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

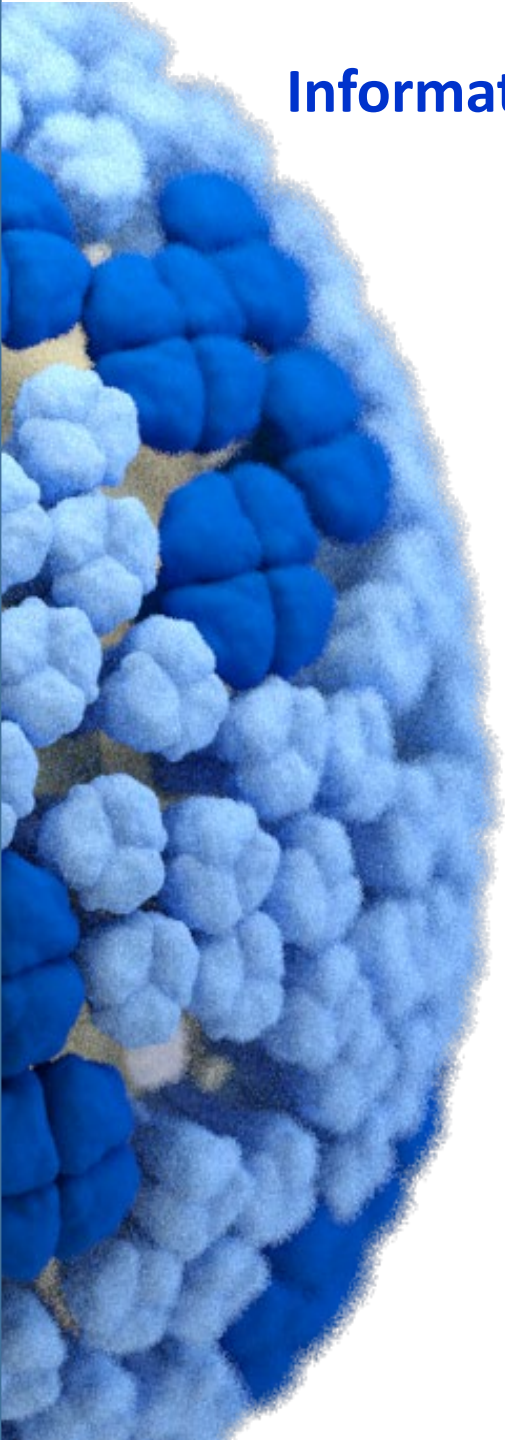
October 10<sup>th</sup>, 2024

## 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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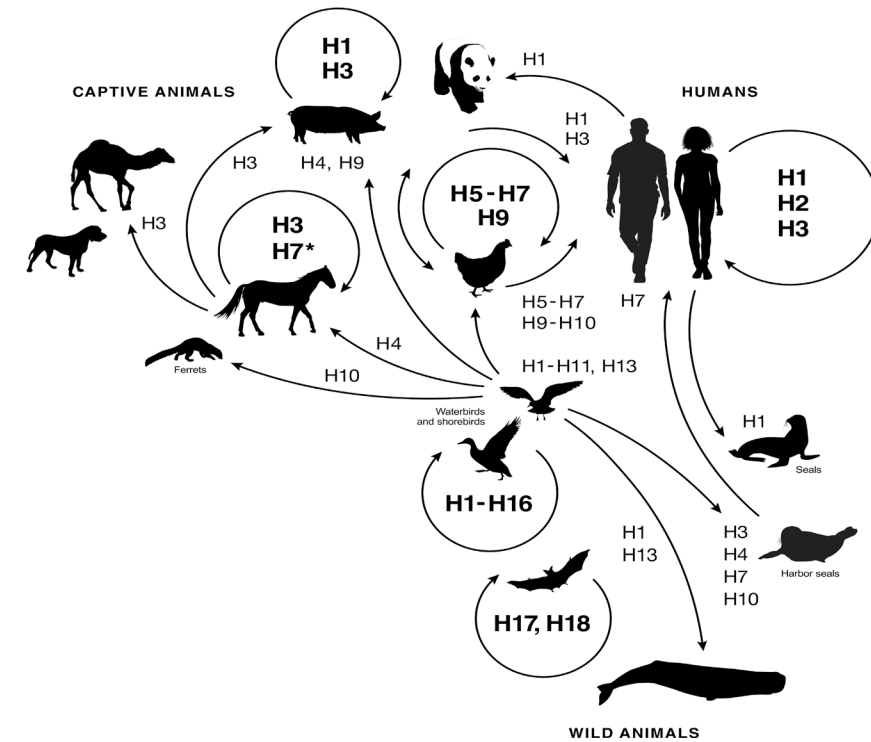
The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.



