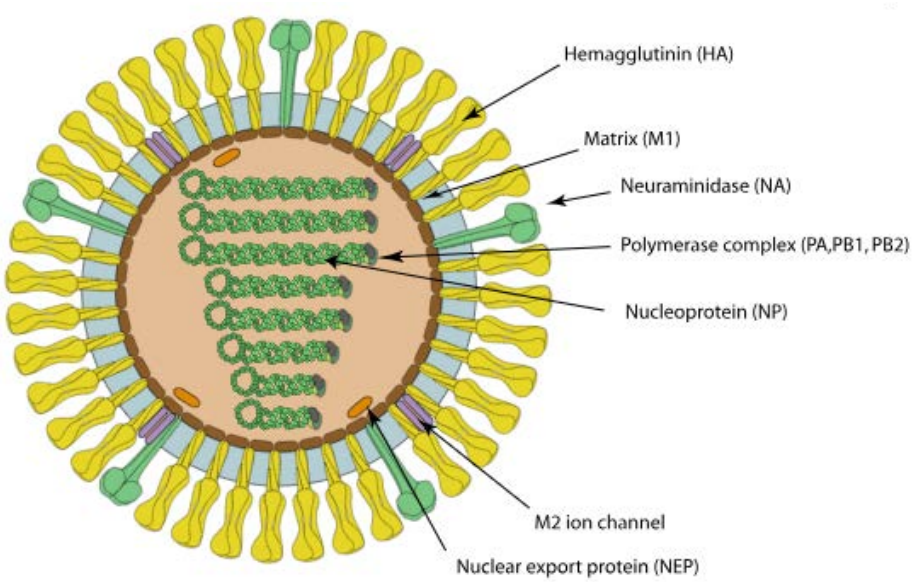

Highly Pathogenic Avian Influenza A(H5N1) Virus Infection in a Dairy Farm Worker

Uyeki TM, Milton S, *et al*. 2024, N Engl J Med (IF 4.7, H-Index 58, Q1)
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FACULTAD DE MEDICINA UASLP

LABORATORIO DE GENOMICA VIRAL Y HUMANA
FACULTAD DE MEDICINA
UASLP

QFB. JM Dávila-Meza
Dra. SE Guerra-Palomares
Dr. CA García-Sepúlveda

Laboratorio de Genómica Viral y Humana
Facultad de Medicina
Universidad Autónoma de San Luis Potosí

Introduction

The avian influenza virus, typically spread among birds, has seen an increase in mammalian cases due to changes in its ecology and epidemiology.

The highly pathogenic H5N1 virus currently circulating in the Americas originated from reassortment events in wild birds in Europe and low pathogenicity strains in wild and domestic birds.

(CDC 2025)

History of HPAI

Since 2020, the H5N1 subtype of clade 2.3.4.4b has caused numerous deaths in wild and domestic birds across Africa, Asia, and Europe.

The virus spread to North America in 2021 and reached Central and South America in 2022.

By 2023, outbreaks were reported in 14 countries and territories, mainly in the Americas.

The risk of infection in mammals and humans increases with contact with infected birds or contaminated environments.

Since 2022, 19 countries across three continents have reported mammalian outbreaks.

Recently, the detection of H5N1 viruses in non-avian species, including terrestrial and marine mammals, has increased.

Introduction

Sporadic human infections with highly pathogenic avian influenza (HPAI) A(H5N1) virus:

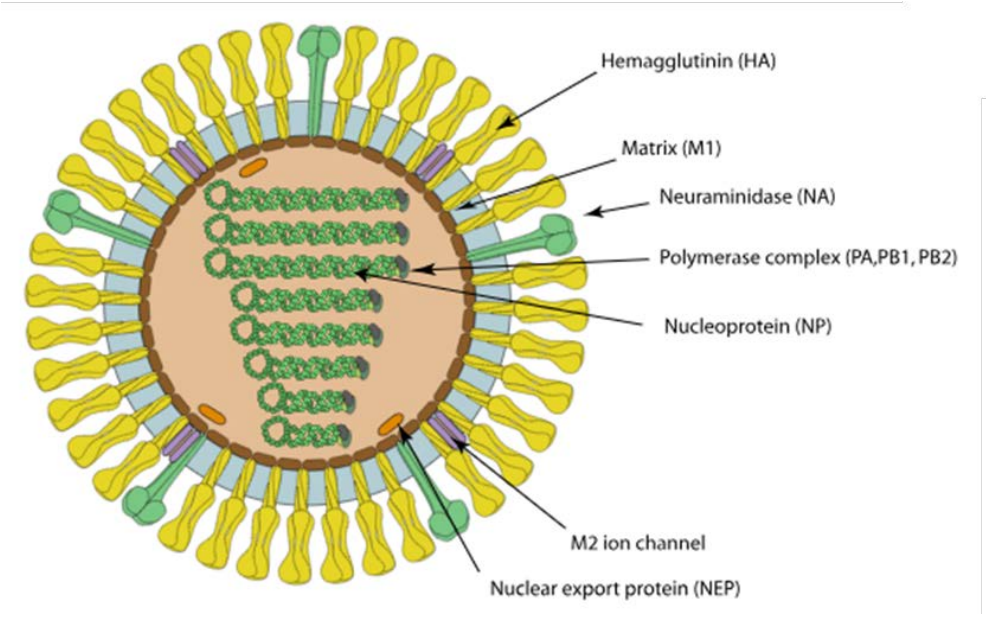
- Wide spectrum of clinical severity
- Case fatality of more than 50%
- Reported in 23 countries over more than 20 years.

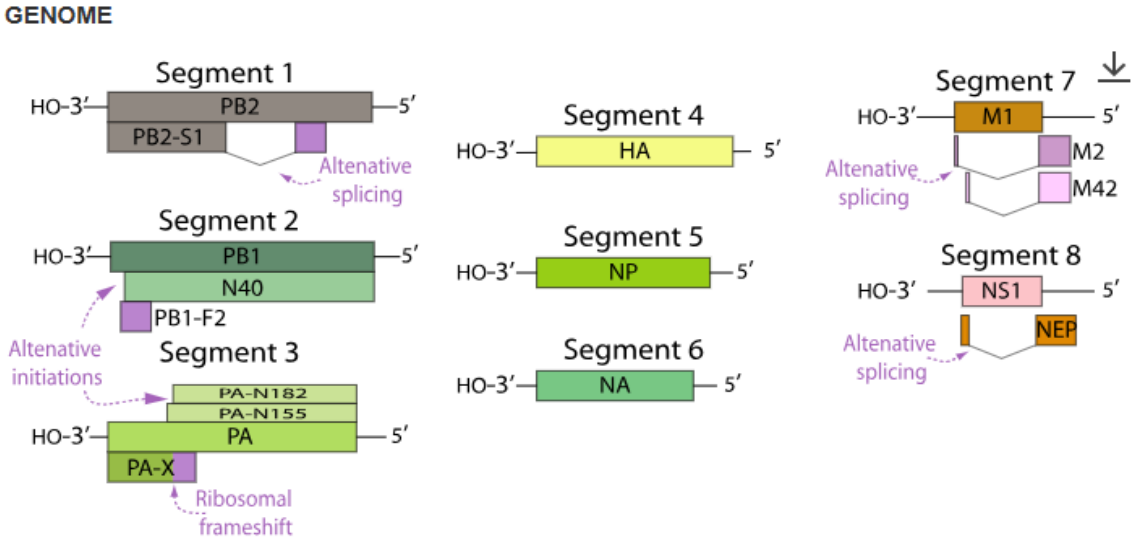
HPAI A(H5N1) clade 2.3.4.4b viruses have spread widely among wild birds worldwide since 2020–2021, resulting in outbreaks in poul try and other animals.

Recently, HPAI A(H5N1) clade 2.3.4.4b viruses were identified in dairy cows, and in unpasteurized milk samples, in multiple U.S. states.

This article discusses a case of HPAI A(H5N1) virus infection in a dairy farm worker in Texas.

Virus structure and genome organization





Viralzone (2024)

Clinical Case

At the end of March 2024, a dairy farm worker presented with redness and discomfort in the right eye, showing subconjunctival hemorrhages and fine serous drainage.

The patient had normal vital signs and clear lungs, with no history of fever, respiratory symptoms, or vision changes.

The worker reported direct contact with healthy and sick dairy cows showing signs of HPAI A(H5N1) infection.

No contact with sick or dead wild birds or poultry.

The worker wore gloves but did not use respiratory or eye protection.

Clinical Case

Conjunctival swab from the right eye and a nasopharyngeal swab were obtained for influenza testing.

RT-PCR results were presumptive for influenza A and A(H5) virus in both specimens.

