The Natural History of Influenza A Viruses in Avian Species

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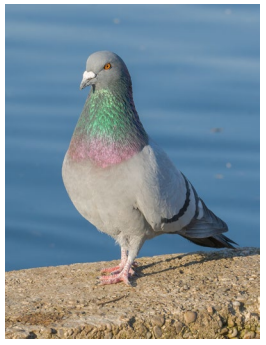
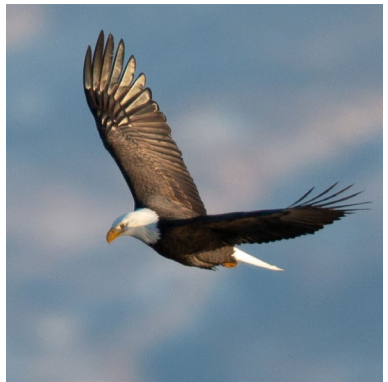
Driven to Discover℠

Dabbling ducks maintain the genetic diversity of influenza A viruses

- There are more than 9000 avian species in the world in 30(ish) orders. They have varied relationships with IAV
- The broad diversity of IAV genetics is maintained in ducks H1N1➡H16N9
- The Gs/GD lineage of H5 IAV is unusual among IAV and has been detected in more avian species than other IAV
  - **Avian host range determinants for Gs/GD**
  - **Avian host pathogenesis (long distance carriers)**


US poultry production systems, biosecurity, and HPAI control strategies

- US poultry are maintained as free of IAV infections with surveillance, depopulation, and prevention with biosecurity
- Biosecurity is the only preventative strategy for IAV infections. Only poultry flocks with biosecurity can be indemnified if they become infected with IAV
  - **Evaluation of the efficacy of various biosecurity strategies: how much virus can they prevent?**
- HPAI is highly pathogenic. It kills chickens and turkeys.
  - Neither infected animals nor their products reach the market
- HPAI infected flocks are quickly eliminated to prevent spread to other populations (difference from 2014/5)
  - **Control strategies targeted to depopulate infected birds only**

H5 in cattle and the challenge of keeping poultry production sustainable

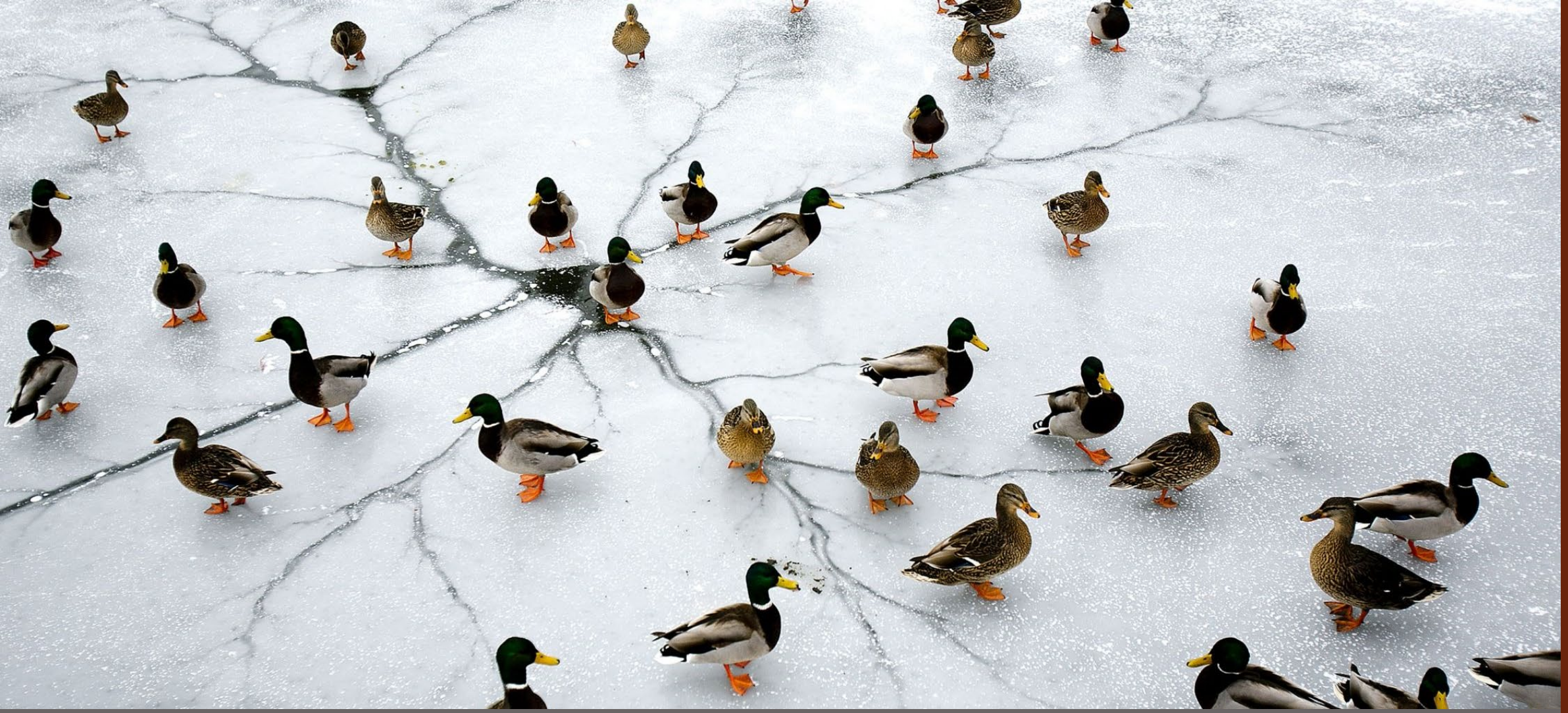
- Poultry HPAI cases since 3/2024 have come from dairy cases
  - Infected poultry farms are indemnified for losses/costs but uninfected farms are not
  - **Understanding the environmental and industry limits on how many poultry flocks can be raised over the course of a year**
- Prior to March 2024, there was one human case linked to poultry infection, now, there have been 13
  - **Better ppe for workers so they can participate in eliminating an important human:animal interface.**
- H5 influenza is in the shared ecosystem, that means more (and different) biosecurity to prevent infections
  - Finding the links between dairy and poultry farms
  - **Methods of manure, mortality, and garbage management that prevent IAV transmission between neighbors**

The requests of the AAAP

- **Risk-based regional surveillance** to efficiently generate the data needed to understand risks and mitigate them with consistent control strategies.
- A consistent, risk-based **national strategy** that adheres to science-based principles of disease control **to reduce further spread of H5 influenza**.
- **Epidemiologic studies and tools to understand connections** among and between susceptible populations
- **Resolution of concerns that impede the utilization of vaccine** needed to control the spread of H5 influenza
- Additional **resource allocation to minimize the long-term impacts of H5 influenza on human health, food security and economic sustainability**

We also need…

- **Diagnostic flexibility.** The virus is dynamic and we need early detection.
  - "If you've seen one flu season, you've seen one flu season" – Nancy Cox
- **Data integration across public/private sources.** To get the data sharing we need, barriers need to be removed.
- **Veterinary education and outreach.** All veterinarians need to know about flu.
- **Ways to protect workers.** Learning to communicate with agricultural workers independent of their employers.



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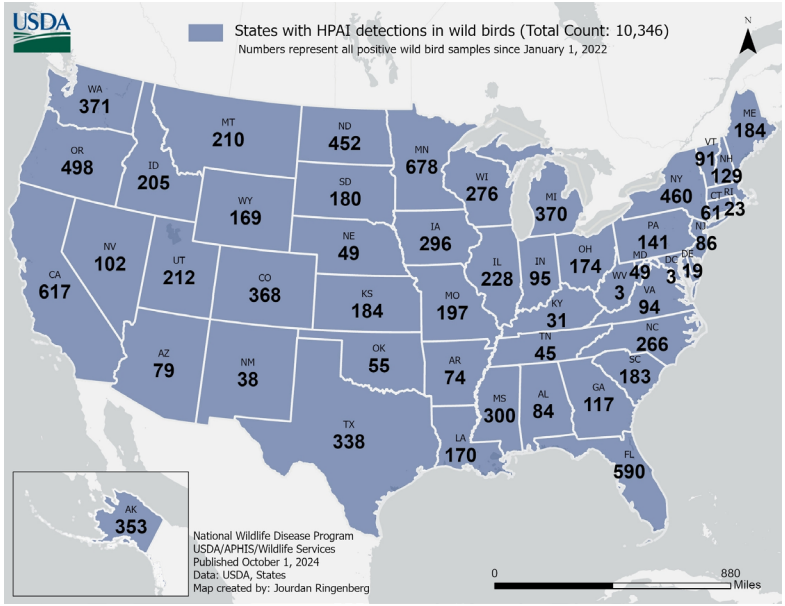
USDA
United States Department of Agriculture

