H5 Influenza Virus ("Bird Flu"):

Is a Pandemic Likely?

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Perelman School of Medicine

The University of Pennsylvania

April 2, 2025

May 1997

May 9, 1997

- A 3-year-old boy in Hong Kong dies of influenza.
- CDC sends a team of scientists to investigate. In a wet market, where local farmers slaughtered and sold their chickens, they found the source of the deadly virus.
- This strain of influenza, H5N1, was particularly deadly, killing 7 of every 10 chickens.
- In December 1997, health officials, trying to control the deadly outbreak, began “a wholesale slaughter of birds.”

Birds slaughtered in bid to contain mystery flu

December 29, 1997
Web posted at: 7:25 a.m. EST (1225 GMT)


(CNN)

HONG KONG, China (CNN) -- Poultry workers and government teams in Hong Kong began the wholesale slaughter of birds Monday, the first step in a plan to contain the mysterious "bird flu" virus that has crossed over to humans and caused four recent deaths.

December 29, 1997

The virus continued to spread

- Bird flu attacked chickens in Japan, Vietnam, Laos, Thailand, Cambodia, China, Malaysia, and Indonesia.
- Then the virus infected 18 more people, killing 6—a mortality rate of 33 percent. Typically, influenza has a mortality rate of less than 1 percent.
- Officials waited for an outbreak among people the following year, but it never came.
- And it didn't come the year after that or the year after that.

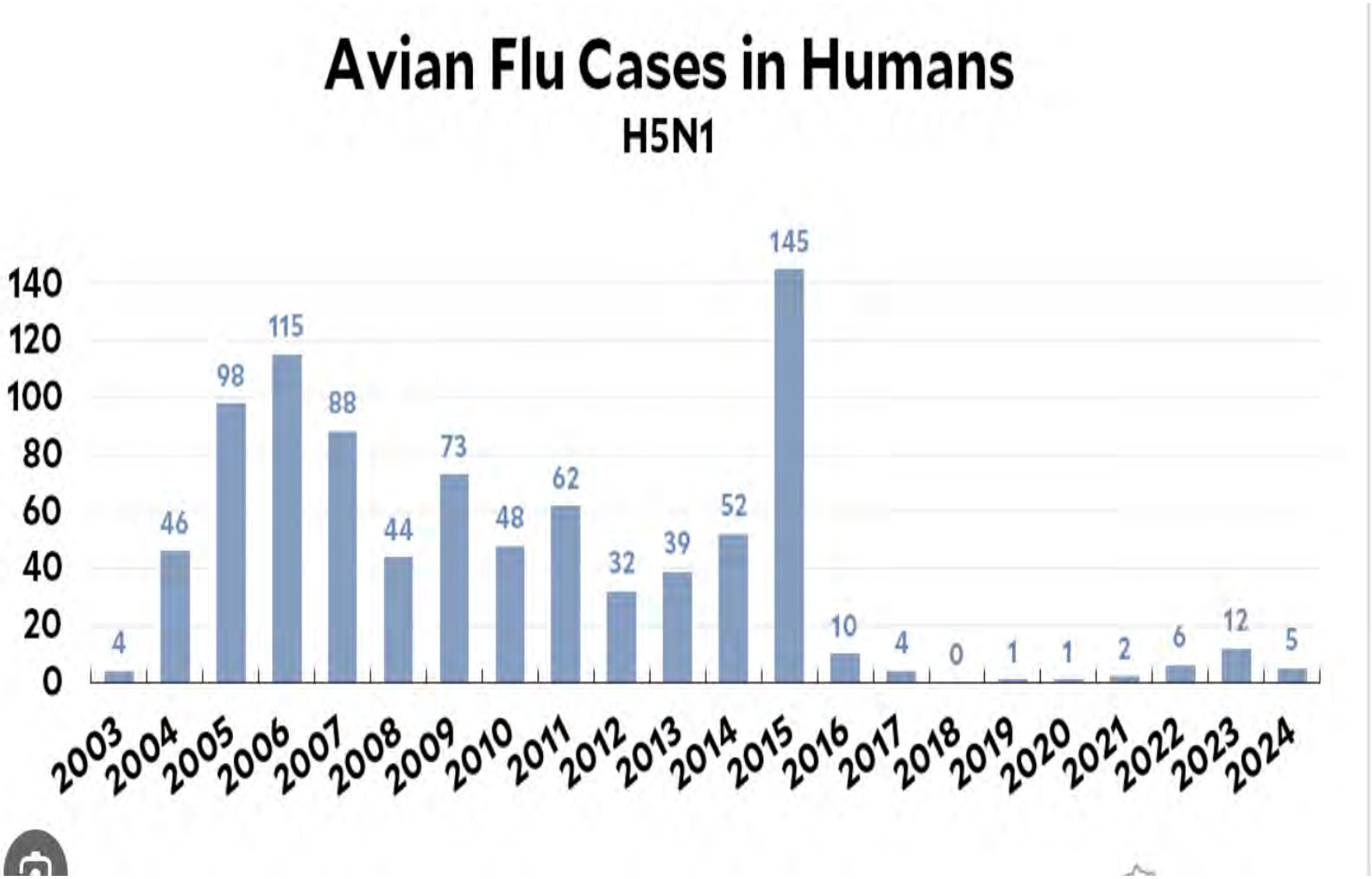
August 2003

August 2003

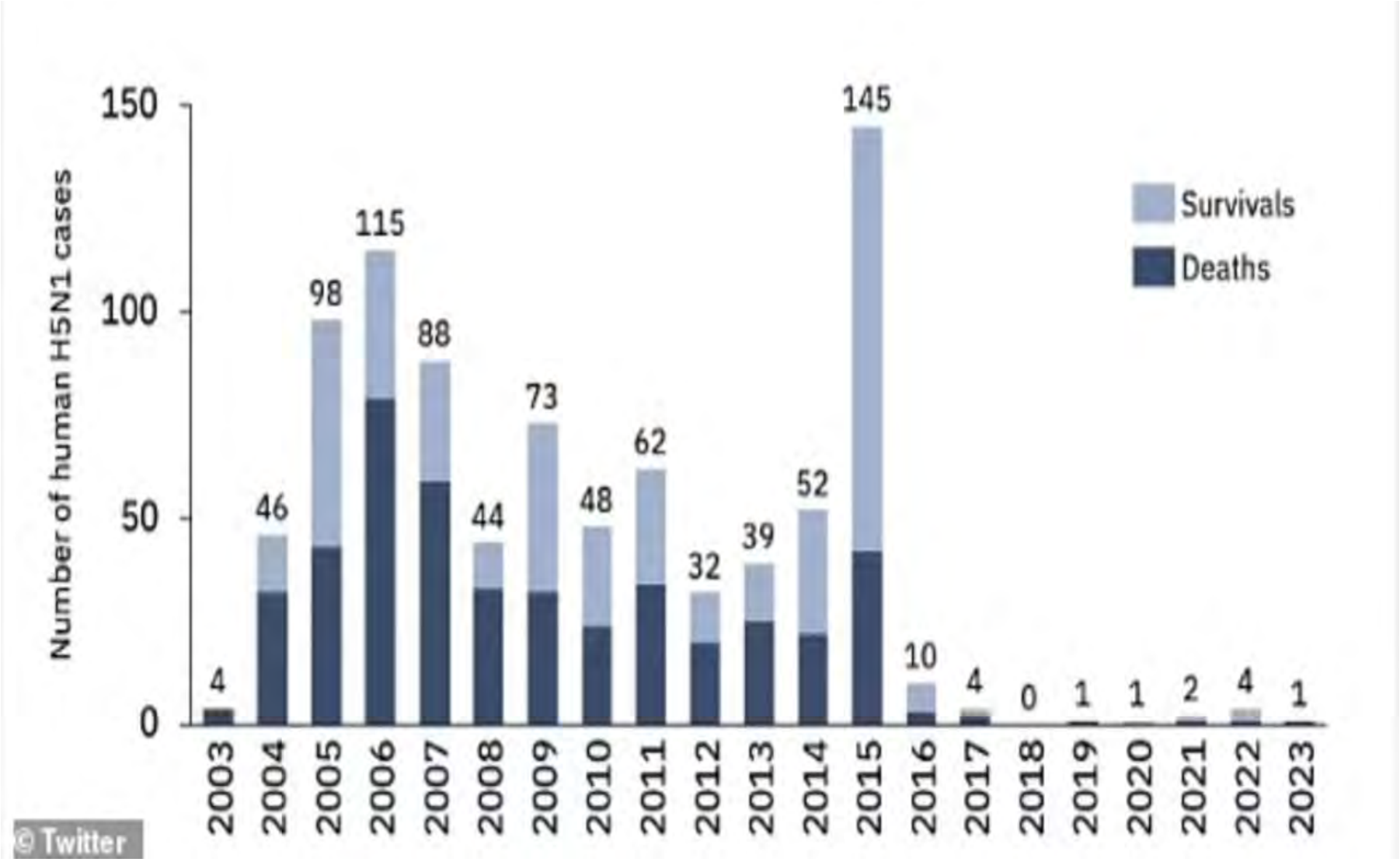
- Six years after the initial outbreak, bird flu reappeared in Southeast Asia. Again, the virus was first detected in chickens. Officials responded by killing hundreds of millions of them.
- Nonetheless, bird flu spread from chickens to ducks, geese, turkeys, and quail.
- Then the virus spread to mammals. First to mice, then to cats, then to a Tiger in a Thai zoo, then to pigs then to humans.
- By April 2005, bird flu had infected 97 people and killed 55, a mortality rate of 57 percent.

