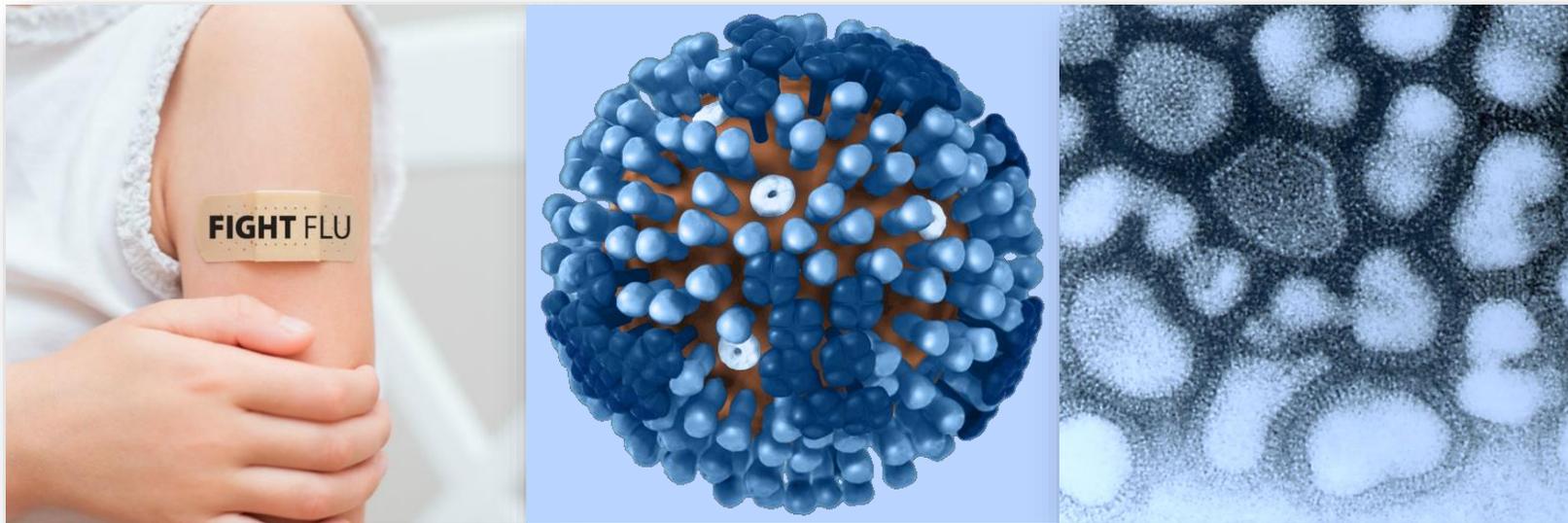


# CDC PUBLIC HEALTH GRAND ROUNDS

## Public Health Response to Severe Seasonal Influenza



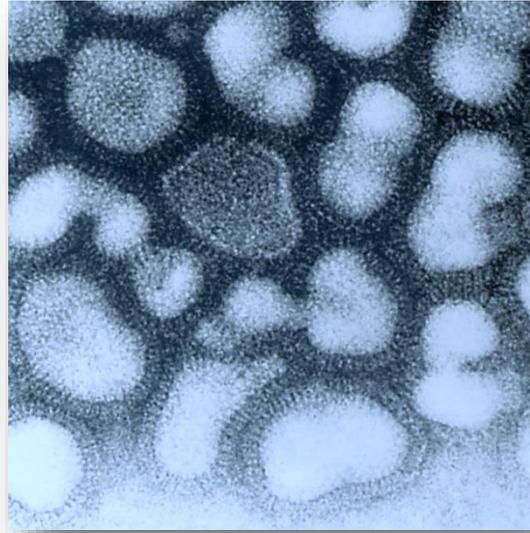
A 508 compliant video is available at:  
<https://youtu.be/azcMZCCr7E>

January 16, 2018



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

# Chasing Flu



**Dan Jernigan, MD, MPH**

*Director, Influenza Division*

National Center for Immunization and Respiratory Diseases



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

# Influenza – Historical Perspective

## ➤ From medieval Italian meaning “influence”

- Originally referring to the astrological influence of the stars
- Later became *influenza del freddo*, “influence of the cold”

## ➤ Epidemics each season, pandemics periodically

- Historians attribute influenza as the cause of pandemics going back centuries
- Two modern pandemics achieving milestones in 2018
  - ❑ 1918 “Spanish” Pandemic (H1N1 ) – 100 years
  - ❑ 1968 “Hong Kong” Pandemic (H3N2) – 50 years

## ➤ Persistence through plasticity

- The influenza virus has evolved to evade human immunity
- Constant changes allow adaptation



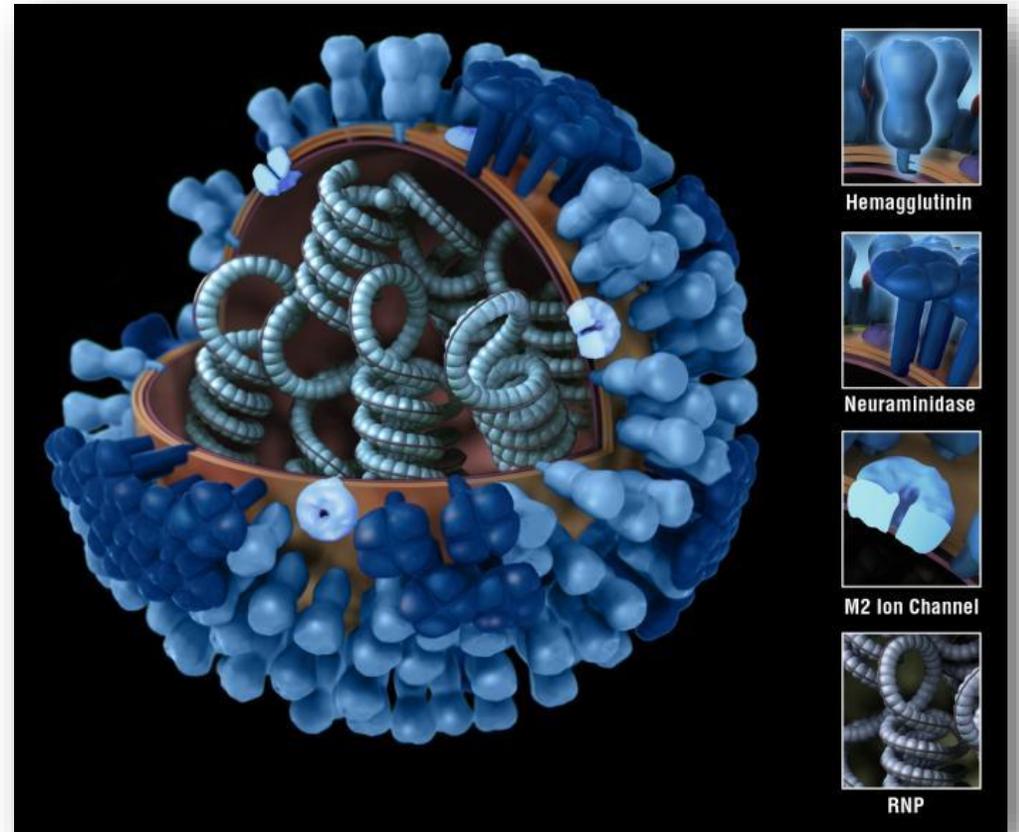
# Influenza Virus

## ➤ Current influenza viruses of humans

- Influenza A(H3N2)
- Influenza A(H1N1)pdm09
- Influenza B/Yamagata
- Influenza B/Victoria

## ➤ Important outer surface proteins

- Hemagglutinin – Vaccines induce antibodies to block this protein
- Neuraminidase – Antiviral drugs inhibit this protein



# Significant Annual Burden of Influenza



**United States**

12,000 – 56,000

140,000 – 710,000

9.2M – 35.6M



**Global**

291,000 – 646,000

3M to 5M

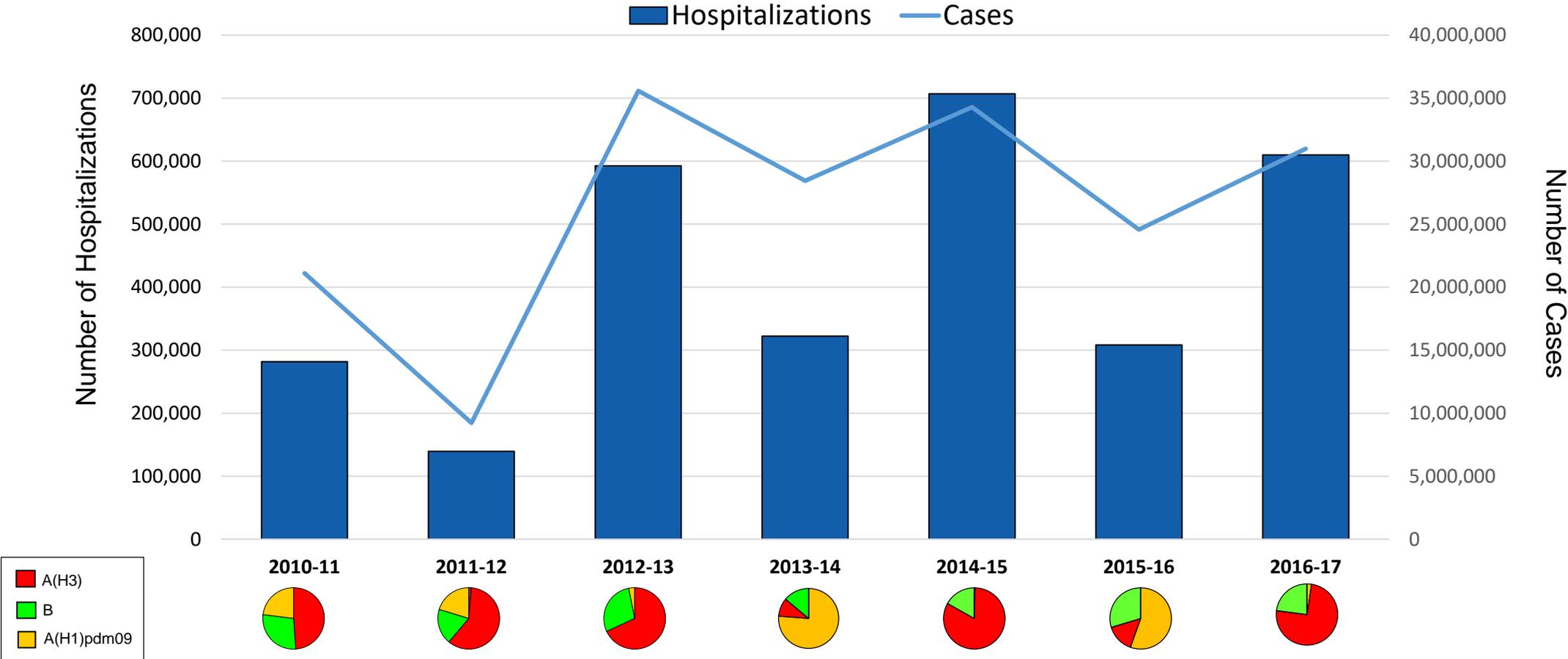
1.0 B



Direct Medical Costs: \$10.4 B per year  
Indirect and Direct Costs: \$87.1 B per year

# Influenza Impact Varies by Season, Highest with H3N2

Estimated Cases, Care-Seeking Cases, and Hospitalizations, U.S. 2010-17 Seasons



# Impact of Current Season

## Colorado Among Worst Hit States For Flu Cases

Filed Under: Banner Health, Centers for Disease Control, Department Of Public Health And Environment, flu, Flu Shot, Flu Vaccine, Greeley, H3-N2, Influenza A, Local TV, North Colorado Medical Center, Weld County



Watch & Listen LIVE  

## Alabama declares state of emergency due to widespread flu cases

Posted: Jan 11, 2018 6:41 PM EST  
Updated: Jan 11, 2018 7:01 PM EST

By WALA Webstaff



**BREAKING NEWS**  
**FLU ALERT**  
WIDESPREAD OUTBREAK ACROSS ALABAMA  
**LOTTERY** -2-8 [FLORIDA.com](http://www.FLORIDA.com) LOTTO: 05-19-20-24-27-!