Highly pathogenic avian influenza virus: a peridomestic wildlife perspective

Jeff Root
USDA/APHIS/WS
National Wildlife Research Center

2022-2024 HP avian influenza virus outbreak

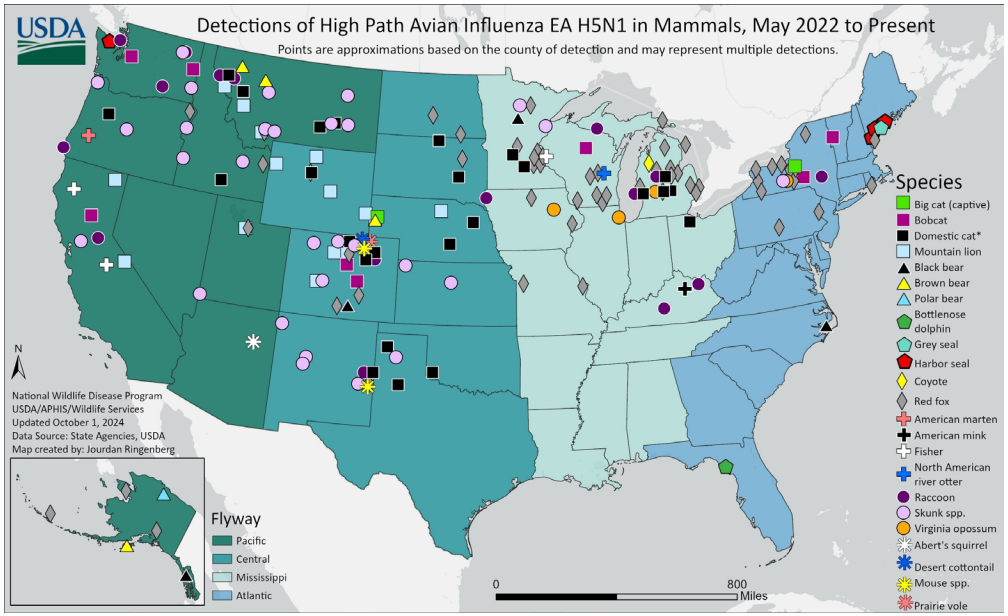
- Large HP AIV outbreak in wild birds and poultry
- Many wild avian species affected/mortality in some species
  - >10,000 detections
    - Significant increase over 2014/15



Source: https://www.aphis.usda.gov/sites/default/files/styles/small_desktop_1024px/public/2024-09/hpai-wild-birds-map.jpg

2022-2024 HP avian influenza virus outbreak

- Several wild mammal species affected
  - Mortality in select species
  - Primarily carnivores and scavengers
- Many states with wild mammal detections
- Virus-laden carcasses
- Examples:
  - Red fox
  - Striped skunks
  - Raccoons
  - Feral cats (primarily at positive premises)



Source: https://www.aphis.usda.gov/livestock-poultry-disease/avian/avian-influenza/hpai-detections/mammals

2022-2024 HP avian influenza virus outbreak

- Viral RNA detections during surveillance activities in rodents and lagomorphs
- Examples:
  - Deer mouse
  - House mouse
  - Prairie vole
  - Desert cottontail

Peridomestic wildlife

Wild or feral animals living within close proximity to humans or human-modified habitats

Potential bridge hosts (Caron et al. Veterinary Research 2015)

HP AIV challenge studies

- Six species selected
  - Striped skunks
  - Virginia opossums
  - Cottontail rabbits
  - House sparrows
  - European starlings
  - Feral pigeons

HP AIV challenge studies

- All species shed virus
- Peridomestic mammals shed higher viral levels than birds
- Striped skunks shed up to $10^{6.3}$

Research priorities

- Experimental studies
  - Viral RNA detections do not necessarily indicate a species can transmit AIV
- Peridomestic wildlife
  - Mobility
  - Natural areas and agricultural facilities
  - Species that can readily get into buildings

Research priorities

- Rodent studies
  - Virus replication
  - Transmission scenarios

Research priorities

- More work on key species
  - Susceptibilities
  - Disease outcomes
  - Shedding profiles
  - Transmission potential

Acknowledgments/co-authors

- A. Bosco-Lauth (CSU)
- J. Ellis (NWRC)
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- S. Porter (NWRC)

Understanding Infection Dynamics Natural History in Animals and Humans

National Academies of Science

Keith Poulsen, DVM PhD, DACVIM

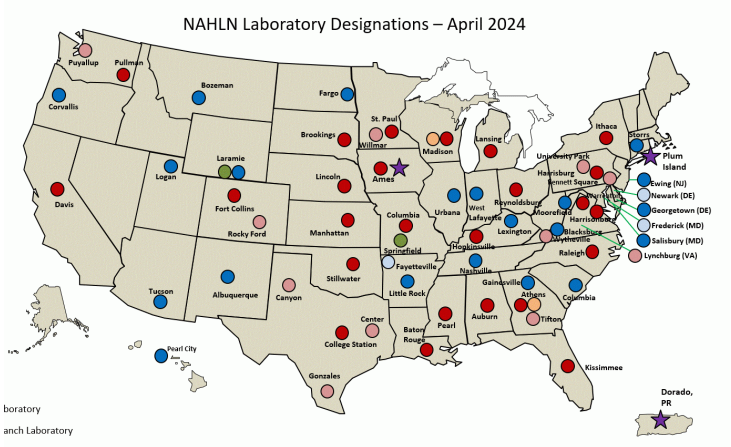
Director, WVDL

- Biosecurity
- Sampling
- Diagnostics
- Moving forward

What we know: Test lactating cattle

Test lactating cattle prior to movement, following guidance.

www.beefmag.com



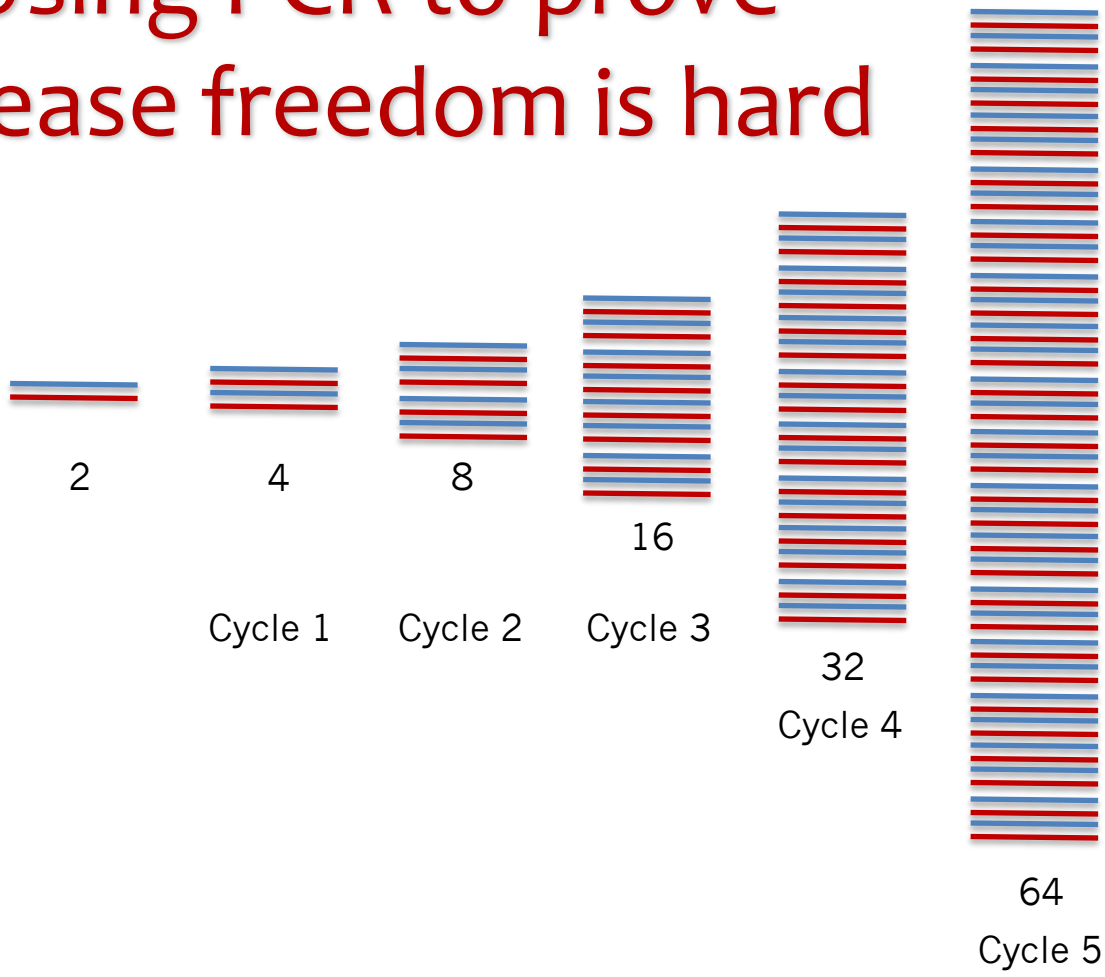
www.farmersweekly.com

www.centralstar.com

www.cornell.edu

www.shutterstock.com

Using PCR to prove disease freedom is hard



	2
Cycle 1	4
Cycle 2	8
Cycle 3	16
Cycle 4	32
Cycle 5	64
Cycle 6	128
Cycle 7	256
Cycle 8	512
Cycle 9	1,024
Cycle 10	2,048
Cycle 11	4,096
Cycle 12	8,192
Cycle 13	16,384
Cycle 14	32,768
Cycle 15	65,536
Cycle 16	131,072
Cycle 17	262,144
Cycle 18	524,288
Cycle 19	1,048,576
Cycle 20	2,097,152
Cycle 21	4,194,304
Cycle 22	8,388,608
Cycle 23	16,777,216
Cycle 24	33,554,432
Cycle 25	67,108,864
Cycle 26	134,217,728
Cycle 27	268,435,456
Cycle 28	536,870,912
Cycle 29	1,073,741,824
Cycle 30	2,147,483,648
Cycle 31	4,294,967,296
Cycle 32	8,589,934,592
Cycle 33	17,179,869,184
Cycle 34	34,359,738,368
Cycle 35	68,719,476,736
Cycle 36	137,438,953,472
Cycle 37	274,877,906,944
Cycle 38	549,755,813,888
Cycle 39	1,099,511,627,776
Cycle 40	2,199,023,255,552

