Published in final edited form as:
Infect Dis Clin North Am. 2008 September ; 22(3): 381–vii. doi:10.1016/j.idc.2008.03.007.

Prevention of Lyme Disease (and other tick borne infections)

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Summary

Prevention is the best method for avoiding potentially serious complications of Lyme disease. In this chapter, we will discuss preventative measures that can be employed by individuals and/or communities. Among the topics discussed are personal protective measures, tick reduction, reservoir reduction and vaccination. Additionally, new preventative measures that are in development including new Lyme disease vaccines, anti-tick vaccines and reservoir-targeted vaccination are discussed.

Keywords

Lyme; Borrelia burgdorferi; prevention; Ixodes; vaccine

Introduction

Since the first recognition of Lyme disease (LD) in the US. in the mid 1970's, there have been many advances in our understanding of how the disease is spread, the biology of the causative organism, *Borrelia burgdorferi*, the ecology of the *Ixodes* tick vector, and of the reservoir hosts (mice, voles, chipmunks, birds). However, despite the explosive growth in our knowledge, the incidence of LD has been increasing at a steady rate and efforts at prevention have been unsuccessful on a population basis.

There are now multiple proven modalities available for preventing Lyme disease transmission, as well as some intriguing new strategies currently under investigation. While this chapter focuses on prevention of Lyme disease, many of the strategies that are used will also be effective for other tick-borne diseases; where applicable, we will also briefly discuss specific preventative measures available for other diseases. Discussed in this chapter are the concepts of post-exposure antibiotic prophylaxis; tick avoidance/personal protective measure; environmental control of ticks, deer, mice and other reservoir hosts; and vaccination. We will also report on new strategies for the prevention of Lyme disease including new human Lyme disease vaccines, anti-tick vaccines (which may provide benefit against a wide variety of organisms), and reservoir targeted vaccines and interventions.

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Post-exposure, antibiotic prophylaxis

There are numerous studies that suggest that early treatment of Lyme disease results in excellent outcomes and prevents the development of long-term sequelae [1–3]. Thus, it is conceivable that treatment at the earliest possible timepoint— just after exposure to an infected tick, when the infection is not yet well established and the numbers of bacteria would be expected to be lowest — could result in good outcomes with shorter courses of antibiotics. The earliest trial of post-exposure prophylaxis was a controlled trial of 387 adults and children who were bitten by *Ixodes scapularis* in Southeastern Connecticut who were randomized to receive either 10 days of amoxicillin vs. placebo. There was no significant difference in the development of erythema migrans (EM) rash or seroconversion, however, there was a very low incidence of EM rashes even in the placebo group (2 cases versus none in the Amoxicillin treated group) [4].

Nadelman et al. randomized 482 patients, living in a highly Lyme disease endemic area in NY, who had removed an *I. scapularis* tick to receive either a single dose of doxycycline or placebo. One person in the treatment group developed erythema migrans rash vs. 8 in the placebo group ($p < 0.04$). [5] Based on this trial, a single dose of doxycycline 200 mg orally may be considered in patients bitten by a tick that can be identified as an *I. scapularis* tick. Current recommendations are to use prophylaxis only in areas with high rates of tick infection (rates >20%). Lyme endemic areas are generally considered to be the eastern seaboard of the United States from Maryland to Maine, as well as Minnesota and Wisconsin [6–10]. Tick bites on the West Coast where I. pacificus is prevalent should generally not be prophylaxed with antibiotics, as the rate of infected ticks is typically below 20% [11]. Before considering antibiotic prophylaxis, it should be established that the tick has been attached for >36 hours, and prophylaxis, if given, should begin within 72 hours of removal of the tick. In a cost effectiveness analysis done in 1992, Magrid et al. determined that in areas of Lyme prevalence of 0.036, prophylactic doxycycline was a cost effective strategy (even when doxycycline was given for 2 weeks as opposed to the single dose now recommended) [12]. Alternatively, the tick bite site can be monitored for erythema migrans rash, which, if it develops can then be treated as early, localized Lyme disease with excellent outcomes. [13]. It is now known that a very high percentage of patients who develop LD from a recognized tick bite will develop a local EM at that site. However, in clinical practice, many clinicians in endemic areas routinely offer antibiotic post-exposure prophylaxis. The efficacy of post-exposure prophylaxis for the Ixodes transmitted diseases Babesiosis and Anaplasmosis has not been well studied; however, given the lower prevalence of tick infection with these organisms in endemic areas in the U.S. and the high incidence of asymptomatic disease, prophylaxis would not be expected to be cost-effective except perhaps in very isolated cases.

