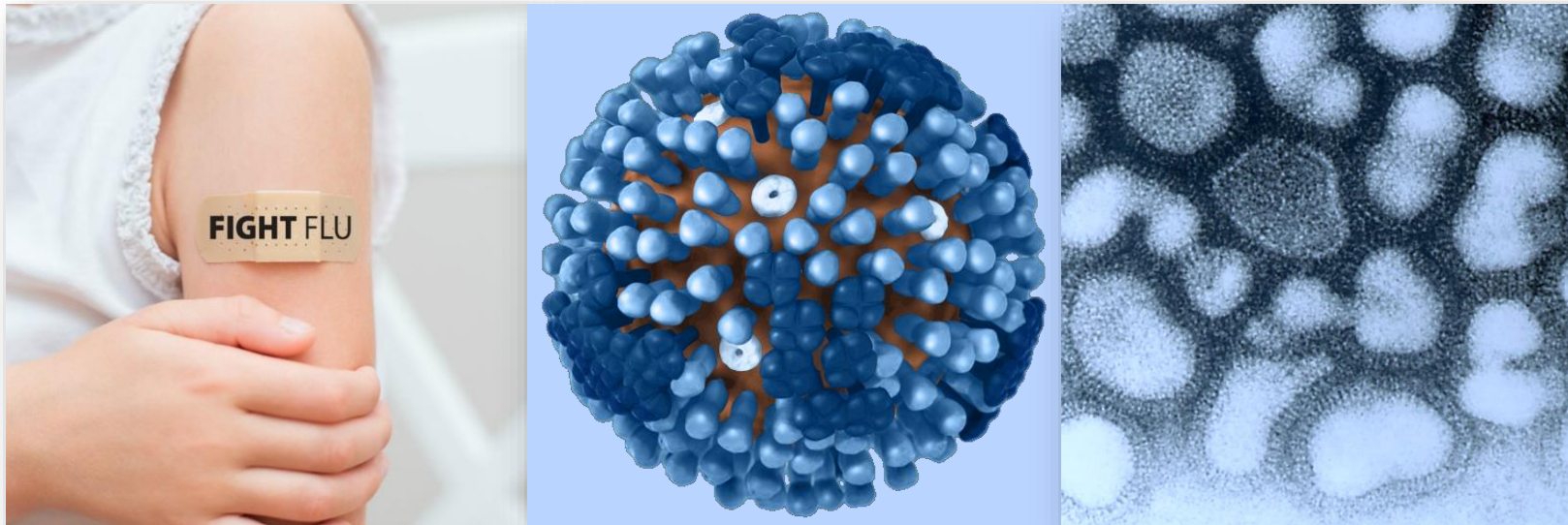


CDC PUBLIC HEALTH GRAND ROUNDS

Public Health Response to Severe Seasonal Influenza



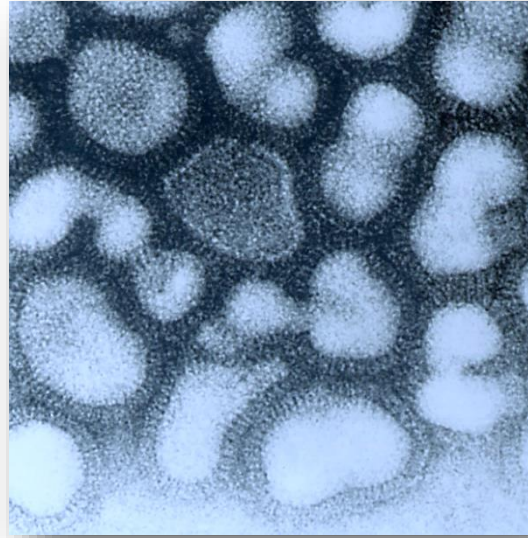
A 508 compliant video is available at:
<https://youtu.be/azcMZCCr7E>

