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The Blacklegged Tick, *Ixodes scapularis*: An Increasing Public Health Concern

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Abstract

In the United States, the blacklegged tick, *Ixodes scapularis*, is a vector of seven human pathogens, including those causing Lyme disease, anaplasmosis, babesiosis, *Borrelia miyamotoi* disease, Powassan virus disease, and ehrlichiosis associated with *Ehrlichia muris eauclarensis*. In addition to an accelerated rate of discovery of *I. scapularis*-borne pathogens over the past two decades, the geographic range of the tick, and incidence and range of *I. scapularis*-borne disease cases, have increased. Despite knowledge of when and where humans are most at risk of exposure to infected ticks, control of *I. scapularis*-borne diseases remains a challenge. Human vaccines are not available, and we lack solid evidence for other prevention and control methods to reduce human disease. The way forward is discussed.

Ixodes scapularis-Borne Disease Agents Are an Increasing Public Health Concern

Among the approximately 50 000 locally acquired vector-borne disease cases reported annually from the contiguous United States, roughly 95% are caused by tick-borne pathogens and >70% are Lyme disease [1]. Lyme disease is caused by the spirochetes *Borrelia burgdorferi* sensu stricto (herein referred to as *B. burgdorferi*) [2], or much less commonly by *Borrelia mayonii* [3]; both are transmitted by the blacklegged tick, *Ixodes scapularis* (including the junior synonym, *Ixodes dammini*) in the eastern United States where the vast majority of cases occur [4,5]. Over the past two decades, we have seen expansions in both the geographic range of *I. scapularis* [6] (Figure 1A,B) and the incidence and geographic range of Lyme disease and other *I. scapularis*-borne diseases [7,8] (Figure 1C,D). In addition, new *I. scapularis*-borne human pathogens continue to be discovered. As of 2017, seven microorganisms transmitted by *I. scapularis* – including five bacteria (*Anaplasma phagocytophilum*, *Bo. burgdorferi*, *Bo. mayonii*, *Bo. miyamotoi*, and *E. muris eauclarensis*), one protozoan parasite (*Babesia microti*), and one virus (Powassan virus) – are known to cause illness in humans [7,9]. The recognition of this diverse guild of *I. scapularis*-borne pathogens over the last five decades marks a significant shift in the perceived medical

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importance of the tick; prior to 1970, *I. scapularis* was not considered an important vector of human pathogens (Figure 2).

Humans are **incidental hosts** (see Glossary) of *I. scapularis* and its associated pathogens; although humans may be bitten [10,11], they are not essential for either the survival of tick populations or pathogen perpetuation (Figure 3). *I. scapularis* is a woodland-associated, three-host tick with a life cycle of 2–4 years [12,13]. Immature ticks (larvae and nymphs) have a broad host range, including rodents, insectivores, birds, lagomorphs, and ungulates [14,15]; whereas adults are restricted to medium- and large-sized mammals, primarily white-tailed deer (*Odocoileus virginianus*) [16]. With the exception of Powassan virus and *Bo. miyamotoi* **relapsing fever spirochetes**, which can be passed **transovarially** as well as acquired through blood-feeding [17,18], the other five human pathogens transmitted by *I. scapularis* are not known to be maintained transovarially, and acquisition by ticks therefore occurs during blood feeding [4,17,19–23].

Many different personal protective measures to prevent tick bites, and control strategies to reduce tick abundance or disrupt pathogen transmission cycles, have been evaluated and demonstrated to be effective at preventing tick bites or reducing the abundance of **host-seeking** ticks or infection rates in ticks or reservoir hosts [24–26]. These approaches include: tick repellents and permethrin-treated clothing to prevent human–tick contact; synthetic chemicals, natural products, and biological agents to suppress host-seeking ticks; deer reduction to suppress tick populations; topical application of pesticides to reduce tick burdens on rodents and deer; and antibiotic treatment or vaccination of rodent reservoirs against Lyme borreliosis spirochetes [27]. However, very few approaches have been evaluated with tick-borne diseases as an outcome measure, and we lack evidence for any currently available personal protective measure or environmentally-based tick/pathogen-control method to consistently reduce *I. scapularis*-borne infections [28,29]. Herein, we describe the rise of *I. scapularis* and its associated diseases, and discuss control opportunities and challenges.

Ixodes scapularis Is Reclaiming Its Historical Range

Tick surveillance is not standardized or routine, thus hampering our ability to monitor changes in the distribution and abundance of *I. scapularis* [6,30]. Retrospective review of *I. scapularis* records reveals remarkable range expansion over the past century, particularly in the northern portion of the eastern United States. The earliest record of the tick in the northeast dates back to the 1920s near Cape Cod, Massachusetts [31]. By 1945, *I. scapularis* was recorded sporadically from states along the northern Atlantic coast, but its core distribution was primarily in the Gulf Coast states and the southeast [10]. In the early 1960s, focal populations were reported along the New England coast and in Rhode Island, and later in that decade records emerged from Long Island, New York, and northwestern Wisconsin. During the 1970s, the reported distribution of the tick expanded, and its abundance increased along the Atlantic coast from New England to the mid-Atlantic states; expansion inland continued through the 1980s and 1990s [30,31].

Moreover, compilations of *I. scapularis* county collection records revealed that over the past two decades the tick's range has expanded substantially in the upper Midwest, northeast and mid-Atlantic states, but remained stable in the southeast (Figure 1A,B). As of 2016, *I. scapularis* had been documented in nearly half (1420 of 3110 counties) of the counties in the contiguous United States; in total, 842 counties across 35 eastern and central states are believed to have established populations [6]. Overall, during the past two decades, the number of counties in which *I. scapularis* is considered to be established has more than doubled. Recent habitat suitability models for *I. scapularis* identified many eastern counties as environmentally suitable for the tick to become established but from which it has not yet been reported, implying that the tick is still under-reported [32,33].