Personal Protection/Tick Avoidance

The first step in prevention of LD is preventing tick bites. For people who frequent tick infested areas there are several steps that can be taken to eliminate or diminish the risk of tick bite and/or transmission of LD. Wearing light colored clothing, as well as keeping long pants tucked into socks provides an effective barrier to ticks, and allows the visualization of dark colored ticks.

Repellants can also decrease the incidence tick bites. Commercially available compounds containing DEET (diethyl-3-methylbenzamide) are currently the most efficacious repellants followed by picaridin (KBR 3023), a piperidine compound. At 1 hour after application, the two compounds each have roughly 85% efficacy in preventing insect bites (including ticks); but at 2, 3 and 4 hours, picaridin was inferior to DEET containing compounds in preventing

tick bites, while having similar protection against mosquitoes [14, 15]. In other *in vitro* studies measuring tick movement along horizontal and vertical filter paper treated with both DEET and AI3-37220 [1-(3-Cyclohexen-1-ylcarbonyl)-2-methylpiperidine – another piperidine compound] DEET had better efficacy in the horizontal paper test, while AI3-37220 performed better on the vertical assay against *Amblyomma* ticks, but not *Ixodes* ticks. [16]

Field studies performed in forestry workers have shown that DEET application can significantly decrease the frequency and number of tick bites. In the U.S., DEET containing products are available in compounds from 5% up to 100%. The higher concentrations provide protection for longer periods of time, (against mosquitoes) up to 12 hours depending on immersion in water, amount of sweating and other environmental factors. An investigational lipid formulation of DEET applied to rabbit ears was effective in preventing attachment of *Amblyomma americanum* and *Dermacentor variabilis* for up to 72 hours and was acaricidal against both species of ticks [17]

Other repellants such as garlic, eucalyptus oil and citronella based products have been tested only against mosquitoes and are inferior to DEET and picaridin [18, 19]. Except for known toxicities in children where high concentrations may cause seizures, DEET containing products have had a good safety record. One caution with DEET containing products is that they can damage certain plastics and synthetic fibers, including eyeglass frames [20]. Piperidine containing compounds are safe for use on plastics.

In addition to insect repellants, certain insecticides/acaricides can be effectively applied to clothing to prevent tick bites. Permethrin, which is commonly used treat human lice infestations, can be applied to clothing and bed nettings to prevent mosquito and tick bites. In fact, the efficacy of permethrin, applied as a spray, or in impregnating clothing was superior to DEET compounds against both Amblyoma and Ixodes ticks in military trials [21]. Permethrin can be applied to clothing by mixing a premeasured container of the product with water and immersing clothing in this solution for 3–4 hours and allowing to dry. The acaricidal properties of permethrin can last through multiple washings depending on the formulation. Some commercial products recommend retreating every 5 or so washings, while the U.S. military's formula can maintain good efficacy through 50 or more washings. Dry cleaning, however will remove the acaricidal properties. Recently, some military clothing is being tested that has a factory applied permethrin polymer that maintains contact acaricidal properties for 100 or more washings, which is roughly equal to the expected life of the uniform.[22–24]

If tick avoidance and repellants fail, daily visual perusal for ticks (tick checks) is an effective way of preventing Lyme disease. Due to the amount of time required for *B. burgdorferi* to transit from the midgut, to the salivary glands and into a new host, if ticks can be detected and removed before 36 hours of attachment, transmission of *B. burgdorferi* can effectively be prevented

Educational programs aimed at teaching susceptible populations to perform tick checks and to apply insect repellants does increase usage. In Baltimore County, MD, subjects were randomized to receive tick related education vs. general health related material. Blood samples from the subjects were checked for antibodies to calreticulin as a marker of tick bites. Those receiving tick education were more likely to use repellants and perform tick checks, but there was no significant difference in serologic evidence of tick bites[25]. In another study, Daltroy *et al.* conducted a randomized controlled trial among some 30,164 ferry passengers traveling to Nantucket Island, providing educational training in tick prevention or bicycle safety education. Those receiving education on tick avoidance were

more likely to wear protective clothing, limit time in tick infested areas, use repellant and perform tick checks than controls. They also showed a 60% risk reduction of tick-borne illness among those who were visiting for longer than 2 weeks [26].

