DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

The Role of the National Institute of Allergy and Infectious Diseases in Research Addressing the Monkeypox Public Health Emergency

Testimony before the

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Stopping the Spread of Monkeypox: Examining the Federal 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 the ongoing monkeypox public health emergency. 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 monkeypox. As the Director of NIAID and the Chief Medical Advisor to the President, I am pleased to discuss NIAID research addressing the U.S. monkeypox outbreak. NIAID is committed to accelerating efforts to answer critical monkeypox research questions in alignment with the U.S. Monkeypox Research Priorities identified by the White House Office of Science and Technology Policy.

Pandemic Preparedness and Prototype Pathogen Approaches for Medical Countermeasures

The monkeypox virus is part of the *Orthopoxvirus* genus, which includes the variola virus that causes smallpox. Available medical countermeasures against monkeypox were made possible by decades of NIAID-supported research on orthopoxviruses. Our orthopoxvirus research is an example of the NIAID prototype pathogen approach to pandemic preparedness, in which basic research and countermeasures for a prototype pathogen within a given family of viruses can be used to help treat and prevent diseases caused by closely related pathogens within that family.

As part of its longstanding investment in biodefense research, NIAID supported early-stage development of the second-generation smallpox vaccine ACAM2000. NIAID further identified the need for a vaccine to overcome the limitations of ACAM2000, which cannot be used by individuals with weakened immune systems. In close collaboration with the Biomedical Advanced Research and Development Authority (BARDA) and the U.S. Food and Drug Administration (FDA), NIAID played a key role in developing a third-generation vaccine against smallpox and

monkeypox now known as JYNNEOS™ (Imvamune or Imvanex).

NIAID-supported research also facilitated the development of an antiviral for smallpox called tecovirimat (TPOXX). This drug is now being used to treat patients with monkeypox under an expanded-access investigational new drug protocol. NIAID is supporting new clinical trials of tecovirimat to gather additional safety and efficacy data to inform clinical and regulatory decision-making on the use of tecovirimat for the treatment of monkeypox. In addition, NIAID-supported scientists continue to conduct basic research to better understand monkeypox virus transmission and disease, and to identify additional antiviral candidates. NIAID researchers at the Vaccine Research Center (VRC) are isolating antibodies for evaluating vaccine-induced immune responses as well as the development of immune assays, diagnostic reagents, and therapeutics in the form of monoclonal antibodies.

Vaccines to Prevent Monkeypox Disease

As noted, NIAID-supported research was essential to the development of the JYNNEOS vaccine made by Bavarian Nordic A/S and approved in the United States and other countries for the prevention of monkeypox (and smallpox). JYNNEOS features a weakened form of live vaccinia virus (modified vaccinia Ankara-Bavarian Nordic [MVA-BN]) that does not replicate or cause disease. MVA is an orthopoxvirus related to the viruses that cause monkeypox and smallpox. NIAID provided significant support for the research and development of JYNNEOS as an alternative to the ACAM2000 smallpox vaccine, which contains replication-competent vaccinia virus and can cause severe adverse events in people with weakened immune systems and individuals with eczema. NIAID has funded studies of JYNNEOS from the preclinical stage through Phase 2 clinical trials to evaluate safety, immunogenicity, duration of protection, and route of administration. NIAID then transitioned the vaccine to BARDA, which supported advanced

clinical evaluation.

In 2019, FDA approved JYNNEOS for individuals at high risk for smallpox or monkeypox virus infection. On August 9, 2022, FDA issued an emergency use authorization (EUA) for JYNNEOS to allow healthcare providers to administer the vaccine by intradermal injection, an alternative to the standard subcutaneous route of administration. The FDA EUA will increase the total number of available JYNNEOS vaccine doses by up to five-fold. The EUA decision was informed by an NIAID-supported clinical study of the vaccine published in 2015 demonstrating that the intradermal route of administration—using just one fifth of the vaccine volume—produced a similar immune response to subcutaneous administration.

NIAID recently launched a clinical study of the JYNNEOS vaccine via different routes of inoculation, including intradermal administration, in adults 18 years of age and older at high risk for monkeypox virus infection. This study may be expanded to provide data to support use of the vaccine against monkeypox for individuals who are pregnant or under the age of 18 years, or to inform potential Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) recommendations for a lower dose vaccination regimen.

NIAID VRC scientists are developing mRNA-based monkeypox vaccines in collaboration with Moderna, Inc., and will conduct efficacy studies in animal models to select lead vaccine candidates. Blood samples from these and other VRC studies will be used to isolate monoclonal antibodies for vaccine antigen design and for evaluation as potential monkeypox therapeutics and diagnostic reagents.

