Prevention of Tick-Borne Diseases*

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Annu. Rev. Entomol. 2008. 53:323–43

The *Annual Review of Entomology* is online at ento.annualreviews.org

This article's doi:
10.1146/annurev.ento.53.103106.093429

0066-4170/08/0107-0323$20.00

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Key Words

Lyme borreliosis, *Ixodes scapularis*, *Borrelia burgdorferi*, tick-borne encephalitis

Abstract

Tick-borne diseases are on the rise. Lyme borreliosis is prevalent throughout the Northern Hemisphere, and the same *Ixodes* tick species transmitting the etiologic agents of this disease also serve as vectors of pathogens causing human babesiosis, human granulocytic anaplasmosis, and tick-borne encephalitis. Recently, several novel agents of rickettsial diseases have been described. Despite an explosion of knowledge in the fields of tick biology, genetics, molecular biology, and immunology, transitional research leading to widely applied public health measures to combat tick-borne diseases has not been successful. Except for the vaccine against tick-borne encephalitis virus, and a brief campaign to reduce this disease in the former Soviet Union through widespread application of DDT, success stories in the fight against tick-borne diseases are lacking. Both new approaches to tick and pathogen control and novel ways of translating research findings into practical control measures are needed to prevent tick-borne diseases in the twenty-first century.

Lyme borreliosis: disease caused by infection with *Borrelia burgdorferi* sensu lato spirochetes

Tick-borne encephalitis: disease caused by a group of related flaviviruses, resulting in potentially fatal encephalitis in focal areas of Europe and Asia

OspA: outer surface protein A

INTRODUCTION

Knowledge in the field of tick-borne diseases has increased rapidly owing to advances in molecular biology, genetics, statistical modeling, and environmental assessment techniques. These advances have allowed for a more in-depth understanding of the intricate relationships between the physical environment, ticks, tick-borne pathogens, and vertebrate hosts. In eastern North America, three important pathogens causing human babesiosis (*Babesia microti*), Lyme borreliosis (*Borrelia burgdorferi*), and human granulocytic anaplasmosis (*Anaplasma phagocytophilum*) are transmitted by a single tick species: the blacklegged tick, *Ixodes scapularis*. Molecular biology tools have allowed us to understand how pathogens such as *B. burgdorferi* and *A. phagocytophilum* regulate the expression of key proteins in tick salivary glands to facilitate their transmission from the tick to the vertebrate host (89, 99, 110). A genomic linkage map for *I. scapularis* has established the groundwork for a genomics project that may someday describe the entire genome of this important tick vector (46, 116, 117). The combination of Geographic Information System and Remote Sensing technology and new statistical modeling techniques has laid the groundwork for a better understanding of associations between environmental factors and spatial patterns of distribution and density of *I. scapularis* and incidence of Lyme borreliosis (7, 22, 29, 40, 52).

Similar examples can be given from other parts of the world. *B. burgdorferi*, which originally was considered the causative agent of Lyme borreliosis across the Northern Hemisphere, was later shown to be a member of a species complex (*B. burgdorferi* sensu lato) including both human pathogens (e.g., *B. afzelii*, *B. burgdorferi*, *B. garinii*) and species that rarely or never have been associated with disease in humans (e.g., *B. bissettii*, *B. sinica*, *B. tanuki*) (6, 119). This finding had significant implications because many older studies had used pathogen-detection techniques not adequate to distinguish between the subsequently described pathogenic and nonpathogenic *B. burgdorferi* sensu lato species. *Rickettsia conorii*, the causative agent of Boutonneuse fever, was previously thought to be the sole member of the spotted fever group rickettsiae that cause human illness in the Mediterranean region of Europe and Africa. Advances in genetic techniques, however, revealed a bewildering array of new spotted fever group rickettsiae that can cause human illness in this area; these include *R. africae*, *R. aeschlimanii*, *R. helvetica*, *R. massiliae*, and *R. slovaca*, to name a few (92). In Eurasia, the complete genome of the tick-borne encephalitis virus has been sequenced, leading to an improved understanding of variation in the pathogenesis of this potentially deadly flavivirus (39, 63). Progress in the control of tick-borne diseases of livestock has been the subject of several recent reviews (35, 78, 121) and is not addressed here. The current review focuses directly on progress in and impediments to the prevention of tick-borne diseases of public health importance (**Table 1**) and discusses potential avenues for future intervention strategies, including personal protection, tick control, vaccination, and information delivery systems.

Unfortunately, the rapid progress in our understanding of key points of attack on tick-borne diseases (**Figure 1**) has translated poorly into successful prevention efforts. Tick-borne diseases of public health importance continue to increase at an alarming rate. In the United States, the number of cases of Lyme borreliosis reported to the Centers for Disease Control and Prevention (CDC) has steadily increased, with more than 23,000 reported cases for the year 2002 (**Figure 2**), despite extensive research efforts aimed at controlling this disease (44, 81). A recombinant vaccine for use in humans, directed against the outer surface protein A (OspA) of the Lyme borreliosis spirochete *B. burgdorferi*, was tested and shown to be effective (109). With the approval of this vaccine by the Food and Drug Administration