Alteration of Environment

Ixodes scapularis ticks undergo a two-year, 3-stage life cycle, feeding once during each stage. They spend most of their lives free in the environment, unattached to a host. Tick eggs hatch in late spring and summer and the six-legged larvae seek out a blood meal, usually from small mammals, including white-footed mice, chipmunks and voles. Birds may also be common feeding hosts for *Ixodes* ticks [27]. As there is little or no transovarial transmission, larvae do not transmit disease and acquire *B. burgdorferi* only when feeding on an infected animal. After the larvae have taken an adequate meal, and drop off onto the forest floor they lie dormant in the leaf litter over the fall and winter, only to emerge the next spring as an eight-legged nymph. If infected, the infection is passed transstadial as the tick progresses to from larva to nymph. In late spring and early summer, questing nymphs will climb onto vegetation and attach to passing animals for its next blood meal. Typically, nymphs also feed on small rodents and birds, but may attach to humans and other targets of opportunity. Feeding on uninfected rodents and birds by infected ticks perpetuates the cycle of *B. burgdorferi*. After the blood meal, the nymphs will molt into adults, which then take their blood meal on larger mammals such as the white tailed deer (*Odocoileus virginianus*). Adult males and females then mate and the cycle begins anew. Over limited areas, such as yards and residential areas, removal of leaf litter and mowing can result in significant reduction in tick numbers by destroying tick habitats. In one study, raking and blowing the leaf litter from a forested residential during March and June community resulted in 72.7 100% reduction in nymphal tick densities [28].

Additionally, controlled burning of vegetation can result in diminished numbers of ticks in localized areas for at least a limited period of time. Researchers in Connecticut [29] performed controlled burns in April and in May of the same year. Subsequent sampling showed reduction of nymphal *I scapularis* of 74% and 100% respectively for moderately burned vs. severely burned areas. However, repeat surveying of the burned areas in the fall of that year showed that the effects of burning are temporary.

Tick eradication

Targeted spraying of acaricides such as permethrin, deltamithrin, carbaryl, chlorpyrifos and others in residential areas can also effectively reduce the tick burden, and thus the chance of contracting LD, for a limited period of time. [30–32]. A single application of granular deltamethrin can effectively reduce ticks by as much as 100% for up to 12 weeks [33]. However, despite the efficacy of spraying, it has not been widely adopted as a tick control measure. One drawback is that this strategy may affect more arthropods than those directly targeted, and have unwanted consequences.[34]. Additionally, ill-timed applications of acaricides may be ineffective, and pose a hazard to human health [35]. Overuse, or inappropriate use of acaricides can increase the incidence of resistance. In the last 2 years, there have been reports of resistance against organophosphates and permethrin developing in *Boophilus* ticks in the U.S [36, 37]. These strategies of tick eradication may prove to be much more effective on island ecologies than on the mainland where ticks can easily infringe on the borders of the treated areas from outside of treatment zones.

Reservoir Hosts

Ixodes scapularis are widely distributed across the United States, in many areas that LD is not found to be endemic. One reason for the lack of Lyme disease in these areas is that in

many parts of the US, lizards are the natural host for *Ixodes* ticks, and *B. burgdorferi* is killed when exposed to lizard blood. Thus, eliminating the hosts, or reducing vector competence for an organism (i.e. preventing the vector from acquiring or transmitting an organism) may be an effective strategy for preventing Lyme disease in humans. The major amplifying host for *Borrelia burgdorferi* in the U.S. is the white footed mouse (*Peromyscus leucopus)* [38, 39]. However, chipmunks (*Tamias striatus*), shrews and other small vertebrates are becoming increasingly recognized as important hosts and birds may also play a major role in amplifying *B. burgdorferi* [40]. As birds can have great territorial range, they have the potential to rapidly disseminate infection into new regions. In 1998–1999, Bunikis *et al* [41] conducted field trials in a highly Lyme endemic area in Connecticut over 2 transmission seasons. Traps were placed in 3 adjacent sites and live mice were tested for seroprevalence of LD. 598 of 801 serum samples (75%) were positive in 514 mice. Logiudice et al. have demonstrated that shrews can play a large role in maintaining *B. burgdorferi* in the environment when mice are scarce or absent [42].

