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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An Update on the Ongoing Federal Response to COVID-19: Current Status and Future Planning

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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 research addressing this once-in-a-lifetime infectious disease pandemic.

The public health response to COVID-19 has required an unprecedented global public-private research effort. NIAID has played a central role in this response by capitalizing on decades of basic, clinical, and applied research to facilitate the rapid development of COVID-19 vaccines, which continue to be important tools to reduce the threat of COVID-19 in the United States and worldwide. NIAID also initiated clinical trials with creative and adaptive designs to evaluate multiple new and existing therapeutics for the treatment of COVID-19.

Responding to Emerging Variants of SARS-CoV-2

The emergence of SARS-CoV-2 variants—some of which demonstrate increased transmissibility and an ability to partially evade the immune response from previous infection and/or vaccination—makes it critical that all eligible individuals remain up to date on their COVID-19 vaccines, including recommended booster doses, to ensure the highest possible level of protection. NIAID has launched collaborative research to rapidly assess the effectiveness of vaccines, monoclonal antibodies, and antiviral drugs against SARS-CoV-2 variants. NIAID also is exploring ways to enhance protection afforded by COVID-19 vaccines and supports and conducts research to understand the impact of SARS-CoV-2 variants on infection- and vaccine-induced immunity. NIH, including NIAID, participates in the HHS-established SARS-CoV-2 Interagency Group (SIG) along with the Centers for Disease Control and Prevention (CDC), U.S. Food and Drug Administration (FDA), Biomedical Advanced Research and Development Authority (BARDA), Department of Defense (DOD), and U.S. Department of Agriculture. The SIG tracks variants in real time to address the potential impact of emerging variants on critical SARS-CoV-2 countermeasures.

NIAID also facilitates the use of cutting-edge tools such as disease modeling and structural

biology to understand how SARS-CoV-2 variants may potentially evade the immune system and/or COVID-19 therapeutics. In addition, NIAID supports the development of next-generation COVID-19 vaccines that could provide protection against disease caused by emerging SARS-CoV-2 variants. Strategies for next-generation COVID-19 vaccines include targeting viral antigens that are highly conserved among SARS-CoV-2 strains and utilizing alternative routes of inoculation, such as intranasal vaccine approaches. NIAID also is conducting research on pan-coronavirus vaccines designed to provide broad protective immunity against emerging SARS-CoV-2 variants and other coronaviruses with pandemic potential. In 2021, NIAID announced awards to four academic institutions to conduct research to develop pan-coronavirus vaccines.

Developing Vaccines to Prevent COVID-19

Sustained research investments by NIAID over decades prior to the emergence of SARS-CoV-2 allowed the unprecedented pace of COVID-19 vaccine development. Longstanding NIAID support enabled the development of versatile vaccine platforms and the use of structural biology tools including cryo-electron microscopy to design specific proteins—called immunogens—that powerfully stimulate the immune system. Prior to the COVID-19 pandemic, scientists at the NIAID Vaccine Research Center (VRC) and their collaborators made the critical scientific discovery of how to mutationally stabilize—in a highly immunogenic form—viral proteins that SARS-CoV-2 uses to infect human cells. This strategy facilitated the design of vaccine candidates that generate robust protective immune responses. As soon as the sequence of SARS-CoV-2 was made available in early January 2020, NIAID 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 of which are now authorized or approved by the FDA, built upon across a range of vaccine platforms including the highly successful mRNA platform.

Through sustained support for fundamental research underlying the vaccine concepts and the establishment and utilization of an extensive clinical trials network, NIAID helped advance the development of six candidate COVID-19 vaccines. NIAID supported the Phase 3 clinical trials for two vaccines that are currently available for use in the United States: the mRNA-1273 vaccine, developed through a collaboration between the NIAID VRC and Moderna, Inc., and the Ad26.COV2.S vaccine candidate from Johnson & Johnson/Janssen. NIAID also is supporting Phase 3 clinical trials of investigational COVID-19 vaccine candidates from AstraZeneca

(AZD1222), Novavax (NVX-CoV2373), and Sanofi/GSK (SARS-CoV-2 adjuvanted recombinant protein vaccine).

