probable case; inclusion of immunohistochemical staining of tissue specimen as confirmatory laboratory criterion; cutoff titers used to determine probable cases defined by individual laboratories; elimination of <em>Proteus</em> OX-2 and OX-19 agglutinin titers as supportive laboratory criteria for a probable case</td>
<td>CDC, 2004</td>
</tr>
<tr>
<td></td>
<td>2008</td>
<td>Confirmation by serologic testing defined as fourfold change in IgG antibody titer; single elevated IgG or IgM titer sufficient for a probable case; ELISA format sufficient only to determine probable cases; inclusion of suspect case classification.</td>
<td>CDC, 2008b</td>
</tr>
<tr>
<td></td>
<td>2010</td>
<td>Change of disease category from “Rocky Mountain spotted fever” to “Spotted fever rickettsiosis”; inclusion of an eschar as clinical evidence of disease; requirement of PCR or cell culture isolation as laboratory confirmation of Rocky Mountain spotted fever.</td>
<td>CSTE 2009b</td>
</tr>
</tbody>
</table>

A well-crafted case definition provides more robust surveillance for the recognized disease and better positions investigators to detect clinically or epidemiologically similar diseases that otherwise might be embedded in data gathered by using a non-specific case definition. Erythema migrans rashes were noted on many patients in the southern and southcentral United States during the late 1980s (Masters et al., 1998), and in 1989, 715 cases of ‘Lyme disease’ were reported from Georgia (CDC, 1990), placing this state among the top 7 in the country for reporting Lyme disease. In the following year, however, only 161 cases were reported from Georgia (CDC, 1991), and even fewer cases in subsequent years. The decline in reported cases reflected the adoption of the CDC surveillance case definition in 1990 by the Georgia Department of Public Health. The abundance of cases reported during 1989 most likely reflected a Lyme disease mimic, associated with bites of lone star ticks, now recognized as Masters’ disease, or southern tick-associated rash illness (Felz et al., 1999; Wormser et al. 2005).
In a similar scenario, investigators in southern Spain identified several patients with atypical 'Lyme borreliosis', who were serologically reactive with *Borrelia burgdorferi* antigens, but who lacked classical erythema migrans skin lesions and who originated from a region of the country where the recognized tick vector of Lyme borreliosis was distributed sparsely. Indeed, blood cultures subsequently revealed a relapsing fevert-Borrelia sp., genetically distinct from *B. burgdorferi* and transmitted by an entirely different tick species. In this case, discovery of a novel disease agent occurred because these patients did not meet the established case definition for Lyme borreliosis (Anda et al., 1996; Guy, 1996). Recent discoveries of rickettsioses in the United States, caused by *R. parkeri* and *Rickettsia* sp. 364D, were precipitated by reports of atypical ‘RMSF’ associated prominently with eschars, which are characteristically absent in the great majority of cases of classical RMSF (Paddock, 2008; Shapiro et al., 2010).

The efforts required to verify that reported data comply with an established case definition are considerable and are magnified further when clinical data and exposure history are uncoupled from laboratory results. Electronic laboratory reporting, used increasingly by states to expand case identification of Lyme disease, captures positive test results, but does not provide supportive information about clinical findings or exposure history. Instead, these data must be collected by public health personnel, creating added burden to surveillance endeavors that often exceeds investigative capacity (Kudish et al., 2007; CDC, 2008c). In response, the Council of State and Territorial Epidemiologists modified the national surveillance case definition for Lyme disease in 2007 to allow reporting of probable cases, i.e., those diagnosed by a health care provider and supported with laboratory evidence of infection (CDC, 2008a).

**Strengths and Limitations of Passive and Active Surveillance**

The most accurate incidence rates are obtained through active surveillance, but these apply to relatively small catchment areas defined for the investigation, and typically provide a snapshot of incidence in a specified region during a relatively short interval of time. This process allows greater control in the selection of clinical specimens and data collected, but is labor-intensive and generally requires a level of funding that is prohibitive to sustain indefinitely. Indeed, most contemporary active surveillance endeavors are supported by federal grants and have a defined period of patient enrollment that spans, at most, only a few years (Ijdo et al., 2000; Olano et al., 2003). In contrast, passive surveillance systems provide data that define endemicity and provide long-term trends over larger geographic regions; however, there is generally less control over the quality and quantity of the acquired data, and this activity requires sustained commitment and appropriate infrastructure at local, state, and national levels to collect, collate, and analyze data collected over broad intervals of time and space.

Inherent differences between these systems preclude direct comparisons of the data generated by each method. By example, prospective active surveillance for ehrlichiosis in southeast Missouri identified 29 confirmed and probable cases from 1997-1999, for a calculated average annual incidence of 3.2 cases per 100,000 population during this 3-year interval (Olano et al., 2003). By comparison, the average annual incidence of ehrlichiosis for the entire state of Missouri, determined by passive surveillance, was only 0.52 cases per 100,000 during 1997-2001 (Gardner et al., 2003), and 0.68 cases per 100,000 during 2001-2002 (Demma et al., 2005b). The nature of active and passive surveillance explains these marked differences in incidence rates. Catchment areas for active surveillance are not chosen at random; rather, these are selected typically by investigators based on passive surveillance estimates that indicate the disease exists
in relative abundance in that region (Wilfert et al., 1984; IJdo et al., 2000). In the case of the Missouri investigation, patient ascertainment was facilitated by a motivated clinician who was skilled at identifying potential cases of ehrlichiosis. Additionally, national surveillance for ehrlichiosis was initiated only in 1997, and several years of maturation may be required before passive surveillance systems reach a level of familiarity and frequent use by clinicians and epidemiologists.