# 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\*

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

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

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

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

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.



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



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



**Phenotypic**  
Antigenic  
Antiviral



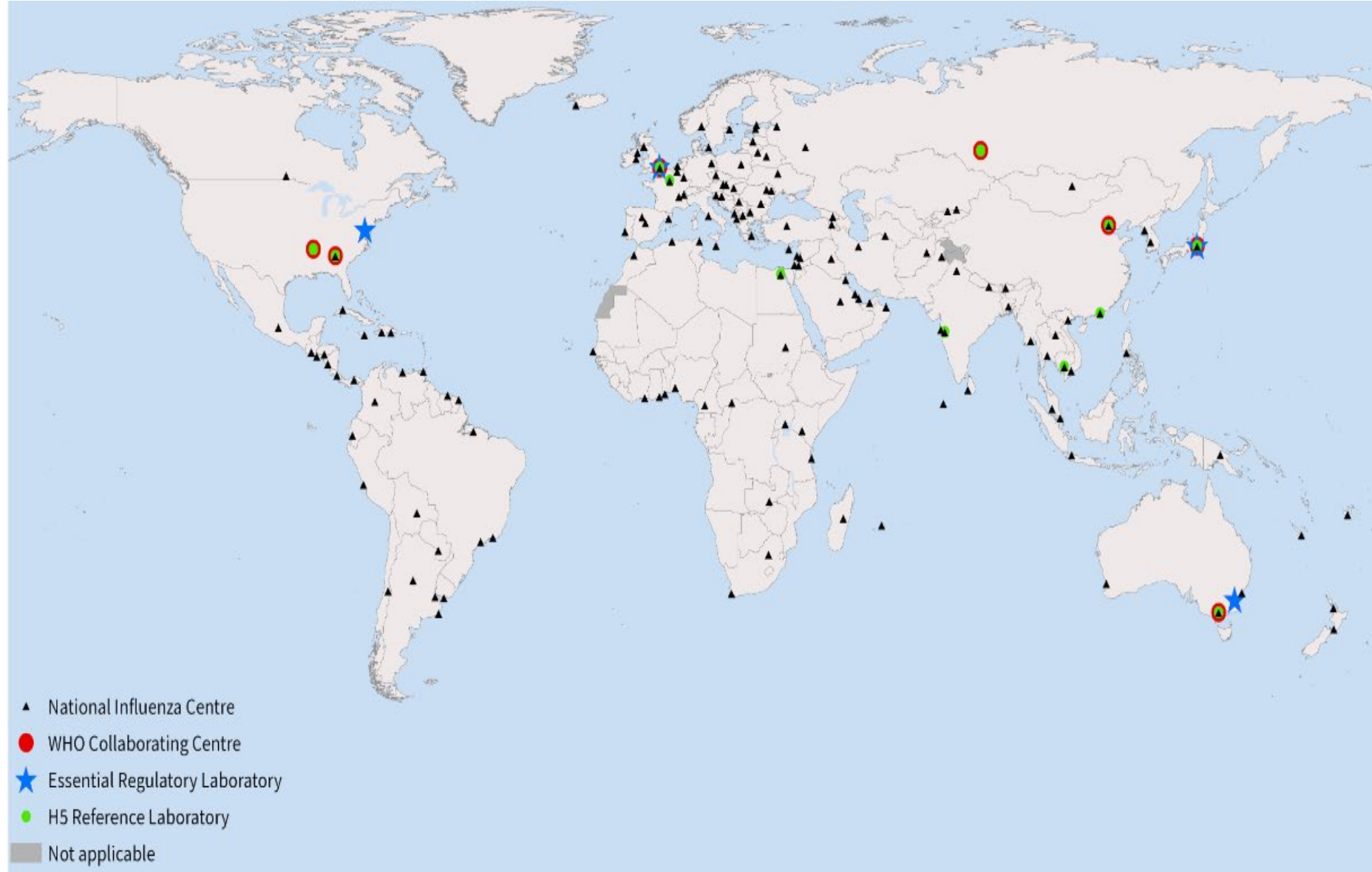
**CVVs**  
Inactivated vaccine  
Egg  
Cell  
Recombinant HA protein  
Live Attenuated Influenza Vaccine



