H5N1 influenza: Who is giving what to whom?

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Speaker Disclosure H5N1 influenza: Who is giving what to whom?

Andrew Bowman

FINANCIAL DISCLOSURE:

Research Support – Centers for Disease Control & Prevention

Research Support – St. Jude Center of Excellence for Influenza Research and Response

UNLABELED/UNAPPROVED USES DISCLOSURE:

I will show use of a diagnostic test for influenza A virus that is currently NOT approved for use in dairy cattle.

Orthomyxoviridae

Types of influenza viruses:

A viruses

- Infect birds and other animals as well as humans
- Are a source of seasonal influenza epidemics and all pandemics

B viruses

- Infect humans only (maybe) and do not cause pandemics (can cause epidemics, but generally less severe than “A”)

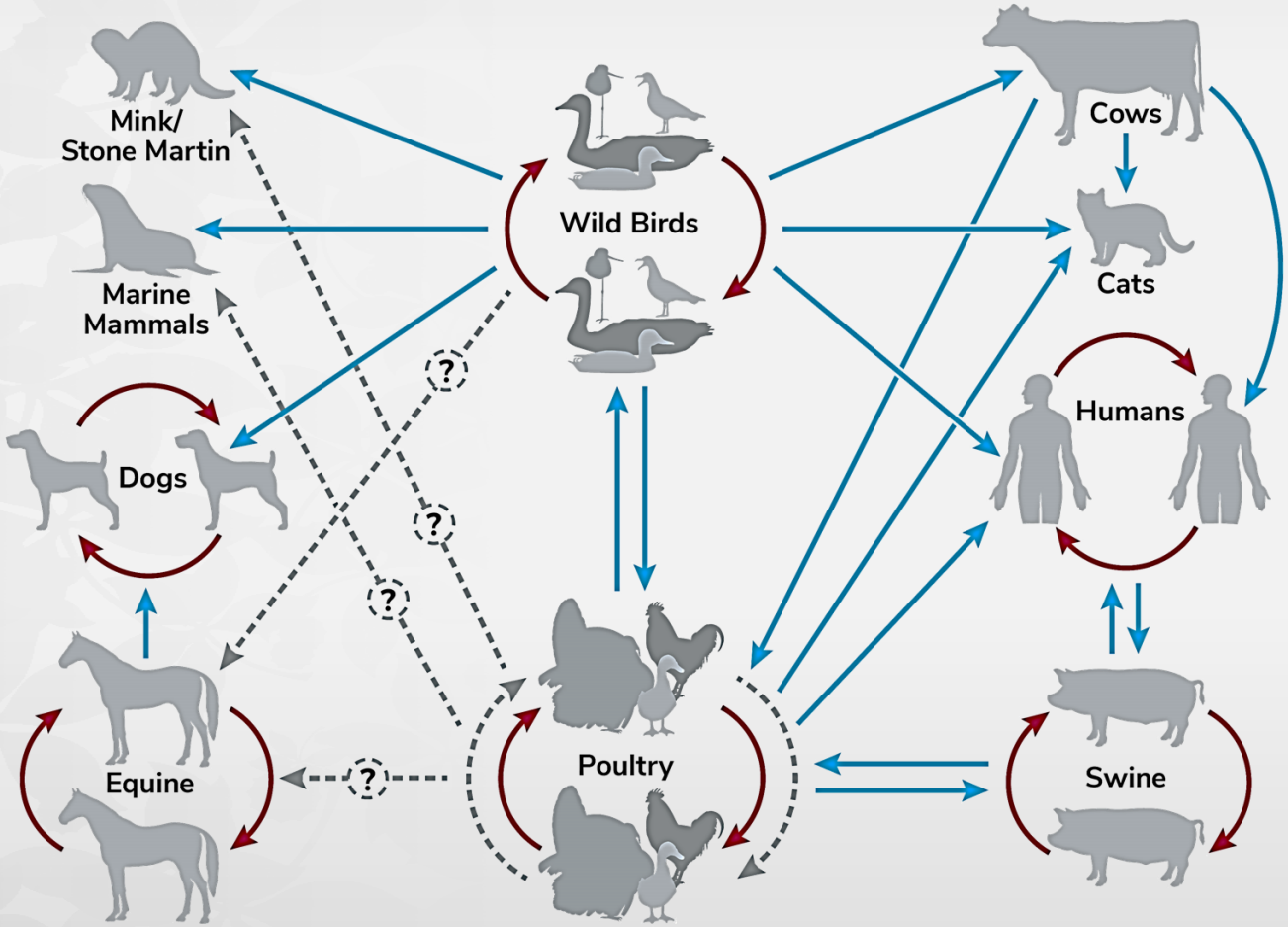
C viruses

- Infect humans and swine and do not cause pandemics
- Usually cause only mild disease

D viruses

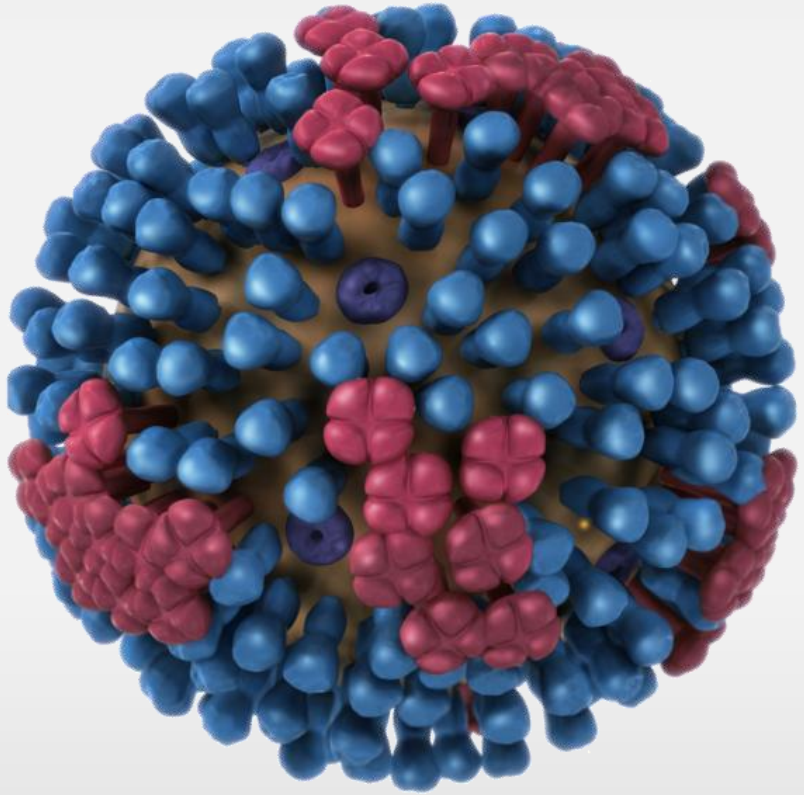
- Identified in swine and cattle. Other species??

Influenza A virus



Influenza A Virus

- (-) Stranded RNA Virus
- Enveloped pleomorphic virus
- Segmented Genome
- Hemagglutinin and neuraminidase are the major surface proteins
  - 18 HA and 11 NA subtypes
    - H17N10 and H18N11 were discovered in bats and these two subtypes appear to be unique to the bat population.



Picture courtesy of :Centers for Disease Control and Prevention, National Center for Immunization and Respiratory Diseases

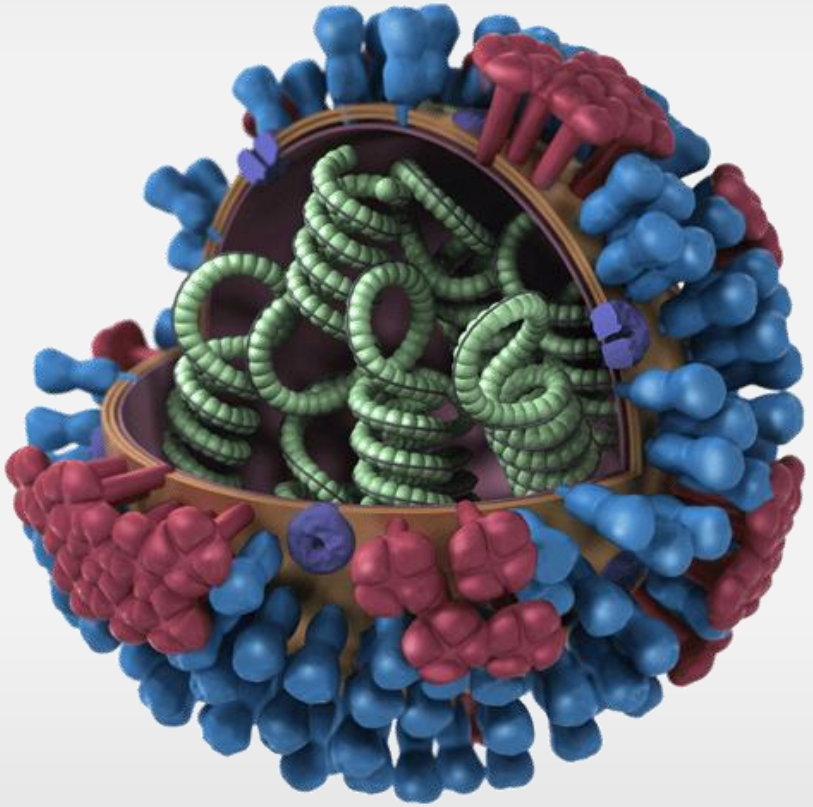
Influenza A Virus

Antigenic Drift

- **Minor antigenic changes over time due to point mutations**
  - Negative sense RNA virus
    - RNA-dependent RNA polymerase
    - No proof-reading during replication

Antigenic Shift

- **Major antigenic changes due to genomic reassortment.**
  - Segmented Genome
    - When one cell is infected by multiple influenza A viruses, gene segments can be shuffled



Picture courtesy of :Centers for Disease Control and Prevention, National Center for Immunization and Respiratory Diseases

Reassortant IAV

HA subtypes = 1 – 16

NA subtypes = 1- 9

Possible HA-NA Combinations Among Type A Influenza Viruses

16 HA X 9 NA =

144 HA-NA combinations

Bat lineage are still in question/pending

HA-NA Combinations by Host

Humans:	**H1N1 H2N2, H3N2**
Swine:	**H1N1, H3N2, H1N2**
Equine:	**(H7N7 disappeared, equi-1), H3N8 (equi-2)**
Canine:	**H3N8, H3N2**
Poultry:	**Many HA-NA combinations recovered** **Not all HA and NA subtypes recovered**
Wild birds:	**> 100 HA-NA combinations recovered** **All 16 HA and 9 NA subtypes recovered**

Pandemics

Pandemic influenza occurs when a new strain of influenza emerges where:

1. there is little or no immunity to the virus in the human population

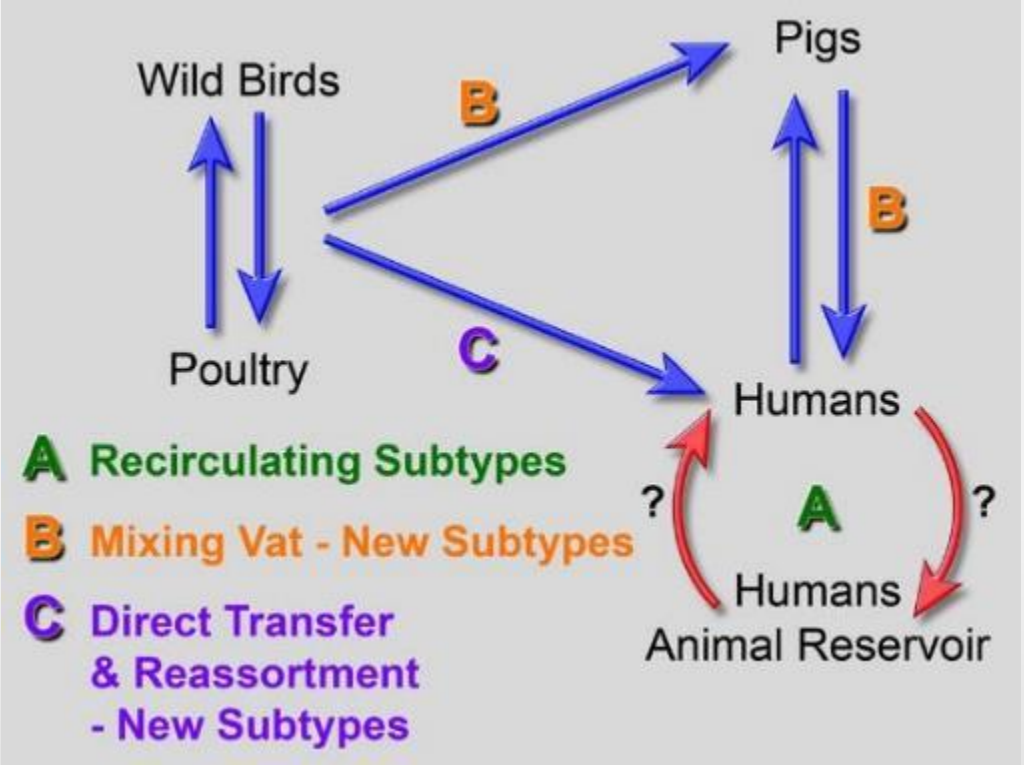
and

2. the virus is able to spread efficiently from person to person.