On the basis of a presumptive A(H5) result:

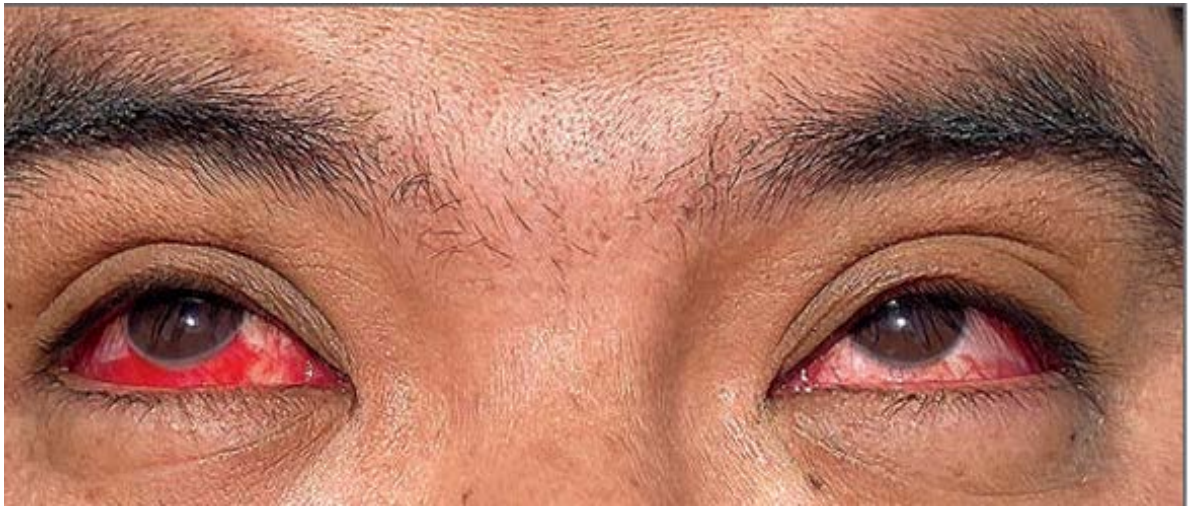
- Home isolation was recommended
- Oral oseltamivir (75 mg twice daily for 5 days) provided for worker
- Oral oseltamivir (75 mg twice daily for 5 days) for postexposure prophylaxis of household contacts.

The next day, the worker reported no symptoms except discomfort in both eyes.

Clinical Case

Reevaluation revealed subconjunctival hemorrhage in both eyes, with no visual impairment.

Over the subsequent days, the worker reported resolution of conjunctivitis without respiratory symptoms, and household contacts remained well.



Clinical Case

On the basis of real-time RT-PCR and sequencing, the Centers for Disease Control and Prevention confirmed HPAI A(H5N1) virus infection in the conjunctival and nasopharyngeal swab specimens obtained on the day of symptom onset.

Additional clinical specimens were not available for influenza testing.

vRNA purified from nasopharyngeal swab specimen (Ct of 33) failed to yield sequence information.

Complete genome sequences from the conjunctival swab specimen (Ct value, 18).

Confirmed that the virus belonged to clade 2.3.4.4b (genotype B3.13),

Virus isolation from both the conjunctival and nasopharyngeal swab specimens yielded identical virus.

Phylogenetic Analysis

Phylogenetic trees were constructed for each viral gene segment by aligning them with related virus sequences from GISAID and GenBank.

Concatenated genome phylogenetic tree.

All gene segments closely related to viruses detected in Texas dairy cattle and genotype B3.13 viruses found in wild birds in Texas during March 2024.

