DHS SCIENCE AND TECHNOLOGY

Master Question List for Highly Pathogenic Avian Influenza (HPAI)

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For comments or questions related to the contents of this document, please contact the DHS S&T Hazard Awareness & Characterization Technology Center at HACTechnologyCenter@hq.dhs.gov.

Science and Technology

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Foreword

The following Master Question List (MQL) was developed by the Department of Homeland Security Science and Technology Directorate (DHS S&T) to provide government decision makers with up-to-date information that will enable appropriate responses to the Highly Pathogenic Avian Influenza (HPAI) outbreak. This MQL summarizes what is known and what knowledge gaps exist to address fundamental questions such as, “What is the infectious dose?” and “How long does the virus persist in the environment?” The information provided is a succinct summary to facilitate structured and scientifically guided discussions across the federal government without the burden of the need to review scientific reports, and to prevent duplication of efforts by highlighting and coordinating research.

Introduction

Of the four types of influenza viruses (A, B, C, and D), influenza A virus (IAV) is the only virus known to cause pandemics. IAV is further classified into subtypes according to the biochemical nature of two proteins on the surface of each virus that help it invade host cells: haemagglutinin (i.e., H or HA) and neuraminidase (i.e., N or NA). IAV subtypes (e.g., H5N1) can be further classified into clades based on genetic similarity. IAVs are found in mammalian species, including humans, swine, canines, and avian across the globe. Avian influenza viruses (AIVs) naturally circulate among waterfowl and other migratory wild aquatic birds including ducks, geese, shorebirds, and gulls.[1] These bird-specific strains of influenza are typically categorized as having low pathogenicity (low pathogenicity avian influenza [LPAI]), meaning that infected birds show no signs of disease or the symptoms expressed are mild. When LPAI is introduced from waterfowl and other wild aquatic birds into domestic poultry such as chickens or turkeys, LPAI can mutate into high pathogenicity (i.e., HPAI), meaning infection causes severe disease in birds and is often fatal. One exception is known, which are the gsGD lineage H5 viruses that circulate in wild migratory birds as HPAI and can be directly transmitted to domestic poultry as HPAI. The distinction between LPAI and HPAI is made based on the lethality of any particular strain of AIV to commercial chickens, as the mutation

from LPAI to HPAI typically occurs upon replication in domestic poultry species.[2] Thus, the primary risk to the Homeland posed by AIVs is to commercial poultry farms within the United States.[3]

Key Facts

- The median infectious dose (ID_{50}) of HPAI in birds depends on virus strain and bird species, but generally ranges from $<10^1$ to $10^{4.6}$ infectious units (estimated average from reported infection values among ducks, chickens, and turkeys infected by intraocular and intranasal inoculation).
- The United States Department of Agriculture (USDA) detected HPAI H5N1 in January 2022, four weeks before the first detection in commercial poultry (turkeys) that signaled the beginning of the 2022/23 U.S. HPAI outbreak, affecting more than 58.7 million domestic birds (as of 06/07/2023).
- The economic impact of the ongoing outbreak has not yet been estimated; however, the 2014-2015 HPAI outbreak resulted in 50.4 million poultry affected at a cost of $850 million to the U.S. government, reduced the economy by $3.3 billion, and impacted international trade relations.[4]
- HPAI strains include variants of H5 and H7. As of June 2023, H5N1, H5N2, and H5N8 have been detected in the United States.
- As of June 2023, there has been one reported detection of HPAI H5N1 in a human in the United States (Colorado), which occurred in an individual who was exposed to the virus while working at a commercial poultry facility.
- There are currently four influenza antiviral treatments approved by the U.S. Food and Drug Administration (FDA) for use in humans: peramivir (Rapivab), zanamivir (Relenza), oseltamivir (Tamiflu), and baloxavir marboxil (Xofluza). These drugs block virus entry, exit, and replication within a host cell.
- No single vaccine is effective against all strains of HPAI; existing vaccines are subtype-specific.

The cutoff date for information gathering related to this document was 06/07/2023.

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Major Findings by Topic Area	
Topic	**Overview of Current Knowledge**
INFECTIOUS DOSE	• The median infectious dose (ID_{50}) of avian influenza (AI) in birds depends on virus strain and host species, but generally ranges from $<10^1$ to $>10^6$ infectious units (estimated average from reported infection values among ducks, chickens, and turkeys infected by intraocular and intranasal inoculation).* • In general, lower doses of AIV are required to infect waterfowl than domestic poultry; however, wild birds show lower mortality than domestic poultry when experimentally infected. • The route of exposure affects the infectious dose in birds. The inhalation route appears more efficacious than the ingestion route. • AIVs are categorized as either having low pathogenicity (LPAI), meaning infected chickens show no signs of disease or the symptoms expressed are mild; or high pathogenicity (HPAI), meaning infection causes severe disease and is often fatal. The distinction between LPAI and HPAI is based on the lethality of a particular strain of AIV when tested against domestic chickens. However, regarding human infection with LPAI or HPAI viruses, high and low pathogenicity designations may not correlate with the severity of illness.
TRANSMISSIBILITY	• AIV is generally transmitted among birds via the fecal/oral route, but respiratory exposure can also lead to AI infection. • On average, infected birds transmit HPAI to approximately 1.5-2.7 additional birds in the same flock and infected poultry farms tend to transmit HPAI to 1.1-2.4 additional farms. • Certain AIV strains transmit more frequently than others, and HPAI viruses are generally more transmissible than LPAI viruses. • During the current HPAI H5N1 global outbreak, there have been several reported cases in humans in close contact with infected birds, but no evidence of sustained human-to-human transmission. • Risk factors for human AI infection include direct contact with or close exposure to sick or dead poultry and visiting live poultry markets.
HOST RANGE	• Waterfowl and other migratory wild aquatic birds are the primary natural reservoir for most subtypes of AIVs. Domestic poultry and other birds can also be infected. Several animal species, including humans, can be incidental hosts to AI. • AIV strains capable of human infection include: H5, H6, H7, H9, and H10 subtypes. Symptoms are typically mild in humans, often presenting 3-5 days after infection, but can progress to upper respiratory tract disease and/or conjunctivitis.

* See the Infectious Dose section on Page 9 for more technical details.

	• Cases of gsGD lineage HPAI H5N6 in humans have presented with severe disease and a corresponding 55% fatality rate; however, to date, there has been no evidence of human-to-human transmission for H5N6. • Between January 2021 and March 2023, gsGD lineage HPAI H5 infections have been reported in over 20 wild and captive mammalian species in the United States and Canada.
INCUBATION PERIOD	• Poultry generally exhibit clinical symptoms of infection hours to days after infection with HPAI virus and can shed virus prior to presentation of disease symptoms. • The flock level incubation period is 14 days, thus for disease control models, a 28-day period is used. • Mammals generally have incubation periods of 1-2 days. Humans infected with H5 AIV generally show clinical symptoms 2-5 days after exposure, though longer incubation periods (≤17 days) are possible.
CLINICAL PRESENTATION	• Categorization of AI is based on its clinical presentation in chickens (i.e., low pathogenicity [LPAI] or high pathogenicity [HPAI]). • Humans infected with an HPAI H5 subtype virus generally exhibit acute respiratory illness including fever, cough, runny nose, headache, and difficulty breathing. • HPAI virus can cause up to 100% mortality in infected chickens. • Clinical signs of HPAI in poultry can include nasal discharge, coughing, sneezing, and general fatigue. More severe symptoms include facial swelling, bluing of comb and wattles, green feces/diarrhea, loss of muscle control, involuntary muscle movements, immobility, soft or misshapen eggs and/or reduced egg production, and death. • Infected mammals can present with clinical signs including fever, coughing, lethargy, diarrhea, and weight loss, with neurological signs such as seizures, ataxia, or tremors also possibly occurring.
BIOSURVEILLANCE AND CLINICAL DIAGNOSIS	• The primary methods of detecting AIV in poultry flocks are real-time polymerase chain reaction (RT-PCR) analyses of oropharyngeal, cloacal, or tracheal swabs, other samples from sick or dead birds, or manure. • Migratory birds that travel long distances have a major role in the global spread of AIVs. • USDA Animal and Plant Health Inspection Service (APHIS) performs AI surveillance in migratory birds. The World Health Organization (WHO) continuously monitors AI and other zoonotic influenza viruses through its Global Influenza Surveillance and Response System, and in collaboration with the World Organization for Animal Health. The Food and Agriculture Organization (FAO) conducts human-animal influenza surveillance.

	• AIV surveillance levels extend beyond normal measures for seasonal influenza, since AIV shedding may wane, and avian species carriers of AIVs may change. • H5 and H7 AIV strains are closely monitored for their ability to evolve from LPAI into HPAI strains-of-concern.
VETERINARY MEDICAL COUNTERMEASURES	• In the United States, the primary method of HPAI control and eradication in poultry is depopulation, rather than veterinary medical countermeasures to treat infected animals. • Amantadine and rimantadine were historically approved for use but are no longer recommended because circulating influenza strains are all resistant to these drugs. • Vaccination has several limitations; however, it is a strategy that can be used alongside other methods to control and prevent the spread of AI.
HUMAN MEDICAL COUNTERMEASURES	• There are currently four FDA-approved antiviral treatments for influenza in humans: peramivir, zanamivir, oseltamivir, and baloxavir marboxil. • For humans that are potentially exposed to or infected with known AIVs (e.g., H5N1), antiviral drugs may be used for treatment and for prophylaxis if given prior to the onset of symptoms. • Humans with a confirmed or suspected novel type of AI should be treated with neuraminidase inhibitor drugs (e.g., oseltamivir). • gsGD lineage HPAI viruses are resistant to amantadine and rimantadine. These drugs should not be used. • Purified antibodies against gsGD lineage H5 viruses have been tested in animal and limited human trials and appear safe. They exhibit some efficacy in *in vitro* studies but are limited against diverse subtypes and clades.
VACCINES	• Globally, several poultry AI vaccines exist, though their use is inconsistent across impacted countries. USDA maintains emergency vaccination guidelines, procedures, and vaccine recommendations. • No single vaccine is effective against all strains of AI; the existing vaccines are subtype and lineage specific. • April 2023 the USDA began HPAI vaccine trials of four candidates to test their efficacy in poultry against gsGD lineage H5N1 clade 2.3.4.4b, the strain causing the current outbreak. • AI vaccines do not prevent infection, but instead reduce clinical signs and mortality. Vaccinated birds can still transmit the infection to other birds, albeit at a lower frequency than unvaccinated birds. • Vaccines exert selective pressures on AIVs, which expedite AIV evolution and vaccine resistance.

DEPOPULATION/ CARCASS DISPOSAL	• USDA-defined standard practice is depopulation within 24-48 hours of HPAI identification on farms, followed by carcass disposal. • USDA-approved methods for depopulation include water-based foam systems (e.g., Kifco Avi-Guard or Spumifer handheld nozzles) or gassing (e.g., carbon dioxide, carbon monoxide, argon, or nitrogen). These methods are generally safe and effective, and gassing is identified as an accepted practice for euthanasia by the American Veterinary Medical Association (AVMA), though efficacy depends on poultry species. • Alternative methods such as Ventilation Shut Down (VSD) are conditionally approved as adjunct methods by USDA but must meet additional policy requirements prior to use. • USDA guidance on carcass disposal methods include composting, burial, incineration, rendering, and landfilling. • Early AIV detection and reporting is essential to limit disease spread and promote successful containment. On average, 12 days are needed for on-site staff to recognize and report the illness.
VIRAL PERSISTENCE AND ENVIRONMENTAL STABILITY	• AIV persistence varies based on the environmental matrix. • AIVs can be 3-4x more persistent, dependent on strain, than human influenza viruses in aerosols, lasting up to 36 hours. This time decreases with increasing ambient temperature, humidity, and sunlight. • Porosity of contaminated surfaces is also a factor in virus stability in the environment. IAVs can persist for 24-28 hours on non-porous surfaces such as stainless steel and plastic, but only 8-12 hours on porous surfaces such as cloth, paper, and tissues. • Moist matrices can induce prolonged stability—up to several months in cold weather, natural wetlands, and on duck feathers and feces. • HPAI virus remains infectious in fresh and frozen poultry products, creating a potential importation hazard.
DECONTAMINATION	• USDA maintains protocols for decontaminating facilities affected by HPAI virus. Decontamination is a crucial component of an HPAI response. • HPAI-affected farms must undergo cleaning and removal of bulk debris, followed by disinfection via drying and heating (i.e., 100-120°F for seven days) or wet disinfection with an approved product. • Different products or materials (e.g., equipment, soil, eggs) require different decontamination methods. • For facilities that cannot be adequately cleaned and disinfected, a fallowing period (i.e., allowing the virus to lie dormant and unoccupied) is required. The fallowing period depends on temperature and season but is typically 120-150 days.

