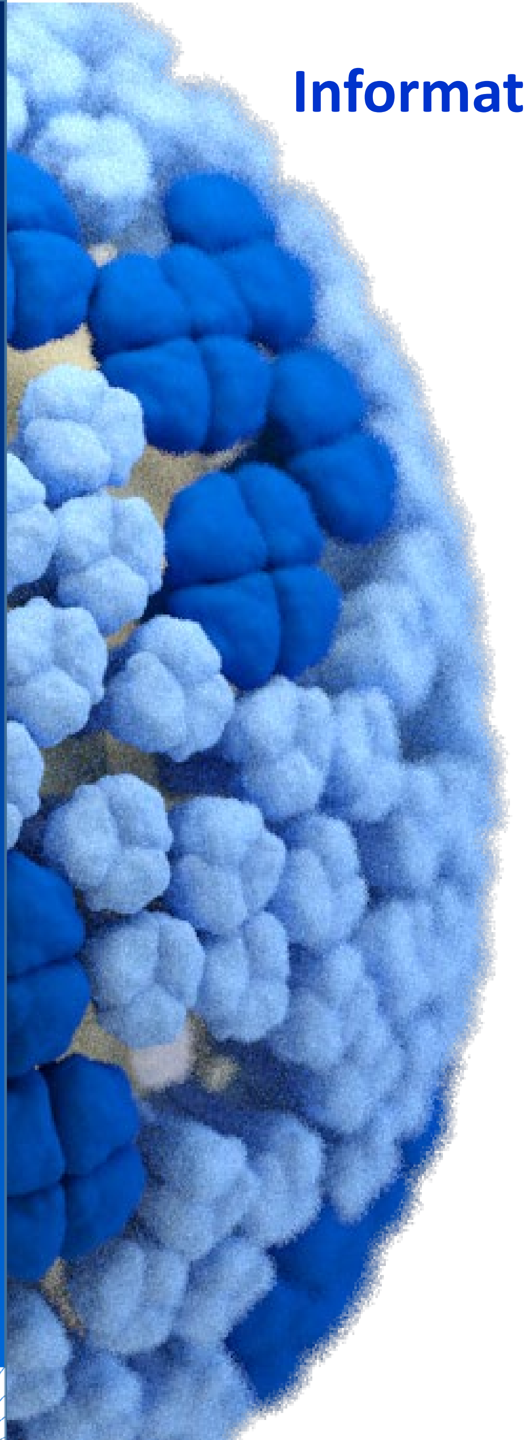
WHO-CC for Influenza | VSDB | Influenza Division | NCIRD



Information For The Vaccine And Related Biological Products Advisory Committee
CBER, FDA

October 10th, 2024

Highly Pathogenic Avian Influenza A(H5Nx) Virus Surveillance and Characterization in the United States and Globally and Recommendations for Candidate Vaccine Virus Development

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Centers for Disease Control and Prevention
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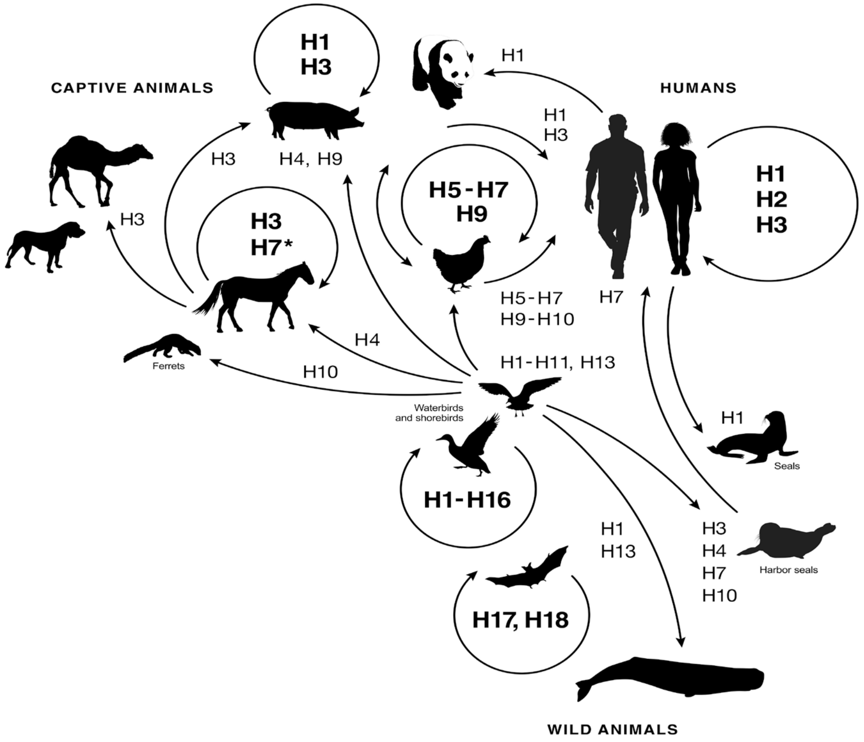
Presentation outline

Introduction

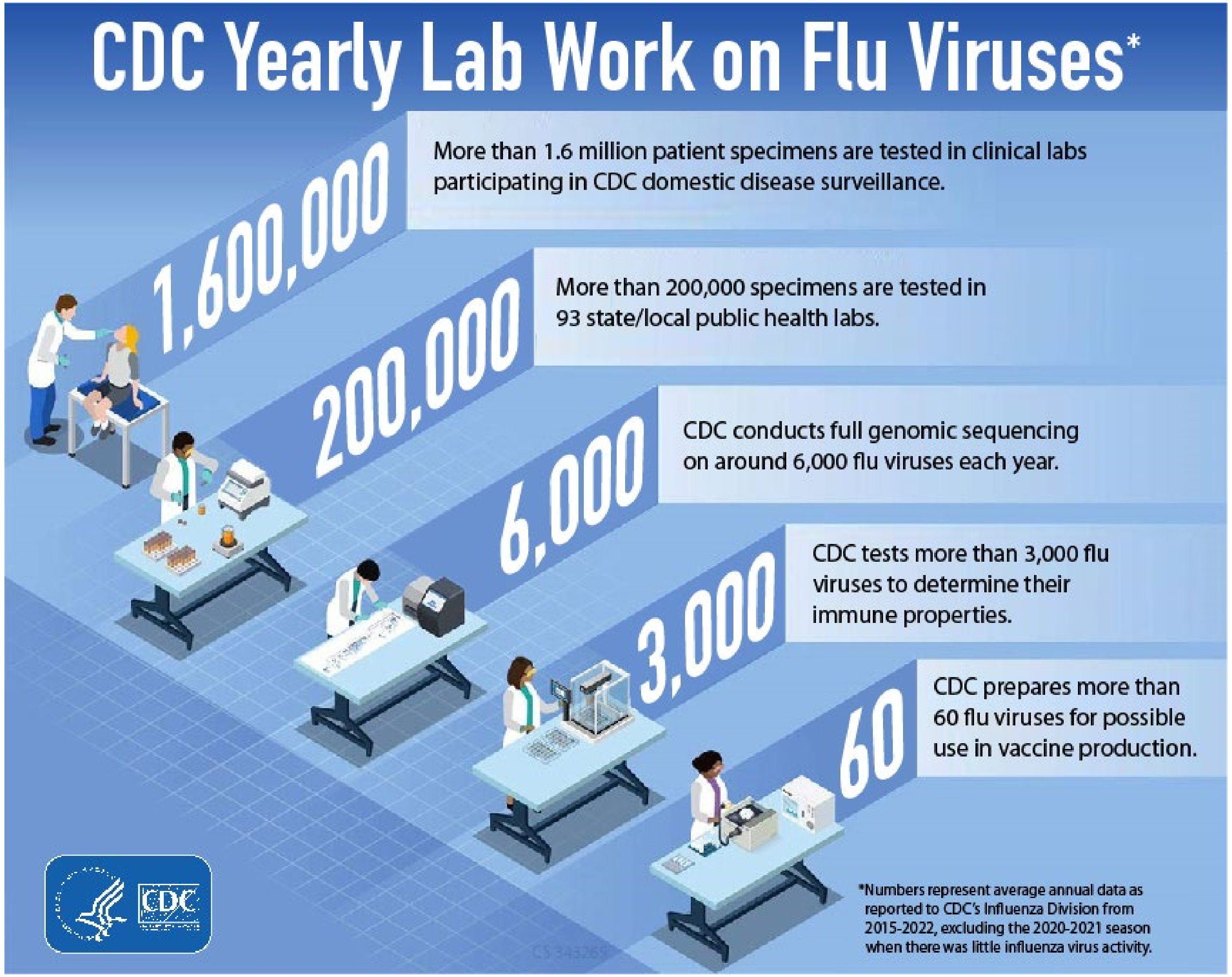
- Overview of Highly Pathogenic Avian Influenza A(H5Nx) virus and process for A(H5Nx) candidate vaccine virus review, recommendations and development
- Epidemiology of U.S. and global human cases, symptoms, surveillance, monitoring in humans and animals
- A(H5Nx) genetic and antigenic characterization; review of circulating clades; review of data from CDC and other CCs, ERLs and H5 Reference Labs



Selected key information supporting committee's recommendations on:

- September 2024 WHO Information Meeting on the 'Antigenic and genetic characteristics of zoonotic influenza A viruses and development of candidate vaccine viruses for pandemic preparedness'
- Recommendations for new A(H5Nx) candidate vaccine virus development; outcome of September 2024 Vaccine Consultation

U.S. Virologic Surveillance - Zoonotic case detection



CDC Yearly Lab Work on Flu Viruses*

1,600,000 More than 1.6 million patient specimens are tested in clinical labs participating in CDC domestic disease surveillance.

