U.S. Highly Pathogenic Avian Influenza A(H5N1) Research Priorities:
October 2024

Introduction

The outbreak of highly pathogenic avian influenza HPAI A(H5N1) has impacted more than 200 dairy cattle herds and led to sporadic human cases in the United States in 2024. So far, human cases in this outbreak have been mild, and the virus has thus far not demonstrated the ability to efficiently bind to receptors that predominate in the human upper respiratory tract. However, influenza viruses have potential to evolve, and A(H5N1) viruses are widely prevalent globally in wild birds. Therefore, continued comprehensive and coordinated, multisectoral surveillance across public health and animal health for these viruses in wild birds, poultry, mammals, and people worldwide, are critical to determine the public health risk. To control this outbreak and minimize its current and potential impacts, we must continue to better understand why and how this is happening, and what actions need to be taken to better protect the health and safety of people and animals, and keep the food supply safe.

Today, the U.S. Government is laying out its clear set of research priorities to address this outbreak.

Experts from across the U.S. Government have outlined a research plan to continue furthering our understanding of the A(H5N1) virus and guide response activities to stop the expansion of the outbreak. These priorities will also guide the broader global scientific community.

This collaborative, whole-of-government, one-health response is focused on addressing scientific questions that have arisen across both animal and human health. For animals, the Agricultural Research Service (ARS), as the in-house research agency of the U.S. Department of Agriculture (USDA), is the leading authority for influenza research in poultry and livestock, partnering with other agencies, academia, and research institutions. Additionally, other USDA agencies including Animal and Plant Health Inspection Service (APHIS), Food Safety Inspection Service (FSIS), the National Institute for Food and Agriculture (NIFA), have been working in coordination with sister agencies and in their respective mission areas through field investigation and epidemiology, diagnostics, food safety, and applied research coordination activities to comprehensively learn as much as possible about A(H5N1) virus transmission and risk factors within herds, between herds, and between dairy and poultry premises.

When it comes to human health, the U.S. Department of Health and Human Services (HHS) is charged with protecting public health and the safety of the food supply. HHS stood up a response team of four HHS agencies – Administration for Strategic Preparedness and Response (ASPR), Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), and National Institute of Allergy and Infectious Diseases (NIAID) within the National Institutes of Health (NIH) – that is working closely with USDA to understand A(H5N1) virus biology, epidemiology, and factors that influence disease pathogenesis and transmission, mitigate risk and prevent the transmission among both people and animals, ensure that America's food supply remains safe, support preclinical and clinical development, regulatory approval, and procure treatments, vaccines, and diagnostics for H5 viruses.

In response to the ongoing A(H5N1) outbreak, the interagency team has prioritized research focusing on the following objectives:

Objective 1: Understand the infections, pathogenesis, transmission and molecular epidemiology of A(H5N1) virus, and mitigate risk to prevent transmission among both people and animals.

Animal health

Focus Area 1.1: Understand A(H5N1) infection, pathogenesis, and transmission in dairy cattle

- Continue to identify and characterize transmission paths and risk factors for A(H5N1) in cattle within farms, between cattle farms, and between cattle and poultry farms. (USDA NIFA and APHIS)
- Determine if A(H5N1) virus is transmitted via aerosolized mucosal virus, or through aerosolized virus laden milk. (USDA ARS)
- Better understand potential transmission of the A(H5N1) virus through the milking machine claw when used on virus-infected lactating cows and then transferred without cleaning and disinfection to naïve lactating dairy cows. (USDA ARS)
- Determine if A(H5N1) virus can infect calves though bucket feeding milk to calves from cows with acute A(H5N1) infections compared to milk from cows later in infection process as the virus quantity declines to low levels. (USDA ARS)

Focus Area 1.2. Understand A(H5N1) infections and pathogenesis in small ruminants

- Challenge goats through intramammary, respiratory, and oral routes to determine if virus infection and illness occurs, the distribution of virus in tissues including mammary glands and meat, and any potential for onward virus spread through shedding in feces, urine, and milk. (USDA ARS)

Focus Area 1.3. Understand A(H5N1) infections and pathogenesis in swine

- Use a swine respiratory challenge model to test multiple A(H5N1) viruses including B3.13 genotype virus from dairy cattle to determine infectivity and severity of disease production, distribution of virus in tissues, and if the viruses can transmit between pigs. (USDA ARS)

Focus Area 1.4: Understand A(H5N1) infections and pathogenesis in poultry

- Use established challenge models for poultry to determine the infectivity, ability to produce disease, and transmissibility of multiple A(H5N1) viruses from dairy cattle and wild birds to chickens and turkeys. (USDA ARS)