# 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

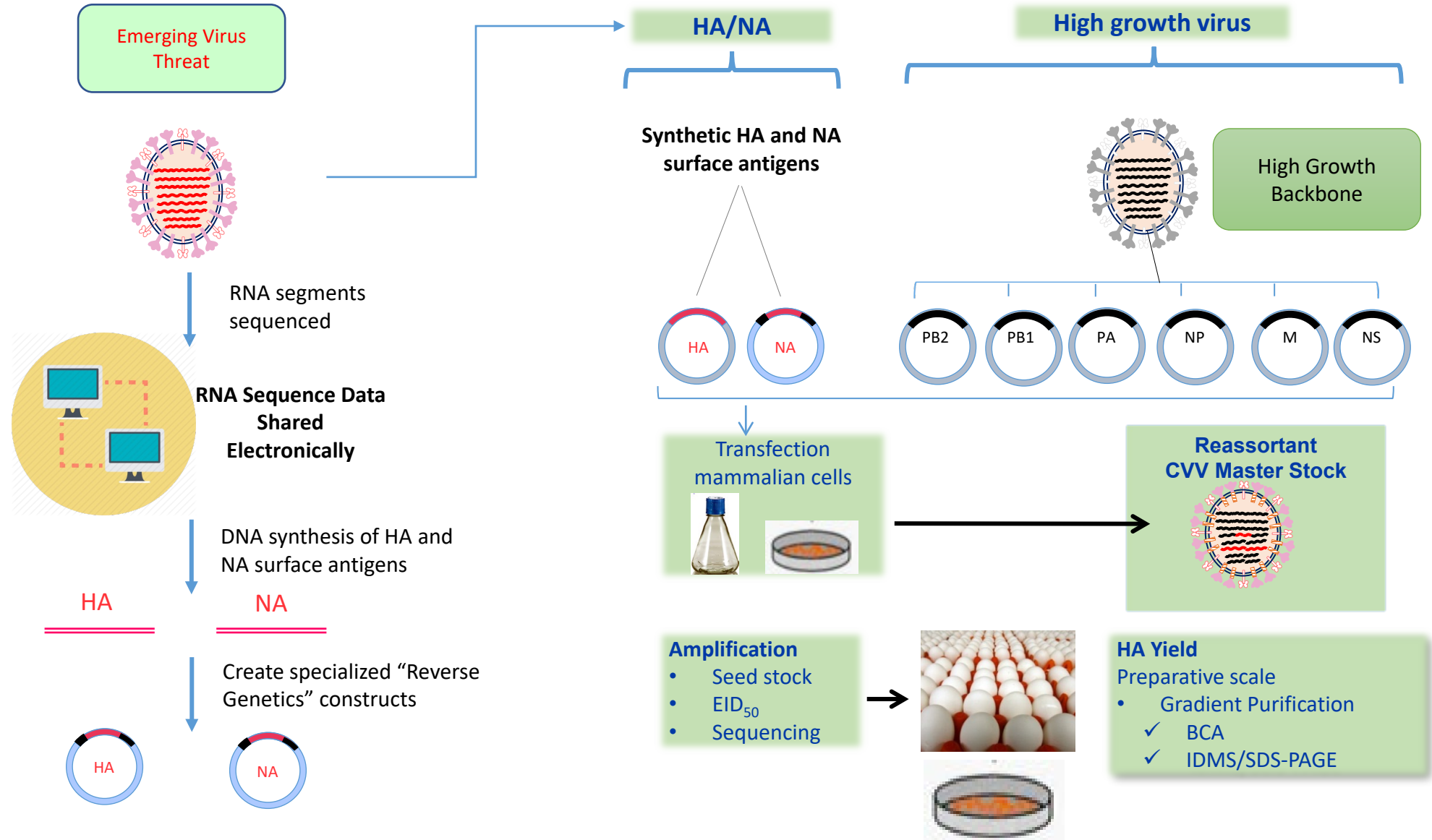
## Goal of WHO committee on influenza vaccine composition

- 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)?