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



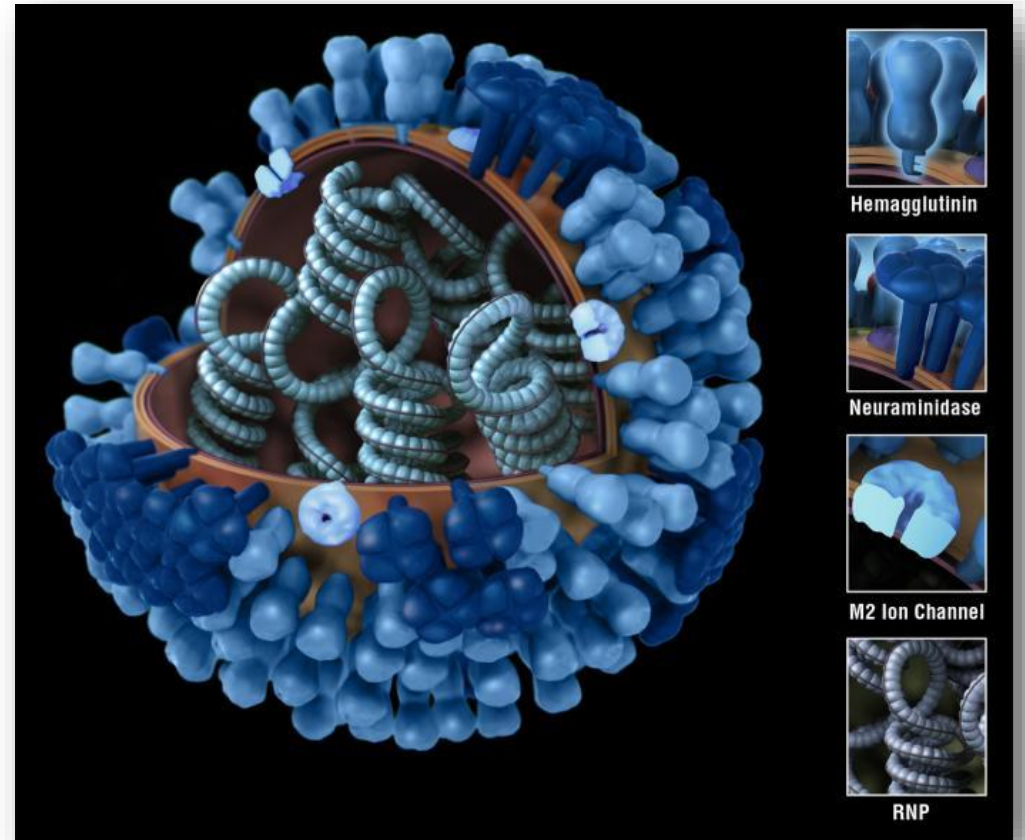
Influenza Virus

➤ 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



12,000 – 56,000

140,000 – 710,000

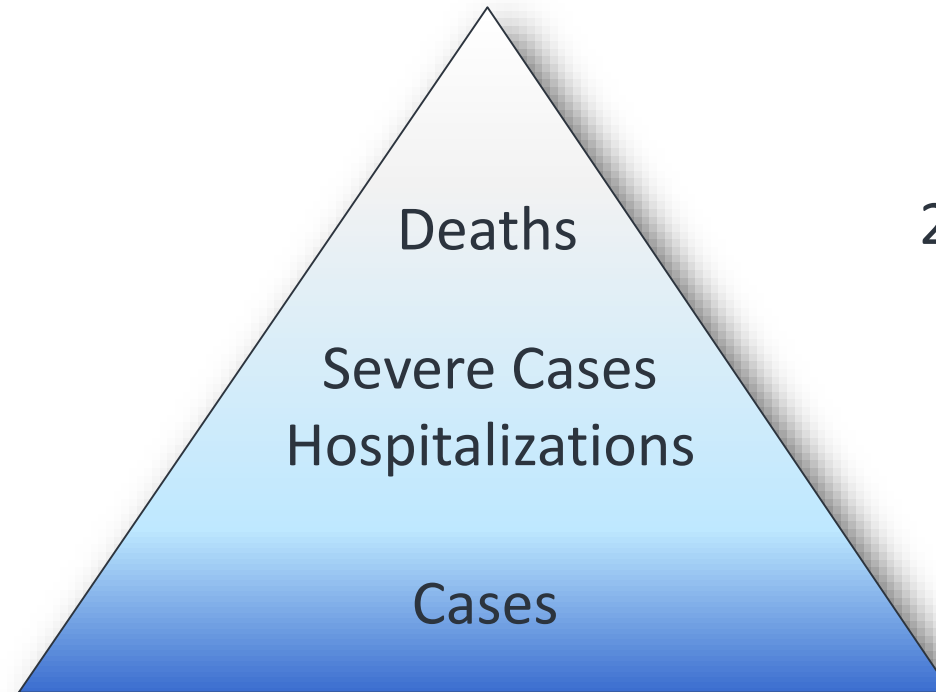
9.2M – 35.6M



291,000 – 646,000

3M to 5M

1.0 B

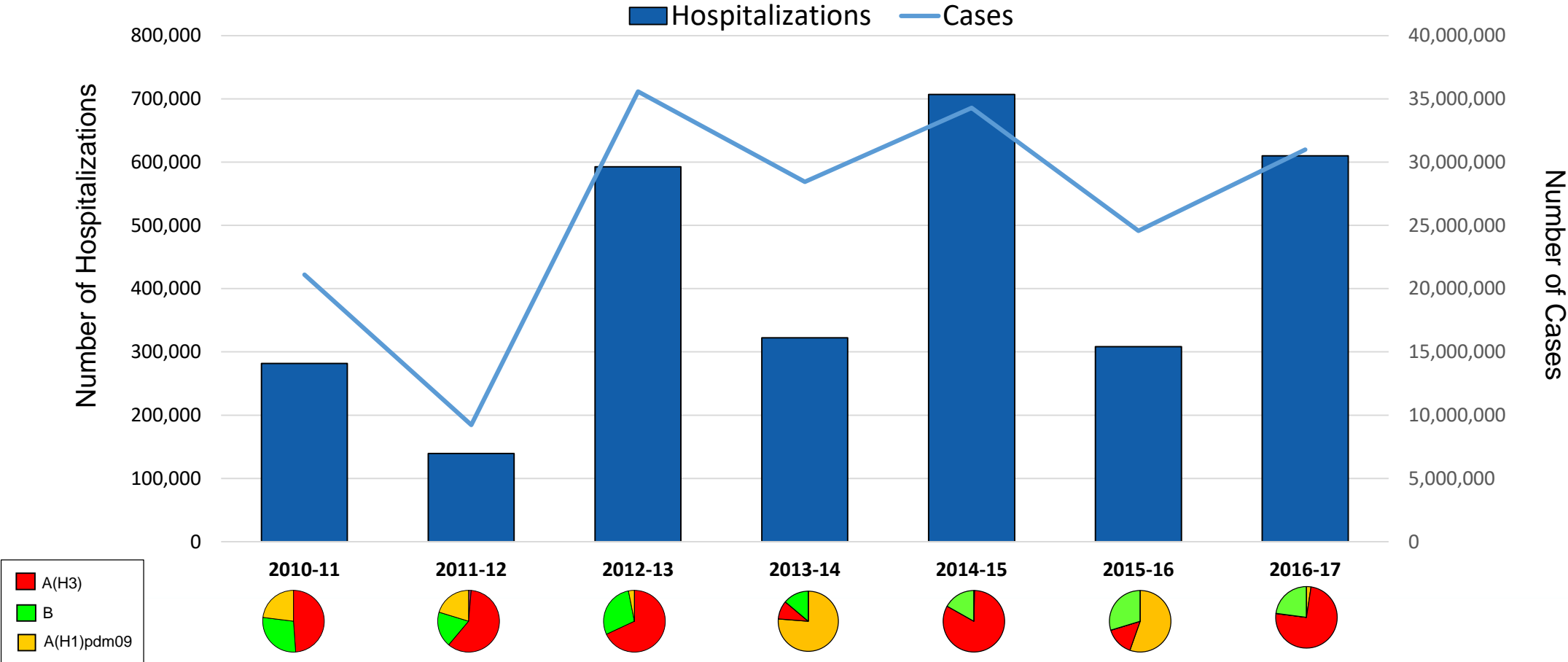


Direct Medical Costs: \$10.4 B per year

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-!

By Jamie Leary

WELD COUNTY, Colo. (CBS4)- The Centers for Disease Control says influenza is now widespread in every state except Hawaii.

