DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

The Role of the National Institute of Allergy and Infectious Diseases Research in Addressing Neglected Tropical Diseases

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Mr. Chairman and Members of the Committee:

Thank you for the opportunity to discuss the global public health threat of infectious diseases, focusing on neglected tropical diseases (NTDs) that affect millions of people worldwide and significant numbers in the United States. I am the Chief of the Parasitology and International Programs Branch in the Division of Microbiology and Infectious Diseases of the National Institute of Allergy and Infectious Diseases (NIAID). NIAID is the lead institute at the National Institutes of Health (NIH) for infectious diseases and supports research and development on medical countermeasures to address these debilitating and sometimes deadly infections.

NIAID OVERVIEW

NIAID conducts and supports basic and applied research to better understand, treat, and ultimately prevent infectious, immunologic, and allergic diseases. As part of its mission, NIAID must address the dynamic scientific challenges that arise from HIV/AIDS, tuberculosis, diarrheal diseases, pneumonia, and malaria; emerging infectious pathogens such as West Nile virus, Ebola virus, and the novel coronavirus emerging in the Middle East (MERS-CoV); and re-emerging infectious diseases such as dengue fever.

NIAID's statutory mandate enables us to conduct and support the research necessary to combat infectious diseases worldwide via our intramural research program and the extramural research community. NIAID is committed to discovering and moving biomedical products along the research and development pathway from "bench to bedside" through support of basic research, identification of drug and vaccine targets, pre-clinical testing, and clinical trials. Critical to this effort are NIAID's public-private partnerships with organizations including non-profits and philanthropies such as the Bill & Melinda Gates Foundation, global research and

development initiatives including the multi-sector "Decade of Vaccines" collaboration, academic institutions, and biotechnology and pharmaceutical companies, as well as coordination and collaboration with Federal agencies such as the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), and the Department of Defense. NIAID offers a broad array of pre-clinical and clinical resources to facilitate research and development partnerships in infectious diseases and to help generate the evidence necessary for FDA's review and approval and licensure of diagnostics, therapeutics, and vaccines.

NIAID EFFORTS AGAINST NEGLECTED TROPICAL DISEASES

The World Health Organization (WHO) has identified 17 infectious diseases as NTDs[1] and has stated that NTDs persist under conditions of poverty and are concentrated almost exclusively in impoverished populations in the developing world. Among these 17 NTDs are several well-known diseases such as dengue fever, African sleeping sickness, schistosomiasis, and Hansen's disease (leprosy). NIAID's mission includes research on these and other infectious diseases that have a disproportionate impact on people worldwide living in resource-poor settings. The NIH contributes the vast majority of the funds that make the United States the largest public funder of NTD-related research and development in the world.[2] We make this effort because the global burden of these neglected diseases is high: over one billion people currently suffer from one or more NTDs. In more than 100 countries, multiple NTDs are endemic and exact an extraordinary human and economic cost in terms of disability and death

[1]The WHO defines the following as neglected tropical diseases: Buruli ulcer, Chagas' disease, dengue, dracunculiasis (guinea-worm disease), echinococcosis, foodborne trematodiases, human African trypanosomiasis (sleeping sickness), leishmaniasis, leprosy, lymphatic filariasis, onchocerciasis (river blindness), rabies, schistosomiasis, soil-transmitted helminthiases, taeniasis/cysticercosis, trachoma, and yaws (endemic treponematoses).
[2]G-finder survey, 2012

every year.[3] NTDs both result from, and contribute to, poverty and they are often co-endemic with other infectious diseases such as HIV/AIDS, tuberculosis, and malaria.

Treatment and prevention options for NTDs are currently limited, and useful point-of-care diagnostics are lacking for many of them. NIAID is working to strengthen the research and development pipeline of such countermeasures by leveraging existing clinical research infrastructure and resources. For example, the NIAID Tropical Medicine Research Centers (TMRCs) are designed to build in-country research capacity and facilitate research on the cause, diagnosis, prevention, and treatment of NTDs. The TMRCs, which are located in disease-endemic areas such as Brazil, the Philippines, Mali, and Ghana, conduct field studies and laboratory research on a variety of infectious diseases including leishmaniasis, schistosomiasis, Chagas' disease, and soil-transmitted helminthiasis. Among other advances, TMRC-supported investigators have identified proteins that may ultimately lead to new, less invasive, point-of-care diagnostics for visceral leishmaniasis, a disease that is currently diagnosed by a an aspirate of the spleen and is fatal if left untreated for severe cases.

