Clinician Update on Human Cases of H5N1 and Influenza A Virus Surveillance

Clinician Outreach and Communication Activity (COCA) Call

Tuesday, May 6, 2025

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- Instructions for how to earn continuing education will be provided at the end of the call.

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- Content will not include any discussion of the unlabeled use of a product or a product under investigational use, with the exception of Dr. Tim Uyeki's discussion of the use of FDA-approved antivirals for treatment of influenza in outpatients, use in hospitalized patients, and higher dosing for treatment and post-exposure prophylaxis.
- CDC did not accept financial or in-kind support from ineligible companies for this continuing education activity.

Objectives

At the conclusion of today's session, the participant will be able to accomplish the following:

1. Provide an update on human infections with avian influenza A(H5N1) viruses in the United States.
2. Discuss CDC's surveillance and monitoring efforts for avian influenza A(H5N1) virus infections in people.
3. Outline the public health implications of avian influenza A(H5N1) virus in animals and the importance of early detection of human infections and control measures.
4. Describe expectations for summertime influenza surveillance activities in the United States, including collecting and testing recommended clinical specimens for influenza viruses, subtyping influenza A positive specimens, and submitting influenza A(H5) positive specimens to CDC.

To Ask a Question

- Using the Zoom Webinar System
  - Click on the “Q&A” button
  - Type your question in the “Q&A” box
  - Submit your question

- If you are a patient, please refer your question to your healthcare provider.

- If you are a member of the media, please direct your questions to CDC Media Relations at 404-639-3286 or email media@cdc.gov.

Today's Presenters

- **Tim Uyeki, MD, MPH, MPP**
  Chief Medical Officer
  Influenza Division
  National Center for Immunization and Respiratory Diseases
  Centers for Disease Control and Prevention

- **Alicia Budd, MPH**
  Team Lead, National Surveillance and Outbreak Response Team
  Epidemiology and Prevention Branch
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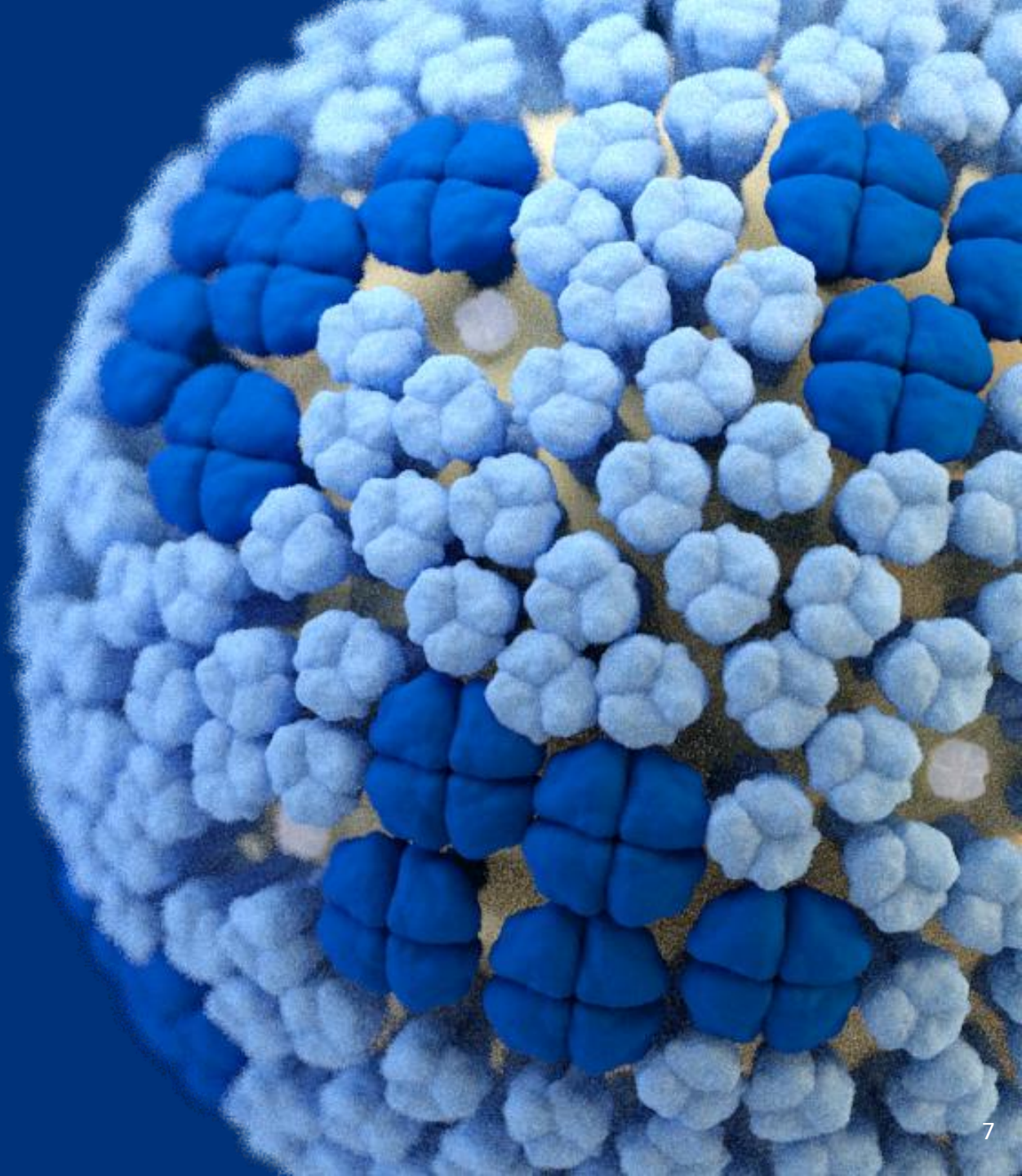
  Centers for Disease Control and Prevention

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

Tim Uyeki, MD, MPH, MPP
Chief Medical Officer, Influenza Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

May 6, 2025

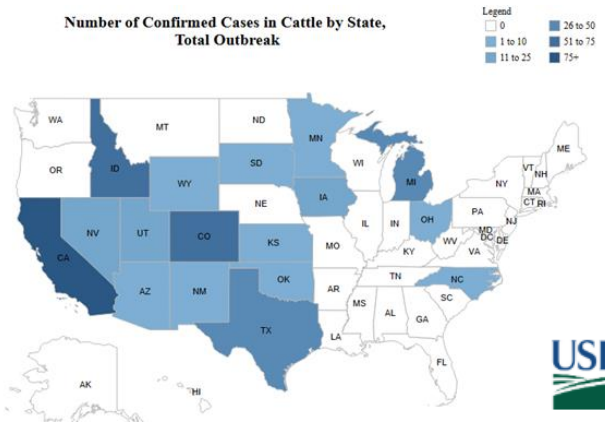


Overview of Highly Pathogenic Avian Influenza (HPAI) A(H5N1) Viruses

- Avian influenza A viruses circulate among wild waterfowl and other wild birds
  - Infect respiratory and gastrointestinal tracts of birds
  - Evolve through exchange of genes (genetic reassortment) and genetic mutations
  - Classified by pathogenicity (based on specific molecular and pathogenic characteristics)
    - Highly pathogenic (HPAI) or Low pathogenic (LPAI) avian influenza A viruses
      - Further classified into virus clades, and subclassified into genotypes
- **HPAI A(H5N1) virus**
  - High mortality in infected poultry
  - Endemic (enzootic) circulation in some countries
  - Spillover to terrestrial (wild, domesticated, farmed) and marine mammals

Overview of Highly Pathogenic Avian Influenza (HPAI) A(H5N1) Virus

- Clade 2.3.4.4b viruses emerged in 2020 in wild birds
  - Unprecedented wide global spread
    - Many bird species infected, poultry outbreaks
    - Many terrestrial and marine mammals infected
  - Detected in wild birds in North America (end of 2021)
  - U.S. poultry outbreaks, wild bird detections since 2022 (ongoing)
    - **>169 million commercial poultry/backyard birds affected (50 states/1 territory)**
    - Wild birds (50 states or territories)
    - Since 2024: **1049 dairy cattle herds (17 states)**



USDA Animal and Plant Health Inspection Service
U.S. DEPARTMENT OF AGRICULTURE

Clade 2.3.4.4b HPAI A(H5N1) Viruses in Dairy Cattle

- **2023-2025: Clade 2.3.4.4b H5N1 viruses in dairy cattle (U.S.)**
  - At least 3 independent introductions from wild birds to dairy cattle
    - Genotypes B3.13 (most prevalent), D1.1
  - Dairy cattle farm-to-dairy cattle farm
  - Dairy cattle farm-to-poultry farm spread
- **Very high levels of H5N1 virus detected in raw cow milk**
  - Experimental Studies:
    - Aerosol inoculation: mild illness; intramammary inoculation: virus isolated for 2 weeks

  ➢**Inactivated by pasteurization; viral RNA can be detected**

  - Viral RNA detectable in raw milk products (e.g., cheese)
    - Detection of viable virus in raw milk cheese reported up to 60 days of aging (preprint)

Burrough et al., Emerg Infect Dis 2024; Spackman et al., J Virology 2024; Spackman et al., J Food Prot 2024; Nooruzzaman et al., Nat Commun 2025; Nooruzzaman et al., bioRxiv March 14, 2025; Halwe et al., Nature 2025; Baker et al., Nature 2025; Nguyen et al., Science April 25, 2025

HPAI in Livestock | Animal and Plant Health Inspection Service (usda.gov)

CDC Recommendations on Raw Milk

- Pasteurization kills A(H5N1) viruses and pasteurized milk is safe to drink.
- People should not drink raw milk or consume products made from raw milk.
- In response to anecdotal reports:
  - CDC recommends against consuming raw milk contaminated with live A(H5N1) virus as a way to develop antibodies against A(H5N1) virus to protect against future disease.