Table 1 Selected tick-borne diseases of public health importance

Disease	Causative agent(s)	Primary vector(s)	Primary geographical distribution
Viral			
Colorado tick fever	*Coltivirus*	*Dermacentor andersoni*	Western North America
Crimean-Congo hemorrhagic fever	*Nairovirus*	*Hyalomma marginatum*	Africa, Asia, Europe
Kyasanur forest disease	*Flavivirus*	*Haemaphysalis spinigera*	Indian subcontinent
Omsk hemorrhagic fever	*Flavivirus*	*Dermacentor marginatus*, *Dermacentor reticulatus*, *Ixodes persulcatus*	Asia
Tick-borne encephalitis	*Flavivirus*	*Ixodes persulcatus*, *Ixodes ricinus*	Asia, Europe
Bacterial			
African tick bite fever	*Rickettsia africae*	*Amblyomma hebraeum*, *Amblyomma variegatum*	Africa, West Indies
Human granulocytic anaplasmosis	*Anaplasma phagocytophilum*	*Ixodes ricinus*, *Ixodes pacificus*, *Ixodes scapularis*	Europe, North America
Human monocytic ehrlichiosis	*Ehrlichia chaffeensis*	*Amblyomma americanum*	North America
Lyme borreliosis	*Borrelia burgdorferi* sensu lato	*Ixodes persulcatus*, *Ixodes ricinus*, *Ixodes scapularis*, *Ixodes pacificus*	Asia, Europe, North America
Mediterranean spotted fever	*Rickettsia conorii*	*Rhipicephalus sanguineus*	Africa, Asia, Europe
Q-fever[a]	*Coxiella burnetii*	Many species of different genera	Africa, Asia, Australia, Europe, North America
Rocky Mountain spotted fever	*Rickettsia rickettsii*	*Amblyomma cajennense*, *Dermacentor andersoni*, *Dermacentor variabilis*, *Rhipicephalus sanguineus*	North, South, and Central America
Tick-borne relapsing fever	*Borrelia* spp.	*Ornithodoros* spp.	Africa, Asia, Europe, North America
Tularemia	*Francisella tularensis*	Many species of different genera	Asia, Europe, North America
Parasitic			
Babesiosis	*Babesia divergens*, *Babesia microti*	*Ixodes ricinus*, *Ixodes scapularis*	Europe, North America

[a] Transmission occurring via infected feces or coxal fluid rather than by the salivary transmission route.

(FDA) in 1999, hopes for combating this tick-borne illness soared. The vaccine, however, was quietly withdrawn from the market by 2002. In Europe, Lyme borreliosis continues to be a growing public health problem. Despite country-to-country variation in reporting criteria, one estimate of Lyme borreliosis cases per year in Europe placed the number at more than 50,000 (73). Moreover, tick-borne encephalitis appears to be an increasing problem in both Europe and Asia due partly to socioeconomic changes resulting in increases in risk behaviors for tick exposure (91) and partly to our increasingly mobile society bringing unvaccinated travelers into endemic regions (57).

One common problem in controlling tick-borne diseases is the difficulty in bridging the gap between research and implementation of control methodology. In the United States, mosquito control commonly is conducted by professional local mosquito control

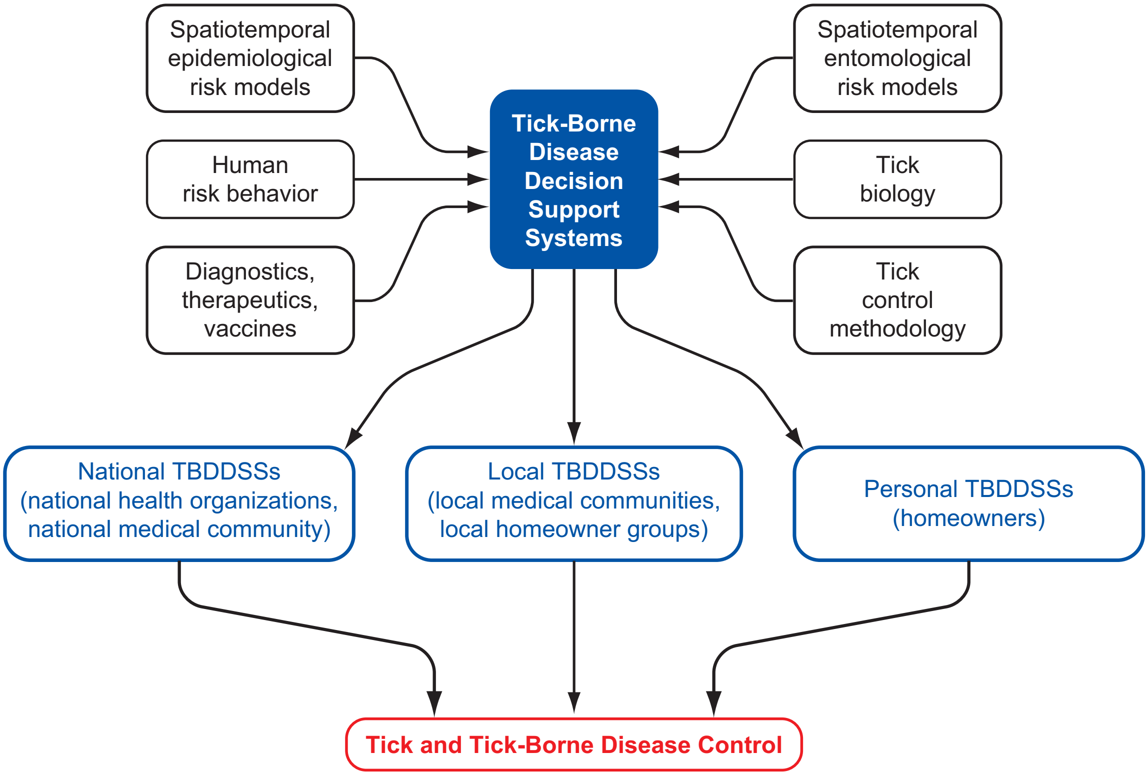

Figure 1

Roadmap to control of ticks and tick-borne diseases.

