Title Figure. Mouth parts of a tick. The center of the mouth (yellow) is covered in tiny barbs that help keep the tick lodged on the host while feeding. Image credit: Igor Siwanowicz, Janelia Farm Research Campus, Howard Hughes Medical Institute, Ashburn, VA. This image is subject to the [creative commons license](#).

NIH STRATEGIC PLAN FOR TICKBORNE DISEASE RESEARCH

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PREPARED BY THE NIH TICKBORNE DISEASES STRATEGIC PLANNING TEAM

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Executive Summary

The U.S. National Institutes of Health (NIH) is committed to addressing the insidious threat to public health posed by the rising incidence of tickborne diseases (TBDs) in the United States. The number of reported TBD cases [more than doubled](#) from 2004 to 2016 , and reached a record high of [59,349](#) cases in 2017. From 2004 to 2016, TBDs represented more than [75 percent](#) of all vector-borne disease cases (642,602 total cases) reported in the United States. Current strategies to address TBDs are hindered by suboptimal diagnostics, a paucity of treatment options for viral and other TBDs, and a lack of vaccines.

This *NIH Strategic Plan for Tickborne Disease Research* proposes building on current trans-NIH efforts to better understand the complex interplay among host, tick, and pathogen factors that contribute to TBDs and the body's defenses against them. The plan aims to leverage this understanding to develop new tools that can more effectively prevent, diagnose, and treat TBDs. These tools will include rapid diagnostics that can discern different TBDs, preventive vaccines, and treatment options for all disease stages of TBDs, in the diverse populations and age groups affected (Figure 1).

Box 1. NIH Strategic Plan for TBD Research Mission
Accelerate efforts across the research spectrum to improve the understanding of TBDs and advance the development of effective tools and strategies for diagnosis, prevention, and treatment

To address the rising threat that TBDs represent, in 2016 the [21st Century Cures Act](#) mandated the establishment of the [HHS Tick-Borne Diseases Working Group](#) to provide expertise, ensure interagency coordination across the Department of Health and Human Services (HHS), and examine research priorities related to TBDs. As part of their directive, the working group developed a [2018 report](#) to Congress that outlined recommendations for TBD research, including a significant emphasis on intensifying research efforts to advance fundamental knowledge of TBDs and enable the development of improved diagnostics as well as treatment and prevention strategies. The 2018 report also called for developing an NIH strategic plan to coordinate a trans-NIH research effort to address TBD research priorities.

The *NIH Strategic Plan for Tickborne Disease Research* highlights the agency's TBD research mission (Box 1), which aligns with the HHS working group recommendations. The plan includes five strategic priorities that capitalize on existing research initiatives and resources to develop the knowledge and tools needed to combat TBDs:

1. **Improve fundamental knowledge of TBDs** to understand the host, vector, and pathogen factors that drive TBD pathogenesis and transmission. Elucidate the host immune mechanisms in response to and exploited by TBD pathogens.

2. **Advance research to improve the diagnosis of TBDs** using both host- and pathogen-targeted approaches, including research for rapid diagnostics and multiplex platform approaches that detect multiple tickborne pathogens.
3. **Accelerate research to improve TBD prevention** by supporting science to design, develop, and evaluate vaccines, vector control strategies, and other prevention approaches.
4. **Promote research to improve treatment for all forms of TBDs**, including studies to develop effective therapies to treat symptoms that persist after TBD treatment, therapies for non-infectious TBDs, and new antimicrobials.
5. **Support tools and resources to advance research in understanding, preventing, diagnosing, and treating TBDs,** including repositories, genomic resources, animal models, and preclinical services to aid the development and assessment of diagnostic, vaccine, and therapeutic candidates.

To accelerate research within these five strategic priorities over the next 5 years and beyond, NIH will leverage current resources and expand collaborations across NIH institutes to promote a multidisciplinary approach to TBD research. These trans-NIH efforts will draw on diverse expertise—from vector biologists to neurologists—to answer complex biological questions and encourage the application of state-of-the-art technologies used successfully in other fields. Furthermore, by supporting systems biology research along with the more traditional approaches, NIH will develop new strategies to help stem the rising incidence of TBDs in the United States.
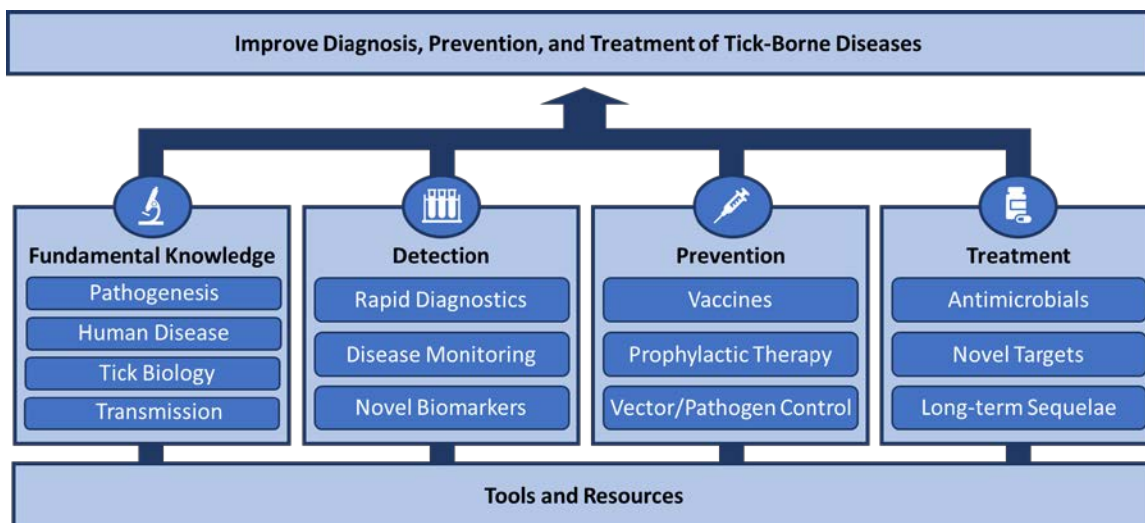

Figure 1. The NIH Strategic Plan for TBD Research builds on the existing foundation of research and resources to advance five TBD research priorities targeted at 1) improving fundamental knowledge, 2) advancing diagnosis, 3) preventing new TBD infections, 4) improving treatment for all forms of TBDs, and 5) supporting tools and resources to advance priorities 1 through 4.