COLD AND FLU - January 7th

Severe flu in California brings medicine shortages, kills 27



HOSPITALS SWAMPED WITH FLU CASES

AMERICA'S NEWS HQ

ted early and is spreading fast

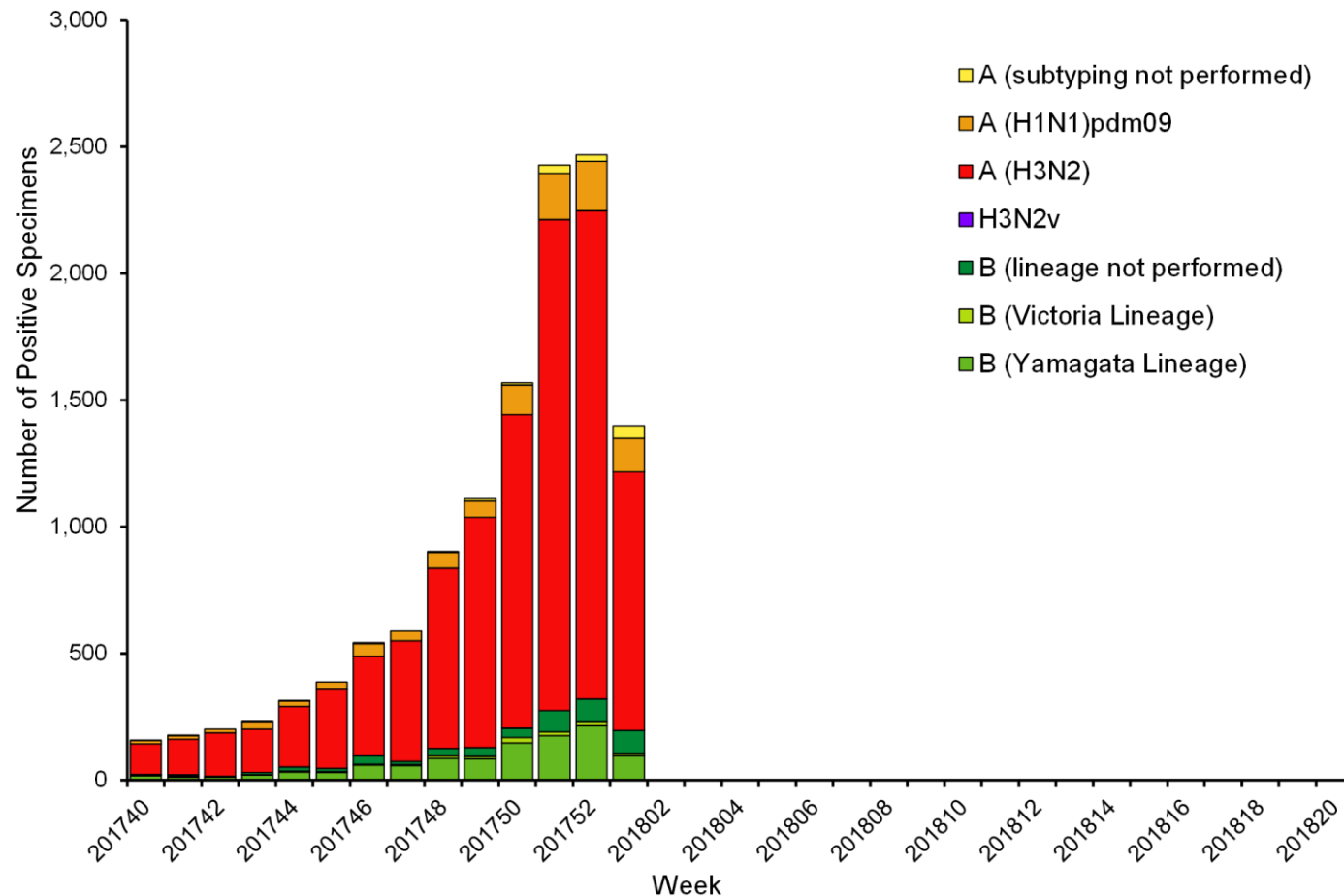
Public Health Surveillance for Influenza in the U.S.