## Severe flu in California brings medicine shortages, kills 27

COLD AND FLU - January 7th



## HOSPITALS SWAMPED WITH FLU CASES

AMERICA'S NEWS HQ

ted early and is spreading fast

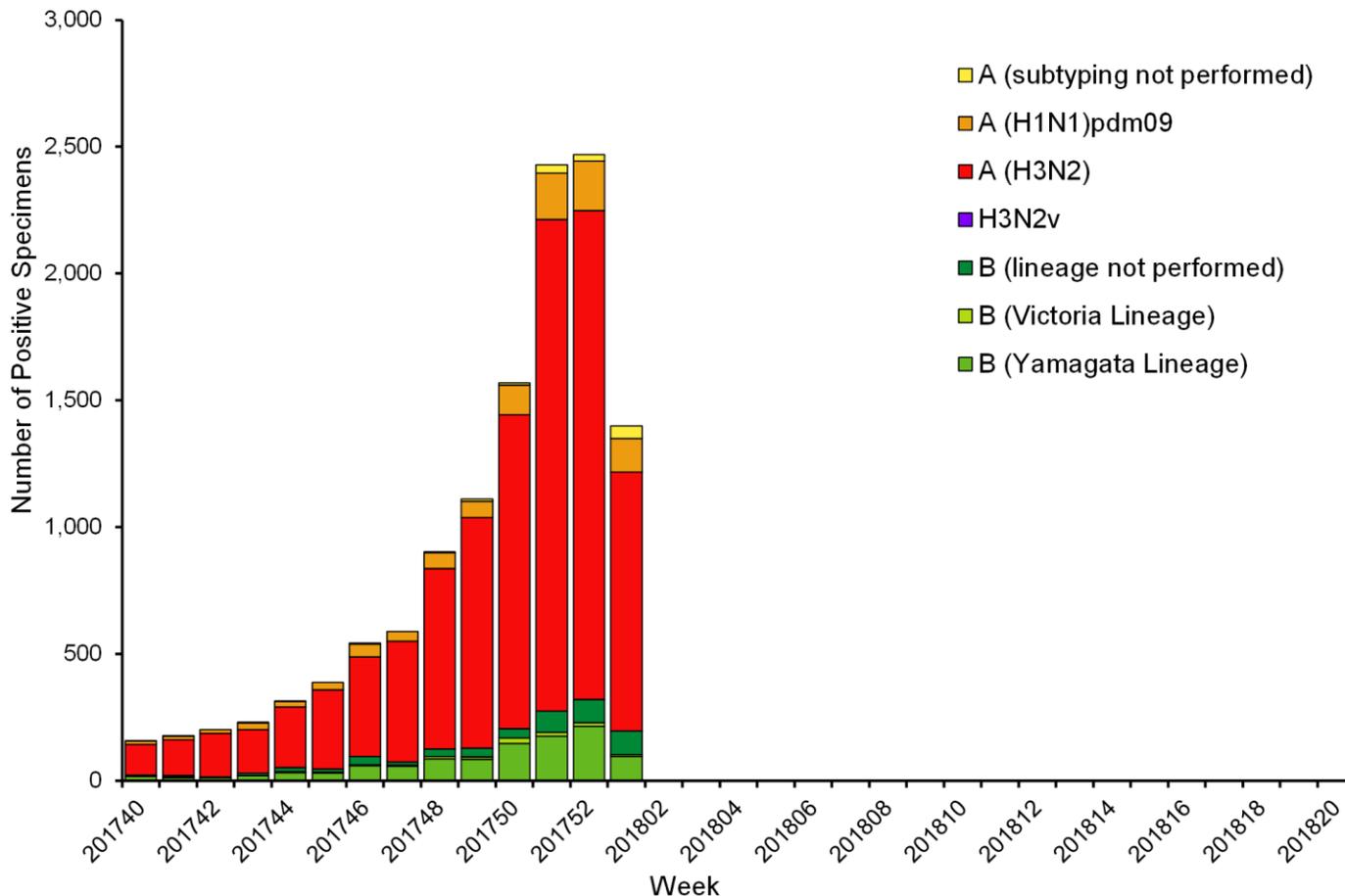
# Public Health Surveillance for Influenza in the U.S.

## ➤ **Surveillance Systems**

- Virus Surveillance
- Geographic Spread
- Outpatient Illness
- Hospitalizations
- Mortality

# Virus Surveillance Shows H3N2 Is Predominant

Influenza Positive Tests Reported to CDC by U.S. Public Health Laboratories, National Summary, 2017-2018 Season



## ➤ H3N2 Infections

- Of all Flu+ (12,474):

- 78%

- Of all Flu A+ (10,874):