Underreporting of true cases is a problem inherent to all passive surveillance systems and can be substantive: in the Marshfield Clinic Epidemiologic Research Study Area, solely 34% of Lyme disease cases were reported to the Wisconsin Department of Public Health during 1992-1998 (Naleway et al., 2002). Even for epidemiological statistics that document outcomes as important as death, there is considerable underreporting to public health authorities. From a capture-recapture study evaluating deaths caused by RMSF in the United States during 1983-1998, approximately 64% of fatal RMSF cases identified by death certificate data were not reported to state health departments or CDC (Paddock et al., 2002).

Prospective cohort studies provide the best estimates of incidence but the resources that are needed to undertake such research preclude their use over larger scales. A good example of the value of a prospective study is that of the clinical trials for SmithKline Beecham's Lymerix Lyme disease vaccine during 1994-1998. Phase II dose-ranging studies were done during 1994-1995 in coastal New England with 353 enrolled subjects. A conservative case definition was adopted, with definite Lyme disease comprising compatible clinical manifestations and laboratory confirmation. Cases of suspected symptomatic Lyme disease comprised erythema migrans without laboratory confirmation and compatible clinical manifestations without other plausible explanation. Such active case finding demonstrated an incidence of 3.4% (95% CI, 1.2-9.5) for either confirmed or suspected Lyme disease among the placebo subjects. This study cost $250,000 (Telford et al., unpublished). Starting in 1995, 10,936 subjects were enrolled in a controlled, double-blind, multicenter Phase III trial in 31 sites in 10 northeastern and middle Atlantic states from Maine to Maryland (Steere et al., 1998). In the placebo group, the incidence of Lyme disease was 1.5% (95% CI, 1.2 - 1.9) during the first year, and 2.0% (1.6 - 2.4) in the second year. Of particular interest were the percentages of asymptomatic seroconversions (16% and 14%, respectively). A study of microbiologically confirmed erythema migrans from the subjects of the Phase III demonstrated that the targetoid or bullseye appearance of erythema migrans was identified in only 9% of patients (Smith et al. 2002). This expensive ($5,000,000) trial provided our best estimates for Lyme disease incidence and provided data on the asymptomatic to symptomatic ratio, a critical statistic to help define burden of disease, as well as refine the perception of what is considered the pathognomonic sign of Lyme disease.

**Accuracy of Surveillance Data**

Underreporting is invariably cited as a limitation to surveillance activities, but over-reporting may be even more damaging to epidemiologic assessments. One of the greatest obstacles to surveillance is ensuring that the data collected represent the disease under consideration. Blended data arise when a single common diagnosis is used to identify multiple related diseases caused by distinct pathogens. This process ultimately creates epidemiological havoc by producing incorrect distributions, hospitalization rates, and case-fatality rates, based erroneously on amalgamated characteristics of several individual diseases.
Most diagnoses of tick-borne infections are diagnosed, and subsequently categorized as ‘confirmed cases’ for epidemiologic analyses, by detecting antibodies in the serum of patients in whom the disease was suspected. Unfortunately, the antibodies generated by humans to specific pathogens often react with other closely related agents that are similar antigenically, but may cause illnesses that differ considerably in disease severity and clinical outcome. Overreliance on serologic methods is also the basis for many non-confirmed cases of tick-borne diseases. It has been demonstrated repeatedly that antibody responses for many of these diseases, including ehrlichiosis and RMSF, often require 7-10 days before a diagnostic titer is detected. Most patients may appear for care during the first few days of the illness, and may never return for subsequent evaluation. From 1 study, approximately two-thirds of culture-confirmed patients infected with *E. chaffeensis* lacked diagnostic IgG titers, as measured by IFA, when they initially presented for care (Childs et al., 1999). Because, diagnostic levels of IgG and IgM antibodies are frequently absent from the serum of patients who die from RMSF, fatal cases of this disease are often not confirmed if appropriate samples are not collected for immunohistochemical, molecular or culture-based diagnostics (Paddock et al., 1999).