➤ **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%

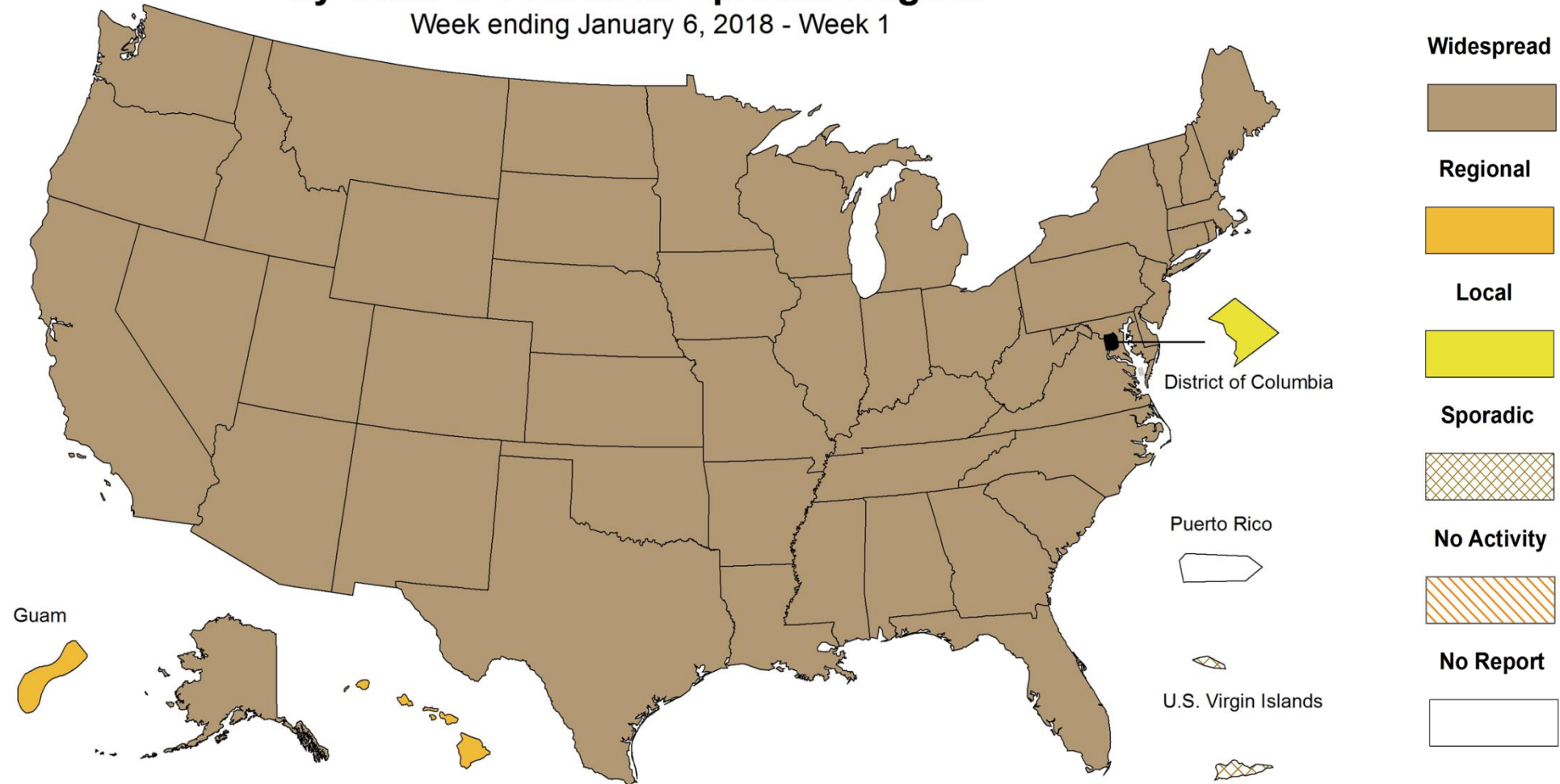
➤ **H1N1 and B continue to increase**

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

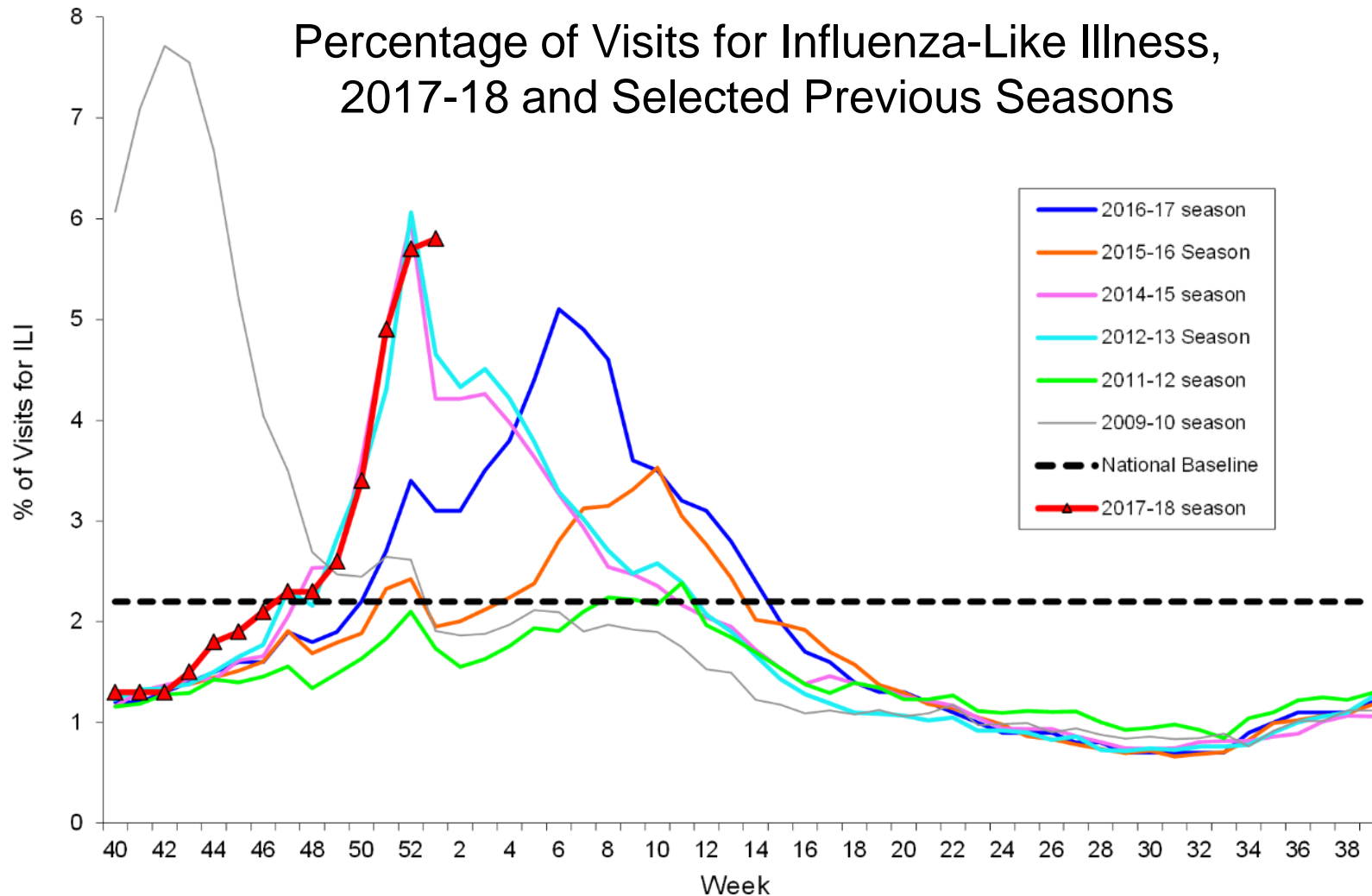
Influenza Is Widespread in 49 States

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

