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March 13, 2019

Francis Collins, MD, PhD
Director
National Institutes of Health
1 Center Drive
Bethesda, MD 20892

Dear Dr. Collins,

The Infectious Diseases Society of America (IDSAs) is writing to provide feedback on NIAID research priorities in response to the Department of Health and Human Services' Tickborne Disease Working Group report. We are pleased to see the NIH taking on these vitally important research questions, as there is much progress still to be made in our understanding of emerging and established tickborne diseases.

We have a sincere appreciation for both patients and their loved ones who suffer from both short- and long-term effects of Lyme disease or other conditions. Our goal as infectious diseases physicians, public health practitioners, and scientists is for all patients to achieve the best possible outcomes.

IDSAs is the largest infectious diseases medical society in the United States, representing more than 11,000 physicians, health care professionals and scientists. Our members care for patients of all ages with serious infections, including tickborne diseases. IDSAs is committed to giving patients the highest quality care for all infectious diseases, including Lyme disease. Society members focus on the research, epidemiology, diagnosis, investigation, prevention, and treatment of infectious diseases in the U.S. and abroad. We would be happy to serve as a resource for any issues surrounding tickborne diseases.

It is essential that research on tickborne diseases meet established standards for scientific rigor to ensure that study results are meaningful and can safely and effectively guide patient care. Attempts to make clinical trials more inclusive or pragmatic must not override the need to ensure that enrolled patients have Lyme disease based on widely accepted standards. IDSAs strongly supports the research agenda outlined by NIAID in their RFI and would like to provide further comments below.

Basic and Translational Research:

With several new tickborne diseases discovered in just the last decade, basic research into these emerging pathogens is vital. Basic research can help determine insights into potential diagnostic approaches, treatments and

prevention techniques for both emerging and existing tick-borne diseases, as well as lead to clues into the ecology, lifecycle, and interactions with humans and animals. Greater research efforts in established infections such as Lyme disease are needed to understand why some patients do not improve after antibiotic therapy. What we do know is that multiple studies have not found significant or durable benefit with prolonged courses of antibiotic treatment based on multiple randomized, placebo-controlled trials. The basis for why these patients do not improve is unclear but may rest within inflammatory mechanisms. Another example lies with late Lyme arthritis, wherein 10% of patients may have persistent inflammation despite antibiotic therapy yet respond to immunomodulatory drugs or synovectomy. The pathogenesis has had some important advances but remains incompletely understood.

Diagnosis and Detection:

IDSA greatly appreciates the Working Group recommendations for increased research to improve Lyme disease diagnostics. Lyme disease is diagnosed by a combination of medical history, physical exam, and if needed, diagnostic testing. The current FDA-approved serologic tests work best for patients who have been infected for at least two to four weeks as this is the typical response time for the human immune system to make antibodies against a bacterial pathogen, such as *B. burgdorferi*. In patients who are just infected, the diagnosis is best made if the characteristic rash, erythema migrans, is present as patients are frequently seronegative—the human antibody-based immune response is not mounted with high efficiency in the first weeks of infection. Current, clinically-validated FDA tests are the best available tests for diagnosis of Lyme disease when the characteristic rash is not present. Scientific advances are needed to improve testing strategies in this earliest phase of Lyme disease.

As serologic tests may remain positive for decades after successful treatment of Lyme disease, development of a test that provides supportive evidence that a patient has been microbiologically cured of infection would also be of great benefit, particularly for patients who do not appear to improve after antibiotic therapy fully. Such improvements in testing would offer clinicians and their patients a helpful adjunct to guard against unnecessary antimicrobial treatment. IDSA has long advocated for increased funding to derive accurate and specific diagnostics that would significantly reduce misdiagnosis and link patients to effective treatments more quickly.

Researching new tests to diagnose and detect emerging tickborne diseases is also critical to developing a better understanding of some of these less well-characterized pathogens.

Prevention:

IDSA greatly appreciates and supports the research priorities laid out in the prevention section. A new vaccine that is safe and effective in humans would be an excellent tool for the prevention of Lyme disease. An effective vaccine is the only way to guard against infection as tick repellents and patient education have not reversed the numbers of patients infected. IDSA also believes further research into vaccines that target the disease reservoirs and vectors would be highly beneficial to prevention efforts for all tickborne diseases. Additionally, IDSA supports studies of effective interventions for reducing the incidence of tickborne diseases in humans, including novel approaches to vector control or anti-tick vaccines. Vector control for ticks is not nearly as well understood as vector control for mosquitoes.

Therapeutics:

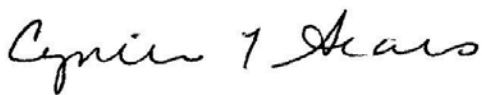
IDSA supports research into therapies for emerging tickborne diseases that do not currently have effective treatment options. IDSA acknowledges that some patients who are successfully treated for Lyme disease continue to suffer from persistent symptoms after treatment. Further research into the mechanism of these symptoms is vital to developing safe and effective treatments for these patients. Federal research funding should be geared toward such studies that will genuinely enhance our understanding of Lyme disease.

Conversely, there is not a pressing need for additional federally supported research on antibiotic treatment for Lyme disease. There is clear, widely accepted scientific evidence indicating that a 10-28 day course of antibiotics, depending on the stage of Lyme disease, will kill the Lyme disease bacterium in humans in all but the rarest of cases. In the setting of patients who have symptoms persisting beyond six months after initial antibiotic therapy, six prospective, randomized, placebo-controlled studies have failed to document sustained or significant benefit, and there is no robust scientific evidence supporting the use of long-term antibiotic therapy in patients with Lyme disease as an approach to help with chronic symptoms such as pain, fatigue, sleep difficulties or subjective neurocognitive complaints. Unnecessary long term antibiotics can be associated with significant harm including selection for antimicrobial resistance, adverse effects such as *C. difficile* infections, and increased healthcare costs. IDSA agrees that effective therapeutics for symptoms that persist after Lyme disease treatment would be beneficial. We support further research that would develop a better understanding of why some patients do not improve after antibiotic therapy so that therapies targeted to the mechanisms of protracted symptoms can be developed and tested.

Another area of study requiring support centers on examining late Lyme arthritis, classically causing a swollen knee. Because this manifestation is less common than early Lyme disease, Lyme arthritis has not been subject to a large, well-designed clinical trial to determine the appropriate type and duration of antibiotic therapy especially as knee swelling tends to persist for weeks or months. As noted above, the 10-15% of patients who experience antibiotic-refractory Lyme arthritis have not been subject to prospective trials to determine the best anti-inflammatory strategies to resolve their condition. A multi-center study to address the best antibiotic treatment for Lyme arthritis would significantly help answer these fundamental questions and also lead to identifying patients who do not adequately respond to antibiotics and could enter a subsequent study for antibiotic-refractory arthritis.

IDSA appreciates NIAID for developing a plan for an important research initiative, and we offer sincere appreciation to the Institute for reviewing our comments. We look forward to the potential developments that could be the result of this research and encourage you to contact Colin McGoodwin (cmcgoodwin@idsociety.org) with any questions.

Sincerely,



Cynthia Sears, MD, FIDSA
President, IDSA