NIAID also supports research to develop improved tools for diagnosis, prevention, and treatment of NTDs by providing researchers with resources they might not otherwise be able to access. These resources include repositories of genomic sequences and samples of parasites, transmission vectors, and hosts as well as services to facilitate early-stage development of countermeasures against NTDs. In addition, NIAID enters into public-private partnerships with host country governments, academic institutions, industry, and global organizations, to leverage opportunities and share the cost—and risk—of developing new and improved vaccines, treatments, diagnostics, and vector control strategies. NIAID research and partnerships leading to recent scientific discoveries related to several important NTDs are highlighted below.

[3] WHO

Dengue fever

Dengue fever affects 50 to 100 million people worldwide every year and is re-emerging as a disease of public health importance in the Americas, including endemic transmission in Puerto Rico and locally acquired cases in Florida. The disease is caused by mosquito-borne viruses that produce high fever, joint and muscle pain, and in severe cases, death. No specific medication exists for dengue fever, and NIAID is working to identify better ways to prevent and treat this infection.

NIAID is funding studies on effective community-based prevention programs, improved laboratory-based surveillance, rapid diagnostic tests and therapies, and the development and testing of several formulations for dengue vaccines. Recently, early-stage clinical trials of dengue vaccines developed by NIAID scientists have identified a lead candidate that was safe and stimulated a strong immune response in most recipients after just one dose. The NIAID vaccine, called TetraVax, was designed to protect against all four dengue viruses and has been licensed by manufacturers in Brazil, India, and Vietnam for production and further evaluation. Phase II clinical trials to evaluate further the safety of TetraVax and its ability to evoke an immune response will begin soon in Brazil and Thailand. If successful, this vaccine could be instrumental in limiting the spread of dengue fever worldwide.

Chagas' disease

Due to increasing migration of populations from endemic areas, Chagas' disease, once confined to the Americas, is now being seen on other continents. The WHO estimates that seven to eight million people worldwide are currently infected with *Trypanosoma cruzi*, the parasite that causes Chagas' disease. Over one-third of those chronically infected suffer serious cardiac,

digestive, or neurological complications. CDC estimates that as many as 300,000 people in the United States are infected with *T. cruzi*, most having acquired their infections in endemic countries, and that 300 infected babies are born each year in the United States. If detected and treated promptly, the disease is curable, so there is an urgent need for better ways to prevent, detect, and more rapidly treat this disease.

The growing pipeline of treatments for Chagas' disease includes a promising drug candidate that has been supported by NIAID. NIAID-funded basic research identified K777, a drug that inhibits an enzyme essential for parasite survival, as a promising treatment for Chagas' disease. NIAID also supported pre-clinical toxicity studies and advanced development including manufacturing, formulation, and pharmacokinetic studies, and will continue clinical development of K777 to determine its safety and efficacy for treating Chagas' disease.

NIAID basic and pre-clinical research is also contributing to efforts toward development of a vaccine against Chagas' disease. NIAID-supported researchers are exploring innovative vaccine designs in the laboratory and in animal models. These include vaccines composed of molecules called glycolipids; vaccines that activate T cells, important components of the immune response; and whole parasite vaccines that have been inactivated so they cannot cause disease but can still generate immunity to Chagas' disease. Together with NIAID's ongoing research to develop and evaluate promising candidates for therapeutics and blood-based diagnostic tests, these efforts show great promise in limiting Chagas' disease worldwide.

Schistosomiasis

Schistosomiasis is a chronic, parasitic disease caused by trematode worms that infected more than 243 million people in 2011.[4] Though mortality from schistosomiasis is relatively low, tens of millions of people worldwide suffer chronic and debilitating consequences. NIAID grantees and scientists are working diligently to identify better ways to treat and prevent various forms of this disease.

NIAID provided resources enabling the sequencing of the genomes of multiple species of *Schistosoma* responsible for different forms of schistosomiasis, including *Schistosoma haematobium*, which causes a form of disease associated with bladder cancer and increased susceptibility to HIV infection. The genome sequence has helped to identify potential cancer-causing genes in this organism as well as targets for new anti-parasitic therapies.

Schistosomes are long-lived parasites that survive for many years in their host and are capable of repairing themselves when damaged. Recent basic biologic studies have provided insight into schistosomes' mechanisms of cellular regeneration that may have far-reaching implications beyond schistosomiasis. NIAID intramural studies of fibrosis, or scarring, resulting from tissue damage caused by schistosomes also provide insights for other diseases that result in harmful fibrosis, such as liver cirrhosis. NIAID scientists are partnering with several companies to study fibrosis and to develop new therapeutic strategies targeting the pathways that lead to fibrotic tissue damage.