Diagnostically relevant levels of antibodies reactive with *R. rickettsii* have been detected in approximately 5%-10% of the U.S. population (Wilfert et al., 1985; Graf et al., 2008; Marshall et al., 2003; Taylor et al., 1985; Hilton et al., 1999). Even more troubling are the frequent descriptions of seroconversions to spotted fever group (SFG) *Rickettsia* and *Ehrlichia* spp. antigens that occur among as many as a 33% of healthy asymptomatic individuals following exposure to tick bites and tick-infected habitats. (Sanchez et al 1992; Yevich, et al., 1995; Hilton et al.,1999; McCall et al., 2001). Nonetheless, serology is used increasingly to diagnose cases of RMSF; as a result, fewer cases are confirmed and a far greater percentage of cases are considered probable (Figure 7). The impact of diagnostic inaccuracy upon epidemiologic observations may be considerable. During 2000-2007, the reported case fatality rate for RMSF in the United States was 0.5%, based on CRF denominator data comprising 7,796 cases, or approximately 1000 cases each year (Openshaw 2010). The validity of this statistic is unreasonable when considered with historical U.S. case-fatality rates of RMSF that typically approach 10%. One explanation for this estimate lies in the composition of the denominator, which is likely populated with patients with milder infections, caused by SFG *Rickettsia* species other than *Rickettsia rickettsii* (Paddock, 2009).

Under some circumstances, serological methods may produce results that divert attention from the true arthropod vector, creating a false portrait of the disease ecology. In this situation, a ‘tick-borne’ disease may in fact be something altogether different. By example, patients infected with *Rickettsia felis*, a flea-borne pathogen, generate antibodies that react with various spotted fever group *rickettsiae*. Because *R. felis* has a cosmopolitan distribution and commonly infects multiple species of wild and commensal human-biting fleas, (Reif and Macaluso, 2009), the potential for human infections is enormous. Recent studies in Kenya and Senegal revealed a prevalence of infection with *R. felis* in approximately 4% of 297 febrile patients from rural areas of these countries; only 1 patient from either series was infected with a tick-borne *Rickettsia* sp. (Socolovschi et al., 2010; Richards et al., 2010). To place these results in context, it is important to recognize that at least 7 pathogenic, tick-borne SFG *Rickettsia* species have been detected in ticks or human patients from the immense and ecologically diverse continent of Africa (Cazorla et al., 2008). If these researchers had not used molecular techniques to correctly identify *R. felis* as the causative agent, and relied only on serologic methods (as many investigators have done for >50 years), the etiology of the disease in these patients could have been ascribed erroneously to
any of multiple tick-borne SFG rickettsial pathogens endemic to this continent. Broader use of similar techniques around the world might change considerably existing notions about the ecology, epidemiology, and clinical presentations of tick-borne rickettsioses.

FIGURE 7 Reported cases of Rocky Mountain spotted fever in the United States, by case classification status, 1992-2007 (Openshaw et al., 2010).

NETWORK APPROACHES FOR DETECTING SHIFTS IN INCIDENCE AND DISEASE SEVERITY: CHALLENGES, PROSPECTS, AND NEW RUBRICS FOR SURVEILLANCE

Any form of surveillance requires sustained and coordinated efforts to provide meaningful data. As with all regional and national services, these programs require continuous funding and prospective governmental commitment, based on public health priorities defined by that state or country. Coordinated national efforts that track these diseases are notably absent in many developed countries. In Germany, an estimated 60,000 new cases of Lyme borreliosis occur each year; however, Lyme borreliosis is not a nationally notifiable disease in this country and precise incidence data do not exist (Mehnert and Krause, 2005). Many countries with active, internationally recognized research programs in rickettsioses, including Australia and France, lack formal national surveillance for tick-borne rickettsioses (Stephen Graves and Philippe Parola, pers. comms). Even in countries where national surveillance exists for one or more of these diseases, the systems are often porous or lack the discriminatory power needed to epidemiologically characterize individual infections. In Italy, tick-borne rickettsioses are lumped in the general category of “rickettsiosis”, without respect to specific disease or arthropod vector species (Ciceroni et al., 2006). In Norway, only cases of disseminated or chronic Lyme borreliosis are notifiable to the Norwegian Institute of Public Health; the majority of infections, represented by erythema migrans, are not tabulated (Nygård et al., 2005).

Not surprisingly, tick-borne diseases are seldom included as nationally notifiable conditions in developing countries with considerable and diverse infectious disease burdens. In the southern Indian state of Karnataka, approximately 400-900 cases of KFD were reported
annually during 2001-2004 (Pattnaik, 2006); however, the lack of national surveillance for this potentially lethal hemorrhagic fever has, in part, has contributed to a belief, likely erroneous, that this disease is confined to a few small districts of a single state in this vast country. This seems highly improbable, considering that the virus as been isolated from or transmitted experimentally by at least 16 species of hard and soft ticks (Boshell, 1969; Pattnaik, 2006), and strains of the flavivirus responsible for the disease have been isolated from patients as far away as Saudi Arabia (Mehla et al., 2009) suggesting that variants of KFD might be found in other parts of India or other countries.