200,000 More than 200,000 specimens are tested in 93 state/local public health labs.

6,000 CDC conducts full genomic sequencing on around 6,000 flu viruses each year.

3,000 CDC tests more than 3,000 flu viruses to determine their immune properties.

60 CDC prepares more than 60 flu viruses for possible use in vaccine production.

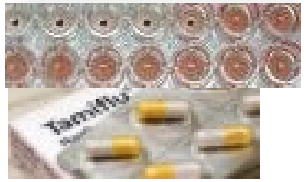
*Numbers represent average annual data as reported to CDC's Influenza Division from 2015-2022, excluding the 2020-2021 season when there was little influenza virus activity.

CS 343289

Diagnostic Kits
Develop, manufacture,
(Flu-SC2/Type/Subtype)

Genotypic (NGS)
'Sequence First'
beginning Fall of 2014

Phenotypic
Antigenic
Antiviral



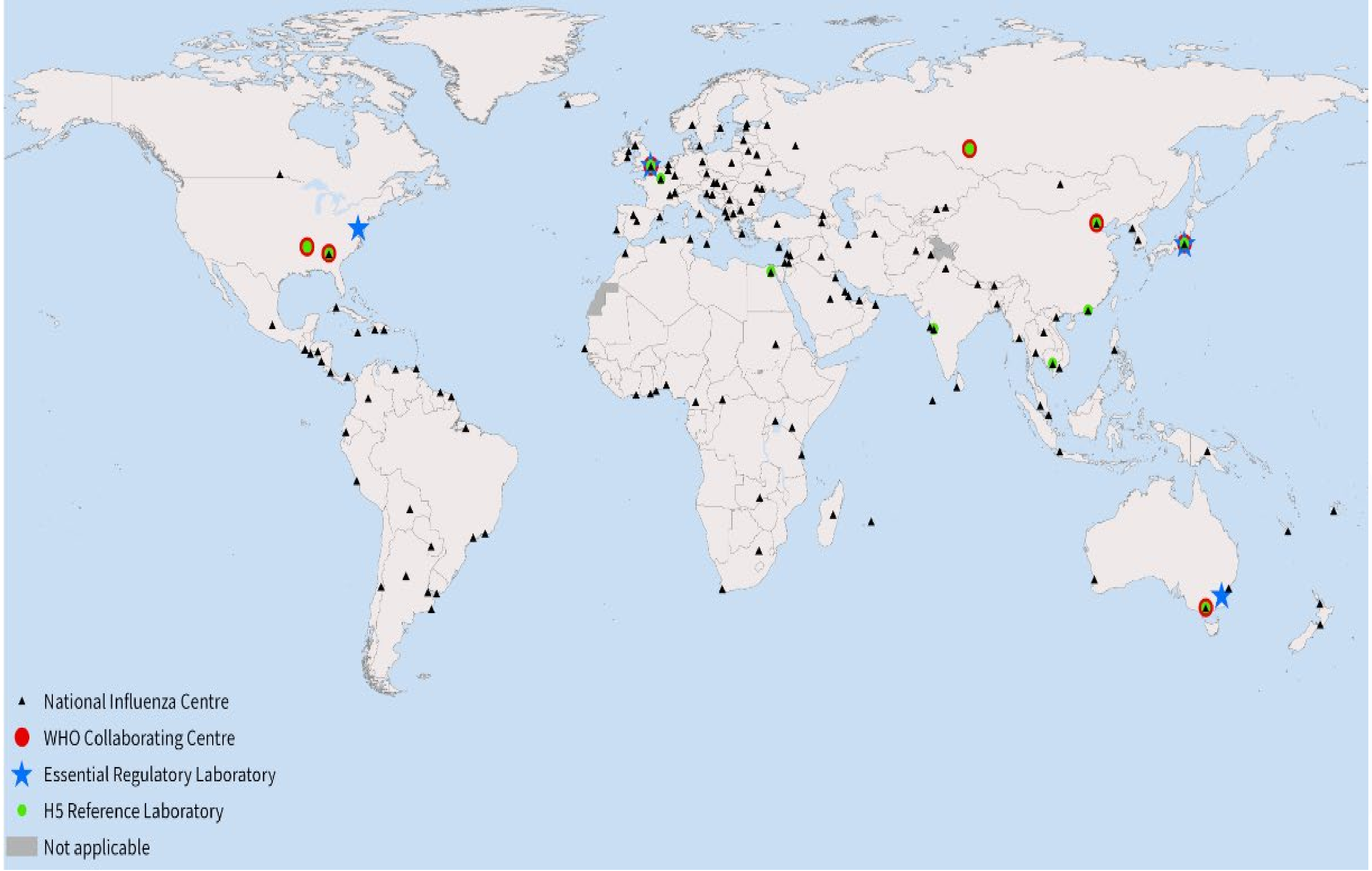
CVVs
Inactivated vaccine
- Egg
- Cell

Recombinant HA protein
Live Attenuated Influenza Vaccine

International Virologic Surveillance in Public Health Labs

CDC supports WHO’s Global Influenza Surveillance and Response System (GISRS)

- **150+ WHO National Influenza Centers in 125 Member States** (CDC Atlanta Influenza Laboratory is one
- **7 WHO Collaborating Centers** for Influenza (CDC is one)
- **12 WHO H5 Reference Laboratories** (CDC is one)



International Virologic Surveillance for Animal Influenza Viruses

H5 Reference Laboratories

- Peter Doherty Institute for Infection & Immunity, Australia
- Institute Pasteur, Cambodia
- National Institute for Viral Disease Control and Prevention, Beijing, PRC
- The University of Hong Kong, Hong Kong SAR
- Centre for Health Protection, Hong Kong SAR
- Institute Pasteur, France
- National Institute of Virology, India
- National Institute of Infectious Diseases, Tokyo, Japan
- State Research Centre for Virology and Biotechnology VECTOR, Russian Federation
- The Francis Crick Institute, London, UK
- Influenza Division, CDC, USA
- St. Jude Children's Research Hospital, Memphis, USA

OFFLU Network

- Food and Agriculture Organization of the UN

- World Organization for Animal Health
  - Animal and Plant Health Agency, UK
  - Animal and Plant Quarantine Agency, South Korea
  - Australian Centre for Disease Preparedness, Australia
  - Institute of Diagnostic Virology, Germany
  - Hokkaido University, Dept. of Disease Control, Japan
  - Istituto Zooprofilattico Sperimentale delle Venezie, Italy
  - Laboratório Nacional Agropecuário em Campinas, Brazil
  - Harbin Veterinary Research Institute, PRC
  - National Centre for Foreign Animal Disease, Canada
  - National Institute of High Security Animal Diseases, India
  - National Reference Laboratory for Avian influenza, Russian Federation
  - National Veterinary Services Laboratories, USDA, USA
  - National Poultry Research Center, USDA, USA
  - Reference Laboratory for Veterinary Quality Control, Egypt
  - The Pirbright Institute, UK

Domestic and International Field Surveillance for Influenza Viruses in Animals

- USDA's IAV-Swine Surveillance Program
- National Veterinary Services Laboratory
- Centers for Excellence for Influenza Research and Response (NIH network)
- The Ohio State University
- Bangladesh (International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b)*
- Cambodia (MOH in collaboration with MOA)*
- Madagascar (MOH with Institute Pasteur and Ministry of Livestock)*
- Vietnam (Department of Animal Health, Ministry of Agriculture and Rural Development)*
- Lao PDR (MOH in collaboration with MOA)*
- Kenya (Wildlife Services)*