	• 70% ethanol is effective at decontaminating surfaces of HPAI H5N1.
PERSONAL PROTECTIVE EQUIPMENT (PPE)	• There is effective personal protective equipment (PPE) for those with a risk of exposure to HPAI virus. The recommended PPE is dependent on the task (e.g., poultry workers, laboratory staff, depopulation workers). • Recommended PPE for poultry workers includes safety goggles, disposable gloves, boots, a respirator (National Institute for Occupational Safety and Health [NIOSH]-certified at N95 or higher), an apron, and disposable fluid-resistant coveralls. The composition of fluid-resistant coveralls should be of a fabric that meets federal regulations (e.g., ISO 16603 ≥ 3.5 kPA). • PPE recommendations for laboratory workers vary by country-specific authorities, but practices defined by USDA, Centers for Disease Control and Prevention (CDC), National Institutes of Health (NIH), and international authorities include high efficiency particulate air (HEPA)-filtered respirators, eye protection, and disposable coveralls. • In addition to frequent handwashing, PPE must be used when in direct contact with infected birds, as well as when handling poultry carcasses, poultry feces or litter, or when entering any premises where diseased or dead poultry may be present.
GENOMICS	• The presence of a polybasic cleavage site within the HA protein is characteristic of HPAI viruses and contributes to increased pathogenicity. • HPAI viral strains include variants of H5 and H7. • Genetic evolution of HPAI viruses is rapid, which contributes to their diversity. • There appears to be a propensity for gsGD lineage HPAI H5 to reassort with LPAI strains. • Emergence of new strains and variants of interest is difficult to predict. There is some evidence for 10-year periodicity of human pandemics. Periodicity of HPAI virus emergence in poultry is weak.
VIRUS IMPORTATION	• A risk factor for virus spillover into domestic poultry is close interactions between wild migratory birds and domestic poultry. • Domestic poultry farms close to migratory bird routes are at risk for HPAI virus infection. Preventive methods include early detection of clinical signs of AI, reducing illegal imports, and using biosecurity to prevent virus introduction and forward transmission. • Once HPAI virus has infected domestic poultry, disease spread can be rapid and losses to poultry flocks and the attendant economic losses can be severe.

Infectious Dose – How much agent will make a healthy individual ill?

What do we know?

Typically, the median infectious dose (ID_{50}) of AI in birds is measured in median egg infectious dose units (EID_{50}) or tissue culture infectious doses ($TCID_{50}$), representing the amount of virus needed to infect 50% of inoculated eggs or tissue cells, respectively. For each measure, lower values indicate greater infectivity, as less virus is needed for infecting a host.

- The ID_{50} of HPAI in birds depends on virus strain and host species, and can range from $<10^1$ to $10^{4.6}$ EID_{50} (estimated from reported values among ducks, chickens, and turkeys infected by intraocular and intranasal inoculation).[5]

In general, lower doses of gsGD lineage HPAI will infect wild fowl compared to domestic poultry, although wild birds also show lower mortality than domestic poultry when experimentally infected with the same HPAI strain.

- Intranasal and intratracheal inoculations of chickens with gsGD lineage HPAI H5N1 (A/turkey/Turkey/1/2005) resulted in an estimated ID_{50} value of $10^{2.5}$ EID_{50}.[6]
- Six-week-old white leghorn chickens (n=10/group) intranasally inoculated with 10^6 EID_{50}/200 µL of gsGD lineage HPAI H5N8 isolated from migratory birds in Eastern China (A/Wildbird/Cixi/Cixi02/2020) began to die three days post-infection (d.p.i.) with all infected chickens dying by five d.p.i.[7]
- Intranasal inoculation of rooks (*Corvus frugilegus)* with gsGD lineage HPAI H5N1 (A/mandarin duck/Miyazaki/22M807-1/2011) determined infection is primarily subclinical, but viral shedding from the oral cavity was $<10^3$ EID_{50} 1-5 d.p.i.[8]
- Intranasal inoculation of ducks with $\geq 10^4$ EID_{50} gsGD lineage HPAI H5N6 (Clade 2.3.4.4e HPAI Tottori/1) caused subclinical infection with low oral viral shedding, but systemic infection from higher dosing (confirmed by immunohistochemical staining) led to higher viral shedding ranging from $10^{4.5}$-$10^{5.7}$ EID_{50}.[9]
- The ID_{50} was determined through oculo-nasal infection of three groups of chickens and ducks (n=6/group) at three doses 10^3, 10^4 and 10^5 EID_{50} of A/chicken/England/053052/2021 (H5N1) strain. The ID_{50} varied between the two species; for ducks, it was determined to be $<10^3$ EID_{50} and was determined to be higher in chickens at $10^{4.67}$ EID_{50}.[10]
- Two-week-old mallards inoculated by the intra-choanal route with gsGD lineage HPAI H5N1 A/American Wigeon/South Carolina/22-000345-001/2022 resulted in an ID_{50} of $<10^2$ EID_{50}.[11]
- The ID_{50} of a non-gsGD lineage HPAI H7N8 strain (A/turkey/IN/16-001403-1/2016) isolated from turkeys post-intrachoanal inoculation varied depending on the host species infected; in chickens, the EID_{50} was $10^{3.2}$, but was lower in turkeys at $<10^2$ EID_{50} and mallards at $10^{2.5}$ EID_{50}.[12]

Poultry exposed to low viral titers of HPAI (10^2 EID_{50}) do not produce fatal infection, but continue to accumulate live virus in skeletal muscles, potentially resulting in food contamination; however, this is likely strain-dependent.

- A 2018 study intranasally challenged 30 ten-week-old Vanaraja chickens with varying concentrations of gsGD lineage HPAI H5N1 (10^2, 10^3, or 10^4 EID_{50}). Birds inoculated with 10^3 and 10^4 EID_{50} died by five d.p.i., but all chickens infected with 10^2 EID_{50} survived and did not show clinical signs of infection until three d.p.i. even though viral antigen was detected 12-24 hours post-infection.[13]

Infectious dose of HPAI and mortality is dependent on HPAI strain and species infected.

- Experimental intrachoanal inoculation of chickens with four different gsGD lineage HPAI H5N2 strains resulted in ID_{50} values of $10^{3.6}$, $10^{3.2}$, $10^{3.5}$, and $10^{5.1}$ EID_{50} for

A/turkey/Minnesota/12582/2015, A/turkey/South Dakota/12511/2015, A/chicken/Iowa/13388/2015, and A/turkey/Arkansas/7791/2015, respectively.[14]

- Estimates of ID_{50} of intrachoanal inoculation in turkeys with gsGD lineage HPAI varied based on virus isolate from 10^3 (A/chicken/IA/13388/2015) to 10^5 EID_{50} (A/northern pintail/WA/40964/2014 and A/turkey/MN/12582/2015), which indicates substantial variation in infectivity among different HPAI strains, even in the same host species.[15]
- Experimental infection of mallard ducks (intranasal inoculation), with three gsGD lineage HPAI H5N2 strains (A/Tk/MN/15, A/Ck/IA/15, and A/Np/WA/14) determined a low infectious dose of $<10^2$ EID_{50} with no mortality observed at low (10^2 EID_{50}) or high (10^6 EID_{50}) doses. In contrast, a gsGD lineage HPAI H5N1 strain (A/Ws/Mongolia/05) had a mortality of 100% at the lowest dose (10^2 EID_{50}) despite having a similar ID_{50} of $<10^2$ EID_{50} dose.[14]

The route of exposure affects the infectious dose, with small particle aerosol exposure and inhalation routes more infectious than ingestion.

- Ferrets, a common model for studying influenza in humans, were inoculated with gsGD lineage HPAI H5N1 viruses (A/Vietnam/1203/2005, A/Muscovy duck/Vietnam/209/05, or A/Whooper swan/Mongolia/244/05) through different routes. Infection with all three viruses was achieved with 10^6 EID_{50} intranasally and $\sim 10^{9.5}$ EID_{50} through consumption of infected meat. Infection occurred with $10^{8.3}$ EID_{50} after direct gastric exposure to meat infected with A/Vietnam/1203/2005.[16]
- Non-human primates (NHPs) exposed to 4 mL of 10^7 plaque forming units (PFU)/mL of aerosolized gsGD lineage HPAI H5N1 (A/Vietnam/UT3040/2004) presented viral titers of $10^{3.60}$, $10^{2.90}$, and $10^{2.34}$ PFU/mL one day post inoculation from nasal swabs. Conventional inoculation of NHPs presented higher or equivalent viral titers of $10^{2.40}$, $10^{2.30}$, $10^{4.53}$, and $10^{4.28}$ PFU/mL one day post inoculation.[17]

Given its highly pathogenic nature, HPAI may have a similar infectious dose to seasonal influenza, <u>but the median human infectious dose (HID_{50}) of HPAI is currently unknown</u>.

- Guinea pigs are regarded as a highly useful model to study influenza. Experimental inoculation with a non-gsGD lineage HPAI H7N9 virus (A/Anhui/1/2013), which caused lethal infection in humans, determined an ID_{50} of three PFU in guinea pigs.[18]

What do we need to know?

- How infectious are AIVs in humans compared to seasonal influenzas?

Transmissibility – How does it spread from one host to another? How easily is it spread?

What do we know?

Phylogenetic analysis of genomes suggest that the emergence of infections is due to invasions of co-circulating variants via wild bird vectors and secondary spread and transmission to backyard and commercial poultry.

- Transmission of HPAI virus to poultry is influenced by multiple risk factors at the local level, with the most critical originating from wild bird populations, the proximity of wetlands, the distance between poultry houses, species composition, and the activities used in raising the poultry. Another important aspect of disease transmission is negligence, or the loose implementation of biosecurity and preventive measures combined with low levels of surveillance.[19]

The main exposure and shedding routes for HPAI virus in birds are via oral and cloacal (i.e., urinary, gastrointestinal, genital tract) routes, although respiratory exposure may also lead to HPAI infection.[20]

- HPAI H5N1 viruses replicate to high titers in the respiratory tract and intestinal tract, and virus is excreted in high titers in both feces and oral secretions.[21]

- Higher cloacal virus shedding of wild ducks may increase transmission between wild birds and poultry.[22] Experimental infection in ducks with an HPAI virus clade 2.3.4.4 showed high levels of infection, high shedding in the environment and efficient transmission in ducks highlighting their role in the spread of disease. However, this strain appears to be duck-adapted as the same strain showed lower rate of infection and transmission in chickens.[10]
- Environmental transmission of HPAI H5N8 virus occurs via fecal contaminated water.[22] The estimated average number of secondary infections from a contaminated environment (R_{env}) was three. When $R_{env} > 1$, this is considered efficient for the transmission of virus to chickens from contaminated water.[22]

On average, infected birds transmit HPAI to between 0.9-3.0 additional birds in the same flock. This range represents the R_0, which is the calculated value for communicable diseases that represents the number of additional birds that one infected bird can infect.

- Analysis of outbreaks between 2003-2018 provided an R_0 estimate by maximum likelihood analysis of 1.69, 1.60, and 1.49 for H5N1, H5N8, and H5N6, respectively.[23]
- Laboratory experiments of airborne transmission rates of HPAI H5N1 strain A/turkey/Turkey/1/2005 between chickens was low: 0.13 and 0.10 new infections per infectious bird at 0.2 meters and 1.1 meters distance, respectively,[24] which suggests bird-to-bird airborne transmission contributes less than other routes.
- Experimental studies on the environmental air samples, dust, feathers, and other fomites suggest that airborne transmission of HPAI clade 2.3.4.4b between premises is low, with the outdoor spread of infectious viral particles in the air at ≤10 m. Other parameters such as indirect contact with wild birds and biosecurity practices pose a greater threat for HPAI.[25]

On average, infected poultry farms tend to transmit HPAI to 1.1-2.4 additional farms at the start of outbreaks.