- 90%

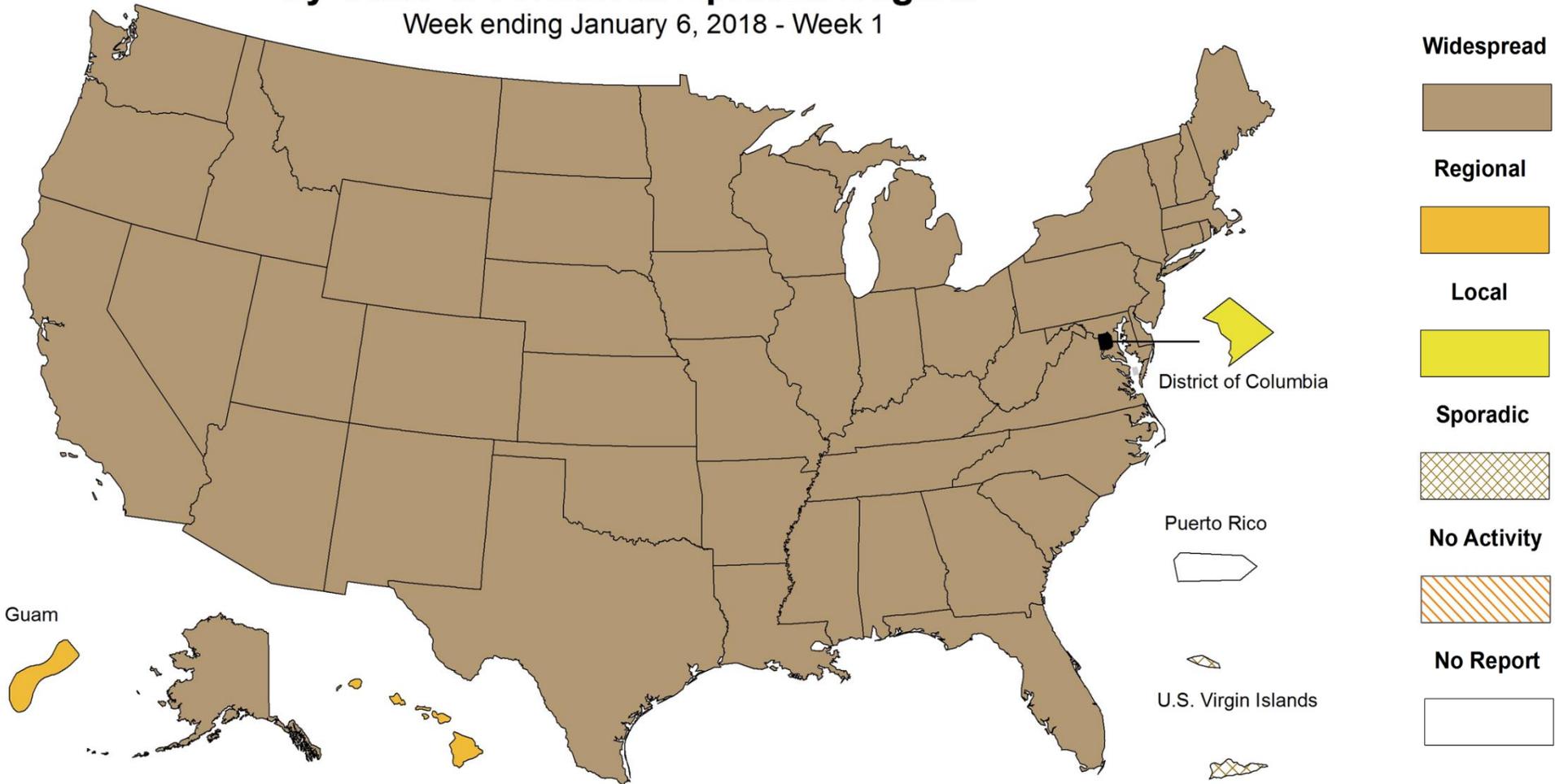
➤ **H1N1 and B continue to increase**

➤ **No evidence of resistance to antiviral drugs among 555 H3N2 viruses tested**

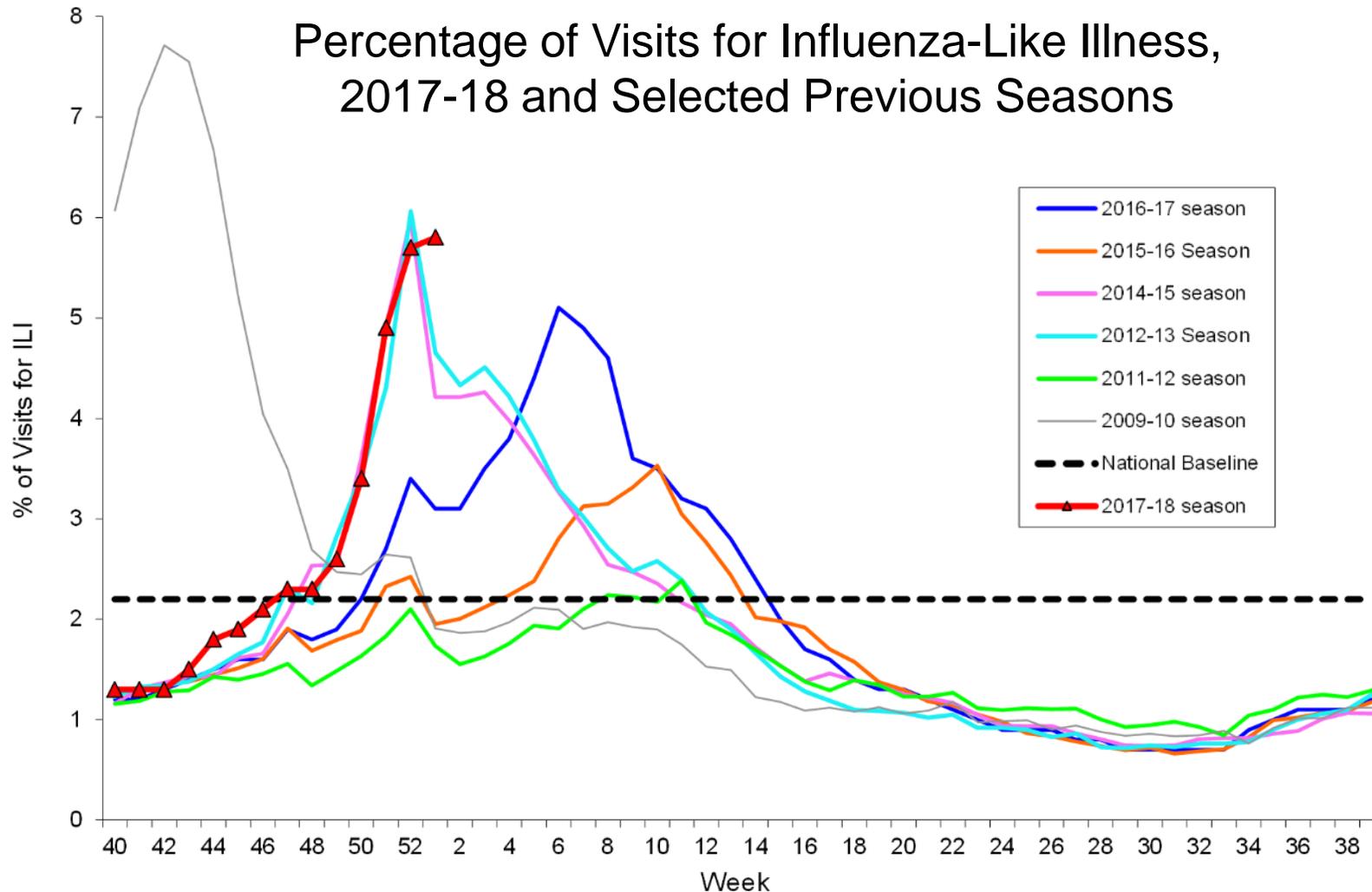
# Influenza Is Widespread in 49 States

## Weekly Influenza Activity Estimates Reported by State & Territorial Epidemiologists\*

Week ending January 6, 2018 - Week 1



# Influenza-Like Illness Is Earlier With Rapid Increase in Visits

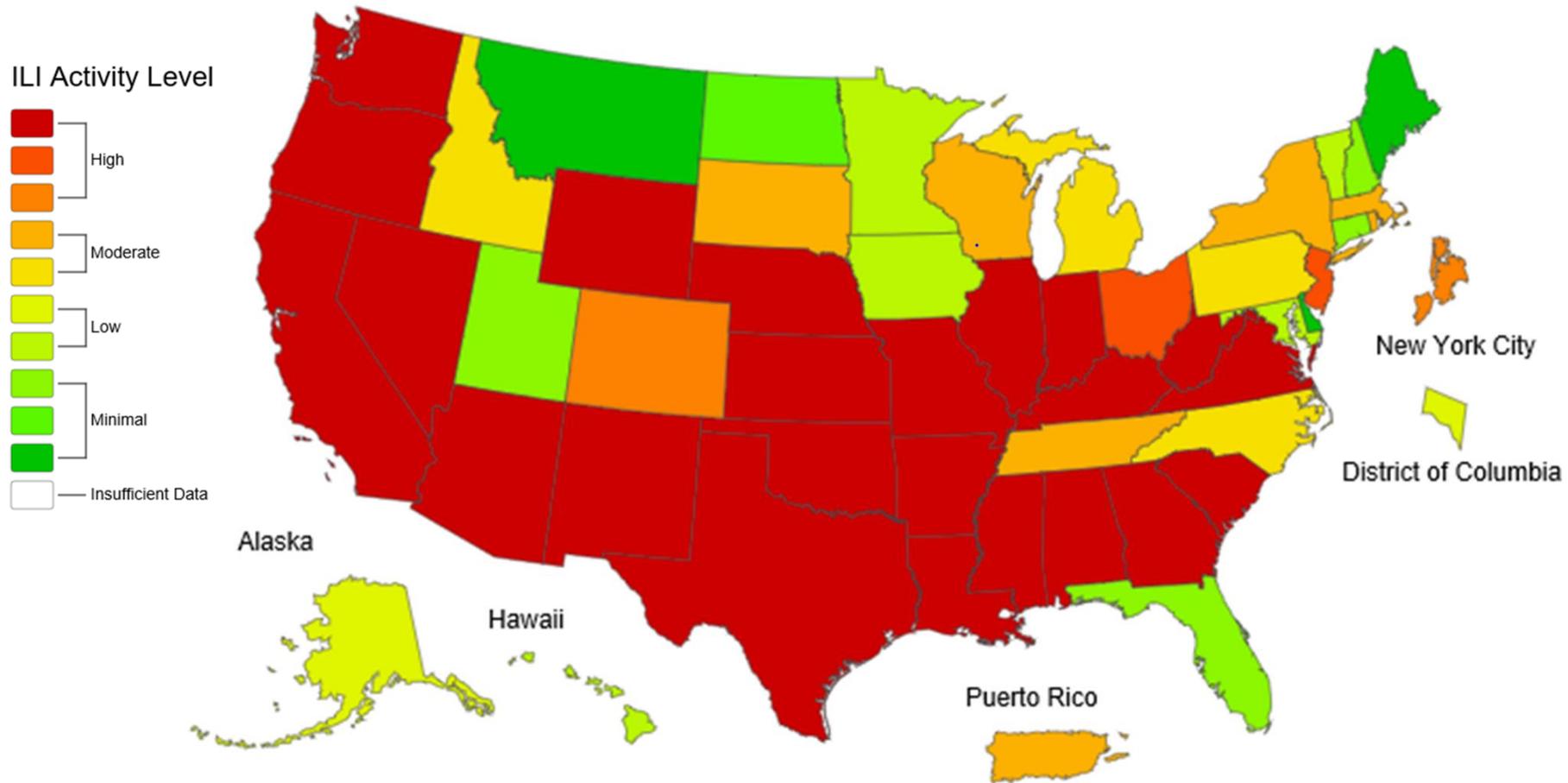


➤ 339,598 visits for ILI reported this season

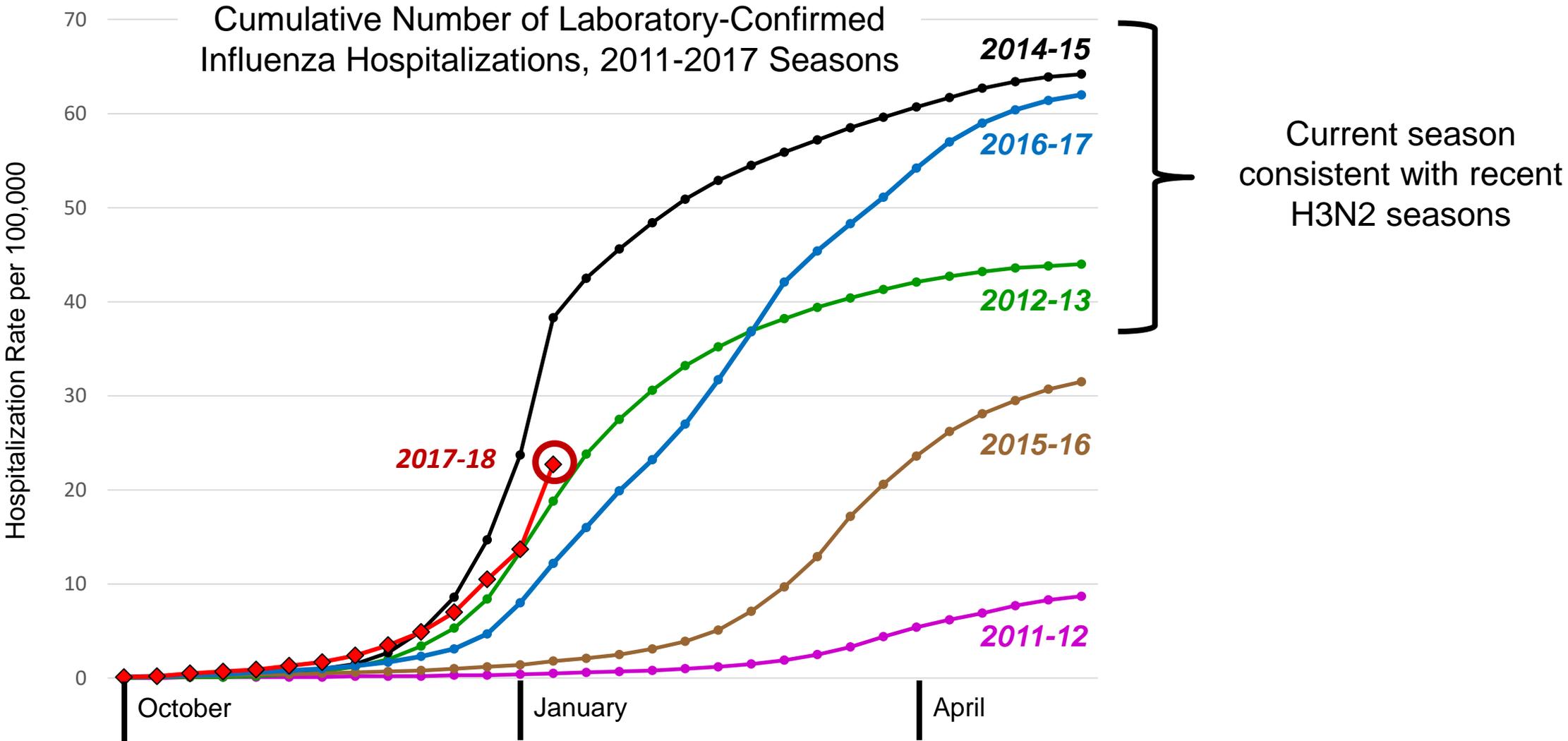
➤ Current season tracking closely to past H3N2 seasons:

- 2014-15
- 2012-13

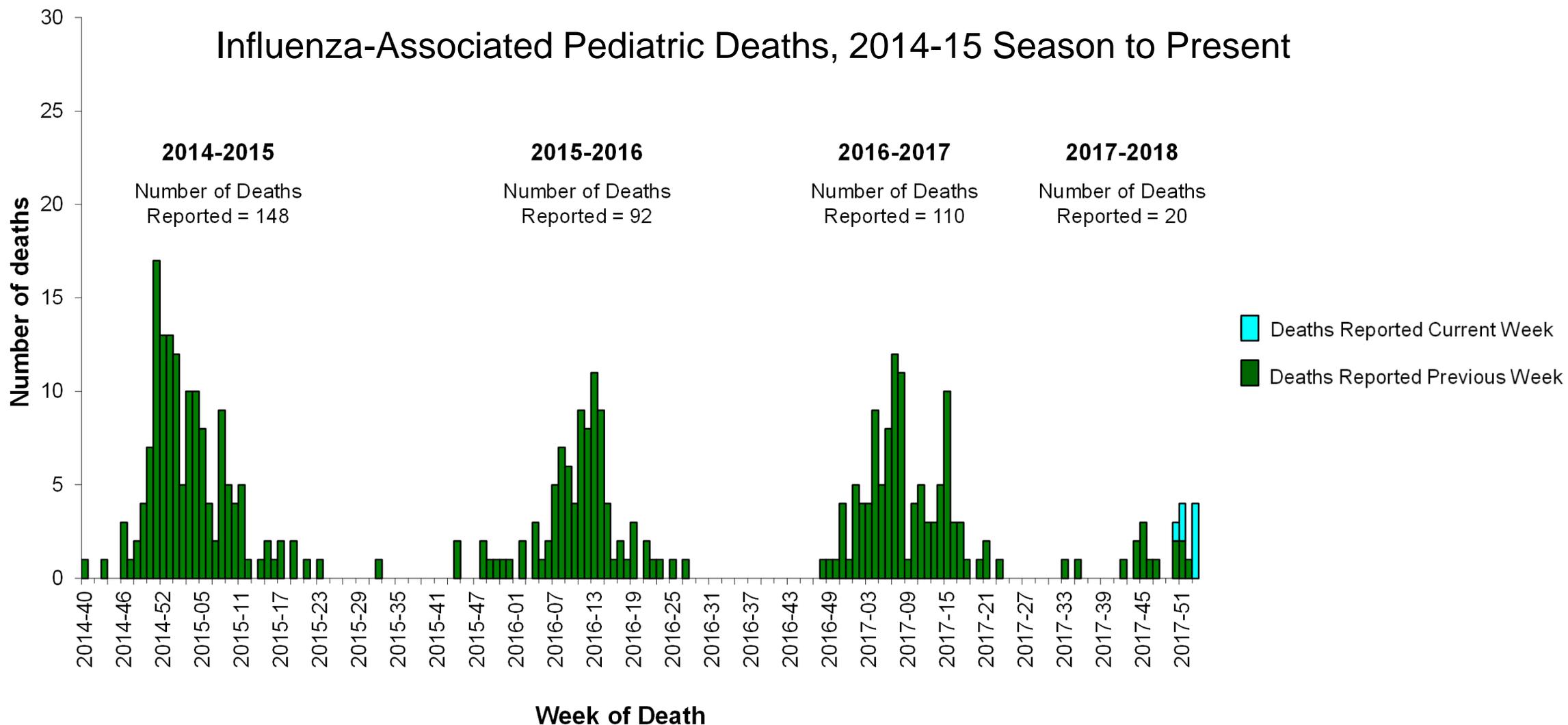
# Highest Influenza-Like Illness reported in South and West



# Hospitalizations Tracking with Recent H3N2 Seasons



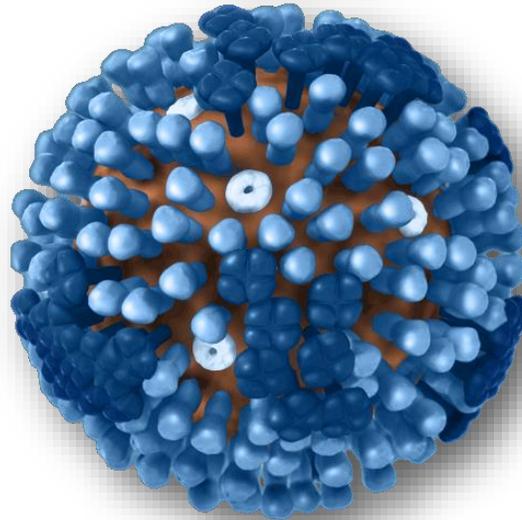
# Twenty Influenza-Associated Pediatric Deaths Reported



# Conclusions

- **Influenza A(H3N2) is predominating this season in the U.S.**
  - Influenza A(H1N1) and influenza B starting to increase
- **Influenza activity began early and has risen quickly**
  - Consistent with past H3N2 seasons: 2012-13 and 2014-15
- **H3N2 seasons have been associated with higher numbers of influenza cases, hospitalizations and deaths**
  - Influenza-associated hospitalization rates this season appear similar to recent H3N2 seasons

# The Problem of H3N2



**David Wentworth, PhD**

*Chief, Virology, Surveillance, and Diagnosis Branch*  
Influenza Division

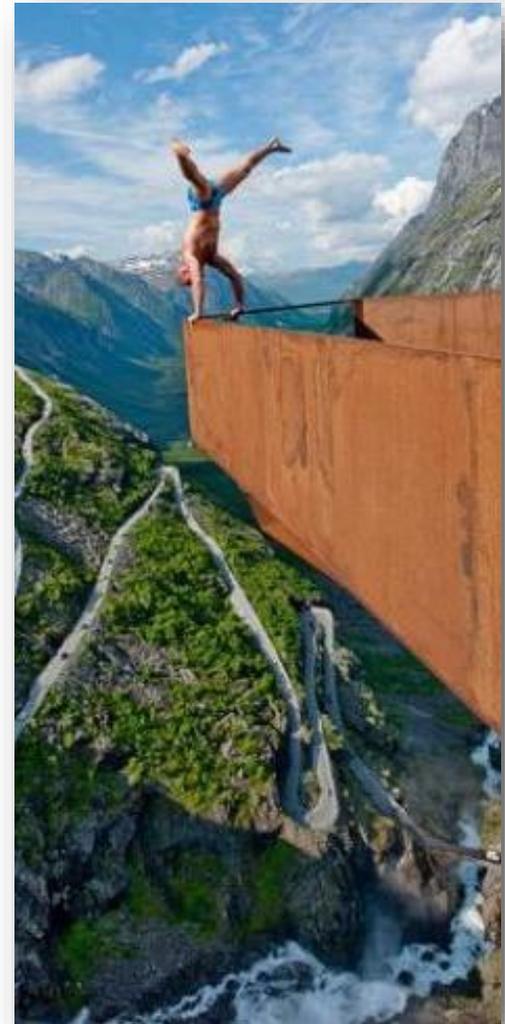
National Center for Immunization and Respiratory Diseases



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Health and Human Services  
Centers for Disease  
Control and Prevention