February 9, 2004

Bird flu continued to spread

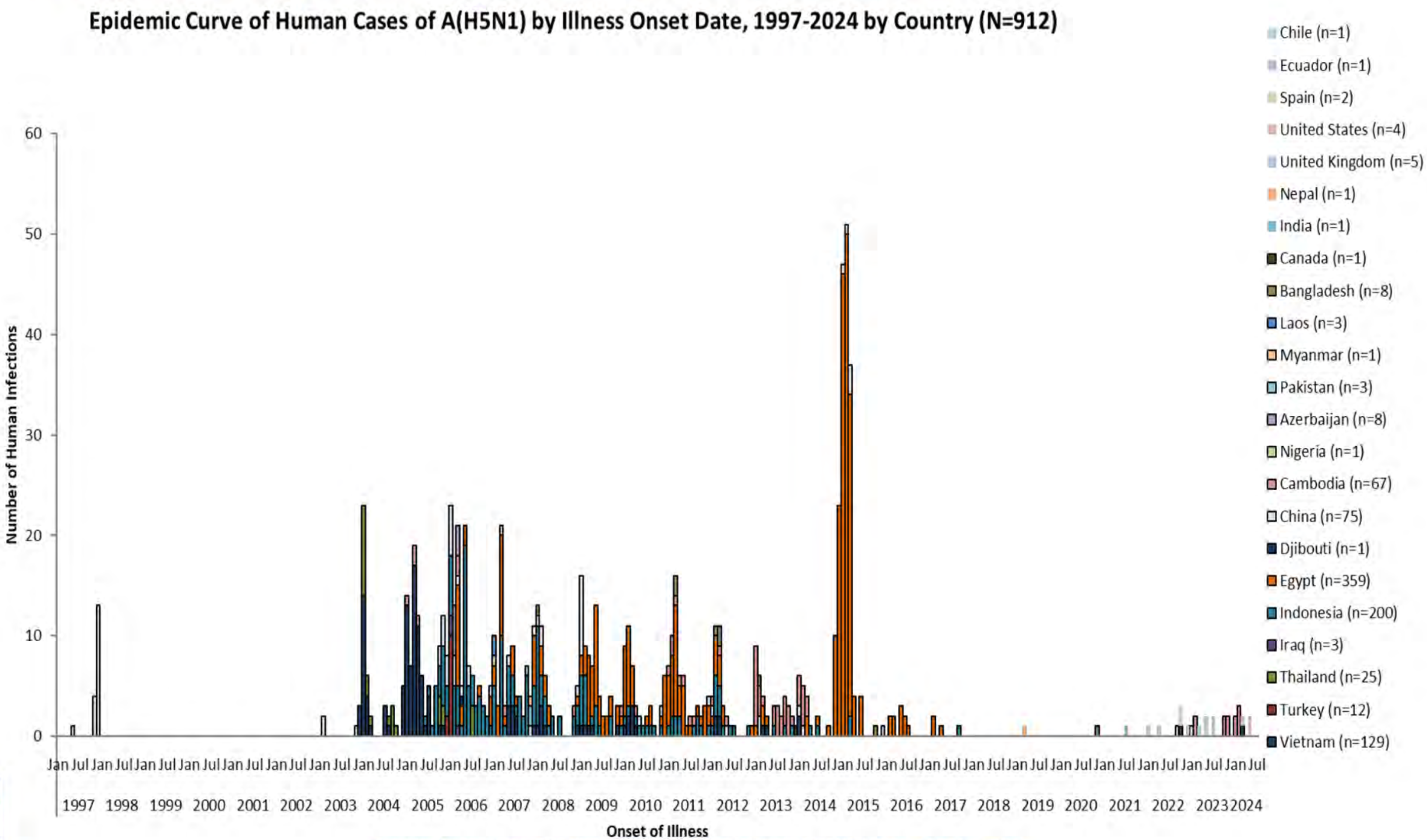


Bird flu continued to spread in people



Bird flu continues to have a high mortality rate

Human A(H5N1) Cases Since 1997



Technical Report: June 2024 Highly Pathogenic Avian Influenza A(H5N1) Viruses | Bird Flu | CDC

CDC Influenza

Bird flu has infected people in 23 countries

March 2024

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

TO THE EDITOR: Sporadic human infections with highly pathogenic avian influenza (HPAI) A(H5N1) virus, with a wide spectrum of clinical severity and a cumulative case fatality of more than 50%, have been reported in 23 countries over more than 20 years.[1] HPAI A(H5N1) clade 2.3.4.4b viruses have spread widely among wild birds worldwide since 2020–2021,[2,3] resulting in outbreaks in poultry and other animals.[2] 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.[4,5] We report a case of HPAI A(H5N1) virus infection in a dairy farm worker in Texas.

ambient air. Auscultation revealed clear lungs. There was no history of fever or feverishness, respiratory symptoms, changes in vision, or other symptoms. The worker reported no contact with sick or dead wild birds, poultry, or other animals but reported direct and close exposure to dairy cows that appeared to be well and with sick cows that showed the same signs of illness as cows at other dairy farms in the same area of northern Texas with confirmed HPAI A(H5N1) virus infection (e.g., decreased milk production, reduced appetite, lethargy, fever, and dehydration[5]). The worker reported wearing gloves when working with cows but did not use any respiratory or eye

Uyeki, T., et al. *New England Journal of Medicine* (2024) 390: 2028-2030

March 2024

- Adult dairy farm worker presents with pain in the right eye with subconjunctival hemorrhage. He didn't have fever or respiratory symptoms; his oxygen saturation was 97% on room air.
- Treated with oral oseltamivir (Tamiflu) with complete resolution of symptoms.

Texas, March 2024

Figure 1. Conjunctivitis with Subconjunctival Hemorrhage in Both Eyes.

Michigan, May 2024

CDC Confirms Second Human H5 Bird Flu Case in Michigan; Third Case Tied to Dairy Outbreak

Risk to general public remains low

Print

Press Release

For Immediate Release: Thursday, May 30, 2024

Contact: Media Relations

(404) 639-3286

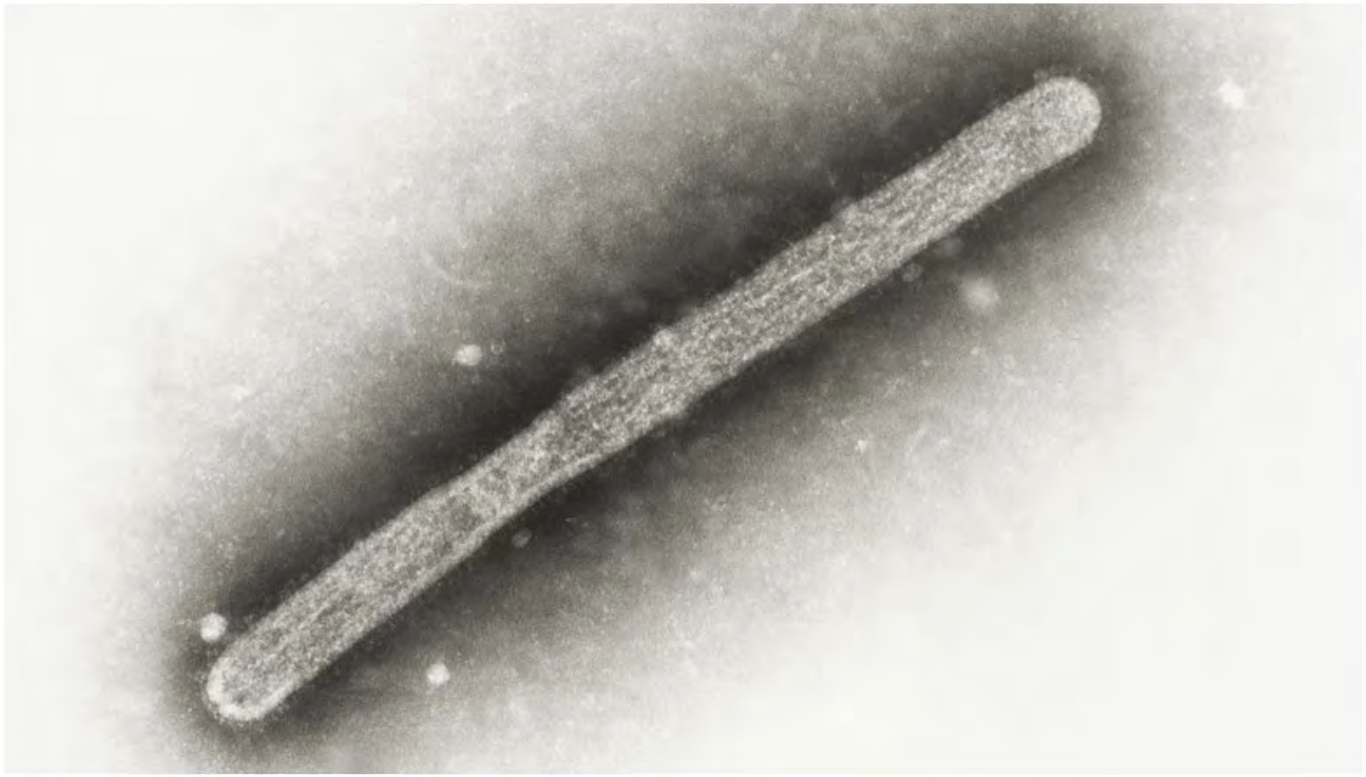
May 30, 2024 – A second human case of highly pathogenic avian influenza (HPAI) A(H5) virus infection has been identified in the state of Michigan. This is the third human case associated with an ongoing multistate outbreak of A(H5N1) in U.S. dairy cows. None of the three cases are associated with the others. As with the previous two cases

Michigan, May 2024

Third person in US tests positive for bird flu in connection to outbreak in dairy cattle

By Brenda Goodman, CNN

5 minute read · Updated 8:13 AM EDT, Fri May 31, 2024



A third person in the US has tested positive for an H5 bird flu virus, health officials announced Thursday.

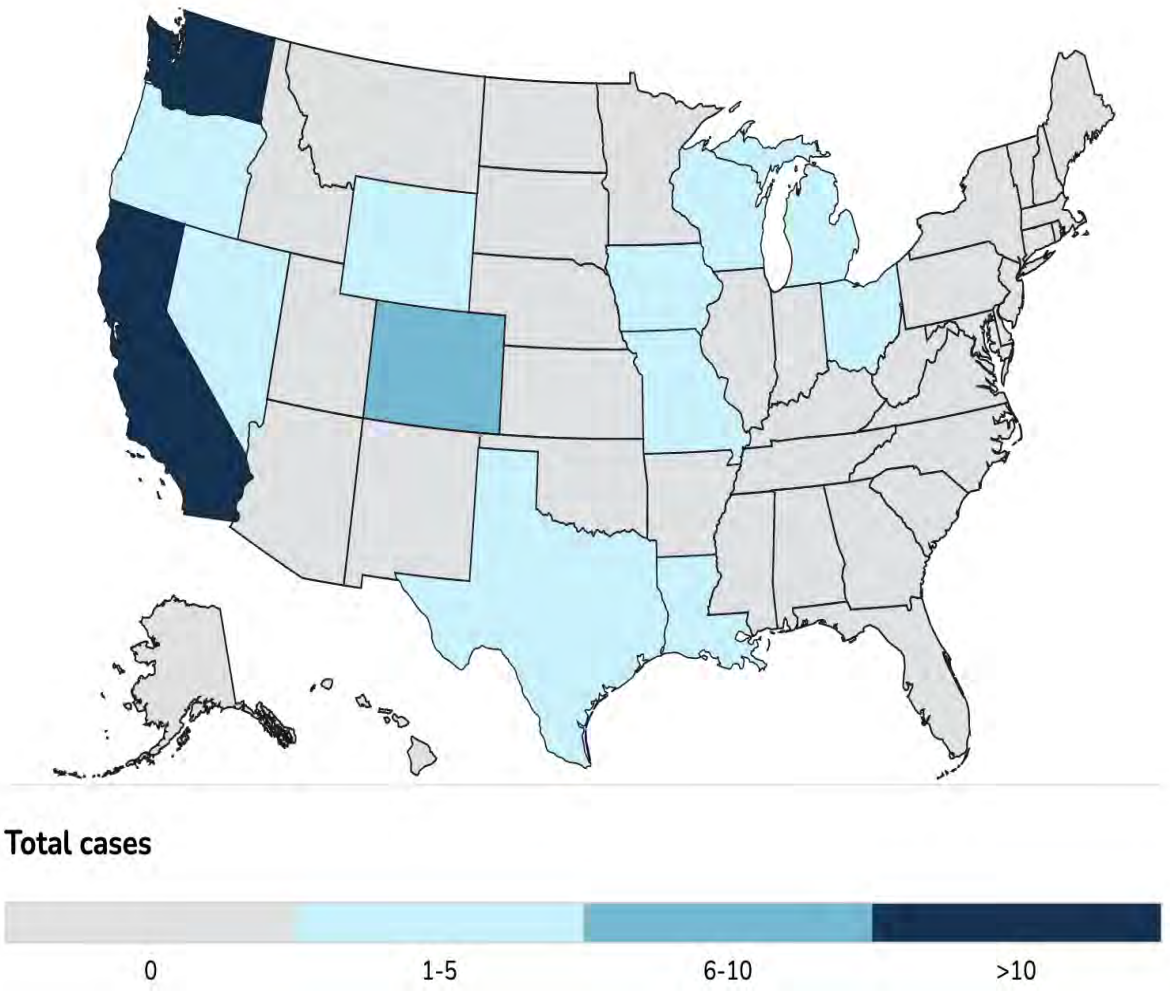
CDC, March 2025

National Total Cases: 70

Cases	Exposure Source
41	Dairy Herds (Cattle)*
24	Poultry Farms and Culling Operations*
2	Other Animal Exposure†
3	Exposure Source Unknown‡

NOTE: One additional case was previously detected in a poultry worker in Colorado in 2022. Louisiana reported the first H5 bird flu death in the U.S.

