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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Addressing New Variants: 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 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 once-in-a-lifetime global infectious disease pandemic.

The public health response to COVID-19 has required an unprecedented global public-private research effort. NIAID has played a central and important role in this response. NIAID capitalized on decades of fundamental basic research, including groundbreaking structure-based vaccine design at the NIAID Vaccine Research Center (VRC), to facilitate the rapid development of COVID-19 vaccines. NIAID also initiated clinical trials with creative and adaptive designs, allowing the evaluation of the safety and efficacy of multiple new and existing therapeutics for the treatment of COVID-19, which has helped support authorization of some of these products by the U.S. Food and Drug Administration (FDA). In addition, NIAID has engaged domestic and international clinical research infrastructure and leveraged highly productive partnerships in the public and private sectors to support multiple COVID-19 vaccine candidates to progress in record time from concept to Emergency Use Authorization (EUA) by FDA. Use of these vaccines throughout the world will continue to play a critical role in reducing the threat of COVID-19 in the United States and globally.

One of the most concerning developments of the ongoing pandemic has been the spread of SARS-CoV-2 variants, including the newly described Omicron variant. The Omicron variant is highly transmissible and is now the predominant variant in much of the United States. Early data suggest that the severity of disease caused by infection with the Omicron variant is lower compared to previous variants. However, the increased transmissibility of Omicron and the large number of new infections may lead to substantial numbers of hospitalizations and deaths, particularly among unvaccinated individuals at highest risk. The emergence of the Omicron variant makes it critical that we continue to vaccinate as many people as we can, as quickly as possible, including with booster doses.

The COVID-19 vaccines authorized or approved in the United States appear to remain

effective against severe disease for most individuals, despite data showing waning of vaccine- and infection-induced immunity. While antibodies generated by the primary COVID-19 vaccine series do not neutralize the Omicron variant as well as prior variants, laboratory studies show that booster doses of COVID-19 vaccines induce high levels of antibodies against the Omicron variant. Early clinical data also show that booster doses of vaccines restore levels of immunity such that people are, at least initially, well-protected against the Omicron variant, particularly against severe disease. Further research to assess immune protection against Omicron is underway, including studies of the durability of protection offered by COVID-19 vaccination and boosters. NIAID efforts to enhance the protection afforded by COVID-19 vaccines and understand the effects of SARS-CoV-2 variants on immunity will help to address the Omicron variant and any future variants that may emerge.

Responding to Emerging Variants of SARS-CoV-2

NIH, including NIAID, participates in the HHS-established SARS-CoV-2 Interagency Group, along with the Centers for Disease Control and Prevention (CDC), FDA, Biomedical Advanced Research and Development Authority (BARDA), Department of Defense (DOD), and U.S. Department of Agriculture to track variants in real time and address the potential impact of emerging variants on critical SARS-CoV-2 countermeasures including vaccines, therapeutics, and diagnostics. Active monitoring of variants has allowed the U.S. Government to optimally deploy therapeutics to treat COVID-19 patients. NIH, CDC, and DOD are assessing the extent to which vaccine-induced immunity or post-infection immunity prevent infection by variants. NIH, BARDA, and DOD also are assessing the efficacy of authorized and candidate therapeutics against emerging variants in cell lines and animal models.

NIAID and our collaborators have rapidly assessed vaccines, monoclonal antibodies, and antiviral drugs to assess their effectiveness against the Omicron variant. Research suggests that although effectiveness of certain monoclonal antibodies against Omicron has been markedly diminished, one of the three monoclonal antibodies authorized for COVID-19 treatment retains its effectiveness against the Omicron variant. A monoclonal antibody authorized for pre-exposure prophylaxis (prevention) in high-risk people also retains its effectiveness. In addition, antiviral drugs used to treat COVID-19 appear to be effective against the Omicron variant.

