

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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Next Steps: The Road Ahead for 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. In this regard, 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 clinical 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 clinical trials network 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 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, though challenges remain such as vaccine hesitancy and extending the durability and breadth of protection provided by COVID-19 vaccination. Currently, more than 69 percent of U.S. adults are fully vaccinated against COVID-19, and more than 10 percent of adults have received an additional booster dose to bolster and prolong vaccine-induced protection, as recommended for key populations by the Centers for Disease Control and Prevention (CDC). It is critical that we continue to vaccinate as many people as we can, as quickly as possible. FDA-authorized and

FDA-approved 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 real-world 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 SARS-CoV-2 variants that may emerge with increased transmissibility or pathogenicity.

One of the most concerning developments of the ongoing pandemic has been the spread of the highly transmissible SARS-CoV-2 Delta variant (B.1.617.2). COVID-19 vaccines distributed in the United States under FDA Emergency Use Authorizations (EUA), and the FDA-approved COVID-19 vaccine, continue to be effective against severe disease caused by these variants, but we must remain vigilant. NIAID continues to conduct research to better understand SARS-CoV-2 variants, how they interact with the immune system, and their implications for COVID-19 therapies and vaccines.

We also know that Americans in underserved and minority communities have been disproportionately affected by this pandemic. NIAID continues to work directly with these communities and has partnered with other agencies in the federal government, and with industry and academia, to ensure that no one in vulnerable communities is left behind as we work 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, 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 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, an investigational 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. This approval followed a review of a biologics license application based on additional data from a Pfizer/BioNTech-supported Phase 3 clinical trial and real-world post-authorization safety surveillance data. The approved vaccine has the same formulation as the vaccine authorized for emergency use in individuals 12 to 15 years of age, and as a third primary series dose for individuals 12 years of age and older who have been determined to have certain kinds of immunocompromise. On October 29, 2021, the FDA authorized the emergency use of the Pfizer/BioNTech COVID-19 vaccine to include children 5 through 11 years of age. 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 through the CoVPN. Two of these vaccine candidates, those from Moderna, Inc., and Johnson & Johnson/Janssen, have been authorized for emergency use.

Utilizing the CoVPN, NIAID is implementing 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 more than 41,000 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 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. CEAL is 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 effectiveness of authorized COVID-19 vaccines.

mRNA-1273 (Moderna)

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 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. On August 13, 2021, FDA amended the EUA to allow for a third primary series dose for individuals 18 years of age or older who have been determined to have certain kinds of immunocompromise.

On September 22, 2021, NIAID scientists and their collaborators published additional results from the Phase 3 trial of mRNA-1273 with a longer duration of follow-up. They reported in the *New England Journal of Medicine* 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.

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 experiencing these conditions who received care have responded well to treatment and rest and usually can return to their normal daily activities after their symptoms improve. Given the significant potential health risk of COVID-19, including a substantially higher risk of myocarditis than with the COVID-19 vaccine, 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. The vaccine is known as Ad26.COV2.S or JNJ-78436735. NIAID has supported 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 efficacious overall at preventing moderate to severe/critical COVID-19 occurring at least 28 days after vaccination and 85 percent efficacy 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. Johnson & Johnson/Janssen recently reported that the immune response from vaccination with Ad26.COV2.S lasts at least eight months.

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 likely exacerbated by the SARS-CoV-2 Delta variant which is much more transmissible than previous strains of the virus.

On September 22, 2021, and October 20, 2021, FDA amended the EUAs for the Pfizer/BioNTech and Moderna COVID-19 vaccines, respectively, to allow for use of a single booster dose at least 6 months after completion of the primary series in the following groups: individuals 65 years of age and older, and those 18-64 years of age at high-risk of severe COVID-19 or with frequent institutional or occupational exposure to SARS-CoV-2. FDA also amended the Johnson & Johnson/Janssen COVID-19 vaccine EUA to include the use of a single booster dose administered at least 2 months after completion of the single-dose primary regimen to individuals 18 years of age and older. In addition, FDA authorized 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. CDC has made recommendations regarding use of these COVID-19 vaccines that are consistent with the FDA authorizations.