40 cycles results in 2.2 trillion copies

Herd-level aggregate testing is key to sustainable surveillance

Ct	Probablity of detection Single cow	1 cow in 100	probability to detect	Ability to detect 1 cow in 1000		Ability to detect 1 cow in 5,000		Ability to detect 1 cow in 10,000	
40	50%	0.04		0.004		0.0008		0.0004	
36.7	90%	0.32		0.032		0.0064		0.0032	
33.4	100%	4	50%	0.32		0.064		0.032	
30.1	100%	32	90%	3.2		0.64		0.32	
26.8	**100%**	**320**	**100%**	**32**	**90%**	**6.4**	**50%**	**3.2**	
23.5	100%	3200		320	100%	64	~90%	32	
20.2	100%	32000		3200		640	100%	320	90%
16.9	100%	320000		32000		6400		3200	100%
13.6	100%	3200000		320000		64000		32000	

Data courtesy of Dr. Suelee Robbe-Austerman, DVM, PhD, Director - NVSL

Gaps for testing:

- Use of bulk tank samples
  - All cows? One sample per week?
- Combination of PCR and ELISA
  - More data to come
- Logistics of sample tube type
  - Biggest logistical barriers
- Logistics of data transfer
  - Biggest logistical barriers

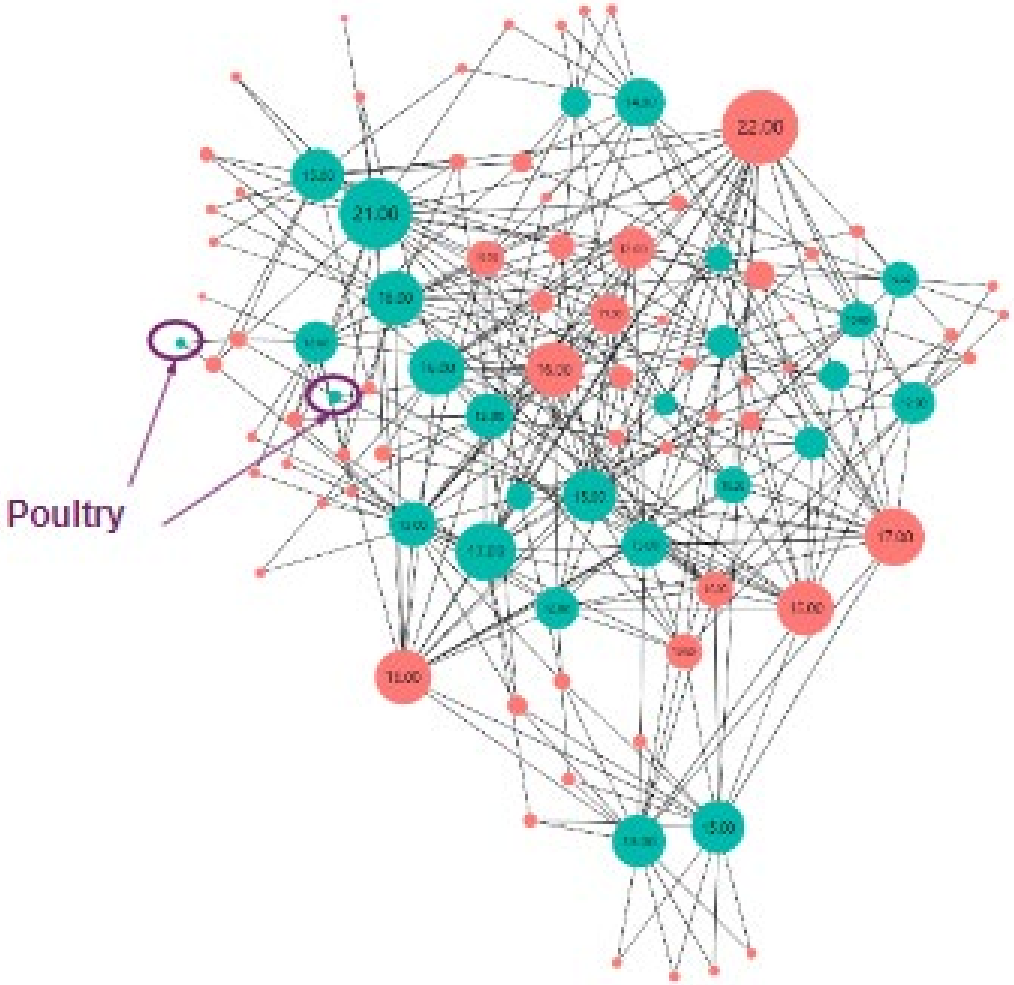
Learning from MI, ID, and CO : repeatable patterns

Colorado Network Visualization

Dairy

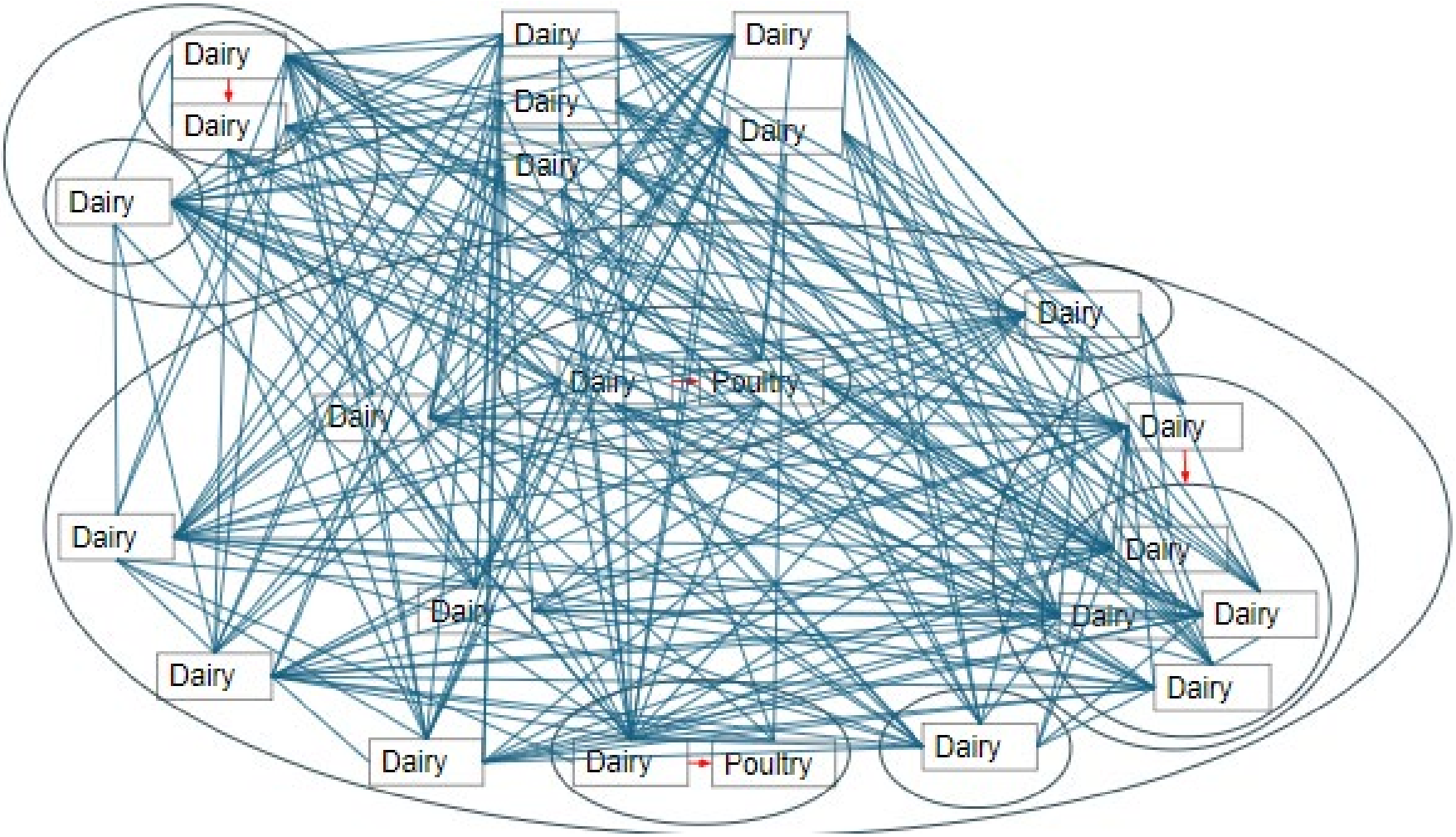
Service Provider

COLORADO
Department of Agriculture



Data courtesy of Dr. Maggie Baldwin, DVM – Colorado State Veterinarian

Learning from MI, ID, and CO : repeatable patterns



Data courtesy of Dr. Maggie Baldwin, DVM – Colorado State Veterinarian

NMPF/AVMA Punch list

Decouple animal disease from milk as a food product

1. Surveillance is critical but needs to be consistent
   National industry with constant movement
2. Antibody testing is valuable and needs to be used in testing strategies
3. Define virus elimination and make it flexible for **business continuity and animal welfare**.