Expanding And Unifying Epidemiologic Coverage

More countries need to adopt national surveillance for tick-borne infections, and work to better harmonize and coordinate case definitions of diseases that cross national borders. Meaningful comparisons of incidence across broad geographical expanses are compromised when a melange of independent and varied case definitions exist for the same disease. Currently there are no standardized case definitions for CCHF notification or contact tracing in European countries, despite a vector tick (*Hyalomma marginatum*) that is distributed broadly across southern and southeastern Europe, and epidemic disease occurring in neighboring parts of Turkey (Figure 8), and in several Territories and Republics of the Russian Federation (Maltezou et al., 2010). From a recent survey of 21 European countries that compared national surveillance efforts for TBE, it was determined that case definitions differed widely across these countries, and for 6 countries where the disease is endemic, there was no officially or clearly formulated case definition (Mantke et al., 2008).

The European Union Concerted Action on Lyme Borreliosis (EUCALB) was established in 1997 to provide information on all aspects of Lyme disease, obtained from peer-reviewed literature and edited by a committee of experienced researchers and clinicians. Despite the intent to provide guidance for obtaining and disseminating the highest standard of information, EUCALB has not been able to standardize surveillance across the European Union, and the compilation of European Union case definitions (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:159:0046:0090:EN:PDF) does not have an entry for Lyme borreliosis. Few European countries have made Lyme disease a compulsorily notifiable condition. Estimates of incidence for this and other tick-borne diseases in many countries are derived from laboratory-based reporting which typically lacks sufficient clinical information to integrate into a robust case definition. Accordingly, many of the same problems for Lyme disease surveillance in the United States are also seen for the European Union as a whole and for most of the member states.
Applying Species-Specific Diagnostics

Robust and predictive epidemiology is predicated on the use of sensitive and specific diagnostic assays. Currently, molecular techniques represent the most widely available standard for species-specific diagnosis. Whenever possible, culture isolation, the microbiological gold standard of diagnosis, should also be attempted to compliment molecular assays. Repeatedly, these methods have leveraged the discovery of novel tick-borne infections and clarified long-standing epidemiologic concerns regarding atypical clinical manifestations, unusual geographic distributions, or exaggerated or diminished severity of diseases that were incorrectly diagnosed. Diligent use of molecular and culture-based diagnostics during a study of 140 Portuguese
patients with MSF enabled investigators to identify specifically a strain of *R. conorii* that was more frequently associated with severe disease in this patient population (de Sousa et al, 2008). The case-fatality rate in this series, determined by using accurate and specific diagnostic assays, was 21%, more than 8 times greater than the previously recognized lethality of this disease (Parola et al., 2005). Molecular techniques were used recently to identify infections with *E. ewingii* and *E. chaffeensis* and dogs and *R. sanguineus* ticks in Cameroon (Ndip et al., 2005: Ndip et al., 2010). These findings provided impetus to search for cases of ehrlichiosis in humans; surprisingly, 12 (10%) of 118 Cameroonian patients with undifferentiated febrile illnesses in whom malaria and typhoid were excluded showed PCR evidence of infection with *E. chaffeensis* (Ndip et al., 2009).

In Missouri, investigators used molecular methods to discriminate infections caused by *E. ewingii* from those caused by *E. chaffeensis* (Buller et al., 1999). Their discovery unveiled a second, clinically and ecologically similar illness, the identity of which was previously obscured because of sufficient overlap of disease manifestations and a shared tick vector. Indeed, surveys examining the relative prevalence of *Ehrlichia* spp. in reservoir hosts and lone star ticks in the United States suggest that *E. ewingii* occurs in these species at frequencies similar to, or in some cases greater than, infection with *E. chaffeensis* (Paddock et al., 2005). However, *E. ewingii* appears to cause a milder illness, and most commonly causes disease in immunosuppressed patients. Without molecular methods, these infections would have remained submerged among those caused by *E. chaffeensis*, contributing to a falsely heterogeneous portrait of *E. chaffeensis* ehrlichiosis. More recently, an *Ehrlichia muris*-like agent, identified by molecular methods from the blood of 4 patients in the Minnesota and Wisconsin, is likely responsible for many other serologically diagnosed cases of ehrlichiosis in the upper Midwestern United States, where neither *E. chaffeensis* nor *E. ewingii* are endemic (McFadden et al., 2010).

Repeatedly, patients with antibodies reactive to multiple SFG *Rickettsia* spp. are found ultimately to be infected with unexpected agents when PCR and cell culture methods are used. In these circumstances, the diagnosis sheds light on clinical or epidemiologic characteristics not conventionally associated with the presumed pathogen, including occurrence of disease in a different geographical region, greater or lesser severity of illness, or presence or absence of prominent cutaneous manifestations. Just a few of the recent discoveries that exemplify the utility of these assays include *Rickettsia heilongjiangensis* in Japan, *R. parkeri* in the southeastern United States, *Rickettsia* sp. 364D in California, *Rickettsia massiliae* in Argentina, and *Rickettsia sibirica mongolotimonae* in southern France (Raoult et al., 1996; Paddock 2009; Shapiro et al., 2010; Ando et al., 2010; García-García et al, 2010). Each of these diagnoses provides a foundation to explain more accurately the epidemiology of the historically recognized SFG rickettsioses for which these were initially confused.