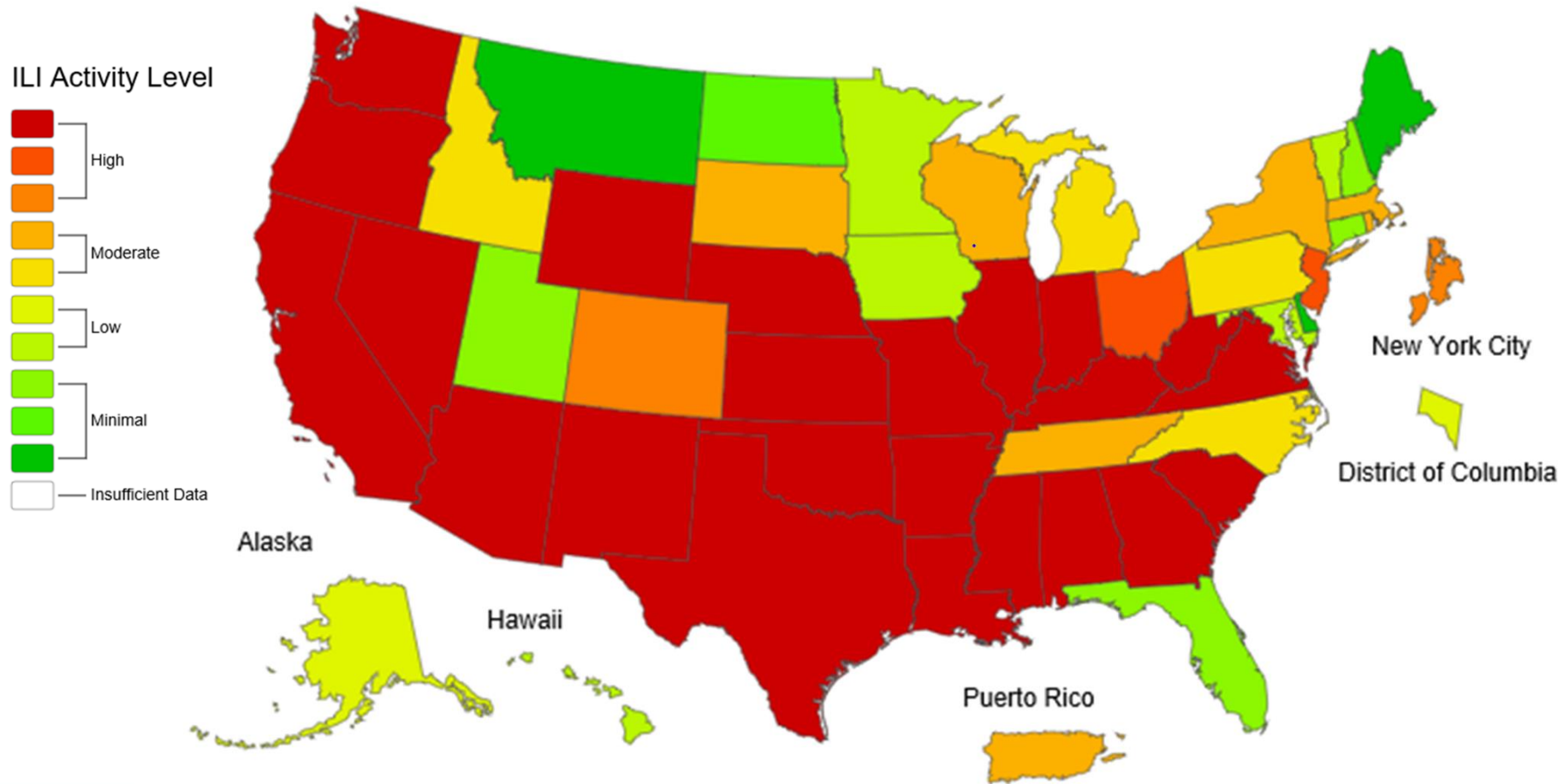


➤ 339,598 visits for ILI reported this season

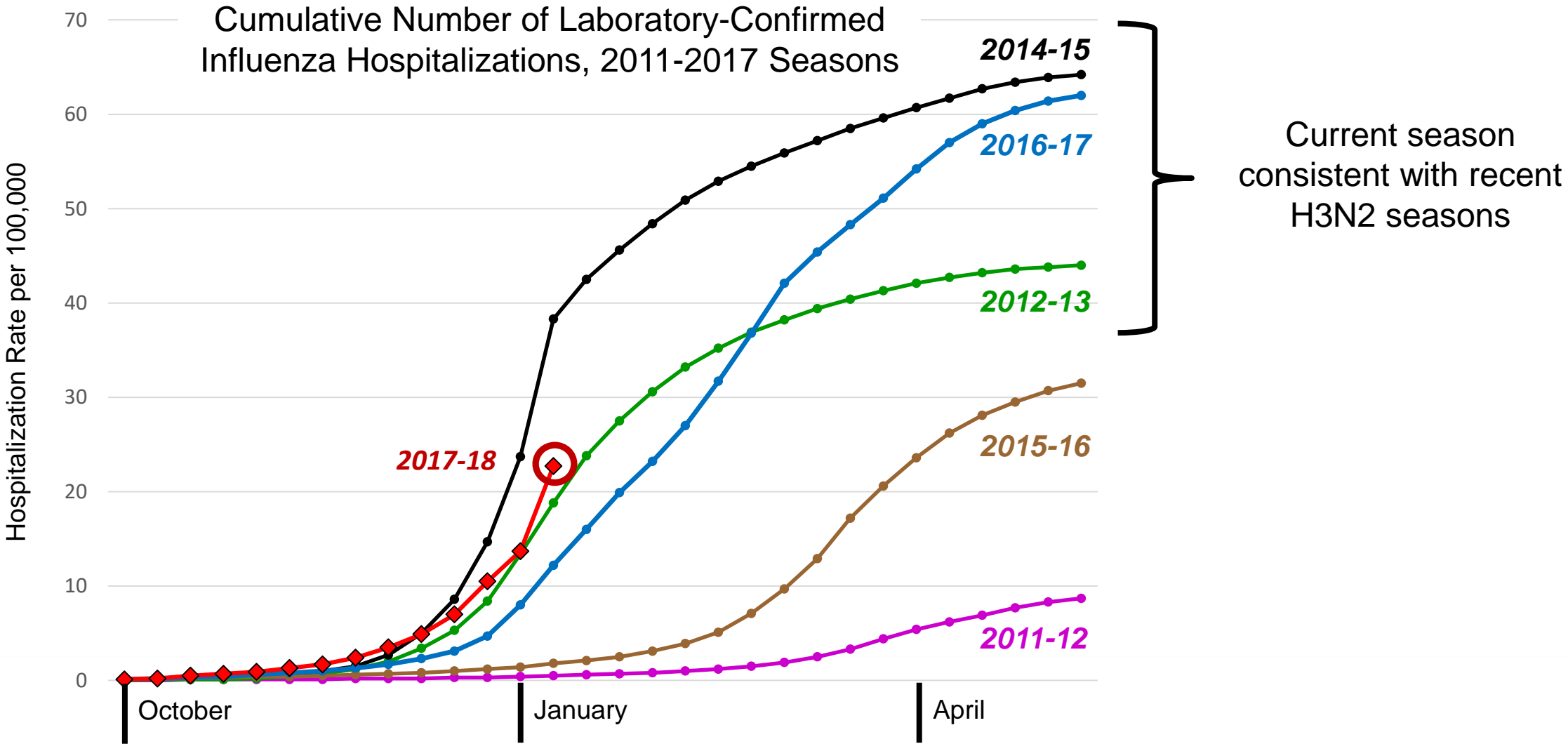
➤ Current season tracking closely to past H3N2 seasons:

- 2014-15
- 2012-13

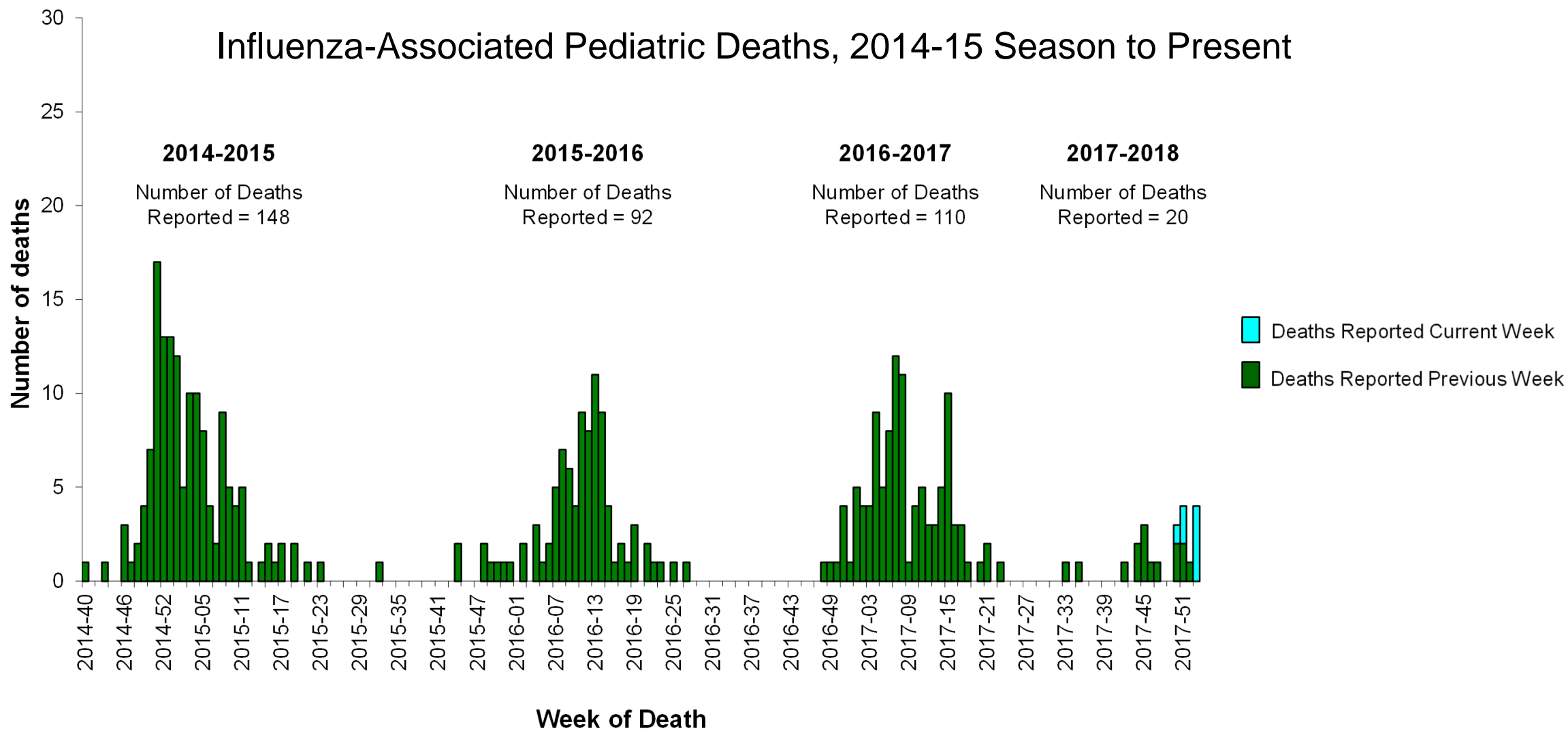
Highest Influenza-Like Illness reported in South and West