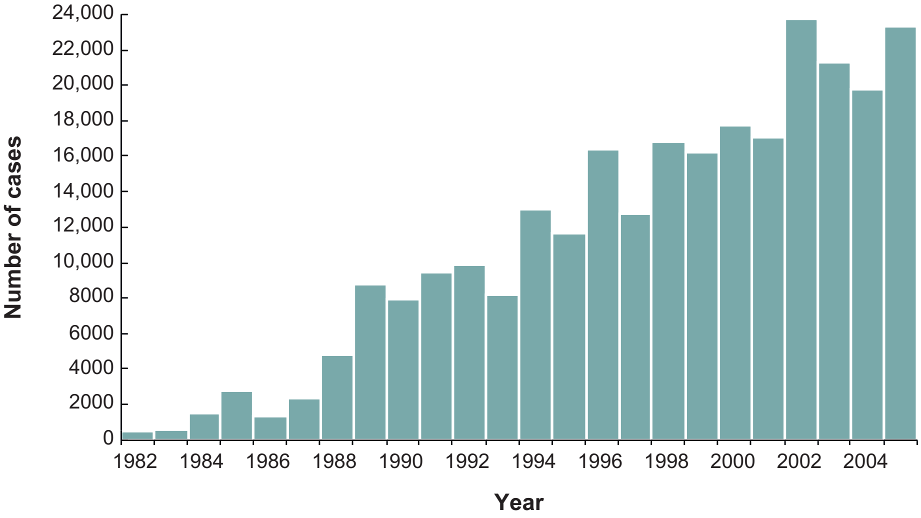

Figure 2

Cases of Lyme borreliosis in the United States reported from 1982 to 2005 to the Centers for Disease Control and Prevention.

programs. As there is no equivalent organizational structure for tick control, the responsibility for control of tick-borne diseases falls squarely on the shoulders of individual physicians and homeowners. Although these individuals can access a multitude of Web-based sources that provide information of variable quality regarding tick-borne diseases, there is a lack of tick-borne disease decision support systems that provide guidance regarding assessment of local risk of acquisition of tick-borne diseases for physicians or personal risk for homeowners (**Figure 1**).

AVOIDING TICK BITES: KNOWLEDGE OF NATURAL SPATIOTEMPORAL RISK PATTERNS FOR TICK EXPOSURE

The first line of defense against tick bites is to avoid high-risk habitats during peak tick activity periods. Below, we use three well-studied tick vectors of Lyme borreliosis spirochetes to explore the potential of and problems associated with avoidance of high-risk areas for tick exposure. The primary vector to humans of *B. burgdorferi* in far western North America, the nymphal stage of the western blacklegged tick, *Ixodes pacificus*, is an excellent example of a tick for which knowledge of spatiotemporal risk patterns for exposure can enable the public to avoid tick bites. This is because exposure of humans to *I. pacificus* nymphs is restricted to an easily recognizable habitat (dense woodland with a ground cover dominated by leaf or fir needle litter and lacking emergent vegetation) during a short time period (mid-April to mid-June) (13, 25, 28, 113). In other cases, avoidance of vector ticks can be far more complicated. For example, a wide range of habitats may present risk of exposure to vector ticks during extended time periods. This is exemplified by the common tick, *Ixodes ricinus*, in Europe, where humans are at risk for exposure to both the nymphal and adult life stages in a variety of habitat types from late spring until early fall (30, 37, 38). Alternatively, high-risk habitats may commonly occur in the peridomestic environment. This is the case in the northeastern United States, where many residential properties include wooded areas infested by *I. scapularis* (15, 67, 98, 105). The high potential for peridomestic exposure to *I. scapularis* likely is a key factor that explains why Lyme borreliosis is common in the northeastern United States.

The importance of peridomestic versus recreational exposure in tick-borne diseases is influenced both by the spatial pattern of clustering of the human population and the availability and actual use of public access lands. The northeastern region of the United States is an example of an area with a relatively scattered suburban population and a high percentage of privately owned land where peridomestic exposure to *I. scapularis* probably is more important than recreational exposure (14, 22, 32). In contrast, recreational exposure predominates in the Colorado Front Range, where the human population is concentrated just to the east of the Rocky Mountains but the only human-biting tick (*Dermacentor andersoni*) occurs primarily in montane areas to the immediate west that are dominated by public access lands and heavily utilized for recreational purposes by the Front Range population (9, 24).

Providing easily understandable and objective information on spatial patterns of risk for exposure to vector ticks (see examples for different spatial scales in **Figures 3** and **4**) is a currently underutilized but cost-effective method of increasing the public's ability to make informed decisions regarding how to avoid high-risk areas and to inform the medical community of circumstances under which a diagnosis of tick-borne disease should be considered. The latter is not a trivial matter because persons afflicted with tick-borne diseases can be unaware of having been bitten by a tick (5, 44, 84). Thus, exposure to habitats recognized as posing risk for contact with vector ticks can be a key component of a diagnosis of possible tick-borne disease.

