Update on H5N1

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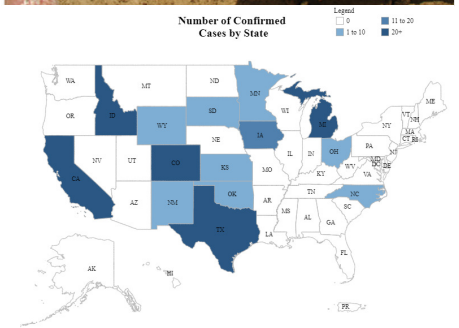
Disclosure and Disclaimer

- No disclosures to report.
- The findings and conclusions in this presentation are those of the speaker and do not necessarily represent the official position of the CDC.

Highly Pathogenic Avian Influenza A(H5N1) Virus

- **HPAI A(H5N1) virus** *(HPAI based on molecular & pathogenicity criteria)*
  - **Infect respiratory and gastrointestinal tracts of birds, high mortality**
  - **Continue to evolve (classified genetically into virus clades)**
- **1997: First human infections identified (Hong Kong)**
- **2003 and ongoing: sporadic human infections worldwide**
- **2020 to date: Clade 2.3.4.4b H5N1 viruses** emerged (spread by wild birds)
  - **Unprecedented wide geographic spread worldwide**
    - Many bird species infected, poultry outbreaks
    - Many terrestrial and marine mammals infected (often fatal)
  - Detected in wild birds in North America (end of 2021)
    - Poultry outbreaks, wild bird detections since 2022 (ongoing)
      - **>100 million commercial poultry/backyard birds affected (48 states); wild birds (49 states)**
      - **>2024: Livestock in the U.S. (goats, alpacas, dairy cattle: >300 dairy cattle herds (14 states)**