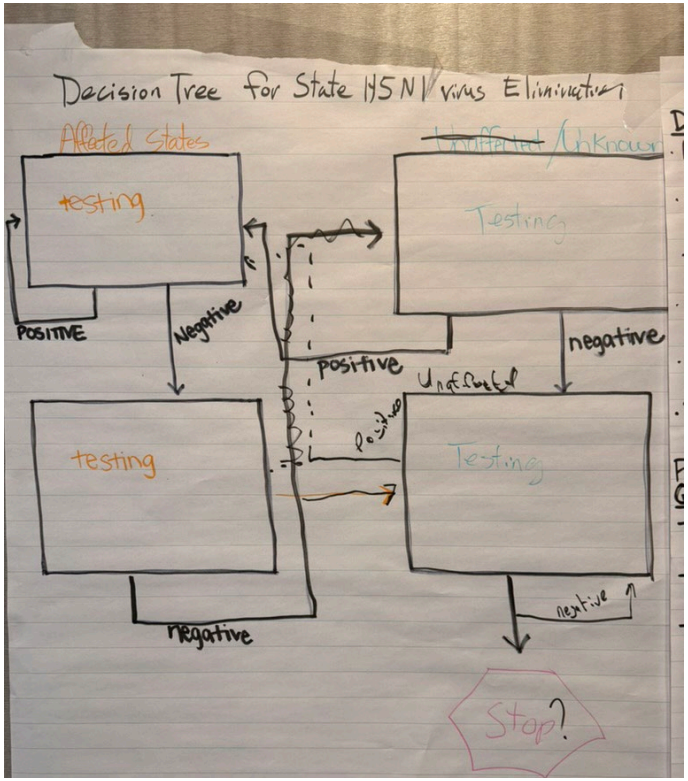
Surveillance → Elimination

Courtesy of National Milk Producers Federation collaboration – Funded by USDA

NMPF/AVMA Punch list

Coordinated national surveillance is required to understand virus elimination

1. Data protection
2. Quarantine
    1. What is it?
    2. How to get out of it?
3. Education and Communication
    1. Farmer to farmer to assuage the fear of the unknown
4. Market Access
    1. Processors must affirm markets will not be lost
    2. This is more a problem in "disease-free states"



Surveillance → Elimination → Coping → Recovery

www.wvdl.wisc.edu

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Highly Pathogenic Avian Influenza A(H5N1) in Humans

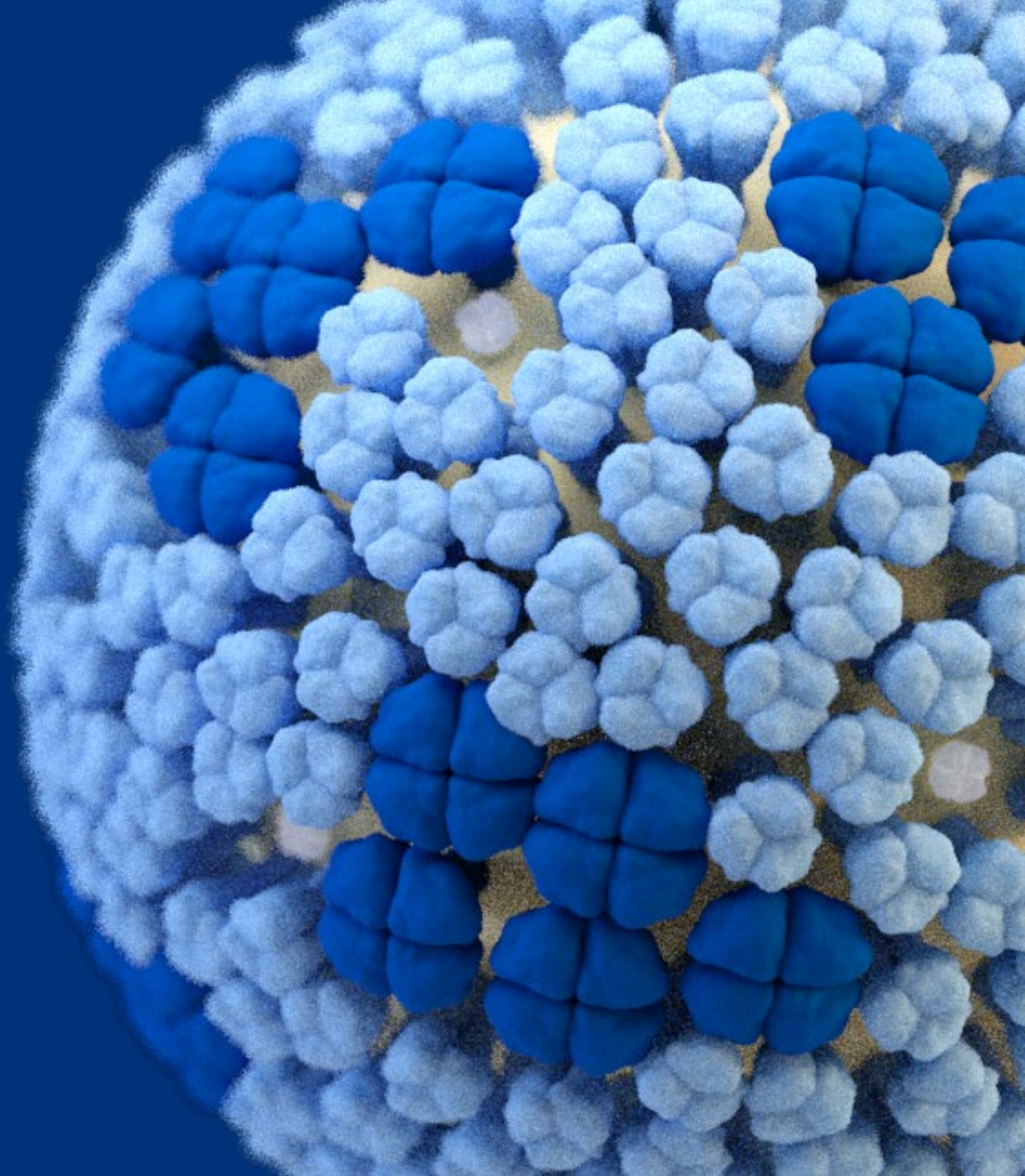
Dr. Carrie Reed

Epidemiology and Prevention Branch Chief

Influenza Division, National Center for Immunization and Respiratory Diseases (NCIRD)