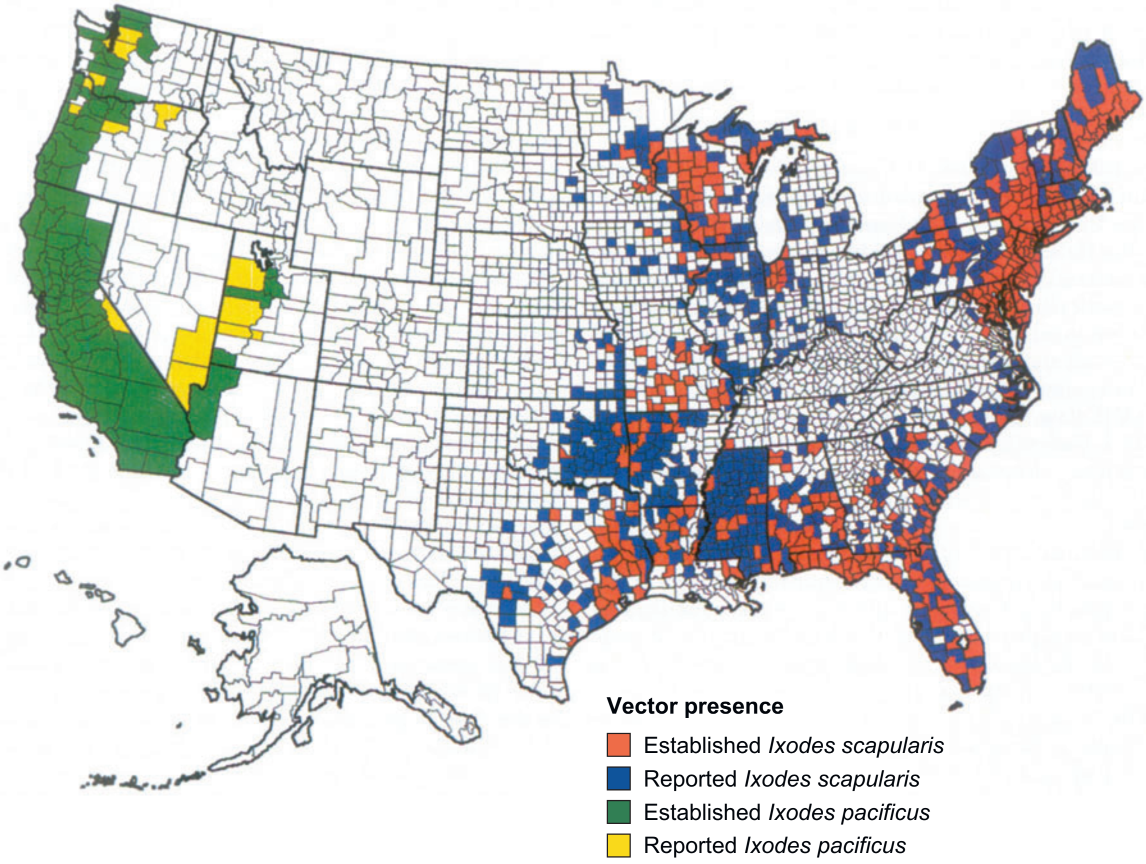

Figure 3

County-based geographical distribution of *I. pacificus* and *I. scapularis* in the United States. Adapted from Reference 18.

AVOIDING TICK BITES: PERSONAL PROTECTION MEASURES

Numerous studies have examined behavioral risk factors for exposure to ticks and tick-borne pathogens (1, 60, 62, 74, 101). If exposure to tick habitats cannot be avoided, there are simple measures that can be taken to minimize the risk of tick bites and pathogen exposure. Wearing appropriate clothing (including socks, long trousers tucked into the socks, and a long-sleeved shirt tucked into the trousers) mechanically decreases the risk that a tick finds a feeding site after having contacted a person. This is because the chances of the tick either being brushed off the clothing or being detected and removed increases with the distance it needs to travel in order to find exposed skin. Repellents have been demonstrated to effectively decrease the risk of bites by a variety of tick species when applied to clothing or bare skin (11, 56, 59, 88, 95, 102). Although DEET (*N*, *N*-diethyl-meta-toluamide) and permethrin-based products are reasonably safe to use, a substantial segment of the population is still unwilling to use them because they are perceived as a potential source of toxicity (45). This conundrum has occasioned a recent surge in research activities focusing on the development of repellents based on natural products, which are thought to be more acceptable to people

DEET: *N*, *N*-diethyl-meta-toluamide

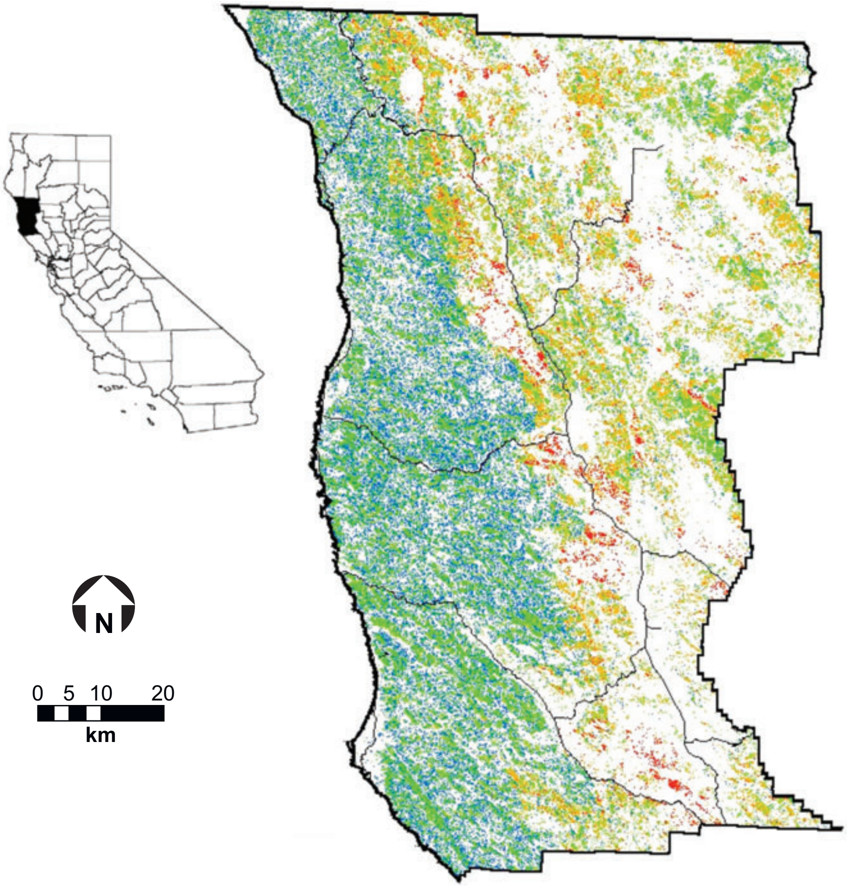

Figure 4

Predicted peak density of *Ixodes pacificus* nymphs in dense woodlands in Mendocino County, California. Areas with risk of nymphal exposure classified as high (>10.50 nymphs per 100 m^2) are shown in red, moderate risk (6.41–10.50 per 100 m^2) in orange, low risk (2.51–6.40 per 100 m^2) in green, very low risk ($\leq$2.5 per 100 m^2) in blue, and minimal or no risk (habitat classified as something other than dense woodland) in white. Map also displays major highways. Inset map shows the location of Mendocino County in California. Adapted from Reference 26.

