

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

The Role of the National Institute of Allergy and Infectious Diseases in Research to Address the
COVID-19 Pandemic

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Leading the Way Forward: Biden Administration Actions to Increase COVID-19 Vaccinations

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Madam Chair, Ranking Member Griffith, and Members of the Subcommittee:

Thank you for the opportunity to discuss the role of the National Institute of Allergy and Infectious Diseases (NIAID) in the research response to coronavirus disease 2019 (COVID-19) and its etiologic agent, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Within the Department of Health and Human Services (HHS) and the National Institutes of Health (NIH), NIAID is responsible for conducting and supporting basic and clinical research on emerging and re-emerging infectious diseases, including COVID-19. As the Director of NIAID and the Chief Medical Advisor to the President, I am pleased to discuss NIAID's research addressing this pandemic.

COVID-19 is a once-in-a-lifetime global infectious disease pandemic requiring an unprecedented public-private research effort. NIAID plays a central and important role in the public health response to COVID-19. NIAID has capitalized on decades of investment in fundamental basic research, including groundbreaking structure-based vaccine design at the NIAID's Vaccine Research Center (VRC); engaged domestic and international research infrastructure; and leveraged highly productive partnerships with industry and longstanding relationships with community partners. NIAID utilized its existing domestic and international clinical trials infrastructure, originally established to conduct research on HIV and influenza, and worked with partners in the public and private sectors to establish the COVID-19 Prevention Network (CoVPN). CoVPN has supported multiple COVID-19 vaccine candidates to progress in record time from concept to authorization for emergency use by the U.S. Food and Drug Administration (FDA). NIAID initiated clinical trials with creative and adaptive designs, allowing the evaluation of multiple new and existing therapeutics for use against COVID-19. Several of these trials demonstrated safety and efficacy of COVID-19 therapeutics and helped support authorization by the FDA. These successes have helped slow the progression of the pandemic. Cases are decreasing, and the administration of FDA-authorized vaccines is increasing rapidly.

While we are cautiously optimistic about the future, we know that many challenges remain; we must continue to employ the proven public health measures that have brought us to where we are today. One of the most concerning developments of the ongoing pandemic is the detection of genetic variants of SARS-CoV-2, some of which appear to be more transmissible than the original virus and less responsive to certain therapeutic agents and vaccine formulations. So far, scientific evidence suggests that the COVID-19 vaccines distributed in the United States under FDA Emergency Use Authorization (EUA) continue to be effective against these variants, but we must

remain vigilant. NIAID is rapidly conducting research to better understand these emerging variants of SARS-CoV-2, how they interact with the immune system, and their implications for COVID-19 therapeutic and vaccine formulations.

We also know that our fellow Americans in underserved and minority communities have been disproportionately affected by this pandemic. NIAID is committed to working directly with these communities and partnering with other agencies in the federal government, and with industry, and academia, to ensure that individuals in underserved and vulnerable communities are not left behind as we move forward towards defeating COVID-19. NIAID also recognizes that while many infections with SARS-CoV-2 resolve after a relatively short time, some individuals continue to suffer longer-term effects even after the virus has been eliminated from the body. NIAID is supporting collaborative efforts to study outcomes in patients across all ages, genders, and co-morbid conditions, who have experienced a wide range of severity of original disease, to identify and characterize these post-acute sequelae of SARS-CoV-2 infection (PASC) and develop effective strategies to address them.

Developing Vaccines and Therapies to Prevent COVID-19

Sustained investments by NIAID in structure-based vaccine design and coronavirus research over the years prior to the emergence of SARS-CoV-2 have enabled the unprecedented pace of COVID-19 vaccine development. Long before the pandemic, NIAID VRC scientists and their collaborators made the critical scientific discovery of how to stabilize in a highly immunogenic form viral proteins that are important for infection, including the spike protein of the Middle East respiratory syndrome coronavirus (MERS-CoV), using a mutation known as S2P. This key finding has facilitated the design of vaccine candidates that generate robust immune responses against coronaviruses and other viruses of public health importance such as respiratory syncytial virus. As soon as the sequence of SARS-CoV-2 was made available, VRC researchers were able to rapidly generate a stabilized SARS-CoV-2 spike protein for use in COVID-19 vaccine development. This crucial breakthrough in structure-based vaccine design for coronaviruses has led to the development of safe and effective COVID-19 vaccines across a range of vaccine platforms.