These geographical trends appear to represent a species reclaiming its historical range. Phylogeographic studies suggest that the tick's historical range likely extended across much of the eastern United States. It is likely that the species originated in the southern United States a half a million years ago, with later expansion into the mid-Atlantic and northeastern United States roughly 50 000 years ago, followed by colonization of the upper Midwest in the last 20 000 years following the retreat of the Laurentide Ice Sheet [34].

Environmental changes over the past 200 years drastically altered the distribution of *I. scapularis*, particularly in the northeast. Rapid deforestation to accommodate agriculture and to provide fuel, coupled with near elimination of white-tailed deer through hunting and habitat loss during the 1800s and early 1900s, likely restricted the range of this woodland tick that strongly depends on deer for blood meals in the adult stage. Refugia sites were restricted to focal areas in the northeast and upper Midwest where forests remained intact [31,35]. By the second half of the 20th century, large portions of the northeast were converted from agricultural to suburban land, leading to reforestation with a spatial mosaic of woods of various ages and patch sizes intermingled with ornamental plants and maintained lawns [36]. During roughly the same time period, the increase in suitable habitat for deer resulted in dramatically increasing abundance of white-tailed deer [35].

Although compilation of presence records provides a reasonably accurate representation of the tick's geographic range, lack of systematic vector surveillance limits accuracy in the estimation of geographic variation in the density of host-seeking *I. scapularis* nymphs, a variable that is more closely associated with Lyme disease incidence than measures of tick presence [37–40]. Roughly a decade ago, a systematic collection effort was undertaken to assess variation in the density of host-seeking nymphal *I. scapularis* ticks throughout the eastern United States [41]. The study revealed that, although *I. scapularis* was widely distributed, the density of host-seeking nymphs was generally higher in the north compared with the south, mirroring the reported distribution of Lyme disease cases in the eastern United States (Figure 1C,D). The findings were consistent with previous reports that, although the tick is present in southern states, host-seeking *I. scapularis* nymphs are rarely collected by **drag sampling** [42–44] and seldom bite people [11,45]. Later studies revealed distinct differences in host-seeking behavior between northern and southern clades of *I. scapularis*. Specifically, southern ticks are less likely than their northern counterparts to ascend vegetation when seeking hosts [46,47], thus reducing the likelihood of tick–human encounters when compared with their northern counterparts. Since the last systematic effort

to document geographic variation in the density of host-seeking *I. scapularis* throughout its range in the United States [41], the tick's range has expanded [6], and northern clade ticks appear to be spreading south [34]. Not surprisingly, the geographic range of counties classified as having high Lyme disease incidence has expanded following similar patterns [48]. A renewed effort to assess spatial variation in the density of host-seeking *I. scapularis* appears justified.

The Number of Recognized Human Disease Agents Transmitted by *I. scapularis* Is Growing

From 1970 through 2017, seven *I. scapularis*-borne human pathogens were described (Figure 2). In 1970, *Ba. microti*, an intraerythrocytic parasite, was first described in an otherwise healthy woman [49], (Figure 2). Shortly thereafter, *Ba. microti* was identified in white-footed mice (*Peromysus leucopus*) and in *I. scapularis*; experimental studies later confirmed that *I. scapularis* nymphs are capable of transmitting *Ba. microti* [50,51].

Lyme disease was first recognized in the United States as a new form of inflammatory arthritis in 1975 [52]. In 1982, a spirochete, later named *Bo. burgdorferi* [53], was identified as the etiological agent and shown to be transmissible by *I. scapularis* [2,5]. Although numerous small mammals and birds have been implicated as **reservoirs** of *Bo. burgdorferi*, the white-footed mouse is among the most important reservoirs in the eastern United States [15,36,54,55].

Human granulocytic anaplasmosis, originally described as human granulocytic ehrlichiosis (*Ehrlichia phagocytophila*), was first identified in six patients from northern Minnesota and Wisconsin presenting with acute febrile illnesses between 1990 and 1993. The timing of onset of cases was consistent with host-seeking activity of *I. scapularis* and *Dermacentor variabilis* and the former was implicated as a vector based on evidence that the closely related *Ixodes ricinus* transmits *E. phagocytophila* in Europe [56]. In 1996, *I. scapularis* was experimentally confirmed as a vector of *E. phagocytophila*, and *P. leucopus* was shown to be a competent reservoir [57]. In 2001, this intraleukocytic bacterium was renamed *A. phagocytophilum* [58].

Powassan virus, a flavivirus, was first recognized as a human pathogen in 1958 when it was isolated from a child who died of encephalitis [59]. *Ixodes marxi*, *Ixodescookei*, and *Ixodes spinipalpis* were implicated as **enzootic vectors** of Powassan virus in the 1960s [60–62], more than 30 years before experimental vector competence was demonstrated for *I. scapularis* [17]. Owing to its greater propensity to bite humans, *I. scapularis* is considered the primary **bridging vector** of Powassan virus (also referred to as 'Deer Tick virus' or 'lineage II Powassan virus') to humans [17,19,63].

In 2011, a novel obligate intracellular Gram-negative bacterium, found in *I. scapularis* from Minnesota and Wisconsin and later described as *E. muris eauclarensis* [64], was recognized to cause ehrlichiosis in humans [65]. *I. scapularis* was demonstrated experimentally to be a vector of *E. muris eauclarensis* [20,66], supporting earlier reports of natural infection in *I. scapularis* from Minnesota and Wisconsin [65,67,68]. *E. muris eauclarensis* has been

detected in naturally infected white-footed mice collected in these two states [69], and reservoir competence was demonstrated in the laboratory [66].

