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

Testimony before the

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Madam Chair, Ranking Member Burr, and Members of the Committee:

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 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). The 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 also has built on its longstanding relationships with community partners to successfully conduct these crucial clinical trials. 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 provided evidence of safety and efficacy of COVID-19 therapeutics and helped support authorization by the FDA.

These successes have helped slow the progression of the pandemic in the United States. Currently, we are vaug

adherence to public health measures are the fundamental tools that will help us head off another COVID-19 surge.

While we are cautiously optimistic about the future, we know that many challenges remain. One of the most concerning developments of the ongoing pandemic is the spread of genetic variants of SARS-CoV-2, some of which appear to be more transmissible than the original virus, more virulent, and/or 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 Authorizations (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 disproportionally affected by this pandemic. NIAID is committed to continuing to work directly with these communities, as well as 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 the COVID-19 pandemic. NIAID also recognizes that while many individuals with SARS-CoV-2 infection fully recover after a relatively short time period, some individuals suffer longer-term effects after the initial phase of illness and after the virus is cleared 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 broad 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 research investments by NIAID in the years prior to the emergence of SARS-CoV-2 enabled the unprecedented pace of COVID-19 vaccine candidate development. Two activities predate successful COVID-19 vaccines: the development

respiratory syndrome coronavirus (MERS-CoV), using a double mutation known as S2P. This key finding 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 in January 2020, VRC researchers rapidly generated 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 vaccine candidates across a range of vaccine platforms.

Five candidate COVID-19 vaccines have been assessed in large-scale Phase 3 clinical trials in the United States thus far, and three have received EUAs 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, those from Moderna, Inc. and Johnson & Johnson/Janssen, 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

vaccine candidate 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. As reported in the *New England Journal of Medicine*, 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 in the Phase 3 trial 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 with Ad26.COV2.S 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. On April 13, 2021, out of an abundance of caution, the FDA and CDC released a joint statement recommending a pause in the use of Ad26.COV2.S in order to review extremely rare case reports of blood clots after vaccine administration. Medical and scientific teams at the FDA and CDC found that available data suggest such blood clots are very rare events. Following their thorough safety review – and in accordance with recommendations fr

children, and people with immune

separate studies, NIAID-supported scientists and collaborators are evaluating the potential impact of emerging SARS-CoV-2 variants on the efficacy of monoclonal antibodies.

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 hospitalized COVID-19 patients with remdesivir plus interferon beta-1a, which is used to treat individuals with multiple sclerosis. ACTT-4, a study assessing baricitinib plus remdesivir versus the glucocorticoid dexamethasone plus remdesivir in adults hospitalized with COVID-19, has closed to enrollment because the study met pre-defined futility criteria.

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. 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 four investigational therapeutics: SAB-185, a fully-human polyclonal antibody produced in cattle; SNG001, an inhalable beta interferon; AZD7442, an investigational long-acting antibody combination; and camostat mesilate, an orally administered drug that may block SARS-CoV-2 from entering cells. ACTIV-3 currently is evaluating the AZD7442 monoclonal antibody combination in hospitalized patients. On April 22, 2021, NIAID and NHLBI launched the ACTIV-3 Critical Care study to test Zyesami and remdesivir (alone and in combination), for their safety and efficacy in hospitalized COVID-19 patients who are experiencing acute respiratory

distress syndrome, a life-threatening condition. Zyesami is a synthetic version of vasoactive intestinal peptide, which is made naturally in the human body and appears to have lung-protective antiviral and anti-inflammatory effects.

On April 13, 2021, NIAID announced the launch of the COVID-19 anti-CD14 Treatment Trial (CaTT) to evaluate the use of a monoclonal antibody known as IC14 in adults hospitalized with COVID-19. IC14 works by binding to and blocking a human protein called CD14 that is associated with the development of severe inflammatory reactions in some COVID-19 patients. In addition, NIAID completed a Phase 3 trial called, "Inpatient Treatment with Anti-Coronavirus Immunoglobulin," or ITAC, to evaluate hyperimmune intravenous immunoglobulin (IVIG) for treatment of COVID-19 in hospitalized adults. The study demonstrated that IVIG plus remdesivir was not superior to remdesivir alone.

NIAID also launched the ACTIV-

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 HHS-established SARS-CoV-2 Interagency Group, along with CDC, FDA, BARDA, the Department of Defense (DOD), and the U.S. Department of Agriculture to address the potential impact of emerging variants on critical SARS-CoV-2 countermeasures. 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 cell lines *in vitro* and in animal models.

NIAID is collaborating with vaccine manufacturers on key areas of research to investigate whether vaccines designed for the original strain of SARS-CoV-2 can maintain efficacy against emerging variants. NIAID also is conducting and supporting comprehensive studies to understand the ability of vaccine-induced antibodies to neutralize the variant viruses. NIAID researchers have analyzed the immune responses of individuals who recovered from COVID-19 prior to the emergence of variants and demonstrated that their T cells – a key component of the immune response to SARS-CoV-2 – also were capable of recognizing the three most widespread SARS-CoV-2 variants, B.1.1.7, B.1.351, and P1. These findings, published in *Open Forum Infectious Diseases*, shed new light on the role of T cells in the development of immunity to SARS-CoV-2 and suggest that these cells also may help protect against emerging variants of concern. On March 25, 2021, NIAID launched a Phase 1 clinical trial in healthy adults to assess the safety and immunogenicity of second-generation COVID

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-

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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 more than 1,200 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, 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. All of these efforts will improve our response to the current pandemic and bolster our preparedness for the next, inevitable viral disease outbreak.