Hospitalizations Tracking with Recent H3N2 Seasons



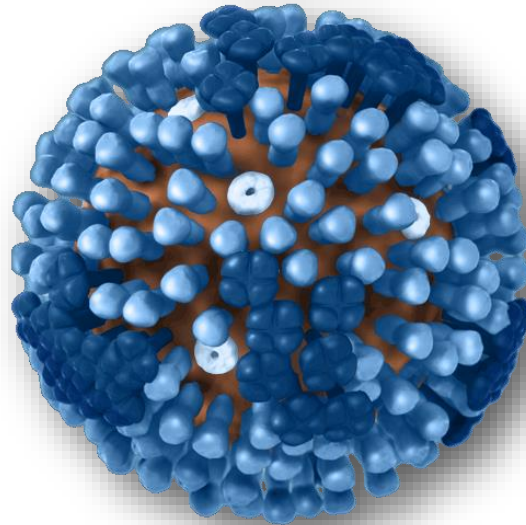
Twenty Influenza-Associated Pediatric Deaths Reported



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



**U.S. Department of
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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

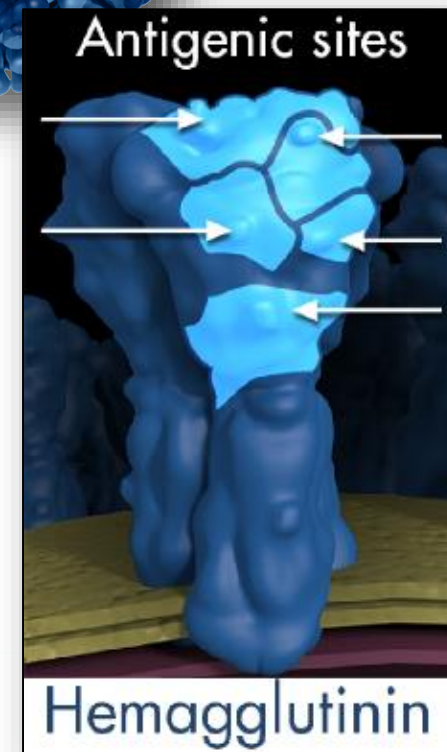
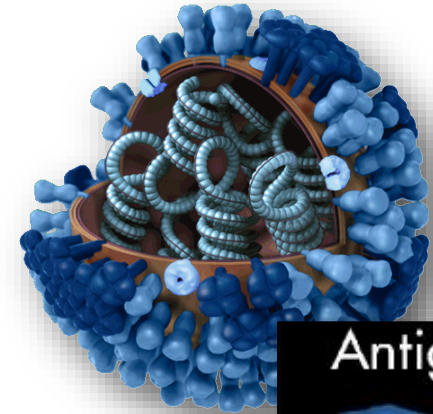
- Segmented genome (enables reassortment)
- CDC uses next-generation sequencing of influenza genome
- Detects all variation – only some are significant changes