Introduction

Tickborne diseases (TBDs) are the most common illnesses transmitted by arthropods (insects, ticks, and mites) in the United States, and the annual number of reported TBD cases continues to increase (Figure 2). In the United States, more than 20 different disease-causing bacteria, viruses, and parasites are transmitted to humans through the bite of a tick (Table 1), and many additional TBDs occur internationally. Most of these TBDs were unknown 50 years ago, and many were only discovered during the past decade.

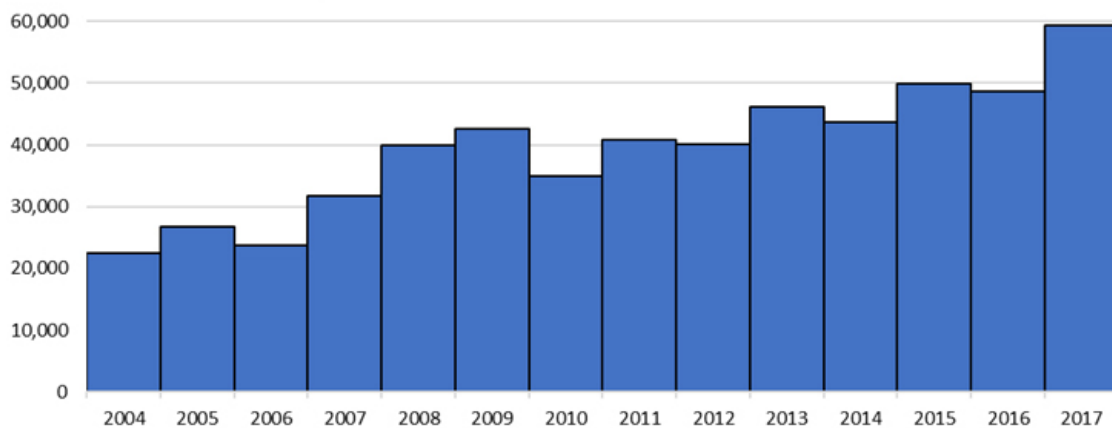**Figure 2. Annual Reported Cases of TBDs in the United States**

Figure 2. Annual reported cases of TBDs in the United States have increased from 2004 to 2017, with a record high number of reported cases in 2017. Figure from CDC: Tickborne Disease Surveillance Data Summary.

Newly identified tick-transmitted pathogens continue to be reported, raising concerns about missed diagnoses, inadequate treatment, and gaps in our understanding of where, when, why, and how TBDs occur. Tick bites are also responsible for the non-infectious disease tick paralysis, and likely the recently discovered alpha-gal allergic syndrome, or "red-meat allergy." Depending on the disease, clinical manifestations of TBDs can range from mild, self-limiting infections to serious illness, extended disability, or even death.

Multiple tick species transmit TBDs, and the changing dynamics and geographic ranges of ticks in the United States and globally have caused additional concerns regarding who is at risk. These changes further reinforce the need for vigilance in responding to new and emerging TBD threats at a time when the true global burden of tickborne infections remains unknown.

TBDs have received increasing public attention given their shifting ranges, increasing incidence, the emergence of new pathogens, and the potential for serious

illness (Box 2). TBDs have been and remain an important research focus at NIH as well. NIH supports a broad range of research studies designed to unravel the biology of ticks and tickborne pathogens and the interactions between ticks, tickborne pathogens, and the mammalian host, with the goal of developing better ways to prevent, diagnose, and treat TBDs.

Tickborne Diseases in the United States

TBDs have been recognized in the United States since at least the late 19th century, and NIH has been involved in their study since early in its history. The Rocky Mountain Laboratories (RML), a component of the NIH National Institute of Allergy and Infectious Diseases (NIAID), traces its origins to the early 1900s as a research station in Montana established to investigate a deadly measles-

> **Box 2. Scope of the U.S. Tickborne Disease Threat**
>
> - Between 2004-2016:
>   - Tickborne pathogens caused more than 75% of 642,602 reported cases of vector-borne disease.
>   - Reported cases for most TBDs at least doubled; some increased up to six-fold.
>   - Lyme disease accounted for more than 80% of TBD cases.
> - TBD cases continue to rise, with 59,349 cases reported in 2017 compared to 48,610 cases in 2016.
> - Approximately 30,000 cases of Lyme disease are reported annually.
> - The Centers for Disease Control and Prevention (CDC) suspects Lyme disease underreporting; actual annual Lyme disease cases are estimated at ~300,000 annually.

like disease. That disease was ultimately identified as Rocky Mountain spotted fever (RMSF), caused by the bacterium *Rickettsia rickettsii* and transmitted by ticks. RML became a component of NIH in 1937 and remains an active site for TBD and other infectious disease research. The causative agent of Lyme disease, for example, was first isolated by RML scientists.

RMSF remained one of only a few recognized human TBDs in the United States for much of the 20th century. The emergence of Lyme disease in the 1970s; however, ushered in a new appreciation for the potential diversity and public health burden of tickborne infections. Within a decade of the identification of *Borrelia burgdorferi*, the causative agent of Lyme disease, researchers began to identify additional tickborne pathogens associated with human disease in the United States. These include human ehrlichiosis (1987), human anaplasmosis (1990), *Rickettsia parkeri* spotted fever (2004), Pacific Coast tick fever (2008), *Ehrlichia muris*–like infection (2009), Heartland virus (2009), *B. miyamotoi* infection (2013), Bourbon virus (2014), and *B. mayonii* infection (2016).

In 2009, researchers reported a novel allergy to red meat associated with certain antibodies against a molecule in meat called galactose-alpha-1,3-galactose (alpha-gal). They soon accumulated evidence that the trigger for this so called red-meat

allergy, or alpha-gal syndrome, was the [bite of the lone star tick](). This was the first report of an arthropod bite leading to food allergy in people.

