CDMRP
DEPARTMENT OF DEFENSE
CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS

Tick-Borne Disease Research Program

Strategic Plan

INTRODUCTION

The Congressionally Directed Medical Research Programs (CDMRP) represents a unique partnership among the U.S. Congress, the military, and the public to fund innovative and impactful medical research in targeted program areas. Programs managed by the CDMRP have formalized strategic plans that identify: program-specific research priorities; how to best address these urgencies; short- and long-term goals; investment strategies; and ways to identify and evaluate program successes with respect to the priorities.

The Tick-Borne Disease Research Program (TBDRP) Strategic Plan identifies the high-impact research goals most important to the program and its stakeholders while providing a framework that is adaptable to changes in the medical research and clinical care environments to address those goals. This plan has been formulated to provide greater clarity of the program's goals over time. Congress appropriates funding for the TBDRP on an annual basis; therefore, there is no guarantee of future funding. The TBDRP Strategic Plan will be reviewed during the program's annual Vision Setting meeting and updated as necessary.

TBDRP BACKGROUND AND OVERVIEW

The TBDRP was established in fiscal year 2016 (FY16), when the efforts of Lyme disease advocates led to a congressional appropriation of $5 million (M). The intent of the TBDRP is to support innovative and impactful research that addresses fundamental issues and knowledge gaps in tick-borne diseases (TBDs). In a letter from the House Lyme Disease Caucus to the Chairman of the Congressional Subcommittee on Defense requesting this appropriation, it was noted that "Lyme and other TBDs are a significant threat to military forces and their dependents, not only at domestic bases and training facilities, but worldwide."[1] The TBDRP was urged to "recognize that tick populations and the diseases they carry are not static, but are emerging and growing threats in many regions, such as the Southeastern and Midwestern U.S.," and that many of these newly discovered TBDs are "becoming more prevalent and deadly." Congress detailed the need for funding "research on TBDs, including to develop more sensitive and accurate diagnostic tests for Lyme and to increase understanding of the full range of Lyme disease processes, as well as the numerous mechanisms that may allow organisms to persist post-treatment." Behind this request is a critical need to accelerate the discovery and development of effective treatments for TBDs, especially treatments that address persistent post-treatment symptoms that create significant health and financial burdens on patients. This long-term tick-borne illness has been most observed in Lyme disease patients and is referred to as persistent Lyme disease/chronic Lyme disease (PLD/CLD), which has clinical similarities to what has been termed as long-COVID.

Approximately 6,000 active-duty Service Members and nearly 56,000 Service Member beneficiaries were diagnosed with a reportable TBD between 2006-2020, with about 80% of these diagnoses attributed to Lyme disease.[2] Lyme disease was the most common vector-borne disease (VBD) reported in Service Members and their beneficiaries from 2016-

2020, accounting for approximately 44% of all reportable medical event cases of VBDs (confirmed, probable, and suspected) during that time.[3] TBDs in Service Members and their beneficiaries present a risk to force readiness. The latest available Centers for Disease Control (CDC) data indicate that over 50,000 cases of TBDs were reported in 2019 [4]; however, reported cases significantly under-represent the total number of infections and a recent study of insurance claims data estimates more than 476,000 annual cases of Lyme disease alone.[5]

The CDMRP patient-centered approach is unique among federal TBD funders and provides a bridge between the science and the most urgent needs of TBD patients. The TBDRP offers a voice to the often unheard individuals living with Lyme disease or other tick-borne illnesses via representation on our peer review and programmatic panels, along with scientists, clinicians, and other reviewers. Through the work of the TBDRP Programmatic Panel, the program has developed the following vision and mission to address congressional intent.

VISION: To prevent the occurrence, better diagnose, and resolve or minimize the impact of Lyme disease and other tick-borne illnesses and conditions.

MISSION: To understand the pathogenesis of Lyme disease and other tick-borne illnesses and conditions, to deliver innovative solutions to prevent, diagnose, and treat their manifestations for the benefit of U.S. Service Members and the American public.

FUNDING HISTORY

The TBDRP has received congressional appropriations of $5M annually from FY16-FY19 and $7M annually from FY20-FY23, for a total of $48M in funding. To date, a total of 48 projects have been funded by the TBDRP.[6]

RESEARCH PORTFOLIO AND ACCOMPLISHMENTS

As shown in Figure 1, the TBDRP has established four Focus Areas to address research gaps in the field of TBDs: Diagnosis, Treatment, Prevention, and Pathogenesis. From FY16-FY22, the TBDRP has invested 26% of its annual research budget on projects focused on Diagnosis, 11% on Treatment, 29% on Prevention, and 34% on Pathogenesis; however, many awards have elements that span more than one area of focus. The TBDRP supports a diverse research portfolio across subject matter/expertise, career stage, and recipient institution.