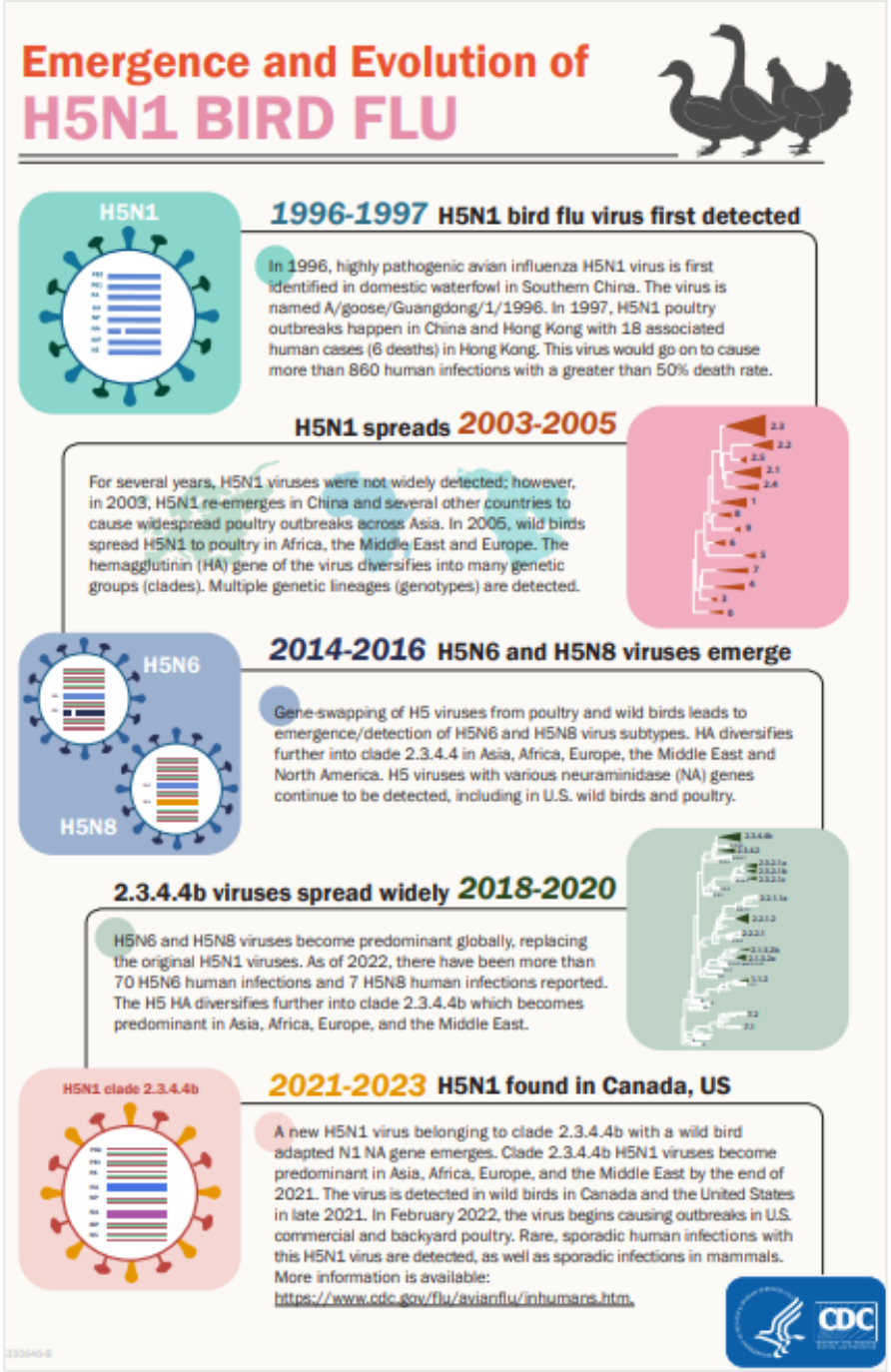
National Academies of Science, Engineering, and Medicine Workshop

October 22, 2024

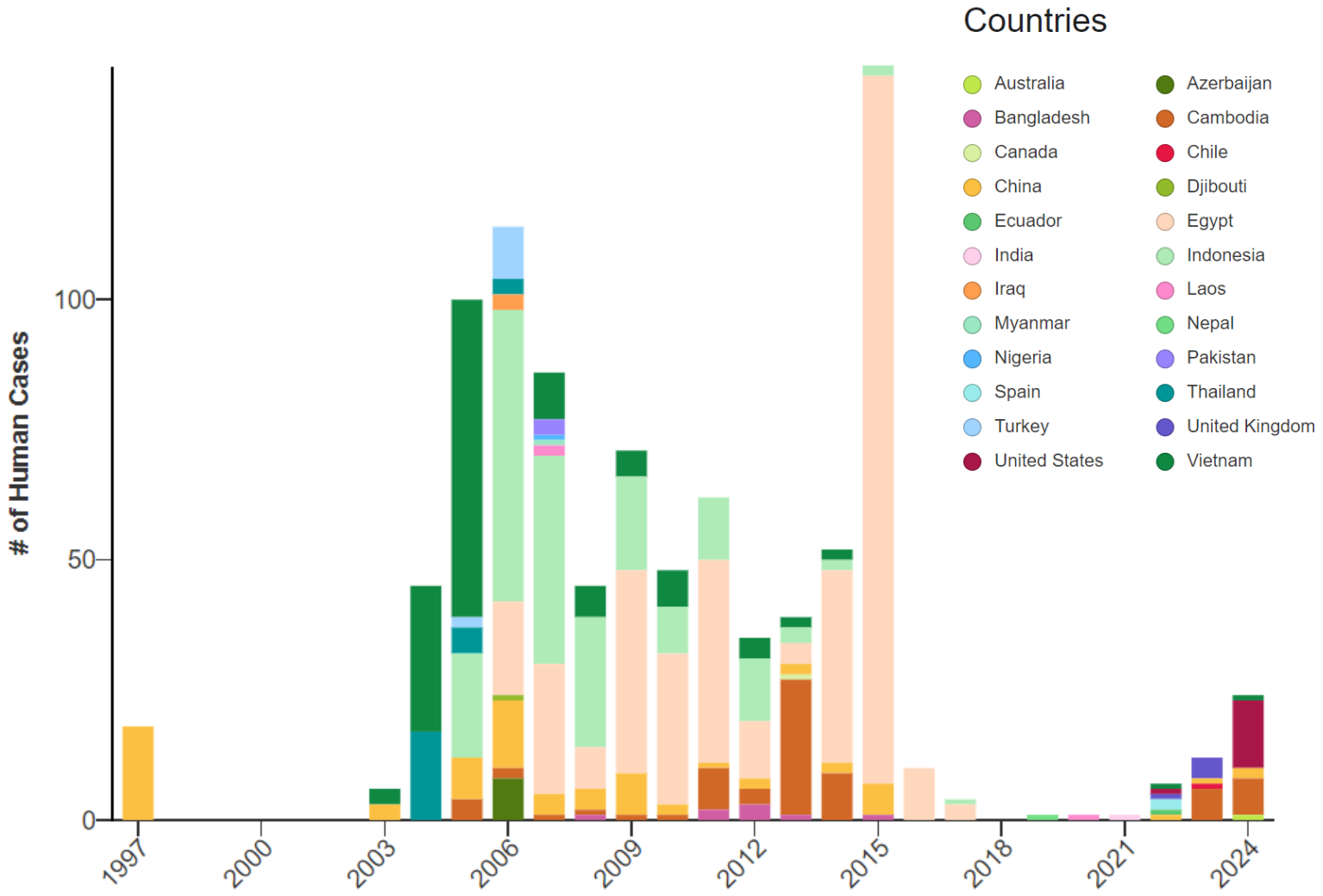


HPAI A(H5N1) over the years

- Highly Pathogenic Avian Influenza A(H5N1) detected in birds in 1996: **H5N1 not a new public health threat**
  - Viruses have continued to evolve, host range expanded
- Sporadic HPAI A(H5N1) virus infections of mammals have been reported since 2003-2004
- Outbreaks of H5N1, H5N2, H5N8 viruses detected in the U.S. in 13 states during 2014-2015; no human cases
- Clade 2.3.4.4b viruses emerged in 2020
  - Unprecedented wide global spread; detected in wild birds in North America in 2021
  - Poultry outbreaks, wild bird & wild mammal detections ongoing since 2022 throughout the U.S. states
  - 2024: Livestock (goats, alpaca, dairy cattle)



HPAI A(H5N1)/HPAI A(H5) Human Cases Since 1997



Sporadic human infections have been reported in 23 countries since 1997 with a case fatality proportion of >50%

