

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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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 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, more than 67% of U.S. adults have received at least one dose of a COVID-19 vaccine, and we must continue to vaccinate as many people as we can, as quickly as possible. FDA-authorized COVID-19 vaccines meet FDA's rigorous standards for safety and efficacy. The high levels of vaccine efficacy observed in the carefully controlled conditions of clinical trials have been subsequently confirmed by their effectiveness in studies of vaccines administered to broad

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 disproportionately 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, some individuals suffer longer-term effects after the initial phase of illness. NIAID is supporting collaborative efforts to study COVID-19 outcomes in patients across all ages, genders, and co-morbid conditions. These studies include people who experienced a broad range of COVID-19 disease severity so we can identify and characterize post-acute sequelae of SARS-CoV-2 infection (PASC) and develop effective strategies to address them.

Developing Vaccines and Monoclonal Antibodies 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 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 key finding 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 for coronaviruses led to the development of safe and effective COVID-19 vaccine candidates across a range of vaccine platforms.

Six candidate COVID-19 vaccines have been or are in the process of being 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. This vaccine is now authorized for emergency use in individuals 12 years of age and older. NIAID has helped to advance five 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 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 periodically reviews data from the ongoing trials to ensure the safety of study volunteers and to determine whether efficacy has been achieved. The CoVPN has enrolled tens of 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 underserved and 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 these clinical studies.

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 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. Early clinical trials demonstrated that mRNA-1273 was generally well tolerated and induced robust immune responses in healthy adults. NIAID and BARDA then began working with Moderna on a Phase 3 clinical trial through 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 for the mRNA-1273 vaccine for prevention of COVID-19 in individuals 18 years of age and older. In subsequent observational studies under “real-world” conditions in broader segments of the population, mRNA-based vaccines continue to display high levels of effectiveness. For example, in an article published in *Morbidity and Mortality Weekly Report (MMWR)*, Centers for Disease Control and Prevention (CDC) researchers and their collaborators showed that among health care personnel, first responders, and other essential workers, the mRNA-1273 and the Pfizer-BioNTech mRNA vaccine were 90 percent effective against SARS-CoV-2 infections 14 or more days after receiving a second dose. Other *MMWR* articles reported that these vaccines were 94 percent effective at preventing symptomatic COVID-19 among health care personnel and reduced the risk of COVID-19 hospitalization by 94 percent among people 65 years of age and older. Recently, NIAID scientists and their collaborators demonstrated that anti-SARS-CoV-2 antibodies persist for at least six months after the second dose of mRNA-1273. On June 26, 2021, FDA updated the EUAs for the Moderna and Pfizer COVID-19 vaccines to include information on the potential risks of myocarditis and pericarditis, particularly following the second dose. According to CDC, reports of

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 *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 in combination with low blood platelets after vaccine administration. Medical and scientific teams at the FDA and CDC found that available data suggest that the chance of this serious adverse event occurring is very low. Following their thorough safety review – and in accordance with recommendations from the CDC’s Advisory Committee on Immunization Practices – the FDA and CDC lifted the recommended pause on the use of Ad26.COV2.S on April 23, 2021. On July 12, 2021, FDA announced revisions to the vaccine recipient and caregivers and vaccination providers fact sheets for the Johnson & Johnson/Janssen COVID-19 vaccine regarding a suggested increased risk of Guillain-Barré syndrome during the 42 days following vaccination. The chance of this occurring following vaccination appears to be very low.

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. 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-19 and 100 percent protection against moderate and severe disease. In addition, the company reported that NVX-CoV2373 showed 91 percent efficacy in preventing symptomatic COVID-19 in people 65 years or older, as well as those with certain comorbidities or those who were identified as being likely to experience regular exposure to SARS-CoV-2. FDA has not yet authorized either of these vaccine candidates.

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, children, and people with immune deficiencies. More than 130,000 pregnant and lactating women already have received the COVID-19 vaccines under FDA EUAs, and early data are promising. These data do not demonstrate any safety concerns for women who are pregnant 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. On March 16, 2021, Moderna, in collaboration with NIAID and BARDA, announced the launch of KidCOVE, a Phase 2/3 study 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. On May 10, 2021, the FDA expanded the EUA for Pfizer's COVID-19 vaccine to include adolescents ages 12 to 15 years of age, and Pfizer also is evaluating their vaccine candidate in younger individuals. Other vaccine developers also have begun, or are planning to begin, trials to test their vaccine candidates in children, adolescents, and other special populations. 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.

Monoclonal Antibodies to Prevent COVID-19

NIAID, collaborating with Regeneron Pharmaceuticals and Eli Lilly and Company, also initiated two Phase 3 clinical trials to evaluate whether their investigational monoclonal antibodies, 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. Regeneron reported in a preprint publication that REGEN-COV prevented symptomatic and asymptomatic infection in household contacts of individuals who had recently tested positive for SARS-CoV-2. Bamlanivimab also was reported to prevent symptomatic and asymptomatic infection in residents and staff of skilled nursing and assisted living facilities, and these findings were published in the *Journal of the American Medical Association*. FDA has not yet authorized the use of either of these drugs for prevention of COVID-19. Clinical trials to test the safety and efficacy of monoclonal antibody therapies for the treatment of COVID-19 are being tested through the ACTIV partnership, and these are discussed below.

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.

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—BRII-196 plus BRII-198 and BMS-986414 plus BMS-986413—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 ensivibep, in hospitalized patients. Ensovibep binds to several sites on the SARS-CoV-2 spike protein, which may inhibit the virus's ability to infect human cells. On April 22, 2021, NIAID and

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 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 (hIVIG) for treatment of COVID-19 in hospitalized adults. The study demonstrated that hIVIG plus remdesivir was not superior to remdesivir alone.

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 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.

NIH recently launched the Antiviral Program for Pandemics, a collaboration between NIH and BARDA that aims to develop safe and effective antivirals to treat and prevent SARS-CoV-2 infection. The program also 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 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 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. 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

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 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. 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. A report from this workshop highlighting the key scientific questions and knowledge gaps regarding PASC was recently published in the *Annals of Internal Medicine*. 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.

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 these efforts will improve our response to the current pandemic and bolster our preparedness for the next, inevitable viral disease outbreak.