National Institute of Allergy and Infectious Diseases

NIAID Research Summary for mpox – Sept 2024

This research agenda outlines near-term (planned) and ongoing projects led by NIAID as part of a broader USG supported mpox research effort. It is not a notice of new funding opportunities. All ongoing and planned studies are contingent upon available funding.

Introduction

Mpox is a viral disease endemic to Central and West Africa that can spread between people and from infected animals. In 2022, spread of the virus that causes mpox (monkeypox virus, MPXV) led the World Health Organization (WHO) to declare a public health emergency of international concern (PHEIC). The disease is transmitted primarily through direct contact with mpox sores or contact with items used by a person with mpox, such as clothing and bed linens. Since January 2023, the Democratic Republic of the Congo has reported more than 22,000 suspected mpox cases. The expanding outbreak and the recent emergence of a new strain, clade 1b, have triggered global concern. In August 2024, travel-associated cases of clade 1b mpox were confirmed in Sweden and Thailand, the first evidence of its spread outside the African continent. In August 2024, the WHO declared mpox a PHEIC for the second time in 3 years.

To support the ongoing public health response, NIAID continues to advance research to enhance the understanding of mpox, aligned with the research objectives below. These efforts include research to further characterize MPXV pathogenesis, disease transmission and spillover; evaluating immunological responses to the disease; and developing and testing mpox investigational and regulatory-approved treatments and vaccines. The NIAID mpox research agenda builds on the Institute's longstanding infectious disease efforts and addresses the significant upsurge of cases in Africa and the global spread of clade Ib MPXV.

Objective 1: Address Gaps in Basic Virology and Immunology

NIAID will continue to conduct and support research to further characterize MPXV and provide the research community with tools and reagents needed to advance the understanding of this virus. Characterizing the natural history of mpox will help inform therapeutic strategies and our understanding the immune response to infection. Ecological studies will help define the reservoir and intermediate hosts of infection, which could inform public health efforts to control the virus.

Focus area: MPXV Epidemiology and Genomic Surveillance

- Performing viral genomic epidemiology studies to better understand, reconstruct, and predict viral evolution, adaptation, and transmission patterns.
- Determining difference in virulence and transmissibility of clades and their genetic basis.
- Developing reagents and assays for characterization of viral isolates and making viral isolates available to the global research community.

Focus Area: MPXV Biology and Pathogenesis

- Supporting large-scale data analysis for basic virology, immunology, and countermeasure development against MPXV and other *Orthopoxviruses*.
- Supporting 3-D structure determination and functional characterization of MPXV proteins for structure-guided countermeasure development.
- Investigating the pathogenesis of the newly identified clade 1b MPXV.

Focus Area: Host-Pathogen Interactions

- Assessing immunological responses and pathophysiology of early MPXV infection.
- Developing animal-challenge models to understand mucosal acquisition and evaluate vaccine-induced immune responses to MPXV.
- Screening human cohorts for seropositivity against MPXV and other *Orthopoxviruses* including smallpox (variola) and vaccinia virus to understand the extent of past infection and immunization in human populations.
- Establishing nonhuman primate and small animal models of MPXV infection.

Focus Area: Drivers of Viral Transmission

- Performing experimental transmission in small animal models (e.g., dormice, prairie dogs, and multimammate rats).

Focus Area: Virus Persistence and Host Reservoirs

- Conducting studies to understand the human-animal interface and suspected reservoir host.
- Characterizing viral persistence and stability in different conditions and matrices, including aerosols and wastewater.
- Conducting inactivation and environmental stability studies of MPXV.