# Influenza Viruses Survive On The Edge of Catastrophe

- **Replication of influenza viruses is error-prone**
  - Disadvantage for the virus
    - ❑ Close to the threshold of extinction (e.g., many defective viruses)
  - Advantages for the virus
    - ❑ Increased adaptability, variants are rapidly selected upon any type of evolutionary pressure (e.g., antiviral drugs, new host, immune)
    - ❑ Evolutionary benefit for evading host immunity
- **Influenza survives as a population of viruses, not as a single virus**
- **Influenza viruses, especially H3N2, are constantly changing**
  - Requires continuous comprehensive virus surveillance
  - Necessitates frequent updates to the vaccine



# Evaluation of Influenza Viruses at CDC

## ➤ Genetic Characterization

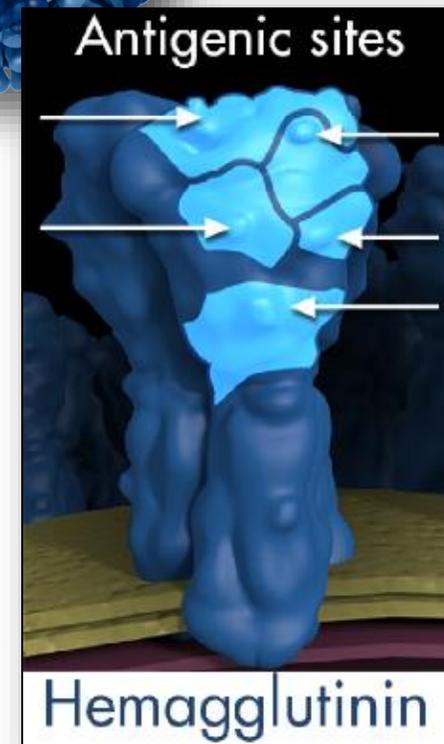
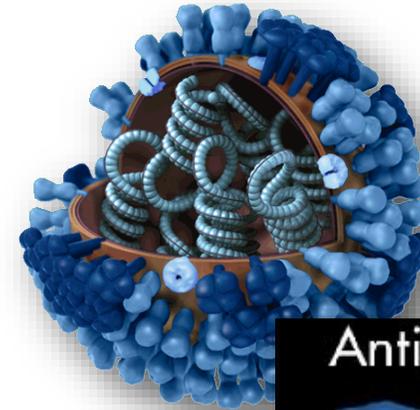
- Segmented genome (enables reassortment)
- CDC uses next-generation sequencing of influenza genome
- Detects all variation – only some are significant changes

## ➤ Antigenic Characterization

- CDC uses multiple tests to evaluate changes in the hemagglutinin surface protein to monitor:
  - Changes in circulating viruses, “drift”
  - Evasion of host immunity to prior infection or vaccination

## ➤ Vaccine virus selection

- Twice annual review of analysis on thousands of viruses
- Choose one each of A(H3N2), A(H1N1), B/Yamagata, B/Victoria

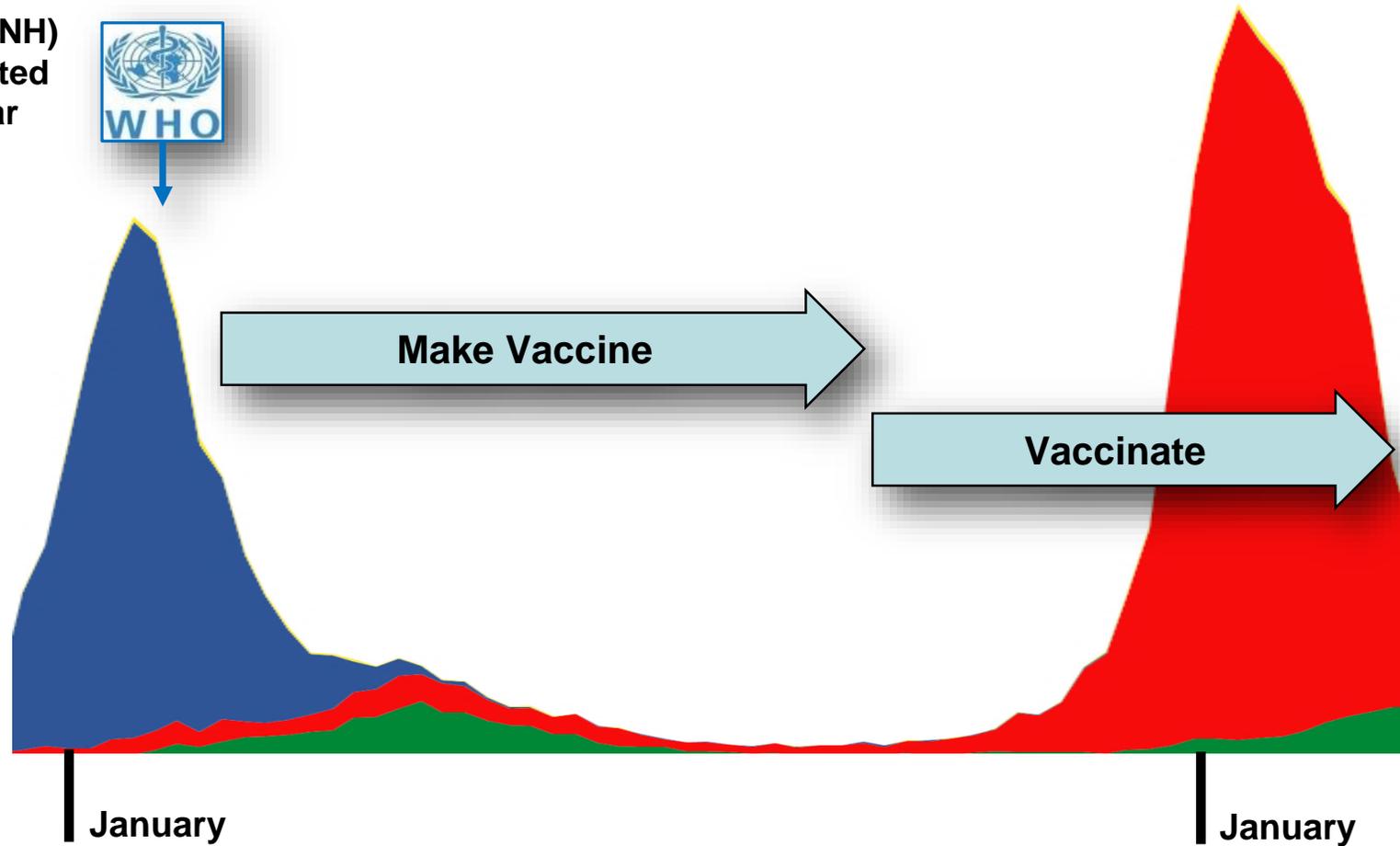


# Vaccine Viruses Need to be Selected Six Months in Advance

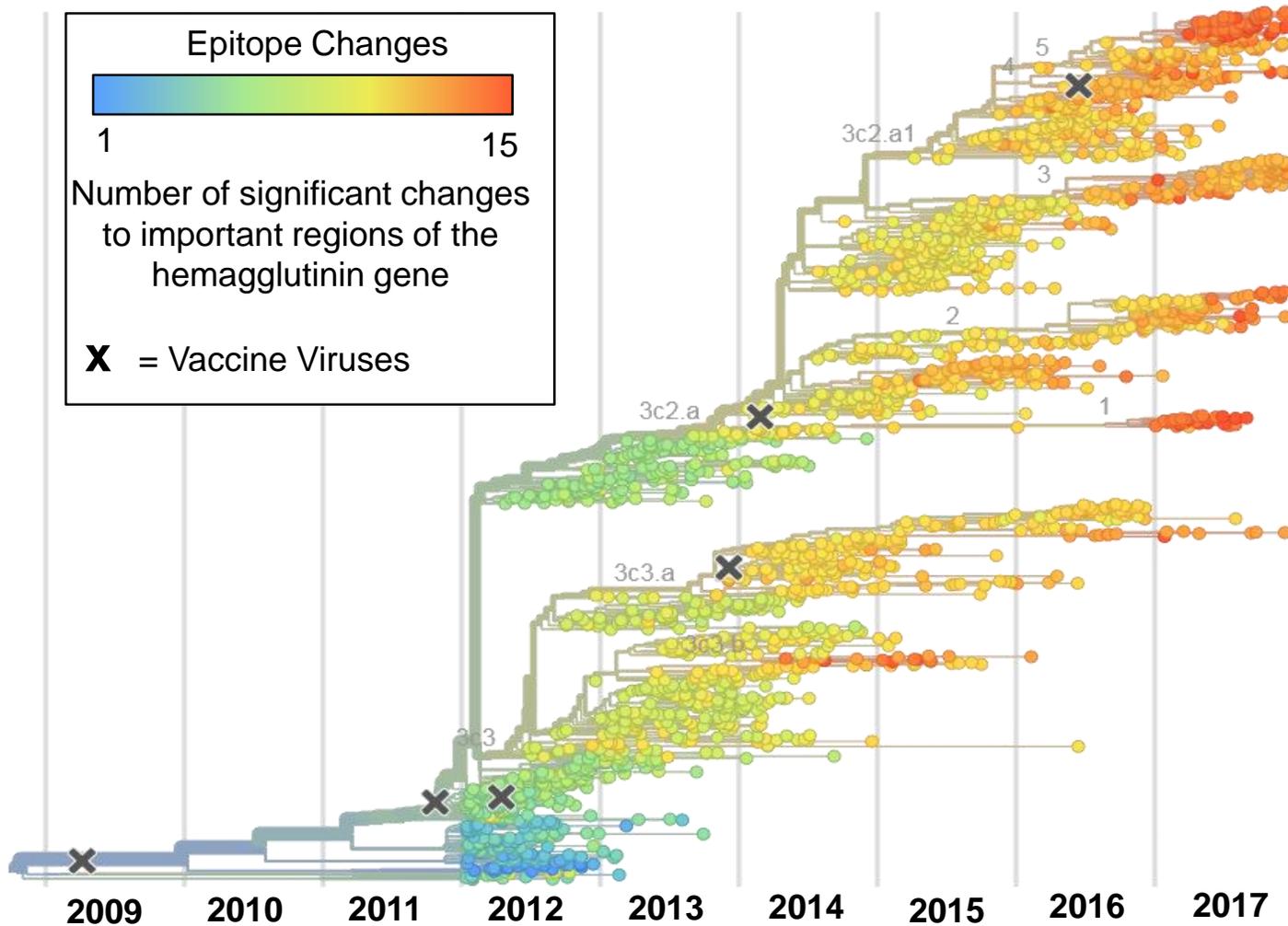
Northern Hemisphere (NH)  
Vaccine Viruses Selected  
in February each year