- Analysis of four commercial poultry HPAI H7 outbreaks estimated the farm-to-farm R_0, pre-intervention mean range 1.1 to 2.4.[26] The generation time between reported infection in one farm and confirmed infected in the next farm in the infection chain varied between 1.9-8.4 days, suggesting substantial variation in farm-to-farm spread.[26] Control measures (i.e., culling of tens of millions of birds, movement restrictions, and pre-emptive destruction of high-risk flocks) reduced farm-to-farm R_0 below 1, effectively ending the outbreaks.[26]
- Modeling studies to evaluate the spread of HPAI from farm-to-farm note that the following steps will reduce virus transmission over time: culling birds on infected farms, culling birds on contiguous premises, banning the restocking of emptied farms, and enforcing restrictions to reduce the number of vehicles and staff on and among farms.[27] Additional studies evaluating the risk of transmission between farms identified that small backyard farms have the highest risk, which is due to the number of people visiting the farm and the other farms on the same day, and they also had the highest amount of direct contact with birds.[28] High risks for HPAI introduction were also noted in layer finisher type poultry due to the increased number of contacts to these farms and the use of cardboard egg trays for removing eggs.[29]
- Analysis of the 2016/17 HPAI H5N8 poultry farm outbreaks in Hungary, Germany, Poland, and the Czech Republic identified there were more farm-to-farm transmission events within countries (estimated R_0 range [0.2-1.3]) than wild bird-to-farm transmission. Wild bird-to-farm transmission did occur in the middle of the epidemic. It was not entirely associated with the start of the epidemic and was most prevalent in the Czech Republic (estimated R_0 4.6). Biosecurity measures prevented more cross-border transmission than local farm-to-farm transmission in Germany, Hungary, and Poland.[30]
- Comparison of the effective R_0 at live bird markets during the fifth wave of infection, when H7N9 became highly pathogenic in China, reached a median estimate of 2.2. The previous

low pathogenic H7N9 waves held medians <1-3.6 between live bird markets, suggesting a higher transmissibility of the highly pathogenic H7N9.[31]

Waterfowl, including ducks, appear to be driving the transmission of LPAI and HPAI to domestic poultry.

- While gsGD lineage viruses are the only HPAI viruses known to circulate in wild birds, HPAI viruses that have emerged from LPAI have been isolated from wild birds during outbreaks in poultry.[32]
- Migratory waterfowl, primarily of the Anatidae family (ducks, geese, and swans), are major carriers of novel virus strains. The identification of new HPAI strains in poultry is more prevalent within migratory pathways.[33]
- Experimental studies have shown that environmental contamination is twice as high for LPAI- than HPAI-infectious ducks.[34]
- Evaluation of viruses from 2017-2018 in Bulgaria of natural infection of gsGD lineage HPAI H5N8 in domestic ducks and poultry have shown, through evaluation of the HA gene, that domestic ducks are potentially driving the transmission to poultry and should be included in regular surveillance, along with wild birds, as outbreaks continue to occur.[35]
- Overall susceptibility varies among wild birds; house sparrows are highly susceptible to gsGD lineage HPAI H5N1 and shed virus for several days prior to onset of symptoms, while rock pigeons are more resistant.[36]
- HPAI viruses can also be transmitted by direct contact and aerosol in mammals.[37-38]

Risk factors for human HPAI infection are direct contact with or close exposure (≤1 meter) to sick or dead poultry in the week before illness onset, or visiting a live poultry market.[39-40]

- Transmission of HPAI to humans in Egypt is likely due to airborne transmission of HPAI virus during home slaughter of poultry. Caregivers of the poultry are infected at a higher rate. A contained poultry slaughter procedure was developed to reduce the airborne transmission and zoonotic infection of HPAI.[41]
- 2022/23 reports to WHO of confirmed human cases all involve close contact with poultry[42] or environmental exposure to sick or dead sea lions and wild birds.[43]
- There is no direct evidence that HPAI viruses are transmitted to humans via consumption of contaminated poultry products,[44] but there is evidence that tigers, leopards, martens, ferrets, and domestic cats and dogs have been infected with H5N1 AIV after eating contaminated poultry meat and blood.[45]
- There is low risk of animal-to-human transmission of HPAI H5 viruses, according to a study examining 60 outbreaks in 13 states; of 164 people exposed to infected birds, five developed acute respiratory infection within 10 days of exposure, but none tested positive for H5N1.[46]
- Human infection from European reassortant HPAI H5N6 is low, despite confirmed incidence among wild birds and human exposures to those birds.[47]
- There is an increased likelihood of gsGD lineage HPAI H5 viruses gaining human-to-human transmissibility.[48]
- Poultry is a source of human infection of HPAI H7.[31, 49]
- The USDA and FDA have assessed the risk of humans becoming infected with HPAI virus through contaminated cooked poultry meat, shell eggs, or egg products to be low.[50]

What do we need to know?

- What is the relative contribution of factors that influence transmissibility between farms (e.g., wild birds, shared farm equipment, human movement)?
- What is the typical generation time or serial interval for infections in poultry? For wild birds?
- Is transmission heterogeneous, in the sense that only a few animals contribute the most to new cases?
- What is the potential for HPAI H7 viruses to transmit to and among humans, and what would further enable it?

Host Range – How many species does it infect? Can it transfer from species to species?

What do we know?

Migratory aquatic birds are the primary natural reservoir for most subtypes of AIVs,[33] but domesticated poultry and other birds can also be infected.[51]

- HPAI virus has been found in gallinaceous poultry (pheasants, quail, guinea fowl), game birds, ducks, geese, ratites, pigeons, vultures, raptors, and cage birds.[51-52]
- Tree sparrows can test positive for H5N1 and can experimentally harbor virus in their respiratory and gastrointestinal tracts. Raptors and carrion birds are also susceptible to H5N1.[53-54]
- Domestic ducks may spread HPAI H5N1 viruses to other poultry and wild birds due to high levels of viral shedding,[22] and both wild waterfowl and ducks may appear clinically normal while harboring systemic infections,[53, 55-56] but this will vary depending on the HPAI strain.[57]

Many animal species, including humans, are susceptible to AIVs, despite not being the primary reservoir hosts.

- gsGD lineage HPAI H5N1 was initially detected in geese (A/goose/Guangdong/1/1996) and emerged among poultry in China;[58-59] and has since been detected in wild and domestic birds.[42, 60]
- The USDA tracks reports of HPAI in mammals and during the ongoing 2022/23 U.S. HPAI outbreak, gsGD lineage HPAI H5N1 has detected the virus in American black bear, grizzly bear, Kodiak bear, American marten, amur leopard, amur tiger, bobcat, bottlenose dolphin, coyote, fisher, grey seal, harbor seal, mountain lion, North American river otter, raccoon, red fox, striped skunk, and Virginia opossum.[61] Detection reports from the United States and Canada have also included Atlantic white-sided dolphin, harp seal, harbor porpoise, mink, muskrat, and North American beaver.[54] Additional reports include detection of gsGD lineage HPAI H5N1 in dogs,[62] tanukis,[63] lynx,[64] domestic cats, stone marten, donkeys, civets, and lions.[53]
- Foxes have tested positive for gsGD lineage HPAI H5 in several U.S. states and Canada,[54, 65-66] as well as in Japan[63] and the Netherlands.[67-68]
- In 2022, gsGD lineage HPAI H5N1 was detected in polecats, a badger, and an otter in the Netherlands[68] and was detected in a harbor porpoise that died from meningoencephalitis in Sweden.[69]
- In October 2022, farmed mink were found to be highly susceptible to gsGD lineage HPAI H5N1 and a mutation in the PB2 gene. Mink-to-mink transmission was indicated to have occurred.[70]
- In January of 2023, it was reported for the first time that three grizzly bears from Montana tested positive for HPAI after being euthanized due to neurological issues.[66]
- WHO has reported several human cases of HPAI H5N1 clade 2.3.4.4b associated with the global outbreak since 2020.[71] One case from China,[72] two from Spain,[73] one case from Vietnam,[72] one case from the UK,[74] and one case from the United States.[71] Recently

another human case was reported from Chile,[75] after the detection of a suspected human case in Ecuador.[76-77]

- Domestic pets such as dogs and cats, who have regular access to the outdoors, can also become infected with HPAI.[78] There is evidence domestic cats and dogs have been infected with H5N1 in multiple locations, including Germany, Thailand, and North America.[79-80]
- Animals most likely become infected by eating the carcasses of HPAI-infected birds.[78]
- Experimental infections of gsGD lineage HPAI H5N1 and reassorted viruses have also occurred in cats, dogs, foxes, pigs, ferrets, laboratory rodents, cynomolgus macaques, and rabbits.[51] gsGD lineage HPAI H5N2 was recovered from a dog and was transmissible to other dogs, chickens, and cats,[51] and has been associated with multiple ostrich outbreaks.[81]
- Experimental gsGD lineage HPAI H5N8 infection has shown low to moderate virulence in ferrets and mice, while black rats did not shed virus or seroconvert,[51] and has been found in serological studies from natural infection of gsGD lineage HPAI H5N8 in pigs.[82] gsGD lineage HPAI H5N8 has appeared in poultry, wigeons, mute swans, gyrfalcon, ostrich, penguins, wild waterfowl, and domestic ducks.[57, 81, 83-87] gsGD lineage HPAI H5N6 has been isolated from pigs[51] and detected in wild birds.[88]
- Reassortants of gsGD lineage HPAI H5N1, including H5N8, are found in poultry, but it is unknown how long wild birds can maintain gsGD lineage HPAI H5N1 viruses or if they can become reinfected. They have been shown to transfer H5N1 and reassortants (including H5N8) to new geographic regions.[51] gsGD lineage HPAI H5N8 has been detected in gray seals in Poland.[89]
- HPAI H7N9 emerged in China in 2016 in poultry and was transmitted to humans. The host range expanded to ducks. A vaccination campaign decreased the detection in poultry and humans, but HPAI H7N9 re-emerged in poultry in Southwest China in 2021.[90]

Sustained transmission in mammal populations is uncommon.

- Although there are cases of mammalian host-to-host transmission of HPAI viruses,[70, 91] sustained transmission is uncommon in mammals.[53] Dogs have experimentally transmitted H5N2 to other dogs, chickens, and cats.[51] Tiger-to-tiger transmission was suspected during outbreak of HPAI H5N1 in a zoo in Thailand.[92] HPAI H5N1 viruses rarely transmit from human to human.[93]
- It is possible for HPAI viruses to adapt to humans. Human infections have been reported from HPAI H5N1 viruses.[53, 75 71, 94] H5N8 was detected in human poultry workers during an outbreak on poultry farms in Russia, although the humans did not have symptomatic disease.[95] Sequence analysis of HPAI H5N1 isolates from mink were shown to have PB2 gene mutations that enhance the polymerase activity of influenza in mammalian cells.[70]
- The risk of people catching HPAI from companion animals is considered extremely low, however it could theoretically be possible.[78-79] A documented case of LPAI transmission from cat to human occurred in NY in 2016.[96]

The primary circulating gsGD lineage HPAI H5N1 clade shifts through time.

- Prior to 2009, gsGD lineage HPAI H5N1 clade 2.2 viruses caused most outbreaks in birds; from 2014, gsGD lineage HPAI H5 clade 2.3.4.4 viruses were the dominant strains, with subtypes H5N1, H5N2, H5N3, H5N4, H5N5, H5N6, and H5N8 detected. Between 2020 and 2021, dominant subtypes have included H5N8, H5N1, H5N3, H5N4, and H5N5.[83] Novel gsGD lineage HPAI H5N8 clade 2.3.4.4b virus was detected in 2020 in wild and domestic birds in Russia, Iraq, Kazakhstan, Europe, Japan, and South Korea.[97-100] In 2017, a novel 2.3.4.4b H5N6 was detected in wild and domestic birds in China.[101]

- HPAI H5N6 viruses have been shown to be less pathogenic in mice and ferrets, but showed a higher level of transmission in ferrets and an enhanced affinity for binding to human receptors.[102] Human cases of H5N6 have occurred with severe disease and 55% fatality rates, but there has been no evidence of human-human transmission.[103]

What do we need to know?