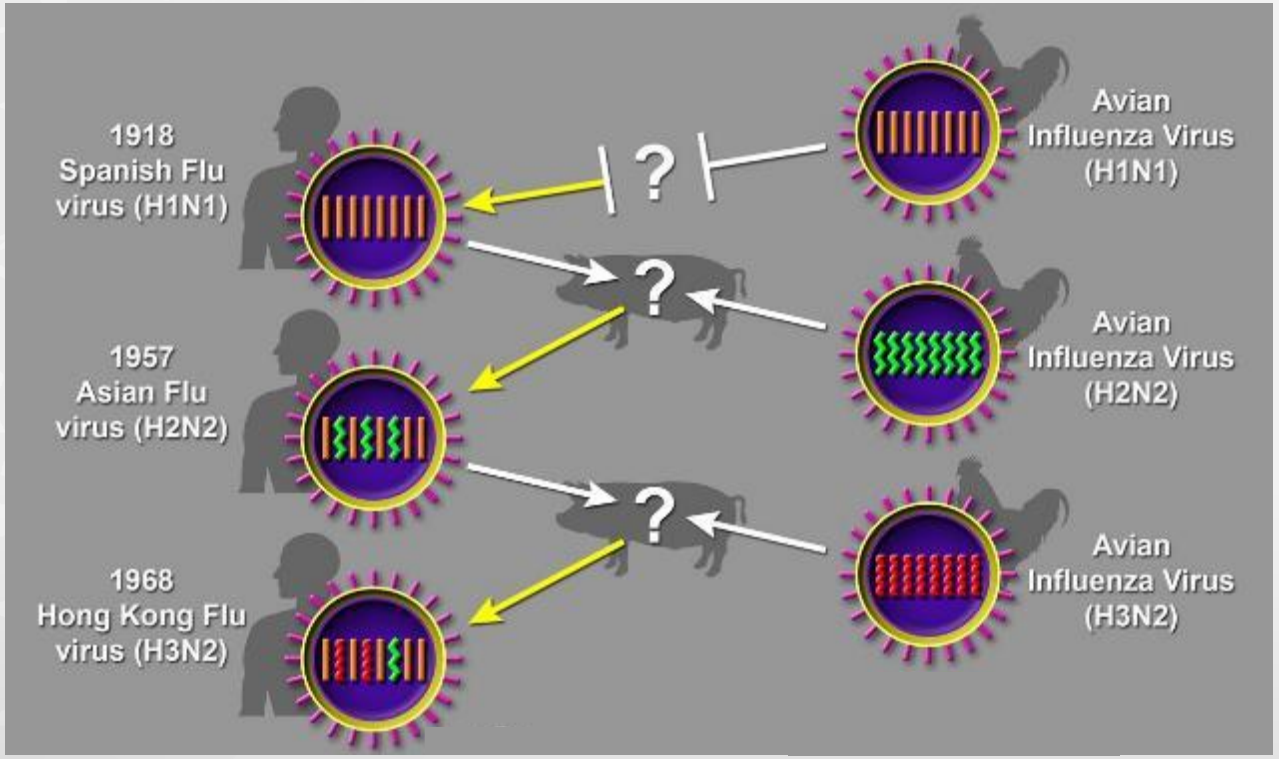
A pandemic virus may cause mild to severe disease.

Pandemics

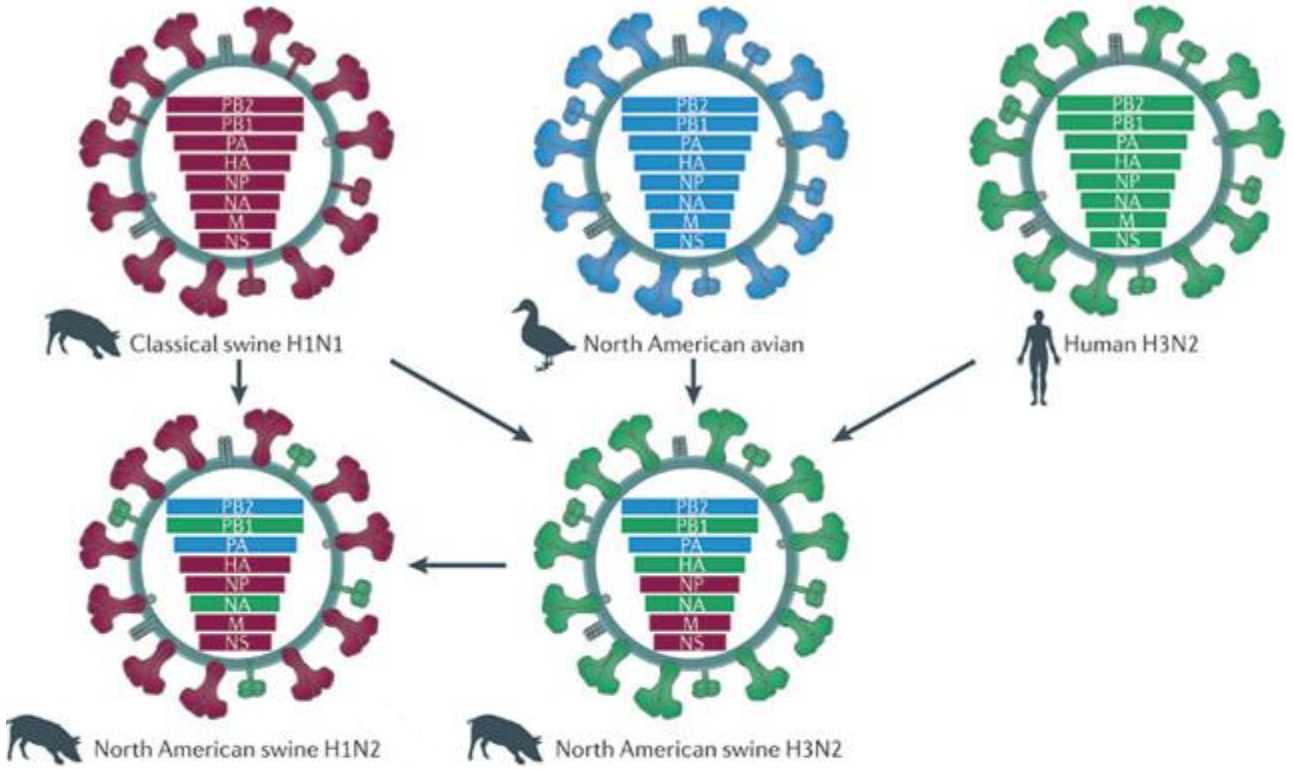
Theories on Origin of Pandemic Influenza A Viruses



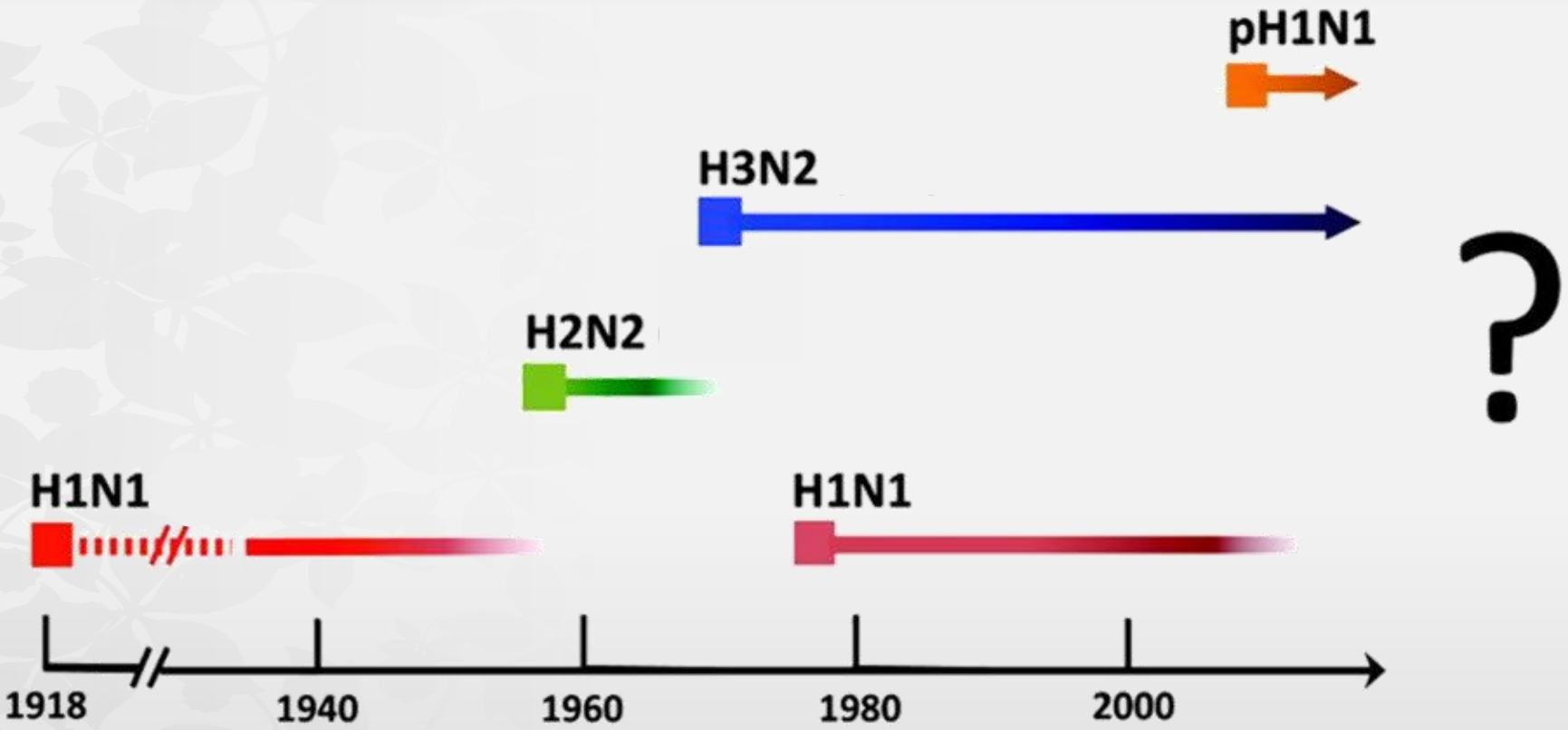
Role of Animals in the Generation of Pandemics



2009 Pandemic H1N1



Fate of a pandemic virus



Peter Palese, and Taia T. Wang mBio 2011;
doi:10.1128/mBio.00150-11

Disease in avian species

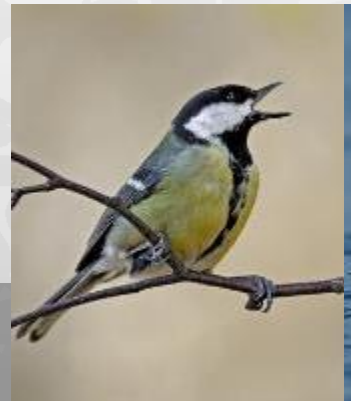
Humans:____

Horses:_____

Pigs:_____

Dogs:_____

Birds:_____




Disease in wild birds

Wild birds are considered to be the primary reservoir for influenza A viruses.

Aquatic birds generally do not show any clinical signs of infection, but the viruses replicate in the intestinal tract of the birds and are shed into the environment.

Disease in domestic poultry

Influenza A viruses can infect a variety of domestic bird species, such as chickens, turkeys, ducks, and quail.

Classified according to the disease severity in domestic chickens, with two recognized forms:

1. Highly pathogenic avian influenza
2. Low-pathogenicity avian influenza

Highly pathogenic avian influenza (HPAI) per 9 CFR 93.100

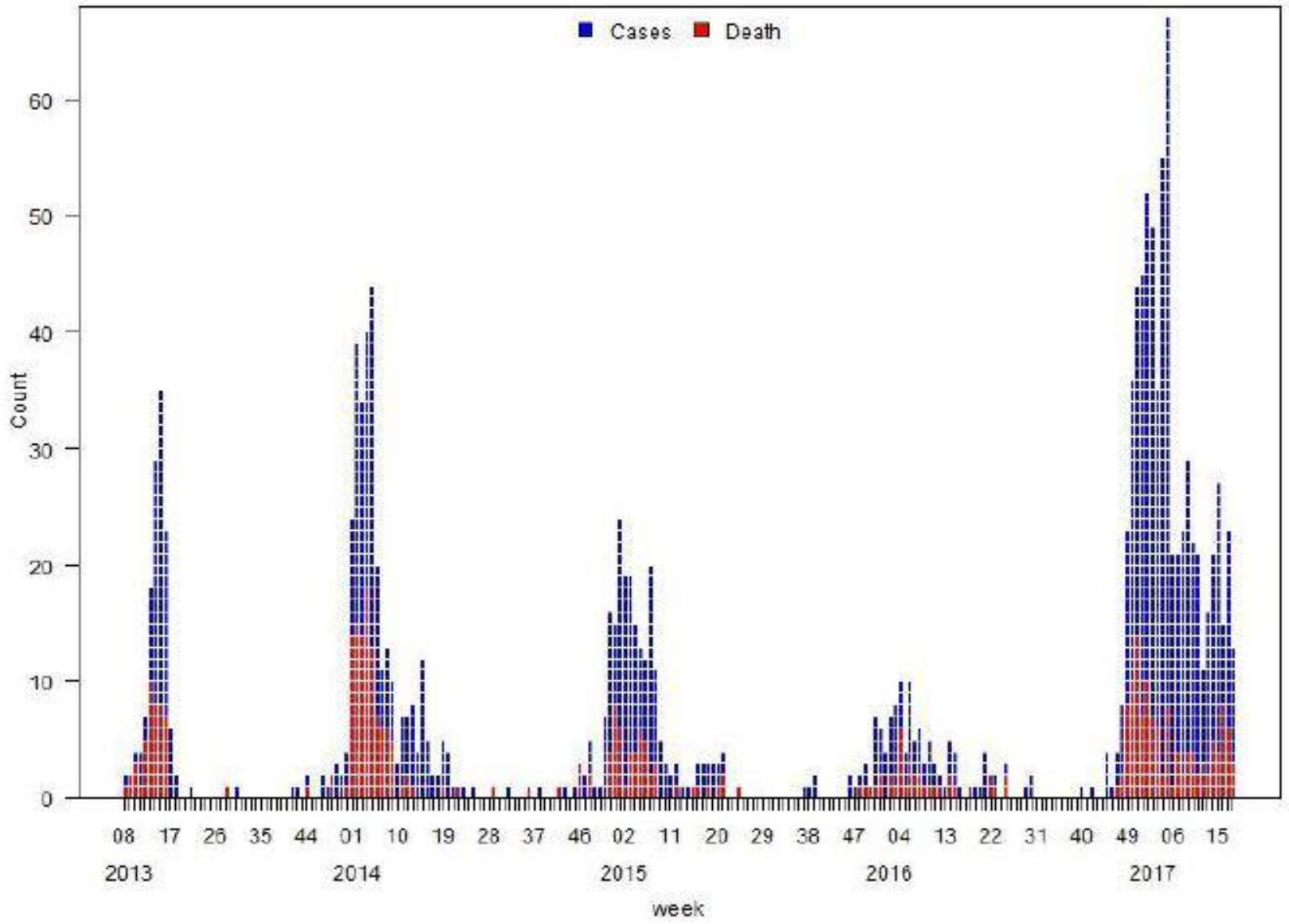
Highly pathogenic avian influenza is defined as follows:

(1) Any influenza virus that **kills at least 75 percent of eight 4- to 6-week-old susceptible chickens** within 10 days following intravenous inoculation with 0.2 mL of a 1:10 dilution of a bacteria-free, infectious allantoic fluid or inoculation of 10 susceptible 4- to 8-week-old chickens resulting in an intravenous pathogenicity index (IVPI) of greater than 1.2;

(2) Any H5 or H7 virus that does not meet the criteria in paragraph (1) of this definition, but has an amino acid sequence at the haemagglutinin cleavage site that is compatible with highly pathogenic avian influenza viruses; or

(3) Any influenza virus that is not an H5 or H7 subtype and that **kills one to five out of eight inoculated chickens** and grows in cell culture in the absence of trypsin within 10 days.

Figure 2: Epidemiological curve of avian influenza A(H7N9) cases in humans by week of onset, 2013-2017



Disease in domestic poultry

Highly pathogenic viruses cause severe disease in domestic poultry and can cause mortality rates of up to 100% in affected flocks.

Low pathogenic viruses generally cause decreased egg production or mild upper respiratory disease in domestic poultry and do not typically cause death.

Confirmed HPAI Detections

Since February 8, 2022

Flocks: 1,712

- Commercial: 789
- Backyard: 923

Birds affected: 174.89 million

- 0.06 million in the past month

Confirmed HPAI Detections (USDA data)

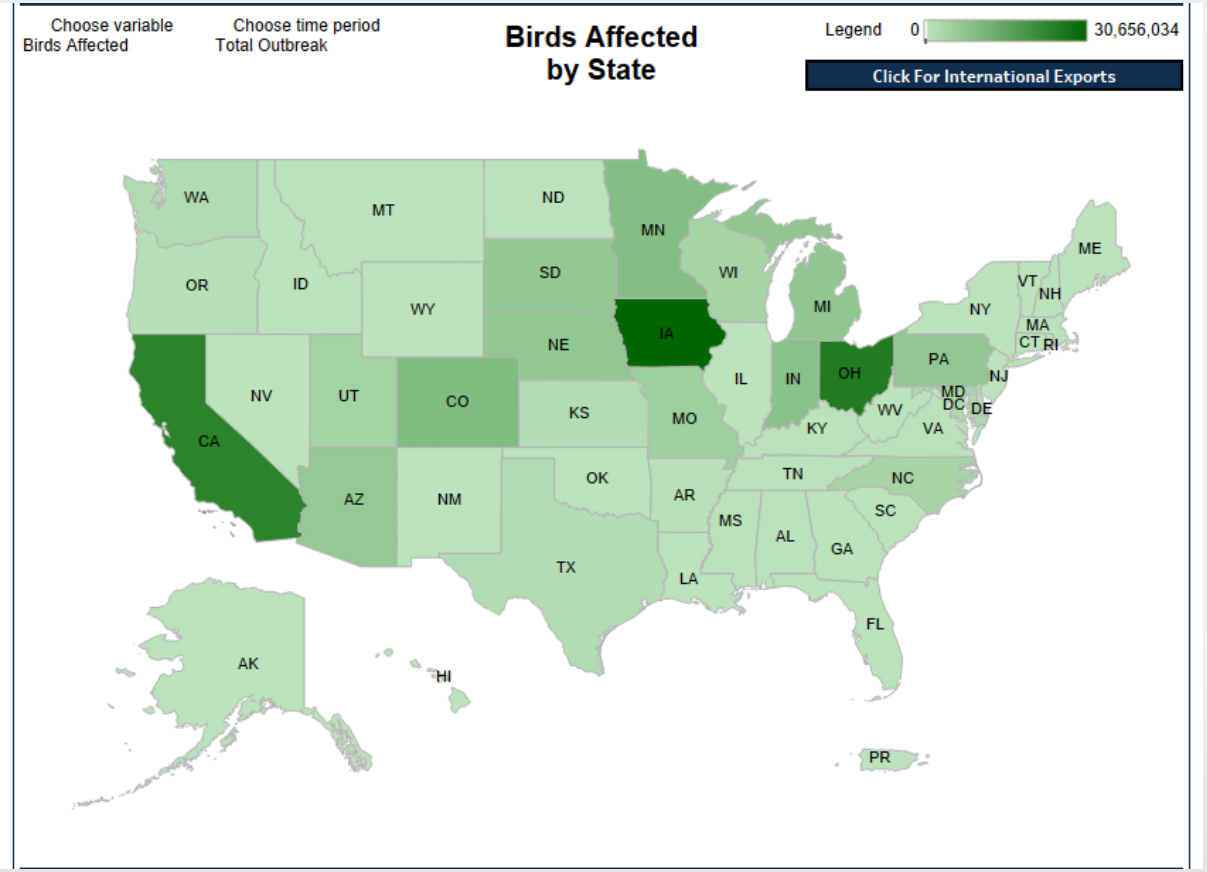
Since February 8, 2022

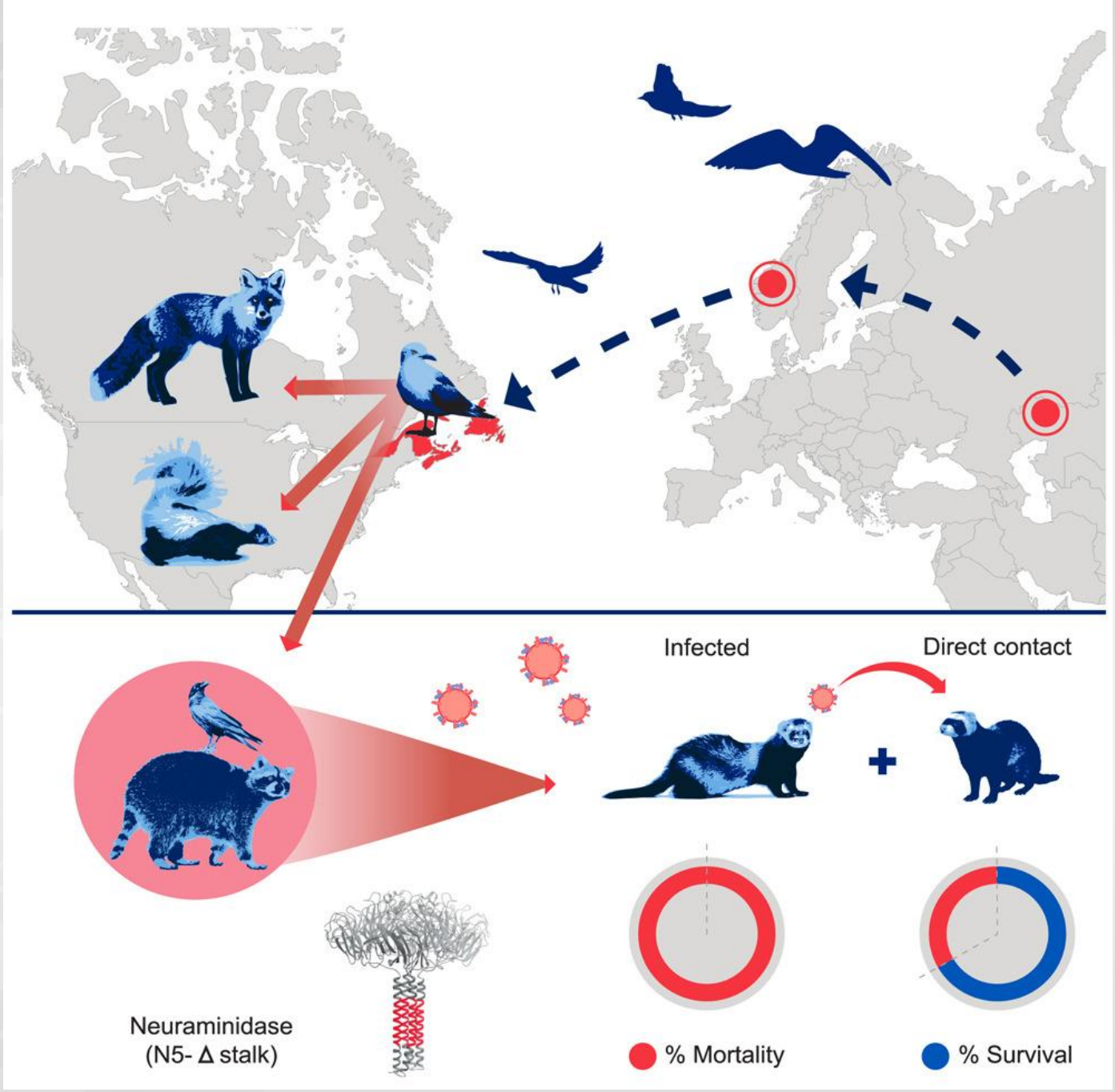
Flocks: 1,592

- Commercial: 757
- Backyard: 835

Birds affected: 162.8 million

- 21.3 million in the past month





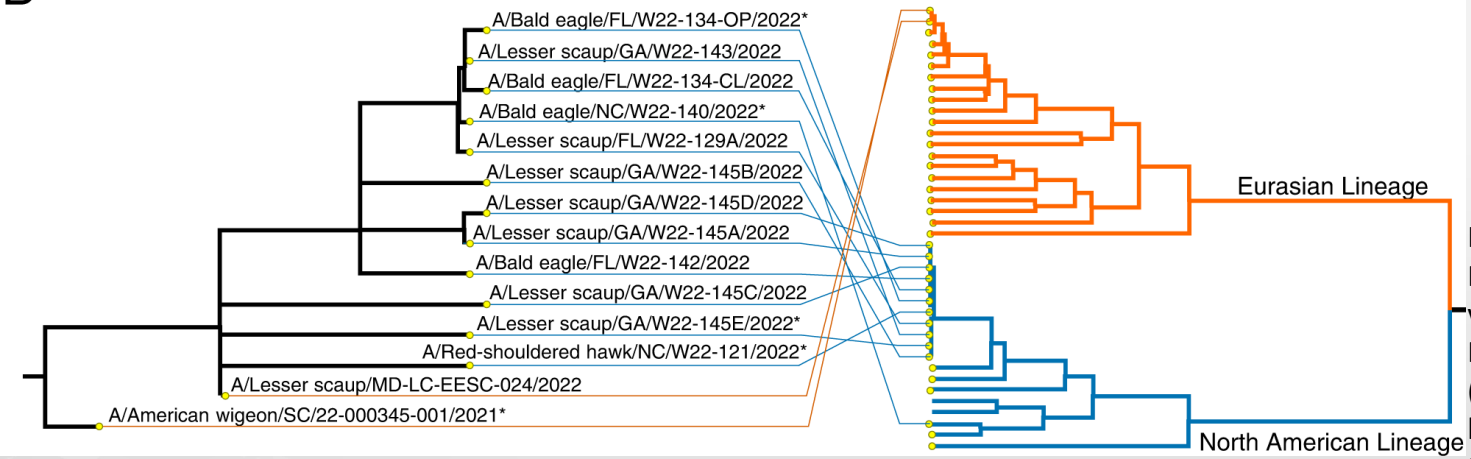
Cell Reports 2024 43DOI: (10.1016/j.celrep.2024.114479)

Rapid evolution of A(H5N1) influenza viruses after intercontinental spread to North America