**Improved Integration of Entomologic and Veterinary Sciences**

For decades, epidemiologists have integrated surveillance of non-human sources, such as mosquitoes, birds, and domesticated animals, in the detection of arboviruses. Similar efforts must be considered with tick-borne infections. Entomologic expertise ensures correct species identification of tick vectors, defines appropriate ecologic associations, and most importantly, provides data otherwise missing that establish the zoonotic bridge and better define incidence.
Epidemiological Entomology

Robust programs in medical entomology at state and national levels are essential to predict and respond to issues relating to tick-borne infections. In 2003, investigators in Mexicali, Mexico conducted an entomologic survey to determine the prevalence of *R. sanguineus* among 94 stray and privately owned dogs in the city, and determined that 60% of these animals were infested with *R. sanguineus*, a prevalence far greater than reported in other areas of Mexico and other parts of the world (Tinoco-Gracia, et al., 2009). In retrospect, these results served as a tocsin to an epidemic of Rocky Mountain spotted fever that occurred in Mexicali and other areas of Baja California during 2009, resulting in 275 confirmed and 734 probable infections (Bustamente Moreno and Pon Méndez, 2010a). In 2009, surveys for *R. sanguineus* identified these ticks in all 14 districts of Mexicali, where 96% of the cases occurred (Sanchez et al., 2009; Bustamente Moreno and Pon Méndez, 2010b). A survey for ticks on dogs from a small community in São Paulo, Brazil in 2005, identified *R. sanguineus*-infested animals at approximately one-third of the households, including specimens infected with *R. rickettsii*. A canine serosurvey conducted in the same community one year later revealed that 70% of the sampled dogs showed high levels of antibodies reactive with *R. rickettsii*, and that human cases were also occurring (Morares-Filho et al., 2008).

Even in the absence of accurate incidence data, entomologic studies can provide objective and quantifiable data to reconcile a real or perceived public health burden. By example, a coastal Maryland community determined by questionnaire that Lyme disease afflicted more than 15% of their residents each year, creating apprehension among residents and local public health officials. Entomologic surveillance, in conjunction with a cross-sectional epidemiologic study, provided objective evidence that Lyme disease was actually rare, and disproportional to the perceived risk. In fact, the community did not know that it was plagued by an infestation of *A. americanum* ticks, that accounted for >90% of all ticks saved by residents, and the majority of ticks collected from vegetation (Armstrong et al., 2001).

Tick-borne infections may be thought of as guilds, or a group of species, not necessarily related, that utilize a common resource. The best example of a tick microbial guild may be found within deer ticks, comprising *B. burgdorferi*, *Babesia microti*, *A. phagocytophilum*, and deer tick virus (Telford et al. 1997). Globally, wherever there are related ticks from the *Ixodes persulcatus* complex, Lyme disease spirochetes, babesiae, *Anaplasma* sp., and a tick-borne encephalitis-group virus may be found. Indeed, detecting one member of the guild is cause for search for all of the others (Telford and Goethert, 2008). Because concurrent or sequential infection with more than one agent is not infrequent (Krause et al., 1996) the guild model has epidemiologic implications. Accordingly, when a patient is diagnosed with Lyme disease, evidence of babesiosis and anaplasmosis should also be sought. When Nantucket Cottage Hospital started using a clinical laboratory that automatically tested for direct molecular evidence of infection with *B. burgdorferi*, *B. microti*, and *A. phagocytophilum* of all patients with a suspected tick-borne illness, the number of confirmed cases of babesiosis and anaplasmosis immediately doubled (T. J. Lepore, pers. comm).

Natural cycles of known pathogens do not necessarily imply a zoonotic risk to humans. By example, *Ixodes dentatus* feeds primarily on rabbits, and only rarely bites humans, yet maintains a diverse guild of pathogens and potential pathogens comprising *Borrelia andersoni*, *B. microti*, a *Babesia divergens*-like parasite, *A. phagocytophilum*, *Anaplasma bovis*, and a Kemerovo-group orbivirus in northeastern U.S. sites (Telford and Spielman 1989; Goethert and...
Telford 2003 a, b, c). However, this guild has minimal epidemiological importance, even when sympatric with human-biting deer ticks, because deer ticks rarely feed on rabbits. Ticks, similar to all multicellular organisms, harbor a diverse array of microbes, and novel high-throughput DNA amplification and sequencing techniques are unveiling the complex microbiome of ticks (Benson et al., 2004; Clay et al., 2008); however, and public health relevance of an agent detected in a tick should never be assumed a priori.