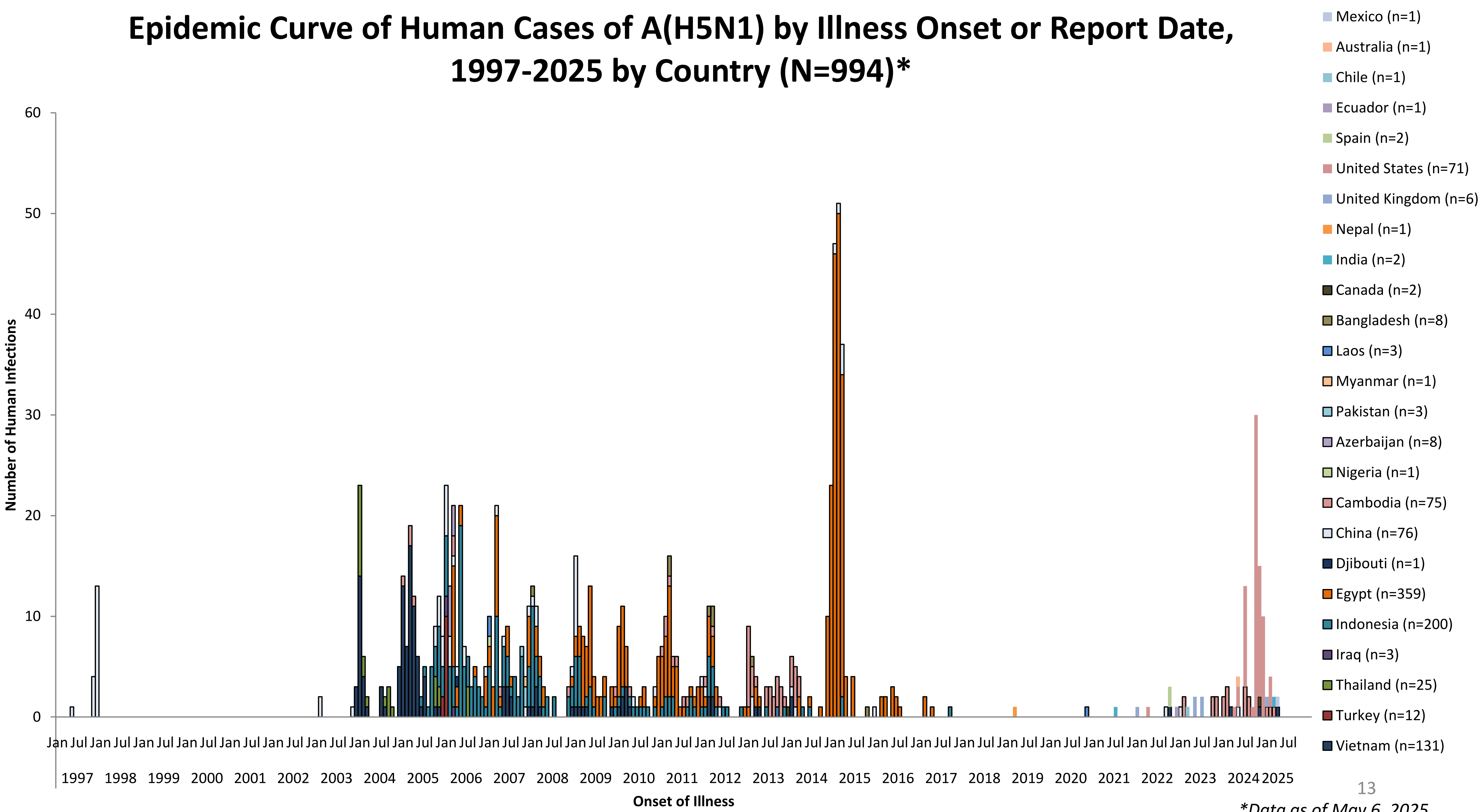
https://www.cdc.gov/food-safety/foods/raw-milk.html

Human Infections with HPAI A(H5N1) Viruses

- **HPAI A(H5N1) viruses lack ability to bind well to receptors most prevalent in the human upper respiratory tract**
  - **HPAI A(H5N1) viruses bind preferentially to receptors most prevalent in the human lower respiratory tract (also found on conjunctivae)**
- First human infections identified in 1997 (Hong Kong)
  - 18 cases, 6 deaths (median age: 17 years (range 1-60)
- 1997 to date: **994 sporadic human cases reported @50% mortality (25 countries)***
  - **Most surveillance worldwide is hospital-based (focused on severe pneumonia)**
  - A(H5N1) cases in 2025 (n=10)
    - Cambodia: 3 cases (3 deaths)
    - India: 1 case (1 death)
    - Mexico: 1 case (1 death)
    - U.K.: 1 case
    - U.S.: 3 cases
    - Vietnam: 1 case

*Data as of May 6, 2025

Epidemic Curve of Human Cases of A(H5N1) by Illness Onset or Report Date, 1997-2025 by Country (N=994)*



Data as of May 6, 2025

Influenza A(H5N1) Cases 2024-2025, United States*

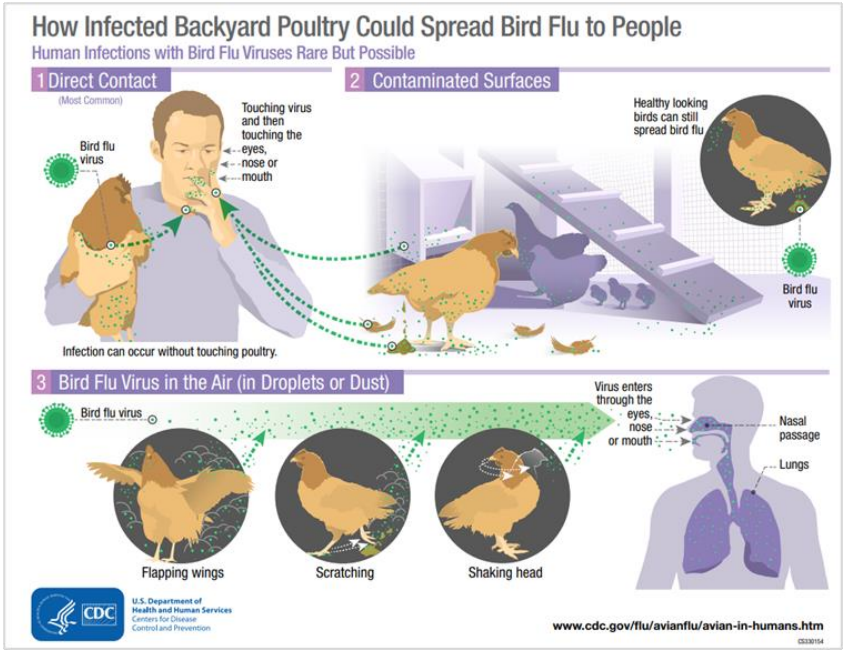
- **70 confirmed A(H5N1) cases, 13 states**
  - **41 cases associated with dairy cow exposures**
    - 5 states: mild illness: conjunctivitis, acute respiratory illness
  - **24 cases associated with commercial poultry exposures**
    - 6 states: mostly mild illness: conjunctivitis, acute respiratory illness
  - **2 cases associated with backyard poultry exposures**
    - 2 states: severe or critical illness
  - **3 cases with <u>unknown exposures</u>**
    - 2 states: mild or moderate illness
  - **4 hospitalized cases**
    - **4 states: 3 pneumonia cases, 1 death**

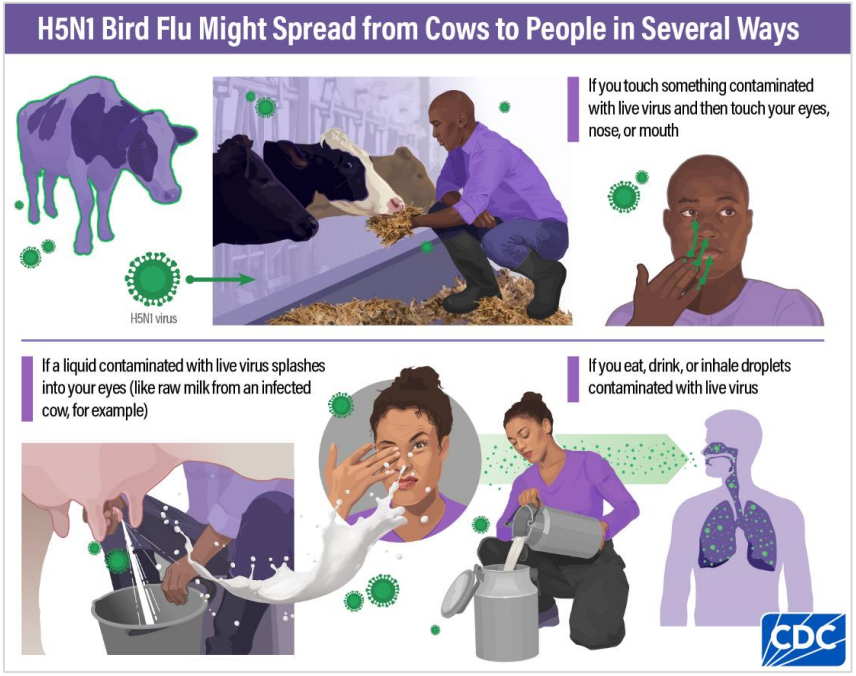
➢**No human-to-human of HPAI A(H5N1) virus identified in the U.S. to date**

As of May 6, 2025; **1 additional case confirmed in 2022; 7 probable cases (not confirmed at CDC)*

Human Infections with HPAI A(H5N1) Virus, Worldwide

- **Unprotected exposures** (without respiratory or eye protection)
  - **Poultry exposures**
    - **Direct/close contact with sick/dead poultry**
    - Visiting a live poultry market
  - **Exposure to other infected animals**
    - **Direct contact or close exposure (dairy cows) or animal products (raw milk)**
  - Limited, non-sustained human-to-human transmission from prolonged exposure to a symptomatic H5N1 patient (last reported 2007)





Clinical Findings in A(H5N1) Cases (Worldwide)

Clinical findings in mild illness (incubation period: mean 3 days (2-7 days)

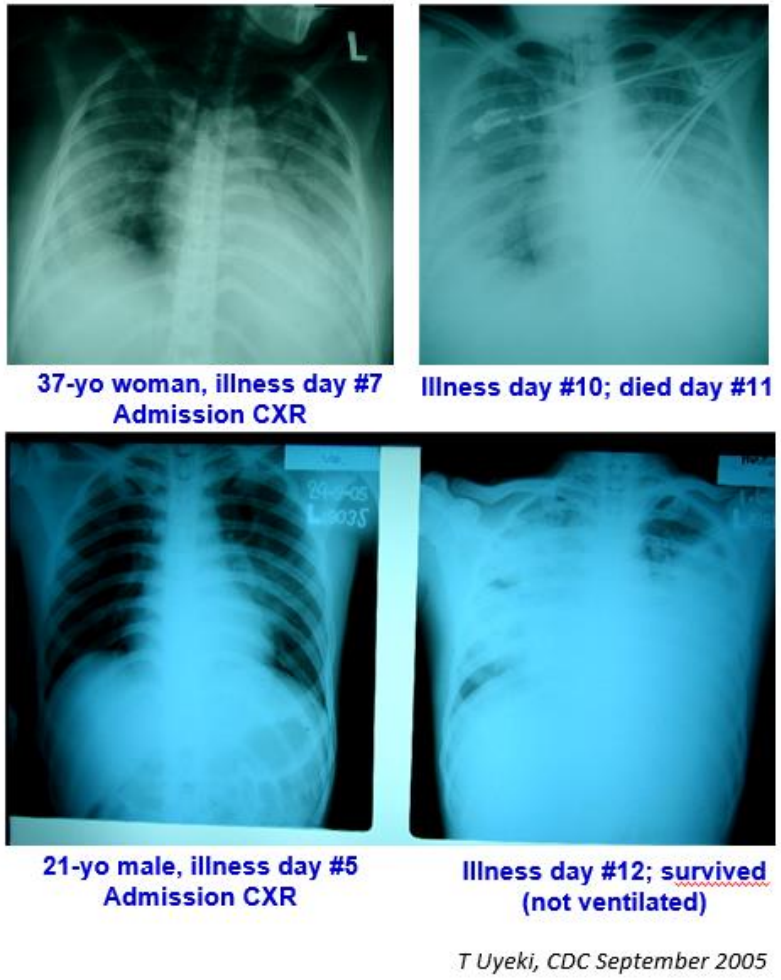
- Fever or feverishness, nonproductive cough, muscle aches, malaise, headache, sore throat, myalgia
  - Abdominal pain; vomiting and diarrhea can occur
  - Eye discomfort/redness/eye discharge (conjunctivitis) can occur 1-2 days after exposure

Progression to lower respiratory tract disease (5-7 days after symptom onset): difficulty breathing, shortness of breath, chest pain, tachypnea

- Hospital admission findings:
  - Clinical: hypoxia, signs of pneumonia
  - Laboratory: leukopenia, lymphopenia, mild-to-moderate thrombocytopenia
  - Radiographic findings: Bilateral pneumonia: patchy, interstitial, lobar, diffuse infiltrates, opacities, consolidation

Figure 1. Conjunctivitis with Subconjunctival Hemorrhage in Both Eyes.