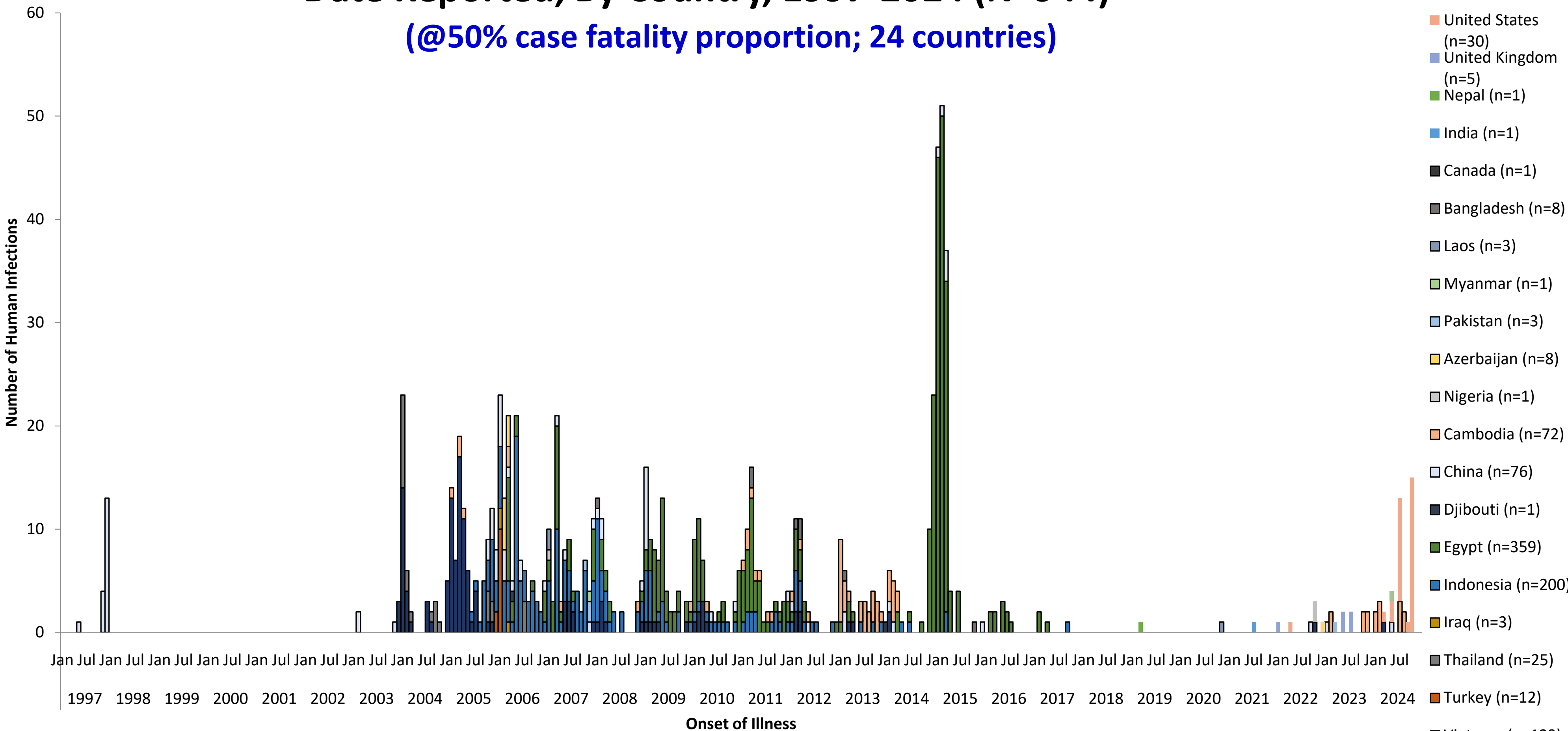
Epidemiology of Human H5N1 Cases

- **First human infections identified: Hong Kong, 1997 (18 cases, 6 deaths)**
  - Median age: 17 years (range 1-60); wide severity: pneumonia: 11; mild illness: 7
- **Re-emergence in humans: 2003-2005 (China, Southeast Asia)**
- **Since 2005: Cases identified in other regions (Middle East, Europe, Africa, Americas)**
- **1997-2024: 944 cases (@50% case fatality; 24 countries)***
  - **Mostly sporadic human cases with pneumonia**
    - Most cases in young adults, some pediatric cases
    - **2023-2024: Clade 2.3.2.1c virus infections in rural villagers (Cambodia: 16 cases, 6 deaths)**
    - **2024: Clade 2.3.2.1a virus infection with critical illness (Australia returned travel to India**
    - **2022-2023: Clade 2.3.4.4b virus infections with critical illness (Chile, China, Ecuador)**
    - **2022-2024: Clade 2.3.4.4b virus infections (mostly conjunctivitis, U.S.)**

**As of October 23, 2024; Chan Clin Infect Dis 2002*

Epidemic Curve of Human Cases of A(H5N1) by Illness Onset Date or Date Reported, By Country, 1997-2024 (N=944)*

(@50% case fatality proportion; 24 countries)



**As of October 23, 2024*

U.S. Cases, 2022-2024* (H5N1 clade 2.3.4.4b viruses)

- **30 Human cases (29 in 2024) (no secondary transmission identified)**
  - **Oseltamivir treatment given/offered; Oseltamivir PEP for close contacts**
  - **Associated with poultry exposures: 10**
    - **April 2022: 1 case reported "fatigue" while depopulating poultry**
    - **July 2024: 9 cases of conjunctivitis in poultry workers depopulating poultry** (one state)
  - **Associated with dairy cattle exposures: 19** (contact transmission)
    - **333 H5N1+ dairy cattle farms in 14 states (March-October 2024)**
    - **March - October 2024: 19 cases in dairy farm workers** (4 states)
    - **Mild illness (18 with conjunctivitis, 1 with respiratory illness)**
  - **Unknown source: 1**
    - **August 2024: 1 case in a person with no exposures to animals or sick persons**
    - **Moderate non-respiratory illness in a person with chronic medical conditions (hospitalized)**
    - **Hospitalized for 3 days, received Oseltamivir treatment; recovered**

Figure 1. Conjunctivitis with Subconjunctival Hemorrhage in Both Eyes.