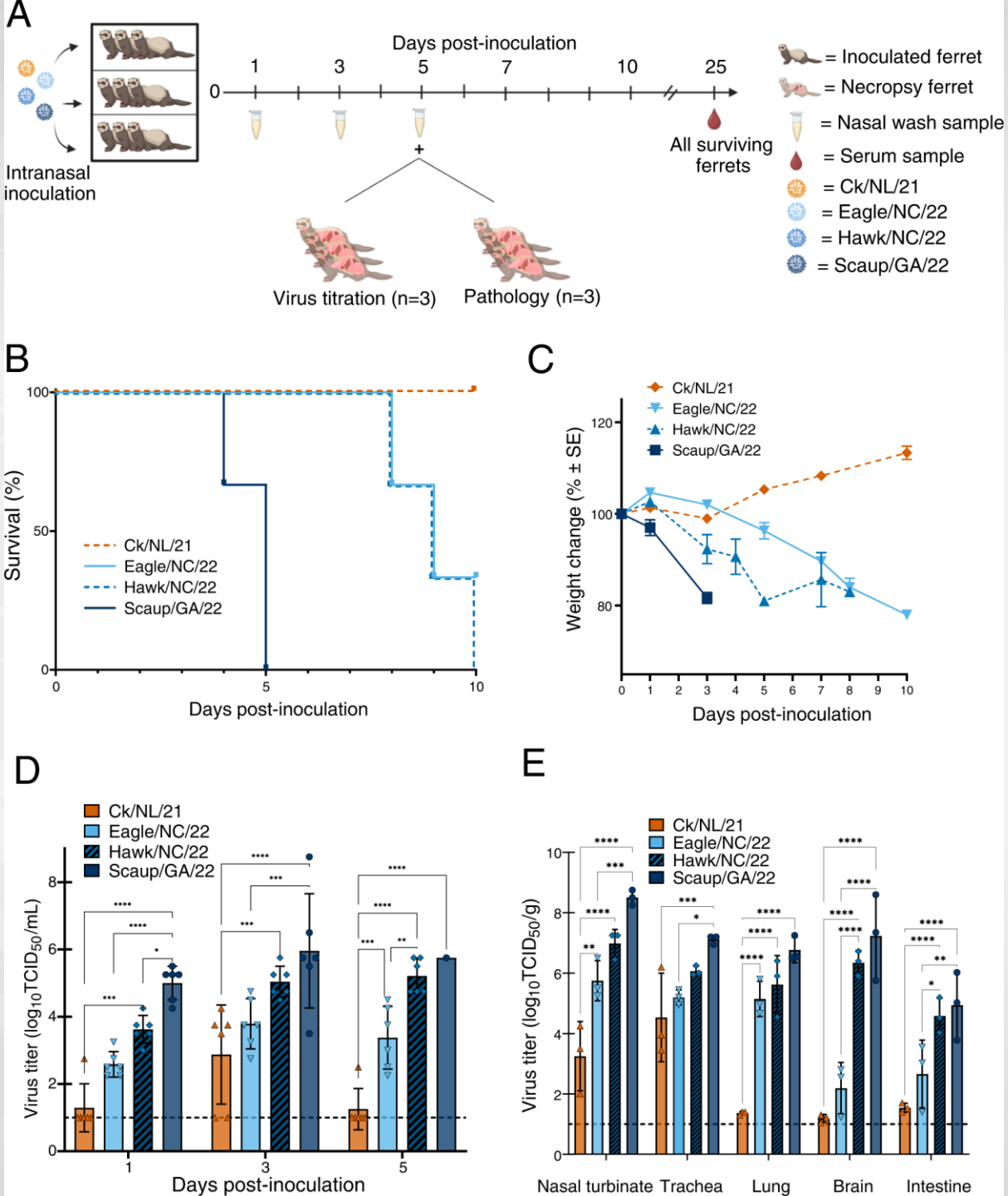
A

Virus	# Isolates	Genotype							
		PB2	PB1	PA	HA	NP	NA	MP	NS
Wigeon/SC/21 Ck/NL/21	12								
Eagle/FL/22 Hawk/NC/22	21								
Eagle/NC/22	16								
Scaup/GA/22	9								

B



Kandeil, A., Patton, C., Jones, J.C. et al. Rapid evolution of A(H5N1) influenza viruses after intercontinental spread to North America. Nat Commun 14, 3082 (2023). https://doi.org/10.1038/s41467-023-38415-7



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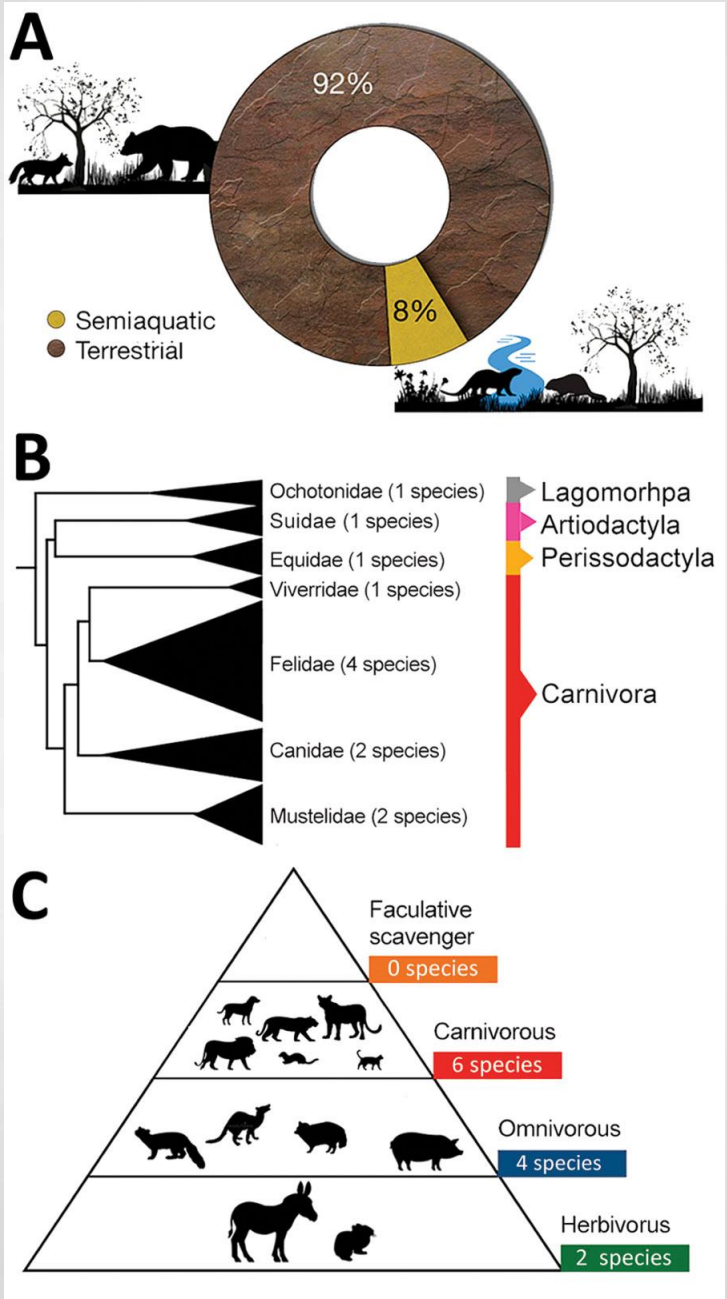
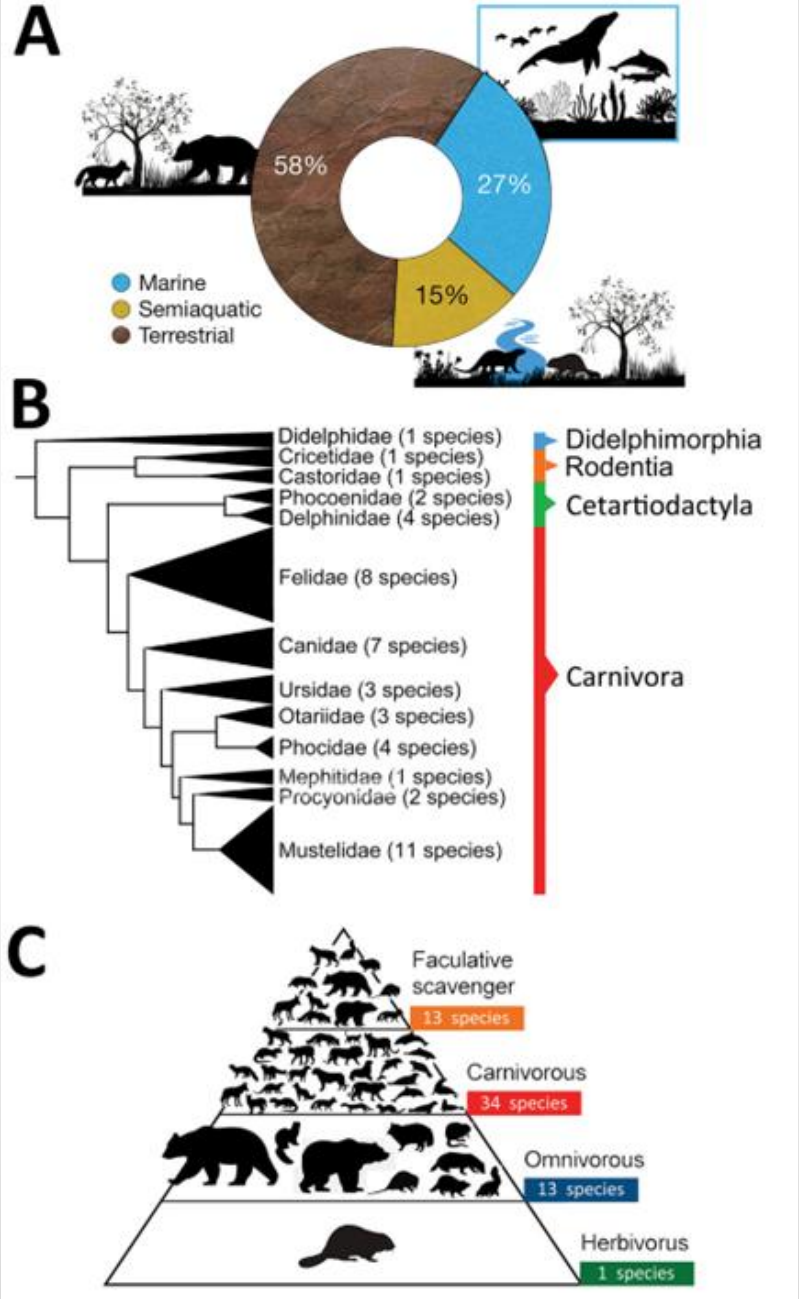
Characteristics of mammal species affected worldwide by highly pathogenic influenza virus A (H5N1)

2003–2019



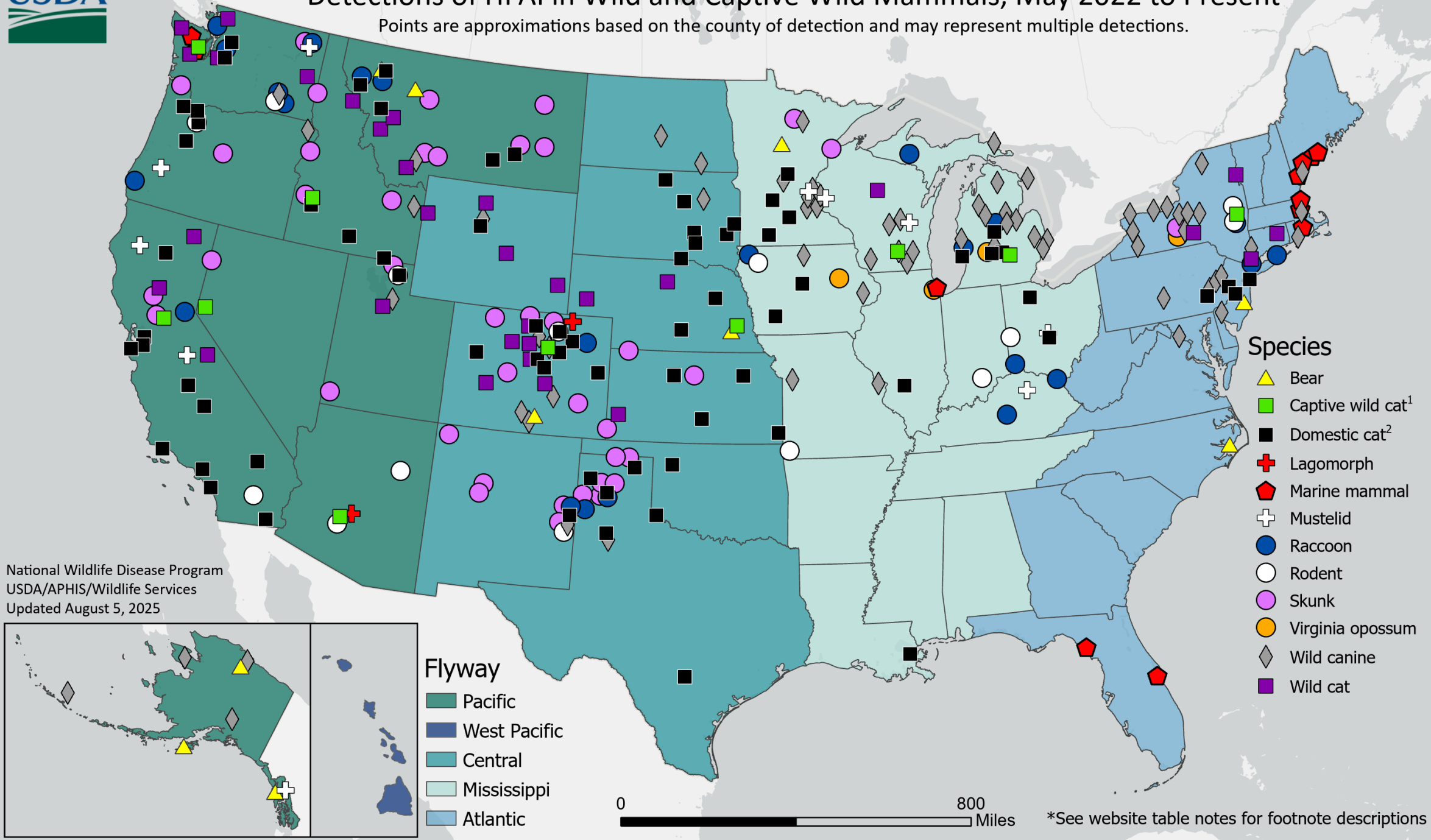
2020–2023



Plaza PI, Gamarra-Toledo V, Euguí J, Lambertucci SA. Recent Changes in Patterns of Mammal Infection with Highly Pathogenic Avian Influenza A(H5N1) Virus Worldwide. Emerg Infect Dis. 2024;30(3):444-452. https://doi.org/10.3201/eid3003.231098

Detections of HPAI in Wild and Captive Wild Mammals, May 2022 to Present

Points are approximations based on the county of detection and may represent multiple detections.