Currently applied entomological risk indices include only the prevalence of infection in host-seeking ticks and the number of ticks collected in an hour (Piesman et al., 1987). However, an epidemiologically predictive risk index will require information on the species of ticks infesting humans, how frequently these attach, and the actual duration of attachment. Although *B. burgdorferi* typically infects 20% of host-seeking nymphal deer ticks in northeastern United States, the median annual incidence of Lyme disease from 9 prospective studies in the most intensely enzootic communities is only 2% (range, 0.4% - 4.0%) (Hanrahan et al., 1984; Steere et al., 1986; Lastavica et al., 1989; Alpert et al., 1992; Shapiro et al., 1992; Krause and Telford, unpublished; Wormser et al., 1998; Steere et al., 1998; Sigal et al., 1998). Fewer than 10% of all Lyme disease cases in the northeastern United States are reported during the fall or winter months when adult deer ticks are most active, even though as many as 50% - 75% of host seeking adult ticks contain spirochetes (Piesman et al., 1986). These apparent paradoxes can be answered answered by entomology: most tick-borne bacterial pathogens require a period of ‘reactivation’ before they attain infectivity (Spencer and Parker, 1923; Piesman et al., 1987; Katavolos et al., 1997). The probability of infection is directly proportional to the duration of feeding and may differ by life stage of the tick, so that 24-48 hours of attachment are generally required for *B. burgdorferi* to be transmitted by nymphal deer ticks; in contrast, adult deer ticks require approximately 3-5 days of attachment to transmit *B. burgdorferi* to a susceptible host (Telford, unpublished).

**Sentinel Species For Tick-Borne Disease**

Despite repeated successes using wildlife and domesticated animals as sentinel species for tick-borne infections, these resources remains under-utilized in formal surveillance programs around the world. Because domestic dogs are frequently parasitized by human-biting ticks, develop robust antibody titers to most agents, are closely associated with human habitation, and are easily sampled, these animals represent exceptional sentinel species for tick-borne pathogens. This technique has been used effectively to predict or corroborate the occurrence, or in some cases, relative absence, of disease burden in human populations, including spotted fever group rickettsiosis in southeastern Australia (Sexton et al., 1991), and Lyme disease and anaplasmosis in the United States (Guerra et al., 2001; Hinrichsen et al., 2001; Duncan et al., 2004; Bowman et al., 2009).

With respect to infections caused by spotted fever group rickettsiae, canine antibodies typically show greater specificity to the infecting agent than to other, antigenically related *Rickettsia* spp. (Nicholson et al., 2006; Demma et al., 2006; Piranda et al., 2008), and may provide greater accuracy than results of human antibody assessments in serologic surveys. Retrospective analysis of 329 archival canine serum specimens, collected from dogs in a community in the White Mountain region of eastern Arizona during 1996, revealed epidemiologically relevant titers of antibodies reactive with *R. rickettsii* in only 2 (0.6%). When dogs were tested 7 years later, following recognition of an RMSF epidemic in this community,
70 (72%) of 97 animals demonstrated epidemiologically relevant antibody titers, and the geometric mean titer was > 84 times higher than observed in 1996 (Demma et al., 2006). Of even greater interest, high antibody titers were also detected in 8 (57%) of 14 dogs sampled at a second community, 60 miles distant, where no cases of RMSF had been reported; however, the following year, an outbreak of RMSF occurred in the second community, involving 9 residents and causing 2 deaths. This approach was later applied to serosurvey of dogs in counties adjacent to the outbreak communities, where approximately 6% of animals demonstrated antibodies to R. rickettsii, primarily among R. sanguineus-infected dogs, suggesting future cases of human disease outside of the recognized boundaries established during the initial outbreak (McQuiston et al, 2009).

Because white-tailed deer are important hosts for several species of ticks that transmit infectious agents to humans, these animals have been used effectively in the United States as sentinels for multiple tick-borne infections, including E. chaffeensis ehrlichiosis and Lyme disease. Among the advantages cited for this species include an extensive and inclusive distribution throughout the range of these diseases, the relatively sedentary nature of deer, rates of exposure to ticks that far exceed those of human exposures, and regulated harvests in all states that facilitates collection of samples from hunter-killed animals (Yabsley et al., 2003; Gill et al., 1994).

Prospecting Other Databases

Tick-borne infections can mimic many other infectious diseases, including meningococccemia, leptospirosis, hantavirus pulmonary syndrome, dengue, and malaria. Recent investigations in Senegal and Togo suggest that tick-borne relapsing fever may be a common cause of fever in many parts of West Africa; however, the diagnosis is seldom considered, because many cases are misdiagnosed with malaria. Indeed, several studies have identified infections with Borrelia spp. in as many as 10% of febrile patients (Vial et al., 2006; Nordstrand et al., 2007).

From a 1993 study of dengue fever in Yucatan and Jalisco states of Mexico, 50 patients with a recent compatible illness had no serologic evidence of infection with dengue virus. Of these, 20 had high levels of antibody reactive to SFG rickettsiae (Zavala-V elazquez et al., 1996). Similar approach in Colombia where 158 serum samples collected from febrile patients during 2000-2004 as part of national or regional surveillance for malaria, dengue, or yellow fever evaluated for SFGR: 21% showed antibodies reactive with SFGR (Hildago et al., 2007).

Evaluations of databases comprising those patients negative for a particular tick-borne disease of interest may be especially fruitful, as many of these patients have been bitten by ticks, reside in tick-infested areas, or present during periods of peak tick activity. From a study conducted by investigators at CDC, paired serum samples collected from 3 (10%) of 29 patients for whom RMSF was suspected, but subsequently showed no serologic evidence of acute disease, were determined retrospectively to have seroconversions to Ehrlichia sp. antigens, and corroborative clinical evidence of ehrlichiosis (Fishbein et al., 1987).