*Exposure Associated with Commercial Agriculture and Related Operations
†Exposure was related to other animals such as backyard flocks, wild birds, or other mammals
‡Exposure source was not able to be identified



March 2025

- 70 confirmed human cases in US.
- H5N1 viruses detected in:
  - 10,917 wild birds (D1.1 genotype)
  - 127,470,312 poultry in 50 states
  - 891 dairy herds in 16 states (B3.13 genotype)
  - All isolates susceptible to oseltamivir

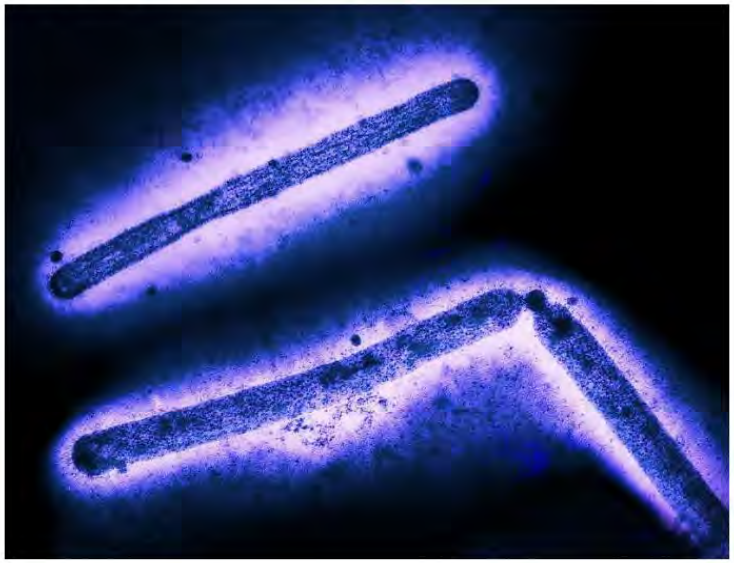
'Exceptionally rare' mutation on H5N1 virus in Canada tied to antiviral drug resistance

News brief | February 21, 2025

Mary Van Beusekom, MS

Topics: Avian Influenza (Bird Flu)

SHARE



NIAID / Flickr cc

In a **research letter** published this week in *Emerging Microbes & Infections*, researchers at the Canada Food Inspection Agency (CFIA) describe their discovery of a mutated H5N1 avian flu strain resistant to the antiviral drug oseltamivir (Tamiflu) on eight chicken farms in British Columbia in October 2024.

When investigating a widespread and ongoing H5N1 outbreak at 45 poultry farms, the CFIA National Centre for Foreign Animal Disease team sequenced the virus, identifying it as a clade 2.3.4.4b A(H5N1) strain. The virus had a neuraminidase surface protein derived from a low-pathogenic flu virus from a North American lineage.

Will H5N1 influenza virus become a human pandemic?

Maurice R. Hilleman, circa 1958

Maurice R. Hilleman (1919-2005), circa 1958. (B014616) (Image courtesy of the National Library of Medicine)

August 1957, Sagamihara, Japan

Japanese girl gargling a water solution for a culture sample in an influenza ward in Sagamihara Hospital, Japan, Aug. 9, 1957. (MIS 58-15573-67) (OHA 233.05: Medical Illustration Service Library)

Maurice Hilleman: The Man Who Predicted a Pandemic

Trenton Streck-Havill, Assistant Archivist | *August 25, 2022* | Share / Save

U.S. Army doctors and scientists cultivate candidate vaccine viruses (CVVs) in fertilized chicken eggs before the virus is killed to use in potential vaccine research. (MIS 58-15573-71) (OHA 233.05: Medical Illustration Service Library)

H2N2 influenza vaccine, 1957

Vial and packaging for the 1957 H2N2 vaccine, at the National Museum of American History. Producing the inoculation required hundreds of thousands of fertilized chicken eggs per day. National Museum of American History

Virologist Maurice Hilleman with his research team at the Walter Reed Army Medical Research Institute in 1957. That year Hilleman and his team would identify and develop 40 million vaccine doses to combat a flu virus from Hong Kong.

PHOTOGRAPH BY ED CLARK, THE LIFE PICTURE COLLECTION/GETTY

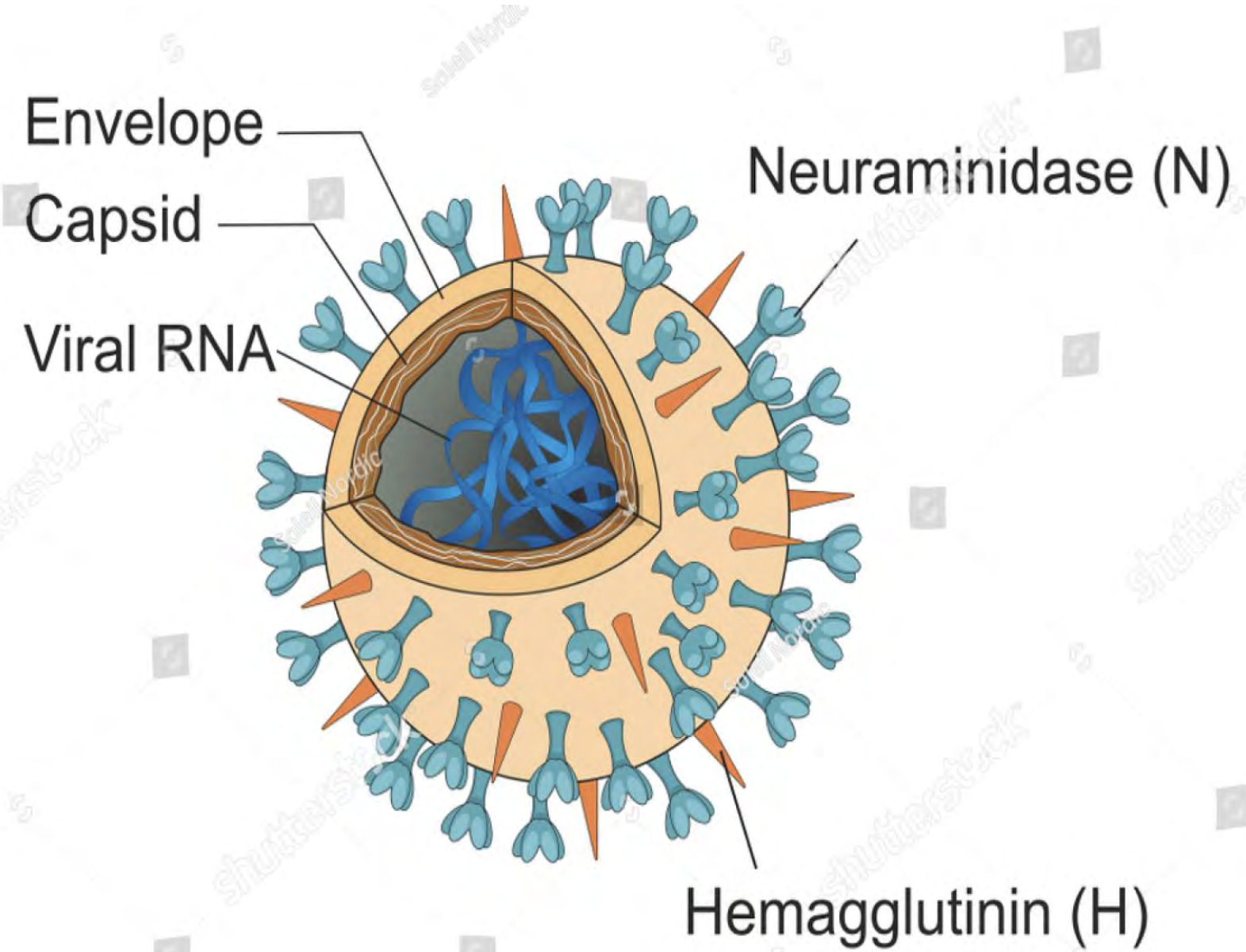
HISTORY & CULTURE | NEWS

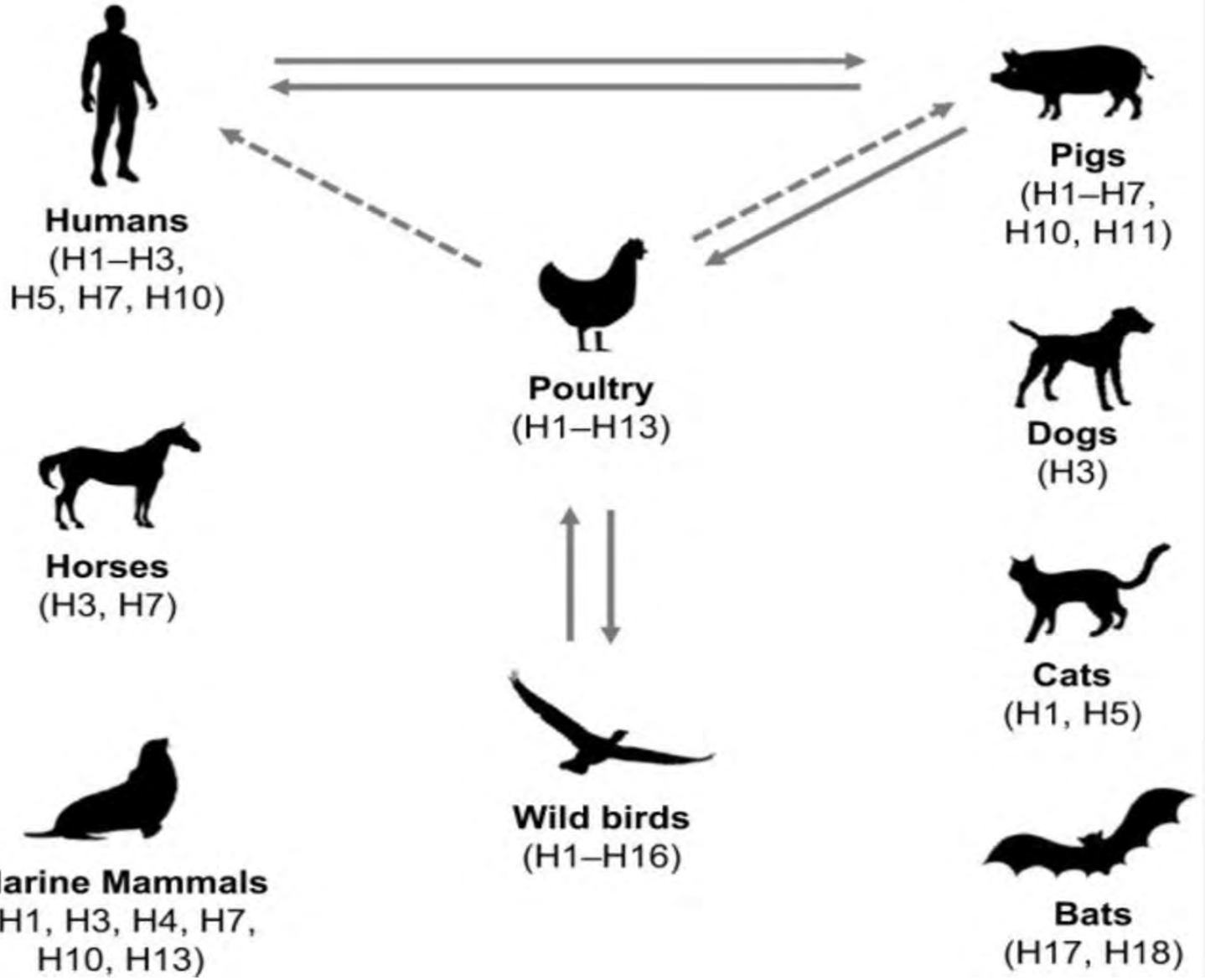
This virologist saved millions of children—and stopped a pandemic