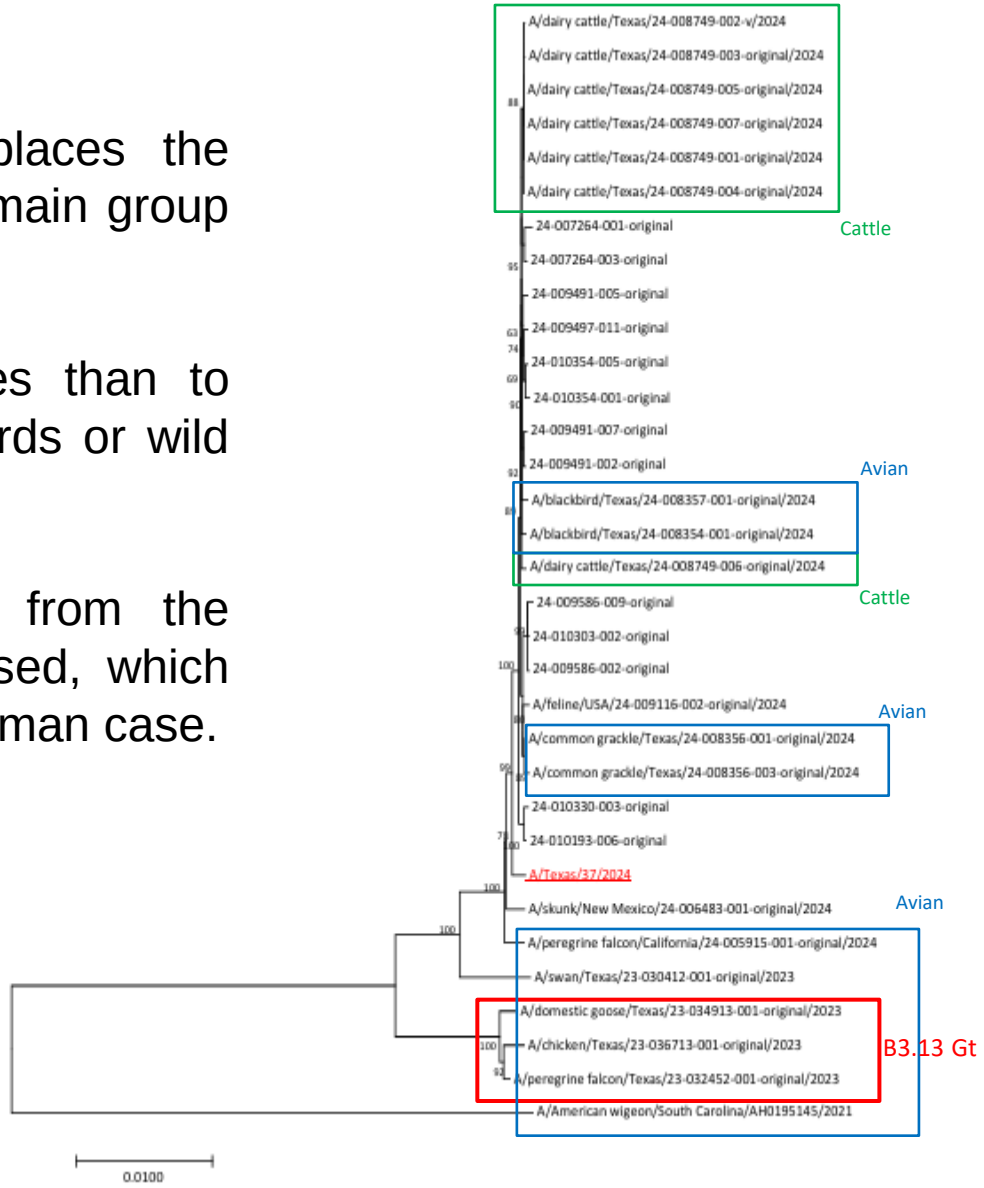
5 bp differences in PB2 gene and 1 bp in HA gene observed vs reference A/Texas/37/2024 (initial bovine outbreak).

Phylogenetic Analysis

A concatenated phylogenetic tree places the human sequence slightly outside the main group of bovine sequences from Texas.

Isolate is closer to Texan sequences than to genotype B3.13 obtained from wild birds or wild mammals.

No sequence data were available from the location where the worker was exposed, which limits the direct comparison with the human case.



Phylogenetic Analysis

Viral sequences from cattle and from the worker maintained primarily avian genetic characteristics and lacked changes in the hemagglutinin gene that would affect receptor-binding specificity (e.g., binding to α2-6–linked sialic acid receptors, primarily located in the human upper respiratory tract) and transmission risk to humans.

The virus identified in the worker's specimen had a change (PB2 E627K) that has been associated with viral adaptation to mammalian hosts and detected previously in humans and other mammals infected with HPAI A(H5N1) viruses and other avian influenza A virus sub types, including A(H7N9) and A(H9N2).

No genetic markers associated with reduced susceptibility to influenza antiviral drugs approved by the Food and Drug Administration (FDA) were identified.

Antigenic Analysis

The A/Texas/37/2024 virus antigenically characterized using ferret antisera generated against pre-pandemic clade 2.3.4.4b. candidate vaccine viruses (CVVs).

Cross-reactivity between A/Texas/37/2024 and these CVVs.