National Wildlife Disease Program
USDA/APHIS/Wildlife Services
Updated August 5, 2025

Domestic Cats

Similar clinical signs and disease progression:

1. An initial complaint of lethargy and inappetence
2. Followed by progressive respiratory signs
3. Progressive neurologic signs in most.

Cases have been often tested for rabies preceding diagnosis with H5N1 infection due to the indistinguishable presentation once neurologic signs presented.

A few cases have been indoor only cats.

H5N1 in cats

Risk Factors

- Cats residing on or near dairy operations
- Owners associated with dairy activities
- Cats being fed raw or discarded milk
- Indoor cats that have escaped for a period of time
- Cats known to hunt or consume rodents or birds

Recommendations to feline owners:

- Limit contact between pets and wild birds as well as ill livestock and environments that could be contaminated with the virus.
- Consider changing clothing and shoes after interacting with animals or birds with unknown health status, and before interacting with personal pets.
- Wash your hands thoroughly after touching or interacting with animals outside your household.
- Avoid contact with sick or dead wildlife.

Recommendations to veterinarians

- Use your clinic's isolation and patient handling protocols for suspected infectious and/or zoonotic disease cases; including negative airflow when possible, contain and disinfect all equipment used in treating the patient, and use PPE and limit staff contact with animals in isolation.
- All veterinary staff should change shoes and clothes prior to leaving the clinic to prevent spreading H5N1 to other pets, family members, and the community

Considerations for Veterinarians: Evaluating and Handling of Cats Potentially Exposed to HPAI

Avoid unprotected close or direct physical contact with sick cats who may have been exposed to animals that tested positive for HPAI A(H5N1) virus infection.

When handling or interacting with cats that might be infected with or have been exposed to bird flu viruses, veterinarians and staff should wear PPE including:

- Disposable or non-disposable fluid-resistant coveralls or gown*, and depending on task(s), add disposable or non-disposable waterproof apron
- Any NIOSH Approved® particulate respirator (e.g., N95® or greater filtering facepiece respirator, elastomeric half mask respirator with a minimum of N95 filters)
- Properly-fitted unvented or indirectly vented safety goggles** or a face shield if there is risk of liquid splashing onto the respirator
- Rubber boots or rubber boot covers with sealed seams that can be sanitized or disposable boot covers for tasks taking a short amount of time
- Disposable or non-disposable head cover or hair cover
- Disposable or non-disposable gloves

Testing for influenza A(H5N1) in felines

The preferred sample is brain tissue.

- Wear PPE when collecting specimens, including mask, face shield, and gloves.
- For deceased or euthanized animals, submit 1” x 2” section of brain (fresh).
- For live animals, submit nasal swab, ocular swab, urine and whole blood.
- Samples should be refrigerated and shipped in an insulated box with ice packs.

H5N1 highly pathogenic avian influenza is a reportable disease in any animal species

Summary of H5N1 in non-poultry species

Wild birds, especially wild waterfowl, are considered to be the primary natural reservoir of influenza A viruses, but various subtypes have become established in different species, including humans, swine, horses, and dogs.

While most influenza viruses are species-specific, the transmission of viruses from one species to another can occur. This may or may not result in sustained transmission in the new species; however, influenza viruses can readily mutate, which can lead to adaptation within the new species.

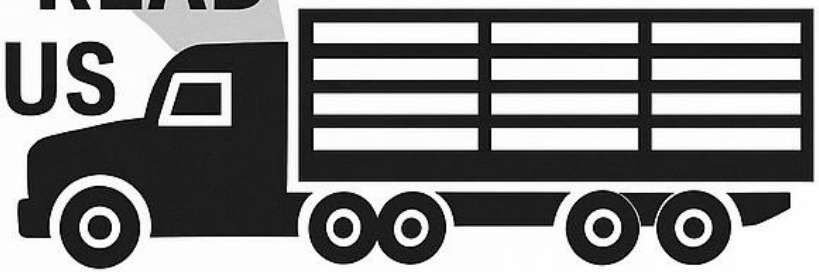
Interspecies transmission can result in the formation of novel pandemic or panzootic viruses.

MARCH 2024

HOLY COW!
H5N1 DETECTED
IN LACTATING DAIRY CATTLE

MASTITIS OF
UNKNOWN ORIGIN

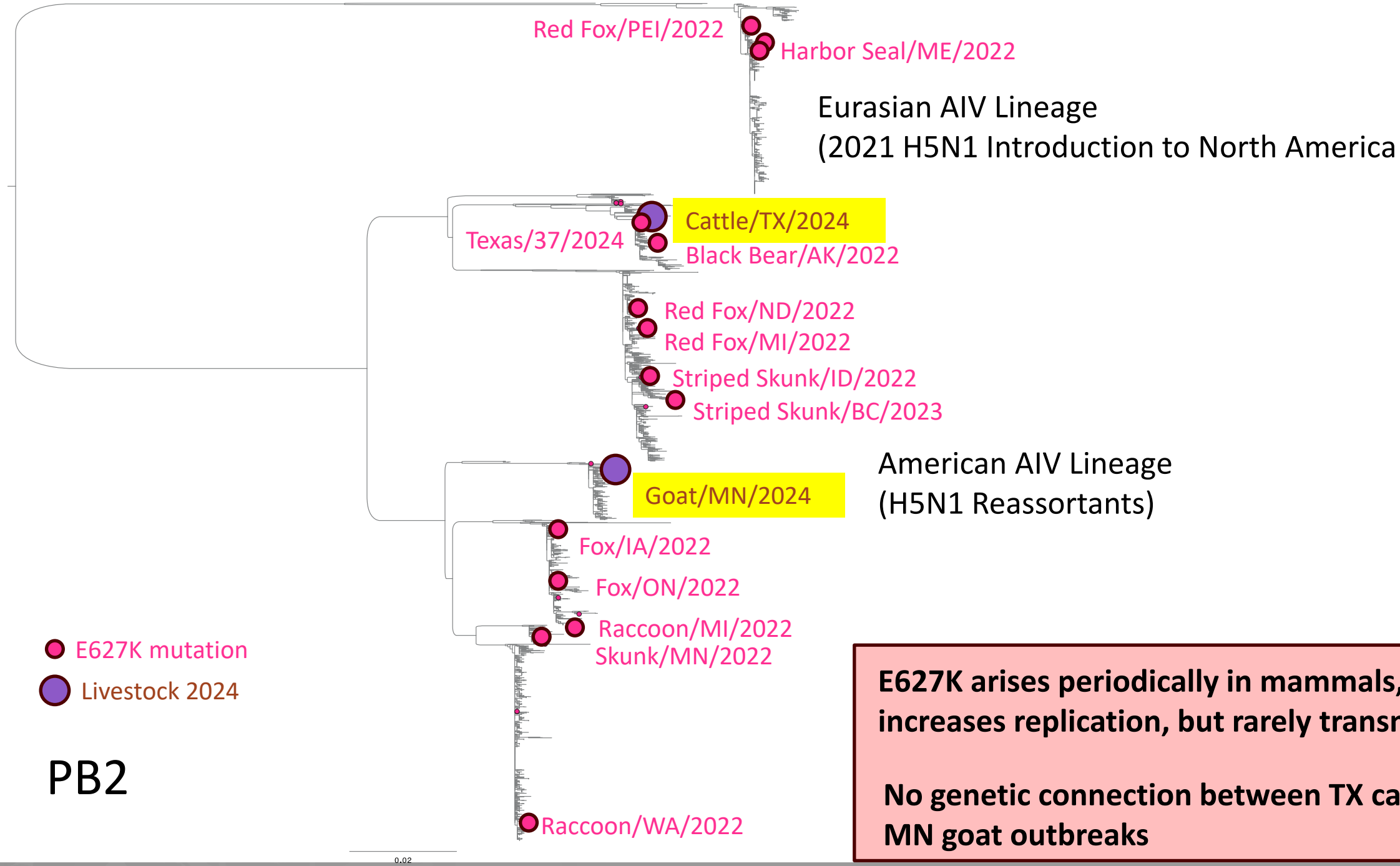
SUBSEQUENT SPREAD
ACROSS THE US



Do the cattle/goat/human viruses have mammalian adapted mutations?

	PB2 Q591K	PB2 E627K	PB2 D701N	HA E190D	HA Q226L	HA G228S
A/dairy cattle/TX/24-008749/2024						
A/goat/MN/24-007234/2024						
A/Texas/37/2024		✓				
A/Chile/25945/2023	✓		✓			
A/sea lion/Argentina/RN-PB011/2023	✓		✓			

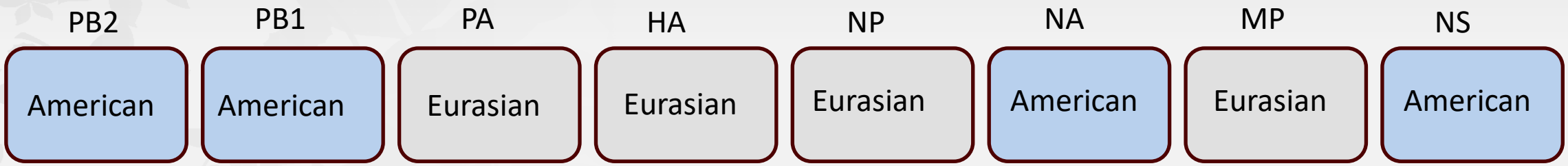
PB2 E627K mutation likely acquired in Texas human case during replication (not transmitted from cattle)



E627K arises periodically in mammals, increases replication, but rarely transmits

No genetic connection between TX cattle and MN goat outbreaks

4:4 reassortants



A/Texas/37/2024

A/dairy cattle/Texas/24-008749-003/2024

A/common grackle/Texas/24-008356-001/2024

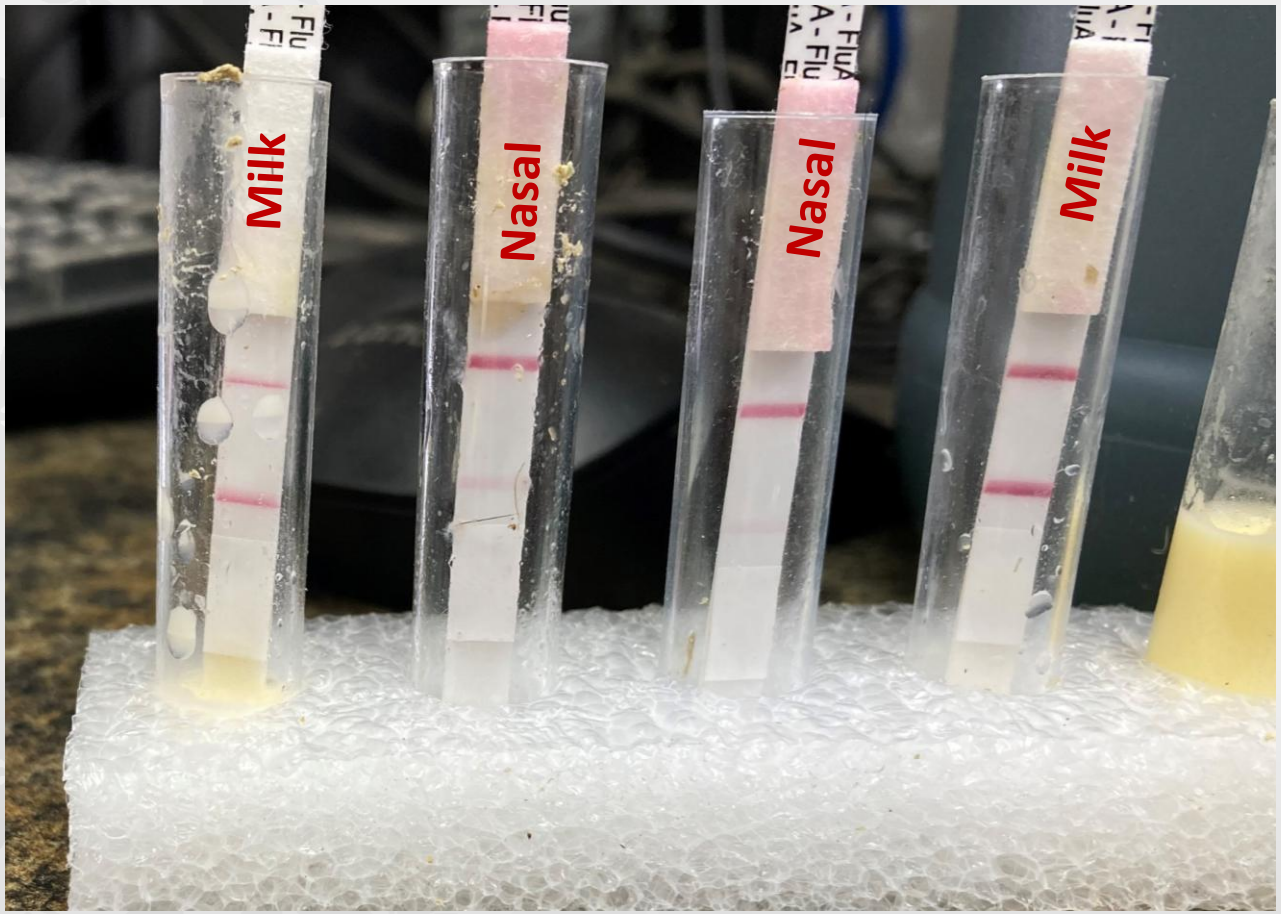
A/blackbird/Texas/24-008354-001/2024

A/goat/Minnesota/24-007234-009/2024

Dominant genotype in 2023 and 2024 in North America

On Farm Experience

On Farm Experience



Outbreak Sample Testing

Milk was the only consistently positive sample type.