A(H3N2)  
A(H1N1)  
B/Yamagata  
B/Victoria

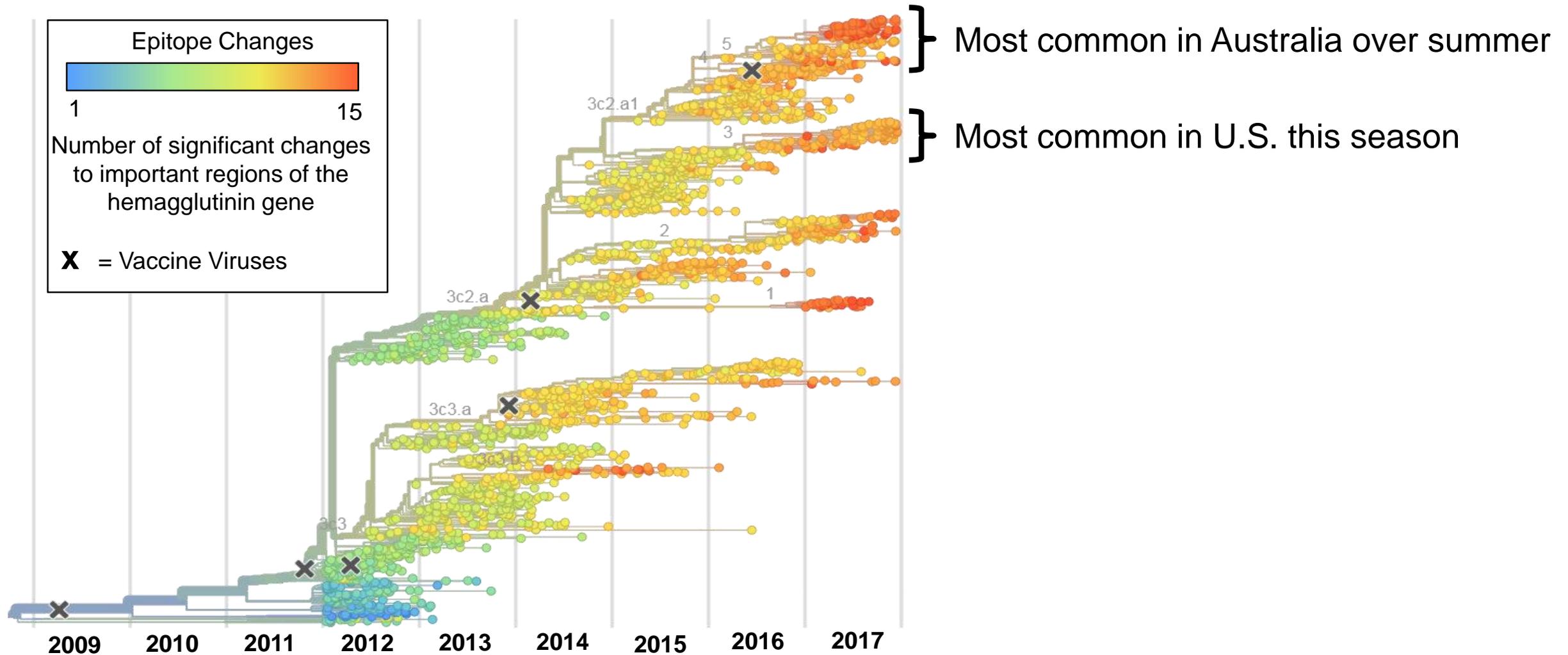


# Improved Genetic Characterization Shows Rapid Evolution and Diversity of H3N2

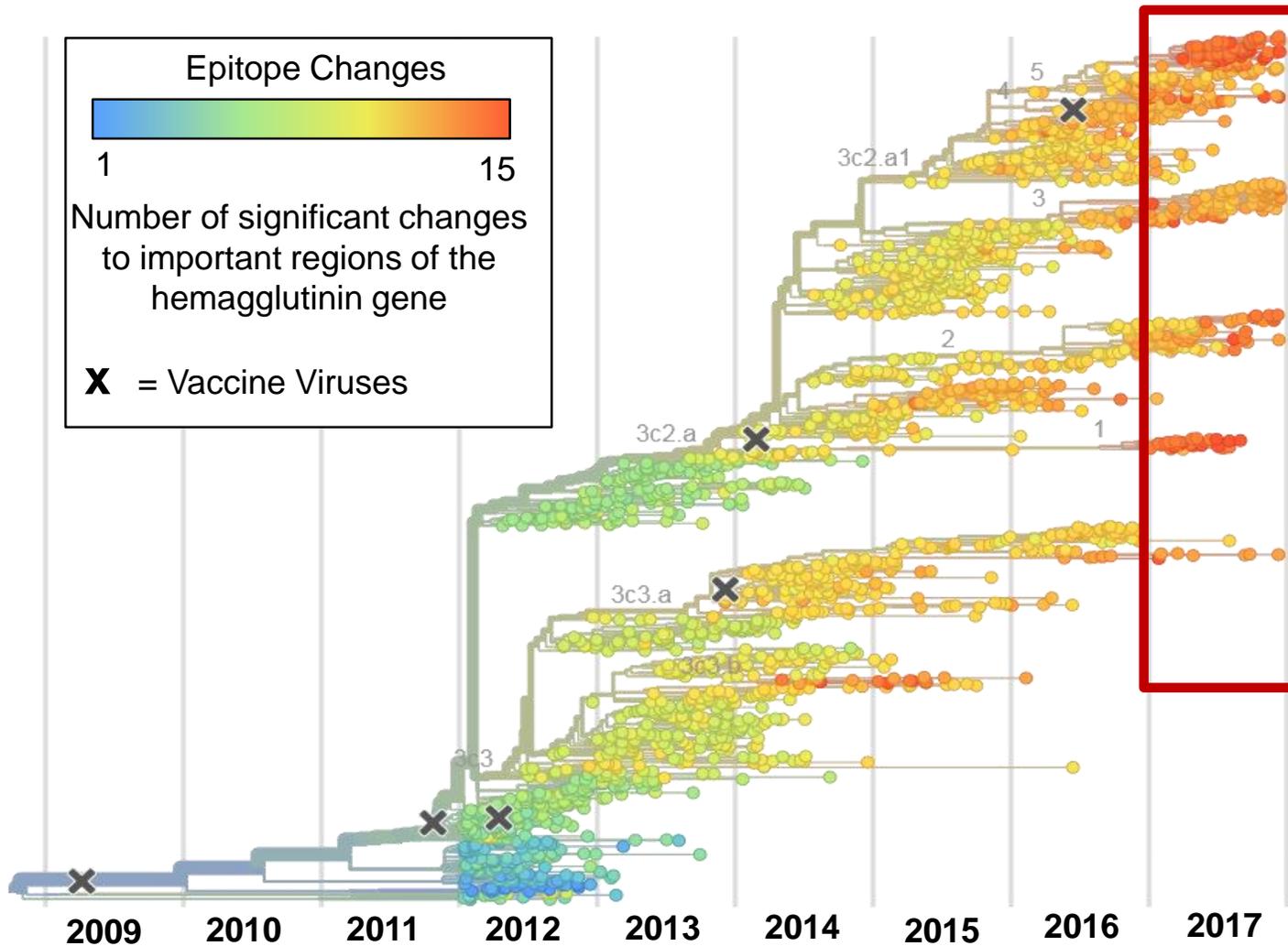


- H3N2 Viruses Evolve More Rapidly than Other Influenza Viruses
- H3N2 has required twice the number of vaccine viruses changes than H1N1
- CDC surveillance shows several H3N2 genetic groups co-circulating this season

# Improved Genetic Characterization Shows Rapid Evolution and Diversity of H3N2

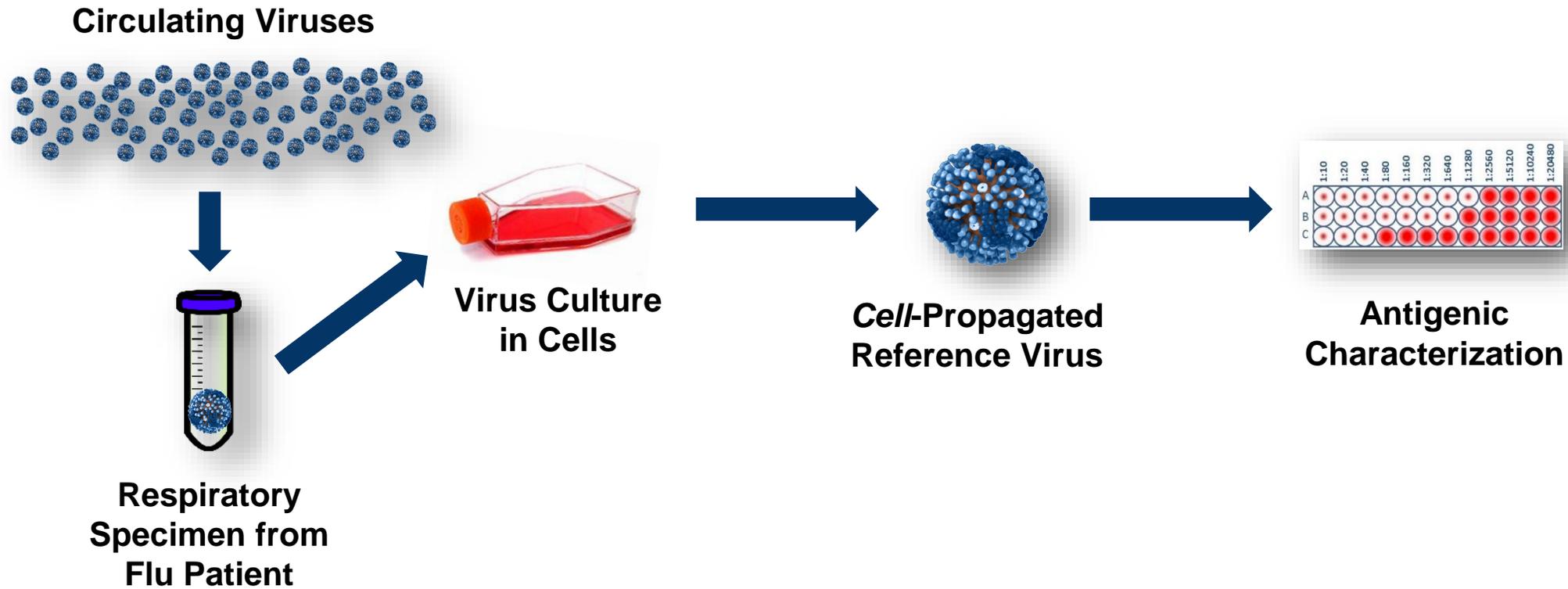


# Improved Genetic Characterization Shows Rapid Evolution and Diversity of H3N2

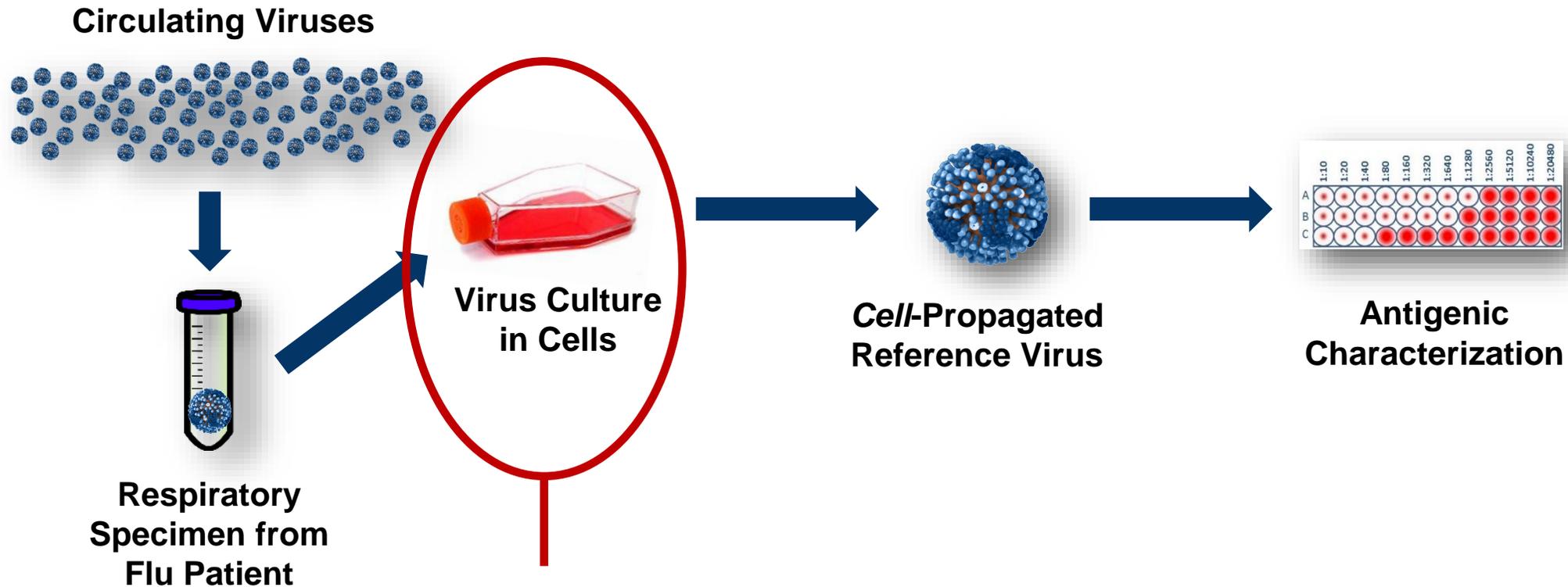


- 97% of circulating H3N2 viruses are similar to the cell-propagated H3N2 reference viruses representing the virus used in the vaccine this season in the U.S.

# Antigenic Characterization of H3N2 Viruses is Increasingly Difficult

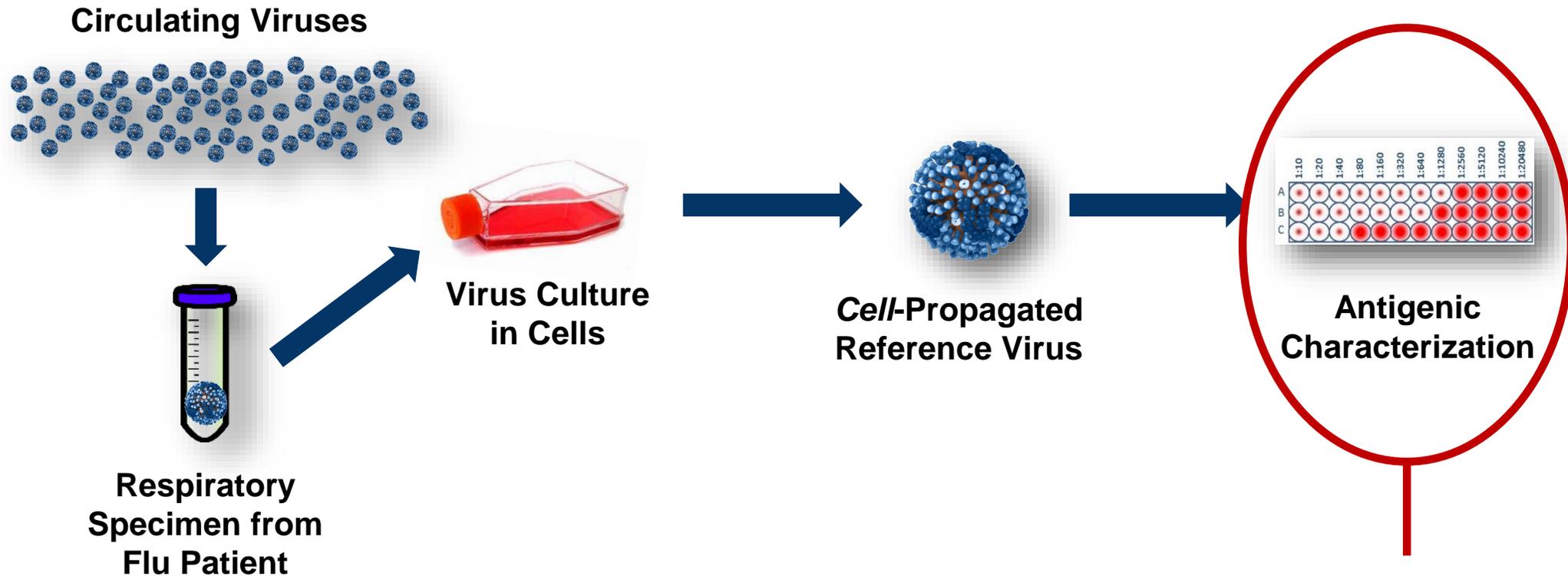


# Antigenic Characterization of H3N2 Viruses is Increasingly Difficult



New methods required for propagating H3N2 viruses in cell culture

# Antigenic Characterization of H3N2 Viruses is Increasingly Difficult



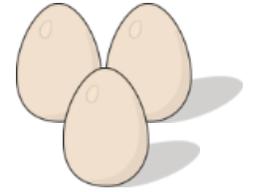
Recent H3N2 viruses require additional and new tests