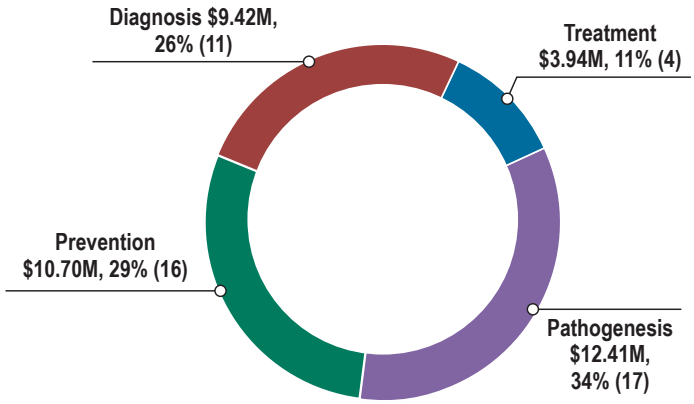


Figure 1: FY16-FY22 Portfolio by Focus Area

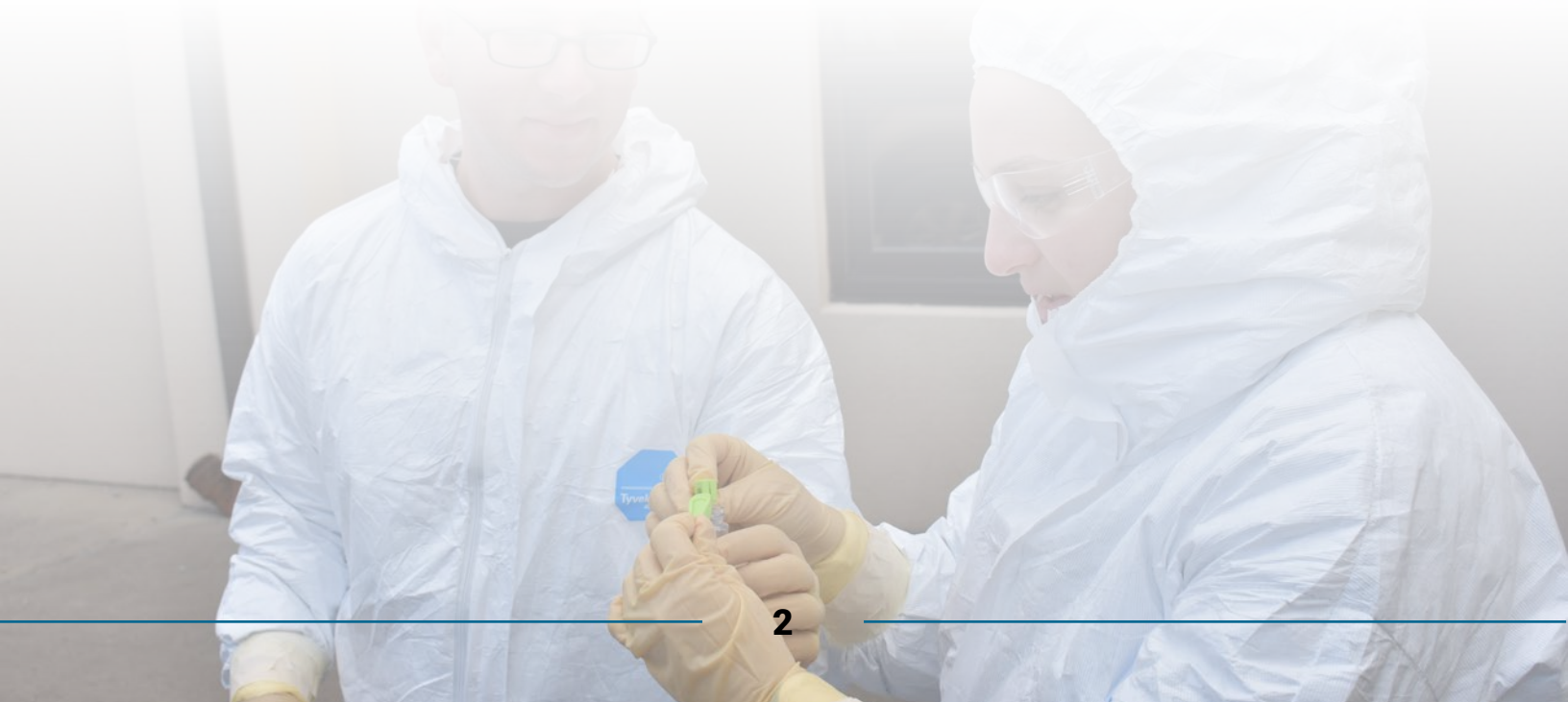
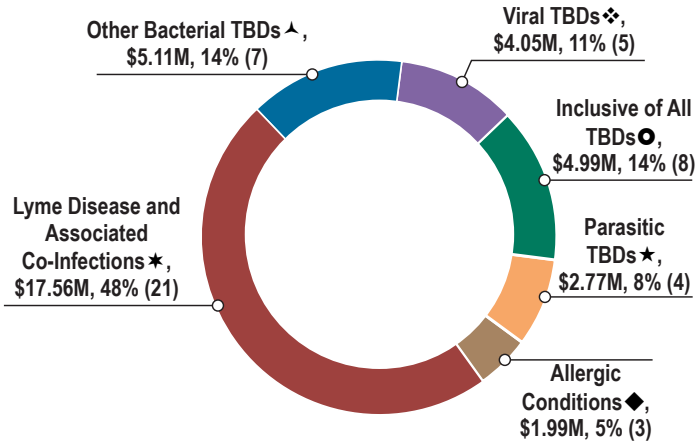


