Update on Seasonal Influenza and Human Infections with Highly Pathogenic Avian Influenza A(H5N1) Virus

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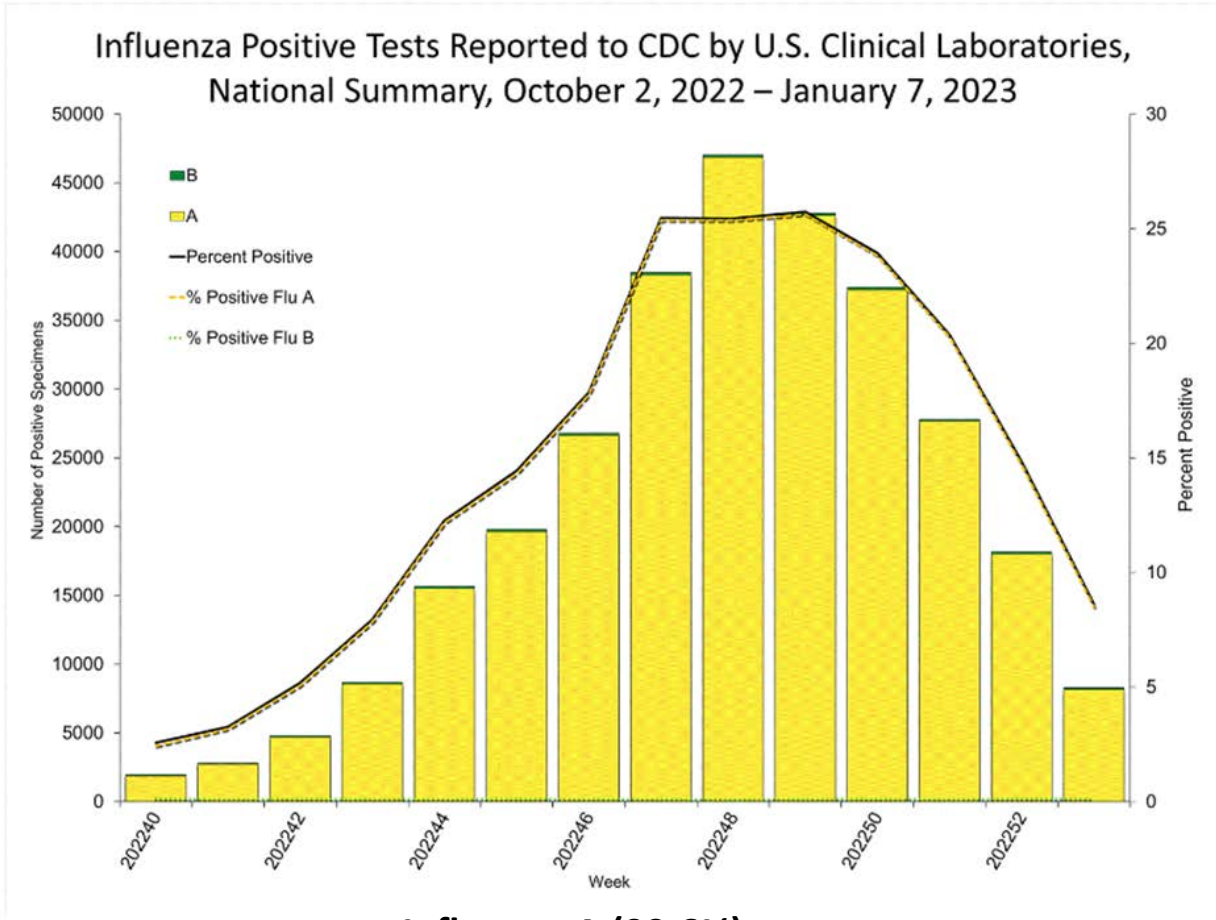
Serious Communicable Diseases Program