Five candidate COVID-19 vaccines have entered Phase 3 clinical trials in the United States thus far, and three subsequently have received an EUA from the FDA. Clinical trials to test COVID-19 vaccine candidates in pediatric populations are ongoing. On December 11, 2020, based

on data from a Pfizer-supported Phase 3 clinical trial, an investigational vaccine developed by Pfizer and BioNTech became the first to receive an EUA from the FDA for the prevention of COVID-19 in individuals 16 years of age and older. NIAID has helped to advance four additional COVID-19 vaccine candidates through support for research on the foundational biology underlying the vaccine concepts as well as for clinical testing through the CoVPN. Two of these vaccine candidates have received EUAs.

Utilizing the CoVPN, NIAID is participating in the implementation of harmonized protocols to test investigational vaccines and preventive interventions against SARS-CoV-2. These protocols were developed in collaboration with the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) public-private partnership, vaccine manufacturers, and the Biomedical Advanced Research and Development Authority (BARDA). NIAID also supports the underlying critical infrastructure for these clinical trials such as a common Data and Safety Monitoring Board (DSMB), an independent group that reviews data from the trials to ensure the ongoing safety of study volunteers and to determine whether efficacy has been achieved. The CoVPN has enrolled thousands of volunteers across the United States and internationally in clinical trials testing multiple investigational vaccines and monoclonal antibodies intended to protect people from COVID-19. The CoVPN also has developed an extensive community engagement framework to reach out to the minority communities disproportionately affected by COVID-19; to better understand their interest in, and concerns about, research participation; and to partner with them to ensure that their vital input is reflected in the conduct of the study.

To further address the critical challenges of participation in clinical trials as well as vaccine acceptance and vaccine hesitancy, NIH established the Community Engagement Alliance Against COVID-19 Disparities (CEAL) initiative, led by the National Heart, Lung, and Blood Institute (NHLBI) and the National Institute on Minority Health and Health Disparities. CEAL brings together trusted community leaders to serve as champions who share information about the importance of participating in COVID-19 research and communicate data on the safety and efficacy of authorized COVID-19 vaccines.

mRNA-1273 (Moderna)

As part of a longstanding collaboration, the NIAID VRC worked with the biotechnology company Moderna, Inc., to develop a vaccine candidate designated as mRNA-1273, which uses a messenger RNA (mRNA) vaccine platform to express the stabilized SARS-CoV-2 spike protein.

Early clinical trials demonstrated that mRNA-1273 was generally well tolerated and induced robust neutralizing antibody responses in healthy adults. NIAID and BARDA then began working with Moderna on a Phase 3 clinical trial utilizing the CoVPN that showed that mRNA-1273 was 94.1 percent efficacious in preventing symptomatic COVID-19. On December 18, 2020, after a thorough review of comprehensive data on mRNA-1273, the FDA issued an EUA of the mRNA-1273 vaccine for prevention of COVID-19 in individuals 18 years of age and older.

Ad26.COV2.S (Janssen/Johnson & Johnson)

Decades of NIAID support for basic, pre-clinical, and clinical research on adenovirus (Ad)-based HIV vaccines underpin the development by Janssen/Johnson & Johnson of a coronavirus vaccine based on the Ad26-vector, known as Ad26.COV2.S or JNJ-78436735. NIAID is supporting a Phase 3 clinical trial of Ad26.COV2.S through the CoVPN and has provided immunological testing of the candidate using NIAID-funded core laboratory infrastructure. In late January 2021, Janssen/Johnson & Johnson released an interim analysis of the Phase 3 clinical trial indicating that the one-dose vaccine candidate was 66 percent effective overall at preventing moderate to severe/critical COVID-19 occurring at least 28 days after vaccination and 85 percent effective overall in preventing severe/critical COVID-19 across several geographical regions, including areas where emerging viral variants predominate. In the United States, the efficacy against moderate to severe/critical disease 28 days after vaccination was 72 percent. On February 27, 2021, the FDA issued an EUA for Ad26.COV2.S for prevention of COVID-19 in individuals 18 years of age and older.