Table 1. Tickborne Diseases of the United States			
Pathogen Type	**Disease**	**Pathogen (U.S.)**	**Tick vector (U.S.)**
Bacteria	Lyme disease	*Borrelia burgdorferi Borrelia mayonii*[1]	Blacklegged tick, western blacklegged tick[1]
	Borrelia miyamotoi infection	*Borrelia miyamotoi*[2]	Blacklegged tick
	Tickborne relapsing fever	*Borrelia hermsii, B. turicata, B. parkeri* and others	Soft ticks (*Ornithodoros* species)
	Anaplasmosis	*Anaplasma phagocytophilum*	Blacklegged tick, western blacklegged tick
	Ehrlichiosis	*Ehrlichia chaffeensis Ehrlichia ewingii Ehrlichia muris eauclairensis*	Lone star tick Lone star tick Blacklegged tick (possible)
	Tularemia	*Francisella tularensis*	American dog tick, Rocky Mountain wood tick, lone star tick
	Rocky Mountain spotted fever	*Rickettsia rickettsii*	American dog tick, brown dog tick, Rocky Mountain wood tick
	Other spotted fever	*Rickettsia parkeri*	Gulf Coast tick
	Pacific coast tick fever	*Rickettsia philipii*	Pacific Coast tick
Virus	Powassan disease	Powassan virus	Blacklegged tick, groundhog tick
	Colorado tick fever	Colorado tick fever virus	Rocky Mountain wood tick
	Bourbon virus	Bourbon virus	Undetermined
	Heartland virus	Heartland virus	Lone star tick
Parasite	Babesiosis	*Babesia microti, B. duncani*	Blacklegged tick
Unknown	Southern tick-associated rash illness	Unknown	Lone star tick
None	Alpha-gal syndrome	None	Lone star tick
	Tick paralysis	None	American dog tick, Rocky Mountain wood tick

Table 1

[1] Borrelia mayonii is a recently discovered pathogen that causes Lyme disease. It has not to date been associated with the western blacklegged tick.

[2] Borrelia miyamotoi is a recently discovered pathogen that causes a relapsing fever and is genetically more similar to the relapsing fever Borrelia species.

An Interplay of Pathogen, Vector, Reservoir, and Host

Unlike infectious diseases that spread directly from person to person or through intermediate surface contact, TBDs are transmitted through a complex interplay of human hosts, pathogens, ticks, and animal reservoirs. A comprehensive strategic research plan therefore requires elements from multiple biological disciplines.

In the United States, nine species of "hard ticks" transmit the majority of tickborne infections, whereas several "soft ticks" primarily transmit bacteria causing tickborne relapsing fever. The recent identification of *Borrelia miyamotoi* infections in the United States represents the unusual transmission of relapsing fever by a hard tick (Table 1).

As the number of tickborne pathogens continues to increase in North America, so has the number of tick species. In 2017, the Asian longhorned tick, *Haemaphysalis longicornis*, was identified in the United States for the first time. The tick, which can transmit human disease in its native Asia, has not yet been shown to carry any known human pathogens in the United States. As of August 2019, Asian longhorned ticks have been identified in 12 states.

In general, the association between a pathogen and a tick is specific, and not every tick can transmit every microbe. This specificity depends on many variables, including the molecular interactions that enable the pathogen to survive and develop within ticks, behavioral factors such as the tick's host-seeking strategy, environmental factors such as temperature and humidity, and human behavior and intrusion into natural tick and pathogen habitats. This complexity makes the study of TBDs and their prevention a challenge.

Similarly, wild and domestic animals, including mammals, reptiles, and birds, are important players in tickborne pathogen survival, reproduction, and spread. As is the case for the tick vectors, these animal reservoirs also vary in their susceptibility to pathogens and their ability to sustain and transmit them.

NIH Strategic Plan for Tickborne Disease Research

The growing health burden of TBDs, along with their underlying biological complexity, warrants a comprehensive strategic research plan. The *NIH Strategic Plan for Tickborne Disease Research* outlines the agency's strategic TBD research priorities to support the understanding of TBDs and advance the development of tools and strategies to prevent, diagnose, and treat TBDs. NIH will continue to support a range of basic, translational, and clinical research to improve our knowledge of illnesses transmitted by ticks and to develop new tools for their prevention, diagnosis, and treatment in all populations, including children.

NIH will support this research through extramural and intramural research programs, including the use of systems biology approaches, to generate a comprehensive understanding of the complex biology of tickborne pathogens.

Strategic Priority 1: Improve Fundamental Knowledge of TBDs

A comprehensive understanding of the biological processes involved in tickborne pathogens' transmission, survival, and ability to cause disease is paramount to developing new tools to combat TBDs. This includes an understanding of the microbial, vector, and host factors and the interactions that contribute to disease. NIH conducts and supports research on tickborne pathogens and their properties associated with human disease. NIH also conducts studies on tick physiology and tick-pathogen interactions, conducts some ecological research, and coordinates these efforts with other agencies.

The emergence of a non-infectious TBD, alpha-gal syndrome, has expanded NIH TBD research to include efforts to better understand the allergic mechanisms behind alpha-gal sensitivity, in addition to research on tick and human factors involved in this disease process.

Figure 3. A Lone star tick. Bites from lone star ticks are associated with alpha-gal syndrome and other TBDs. Image credit: NIAID.

Objective 1.1: Understand the fundamental biology of tickborne pathogens

- **Determine biochemical mediators of pathogen survival.** All microbes have evolved genetic pathways enabling them to thrive within their environments. Tickborne pathogens must adapt to survive within ticks, as well as in human and animal reservoirs. Elucidating the genes and gene products that are important for pathogen transmission, tissue invasion, and other key elements of survival is key to developing a complete picture of their life cycles. As with most pathogens, scientists have an incomplete understanding of the microbial genetic and biochemical pathways required for the survival of tickborne bacteria, viruses, and parasites. NIH will continue to support basic research to expand our knowledge of known microbial genetic and biochemical pathways, to identify new ones, and to exploit those findings for new approaches to preventing, diagnosing, and treating TBDs.

- **Elucidate microbial structural biology.** The functions of microbes, including their abilities to invade, reproduce, and cause disease in their hosts, depend in part on their structural makeup. Tickborne bacteria, viruses, and parasites all have biological structures that enable them to interact with tick and host cells and tissues. Those structures may enable the microbes to invade host cells, acquire nutrients, suppress immune responses, bind to specific tissues, move about the host, replicate their DNA, or any other property critical for survival. Understanding the structural

biology may assist in developing targeted interventions to disrupt pathogen transmission or survival within the host. NIH will support research to advance our understanding of the underlying microbial structures that are required for pathogen survival.

- **Investigate the ways in which intracellular TBD pathogens interact with the host cell .** Many tickborne pathogens—such as viruses and some bacteria—reside inside host cells. Viruses and intracellular bacteria, such as those that cause Rocky Mountain spotted fever, anaplasmosis, and ehrlichiosis, co-opt the host cell and manipulate its genetic and biochemical components to ensure their reproduction or survival. Knowledge of the needs of intracellular pathogens and the mechanisms they employ to satisfy those needs will shed light on potential new targets for drugs to combat TBDs. NIH will support research on the biological processes required for the survival of tickborne viruses and bacteria within cells, including efforts to develop improved technologies for studying intracellular bacteria.