*Currently funded CDC projects

Data used to address key vaccine update questions

- **Epidemiologic and clinical data**
  - Where are recent animal outbreaks and human cases occurring? Are they unusual in magnitude, disease presentation, duration?
- **Virus surveillance (GISRS: Global Influenza Surveillance and Response System)**
  - GISRS labs test >10,000 animal and human samples per 6 months suspected of containing non-seasonal influenza viruses
    - **Multiple virus groups**: **A(H1)v, A(H3N2)v, H5Nx, H7Nx, H9N2 H10Nx**
    - GISRS labs regularly share representative specimens among WHO CCs
- **Genomic characterization of viruses (influenza changes rapidly and multiple clades of interest continually emerge)**
  - Primary focus is HA gene genetic diversity; conduct genome constellation analysis and identify reassortment
- **Antigenic characterization of representative emerging viruses**
  - Naïve ferrets used to determine level of antigenic variation ("drift"); understand immune response triggered by the HA protein on the surface of influenza virus to determine if they would be neutralized by an existing CVV or have the potential to be a new vaccine
  - Emerging antigenically distinct viruses are selected as new reference viruses for serology and as candidate vaccines
- **Post vaccination human serologic analysis**
  - Comparative analysis of circulating viruses to identify those that pose the greatest risk of immune escape
- **Data integration and comparison among WHO CCs (shared SOPs, reagents, and viruses)**
  - Influenza epidemiology, surveillance, phylogenetics, phylogeography, and antigenic data integration
- **Availability and characteristics of new candidate vaccine virus antigens**
  - Data generated that illustrates the new antigens induce antibodies that neutralize or cross-react with circulating viruses

Goal and key questions addressed for zoonotic candidate vaccine virus development recommendations

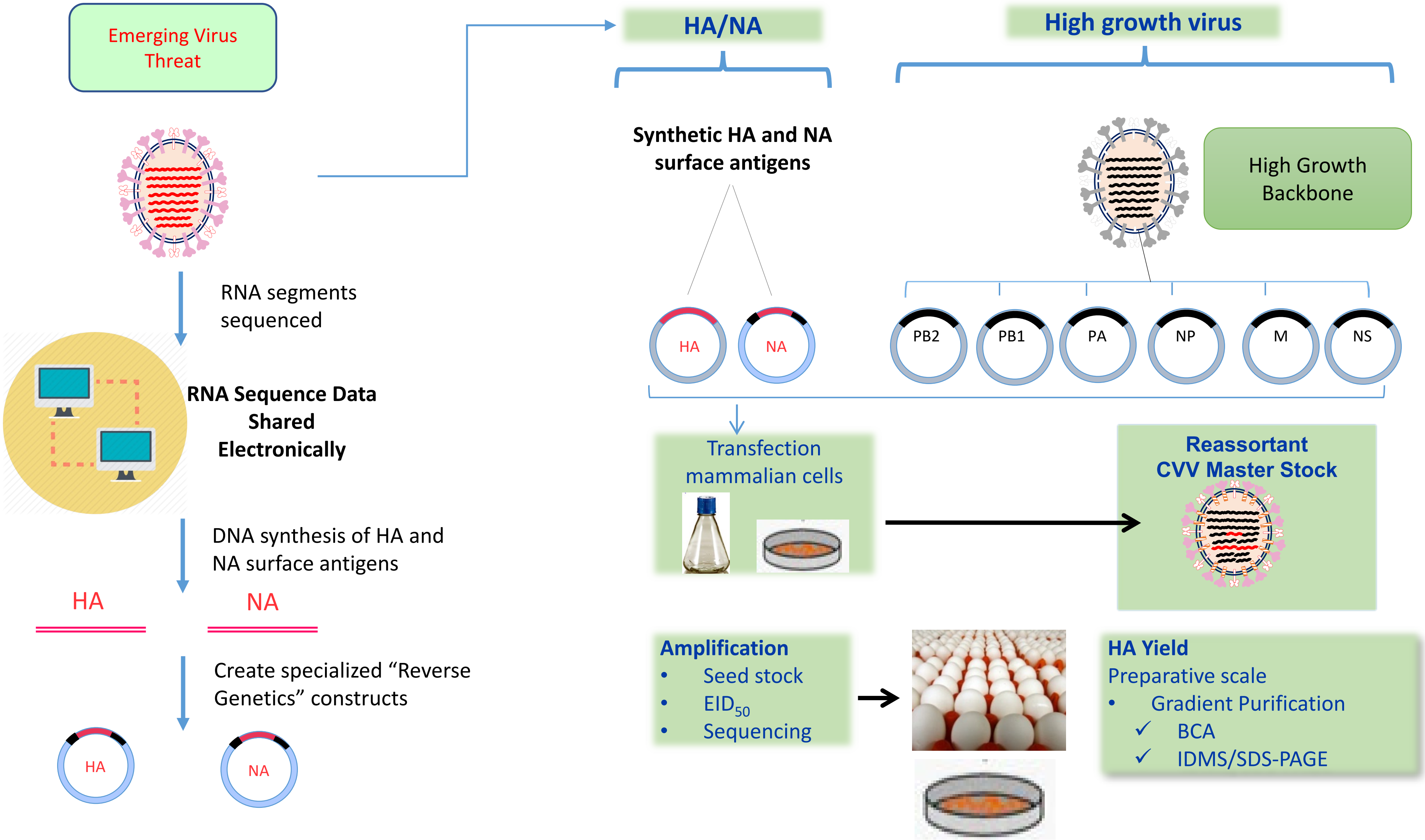
Goal of WHO committee on influenza vaccine composition

- Identify influenza virus antigen(s) that will elicit immunity against diverse/diverging viruses that will likely co-circulate in the future. Ideal antigens confer breadth of immunity to multiple subclades of viruses and reduce risk(s). It is not trying to “match” just one strain of influenza virus that will circulate.

Key questions for each of the relevant clades of concern

- Are there significant epidemics and where were they?
- What are the avian and swine influenza A clades circulating?
    - What are the genetic clades/subclades in circulation and where?
    - What genetic diversity has been observed within subclades (surface proteins/genome)?
    - Are the viruses with new genetic changes spreading geographically?
    - Are the viruses with new genetic changes antigenically distinct from prior or contemporary viruses?
    - What is the proportion of the new group(s) and what group(s) are likely to predominate?
    - Do current vaccines induce antibodies in humans that protect against co-circulating viruses and/or emerging strains?
    - If new vaccine antigen is warranted, does it elicit antibodies with breadth which recognize multiple important subclades (i.e., does it confer breadth of protection)?