To better understand the risk of transmission to species other than birds, we need more information on the role of viral diversity on host susceptibility:

- What is the risk of human and animal infection and subsequent transmission due to natural diversity of H5N1 subtypes?[53]
- What is the role of domestic animals in transmitting and maintaining H5N1?[53]

Incubation Period – How long after infection do symptoms appear? Are animals infectious during this time?

What do we know?

Birds generally exhibit clinical symptoms of infection such as coughing, sneezing, and nasal discharge hours to days after becoming infected with an HPAI virus, however they can shed HPAI virus during the incubation period prior to clinical signs.

- Incubation periods for HPAI vary and are dependent on infectious dose, transmission acquisition, and environmental factors. Determination of infection duration and incubation time is confounded when no clinical symptoms are present. Naturally infected chickens have an incubation period from 3-14 days.[104]
- In poultry, the incubation period can range from hours to days. For disease control considerations, a 28-day incubation period is used for avian populations.[105] Mammals are thought to have short incubation periods of 1-2 days.[51]
- The duration of infection depends on the host species, virus strain, and severity of infection.[51] Waterfowl can shed virus before clinical signs appear.[51, 53] Studies have found virus shedding in chickens and wild birds within 1-2 days following exposure.[106-107]
- The incubation period in individual birds can be a few days, whereas herd incubation (the incubation period through a flock of birds) can be a couple of weeks with ongoing transmission between the birds of the flock occurring through inhalation or ingestion.[108-109]

Humans infected with H5N1 AI generally show clinical symptoms 2-5 days after exposure, though longer incubation periods (≤17 days) are possible.

- For AIV (H5N1) infections in humans, incubation periods average 2-5 days after virus contact or contact with exposed live poultry, often being described as “within the week prior” [110-112,113] and while rare, on the high end can range from 8-17 days.[51, 95, 114] For human infections with the HPAI (H7N9) virus, incubation period ranges from 1-13 days,[51] with an average of 3-5 days.[111]
- No epidemiological evidence supports the food chain as a source of transmission for HPAI H1N5 in humans; however, it remains hypothetical based on virus detection in fecal and rectal swab samples.[16] This route of exposure is poorly described and it is unknown if the incubation period is different than for a respiratory route of exposure.[110]
- There are limited examples of possible human-to-human transmission of HPAI[115] however in the few documented cases of likely spread, the incubation period was measured at 3-5 days, with one instance of an incubation period of 8-9 days.[116]

What do we need to know?

- How infectious are individuals during the incubation stage relative to the symptomatic stage?
- Consumption of infected tissue or water has been suggested as a source of human infection.[110] If infection is acquired this way, does it alter the incubation period?
- To inform sensitivity of diagnostic tests and improve modeling, to what extent is HPAI H5N1 shed during the incubation period?

Clinical Presentation – What are the signs of infected individuals?

What do we know?

HPAI and LPAI refer to high or low pathogenicity in chickens (respectively), not humans or other animals.[117]

- LPAI viruses can cause serious illness in humans, but generally not in chickens.[117] Clinical symptoms of LPAI in humans can include conjunctivitis, fever, runny nose, sore throat, cough, and severe respiratory symptoms such as pneumonia and respiratory failure, even death. Few cases are asymptomatic.[118]

HPAI can cause up to 100% mortality in infected chickens. Clinical presentation in birds can include mild to severe respiratory disease signs as well as neurological issues, problems with egg production and formation, and even sudden death. Mortality can also occur without any other external clinical signs of infection in birds.

- Clinical signs of HPAI in birds can include common respiratory illness signs such as nasal discharge, coughing, sneezing, and general fatigue. More severe symptoms are facial swelling, comb and wattles turning blue,[119] green feces/diarrhea, loss of muscle control, involuntary muscle movements and spasms, immobility, death,[120] and egg abnormalities such as soft or misshapen eggs, reduced egg production,[121,122,51] or eggs without shells.[123] Mortality can occur without external clinical signs of infection, and an increase in mortality within flocks is sometimes the only sign of this virus.[122]
- Inoculations of HPAI H5N8 in chickens causes 50-100% mortality.[124] Necropsy examination reveals edematous, hemorrhagic, and necrotic abdominal organ lesions.[124]
- HPAI H5N1-affected chickens can also die without outward clinical signs.[125] Histologically, these birds show necrosis in the spleen, brain stem, cerebrum, cerebellum, pancreas, and lymphoid tissues in intestinal lamina propria.[125] HPAI virus is thought to be excreted primarily from the digestive tract.[125]
- HPAI-infected wild birds such as waterfowl or migratory birds are often asymptomatic; however, recent surveillance shows the possibility that a clinical sign of HPAI infection in wild birds could be a reduction in the number of movements over a time period or decreased flight distance.[126] As the spread of HPAI infection between wild and farmed birds is becoming more documented, and is believed to have played a large role in the 2021-2022 epidemic, defining and understanding clinical presentation of wild and migratory birds will be crucial in controlling transmission to domestic poultry.[127-131]

While rare, it is possible for other animals to become infected with AIVs.[78-79]

- Infected mammals can present with clinical signs often found in other diseases, including fever, coughing, lethargy, diarrhea, and weight loss,[79, 132] with neurological signs such as seizures, ataxia, or tremors also possibly occurring.[133] Laboratory animal models show these clinical signs can range from mild to fatal.[132]

Humans infected with HPAI H5 virus generally exhibit acute illness including fever, upper respiratory tract symptoms, myalgia, and lower respiratory tract illness.[121] However, humans can present with more severe symptoms including pneumonia, gastrointestinal issues, encephalitis, septic shock, multi-organ failure, and even death.[95, 121]

- Fever is common, but not always present. The less common symptoms to be aware of include nausea or vomiting, diarrhea, or seizures.[134]
- Significant clinical human illness is the feature of a pandemic IAV strain.[135]
- A strong index of suspicion of human H5N1 virus infection is warranted with cases of rapid onset fever and respiratory illness after having exposures to potentially infected poultry.[39]
- Current CDC HPAI H5 or H7 virus human exposure monitoring guidance for avian outbreak responders: self-reporting illness (passive monitoring) for those wearing adequate PPE. For those with inadequate or lacking PPE, active disease monitoring is advised. For those responding to an AIV of unknown origin, active monitoring during exposure and continuing for 10 days post-exposure are recommended, regardless of PPE use.[136]
- Personnel involved in culling operations or others with close contact of known infected birds should monitor closely for neurological or respiratory symptoms, as well as conjunctivitis, for at least 10 days following the exposure.[129]

Prior to 2022, there were no confirmed HPAI H5 infections in humans in the United States,[121] though sporadic human infections have been reported in other countries (e.g., H5N8 in Russia,[137] H5N6 in China,[138] H5N1 in China,[139] Cambodia, Vietnam, Laos, Egypt, and Indonesia).[140] However, in April 2022, a case of H5N1 was identified in a poultry worker in Colorado.[141]

- The U.S. patient was involved with culling infected poultry at a Colorado farm with confirmed H5N1 cases in the poultry. He presented with fatigue and was confirmed positive for H5N1 by the Colorado Department of Public Health and Environment Laboratory Services as well as the CDC. He was treated with antivirals and recovered without hospitalization, with no further spread to close contacts.[141]
- In December 2022, there was one case of human infection from backyard poultry in Ecuador, the first in Latin America or the Caribbean.[76] In February 2023 in Cambodia, a father and daughter both tested positive for H5N1 after exposure to village poultry, with the infection being fatal to the daughter.[142-143] In March 2023, Chile had its first case of human infection as well.[75] Since 2020, there have been five cases of humans infected with H5N1 in the WHO European region, including two poultry workers testing positive in the UK in May 2023.[144]
- The WHO tracks all human cases of H5N1, which as of 6/07/2023 includes data from 2003 through April 24, 2023.[145]

What do we need to know?

- To what extent have subclinical or asymptomatic HPAI infections been underreported in humans?
- Is there any discernable pattern based on timing or progression of symptoms that would allow farmers to recognize HPAI infections more quickly in their flocks?

Biosurveillance and Clinical Diagnosis – Are there tools to diagnose infected individuals? When during infection are they effective? Are there ongoing surveillance efforts to detect HPAIs?

What do we know?

The primary method of detecting AI in poultry flocks is real-time reverse transcription polymerase chain reaction (rRT-PCR) from cloacal and oropharyngeal/tracheal swabs,[146] sampling from sick and dead birds,[147] and manure.[148]

- RT-PCR is used for evaluating the presence of HPAI in manure from commercial flocks,[148] and, along with sequencing, provide confirmatory testing for HPAI presence.[33] Validated RT-

PCR assays allow for detection of HPAI H5 viruses and co- circulating LPAI viruses, and considerably reduce diagnosis times.[149]

- RT-PCR viral detection is typically possible within a few days of disease onset.[150]

Laboratory diagnoses also include immunodetection of virus antigen/antibody.

- HPAI virus can be identified by the presence of IAV using agar gel immunodiffusion, enzyme immunoassay, immunofluorescence assays, and enzyme-linked immunoadsorption assays.[151]
- Antigen detection is widely used globally for AI identification in poultry flocks for early detection and containment initiation.[2, 152]
- According to CDC and WHO guidelines, rapid antigen detection tests, such as immunofluorescence or enzyme immunoassay, should not be the diagnostic method of choice in the event of a suspected outbreak of AI.[95, 153] Rapid antigen testing for HPAI is often falsely negative in confirmed cases.[150]
- Farmers and staff can play a key role in the elimination of AIVs, in part through basic education on early detection and biosecurity.[154] The use of disinfection booths for farm visitors or workers was associated with lower risk of H5N6 infection in individual farms during an outbreak in Korea.[155]

Migratory birds that travel long distances have a major role in the global spread of AIVs.[156]

- An important component of biosurveillance is wild bird carcass surveillance from target species.[157] In wild birds, passive surveillance (from dead birds) is an appropriate method for HPAI surveillance when HPAI infections are associated with bird mortality, whereas active surveillance (from live birds) has an extremely low efficiency for detecting HPAI virus.[158]
- When positive cases of HPAI are detected in a country or region, surveillance protocols for wild birds should be initiated, as the movement of migratory waterfowl is considered a potential risk for virus transmission into non-infected areas.[151]
- Birds in Anseriformes (ducks, geese, and swans) and Charadriiformes (shorebirds) orders are considered natural reservoirs for all AIVs; AIVs have been most frequently isolated from these birds.[159] Spillover of gsGD lineage HPAI H5 from wild to domestic birds is complex. Wild gulls and ducks play a large role in geographic spread of HPAI H5, but primarily transmit to other wild birds as opposed to domestic poultry directly.[160] Wild land birds (e.g., crows, songbirds, raptors), on the other hand, were observed more often to transmit directly to domestic ducks, chicken, and turkey compared to other wild HPAI H5 sources.[160] Similarly, wild geese were responsible for more transmission to domestic poultry than wild ducks, suggesting that wild geese and swans are an underappreciated source of HPAI H5 spillover.[160]
- HPAI vigilance must be continuous, since HPAI disease severity may wane and avian species carriers of HPAI viruses may change.[161] Additionally, the presence of important long-range HPAI vectors is generally seasonal, which should influence active sampling schemes to supplement passive sampling.[55]
- Mutation from an LPAI H5 or H7 virus to an HPAI virus occurs in poultry, warranting periodic virus surveillance in domestic flocks.[162]

Monitoring for HPAI is conducted by the USDA in the United States, as well as by international partners in their respective regions.