Objective 1.2: Understand host interactions with tickborne pathogens

- **Understand the human immune response to tickborne pathogens**. A better understanding of human immune defenses is vital to developing vaccines and other technologies to prevent TBDs. Detailed knowledge of the human host response to infection will not only provide insights into new approaches for diagnosis, treatment, and prevention, but will likely elucidate why individuals may respond to the same pathogen in different ways. NIH will support research on the human response to infection, including both the innate and adaptive immune systems, with a focus on the factors that lead to protective immunity.

- **Understand how TBDs interact with and affect human organ systems.** In addition to better understanding the interplay of the human immune response to tickborne pathogens, it is crucial to understand how TBDs affect other organ systems. For example, in rare cases Lyme disease can affect the heart, a process that is poorly understood. TBD impacts on respiratory, hepatic, musculoskeletal, and other organ systems have also been reported. A few tick-borne pathogens, such as Powassan virus, can cause fatal or disabling meningoencephalitis, an inflammation of the brain and surrounding tissue, due to their ability to infect the brain and nervous system. TBDs can also contribute to neuropsychiatric complications that can persist after the TBD is treated. In addition, changes to the host immune system as a result of TBD infection can trigger and propagate other immune pathways and contribute to the development of sequelae, such as Lyme arthritis. Research supported by NIH will provide insights into how TBDs affect the health of multiple organ systems, and the implications for persistent symptomology. This includes developing animal and cell models

that will facilitate studies of human organ system pathogenesis to better address the full range of TBD sequelae.

- **Understand how tickborne pathogens spread within the body following infection**. Following infection, most tickborne pathogens spread to specific cells or tissues within the body. Understanding the host and microbial factors that determine where pathogens migrate will provide insight into potential mechanisms to interrupt the disease process. Taking advantage of established procedures and emerging imaging technologies, NIH will support studies to identify where tickborne pathogens go following initial infection, how they get there, and the microbial and human factors that enable that movement.

Figure 4. Black-legged tick. Bites from black-legged ticks are associated with Lyme disease and other TBDs. Image credit: CDC; Michael L. Levin, PhD.

- **Understand how tickborne pathogens evade human immune defenses.** Many pathogens have evolved to evade or shut down elements of human immune responses. While many mechanisms have been identified, scientists do not fully understand the role of immune evasion for different tickborne pathogens, or how that evasion is accomplished. NIH will support research to identify the complete spectrum of immune evasion strategies with the goal of developing countermeasures to enable improved treatment and prevention.

- **Determine the cause of persistent symptoms in humans infected with TBDs**. For some TBDs, such as Lyme disease, some individuals report continuing, sometimes debilitating, symptoms following standard treatment, or in cases where the infection has not been promptly treated. The cause(s) of these symptoms remain unknown but have been postulated to be due to persistent infection, an autoimmune response, lingering inflammatory processes triggered by nonliving bacterial components, or even other diseases unrelated to tickborne infections. NIH will continue to support research into the causes of long-term symptoms attributed to TBDs, including treatment-refractory infections.

Objective 1.3: Understand the pathogenesis of noninfectious TBDs

- **Understand the factors underlying the development of alpha-gal syndrome.** Alpha-gal syndrome is the only known food allergy that can be induced by an arthropod bite, in this case, the lone star tick. Understanding the host immune–mediated and vector-associated mechanisms that lead to alpha-gal syndrome will help develop tools to predict who will develop an allergic reaction, as well as interventions to counteract this condition. NIH will continue to support fundamental studies to understand the impact of

blood feeding by ticks and insects on immunologic events and TBD pathogenesis, including alpha-gal syndrome.

- **Unravel tick-pathogen interactions**. Identifying and characterizing the factors and biochemical processes—both of the pathogen and tick—that allow bacteria, viruses, or parasites to invade and survive within their vector are critical components to understanding TBDs. The specificity of pathogens for their tick vectors, and the competency of those vectors to support the pathogen, are regulated by a host of biochemical structures and pathways. NIH will support research aimed at understanding and potentially interrupting these pathways, with the goal of stopping TBDs at the level of the tick before a person has been bitten.

- **Understand pathogen transmission.** Pathogen transmission between tick and vertebrate hosts (human and reservoir) is a complex process. That process requires genetic signals from both the tick and the microbe, resulting in biological changes in both that enable the pathogen to move from an invertebrate to a vertebrate host. Furthermore, not all pathogens are retained within a tick as it molts from one developmental stage to another, nor are all passed from a female tick to her eggs. In addition, environmental factors are important in the biology of ticks and reservoir species. NIH will support research to determine additional avenues to interrupt transmission throughout the reservoir-tick-human life cycle.

- **Characterize the tick immune system**. Ticks have their own immune systems that protect them from infection. Tickborne pathogens have evolved to partially avoid these defenses as they establish themselves within the vector. The resulting state of mutual tolerance, where ticks elicit a sufficient immune response to keep microbe numbers in check, is carefully regulated and incompletely understood. Disrupting this regulation may provide an avenue for tick-targeted interventions to prevent TBDs. NIH will support research to identify key components of tick immunity and pathogen attempts to overcome those defenses.

- **Assess the role of the tick microbiome in pathogen acquisition and transmission.** As with humans, ticks normally carry a number of commensal microbes within their midguts and other organ systems. They may also be coinfected with other pathogens, including other bacteria, viruses, or protists that they can transmit to people. Research has shown that the presence of some microbes, whether harmful or harmless, can affect the ability of ticks to acquire and harbor others. Studies with other insect vectors have also demonstrated that genetically modified commensal microbes can deliver toxic compounds to those vectors and interfere with pathogen transmission. NIH will support research to elucidate the tick microbiome to examine the impact of multipathogen infections in ticks and to explore the potential

application of genetic approaches developed for non-tick vectors to TBD pathogen elimination.

- **Understand how tick-derived factors contribute to the establishment and severity of TBDs.** Tick-derived factors, such as salivary proteins that are co-delivered with tickborne pathogens during a blood meal, can contribute significantly to TBDs. Pathogens have evolved to take advantage of these molecules, exploiting them to facilitate the infectious process by modulating and suppressing the immune response at the bite site and assisting the pathogen in spreading within the host. Understanding how tick salivary proteins contribute to TBDs could help identify novel targets for vaccines and therapeutics with the potential to prevent and treat a range of TBDs, respectively. NIH will continue to support fundamental studies to understand the impact of blood feeding by ticks on immunologic events and TBD pathogenesis.

Figure 5. Tick salivary gland. NIH scientists are exploring tick salivary glands as a tool to study virus and bacteria transmission and infection.