One method that has been employed for reducing local tick burden is to apply acaricides to mice, thus killing attached larval and nymphal ticks on the major amplifying host. Cardboard tubes filled with acaricide impregnated cotton can be placed around a yard or other area where mice are known to thrive. The mice then utilize the cotton in lining their nest, coating themselves with the acaricide and eliminating ticks from themselves and their nest-mates. This product appears to be effective in some environments, such as island ecologies and not in others (mainland) perhaps due to the differential impact of alternative hosts [43–45].

Although they are not important as an amplifying reservoir of *B. burgdorferi*, deer are an important host for maintenance of tick populations. Adult ticks prefer the white-tailed deer (*Odocoileus virginianus*) as the major host. The effect on *Ixodes* population by removal or culling of deer has been mixed. On Great Island, Cape Cod Massachusetts, and Monhegan Island, ME, the virtual elimination of deer resulted in a marked decrement in both tick population and cases of Lyme disease [46, 47]. Subtotal deer reduction did not result in a meaningful decrease in *I. scapularis* ticks [48]. A recent study conducted in northern New Jersey measured the number of questing *Ixodes* ticks during a 3 year period of active culling of the deer population. A reduction in deer density of 46.7% resulted in no decrement of tick population. In addition, human cases of LD were not affected to any discernable degree during the study period. [49]. Thus, the impact of subtotal removal of deer on Lyme disease transmission may be minimal.

Application of acaricides to deer has also been tested. One device, called a “four-poster device,” attracts deer through a large feed reservoir. In order for the deer to access the feed, they must insert their head and neck between 2 vertical rollers that are impregnated with an acaricide. The vast majority of ticks attach themselves to the head and neck of deer. Deer have been shown to readily utilize this device and this method has proved successful in reducing ticks from deer. In areas where the deer population is burgeoning, however, there is some reluctance to employ any device that feeds deer, and aids in their survival and propagation. In addition, as deer will congregate around food sources, there is the potential for increasing the spread of deer wasting disease. One benefit from this and other strategies for targeting ticks is that other tick-borne diseases such as Babesiosis and Anaplasmosis would similarly be affected.

Human vaccination

In December of 1998, Smith-Kline Beecham (now known as GlaxoSmithKline) gained FDA approval for its *B. burgdorferi* outer surface protein A (OspA) based Lyme disease vaccine,

LYMErix. This vaccine used a unique mechanism of protecting the immunized person from acquiring the disease. OspA plays an important role in allowing *B. burgdorferi* to survive in the tick midgut by binding to the tick midgut protein, TROSPA [50]. As the tick takes its blood meal, OspA expression on *B. burgdorferi* is rapidly turned off so that there is minimal expression of OspA in organisms entering mammalian hosts. Thus, natural infection rarely produces an antibody response to OspA. In vaccination with OspA, antibodies circulating in the vaccinated person/animal are taken up by the tick with the blood meal. These antibodies kill *B. burgdorferi* while it is still in the tick midgut, thus preventing transit to a new host.