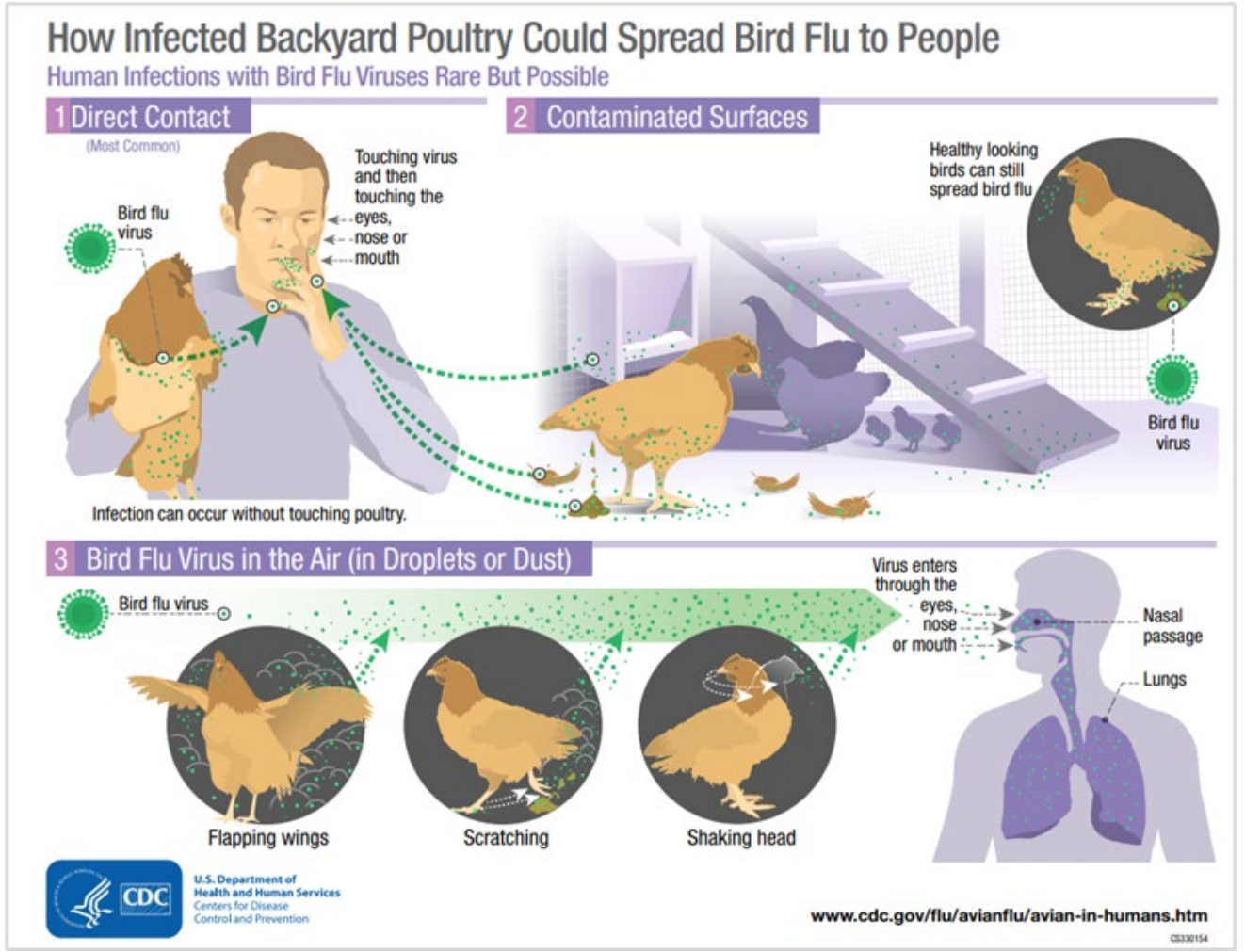
Since January 2022: 58 human cases have been detected globally

- U.S. (28), Cambodia (16), U.K. (5), Spain (2), Vietnam (2), China (2), Ecuador, Chile, Australia
- 15 cases of severe/critical illness, seven deaths

[Past Reported Global Human Cases with Highly Pathogenic Avian Influenza A(H5N1) (HPAI H5N1) by Country, 1997-2024 | Bird Flu | CDC] (Thru Aug 7, 2024; may include A(H5)+, presumed H5N1 cases)

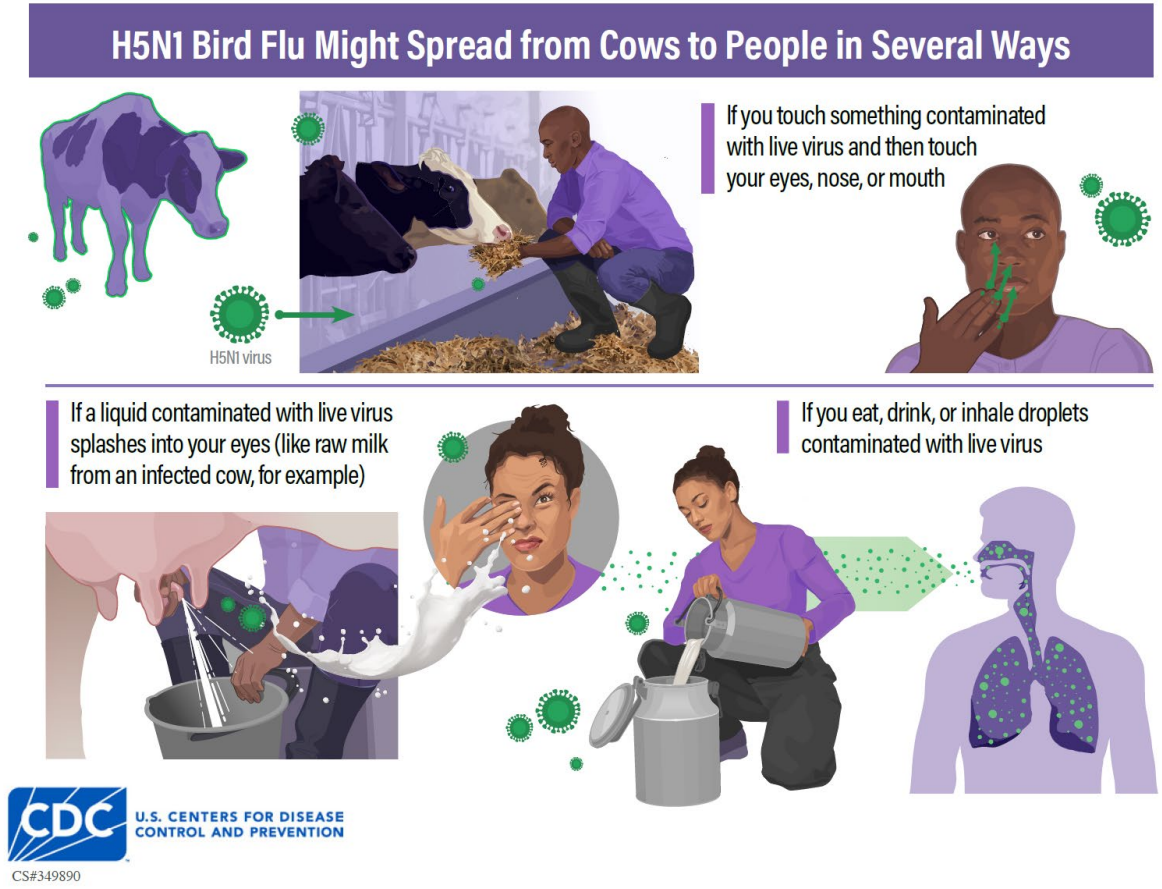
Historical Human Exposures to HPAI A(H5N1) Viruses

- Historically, human infections have been the result of:
  - Direct/close contact with sick or dead poultry or wild birds
  - Visiting a live poultry market as commonly identified risk factor
  - Limited, non-sustained human-to-human transmission has occurred globally in the past (not in U.S.)



HPAI A(H5N1) in U.S. Cattle during 2024

- March 25: USDA reported HPAI confirmed in cows and milk samples from TX and KS
- USDA has confirmed HPAI in dairy herds on 330 farms across 14 states
  - HPAI positive farm cats, mice, birds confirmed on/near multiple farms
  - Further detections of the B3.13 genotype in poultry flocks in multiple states
- **New reservoir of exposure and potential routes of infection to humans**
  - **Does this change human risk?**
  - **Or spectrum of disease in humans?**



Priorities for public health investigations

Top priority:

- Monitoring of people exposed to infected/sick animals,
- Testing of people that develop signs/symptoms of possible infection after exposure
- Robust surveillance through public health laboratories to detect novel influenza virus infections more broadly in the community
- Case/contact investigation if cases are identified

Additional epidemiologic investigations:

- More systematic studies of human risk, clinical manifestation, exposures, and risk/preventative factors associated with infection

HPAI A(H5) Human Cases, United States, 2022-2024

Human cases (n=28), 27 cases in 2024

- **No human-to-human transmission**
- **Associated with dairy cattle exposures: 15**
  - March - July 2024: 4 cases in dairy farm workers (TX, MI (2), CO) with exposure to infected or presumed infected dairy cattle
  - October 2024: 13 cases in dairy farm workers (CA) with occupational exposure
  - All cases were clinically mild, offered antivirals, not hospitalized
- **Associated with poultry exposures: 10**
  - April 2022: 1 case in worker depopulating poultry (CO)
  - July 2024: 9 cases in workers depopulating poultry (CO)
  - All cases were clinically mild, offered antivirals, not hospitalized
- **Unknown source of exposure: 1**
  - September 2024: Missouri patient hospitalized, had underlying medical conditions, given antivirals, discharged and recovered; surveillance testing at public health laboratory identified influenza A/H5
  - Results of serology at CDC pending

Field Investigation: Colorado Poultry Farms

- State health department and deployed CDC staff conducted systematic worker monitoring at two affected poultry farms
- Field team conducted on-site worker symptom screening / specimen collection, provide oseltamivir to exposed workers, case & contact investigations, assess PPE usage
- Over 600 workers were screened for symptoms;
  - 109 people reported symptoms, received empiric antiviral treatment, and were tested
  - 19 people were positive for SARS-CoV-2
  - 9 were positive for influenza A(H5)
    - 6 cases (2.3% of workers) at Farm 1
    - 3 cases (0.8% of workers) at Farm 2
    - All reported conjunctivitis, some had additional respiratory symptoms; all mild illness, no hospitalization