Uyeki NEJM 2024



T Uyeki, CDC September 2005

Clinical Complications of HPAI A(H5N1) Virus Infection

- **Pneumonia is the most common complication**
  - Progression to respiratory failure, and acute respiratory distress syndrome
  - Community-acquired bacterial co-infection is rare; ventilator associated pneumonia in intubated patients
- **Other complications**
  - Acute kidney injury
  - Sepsis, shock, disseminated intravascular coagulation, multi-organ failure (respiratory & renal failure)
  - Cardiac failure
  - Atypical complications
    - Encephalitis, meningoencephalitis
    - Reye syndrome with salicylate exposure
    - Spontaneous abortion

Influenza Testing (Outpatients)

- **If A(H5N1) virus infection is suspected (use recommended PPE*):**
  - **<u>Patients with acute respiratory symptoms</u>:**
    - **Collect (1) a nasopharyngeal swab, and (2) combined nasal and throat swab specimens**
      - **Place each specimen into separate tubes of viral transport media**
  - **<u>Patients with conjunctivitis</u>:**
    - **Collect (1) a conjunctival swab, and (2) a nasopharyngeal swab**
      - **Place each specimen into separate tubes of viral transport media**

➢ **Influenza A virus subtyping and A(H5) virus testing at a public health laboratory**

<u>Nearly all influenza tests in clinical settings</u> cannot specifically identify A(H5N1) virus

- ***Cannot differentiate A(H5N1) virus from seasonal influenza A(H3N2) and A(H1N1)pdm09 viruses***
  - ***Need to perform subtyping of influenza A viruses (H1, H3), and A(H5) assays***
  - ***A(H5) RT-PCR testing is available from 3 companies***
    - ***Quest*** *(NP, anterior nasal, oropharyngeal swab, conjunctival swabs, BAL fluid)*
    - ***ARUP*** *(respiratory or conjunctival swabs)*
    - ***Labcorp*** *(NP swab) influenza A & B with reflex to A(H5)*

*PPE: gown, gloves, NIOSH approved N95 filtering facepiece respirator, eye protection

Influenza Testing (Hospitalized Patients)

- **Infection Prevention and Control Measures**
  - Place patient in an **airborne infection isolation room with negative pressure**
  - Recommended PPE: **gown, gloves, NIOSH approved N95 filtering facepiece respirator, eye protection**

- **Patients with lower respiratory tract disease**
  - Collect **upper respiratory specimens** (NP swab, combined nasal & throat swabs), and **sputum** for influenza A and A(H5) virus testing at public health laboratories
  - Intubated patients: Also collect **endotracheal aspirate specimens (or BAL fluid)**

➢ ***Collect multiple respiratory specimens from different sites on multiple days for patients with suspected HPAI A(H5N1) virus infection to maximize potential for diagnosis***

Antiviral Treatment

- **Oseltamivir treatment is recommended as soon as possible for patients who are suspected, probable or confirmed cases of A(H5N1)**
  - Current HPAI A(H5N1) clade 2.3.4.4b viruses are generally susceptible to oseltamivir and other FDA-approved antivirals for seasonal influenza
  - **Observational studies suggest survival benefit with early initiation of oseltamivir treatment compared to no treatment or later initiation of treatment**
- No data for baloxavir treatment of A(H5N1) patients, optimal dosing and duration are unknown

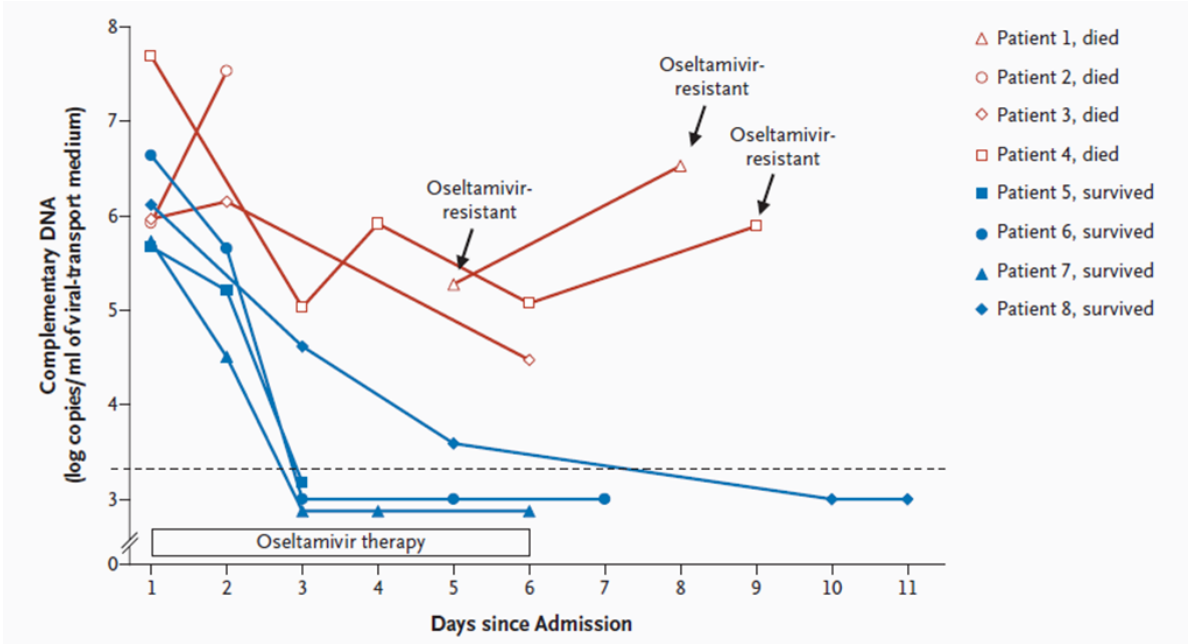
Adisamito J Infect Dis 2010; Adisamito J Infect Dis 2011; Kandun Lancet 2008; Liem Clin Infect Dis 2009; Yu PLoS ONE 2008

Antiviral Treatment For Clinically Mild Illness

- **If A(H5N1) virus infection is suspected:**
  - **Start empiric antiviral treatment with Oseltamivir as soon as possible** (while awaiting testing results)
  - **Recommend home isolation for mild illness, notify local and state public health for testing, monitoring and follow-up as soon as possible**
  - **If A(H5N1) virus infection is confirmed: home isolation**
    - Consider: until clinically improved or repeat respiratory specimens are negative for influenza

Antiviral Treatment For Hospitalized A(H5N1) Patients

- **Consider combination antiviral treatment for hospitalized patients (and immunocompromised)**
  - **Higher dosing of oseltamivir?**
  - **Oseltamivir resistance reported with critical illness and fatal outcomes**
- **Combination antiviral treatment given to some hospitalized A(H5N1) patients**
  - **Oseltamivir, Baloxavir, Amantadine or Rimantadine**
  - **Adjust dosing for Oseltamivir, Amantadine, Rimantadine for acute kidney injury**
- **Gap: Very limited human data on combination antiviral treatment of A(H5N1) patients to inform recommendations (1 case report)**



de Jong NEJM 2005; Jassem NEJM 2025

Antiviral Post-Exposure Prophylaxis

- **Post-exposure antiviral prophylaxis**
  - If A(H5N1) virus infection is confirmed, **household and other close contacts are recommended to receive Oseltamivir at treatment dosing as soon as possible** (twice daily x 5 days; longer duration for ongoing exposures)
    - » **Monitor for any illness signs/symptoms x 10 days after the last exposure**
    - » **Offer to persons with high-risk exposures to infected animals**

Clinical Management: Hospitalized Patients

- **Place patient in airborne infection isolation room**
  - **Personal protective equipment: gloves, gown, eye protection, respiratory protection as least as protective as an N95 filtering facepiece respirator**
- **Start oseltamivir treatment ASAP, consider combination treatment**

➢ **Supportive care of complications**

  - Advanced organ support, critical care

- **Immunomodulators**
  - **Avoid moderate to high-dose corticosteroids**
    - Associated with prolonged viral shedding
    - May increase risk for ventilator-associated pneumonia and death
  - No data for other immunomodulators (e.g., IL-6 receptor blockers, JAK inhibitors)

Self-knowledge Check: What are risk factors for HPAI A(H5N1) Virus Infection in humans in the United States to date?

A. Consumption of unpasteurized (raw) cow milk
B. Direct or close unprotected contact with sick pigs
C. Direct or close unprotected contact with sick/dead poultry
D. Consumption of raw or undercooked beef
E. Direct or close unprotected contact with dairy cattle or raw milk
F. A and E
G. C and E
H. A, C, and E

Answer: What are risk factors for HPAI A(H5N1) Virus Infection in humans in the United States to date?

A. Consumption of unpasteurized (raw) cow milk
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D. Consumption of raw or undercooked beef
E. Direct or close unprotected contact with dairy cattle or raw milk
F. A and E
G. C and E
H. A, C, and E

Rationale: Direct or close unprotected exposure to sick or dead poultry or dairy cattle or raw cow milk have been reported for cases of influenza A(H5N1) in the United States.