unwilling to use currently available repellents based on synthetic chemicals. A product derived from lemon-scented eucalyptus oil (Citriodiol, or p-menthane-3,8-diol) is currently on the market for use as a tick repellent and has been shown to be somewhat effective in the field (34); several other plant-derived compounds including geranium oil, lavender oil, and Alaska yellow cedar oil also show potential as tick repellents (21, 50).

An antitick vaccine for cattle ticks directed against midgut antigens already has been developed and applied with variable success under field conditions (20, 83, 118). Although an intriguing concept based on its potential for suppressing multiple tick-borne diseases caused by different pathogens transmitted by a single tick species, the development of a similar antitick vaccine for humans is far more complicated. To serve its ultimate purpose, such a vaccine will need to be efficient not only in disrupting tick feeding but also in preventing pathogen transmission by an infected tick. This may become a race between how rapidly

Acaricides: insecticides used to kill ticks and other Acarines

DDT: dichloro-diphenyl-trichloroethane

the antitick vaccine disrupts feeding versus how quickly the tick starts to transmit the pathogen. Antitick vaccines targeting midgut antigens have potential for controlling tick-borne pathogens exhibiting a significant time-lag between tick attachment and pathogen transmission, as seen for *B. burgdorferi* (79, 82). Pathogens likely to be transmitted shortly after tick attachment, such as tick-borne encephalitis virus, will require antitick vaccine strategies that target tick attachment rather than feeding; recently, an antitick cement substance has been employed against tick-borne encephalitis virus (58). From a societal perspective, antitick vaccines may be more likely to succeed commercially in Europe, where the population already is accustomed to a safe and efficacious vaccine against tick-borne encephalitis virus, than in the more litigation-prone North American arena, which has already experienced the commercial downfall of a Lyme disease vaccine. The current frontier in research on antitick vaccines targeting key human-biting ticks is focused primarily on identifying potential protein targets useful in future vaccine development (49, 69, 72, 114, 120).

STRATEGIES FOR SUPPRESSION OF HOST-SEEKING TICKS

Acaricides have been applied to vegetation to decrease tick populations in recreational and agricultural settings. The use of area-wide acaricides to combat human tick-borne disease has had few well-established success stories. Perhaps the one demonstration of the potential power of the employment of area-wide acaricides to decrease the public health impact of a tick-borne agent was in the former Soviet Union. From 1965 to 1971, the incidence of tick-borne encephalitis in the former Soviet Union was decreased by two-thirds mainly because of the widespread use of DDT (dichloro-diphenyl-trichloroethane) to kill the principal vector tick (*Ixodes persulcatus*) (54). With the worldwide abandonment of DDT, this campaign ended and the incidence of human infection with tick-borne encephalitis virus in the former Soviet Union gradually returned to preintervention levels over the next two decades.

Public health efforts to demonstrate the potential of area-wide acaricides to control *I. scapularis* nymphs (the key vector stage) are ongoing in Lyme disease–endemic regions of the United States. Originally, older, second-generation pesticides such as carbaryl, diazinon, and chlorpyrifos were employed to kill *I. scapularis*. Over time, pest-control operators in the northeastern United States have moved toward less-toxic but highly effective synthetic pyrethroids (e.g., cyfluthrin, permethrin, and deltamethrin) for controlling *I. scapularis* in the peridomestic environment. Interestingly, a single well-timed application of deltamethrin applied at the forest-lawn interface of residential properties can kill 95% of host-seeking *I. scapularis* nymphs (97). Such an application would, presumably, dramatically reduce the risk of acquiring infection with the agents causing Lyme borreliosis, human granulocytic anaplasmosis, or human babesiosis. But yet, most residents in areas highly endemic for these *I. scapularis*–transmitted pathogens decline to use area-wide acaricides on their properties owing to perceived concerns regarding the products capacity to cause mammalian toxicity and environmental damage. In fact, less than 25% of residents in highly Lyme borreliosis–endemic regions of Connecticut, New Jersey, New York, and Massachusetts reported spraying their properties to control ticks (81). This reality has forced public health entomologists to look broadly for alternative interventions to reduce the risk of tick-borne diseases. One of the first alternative avenues pursued was vegetation management.

Vegetation management has been part of tick control for centuries. Native Americans were reported to conduct controlled burns in part to reduce tick populations; pasture rotations have long been part of tick control in livestock management. Different types of vegetation management (brush removal, mowing, and removal of overstory vegetation) were explored in the late 1960s in the southeastern United States to control the exceptionally abundant and vigorous lone star tick, *Amblyomma americanum*, which then was known as a vector of the tularemia agent *Francisella tularensis* and later has been implicated in the transmission of the causative agent of human monocytic ehrlichiosis (*Ehrlichia chaffeensis*) (31, 41, 47, 75). The emergence of Lyme borreliosis reinvigorated the science of vegetation management for tick control. The principal vector of *B. burgdorferi* in the eastern United States, *I. scapularis*, is found mainly in forest habitats associated with leaf litter. Removal of leaf litter from the forest floor exposes these ticks to desiccation and dramatically reduces the overall population of host-seeking ticks (96). Brush removal and burning also reduces *I. scapularis* populations but the effect is short-lived (64, 108, 124). More long-lasting landscape management strategies might include placing a border between naturally tick-infested forested habitats and adjacent lawns on residential properties (67); Alaska yellow cedar sawdust may be an appropriate material for such borders owing to its repellent properties (80).