Other COVID-19 Vaccine Candidates

NIAID, through the CoVPN, is supporting Phase 3 clinical trials of COVID-19 vaccine candidates from AstraZeneca (AZD1222) and Novavax (NVX-CoV2373). AstraZeneca's AZD1222 COVID-19 vaccine candidate uses a chimpanzee adenovirus-vectored vaccine approach developed by researchers at the University of Oxford in collaboration with scientists at NIAID's Rocky Mountain Laboratories. AstraZeneca has reported promising results from their international Phase 3 clinical trial of AZD1222; data from the U.S. trial of AZD1222 are pending.

Monoclonal Antibodies to Prevent COVID-19

NIAID scientists, collaborating with Regeneron Pharmaceuticals and Eli Lilly and

Company, also initiated two Phase 3 clinical trials to evaluate whether their investigational monoclonal antibodies, known as REGEN-COV and bamlanivimab respectively, can prevent infection or symptomatic disease in people at high risk of exposure due to their living or working conditions. Each company recently reported promising initial results, and further analysis of the data from the trials is ongoing.

Identifying Therapeutics to Treat COVID-19

Safe and effective therapeutics are urgently needed to treat patients with COVID-19. NIAID launched a multicenter, randomized placebo-controlled clinical trial, the Adaptive COVID-19 Treatment Trial (ACTT), to evaluate the safety and efficacy of multiple investigational therapeutics for COVID-19. ACTT-1 examined the antiviral drug remdesivir for treatment of severe COVID-19 in hospitalized adults. Based on positive data from ACTT-1, the FDA approved the use of remdesivir for treatment in adults and children 12 years of age and older and weighing at least 40 kg hospitalized due to COVID-19. ACTT-2 evaluated the anti-inflammatory drug baricitinib in combination with remdesivir, and based on favorable data from ACTT-2, the FDA issued an EUA for the use of baricitinib in combination with remdesivir for treatment of adults and children older than 2 years hospitalized with COVID-19 and requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation. ACTT-3 is currently evaluating treatment of patients hospitalized with COVID-19 with remdesivir plus interferon beta-1a, which is used to treat individuals with multiple sclerosis. ACTT-4 is currently enrolling adults hospitalized with COVID-19 to assess baricitinib plus remdesivir versus the glucocorticoid dexamethasone plus remdesivir.

NIAID, in collaboration with other NIH Institutes, also launched two clinical trials as part of the ACTIV partnership, which utilizes master protocols allowing the addition of other investigational therapeutics as the trials continue. The two studies, ACTIV-2 and ACTIV-3, initially evaluated the use of the monoclonal antibody bamlanivimab to treat COVID-19 in outpatient and inpatient settings, respectively. Bamlanivimab was discovered by the company AbCellera in collaboration with the NIAID VRC and developed by Eli Lilly. Bamlanivimab received an FDA EUA in November 2020 for treatment of mild-to-moderate COVID-19 in patients with high risk for COVID-19 disease progression, based on data from a Lilly-sponsored Phase 2 clinical trial. ACTIV-2, which is focused on outpatients, has since been expanded to evaluate a combination monoclonal antibody therapy, BRII-196 and BRII-198, as well as three

investigational therapeutics: SNG001, an inhalable beta interferon; AZD7442, an investigational long-acting antibody combination; and camostat mesilate, an orally administered molecule that may block SARS-CoV-2 from entering cells. ACTIV-3 currently is evaluating the AZD7442 monoclonal antibody combination in hospitalized patients. In addition, NIAID launched a Phase 3 trial called, “Inpatient Treatment with Anti-Coronavirus Immunoglobulin,” or ITAC, to evaluate hyperimmune intravenous immunoglobulin for treatment of COVID-19 in hospitalized adults. NIAID also began a Phase 3 CoVPN trial of an Eli Lilly combination therapy, bamlanivimab and etesevimab, for treatment of mild to moderate COVID-19.