- Focus-reduction and microneutralization assays
- Developing “nano-neutralization” assay

# Influenza Vaccine Manufacturing Requires Specially Prepared Viruses

## ➤ Egg-Based Influenza Vaccines

- Primary manufacturing technology for over 50 years
- Majority (~87%) of available vaccines in the U.S. use eggs
- CDC and other laboratories isolate viruses directly from human respiratory specimens in eggs
  - ❑ Influenza viruses can undergo changes as they are grown in eggs

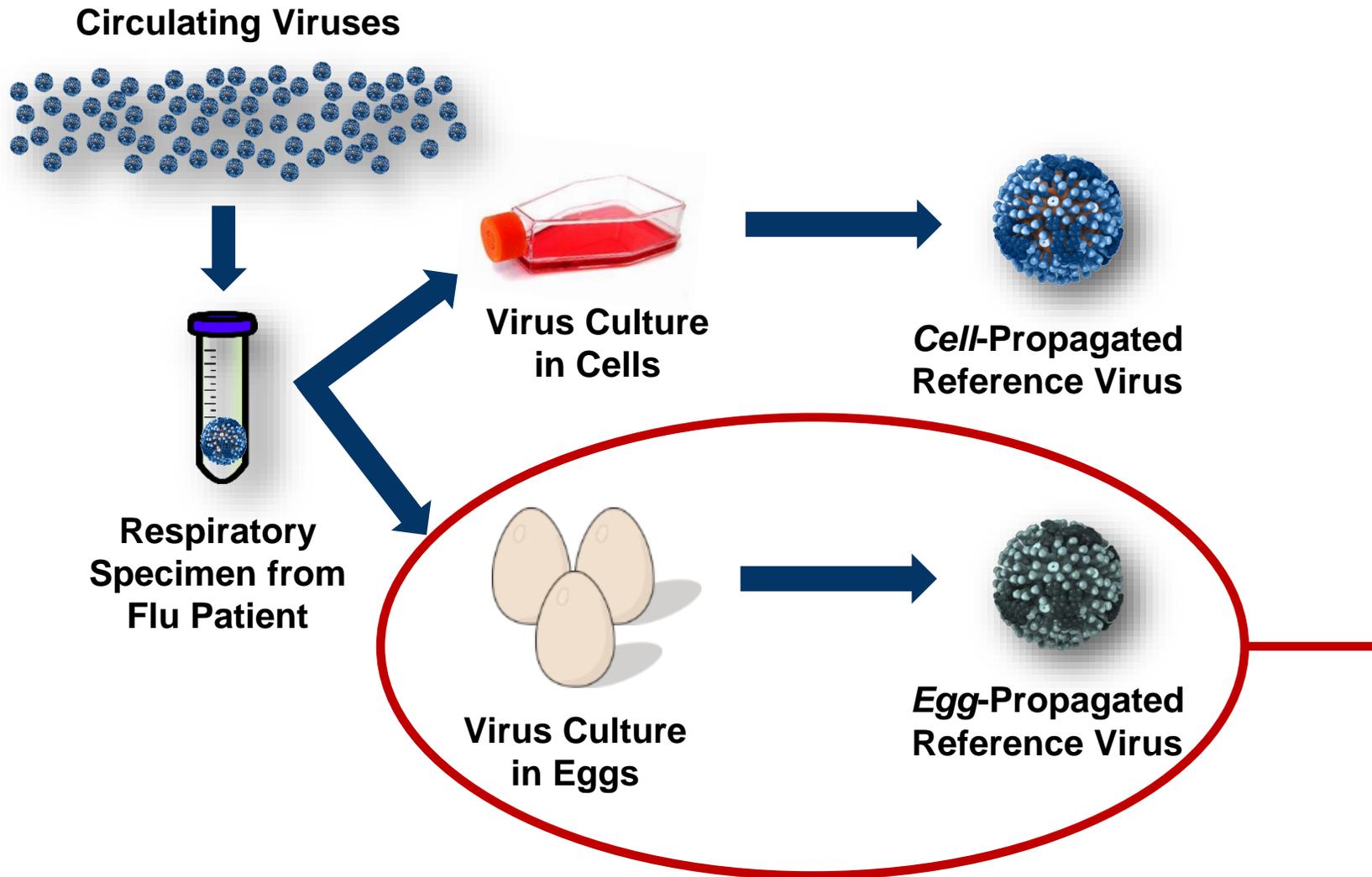


## ➤ Influenza Vaccines Made Without Eggs

- Cell-Based Manufacturing
  - ❑ CDC provides cell-propagated candidate vaccine viruses to the cell-based manufacturer
- Recombinant Protein Manufacturing
  - ❑ CDC provides gene segment sequences to manufacturer which then generates protein using insect cells

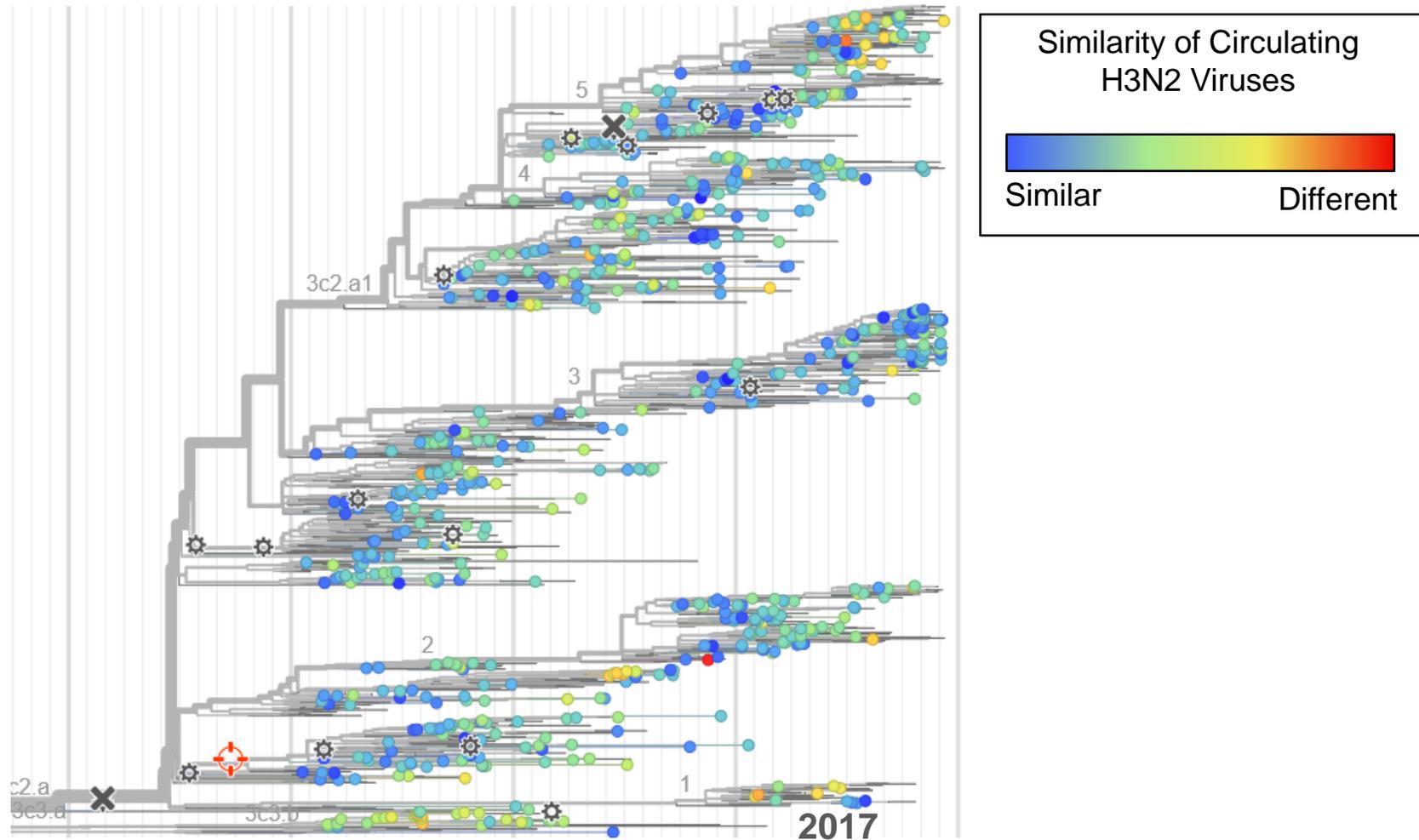


# H3N2 Virus Growth in Eggs Is Increasingly Challenging



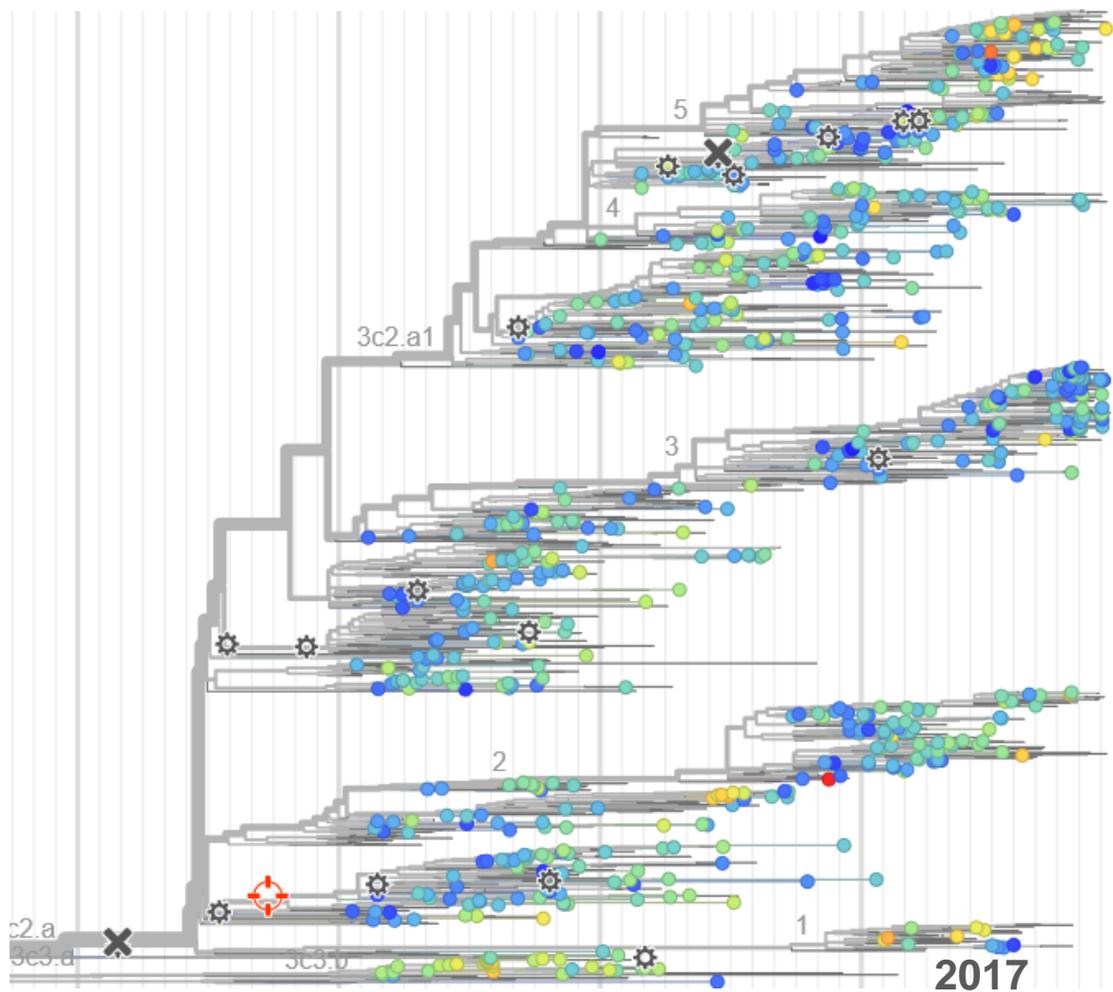
- **Poor Propagation:** H3N2 viruses are difficult to propagate in eggs.
- **Egg Propagation Can Change Antigenicity:** Contemporary H3N2 (3C.2a) viruses acquire changes on the hemagglutinin protein upon propagation in eggs and this can impact the antigenic properties.