Bo. miyamotoi, a relapsing fever spirochete, was first described in *Ixodes persulcatus* in Japan [70]. In 2001, the ability of *I. scapularis* to transmit *Bo. miyamotoi* while feeding, and to pass spirochetes transovarially, was demonstrated under laboratory conditions [71]. A decade later, *Bo. miyamotoi* was recognized as a human pathogen in a report of 46 cases from Russia [72]. Shortly thereafter, the first recognized case of *Bo. miyamotoi* disease in North America was described in an 80-year-old woman from New Jersey [73]. The first large case series from the northeastern United States revealed that the peak onset of illness occurs from July through August – 1 month later than for Lyme disease, anaplasmosis, and babesiosis – and thus corresponds with the peak host-seeking activity of larval rather than nymphal *I. scapularis* ticks [74,75]. Although white-footed mice support short-lived infections of *Bo. miyamotoi* transmissible to feeding ticks and likely play a role in amplification of infections [71,76], transovarial transmission may be the primary route of enzootic maintenance [76–79].

Until 2016, when *Bo. mayonii* was described and recognized as a causative agent of Lyme disease in Minnesota and Wisconsin [3,80], *Bo. burgdorferi* had been considered the sole agent of Lyme disease in the United States. *Bo. mayonii* has been detected in field-collected *I. scapularis* from Minnesota and Wisconsin [3], and vector competence has been demonstrated under laboratory conditions [4]. *Bo. mayonii* also was isolated from white-footed mice and an American red squirrel (*Tamiasciurus hudsonicus*) in Minnesota, but reservoir competence has not yet been demonstrated experimentally [81].

Coinfections Are Common in *I. scapularis* and May Increase Severity of Illness in Humans

Coinfections are commonly reported in *I. scapularis*, most often dual infections of *Bo. burgdorferi* with either *A. phagocytophilum* or *Ba. microti* [82–91]. Because of small sample sizes and lack of systematic efforts to assess trends over the geographic range of *I. scapularis*, the true prevalence of coinfections remains unknown. Based on limited data, prevalence of dual infections varies over time and by geographic region and has been reported in 1–28% of ticks tested, but commonly less than 5–10% of ticks are coinfected [89–91].

Bo. burgdorferi and *Ba. microti* share a common reservoir, the white-footed mouse, explaining the increased likelihood of finding coinfections more often than expected by chance [85,86,91]. Recent evidence suggests that *Bo. burgdorferi* promotes transmission of *Ba. microti*, and the former typically becomes established in new foci before the latter [85,86,91,92]. By contrast, coinfection with *Bo. burgdorferi* and *A. phagocytophilum* are typically observed at rates expected based on prevalence of each infection individually, suggesting independent enzootic transmission maintenance cycles [83,84,87,93]. Although, the efficiency of *I. scapularis* to transmit *Bo. burgdorferi* or *A. phagocytophilum* is not affected by coinfection [84], coinfection in mice has been shown to increase pathogen acquisition by feeding larvae, compared with rates observed when feeding on singly infected

mice [94]. The relative abundance of various hosts in a community likely influences the probability of coinfections occurring. Although reported less commonly as a coinfection with *Bo. burgdorferi* compared with *A. phagocytophilum* or *Ba. microti*, coinfection with *Bo. miyamotoi* appears to occur at rates expected by chance, or lower, again suggesting independent mechanisms of persistence [76,82].

Coinfections with *I. scapularis*-borne pathogens in humans can arise from the bite of a single coinfected tick, or from concurrent bites by multiple singly-infected ticks. Although differences in methods of detecting infections differ across studies of persons diagnosed with tickborne diseases, and across studies from the northeastern and upper Midwestern United States, coinfection rates ranged from 0 to 67% for Lyme disease and babesiosis, 0 to 26% for Lyme disease and anaplasmosis, and 0 to 7% for anaplasmosis and babesiosis [90]. As reviewed previously, concurrent infections with *Bo. burgdorferi* and *Ba. microti* or *A. phagocytophilum* appear to increase severity of illness [90,91].

Incidence and Ranges of Diseases Caused by *I. scapularis*-Borne Pathogens Are Increasing

I. scapularis-borne pathogens are associated with four nationally notifiable diseases. Lyme disease was added to the list of notifiable conditions in 1991; anaplasmosis, Powassan virus disease, and babesiosis were included in 2000, 2002, and 2011, respectively. Case counts have generally increased for each of these conditions since they became notifiable (Figure 4). From 2002 to 2016, a total of 102 Powassan virus disease cases have been reported, with annual case counts ranging from 0 to 22 cases[i]. By contrast, since 2008, annual reported cases of Lyme disease have exceeded 30 000, marking a near tripling of reported cases since it was first notifiable in 1991 [8,95]. Notably, the number of cases reported is estimated to be approximately tenfold lower than the number of Lyme disease cases that are diagnosed annually [96,97]. Reported cases of anaplasmosis increased from 351 in 2000 to 4151 in 2016, and reported cases of babesiosis have increased from 1128 in 2011 to 1910 in [i].

Compared with Lyme disease, the incidence of reported anaplasmosis, Powassan virus disease, and babesiosis is several orders of magnitude lower, and their geographic distribution appears to be similar but more restricted; like the distribution of Lyme disease cases, the geographic range of anaplasmosis and babesiosis has similarly spread over time (Figure 4) [7,19,95,98,99]. Over 96% of Lyme disease cases are reported from just 14 states in the northeast, mid-Atlantic and the upper Midwest [95]. Since the mid-1990s, the number of counties with a high incidence of Lyme disease has increased by approximately 300% [48]. As it is not a notifiable condition, trends in incidence and geographic range of *Bo. miyamotoi* disease cases are not well characterized, but the geographic range is likely similar to that of Lyme disease [100]. By contrast, ehrlichiosis, caused by *E. muris eauclarensis*, thus far has been reported only from the upper Midwest [65].