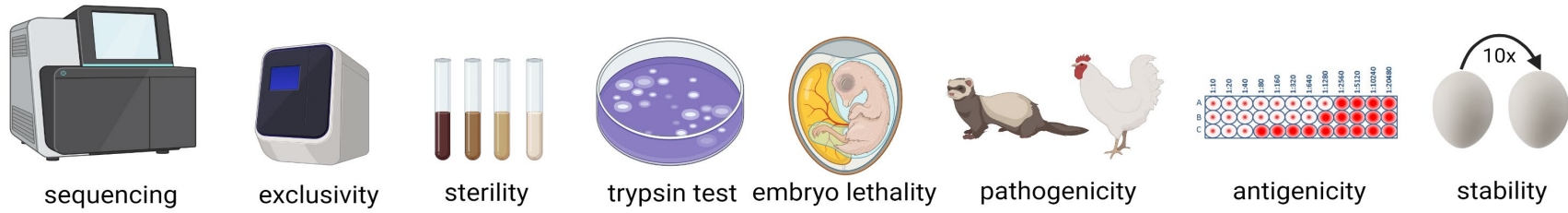
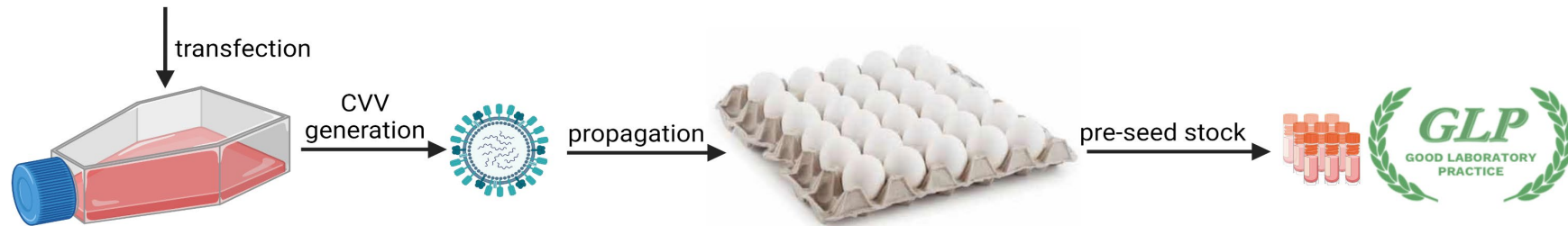
# Generation of pre-pandemic CVVs for A(H5Nx) by CDC, Influenza Division



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

Gene synthesis, CVV production

QC, QA, submission, listing, distribution





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## Zoonotic influenza: candidate vaccine viruses and potency testing reagents