Strategic Priority 2: Advance Research to Improve Detection and Diagnosis of TBDs

Rapid, accurate diagnosis is critical for the optimal treatment of TBDs. Diagnosis of tickborne infections utilizes the same technologies as diagnosis of many other infectious diseases. Serological tests, which detect host antibodies to the infectious agents, tests to identify pathogen nucleic acids in blood or tissues, and, for some TBDs, blood smear examination for direct detection of the pathogen itself, are the first-line approaches. While these tests are clinically useful, they all have limitations. By looking for antibodies as a marker of infection, serological tests do not detect the presence of a pathogen directly. They therefore may miss an early infection, when antibodies have not yet been produced. Conversely, in certain clinical contexts, it may be difficult to distinguish between an active infection and past infection when antibodies remain in the blood following clearance of the pathogen.

Molecular diagnostics to detect pathogen nucleic acids must be carefully designed to avoid false positive or false negative results. In addition, these tests only indicate the presence of a microbe's DNA or RNA, rather than of the microbe itself. Furthermore, both approaches may detect the presence of both the targeted pathogen and a closely related microbe, thereby confusing diagnosis.

For alpha-gal syndrome, blood tests can measure the level of antibodies to alpha-gal in the bloodstream, and a skin test can confirm sensitivity to the antigen.

NIH will support research to improve TBD diagnostic tests and develop multiple diagnostic technologies, including both pathogen- and host-targeted approaches, that can be implemented in all populations affected by TBDs.

Objective 2.1: Develop new or improve existing diagnostic tests for TBDs

- **Support research on new rapid diagnostic tests.** While diagnostic tests exist for all known TBDs, new tests are needed that are rapid and easy to interpret while maintaining high specificity (low chance of a false positive test) and high sensitivity (low false negatives). For example, in the case of most tick-borne encephalitides, diagnosis is often delayed until after significant brain injury has occurred. The tests should also be able to detect a pathogen both early and late in the infectious process, and to differentiate between active and past infection. Multipathogen diagnostic tests are an ultimate goal because of their clinical potential to provide a single-test answer when a TBD is suspected. NIH will continue to support research on novel tests to address current diagnostic gaps.
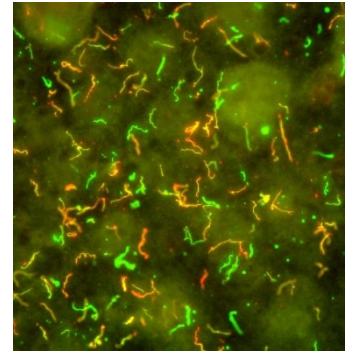
Figure 6. Spirochetes of the Lyme disease bacteria, Borrelia burgdorferi. *Image credit: NIAID.*

- **Support research on direct-detection technologies.** Antibody tests do not detect a pathogen in the earliest stages of infection, which can lead to delays in treatment. Direct-detection technologies could potentially provide rapid diagnostic identification of pathogens during different stages of infection, including early phases. NIH will continue to support novel approaches to developing direct-detection diagnostic tests for TBDs.

Objective 2.2: Develop diagnostic tests capable of predicting treatment success

- **Develop diagnostics to monitor treatment response or success**. The success of treatment protocols for TBDs varies and typically is determined by the sustained absence of symptoms and long-term complications. In Lyme disease, patients sometimes report continuing or recurrent symptoms long after treatment has been completed. Tests that can monitor treatment response or determine the presence of physiologic or biochemical factors that mediate that response could help predict whether a person will respond to standard therapy or require adjunct treatments. NIH will support research on diagnostic methods that can predict response to treatment.

- **Develop diagnostics to differentiate TBD signs and symptoms from those caused by other diseases.** Many symptoms, including musculoskeletal, cardiovascular, rheumatologic, neurologic, and neuropsychiatric symptoms, have been attributed to TBDs. Those symptoms may occur in the absence of a clear diagnosis of a tickborne infection, leading to uncertain treatment approaches and poor response to therapy. NIH will support the development and use of diagnostic tests that can clearly

differentiate between TBDs and the most common confounding diagnoses, thereby improving patient outcomes.

Objective 2.3: Develop host-based diagnostic tests

- **Identify human biomarkers that detect infection**. Infection with tickborne pathogens can affect multiple organ systems and trigger or perturb multiple biochemical pathways, depending on the infectious agent. These pathogen-specific alterations in host biochemistry may leave molecular biosignatures that can be detected and used to diagnose infection. NIH will continue to support research to differentiate between early and late stages of infection and to distinguish TBDs from other diseases with similar symptoms.

- **Discover biomarkers of persistent symptoms**. Biomarker studies typically take a whole-system approach to detecting how the body interacts with infectious agents, both immunologically and through other biochemical processes. For TBDs, biomarkers may prove useful in predicting the likelihood that persistent symptoms will emerge, or in assessing the cause of continued symptoms in those individuals. NIH will support research on the potential of biomarkers to expand our knowledge of the effects of tickborne pathogens on humans, including the emergence of persistent symptoms.

Strategic Priority 3: Accelerate Research to Improve Prevention of TBDs

Prevention of TBDs in the United States and globally is focused on reducing or eliminating ticks in the environment, avoiding areas where ticks are present, or using clothing, repellents, and personal surveillance to prevent tick bites.

Vaccines are among the most effective public health tools for combating infectious diseases, yet there are no currently licensed vaccines in the United States for any TBD. A vaccine to prevent tickborne encephalitis—a viral disease occurring primarily in parts of Europe and northern Asia—is available in countries where the disease is a threat.

In 1998, an FDA-approved vaccine that reduced the chance of contracting Lyme disease by 76% became available in the United States. The vaccine's manufacturer later ceased production, a decision that generated considerable discussion.

In cases where an individual notices a tick bite, a single dose of doxycycline taken within 72 hours of the bite has been shown to prevent Lyme disease. Doxycycline is also the first-line treatment for many other tickborne bacterial diseases, and its use as a prophylactic for each TBD is yet to be assessed.

There is no current prevention for alpha-gal syndrome in those with prior episodes, other than avoidance of red meat for food-induced disease.

NIH will support research on the prevention of TBDs that includes vaccines and other immune-based technologies as well as approaches that reduce transmission of tickborne pathogens in the wild.

Objective 3.1: Support the discovery, design, development, and evaluation of safe and effective vaccines and other preventive interventions

- **Support research and development of vaccines to prevent TBDs**. Safe and effective vaccines for some TBDs have been developed in the past, and those approaches could be revisited in moving toward next-generation vaccines. Furthermore, multiple vaccine strategies—attenuated, nucleic acid, and peptide—have been pursued for other pathogens and may be applied to TBDs. In addition to pathogen-targeted approaches, vaccines that target tick salivary components or other tick proteins introduced during feeding could be developed as antigens for "anti-tick" vaccines. NIH will continue to support antigen discovery and vaccine development for TBDs.