[i]Resources
wwwn.cdc.gov/nndss/default.aspx

Controlling *I. scapularis* and Reducing Tick-Borne Diseases Is Challenging

The Evidence Base for Existing Interventions to Reduce Human Tick-Borne Disease Is Weak

Perhaps the most vexing aspect of control of *I. scapularis*-borne diseases, as exemplified by Lyme disease, is that we already know (i) the geographic areas in which the majority of cases will occur each year, and (ii) the months of the year during which most of the infections will be acquired [95]. In the Lyme disease focus in the northeast, we also know that humans most often encounter *I. scapularis* ticks in peridomestic settings, including on their own residential properties [26,37]. Despite this detailed knowledge of when and where humans are most at risk for exposure to infected ticks, we remain unable to control *I. scapularis*-borne diseases.

Previous reviews have addressed (i) personal protective measures to reduce human contact with *I. scapularis* ticks and environmentally based control methods to suppress host-seeking ticks and reduce infection with Lyme disease spirochetes in tick vectors and rodent reservoirs [25–27,101]; (ii) the evidence base for such measures, and methods to reduce Lyme disease [28,29,102,103]; and (iii) the prospect for a human Lyme disease vaccine to re-emerge in the wake of the rise and fall of Lymerix, an effective licensed vaccine that was removed from the US market in 2003 [104,105]. Despite the emergence of a wide array of approaches to avoid contact with ticks through personal protective measures, suppress host-seeking *I. scapularis,* or disrupt enzootic *B. burgdorferi* transmission, we unfortunately still lack robust evidence for any method other than a human Lyme disease vaccine to reduce disease cases. When thinking about strengths and weaknesses of methods to prevent *I. scapularis*-borne infections, we find it useful to illustrate the chain of events leading to a case of *I. scapularis*-borne infection (using Lyme disease as an example) and, working backwards from the human infection, define and discuss the points where we can potentially intervene (Figure 5).

Disease Resulting from Bites by Infected Ticks Can Be Prevented by Early Tick Detection and Removal, Antibiotic Prophylaxis, and, in the Future, Hopefully Also by Vaccines

The most proximate intervention to prevent a human infection caused by an *I. scapularis*-borne pathogen is to ensure that the bite of an infected tick does not result in illness (Figure 5). Although this intuitively is the most impactful intervention point, all currently available intervention methods suffer from the shortcoming of being reliant on detection of attached ticks. The fact that *I. scapularis* nymphs are notoriously difficult for people to detect while biting [106] limits the usefulness of both removal of an attached infected nymph before it can transmit a pathogen [107] and antibiotic prophylaxis following a recognized tick bite [108]. This could potentially be overcome with a new type of consumer product to kill attached ticks without first having to detect their presence, such as an acaricidal skin lotion or shower soap. However, even this solution has practical limitations because it will require daily use and would be effective only if the soap or lotion is applied directly onto an unrecognized biting tick. Moreover, the tick would be attached for some period of time before being impacted, thus increasing the risk for pathogen transmission.

Potential future **magic bullet** solutions, capable of both ensuring that the bite of an infected tick does not result in illness and having the potential to rapidly and dramatically reduce *I. scapularis*-borne human infections at the population level, include (i) human vaccines or prophylactic antibody treatments against Lyme disease spirochetes or other *I. scapularis*-borne pathogens [104,105,109,110], and (ii) transmission-blocking anti-tick vaccines for human use with potential for simultaneous protection against multiple *I. scapularis*-borne pathogens [111–115]. These approaches would not require daily action and vigilance, and they would be effective regardless of whether or not bites by infected ticks are noticed. If proven to be safe, effective, and acceptable for widespread use, there is no question that the re-emergence of a human vaccine against *Bo. burgdorferi*, or the emergence of a prophylactic antibody treatment, would be the most effective ways to rapidly reduce Lyme disease cases. However, neither approach would address the remaining *I. scapularis*-borne pathogens, several of which are on the rise (Figure 4). A transmission-blocking anti-tick vaccine could potentially address that shortcoming, but only if it proves to act quickly and effectively enough on an infected tick to prevent or substantially reduce the likelihood of pathogen transmission occurring before the tick is incapacitated. These urgently needed approaches merit greater resources to expeditiously move them forward in a pipeline from prevention concept to proven solution and become, should they be successful, cornerstones in public health programs to reduce *I. scapularis*-borne infections.

Use of Repellents and Permethrin-Treated Clothing Can Reduce the Risk of Tick Contact Resulting in Bites

The next point of intervention to prevent a human infection is to ensure that ticks making contact with human skin or clothing do not get an opportunity to bite (Figure 5). This can be achieved by the use of tick repellents on skin and clothing, or the use of permethrin-treated clothing [27,116], combined with regular checks for crawling ticks, changing clothes when coming inside (and drying removed clothing articles at high heat), and taking a shower (ensuring removal of clothes worn outside, increasing the likelihood of detecting crawling ticks, and perhaps also dislodging crawling ticks while showering) [25,29,95]. The main problem is that all of these actions require a level of daily vigilance and effort that is hard to keep up for the period of 2–3 months during which *I. scapularis* nymphs are most active. Another problem is that we lack knowledge of how specific use patterns for repellents and permethrin-treated clothing, including frequency of use and extent of the body protected, may impact their protective effect against tick bites.