Cross-reactivity equivalent to homologous virus titers for ferret antisera generated against IDCDC-RG78A (A/American Wigeon/South Carolina/22-000345-001/2021-like CVV) and IDCDC-RG80A (A/chicken/Ghana/AVL-763_21VIR7050-39/2021-like CVV).

However, the cross-reactivity of the antiserum generated against IDCDC-RG71A (A/Astrakhan/3212/2020-like CVV) was 2 to 4 times lower compared to the homologous virus titers.

Supplemental Table 1. Hemagglutination inhibition assay of HPAI A(H5Nx) viruses

REFERENCE ANTIGENS	Subtype	Clade	IDCDC-RG71A	IDCDC-RG78A	IDCDC-RG80A
IDCDC-RG71A (A/Astrakhan/3212/2020-like)	H5N8	2.3.4.4b	**160**	80	160
IDCDC-RG78A (A/American Wigeon/South Carolina/22-000345-001/2021-like)	H5N1	2.3.4.4b	80	**160**	320
IDCDC-RG80A (A/chicken/Ghana/AVL-763_21VIR7050-39/2021-like)	H5N1	2.3.4.4b	40	40	**320**
TEST ANTIGENS					
A/Texas/37/2024, conjunctival swab isolate	H5N1	2.3.4.4b	80	160	320
A/Texas/37/2024, nasopharyngeal swab isolate	H5N1	2.3.4.4b	40	160	320

Discussion

Conjunctivitis is rare in human cases of HPAI A(H5N1) infection.

vRNA levels were lower in the nasopharynx compared to the conjunctiva, indicating differences in viral replication.

Conjunctival infection might have occurred through contact with contaminated hands or aerosols from infected cows.

Fomite transmission cannot be ruled out.

If cow-to-human transmission occurred, it would be the first documented case globally.

Although conjunctivitis is mild, H5N1 has pandemic potential and can cause severe disease.

It is recommended to avoid unpasteurized milk and strengthen preventive measures on infected farms.

Discussion

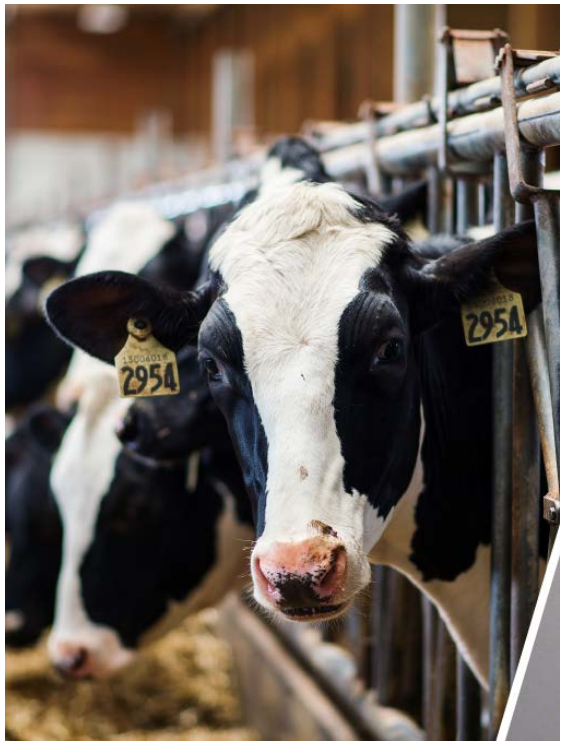
There are significant knowledge gaps regarding how the virus affects cows, including pathogenesis, transmission, and duration of viral shedding.

Genetic differences between human and bovine viruses are expected, as wild birds are the initial source.

The virus may have circulated undetected in farms, increasing its genetic diversity.

The human virus showed good cross-reactivity with current candidate vaccines, suggesting they would likely provide protection.

However, monitoring the genetic evolution of the virus in cows is critical to ensure that vaccines remain effective.



Comments and perspectives

From early 2003 to November 1, 2024, 939 human cases of avian influenza A(H5N1), including 464 deaths (a fatality rate of 49.4%), were reported to the World Health Organization (WHO) from 24 countries worldwide.

From 2022 to December 2, 2024, 61 human infections caused by avian influenza A(H5N1) were reported in four countries in the Americas:

- 58 cases in the United States,
- 1 case in Canada confirmed on November 13, 2024,
- 1 case in Chile reported on March 29, 2023, and
- 1 case in Ecuador reported on January 9, 2023.

Comments and perspectives

In 2024, 58 human cases were reported:

- 1 in Canada
- 57 in the United States.
    - Of these cases, 74% (n=43) reported between October and November 2024.