Two large trials of an OspA vaccine showed good efficacy in the prevention of Lyme disease (76% and 92% after 3 doses) [51, 52]. An OspA vaccine, as well as other *B. burgdorferi* vaccines have been available for dogs since the early 1990's and these remain in use. The human vaccine, however was voluntarily withdrawn from the market due to poor sales. There were several factors involved in the lack of sales including the expense, the need for frequent revaccination and widely publicized concerns about a potential relationship with the development of autoimmune arthritis in patients with a specific HLA haplotype (DRB 0401) ref. A region of OspA that spans the amino acid residues 165–173 ($OspA_{165–173}$) was postulated to be a molecular mimic of human leukocyte function associated antigen - $1_{\alpha L326–345}$ (LFA-1) capable of inducing proliferation of autoreactive T cells [53, 54]. However, since then, multiple lines of evidence have not supported this hypothesis and molecular mimicry of LFA-1 is no longer felt to be a mechanism of antibiotic resistant Lyme arthritis, although other cross-reactions with OspA cannot be ruled out [55]. Post-hoc analysis of the two large trials of OspA vaccination have not revealed any increased incidence of autoimmune arthritis to date. In Europe, an Austrian company (Baxter Vaccines) is currently testing a re-engineered OspA with the LFA-1 cross-reacting epitope removed from the sequence to avoid this controversy. Use of an OspA vaccine in Europe is complicated by the fact that there is greater sequence diversity in OspA among strains of *B. burgdorferi* circulating in Europe—necessitating the use of a multivalent OspA vaccine.

Of note, in patients who received the human OspA vaccine while it was available, there are additional considerations in interpreting serologic test results for Lyme disease. Older ELISA tests that used whole *in vitro* grown organisms as the antigen for the test may be falsely positive in patients who have received OspA vaccination. Newer tests using specific recombinant antigens and/or peptides (such as the C6 peptide test) should not be affected by OspA vaccination. Similarly, OspA is not a diagnostic antigen on standard Western blot tests and thus Western blot testing for Lyme disease is also not affected. Because antibody responses to OspA fade quickly without revaccination, issues of cross-reactivity, even in the older ELISA tests, are likely no longer relevant (although it would certainly be logical to use the newer, more specific tests regardless).

There is currently only one other vaccine that is approved and available for a tick borne disease, tick-borne encephalitis (TBE). TBE virus is a flavivirus that is endemic throughout most of Europe, and is especially prevalent in Eastern Europe, striking a wide swath through Russia eastward all the way to Northeastern China. The majority of disease caused by TBE virus is of the European (Type 1) subtype, associated with the tick *Ixodes ricinus*, while cases in Eastern Russia and Northeastern China are of the Far-Eastern subtype (Type 2). The Far-Eastern subtype of the virus is closely associated with *Ixodes persulcatus* as the main vector. In addition to being transmitted by tick vectors, TBE has been noted to be caused by ingesting unpasteurized mild, mainly from goats. [56–58].

There are 2 forms of the vaccine available in Europe. The most commonly used vaccine is FSME-Immun (Baxter Vaccine AG, Vienna, Austria) based on TBE virus initially derived

from virus pooled from several ticks from Neudörfl, Austria. This vaccine has undergone several iterations since it was initially approved for use in 1976. Initial versions of the vaccine suffered from a high incidence of associated side effects. In 1999 thiomersol was removed as a preservative and in 2000, the source of virus seed was changed from mouse brain suspension to chick embryo cell supernatant. At this time albumin was removed as a stabilizer, with an unexpected increase in adverse events. These consisted chiefly of high fever and febrile seizures in young children In 2001, the current version appeared using chick embryo cells as a source of viral seed, and the re-addition of albumin stabilizer [59]. A pediatric version (consisting of strength active ingredient) was added in 2002. This vaccine is also available in Canada. This version of the vaccine has shown a high degree of cross reactivity with the Siberian strains and the Far Eastern strains of the virus

The other European TBE vaccine, Encepur (Chiron-Behring, Marburg, Germany) is derived from the K 23 strain of TBE virus. An earlier version of this vaccine had numerous reports of IgE mediated immune reactions in the ½ dose pediatric version. This vaccine, as well as the adult formulation has been replaced by newer versions that do not use gelatin as a stabilizer and are now better tolerated.

Both of these vaccines use a standard and an accelerated schedule for dosing. The standard schedule consists of an initial injection followed by a 2nd dose in 1–3 months. Nine to twelve months after the second dose, a third dose is given. The accelerated dose (used mostly in travelers) is given as 3 doses given on days 0, 7, and 21. A protective immunity is elicited in approximately 2 weeks following either dosing regimen [60, 61].