Risk of Contact with Host-Seeking Ticks Can Be Minimized by Behavioral Change, Environmental Modification, and Killing of Host-Seeking Ticks

Even further distant from the human infection, we can intervene by minimizing contact with host-seeking ticks (Figure 5) through (i) avoidance of habitats with a high risk for tick contact (easier said than done if it includes your backyard), (ii) reduction in longevity or survival of desiccation-sensitive host-seeking *I. scapularis* ticks in the peridomestic environment (e.g., xeriscaping, hardscaping, and vegetation management, including keeping grass short, clearing brush and removing leaf litter), or (iii) direct killing of host-seeking ticks with acaricides or biological control agents [24,25,27,29,117]. Here we introduce increased complexity by relying on solutions that are highly sensitive to human movement

patterns. For example, controlled experimental spring applications of pyrethroids typically reduce host-seeking *I. scapularis* nymphs by >85% [27]. Nevertheless, a recent effort to reduce tick bites and human *I. scapularis*-borne infections by spraying pyrethroids along the lawn–wood interface on residential properties, rather than treating all the wooded and brushy high-risk habitat on the properties, achieved 50–70% suppression of host-seeking *I. scapularis* nymphs within the areas sprayed but failed to reduce either tick bites or human infection [118]. Suppression of host-seeking *I. scapularis* nymphs across all wooded or brushy habitats on a property, thereby getting closer to a desired goal of complete absence of ticks in this high-risk environment, intuitively should be more impactful but it is also more expensive and may come at higher environmental costs. It remains to be evaluated to what extent such an intervention can reduce tick-borne disease.

Production of Infected Ticks Can Be Suppressed by Targeting Important Tick Hosts and Pathogen Reservoirs

Finally, we can intervene by suppressing production of infected *I. scapularis* nymphs by disrupting enzootic pathogen transmission among tick immatures and vertebrate hosts acting as pathogen reservoirs (particularly rodents) and targeting key hosts for the adult stage (particularly white-tailed deer) to reduce overall tick populations (Figure 5). There is little doubt that the white-tailed deer is the engine that drove the remarkable surge in populations of *I. scapularis* seen across the northeast and upper Midwest over the last 50 years [31,35]. Intuitively, adult *I. scapularis* ticks feeding on white-tailed deer is the weakest point in the chain leading to tick population build-up and, ultimately, intensified enzootic transmission among tick immatures and pathogen reservoirs, and production of pathogen-infected *I. scapularis* nymphs. It therefore has been reasonably argued that addressing deer, either by population reduction to very low levels or topical/oral application of acaricides to a large proportion of the deer, should be viewed as a cornerstone of area-wide environmentally based integrated management programs for *I. scapularis* [25,26,101,103]. Although numerous methods targeting rodent reservoirs and white-tailed deer have emerged in the last 30 years [27], questions remain about the extent of available animals within a given area that need to be removed or treated to achieve reduction of human tick bites and human disease [26,28,102,103]. These methods also can be sensitive to local vertebrate community structure (if alternative pathogen reservoirs are readily available for tick immatures or alternative hosts for adult ticks are abundant) or, when relying on food baits in the implementation, to natural variation in food sources for rodents or deer over time.

Integrated Intervention Approaches Need to Be Evaluated with Human Disease Outcome Measures

Barring the emergence of a magic bullet solution (human vaccine, prophylactic antibody treatment, or transmission-blocking anti-tick vaccine), no single personal protective measure or environmentally based tick/pathogen control method is likely to substantially reduce *I. scapularis*-borne infections when used in isolation [28]. A few integrated intervention approaches that combine two or three environmentally based control methods have been shown to effectively reduce abundance of host-seeking *I. scapularis* nymphs [26,27,119–121], but none of these integrated approaches have yet been evaluated with the gold standard of human infection with an *I. scapularis*-borne pathogen as an outcome measure [28]. As

suggested by the chain of events outlined in Figure 5, we also need to think outside the box and consider integrated intervention approaches that – rather than just combining two or more environmentally-based control methods – also include changes in human behavior and the use of existing personal protective measures.

We Need to Better Understand the Issues Relating to Cost, Acceptability, and Feasibility of Different Intervention Approaches

Another major challenge arises because control of *I. scapularis* and prevention of infection with its associated pathogens remains the responsibility of individual homeowners. Families therefore must make decisions regarding personal protective measures and environmentally based tick control on their properties, taking into consideration how much money they are willing to spend, under which circumstances (when and where) they wish to be protected, the level of daily effort required to achieve protection, and whether a given measure or method is acceptable to use. As illustrated in Figure 6, an ideal tick-borne disease prevention method should, from the perspective of a family, incur low cost, require minimal effort, and be globally effective (i.e., protective everywhere, all the time, and regardless of type of activity). It also must be acceptable for use. The scope of this challenge is illustrated by the most recently published survey of willingness to pay for tick control [122], which found that most residents in a Lyme disease endemic setting in Connecticut were unwilling to spend more than $100 per year and that acceptability was limited for some methods, including the use of acaricides to kill host-seeking ticks.

The magic bullet approaches discussed above (human vaccine, prophylactic antibody treatment, or transmission-blocking anti-tick vaccine) come closest to solving the ‘impossible tribar’ of low cost, minimal effort, and global effectiveness, should they emerge and prove to be safe, effective, and widely acceptable for use (Figure 6). All currently available personal protective measures or environmentally based control methods fall short for at least one of the three desired characteristics, and some likely also will have limited acceptability. This, in turn, raises the intriguing question of which characteristic a majority of families is willing to give up: low cost, minimal effort, or global effectiveness? We therefore need to consider not only whether solutions to reduce *I. scapularis*-borne infections can be applied by individual families/on individual properties or may require implementation at a neighborhood/community scale, but also which solutions can achieve specific combinations of at least two desired characteristics: low cost–minimal effort, low cost–global effectiveness, or minimal effort–global effectiveness. Finally, we note that the process of moving promising solutions to reduce *I. scapularis*-borne infections forward in a pipeline from prevention concept to proven solution and successful public health program currently is impeded by an order of magnitude shortcoming in the financial resources available to achieve this effectively and expeditiously.