NIAID also announced the ACTIV-5/Big Effect Trial (BET), which is designed to streamline the identification of experimental COVID-19 therapeutics that demonstrate the most promise. BET, an adaptive Phase 2 clinical trial, compares different investigational therapies to a common control arm to identify treatments with relatively large effects as promising candidates for further study in large-scale trials. BET initially is evaluating two therapeutics: risankizumab, an immunomodulatory monoclonal antibody developed by Boehringer Ingelheim and AbbVie, which is FDA-approved for the treatment of severe plaque psoriasis; and lenzilumab, an investigational immunomodulatory monoclonal antibody developed by Humanigen.

The NIH also has established the COVID-19 Treatment Guidelines Panel to provide recommendations to health care providers regarding specific COVID-19 treatments based on the best available science. The Guidelines also address considerations for special populations, including pregnant women and children. Each Treatment Guidelines section is developed by a working group of Panel members with expertise in the area addressed in the specific section; these members conduct systematic, comprehensive reviews of relevant information and scientific literature. The Panel comprises representatives of NIH and five other federal agencies along with representatives of nine professional organizations, academic experts, and treating physicians including providers from high COVID-19 incidence areas, and community representatives. The Panel meets regularly to evaluate possible treatment options for COVID-19 and update the Treatment Guidelines as new clinical evidence emerges.

Responding to Emerging Variants of SARS-CoV-2

NIAID is fully engaged in efforts to mitigate the potential impact of emerging variants of SARS-CoV-2. NIH, including NIAID, participates in the SARS-CoV-2 Interagency Group (SIG), which works to detect and characterize these new variants and to develop and adapt

countermeasures to address them. The SIG was established by HHS to facilitate coordination among NIH, the Centers for Disease Control and Prevention (CDC), FDA, BARDA, the Department of Defense (DOD), and the U.S. Department of Agriculture (USDA) to detect and address SARS-CoV-2 variants as they emerge. NIH, CDC, and DOD are assessing whether vaccine-induced immunity, or natural immunity from prior infection, can be effective in combating the variants. NIH, BARDA, and DOD also are determining the efficacy of certain authorized therapeutics against emerging variants in cells and in animal models. In addition, NIAID is collaborating with vaccine manufacturers on key areas of research to investigate whether vaccines designed for the original strain of SARS-CoV-2 could maintain efficacy against emerging variants. NIAID also plans to test new vaccine formulations designed specifically to protect against certain variants that show early indications of reduced sensitivity to existing countermeasures.

NIAID, the National Human Genome Research Institute, and the National Library of Medicine are participating in the SARS-CoV-2 Sequencing for Public Health Emergency Response, Epidemiology, and Surveillance (SPHERES) initiative. SPHERES is a national genomics consortium led by CDC that helps to coordinate SARS-CoV-2 sequencing across the United States. NIAID is working with partners to identify, monitor, and calculate the frequency of current variations in the SARS-CoV-2 genome to help predict emerging variants. NIAID also facilitates the use of cutting-edge modeling and structural biology tools to understand how variants might affect interactions between the virus and the immune system or COVID-19 therapeutics. NIAID scientists are helping to inform our understanding of transmissibility of the variants by studying their stability in the environment of infected individuals and their ability to grow in human lung cells. These efforts add to a growing body of knowledge about SARS-CoV-2 variants and our ability to combat them.

Understanding the Immunology and Pathogenesis of COVID-19

NIH is supporting studies to understand the incidence of SARS-CoV-2 infection in specific populations, including children, as well as certain aspects of the clinical course of infection, including thromboses, strokes, heart attacks, and other sequelae of infection. NIAID is working with partners to delineate biological and immune pathways responsible for the varied manifestations of COVID-19. NIAID also will examine the quality and durability of the immune response to SARS-CoV-2; this information may be leveraged to develop novel SARS-CoV-2 therapeutics or vaccines.