Least-toxic approaches for area-wide tick control include chemicals such as soaps and desiccants (76). Another environmentally friendly approach to tick control involves the use of biological agents (e.g., parasitoid wasps, nematodes, bacterial and fungal agents, and vertebrate and invertebrate predators of ticks) to kill ticks; this was the subject of a previous extensive review (93). Recently, much work has focused on developing fungal agents that can be sprayed at spore concentrations that kill *I. scapularis* (3, 48). The prime candidate for a commercially available fungal agent to kill *I. scapularis* is *Metarhizium anisopliae*. This fungus, however, is still not widely available for tick control in high volume with sufficient viable spore concentrations to kill ticks for Lyme borreliosis prevention.

To minimize the amount of acaricides needed to control ticks, researchers have developed host-targeted approaches to tick control. Compared with area-wide broadcasts of acaricides to vegetation, only minute amounts of acaricides are used in these host-targeted efforts when calculated on a per-acre basis. Perhaps the largest effort to employ host-targeted approaches to prevent tick-borne diseases in humans began when the USDA group at Kerrville, Texas, began to adapt bait station technology originally developed for control of the Southern cattle tick *Rhipicephalus* (*Boophilus*) *microplus* for use against tick vectors of human pathogens. First, they tested a device that lured white-tailed deer into corn-feeding stations that contained four paint rollers laden with acaricide. To get the corn, these deer had to rub their heads against the paint rollers and self-apply a test acaricide (amitraz). This device was called the 4-poster device. Initial trials against the lone star tick, *A. americanum*, were highly successful (86, 87) and the device was subsequently tested against *I. scapularis* (10, 103). Because the devices are mainly targeted at the adult stage of *I. scapularis*, there is a delayed effect before the principal pathogen vector stage, the nymph, is reduced. But, in initial trials in Maryland using both amitraz (10) and 10% permethrin (103), *I. scapularis* populations were dramatically reduced over a wide area. A field test of this technology in several states where Lyme borreliosis is hyperendemic has been conducted and is currently being analyzed.

Potential regulatory concerns about bringing deer to feeding stations and the high cost of labor required to maintain the bait and acaricide on the 4-poster devices must be addressed before this technology comes into widespread use. Attempts to control ticks by limiting deer populations through fencing or hunting have had mixed success. On an island off the cost of Maine, researchers recently demonstrated that eradication of the deer herd led to a dramatic reduction in populations of *I. scapularis* (90). There is, however, still a need to establish a cutoff for deer populations below which we are certain tick populations and Lyme disease spirochete transmission risk will be reduced.

Targeting the rodent hosts that support populations of the immature stages of ticks or serve as key pathogen reservoirs has also received research attention. An early study from Virginia (104) used a bait box that dispensed either 5% carbaryl or 1% diazinon and targeted a principal host, the meadow vole, *Microtus pennsylvanicus*, of the immature stages of the American dog tick, *Dermacentor variabilis*, which is a key vector of both the tularemia agent *F. tularensis* and the Rocky Mountain spotted fever agent *Rickettsia rickettsii* in the eastern United States (8, 51). Subsequently, it was observed that the white-footed mouse, *Peromyscus leucopus*, a principal host for immature *I. scapularis*, would take cotton from experimental nesting boxes on the ground back to their own nests. Researchers treated these cotton balls with permethrin, thereby treating both the mouse taking the cotton balls and all its nest mates. Cardboard tubes containing permethrin-treated cotton balls were field tested in Massachusetts and dramatically reduced both the number of *I. scapularis* larvae and nymphs on white-footed mice and the density of infected host-seeking nymphs (17, 65, 66). Unfortunately, field studies conducted in New York and Connecticut did not show similar dramatic efficacy (16, 106, 107). One reason for variation from site to site may be the diversity of vertebrates that serve as hosts for *I. scapularis* immatures or as reservoirs of *B. burgdorferi*. In some locations, chipmunks, shrews, or even birds may be significant contributors as tick hosts and key players in enzootic transmission of *B. burgdorferi*. New designs for bait boxes that contain wicks that deliver fipronil, a highly effective acaricide that renders treated animals free of ticks for up to 7 weeks, have been tested in coastal Connecticut and show some promise for reducing the number of host-seeking *I. scapularis* infected with *B. burgdorferi* (23). The utility of these fipronil-treated bait boxes in diverse ecological settings needs to be established, and the boxes must be made resistant to vandalism by squirrels.

STRATEGIES FOR SUPPRESSION OF PATHOGEN-INFECTED TICKS

Host-targeted approaches that specifically kill vector-borne pathogens within vertebrate reservoirs are an alternative to the above-mentioned host-targeted approach in which an acaricide is used to kill ticks attached to a reservoir host. In one pilot study in Connecticut, white-footed mice were captured and inoculated with a recombinant vaccine directed against the OspA of *B. burgdorferi* (115). An attempt to vaccinate all the mice caught within a woodlot resulted in a 16% decrease in the *B. burgdorferi* infection rate of host-seeking *I. scapularis* nymphs the following year (115). A more practical approach to disseminating a wildlife vaccine against the OspA protein of *B. burgdorferi* would utilize an oral vaccination approach. Oral OspA vaccines based on recombinant vaccinia virus (94) or *Escherichia coli* (36) are highly effective when tested on rodents in the laboratory. Field trials of candidate rodent-targeted OspA vaccines are needed to explore the promise of this technology. An additional pathogen-host-targeted approach to prevention of tick-borne diseases would be to place doxycycline into an oral bait formulation. This would have the added benefit of attacking not only *B. burgdorferi* but also other tick-borne pathogens such as *A. phagocytophilum*. The ability of doxycycline prophylaxis to block transmission of *B. burgdorferi* to rodents in the lab has been demonstrated (125). However, the environmental impact of using doxycycline-treated baits for the prevention of tick-borne diseases, especially the risk of emergence of doxycycline-resistant bacteria through large-scale introduction of this antibiotic into populations of rodents, needs to be assessed before this technology is acceptable for widespread use.

