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STATEMENT OF

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Background on trials networks

The COVID-19 Prevention Network (CoVPN) was formed by the National Institute of Allergy and Infectious Diseases (NIAID) at the US National Institutes of Health (NIH) to respond to the global pandemic (coronaviruspreventionnetwork.org/about-covpn/). Using the infectious disease expertise of their existing research networks and global partners, NIAID has directed the networks to address the pressing need for vaccines and monoclonal antibodies against SARS-CoV-2. The CoVPN is led by Dr. Lawrence Corey, University of Washington and Fred Hutchinson Cancer Research Center and Dr. Kathleen Neuzil, University of Maryland School of Medicine. The CoVPN works in partnership with NIH, manufacturers and other organizations to develop and conduct studies to ensure rapid and thorough evaluation of US government-sponsored COVID-19 vaccines and monoclonal antibodies for the prevention of COVID-19 disease. The CoVPN brings together experienced NIH-funded clinical trial networks including the HIV Vaccine Trials Network (HVTN), hvtn.org, the HIV Prevention Trials Network (HPTN) hptn.org, the Infectious Disease Clinical Research Consortium Vaccine Treatment and Evaluation Units (IDCRC VTEU), idcrc.org, and the AIDS Clinical Trials Group (ACTG), actgnetwork.org.

Statement

By February 16, 2021, the global COVID-19 pandemic had claimed more than 2.4 million lives, with more than 108 million SARS-CoV-2 infections. The economic and social consequences have been equally staggering, with unemployment in the United States hitting a yearly total of nearly 9% in 2020 after a decade of jobs expansion. The commercial airline industry, the hospitality sector, pedestrian retail industry and the global tourism industry, among others, have suffered. The closure of schools and lack of extracurricular activities is impacting the academic, social and physical development of children, with a disproportionate impact on minorities. Persons of all ages are struggling with the effects of isolation, extreme lifestyle changes, and increased anxiety related to the pandemic and mitigation factors to contain it.

The U.S. government effort known as “Operation Warp Speed” (OWS) was officially announced in late April 2020 as a public-private partnership to facilitate and accelerate the development, manufacturing, and distribution of COVID-19 vaccines, therapeutics, and diagnostics. However, work was already underway as early as January 2020 among scientists, public health and government officials, and vaccine manufacturers, who recognized the urgent need for preventive and therapeutic options to curb the spread of the infection and to mitigate the devastating consequences of COVID-19. The result was the initiation of vaccine development and testing that resulted in the approval of two vaccines through FDA Emergency Use Authorization (EUA) in December 2020. **In this statement, I will describe how foundational science, effective partnership, and resource allocation enabled the unprecedented vaccine development achievements. Further, I will emphasize investments that are needed to ensure we are better prepared for the next pandemic.**

Vaccine development is a lengthy, risky, and expensive process that proceeds in deliberate stages, with evaluation after each step before proceeding to the next one. **The typical vaccine development process may take 10-20 years or more from early scientific discovery to licensure and distribution.** Researchers first evaluate experimental vaccines in the laboratory and animal models. If a vaccine candidate is safe and appears promising in these preclinical experiments, it may go on to be carefully tested in people, but only if there is funding to do so. Many vaccines never move beyond preclinical testing simply because there is no perceived market value and no funding.

Clinical testing begins with Phase 1 studies to establish safety and immune responses in small numbers of healthy adults. With satisfactory results, and the funding to do so, studies move to Phase 2, where larger numbers of people in the target population (the population that will benefit from the vaccine, e.g., older people or people with underlying diseases) are included, with careful safety assessment and further assessment of immune responses. Finally, Phase 3 studies are conducted. Phase 3 studies include large numbers of people, and their goal is to show an effect of the vaccine on clinical disease – either preventing the disease or lessening the severity of the disease- while demonstrating safety in larger numbers of people. Phase 3 studies are very expensive- generally in the tens to hundreds of millions of dollars. These expenses include developing and maintaining the infrastructure at the clinical trial sites, the staffing and investigator costs to conduct the trial and closely follow the volunteers, participant costs for their time and transportation, database set-up and data management and statistical analysis, regulatory oversight and monitoring costs, equipment and supply costs, and laboratory costs related to specimen collection, processing and performance of assays. Thus, many vaccines never make it to Phase 3 testing based on funding decisions alone. After a vaccine is licensed, FDA, CDC, and other federal agencies continue to monitor its safety and effectiveness. There is generally a lag time between licensure and full roll-out of a vaccine, as manufacturers generally do not take the risk of making vaccines at scale until they are licensed and recommended for use.