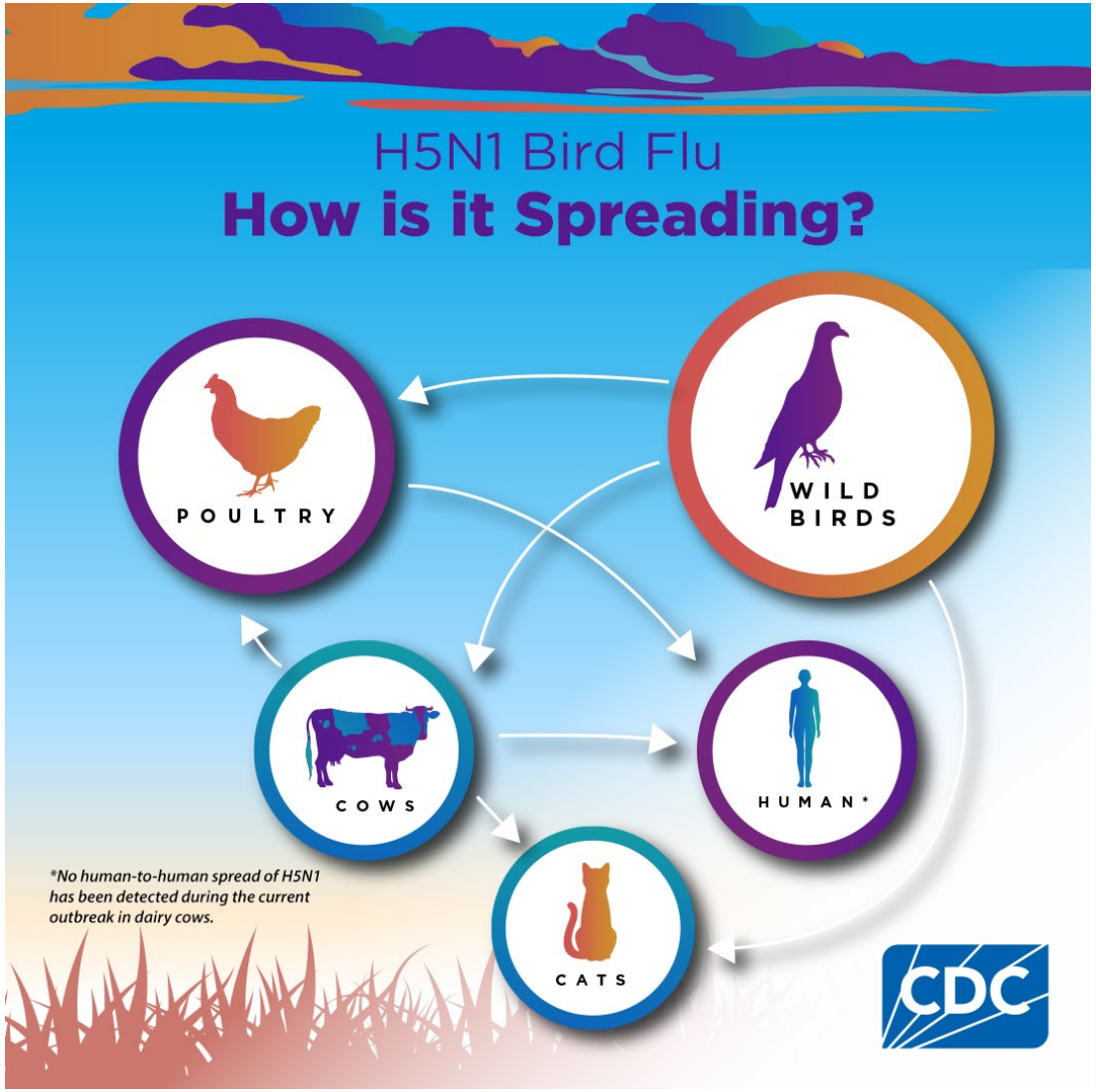
https://www.cdc.gov/mmwr/volumes/73/wr/mm7334a1.htm

Other Field Investigations

- State-led dairy worker serosurvey
  - State + CDC teams enrolled >100 dairy farm workers at H5N1-confirmed farms in two U.S. states (Michigan and Colorado); most worked directly with sick cows
- Veterinary serosurvey
  - Enrolled 150 veterinarians, technicians, and students at an annual professional conference who had recent contact with cows in 45 states
- Both investigations included:
  - Survey/interview about relevant exposures, job duties, PPE use, recent illnesses
  - Blood collection for serologic testing with HI and MN assays (testing in progress)

Public Health Risk

- Overall risk to the public remains **low**
- Increased risk with exposure to infected animals or environment – occupational, recreational
- Key epidemiologic questions:
  - What is the risk of infection with HPAI A(H5N1) virus in exposed populations?
  - What is the spectrum of illness?
  - What are the types of exposure to HPAI A(H5N1) virus on farms/dairies?
  - What exposures, activities, behaviors are associated with human infections with HPAI A(H5N1) virus or protection from infection?



Thank you

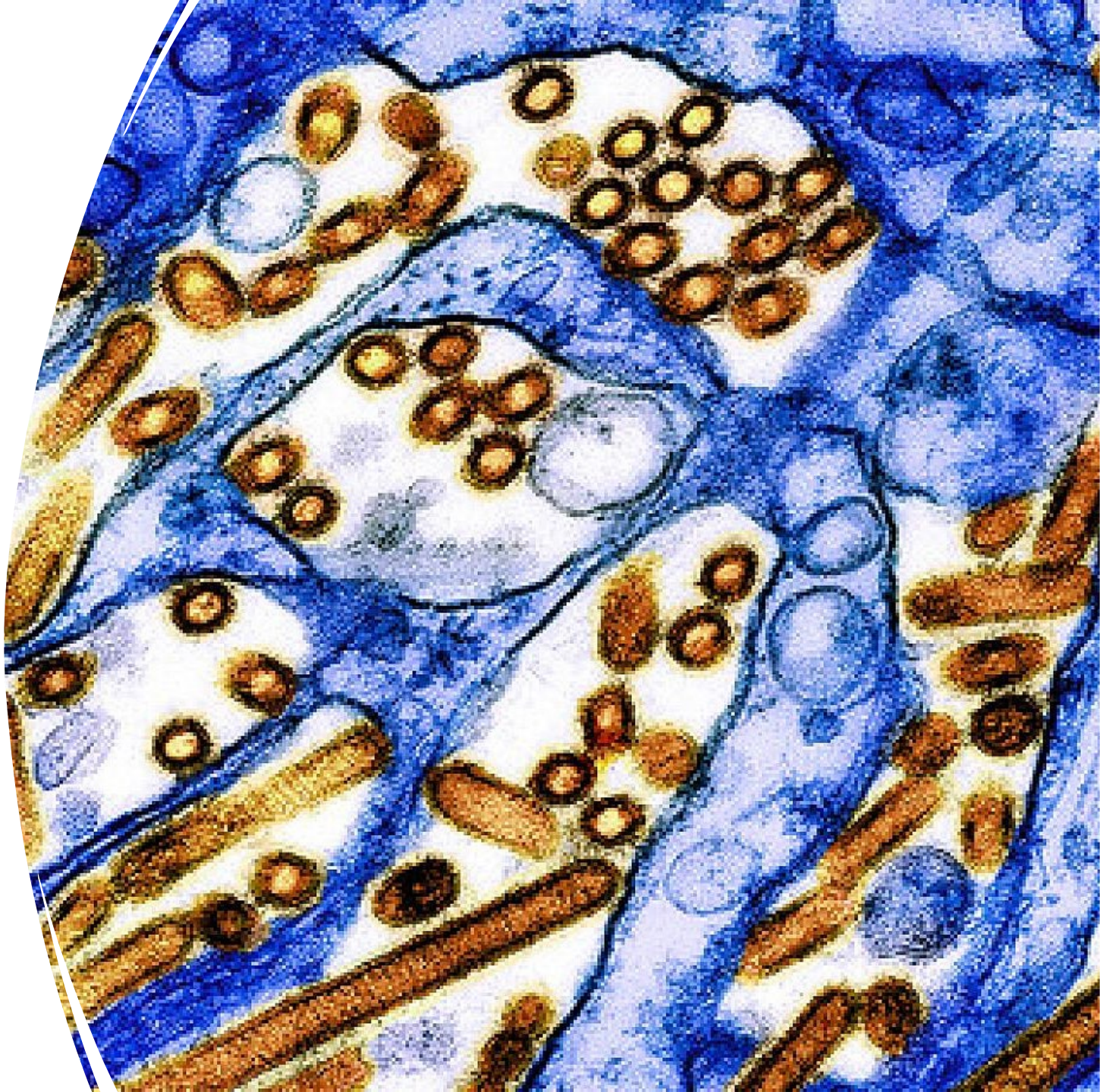
For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

Human Avian Influenza A H5N1 Cases in California

Erica Pan, MD, MPH, FIDSA FAAP
State Epidemiologist
California Department of Public Health