Figure 2 shows that the majority of awards in the TBDRP portfolio are focused on Lyme disease, which has the highest burden and incidence of any TBD in the U.S. Comprising 48% of the portfolio, 21 awards are classified as "Lyme disease and associated co-infections", which refers to studies of Lyme disease alone or with various co-infections commonly diagnosed with Lyme disease, including babesiosis and anaplasmosis. Importantly, about half of these awards directly investigate or have implications in PLD/CLD, the condition that involves persistent debilitating symptoms after treatment for Lyme disease and is a top patient priority.



✶ Indicative of studies of Lyme disease alone or with various co-infections commonly diagnosed with Lyme disease.

✦ Currently includes Rickettsiosis and Ehrlichiosis

❖ Currently includes Powassan, Crimean-Congo Hemorrhagic Fever, and Tick-Borne Encephalitis viruses

○ Indicative of studies involving approaches applicable to any/all TBDs

★ Currently refers to Babesiosis

◆ Currently refers to Alpha-Gal Syndrome

Figure 2: FY16-FY22 Portfolio by Pathogen/Disease

The TBDRP strives to solicit, fund, and manage research toward the discovery and development of health care solutions to prevent the occurrence, better diagnose, and resolve or minimize the impact of Lyme disease and other tick-borne illnesses and conditions. As a part of the strategy toward this vision, the TBDRP aims to support the translation of promising preclinical findings into products for clinical application that will directly impact and improve the quality of life for people suffering from TBDs. Products in development are intended to be responsive to the healthcare needs of military Service members, Veterans, and/or beneficiaries and the American public. Impactful products or outcomes currently under development in the TBDRP portfolio include the following:

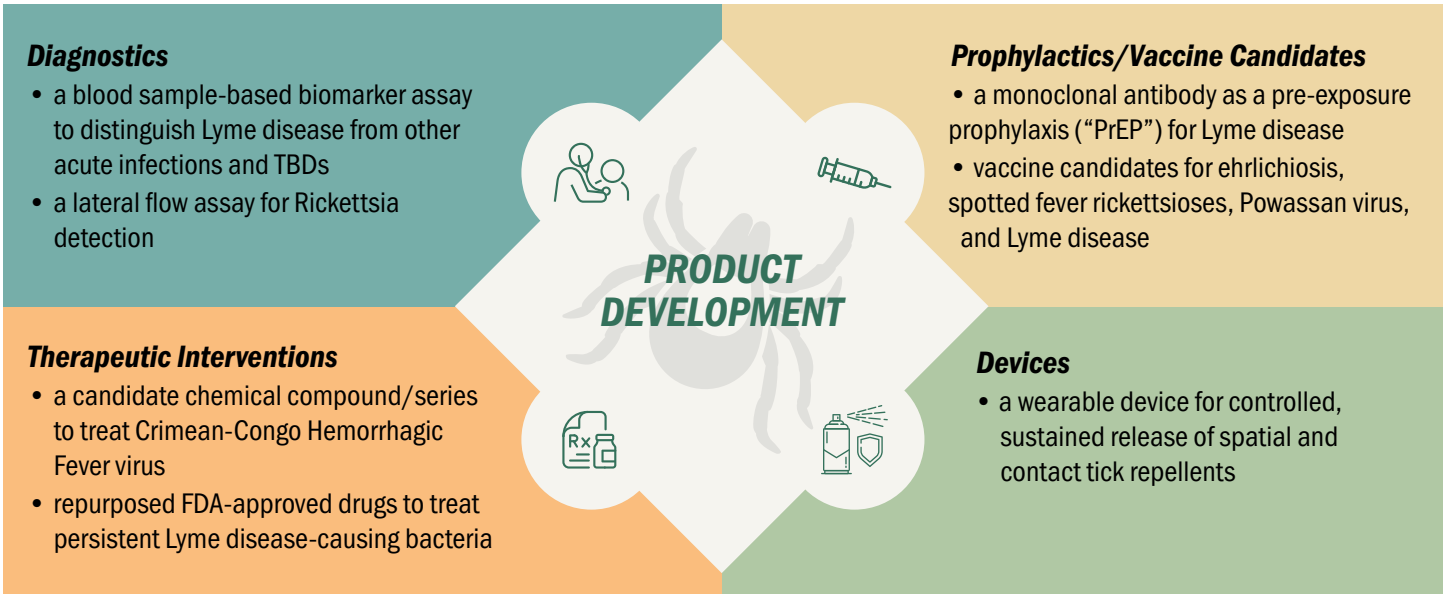


Figure 3: TBDRP Responsively and Responsibly Developing Products to Lessen the Burden of Tick-Borne Diseases

RESEARCH AND FUNDING ENVIRONMENT

STATE OF THE SCIENCE

As tick populations increase and expand geographically, new TBDs continue to emerge. The study of these TBDs is complicated not only due to the breadth of diseases and conditions that occur due to various bacterial, viral, and parasitic tick-borne pathogens (summarized in Figure 4), but also because a single tick bite can transmit more than one of these pathogens at a time.