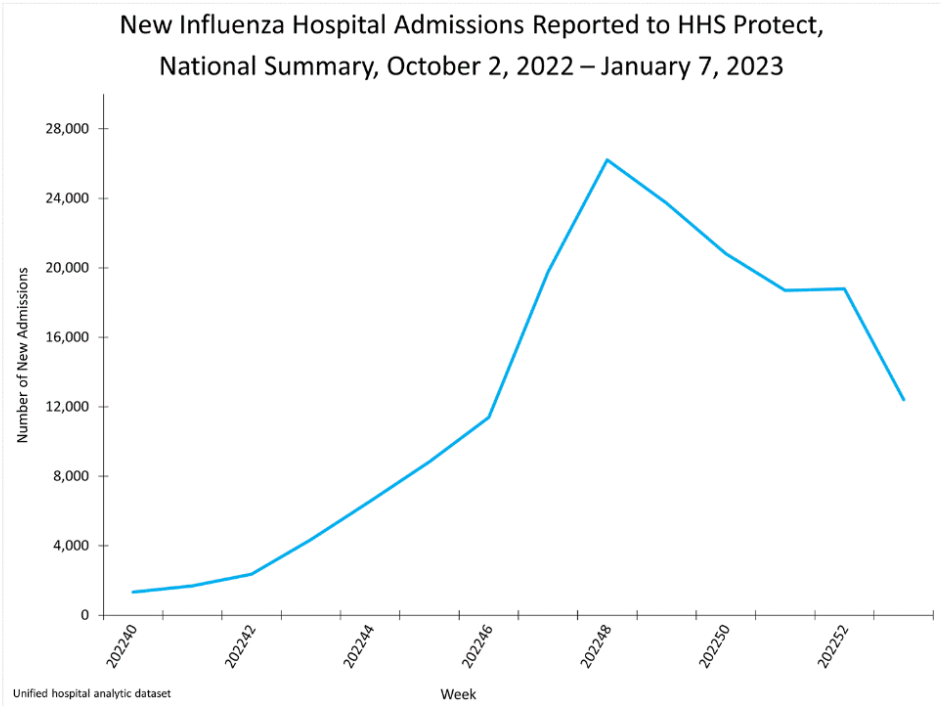
Disclosures

- None

Seasonal Influenza 2022-2023

2022-2023 U.S. Influenza Season



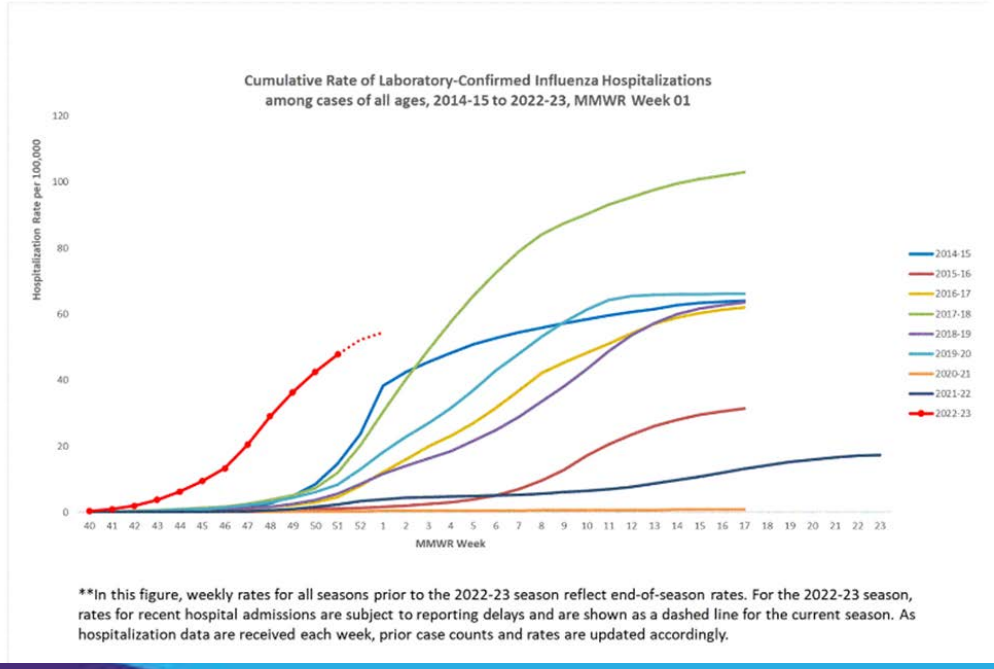


Influenza A (99.6%)

***77% A(H3N2) viruses**

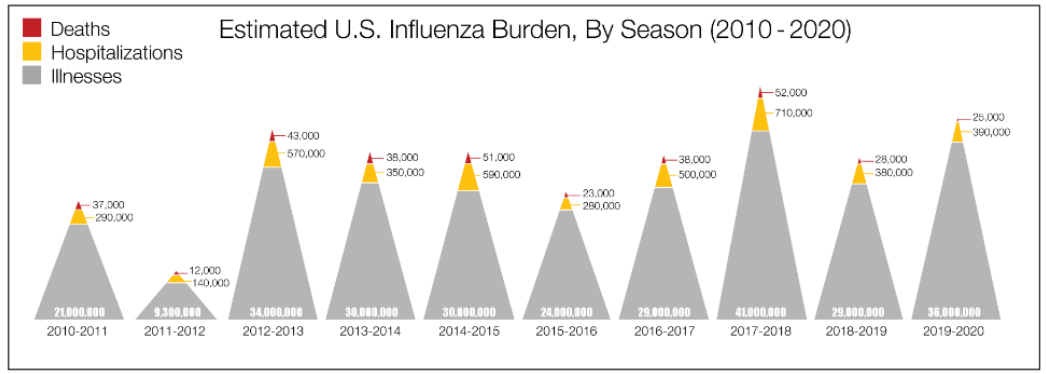
***23% A(H1N1)pdm09 viruses**

Influenza B (0.4%)



https://www.cdc.gov/flu/weekly/index.htm

Preliminary In-Season Burden Estimates, 2022-2023



CDC estimates* that, from **October 1, 2022** through **January 7, 2023**, there have been:

24 – 47 million
flu **illnesses**

11 – 23 million
flu **medical visits**

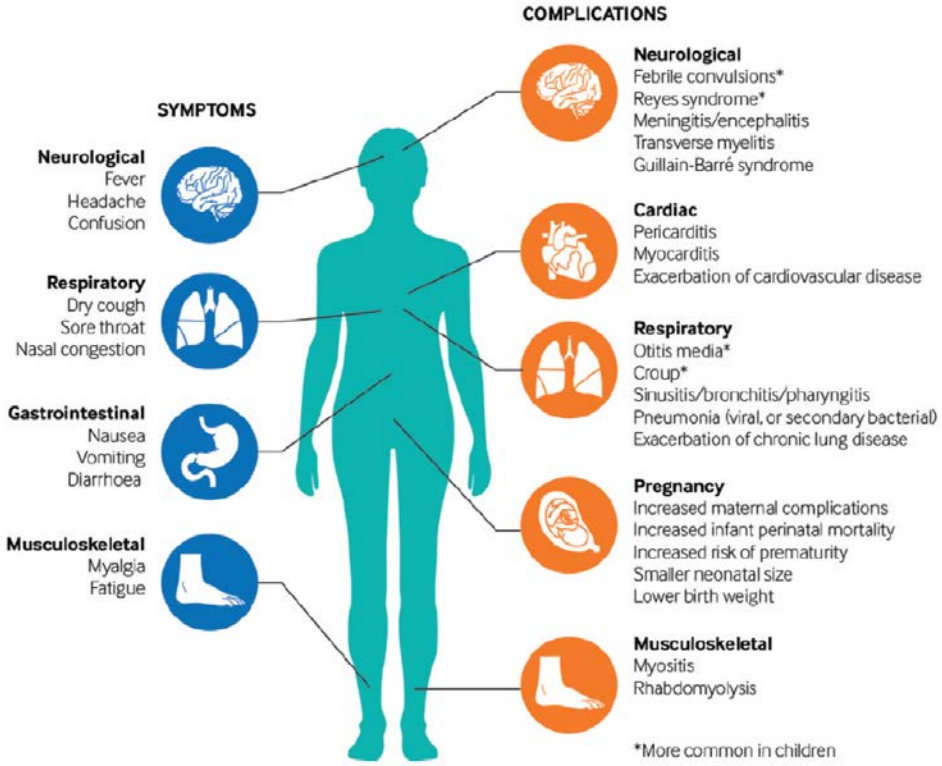
260,000 – 560,000
flu **hospitalizations**