- The United States Geological Survey National Wildlife Center in Wisconsin conducts enhanced HPAI surveillance and has identified lethal HPAI infections in diverse raptor populations.[163] USDA APHIS performs AI surveillance in migratory birds.[52, 164] WHO

continuously monitors AIV and other zoonotic influenza viruses through its Global Influenza Surveillance and Response System, and in collaboration with the World Organization for Animal Health and the FAO, conducts human-animal surveillance.[95]

  - USDA, together with the Center for Food Security and Public Health, implemented a biosecurity resource based off of the Checklist for Self-Assessment of Implementing Poultry Biosecurity as part of initial response.[165]
  - Appraisal and Indemnity resources are available for backyard flocks affected by HPAI.[166]

- Wild bird LPAI/HPAI viral sampling is primarily from several genera from the family Anatidae.[167] USDA determines which watersheds to conduct virus surveillance based on significant historic influenza clusters, identification of flyway mixing of dabbling ducks within the lower 48 states and watersheds with high quantity of domestic chickens and turkey, as well as the median annual number of days above and below 0°C in a watershed.[167]
- USDA detected gsGD lineage HPAI H5N1 in January 2022 (via hunter-harvested bird sampling),[52] four weeks before the first detection in commercial poultry (turkeys)[168] that signaled the beginning of the 2022/2023 U.S. HPAI outbreak affecting more than 58.7 million domestic birds (as of 06/07/2023).[168]
- The National Wildlife Disease Program (USDA/APHIS/Wildlife Services) monitors HPAI in mammals across the country.[61] As of 6/07/2023, over 195 HPAI H5N1 virus detections in mammals have been reported as part of the 2022/2023 U.S. outbreak.[61]
- The 25 member nations in the Global Consortium for H5N8 and Related Influenza Viruses monitor global circulating AIVs.[156] Similarly, 31 European countries routinely sample commercial and backyard poultry flocks, as well as wild birds for circulating LPAI and HPAIs.[169] This type of surveillance can help establish, for instance, whether new genomic variants likely arose from locally circulating strains, or whether they were imported from other sources.[170]
- AIV surveillance in wild waterfowl is accomplished via RT-PCR from oropharyngeal, cloacal, and feather swabs, alongside sequencing and serological analysis of antibodies against IAV.[55] Swabs from feathers may be more sensitive than cloacal or tracheal swabs, though this advantage may be restricted to later stages of infection (≥3 d.p.i.).[171]
- Clinical signs alone cannot distinguish an LPAI from HPAI.[172]

What do we need to know?

- How effective are methods for identifying LPAI with the potential to develop into HPAI?[173]
- Are there inexpensive, effective, field-based diagnostic methods that can be widely deployed?

Veterinary Medical Countermeasures – Are there effective treatments?

What do we know?

In the United States, the primary method of HPAI virus control and eradication in poultry is depopulation, rather than use of veterinary countermeasures to treat infected animals.[104]

- USDA instructs responsiveness to HPAI virus by isolating and depopulating an infected population. In extreme cases, emergency vaccinations can be administered to the animals.[104]

There are several medications available that reduce clinical signs and potential for transmission in infected poultry,[174] though they are not used in the United States.

- Experimental intranasal infections in chickens with HPAI H5N6 were treated with oral baloxavir marboxil or peramivir either immediately or 24 hours post-challenge. Only those

chickens treated immediately post-challenge with baloxavir marboxil showed significant reduction in viral titers and protection from death.[175]

- Methylated soy protein has potential to prevent or treat HPAI in some chickens.[176]
- Oseltamivir reduced mortality and transmission when administered to chickens infected with HPAI H5N2, but transmission resumed once antiviral treatment ended.[177] Zanamivir was ineffective at reducing HPAI mortality or transmission between chickens.[177]
- Resistance to amantadine has been resolved to a single mutational polymorphism at the S31N location of the second matrix proton channel (M2) protein, which is present in AI H5N1 and H7N9 subtypes.[178-179] Experimental studies using site-directed drug development have shown that M2-inactivation drugs can still be used against resistant strains and remain viable future treatment options.[178-179]

Vaccination efficacy is typically limited to the same subtype and clade; however, it is a strategy that can be used alongside other methods to control and prevent the spread of AI.[180]

- Vaccinations using plant-derived HPAI proteins has shown to be effective in protecting chickens from HPAI infections.[181]

What do we need to know?

- Are there effective measures for reducing viral load in infected poultry aside from vaccines?
- Can currently resistant strains of influenza develop additional resistance to existing treatments for animals?

Human Medical Countermeasures – Are there effective treatments?

What do we know?

For humans with confirmed or suspected IAV caused by relevant strains (e.g., H7N9, H5N1), antiviral drugs may be used for treatment and prophylaxis if given early in symptom progression or before symptoms begin.

- Humans with confirmed or suspected novel influenza should be given neuraminidase inhibitor drugs (e.g., oseltamivir, peramivir, and zanamivir) for treatment.[182]
- Oseltamivir is most effective when given within 48 hours of symptom onset and before respiratory failure,[183] though some benefits occur if given within 6-8 days of symptoms.[184]
- Household or close family members with highest risk of exposure to individuals having confirmed IAV caused by H7N9 or H5N1 viruses should be given oral oseltamivir or inhaled zanamivir as chemoprophylaxis within 48 hours of exposure to reduce likelihood of additional transmission, according to the CDC.[185]
- Some HPAI strains H7N9, H5N6, and H5N1 are resistant to antiviral medications amantadine and rimantadine, which should not be used.[186]
- Oseltamivir given to mice prior to experimental challenge with HPAI reduces mortality,[187] although the dose required depends on the virulence of the HPAI strain.[188]
- The antiviral medication peramivir demonstrates protective efficacy against various AIVs in mice (e.g., H5N1, H9N2),[189-190] and eliminates virus from the respiratory tract and prevents development of clinical signs of infection.[191] Peramivir shows similar efficacy as oseltamivir in humans when used to treat seasonal influenza,[192] but is untested in humans having novel AIs.
- The anti-influenza drug, favipiravir, a chain terminator of viral RNA only approved for use in Japan, has demonstrated protective efficacy against H5N1 infection in mice[193] and is in Phase III clinical trials to determine human efficacy.[194]

- Purified antibodies against H5N1 have been tested in animal and small human trials and appear safe, with some efficacy in *in vitro* studies.[195-196]
- In a case study, a severely ill patient was treated with convalescent plasma that led to a reduction in viral load.[197] Clinical trials are needed to better understand the effectiveness and assess general safety.

What do we need to know?

- Antiviral treatments are limited to the same four drugs (oseltamivir, zanamivir, peramivir, and baloxavir marboxil) for both humans and animals. What is the barrier against species-specific treatments?
- Can current therapeutic options be modified to counter resistance to amantadine-class drugs?

Vaccines – Are there effective vaccines?

What do we know?

Globally, there are several existing vaccines against AI in poultry, though their use is not consistent across impacted countries.[198] USDA maintains emergency poultry vaccination guidelines, procedures, and vaccine recommendations.[104]

- The role of vaccines in the prevention and control of HPAI is a topic being actively explored,[199] with the European Council releasing a press release in May 2022 regarding the decision by the agriculture ministers on a strategic vaccination approach.[200] Vaccination has often been thought of as a last resort, but the 2021-2023 epidemic is causing countries to debate revising their vaccination strategies.[131, 201]
- Vaccines have been used to help control outbreaks of HPAI in poultry flocks (e.g., H5N2 in Mexico, H7N3 in Pakistan, and H9N2 and H5N1 in Asia), with inactivated whole virus vaccine most commonly used, as well as vaccines made from recombinant viruses with specific AIV genes.[198]
- Due to the 2023 spread of HPAI within the United States, in April 2023, the USDA began HPAI vaccine trials of four candidates to test their efficacy in poultry against gsGD lineage H5N1 clade 2.3.4.4b, the strain causing the current outbreak.[202-203]
- Recombinant or reverse genetics have also been used to create vaccines, where AIV genes are inserted into other viral genomic backbones (e.g., Newcastle disease virus, fowl poxvirus).[198]
- Various poultry species can be vaccinated,[104] though vaccine efficacy and effective doses differ among species.[204] For example, vaccines developed in ducks may inhibit HPAI H5N1 infection,[205] although different species of ducks show different responses to the same vaccine.[206]
- China (91%), Egypt (4.65%), Indonesia (2.3%), and Vietnam (1.4%) have historically conducted the majority of AIV vaccinations,[207] although current rates of vaccination are not known. Vaccination of poultry was initiated in September 2017 in China. Even though the globally circulating H5 viruses have been detected in many species of wild birds and occasionally in ducks or geese in recent years, issues have not been reported on routinely vaccinated poultry farms in China, and the pervasive H7N9 viruses have been nearly eliminated in China.[208]
- Eradication of HPAI through vaccination campaigns, in coordination with other measures, has occurred in a few countries, and typically where either a high level of competence in veterinarian services exists, or where the geography and density of bird populations have helped lead to the success.[209]

- One complication in vaccination campaigns is vaccinated birds become difficult to differentiate from infected birds.[209-210] An International Alliance for Biological Standardization international meeting was held in October 2022 to discuss challenges and barriers to AIV vaccine use, such as trade concerns and availability of suitable vaccines, and recommendations have been made to support greater use of vaccination to help control the spread of HPAI.[211]
- After 19 critically endangered California condors were found dead due to HPAI infection, APHIS approved the emergency use of an HPAI vaccine. Since the inactivated vaccine, which had been conditionally licensed by APHIS Center for Veterinary Biologics in 2016, has not been tested against the current strain, it will be pilot tested in vultures first. Vaccination will be limited to the condors, which are wild birds and not poultry, so it will not impact trade.[212-214]

There are multiple vaccines for use in humans for protection against IAV (H5N1), however they have typically been developed for the Strategic National Stockpile or for pandemic preparedness and are not produced in large quantities, nor are they available for general population use.[215]

- There are some older approved or conditionally approved vaccines for use in humans by the FDA, such as Sanofi Pasteur's inactivated "H5N1 Influenza Virus Vaccine" licensed by the FDA in 2007,[216] and GlaxoSmithKline's "Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted" licensed in 2013.[215]
- In January 2020, the FDA approved use of CSL Segirus's cell-based monovalent IAV H5N1 vaccine "Audenz," in people six months and older, who may be at high risk of exposure.[217]
- The European Union has also approved or temporarily approved several H5N1 vaccines,[218] including Novartis's "Foclivia" in 2009,[219] GlaxoSmithKline's "Adjupanrix" in 2009,[220] and Novartis's "Aflunov" in 2010.[221]
- The CDC, in coordination with the WHO, developed a curated bank of Candidate Vaccine Viruses (CVVs) that are a library of influenza viruses, including both seasonal and HPAI influenza viruses, which can be used for expedited development of human vaccines if needed. The CVV library contains virus nearly identical to the H5N1 (clade 2.3.4.4b) currently circulating.[222-225]
- The U.S. Biomedical Advanced Research and Development Authority (BARDA), is working with multiple vaccine manufacturers, including GSK and CSL Seqirus, to test the safety of H5 vaccine candidates more similar to the current outbreak strain.[226]

There is no single AI vaccine for birds that is effective against all hemagglutinin (H1-16) and neuraminidase (N1-9) subtypes; existing vaccines are subtype- or even clade-specific.[198]

- Vaccines used in birds are either "homologous," (the HA and subtypes both match the virus to be protected against), or "heterologous" (where the NA subtype differs). For all inactivated AIVs, the HA vaccine strain subtype needs to match the wild virus strain HA subtype. Heterologous vaccines are most often used for HPAI, and permit differentiation of birds infected with vaccine or field strains.[198]
- Birds vaccinated with an H5 virus were protected from subsequent challenge with an HPAI H5 strain, while those vaccinated with H7-subtype virus were not protected from subsequent H5 challenge, which demonstrates the need to match the HA subtype of the vaccine and the virus causing infections.[32]
- Inactivated vaccines are broadly protective against historic virus strains, in contrast to seasonal human influenza where vaccines are changed annually.[32]

- A new study shows an effective HPAI vaccine in ducks. All vaccines tested were efficient in reducing, at least to some extent, virus shedding following challenge with gsGD lineage HPAI H5N8 clade 2.3.4.4b virus. The study was based on experimental vaccines, but showed proof of concept that vaccine control of HPAI can be achieved in ducks.[227]
- Significant antigenic differences between commercially available poultry vaccines and currently circulating HPAI viruses suggests that vaccines may be suboptimal in controlling current poultry outbreaks.[100]
- Cross-group protective immunity was shown to be elicited in mice, ferrets, and NHPs by co-immunization with HA immunogens. Protection included HPAI H5N1 and H7N9.[228]

AI vaccines for birds do not prevent infection but reduce clinical signs and mortality. Vaccinated birds can still transmit infection to other birds, albeit at a lower rate than unvaccinated birds.