Uyeki NEJM 2024

**As of October 23, 2024; Morse NEJM 2024; Uyeki NEJM 2024; Drehoff MMWR 2024*

Risk Factors for Human Infection with H5N1 Virus

- **Exposure to infected poultry**
  - **Direct/close unprotected exposure to sick/dead backyard poultry (rural areas)**
  - **Visiting a live poultry market**
- **Exposure to infected wild birds**
  - **Defeathering wild swans that died** (2 case clusters, Azerbaijan, 2006)
- **Some cases with no known source of infection**
  - (e.g., returned traveler to Canada Dec. 2013; one case in August 2024, U.S.)
- **2024: Sporadic mammal-to-human H5N1 virus transmission**
  - **First cases of dairy cattle-to-human transmission (U.S.)**
- **Limited, non-sustained human-to-human transmission (rare)**
  - **Not reported since 2007 (has occurred after prolonged, unprotected exposures)**

WHO NEJM 2008; Zhou J Infect Dis 2009; Mounts J Infect Dis 1999; Gilsdorf Eurosurveillance 2006; Ungchusak NEJM 2005; Wang Lancet 2007

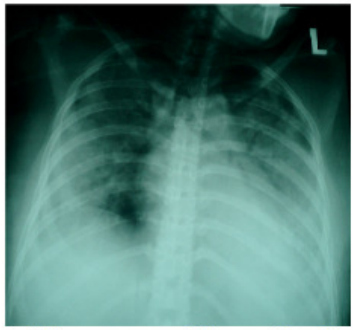
Signs & Symptoms of HPAI A(H5N1) Virus Infection

Clinical findings in mild respiratory illness

- **Incubation period: mean: 3 days (2-7 days)**
- **Fever or feverishness, nonproductive cough, myalgia, malaise, headache, sore throat**
  - ➢ **Abdominal pain; vomiting, diarrhea**
  - • **Conjunctivitis can occur 1-2 days after exposure**

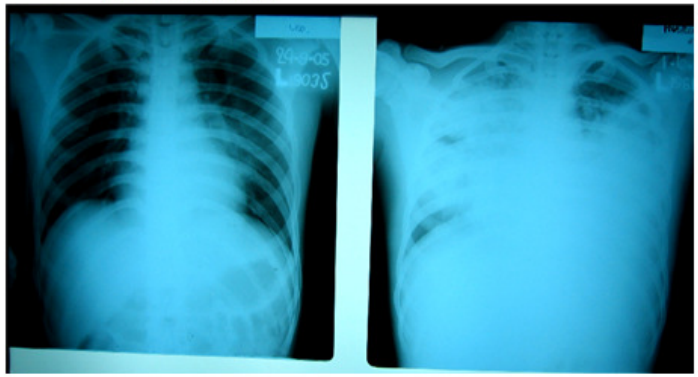
Progression to pneumonia (5-7 days after symptom onset)

- **Hospital admission findings:**
  - • **Clinical: hypoxia, signs/symptoms of pneumonia**
    - • **Radiographic findings of pneumonia**
  - • **Laboratory: leukopenia, lymphopenia, mild-to-moderate thrombocytopenia**



37-yo woman, illness day #7
Admission CXR

Illness day #10; died day #11



21-yo male, illness day #5
Admission CXR

Illness day #12; survived
(not ventilated)

T Uyeki, CDC September 2005

Complications of H5N1 Virus Infection

- **Pneumonia is the most common complication**
  - **Progression to respiratory failure, ARDS**
    - **Community-acquired bacterial co-infection is rare**

- **Other severe complications**
  - **Acute kidney injury**
  - **Cardiac failure**
  - **Sepsis, shock, DIC, multi-organ failure (respiratory and renal failure)**
  - **Atypical complications**
    - **Encephalitis** with diarrhea and pneumonia; encephalitis with obstructive hydrocephalus; meningoencephalitis with pneumonia
    - **Reye syndrome** with salicylate exposure
    - **Spontaneous miscarriage** in a pregnant woman
    - **Vertical transmission** (mother-to-fetus)