# Cell-Propagated H3N2 Reference Viruses Show Limited Antigenic Drift Compared to Circulating H3N2 Viruses

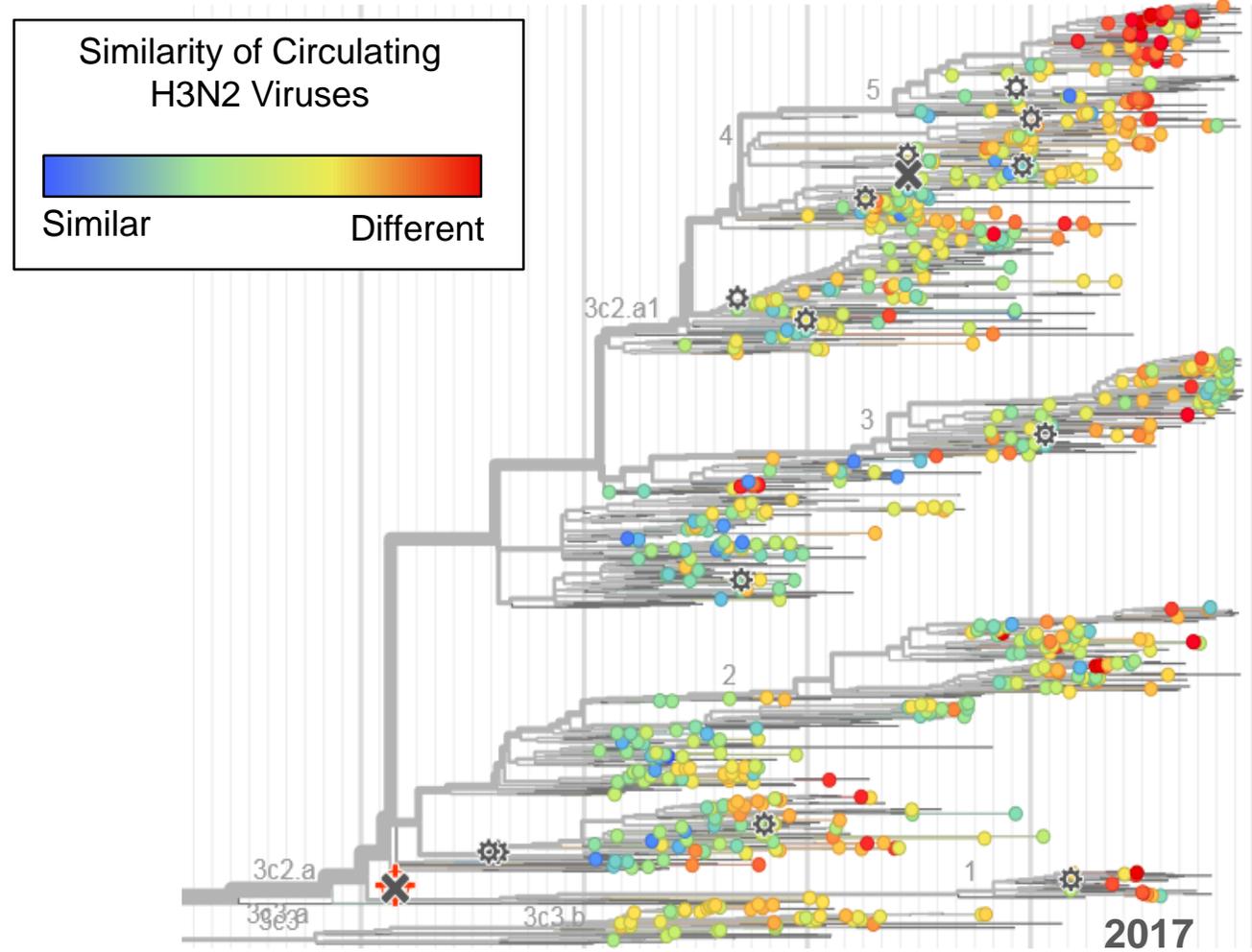


**Cell-Propagated H3N2 Reference Virus**

# Egg-Propagated H3N2 Reference Viruses Are Less Similar to Circulating H3N2 viruses Than Cell-Propagated



**Cell-Propagated H3N2 Reference Virus**



**Egg-Propagated H3N2 Reference Virus**

# H3N2 Summary

- **H3N2 viruses rapidly evolve and evade immunity generated from prior exposure and or vaccines**
  - Many divergent populations are co-circulating
  - H3N2 changes rapidly to adapt to selective pressures
- **Efforts are underway to overcome contemporary H3N2 vaccine challenges**
  - Improving virus strain selection
    - Increased use of Next-Generation sequencing and fitness forecasting
    - Development of new assays
  - Manufacturers employing new technologies
    - ❑ Cell-propagated vaccine viruses
    - ❑ Recombinant protein vaccines

# Mitigating Influenza with Vaccines and Antivirals



**Alicia Fry, MD, MPH**

*Chief, Epidemiology and Prevention Branch*  
Influenza Division

National Center for Immunization and Respiratory Diseases



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Health and Human Services**  
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Control and Prevention

# Influenza Vaccination

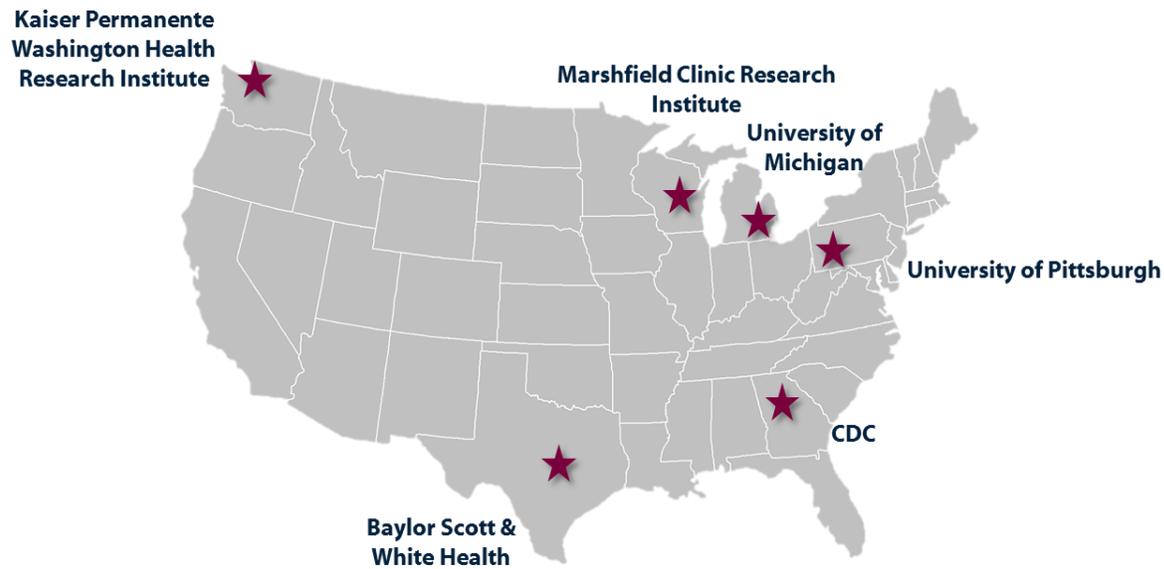
- Influenza vaccination is recommended for all persons aged 6 months and older *each year*
- The 2017-18 influenza vaccine contains a similar H3N2 virus as last season, only the H1N1 virus was updated

## 2017-18 Influenza vaccine composition:

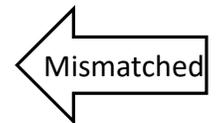
- A/Michigan/45/2015 (H1N1)pdm09-like virus (updated);
  - A/Hong Kong/4801/2014 (H3N2)-like virus (same)
    - B/Brisbane/60/2008-like virus (same)
- B/Phuket/3073/2013-like virus (same, only in quadravalent)

# We monitor influenza Vaccine Effectiveness (VE) every year with the US Flu VE Network

## US Flu VE Network\*

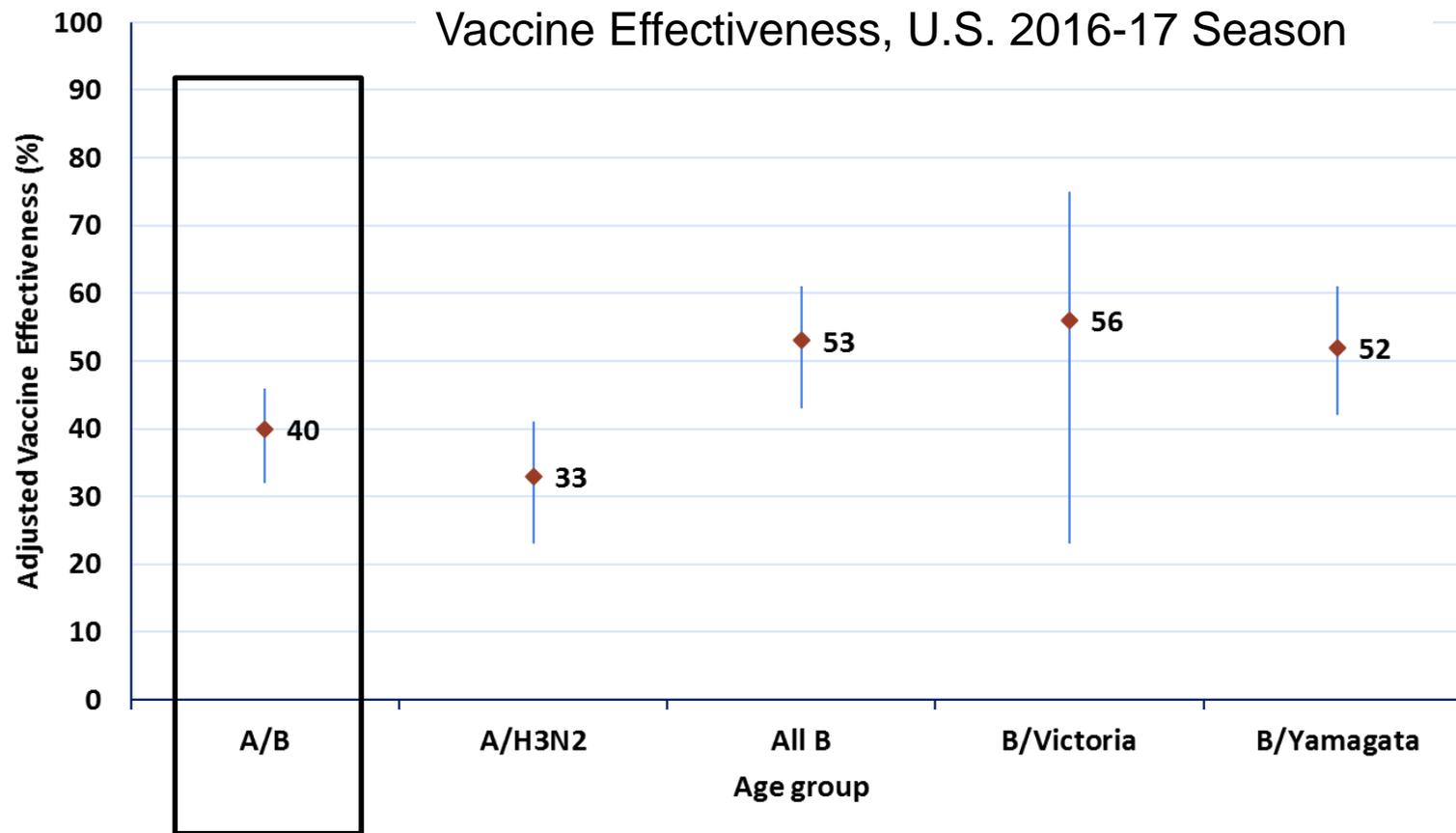


Season	VE against A/B influenza viruses (95% CI)
2010-11	60% (53, 66)
2011-12	47% (36,56)
2012-13	49% (43, 55)
2013-14	52% (44,59)
2014-15	19% (10,27)
2015-16	48% (41, 55)
2016-17	40% (32, 46)