AVOIDING DISEASE FOLLOWING A BITE BY AN INFECTED TICK

There are at least three general approaches to avoiding disease following a bite by an infected tick. First, clinical disease can be suppressed by a previously administered vaccine. This is currently only applicable to tick-borne encephalitis for which there is a commercially successful vaccine that has been used widely in Europe for several decades (2, 4, 12). In contrast, the Lyme borreliosis vaccine for use in humans (LYMErix^{TM}) that was introduced in North America in 1998 was retracted from the market in 2002 despite being relatively safe and efficacious (61, 85, 109, 123). Primary factors leading to low sales and, ultimately, the downfall of this vaccine included the need for frequent boosters, a high vaccination cost, exclusion of children from vaccination, fear of vaccine-induced musculoskeletal symptoms, and litigation related to the vaccine (42, 44). Although there is progress toward new and improved Lyme borreliosis vaccines (53, 122), the commercial failure of LYMErix likely will slow the development process for replacement vaccines. Second, daily tick checks following exposure to high-risk habitats and subsequent prompt removal of attached ticks may prevent pathogen transmission by infected ticks for some tick-borne diseases. For example, it is well established that *B. burgdorferi* is not commonly transmitted until >24 h after attachment of infected *I. pacificus* or *I. scapularis* ticks (77, 79, 82). Third, in the case of Lyme borreliosis, administering an appropriate antibiotic shortly after a tick bite decreases the risk of developing clinical symptoms (55, 70). A similar approach may prove effective for other tick-borne bacterial pathogens.

COST-EFFECTIVENESS OF PREVENTION OF TICK-BORNE DISEASES

A cost-benefit analysis of vaccination against tick-borne encephalitis virus among French troops on tour in the Balkans showed a negative economic benefit; the cost of a vaccination program including all military personnel (€10.05 million) far exceeded the economic benefit (€4.37 million) of preventing an estimated 121 tick-borne encephalitis cases through the vaccination program (19). In the United States, a study of test-treatment strategies for patients suspected of having Lyme borreliosis showed that neither testing nor antibiotic treatment is cost-effective if the pretest probability of Lyme borreliosis is low (71). Empirical antibiotic therapy was recommended if the pretest probability is high. Evaluations of cost-effectiveness of vaccinating against Lyme borreliosis, conducted while a vaccine was still commercially available, indicated that few communities had disease probability rates (>0.005) great enough for mass-vaccination to be economically beneficial and that vaccination should be based on estimates of individual risk, with vaccination recommended for persons whose probability of contracting Lyme disease is ≥0.01 (68, 100). Although society may seek to balance the cost of Lyme borreliosis (126) against the potential benefit of control technologies (43, 44), homeowners must make these decisions themselves each year. It is incumbent upon public health authorities to provide timely information about the risk of tick-borne diseases and to guide homeowners toward resources outlining the latest developments in tick-borne disease control methodologies.

TRANSFER OF INFORMATION TO THE MEDICAL COMMUNITY AND THE GENERAL PUBLIC

Transfer of research-derived information in easily understandable formats to the public and the medical community, e.g., in the format of decision support systems for tick-borne disease risk assessment, is an important but inadequately studied aspect of prevention of tick-borne diseases. The importance of reliable and user-friendly Web-based information resources cannot be overstated in light of the constantly increasing usage of the Internet as the first option for retrieving information on any given topic. Long-established Web-based information resources for Lyme borreliosis providing a classical one-way flow of information from source to user are now complemented by novel Web-based resources that provide a more interactive two-way flow of information between the source and the end user. This is exemplified by the University of Rhode Island (URI) Web-based Tick Encounter Resource Center (**http://www.tickencounter.org/**), which not only provides a variety of objective information on Lyme borreliosis for Rhode Islanders and others but also aims to serve as a conduit for two-way information flow between URI researchers, the local community, and beyond that will allow for continual improvement of the provided Web-based knowledge resource.

Web-based information resources also are well suited to incorporate risk maps for tick-borne diseases. For example, risk maps for tick-borne encephalitis in Europe are used as a decision support tool for the medical community and the public when determining the benefit of receiving vaccination against tick-borne encephalitis virus (111, 112). As illustrated in **Figure 5** for Lyme borreliosis in California, risk maps also can combine independently derived information on fine-scale incidences of tick-borne disease and acarological risk of tick exposure (27). This approach not only confirmed that north coastal California and the