Uyeki Clin Infect Dis 2009

Potential Exposures to H5N1 Virus

- **People with close, prolonged, or unprotected exposures to infected animals (including livestock), or to environments contaminated by infected animals, are at greater risk of infection**
- **Potential occupationally exposed persons**
  - **Dairy farm workers**
  - Slaughterhouse workers
  - Milk processing facility employees
  - **Poultry workers**
  - Veterinarians, veterinary assistants

  - Monitor for signs or symptoms of acute respiratory illness and/or conjunctivitis and seek clinical care if signs/symptoms occur (testing, potential antiviral treatment)
- **Unprotected exposure to a symptomatic person with H5N1 virus infection**

CDC Influenza

Influenza Testing (Outpatients)

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

➢ **Influenza A virus and A(H5) virus testing must be done at a public health laboratory****

Influenza tests available in clinical settings

- ***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***

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

**Confirmation at CDC

CDC Influenza

Influenza Testing (Hospitalized Patients)

- **Patients with lower respiratory tract disease (use recommended PPE*)**
  - 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***

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

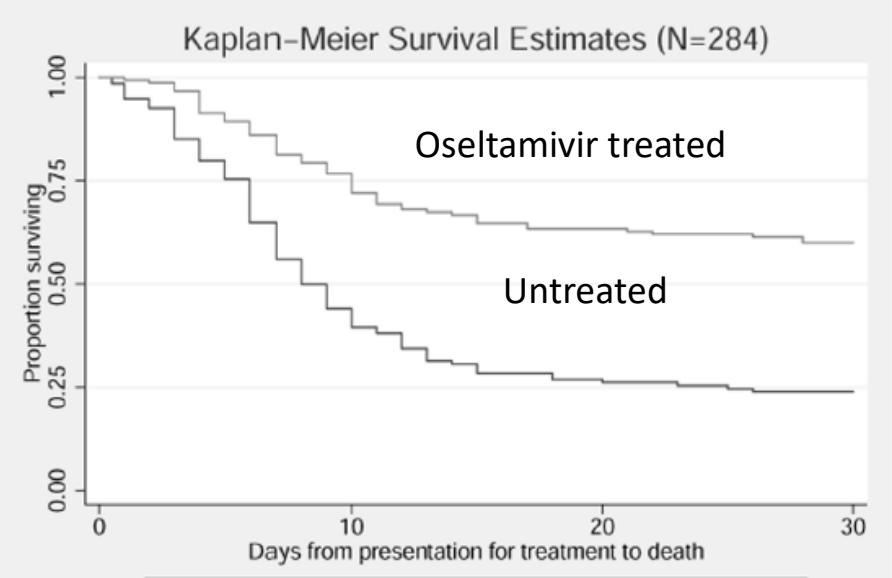
(Place patient in an airborne infection isolation room with negative pressure)

**Confirmation at CDC

CDC Influenza

Clinical Management: Antiviral Treatment for H5N1

- **No RCTs of antivirals for H5N1 patients**
- **Limited observational data**
  - **Oseltamivir treatment versus no treatment and starting treatment early after symptom onset is associated with lower mortality**