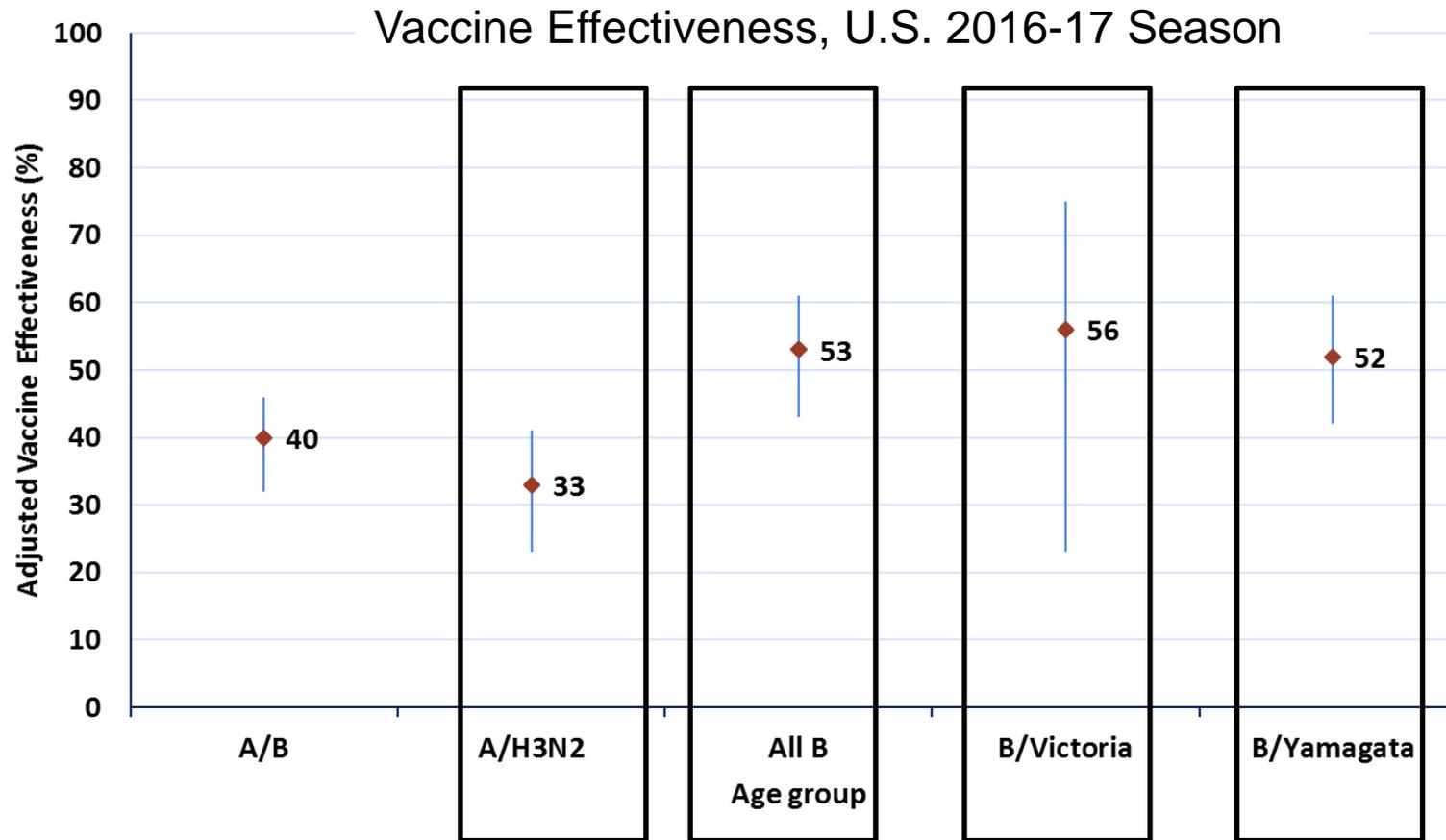


\*Enrolls outpatients aged  $\geq 6$  months old with acute respiratory illness from 66 clinics. Uses a test-negative case-control design where PCR positive flu = case and PCR negatives = control

# Last Season (2016-17), Vaccination Reduced Influenza-Associated Outpatient Visits by 40%



# Vaccine Effectiveness Varied By Vaccine Component Last Season

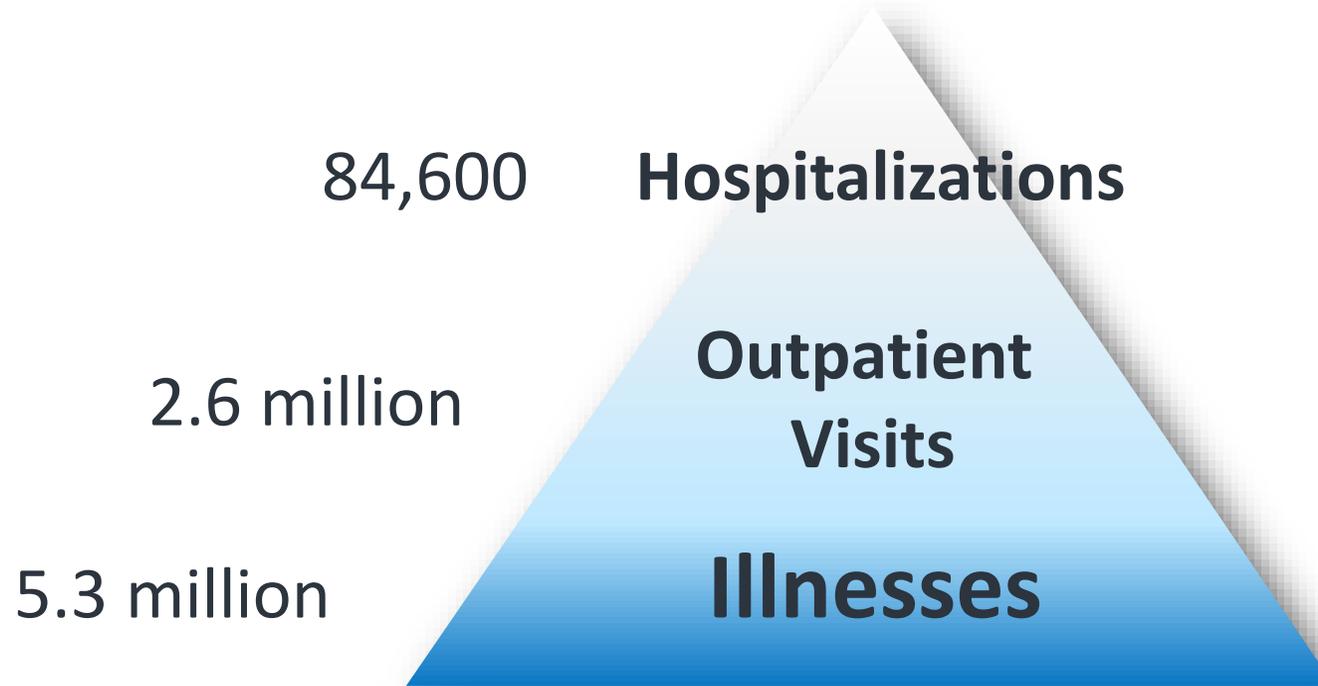


# In recent years, the H3N2 vaccine component has not worked as well as H1N1 or B vaccine components

- **Meta-analysis of observational VE studies conducted in ambulatory care settings, 2004-2015**
  - Pooled VE against influenza B viruses was 54%
  - Pooled VE against influenza A(H1N1)pdm09 viruses was 61%
  - Pooled VE against H3N2 viruses was 33%

# Current influenza vaccines reduce the burden of illnesses in the US

➤ In 2016-17, vaccination provided substantial prevention:



Modeled using estimates of disease burden, vaccine coverage and effectiveness, based on Reed et al <https://www.cdc.gov/flu/about/disease/2015-16.htm>

# Our second line of defense after vaccination: antiviral medications for treatment of influenza

## ➤ 3 FDA-approved neuraminidase inhibitors\* (NAIs) are recommended

- Oral oseltamivir (Tamiflu® or generic formulation)
  - Approved for treatment age  $\geq 14$  days (*recommended for all ages*)
- Inhaled zanamivir (Relenza®)
  - Approved for treatment age  $\geq 7$  years
- Intravenous peramivir (Rapivab®)
  - Approved for treatment age  $\geq 2$  years



\*Only medications active against circulating influenza viruses. Not effective against other viruses.

# Evidence for neuraminidase inhibitors (NAI) efficacy

- **Randomized placebo-controlled clinical trials (RCTs) in outpatients with lab-confirmed influenza:**
  - Early treatment (within 2 days of illness onset) shortened duration of fever and illness symptoms by ~1 day
- **No placebo controlled clinical trials for *prevention of severe outcomes***

# Evidence for NAI effectiveness against severe outcomes from meta-analyses and observational studies

- **Evidence from meta-analyses of RCTs in outpatients and observational studies in hospitalized and outpatients demonstrate that early treatment reduces severe illness**

**Outpatients with lab-confirmed influenza:** Reduction in subsequent otitis media (34%) in children, and lower respiratory tract illnesses requiring antibiotics (37-44%) and hospitalizations (63%) in adults, and reduction of hospitalizations (75%) in high risk persons (all ages)

**Hospitalized patients:** Reduction in mortality in adults (50%) and shortened length of PICU stay (18%) and post admission mechanical ventilation (34-77%) in children

# CDC Antiviral Guidance focuses on severe illness

- **Antiviral treatment is recommended as early as possible for any patient with suspected or confirmed influenza who is:**
  - Hospitalized
  - Has severe, complicated, or progressive illness
  - Is at high risk for influenza complications
- **Antiviral treatment can be considered for any previously healthy, symptomatic outpatient not at high risk with confirmed or suspected influenza on the basis of clinical judgment**
  - If treatment can be initiated within 48 hours of illness onset

# Persons at High Risk for Influenza Complications

- Children <2 years
- Adults  $\geq 65$  years
- Pregnant and postpartum women
- Persons with immunosuppression
- Persons with underlying medical conditions: chronic pulmonary, cardiovascular, renal, hepatic, hematologic, and metabolic disorders (i.e., diabetes), or neurologic/neurodevelopment conditions, morbid obesity
- American Indians and Alaska Natives
- Persons <19 years who are receiving long-term aspirin therapy



# Antiviral Supply This Season

- **There is adequate national supply to meet the high demands from this season**
- **Spot shortages have been reported in areas with high influenza activity**
  - We are working with manufacturers to address existing gaps
    - CDC has a webpage on antiviral drug supply with manufacturer information for inquiries related to antiviral purchases/availability.
- **Consider advising patients seeking to fill prescriptions to call ahead to make sure their pharmacy has the medication (may need to call more than one)**
  - Antiviral drugs work better the earlier you begin taking them so prompt action is important.**

# Summary

- **Annual influenza vaccination is the best way to protect against influenza - as long as influenza viruses are circulating CDC recommends vaccination**
  - A substantial burden of illnesses are averted with current vaccines
- **Influenza antivirals are an important second line of defense, especially for patients with severe illness and those at increased risk for severe disease**

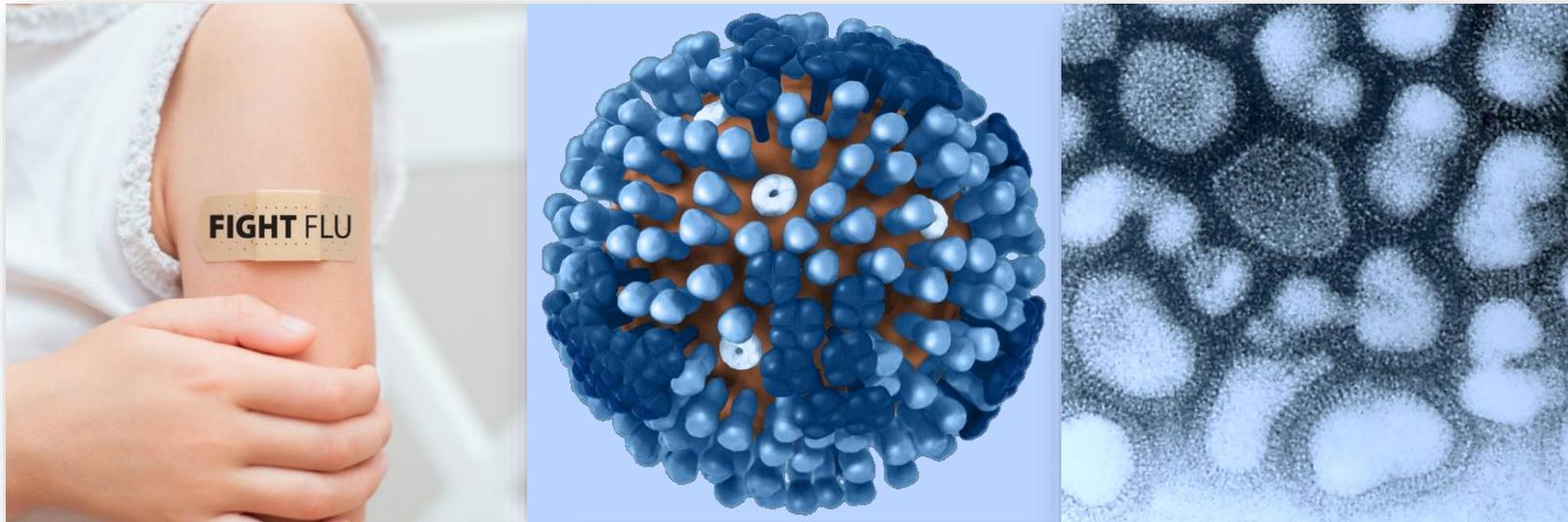
# Conclusions

- Influenza is affecting most of the country
- Peak activity may be occurring now, but influenza will circulate for many more weeks
- Urge your friends, family, and patients to get vaccinated if they have not done so yet
- Think flu - treat hospitalized patients and high risk outpatients with influenza antivirals as soon as possible



# CDC PUBLIC HEALTH GRAND ROUNDS

## Public Health Response to Severe Seasonal Influenza



January 16, 2018



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