An additional complexity is that TBDs and conditions can impact multiple body systems and may unfortunately have long-term health implications (see Figure 4). Neurologic complications following tick-borne infection can negatively impact many aspects of daily living. Viral TBDs in particular are so deadly because they can cause fatal meningitis and encephalitis. Failed diagnosis or misdiagnosis of Lyme disease, resulting in lack of treatment or improper treatment, may lead to complications, such as Lyme arthritis, potentially fatal impacts on heart function due to Lyme carditis, and or/neurological problems. While some cases of Lyme disease may be properly diagnosed and resolved within several weeks of antibiotic treatment, if treatment is administered too late or if the treatment protocol fails, patients may develop PLD/CLD. Many patients with PLD/CLD experience long-term pain, fatigue, neurological and cognitive issues, and/or altered immune function.[7]

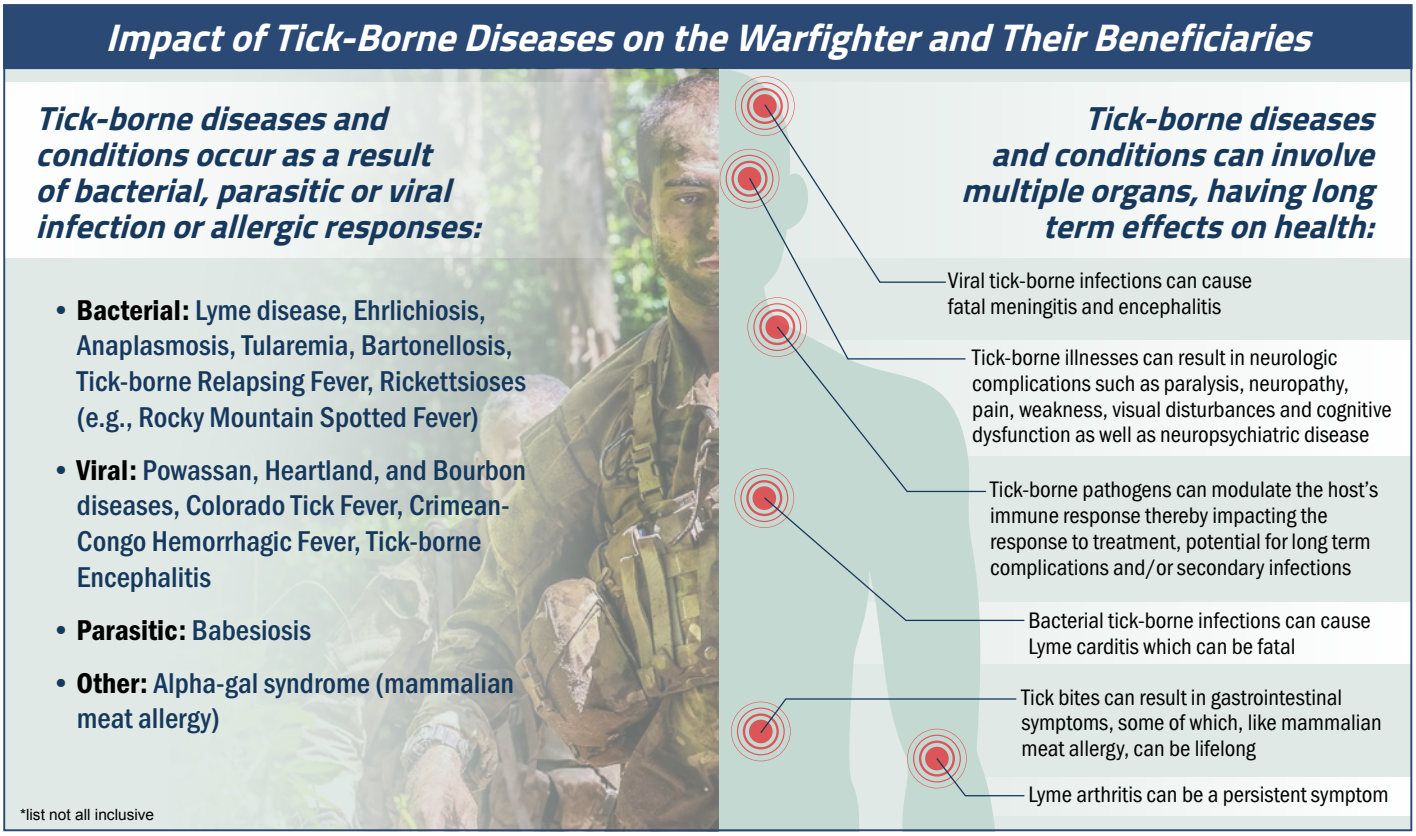


Figure 4: Impact of TBDs on the Warfighter and Their Beneficiaries

Despite funding efforts of the primary federal funders of TBD research, the National Institutes of Health (NIH) and the CDC, there are still numerous challenges and gaps in knowledge associated with research related to the diagnosis, treatment, prevention, and pathogenesis of Lyme disease and all other TBDs. All of these gap areas have been extensively reviewed by the U.S. Department of Health and Human Services (HHS) Tick-Borne Disease Working Group (TBDWG) and its subcommittees and published in their 2018, 2020, and 2022 Reports to Congress.[8-10]