Maurice R. Hilleman prediction

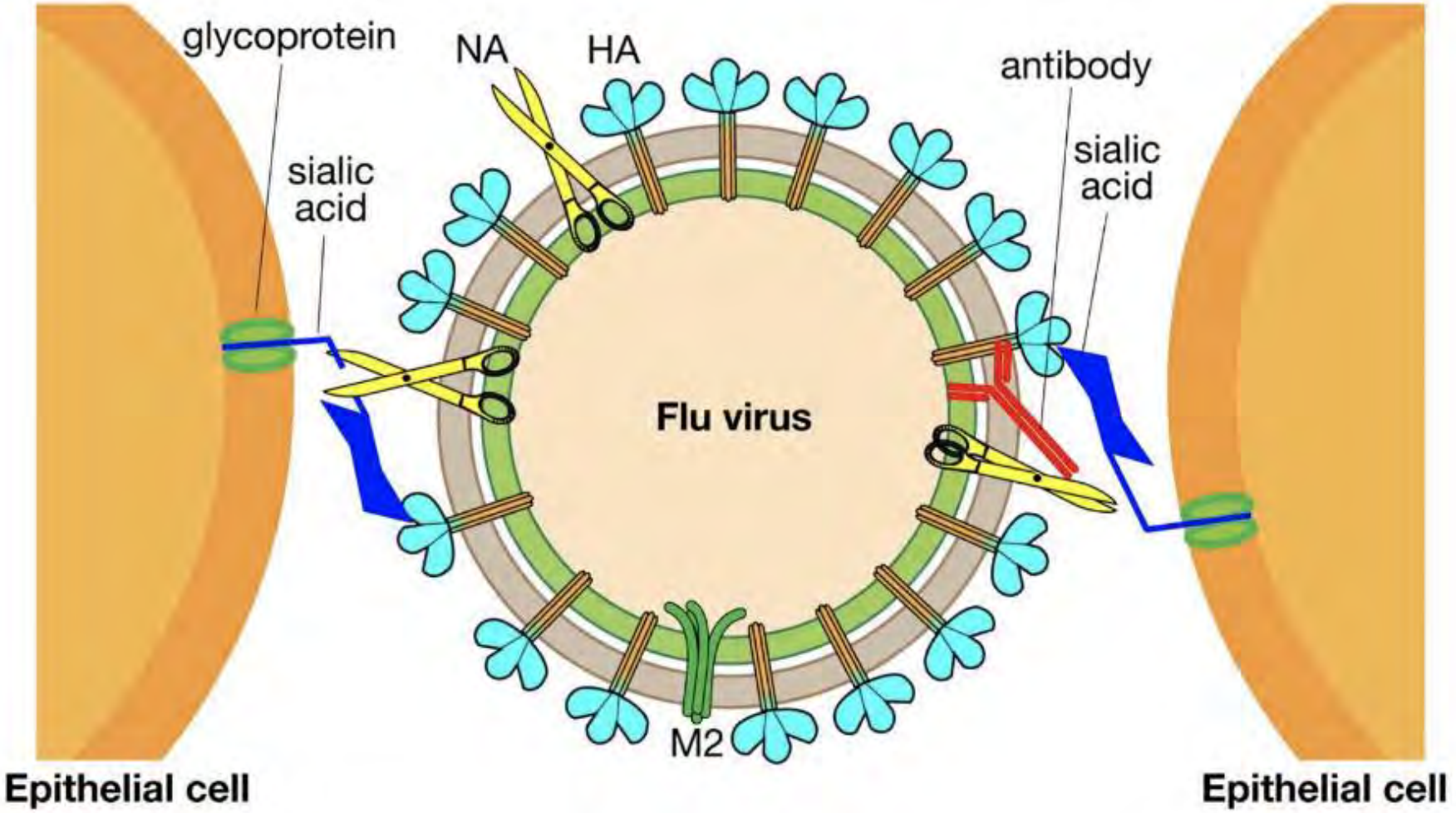
- Influenza viruses have been circulating in people since the mid-1300s.
- About 2-3 pandemics per century.
- Every pandemic has been caused by either H1, H2, or H3 viruses.
- H5 viruses have never caused a human pandemic. And Hilleman believed that they never would.

Why?

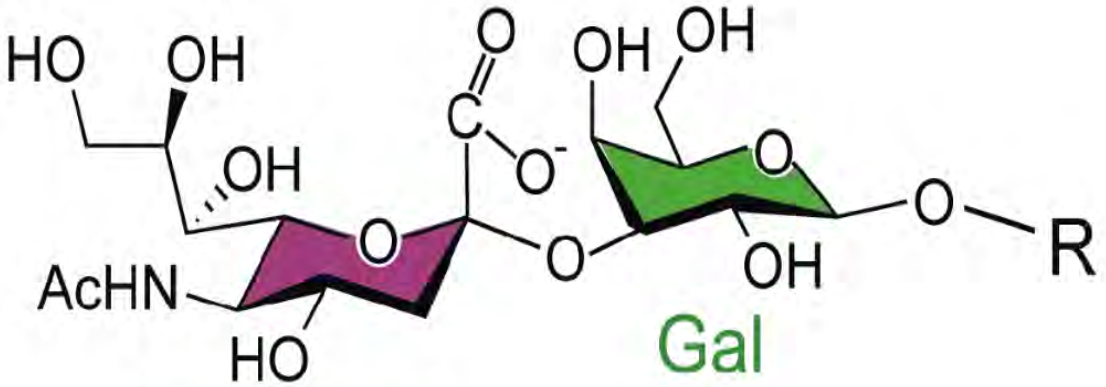

Envelope
Capsid
Viral RNA
Neuraminidase (N)
Hemagglutinin (H)


Humans
(H1–H3,
H5, H7, H10)
Pigs
(H1–H7,
H10, H11)
Poultry
(H1–H13)
Dogs
(H3)
Horses
(H3, H7)
Cats
(H1, H5)
Wild birds
(H1–H16)
Marine Mammals
(H1, H3, H4, H7,
H10, H13)
Bats
(H17, H18)

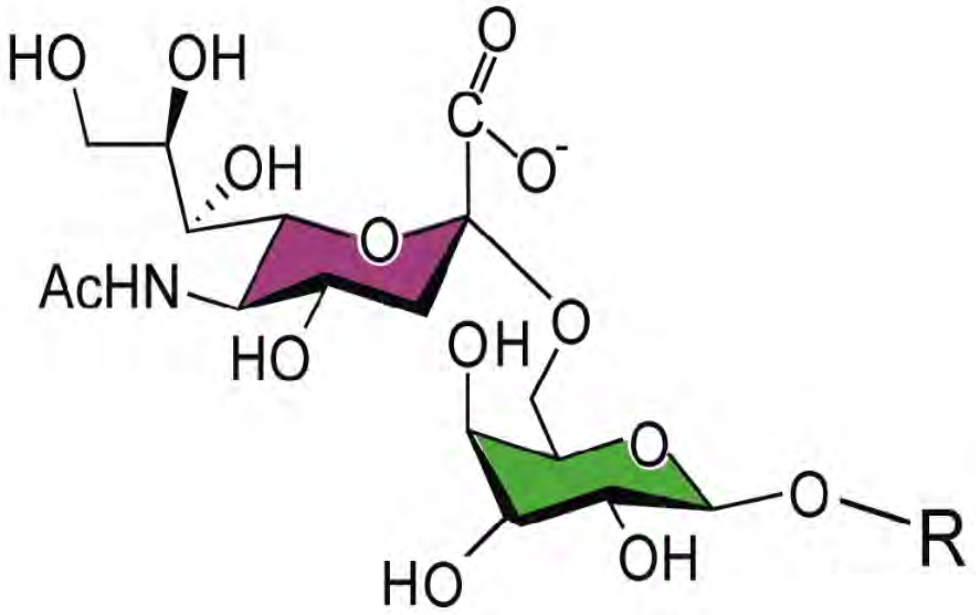
Viral hemagglutinin binds to a sialic acid receptor on the surface of cells



α2,3-linked Sia



α2,6-linked Sia



viruses

MDPI

Review

Sialic Acid Receptors: The Key to Solving the Enigma of Zoonotic Virus Spillover

Suresh V Kuchipudi [1,2,*], Rahul K Nelli [3], Abhinay Gontu [1,†], Rashmi Satyakumar [1,†], Meera Surendran Nair [1,†] and Murugan Subbiah [4]