Focus Area 1.5: Continue molecular epidemiology studies

- Study the A(H5N1) virus to better understand the mechanisms for movement of the virus between farms, including between dairy cattle herds, dairy cattle to poultry, and dairy cattle to wildlife. These studies incorporate phylodynamic and other studies using genomic epidemiology methods with sequence data to identify how spread can be mitigated. (USDA ARS)

Focus Area 1.6: Dairy waste

- Examine different matrices of dairy waste and effluent for microbial action and thermal inactivation of A(H5N1) virus over time and under varying temperatures including generation of D and Z values. (USDA ARS)

Focus Area 1.7: Additional research related activities

- Data collection and analysis of affected dairy and poultry farms to understand the A(H5N1) virus transmission and risk factors at the herd/flock and inter-herd/flock levels; Sample collection of wild birds and mammals and peridomestic birds on and around affected premises to better understand their role in disease transmission. (USDA APHIS)
- Funding multiple real-time, applied field research projects with State, universities and laboratories to answer key questions related to active infection, virus transmission, and recovery. (USDA NIFA and APHIS)

Human health

Focus Area 1.8: Understand A(H5N1) virus biology.

- Continue to identify and monitor virologic characteristics of A(H5N1) viruses. (CDC, NIAID)
- Identify genetic markers associated with increased infectivity, transmissibility or reduced antiviral susceptibility. (CDC)
- Track genetic changes that occur in the virus during animal and human infections. (CDC)
- Enable tracking of pathogen evolution through Nextstrain, a collection of open-source tools for real-time phylogenetic analysis of viral outbreaks. (NIAID)
- Conduct comprehensive antigenic, phenotypic, genotypic, and evolutionary characterization of A(H5N1) viruses detected in humans and animals. (CDC, NIAID)

Focus Area 1.9: Understand virus and host factors that influence disease pathogenesis and lead to transmission.

- Better understand the primary means of transmission for A(H5N1) human infections. This includes animal-to-human zoonotic transmission and transmission via fomites. It also includes assessment of how the virus gains entry and replicates in humans. (CDC, NIAID)
- Characterize the spectrum of human clinical illness, including potential prevalence of severe illness, illness resulting in hospitalization or death, and asymptomatic and pauci- symptomatic cases. (CDC)
- Outline parameters important to human infection and resolution of illness, including estimated incubation period and duration of infectiousness. (CDC)
- Determine virus and host factors that impact virulence and transmission of novel influenza viruses, to include serology studies to determine the population immunity among the general population to A(H5N1) viruses. (CDC)
- Employ animal models to help describe clinical presentation, virulence, sites of viral replication, and transmissibility following different routes of exposure for these A(H5N1) viruses compared to seasonal and other zoonotic influenza viruses. (CDC, NIAID)
- Determine the biology of transmission in cattle (cow to cow, cow to calf via milk consumption), characterize infection in other animal models, and determine if consumption of infected milk is a viable method of transmission. (NIAID)
- Conduct immunologic and virologic pandemic risk assessment of novel influenza viruses in animal models and other model systems. (CDC)
- Characterize immune responses to the A(H5N1) virus in cattle and other animal models, and how the immune response may shape pathology. In addition, human sera collected from clinical trial volunteers immunized with existing vaccines and vaccine candidates will be tested against the A(H5N1) virus. (NIAID)

Focus Area 1.10: Mitigate risk and prevent the transmission of A(H5N1) virus among both people and animals.

- Continue monitoring for human infections using existing influenza surveillance platforms and develop strategies for enhanced surveillance and laboratory testing. (CDC)
- Continue monitoring how widespread human exposure and infection are, to include estimating the prevalence and incidence of human infections. (CDC)
- Continue tracking the risk of infection among people exposed to infected dairy cattle, other animals, and their environment or contaminated animal products (e.g., raw milk). (CDC, NIAID)
- Better understand what measures most minimize the risk of infection among exposed persons. This includes personal protective equipment (PPE), and administrative and engineering controls. (CDC)
- Identify host, pathogen, and exposure risk indicators for severe illness. (CDC)
- Continue to monitor the pandemic potential of this A(H5N1) virus with the Influenza Risk Assessment Tool (IRAT). (CDC)
- Estimate the impact of nonpharmaceutical interventions and medical countermeasures, including pre-pandemic H5 vaccines and potential H5 vaccines made using existing candidate vaccine

viruses, in preventing infection and/or severe illness, should widespread person-to-person transmission occur. (CDC)
- Monitor and evaluate the effectiveness of influenza antiviral medications in preventing and attenuating illness, and public health interventions, including A(H5N1) vaccine (should it be employed). (CDC, NIAID)
- Evaluate strategies to increase uptake of public health interventions such as diagnostics, treatments, and vaccines. (CDC)
- Coordinate with the WHO's Global Influenza Programme and the Global Influenza Surveillance and Response System (GISRS) and the OFFLU animal health network (World Organization for Animal Health, Food and Agriculture Organization, and reference laboratories) to support rapid information and resource sharing. (CDC)

Objective 2: Ensure that the Nation's food supply remains safe.