➤ 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

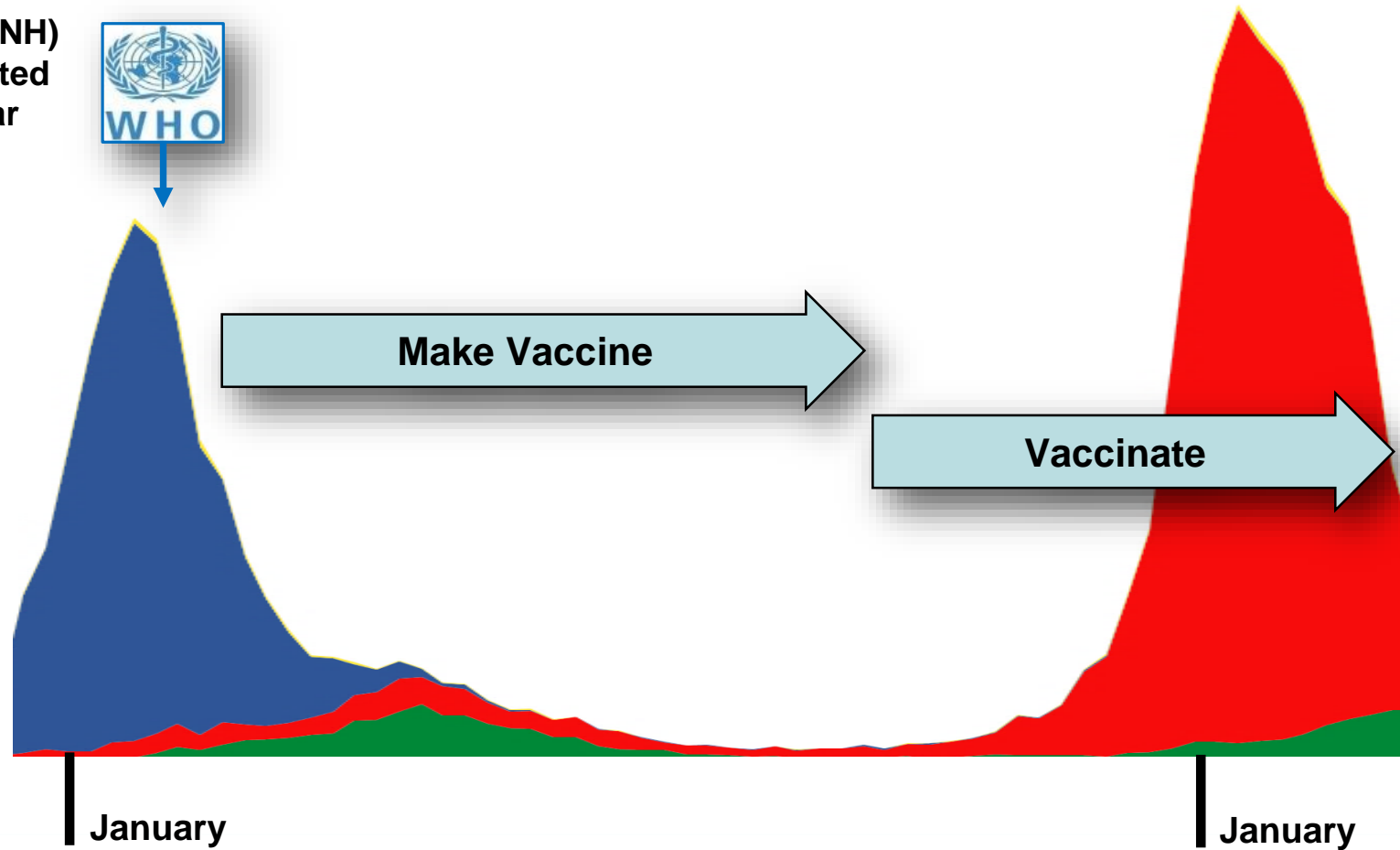


Vaccine Viruses Need to be Selected Six Months in Advance

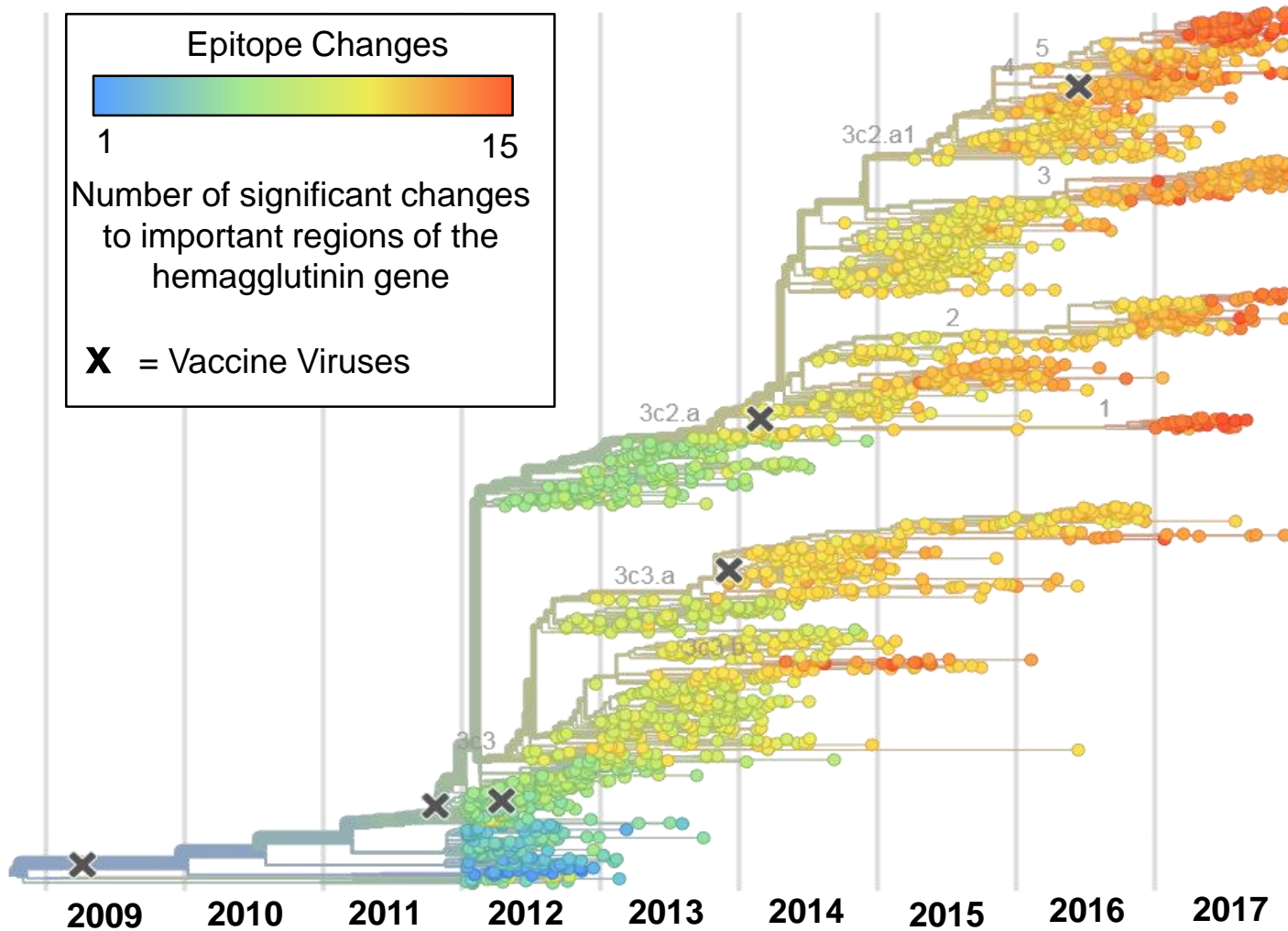
Northern Hemisphere (NH)
Vaccine Viruses Selected
in February each year