Figure 7. Syringe and vaccine vial. Image credit: NIAID

- **Support research on adjuvants to improve TBD vaccine efficacy**. The effectiveness of many vaccines is enhanced by the presence of adjuvants that stimulate host immune responses or direct the response towards certain immune cell types or pathways. Adjuvants vary depending on the pathogen and vaccine. NIH will support research to identify safe and effective adjuvants for TBD vaccines.

- **Support research on post-exposure prophylaxis**. For Lyme disease, a course of common antibiotics can prevent illness if given shortly after infection. NIH will continue to support research on prophylactic use of antimicrobials or other post-exposure approaches to prevent TBD infections or reduce the severity of disease.

Objective 3.2: Develop or improve approaches to interrupt pathogen acquisition, transmission, or survival in ticks and reservoir species

- **Discover and advance biological approaches to reduce transmission**. A tickborne pathogen depends on its tick vector for survival, providing a target outside of the human body for prevention efforts. Paratransgenic approaches, which involve modifying other microbes that coinfect vectors, have been used for some insect vectors and may be effective in blocking pathogen transmission to humans or among tick developmental stages. Transgenic approaches, which have been studied most extensively in mosquitoes, provide another approach to reduce transmission. NIH will continue to support research on strategies that reduce the capacity of ticks to acquire, support, or transmit infectious pathogens to humans.

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- **Investigate reservoir-targeted vaccines.** Not all tickborne pathogens are transmitted from a female to her eggs. In some cases, ticks acquire the pathogen through feeding on reservoir animals such as mammals or birds. The central role played by those reservoirs in maintaining pathogen transmission cycles makes them a promising target for intervention. Oral vaccines inserted into baits, may prevent mice from carrying a pathogen, thereby reducing the numbers of ticks carrying the microbe as well. NIH will support research on novel approaches to interrupting the tickborne pathogen life cycle in the animal reservoir.

Objective 3.3: Vector control

- **Support biological strategies to reduce tick populations.** Tick control approaches are an important tool for preventing and controlling tickborne diseases. Novel biological interventions, such as the transgenic and paratransgenic approaches described above, can be used for vector control. NIH will continue to support research aimed at reducing vector populations as a means of reducing TBDs in people.

Strategic Priority 4: Support Research to Advance the Treatment of TBDs

For infectious diseases, effective treatment varies depending on the pathogen involved, and additional therapeutic strategies may be needed to manage post-infectious symptoms.

Furthermore, treatment regimens for many TBDs have not been optimized for all patient populations. While bacterial TBDs can typically be treated with standard antibiotic therapies, drugs that specifically target viral TBDs have not yet been developed. Lyme disease, which usually resolves following a course of antibiotics, has been associated with continuing symptoms in some individuals. In addition, there are currently no known effective treatments for encephalitis caused by tick borne pathogens.

No ideal drugs exist for treating alpha-gal syndromes, including red meat allergy. Avoidance of foods that cause a reaction is currently the best strategy for disease management. However, as the triggering allergen is also found in non-dietary sources, including some medications, effective therapies beyond dietary restriction are needed for controlling alpha-gal allergic reactions. Developing effective treatment options will require therapeutic expertise different from that needed for antimicrobial development.

- **Identify and characterize new molecular targets for therapeutics.** Current antimicrobial drugs generally target a limited set of biochemical processes in pathogens. The need for new drug targets for most infectious diseases is widely accepted, including tickborne pathogens, most of which have limited therapeutic options. NIH will support research to identify drug targets for TBDs and develop them into therapeutic interventions for tickborne infections.

Figure 8. Bottle of doxycycline capsules. Oral antibiotics, such as doxycycline, are often prescribed after exposure to tickborne Lyme disease. Image credit: NIAID.

- **Develop antivirals for tickborne viruses**. No antiviral drugs are currently approved for treating domestic tickborne viruses, and treatment options for most non-domestic tickborne viruses are limited. NIH will support research toward the development of new antivirals, as well as testing the effectiveness of existing antivirals against related tickborne viruses.

- **Assess safety and efficacy of new therapies for TBDs**. Moving potential new therapies from their discovery in the laboratory to their use in the clinic requires extensive studies of dosing, efficacy, and safety. NIH will utilize its resources to advance promising new treatments through the pipeline, with the goal of hastening product development and acceptance.

- **Identify safe and effective complementary and integrative health therapies for TBDs**. Currently, the efficacy of complementary approaches for TBDs have not been supported by scientific evidence, and in some cases the treatments (e.g., peroxide, bismuth therapy) are potentially unsafe. NIH aims to stimulate new research on the safety and usefulness of complementary and integrative health approaches for TBD and post-TBD symptom treatment strategies, and support research to develop a mechanism- and evidenced-based approach to TBD care.

Objective 4.2: Advance research on treatment for extended symptoms and post-infectious sequelae

- **Assess treatment strategies for extended or long-term symptoms attributed to TBDs.** For some TBDs, patients report long-term symptoms following treatment or in the absence of prompt treatment. Reported illnesses often include musculoskeletal, rheumatological, cardiovascular, neurological, and neuropsychiatric symptoms, among others. For TBDs, optimal treatment of these symptoms may involve antibiotic and/or other treatment regimens. NIH will support research on the mechanisms leading to

these symptoms and on treatments to improve outcomes for long-term sequelae of tickborne infections.

Strategic Priority 5: Develop Tools and Resources to Advance TBD Research

Enhanced access to reagents, pathogens, vectors, data, and analytical tools can accelerate research progress for TBDs. Many resources for studying TBDs are difficult to maintain through investigator grants due to the limited time restrictions of such grants. In some cases, centralized repositories or research resources will be important components of the NIH research support effort.

Objective 5.1: Support sample and reagent repositories to enable fundamental research and product development

- **Facilitate access to biological samples to assist research on TBDs**. Well-characterized biological samples and reagents are critical to the effective conduct of research on TBDs. Consistent samples are required for development of new diagnostic tests, as well as for early validation of new treatments or vaccines. NIH will support pathogen and clinical sample repositories as well as reagent repositories to ensure that these resources are readily available to researchers**.**

Objective 5.2: Support genomics resources

- **Support access to and generation/analysis of TBD genetic data.** Understanding the biology of tickborne pathogens and their reservoirs is enhanced by the availability of genomic information. This information can be used to provide a comprehensive understanding of the genes and proteins critical in maintaining tick-pathogen-reservoir-host life cycle interactions. NIH will continue to directly support DNA sequencing and functional genomics efforts, in addition to providing access to bioinformatics resources.