Testing and Treatment Resources from CDC

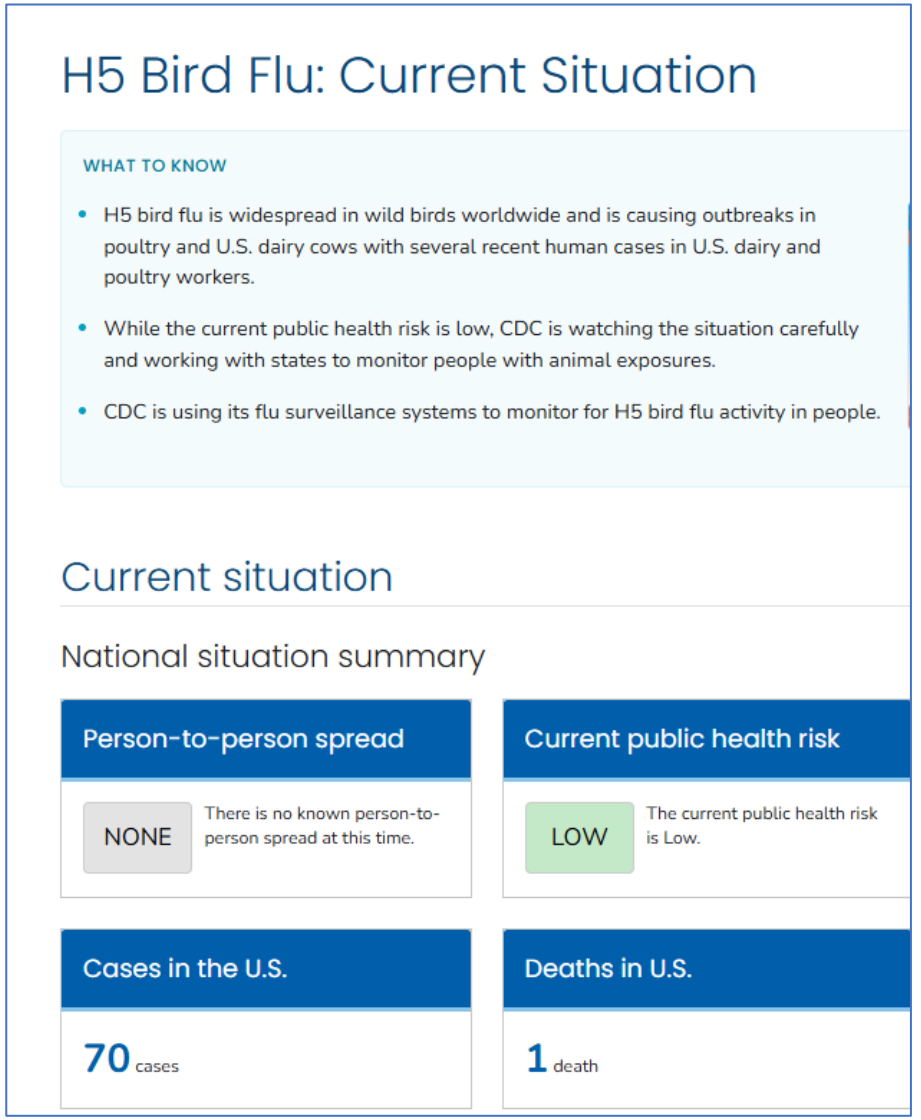
- **Testing and Specimen Collection**
  https://www.cdc.gov/bird-flu/php/severe-potential/index.html

- **Antiviral Treatment**
  https://www.cdc.gov/bird-flu/hcp/novel-av-treatment-guidance/index.html

- **Infection Prevention and Control Measures**
  https://www.cdc.gov/bird-flu/hcp/novel-flu-infection-control/index.html

- **Antiviral Post-Exposure Prophylaxis**
  https://www.cdc.gov/bird-flu/php/novel-av-chemoprophylaxis-guidance/index.html

  https://www.cdc.gov/bird-flu/hcp/guidance-exposed-persons/index.html



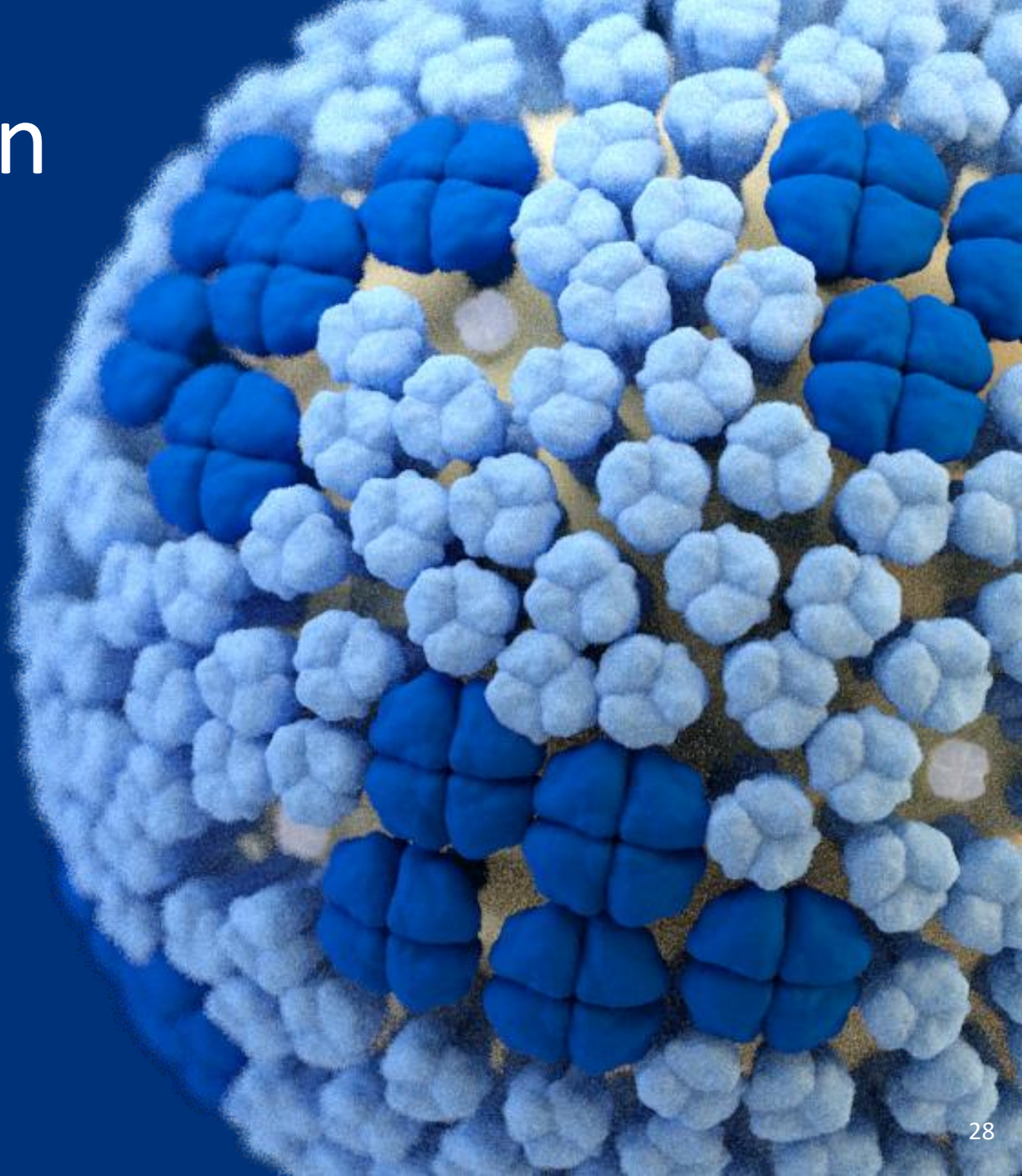
Highly Pathogenic Avian Influenza A (H5N1): Surveillance and Monitoring

Alicia Budd, MPH

Influenza Division

Centers for Disease Control and Prevention (CDC)

May 6, 2025



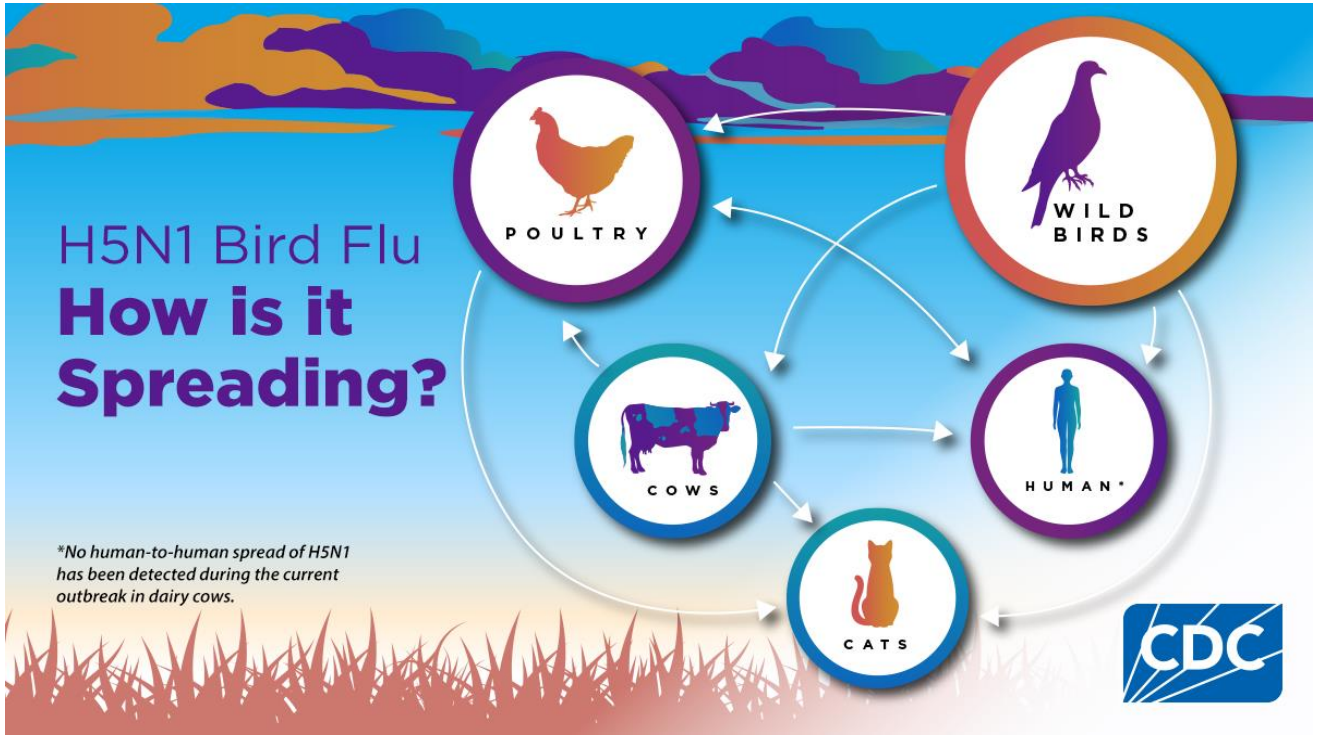
Public Health Risk

- Overall risk to the public remains low

https://www.cdc.gov/cfa-qualitative-assessments/php/data-research/h5-risk-assessment.html