In Russia, two vaccines are available against TBE. These are both prepared from Far-Eastern subtypes of the virus (strains Sofjin and 205). The Instituite of Poliomyelitis and Viral Encephalitis (Moscow, Russia) has produced a vaccine that has been in production since 1984. The second vaccine given the brand name ENCIVIR (Virion, Tomsk, Russia) has been in production since 2001. Both vaccines use a schedule of 3 doses for primary inoculation, and both are approved for use in children.

Tick-borne encephalitis virus specific immunoglobulin is used in Russia, both as a pre-exposure prophylaxis and post-exposure treatment. TBE immunoglobulin was withdrawn from use in Europe due to concern over possible severe side effects.

Use of the vaccine has proven very effective in reducing the incidence of TBE. Austria, which previously had the highest rates of TBE in Europe, began a mass vaccination campaign in 1981. By 2001, greater than 86% of the population had been vaccinated for TBE with seroconversion rates of greater than 99%. The number of TBE cases in Austria has decreased from almost 700 cases per year to approximately 50 cases per year. During this same period, the number of cases in the neighboring Czech Republic, which has a vaccination rate of approximately 10%, has increased from 300 cases per year to over 600 cases per year [62].

Unfortunately, no human vaccines currently exist for other important tick-borne infections (Babesiosis, Anaplasmosis, other TBE complex diseases), which has necessitated the search for new strategies for controlling disease.

The Future

With the withdrawal of the human Lyme disease vaccine, researchers have been exploring new ways of reducing the incidence of Lyme disease. New vaccines based on other *B. burgdorferi* antigens are currently undergoing testing. Unfortunately, the majority of *B. burgdorferi* proteins that have been tested for protective efficacy in a vaccine do not elicit

protective responses. Decorin binding protein A (DbpA) has been studied as a potential antigen with mixed results. As an antigen expressed by *B. burgdorferi* while in its mammalian host, there were initially high hopes for DbpA to be an ideal partner to the tick expressed OspA antigen in a vaccine. However, after encouraging results in DbpA vaccinated mice infected by needle inoculation, subsequent studies using a more natural infected tick challenge showed poor efficacy [63]. The exact reason for the lack of efficacy is unknown, but may be due to low expression of DbpA in the tick host and/or differences in post-translational processing of recombinant E. coli produced protein compared with natural DbpA [64]

Another potential candidate antigen is *B. burgdorferi* outer surface protein C (OspC). OspC is essential early in the transition from tick to mammalian host and is then subsequently down regulated by the organism. Early vaccine studies with OspC showed good protective efficacy against isogenic strains of the organism [65] However, there is significant sequence diversity in OspC among strains of *B. burgdorferi* and no protection was seen against different strains of *B. burgdorferi* expressing different variants of OspC. A phylogenetic analysis by Earnhardt and Marconi demonstrated on average a 65% sequence identity within different types of OspC, while having >97% identity within types with approximately 34 distinct sequences required for a broadly effective vaccine [66]. Recently, tetra and octa valent preparations of an OspC vaccine have shown promise in offering broader protection against a variety of *B. burgdorferi* strains [67, 68].

With very limited targets in development for an anti-*B. burgdorferi* targeted vaccine and no advanced vaccine candidates for Babesiosis or Anaplasmosis, researchers have also begun to investigate the possibility of vaccinating against the vector itself. Burke et al, made the observation that people who have cutaneous hypersensitivity to a tick bite (i.e. an immune reaction to the tick bite, likely due to prior exposure to multiple tick bites) have a decreased incidence of contracting Lyme disease [69]. While this may be due to earlier recognition and removal of the tick, there is laboratory evidence to support the possibility that exposure to tick antigens may decrease tick feeding. The conceptual groundwork for an anti-tick vaccine was established over 65 years ago when Trager first showed that guinea pigs developed resistance to tick feeding after even a single infestation with *Dermacentor variabilis* [70]. In conjunction with the resistance, upon subsequent feedings the guinea pigs showed significant evidence of an inflammatory immune response at the site of the tick bites suggesting that components of the immune response were responsible for incomplete feeding and detachment by the tick.