In addition, NIAID supports research on COVID-19 vaccines in special populations, such as children and individuals who are pregnant or lactating. NIAID and BARDA are collaborating with Moderna on the Phase 2/3 KidCOVE study to evaluate the safety and efficacy of mRNA-1273 in children ages 6 months to less than 12 years. KidCOVE investigators recently reported positive initial results, and Moderna has submitted to FDA a request for an Emergency Use Authorization of the vaccine in this population. NIAID will continue to explore opportunities to support additional trials to test vaccine candidates in children, adolescents, and other special populations.

Ensuring Protection by the use of COVID-19 Vaccine Boosters

FDA-authorized and FDA-approved COVID-19 vaccines have maintained their effectiveness in preventing severe COVID-19. However, we have seen with both the Delta and Omicron variants that protection against mild and moderate disease begins to decrease over time following the primary vaccine series. NIAID quickly established that boosting with the same vaccine that was used for the primary vaccine series could significantly increase levels of antibodies against all current variants, compared to levels in individuals who received the primary regimen alone. This "homologous" boosting has translated into increased protection against severe disease as well as mild infection. In addition, an NIAID-led study showed that boosting with a COVID-19 vaccine different than the one used for the primary vaccine series ("mix and match") was safe and prompted a robust immune response. Data from this study were evaluated by FDA in their decision-making to authorize the use of a "mix and match" approach to boosters for FDA-authorized or approved COVID-19 vaccines.

As SARS-CoV-2 variants have emerged, NIAID moved rapidly to investigate the potential of targeted boosters to enhance immune responses to emerging variants. Shortly after the Omicron variant was first described, the NIAID VRC began conducting preclinical testing of an Omicron-specific booster candidate. NIAID scientists showed in animals that boosting with either the existing mRNA-1273 vaccine or an Omicron-specific vaccine enhanced antibodies against Omicron and increased protection following challenge with the Omicron variant. NIAID now will examine whether people who received boosters—either mRNA-1273 or variant-specific COVID-19 boosters—generate antibodies that can bind to and neutralize the Omicron variant and its sublineages.

NIAID also 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. In 2021, NIAID launched multiple trials assessing the response to COVID-19 vaccination in people with immune systems weakened due to a variety of diseases or organ transplantation. Additionally, NIAID recently launched the Phase 2 COVID-19 Variant Immunologic Landscape (COVAIL) trial to learn whether different vaccine booster regimens can broaden and increase the durability of immune responses in adults who already have received a primary vaccination series and a first booster shot.

Identifying Therapeutics to Treat COVID-19

Additional 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.

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. Data from ACTT were critical for FDA approval of the antiviral drug remdesivir and the anti-inflammatory drug baricitinib for treatment of COVID-19. NIAID, in collaboration with other NIH Institutes, also launched the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) public-private partnership, which is focused on late-stage clinical trials investigating candidate drugs for outpatient and inpatient settings. ACTIV uses flexible master protocols for clinical trials, allowing the inclusion of additional investigational therapeutics as the trials continue.

The widespread availability of highly effective oral antivirals that can be taken at home early in the course of infection could help prevent SARS-CoV-2 transmission, mitigate overwhelming surges in hospitalizations, and save lives. In collaboration with the DOD Defense Threat Reduction Agency, NIAID supported basic research and product development for the oral antiviral drug molnupiravir (Lagevrio), which the FDA authorized for the treatment of mild-to-moderate COVID-19 in certain populations and situations. NIAID also provided expert advice for clinical trials of Pfizer's oral antiviral Paxlovid, which the FDA authorized for the treatment of mild-to-moderate COVID-19 in certain populations. Paxlovid is now the leading antiviral drug for the treatment of COVID-19, with an almost 90 percent efficacy in preventing severe disease resulting in hospitalization if administered early in the course of infection.

