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

United States Senate Committee on Health, Education, Labor, and Pensions

Hearing Titled:

The Path Forward: A Federal Perspective on the COVID-19 Response

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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

segments of the public in the United States and other countries. Vaccination and adherence to public health measures are the proven interventions that will be particularly important as we work to address the SARS-CoV-2 Delta (or B.1.617.2) variant and other variants with increased transmissibility or pathogenicity that may emerge.

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 variants of SARS-CoV-2 such as the Delta (B.1.617.2) variant. 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 severe disease caused by these variants, but we must remain vigilant. NIAID is rapidly conducting research to better understand these emerging variants, 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 and partnering with other agencies in the federal government, and with industry and academia to ensure that nobody in vulnerable communities is 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,

myocarditis and pericarditis following vaccination with mRNA COVID-19 vaccines are rare. Most patients who received care have responded well to treatment and rest, and patients usually can return to their normal daily activities after their symptoms improve. Given the significant potential health risk of COVID-19, the CDC continues to recommend that individuals ages 12 and older be vaccinated with the relevant FDA-authorized COVID-19 vaccine.

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

Decades of NIAID support for basic, preclinical, and clinical research on adenovirus (Ad)-based HIV vaccines underpin the development by Johnson & Johnson/Janssen of a coronavirus 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

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. Rocky Mountain Laboratories. On March 25, 2021, AstraZeneca announced an updated interim analysis of AZD1222 reporting that the vaccine candidate was 76 percent effective at preventing symptomatic COVID-19, including 85 percent effective in participants aged 65 years and over. Importantly, the efficacy of AZD1222 against severe COVID-19 disease was reported to be 100 percent. Novavax's NVX-CoV2373 COVID-19 vaccine candidate uses a protein nanoparticle vaccine approach. On June 14, 2021, Novavax announced that NVX-CoV2373 demonstrated 90.4 percent efficacy in preventing symptomatic COVID-

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TeenCOVE study of mRNA-1273 in adolescents between the ages of 12 and 17. On May 10,
WKH)'$ H[SDQGHG WKH (8$ vaccine to include adolescents ages 12
to 15 years of age, and Pfizer also is evaluating their vaccine candidate in younger individuals.

The Adaptive COVID-19 Treatment Trial

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 currently is 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.

The ACTIV Public-Private Partnership

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 two combination monoclonal antibody therapies ² BRII-196 plus BRII-198 and BMS-986414 plus BMS-986413 ² as well as four additional investigational therapeutics: SAB-185, a fully-human polyclonal antibody produced in cattle; SNG001, an inhalable beta interferon; and AZD7442, an investigational long-acting monoclonal antibody combination. Camostat mesilate, an orally administered drug that may block SARS-CoV-2 from entering cells, was evaluated but ultimately not included in ACTIV-2 efficacy studies, as it failed to induce early changes in viral shedding or improvement in symptoms. ACTIV-3 currently is evaluating the AZD7442 monoclonal antibody combination, as well as the small molecule ensovibep, in hospitalized patients. Ensovibep binds to several sites on the SARS-CoV-2 spike

NHLBI launched a new trial, known as ACTIV-3 Critical Care, 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.

Three monoclonal antibody therapies currently have FDA EUAs for the treatment of COVID-19 in outpatients. Due to concerns of variant resistance to monoclonal antibody therapies, the FDA now includes information on the susceptibility of SARS-CoV-2 variants in its fact sheets for health care providers for each of these therapies. NIAID-supported scientists and collaborators are evaluating the potential impact of emerging SARS-CoV-2 variants on the efficacy of monoclonal antibodies.

Additional NIAID-supported Therapeutics Activities

On April 13, 2021, NIAID announced the launch of the COVID-19 anti-CD14 Treatment Trial (CaTT) to evalu

development of antivirals directly targeting viruses with pandemic potential. As part of this effort, NIAID will establish Antiviral Drug Discovery Centers for Pathogens of Pandemic Concern. These multidisciplinary research centers will create platforms that will initially target coronaviruses, and then could be expanded to other viruses with pandemic potential ±helping to better prepare the nation for future viral threats.

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 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 at the time, Alpha (also known as B.1.1.7), Beta (B.1.351), and Gamma (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-19 vaccine FDQGLGDWHV GHYHORSHG E\ *ULWVWRQH2QFRORJ\ ,QF *U candidates. The vaccine candidates utilize a strategy aimed at inducing both neutralizing antibodies and T cell responses to elicit a broad immune response. This approach could provide protection against emerging SARS-CoV-2 variants by targeting several viral antigens, all of which are highly conserved among viral strains.

NIAID also plans to test new vaccine formulations that may protect against certain variants that show early indications of reduced sensitivity to existing countermeasures. On March 31, 2021, NIAID launched a Phase 1 clinical trial of an investigational Moderna vaccine based on its FDA-authorized COVID-19 vaccine, designed specifically to target the Beta (B.1.351) SARS-CoV-2 variant first detected in South Africa. NIAID and Moderna are evaluating this vaccine candidate as a precautionary measure as we gain more data to confirm that current vaccines provide an adequate degree of protection against currently circulating SARS-CoV-2 variants. In addition, NIAID is leading a study in fully vaccinated individuals to determine the safety and efficacy of boosting with a COVID-19 vaccine different than the one used for the initial vaccination. The results of this trial are intended to inform public health policy decisions on the potential use of mixed vaccine schedules should booster doses be needed.

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 and inform public health measures.

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.

Early in the pandemic, the intramural research programs of NIAID, NCI, the National Center for Advancing Translational Sciences, and the National Institute of Biomedical Imaging and Bioengineering partnered to rapidly deploy the SARS-CoV-2 Pandemic Serosurvey. The study investigated whether adults in the United States without a confirmed history of SARS-CoV-2 infection have antibodies to the virus, thus indicating prior infection. Findings from the first time point of this longitudinal study suggest that the prevalence of COVID-19 in the United States during the spring and summer of 2020 may have far exceeded the number of cases medically diagnosed. Extrapolating from analyses of blood samples from people who did not have a previously diagnosed SARS-CoV-2 infection, along with socioeconomic, health, and demographic data, the researchers estimate that there may have been an additional 16.8 million undiagnosed SARS-CoV-2 infections through mid-July 2020. Continued analysis of the 1-year follow-up data from the study will be very important in better understanding mortality rates, prevalence of immunity, and the impact SARS-CoV-2 has had on various communities in the United States.

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

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