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2 Center for Infectious Disease Dynamics, Pennsylvania State University, University Park, PA 16801, USA
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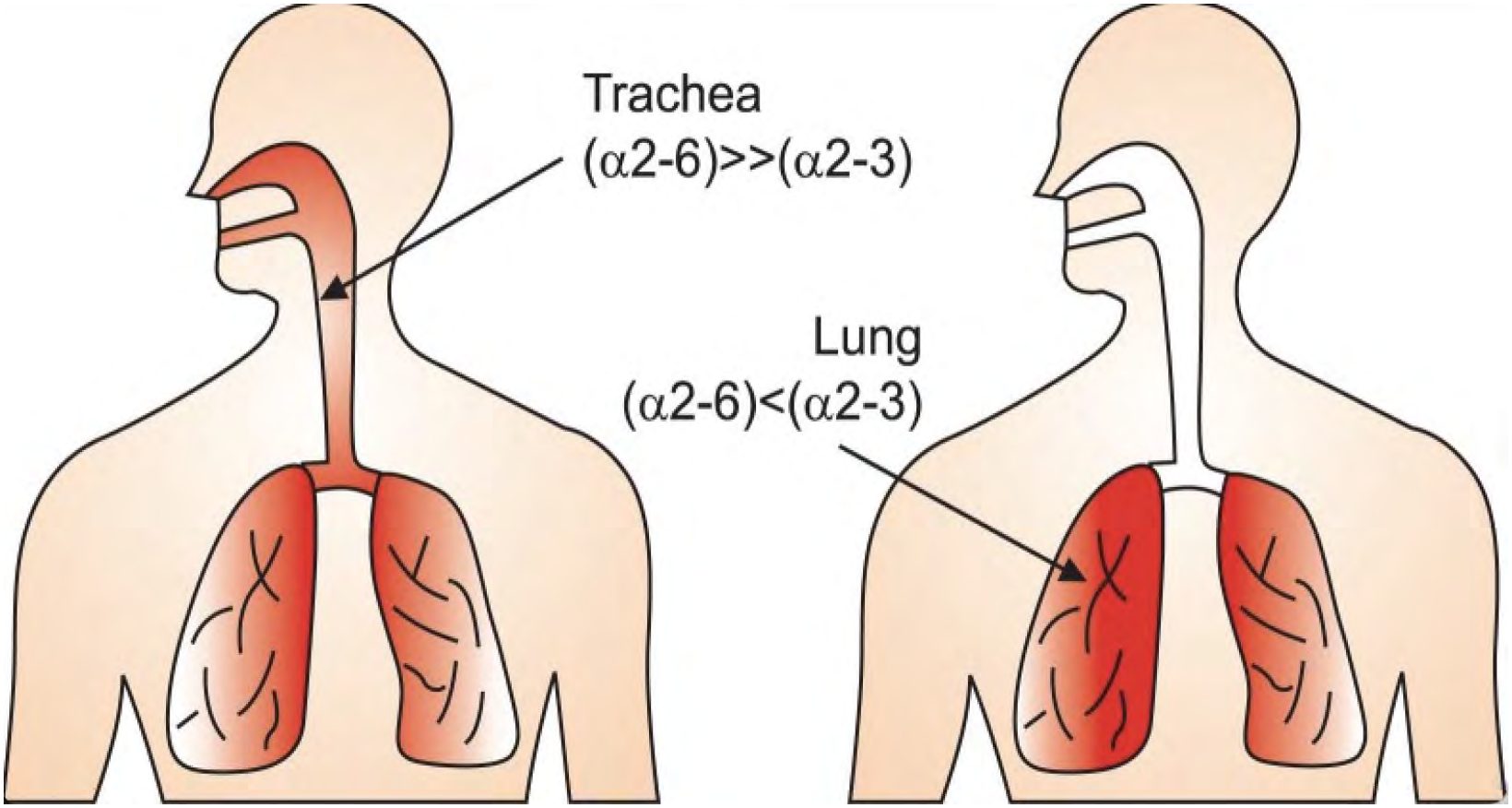
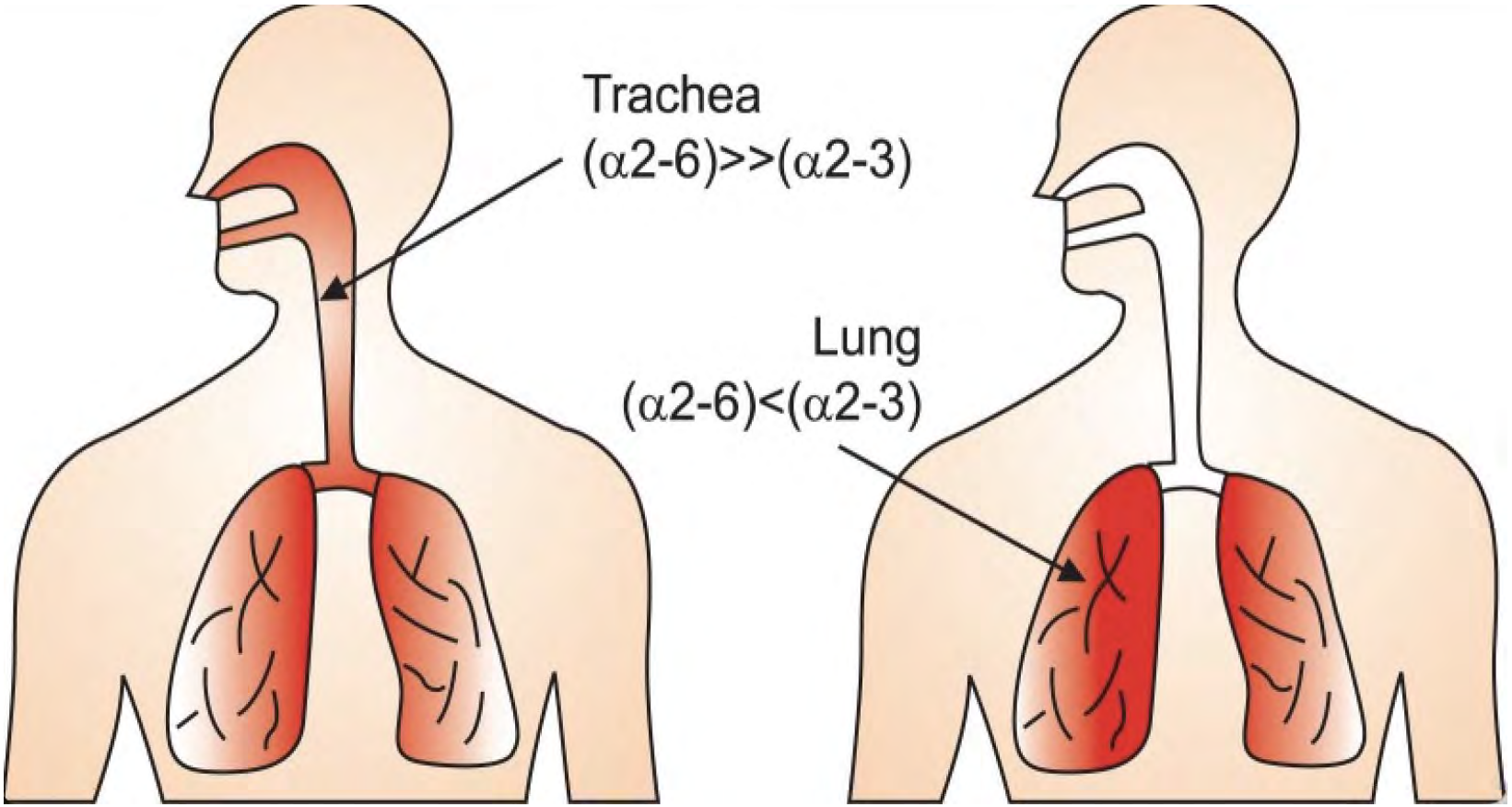
* Correspondence: skuchipudi@psu.edu
† These authors contributed equally to this work.

Kuchipudi, S.V., et al. *Viruses* (2021) 13: 262

H1, H2, and H3 influenza viruses bind to alpha 2-6 sialic acid receptors



H5 influenza viruses bind to alpha 2-3 sialic acid receptors



Sialic acid receptors in humans

- Humans express **α**-2,6 sialic acid receptors in the upper respiratory tract and **α**-2,3 sialic acid receptors in the lower respiratory tract (i.e., lungs).
- Therefore, H5 viruses, which bind to **α**-2,3 sialic acid receptors can't replicate in the upper respiratory tract.
- Because H5 viruses don't replicated well in the upper respiratory tract, they are not easily spread from person-to-person.

Sialic acid receptors in humans

- Influenza infection of the upper respiratory tract by H1, H2, and H3 viruses allows for amplification of virus from hundreds of viral particles to millions of virus particles, which then travel to the lungs causing pneumonia.
- People with pneumonia caused by H5 viruses are typically exposed to large quantities of virus from another source (most likely poultry), obviating the necessity of viral replication in the upper respiratory tract.

Why dairy farm workers?

> Emerg Infect Dis. 2024 Sep;30(9):1907-1911. doi: 10.3201/eid3009.240696. Epub 2024 Aug 10.

Avian and Human Influenza A Virus Receptors in Bovine Mammary Gland

Charlotte Kristensen, Henrik E Jensen, Ramona Trebbien, Richard J Webby, Lars E Larsen

PMID: 39127127 PMCID: PMC11347012 DOI: 10.3201/eid3009.240696

Abstract

An outbreak of influenza A (H5N1) virus was detected in dairy cows in the United States. We detected influenza A virus sialic acid -α2,3/α2,6-galactose host receptors in bovine mammary glands by lectin histochemistry. Our results provide a rationale for the high levels of H5N1 virus in milk from infected cows.

Kristensen, C. et al. *Emerging Infectious Diseases* (2024) 30: 1907-11.

Sialic acid receptors in cows

- Both alpha 2-3 and alpha 2-6 sialic acid receptors are expressed in the mammary glands (utters) of cows.
- H5N1 influenza viruses are contained in milk of infected cows and the virus can be aerosolized during milking, putting dairy farm workers at risk.

Why do dairy farm workers suffer from conjunctivitis?

Texas, March 2024

Figure 1. Conjunctivitis with Subconjunctival Hemorrhage in Both Eyes.

Influenza Other Respir Viruses. 2008 Aug 8;2(5):147–154. doi: 10.1111/j.1750-2659.2008.00051.x

Sialic acid tissue distribution and influenza virus tropism

Urban Kumlin [1], Sigvard Olofsson [2], Ken Dimock [3], Niklas Arnberg [1]

Author information Article notes Copyright and License information

PMCID: PMC4941897 PMID: 19453419

Abstract

Abstract Avian influenza A viruses exhibit a strong preference for using α2,3-linked sialic acid as a receptor. Until recently, the presumed lack of this receptor in human airways was believed to constitute an efficient barrier to avian influenza A virus infection of humans. Recent zoonotic outbreaks of avian influenza A virus have triggered researchers to analyse

Kumlin, U., et al. *Influenza Other Respiratory Viruses* (2008) 2: 147-54.

Sialic acid receptors in people

- Although alpha 2-6 sialic acid receptors are predominant in the nose, throat, and windpipe of people, the alpha 2-3 sialic acid receptors are predominant in human conjunctiva.
- This explains why conjunctivitis was a prominent feature of disease in infected dairy farm workers.

March 2025

- In early 2025, there was no evidence that circulating H5 viruses either in the United States or the world had spread from person-to-person.
- There was also no evidence that the gene that coded for the hemagglutinin of H5 viruses had mutated to allow binding to alpha 2-6 sialic acid receptors in a manner identical to H1, H2, or H3 influenza viruses.