The early focus of development of tick vaccines has been on salivary gland proteins. These are sometimes referred to as “exposed” antigens because the host comes in direct contact with them and develops a natural antibody response [71]. Tick saliva is a complex mixture of components that serve multiple functions, including modulation of the host immune response by induction of different cytokines and chemokines, inhibition of host hemostasis, maintenance of attachment and digestion of proteins. Vaccines against salivary proteins may produce protection by blocking any or all of these functions and have the advantage that, by working at an early stage of infection, may be able to more effectively interfere with tick attachment or transmission of pathogens. Several groups have reported decreased transmission of *B. burgdorferi* when infected ticks are fed on mice that have previously been fed upon by pathogen free *Ixodes* [72, 73].

“Concealed” tick antigens may also provide protective immunity. Concealed antigens are those to which tick hosts do not develop an immune response against during the course of (repeated) tick infestations [71]. Concealed antigens that are potential vaccine targets are often proteins that play critical roles in the tick midgut such as proteases involved in

digestive processes. One potential disadvantage of concealed antigens is that because they are not injected into the host, anamnestic responses boosting antibody titers against the vaccine antigen do not occur in the course of natural exposure to the ticks. A concealed antigen of the tick *Boophilus microplus*, Bm86, has been developed into the first commercially available anti-tick vaccine and has had a large economic impact on the cattle industry in Australia and South America where *B. microplus* is prevalent [74]. Vaccination with Bm86 has been shown to decrease transmission of Babesia to vaccinated cows. Because all three of the Ixodes transmitted human pathogens, *B. burgdorferi*, *A. phagocytophilum* and *B. microti*, require a minimum of 36–48 hours to be transmitted from a tick to a human, vaccines that decrease feeding time have the potential for preventing acquisition of infection by vaccinated humans. Three very promising tick antigens of *Ixodes scapularis* have been identified—TROSPA, subolesin, and 64Trp. TROSPA is a tick midgut protein that serves as the binding partner for *B. burgdorferi* OspA. Antibodies to TROSPA do not appear to kill ticks, but does reduce vector competence for *B. burgdorferi* and subsequent transmission to new hosts [50]. Vaccination with subolesin or 64Trp have both been shown to diminish tick feeding and/or survival and have been shown to decrease transmission of *A. phagocytophilum* and tick borne encephalitis virus respectively [75, 76]. Vaccination with another *Ixodes* tick antigen, Salp25D, impaired acquisition of *B. burgdorferi* by ticks, but did not affect transmission of *B. burgdorferi* from infected ticks to uninfected mice [77]. While this renders Salp25D less useful as a candidate human vaccine, it may have uses as a reservoir vaccine.

In the absence of an available human vaccine, researchers have been investigating the vaccination of reservoirs of *B. burgdorferi* to reduce carriage of the organism. Tsao et al. performed an ambitious study where *Peromyscus* mice were captured and hand vaccinated with either OspA or a control vaccine. Vaccination significantly reduced the prevalence of *B. burgdorferi* the following year in ticks collected from sites where OspA was given compared with control [78]. Several groups are now developing methods for oral distribution of an OspA vaccine to mice and other reservoir hosts [79, 80]

In summary, multiple approaches to the prevention of human Lyme disease have now been tested and proven efficacious. However, despite their successes in trials or on a personal basis, none have been successfully employed to reduce either the geographic spread of Lyme disease or the increasing incidence of human infection on a population level. While the development of a human vaccine would be welcome, given the relatively localized areas of risk and the specific behaviors associated with exposure, even a highly efficacious human vaccine is unlikely to alter the dynamics of the disease—although it will be of great benefit to certain segments of the population—and the cost-benefit ratio may be prohibitive. Development of anti-tick vaccines that may protect against more than one agent may alter the cost-benefit ratio, particularly where potentially fatal diseases are involved. More promising would be the employment of community-wide approaches to reduction of disease reservoirs in the wild. Some simple models of tick ecology and *B. burgdorferi* transmission have suggested that combinations of currently available technologies (acaricides, 4-poster devices, deer reduction and vegetation reduction) on a widespread and yearly basis would be predicted to reduce the carriage of *B. burgdorferi* below the transmission threshold in 5–7 years depending upon the efficacy of the intervention [81, 82]. Further trials of these strategies hold the best hope for reduction of tick borne diseases in the future.

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