- The absence of clinical signs and mortality can enable "silent spread" of AIVs in vaccinated flocks, which can occur even when vaccines are effective in individual birds.[229]
- A single vaccination of chickens was insufficient to prevent antibody titer increase following challenge with HPAI H5N1, which suggests that animals were still becoming infected despite a reduction in clinical signs.[230]

Vaccines exert selective pressures on AIVs,[231] hastening evolution and vaccine resistance.[232]

- Antigenic drift in Egypt has reduced the efficacy of an existing H5N2 vaccine against circulating HPAI H5N1 strains.[233]
- Similarly, researchers have found novel HPAI H7N9 strains in China have the ability to partially escape neutralization by vaccines, with those vaccines introduced only six months prior,[234] which is suggestive of rapid evolution due to vaccine-induced selective pressures. The control of H5N1 in China has resulted in seven different vaccines being introduced over a 10-year period.[209]
- The World Organisation for Animal Health's (WOAH's) General Assembly debated the use of vaccination as a complementary tool and extensively discussed its associated implementation challenges.[235] It was recognized that a successful vaccination strategy must rely on authorized vaccines that closely match the virus strains in circulation. Furthermore, it must be accompanied by robust disease surveillance, which is able to demonstrate freedom from infection in the domestic animal population as recommended by WOAH Terrestrial Animal Health Code.[235]
- USDA's Agricultural Research Service has begun AI vaccination trials in April 2023. The researchers expect to have two-dose vaccine challenge studies with results in June 2023.[203]

What do we need to know?

- For increased resistance to infection as the influenza strains change over time, and reduced time for production of new strain-specific vaccines, could a "universal" AI vaccine be developed?
- How effective is prophylactic vaccination at reducing depopulation needs? (To understand the cost and risk benefit of vaccination versus mandatory culling if a farm's flock becomes infected).

Depopulation / Carcass Disposal – What are safe and effective ways to minimize the spread of HPAI in agricultural settings?

What do we know?

Within 24-48 hours of HPAI notification on farms, the USDA-defined standard practice is depopulation with water-based foam systems (e.g., National Veterinary Stockpile Kifco

Avi-Guard, or Spumifer handheld nozzles) for floor-raised birds or gassing (e.g., carbon dioxide, carbon monoxide, argon, or nitrogen) for caged birds. These processes are generally safe and effective, and gassing is identified as an accepted practice for euthanasia by the American Veterinary Medical Association (AVMA),[236] though efficacy depends on poultry species.[237-238]

- Efficacy of foam versus gassing for depopulation is species-dependent. While water-based foam (Spumifer with 1% Phos-Chek and water foam) resulted in more rapid brain death in turkeys,[239-240] while 100% CO_2 gas outperformed water-based foam in four physiological categories (time to unconsciousness, motion cessation, brain death, and altered terminal cardiac activity) in ducks.[240-241]
- Gas concentration in depopulation is also species-dependent; 40% CO_2 concentrations are effective euthanasia for chickens within 2-4 minutes, although >70% concentration is required for ducks and geese.[236-237]
- Cervical dislocation is another method for euthanasia. This is a non-invasive method; however, it requires trained personnel and is inefficient for large flocks or birds, in addition to the long exposure time of the responsible personnel.[151]

Alternative methods such as Ventilation Shut Down (VSD) are conditionally approved as adjunct methods by USDA, but must meet additional policy requirements before use.[238]

- VSD is considered a controversial practice by some veterinarians.[242]
- Continuing research shows improvement of VSD efficacy with addition of supplemental heat.[243-245]

USDA disposal methods include composting, burial, incineration, rendering, and landfilling.

- The disposal method to be used is selected by the disposal group composed of federal partners and incident command staff.[246] Methodology is evaluated for each incident leveraging containment efficacy, environmental considerations, stakeholder acceptance, and cost burden.[246]
- Research indicates increasing temperature from 35- 55°C during carcass composting reduces the time required to achieve greater than 99.999% reduction in viral activity from 6.4 hours to 29 minutes.[247] USDA suggests maintaining a temperature of 135-140°F for 3-12 weeks to ensure full decomposition.[246]

Early influenza virus detection and reporting and time to depopulation directly impacts the spread of HPAI and successful containment. On average, 12 days are needed for on-site staff to recognize illness and initiate reporting.[248-251]

- Expedited bird depopulation can greatly impact HPAI spread.[237, 250]
- During a 2015 HPAI outbreak in Ghana, reporting and subsequent management averaged 12.3 days. Reporting delays resulted in increased culling (94.2% culled across five regions and 35 farms).[251]
- The U.S. 2014-2015 HPAI outbreak observed 70% and 12% of commercial egg-laying hens and young hens culled across 232 farms in 15 states, resulting in the loss of approximately 51 million birds at a cost of $879 million.[249]
- Farm-to-farm horizontal transmission was found to be a major factor in a South Korean review of HPAI outbreaks from 1998-2014, and control and reporting mechanisms had not been effectively implemented.[252]
- Geographic containment zones are established immediately upon HPAI notification per USDA guidance control strategies.[246]

- During the Serbia outbreak (May 2022), strict measures were applied to prevent the spread of the disease through thorough cleaning, disinfection of facilities, and testing of poultry from contact holdings where no new cases of disease or death were recorded.[253]
- Air filtration and quick depopulation improve efficacy of HPAI containment strategies.[254]
- Depopulation or carcass disposal strategies have not been determined for migratory and wild birds, but USDA recommends separating and securing water, food, and other materials in locations difficult for wild birds to access.[255]

What do we need to know?

- What are the current barriers to on-site recognition of illness and initiation of reporting?
- What is the risk of on-site handling procedures during culling and disposal for accidental contamination?
- Would further evaluation of alternative depopulation methods provide[256] time-savings, efficacy, or cost burden benefits?[238]
- What efforts have been exerted to control disease spread from wild birds to domestic species?

Viral Persistence and Environmental Stability – How long does the virus live in the environment?

What do we know?

Avian influenza virus persistence varies based on the environmental matrix and exposure to natural environmental factors (heat, ultraviolet [UV] exposure, salinity, and pH).

- Avian influenza virus can persist in aerosols for 24-36 hours, which is longer than human influenza viruses (6-15 hours).[257, 258-259]
- The persistence of AIVs, which include HPAI, was 30 minutes at 56°C,[260-261] and persistence time has been shown to decrease with higher temperatures. Ultraviolet light exposure for 30 minutes and pH of less than two for 30 minutes have been shown to inactivate H7N9.[260]
- Three Korean H5N1 HPAI viruses [(A/chicken/Korea/ES/03), (A/chicken/Korea/IS/06), and (A/chicken/Korea/Gimje/08)] were used to experimentally study virus survival rates at 4°C, 20°C, and 30°C in PBS. The Gimje/08 strain survived the longest at all temperatures (3213 at 4°C, 293 at 20°C, and 58 days at 30°C). The duration of virus persistence decreased with increasing temperature.[258-259, 262-263]

Avian influenza viruses are extremely stable in water, showing infectivity after several months in cold weather natural wetlands.

- Using a combination of field- and laboratory-based approaches, AIVs (five subtypes) were found to be infectious after at least seven months in Alaskan and Minnesotan wetlands (using filtered surface water samples),[264] suggesting a key source of natural infection in waterfowl.
- LPAIs are most stable in water with basic pH (7.4-8.2), cool temperatures (4-17°C), and low salinity.[265]
- The half-life of several avian influenza strains in distilled water decreased from 7.7 ± 1.5 days at 17°C to 3.8 ± 1.4 days at 28°C.[266]
- Eurasian HPAI H5N1 showed persistence in water similar to several LPAI strains,[267] though HPAI persistence depends on the specific strain.[268] All avian influenza viruses appear more stable in cooler, less acidic water with low salinity.[265, 267]
- Avian influenza viruses are likely more stable in lake sediment than in water.[269]

- The clade 1, genotype Z, HPAI H5N1 viruses (A/Cambodia/ 408008/2005) and (A/chicken/Cambodia/LC1AL/2007) were used to experimentally inoculate artificial simple and complex aquatic biotopes (water, mud, aquatic flora and fauna, mix) with parameters close to those in Cambodia. Infectious virus was only recovered from rainwater four days post-contamination at 25°C. Viral RNA persisted up to 20 days in rainwater, seven days in pond or lake water, and up to 14 days post-contamination in several mud samples. Infectious virus and viral RNA was detected in few cases in the aquatic fauna and flora, especially in bivalves and labyrinth fish.[270]
- The infectivity of 12 IAVs that were isolated from naturally infected ducks were monitored for approximately one year, with each virus tested in distilled water held in the laboratory at 4°C and filtered surface water from four Alaska sites maintained in the field at ambient temperature. A single replicate from two viruses tested remained viable for 361-377 days post-sample collection when maintained in surface waters under ambient temperatures.[271]

HPAI viruses are relatively stable in duck feathers and poultry feces, maintaining infectivity for up to 160 days in experimental trials.

- Experimental inoculation of domestic ducks with two strains of gsGD lineage HPAI H5N1 (Ck/Miya/K11/07 and Ws/Akita/1/08) showed infectivity persistence for ≤160 days in detached feathers (at 4°C), longer than persistence in water (≤30 days) or feces (≤6 days).[272] Virus persistence declined with increasing temperature from 4°C to 20°C.[272]
- Duck feathers either containing or devoid of preen oil were experimentally inoculated with gsGD lineage HPAI H5N1 (A/crow/India/11TI16/2011) and stored at 37°C, 25°C, and 10°C. Samples were tested at regular intervals for percent infectivity and viral load – values were higher in naturally preened duck feathers versus the preen oil deficient controls at both low and high initial concentrations of virus (10^4 EID_{50} and 10^6 EID_{50}). Maximum persistence was observed at 10°C in naturally preened duck feathers spiked with virus at 10^6 EID_{50}.[273]
- In duck feces, LPAI virus infectivity (H4N6 A/Mallard/Wv1732-34/03, H5N1 A/Teal/Wv632/Germany/05, and H6N8 A/Mute Swan/Germany/R2927/07) declined by 90% after two, five, 17, or 62 days on average, and is dependent on temperature (30°C, 20°C, 10°C, and 0°C, respectively).[269]
- Wet or dry chicken feces were experimentally inoculated with 10^6 EID_{50} HPAI H5N1 (A\Ck\Sikkim\151466\2008H5N1) and stored at 42, 37, 24, and 4°C. In both dry and wet feces, the virus survived up to 18 hours at 42°C, 24 hours at 37°C, five days at 24°C, and eight weeks at 4°C.[274]\
- Simulated sunlight significantly reduces the persistence of HPAI (H5N1) on surfaces and in feces.[275]

IAVs can persist for 24-48 hours on non-porous surfaces such as stainless steel and plastic, and for <8-12 hours on cloth, paper, or tissues.[276]

- AIV (Influenza A/Herring gull/Delaware 471/86 (H13N7)) was no longer infectious nine days after experimental inoculation on porous and non-porous surfaces, but infectivity persisted for ≥6 days on latex and feathers; ≥3 days on steel, tile, rubber gumboots, rubber tires, egg shells, and plastic; ≥2 days on wood; ≥1 day on cotton fabric; and ≤1 day on egg trays and polyester fabric.[277]
- The persistence of H9N2 AIV (A/mallard/Jiangxi/39/2011) on the surfaces of plastics was studied under different environmental conditions (various temperatures, humidity, and salinity) using glass and stainless steel for comparison for 1-14 days. Infectivity was lost by approximately 90% in one day and completely lost in three days after the virus was placed on materials.[278]

- H5N1 subtype strains (H5N1-Ky and H5N1-Eg) were infectious on a plastic surface after 10 hours but were inactive by 24 hours. The H5N1-Ky and H5N1-Eg strains were active on the human skin surface after 1.5 hours, but were inactive within three hours.[279]

In poultry litter, HPAI persists longer than LPAI.[280]

- In poultry litter, HPAI (A/Chicken/California/15-004912/2015 (H5N8)) persisted for up to 60 hours at room temperature (21-27°C, litter dependent) and 30-85% relative humidity (litter dependent), while LPAI (A/Chicken/California/2000 (H6N2)) persisted for only 24 hours.[280]

HPAI maintains infectivity in fresh and frozen poultry products, creating a potential importation hazard.

- Outbreaks in domesticated poultry[281] have been linked to imported contaminated carcasses, as imported HPAI can maintain infectivity in fresh[282-283] and frozen poultry products.[281-282]
- H7N9 on raw chicken remained viable at -20°C for nine days, 4°C for seven days, and 25°C for four days; therefore, H7N9 on raw chicken could be a potential source of transmission domestically and internationally.[284]

What do we need to know?

- How long do HPAI strains maintain infectivity in frozen poultry carcasses?