Therapeutics to Treat Monkeypox Disease

Currently, no specific treatment is approved by the FDA for monkeypox virus infection. However, the antiviral tecovirimat (TPOXX), developed to treat smallpox, is being used to treat

patients with monkeypox under an expanded-access investigational new drug protocol. NIAID funded the discovery of tecovirimat as well as preclinical studies to determine its mechanism of action and its safety and efficacy in animals. NIAID and BARDA also have funded Phase 1 and Phase 2 clinical trials to test the safety and pharmacokinetics of an oral formulation of tecovirimat. The FDA approved the oral formulation of tecovirimat in 2018 for treating smallpox in adults and children and this formulation is part of the U.S. Strategic National Stockpile. An intravenous formulation of tecovirimat subsequently received FDA approval. Although this antiviral was approved for the treatment of smallpox, the drug's FDA approval was based on studies in animals infected with monkeypox virus. Clinical trials to evaluate tecovirimat in humans with monkeypox are needed to gather additional data about the safety and efficacy of the drug in the context of the current outbreak to aid clinical and regulatory decision-making.

In this regard, NIAID-supported investigators have launched a Phase 3, randomized, placebo-controlled, double-blind trial of tecovirimat for the treatment of monkeypox in outpatient settings in the United States through the AIDS Clinical Trials Group (ACTG). Using this established and successful HIV clinical trials infrastructure will facilitate community engagement and help researchers ensure that vital community input is reflected in the conduct of the study. The study also has an open-label component to ensure that certain high-risk populations (e.g., pregnant or breastfeeding individuals, those who are heavily symptomatic, and those with severe immune deficiencies) are not randomized to placebo, while also providing a means to collect important data on the safety and pharmacokinetics of tecovirimat in these populations.

NIAID, in collaboration with Institut National de Recherche Biomédicale of the Democratic Republic of Congo (DRC), also is planning a double-blind, randomized controlled trial of the safety and efficacy of tecovirimat for treating adult and pediatric patients diagnosed with monkeypox. The study in the DRC was planned prior to the current global outbreak as part of

NIAID preparedness efforts to study high-consequence pathogens in key international locations where they are endemic.

NIAID also supports early-stage research to help identify additional candidate antivirals for monkeypox. It is possible that monkeypox virus will develop resistance to tecovirimat. This is one of the reasons NIAID-supported scientists are screening novel compounds to help find new antiviral candidates to treat monkeypox.

Understanding Monkeypox Transmission and Reservoirs

Monkeypox is disproportionately affecting men who have sex with men in non-endemic countries. However, anyone exposed to the circulating virus can get monkeypox regardless of their age, gender identity, or sexual orientation. Of note, the previous outbreak of monkeypox in the United States in 2003 was driven by animal-to-person spread and involved domesticated prairie dogs that were infected by small mammals imported from West Africa. NIAID scientists are conducting animal studies to understand the human-animal interface with monkeypox virus and its suspected reservoir hosts, such as Gambian pouched rats, rope squirrels, and dormice. NIAID also is supporting the development of animal models to evaluate vaccine-induced immune responses to monkeypox virus.

In addition, NIAID-supported scientists are performing genomic sequencing to better understand the monkeypox virus and its various strains. Investigators with the NIAID-funded Centers for Research in Emerging Infectious Diseases (CREID) are supporting clinical surveillance in the DRC, Nigeria, and Sierra Leone. CREID investigators also are providing validated molecular primers and probes to help strengthen diagnostic capacity in Kenya, Tanzania, Panama, and Brazil. In addition, the NIAID International Centers for Excellence in Research (ICER) program has helped enhance diagnostic capacity in Mali, Ghana, Republic of the Congo, and

Cambodia.

NIAID scientists also are developing a high-throughput serologic assay that can distinguish between individuals infected with monkeypox virus and people who may have received a vaccinia-based vaccine, such as JYNNEOS or ACAM2000. In collaboration with the CDC and other U.S. and international researchers, NIAID will use this assay to conduct retrospective and prospective serological studies to better understand the extent of monkeypox virus circulating in the United States and worldwide. In addition, NIAID is making viral isolates available, free-of-charge, for distribution to the global research and surveillance community via the NIAID-funded BEI Resources repository. Distribution of these resources will facilitate additional priority research throughout the broader scientific community, particularly in the areas of diagnosis and surveillance.

Conclusion

NIAID continues to expand research on the biology, pathogenesis, and clinical manifestations of monkeypox virus infection as well as studies of existing and potential interventions to diagnose, treat, and prevent monkeypox. NIAID also is committed to working in partnership with those populations, including men who have sex with men, that currently are most at-risk of monkeypox to help identify and address key monkeypox research questions. These efforts will improve our response to the ongoing public health emergency.