Generation of pre-pandemic CVVs for A(H5Nx) by CDC, Influenza Division



Emerging Virus Threat

RNA segments sequenced

RNA Sequence Data Shared Electronically

DNA synthesis of HA and NA surface antigens

Create specialized "Reverse Genetics" constructs

HA/NA

Synthetic HA and NA surface antigens

High growth virus

High Growth Backbone

Transfection mammalian cells

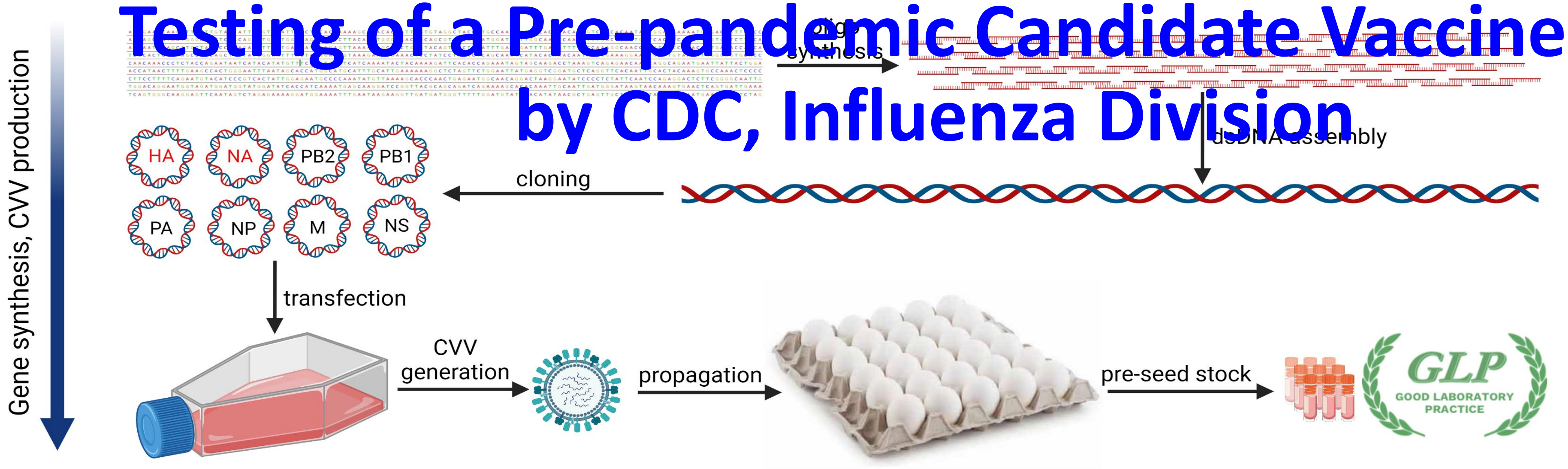
Reassortant CVV Master Stock

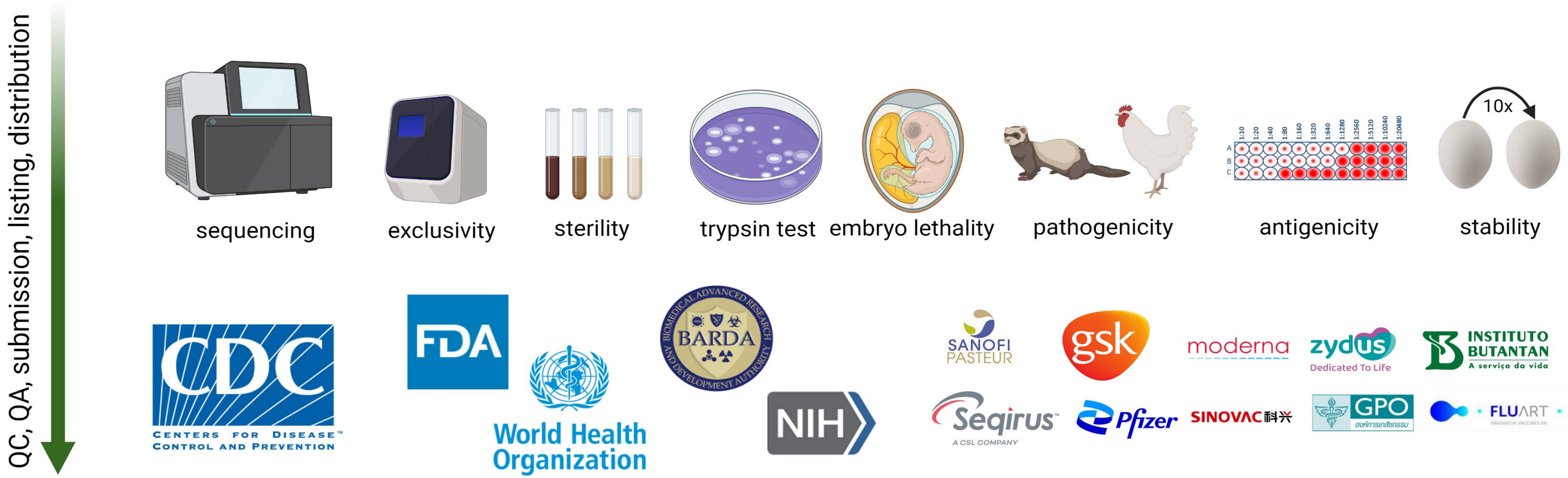
Amplification
- Seed stock
- EID_{50}
- Sequencing

HA Yield
Preparative scale
- Gradient Purification
  - ✓ BCA
  - ✓ IDMS/SDS-PAGE

Courtesy Dr. Bin Zhou, Vaccine Preparedness Team/VSDB, Influenza Division

Testing of a Pre-pandemic Candidate Vaccine Virus by CDC, Influenza Division





CDC CENTERS FOR DISEASE CONTROL AND PREVENTION

FDA

World Health Organization

BARDA

NIH

SANOFI PASTEUR

gsk

moderna

zydus Dedicated To Life

INSTITUTO BUTANTAN A serviço da vida

Seqirus A CSL COMPANY

Pfizer

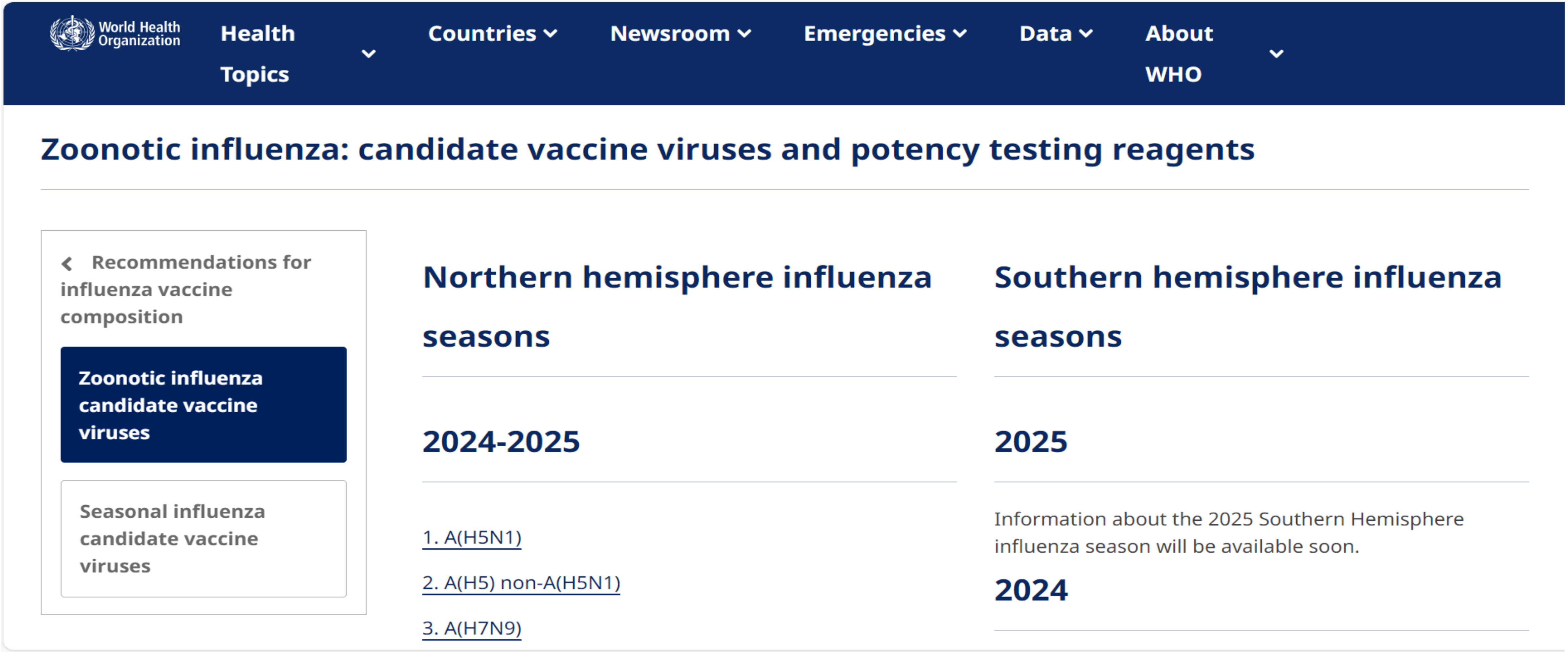
SINOVAC科兴

GPO

FLUART

Courtesy Dr. Bin Zhou, Vaccine Preparedness Team/VSDB, Influenza Division

Pre-pandemic candidate vaccine viruses (CVVs) & public information



Zoonotic influenza: candidate vaccine viruses and potency testing reagents

Northern hemisphere influenza seasons

2024-2025

1. A(H5N1)
2. A(H5) non-A(H5N1)
3. A(H7N9)

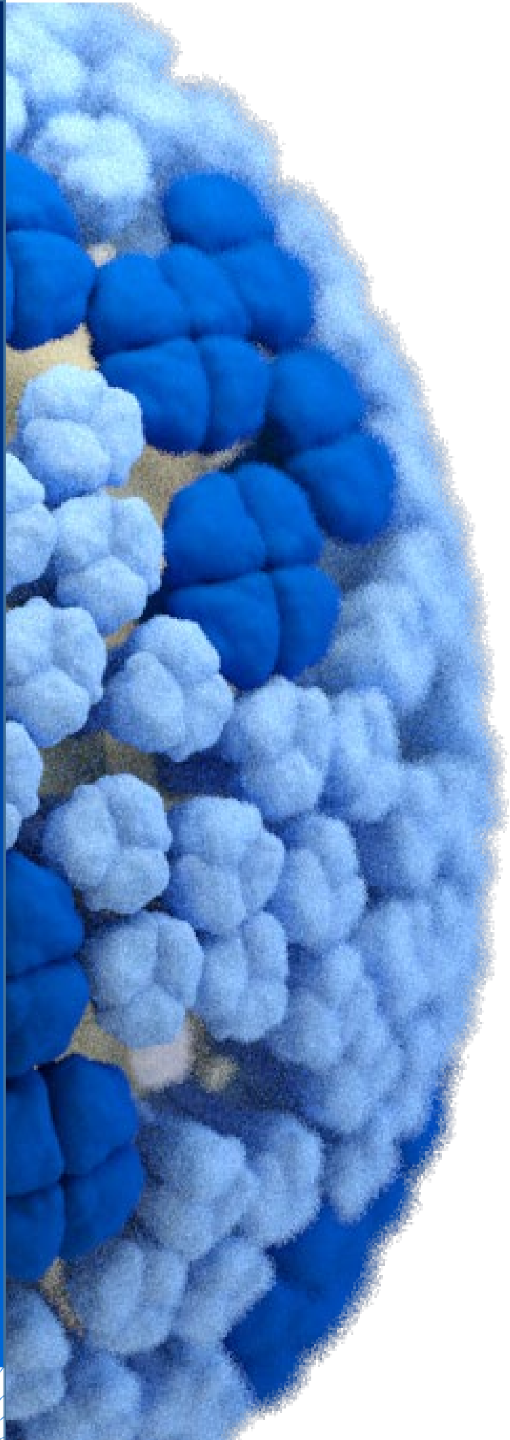
Southern hemisphere influenza seasons

2025

Information about the 2025 Southern Hemisphere influenza season will be available soon.