← Recommendations for influenza vaccine composition

Zoonotic influenza candidate vaccine viruses

Seasonal influenza candidate vaccine viruses

### 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**

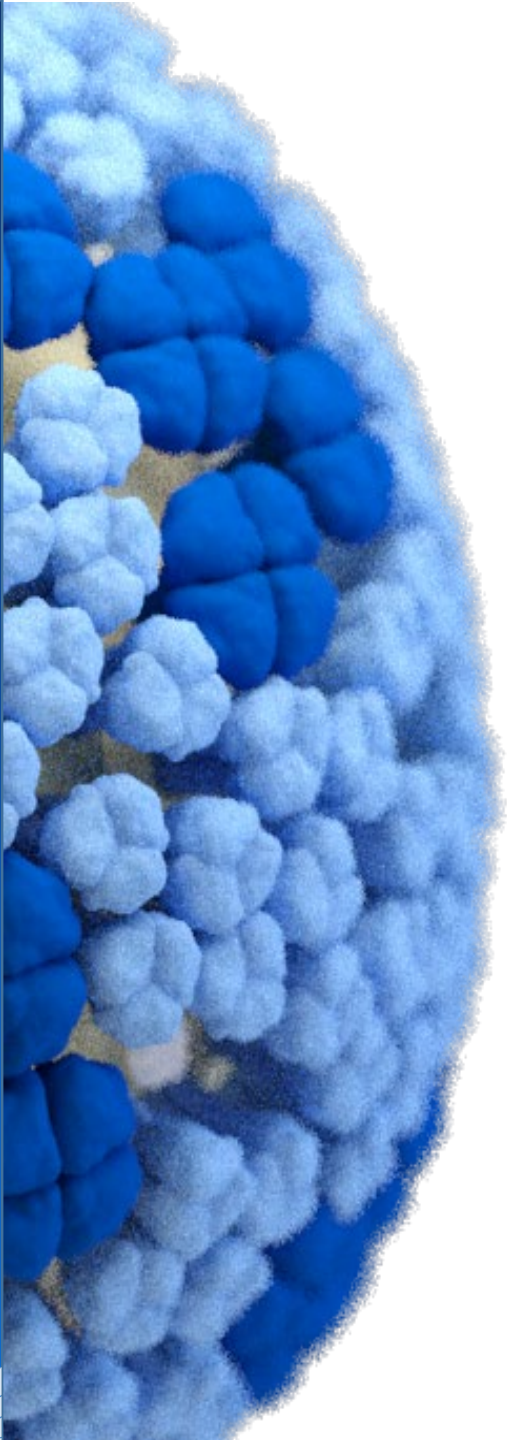
- <https://www.who.int/teams/global-influenza-programme/vaccines/who-recommendations/candidate-vaccine-viruses>

- **Zoonotic influenza summary reports and candidate vaccine viruses for zoonotic influenza vaccine viruses:**

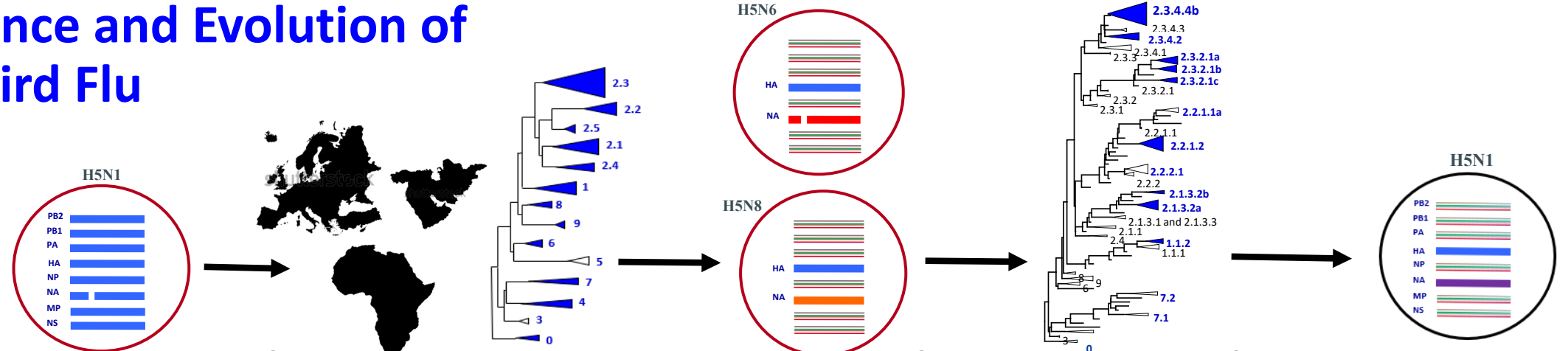
- <https://www.who.int/teams/global-influenza-programme/vaccines/who-recommendations/zoonotic-influenza-viruses-and-candidate-vaccine-viruses>