Milk from clinical cows contained up to $10^{8.5}$ $TCID_{50}$/mL

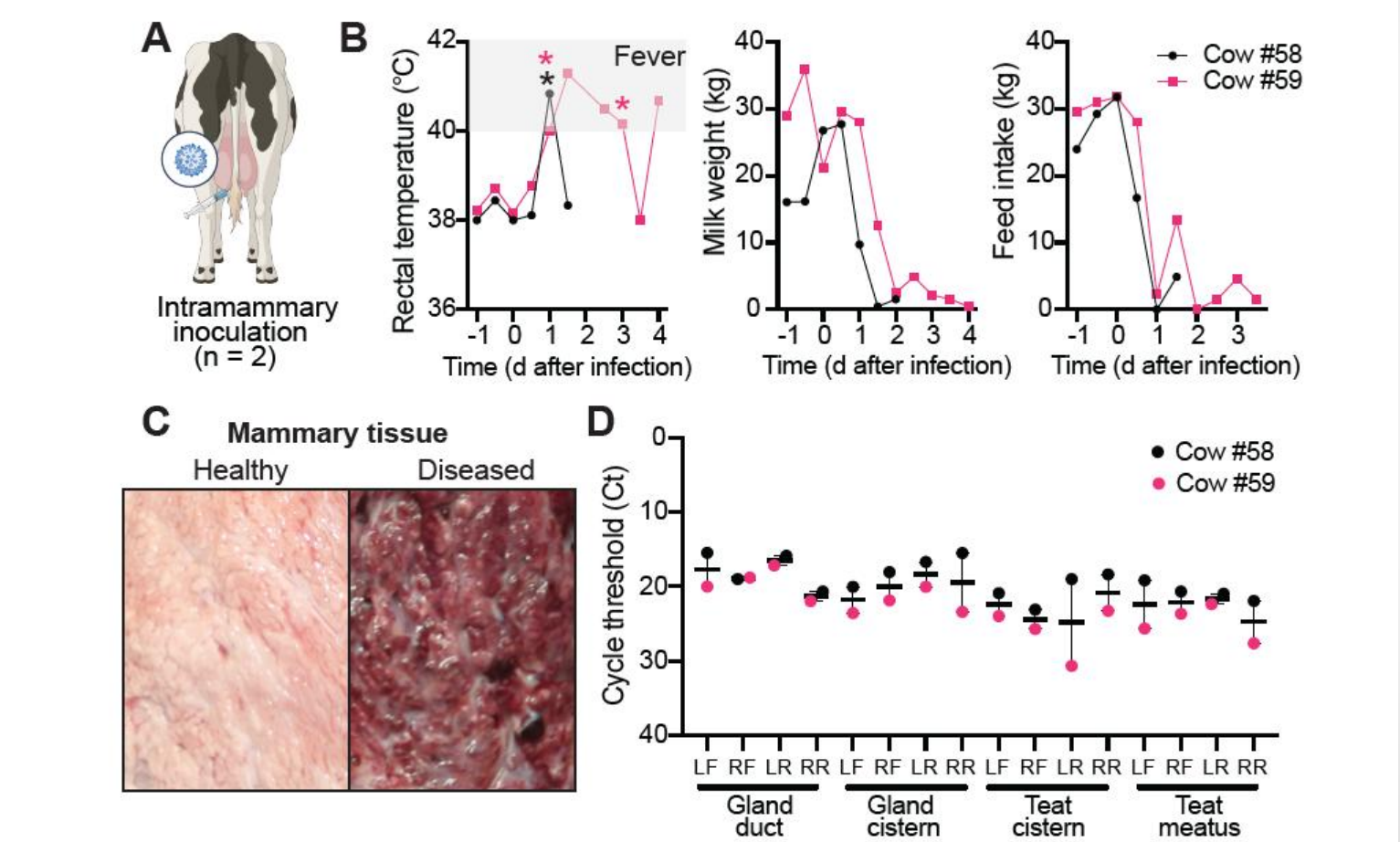
In the milking parlor:

- Udder wipes
  - 8/128 [6.3%] positive pre-milking
  - 6/128 [4.7%] positive post-milking
  - Only 2 cows positive pre and post milking

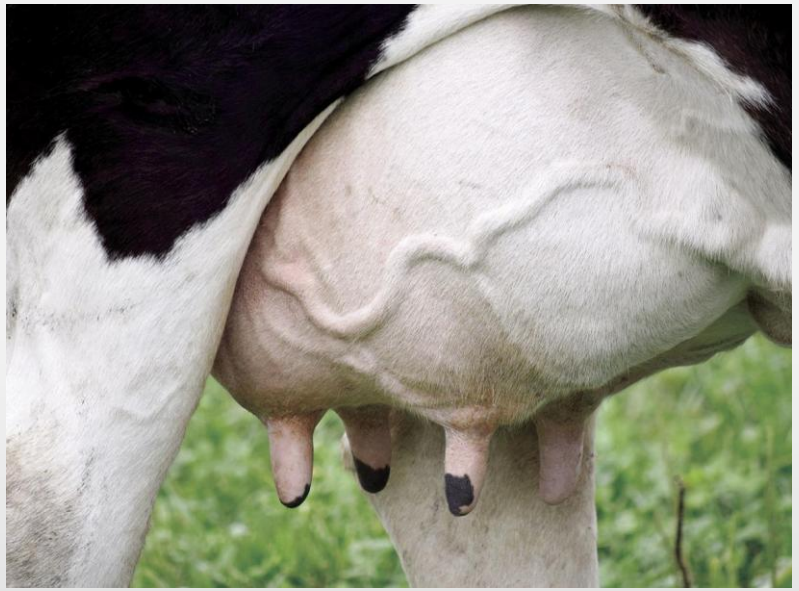
Teat cup liners and parlor floor were positive

Preprint available at https://doi.org/10.21203/rs.3.rs-6900680/v1

Intramammary Inoculation



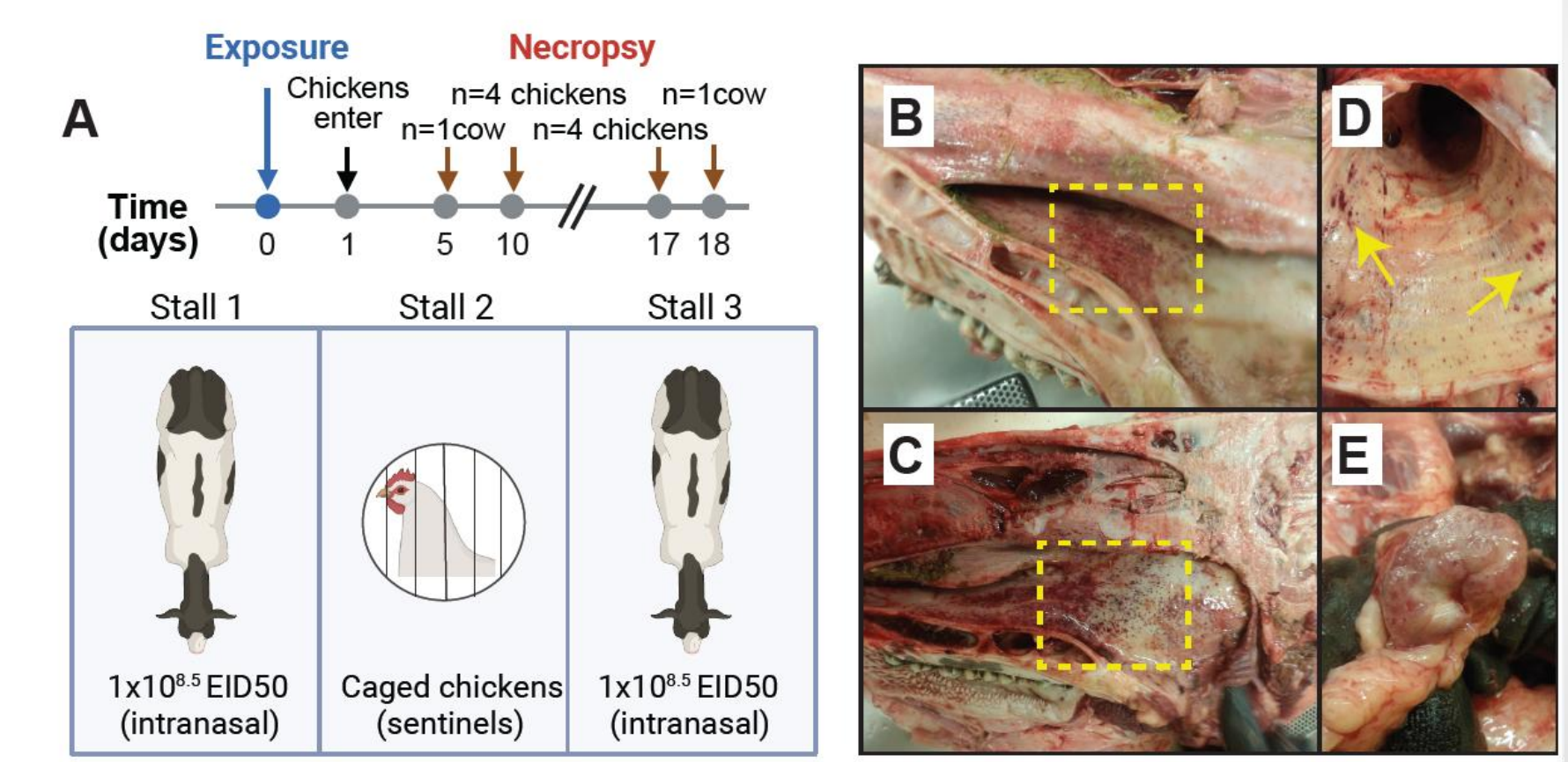
10^7 PFU per teat
(inoculated all 4 quarters)



Preprint available at https://doi.org/10.21203/rs.3.rs-6900680/v1

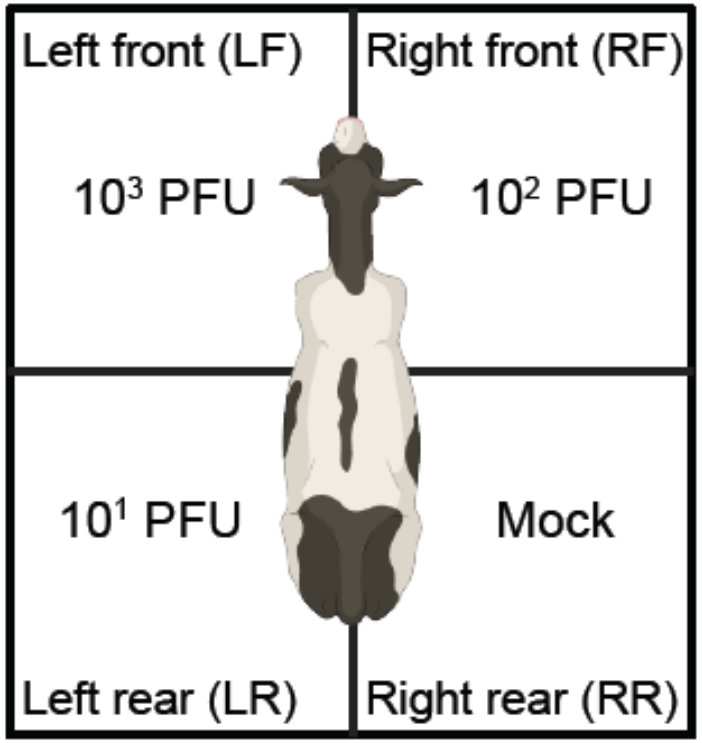
Intranasal Inoculation

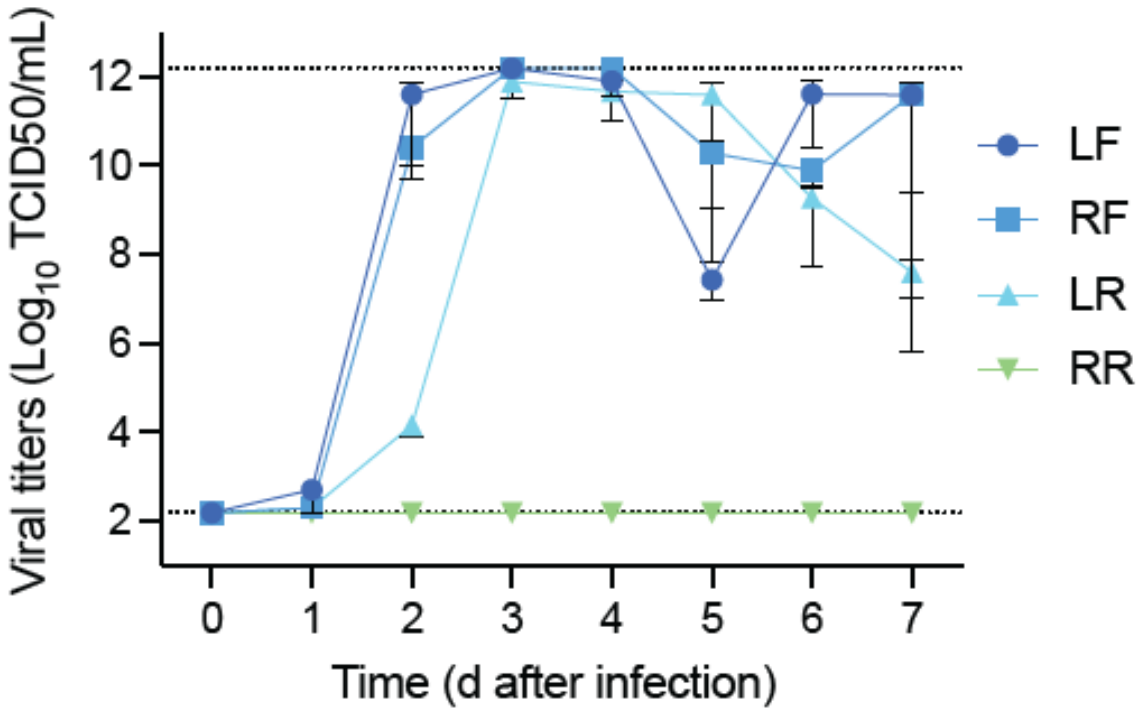
- Only minimal replication in the upper respiratory tract
- No virus in the milk (or elsewhere)
- No transmission to chickens in the room