Diagnosis of tick-borne illnesses and determining appropriate treatment and therapy remain a challenge. Current diagnostic methods have limitations in sensitivity and, because they largely rely on the development of a host-antibody response to infection, run the risk of false negative results due to lack of antibody response at the very early stages of infection. Developing more sensitive and accurate diagnostic tests has the potential to remove barriers to patients receiving the appropriate course of treatment.

TBD treatment options are limited, can be expensive, ineffective, in some cases require IV administration, and can depend on whether the infection is caught at an early stage or at a late stage with persistent symptoms. Currently, the most efficacious treatments for Lyme disease are combination therapy regimens using antibiotics, but these treatments may not address long-term or persistent complications of infection. Investigating new and optimized therapeutic options in animal models can be used, first to elucidate the mechanisms underlying how the drugs work, and second to better guide treatment protocols for acute and persistent illnesses.

There is a lack of adopted prevention strategies to limit tick populations and prevent human infection biologically (vaccines or prophylactics) or via the use of novel barriers. Developing more acceptable and proven methods of prevention that are safe for humans and the environment, affordable, and easy to use can minimize the public health burden of TBDs.

Like other infection-associated chronic illnesses, the mechanisms of TBD pathogenesis remain incompletely understood, and with the emergence of new tick-borne pathogens, continued research efforts are needed. Understanding the pathology underlying tick-borne infection and persistent symptoms or long-term effects on health will aid in diagnosing patients with Lyme disease and differentiating between patients with Lyme disease and those with other diseases presenting similar symptoms. In addition to improved diagnosis, understanding host-pathogen interactions, including pathogen evasion of the immune system, as well as the human immune response to these pathogens could lead to identification of more effective therapeutics, which can potentially provide the basic knowledge needed to develop effective vaccines.

FEDERAL RESEARCH FUNDING LANDSCAPE

To maximize the TBDRP's ability to fill research gaps and leverage the findings of others, it is important for the program to understand the focus and successes of other major funders of TBD-related research. The program's approach to coordinate with other major funding agencies is facilitated by incorporating individuals from those federal organizations into the TBDRP Programmatic Panel. These representatives can provide data to supplement what is publicly available (via sources such as Federal RePORTER) and can provide more information about the efforts being funded by their agencies and how to work synergistically, while avoiding duplication of effort. The majority of NIH TBD research investments are in pathogenesis/basic research, and although the CDC does fund some research awards, their funding is largely for the implementation of programs focused on TBD surveillance and prevention.

Figure 5 shows that the NIH and CDC invested approximately $906M toward extramural and intramural TBD efforts during the period FY14-FY21,[11] with 60% of the total investment attributed to the NIH and 40% to the CDC. The Kay Hagan Tick Act of 2019 and other related efforts were responsible for a subsequent significant increase in NIH and CDC funding for TBD-related activities; however, federal funding for TBD research is still orders of magnitude lower, per case, versus other infectious diseases, such as hepatitis C, HIV, and influenza. [8,9]