16,000 – 48,000
flu **deaths**

https://www.cdc.gov/flu/about/burden/preliminary-in-season-estimates.htm

Influenza Complications

- **Moderate Illness**:
  - Otitis media in young children, sinusitis
  - Exacerbation of chronic disease
- **Severe to Critical Illness:**
  - **Exacerbation of chronic disease**
  - **Respiratory:** viral pneumonia, croup, status asthmaticus, bronchiolitis, tracheitis, ARDS
  - **Cardiac:** myocarditis, pericarditis, myocardial infarction
  - **Neurologic:** encephalopathy & encephalitis, cerebrovascular accident, Guillain-Barre syndrome (GBS), Acute Disseminated Encephalomyelitis (ADEM), Reye syndrome
  - **Bacterial co-infection:** invasive bacterial infection (e.g. community-acquired pneumonia)
    - *Staphylococcus aureus* (MSSA, MRSA), *Streptococcus pneumoniae*, Group A *Strept*
  - **Musculoskeletal:** myositis, rhabdomyolysis
  - **Multi-organ failure** (respiratory, renal failure, septic shock)
  - **Healthcare-associated infections** (e.g. bacterial or fungal ventilator-associated pneumonia)



Ghebrehewet BMJ 2016

Groups at Increased Risk for Influenza Complications and Severe Illness

- **Children aged <2 years and adults aged ≥65 years**
- **Persons with chronic medical conditions**, including pulmonary (including asthma) or cardiovascular (excluding isolated hypertension), renal, hepatic, neurologic (including persons who have had a stroke) and neurodevelopmental, hematologic, metabolic or endocrine disorders (including diabetes mellitus)
- **Persons who are immunocompromised**
- **Persons with extreme obesity (BMI ≥40)**
- **Children and adolescents who are receiving aspirin-or salicylate-containing medications** (who might be at risk for Reye syndrome after influenza virus infection)
- **Residents of nursing homes and other long-term care facilities**
- **Pregnant persons and people up to 2 weeks postpartum**
- **People from certain racial and ethnic minority groups, including non-Hispanic Black, Hispanic or Latino, and American Indian or Alaska Native persons**

https://www.cdc.gov/flu/highrisk/index.htm

SARS-CoV-2 and Influenza Virus Co-infection Can Cause Severe Disease

- U.K. study from January 20-April 25, 2020 (N = 19,256)
  - **SARS-CoV-2 and influenza virus co-infection** (n = 58) **was associated with 2 times higher odds of ICU admission** (adjusted OR, 2.08;95%CI, 1.17-3.70) **or death** (adjusted OR, 2.27; 95% CI, 1.23-4.19) **compared with SARS-CoV-2 infection alone**
- U.K. study of hospitalized COVID-19 patients (Feb. 2020-Dec. 2021)
  - N=212,446 adults; n=6,965 had other respiratory virus testing results
    - 8.4% had respiratory viral co-infections; Influenza virus: 227; RSV: 220; Adenoviruses: 136
    - **SARS-CoV-2 and influenza virus co-infection was associated with 4 times higher odds of invasive mechanical ventilation** (weighted OR: 4.14,2.00-8.49; p<0.0001) **versus SARS-CoV-2 infection alone** (RSV, Adenoviruses: not significant)
    - **SARS-CoV-2 and influenza virus co-infection was significantly associated with 2.35 times the odds of in-hospital mortality** (weighted OR: 2.35, 1.07-5.12; p<0.031) **versus SARS-CoV-2 infection alone**
- U.S. Study of hospitalized pediatric influenza patients (2021-2022)
  - N=525 children; 32 (6%) with SARS-CoV-2 and influenza virus co-infection
    - **SARS-CoV-2 and influenza virus co-infected patients had significantly higher frequency of invasive mechanical ventilation** (13% versus 4%, p=0.03) **and non-invasive ventilation** (16% versus 6%, p=0.05) **versus influenza alone**

Stowe Int J Epidemiology 2021; Swets Lancet 2022; Adams MMWR 2022

Influenza Diagnostic Tests*

Test	Method	Time to Results	Performance	Notes†
Rapid diagnostic test	Antigen detection	10 min	Low to moderate sensitivity; high specificity	Negative results may not rule out influenza; most assays are approved for point-of-care use; multiplex assays can identify and distinguish among influenza A, influenza B, and SARS-CoV-2
Rapid molecular assay	Viral RNA detection	15–30 min	Moderately high to high sensitivity; high specificity	Negative results may not rule out influenza; some assays are approved for point-of-care use; multiplex assays can identify and distinguish among influenza A, influenza B, and SARS-CoV-2
Immunofluorescence assay	Antigen detection	2–4 h	Moderate sensitivity; high specificity	Negative results may not rule out influenza; requires trained laboratory personnel with fluorescent microscope in a clinical laboratory
Molecular assay	Viral RNA detection	60–80 min for some assays; up to 4–6 h for others	High sensitivity; high specificity	Negative results may not rule out influenza; multiplex assays can identify and distinguish among influenza A, influenza B, and SARS-CoV-2
Tissue cell virus culture	Virus isolation	3–10 d	Generally high sensitivity (can vary by virus); high specificity	Negative results may not rule out influenza

** Respiratory tract specimens should be collected as close to illness onset as possible for testing. Serologic testing requires paired acute and convalescent sera and is not recommended except for public health investigations and research. Updated information and guidance on the use of influenza diagnostic tests and interpretation of results are available at www.cdc.gov/flu/professionals/diagnosis/index.htm.*

† These tests are FDA-cleared or are available through FDA EUAs for high- or moderate-complexity clinical laboratories or point-of-care use, including by Clinical Laboratory Improvement Amendments waiver.