2024

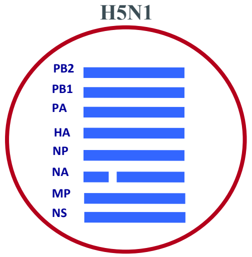
- **Candidate vaccine viruses and reagents**
  - https://www.who.int/teams/global-influenza-programme/vaccines/who-recommendations/candidate-vaccine-viruses
- **Zoonotic influenza summary reports and candidate vaccine viruses for zoonotic influenza vaccine viruses:**
  - https://www.who.int/teams/global-influenza-programme/vaccines/who-recommendations/zoonotic-influenza-viruses-and-candidate-vaccine-viruses

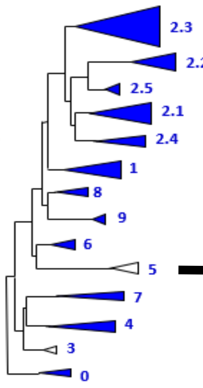


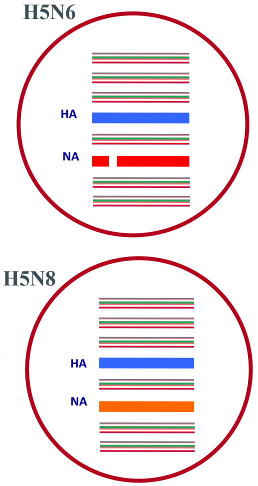
HPAI A(H5Nx) Viruses

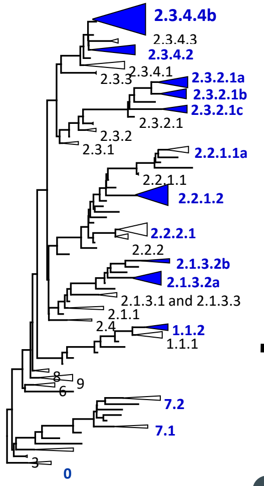
Overview of current circulation

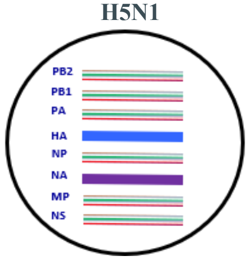
Emergence and Evolution of H5N1 Bird Flu











1996-1997

H5N1 bird flu virus first detected

In 1996, HPAI H5N1 virus first identified in domestic waterfowl in Southern China. Virus is named A/goose/Guangdong/1/1996.

In 1997, poultry outbreaks detected in China and Hong Kong; 18 human cases (6 fatal) identified.

The original H5N1 virus caused over 860 reported human infections with over 50% mortality.

2003-2005

H5N1 spreads to Africa, the Middle East and Europe

H5N1 re-emerges in 2003 resulting in widespread poultry outbreaks across Asia.

In 2005, wild birds spread H5N1 to poultry in Africa, the Middle East and Europe.

HA gene diversifies into many genetic groups called clades.

Multiple genetic lineages (genotypes) are detected across the Eastern hemisphere.

2014-2016

H5N6 and H5N8 viruses emerge

Reassortment (gene-swapping) of H5 viruses from poultry and wild bird leads to emergence and detection of H5N6 and H5N8 virus subtypes.

HA diversifies further into clade 2.3.4.4 in Asia, Africa, Europe, the Middle East and North America.

H5 viruses with various NA genes continue to be detected, including in U.S. wild birds and poultry.

2018-2020

Clade 2.3.4.4b viruses spread widely

H5N6 and H5N8 viruses become the predominant subtypes detected globally replacing majority of original H5N1 virus.

HA diversifies further into clade 2.3.4.4b and it becomes the predominant clade circulating in Asia, Africa, Europe, and the Middle East.

2021-2022

H5N1 Identified in Canada, United States

Reassortment leads to emergence of new H5N1 virus belonging to clade 2.3.4.4b with a wild bird adapted N1 NA gene.

Clade 2.3.4.4b H5N1 viruses become the predominant subtype in Asia, Africa, Europe, and the Middle East by the end of 2021.

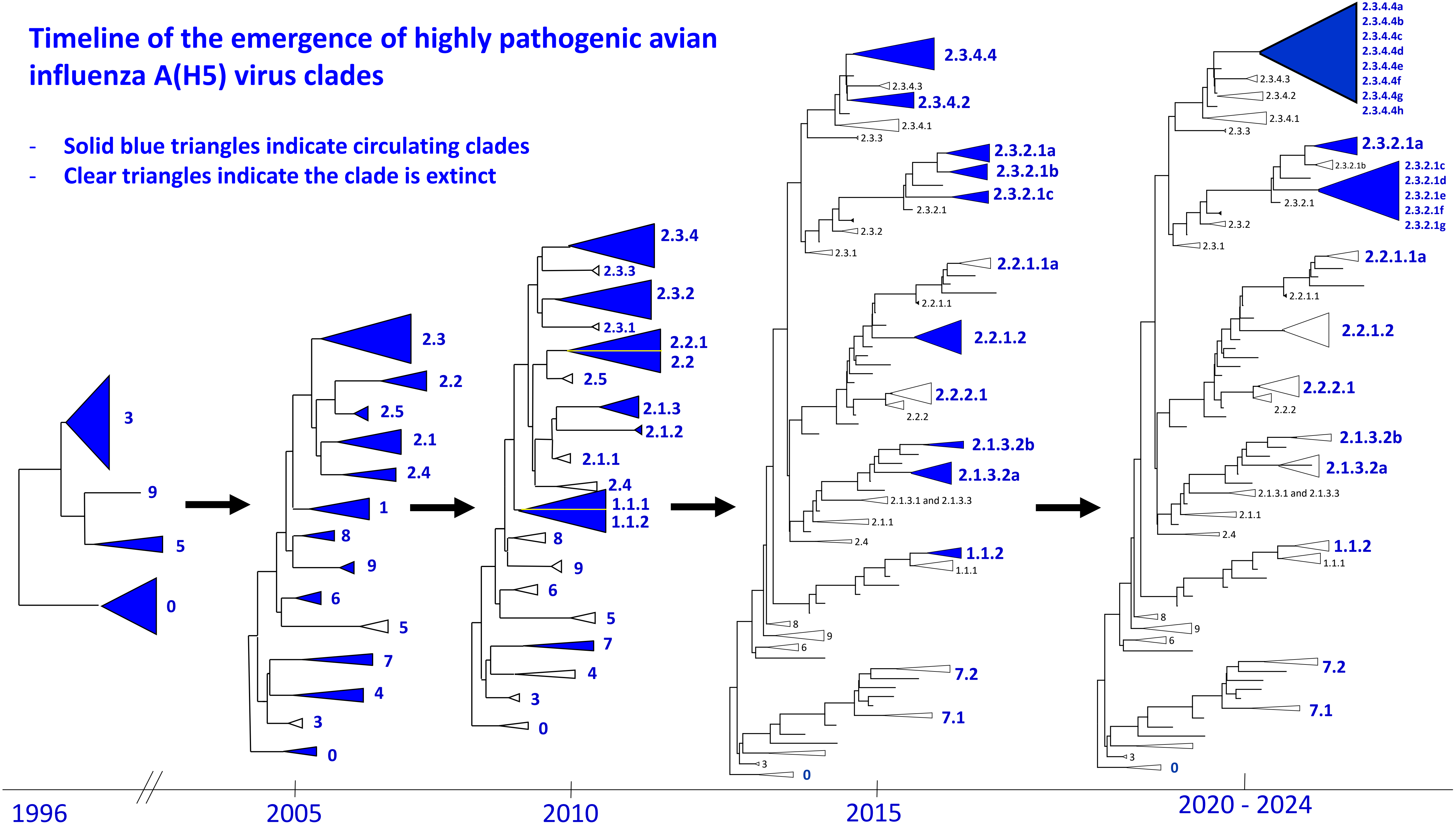
The virus is detected in Canada and U.S. wild birds in late 2021. In February 2022, the virus begins causing outbreaks in U.S. commercial and backyard poultry.