NIAID also is supporting the development of next-generation vaccines that could provide protection against emerging SARS-CoV-2 variants by targeting several viral antigens, all of which

are highly conserved among viral strains. 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 candidates developed by Gritstone Oncology, Inc. Gritstone's COVID-19 vaccine candidates utilize a strategy aimed at inducing both neutralizing antibodies and T cell responses to elicit a broad immune response against conserved viral antigens. NIAID also is conducting early-stage research on pan-coronavirus vaccines designed to provide broad protective immunity against multiple coronaviruses, especially SARS-CoV-2 and other viruses with pandemic potential. In 2021, NIAID announced awards to four academic institutions to conduct research to develop vaccines to protect against multiple types of coronaviruses and viral variants.

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. These efforts add to our knowledge about SARS-CoV-2 variants and our ability to combat them.

Developing Vaccines to Prevent COVID-19

Sustained domestic and international research investments by NIAID prior to the emergence of SARS-CoV-2 enabled the unprecedented pace of COVID-19 vaccine development. Two activities in particular predate successful COVID-19 vaccines: the development of versatile vaccine platforms and the adaptation of structural biology tools to design specific proteins (immunogens) that powerfully stimulate the immune system. 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. These included the spike protein of Middle East respiratory syndrome coronavirus (MERS-CoV), which was stabilized using a double mutation known as S2P. This strategy facilitated the design of vaccine candidates that generate robust immune responses not only against coronaviruses but also 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 led to the development of safe and effective COVID-19 vaccine candidates, several now authorized or approved by the FDA, across a range of vaccine platforms.

Six candidate COVID-19 vaccines have been assessed in completed or ongoing large-scale Phase 3 clinical trials in the United States. Clinical trials assessing COVID-19 vaccine candidates in certain pediatric populations have been completed or are still ongoing. On August 23, 2021, a candidate vaccine developed by Pfizer and BioNTech became the first to be approved by the FDA for the prevention of COVID-19 in individuals 16 years of age and older. The vaccine also is authorized for emergency use and is available under the EUA as a two-dose primary series for individuals 5 years of age and older, as a third primary series dose for individuals 5 years of age and older who have been determined to have certain kinds of immunocompromise, and as a single booster dose for individuals 12 years of age and older 5 months after completing a primary series of the Pfizer/BioNTech COVID-19 vaccine. The Pfizer/BioNTech COVID-19 vaccine also is authorized for use as a heterologous single booster dose following completion of primary vaccination with a different available COVID-19 vaccine. The Pfizer/BioNTech vaccine is one of six COVID-19 vaccine candidates NIAID has helped advance through support for the fundamental research underlying the vaccine concepts, as well as for clinical testing. Two additional vaccine candidates, from Moderna, Inc., and Johnson & Johnson/Janssen, are available under an FDA EUA.

<u>mRNA-1273 (Moderna)</u>

As part of a longstanding collaboration, the NIAID VRC collaborated with the biotechnology company Moderna to develop a vaccine candidate designated mRNA-1273, which uses a messenger RNA (mRNA) vaccine platform to express the stabilized SARS-CoV-2 spike protein. After promising results in early clinical trials, NIAID and BARDA began working with Moderna on a Phase 3 clinical trial. NIAID scientists and their collaborators published updated results from this trial indicating that the vaccine had 93.2 percent efficacy in preventing COVID-19 illness, 98.2 percent efficacy in preventing severe disease, and 63 percent efficacy in preventing asymptomatic infection. Importantly, the efficacy of mRNA-1273 in preventing COVID-19 four months or more after the second dose was maintained at greater than 90 percent. In addition, in observational studies in “real-world” conditions in broader segments of the population, mRNA-

based vaccines continue to display high levels of effectiveness.

FDA has authorized mRNA-1273 for emergency use for prevention of COVID-19 in individuals 18 years of age and older as a two-dose primary series, as a third primary series dose for individuals 18 years of age and older who have been determined to have certain kinds of immunocompromise, and as a single booster dose in people 18 years of age and older 5 months after completing a primary series of the vaccine. mRNA-1273 also is authorized for use as a heterologous single booster dose for individuals 18 years of age and older following completion of primary vaccination with a different available COVID 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. The vaccine is known as Ad26.COV2.S or JNJ-78436735. NIAID has supported a Phase 3 clinical trial of Ad26.COV2.S 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 efficacious overall at preventing moderate to severe/critical COVID-19 occurring at least 28 days after vaccination and 85 percent efficacious overall in preventing severe/critical COVID-19 in the Phase 3 trial across several geographical regions, including areas where viral variants predominated. In the United States, the efficacy against moderate to severe/critical disease 28 days after vaccination with Ad26.COV2.S was 72 percent. FDA has authorized Ad26.COV2.S for emergency use for prevention of COVID-19 in individuals 18 years of age and older as a single primary vaccination dose and as a single booster dose for individuals 18 years of age and older two months after completing primary vaccination with the vaccine.