Uyeki Annals of Int Med 2021

Multiplex Assays for Influenza Viruses and SARS-CoV-2

- **Multiplex Antigen Detection Assays**
  - **Assays that can detect Influenza A and B and SARS-CoV-2 antigens simultaneously in respiratory specimens have received FDA Emergency Use Authorization (EUA)**
    - **Results in 15 minutes**
    - **High complexity, moderate complexity, CLIA-waived**

- **Multiplex Nucleic Acid Detection Assays**
  - **Assays that can detect Influenza A and B and SARS-CoV-2 nucleic acids simultaneously in respiratory specimens have received FDA EUA or De Novo 510(k) clearance or premarket approval (PMA)**
    - **Variable turnaround time to results (20 minutes to 8 hours)**
    - **High complexity, moderate complexity, CLIA-waived**

https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/vitro-diagnostics-euas#individual-molecular;
https://www.cdc.gov/flu/professionals/diagnosis/table-flu-covid19-detection.html

Recommended Antivirals for Treatment of Influenza, 2022-2023

Four FDA-approved antivirals are recommended:

- **All have demonstrated efficacy and are FDA-approved for early treatment (<2 days of illness onset) in outpatients with uncomplicated influenza**
- **Neuraminidase inhibitors (NAIs):**
  - **Oseltamivir** (oral, twice daily x 5 days)
  - **Zanamivir** (inhaled, twice daily x 5 days) [investigational IV zanamivir is not available in the U.S.]
  - **Peramivir** (intravenous: single dose)
- **Cap-dependent endonuclease inhibitor: Baloxavir marboxil** (oral: single dose)

Antiviral Drug	Route of Administration	Recommended Ages for Treatment
Oseltamivir	Oral (twice daily x 5d)	All ages
Zanamivir	Inhaled (twice daily x 5d)	≥7 years
Peramivir	Intravenous (single infusion)	≥6 months
Baloxavir	Oral (single dose)	≥5 years (otherwise healthy) ≥12 years (high-risk)

https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

CDC Antiviral Treatment Recommendations

- **Focused on prompt treatment of persons with severe disease and those at increased risk of influenza complications**
- **Antiviral treatment is *recommended as soon as possible*** for **any patient with confirmed or suspected influenza who is:**
  - **Hospitalized** (without waiting for testing results)
    - **Oseltamivir**
  - **Outpatients with complicated or progressive illness of any duration**
    - **Oseltamivir**
  - **Outpatients who are at high risk for influenza complications**
    - **Oseltamivir, Baloxavir, Zanamivir, Peramivir**
- Antiviral treatment can be considered for any previously healthy, non-high-risk outpatient with confirmed or suspected influenza (e.g. with influenza-like illness) on the basis of clinical judgment, if treatment can be initiated within 48 hours of illness onset; including empiric treatment (e.g. in-person visit or via telemedicine)

https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

Human Infections with Highly Pathogenic Avian Influenza A(H5N1) Virus

Human Infections with Highly Pathogenic Avian Influenza A(H5N1) Virus

- First infections identified in Hong Kong, 1997 (18 cases, 6 deaths)
- Re-emergence in humans: 2003-2005 (Southeast Asia)
- Sporadic cases of avian-to-human transmission, rare human-to-human spread
- 2003-2023: 868 cases, 457 deaths (53%) reported from 21 countries*
- 2022: H5N1 virus detected in respiratory specimens
  - 1 worker involved in culling poultry (fatigue), U.S.
  - 2 poultry workers (asymptomatic), Spain
  - 1 person with poultry exposure (fatal), China
  - A(H5) virus detected in 1 child with poultry exposure (critically ill), Vietnam
- 2023: H5N1 virus detected in a child (critically ill), Ecuador

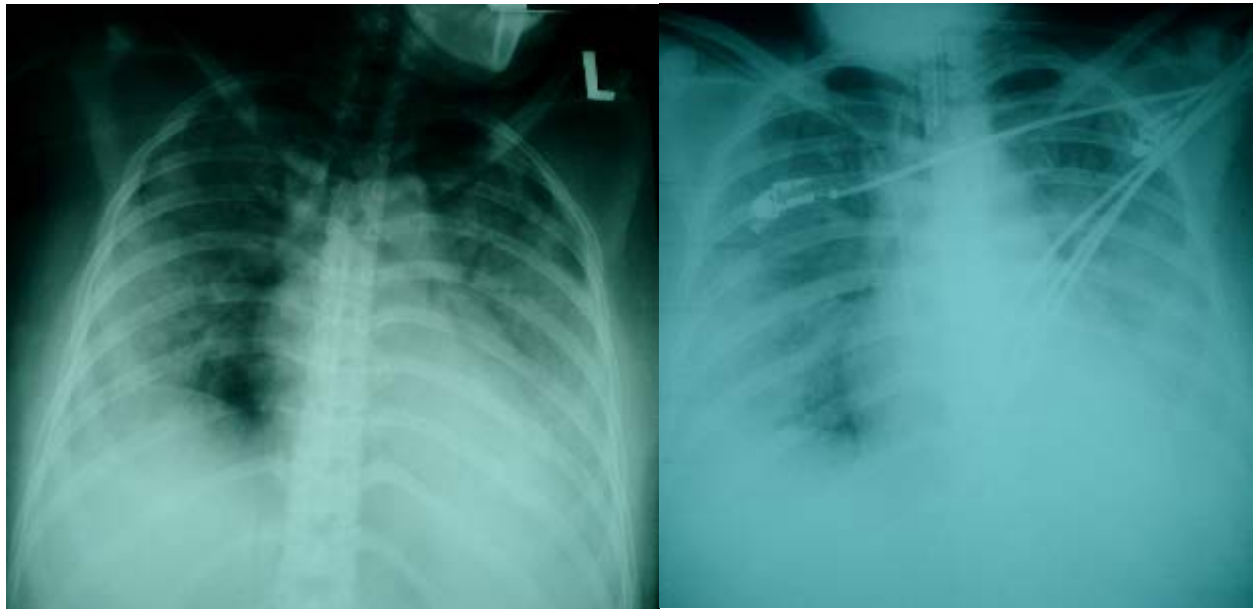
*https://cdn.who.int/media/docs/default-source/influenza/human-animal-interface-risk-assessments/cumulative-number-of--confirmed-human-cases-for-avian-influenza-a(h5n1)-reported-to-who--2003-2023.pdf?sfvrsn=c6600b55_1&download=true