Animal health

Focus Area 2.1: Continue evaluation of the variability/infectivity of A(H5N1) virus in food systems
- Conduct collaborative studies to quantify viability/infectivity of A(H5N1) in both model food systems (i.e., meat slurries, meat juice, meat tissues, raw milk, etc.), as well as in dairy foods (i.e., yogurt, Hispanic-style cheese, raw milk cheese, etc.), and fermented and dried meats (i.e., salami, biltong, pepperoni, etc.) in response to varying intrinsic and extrinsic food relevant parameters (i.e., temperature, time, pH, salt, fat, moisture, etc.). (USDA ARS)

Focus Area 2.2: Determine the pathogenesis and tissue distribution of A(H5N1) virus in dairy cattle
- Conduct studies to determine the full tissue distribution of A(H5N1) in infected dairy cattle over the 3-week infection period to better understand levels and distribution of A(H5N1) in tissues from end-of-production dairy cattle. (USDA ARS)
- Address gaps in virus pathogenesis, tissue tropisms, and animal species susceptibility of B3.13 and other genotypes. (USDA NIFA and APHIS)

Focus Area 2.3: Conduct mid- and long-term research to enhance predictive analytics capabilities, validate processing technologies, and develop interventions
- Enhance capacity of the Food Safety National Program to respond to emerging viral contaminants by building capacity related to needed expertise (i.e., virus propagation and assay technologies and clearance/training for scientists to work in BSL-3 laboratories) via the recruitment, mentoring, and training of students and post-docs to be shared among collaborators. Efforts will be directed to utilize the capacity generated to validate processing technologies, improve predictive analytics capabilities, and identify processing plant interventions effect on virus reduction and product safety. (USDA ARS)

Human health

Focus Area 2.4: Understand characteristics of inactivation methods for A(H5N1) in dairy products. (FDA)
- Continue to test pooled raw milk samples to characterize potential virus levels that pasteurization may encounter. (FDA)
- Conduct additional bench-top equipment studies to estimate the precise time and temperature needed for inactivation of A(H5N1) virus in milk and milk products. (FDA)
- Conduct additional studies using continuous flow pasteurization equipment, reflective of those in commercial use, to confirm pasteurization parameters effective at inactivating A(H5N1) virus in milk processes. (FDA)

- Assess the survival of A(H5N1) virus in raw milk cheeses under various parameters over the aging process. (FDA)
- Examine 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. (NIAID)

Focus Area 2.5: Monitor the safety of retail dairy products

- Sample retail dairy products to determine if any viable A(H5N1) virus survives commercial processing. (FDA)

Focus Area 2.6: Develop One Health interventions to prevent, control, or eliminate A(H5N1) in animals, milk, and the environment.

- Develop strategies to decrease the impact of A(H5N1), interventions to prevent or control spread of A(H5N1) (FDA)
- Develop alternative viral inactivation and disposal methods for discarded milk. (FDA)

Objective 3: Support preclinical and clinical development, regulatory approval, and, if needed, procurement of treatments, vaccines, and diagnostics for H5 viruses.

Animal health

Focus Area 3.1: Develop an A(H5N1) vaccine efficacy challenge model and testing vaccines in dairy cattle

- Continue to develop an influenza vaccine challenge model for lactating dairy cows exploring intramammary, respiratory, and oral challenge by A(H5N1) virus and will use the best challenge model for testing multiple vaccines including mRNA vaccines for protection. (USDA ARS)

Focus Area 3.2: Develop H5 HPAI vaccines for poultry, cattle, and other livestock

- Multiple commercial companies are investing in the development of A(H5N1) vaccines for a variety of species. USDA is also able to use its extensive experience in animal influenza vaccine development to design vaccines that address the target product profile and are fit for purpose. (USDA)
- Evaluate vaccines for protecting turkeys against A(H5N1) including inactivated whole avian influenza virus vaccine, RNA vaccine, turkey herpesvirus vectored vaccines, and newly developed live avian influenza virus vaccines with genomic changes to reduce reassortment risk. Serological tests are being validated to identify A(H5N1) infections in vaccinated poultry. Studies are ongoing to antigenically match the vaccine seed strain to the field virus to produce optimal protection. (USDA ARS)
- Conduct vaccine studies using the goat infection model from Objective 1 as a vaccine challenge model to determine if vaccines are effective at protecting goats and as a potential surrogate model for screening vaccines for protection against HPAI in cattle. USDA ARS also plans to conduct vaccine studies in swine using the challenge model from Objective 1 to assess protection of existing and new vaccines to protect livestock. (USDA ARS)
- Expand knowledge on vaccinology of HPAI in dairy cattle, vaccine development, and product evaluation for USDA licensure. (USDA ARS, NIFA, and APHIS)

Focus Area 3.3: Validate and improve HPAI diagnostics for use in livestock.