Ensuring Protection with COVID-19 Vaccine Boosters

FDA-authorized and FDA-approved COVID-19 vaccines have maintained remarkable effectiveness in preventing severe COVID-19. However, protection against mild and moderate disease begins to decrease over time following the primary vaccine series; this effect is seen with both the Delta and Omicron variants circulating in the United States. As noted, the Omicron variant appears to be more transmissible than previous variants and more apt to evade immunity. Individuals who receive a booster dose of a COVID-19 vaccine have markedly higher levels of

antibodies against SARS-CoV-2 variants compared to levels in individuals who received just the primary regimen, and early clinical data still being evaluated suggest these boosted individuals are, at least initially, well-protected against the current Delta and Omicron variants, particularly against severe disease.

FDA amended the EUAs for the Moderna and Johnson & Johnson/Janssen COVID-19 vaccines, respectively, to allow for use of a single booster dose for individuals 18 years of age and older. FDA also amended the EUA for the Pfizer/BioNTech COVID-19 vaccine to allow for the use of a single booster dose for individuals 12 years of age and older. CDC recommends receiving a booster dose of the COVID-19 vaccine at least 5 months after completion of the primary series of the Pfizer/BioNTech and Moderna COVID-19 vaccines, and at least 2 months after completion of the single-dose primary regimen of the Johnson & Johnson/Janssen COVID-19 vaccine.

NIAID has initiated several studies to specifically address the Omicron variant and has several more in planning stages. For example, NIAID is testing the impact of a higher dose of the Moderna vaccine as a booster. In addition, the NIAID VRC is conducting preclinical testing of an Omicron-specific booster candidate (mRNA-1273.529) and of mixed (bivalent) booster candidates (mRNA-1273 plus a Beta variant-specific booster) against the Omicron variant. NIAID also plans to examine whether individuals who received boosters—either mRNA-1273 or investigational COVID-19 vaccine boosters designed to incorporate mutations found in emerging variants—generate antibodies that can bind to and neutralize the Omicron variant.

NIAID is leading a study in fully vaccinated individuals to assess the safety and immune responses following boosting with a COVID-19 vaccine different than the one used for the initial vaccination ("mix and match"). This trial includes a booster candidate (mRNA-1273.211) that incorporates several mutations that are present in the Omicron variant. NIAID released early data from this trial demonstrating that administering the Pfizer, Moderna, or Johnson & Johnson/Janssen COVID-19 vaccines at least 12 weeks after individuals received a different vaccine regimen effectively enhanced the immune response to SARS-CoV-2. Additionally, no safety concerns were identified. The results of this trial were made available to FDA during FDA's decision-making process to authorize the use of heterologous, or "mix and match," booster dosing in eligible individuals following completion of primary vaccination with a different available COVID-19 vaccine for persons 18 years of age and older.

NIAID is supporting additional preclinical and clinical research to assess the durability of immunity induced by COVID-19 vaccines, as well as the effect of COVID-19 vaccine boosters.

On April 23, 2021, NIAID launched an observational study at the NIH Clinical Center assessing how people with immune system deficiencies or dysregulations respond to COVID-19 vaccination. NIAID investigators also will gather information about COVID-19 illness in these individuals. This study will inform decision-making about COVID-19 vaccination in people with immune deficiencies and dysregulation conditions. In August 2021, NIAID launched multiple additional studies to assess and enhance the immune response to COVID-19 vaccines in immunocompromised individuals with autoimmune diseases as well as solid organ transplant recipients. This effort features a study with a multicenter, adaptive design to assess the immune responses to an additional dose of the COVID-19 vaccine in immunocompromised individuals. Data from this research will inform future considerations of additional doses of COVID-19 vaccines for these populations. CDC has made a recommendation, after review of the available scientific data, that people with moderately to severely compromised immune systems receive an additional dose of mRNA COVID-19 vaccine at least 28 days after a second dose of Pfizer/BioNTech COVID-19 vaccine or Moderna COVID-19 vaccine.