Human Infections with Highly Pathogenic Avian Influenza A(H5N1) Virus

- **Risk factors:**
  - **Direct/close exposure to sick/dead infected poultry, visiting a live poultry market**
  - **Prolonged, unprotected, close exposure to a symptomatic case**
- **Clinical features (a few asymptomatic infections reported)**
  - **Upper respiratory tract illness, pneumonia, respiratory failure, sepsis, ARDS, and multi-organ failure with high mortality**
  - **Rare complications: encephalitis, encephalitis with obstructive hydrocephalus**
- **Clinical management:**
  - **Antiviral treatment (oseltamivir), avoid high-dose corticosteroids**
  - **Supportive care, advanced organ support**
  - **IPC: Airborne Isolation room (negative pressure), contact and airborne precautions**

Uyeki and Peiris Infect Dis Clinics N America 2019

CXRs of H5N1 Patients Indonesia, September 2005



37-year old woman
Illness day #7
Admission CXR

Illness day #10;
died day #11

21-year old male
Illness day #5
Admission

Illness day #12
Not ventilated
Fully recovered

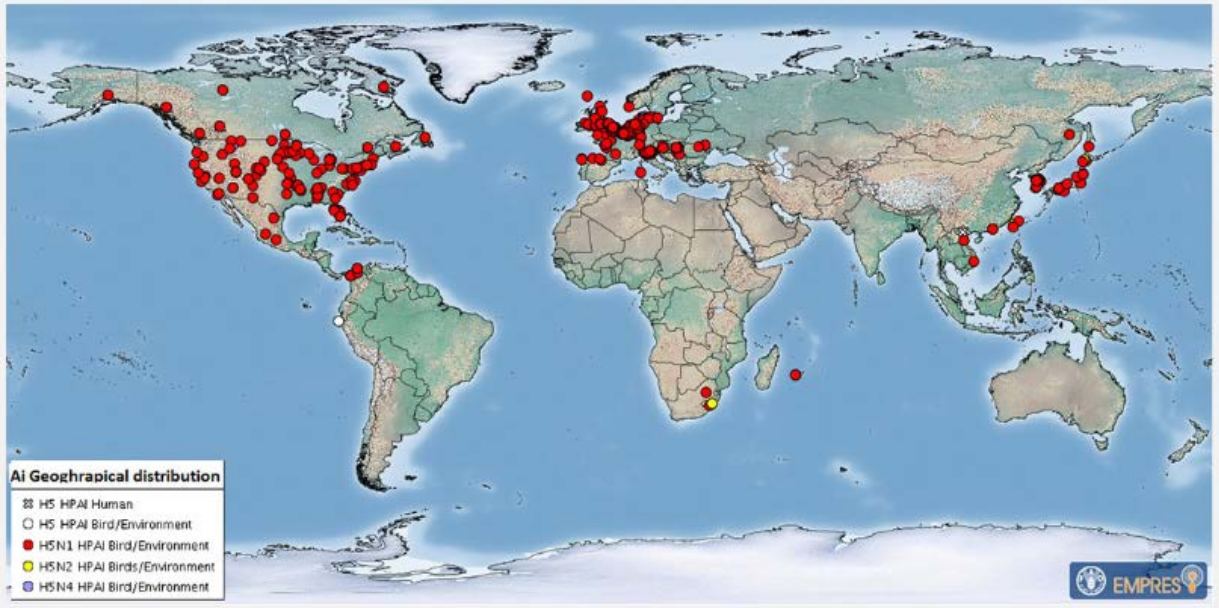
T Uyeki CDC

Human Infections with Highly Pathogenic Avian Influenza A(H5N1) Virus

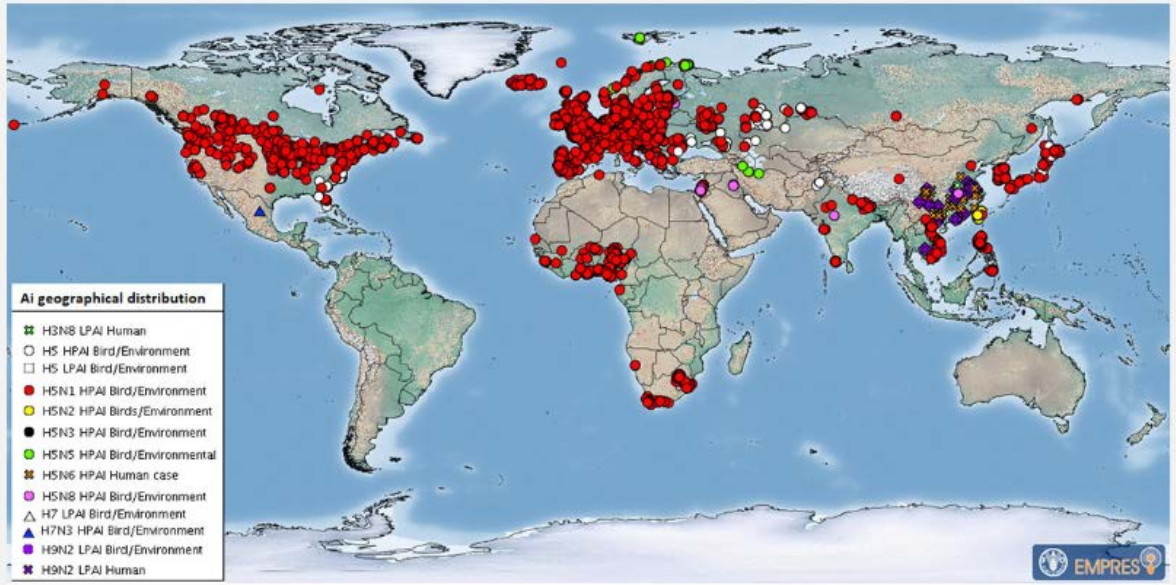
- **H5N1 virus evolution:**
  - **Since 1997, H5N1 viruses have continued to evolve into clades and subclades**
    - **Since 2020, highly pathogenic avian influenza (HPAI) A(H5N1) clade 2.3.4.4b viruses have spread via migratory birds in Africa, Asia, and Europe**
    - **Late 2021-2022, spread to North America: poultry outbreaks, wild bird detections (hawks, eagles, owls, vultures, raven, crows, geese, ducks, grebes, pelicans, swans, shovelers, teal, cormorants, kestrels, gulls, others)**
    - **Late 2022: spread to South America**
  - **Transmission to mammals**
    - **Terrestrial mammals (red fox, raccoon dog, coyote, otter, badger, polecat, ferret, mink, lynx, bobcat, fisher cat, amur leopard, raccoon, skunk, black bear, brown bear, grizzly bear, opossum)**
    - **Marine mammals (seals, porpoise, dolphin)**