H5 influenza viruses will not become a pandemic until the virus binds to alpha-2,6 sialic acid receptors

The Louisiana Case

CDC Confirms First Severe Case of H5N1 Bird Flu in the United States

Since April 2024, there have been a total of 61 reported human cases of H5 bird flu reported in the United States

PUBLISHED ON **DECEMBER 23, 2024**

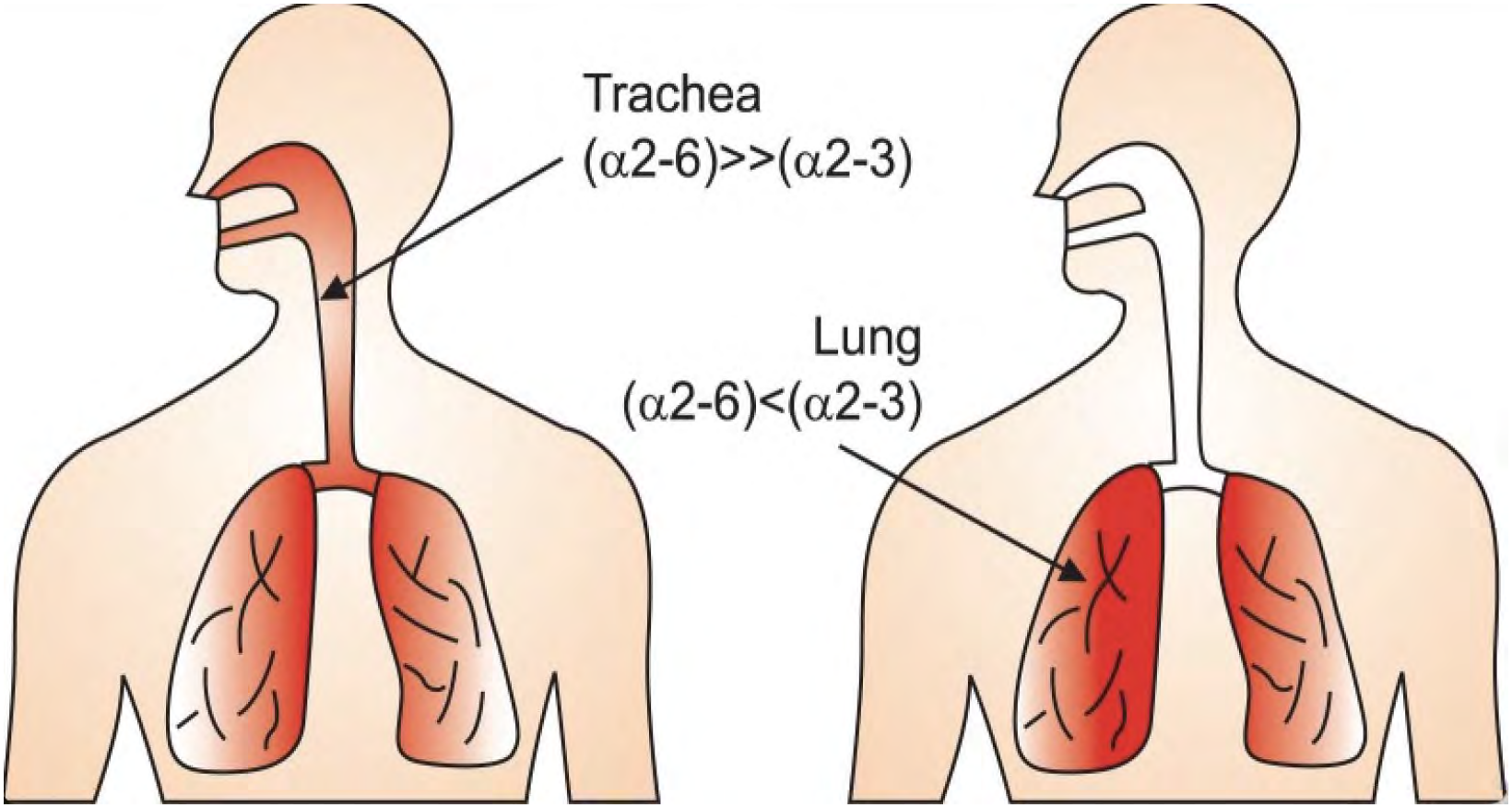

NEWSROOM
NEWSROOM
CNN
GROWING OUTBREAK
FIRST SEVERE U.S. CASE OF BIRD FLU CONFIRMED IN LOUISIANA
CNN
NEWSROOM
960 × 540

The Louisiana Case

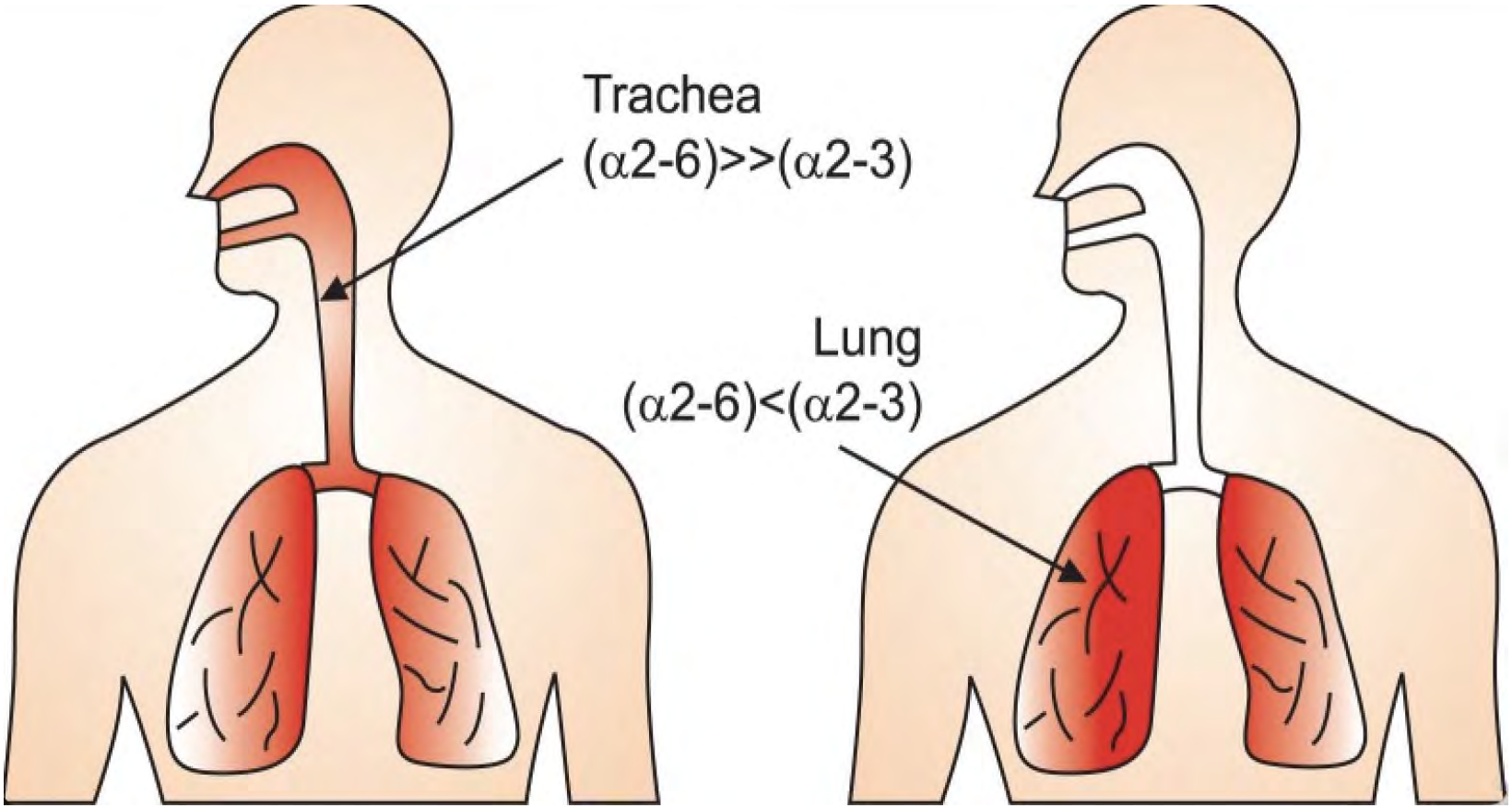
- Genetic analysis of the H5N1 virus revealed three amino acid changes that "may result in increased binding to alpha 2-6 sialic acid receptors."
- These mutations occurred during infection and were not found in the bird that infected this man. These amino acid changes were not detected in any other poultry.
- No person-to-person transmission has occurred with this virus.
- Analysis of the neuraminidase (NA), polymerase (P), or matrix genes showed no mutations associated with decreased susceptibilities to oseltamivir.

Why was the mortality rate so high in the 1997 and 2003 outbreaks but not in the 2024 outbreak in the United States?

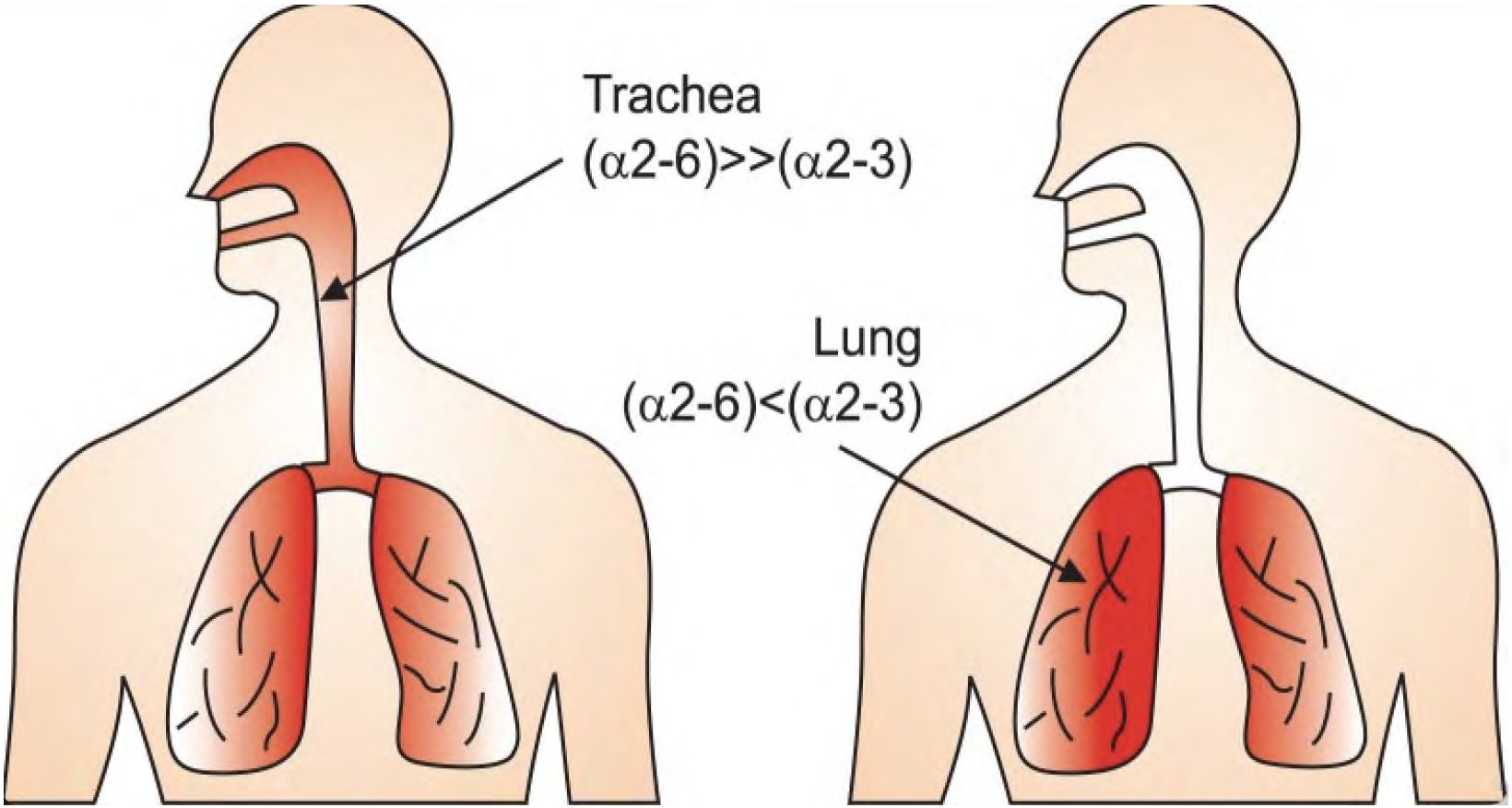
Pathogenesis of infection determines severity