# 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.*

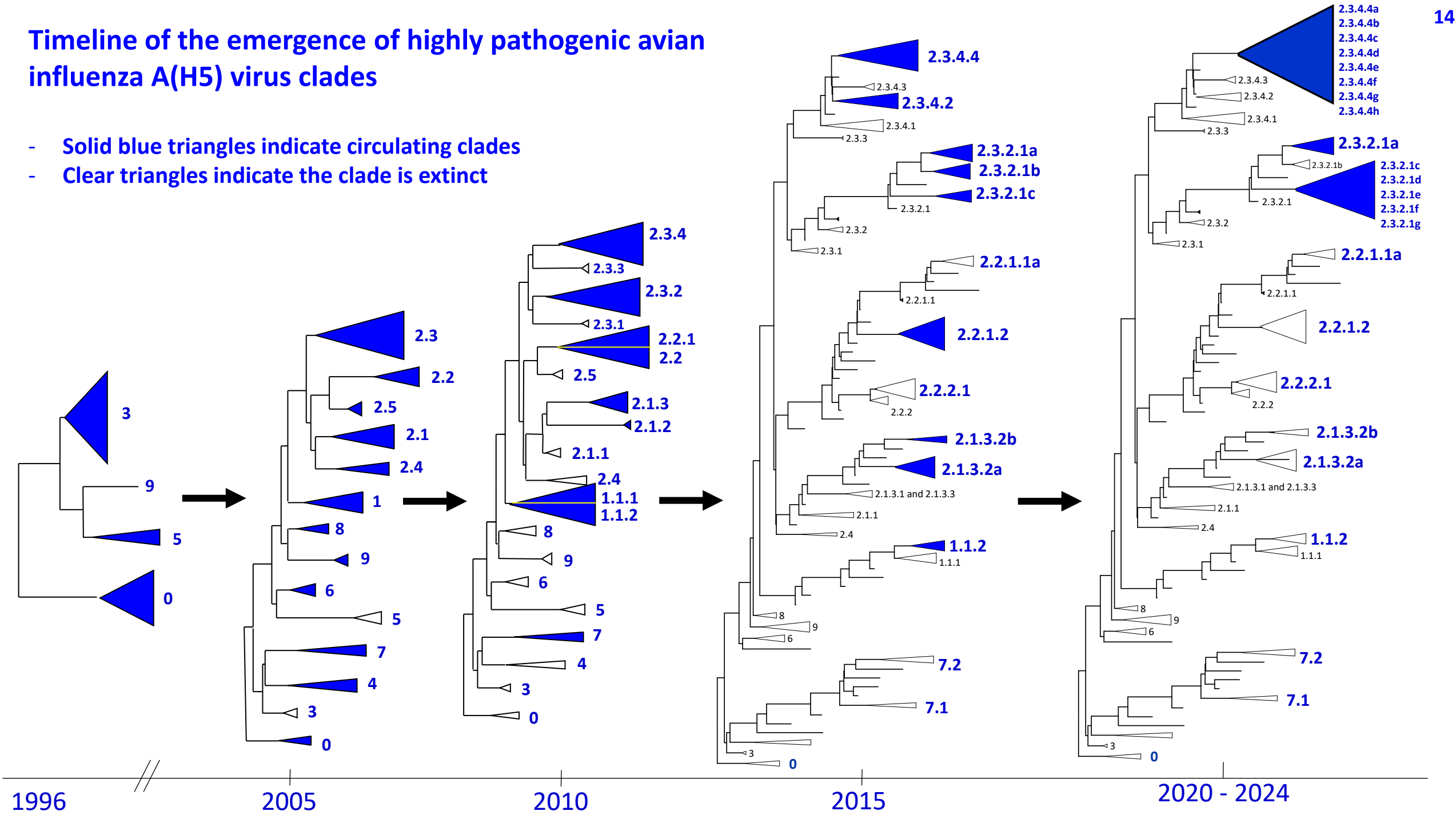
*The virus is detected in Canada and U.S. wild birds in late 2021. In February 2022, the virus begins causing outbreaks in U.S. commercial and backyard poultry.*