Recent Spread of Highly Pathogenic Avian Influenza A(H5N1) Virus in Birds

Map 1. *Global distribution of AIV with zoonotic potential* observed since 1 October 2022 (i.e. current wave)*



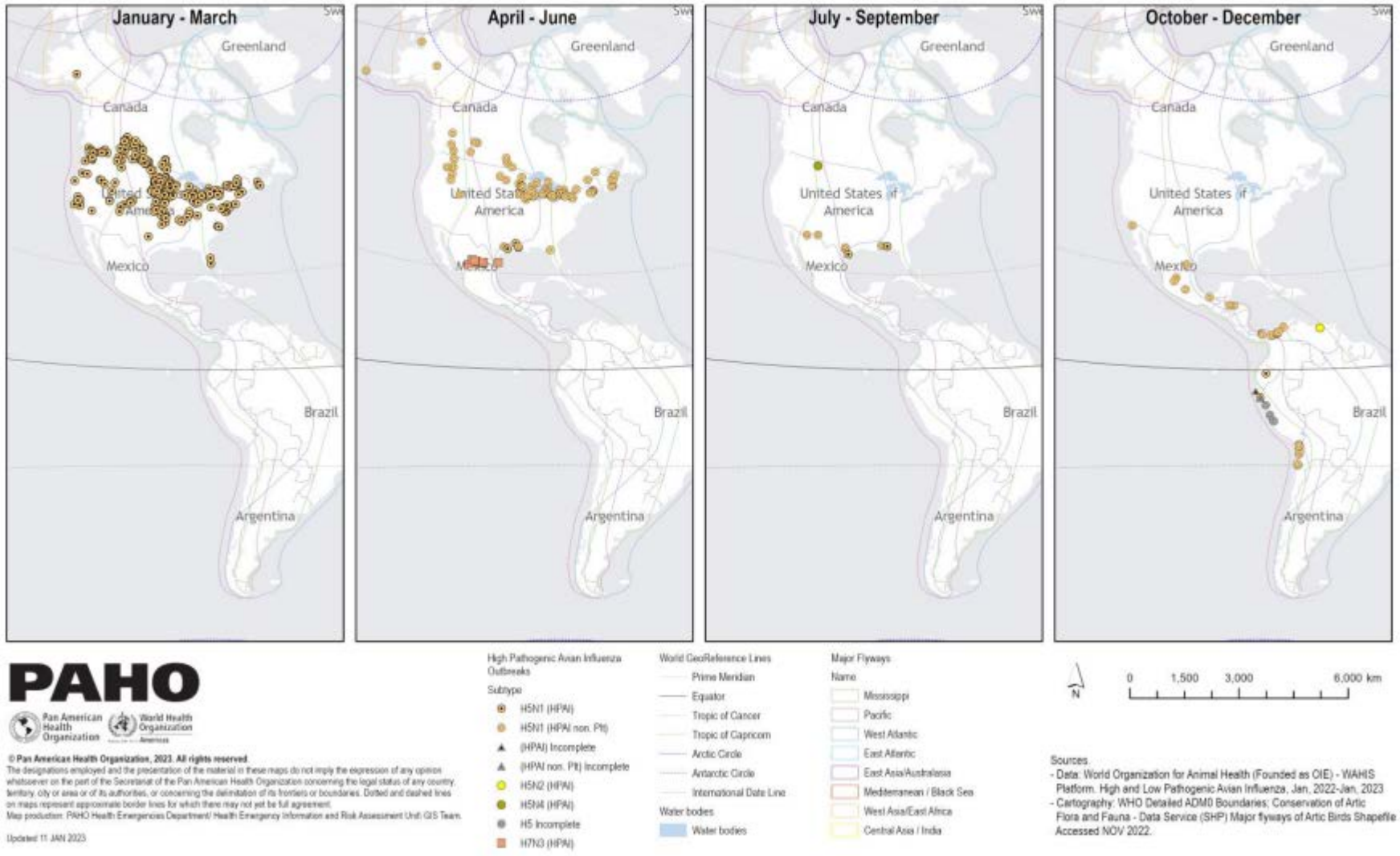
Map 2. *Global distribution of AIV with zoonotic potential* observed in the period 1 October 2021 to 30 September 2022 (i.e. previous wave)*



https://www.fao.org/animal-health/situation-updates/global-aiv-with-zoonotic-potential/en