Every year, spider bite statistics are collected by poison control centers across the United States; however, these accuracy of these data have been questioned by prominent arachnologists, who convincingly argue that in many states, hundreds of reports of necrotic arachnidism attributed to the brown recluse spider (Loxosceles reclusa) occur in areas where these spiders are
absent (Vetter and Furbee, 2006), including much of Georgia, Florida, and South Carolina (Vetter et al., 2004; Vetter et al. 2009). Because necrotic arachnidism is occasionally considered by physicians as a diagnosis for patients with eschar-associated rickettsioses (Paddock et al., 2008) and Lyme disease (Rosenstein and Kramer, 1987; Osteroudt et al., 2002), closer inspection of these databases could uncover many previously undiagnosed and uncounted cases of tick-borne disease. This approach could also yield interesting results in other parts of the world, including Australia and Brazil, where necrotic skin lesions are often attributed erroneously to spiders that do not exist in the reporting area (Ibister, 2004).

Extracting New Data From Existing Surveillance Systems

Increasingly, physicians and scientists are identifying specific genetic characteristics and co-morbid or infectious conditions in patients that predispose these individuals to particularly severe forms of certain tick-borne infections. These include life-threatening disease in HIV-infected patients who become co-infected with \textit{E. chaffeensis}, fulminant \textit{R. rickettsii} and \textit{R. conorii} infections in patients with glucose-6-phosphate dehydrogenase deficiency, fatal MSF in alcoholics, and increased severity of TBE in patients with a specific deletion in the chemokine receptor CCR5 (Walker et al., 1983; Raoult et al., 1986; Paddock et al., 2001; Kindberg et al., 2008; de Sousa et al., 2008). These observations have been identified in relatively small cohorts of patients who have been evaluated by small groups of clinicians who become cognizant of a specific characteristic that places these patients at increased risk for more severe infection; to identify similar characteristics among the total number of counted cases in a state or country poses a great challenge for future surveillance efforts (Childs and Paddock, 2002).

Age-specific incidence data gained from the first several years of national surveillance (Demma et al., 2005b; CDC, unpublished data) for ehrlichiosis and anaplasmosis show a striking age-related increase in frequency of these infections among older persons (Figure 9). One plausible hypothesis for this observation suggests that cholesterol dependence by \textit{E. chaffeensis} and \textit{A. phagocytophilum} may correlate with greater disease severity in older patients, because cholesterol levels typically rise with increasing age, and these bacteria lack the all of the genes necessary for the biosynthesis of lipid A (Lin and Rikihisa, 2003). A direct association between cholesterol levels and the clinical severity of other forms of gram-negative sepsis add support to this hypothesis (Ayyadurai et al., 2010); in this context, serum cholesterol levels, collected as supplemental data on CRFs, could ultimately provide important clues to the pathogenesis of these diseases.

In Silico Analytic Methods

Molecular phylogenetic tools have refined our understanding of the etiology of tick-borne infections. Advances in data analysis, made possible by tremendous computing power, should provide similar refinement of our understanding of transmission dynamics and environmental correlates of risk. Predictive models for guiding intervention and proactively studying new zoonotic sites are currently untenable. Validation of these models would require incidence data at the same scale as that for enzootic parameters; it is not axiomatic that the case counts for an entire state would be predicted by regressors, such as an entomological risk index, estimated from solely one town in that state. Although some analyses demonstrate correlations between measured tick density and Lyme disease case reports (Stafford et al., 1998; Mather et al., 1996), a priori predictions are not currently possible.
Vector-borne infections are considerably complex to model. Sir Ronald Ross initiated mathematical modeling for malaria risk in 1909, but it was not until coordinated efforts in the 1950s (MacDonald, 1957) promoted enough quantitative understanding of malaria epidemiology that the effects of interventions such as vaccination could be predicted (Molineaux, 1985). In this respect, considerably more attention needs to be directed toward studies that provide needed data for quantitative models of tick-borne diseases. These efforts could also help develop testable hypotheses on critical aspects of tick life cycles or pathogen transmission cycles. Given the difficulty of finding study sites for longitudinal ecology study of *R. rickettsii*, for example, the role of transovarial transmission in perpetuating this agent in nature could be explored by modeling; currently, the importance of transovarial transmission remains debated (Telford, 2009).

Great advances in remote sensing of environmental parameters and data analysis algorithms such as Geographic Information Systems (GIS) may allow prediction of the distribution of infection, or even incidence. However, given the extremely focal nature of transmission for most tick-borne infections, the utility of GIS would be a function of the scale of the analyses, which would depend on the availability of satellite data of a useful scale. For GIS analyses, as with mathematical models, the bridge from nature to human risk requires the filter of human behaviors; in the absence of this filter, associations of environmental variables with...
incidence data, even when available at the correct scale and duration, are less robust. In this context, GIS analyses are potentially powerful tools, whose practical utility are currently limited by our understanding of the basis for and measurement of human risk.