Exposure to dairy cattle was associated with 59% of the cases, and in 5% (n=3), the source of exposure has not yet been determined.

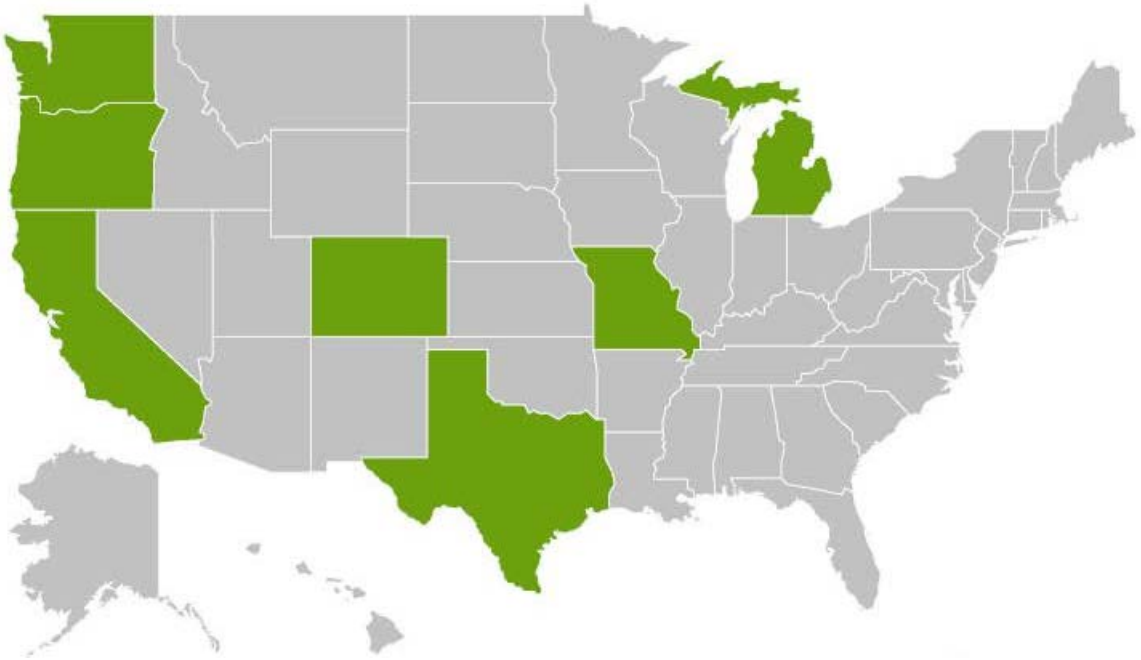
96% (n=56) of the cases involved individuals > 18 years of age, 2 cases were reported in individuals under 18, 1 in Canada and one in the United States.

Regarding the subtype:

- 21% (n=12 cases) were confirmed as H5N1
- 21% (n=12 cases) were identified as clade 2.3.4.4b.
    - For three of these cases, the genotype was B3.13. (WHO, 2024)

Comments and perspectives

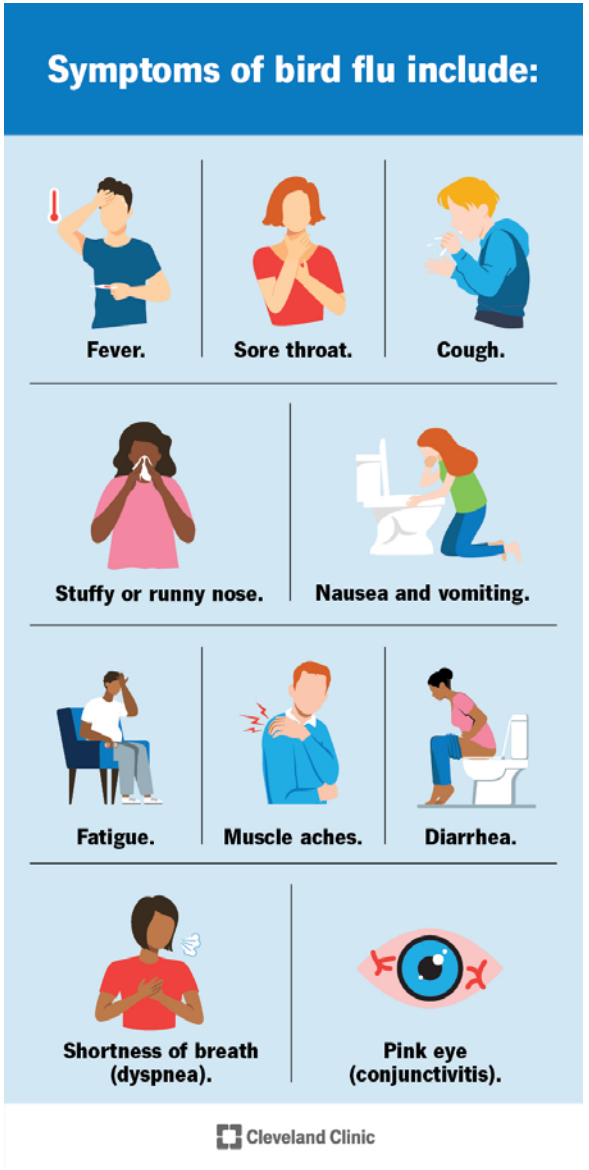
In the United States, from January to December 2, 2024, 57 human cases of influenza A(H5N1) were confirmed in seven states: California (n=31), Colorado (n=10), Michigan (n=2), Missouri (n=1), Texas (n=1), Oregon (n=1), and Washington (n=11). Ninety-eight percent (n=56) of the cases involved individuals over 18 years of age.