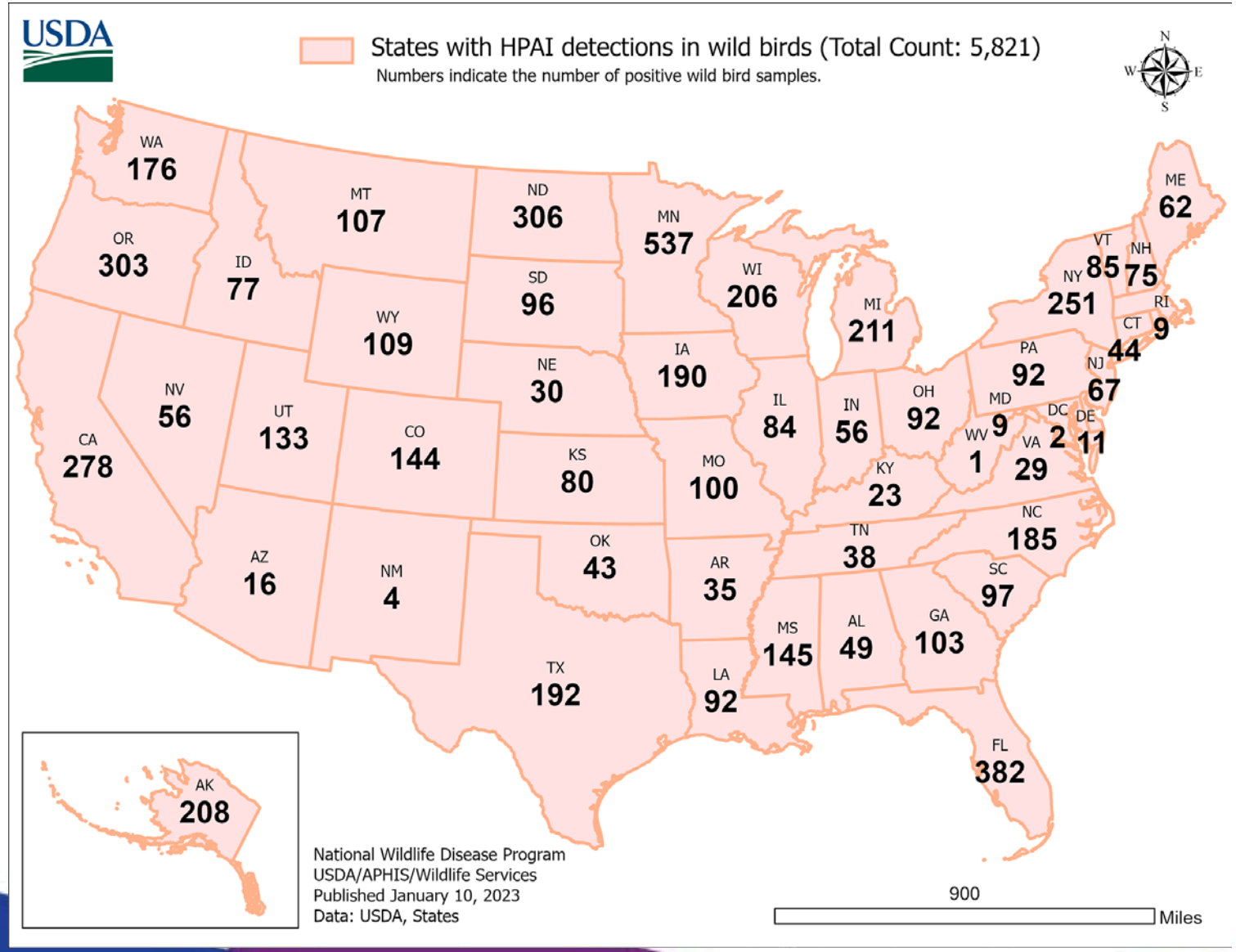
Spread of Highly Pathogenic Avian Influenza A(H5N1) Virus in Birds in the Americas, 2022-2023

Figure 1. Avian influenza outbreaks and main migratory routes of wild birds. Region of the Americas, as of EW 1 of 2023.



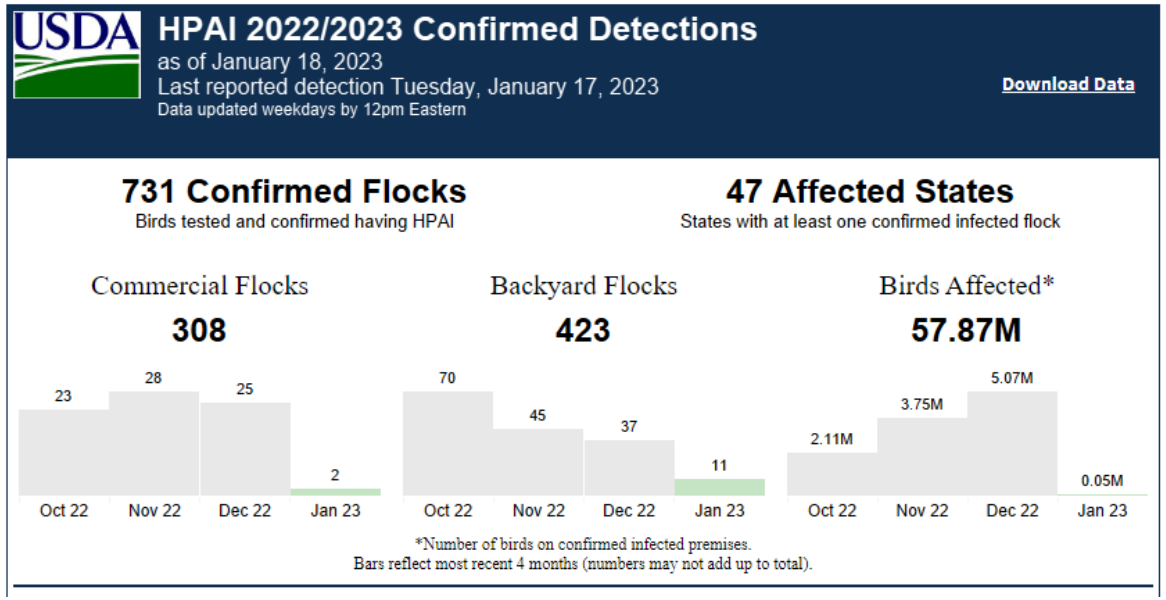
https://www.paho.org/en/documents/epidemiological-update-outbreaks-avian-influenza-and-public-health-implications-region-0