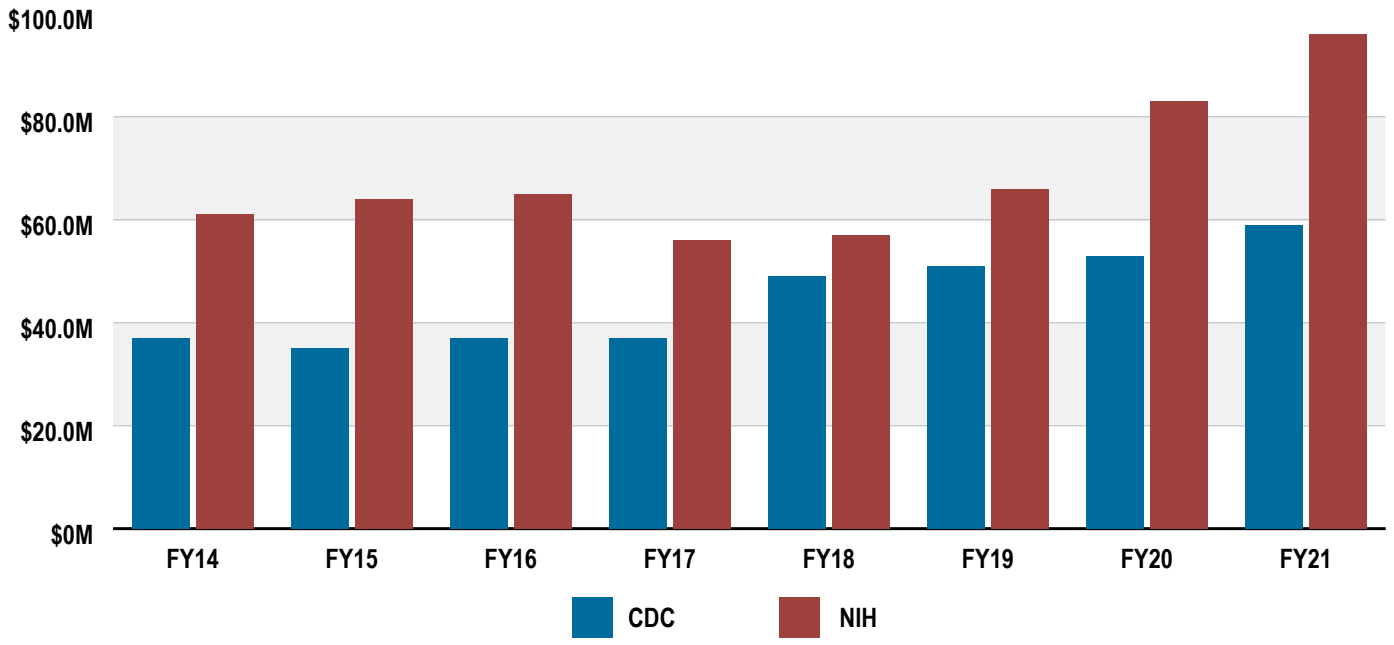


Figure 5: CDC and NIH Funding of TBD, FY14-FY21

OTHER MAJOR FUNDING AND RESEARCH-RELATED INITIATIVES

There are a number of funding and research programs aligned with the vision and mission of the TBDRP. In addition to the primary federal funders noted previously, the National Science Foundation, Biomedical Advanced Research and Development Authority (part of the HHS), and the Deployed Warfighter Protection Research Program (part of the Department of Defense [DOD]) provide a nominal amount of funding for TBD research.

In addition, private funding initiatives (non-governmental organizations) are spearheaded by advocacy groups that provide a voice to individuals living with Lyme disease or other tick-borne illnesses who may otherwise be unheard. These initiatives include, but are not limited to, Bay Area Lyme Foundation, Global Lyme Alliance, the Lyme Disease Association, LymeDisease.org, and the Steven & Alexandra Cohen Foundation. The LymeX Innovation Accelerator, a public-private partnership between the HHS and the Cohen Foundation, was recently launched as well and has uniquely used prize challenges to accelerate Lyme disease diagnostics development.

Information on TBD surveillance and/or management from many established organizations is used to help inform TBDRP strategy. Such groups within the DOD include the Global Emerging Infections Surveillance section of the Armed Forces Health Surveillance Branch, as well as the Armed Forces Pest Management Board. Additionally, surveillance and/or management efforts are underway by the U.S. Department of Agriculture, U.S. Geological Survey, National Park Service, Environmental Protection Agency, and the CDC, including their regional Centers of Excellence.

As a result of efforts by these various federal and private programs and others, several valuable resources are aligned with the TBDRP vision and mission and are available to investigators. The DOD has developed VectorMap, which provides disease maps, mapped collection data, and distribution models for disease vectors, including ticks, while the CDC maintains a passive arbovirus surveillance system known as ArboNet. TBD biorepositories include the CDC/NIH Lyme Serum Repository, the Columbia Specimen Bank[12] at the Columbia University Lyme and Tick-Borne Diseases Research Center, the Johns Hopkins Lyme Disease Clinical Research Center SLICE Study Biorepository,[13] and the Lyme Disease Biobank[14] established by the Bay Area Lyme Foundation. In addition, MyLymeData[15] has established an extensive, big data-driven Lyme disease patient registry. The transformational research at these centers and the data available via these resources further shape the environment in which the TBDRP operates.

STRATEGIC DIRECTION

Lyme and other TBDs are a significant burden on the health and welfare of the American public and a particular threat to military Service Members and their families at military installations and training facilities. Because there is no clear understanding of the full range of these disease processes, including the implications of simultaneous co-infections, the diagnosis and treatment of civilians and military personnel are further complicated.

The strategic priorities of the TBDRP remain focused on supporting new ideas and discovery, as well as established research to advance the development of improved methods of prevention, direct detection, and treatment to reduce the public health burden of TBDs. As the underlying pathogenesis of TBDs (including the cause of persistent symptoms in Lyme disease) continues to be elucidated, the TBDRP aims to support researchers in building on their findings to pursue further optimization and preclinical development, as well as eventual validation and translation of these advancements.