NIH has prioritized and accelerated the development of oral antivirals against potential pandemic pathogens by collaborating with BARDA to launch the Antiviral Program for Pandemics (APP). APP aims to develop safe and effective oral antivirals for broad use in outpatient settings to treat and prevent infection with RNA viruses of pandemic potential. The program will build sustainable approaches for targeted antiviral discovery and development. As part of APP, NIAID recently established nine multidisciplinary Antiviral Drug Discovery (AViDD) Centers for Pathogens of Pandemic Concern with the goal of creating platforms that will target RNA viruses with pandemic potential, helping to better prepare the nation for future viral threats.

NIAID also conducts and supports research to determine the impact of SARS-CoV-2 variants on the effectiveness of monoclonal antibodies and other therapeutics. For example, research suggests that although effectiveness of certain monoclonal antibodies against Omicron is markedly diminished, the monoclonal antibody bebtelovimab, discovered by AbCellera in collaboration with the NIAID VRC, is active *in vitro* against all circulating Omicron subvariants. In addition, NIAID is working to develop new drugs, including therapeutics that inhibit essential processes in the virus replication cycle or that address the host response to COVID-19, with an eye toward agents that maintain their effectiveness against emerging variants.

NIH also 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. Each Treatment Guidelines section consists of recommendations 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 meets regularly to evaluate possible treatment options for COVID-19 and update the Treatment Guidelines as new clinical evidence emerges.

Understanding COVID-19 Immunity and Pathogenesis

Data on immunity induced by infection with SARS-CoV-2, including studies by NIAID scientists and NIAID-supported researchers, clearly demonstrate that following infection most people generate a protective immune response. NIAID continues to support research to understand immune responses to SARS-CoV-2 infection and COVID-19 vaccination, including projects investigating the durability of immune responses; whether immunity differs in certain populations; and how SARS-CoV-2 variants may evade immunity. These studies include research across the range of immune components, including the role of memory T and B cell responses in preventing

progression of disease during SARS-CoV-2 infection.

In addition, NIAID 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 is supporting multiple studies to evaluate acute and long-term clinical and immunological aspects of MIS-C and SARS-CoV-2 infection in children. NIAID also is participating in a trans-NIH effort to coordinate MIS-C research, the Collaboration to Assess Risk and Identify Long-term Outcomes for Children with COVID (CARING for Children with COVID). This effort supports data sharing across studies funded by multiple NIH Institutes to determine the spectrum of illness and predict long-term consequences of infection in children.

Addressing the Long-term Effects of COVID-19

While most people recover quickly and fully from infection with SARS-CoV-2, some experience ongoing or new symptoms or other health effects after the acute infection has resolved; this syndrome is referred to as post-acute sequelae of SARS-CoV-2 infection (PASC). NIH supports research to inform estimates of PASC prevalence as well as to understand the pathogenic mechanisms underlying the wide range of observed symptoms and the risk factors for developing PASC. NIH also launched the Researching COVID to Enhance Recovery (RECOVER) Initiative, a trans-NIH effort that includes targeted funding for research in this critical area. The NIH RECOVER Initiative complements ongoing NIAID studies to better understand the various post-acute manifestations of COVID-19 and will 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.

Conclusion

NIAID continues to expand efforts to elucidate the biology, pathogenesis, and clinical manifestations of SARS-CoV-2 infection, including with variants of concern such as Delta and Omicron, and to apply this knowledge to develop safe and effective interventions to diagnose, treat, and prevent SARS-CoV-2 infection and/or COVID-19. NIAID also supports early-stage research on candidate vaccines that could protect against multiple strains of coronaviruses. These efforts will improve our response to the current pandemic and bolster our preparedness for the next inevitable emerging infectious disease outbreak.