NIAID also supports research on the organisms that serve as environmental reservoirs of schistosome parasites. For example, NIAID-supported scientists recently investigated the environmental conditions that facilitate growth of *S. mansoni* within the snail *Biomphalaria glabrata*. The parasites multiply within freshwater snails and are released into the water, where

[4] WHO

people engaged in agricultural, domestic, and recreational activities are infected. The scientists found that temperature influences whether the parasites can grow within the snail. This finding contributes to understanding of how these parasites survive in the environment and may help uncover methods to prevent the spread of *S. mansoni* and other schistosome parasites.

NIAID also pursues the development of vaccines against schistosomiasis to help prevent schistosome infections. Recently, NIAID-supported researchers identified a promising vaccine candidate targeting the Sm-p80 antigen of *S. mansoni.* The Sm-p80 vaccine generated robust immune responses when tested in an animal model of schistosomiasis. NIAID is partnering with a small business under NIH's Small Business Innovation Research program to continue the pre-clinical development of this vaccine candidate. NIAID will continue to seek collaborations and partnerships to support vaccine development for schistosomiasis and other NTDs. Together with the Bill & Melinda Gates Foundation, NIAID co-sponsored a meeting earlier this year to assess the landscape of schistosomiasis vaccine candidates and to provide strategic guidance for future vaccine research and development priorities.

Amebiasis

Amebiasis, caused by the parasite *Entamoeba histolytica*, is acquired through contaminated food and water, and generates symptoms that range from mild diarrhea to dysentery. More than 50 million people worldwide are affected each year, leading to as many as 100,000 deaths.[5] Emerging resistance to the current treatment for amebiasis has generated great interest in the development of new therapeutics for amebiasis and related infections. In response, NIAID provided funding to academic partners to screen a library of FDA-approved drugs for activity against *E. histolytica.* The screen identified auranofin, a drug currently used to treat

[5] CDC

rheumatoid arthritis, as a potential drug for amebiasis. Follow-up tests in animals confirmed its promise. Auranofin has been designated as an orphan drug by FDA for the treatment of amebiasis, which will facilitate its testing for efficacy in humans. NIAID will continue to support clinical development of this promising drug. In addition, NIAID also has provided early-stage research support for amebiasis vaccine candidates.

Trachoma

Trachoma, caused by the bacterium *Chlamydia trachomatis,* is a leading cause of blindness worldwide. The disease affects more than 20 million individuals and continues to be hyperendemic in many of the poorest areas of Africa, Asia, Central and South America, Australia, and the Middle East.[6] NIAID conducts and supports research on vaccines to prevent this debilitating infection. NIAID researchers developed a vaccine candidate shown to be safe and effective in an animal model. If this vaccine is efficacious in planned human studies, epidemiological models indicate that it could significantly reduce the prevalence of trachoma and could help limit the spread of the disease in endemic areas.

Hansen's disease (leprosy)

Hansen's disease (also known as leprosy) is a chronic bacterial disease caused by *Mycobacterium leprae* that affects the skin, peripheral nerves and upper airway and often leads to life-long disability. Hansen's disease has long been associated with social stigma and discrimination, contributing to the negative effects of this disfiguring disease. The WHO reports that nearly 230,000 new cases of Hansen's disease were identified globally in 2010. The National Hansen's Disease (Leprosy) Registry reported 213 cases of Hansen's disease in the

[6] WHO

United States in 2009. This number includes cases in Texas and Louisiana thought to result from transmission to humans from nine-banded armadillos living in the region. NIAID has been supporting Hansen's disease research around the world for many years. Research efforts are focused on early detection, prevention of nerve damage, and development of genomic tools to aid in the surveillance of emerging drug resistance to current treatments. Furthermore, NIAID has been supporting the development of novel diagnostics for Hansen's disease to identify the disease prior to the development of symptoms and disability.

NIAID also works to provide critical research resources to facilitate study of Hansen's disease. Armadillos, the only animal known to be susceptible to Hansen's disease, are an important tool for research on the disease. Since 1978, NIAID has supported the only globally available contracts for the preparation of research reagents from *M. leprae* that is propagated in armadillos to produce sufficient quantities of the bacteria. These NIAID-funded efforts also support the development of the armadillo as an animal model of Hansen's disease and associated nerve damage to evaluate the efficacy of new drugs and vaccines.