These TBDRP priorities are based on the current state of the science, as well as the current research funding landscape and congressional intent, as described above. Taking into consideration the TBDRP appropriation amount and the mission of other aligned research programs, this approach is not intended to address all the needs of the community. With a broad array of tick-borne pathogens and associated diseases/conditions, the program must consider the incidence and public health burden of any given TBD/condition in prioritizing research investments. The program particularly encourages applications focused on persistent Lyme disease, as well as other TBDs and conditions endemic to the U.S.[16] TBDRP-funded research must focus on directly impacting the health of the U.S. military (active-duty or Veteran), their beneficiaries, and/or the American public.

STRATEGIC GOALS

The TBDRP's strategic goals are aimed toward addressing the gaps related to the diagnosis, treatment, prevention, and pathogenesis of the numerous TBDs that increasingly impact civilian and military populations. The TBDRP seeks to invest in and make progress toward the following goals/priorities; however, investigators are encouraged to propose their own best ideas. The program does not define what types of knowledge products or technologies will be funded and is open to any aspect of the current needs defined by the state of the science at any particular time. Near-term and medium- to long-term strategic goals are detailed below.

Near-Term

The TBDRP will address its Focus Areas (diagnosis, treatment, prevention, and pathogenesis) via the following near-term strategic goals:

Support research toward improving detection and diagnosis of TBDs, including the following:

- Innovative approaches that provide diagnosis for a single or for multiple tick-borne pathogens in human samples, with priority given to direct detection assays
- Novel diagnostics capable of distinguishing active Lyme disease infection from previous exposure
- Approaches focused on the detection/diagnosis of maternal-to-fetal transmission of Lyme disease and/or other tick-borne infections, including the development of relevant animal models

Support research toward elucidating new and effective TBD treatments, including the following:

- Novel preclinical therapeutic strategies for TBDs, with priority given to Lyme disease and other TBDs endemic to the U.S. that have a documented need for additional therapeutic options
- Preclinical evaluation of FDA-approved or -cleared drugs to support additional intended use(s) in the treatment of TBDs

Support research toward more effective and widely acceptable measures for the prevention of TBDs, including the following:

- Drugs and/or prophylactic antibodies, or other novel non-vaccine approaches that can be utilized prophylactically to prevent human TBDs
- Identification, validation, and/or improvement of tick- or reservoir-targeted prevention and control interventions that are safe and nontoxic to nontarget species

Support research toward better understanding the pathogenesis of TBDs at the cellular and molecular level, including the following:

- The interaction among tick-borne pathogens in ticks and/or mammals, and consequences on pathogen synergy and competition, the local and systemic immune response, or disease severity, with an emphasis on Lyme disease and its associated coinfections
- Mammalian immune evasion, host tolerance, or pathogen-host immunosuppression associated with Lyme disease and/or other tick-borne infections
- Persistent clinical manifestations associated with Lyme disease, with studies providing insight into neurologic symptoms particularly encouraged
- Understanding the role of TBDs on maternal health and pregnancy outcomes or the long-term impact on children with maternal-to-fetal transmission of tick-borne infections

For FY23, for example, applications proposing human vaccine work, field work of tick or reservoir hosts, studies related to mammalian meat allergy (allergic response to galactose-alpha-1,3-galactose [alpha-gal]), or studies related to Lyme arthritis are considered nonresponsive to the TBDRP funding opportunities. Like areas of focus, areas of exclusion may vary year-to-year and are determined by an assessment of the TBDRP portfolio as well as research investments of other major TBD funders.

Medium- to Long-Term

Beyond the near term, the TBDRP anticipates continuing to build its funding efforts to address the major areas of focus detailed above (diagnosis, treatment, prevention, and pathogenesis). Strategic goals (specific Focus Areas) will evolve on an annual basis. For example, as a medium- to long-term priority, the TBDRP will consider soliciting studies that specifically involve a military population or use military data, studies that use big data to aid in diagnosis, studies that lend insight into Lyme carditis and the diagnosis of this condition in the emergency room environment, or studies that shed light on the psychiatric manifestations of neurological Lyme disease.

As another potential medium- to long-term priority, the TBDRP will support the development of accepted experimental models of diagnosis and treatment to aid in solving the challenges associated with providing patient care. For example, the program anticipates funding translational research to develop experimental treatment models to support the identification of novel targets related to the development of TBDs during pregnancy (i.e., maternal-to-fetal transmission). The preliminary results from this model can later translate to the clinical setting to provide patients access to effective treatment and mitigate adverse outcomes on both maternal and fetal health.

Potential long-term supporting goals will be added to or possibly replace some of the near-term strategic goals should advances in the research of TBD pathogenesis make them more viable and impactful to the program and the community. However, the scope and scientific nature of medium- to long-term goals will depend on the funding available in the future and the progress made in the field as a whole. The TBDRP will continue to reference overarching TBD research (state-of-the-science) and funding landscape analyses, such as those carried out the by the HHS TBDWG.

INVESTMENT STRATEGY

The TBDRP's annual investment strategy outlines the program's approach to soliciting the type of research that will facilitate its near-term strategic goals, while ensuring synergy of program investments with other funding agencies. The program aims to invest in basic, translational, or clinical studies through various mechanisms that promote idea development across the entire career-development pipeline. This investment strategy will be re-evaluated and updated as necessary during the annual TBDRP Vision Setting meeting, considering the state of the science and available appropriations in the future.

