

A tick too close: the emerging threat of tick-borne diseases

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It's that time again - the season for hiking, bathing, grilling... and a badly needed blood meal. The mosquitoes are thrilled! We – as the blood meal – don't share their excitement, but for those of us living in temperate regions (in contrast to the tropics and subtropics), mosquitoes are – with a few exceptions (e.g. West Nile virus) - a nuisance but not much of a health threat. But don't put down your defenses! Another bloodsucker is on the prowl. In mild, moist climates, ticks are in their element and are vectors of some nasty diseases.

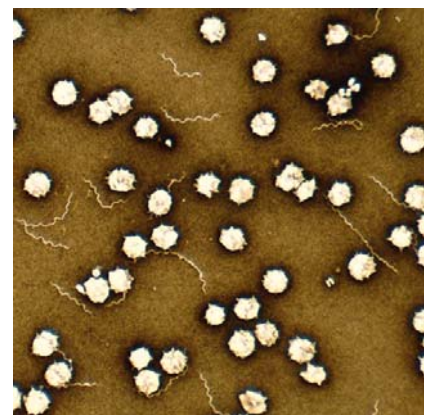
The tick lifestyle must be a successful one; they've been around in pretty much the same form for approximately 200 million years. Plenty of time to specialize. When it comes to the "attack", ticks don't get points for creativity; most species wait patiently on vegetation until somebody brushes by, at most stretching their legs out a little when they detect a potential vertebrate host (movement, carbon dioxide, heat). But once a host is found, there are real tricks to the tick trade: special mouthparts that prevent easy removal, a cement-like substance that glues the tick in place, saliva containing analgesic, anti-inflammatory and coagulation-inhibiting substances. The blood-collecting procedure is painless and often goes unnoticed.



A tick of the genus "Ixodes ricinus" © www.zecken.de

Like mosquitoes, ticks can carry and transmit a wide variety of pathogens – bacteria, viruses and parasites. Ticks don't target humans in particular, they're just looking for blood: during each stage of development – from larva to nymph to imago (adult) – ticks have to feed before they can develop to the next stage, and pretty much any vertebrate host will do. All tick-borne diseases with the exception of *Borrelia duttoni* are zoonoses, or diseases of animal origin: humans are accidental victims and dead-end hosts that do not act as reservoirs of disease.

For more than a century it has been known that ticks transmit human disease; ten years after ticks were shown to be vectors for Texas cattle fever, J.E. Dutton found in 1903 that relapsing fever is a tick-borne illness caused by *B. duttoni*. From the earliest research on tick-borne illnesses it has been clear that they are dangerous (a number of pioneering scientists – including Dutton - succumbed to the pathogens they were studying), but the perceived threat to public health remained low. This has changed over the last decades: the dramatic emergence of tick-borne diseases (e.g. Lyme borreliosis) has brought ticks into the "lymelight".



Borrelia is a spirochaete bacterium and the causative agent of relapsing fever © WellcomeTrust

Lyme disease

- **Causative agents:** pathogenic *Borrelia* species (*B. afzelii*, *B. burgdorferi*, *B. garinii*); *B. burgdorferi* isolated in 1982
- **History:** accounts from Europe as early as 1764, syndrome as recognized today identified in the mid-1970s around Lyme, Connecticut
- **Vector:** hard-bodied *Ixodes* ticks (*Ixodes persulcatus*, *I. ricinus*, *I. pacificus*, *I. scapularis*)
- **Geographic distribution:** primarily temperate regions of the Northern hemisphere
- **Incidence:** most common tick-borne disease in North America and Europe; in 2007 27,444 cases (38% more than in 2006) were reported to the CDC, which estimates that this represents ~10% of infections; in most prevalent areas, >30 individuals/100,000 infected; infection rates in Europe may be comparable
- **Symptoms:** fever, headache, fatigue, characteristic skin rash called erythema migrans; if left untreated, infection can spread to joints, the heart and the nervous system
- **Prophylaxis:** transmission of *Borrelia* usually doesn't occur until the tick has been attached for more than 24 hours; prompt tick removal can prevent infection
- **Treatment:** oral antibiotic treatment (e.g. with doxycycline, amoxicillin) for several weeks; intravenous treatment for patients with cardiac or neurological symptoms
- **Vaccine:** immunization with OspA induces antibodies that enter a biting tick and kill OspA-coated *Borrelia* there; LYMERix™ was introduced in North America in 1998 but retracted in 2002 due to problems including low sales (high vaccination costs, need for frequent boosters, exclusion of children from vaccination) and concerns over serious side effects (particularly arthritis); new vaccines are under development

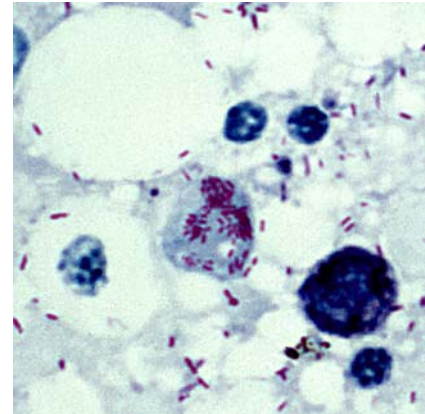
Coming out of nowhere?