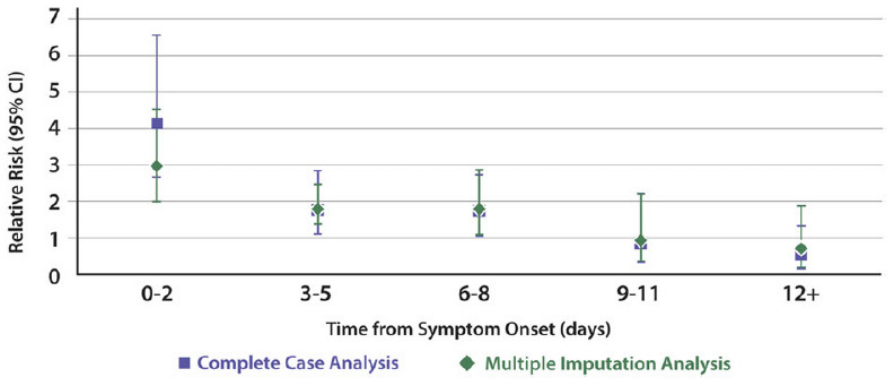


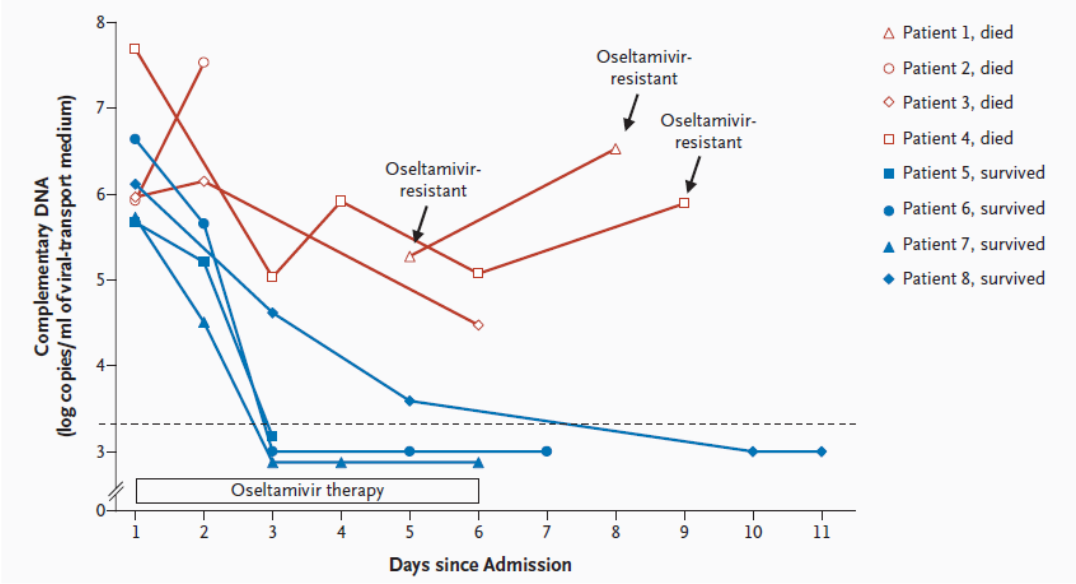
Figure 1. Comparison of relative risk of survival by timing of oseltamivir initiation between complete case and multiple imputation analysis. Squares, complete case analysis; diamonds, multiple imputation analysis. CI, confidence interval.

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

Clinical Management: Antiviral Treatment

- **H5N1 viruses infecting patients in 2024 are susceptible to Oseltamivir**
- **Start Oseltamivir treatment empirically as soon as possible for suspected H5N1 virus infection (based on history of exposures)**
  - **Oseltamivir standard dosing: twice daily x 5 days (*no data for Baloxavir*)**

- **Lower respiratory tract disease:**
  - **Optimal Oseltamivir dosing/duration unknown; longer treatment for severe disease, prolonged shedding**
  - **Emergence of oseltamivir resistance reported during or after treatment**
  - **Combination antiviral treatment?**
    - **Oseltamivir + Baloxavir?**



de Jong NEJM 2005

Clinical Management: Hospitalized Patients

- Isolate patient, follow recommended infection prevention and control measures, use recommended PPE
- Oseltamivir treatment
- Supportive care of complications
  - Advanced organ support, critical care
- Adjunctive therapy - 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)

Case Presentation

Clinic visit

- 37-yo male presents with 3-day history of bilateral eye discomfort, photophobia, sore throat, headache, feverishness, non-productive cough, myalgia, diarrhea.
- Works at a poultry farm in Georgia
  - [HPAI A(H5N1) virus has not been identified in poultry or dairy farms in Georgia in 2024]
- Past medical history: unremarkable; never hospitalized, no surgeries, not up to date on adult immunizations, not received 2024 COVID-19 vaccine or 2024-2025 influenza vaccine; no current medications, non-smoker, no vaping
- Exam findings: afebrile, unremarkable vital signs, SpO2 96% RA
- Pertinent findings on physical exam:
  - Eyes: bilateral palpebral/tarsal inflammation, right eye subconjunctival hemorrhage, right eye purulent drainage
  - Throat: erythematous, no exudates
  - Lungs: good air exchange, slightly diminished breath sounds bilaterally

Differential Dx

- Community-acquired respiratory virus infection?
- Psittacosis?
- H5N1?
- Group A Streptococcal infection?
- Above with bacterial conjunctivitis?