Decontamination – What are effective methods to kill the agent in the environment?

What do we know?

The U.S. Environmental Protection Agency maintains a list of registered chemical compounds for use in disinfection against avian influenza on farm settings, including bleach, alcohol, and quaternary ammonium-based compounds.[285]

- The U.S. Environmental Protection Agency's (EPA's) List M for registered antimicrobial products with label claims against AI: List M: Registered Antimicrobial Products with Label Claims for Avian Influenza | U.S. EPA.[286]

The Animal and Plant Health Inspection Service (APHIS) of the USDA maintains protocols for cleaning and disinfection of facilities affected by HPAI, and decontamination is a crucial component of HPAI response. HPAI-affected farms must undergo cleaning and removal of bulk debris, followed by disinfection by drying and heating (100-120°F for seven days) or wet disinfection with an approved product, and fumigation if needed.[287]

- A Virkon®S and propylene glycol mixture can be used for outdoor disinfection of non-porous surfaces under freezing conditions (e.g., trucks, tractors, equipment, footwear).[288]
- Sodium bisulfate is used to acidify poultry litter, and is largely effective at inactivating LPAI within 36 hours.[280] Acidification (exposure to pH of 1 or pH of 3 for six hours) is known to inactivate low levels of HPAI (H5N1) when suspended in peptone water.[261]
- Soap, detergent, and alkali (Surf Excel®, Life bouy®, and caustic soda) at 0.05% concentration at 28°C was not sufficient in destroying H5N1 virus, but increasing concentrations above 0.1% inactivated the virus after five minutes contact time at 28°C.[261]
- Chemical disinfectants (formalin, iodine crystals, phenol crystals, CID 20, Virkon-S, Zeptin, KEPCIDE 300, and KEPCIDE 400) can inactivate H5N1 at the recommended concentrations at 28°C.[261]
- Burning of contaminated poultry carcasses, litter, and feed in pyres or incinerators is another option for the decontamination and disposal of large amounts of contaminated waste resulting from HPAI outbreaks, if other methods are not feasible.[104, 289]

For facilities that cannot be adequately cleaned and disinfected, a fallowing period (allowing to lie dormant and unoccupied) is required.[287]

- The fallowing period is typically 120 days, but is dependent upon temperature and season.[287] Research comparing two U.S. farms that had been exposed to HPAI H5N2

demonstrated that the farm that immediately depopulated after abnormal mortality was detected was able to begin repopulation 37 days sooner than the farm that began depopulation late after detection of abnormal mortality. The lost profit for the farm with late response was estimated to be 3.3 million U.S. dollars.[290]

- Assessment of duck transportation vehicles and crates during H5N8 outbreaks revealed variable decontamination efficacy, dependent upon initial viral contamination load, cleaning and disinfection protocols, and protocol implementation.[291] It is important to consider that the samples collected were analyzed through rRT-PCR for type A influenza; no information was provided for an infectivity assay.

Various decontamination methods have been evaluated for poultry products to control the spread of AI.

- Cooking eggs to a temperature of 71°C is stated to kill AIVs, while dried egg white requires exposure to 67°C for 15 days to inactivate HPAI and maintain properties of egg products.[292]
- According to USDA, AIVs can be inactivated in egg products and poultry meat by heating processes (e.g., 60°C for 188 seconds for whole eggs, 65°C for 42 seconds for poultry meat).[104] A 4-log decrease in the titer for HPAI H7N7 was observed in cell culture after an exposure of 63°C for 90 sec.[293]
- The guidelines provided by USDA Food Safety and Inspection Service time and temperature for cooking chicken meat to achieve a 7-log reduction of *Salmonella* is also applicable to AIV strains. AIV strains including HPAI were effectively inactivated in chicken meat held at 70 or 73.9°C for less than one second.[294]
- Meat and egg white contaminated with AIV can be treated with E-Beam irradiation at 10.4 kGy and 8.2 kGy to accomplish a 4-log reduction in viability of infectious virus.[295]
- Ultraviolet light emitting diodes (UV-LEDs) have been shown to inactivate IAVs by inhibiting host cell replication and transcription of viral RNA.[296]
- During 2014-2015 outbreak, APHIS found that dry cleaning and heat disinfection of barns was most cost- and time- effective.[297]
- Due to the surface extension of poultry facilities, international and local guidelines suggest that cleaning with clean water and neutral detergents should be followed by antioxidant agents such as disinfectants. [151] It is important to maintain the appropriate times for each period. This method is a viable alternative for virus elimination in poultry facilities where dry disinfection is not available.
- The EPA has reviewed required laboratory testing data to certify disinfectant products registered for use to kill AI.[286]

What do we need to know?

- What are additional cost-effective means of HPAI poultry virus decontamination?
- What are the risks of reinfection given different means of decontamination?

Personal Protective Equipment (PPE) – What PPE is effective and who should be using it?

What do we know?

There is effective PPE for those with potential exposures to HPAI, with the recommended type of PPE dependent on the type of exposure (e.g., poultry workers, laboratory staff, depopulation workers).

- The greatest risk for AIV infection are those who have direct physical contact or close proximity (two meters) to infected birds, contact with contaminated surfaces, or at a live poultry market.[298] In addition to frequent handwashing, PPE must be used when in direct contact with possibly infected birds as well as poultry carcasses, poultry feces or litter, or when entering any premises with diseased or dead poultry.[298]

Recommended PPE for poultry workers includes safety goggles, disposable gloves, boots, a respirator (NIOSH-certified at N95 or higher), apron, disposable head/ hair cover, and disposable fluid-resistant coveralls.[298]

- Respirators should be used in a comprehensive respiratory protection program in accordance with the Occupational Safety and Health Administration (OSHA) Respiratory Protection standard (29 CFR 1910.134) and other requirements. Staff required to wear N95 (or higher) respirators require medical clearance, training, and fit-testing for respirator use.[298]
- Reusable PPE (e.g. rubber boots, rubber apron) should be cleaned until visible dirt is removed, and then disinfected with an EPA-approved disinfectant.[298]
- Poultry workers involved in depopulation should wear full PPE consisting of lightweight, disposable, or heavy-duty rubber work gloves that can be disinfected; disposable outer garments, coveralls, or surgical gowns with long, cuffed sleeves and a sealed apron; disposable shoe covers or boots that can be cleaned and disinfected; safety goggles and disposable head/hair cover; and an N95 or higher respirator.[299]
- To reduce risk of HPAI virus infection, landfill workers having contact with AIV-infected carcasses or potentially infected materials should use appropriate PPE when disposing of poultry carcasses during HPAI outbreaks,[298] including disposable gloves, boots, protective disposable fluid-resistant coveralls, goggles, and a NIOSH-certified respirator (e.g., N95 or higher) when in direct contact with infected birds, poultry carcasses, and/or poultry feces or litter.[298]

Recommended PPE for laboratory workers depends on the purpose of the work, the biosafety level of the laboratory, and the country of operation.

- Laboratory research with HPAI requires development and implementation of a written biosafety plan proportionate to the risk of the select agent (9 CFR §121.12(a)).[300-301]
- Biosafety Level-2 (BSL-2) Laboratories: Laboratories such as veterinary diagnostic laboratories conducting routine screening surveillance on samples collected from wild birds and domestic poultry. In the United States and regions known to be HPAI-free, these are considered low-risk materials, and this work can be conducted in a BSL-2 laboratory. [302] Personnel are required to use disposable gloves, laboratory coat, and eye protection.[301]
- Biosafety Level-3 (BSL-3) Laboratories: In addition to standard BSL-2 practices, the following additional PPE and laboratory practices are used: powered air-purifying respirators, protective suit (e.g., wrap-back disposable gown, protective suit, disposable Tyvek gown), and double disposable gloves. For research with mammalian-transmissible HPAI viruses, disposable sleeves are worn over the gown while working in a biosafety cabinet, as well as shoe coverings (e.g., double disposable shoe coverings; single disposable shoe coverings if worn with footwear dedicated to BSL-3 enhanced laboratory use, or impervious boots or shoes of rubber or other suitable material that can be decontaminated), and protective eyewear.[300-301]
- Biosafety Level-4 (BSL-4) Laboratories: Additional measures beyond the facility requirements for BSL-3 are not needed. The BSL-3 criteria are sufficient for appropriate HPAI biocontainment.[300]
- A cross-contamination event occurred in 2014 at the CDC between LPAI H9N2 (non-select agent) and HPAI H5N1 (select agent) viruses. Because proper biocontainment and PPE procedures were followed, the virus remained contained and no illness or injury occurred.[303]

What do we need to know?

- If HPAI is identified in routine screening, is the BSL-2 PPE enough to prevent infection?

Genomics – How does the disease agent compare to previous strains?

What do we know?

AI viruses are defined by the presence (HPAI) or absence (LPAI) of a polybasic cleavage site in the HA gene.

- LPAI viruses contain HA proteins that can only be cleaved (required for cell entry) by a limited number of enzymes; however, HPAI viruses contain HA that can be cleaved by a broader set of enzymes.[304] The transition from LPAI to HPAI can occur from mutations inserting basic amino acid residues (e.g., arginine, lysine, and histidine) at the HA cleavage site during routine circulation of the virus in natural hosts, and these transitions can be documented by identifying the LPAI ancestors of HPAI strains in phylogenetic studies.[305]
- Between 1959 and 2019, there have been 42 observed transition events from LPAI to HPAI in H5 and H7 AIs.[304] While most led to restricted outbreaks, several, including H5 HPAI, continue to cause outbreaks in poultry.[304]
- Interspecies transmission of HPAI was enhanced through genetic reassortment of H5N8 with a North American avian origin LPAI virus resulting in the generation of H5N2 HPAI virus responsible for the outbreaks in Canada and the United States in 2015.[306]
- Insertion of a polybasic cleavage site found in a human H7N9 infection into an H7N9 LPAI caused high mortality rates in mice, demonstrating the importance of the HA cleavage site in AIV virulence.[307] However, the high mortality of gsGD lineage HPAI H5N8 clade 2.3.4.4b virus in ducks is associated with a number of genome segments, not just HA,[57] and amino acid substitutions in polymerase genes have also been linked to elevated mortality.[56]
- gsGD lineage HPAI H5 clade 2.3.4.4b viruses were initially identified in Europe and were detected in North America in late 2021.[126] These viruses are responsible for the current 2022 HPAI outbreak in the United States.[308]

As with all influenza viruses, evolution of HPAI viruses is rapid, which contributes to the diversity of these viruses.

- The nomenclature for variants is complex and requires continuous revision, considering their rapid development. The H5N1 Evolution Working Group was established in 2007 to develop a unified nomenclature.[309] An influenza clade or group is an additional classification beyond subtypes or lineages. For gsGD lineage HPAI H5, several viral clades have been identified (0 to 9) based on phylogenetic characterization, with respective hierarchical orders denoted using decimals. For example, subclades 2.2 and 2.3 are genetically similar and part of clade 2, and 3rd and 4th order subclades have been identified (e.g., 2.3.2 and 2.3.2.1, respectively) denoting further genetic variation within the subclade 2.3.[310]
- Most of the continuously evolving and circulating gsGD lineage HPAI H5 variants belong to clade 2, according to the WHO. As of 2014, clades 1.1.1, 1.1.2, 2.1.3.2a, 2.2.1, 2.2.1.1a, 2.2.2.1, 2.3.2.1a, 2.3.2.1b, 2.3.2.1c, 2.3.4.2, and 7.2 were in circulation globally.[310] In 2015, three new clades were designated: 2.1.3.2a, 2.2.1, and 2.3.4,[311] the last of which has further diversified resulting in the 2.3.4.4b clade that is circulating in Europe,[123] Asia,[312] Africa,[313] and North America[126] as of December 2022. The Republic of Korea has reported outbreaks of HPAI caused by subtypes of clades 2.5, 2.2, 2.3.2, 2.3.2.1, 2.3.4.4c, d, and e since 2003 with more recent reports of clades 2.3.4.4d and 2.3.4.4b.[314] HPAI H5N1 clade 2.3.2.1c was reported to have caused human infections in Cambodia and infected a chicken in Indonesia.[315-317] Recently, a new reassortant HPAI H5N1 with the HA belonging to clade 2.3.4.4b.2 was reported from China.[318]

Exchange of genetic material among co-circulating AI strains is a primary driver of evolutionary change.