Objective 5.3. Incentivize product development through preclinical services

- **Support pre-clinical development of promising products.** Developing new drugs, vaccines, and diagnostic tests is a time-consuming and expensive endeavor. Resources to provide support for different steps along the product development pathway can be valuable in ensuring that promising products continue to move forward. NIH will utilize NIAID preclinical services and animal models contracts to offer critical screening and testing services needed for identifying and developing new products for the prevention, diagnosis, and treatment of TBDs without additional cost.

Conclusion

The increase in TBD incidence in the United States represents a growing public health threat as new pathogens emerge and the geographic distributions of tick vectors expand. This calls for a renewed strategic approach to TBD research and control that will improve our understanding of tickborne pathogens, ticks, reservoir

animals, and humans—and the interactions among them. The resulting information will be used to develop new or improved tools for disease prevention, diagnosis, and treatment.

A comprehensive strategy will require a coordinated effort among governmental, nongovernmental, and community-based organizations. *The NIH Strategic Plan for Tickborne Disease Research* defines the areas of TBD research within the NIH mission and outlines the agency's research priorities and goals. This strategic plan builds on other national efforts, such as the [HHS Tick-Borne Disease Working Group](#) and A National Strategy for Vector-borne Disease Prevention and Control in the United States, currently being developed by the CDC.

Collectively, these reports and working groups highlight a commitment from multiple government agencies to improve coordination of TBD research and discovery efforts, disease and vector surveillance, and public and medical provider education. NIH reaffirms its commitment to conduct research to improve knowledge of these diseases and develop new tools for their prevention, diagnosis, and treatment. NIH aims to address these needs through a comprehensive scientific agenda that will strengthen TBD research.

Appendices

Appendix 1. Developing the Strategic Plan

Introduction

In response to the growing public health threat that tickborne diseases (TBDs) represent in the United States, and in accordance with recommendations from the United States Department of Health and Human Services (HHS)–supported [Tickborne Disease Working Group](#) (established in 2016 as part of the [21st Century Cures Act](#)), NIH convened a trans-NIH strategic planning team with subject matter and policy experts from five NIH institutes and the NIH Office of the Director (see Appendix 2) to develop a strategic framework to advance TBD research for the next 5 years and beyond. The framework outlined five areas of opportunity in TBD research, including improving fundamental knowledge, diagnosis, prevention, treatment, and research tools and resources.

Using a Request for Information (RFI) ([NOT-OD-19-077](#); see [Appendix 1](#)), NIH sought input from stakeholders in the scientific research community, industry, and the general public regarding the proposed framework. Comments were submitted through a web-based form from February 13 to March 13, 2019, on, but not limited to, the following three focus areas:

- Significant research gaps and/or barriers not identified in the framework
- Resources required or lacking that may be critical to advancing the areas of research opportunity
- Emerging scientific advances or techniques in basic research, diagnostics, prevention, therapeutics, or resources that may accelerate NIH research priorities detailed in the framework

NIH staff categorized the responses into cross-cutting themes when possible or otherwise summarized the responses by each of the areas identified in the bulleted points above.

Characteristics of Respondents

NIH received 92 responses to the RFI. The majority of responses were from members of the public (36) and members of academic institutions (33). Other respondents included individuals from advocacy organizations (8), private healthcare practice (6), government (3), and industry (2). One response each was received from a professional society, a private foundation, and a public online Lyme disease support group. One response did not include any identifiable information and could not be classified.

Cross-Cutting Themes

Several themes emerged from comments submitted on the topic areas identified in the RFI. Overall, the submissions were positive and supportive of the framework. More than 30 respondents agreed that detection and diagnosis of TBDs is a key

strategic priority. Specifically, respondents were supportive of research for direct detection of tickborne pathogens and multipathogen platform testing. Other responses highlighted the need for diagnostics to determine treatment success or eradication of the pathogen, differentiation among different stages or manifestations of Lyme disease, biomarkers to detect the likelihood of disease persistence, and detection of emerging tickborne pathogens.

Consistent with topics included in the strategic framework, 18 respondents were strongly in favor of advancing therapeutic discovery, with objectives varying from treating persistent Lyme disease and associated sequelae to identifying therapeutic alternatives to antibiotics for Lyme disease (e.g., biologics, immunotherapies, and natural and nonpharmaceutical interventions). Two respondents also drew attention to the paucity of viral TBD treatments (e.g., viral replication inhibitors). Two other treatment-related topics mentioned included the need to understand treatment failure and to determine appropriate means for treating TBD coinfections. Finally, several respondents mentioned the need to conduct therapeutic clinical trials in Lyme disease patients whose symptoms persist after antibiotic treatment or in Lyme disease patients who are not diagnosed/treated during the acute phase of the disease.

Fifteen respondents called for research emphasizing persistent TBD, with a primary focus on improving diagnosis and treatment of persistent Lyme disease. Other major themes regarding persistent TBD were understanding disease pathogenesis and factors that contribute to or may predict post-treatment Lyme disease syndrome. Respondents also requested research on disease pathogenesis in people who are infected with Lyme disease for greater than 6 months without receiving treatment and research investigating bacterial persistence in disease reservoirs.

Respondents also highlighted several perceived organizational barriers to advancing TBD research, including inadequate funding for TBD research (10 responses) and the lack of dedicated study sections or inclusion of multidisciplinary reviewers for TBD research grant applications (4 responses). Other barriers mentioned in the responses included a lack of collaboration among NIH institutes and centers and across government agencies (1 response) and inconsistencies in surveillance and diagnostic testing criteria among states and healthcare systems (2 responses).

Significant Research Gaps and/or Barriers Not Specifically Identified in the RFI
Although many respondents approved of the proposed research foci, several people identified gaps and barriers that were absent from or not emphasized in the framework. Specifically, comments focused on increasing the understanding of vector ecology (11 responses), the pathogenesis and treatment of TBD coinfections (11 responses), and transmission dynamics (5 responses). Respondents cited the need for tickborne virus ecological field studies to determine how native and non-native tick species become invasive and share hosts/pathogens; the impact

environmental change and entomopathogens have on tick abundance and TBD emergence, spread, and persistence; and how anthropogenic disturbances influence these factors. Nine respondents also noted the need for research on vector control strategies, including gene drives, and non-pesticide alternatives.