- Greater risk for people with close, prolonged, or unprotected exposures to HPAI A(H5) infected animals, or to environments contaminated by infected animals
- Exposed individuals should monitor for symptoms after first exposure and for 10 days after last exposure

HPAI (H5) risk assessment: https://www.cdc.gov/cfa-qualitative-assessments/php/data-research/h5-risk-assessment.html



Avian Influenza Social Media Toolkit | Bird Flu | CDC

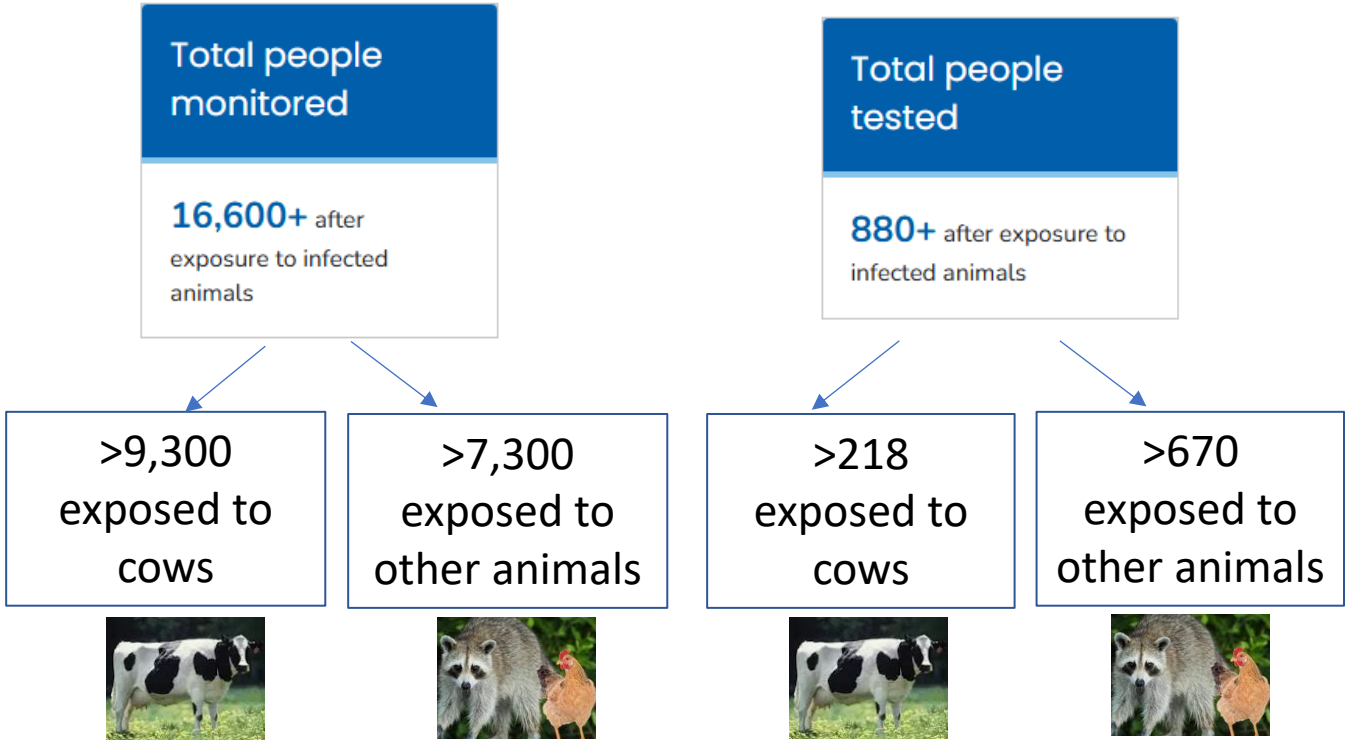
Monitoring of Exposed Persons in the United States

- Active monitoring of people exposed to infected birds, poultry or other animals for 10 days after last exposure

❖ Since February 2022

- >25,900 people monitored
- >1,170 people tested for influenza A

❖ Current HPAI Outbreak (since March 2024)



H5N1 Bird Flu Surveillance and Human Monitoring | Bird Flu | CDC

H5 Bird Flu: Current Situation | Bird Flu | CDC

Ongoing Human Monitoring (1/2)

Targeted H5 surveillance (since March 24, 2024)

Total people monitored	Total people tested	Human cases
16,600+ after exposure to infected animals	**880+** after exposure to infected animals	**64** cases detected through targeted H5 surveillance

H5 Bird Flu: Current Situation | Bird Flu | CDC

Ongoing Human Monitoring (2/2)

Targeted H5 surveillance (since March 24, 2024)

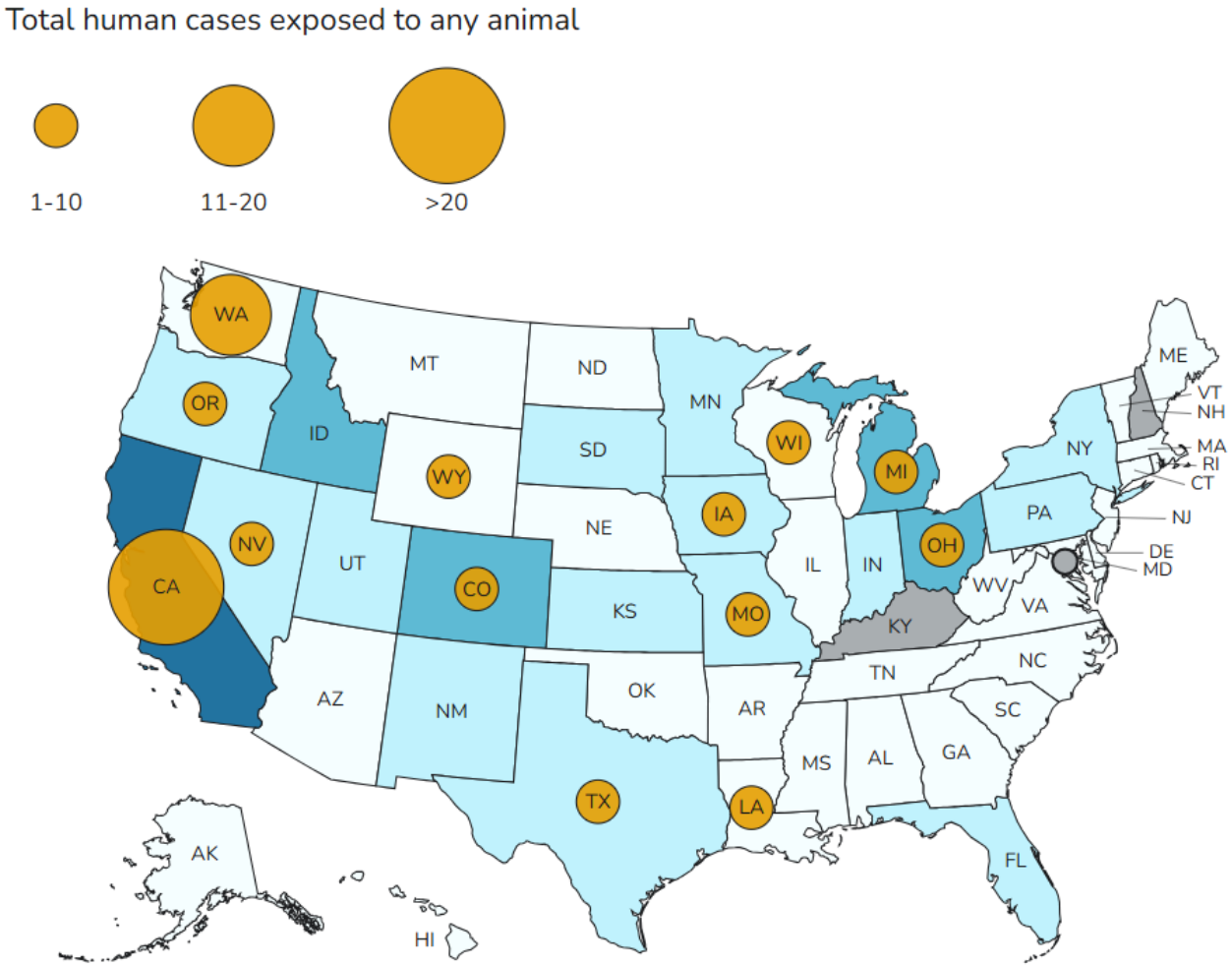
Total people monitored	Total people tested	Human cases
16,600+ after exposure to infected animals	**880+** after exposure to infected animals	**64** cases detected through targeted H5 surveillance

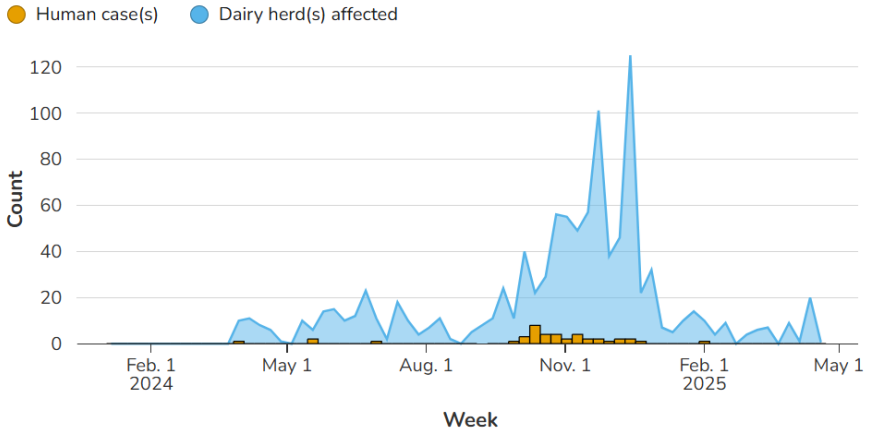
National flu surveillance (since February 25, 2024)

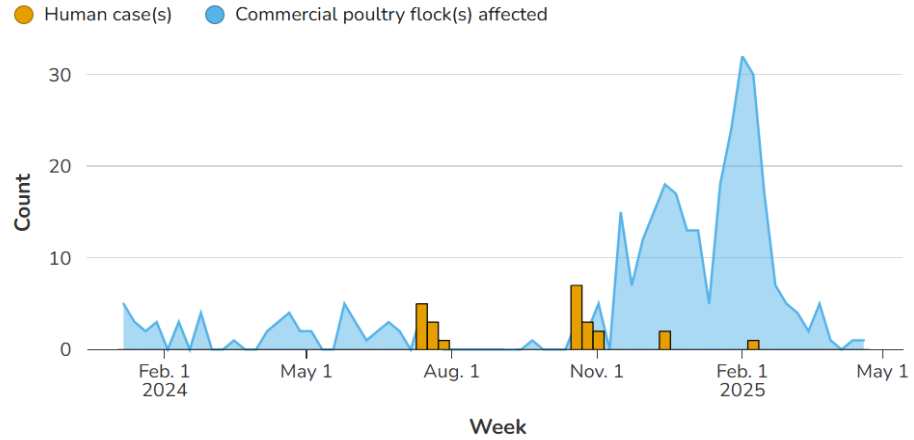
Specimens tested	Human cases
181,476+ specimens tested that would have detected influenza A(H5) or other novel influenza viruses	**6** case detected through national flu surveillance