Objective 2: Evaluate, Optimize and Advance mpox Vaccine Candidates

A safe and effective mpox vaccine is needed to prevent the spread of MPXV. In 2019, the U.S. Food and Drug Administration (FDA) approved a modified vaccina Ankara (MVA) vaccine, MVA-BN (JYNNEOS), for prevention of smallpox and mpox. The vaccine is recommended in the U.S. for pre-exposure prophylaxis among individuals at high risk for acquisition of mpox. In addition, vaccination with MVA-BN is part of the public health response to a growing outbreak in Africa. Given the relatively limited supply of MVA-BN and growing public health needs, NIAID currently supports studies to evaluate dosing regimens to stretch the vaccine supply, expand the populations in whom the vaccine is approved, and promotes development of novel vaccine candidates and discovery of vaccine adjuvants. In addition, NIAID supports research on the immunology of poxvirus infections and vaccines.

Focus Area: Epitope and Antigen Discovery

- Determining viral targets of protective antibodies and T cells.

Focus Area: Vaccine Testing and Validation

- Evaluating MVA-BN (JYNNEOS) vaccine reactogenicity and immunogenicity when administered either subcutaneously or intradermally in adolescents compared to adults (DoSES study). This is a Phase 2 randomized, open-label, non-placebo controlled clinical trial in two stages:
    - Stage 1 evaluates the reactogenicity and immunogenicity of two intradermal regimens of the vaccine compared to the standard subcutaneous regimen in adults.
    - Stage 2 evaluates the standard subcutaneous regimen in adolescents compared to adults.

Focus Area: Vaccine Platform Discovery

- Exploring novel vaccine platforms including mRNA, nanoparticle, and other technologies.

Focus Area: Adjuvant Development and Testing

- Conducting basic and clinical research on adjuvants for poxvirus vaccines to enhance their safety and immunogenicity.

Objective 3: Advance Existing and Novel mpox Treatment Strategies

Prior to the current mpox outbreak, the FDA approved several safe and effective treatments for smallpox. Animal studies demonstrated efficacy of these countermeasures against MPXV, but human studies were lacking. NIAID recently conducted an initial analysis of results from a double-blind, randomized, controlled trial of the safety and efficacy of tecovirimat for the treatment of adult and pediatric patients diagnosed with mpox (PALM007 trial). This analysis found that tecovirimat did not reduce the duration of mpox lesions among children and adults with clade 1 mpox, but demonstrated reduced mortality, with or without tecovirimat, when patients were provided high-quality supportive care. Further analyses are planned to better understand outcomes observed in the study. NIAID also is advancing the discovery of novel therapeutic candidates and pursuing multiple strategies to develop antibody-based therapeutics to use as pre-exposure prophylaxis or treatment.

Focus Area: Direct Acting Therapeutics

- Evaluating tecovirimat for the treatment of mpox, including an open-label arm for treatment of high-risk populations (e.g., pregnant or breastfeeding individuals and those with severe immune deficiencies) (STOMP TRIAL).
- Advancing discovery of early stage, novel therapeutics with activity against MPXV.

Focus Area: Monoclonal Antibodies

- Developing broadly neutralizing antibodies (which target multiple strains/clades) and more targeted monoclonal antibodies that neutralize different poxviruses, including MPXV.

Objective 4: Support Development of Newer Diagnostics and Assays

The development and tes ting of rapid, specific, and sensitive diagnostic assays are critical for prompt identification and isolation of cases and epidemiological surveillance during a public health crisis and epidemic. Diagnostics are essential tools when evaluating candidate medical countermeasures. NIAID collaborates with public health partners to enable and conduct serological testing of research specimens.

Focus Area: Biomarker Discovery and Validation

- Developing high-throughput serologic assays that can distinguish between *Orthopoxvirus* immunization and infection.

Focus Area: Diagnostic Platform Technologies

- Validating existing diagnostic assays for MPXV, including qRT-PCR based and rapid diagnostics and next-generation sequencing technologies for MPXV genomic analysis, including portable nanopore sequencing devices for use in endemic countries.

Focus Area: Sensitive Detection Chemistries

- Developing, testing, and validating diagnostic assays that detect all clades of MPXV.