U.S. Department of
Health and Human Services
Centers for Disease
Control and Prevention

https://archive.cdc.gov/www_cdc_gov/flu/avianflu/communication-resources/bird-flu-origin-infographic.html#:~:text=In%201996,%20highly%20pathogenic%20avian%20influenza

Timeline of the emergence of highly pathogenic avian influenza A(H5) virus clades

- Solid blue triangles indicate circulating clades
- Clear triangles indicate the clade is extinct



A(H5Nx) clade 2.3.4.4 activity

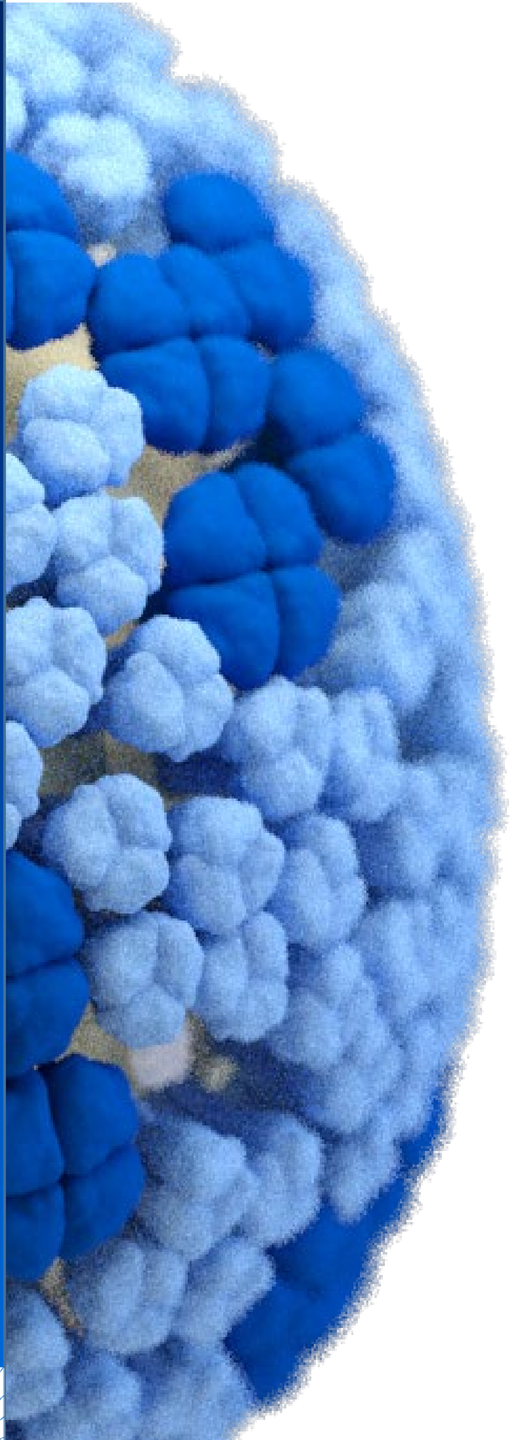
China

Indonesia

Wild birds, dairy cattle, domestic birds and mammals in:
Africa, Asia, Europe and the Americas

A(H5Nx) Clade 2.3.4.4 Candidate Vaccine Virus Development

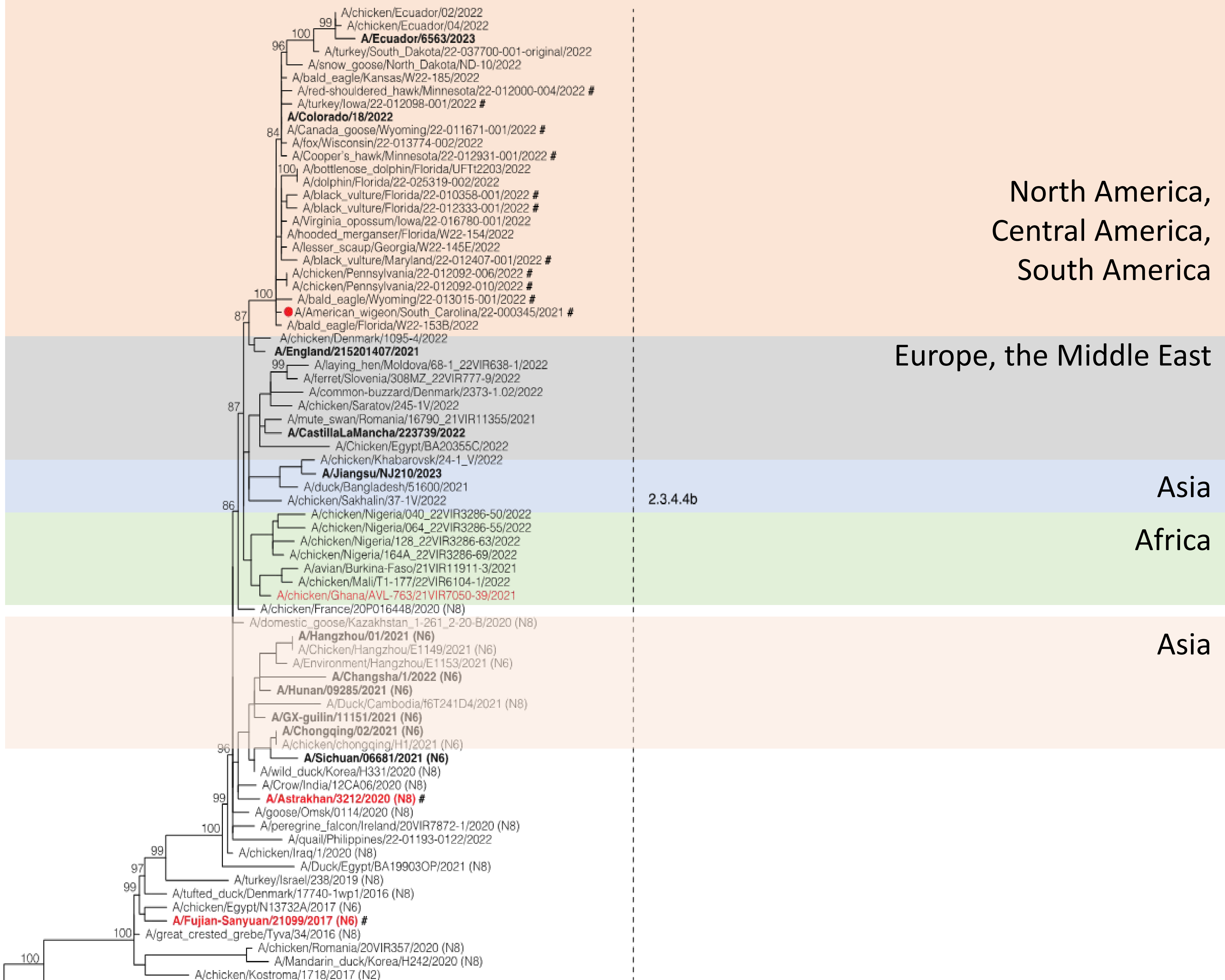
Candidate vaccine viruses	Subtype	Clade	Institution	Availability
IDCDC-RG42A (A/Sichuan/26211/2014-like)	H5N6	2.3.4.4a	CDC	Yes
China CDC (A/Fujian-Sanyuan/21099/2017-like)	H5N6	2.3.4.4b	China CDC	Pending
IDCDC-RG71A (A/Astrakhan/3212/2020-like)	H5N8	2.3.4.4b	CDC	Yes
CBER-RG8 (A/Astrakhan/3212/2020-like)	H5N8	2.3.4.4b	FDA	Yes
IDCDC-RG80A A/chicken/Ghana/AVL-763/21VIR7050-39/2021-like	H5N1	2.3.4.4b	CDC	Pending
IDCDC RG78A A/American Wigeon/South Carolina/22-000345-001/21-like	H5N1	2.3.4.4b	CDC	Yes
IDCDC-RG43A (A/gyrfalcon/Washington/41088-6/2014-like)	H5N8	2.3.4.4c	CDC	Yes
China CDC (A/Hubei/29578/2016-like)	H5N6	2.3.4.4d	China CDC	Pending
NIID-001 (A/duck/Hyogo/1/2016-like)	H5N6	2.3.4.4e	NIID	Yes
A/chicken/Vietnam/NCVD-15A59/2015-like	H5N6	2.3.4.4f	SJCRH	Pending
IDCDC-RG69A (A/chicken/Vietnam/RAHO4-CD-20-421/2020-like)	H5N6	2.3.4.4g	CDC	Yes
IDCDC-RG56A (A/Guangdong/18SF020/2018-like)	H5N6	2.3.4.4h	CDC	Yes