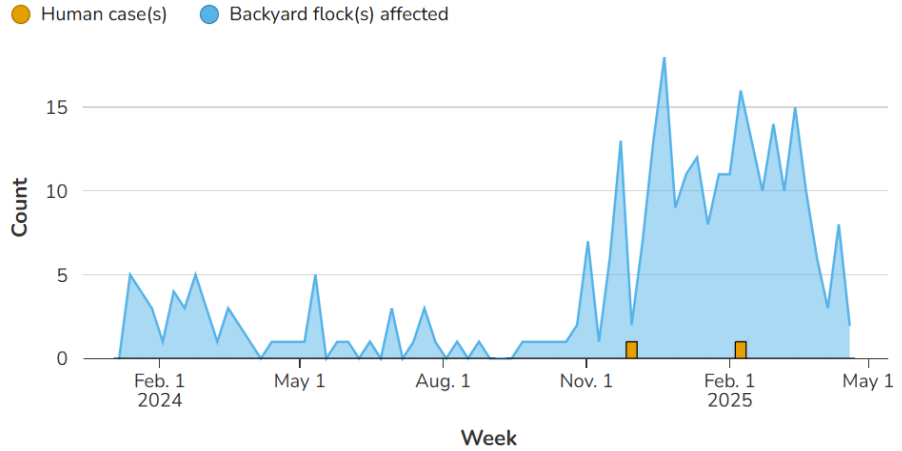
H5 Bird Flu: Current Situation | Bird Flu | CDC

Human Cases Exposed to Infected Animals



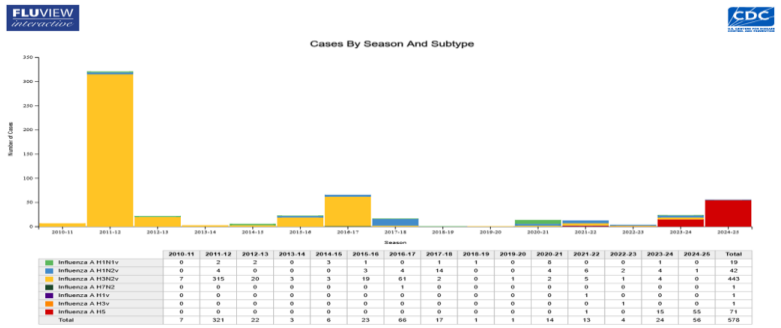






https://www.cdc.gov/bird-flu/h5-monitoring/index.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fflu%2Favianflu%2Fh5-monitoring.html

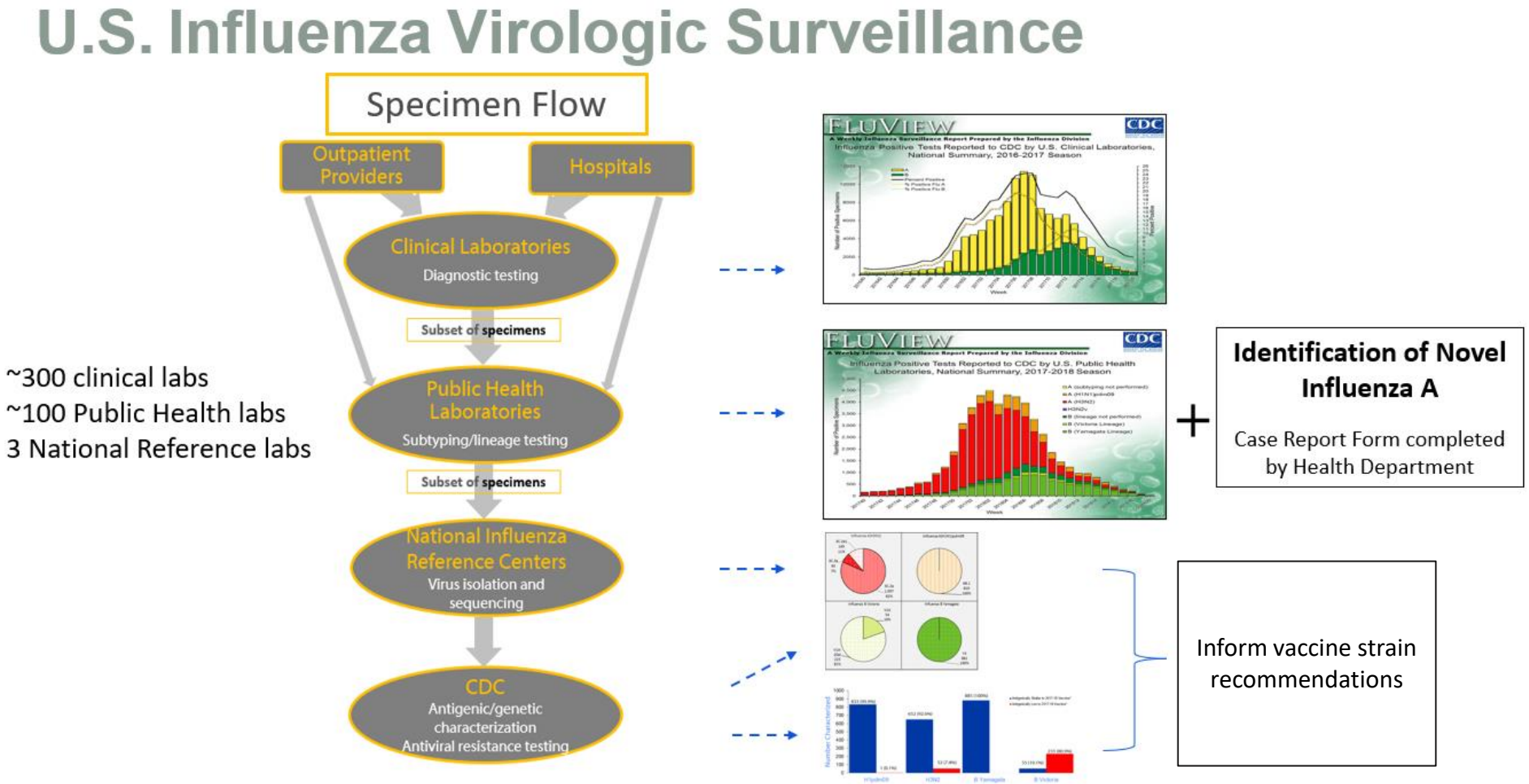
Summer Influenza Surveillance: What Clinicians Can Do



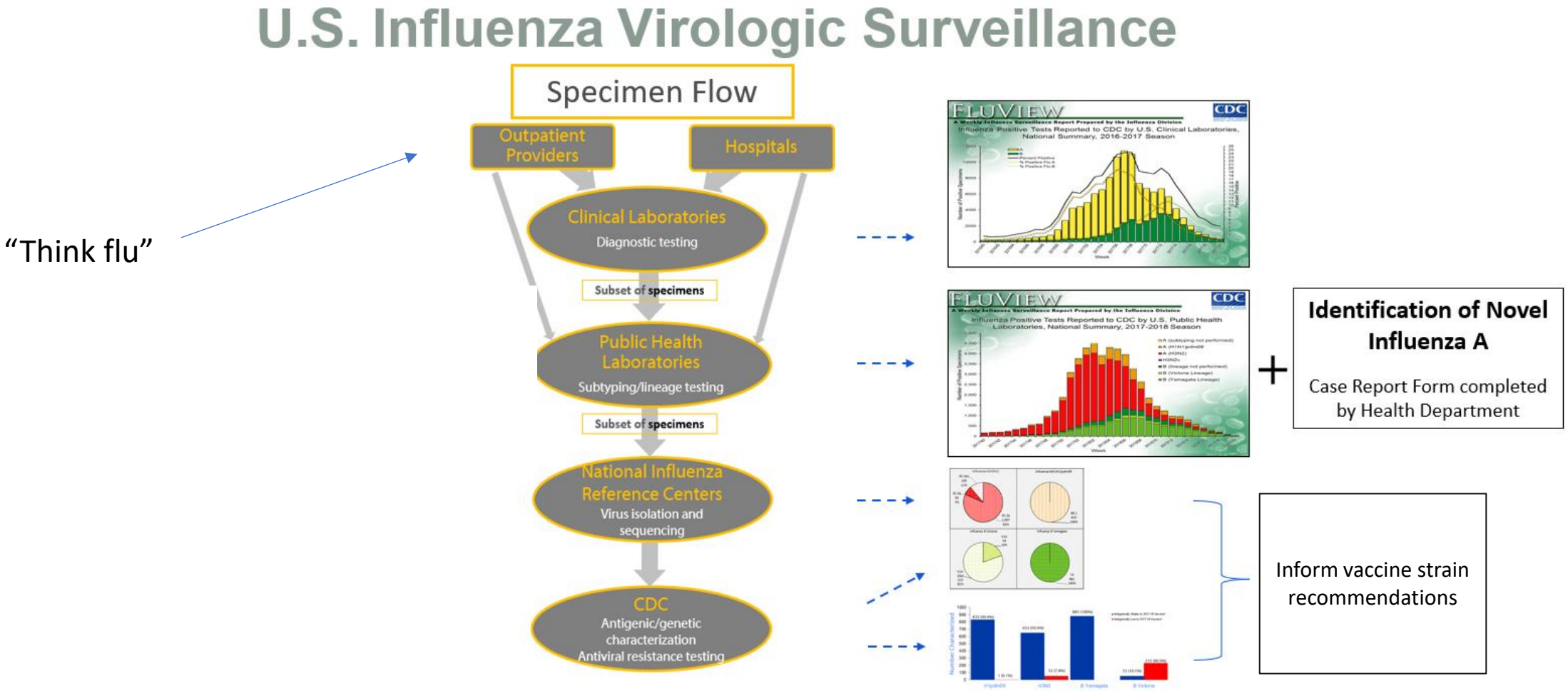
- Goal: Continue influenza testing throughout the summer especially if
  - Recent history of relevant exposures (e.g., dairy cattle, raw milk, wild birds, poultry, agricultural fair attendance)
  - Participating in communal activities/settings, such as summer camps
  - Severely ill