As part of the team that designed the first Phase 1 of the NIH-Moderna messenger RNA (mRNA) vaccine and the later Phase 3 studies, and as part of the investigative team that conducted the first Phase 1 trial of the Pfizer mRNA vaccine in the U.S., I witnessed firsthand how the pandemic urgency considerably shortened the vaccine development timeframe. Investments in basic science were the foundation to this success. Decades of work on understanding the structural biology and pathogenesis of coronaviruses and other viruses enabled scientists at the Vaccine Research Center at the NIH to identify the appropriate structural target for the vaccine (the outer spike or S glycoprotein of the coronavirus), stabilize that protein, and have an mRNA genetic sequence ready to test in animals and to send to a vaccine manufacturer to make clinical trial material within days. Prior partnerships with the vaccine manufacturer- Moderna- meant that the mRNA for this vaccine could be inserted into a lipid coat at dose ranges that had already been established and tested for other vaccines. Further, the investment by NIH in clinical trials infrastructure and networks allowed access to experienced and capable clinical scientists, like myself, who stepped forward to design, execute and analyze the studies in partnership with government and industry. Importantly, all of these stages, were conducted in parallel. Likewise, NIH-funded researchers who had studied coronaviruses for their entire careers were prepared to provide guidance on

coronavirus biology and to conduct the immunology assays, which would serve as the first indication that the vaccine could elicit an immune response in humans. Other NIH-funded researchers had developed animal models and innovative ways to assess immune responses to other pathogens and were able to transfer their learnings to the study of SARS-CoV-2. To do so required specialized skills, laboratories and equipment- without this prior research capacity and infrastructure, the effort would have slowed considerably. No one waited for the results of the animal studies to begin to prepare the laboratory to conduct the assays, or to design and plan the human studies; Phase 3 studies were planned "at risk" before Phase 1 results were available. Vaccines were manufactured "at risk" before animal results were available. This was all possible due to the resources provided for this effort; the dedication of laboratory and clinical scientists; the prior partnership between Moderna and NIH, and prior pandemic preparedness efforts that enabled regulatory teams to establish frameworks for reviews in record time.

We followed all required processes to ensure these vaccines were held to extremely high safety standards because they would be deployed broadly if successful. All trial designs were reviewed by independent ethics boards, and the FDA. Data safety and monitoring boards were convened and consisted of experts with no direct ties to the product or the trials to monitor trial safety. None of the vaccine platforms chosen for early testing in the U.S. consisted of the full virus or a weakened virus- so it was impossible for these vaccines to cause COVID-19. The vaccines being tested in the U.S. comprise either the protein or a piece of the virus to induce an immune response, or a genetic sequence to instruct our cells to make the desired protein antigen. In either case, the vaccine cannot cause SARS-CoV-2 infection.

Given my involvement from the start in the NIH-Moderna development effort, I can attest that safety was never compromised by the speed of this effort. While the usual stages of development were compressed, the confidence in the safety of the vaccines was established. The first-in-human trial of the NIH-Moderna SARS-CoV-2 mRNA vaccine began based on 1) historical safety data on the mRNA platform from previous and ongoing clinical trials using vaccines targeting a variety of viral pathogens such as influenza and Zika which indicated the platform was safe in humans; 2) historical safety and immunogenicity data of other coronavirus vaccines (e.g. SARS-1 and MERS) using coronavirus spike proteins, suggesting that the protein was safe and should elicit a robust immune response; and 3) previous experimental data using other coronavirus vaccines in animals confirming the immunogenicity and efficacy of vaccines against the spike protein. Data in animals for this construct were generated as Moderna worked to make the vaccine for human testing.