NIAID is supporting preclinical and clinical research to assess the durability of immunity induced by COVID-19 vaccines and to help determine whether boosters will be necessary for additional populations. 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”). On October 13, 2021, NIAID posted a preprint outlining the results of the study on *medRxiv* that showed 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 informed decisions on the use of mixed vaccine schedules for additional doses of COVID-19 vaccines, as described above.

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 multicenter, adaptive design study to assess the immune responses

to an additional dose of the COVID-19 vaccine in immunocompromised individuals. Data from these studies 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, children, and people with immune deficiencies. More than 169,000 pregnant and lactating women already have received the COVID-19 vaccines under EUAs. 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. 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. Pfizer also is evaluating their vaccine candidate in children younger than age 5. Other vaccine developers also 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

In addition to the FDA-authorized and FDA-approved COVID-19 vaccines described above, 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 100 percent effective at preventing severe COVID-19 disease. Novavax's NVX-CoV2373 COVID-19 vaccine candidate uses a protein nanoparticle vaccine approach. On September 23, 2021, Novavax published data in the *New England Journal of Medicine* showing that NVX-CoV2373 demonstrated 89.7% protection against SARS-CoV-2 infection and 100 percent protection against moderate and severe COVID-19 disease. FDA has not yet authorized either of these vaccine candidates for emergency use.

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. On September 28, 2021, NIAID announced awards to three academic institutions to conduct research to develop vaccines to protect against multiple types of coronaviruses and viral variants.

Monoclonal Antibodies to Prevent COVID-19

NIAID, collaborating with Regeneron Pharmaceuticals and Eli Lilly and Company, 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. On September 23, 2021, Regeneron reported in the *New England Journal of Medicine* that REGEN-COV prevented symptomatic and asymptomatic infection in household contacts of individuals who had recently tested positive for SARS-CoV-2. Bamlanivimab also prevented symptomatic and asymptomatic infection in residents and staff of skilled nursing and assisted living facilities as reported in the *Journal of the American Medical Association*. On August 10, 2021, FDA expanded the EUA for REGEN-COV to include post-exposure prophylaxis for COVID-19 in certain adults and pediatric individuals (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death. On September 16, 2021, FDA expanded the EUA for bamlanivimab and etesevimab, administered together, to include post-exposure prophylaxis in these same populations. Clinical trials to test the safety and efficacy of monoclonal antibody therapies for the treatment of COVID-19 are being conducted through the ACTIV partnership, and these are discussed below.

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 protecting against COVID-19 and COVID-19 disease progression. For example, 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—one led by researchers from NIAID and Johns Hopkins Hospital and another by scientists from the La Jolla Institute for Immunology—examining the 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. 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.

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 immune responses to SARS-CoV-2 and suggest that these cells also may help protect against emerging variants of concern.

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.

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. On July 29, 2021, the FDA revised the existing EUA for baricitinib to remove the requirement that baricitinib be administered in combination with remdesivir. This revision was supported by data from a Lilly-supported Phase 3 trial. 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, a study assessing baricitinib plus remdesivir versus the glucocorticoid dexamethasone plus remdesivir in adults hospitalized with COVID-19 and requiring oxygen, showed 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 combination monoclonal antibody therapies—BRII-196 plus BRII-198 and BMS-986414 plus BMS-986413—as well as three 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. Brio Biosciences recently announced 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, as well as the small molecules ensovibep and PF-07304814, 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. PF-07304814 inhibits a critical part of the replication process of SARS-CoV-2. 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 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.

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.

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 evaluated 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. 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 Department of Defense (DOD) Defense Threat Reduction Agency, supported basic research and product development for the oral antiviral drug molnupiravir. On October 1, 2021, 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 50 percent in at risk, non-hospitalized adult patients with mild-to-moderate COVID-19. Merck announced on October 11, 2021, that they have submitted an EUA for use of molnupiravir for the treatment of mild-to-moderate COVID-19 in adults who are at risk for progressing to severe COVID-19 and/or hospitalization.

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 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.

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 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 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.

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, 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 the extent to which vaccine-induced immunity, or post-infection immunity, prevent infection by 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 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. 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.

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 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, 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 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 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 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 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. 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. This funding, supported by the American Rescue Plan Act of 2021 (P.L. 117-2), will enable NYU to engage 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, 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.