- Actions for clinicians
  - "Think flu" even though it's summer
  - Talk to patients about their exposures and risk
  - Collect specimens for influenza testing from symptomatic patients
  - Facilitate subtyping of influenza A positive specimens
  - Notify state or local public health
    - Virus is "unsubtypeable"
    - Exposure history + flu A positive and subtyping not known
    - Severely ill + flu A positive and subtyping not known

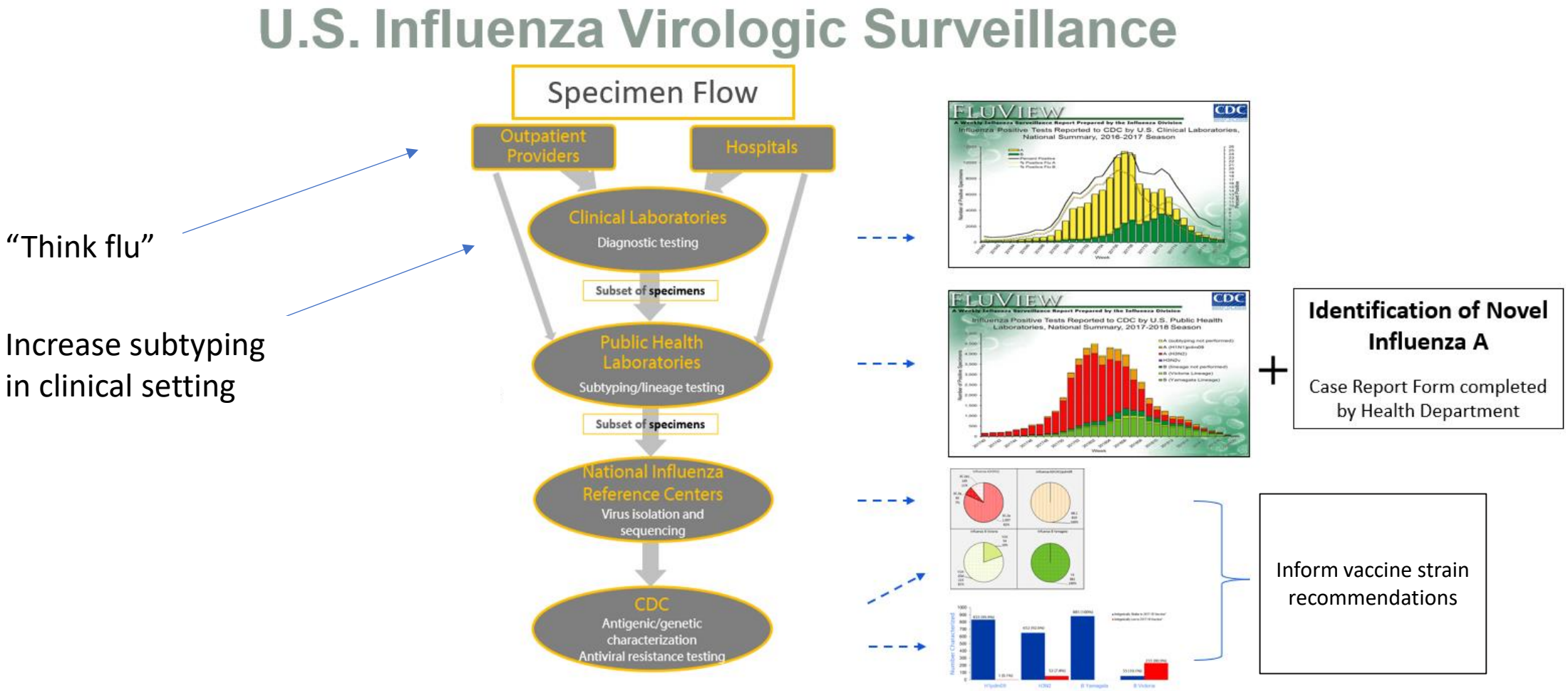
Summer Influenza Surveillance: Maintain Influenza A Subtyping (1/3)



Summer Influenza Surveillance: Maintain Influenza A Subtyping (2/3)



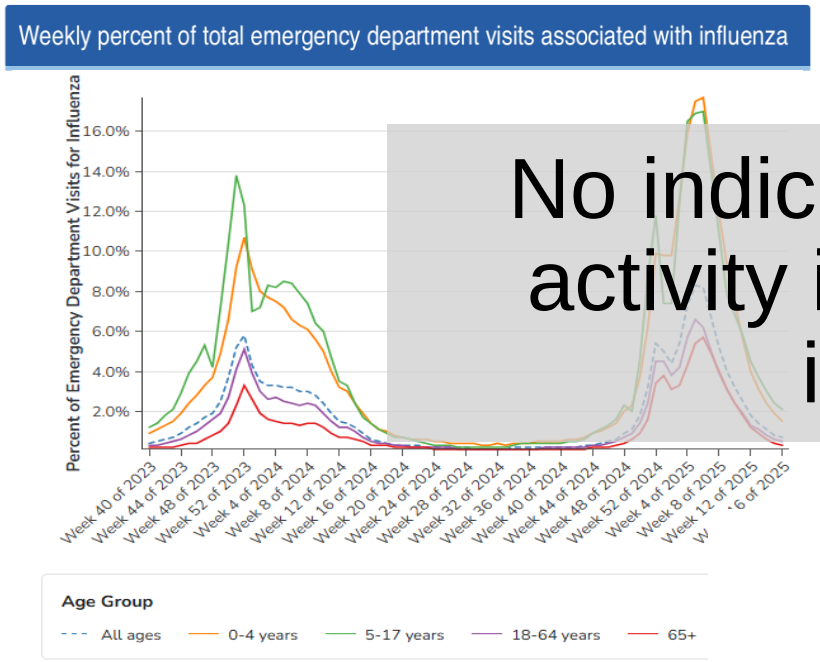
Summer Influenza Surveillance: Maintain Influenza A Subtyping (3/3)



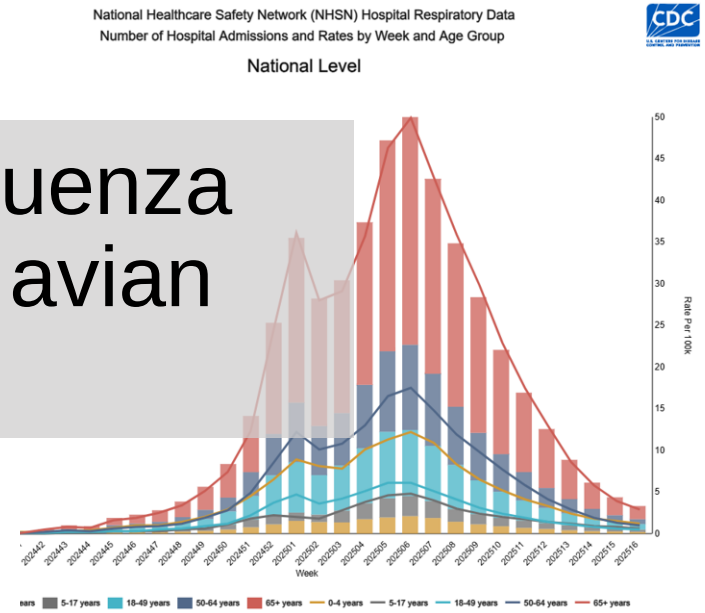
"Think flu"