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

# 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*



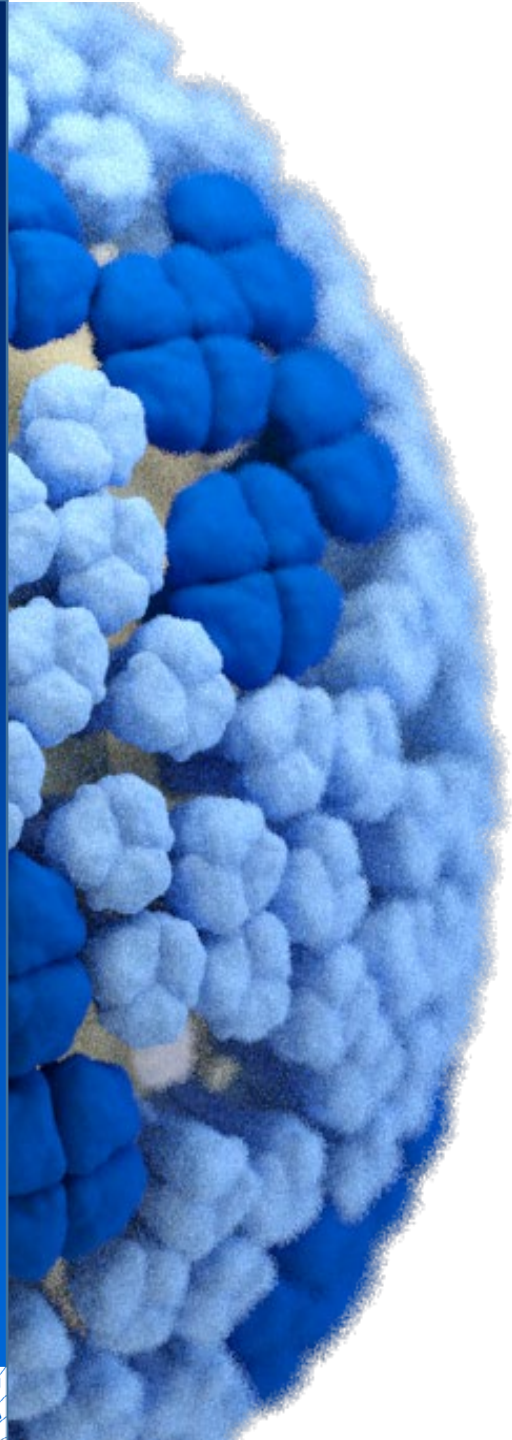


# A(H5Nx) Clade 2.3.4.4 Candidate Vaccine Virus Development

| 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

North America,  
Central America,  
South America

Europe, the Middle East

Asia

Africa

Asia



2.3.4.4b

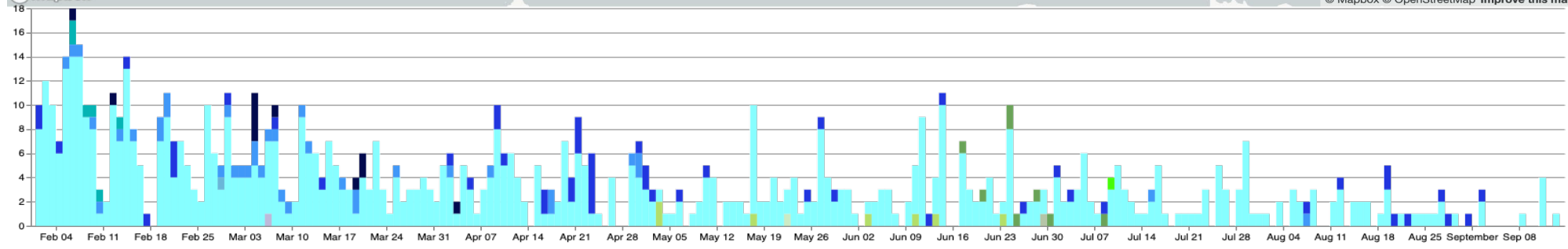
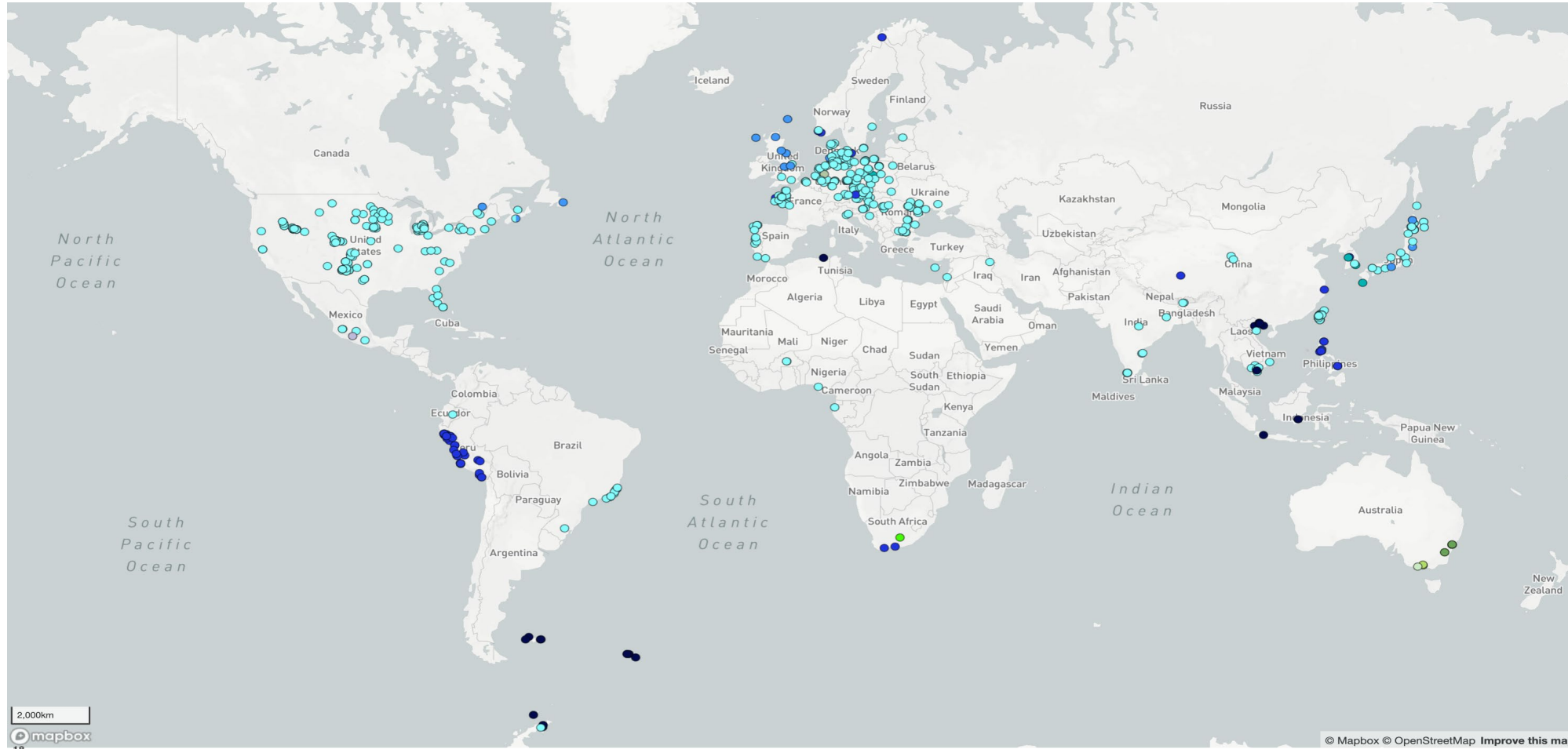
# Clade 2.3.4.4b A(H5) Candidate Vaccine Virus Development

| 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



# 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

| #   | Strain |
|-----|--------|
| 51  | I      |
| 54  | D      |
| 84  | N      |
| 88  | D      |
| 96  | N      |
| 97  | D      |
| 115 | L      |
| 120 | S      |
| 127 | T      |
| 131 | V      |
| 136 | P      |
| 155 | D      |
| 156 | A      |
| 158 | P      |
| 161 | K      |
| 162 | I      |
| 195 | T      |
| 210 | A      |
| 214 | A      |
| 218 | Q      |
| 226 | M      |
| 234 | K      |
| 320 | S      |
| 510 | V      |

Antigenic site E

Antigenic site A  
Antigenic site B

Antigenic site B; gain of glycosylation

Antigenic site D  
Antigenic site D

vs IDCDC-RG78A (A/Am. Wigeon/South Carolina/22-000345-001/2021)





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

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

# 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 | <u>160</u>  | 10          | 2560        | 40            |
| IDCDC-RG78A (A/American Wigeon/South Carolina/22-000345-001/2021) | H5N1    | 2.3.4.4b | 320         | <u>80</u>   | 2560        | 320           |
| IDCDC-RG80A (A/chicken/Ghana/AVL-763_21VIR7050-39/2021)           | H5N1    | 2.3.4.4b | 40          | 20          | <u>2560</u> | 40            |
| rg-A/bald eagle/Florida/W22-134-OP/2022                           | H5N1    | 2.3.4.4b | 160         | 40          | 2560        | <u>160</u>    |
| <b>Test antigens</b>  |         |          |             |             |             |               |
| 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            |

## 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.**

# Support and Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