Comments and perspectives

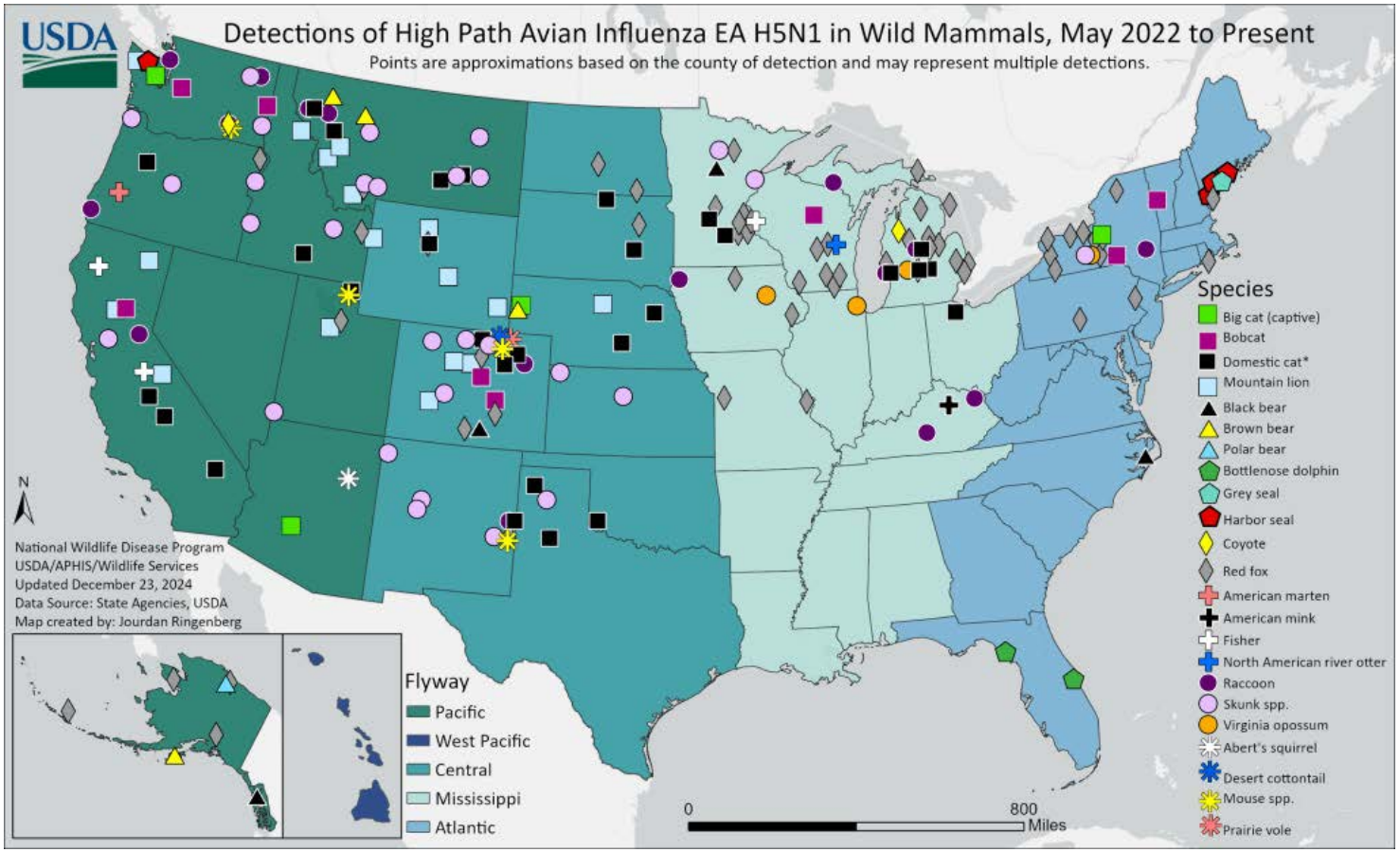
Of the 51 cases with symptom information available:

