NIAID Research Agenda for 2024 H5N1 Influenza – May 2024

Introduction

In March 2024, H5N1 highly pathogenic avian influenza A was detected in clinical samples of unpasteurized milk isolated from sick dairy cows in the United States. In April, the first human infection in a worker exposed to dairy cattle was reported. In response to this growing public health concern, the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), mobilized its intramural and extramural-supported research infrastructure, including the Vaccine Research Center (VRC), the Bacterial and Viral Bioinformatics Resource Center (BV-BRC), the Centers for Excellence for Influenza Research and Response (CEIRR) network, and the Collaborative Influenza Vaccine Innovation Centers (CIVICs), among others, to provide scientific support to the U.S. Department of Agriculture (USDA) and the Department of Health and Human Services (HHS) including several of its other agencies.

The primary responsibility at HHS is to protect public health and the safety of the food supply, which is why the Department continues to approach the outbreak with urgency. HHS stood up a response team which includes four HHS agencies – the Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), NIH/NIAID, and Administration for Strategic Preparedness and Response (ASPR) – which are working closely with USDA to:

- Ensure all communities are kept healthy, safe, and informed
- Ensure that the Nation's food supply remains safe
- Safeguard American agriculture and the livelihood and well-being of American farmers and farmworkers
- Monitor trends to mitigate risk and prevent the transmission of H5N1 virus among both people and animals.
- Ensure clinical research infrastructure is available to study natural history and evaluate candidate medical countermeasures if necessary.

To support a robust HHS response, NIAID continues to leverage its domestic and international infrastructure dedicated to advancing basic and translational research on the H5N1 virus aligned with the following objectives:

Objective 1: Increase understanding of H5N1 virus biology and factors that influence disease pathogenesis and transmission

NIAID supports multiple efforts to improve understanding of H5N1 virus epidemiology, transmission, natural history, and pathogenesis, as well as the host response to the virus. NIAID is also assisting with surveillance and virus characterization activities as requested by state and federal partners. Improving the understanding of the basic biology of the H5N1 virus will be crucial to developing promising strategies to prevent, detect, and treat the virus in the event of human-to-human transmission of H5N1 virus.

- *Focus Area 1: H5N1 Virus Epidemiology and Genomic Surveillance*

  In addition to studies to understand how H5N1 virus is spreading within and between farms, NIAID-supported investigators also are examining the genetic sequences of viruses collected to assist efforts assessing H5N1 virus transmission. Investigators are preparing to release a phylogenetic tree using the most recent viral isolates available in GenBank, the publicly available NIH database of annotated genetic sequences. NIAID-supported investigators are continuing to

enable tracking of pathogen evolution through Nextstrain, a collection of open-source tools for real-time phylogenetic analysis of viral outbreaks. Viral evolution is being carefully monitored for evidence of changes in pathogenesis and impacts on the effectiveness of vaccines, therapeutics, and diagnostics.

- *Focus Area 2: H5N1 Virus Biology and Pathogenicity*

  NIAID continues to support efforts to enhance understanding of H5N1 virus biology, including where the virus can be detected following different routes of exposure in animal models and the sites of viral replication in cattle. In addition, these models will be used to understand viral replication, clinical signs of illness, location and duration of viral shedding.

- *Focus Area 3: Drivers of Viral Transmission*

  NIAID is using animal models to understand potential routes of transmission. This effort includes determining the biology of transmission in cattle (cow to cow, cow to calf via milk consumption), characterizing infection in other animal models, and determining if consumption of infected milk is a viable method of transmission.

- *Focus Area 4: Virus Persistence and Reservoirs*

  Ongoing studies by NIAID intramural and extramural-supported investigators include characterization and risk assessment studies of virus isolated from milk samples and generating reagents for further research and response efforts. Information from these studies is being shared with other HHS agencies, as well as USDA. In addition, investigators are examining factors required for infectious virus persistence in raw milk, the parameters for heat inactivation of virus in milk, and virus stability in milk on various surfaces and in aerosols.

- *Focus Area 5: Immune Response to H5N1 Viral Infection*

  NIAID is advancing our understanding of H5N1 virus pathogenesis and the immune responses to infection, treatment, or vaccination. Studies include characterizing immune responses to the H5N1 virus in cattle and other animal models, and how the immune response may shape pathology. These efforts will be critical to understanding the underlying mechanisms of infection and accelerating advances in preventing or treating disease. In addition, human sera from existing vaccines and vaccine candidates in clinical studies will be tested against the H5N1 virus currently being detected in this outbreak.

Objective 2: Develop and evaluate prevention strategies for H5N1 influenza

The development of a safe and effective vaccine is a priority for preventing spread of the virus to certain at-risk populations (e.g., farm workers). NIAID currently supports the development of multiple vaccine candidates against avian influenza, including several in early-stage clinical trials. In addition, NIAID supports research on the immunology of influenza infections and vaccines, including vaccine adjuvant discovery and influenza immune epitope discovery related to other H5 influenza viruses.

- *Focus Area: Antigen Discovery and Vaccine Development*

  A key focus of the NIAID influenza research program is the development of a universal influenza vaccine—a vaccine that can protect against multiple subtypes, including H5N1 virus. NIAID intramural and extramural-supported investigators will continue efforts to develop and test universal vaccine candidates, including several promising candidates which are in early-stage clinical development.

- *Focus Area: Adjuvant Research*

  NIAID conducts and sponsors basic and clinical research on adjuvants for influenza vaccines to enhance their safety and efficacy against H5N1 virus.

Objective 3: Advance existing and novel H5N1 influenza treatment strategies

Antivirals are considered a first line of defense for controlling novel influenza virus outbreaks, as little immunity is present in the human population and vaccine development is a prolonged process. NIAID is developing and testing safe and effective antivirals to treat influenza infections and prevent serious complications.

- *Focus Area: Direct Acting Therapeutics*

  The emergence or re-emergence of influenza viruses potentially resistant to existing antiviral drugs is a serious and ongoing threat necessitating the development of new, broad-spectrum antiviral drugs with novel mechanisms of action and host-directed therapeutics to treat influenza. NIAID will continue to investigate the safety and efficacy of broad-spectrum direct acting antivirals. Additionally, pan-influenza host-targeted molecules that can target multiple influenza viruses are being evaluated.

- *Focus Area: Monoclonal Antibodies*

  NIAID also continues to pursue multiple strategies to develop antibody-based therapeutics for use as pre-exposure prophylaxis (PrEP) or treatment for influenza infection. These include broadly neutralizing antibodies (which target multiple strains) and more targeted monoclonal antibodies aimed at H5N1-specific surface components that could protect from death or severe respiratory disease from H5N1 influenza.

Objective 4: Support strategies for H5N1 virus detection

Rapid and sensitive diagnostic assays are a critical component in the epidemiological monitoring of an outbreak. They are also essential to evaluate candidate countermeasures. Ideally, diagnostic assays should be able to promptly (within minutes) distinguish one influenza strain from another, as different strains respond differently to available antivirals.

- *Focus Area: Development of Diagnostics*

  The NIAID Diagnostics Development Services is available to support *in vitro* diagnostics product developers as they upgrade existing tests for H5N1. Additionally, the BEI Resources Repository is working to make H5N1 virus-specific reagents available for diagnostics development.