In designing the Moderna Phase 1, we specified that the first participants in the trial must be young and middle-aged healthy adults, who would be the least likely to suffer ill effects of a vaccine. The trials began with low doses and worked up to higher doses. Experienced investigators throughout the U.S. conducted the studies. The volunteers were observed for several hours after receiving the first vaccine and followed carefully with clinical and laboratory assessments in the days after receiving the vaccine before another small group of individuals was vaccinated. At my center, we were the first to vaccinate with the Pfizer-BioNTech vaccine and we followed this same pattern. Participants were counseled on how to recognize side effects of the vaccine, to recognize if they have any signs or symptoms of COVID-19 and were counseled in how to reduce their risk of acquiring COVID-19. Physicians

and other study personnel were available to the participants, as needed, 24 hours per day. Through this careful Phase 1 evaluation we learned that the vaccine caused more side effects at the highest dose, but the immune response was not as good at the lowest dose. So, a "middle dose" that had mild to moderate, self-limited side effects and induced a hearty immune response was chosen to take forward into Phase 2 and eventually Phase 3 testing.

It was clear from the start that given a pandemic of this severity and magnitude, multiple vaccines would be needed to vaccinate the U.S. and the global population. Further, the risky nature of vaccine development necessitated the parallel development of many vaccines, with the hopes that at least one would make it to the approval stage. Thus, a mechanism to harmonize protocols and share lessons learned was established early on. A critical collaborative program was spearheaded by NIH: the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) public-private partnership (nih.gov/research-training/medical-research-initiatives/activ). At this time of global urgency, this effort brought together the individual strengths of all sectors – Department of Health and Human Services (BARDA, CDC, FDA); other government agencies (Department of Defense and Veterans Affairs); and representatives from the European Medicines Agency, academics, philanthropic organizations, and numerous biopharmaceutical companies. The goal was to develop a coordinated strategy for prioritizing and speeding development of the most promising treatments and vaccines. I was part of this effort, serving on the Vaccines subgroup. The group shared lessons learned, debated challenges in the field, and publicly shared outputs from the group to benefit all. Involvement of regulators from the beginning facilitated the effort.

A further element of the effort was to establish a framework for conducting harmonized, vaccine efficacy trials that adhered to published regulatory guidance. The Phase 3 trials were large – at least 30,000 people per trial. This size ensured that results would be obtained quickly, and that a diverse population of Americans would be enrolled, including the elderly, minority populations and those with chronic illness. With a large trial, an understanding of the safety and efficacy of the vaccine in these subgroups would be possible. NIH-funded clinical trials networks worked in partnership with manufacturers and clinical research organizations to enroll the large trials quickly and with attention to safety detail and scientific rigor. Common laboratories and methodologies will allow for comparisons across trials to inform decisions on improving vaccines, if necessary; moving to broader populations (e.g., children, persons with weak immune systems); and vaccine policy recommendations. Likewise, statistical groups worked collaboratively to evaluate data in similar ways, and in the future to combine data from the trials to have statistical power to understand how well the vaccines work against less common outcomes, such as preventing death from COVID-19.

The rapid conduct of the trials and achieving an early answer on the efficacy of these vaccines was critical given the extreme need for a vaccine during this pandemic. The first results of the mRNA vaccines were remarkable – showing greater than 90% efficacy against any symptomatic COVID-19, and importantly against severe COVID-19. The prevention of severe disease is critically important, as severe COVID leads to health care encounters and hospitalizations that stress the health care system and lead to delays in receiving care for other reasons. As most vaccine adverse events occur shortly after vaccination, the FDA required a median of two months follow-up before EUA would be granted. However, a consequence of the rapid conduct of the trials is that at the time of EUA, only short-term effectiveness and safety data are available on the vaccines. The participants continue to be

followed as part of the trials, for at least 2 years. Further, as with all vaccines in the U.S., assessment does not stop at the time of approval. Systems are in place through the CDC, the FDA and the vaccine manufacturers for follow-up beyond EUA and licensure. Through these systems, we are learning more about the rare allergic reactions occurring after administration of the mRNA vaccines, for example. These anaphylactic reactions, with a rate of approximately 4-11 per million, were not seen in the trials of 30,000 people. Likewise, CDC has studies in place to ensure that vaccines work well "in the real world" as they are distributed broadly. Ensuring the capacity of the CDC and FDA to conduct this postmarketing follow-up is critical.