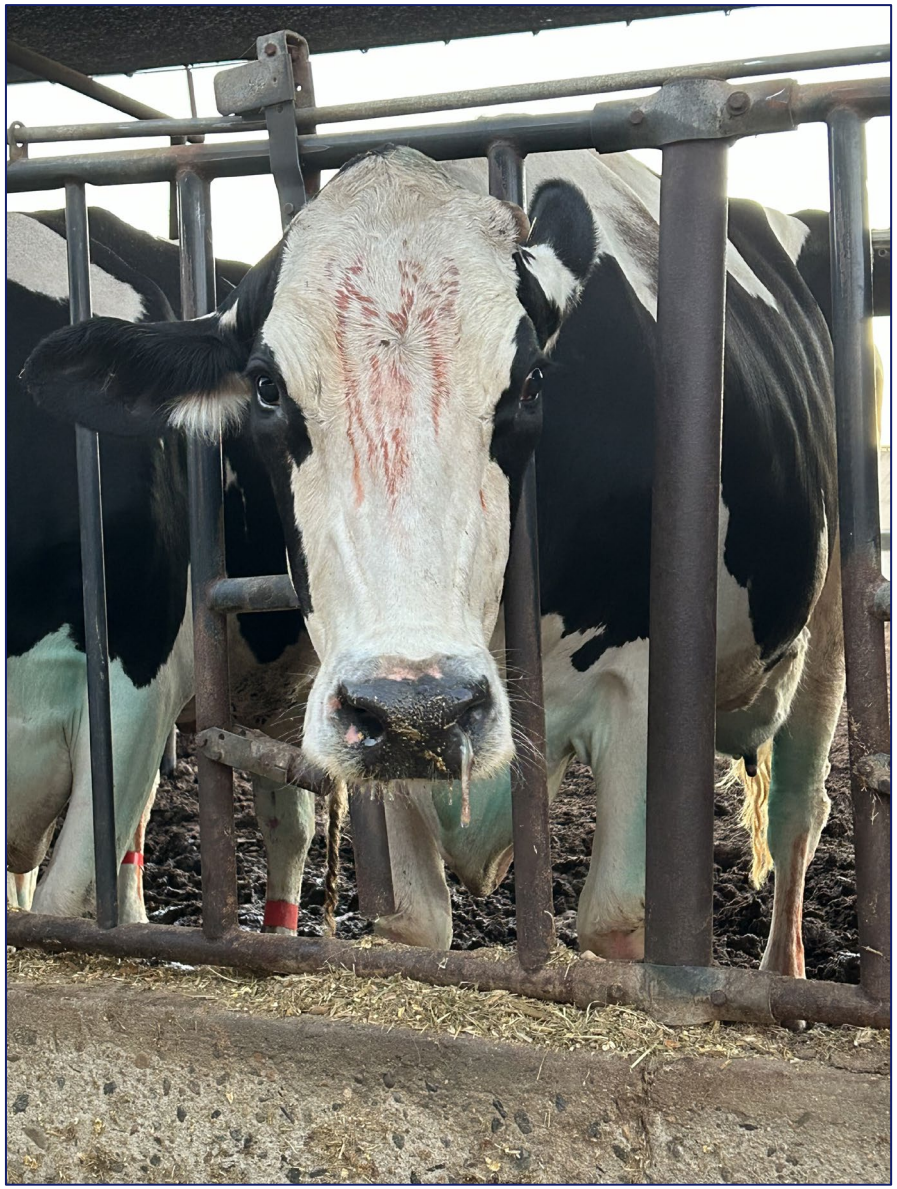
October 22, 2024

NASEM H5N1 Research Workshop



H5N1 Detections in in California

- There are >1100 dairy farms in California with >1.7M cows and >17,500 workers
- The first 3 California dairy farms with infected cows were identified August 30, 2024
- The first 2 human cases of H5N1 in California were confirmed by CDC on 10/3/2024
- As of 10/18:
  - H5N1 had been confirmed in dairy cows in 124 dairies in central California; AND
  - in 13 human cases in 11 dairies



CDPH

Human H5N1 Cases in California, continued

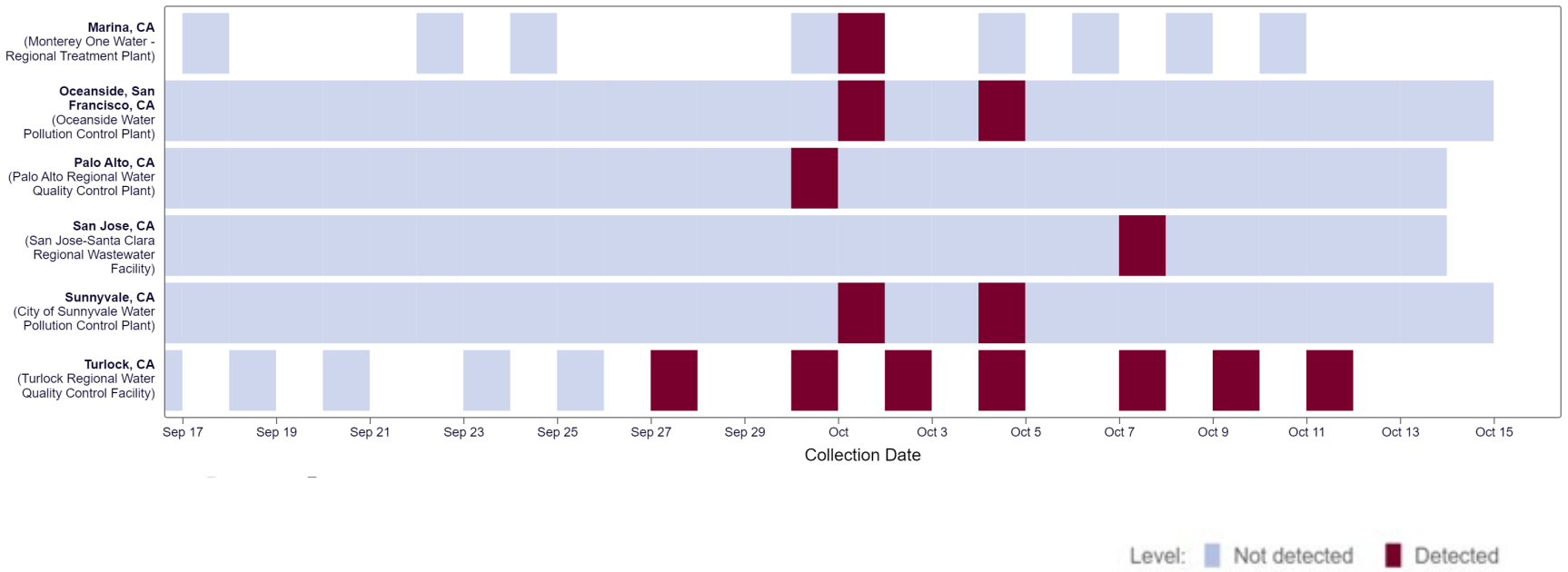
- All 13 confirmed cases are male
- Age range = 21-54
- Of the 7 cases with job information; 6 are milkers, 1 took care of sick cows
  - Presumed exposure was raw milk in eyes, either by splashes/sprays or by touching eyes with contaminated hands
- All have had mild illness; none have been hospitalized
- All reported eye infection/redness; 6 reported fever, some had additional mild symptoms
- Test results
  - 12 /13 (92%) had positive conjunctival swabs (the case without a positive conjunctival swab had a positive nasal swab)
  - 5/11 (45%) had positive nasal/OP swabs
  - 2/13 (15%) had positive NP swabs
- Of the 11 cases with PPE information; 11 reported they used PPE
  - 4 reported using goggles (1 reported goggles + face shield)
  - 5 reported using a facemask
  - 8 reported using gloves

CDPH

H5 Wastewater detections in California

CALIFORNIA INFLUENZA A & H5 MONITORING

- **Ongoing influenza A monitoring in 73 sites in California**
- **Ongoing H5 monitoring in 54 sites in California**
  - 3 sites in the Central Valley: Turlock, Merced, Lodi
- **Sporadic H5 WW detections in 9 California sites, to date**



- Mid-July to August: No detections in California
- September: Detections in 3 sites
  - Turlock, San Diego and Palo Alto
- **Since Oct 1st (past 2 weeks):**
  - Detections in 5 sites
    - **4 sites in SF Bay Area:**
      - No obvious large-volume dairy inputs to wastewater plants
      - Ongoing investigation
    - **Turlock:** Consistent detections at high concentrations
      - Multiple dairy processing plants, including plants servicing H5 cattle impacted regions

CDPH

Available data as of 10/16/24

Priority Research Questions

- Transmission
- **Prevention/Mitigation**
- Diagnosis & Testing
- Immunity
- Wastewater Surveillance

- Barriers to implementation of best practices & ideal prevention measures
  - PPE
  - Biosecurity/separation of ill cows
  - Reporting of symptoms
  - Testing
  - Treatment
- Factors supporting trust & collaboration
- Economic impacts
  - Farms, Industry, Economy
- Appropriate Level of Resources
  - Depts of Ag, Public Health, Lab networks
  - Workforce Infrastructure
  - Base surveillance & Data systems to detect/respond/plan