Concluding Remarks

In recent decades, *I. scapularis* has become more widespread, and an increasing number of microorganisms transmitted by this tick have proven to be pathogenic in humans. In parallel, both the incidence and geographic range of reported cases of *I. scapularis*-borne diseases

have increased, and coinfections are increasingly being recognized to contribute to severity of illness. Moreover, habitat suitability models suggest that the tick's potential range exceeds the current reported distribution, suggesting either under-reporting of the tick's current range or the potential for range expansion (see Outstanding Questions). Because the presence of the **vector tick** is a prerequisite for human tick-borne infections, we recognize a need to monitor changes in the distribution of *I. scapularis*. Recognizing that the density of host-seeking infected nymphs provides a better estimate of human risk for bites by infected ticks than measures of tick presence, we emphasize the need to assess spatial variation in the density of infected host-seeking nymphs in order to educate the public of changing risk patterns. Such studies should (i) use standardized sampling methodology, (ii) be conducted during the expected peak in nymphal host-seeking, (iii) use sensitive and specific pathogen-detection assays that are capable of detecting coinfections, (iv) report the density of pathogen-infected host-seeking nymphs (the life stage most often associated with human infections) per sampling site, and (v) use appropriate statistical methods to extrapolate predictions about the measured outcomes to areas that were not sampled. Moreover, there is a critical need for intervention approaches with proven capacity to reverse the growing public health problem imposed by *I. scapularis* (see Outstanding Questions). We need intensified and sustained efforts to develop safe and effective human vaccines, prophylactic antibody treatments, and transmission-blocking anti-tick vaccines, as well as a stronger evidence base for the capability of other already available personal protective measures and environmental control methods to reduce tick-borne disease, especially for integrated intervention approaches. Although proof-of-concept studies will logically focus on acarological or zoonotic outcomes (e.g., tick or host abundance, infection rates in ticks or hosts), ultimately evaluations of prevention strategies with human disease outcomes are needed.

Outstanding Questions

How widespread is *I. scapularis*?

How does the density of infected host-seeking nymphs change across the species' range?

Are *E. muris eauclarensis* and *Bo. mayonii* restricted to the upper Midwest and, if so, why?

As previously distinct northern *I. scapularis* foci in the upper Midwest and northeast are merging, how will this affect the distribution of *I. scapularis*-borne pathogens?

Why is the prevalence of *Bo. miyamotoi* in ticks so low compared with *Bo. burgdorferi*, given that the former is transmitted transtadially and transovarially and the latter is transmitted only transtadially?

Among the potential control strategies, which has the greatest potential to reduce the incidence of *I. scapularis*-borne disease cases? Given that none of the current options can combine low cost, minimal effort, and global effectiveness, which

characteristic is a majority of families willing to give up: low cost, minimal effort, or global effectiveness?

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Glossary

Bridging tick vectors
ticks that acquire pathogens from zoonotic hosts involved in enzootic transmission cycles and later transmit pathogens to incidental hosts, which, in the case of tick-borne pathogens, include humans.

Coinfection
simultaneous infection with two or more pathogens within the same vector or host.

Drag sampling
a method of collecting host-seeking ticks in which a blanket is dragged across vegetation, typically over fixed distances or amounts of time, usually in an effort to quantify the abundance or density of host-seeking ticks. It is generally considered a better measure of the risk for human encounters with ticks than measures of tick abundance on hosts.

Enzootic tick vectors
ticks that transmit the pathogen of interest among zoonotic hosts.

Host-seeking
behavior displayed by a tick in an attempt to find a bloodmeal host (e.g., ascending vegetation and waiting for a host to pass by).

Incidental hosts
hosts that are not essential to the tick's life cycle or perpetuation of tick-associated pathogens.

Magic bullet
something providing an effective solution to a difficult or previously unsolvable problem.

Relapsing fever spirochetes
phylogenetically related to Lyme disease spirochetes, but relapsing fever spirochetes are typically transmitted by soft (argasid) ticks (with the notable exception of a few hard-tick-borne species, including *Borrelia miyamotoi*), and transovarial transmission is common. In contrast, Lyme disease spirochetes are transmitted by hard (ixodid) ticks and are not maintained transovarially.

Reservoirs
organisms in which a pathogen can survive and reproduce, for some period of time, and that contribute to enzootic maintenance.

Transovarial transmission

passage of infection from an infected adult female tick to her eggs.

Vector ticks

ticks capable of acquiring infection during blood-feeding or transovarially, remaining infected through transition to subsequent life stages, and infecting a susceptible host while feeding.

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Highlights

The blacklegged tick, *Ixodes scapularis*, is becoming more widespread in the eastern United States.

The number of *I. scapularis*-borne microorganisms recognized to be pathogenic in humans is increasing.

The incidence of *I. scapularis*-borne disease cases continues to increase.

The geographic distribution of human cases of *I. scapularis*-borne diseases is expanding.

There is a critical need for control approaches with proven capacity to reverse the growing public health problem imposed by *I. scapularis.*