Clinical Trials of COVID-19 Vaccine Candidates in Special Populations

To effectively end the COVID-19 pandemic, it will be important to vaccinate as many people as possible, including those in special populations, such as pregnant and lactating women and children. Many pregnant and lactating women already have received the available COVID-19 vaccines. Data from these individuals demonstrate no safety concerns for pregnant women or their babies. In addition, protective antibodies against SARS-CoV-2 have been detected in babies born to pregnant women who received mRNA COVID-19 vaccines. On June 23, 2021, NIAID launched an observational study, MOMI-VAX, to evaluate the immune responses generated by COVID-19 vaccines administered to individuals during pregnancy or up to two months postpartum. The study also will assess vaccine safety and evaluate the transfer of vaccine-induced antibodies to infants across the placenta and through breast milk.

Efforts to evaluate COVID-19 vaccines in pediatric and other special populations are ongoing. This includes KidCOVE, a Phase 2/3 study launched by Moderna, in collaboration with NIAID and BARDA, to evaluate the safety and efficacy of mRNA-1273 in children ages 6 months to less than 12 years. This study is in addition to Moderna's ongoing TeenCOVE study of mRNA-1273 in adolescents between the ages of 12 and 17. Pfizer also is evaluating their vaccine candidate in children younger than age 5, including a three-dose primary series. Other vaccine

developers have begun, or are planning to begin, trials to test their vaccine candidates in children, adolescents, and other special populations.

Other COVID-19 Vaccine Candidates

NIAID also is supporting Phase 3 clinical trials of COVID-19 vaccine candidates from AstraZeneca (AZD1222) and Novavax (NVX-CoV2373). FDA has not yet authorized either of these vaccine candidates for emergency use.

Understanding the Nature of Immunity to SARS-CoV-2

NIAID is conducting and supporting research to enhance our knowledge of immunity against SARS-CoV-2 and to identify components of the immune response that provide protection against COVID-19. NIAID also is examining the quality and durability of the immune response to SARS-CoV-2, generating information that may be leveraged to develop novel SARS-CoV-2 therapeutics or vaccines and inform public health measures.

Data on infection-induced immunity from natural infection with SARS-CoV-2, including studies by NIAID scientists and NIAID-supported researchers, clearly demonstrate that most individuals generate a protective immune response to COVID-19 after infection. However, uncertainty surrounds several variables that can affect the generation of a protective immune response to SARS-CoV-2 following either infection or vaccination. Variables affecting the immune response include the age of the individual; their immune status; the medical treatments they have received; the impact of SARS-CoV-2 variants; and the impact of the severity of initial infection and time since infection, if applicable. Given that COVID-19 vaccination after infection with SARS-CoV-2 is safe and markedly enhances immune responses, COVID-19 vaccination is recommended for eligible individuals regardless of history of symptomatic or asymptomatic SARS-CoV-2 infection. NIAID continues to support research to understand immune responses to SARS-CoV-2 infection and/or COVID-19 vaccination, including projects investigating the durability of immune responses; whether immunity differs in certain populations; and how SARS-CoV-2 variants may affect immunity.

NIAID also is supporting research to improve understanding of the role of T cells in protection against COVID-19 and COVID-19 disease progression. NIAID supported a collaborative longitudinal study by researchers at Emory University and the Fred Hutchinson Cancer Research Center that demonstrated that SARS-CoV-2-specific T cells were detectable for

up to 8 months in patients after mild to moderate COVID-19. NIAID also supported two separate studies examining T cell responses in recovered COVID-19 patients and individuals vaccinated against COVID-19. They found robust immune responses to the original strain as well as multiple variants of SARS-CoV-2 in both groups. Additional work by NIAID researchers and grantees showed that most individuals with existing T cell responses against SARS-CoV-2 should generate a T cell response against the Omicron variant, and that SARS-CoV-2 has thus far not evolved extensive T cell escape mutations. Other work from NIAID-supported investigators has shown that vaccine-induced T cell responses recognize the Omicron variant. In another NIH-supported study, researchers uncovered features of T cells that distinguish fatal from non-fatal cases of severe COVID-19, which could lead to new treatments for this disease. However, it is important to note that although we are learning important information about T cell responses in SARS-CoV-2 infected and vaccinated individuals, we still do not know the extent to which T cell responses mediate protection against COVID-19.