Other comments focused on determining and exploiting vulnerabilities in the host-pathogen-vector life cycle, including targeted genetic analyses that may identify co-adaptations and regulation of transmission. Additional comments cited the need for studies to determine the impact of the tick microbiome and innate immunity on vector-pathogen interactions. Respondents also requested or proposed strategies to determine the best treatment course for TBD coinfections and the impact of concurrent TBDs on vector dynamics and disease presentation, severity, and recovery potential. The need for computational models of ecological systems and aspects of TBD pathogenesis and immune dynamics also featured in several responses.

Widening the focus to broader U.S. government TBD activities coordinated by the CDC, nine respondents pointed out the need for more comprehensive surveillance efforts nationwide.

Seven respondents recognized a lack of studies on TBD immune dynamics, particularly for mechanisms that TBDs use to subvert or evade the immune system. Three respondents thought molecular signaling pathways, including G protein–coupled receptors, warranted study to help identify therapeutic targets and understand disease pathogenesis.

Requests for research to understand and treat Lyme disease sequelae featured in nine responses, including neuropsychiatric sequelae (e.g., depression, anxiety, and mania), Lyme-induced encephalitis, Lyme arthritis, and Lyme neuroborreliosis.

Resources Required that May be Critical to Advancing the Areas of TBD Research

Respondents identified several resources that are key to progress in TBD biomedical research. Seven suggestions focused on creating new avenues to promote multidisciplinary TBD research, including a collaborative research network, workshops or forums to encourage interaction among TBD investigators, and early investigator awards to draw new talent into the TBD research field.

Seventeen respondents indicated a lack of resources for conducting "big data" analyses, including databases for fully annotated tick and bacterial genomes, curated microbial databases for tick gut microbiome analysis, a database of human genetic analyses pre- and post-Lyme disease treatment, comparative genomic analysis resources, and data-sharing platforms. Respondents suggested building new genetic and bioinformatic tools as well as computational models to aid in studies of TBD disease pathogenesis, epigenetics, population genetics, and development of assays and reagents.

Six respondents cited a need for models and supporting tools to conduct TBD research. Specifically, submissions requested genetic knockout tick models for functional genomic studies. Other responses noted the need for *in vitro* models for therapeutic target screening and animal models for viral TBDs and coinfection studies. Others requested models that accurately reflect human disease. One respondent noted a need for a system for membrane feeding of ticks to reduce dependence on live animals.

Another need identified by several submissions (nine responses) was repositories to support TBD research. Most prominently, submissions indicated a need for a free or low-cost U.S. resource center for TBD strains (e.g., emerging tick species and infected and uninfected ticks) to aid TBD research. Other responses focused on the need for clinically well-defined patient samples for basic research studies and validation of assays/biomarkers (e.g., skin biopsies, serum, and cerebrospinal fluid).

Lastly, four respondents noted the need for reagents to support TBD research, including antibodies and molecular tools for imaging studies and reagents that can be used in multiplex assays.

Emerging Scientific Advances or Techniques in Basic Research, Diagnosis, Prevention, Therapeutics, or Resources That May Accelerate NIH Research Priorities

NIH provided an opportunity to RFI respondents to identify any new developments in the areas of basic, diagnostic, therapeutic, or vaccine research that would accelerate TBD research priorities. Respondents suggested incorporating several technological advances into various aspects of the strategic plan. One respondent suggested using 3D printing to generate human skin and organoid models to study localized immune and microbiome milieus. Another submission suggested leveraging machine learning into computational models of TBD. A few respondents also cited the potential benefits of using advanced imaging techniques and single-cell analyses to gain more comprehensive insights into disease pathogenesis and immune dynamics. Gene-editing tools featured in three responses, indicating this may be a beneficial avenue for developing vector control strategies and genetically modified tick models for functional genomic studies. Finally, one respondent suggested that next-generation sequencing of nucleic acids, metagenomic analysis, protein-peptide affinity capture, and tandem mass spectrometry could be used to guide the development of new diagnostics.

Other Comments

Some respondents expressed a desire for greater transparency in the research planning and implementation processes, whereas others suggested changes to the peer review process to include wider representation from the TBD community, such as advocacy group representatives, community physicians, or members of the general public.

Provider and public education about TBD prevention, diagnosis, and treatment featured in 14 RFI responses. Respondents requested public education materials on preventing tick bites as well as training for medical professionals in the proper diagnosis and treatment of Lyme disease.

Conclusion

NIH solicited feedback using an RFI (NOT-OD-19-077) on a draft strategic framework to advance TBD research and development for the next 5 years and beyond. The responses were submitted by a wide array of stakeholders, including scientists, patient advocacy groups, industry, and members of the general public. Many of the remarks included strong support for efforts to identify the knowledge and tools needed to advance TBD research, diagnosis, prevention, and treatment. They also provided numerous suggestions and commentary that informed the development of and reinforced the TBD research priorities detailed in the strategic framework. The NIH Tickborne Diseases Strategic Planning Team carefully considered the suggestions and incorporated them, where appropriate, in the *NIH Strategic Plan for Tickborne Disease Research*.

Appendix 2. NIH Tickborne Diseases Strategic Planning Team

First Name	Last Name	Institute
Yisong	Wang	NCCIH[1]
Lillian	Abbey	NIAID[2]
Nick	Bushar	NIAID
Thomas	Calder	NIAID
Adriana	Costero-Saint Denis	NIAID
Maliha	Ilias	NIAID
Wolfgang	Leitner	NIAID
Adriana	Marques	NIAID
Sarah	Miers	NIAID
Samuel	Perdue	NIAID
Johanna	Schneider	NIAID
Meredith	Shaffer	NIAID
Cindy	Caughman	NIAMS[3]
Van	Nguyen	NIAMS
Reaya	Reuss	NIAMS
Rosanna	Ng	NIH OD[4]
Sarah	Rhodes	NIH OD
Ajay	Vatave	NIH OD
Marina	Volkov	NIH OD
Elizabeth	Walsh	NIH OD
Phyllis	Ampofo	NIMH[5]
Mindy	Chai	NIMH
Meredith	Fox	NIMH
Rachel	Scheinert	NIMH
Paul	Scott	NINDS[6]
Christine	Torborg	NINDS
May	Wong	NINDS

Table Legend
[1] *National Center for Complementary and Integrative Health*
[2] *National Institute of Allergy and Infectious Diseases*
[3] *National Institute of Arthritis and Musculoskeletal and Skin Diseases*
[4] *National Institutes of Health, Office of the Director*
[5] *National Institute of Mental Health*
[6] *National Institute of Neurological Disorders and Stroke*