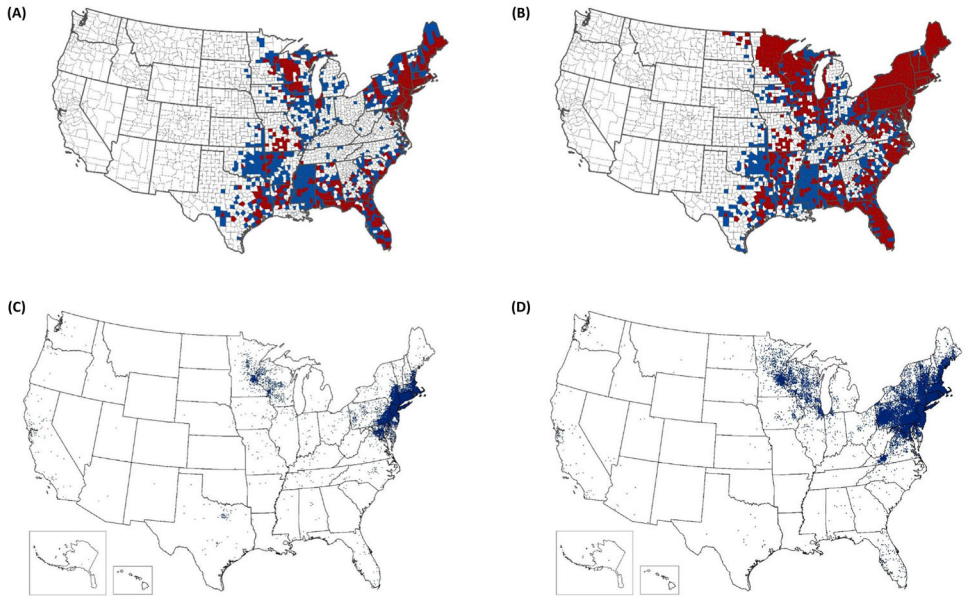

Figure 1.

Reported Distribution of *Ixodes scapularis* in 1996 (A) and 2016 (B); and Reported Cases of Lyme Disease in 2001 (C) and 2015 (D).

Counties classified as established, based on <6 individual ticks of a single life stage or >1 life stage reported per county in a year are shown in red. Counties classified as reported based on <6 individual ticks reported in a year are shown in blue. Data from A and B are derived from Dennis *et al.* [30] and Eisen *et al.* [6], respectively. In panels C and D, one dot was placed randomly within the county of residence for each reported case. In the far-western United States, *Ixodes pacificus* serves as a vector of *Borrelia burgdorferi*.

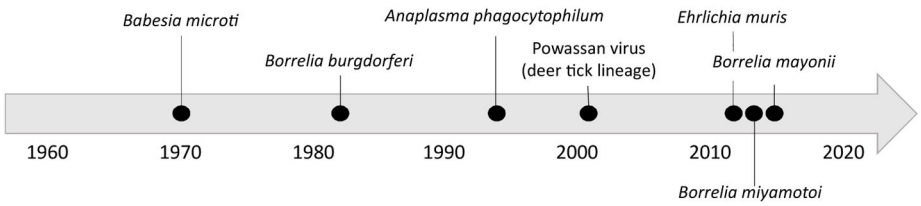

Figure 2.
Timeline Showing Discovery of the Seven Human Pathogens Transmitted by *Ixodes scapularis*.

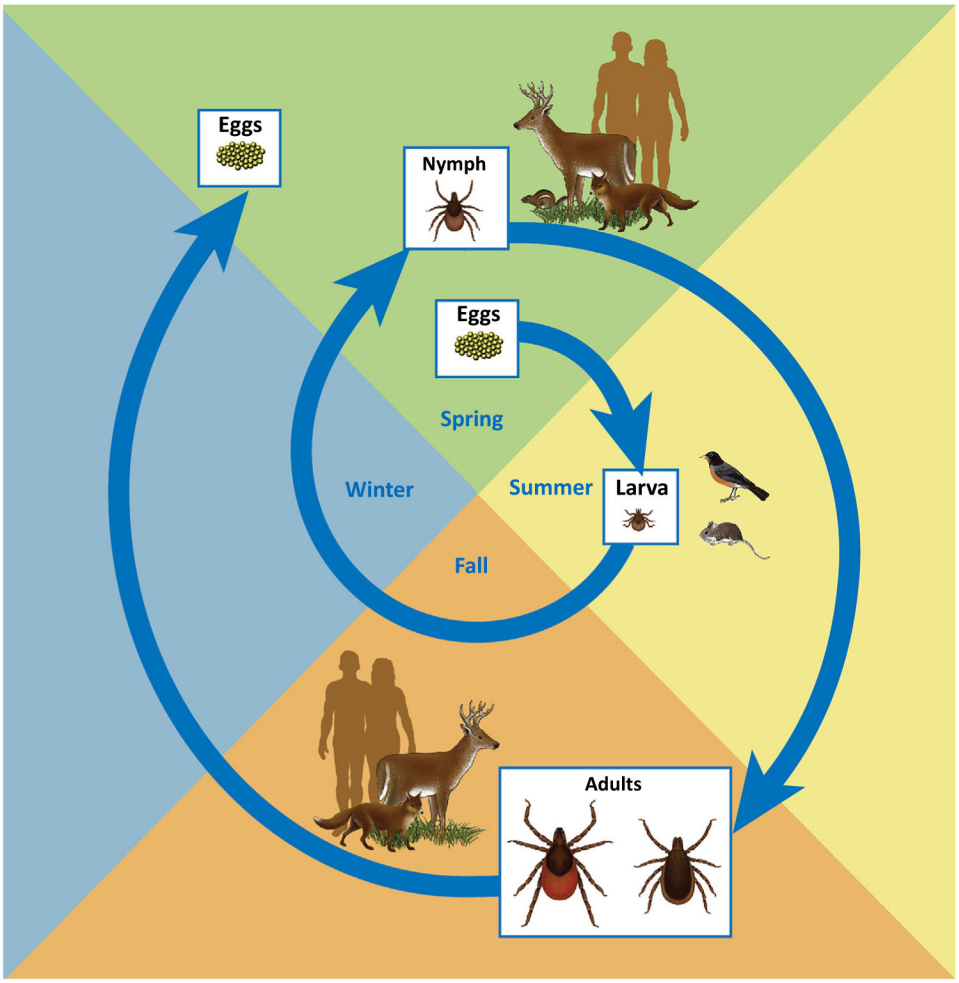

Figure 3.
Life Cycle of *Ixodes scapularis*.