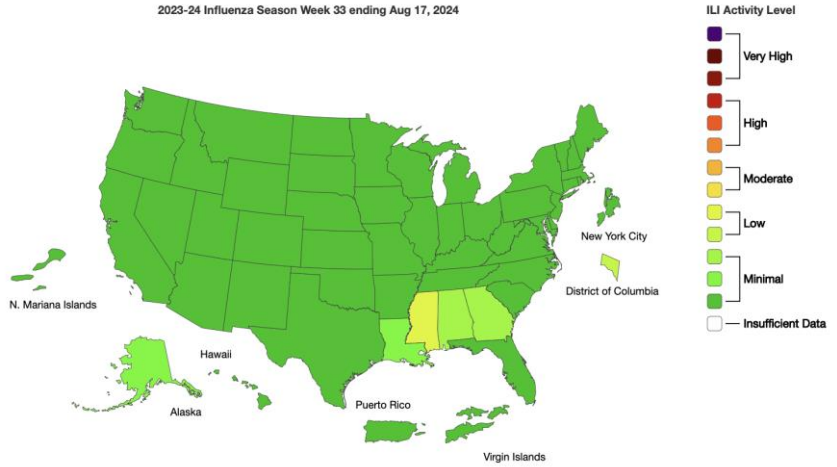
Increase subtyping in clinical setting

Summer Influenza Surveillance: Monitor for Unexpected Patterns

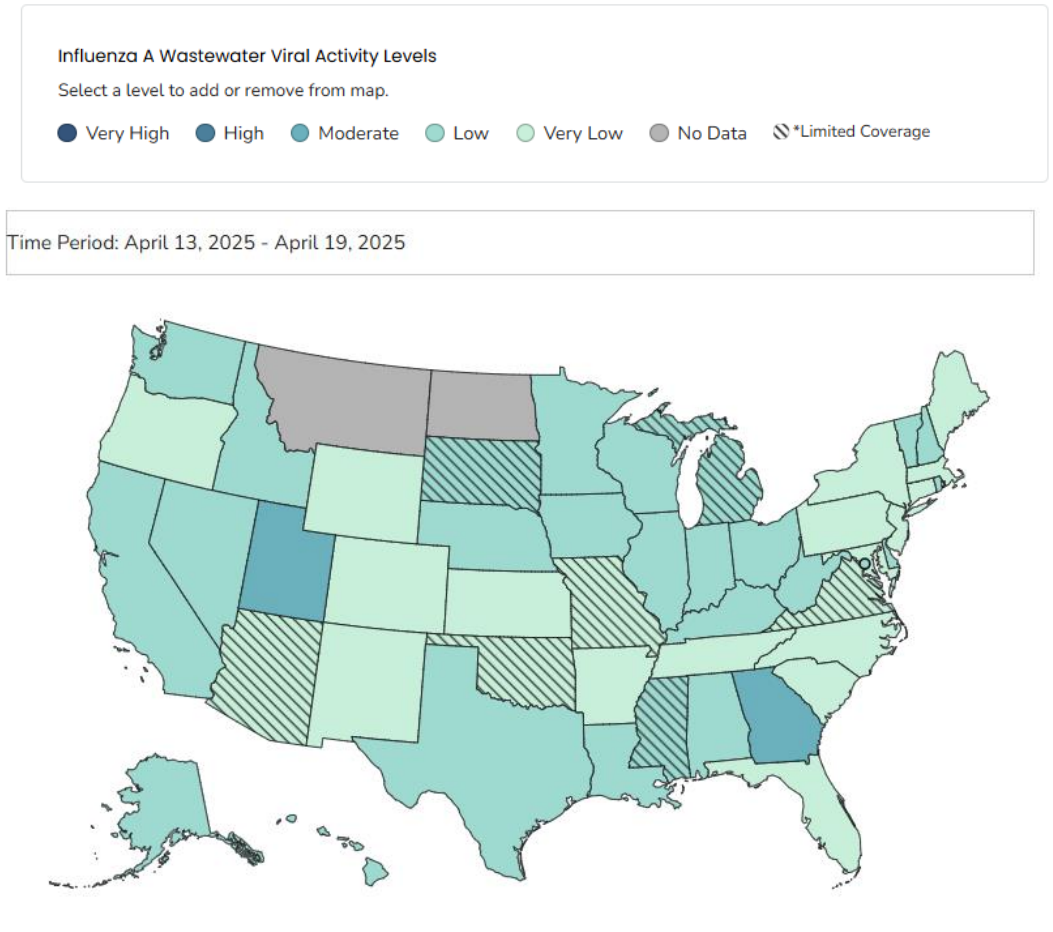


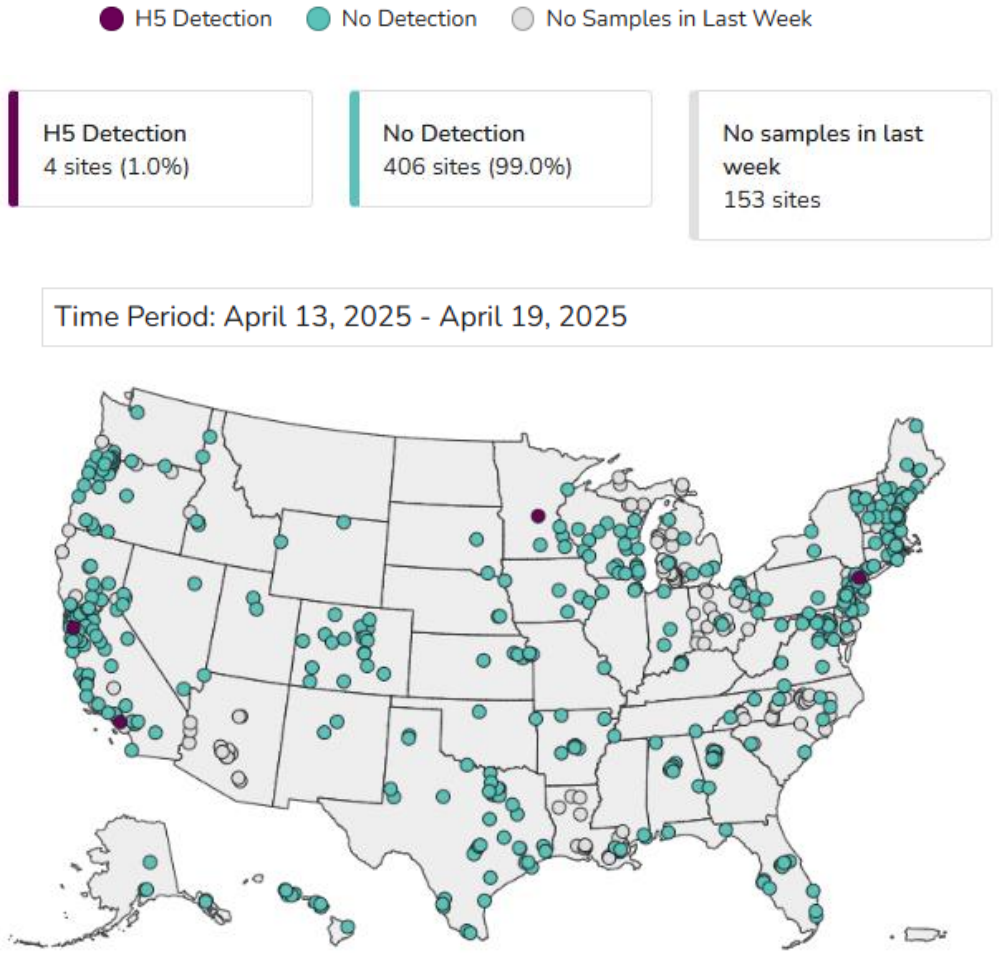
No indicators of unusual influenza activity in people, including avian influenza A(H5N1)





Wastewater Surveillance for Influenza Virus





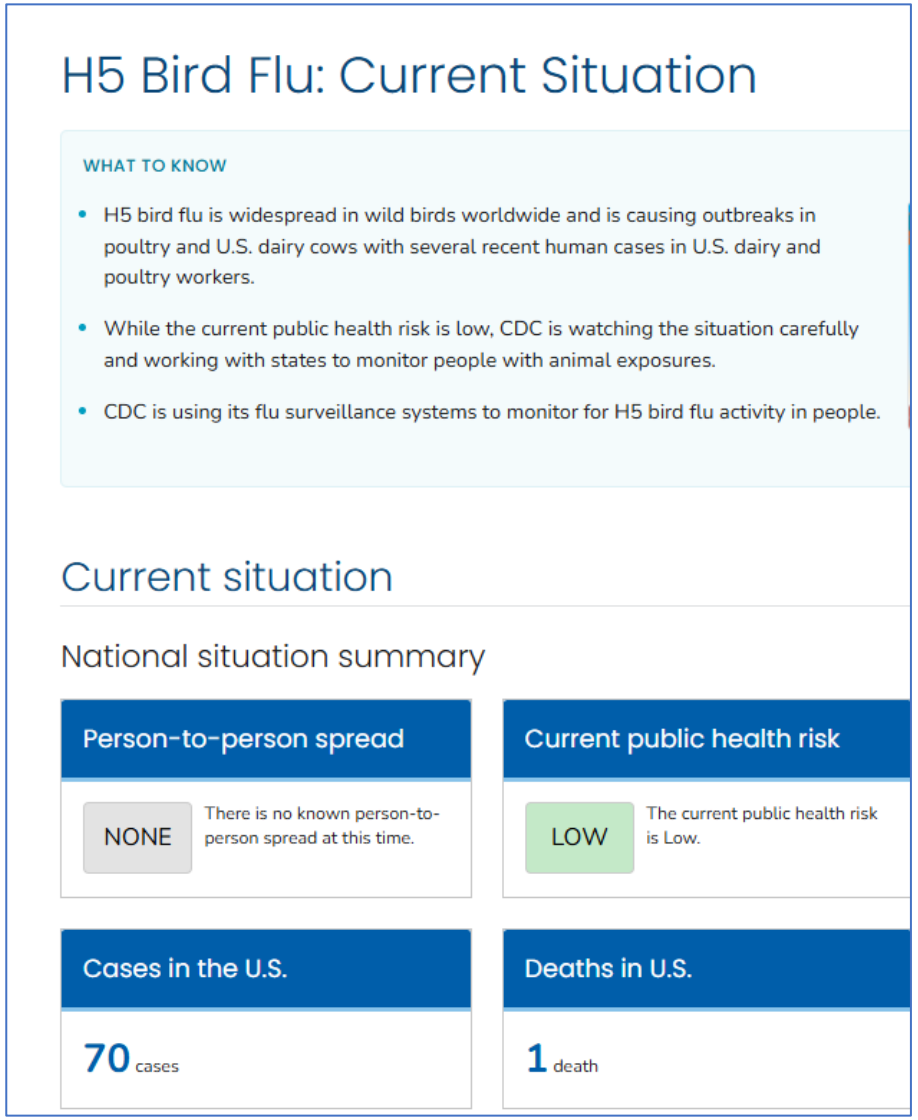
Monitoring and Surveillance Resources from CDC

- **Current Situation**
  https://www.cdc.gov/bird-flu/situation-summary/index.html#human-cases

- **H5 Flu Surveillance and Human Monitoring**
  https://www.cdc.gov/bird-flu/h5-monitoring/index.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fflu%2Favianflu%2Fh5-monitoring.html

- **Reducing Exposure for People Working with Animals**
  https://www.cdc.gov/bird-flu/prevention/worker-protection-ppe.html

- **Prevention, Monitoring and Public Health Investigations**
  https://www.cdc.gov/bird-flu/prevention/hpai-interim-recommendations.html



Self-knowledge Check: Clinicians can perform which of the following activities to help detect novel influenza viruses this summer?

A. “Think flu” even though it’s not respiratory virus season
B. Ask patients about any recent relevant exposures (e.g., dairy cattle, raw milk, wild birds, poultry, agricultural fair attendance)
C. Collect a specimen for flu testing from symptomatic patients, especially if they have a recent relevant exposure
D. All of the Above

Answer: Clinicians can perform which of the following activities to help detect novel influenza viruses this summer?

A. “Think flu” even though it’s not respiratory virus season
B. Ask patients about any recent relevant exposures (e.g., dairy cattle, raw milk, wild birds, poultry, agricultural fair attendance)
C. Collect a specimen for flu testing from symptomatic patients, especially if they have a recent relevant exposure
D. **All of the Above**

Rationale: All of these activities are important for detecting novel influenza viruses.

Joining for Q&A

- **Todd Davis, PhD, MSPH**
  Team Lead, National Surveillance and Outbreak Response Team
  Influenza Division
  National Center for Immunization and Respiratory Diseases
  Centers for Disease Control and Prevention

- **Marie Kirby, PhD**
  Team Lead, Genomics and Diagnostics Team
  Influenza Division
  National Center for Immunization and Respiratory Diseases
  Centers for Disease Control and Prevention

To Ask a Question

- Using the Zoom Webinar System
  - Click on the “Q&A” button
  - Type your question in the “Q&A” box
  - Submit your question

- If you are a patient, please refer your question to your healthcare provider.

- If you are a member of the media, please direct your questions to CDC Media Relations at 404-639-3286 or email media@cdc.gov.

TRAIN

- CDC has fully transitioned from Training and Continuing Education Online (TCEO) to **CDC TRAIN** (https://www.train.org/cdctrain).
- **Transcripts & Certificates**: You can access and download CE transcripts and certificates in TCEO through the end of 2025.
- Instructions will be available on both platforms and a learner support team will be available to answer questions.

Continuing Education

- All continuing education for COCA Calls is issued online through CDC TRAIN at CDC TRAIN (https://www.train.org/cdctrain).

- Those who participate in today's COCA Call and wish to receive continuing education please complete the online evaluation by **June 9, 2025,** with the **course code WC4520R-050625.** The **registration code** is **COCA050625.**

- Those who will participate in the on-demand activity and wish to receive continuing education should complete the online evaluation between **June 10, 2025,** and **June 10, 2027,** and use **course code WD4520R-050625.**

Today's COCA Call will be Available to View On-Demand

- **When:** Next week
- **What:** Closed caption recording and transcript
- **Where:** On the COCA Call webpage
  https://www.cdc.gov/coca/hcp/trainings/h5n1_influenza_a_virus_surveillance.html

Additional Resources

- Continue to visit https://www.cdc.gov/coca/hcp/trainings/index.html to get more details about upcoming COCA Calls.

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Thank you for joining us today!

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.