HPAI A(H5Nx) Viruses
Clade 2.3.4.4b

Epidemiology and Genetic/ Antigenic Characterization

Geographic clustering of A(H5Nx) 2.3.4.4b viruses



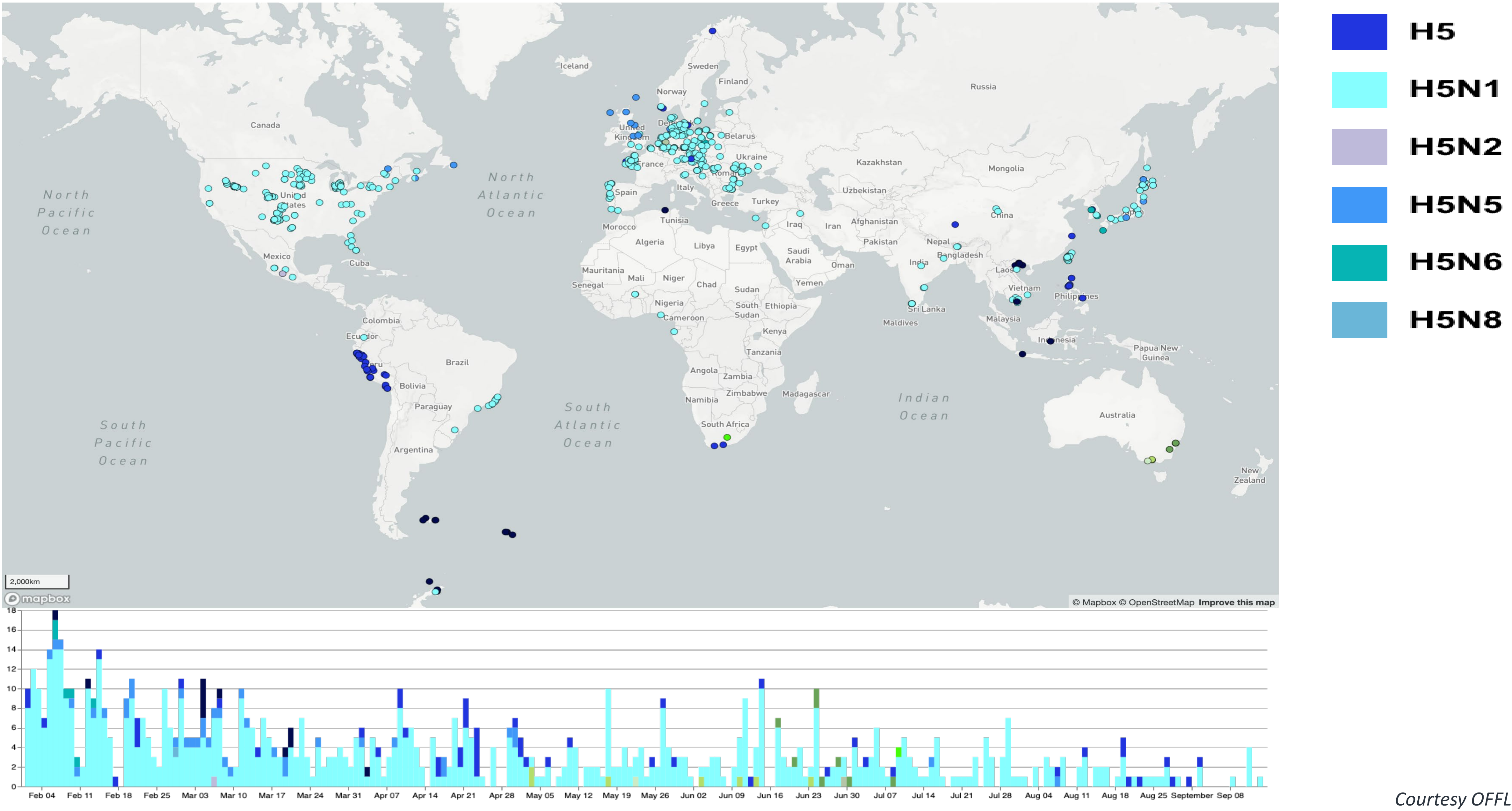
Clade 2.3.4.4b A(H5) Candidate Vaccine Virus Development

Candidate vaccine viruses	Subtype	Institution	Availability	Date selected	Date available
IDCDC-RG71A (A/Astrakhan/3212/2020-like)	H5N8	CDC	Yes	February 2021	January 5, 2022
CBER-RG8 (A/Astrakhan/3212/2020-like)	H5N8	FDA	Yes	February 2021	November 9, 2021
IDCDC-RG80A A/chicken/Ghana/AVL-763/21VIR7050-39/2021-like	H5N1	CDC	Pending	September 2022	Pending*
IDCDC RG78A A/American Wigeon/South Carolina/22-000345-001/21-like	H5N1	CDC	Yes	February 2023	September 18, 2023

***IDCDC-RG80A (A/chicken/Ghana/AVL-763/21VIR7050-39/2021-like)**

- Pending Master File submission

Avian influenza activity in animals since February 2024



Courtesy OFFLU

HPAI A(H5Nx) human infections since February 2024

Subtype (clade)	Country reporting	Cases	Clinical severity	Exposure
H5N1 (2.3.2.1c)	Cambodia	6	Severe/Fatal	Poultry
	Viet Nam	1	Fatal	Poultry
H5 (2.3.4.4b)	USA	16	Mild	Dairy cattle / poultry / unknown
	China	1	Fatal	Poultry
H5N6 (2.3.4.4h)	China	2	Fatal	Poultry
H5N1 (2.3.2.1a)	Australia	1	Mild	Travel from India
H5N1 (unknown)	China	1	Severe	Travel from Viet Nam

Cumulative numbers globally

- 8 A(H5), 7 A(H5N8), 93 A(H5N6) and 906 A(H5N1)

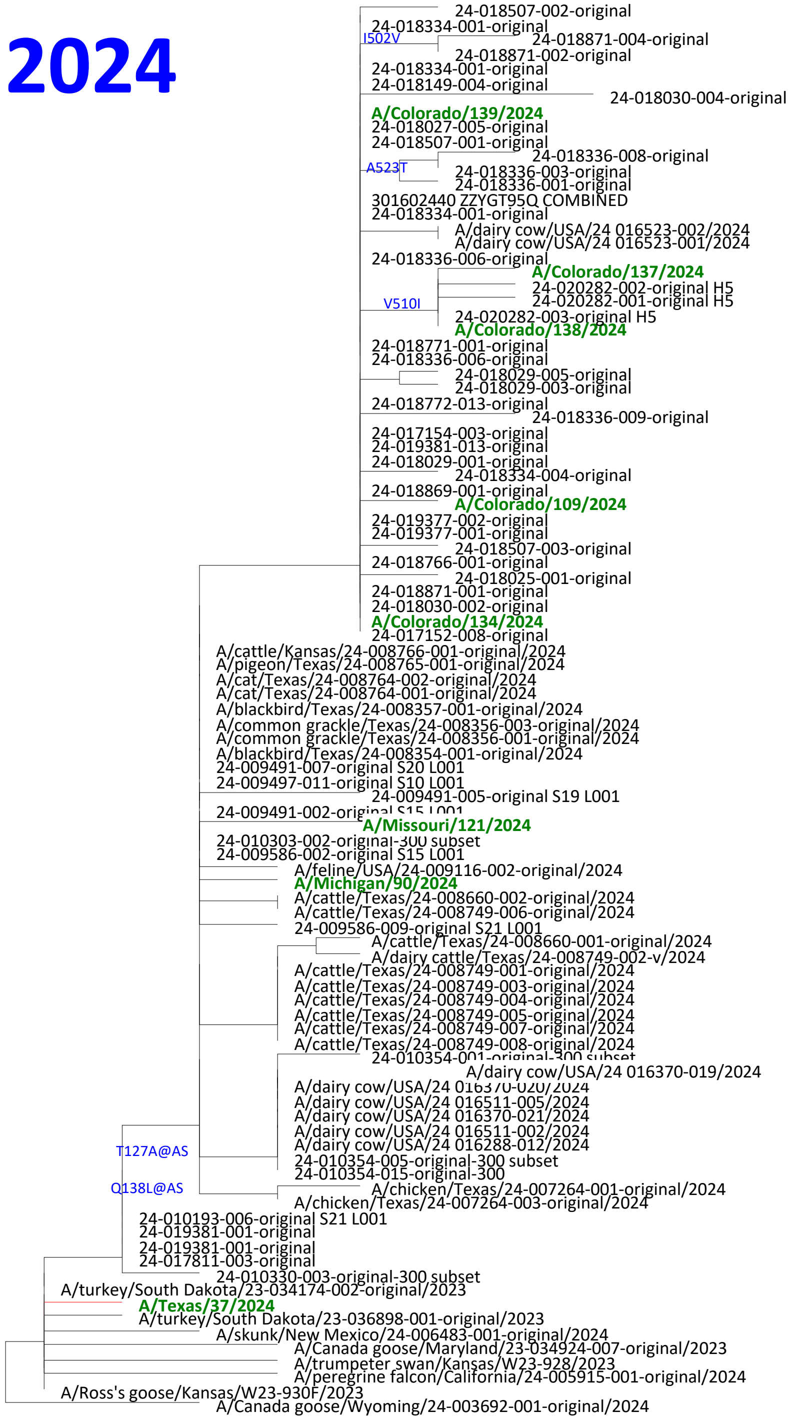
A(H5) human cases detected in the USA in 2024

- Viruses (with some exceptions that could not be sequenced) are genotype B3.13 clade 2.3.4.4b HPAI A(H5) closely related to each other and viruses detected in dairy cattle and related spillover events into poultry

- The genome sequences maintain primarily avian genetic characteristics and lack changes that would be expected to make the virus better adapted to infect or spread among humans.