Near-Term

To achieve the vision of the TBDRP, the near-term investment strategy includes an idea development mechanism for TBD prevention and pathogenesis-related topics, as well as a more product-driven funding mechanism for TBD treatment and diagnosis-focused research, both of which have an option for a career development-focused approach to the proposed research and both of which align with the near-term strategic goals. Current and archived funding opportunities can be accessed via the CDMRP website.[17]

First offered in FY20, the **Idea Development Award (IDA)** supports conceptually innovative (non-incremental) research that may lead to impactful discoveries or significant advancements that will accelerate progress toward improving TBD research, patient care, and/or quality of life. Starting with FY22, the IDA mechanism has been focused only on topics aligned with the TBDRP prevention and pathogenesis strategic goals.

With the goal of adding more patient-focused TBD solutions to the portfolio, the **Therapeutic/Diagnostic Research Award (TDRA)** was first offered in FY22 for topics aligned with the TBDRP treatment and diagnosis strategic goals. Research proposed under the TDRA should demonstrate translational potential, with studies expected to be empirical in nature and product-driven. The TDRA encourages partnerships between experienced TBD investigators and those with expertise in therapeutic or diagnostic development and transition to commercialization, particularly those from the commercial sector.

To grow the field of TBD researchers, both the IDA and the TDRA have included a **Career Development Option (CDO)** to support investigators that are early in their TBD research career and working under the mentorship of an experienced TBD researcher. Preliminary data is not required for this option and emphasis is placed on the career development plan of the applicant and their potential for advancement in the TBD research field. Applications submitted under the CDO are reviewed via separate, career development-specific evaluation criteria by a separate, dedicated peer review panel.

Medium- to Long-Term

In the medium- to long-term, the TBDRP intends to continue funding research covering a wide range of TBDs with a broad set of unanswered research questions via idea- and product-focused award mechanisms. The TBDRP will also continue to foster bringing new investigators into the field of TBD research. Scientific priorities will be assessed annually during the Vision Setting meeting and may change over time. Depending on the progression of the field and availability of funds, the TBDRP may move toward funding more translational or clinical research via appropriately more complex and tailored award mechanisms. The program also may consider promoting expansion awards to build on the progress made through efforts already initially funded by the TBDRP, or it may consider promoting team science-focused award mechanisms to encourage collaboration among TBD investigators and/or partnerships between academia and the commercial sector (industry).

In line with TBDRP strategic goals, the program investment strategy is designed to promote patient-centered research geared toward developing ideas and solutions that have strong potential to reduce the incidence and alleviate the burden of tick-borne illnesses and conditions on patients and their families. Research investments in the medium- to long-term will continue to further knowledge and/or technology toward improved patient care and/or quality and advance evidence-based treatments, therapeutics, or diagnostics toward dissemination and clinical implementation.

MEASURING PROGRESS

Near-Term Outcomes

The TBDRP will measure its near-term success by assessing the receipt, funding, and management of high-quality applications that contribute toward meeting the program's Focus Areas and strategic goals. In the near-term, the TBDRP will monitor the responses to award mechanisms and the number of funded applications for each of its overarching program priorities.

Award technical/research progress, including near-term publications and other outcomes, as well as the development of products, will be tracked on a quarterly basis and will vary based on the stage of the funded research project. Progress toward career development goals will also be assessed by surveying applicable investigators about gaining training/skills/expertise in TBD research, attending TBD-related meetings, obtaining mentorship that helped to advance their TBD research career, obtaining additional funding for TBD research, and planning to continue careers in TBD research over the next 5 years. All progress will be provided to the TBDRP Programmatic Panel as a tool to aid in their development of the annual program investment strategy. As the TBDRP evolves, the program will encourage more research in Focus Areas that are understudied.

Medium- to Long-Term Outcomes

Medium- to long-term success will be evaluated based on how research funded by the TBDRP advances the strategic goals or contributes to progress in the field of TBD research and patient care. Contributions to progress in the field include measurable long-term outcomes aligned with each strategic goal, such as publications, patents, clinical trials, commercialization, and changes in standard of care.

The TBDRP will work with the major federal funders of TBD-related research, as well as other major research initiatives, to monitor the overall TBD research funding landscape. Importantly, private, non-governmental funding initiatives play a prominent role in the tick-borne disease research funding landscape, supporting projects that will produce the preliminary data needed to feed the pipeline toward federally-funded efforts. The program will continue to coordinate with these non-governmental organizations that have complimentary goals to the TBDRP. The program will organize in-progress review meetings of TBDRP-funded investigators and/or partner with major federal funders, such as the NIH, to participate in larger progress review (state-of-the-science) meetings. Together, the overall research and funding environment, as well as the TBDRP's research portfolio and research accomplishments, will drive the program's strategy moving forward at both the annual near-term investment strategy level and the long-term strategy levels.

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13 https://www.hopkinslyme.org/

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