The emergence of Lyme borreliosis is particularly striking; before the 1970s the disease wasn't even recognized to exist, and it now affects more people in North America and Europe than any other tick-borne disease. However, ticks are vectors for a number of other diseases that are also on the march: in Europe, cases of tick-borne encephalitis (TBE) are – despite the availability of an effective vaccine – increasing steadily. And the number of *Rickettsia* species – both those recognized to cause human disease and those with unknown pathogenicity – have grown dramatically over the past years (more in the next Perspective). The list goes on...

A portion of the growing incidence of tick-borne diseases may be attributable to heightened awareness and improved diagnosis. And improved techniques in genetics and molecular biology have enabled the differentiation of some tick-borne pathogens – most notably *Borrelia* and *Rickettsia* – into an array of new species. Nevertheless, there is no doubt that more and more humans are being exposed to disease-transmitting ticks. The main reason for the increasing impact of tick-borne diseases on human health is almost certainly changes in human activity. In the northeastern United States, humans have increasingly moved “into the woods” - tick habitat – and most exposures to disease are thought to occur near home. In contrast, it has been hypothesized that the massive rise in the incidence of TBE in Eastern Europe after the fall of Commu-

nism is due to increased use of woodlands for gathering food or recreational activities. Movement of housing into wooded suburban areas, changing leisure habits, altered agricultural habits and reforestation, travel into endemic areas...these and other human behaviors greatly influence exposure to tick-borne diseases.

Some studies indicate that climate change may also be playing a role in the increased incidence of some tick-borne diseases. For example, TBE and Lyme borreliosis are reaching new heights; corresponding with the spread of *Ixodes ricinus* to higher latitudes (e.g. Sweden) and altitudes (e.g. Czech Republic), new risk areas for the diseases have been identified. On the other hand, decreasing rainfall and increased temperatures may reduce or even eliminate tick populations in other areas. Climate also affects tick activity, and a recent study (see Gatewood et al. below) indicates that the seasonal cycle of tick feeding determines the severity of Lyme disease in a particular region; in mild climates, where ticks have a longer opportunity to feed between the nymph and adult stages, the bacterial strains cause more severe disease in humans. In areas where temperature changes are more extreme and the feeding window shorter, milder disease forms are seen. Increasing global temperatures could really mix things up.



Rickettsia rickettsii bacteria, which are the cause of Rocky Mountain spotted fever (RMSF).
© CDC/ Billie Ruth Bird

Tick-borne encephalitis (TBE)/ Frühsommer-Meningoenzephalitis (FSME)

- **Causative agent:** TBE virus (TBEV), a flavivirus; different subtypes (Western, Far-Eastern, Siberian) exist
- **History:** symptoms described as early as 1931
- **Vector:** *Ixodes ricinus* and *Ixodes persulcatus*
- **Geographic Distribution:** Western/Central Europe, Scandinavia, former USSR, Asia
- **Incidence:** incidence increasing steadily throughout Europe (except Austria); at least 10,000 hospitalized cases each year (13,000 in 2007)
- **Symptoms:** clinical cases are typically biphasic: non-specific influenza-like symptoms are followed by an asymptomatic period and then meningitis/meningoencephalitis of varying severity; mortality rate of ~1% in adults and lasting neurological sequelae in 30–80% of patients (severe in ~10%)
- **Treatment:** none
- **Vaccine:** a highly effective inactivated vaccine exists; TBE incidence has decreased dramatically in Austria, where more than 88% of the population is vaccinated, but vaccination rates are significantly lower in other countries

Future outlook

Between 1965 and 1971, the incidence of TBE in the former Soviet Union decreased by two-thirds after widespread use of DDT. Sounds like a success story! If one could ignore the devastating effects DDT had – and still has – on the environment and human health. When application of the highly toxic insecticide was discontinued, it took only two decades for TBE to return to previous levels. Since that time tick-borne diseases have become an even greater public health threat, and – with the exception of the vaccine against TBE – we haven't come up with any really good answers.

Less toxic but highly effective acaricides have been developed but are not in widespread use. DDT has left a legacy: there is strong resistance to spraying due to reservations with regard to toxicity and environmental damage. To control tick populations using minimal amounts of acaricide, researchers have developed host-targeted approaches such as devices to paint deer with acaricide or setting out treated cotton balls that mice take back to their nests. Host-targeted methods are complicated by the diversity of reservoir hosts that can exist, and reports of success are highly varied.