**SUMMARY AND PERSPECTIVE**

Tick-borne diseases are the Cinderella of vector-borne disease (VBD) systems: always beautiful, but for so long over-shadowed by the big ugly sisters of insect-borne malaria, trypanosomiasis, dengue, etc. In traditional happy-ending style, they are now emerging as the princess of VBDs, their full significance appreciated: as important in temperate as tropical regions, as much a veterinary as a medical problem to fit neatly into the 'one world, one health' maxim, and with an exquisite complexity to keep many a scientist fully occupied over a lifetime.

*S. E. Randolph, 2009b*

Predicting the future is an imprecise science; nonetheless, a clear association exists between human disturbance of natural habitats and the emergence and expansion of tick-borne diseases, and it is precisely this link that portends important increases in the scope and range of these zoonoses in the years to come. Remarkable scientific and medical discoveries during the last several decades have expanded considerably the known spectrum of tick-borne infections. Fundamental surveillance efforts for these infections, curiously, have not made similar strides. There are many practical reasons to explain the paucity of effective surveillance systems for tick-borne diseases around the world, including perceived need, long-term interest, and monetary commitments necessary to sustain these programs. These factors provide the longevity necessary for fine-tuning of case definitions and collection instruments, and ultimately, meaningful interpretations of the collected data; however, as more unique pathogens are identified, distinctions among the diseases caused by these agents may become increasingly subtle. In the end, the effort required to discover a new disease is generally far less than the subsequent endeavors required to establish and maintain long-lasting and accurate surveillance for that disease.

The measurement of incidence is important because it can be used to quantify and rank the causes of ill health so that scarce resources may be allocated. Incidence is critical to refine and validate predictive or explanatory models, which help develop new testable hypotheses or identify critical breakpoints. Changes in incidence may point to fundamental alterations of ecology or human behavior. Measuring incidence accurately, however, can be prohibitively expensive, as seen with the Lymerix Phase III trials. Indeed, surveillance will become increasingly important in the places that have the least existent infrastructure and the fewest resources to devote to establishing such programs. In Africa, scientific and medical concerns for tick-borne diseases are vastly overshadowed by other arthropod-borne infections; nonetheless, the unrecognized burden of these infections could be considerable. By example, the incidence of tick-borne relapsing fever in Senegal has been estimated at 5.1% (Trape et al., 1996), and the spread of infections with *Ehrlichia* spp. among an expanding and highly vulnerable HIV-infected cohort on this continent could have devastating consequences (Ndip et al., 2009).

Our challenge is to improve the measurement of incidence within the limits of available resources and capacities. With technological advances, global disparities in the capacity to
Global Incidence of Tick-Borne Disease

Collect this information may lessen; today, even the poorest countries are rapidly gaining access to thermal cyclers and the Internet, and the coverage of such critical technology will only increase. In the interim, our use of the currently available data—a dark glass—can be enhanced if we understand its limitations and frame our interpretations accordingly.

Acknowledgments

We thank the following individuals who generously provided data and input to this work: Marcelo Labruna (Cidade Universitária São Paulo, São Paulo, Brazil); Elba de Lemos (Instituto Oswaldo Cruz, Rio de Janeiro, Brazil); Rita de Sousa (Instituto Nacional de Saúde Dr Ricardo Jorge, Lisboa, Portugal); José Oteo (Hospital San Pedro, Logroño, Spain); Shuji Ando (National Institute of Infectious Diseases, Tokyo, Japan); Agustín Estrada-Peña (University of Zaragoza, Zaragoza, Spain); Claudia Colomba (Università di Palermo, Palermo, Italy); Philippe Parola (Université de la Méditerranée, Marseille, France); Robert Swanepoel (National Institute for Communicable Diseases, Sandringham, South Africa); Stephen Graves (Hunter Area Pathology Service, New South Wales, Australia); Scott O’Dee and Richard Gary (Zoonotic Disease Program, Ohio Department of Health), and; Scott Dahlgren and Robert Holman (Division of High Consequence Pathogens and Pathology, CDC). Finally, we are indebted to Paul Mead, and Jennifer McQuiston (Division of Vector-Borne Infectious Diseases, CDC) for their thoughtful review and invaluable comments to the manuscript. SRT is supported by NIH R01 AI 064218.

References


Estrada-Peña, A., Z. Vatansever, A. Gargili, and Ö. Ergönul. 2010. The trend towards habitat fragmentation is the key factor driving the spread of Crimean-Congo haemorrhagic fever. *Epidemiology and Infection* 138: 1194-1203.


GLOBAL INCIDENCE OF TICK-BORNE DISEASE


Global Incidence of Tick-borne Disease


GLOBAL INCIDENCE OF TICK-BORNE DISEASE


Randolph, S. E. 2010. To what extent has climate change contributed to the recent epidemiology of tick-borne diseases? Veterinary Parasitology 167: 92-94.


Randolph, S. E., on behalf of the EDEN-TBD sub-project team. 2010. Human activities predominate in determining changing incidence of tick-borne encephalitis in Europe. Eurosurveillance 15: pii=19606.


GLOBAL INCIDENCE OF TICK-BORNE DISEASE