Preprint available at https://doi.org/10.21203/rs.3.rs-6900680/v1

Remarkably low infectious dose (B3.13)





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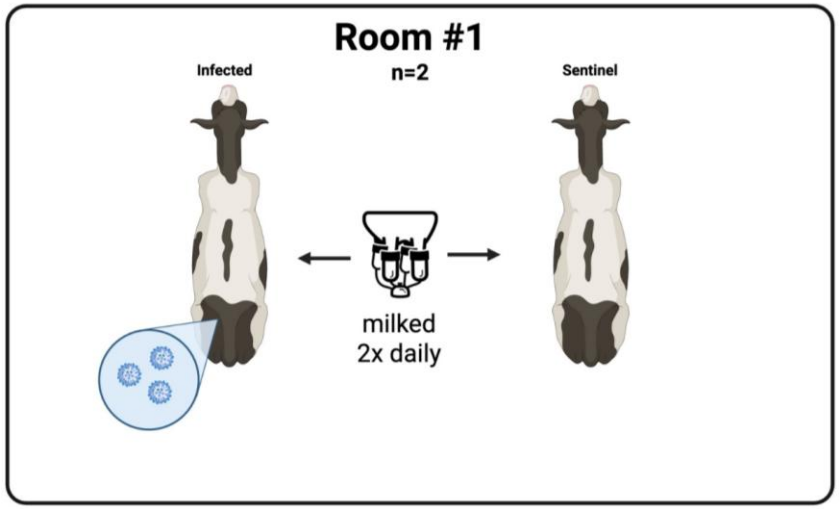
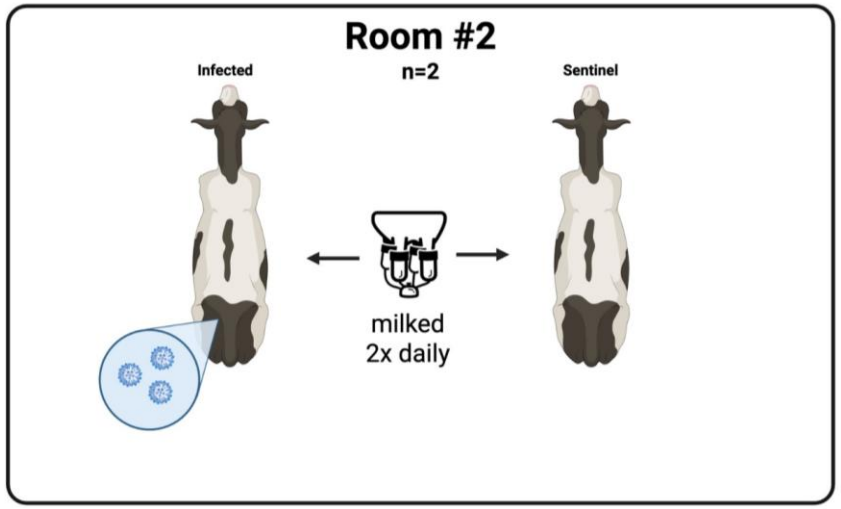
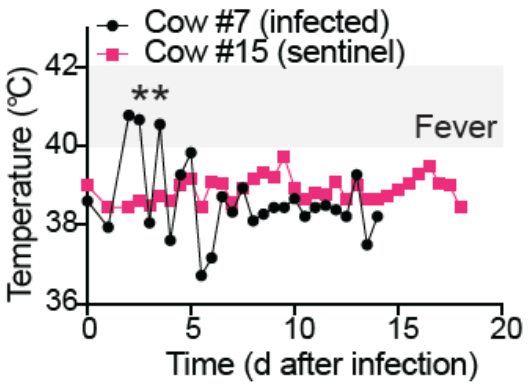
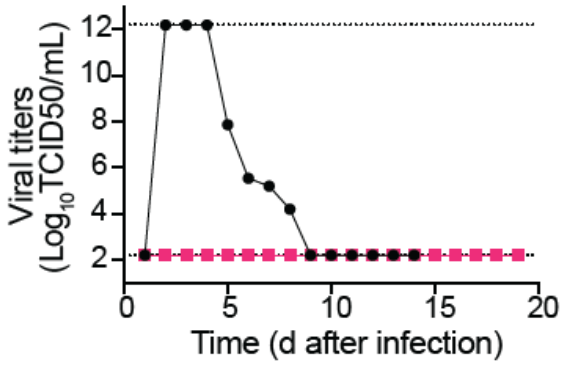
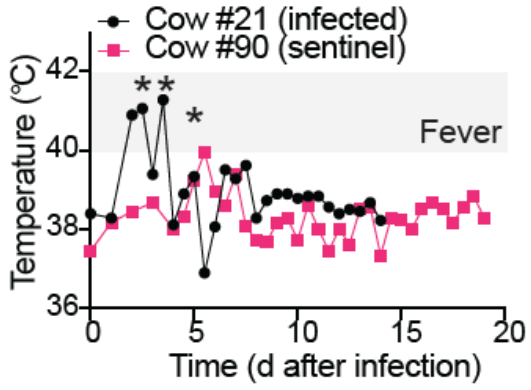
Lack of transmission

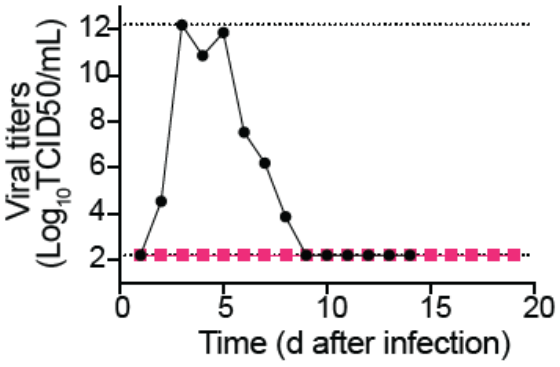












US dairy industry

- 9.3 million cows
- 18,830 dairy farms
- 80 billion liters of milk annually

Retail Milk

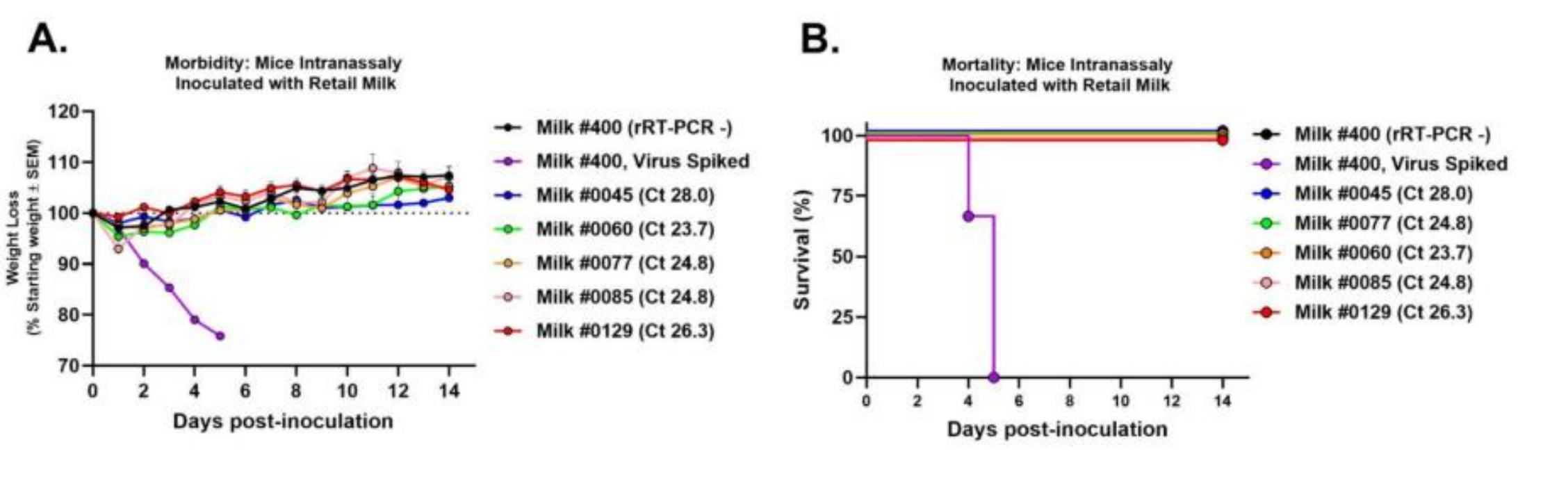
April 13, 2024 (29 reported cases in the US)

- 168 whole milk samples
- Bottled in 18 states
  - Purchased in 12 states

- 36.3% (61) PCR positive
  - Ct values ranged from 23.7- 36.9
  - Bottled in 10 states
  - 20 processing plants

Pasteurization is effective

NO viable virus detected in retail milk



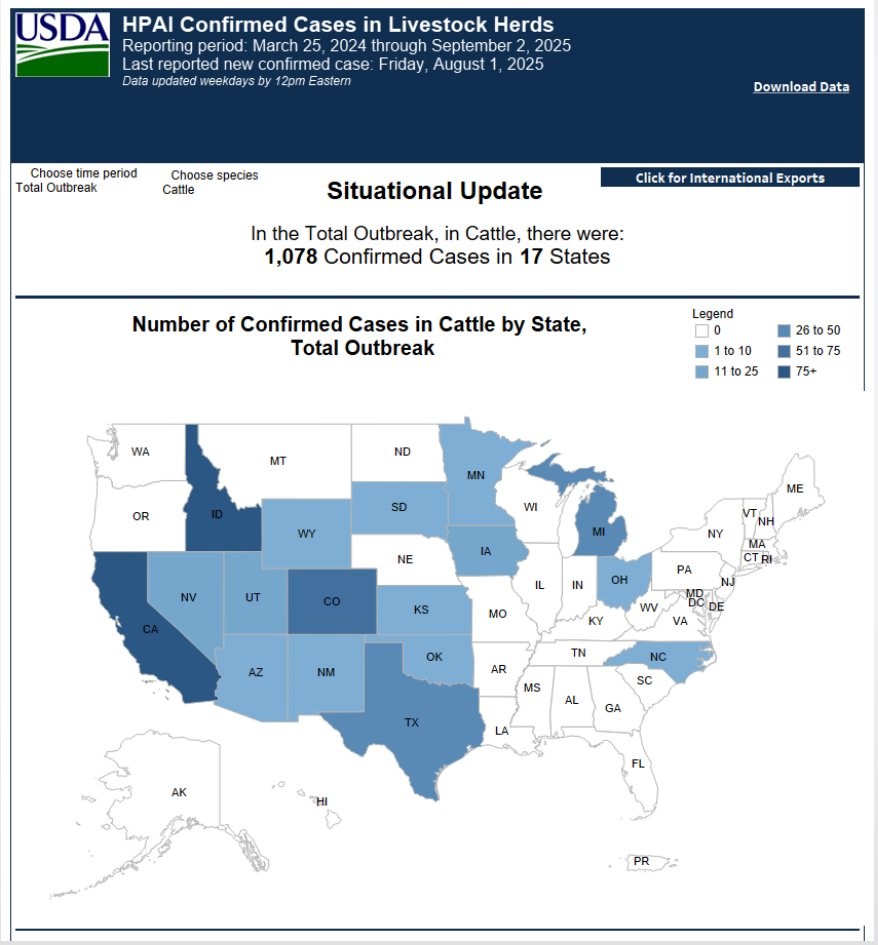
Current Status

Federal Order (April 24, 2024)

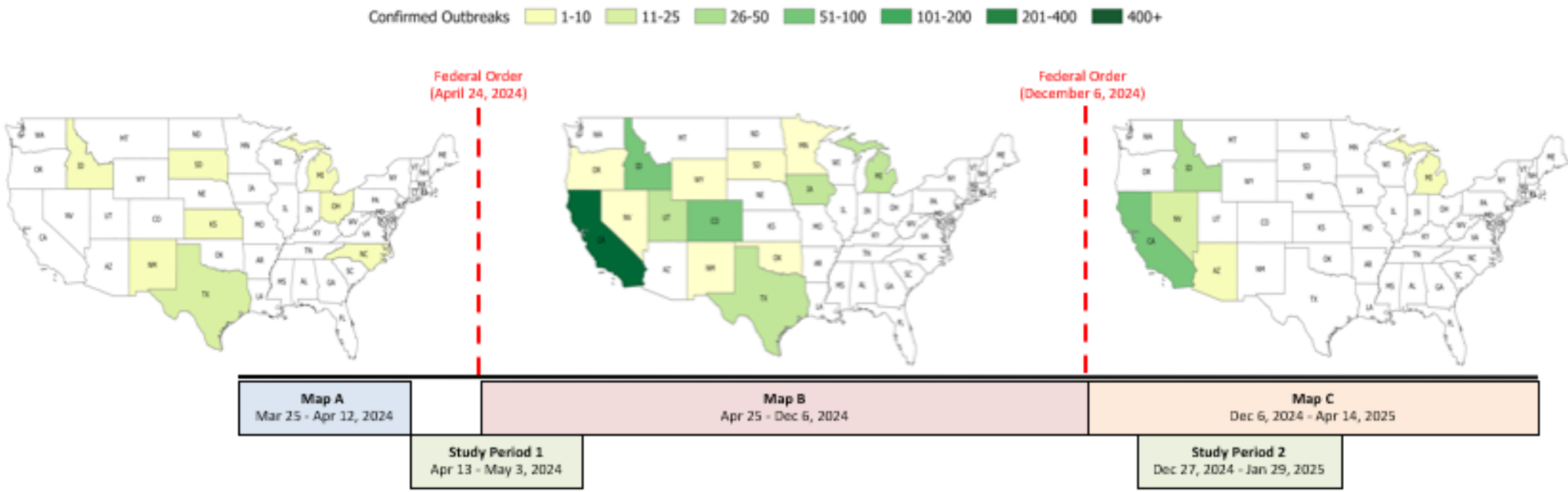
- A negative influenza A virus test is required for lactating dairy cattle before interstate movement.