Laboratory Testing

- Rapid SARS-CoV-2 antigen (nasal swab): negative
- Rapid Influenza A/B antigen (nasal swab): negative
- Rapid GAS antigen (throat swab): negative
- CXR: unremarkable

Management Plan

- Discharge home
- Erythromycin ophthalmic ointment

2nd Patient Encounter

- Patient returns 2 days later with worsening cough
- New history: was participating in poultry culling work at a commercial poultry farm in another state ("almost all the chickens died, I was helping to dispose of the dead chickens"), returned one day before the first clinic visit.
- Physical exam: afebrile, unremarkable vital signs, SpO2 94% RA
- Pertinent findings on physical exam:
  - Eyes: resolving bilateral palpebral/tarsal inflammation, resolving right eye subconjunctival hemorrhage, no drainage
  - Throat: erythematous, no exudates
  - Lungs: good air exchange, slightly diminished breath sounds bilaterally, non-focal exam

Differential Dx, Management Plan

- Rapid SARS-CoV-2 antigen (nasal swab): negative
- Rapid Influenza A/B antigen (nasal swab): negative
- Rapid GAS antigen (throat swab): negative
- CXR: Mild bilateral interstitial infiltrates

- Referred to local public health department for suspected H5N1
  - Collected conjunctival swabs, NP swab, combined nasal/throat swab and sent to GA Department of Public Health laboratory for influenza A, B, and subtyping: A(H1N1)pdm09, A(H3), A(H5)
  - Prescribed empiric oseltamivir treatment
  - Close monitoring - referral to ED?
  - Local public health to f/u on testing results, household contacts

Take Home Points

- Rapid Influenza A/B antigen tests have low sensitivity to detect seasonal influenza A and B viruses, and to detect novel influenza A viruses in respiratory specimens, and cannot specifically identify A(H5) virus
- If H5N1 is suspected:
  - Contact local and state public health
  - Start empiric Oseltamivir treatment as soon as possible
  - Isolate patient; collect recommended clinical specimens for testing at a public health laboratory (CDC rRT-PCR influenza assay), if influenza A+, run subtyping for A(H1) and A(H3): if negative, then run A(H5); confirm A(H5)+ results at CDC
  - Monitor patient for clinical worsening, monitor close contacts (household) and start oseltamivir PEP if patient tests A(H5)+

Resources

- H5 Bird Flu: Current Situation | Bird Flu | CDC
- Case Definitions for Investigations of Human Infection with Avian Influenza A Viruses in the United States | Bird Flu | CDC
- Clinician Brief: Evaluating and Managing Patients Exposed to Animals or Persons Infected with Novel Influenza A Viruses of Public Health Concern | Bird Flu | CDC
- Interim Guidance for Infection Control Within Healthcare Settings When Caring for Confirmed Cases, Probable Cases, and Cases Under Investigation for Infection with Novel Influenza A Viruses Associated with Severe Disease | Bird Flu | CDC
- Interim Guidance on Specimen Collection and Testing for Patients with Suspected Infection with Novel Influenza A Viruses Associated with Severe Disease or with the Potential to Cause Severe Disease in Humans | Bird Flu | CDC
- Interim Guidance on the Use of Antiviral Medications for Treatment of Human Infections with Novel Influenza A Viruses Associated with Severe Human Disease | Bird Flu | CDC
- Interim Guidance on Influenza Antiviral Post-exposure Prophylaxis of Persons Exposed to Birds or Other Animals with Novel Influenza A Viruses Associated with Severe Human Disease or with the Potential to Cause Severe Human Disease | Bird Flu | CDC
- Interim Guidance for Follow-up of Close Contacts of Persons Infected with Novel Influenza A Viruses Associated with Severe Human Disease or with Potential to Cause Severe Human Disease, and Use of Antiviral Medications for Post-exposure Prophylaxis | Bird Flu | CDC