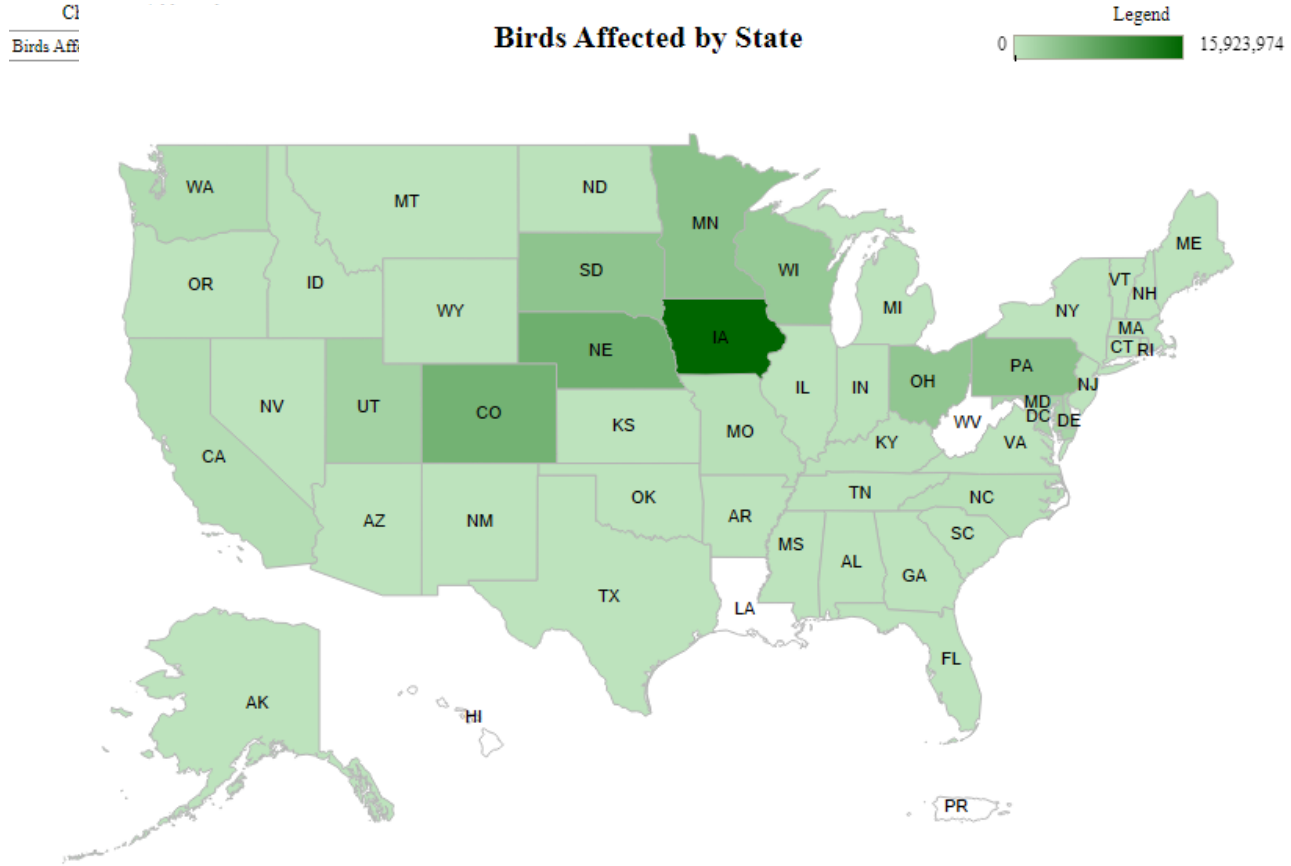
Highly Pathogenic Avian Influenza A(H5N1) Virus Detections in Wild Birds, U.S. January 2022-January 2023



https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/animal-disease-information/avian/avian-influenza/hpai-2022/2022-hpai-wild-birds

Highly Pathogenic Avian Influenza A(H5N1) Virus Detections in Commercial Poultry and Backyard Flocks, U.S. January 2022-January 2023





https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/animal-disease-information/avian/avian-influenza/hpai-2022/2022-hpai-commercial-backyard-flocks

Summary

- Influenza activity has declined nationally recently but seasonal influenza viruses are expected to continue to circulate for weeks
  - Influenza A(H3N2) viruses have predominated with some A(H1N1)pdm09 virus circulation, with very little influenza B virus circulation to date
- Influenza testing can help inform clinical decisions; multiplex assays are available that detect influenza A/B viruses and SARS-CoV-2
- Prompt antiviral treatment is recommended for outpatients at high-risk for influenza complications, and oseltamivir is recommended as soon as possible for hospitalized patients with suspected/confirmed influenza
- Highly pathogenic avian influenza AH5N1) viruses have caused poultry outbreaks and infections in wild birds and mammals in the U.S. and worldwide
- The overall risk to public health is low, but a small number of sporadic human infections with highly pathogenic avian influenza A(H5N1) virus resulting from poultry exposures have occurred to cause a wide range of disease severity

References

CDC. Weekly U.S. Influenza Surveillance Report. https://www.cdc.gov/flu/weekly/index.htm

CDC. Information for Clinicians on Influenza Virus Testing. https://www.cdc.gov/flu/professionals/diagnosis/index.htm

CDC. Influenza Antiviral Medications: Summary for Clinicians. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

USDA. 2022-2023 Detections of Highly Pathogenic Avian Influenza. https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/animal-disease-information/avian/avian-influenza/2022-hpai

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World Health Organization. Assessment of risk associated with recent influenza A(H5N1) clade 2.3.4.4b viruses. https://www.who.int/publications/m/item/assessment-of-risk-associated-with-recent-influenza-a(h5n1)-clade-2.3.4.4b-viruses