- Evaluate and validate available serological and pen side influenza diagnostic assays to fully understand their performance characteristics and appropriate use in livestock. (USDA APHIS)

Human health

Focus Area 3.4: Advance H5Nx vaccines

- Identify additional candidate vaccine viruses (CVVs) expected to provide protection against currently circulating A(H5N1) viruses in animals. (CDC)
- Support clinical trials and manufacturing of antigenically well-matched vaccine candidates stored in the National Pre-pandemic Influenza Vaccine Stockpile (NPIVS) to enable regulatory action and distribution, if needed. (ASPR)
- Partner with laboratories with existing capabilities to perform centralized immune assays using samples collected from nonclinical studies and from subjects enrolled in influenza vaccine clinical trials conducted under FDA Investigational New Drug (IND) applications and to perform cross-reactive immune response testing of clinical samples for pandemic preparedness and response. (ASPR)
- Continue supporting development of mRNA-based pandemic influenza vaccines for influenza viruses of pandemic potential, e.g., H5Nx and H7Nx, and following regulatory approval, incorporate into the NPIVS, to add a more rapid option to the arsenal for the nation's pandemic influenza preparedness and response. (ASPR)
- Partner with companies to advance needle-free vaccine technologies, including oral, intranasal, transdermal, and subcutaneous microarray patches (MAPs), which offer several advantages over injectable preparations, including the potential for rapid delivery, ease of administration, and improved vaccine performance. (ASPR)
- Support decentralized clinical trials (DCTs) where various trial elements will occur either in the home or at a retail pharmacy location to increase the breadth and diversity of participants and improve accessibility by reducing the participation barrier. (ASPR)
- Research universal and supra-seasonal vaccines that incorporate broadly conserved immunogens into existing seasonal vaccine to mitigate the impact that any influenza pandemic would have during the time needed to develop and deploy a matched vaccine, decreasing severe disease and death for the entire population and potentially delaying incidence and spread. (ASPR, NIAID)
- Conduct and sponsor basic and clinical research on adjuvants for influenza vaccines to enhance their safety and efficacy against A(H5N1) virus. (NIAID)

Focus Area 3.5: Advance treatments for influenza diseases, including antiviral drugs and monoclonal antibodies.

- Evaluate antiviral drugs to assess the emergence of drug-resistant viruses. (CDC, NIAID)
- Investigate the safety and efficacy of broad-spectrum direct acting antivirals as well as pan-influenza host-targeted molecules that can target multiple influenza viruses. (NIAID)
- Conduct a phase 2 platform clinical trial investigating host-directed therapeutics for the treatment of Acute Respiratory Distress Syndrome (ARDS), including ARDS caused by influenza infections. In addition to collecting safety and efficacy data on enrolled patients, biomarker data investigation to aid in the planning of pivotal phase 3 clinical studies by identifying specific patients that may benefit from a specific therapeutic or therapeutic mechanism of action. (ASPR)
- Invest in pre-exposure prophylaxis (PrEP) therapeutic candidates that require one dose to provide six months of protection (the entire influenza season) to provide an FDA-licensed PrEP therapeutic to protect healthcare workers and first responders. (ASPR)
- Pursue multiple strategies to develop antibody-based therapeutics for use as PrEP or treatment for influenza infection, to include broadly neutralizing antibodies (which target multiple strains) and more targeted monoclonal antibodies aimed at A(H5N1)-specific surface components that could protect from death or severe respiratory disease from A(H5N1) influenza. (NIAID)

Focus Area 3.6: Develop diagnostic tests and assays to rapidly and accurately identify A(H5N1) infections.

- Support in vitro diagnostics product developers as they upgrade existing tests for A(H5N1) through the NIAID Diagnostics Development Services and make A(H5N1) virus-specific reagents available for diagnostics development through the BEI Repository. (NIAID)
- Continue investing in home-use/remote use molecular flu tests that move testing closer to the patient, both speeding up test results and increasing testing access. Investments will focus on tests that are lower cost to manufacture, and more affordable to the patient, have an increased ability to multiplex, providing more test results in a single testing action (e.g., Flu A, Flu B, COVID-19, RSV in a single test). (ASPR)
- Invest in Next Generation Sequencing (NGS) platforms as diagnostics to inform clinical patient care. (ASPR)