To help prepare for future pandemic threats, the NIAID VRC has established the Pandemic Response Repository through Microbial/Immune Surveillance and Epidemiology (PREMISE) program. The program will use data from the measurement of T and B cell immune responses to inform the discovery and development of diagnostic, prophylactic, and therapeutic countermeasures and accelerate the global response to pandemic threats. NIAID anticipates the research conducted by PREMISE will advance our knowledge of immune response to vaccination and infection and help inform the response to future pandemic threats.

Identifying Therapeutics to Treat COVID-19

Safe and effective therapeutics are urgently needed to treat patients with COVID-19. NIAID has worked quickly from the earliest days of the pandemic to evaluate promising therapeutics for COVID-19 in rigorous, randomized, controlled clinical trials. COVID-19 therapeutics that inhibit essential viral processes or address the host response to COVID-19 are expected to maintain their effectiveness against emerging variants, such as the Omicron variant. As noted above, some monoclonal antibodies appear to be ineffective against Omicron, while others maintain their activity. NIAID is conducting and supporting additional research to determine how Omicron and other variants impact the effectiveness of monoclonal antibodies and other therapeutics as well as working to develop new drugs.

The Adaptive COVID-19 Treatment Trial

Early in the outbreak, 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. The FDA subsequently revised the EUA for baricitinib to remove the requirement that baricitinib be administered in combination with remdesivir. ACTT-3 evaluated the treatment of hospitalized COVID-19 patients with remdesivir plus interferon beta-1a, which is used to treat individuals with multiple sclerosis, and found no clinical benefit from the addition of interferon beta-1a. ACTT-4 assessed baricitinib plus remdesivir versus the glucocorticoid dexamethasone plus remdesivir in adults hospitalized with COVID-19 and requiring oxygen, showing that these two regimens led to similar outcomes.

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. 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 been expanded and is currently evaluating two investigational therapeutics: SAB-185, a fully-human polyclonal antibody produced in cattle, and SNG001, an inhalable beta interferon. After completing the Phase 2 portion of the ACTIV-2 trial, AstraZeneca is independently pursuing a Phase 3 trial of their investigational long-acting monoclonal antibody combination, AZD7442. Brii Biosciences announced a rolling EUA submission for their combination monoclonal antibody therapy, BRII-196 plus BRII-198, based on promising results from ACTIV-2 for the treatment of COVID-19. Among patients at high risk of clinical progression, those receiving BRII-196 plus BRII-198 had

78 percent decreased risk in hospitalization and death. On September 24, 2021, SAB Biotherapeutics announced the graduation of SAB-185 into Phase 3 efficacy studies in ACTIV-2.

ACTIV-3 currently is evaluating the AZD7442 monoclonal antibody combination and PF-07304814, a protease inhibitor, in hospitalized patients. PF-07304814 inhibits a critical part of the replication process of SARS-CoV-2. On April 22, 2021, NIAID and the National Heart, Lung, and Blood Institute (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 to various monoclonal antibodies in its fact sheets for health care providers. NIAID-supported scientists and collaborators are evaluating the potential impact of emerging SARS-CoV-2 variants on the efficacy of monoclonal antibodies. NIAID and BARDA have shared their expertise with FDA as FDA has modified EUAs for monoclonal therapies regarding the testing of these products against variants and the conduct of independent assessments of potency against variants as they emerge.