Epidemic influenza infection

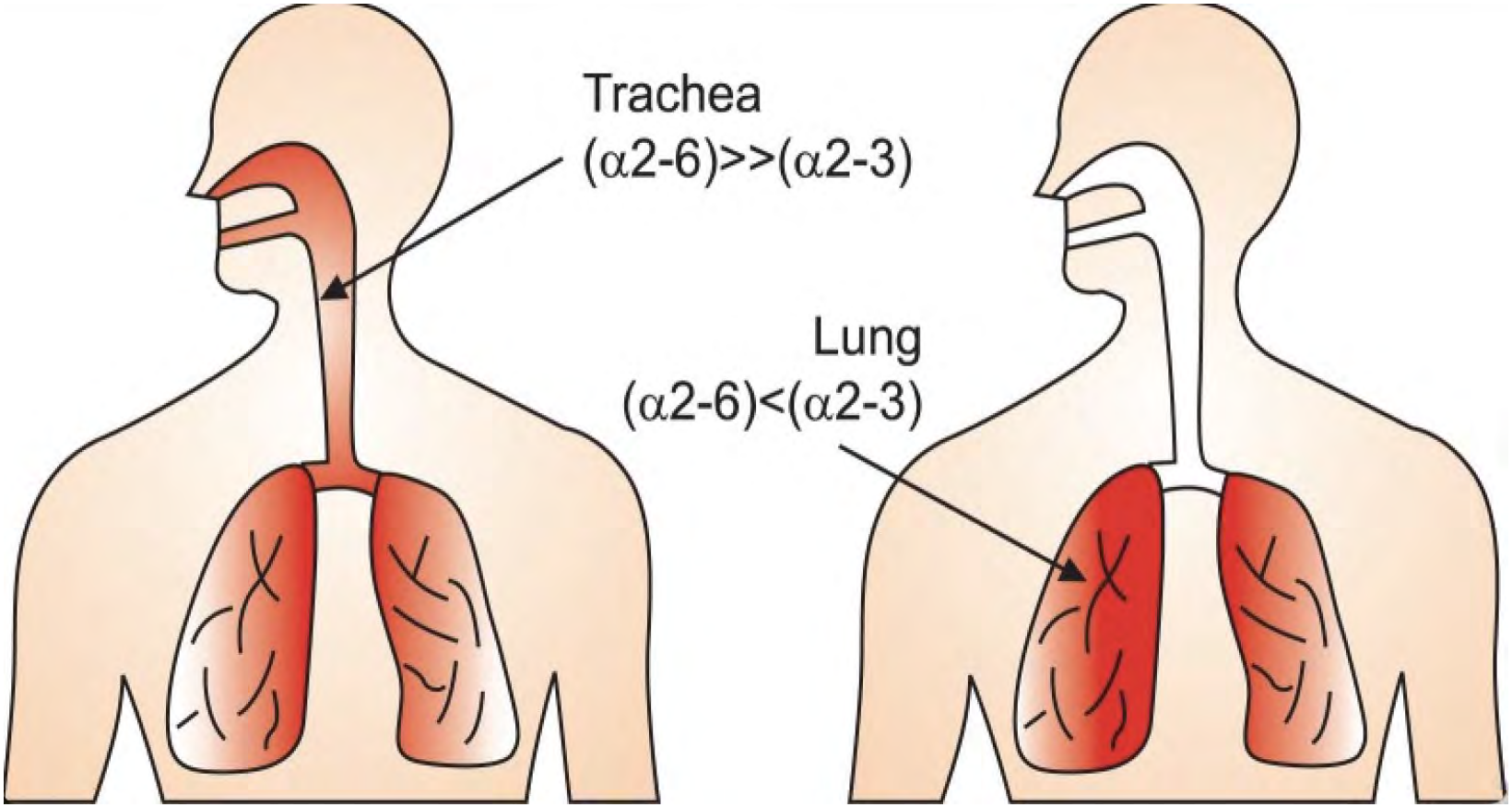


Louisiana case of poultry exposure

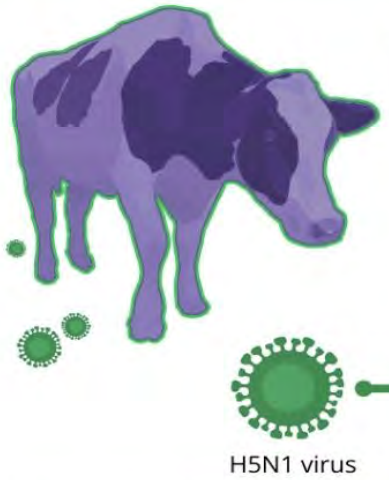


Chickens suffer upper and lower respiratory tract infection with H5 influenza viruses

Dairy farm workers



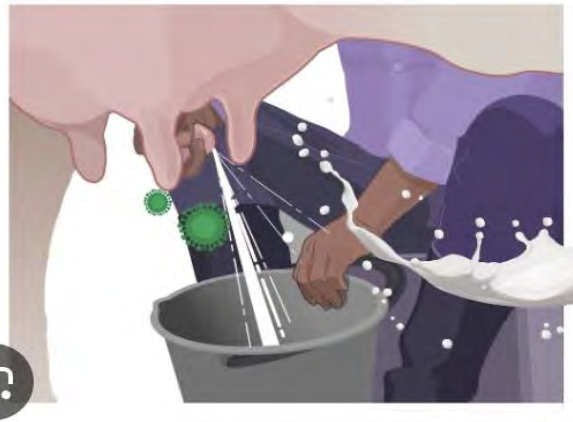
H5N1 bird flu might spread from cows to people in several ways



H5N1 virus

If you touch something contaminated with live virus and then touch your eyes, nose, or mouth

If a liquid contaminated with live virus splashes into your eyes (like raw milk from an infected cow, for example)



If you eat, drink, or inhale droplets contaminated with live virus

CDC

349850-A

1,650 × 1,275

Raw vs. pasteurized milk

Influenza virus can persist up to 5 days in raw milk

Environmental Science & Technology Letters > ASAP > Article

Open Access

Cite Share Jump to Expand

ECOTOXICOLOGY AND PUBLIC HEALTH | December 12, 2024

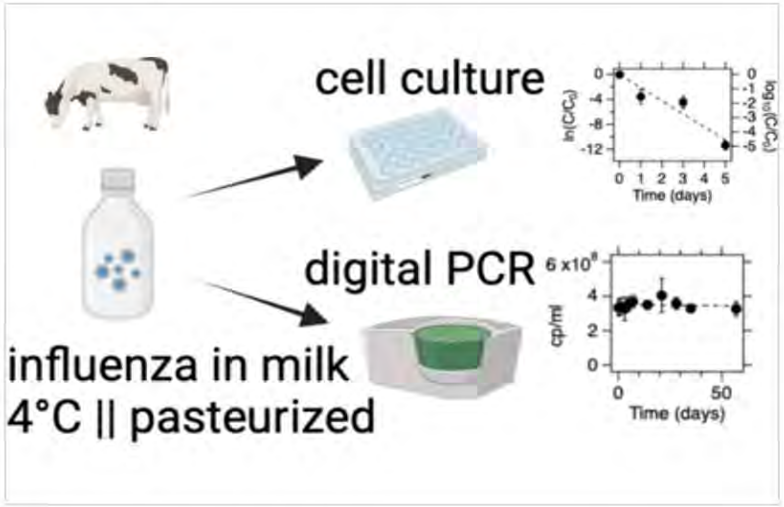
Infectivity and Persistence of Influenza A Virus in Raw Milk

Alessandro Zulli, Mengyang Zhang, Sehee Jong, Catherine Blish, and Alexandria B. Boehm*

Open PDF | Supporting Information (1)

Abstract

Influenza A viruses present important public health risks, with recent outbreaks of highly pathogenic avian influenza (HPAI) H5N1 in dairy cattle raising concerns about potential transmission through raw milk consumption. This study investigated the persistence of influenza A virus H1N1 PR8 (IAV PR8) in raw cow milk at 4 °C. We found a first-order decay rate constant of −2.05 day^{-1} equivalent to a T_{99} of 2.3 days. Viral RNA remained detectable for at least 57 days with no degradation. Pasteurization (63 °C for 30 min) reduced infectious virus to undetectable levels and reduced viral RNA concentrations, but reduction was less than 1 log_{10}. These findings highlight the potential risk of



December 18, 2024

UPDATED: Confirmed H5 Bird Flu Detected in Los Angeles County Cats That Consumed Recalled Raw Milk - Public Health Investigating Additional Possible Cases in Cats

The Los Angeles County Department of Public Health has confirmed two cases of H5 bird flu in cats that consumed recalled raw milk from Raw Farm, LLC. In addition, Public Health is investigating three other possible cases of H5 bird flu in three cats from a different household.

CDC recommendations

- "The CDC recommends that people avoid drinking raw milk, including products made from raw milk, due to the risk of avian influenza A(H5N1) virus contamination."
- Rather, the CDC recommends drinking pasteurized milk only, which also avoids the risk of Listeria, Campylobacter, Salmonella, and E. coli infections.

BREAKING DOWN THE HTST PROCESS.