NIAID, along with FDA, is supporting a National Cancer Institute (NCI) effort to determine the sensitivity and specificity of certain SARS-CoV-2 serological tests, which can detect antibodies indicative of a prior exposure to SARS-CoV-2. NCI and NIAID also are working to establish a collaborative network to increase national capacity for high-quality serological testing with rapid return-of-results to subjects. These efforts include the use of serological testing to support clinical trials of convalescent serum and the establishment of registries for seroprotection studies. NIAID, NCI, the National Center for Advancing Translational Sciences, and the National Institute of Biomedical Imaging and Bioengineering are partnering on a study, called the Serological Sciences Network or SeroNet, to investigate whether adults in the United States without a confirmed history of SARS-CoV-2 infection have antibodies to the virus, thus indicating prior infection. The study is evaluating the durability of the immune response and aspects of the immune response that contribute to protection against COVID-19.

NIAID scientists are participating in leadership of the COVID Human Genetic Effort, an international consortium of hospitals and genetic sequencing hubs that aim to discover genetic factors conferring resistance to SARS-CoV-2 infection or predisposing to severe COVID-19 disease. The consortium has identified a subgroup of patients with severe COVID-19 that have ineffective immune responses to SARS-CoV-2, some of whom have identifiable mutations in key immune pathways. NIAID also supports efforts to understand the rare but extremely serious multisystem inflammatory syndrome in children (MIS-C) that has been associated with SARS-CoV-2 infection in children and adolescents. NIAID hosted a virtual workshop on MIS-C with scientists and clinicians from academia, NIH, FDA, and industry, and a report of the workshop recommendations was published on November 2, 2020. NIAID also supports the Pediatric Research Immune Network on SARS-CoV-2 and MIS-C (PRISM) to evaluate acute and long-term clinical and immunological effects of MIS-C and SARS-CoV-2 infection in children. In addition, NIAID is collaborating with Children's National Medical Center to follow 1,000 children with a history of SARS-CoV-2 infection, including those with MIS-C, to determine long-term effects of the illness. NIAID is participating in a trans-NIH effort to coordinate MIS-C research led by NHLBI and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development. This centralized effort, the Collaboration to Assess Risk and Identify Long-term Outcomes for Children with COVID (CARING for Children with COVID), will permit data to be shared across studies to determine the spectrum of illness and predict long-term consequences of infection.

Monitoring the Long-term Effects of COVID-19

Many people who have had COVID-19 report continued symptoms as they transition from the acute to post-acute phases of the disease, and we continue to learn more about the duration and manifestations of COVID-19 as we hear from these patients. In December 2020, NIAID hosted a Workshop on Post-Acute Sequelae of COVID-19 with clinicians, immunologists, virologists, and members of the patient community to present existing data, identify key knowledge gaps, and explore different perspectives on this heterogeneous condition. Subsequently, NIH announced a trans-NIH effort to address PASC, including targeted funding for research in this critical area. The NIH PASC Initiative will complement ongoing NIAID studies to better understand the various post-acute manifestations of COVID-19 in various populations.

NIAID intramural scientists initiated the Longitudinal Study of COVID-19 Sequelae and Immunity to better understand PASC and determine whether people who have recovered from acute SARS-CoV-2 infection develop an immune response to SARS-CoV-2 that provides protection against reinfection. NIAID-supported investigators also have established the Immunophenotyping Assessment in a COVID-19 Cohort (IMPACC) to determine how immunological markers correspond to, or may even predict, the clinical severity of COVID-19. Since May 1, 2020, IMPACC researchers have collected detailed clinical data along with blood and respiratory samples from 1,800 hospitalized COVID-19 patients of diverse race and ethnicity at approximately 20 hospitals nationwide. The cohort will be followed during hospitalization and up to one year after discharge to assess their functional and immunologic recovery.

Conclusion

NIAID continues to expand efforts to elucidate the biology, pathogenesis and clinical manifestations of SARS-CoV-2 infection, including emerging variants, and to employ this knowledge to develop safe and effective interventions to diagnose, treat, and prevent SARS-CoV-2 infection and COVID-19. NIAID is focused on developing safe and effective SARS-CoV-2 vaccines and therapeutics and sensitive, specific, and rapid point-of-care molecular diagnostic and serological tests. NIAID also is conducting early stage research on candidate vaccines that could protect against multiple strains of coronaviruses. These efforts will improve our response to the current pandemic and bolster our preparedness for the next, inevitable viral disease outbreak.