Additional NIAID-supported Therapeutics Activities

NIAID also launched 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 therapeutics to a common control arm to identify treatments with relatively large effects as promising candidates for further study in large-scale trials. BET initially evaluated two therapeutics: risankizumab, an immunomodulatory monoclonal antibody developed by Boehringer Ingelheim and AbbVie that is FDA-approved for the treatment of severe plaque psoriasis; and lenzilumab, an investigational immunomodulatory monoclonal antibody developed by Humanigen. Recently, a third therapeutic was added: danicopan, an oral drug that inhibits a key inflammatory pathway and was originally designed to treat a rare but serious disorder called Paroxysmal Nocturnal Hemoglobinuria.

NIAID, in collaboration with the DOD Defense Threat Reduction Agency, supported basic research and product development for the oral antiviral drug molnupiravir. Merck and

Ridgeback Biotherapeutics announced clinical data from their Phase 3 trial which showed that molnupiravir reduced the risk of hospitalization or death by approximately 30 percent in at risk, non-hospitalized adult patients with mild-to-moderate COVID-19. In December 2021, FDA authorized the use of molnupiravir for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19 and for whom alternative COVID-19 treatment options authorized by the FDA are not accessible or clinically appropriate. NIAID also provided support for the development of Paxlovid, an oral antiviral candidate developed by Pfizer. In a Pfizer-supported Phase 2/3 clinical trial, a course of Paxlovid given within the first 3 days of symptoms reduced the risk of COVID-19-related hospitalization or death by 89 percent among non-hospitalized adults with COVID-19 at high risk of progressing to severe illness. In December 2021, FDA authorized the use of Paxlovid for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients 12 years of age and older weighing at least 40 kilograms who are at risk for progressing to severe COVID-19 and/or hospitalization.

NIH has launched the Antiviral Program for Pandemics, an NIH-BARDA collaboration that aims to develop safe and effective antivirals to treat and prevent SARS-CoV-2 infection. The program will build sustainable platforms for targeted drug discovery and 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 target coronaviruses and additional RNA viruses with pandemic potential, helping to better prepare the nation for future viral threats. Oral drug candidates for broad use in outpatient settings are the primary focus of this effort.

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 address considerations for hospitalized and non-hospitalized patients as well as 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 eleven 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.

Understanding the Incidence 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 also is working with partners to delineate biological and immune pathways responsible for the varied manifestations of COVID-19.

Early in the pandemic, the intramural research programs of NIAID, the National Cancer Institute, 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 may have exceeded the number of cases medically diagnosed by an additional 16.8 million infections through mid-July 2020. Continued analysis of the 1-year follow-up data from the study will be 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 aims to discover genetic factors conferring resistance to SARS-CoV-2 infection or predisposing to severe COVID-19. The consortium identified a subgroup of patients with severe COVID-19 that have ineffective immune responses to SARS-CoV-2, some of whom have mutations in key immune pathways.

NIAID also is engaged in 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 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.

Addressing the Long-term Effects of COVID-19

Many people who have had COVID-19 experience continued symptoms or other sequelae 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.

NIH has announced the Researching COVID to Enhance Recovery (RECOVER) Initiative, a trans-NIH effort to address PASC, including targeted funding for research in this critical area. The NIH RECOVER Initiative will complement ongoing NIAID studies to better understand the various post-acute manifestations of COVID-19 in various populations. On June 10, 2021, NIH announced awards to New York University (NYU) to build the RECOVER research consortium, harmonize and coordinate data within the consortium, and develop methods for monitoring protocols; and to Massachusetts General Hospital to provide statistical analyses and coordinate data standardization, access, and sharing among RECOVER projects. On September 15, 2021, NIH announced, through NHLBI and the National Institute of Neurological Disorders and Stroke, awards to NYU to develop the RECOVER Cohort with funding from the American Rescue Plan Act of 2021 (P.L. 117-2). NYU is engaging more than 100 researchers at more than 30 institutions to build a diverse national study population and support large-scale studies on the long-term effects of COVID-19.

NIAID intramural scientists initiated the Longitudinal Study of COVID-19 Sequelae and Immunity to better understand PASC and determine the extent to which people who have recovered from acute SARS-CoV-2 infection develop an immune response 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 such as Delta and Omicron, 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 these efforts will improve our response to the current pandemic and bolster our preparedness for the next, inevitable viral disease outbreak.