- The HA sequences of the viruses from humans share the same amino acid changes as those identified in dairy cattle and other animals
  - Missouri case contains two additional mutations in HA1 protein
    - P136S; Antigenic site not expected to impact cross-reactivity to clade 2.3.4.4b CVVs
    - A156T; Antigenic site that has resulted in reductions in cross-reactivity to ferret antisera raised to available clade 2.3.4.4b CVVs

- There are no mutations known to be associated with reduced susceptibility to FDA approved antiviral drugs identified in the virus sequences from the patients' specimens.



HA comparison to 2.3.4.4b CVVs

	IDCDC-RG78A	A/Missouri/121/2024	A/Colorado/109/2024	A/chicken/USA/24-019377-001/2024	A/chicken/USA/24-019377-002/2024	A/Colorado/134/2024	A/chicken/Colorado/24-020282-001/2024	A/chicken/Colorado/24-020282-002/2024	A/chicken/Colorado/24-020282-003/2024	A/Colorado/138/2024	A/Colorado/139/2024	A/Michigan/90/2024	A/Texas/37/2024	A/Colorado/137/2024	A/cattle/CO/24-018028-007/2024	A/cattle/NM/24-010512-001/2024	A/cattle/TX/24-014545-002/2024	A/cattle/TX/24-014545-007/2024	A/cattle/CO/24-020940-002/2024	A/cattle/CO/24-020940-006/2024	A/chicken/ID/24-019884-002/2024	A/cattle/TX/24-009499-001/2024	A/cattle/SD/24-010354-007/2024	A/turkey/MN/24-014760-002/2024	A/turkey/MN/24-014760-003/2024	A/cattle/MN/24-016370-008/2024	A/domestic cat/NM/24-009116-004/2024	A/domestic cat/NM/24-009116-005/2024	A/cattle/MI/24-010231-001/2024	A/cattle/ID/24-015196-012/2024	A/cattle/IA/24-018873-002/2024	A/cattle/TX/24-017473-002/2024	A/cattle/TX/24-015973-009/2024	A/cattle/MN/24-020731-004/2024	A/cattle/MN/24-020731-005/2024	A/cattle/TX/24-019890-006/2024	
51	I																															L					
54	D																				N																
84	N																													D							Antigenic site E
88	D																																	G			
96	N																		S																		
97	D																						N														
115	L	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q	
120	S																			R																	
127	T																						A	A	A	A								A	A		
131	V																															E					
136	P	S																																			Antigenic site A
155	D																							N	N												Antigenic site B
156	A	T																				T															Antigenic site B; gain of glycosylation
158	P																										Q	Q									
161	K																																R				
162	I							I/V									V	V																			
195	T	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	
210	A														T																						Antigenic site D
214	A																																			T	Antigenic site D
218	Q																														R						
226	M																									I											
234	K																												N								
320	S															N																					
510	V						I	I	I	I				I																							
#aadiff		4	2	2	2	2	3	4	3	3	2	2	2	3	3	3	3	3	3	3	3	3	4	4	4	4	3	3	3	3	3	4	3	4	3	3	vs IDCDC-RG78A (A/Am. Wigeon/South Carolina/22-000345-001/2021)

Influenza

Hemagglutination inhibition assay of human cases of A(H5) clade 2.3.4.4b viruses

			Post-infection ferret antisera					
Reference antigens	Subtype	Clade	VN/ 1203	CNIC-21099	IDCDC-RG71A	IDCDC-RG78A	IDCDC-RG80A	TX/37
A/Viet Nam/1203/2004	H5N1	1	2560	<10	<10	<10	<10	<10
CNIC-21099 (A/Fujian-Sanyuan/21099/2017)	H5N6	2.3.4.4b	20	80	160	80	1280	40
IDCDC-RG71A (A/Astrakhan/3212/2020-like)	H5N8	2.3.4.4b	10	80	320	160	1280	80
IDCDC-RG78A (A/American Wigeon/SC/22-000345-001/2021)	H5N1	2.3.4.4b	10	80	640	320	1280	80
IDCDC-RG80A (A/chicken/Ghana/AVL-763_21VIR7050-39/2021)	H5N1	2.3.4.4b	<10	10	80	40	1280	80
A/Texas/37/2024	H5N1	2.3.4.4b	10	40	320	160	1280	80
Test antigens								
A/Colorado/109/2024	H5N1	2.3.4.4	10	10	320	320	1280	80
A/Colorado/134/2024	H5N1	2.3.4.4	10	10	160	160	1280	80
A/Colorado/137/2024	H5N1	2.3.4.4	10	10	160	320	1280	80
A/Colorado/138/2024	H5N1	2.3.4.4	10	40	160	160	1280	80
A/Michigan/90/2024	H5N1	2.3.4.4	10	40	160	320	1280	80

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Hemagglutination inhibition assay of A(H5) clade 2.3.4.4b viruses in dairy cattle

Reference antigens	Subtype	Clade	IDCDC-RG71A	IDCDC-RG78A	IDCDC-RG80A	bald eagle/FL
IDCDC-RG71A (A/Astrakhan/3212/2020-like)	H5N8	2.3.4.4b	160	10	2560	40
IDCDC-RG78A (A/American Wigeon/South Carolina/22-000345-001/2021)	H5N1	2.3.4.4b	320	80	2560	320
IDCDC-RG80A (A/chicken/Ghana/AVL-763_21VIR7050-39/2021)	H5N1	2.3.4.4b	40	20	2560	40
rg-A/bald eagle/Florida/W22-134-OP/2022	H5N1	2.3.4.4b	160	40	2560	160
Test antigens						
A/bovine/USA/C-5/2024	H5N1	2.3.4.4b	160	40	2560	160
A/bovine/USA/12/2024	H5N1	2.3.4.4b	160	20	2560	160
A/bovine/USA/A-1/2024	H5N1	2.3.4.4b	80	40	2560	160
A/bovine/USA/K-6/2024	H5N1	2.3.4.4b	20	10	2560	80
A/bovine/Ohio/B24OSU-368/2024	H5N1	2.3.4.4b	<10	10	640	20

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Clade 2.3.4.4b A(H5) Candidate Vaccine Virus Development

Candidate vaccine viruses	Subtype	Institution	Availability	Date selected	Date available
IDCDC-RG71A (A/Astrakhan/3212/2020-like)	H5N8	CDC	Yes	February 2021	January 5, 2022
CBER-RG8 (A/Astrakhan/3212/2020-like)	H5N8	FDA	Yes	February 2021	November 9, 2021
IDCDC-RG80A A/chicken/Ghana/AVL-763/21VIR7050-39/2021-like	H5N1	CDC	Pending	September 2022	Pending
IDCDC RG78A A/American Wigeon/South Carolina/22-000345-001/21-like	H5N1	CDC	Yes	February 2023	September 18, 2023

No new clade 2.3.4.4b CVVs recommended during September 2024 VCM

HPAI A(H5Nx) clade 2.3.4.4b summary

Epidemiology and surveillance

- **Detected in birds in many regions in Africa, Antarctica, Asia, Europe, North America and South America.**
- **A(H5N1) viruses have continued to circulate in birds in most regions of the world.**
    - A(H5N6) viruses have been detected in China and Japan.
    - A(H5N5) viruses have been detected in Asia, Europe and North America.
- **Infections in wild and captive mammals have continued to be reported,** as well as the ongoing outbreak in dairy cattle with subsequent spread to poultry and peri-domestic birds and mammals in the USA.

Genetic analysis

- **Sequence analyses for viruses from dairy cattle indicate the ongoing outbreak was caused by a single introduction of a genetically stable virus** that has subsequently spread to over 255 farms in 14 states.
- The majority of HAs from the characterized 2.3.4.4b viruses in the US had **fewer than 4 amino acid substitutions** compared to closest 2.3.4.4b CVV.
- Continued genetic analysis is critical to identify viruses with changes that may impact antigenicity.

Antigenic Analysis

- **Most viruses tested reacted well to at least one post-infection ferret antisera raised against the 2.3.4.4b CVVs.**
    - A small number of dairy cattle viruses with HA substitutions in antigenic sites showed reduced reactivity to post-infection ferret antisera to available CVVs.
    - Viruses with HA changes are sporadically detected and do not currently represent sustained circulation.
- **The data supported no recommendation to develop a new candidate vaccine virus to 2.3.4.4b viruses.**

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