- H5 AIVs (H5N1, H5N2, H5N6, and H5N8) infecting wild birds in China acquired different NA types through reassortment with other strains (H3N2, H6N6, H3N8).[319] These new H5 subtypes showed high mortality in chickens, but variable mortality in mice and ducks.[319]
- HPAI H5 clade 2.3.4.4b reassortant viruses were detected in wild birds in The Republic of Korea in 2022. The PB1, PA, NP, NS, or PB2 genes were from LPAI while the HA, NA, M genes were from HPAI strains. Mutations in the HA gene were detected that are associated with increased binding to human sialic acid receptors.[320] Similarly, sequencing of strains from the Czech Republic showed a high propensity of HPAI H5 to reassort with LPAI strains.[321]
- AI viruses circulating in wild birds have been described as loose "genome constellations" characterized by extensive reassortment, rather than more stable, isolated evolutionary lineages,[322] which, in turn, may facilitate the emergence of new subtypes, suggesting that outbreaks of novel avian influenzas in wild birds may be related to the timing of reassortment events in natural populations.[323]

HPAI strains include variants of H5 and H7;[304] an outbreak of HPAI H5N1 has been detected in U.S. wild birds and commercial poultry since early 2022.[324] While rare, a human case of H5N1 in the United States has been associated with this outbreak.[325] Only four human infections of LPAI H7N9 have ever been identified in the United States.[325]

- In February 2021, seven workers in a Russian poultry farm were confirmed to have acquired HPAI H5N8, though all had mild or asymptomatic illness.[326]
- During the current global 2021-2022 HPAI H5N1 outbreak, there have been fewer than 10 reported cases in humans in close contact with infected birds, but there was no evidence of sustained human-to-human transmission.[118, 327]
- HPAI H7N9 emerged in China in May 2016 from a H7N9 low pathogenic avian (LPAI) strain due to four amino acids (Lys-Arg-Thr-Ala) inserted into the hemagglutinin cleavage site. Within 14 months, 28 human cases were detected with a 50% mortality rate and 60,000 poultry had died of H7N9 infection with 300,000 chickens culled.[328]
- The receptor binding preference could influence the probability of spillover events from avian species to humans. Avian-lineage influenza viruses differ from human-lineage influenza viruses in that they generally prefer to bind different sialic acids on cell surfaces, but adaptations and mutations have been documented in H5N1, H7N2, and H9N2 avian-lineage isolates recovered from humans.[329]
- Mutations to some gene segments (HA) have been associated with increased affinity for human-type receptors as opposed to avian-type receptors. Mutations in other gene segments (PB2, M1) have been shown to enhance replication in mammalian cells.[68, 315, 321, 330]

The global diversity of HPAI viruses is not fully characterized, but the gsGD lineage HPAI H5Nx lineage is known to frequently reassort and have a relatively high evolutionary rate compared to LPAI, resulting in high virus diversification.[117] Emergence of new strains and variants of interest is difficult to predict but might exhibit regular periodicity. Selection pressures, for instance from vaccines, can drive evolutionary change.

- A weak 2-8 year cyclic pattern in the occurrence of influenza subtypes in North American ducks has been observed with high prevalence one year, followed by reduced prevalence the subsequent years.[331]
- Evidence suggests that control measures, primarily in China, aimed at reducing the global spread of gsGD lineage HPAI H5N1 may have facilitated the emergence of novel H5Nx

lineages,[332] which could have been due either to antigenically-distinct H5Nx viruses avoiding immunity from widespread H5N1 vaccines, or stochastic genetic drift after severe H5N1 population bottlenecks allowing for rapid fixation and emergence of H5Nx strains.[332]

- Screening of novel influenza strains for reactivity against banked human serum can indicate if the general population has immunity to the strain; and if no immunity is detected, then the strain poses a greater threat to human health.[333]

What do we need to know?

- What biological factors influence spillover probability?
- What factors lead to LPAI viruses becoming HPAI viruses?
- What fraction of the global genetic diversity of HPAI poses a threat to human and animal health?
- How can we predict which HPAI viruses pose a pandemic threat?
- What conditions favor genomic reassortment between HPAI H5 viruses?[334]

Virus Importation – What are the main routes of entry into the United States? Are there effective mitigation strategies to limit HPAI importation?

What do we know?

Importation occurs via close interactions between wild migratory birds and domestic poultry,[335,336] though other sources may also play a role.

- Northern Mexican poultry farms have experienced HPAI H7N3 outbreaks occurs since 2012, which may be a risk to U.S. poultry.[337]
- HPAI H5N1 outbreaks with novel genetic mutations have recently occurred in farmed American mink, suggesting that both imported and domestic mink farming are potential sources of HPAI importation.[70, 338]
- The 2016-2017 HPAI H5 outbreak was the largest in Europe by both the number of nations and farms, and the diversity of wild birds affected.[339] Phylogenetic analysis revealed two main pathways into Europe.[339]
- Korea appears vulnerable to HPAI outbreaks due to the East Asian-Australasian migratory flyway for waterfowl and the high density of duck farming in locations that overlap with migratory bird habitats.[340]
- During the 2016-2017 HPAI H5N6 epidemic, South Korean researchers found a potential role of sedentary waterfowl as a bridge host in facilitating HPAI transmission between migratory waterfowl species and poultry farms.[130]
- The outbreaks of HPAI on the gamebird industry in Great Britain were explored via risk assessment. Overall, HPAI transmission into gamebird rearing sites was considered low (through hatching egg and day-old chick movement), though there is a paucity of data especially concerning biosecurity measures taken at the gamebird farms.[341]
- During 2005, HPAI H5N1 virus spread rapidly from Central Asia to Eastern Europe through infected ducks, geese, and swans.[342]
- Imported HPAI H5N1 viruses from China significantly contribute to outbreaks in Vietnam.[343]
- In 2014, clade 2.3.4.4 H5N8 HPAI viruses spread across Korea and to China, Japan, Russia, and Europe, and were eventually discovered in wild birds in Canada and the Northwestern United States.[344]
- In West Africa (Burkina Faso), both domestic poultry and hooded vultures were found to harbor HPAI (H5N1). Vultures may be a vector or sentinel for H5N1.[345]

- gsGD lineage HPAI H5 clade 2.3.4.4b viruses are currently circulating in wild birds in the United States.[52] Migration studies indicate that this virus has been imported into the United States across the Atlantic Ocean via Iceland, Greenland/Arctic and/or pelagic routes.[346]
- Modeling suggests that wild bird migration and illegal poultry trade are primary forms of HPAI introduction, and that the legal poultry trade is not a major importation risk.[156]
- There is an extremely low risk that HPAI could be transmitted to domestic poultry from corn or feed contaminated by feces of infected wild migratory birds.[347] Nevertheless, securing poultry food bins and cleaning up wasted or spilled feed is recommended.[348]

HPAI outbreaks are associated with wildfowl migratory seasons.[349]

- Genomic characterization of AIVs is becoming increasingly important to the rapid identification of circulating HPAI viruses.[350]
- In April 2020, two Whooper Swans (*Cygnus cygnus*) and one Swan Goose (*Anser cygnoides*) were found dead at three different locations in Western Mongolia. Analysis of H5N6 isolates indicated that the overlap of three flyways (East Asian-Australian, Central Asian, and East African-West Asian) over Mongolia and Siberia may have played a role in dissemination of H5N6 in Europe and East Asia in 2017-2018.[351]
- Eurasian-origin HPAI H5N1 virus clade 2.3.4.4b was detected in wild waterfowl in Atlantic coastal states in the United States. Bird banding data showed widespread movement of waterfowl within the Atlantic Flyway and between neighboring flyways and northern breeding grounds.[352]

After importation, spread can be rapid, and losses to poultry flocks and the economy can be severe.

- The 2014-2015 HPAI H5 outbreak affected 21 Western and Upper Midwestern States and had a $3.3 billion impact on the economy.[4] It had originated from wild waterfowl in the Pacific Flyway.[4] Later cases were introduced into commercial turkey and laying chicken farms and spread between these commercial enterprises through human activities.[4]
- Upon importation in one African nation (Nigeria, 2006), HPAI spread to seven other countries in three months.[353]
- Commercial avian enterprises must be vigilant regarding potential interactions with infected wildfowl.[349] [130]

What do we need to know?

- Illegal poultry trade is significant for importation and spread of HPAI. How can illegal poultry trade be addressed to reduce the risk of HPAI importation?[343]
- Novel H5N8 and H5N1 reassortment (HPAI) viruses have been detected in Iran and has been identified as a hotspot for virus introduction, dissemination, and generation of new HPAI variants throughout the Middle East.[354] How extensive is the global seeding from this hotspot?

Definitions of Commonly Used Acronyms and Names

Acronym/Term	Definition	Description
AI	Avian Influenza	Disease caused by an avian virus
AIV	Avian Influenza Virus	Virus responsible for causing avian influenza
APHIS	Animal and Plant Health Inspection Service	N/A
AVMA	American Veterinary Medical Association	N/A
BSL	Biosafety Level	N/A
CDC	Centers for Disease Control and Prevention	N/A
Clade	Closely related viruses based on the similarity of their HA genes	Influenza A virus subtypes are based on two proteins on the surface of the virus: hemagglutinin (HA) and neuraminidase (NA). Subtypes are further divided into clades, which are based on the genetic similarity of the HA gene.
d.p.i.	Days Post-Infection	N/A
DHS S&T	U.S. Department of Homeland Security	N/A
EID_{50}	Median egg infectious dose	The dose at which 50% of the inoculated eggs become infected. Used as a standard measure of infectivity.
EPA	U.S. Environmental Protection Agency	N/A
FAO	Food and Agriculture Organization	N/A
FDA	U.S. Food and Drug Administration	N/A
gsGD lineage HPAI	A/Goose/Guangdong/1/96 (GsGd) lineage of HPAI H5 virus	gsGD lineage HPAI circulates in waterfowl and other migratory wild birds as HPAI. This lineage is unique as other HPAI viruses typically emerge from LPAI after replication in a domestic poultry species.
Hemagglutinin (H or HA)	A glycoprotein found on the surface of cells and viral envelopes	Hemagglutinin on the surface of influenza binds to sialic acid to facilitate importation of the virus.
HID_{50}	Median Human Infectious Dose	The dose at which 50% of humans become infected. Used as a standard measure of infectivity.
HPAI	Highly Pathogenic Avian Influenza	Disease caused by a highly pathogenic avian influenza virus
IAV	Influenza A Virus	Virus responsible for causing influenza A
ID_{50}	Median Infectious Dose	The dose necessary to infect 50% of the target population (e.g., birds). Generally, assumes typical, healthy, adult individuals.
ISO	International Organization for Standardization	N/A
LPAI	Low Pathogenicity Avian Influenza	N/A

Acronym/Term	Definition	Description
MQL	Master Question List	N/A
Neuraminidase (N or NA)	An enzyme that cleaves neuraminic acids	Newly replicated viral particles use neuraminidase to cleave sialic on the surface of the host cell, which allows the viral particle to be released from the host cell.
NHP	Non-Human Primate	N/A
NIH	National Institutes of Health	N/A
NIOSH	National Institute for Occupational Safety and Health	N/A
PFU	Plaque Forming Unit	A measure of virus infectivity per unit volume. Infectious virus particles form a plaque in cultured cells.
PPE	Personal Protective Equipment	N/A
R_0	Calculated value for communicable diseases that represents the number of additional animals that one infected animal can further infect	N/A
Reassortant	Strain having genetic material from two or more related strains	Reassortment occurs when individual hosts are infected with multiple related virus strains simultaneously and those strains exchange genetic material; this genetic mixing leads to reassortants, which are the strains that result from such exchange.
R_{env}	Average number of secondary infections from a contaminated environment	N/A
RT-PCR	Real-Time Polymerase Chain Reaction	N/A
$TCID_{50}$	Median Tissue Culture Infectious Dose	The dose necessary to infect 50% of tissue cells. Used as a standard measure of infectivity (e.g., it required 10^3 $TCID_{50}$ to produce clinical signs in exposed chickens).
USDA	U.S. Department of Agriculture	N/A
UV	Ultraviolet	N/A
UV-LED	Ultraviolet Light Emitting Diode	N/A
VSD	Ventilation Shut Down	N/A
WHO	World Health Organization	N/A
WOAH	World Organisation for Animal Health	N/A

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