Onchocerciasis and filarial infections

NIAID conducts and supports research on infections caused by parasitic filarial worms. These filarial infections include NTDs such as onchocerciasis and lymphatic filariasis. Onchocerciasis, or river blindness, is caused by the parasite *Onchocerca volvulus*, which is transmitted to humans via the bite of *Simulium* blackflies. The parasite is currently estimated to infect at least 25 million people, primarily in sub-Saharan Africa, leading to 300,000 cases of blindness.[7] Technology to detect the OV-16 antigen of *O. volvulus,* initially developed by NIAID researchers in the early 1990s, is moving forward to commercial development as a

[7] CDC

diagnostic tool. Using NIAID's technology, the non-profit organization PATH will partner with Standard Diagnostics, Inc., to manufacture and distribute a rapid test to detect the parasite. PATH plans additional public-private partnerships with the WHO and others to assess the diagnostic test at field sites in Africa. Such technologies can expand our capability to detect and treat river blindness and other NTDs.

NIAID supports a broad range of activities for filarial infections, including a research resource center that provides critical reagents to the scientific community. NIAID researchers have developed improved treatment regimens for filarial infections and have advanced the molecular diagnosis of blood- and skin-borne filarial infections. In particular, NIAID researchers have worked to uncover the genetic sequence of *Brugia malayi*, one of the causes of the disfiguring disease lymphatic filariasis. The WHO estimates that 120 million people in tropical regions of the world have this disease, which can lead to elephantiasis, or disfiguring swelling of the limbs. NIAID scientists are using genetic information to map the expression of *B. malayi* proteins at various stages of the parasite's life cycle. This research contributes to better understanding of the parasite and could be used to identify targets in the parasite for new drugs or vaccines. NIAID scientists also are examining the response of the human hosts of *B. malayi* to understand the progression of the disease and develop treatments to prevent its debilitating effects. In addition, NIAID is currently supporting development of a recombinant fusion protein vaccine for lymphatic filariasis, which could help prevent many cases of this devastating disease.

NIAID scientists also are conducting clinical trials on loiasis, a filarial infection caused by the Loa loa parasite that affects several million individuals in West and Central Africa. While mass drug administration of deworming agents has been used to control other filarial infections,

these treatment campaigns have led to serious adverse effects in individuals infected with Loa loa. The goal of the NIAID clinical studies is to understand and prevent the adverse drug reactions, which will ultimately allow the restoration of mass drug administration to limit the effects of loiasis in these regions.

Leishmaniasis

Leishmaniasis is a poverty-related disease that in some settings is associated with increasing urbanization and associated migration. The WHO estimates that 12 million people around the world are currently infected with *Leishmania* parasites. The parasites, transmitted by the bites of infected sand flies, cause various forms of disease. Cutaneous leishmaniasis causes skin sores, and the more severe visceral leishmaniasis affects internal organs such as the spleen, liver, and bone marrow. NIAID conducts leishmaniasis research in the laboratory and at field sites in Mali, where NIAID scientists are studying cutaneous leishmaniasis in two villages endemic for *Leishmania major* infection. This field research will contribute to a better understanding of the epidemiology of the disease and immune protection against infection. NIAID also has supported pre-clinical development of a vaccine for visceral leishmaniasis, and is currently supporting a clinical trial of a leishmaniasis vaccine. In addition, funding from the Bill & Melinda Gates Foundation is supporting NIAID researchers' assessment of the efficacy of leishmania vaccines against visceral leishmaniasis. NIAID scientists also have partnered with the animal health company Merial Ltd. to develop a canine leishmania vaccine. Dogs in some regions can be an important reservoir of infection, and sand flies can transmit leishmania parasites to humans after biting an infected dog. Such vaccines, if successful, could help prevent *Leishmania* infections and limit the spread of this disease.

CONCLUSION

NIAID conducts critical basic and translational research on numerous neglected tropical diseases that is leading to new interventions to improve global health. NIAID will continue its longstanding investment throughout the product development pipeline from basic to pre-clinical and clinical research to tools to diagnose, treat, prevent, and control NTDs. The effective transition from basic research to product development to implementation of global infection control programs requires that we focus on research and development of improved diagnostics, therapeutics, and vaccines, and capitalize on public-private partnerships and fruitful collaborations with academia, non-profit organizations, and industry.