Summary

Our investments in pandemic preparedness, and in basic, translational, regulatory, and clinical science enabled the historic vaccine development achievements in response to the COVID-19 pandemic. Leadership at the federal government level united partners from different sectors around the common goal of combatting a global crisis – this partnership was key to success. Finally, the available resources and efficient use of those resources through harmonized efforts allowed this enormous undertaking to proceed without the usual delays. We have two COVID-19 vaccines currently – to prevent disease it must be delivered to people. We are seeing weaknesses in the system in two main areas – vaccine distribution, due to chronic underfunding of state and local health departments, and public confidence in vaccines, leading to suboptimal uptake in certain populations. Investments in public health, understanding vaccine hesitancy, and building trust in communities must complement our investments in science to optimally mitigate the effects of COVID-19 and future pandemics. Finally, the emergence of variant strains around the world emphasizes that this must be a global response to be successful.

Future Investments

- NIH must be well-funded. Investments and advances in science over the past several decades were the foundation of the successful COVID-19 pandemic response. We must continue to invest in basic, clinical, and epidemiologic science. This includes funding research in the areas of coronavirus immunology, pathogenesis, and the interaction between coronaviruses; and to better understand other pathogens with pandemic and outbreak potential – influenza, certainly, as well as lesser studied pathogens including other coronaviruses, arenaviruses (e.g. Lassa fever), filovirus (e.g. Ebola) and togaviruses (e.g. Chikungunya).
- The emergence of three severe coronaviruses in the past two decades should prompt an integrated, multidisciplinary effort to develop countermeasures for coronaviruses. This would include antivirals and "pan-coronavirus" vaccines that could work preventing all coronaviruses.
- We need continued investments in clinical trial infrastructure. The NIH-funded clinical trial networks have played a key role in this pandemic response and in the previous response to the H1N1 influenza pandemic. These networks advance our understanding of many vaccine-preventable diseases and allow for surge capacity during a pandemic.

- We need investments in the CDC, FDA and public health – the lack of funding and decline in state and local health departments has been evident in the challenges of vaccine distribution.
- We need investments in better understanding vaccine hesitancy in order to design programs that will restore confidence in vaccines and increase vaccine coverage.
- Finally, and importantly, a global pandemic requires a global response. Variants are emerging around the world in the absence of vaccines. We need an integrated global surveillance system for SARS-CoV-2 that can be modelled after the global influenza surveillance effort. Furthermore, the U.S. must fully participate in the activities of the WHO to ensure global equitable access to COVID-19 vaccines.

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Speaker biography

Kathleen Neuzil, MD, MPH is the Myron M. Levine MD DTPH Professor in Vaccinology, Professor of Medicine and Pediatrics, and the Director of the Center for Vaccine Development and Global Health at the University of Maryland School of Medicine (UMSOM, medschool.umaryland.edu/cvd/). She is an internationally recognized research scientist and advocate in the field of vaccinology. Throughout her career, Dr. Neuzil has conducted clinical and epidemiologic studies on vaccine-preventable diseases, yielding high-profile publications that inform policy decisions and public health actions. Dr. Neuzil has conducted research in the United States (U.S.) and around the world on multiple vaccines, including influenza, rotavirus, human papillomavirus, Japanese encephalitis, typhoid conjugate vaccines, and most recently, SARS-CoV-2. Dr. Neuzil has been central to the domestic response to COVID-19. In her role as Co-Director of the COVID-19 Prevention Network (CoVPN), described below, she is part of the leadership team designing and overseeing the clinical evaluation strategy for COVID-19 clinical trials in the U.S. She is a co-Principal Investigator of the NIH-funded Leadership Group for the Vaccine and Treatment Evaluation Unit network. In her role at UMSOM she is an investigator on COVID treatment, prevention, and post-exposure prophylaxis trials. Dr. Neuzil has more than 230 scientific publications on vaccines and infectious diseases. Dr. Neuzil's research capabilities are complimented by 20 years of involvement in domestic and international policy, including past membership on the US Centers for Disease Control and Prevention’s Advisory Committee on Immunization Practices (ACIP). She is a member of the World Health Organization Strategic Advisory Group of Experts on Immunization and the ACIP working group on coronavirus vaccines. Dr. Neuzil was named the Baltimore Sun “Marylander of the Year” for her role in the response to the COVID-19 pandemic.