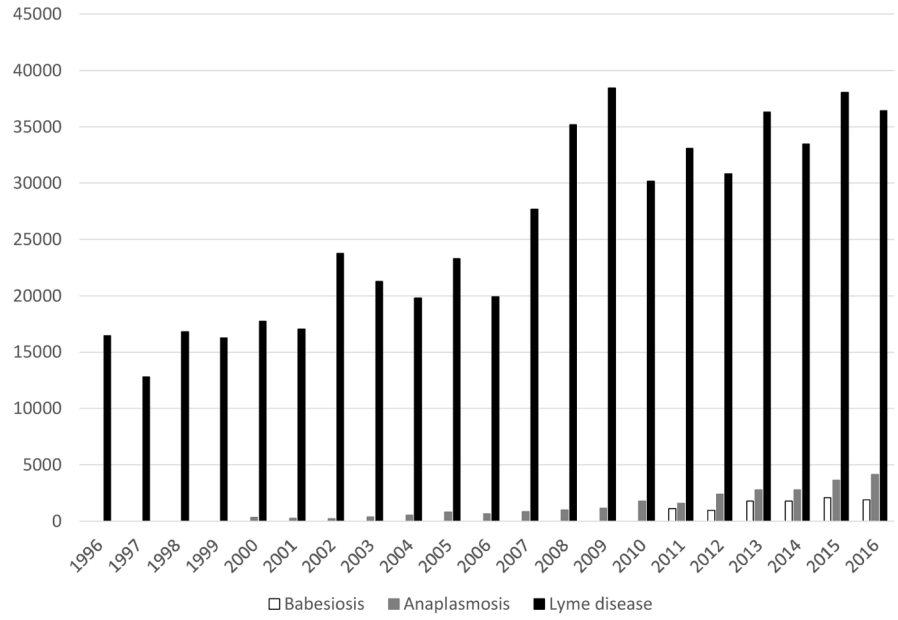

Figure 4.

Reported Cases of Babesiosis, Anaplasmosis, and Lyme Diseases in the United States, 1996–2016. Source: https://wwwn.cdc.gov/nndss/data-and-statistics.html (last referenced November 13, 2017).

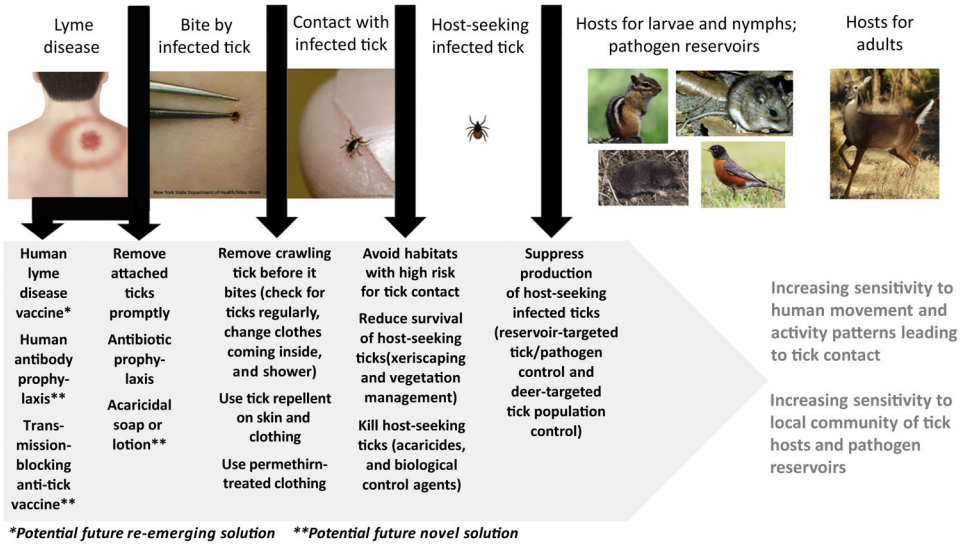

Figure 5.

Chain of Events Leading to a Lyme Disease Infection, with Possible Intervention Points for Different Control Approaches.

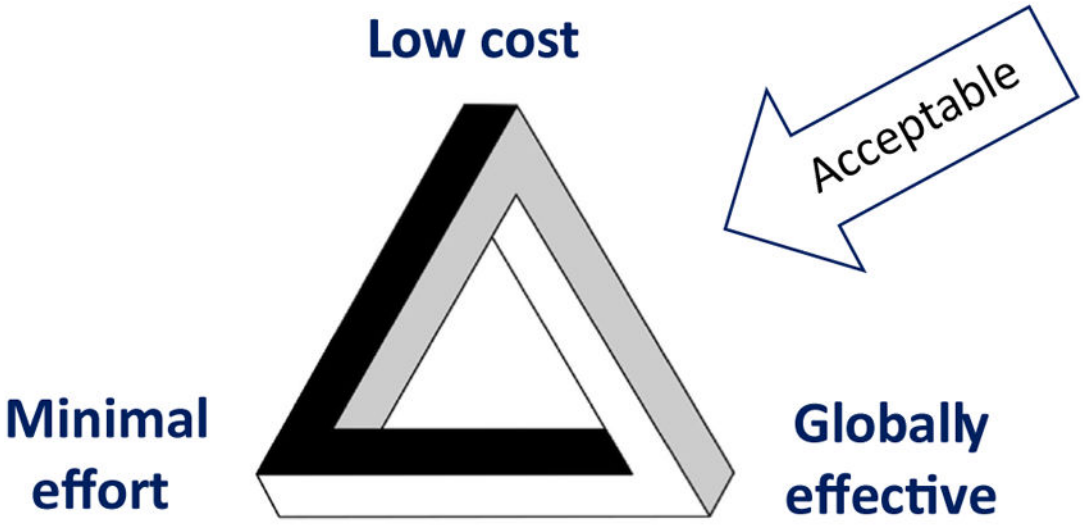

Figure 6.
Desired Characteristics of an Ideal Tick-Borne Disease Prevention Method.