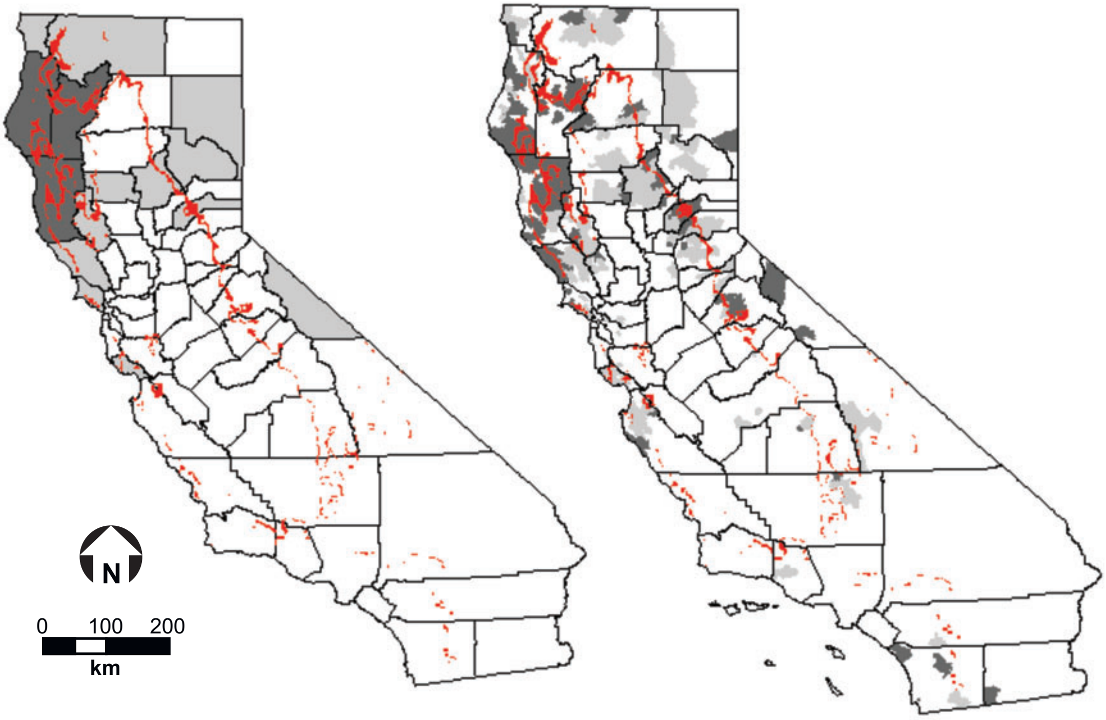

Figure 5

California (*left*) counties and (*right*) zip codes with Lyme borreliosis incidence exceeding 1 case (*light gray*) or 5 cases (*gray*) per 100,000 persons—during the years 1993–2005, in relation to the distribution of areas with high projected acarological risk of exposure to *Ixodes pacificus* nymphs (shaded *red*). Adapted from Reference 27.

northern foothills of the Sierra Nevada mountain range are the primary Lyme borreliosis foci in the state (33) but also revealed the presence of small, isolated high-risk "islands" in the southern part of the state where the occurrence of locally acquired Lyme borreliosis has been contentious.

PREVENTION OF TICK-BORNE DISEASE IN THE TWENTY-FIRST CENTURY

Decisions concerning the prevention of many vector-borne diseases (e.g., malaria, trypanosomiasis, dengue, West Nile virus disease) are made at the national, regional, local, or mosquito control district level. When dealing with tick-borne diseases, such decisions are made at the family or individual level. Mosquito control is a community responsibility; tick control is an individual homeowner responsibility. This may explain why currently in the United States, several thousand people are dedicated to mosquito control, whereas only a few dozen are dedicated to public health–related tick control. Nevertheless, the research community has been ingenious in devising a plethora of novel methods for tick and tick-borne disease control including vaccines, area-wide acaricide application, least-toxic pesticides, host-targeted devices for acaricide application, host-targeted vaccines, biological control methods, and personal protection strategies. But, except perhaps for the focal use of vaccine against tick-borne encephalitis virus in Europe and eastern Russia, methods for the prevention of tick-borne diseases are not widely employed, even in the face of an increasing surge of Lyme borreliosis, human granulocytic anaplasmosis, and human babesiosis. We must bring academic research on tick-borne diseases into the real world and make effective methods for the prevention of tick-borne diseases cheap, safe, and easy for the homeowner to apply. We must also ensure ready access (e.g., through Web-based decision support systems for tick-borne diseases) to information empowering individuals to (*a*) make rational and informed decisions regarding their personal risk of exposure to tick-borne pathogens and (*b*) take appropriate actions to mitigate risk of tick bites and pathogen exposure. Those are our challenges at the beginning of the twenty-first century in the field of prevention of tick-borne diseases.

SUMMARY POINTS

1. Tick-borne diseases are on the rise.
2. Despite an explosion of knowledge in the fields of biology and genetics of ticks and tick-borne pathogens, measures to combat tick-borne diseases are lagging.
3. Past successes include the tick-borne encephalitis virus vaccine and widespread application of DDT in the former Soviet Union.
4. Promising prevention approaches have emerged in the arena of host-targeted tick control and oral vaccination of reservoir hosts.
5. The current frontier in anti-tick vaccines is focused on identifying target antigens for future vaccine development.
6. Progress toward new and improved Lyme borreliosis vaccines has been slowed by the commercial failure of LYMErix.
7. Reluctance by the public to use synthetic repellents and acaricides has led to the exploration of natural products for this use.

8. Decision support systems for the assessment of tick-borne disease risk are needed to help the medical community and general public make choices concerning the prevention of tick-borne diseases.

FUTURE ISSUES

1. There is a need for development of integrated pest management approaches highlighting least-toxic methods for tick control and prevention of tick-borne diseases.
2. Academic research on tick-borne diseases must be brought into the real world and effective methods for the prevention of tick-borne diseases must be made cheap, safe, and easy for the homeowner to apply.
3. We need to ensure ready access to objective information empowering the individuals de facto responsible for control of ticks and tick-borne diseases to make rational and informed decisions regarding their personal risk of exposure to tick-borne pathogens and to take appropriate actions to mitigate risk of tick bites and pathogen exposure.

DISCLOSURE STATEMENT

The authors are not aware of any biases that might be perceived as affecting the objectivity of this review.

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Annual Review of Entomology

Volume 53, 2008

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