Research is also continuing on the vaccine front. New Lyme disease vaccines are being developed and there is also preliminary research into an “anti-tick” vaccine – one exists already for cattle – that could prevent multiple tick-borne diseases in the future. Vaccination of reservoir hosts is being tested as a means to reduce the number of infected ticks.

In the mean time, the most effective weapon against tick-borne disease may be the effective gathering of information and its distribution to the public. A recent survey of TBE in European countries showed that diagnosis and surveillance/notification of cases are not consistent among different nations, and standardized measurement of the pathogen in tick populations or vertebrate reservoirs has yet to be established. The latter is of crucial importance, as the identification of endemic foci enables the local population – citizens, medical community as well as visiting travelers – to be targeted for notification of regional risk (*e.g.* the FSME risk map published periodically by the Robert Koch Institute). Tick-borne diseases don't show any sign of going away, but – until science comes up with something better – a good flow of information may be the best medicine.

References and additional reading:

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- Extensive information about TBE – etiology, epidemiology, diagnosis, therapy...– is available in a booklet from Baxter AG (maker of the vaccine): http://www.isw-tbe.info/tbe.aspx_param_target_is_51410_and_1_is_2.v.aspx (monograph TBE)
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- (Gatewood *et al.* Climate and tick seasonality are predictors of *Borrelia burgdorferi* genotype distribution. *Appl. Environ. Microbiol.* (2009) 75: 2476-2483. DOI: 10.1128/AEM.02633-08 summary: www.opa.yale.edu/news/article.aspx?id=6615)
- Ticks and politics: The rise of tick-borne diseases in Eastern Europe. <http://www.wellcome.ac.uk/News/2003/Features/WTD004548.htm>

Table of some important tick-borne human diseases

Disease	Pathogen(s)	Main vector(s)*	Reservoir Host(s)	Geographical Distribution
Bacterial				
Lyme borreliosis	<i>Borrelia burgdorferi</i> , <i>B. afzelii</i> , <i>B. garinii</i>	<i>Ixodes persulcatus</i> , <i>I. ricinus</i> , <i>I. pacificus</i> , <i>I. scapularis</i>	Rodents, birds	North America, Europe, Asia
Tick-borne re-lapsing fever	<i>Borrelia</i> spp.	<i>Ornithodoros</i> spp.	Rodents, hares/ rabbits, humans (<i>B. duttoni</i>)	North America, Europe, Africa Asia
Spotted fevers and tick typhuses	<i>Rickettsia rickettsii</i> , <i>R. conorii</i> , <i>R. sibirica</i> , <i>R. japonica</i> , <i>R. africae</i> , <i>R. australis</i> & others	<i>Dermacentor</i> spp., <i>Amblyomma</i> spp., <i>Rhipicephalus sanguineus</i> & others	Rodents, hares/rabbits, hedgehogs, dogs	Worldwide (except Antarctica)
Q-fever	<i>Coxiella burnetii</i>	Many species of different genera	Domestic livestock	North America, Europe, Africa, Asia, Australia,
Human granulocytic anaplasmosis	<i>Anaplasma phagocytophilum</i>	<i>I. ricinus</i> , <i>I. pacificus</i> , <i>I. scapularis</i>	Rodents and other small mammals	North America, Europe
Human monocytic ehrlichiosis	<i>Ehrlichia chaffeensis</i>	<i>A. americanum</i> , <i>D. variabilis</i>	Deer, dogs	North America
Tularemia	<i>Francisella tularensis</i>	Many species of different genera	Rodents, hares/ rabbits, others	North America, Europe, Asia
Viral				
Tick-borne encephalitis	<i>Flavivirus</i>	<i>Ixodes persulcatus</i> , <i>Ixodes ricinus</i>	Rodents, insectivores	Europe, Asia
Kyasanur forest disease	<i>Flavivirus</i>	<i>Haemaphysalis spinigera</i>	Monkeys, small mammals	Indian subcontinent
Crimean-Congo hemorrhagic fever	<i>Nairovirus</i>	<i>Hyalomma marginatum</i>	Hares, hedgehogs, small mammals	Europe, Asia, Africa
Colorado tick fever	<i>Coltivirus</i>	<i>D. andersoni</i>	Rodents	Western North America
Parasitic				
Babesiosis	<i>Babesia divergens</i> , <i>B. microti</i>	<i>I. ricinus</i> , <i>I. scapularis</i>	Rodents, cattle, deer (?)	North America, Europe

*co-transmission of multiple pathogens by *Ixodes* ticks can complicate disease diagnosis and epidemiology. In addition to Lyme borreliosis and TBE, *Ixodes* spp. can transmit *Babesia divergens* and *Babesia microti* (cause babesiosis in Europe and North America, respectively), *Coxiella burnetii* (Q fever), *Anaplasma* spp. (erlichiosis; previously named *Ehrlichia* spp.), *Francisella tularensis* (tularaemia) and *Rickettsia helvetica* (perimyocarditis, sarcoidosis?)