National Milk Testing Strategy (December 2024)

- Comprehensive H5N1 surveillance of the milk supply.
- Identified D1.1 in Nevada and Arizona

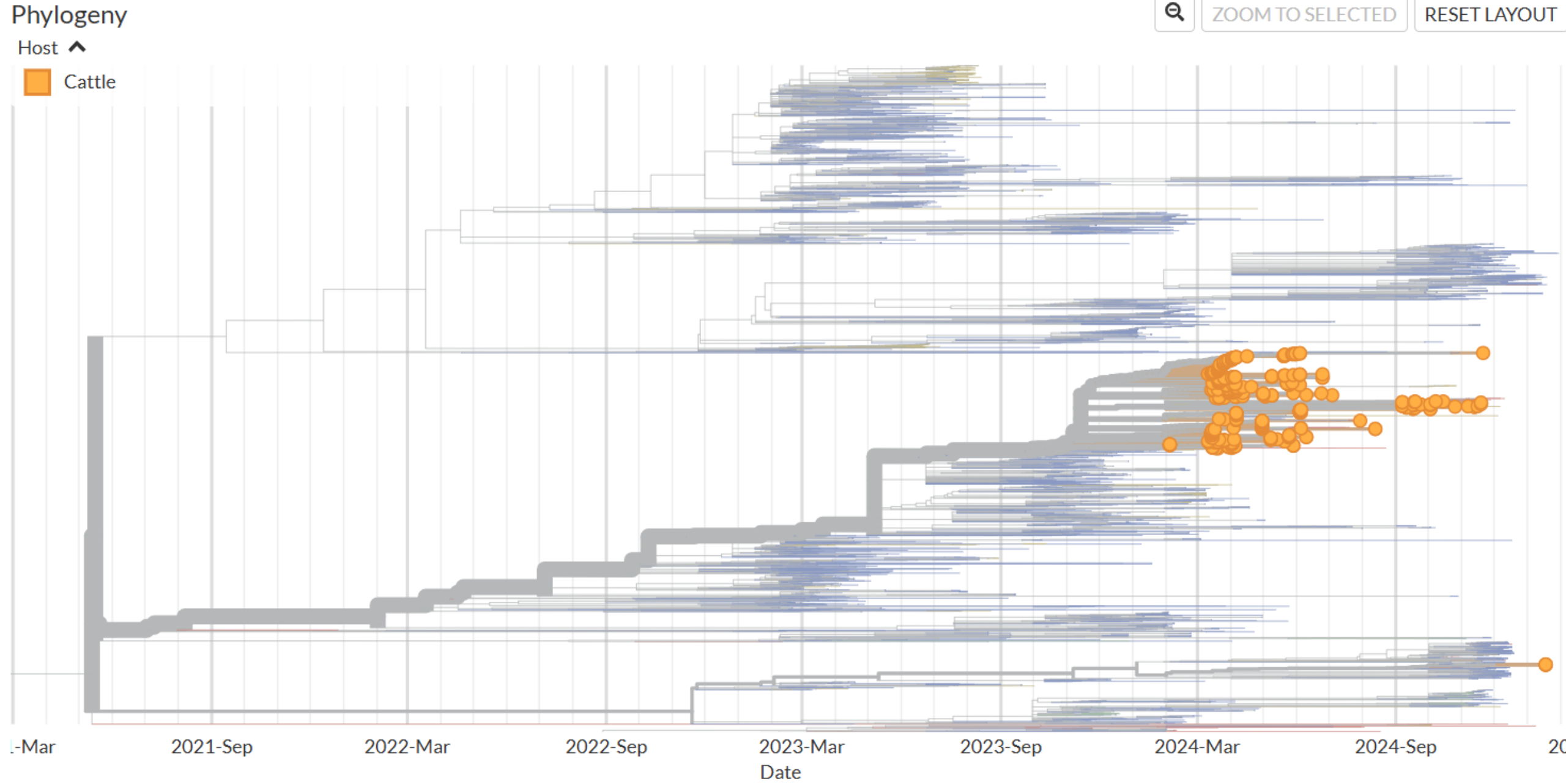


Retail Milk Detections



36.3% (61/168)

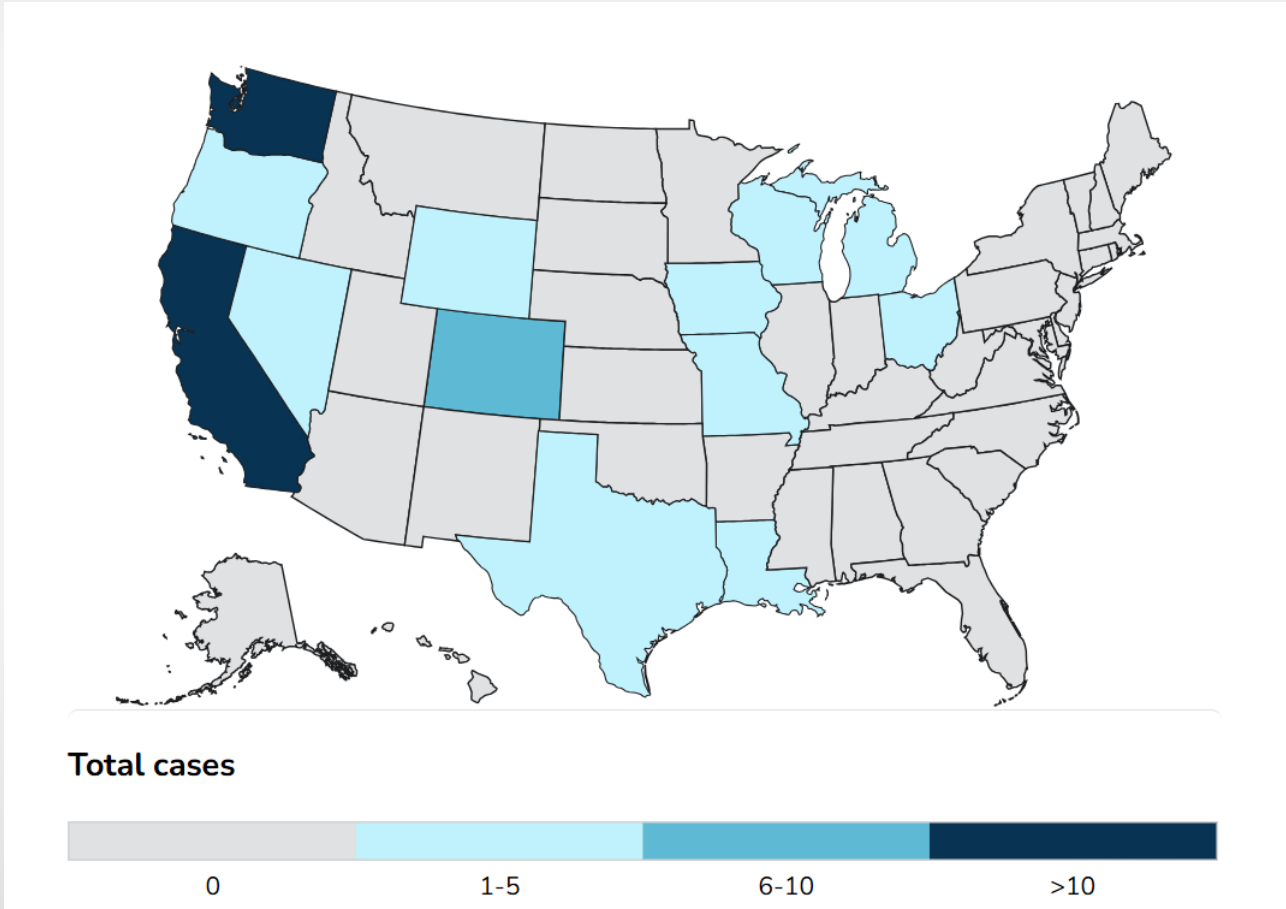
6.9% (33/477)


Phylogeny
ZOOM TO SELECTED
RESET LAYOUT
Host
Cattle
-Mar
2021-Sep
2022-Mar
2022-Sep
2023-Mar
2023-Sep
2024-Mar
2024-Sep
Date

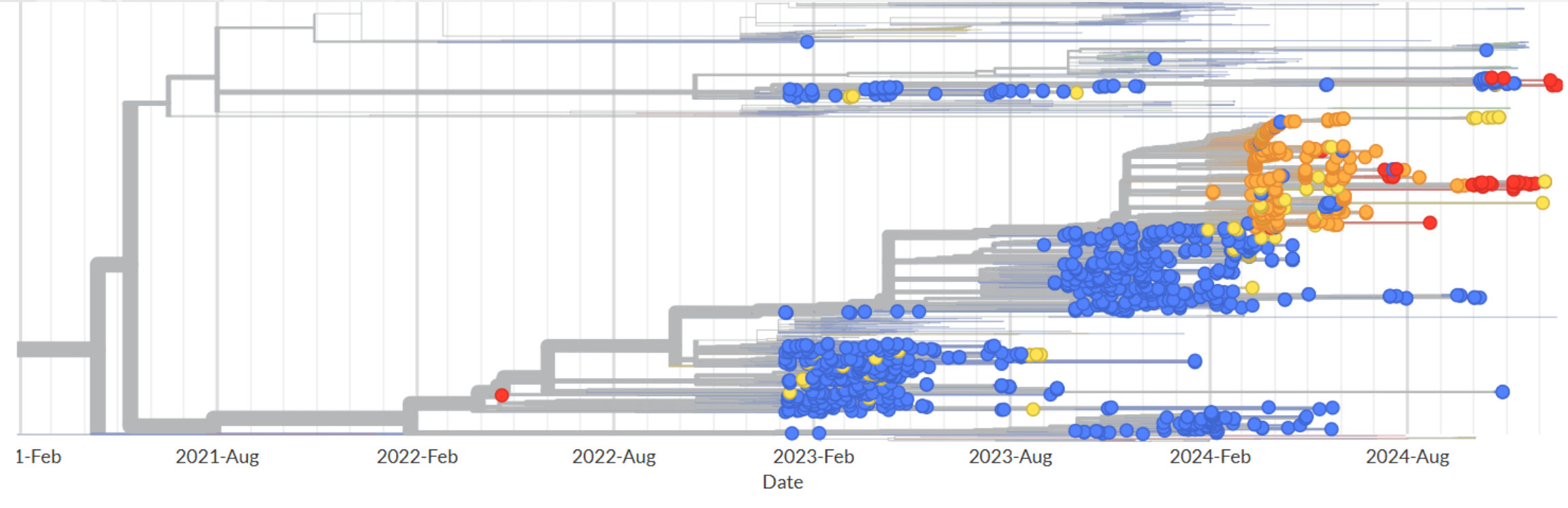

RAW FARM
TRULY
RAW
CHEDDAR
GRASS-GRAZED
GLUTEN FREE

70 Total Reported Human Cases in the United States

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



H5 in North America



H5N1 detected in swine

First-ever known US case of bird flu found in a pig in Central Oregon farm

By **Alejandro Figueroa** (OPB)
Oct. 30, 2024 4:03 p.m. **Updated:** Oct. 30, 2024 8:11 p.m.

U.S. Department of Agriculture officials say there is no concern about the safety of the nation's pork supply

What is pork doing?

Draft H5N1 Swine Industry Response Plan

A. Background

a. Currently, an Influenza A (HPAI H5N1 clade 2.3.4.4b virus is circulating in various domestic and wildlife species. It has had a negative impact on the dairy industry, creating an economic burden to dairy farmers and leading to loss of trade as well as concern regarding food safety of milk and meat since it was first identified in a dairy herd in Texas in March 2024. The continued spread of this virus through dairy cattle has also created an increased exposure risk for poultry flocks and swine herds. Whole genome sequencing (WGS) analysis suggests an initial single spillover event of the HPAI H5N1 clade 2.3.4.4b, genotype B3.13 from wild birds to dairy cattle, most likely occurring in the Texas panhandle in December 2023, with onward spread of the virus to other states (Nguen et al, 2024). The Federal Order released by USDA mandates a 30-day quarantine in the event of a positive detection via PCR in lactating cattle moving across state lines.
The pork industry is concerned about the potential response following a discovery of the H5N1 HPAI virus in the U.S. swine population, given the significant differences between the swine and dairy industries. Implementing similar

What can people do?

1. Biosecurity
2. Biosecurity
3. Biosecurity
   - Add dairy cattle to the list of things to avoid
4. Get a flu vaccine
5. Look for and report abnormalities

Ohio State Team

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FUNDED BY NIAID

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