- 90% (n=46 cases) presented conjunctivitis
- 29% (n=15 cases) had fever, and
- 20% (n=10 cases) experienced headaches.



Comments and perspectives

Of the total cases in the United States, 60% (n=34 cases) were linked to exposure to sick or infected dairy cattle, while 37% (n=21 cases) were associated with exposure to poultry. In two cases, the source of exposure could not be determined.



Comments and perspectives

Epidemiological Situation in Mexico

As of epidemiological week 46 of the 2024-2025 seasonal influenza season, Mexico has seen:

- 71.7% Influenza A (H3N2).
- 14.5% influenza A (H1N1)
- 8.1% influenza B
- 5.7% unsubtyped influenza A.

No human cases of avian influenza A (H5N1) have been reported. (yeah right!)

From 2022 to week 46 of 2024, Mexico has reported 46 outbreaks of avian influenza in wild and domestic birds, 28 occurring in 2024.

During this period, 524 combined samples were processed by InDRE:

- 523 tested negative for influenza A (H5N1) and A (H7N3).
- One sample tested positive for influenza A (H5N2).

Conclusions

This is the first potential case of A(H5N1) virus transmission from cattle to a human, highlighting the virus's adaptability to new hosts.

The infection showed tropism for conjunctival tissue, suggesting non-respiratory transmission routes, such as direct contact.

Agricultural workers face higher zoonotic risks due to contact with infected animals and inadequate protective measures.

The PB2 E627K marker indicates mammalian adaptation and underscores the virus’s pandemic potential.

The cattle outbreak underscores risks to food safety and the need to avoid unpasteurized dairy products in affected areas.

Conclusions

Strengthening collaboration among public health, veterinary, and environmental sectors is crucial to mitigate zoonotic risks.

Continuous monitoring and biosecurity measures are necessary to address questions about the virus's evolution in cattle.

Current vaccines demonstrate cross-reactivity with the virus, providing hope for effective outbreak responses.

Implementing surveillance, farm controls, and education on zoonotic risks is essential to prevent the spread of the virus.

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LANCOBI IPN UNAM UASLP

Laboratorio de Genómica Viral & Humana BSL-3, Facultad de Medicina UASLP

- Dr. Christian A. García-Sepúlveda (Operaciones BSL-3, Virología Molecular)
- Dra. Sandra E. Guerra-Palomares (Operaciones BSL-3, Virología Molecular)
- LTS. Dulce M. Hernández Piña (Lab Manager)
- Dr. Andreu Comas García (Epidemiología molecular)
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- MVZ. Carolina Escalante Vargas (Trabajo de campo con murciélagos)

Laboratorio Nacional de Vacunología y Virus Tropicales, Escuela Nacional de Ciencias Biológicas IPN

- Dra. Ma. Isabel Salazar Sánchez (Virología molecular e inmunología)
- Dr. Jesús Miguel Torres Flores (Operaciones BSL-3)
- Dr. Joel Armando Vázquez Pérez (Virólogo especializado en Influenzavirus)
- Dr. Rosa Elena Sarmiento Silva (Viróloga especializada en virus respiratorios)

Departamento de Inmunología del Instituto de Investigaciones Biomédicas UNAM

- Dra. Clara Inés Espitia Pinzón (Operaciones BSL-3)
- Dr. Antonio García Knight (Inmunólogo viral con énfasis en virus emergentes)
- Dr. Renato León Rodríguez (Virología molecular)
- Dr. Wenceslao Coronado Aceves (Evaluación de fármacos in vitro e in vivo)
- Dra. Georgina Diaz Herrera (Médica Veterinaria pequeñas especies)
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Viral & Human Genomics Laboratory

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