1. COW IS MILKED

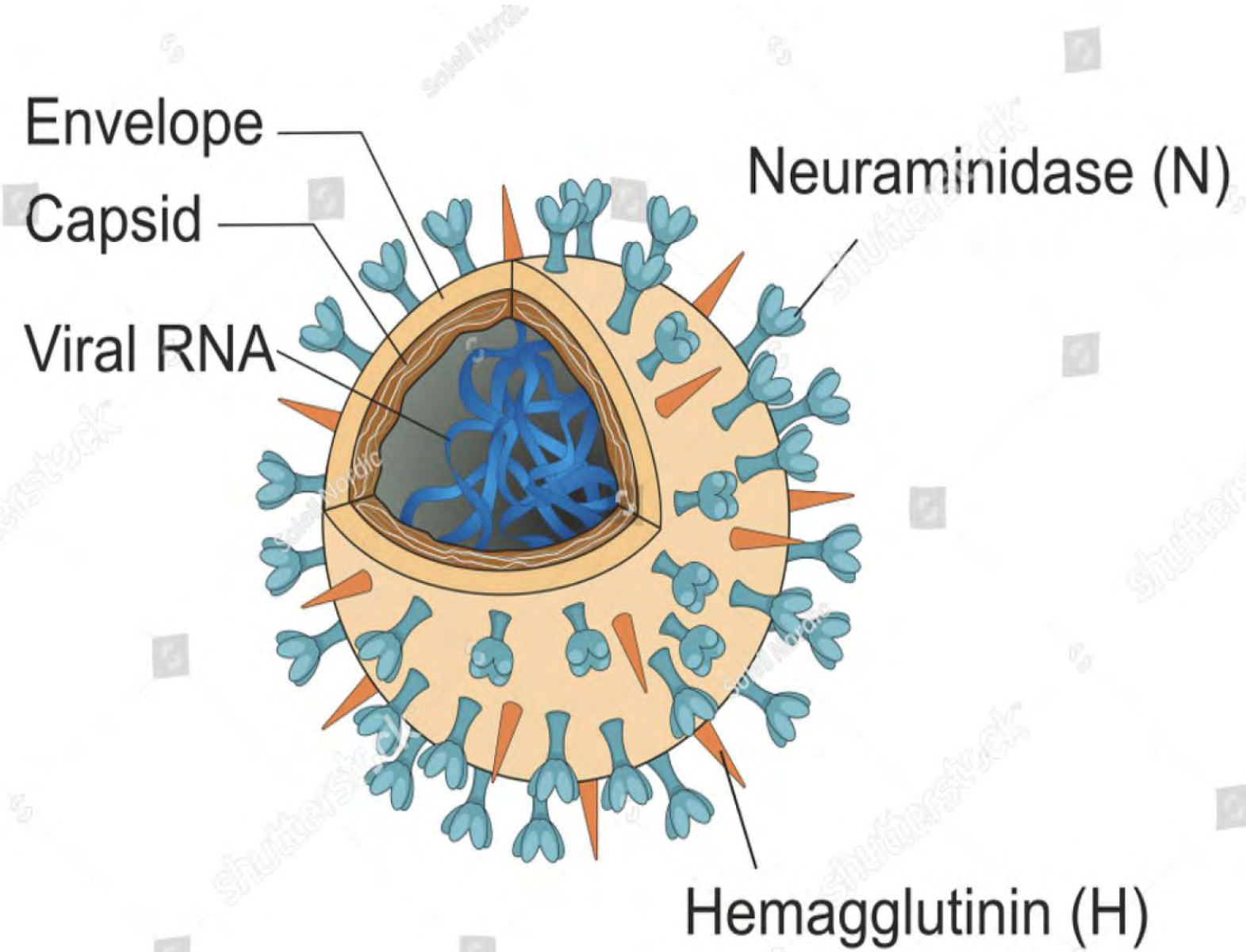
2. PRODUCT IS KEPT CHILLED AT 39°F

3. MILK ARRIVES AT PLANT

4. MILK IS HEATED TO 161°F FOR 15 SECONDS

5. MILK IS COOLED TO SUPPORT THE NEXT STEP IN THE PROCESS

6. MILK HEADS DOWNSTREAM IN THE PRODUCTION LINE


Envelope
Capsid
Viral RNA
Neuraminidase (N)
Hemagglutinin (H)

THE JOURNAL OF BIOLOGICAL CHEMISTRY

Vol. 262, No. 36, Issue of December 25, pp. 17744-17749, 1987
Printed in U.S.A.

Effects of Low pH on Influenza Virus

ACTIVATION AND INACTIVATION OF THE MEMBRANE FUSION CAPACITY OF THE HEMAGGLUTININ*

(Received for publication, April 20, 1987)

Toon Stegmann‡§, Frank P. Booy¶, and Jan Wilschut‡‖

From the ‡Laboratory of Physiological Chemistry, University of Groningen, Bloemsingel 10, 9712 KZ Groningen, The Netherlands and the ¶Biochemical Laboratory, University of Groningen, Nijenborgh 16, 9747 AG Groningen, The Netherlands

The hemagglutinin of influenza virus undergoes a conformational change at low pH, which results in exposure of a hydrophobic segment of the molecule, crucial to expression of viral fusion activity. We have studied the effects of incubation of the virus at low pH either at 37 or 0 °C. Treatment of the virus *alone* at pH 5.0 induces the virus particles to become hydrophobic, as assessed by measuring the binding of zwitterionic liposomes to the virus. At 37 °C this hydrophobicity is transient, electron microscopic examination of the virus reveals a highly disorganized spike layer, and fusion activity toward ganglioside-containing

and HA_2 (Klenk *et al.*, 1975). At the pH threshold of fusion (Doms *et al.*, 1985, 1986; Daniels *et al.*, 1985) an irreversible conformational change takes place in the hemagglutinin (Skehel *et al.*, 1982), leading to exposure of the hydrophobic N terminus of the HA_2 subunit. Thereby the isolated hemagglutinin acquires the ability to bind to nonionic detergents or lipid vesicles (Skehel *et al.*, 1982; Doms *et al.*, 1985). Strains or mutants of influenza virus with different pH dependences of fusion activity also show a corresponding shift in the pH dependence of the conformational change (Doms *et al.*, 1986; Daniels *et al.*, 1985). Therefore, the conformational change in

Stegmann, T. *Journal of Biological Chemistry* (1987) 262: 17744-49.

Vaccines to prevent H5 influenza disease

Sanofi Pasteur (H5N1)

- In April 2007, the FDA approved an H5N1 vaccine made by Sanofi Pasteur.
- Two dose vaccine given 28 days apart in persons 18 to 64 years of age.
- This vaccine is made in a manner analogous to Fluzone. Specifically, the virus is propagated in eggs, inactivated with formaldehyde, and chemically disrupted with a non-ionic surfactant (so-called “split virus”). This vaccine is now part of the National Stockpile.

GlaxoSmithKline (H5N1)

- In 2013, the FDA approved an H5N1 vaccine made by ID Biomedical Corporation of Quebec but distributed by GSK.
- Two dose vaccine given 21 days apart in persons greater than 6 months of age.
- This vaccine is made in a manner analogous to FluLaval. Specifically, the virus is propagated in eggs, inactivated with formaldehyde and UV light, and chemically disrupted with sodium deoxycholate. The vaccine is adjuvanted with an oil-in-water emulsion containing squalene, vitamin E, and polysorbate 80. This vaccine is also part of the National Stockpile.

CSL Seqirus (H5N1)

- In February 2020, the FDA approved a vaccine made by CSL Seqirus for anyone over 6 months of age as a two-dose vaccine with the second dose given 21 days apart.
- H5N1 influenza virus grown in MDCK (canine kidney) cells, inactivated with beta-propiolactone, treated with detergent in a manner identical to Flucelvax, and adjuvated with a squalene-based, oil-in-water emulsion (MF59) in a manner similar to Fluad.

Do H5N1 vaccines prevent severe infections?

Because of the rarity of H5 influenza infections, efficacy data are not currently available

Brief Communication | Published: 16 July 2024

Licensed H5N1 vaccines generate cross-neutralizing antibodies against highly pathogenic H5N1 clade 2.3.4.4b influenza virus

Surender Khurana ✉, Lisa R. King, Jody Manischewitz, Olivia Posadas, Ashish K. Mishra, Dongxiao Liu, John H. Beigel, Rino Rappuoli, John S. Tsang & Hana Golding

Nature Medicine **30**, 2771–2776 (2024) | Cite this article

Abstract

The emergence of highly pathogenic avian influenza (HPAI) H5N1 clade 2.3.4.4b viruses and their transmission to dairy cattle and animals, including humans, poses a major global public health threat. Therefore, the development of effective vaccines and therapeutics against H5N1 clade 2.3.4.4b virus is considered a public health priority. In the United States, three H5N1 vaccines derived from earlier strains of HPAI H5N1 (A/Vietnam, clade 1, and A/Indonesia,

Khurana, S., et al. *Nature Medicine* (2024) 30: 2771-2776.

Does the CDC currently recommend H5N1 vaccines for those at high risk?

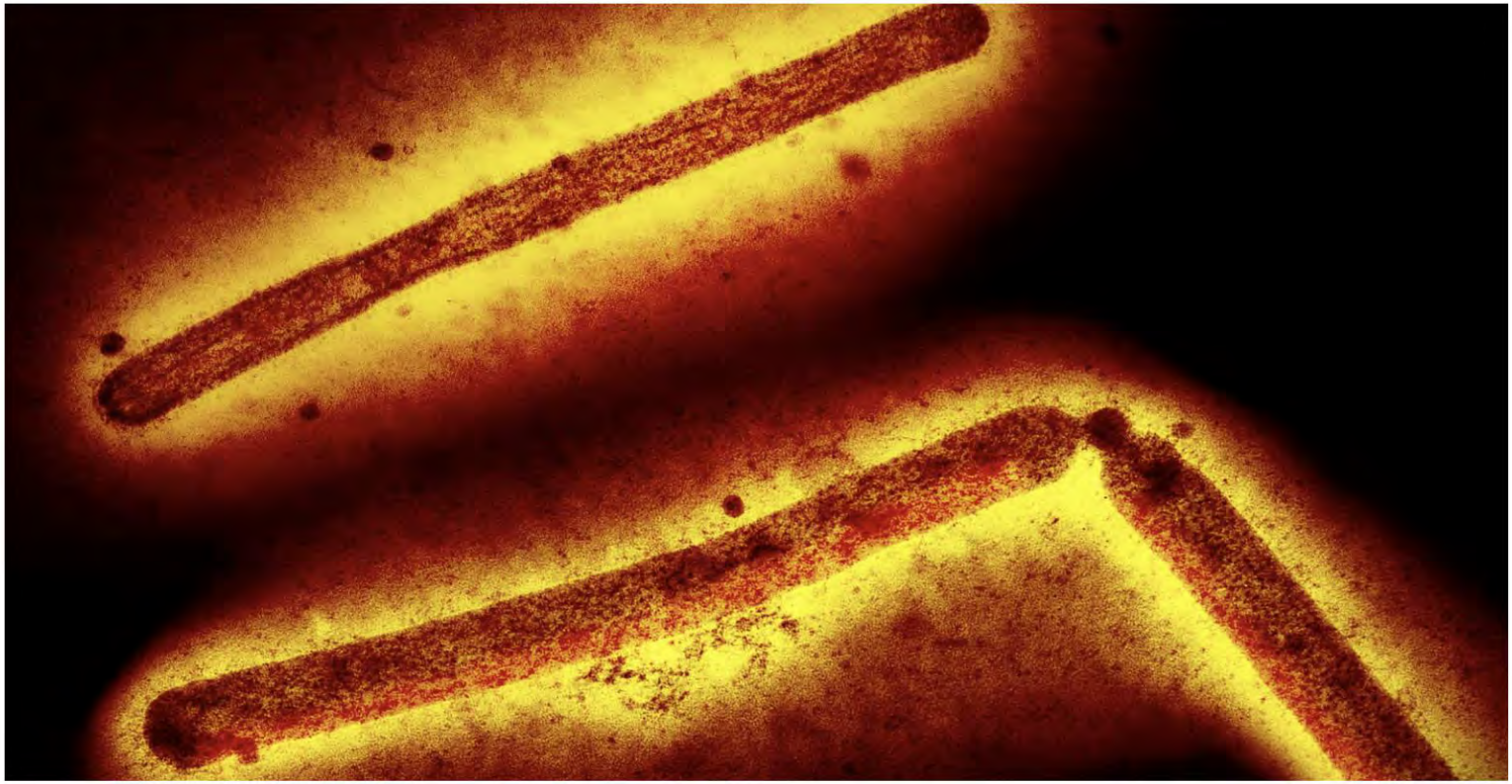
CDC and H5N1 vaccines

- As of December 26, 2025, the CDC states, “No human vaccines for prevention of highly pathogenic avian influenza (H5N1) virus infections are currently available in the United States. Seasonal influenza vaccines so not provide protection against human infection with H5N1 viruses.”
- The CDC is waiting to determine whether H5N1 vaccines cause severe disease in people at high risk before making a recommendation.

Finland to offer bird flu vaccine to select groups of people, a possible global first

By Andrew Joseph June 5, 2024

Reprints



H5N1 bird flu particles

Zoonotic influenza vaccine (H5N8)

- Made by CSL Seqirus. Available for anyone over 18 years of age as a two-dose vaccine with the second dose given 3 weeks later.
- H5N8 influenza virus grown in eggs, inactivated with beta-propiolactone, treated with detergent and adjuvated with a squalene-based, oil-in-water emulsion (MF59).
- European Union purchased 40 million doses for 15 countries. Finland first to recommend vaccine for poultry, dairy, and farmers (mink, foxes), veterinarians, and scientists at highest risk of disease.

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