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

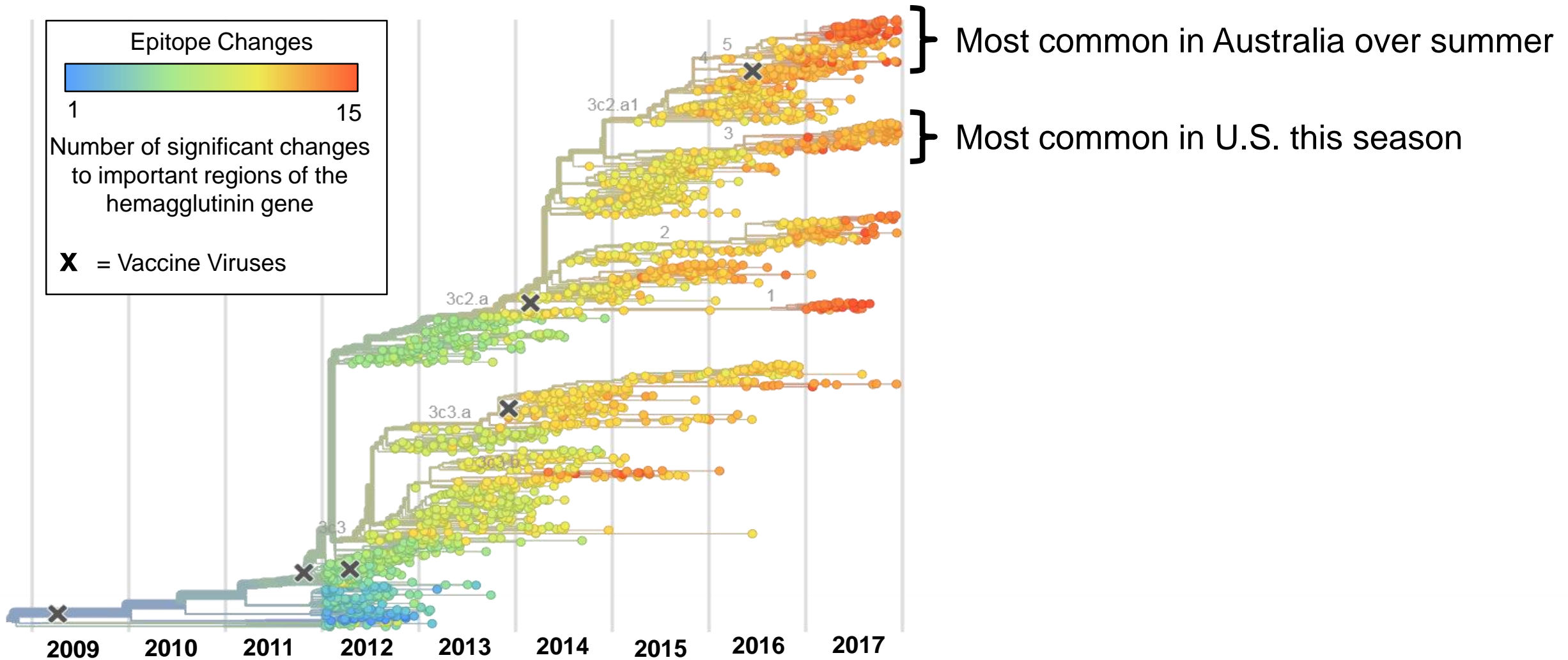


Improved Genetic Characterization Shows Rapid Evolution and Diversity of H3N2

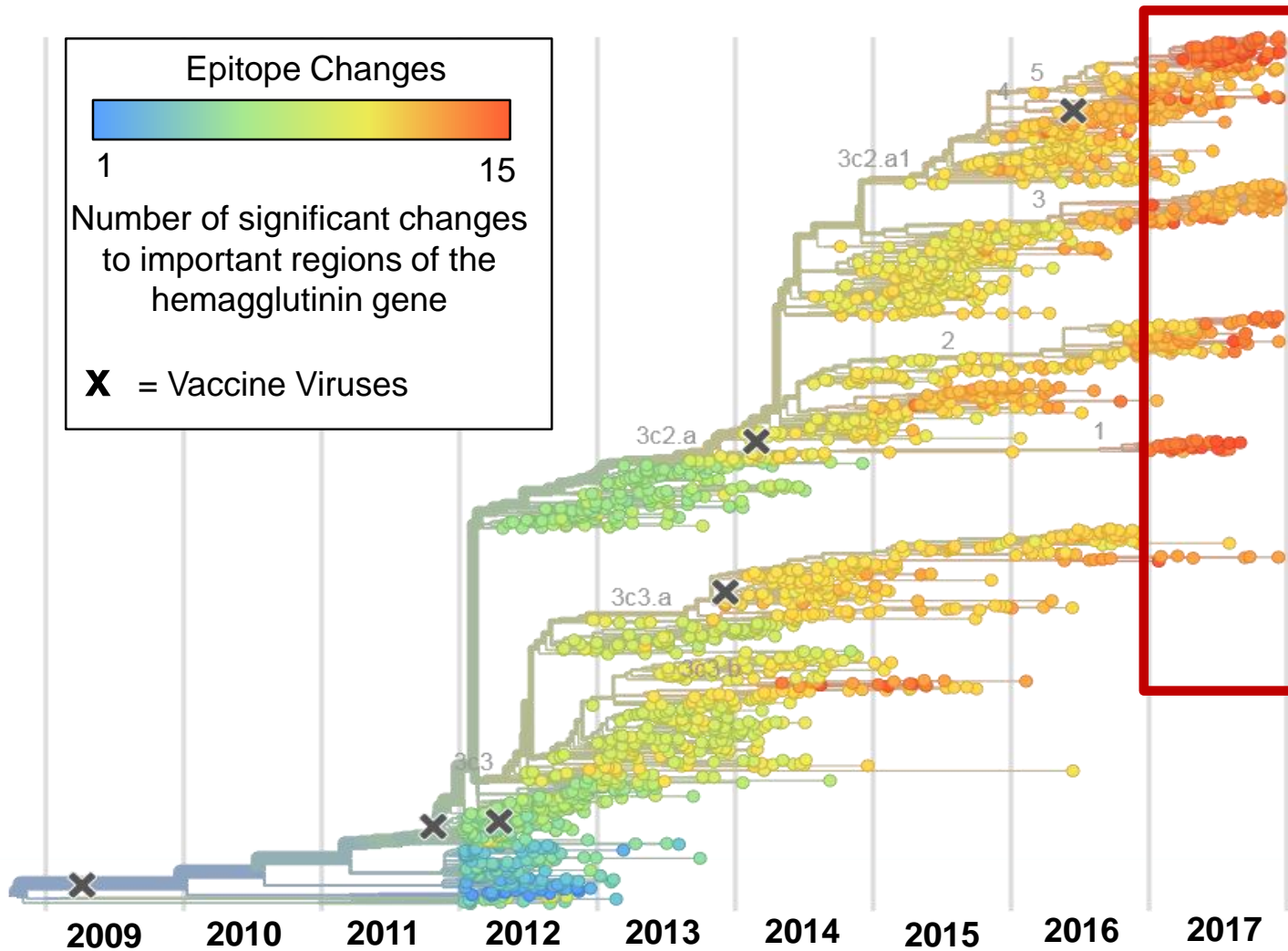


- H3N2 Viruses Evolve More Rapidly than Other Influenza Viruses
- H3N2 has required twice the number of vaccine viruses changes than H1N1
- CDC surveillance shows several H3N2 genetic groups co-circulating this season

Improved Genetic Characterization Shows Rapid Evolution and Diversity of H3N2

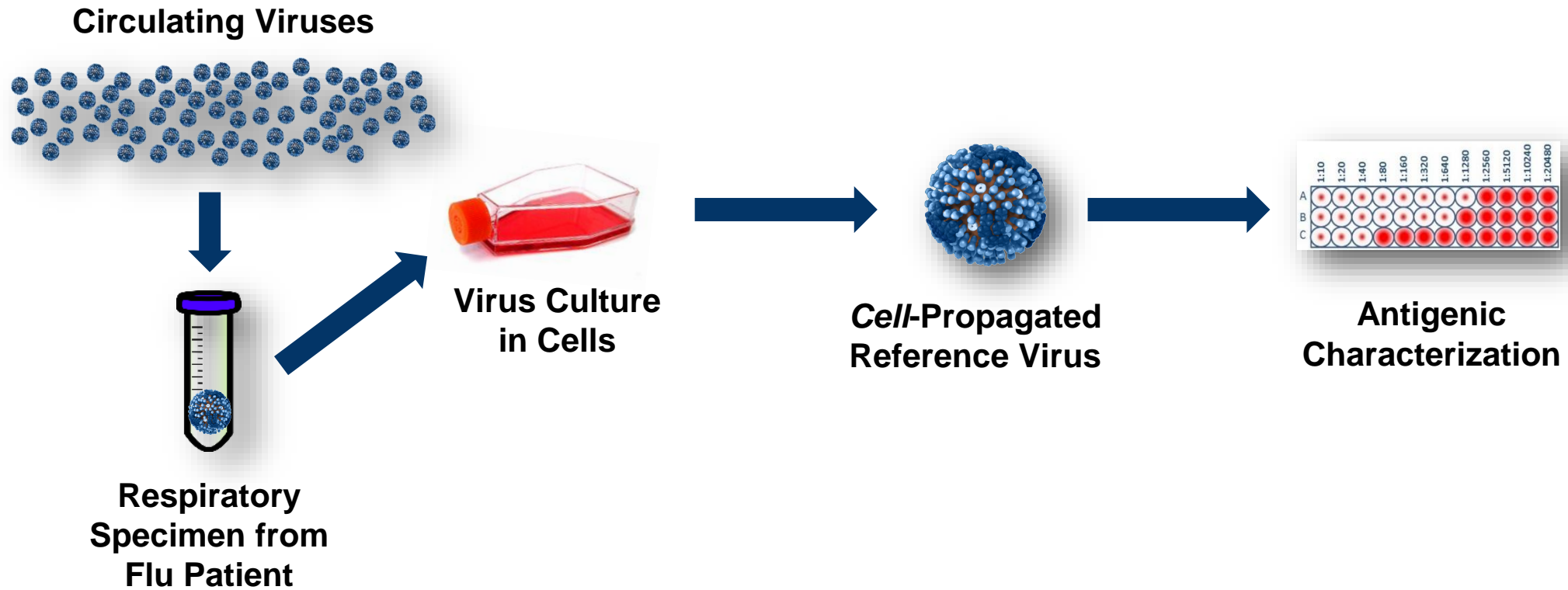


Improved Genetic Characterization Shows Rapid Evolution and Diversity of H3N2

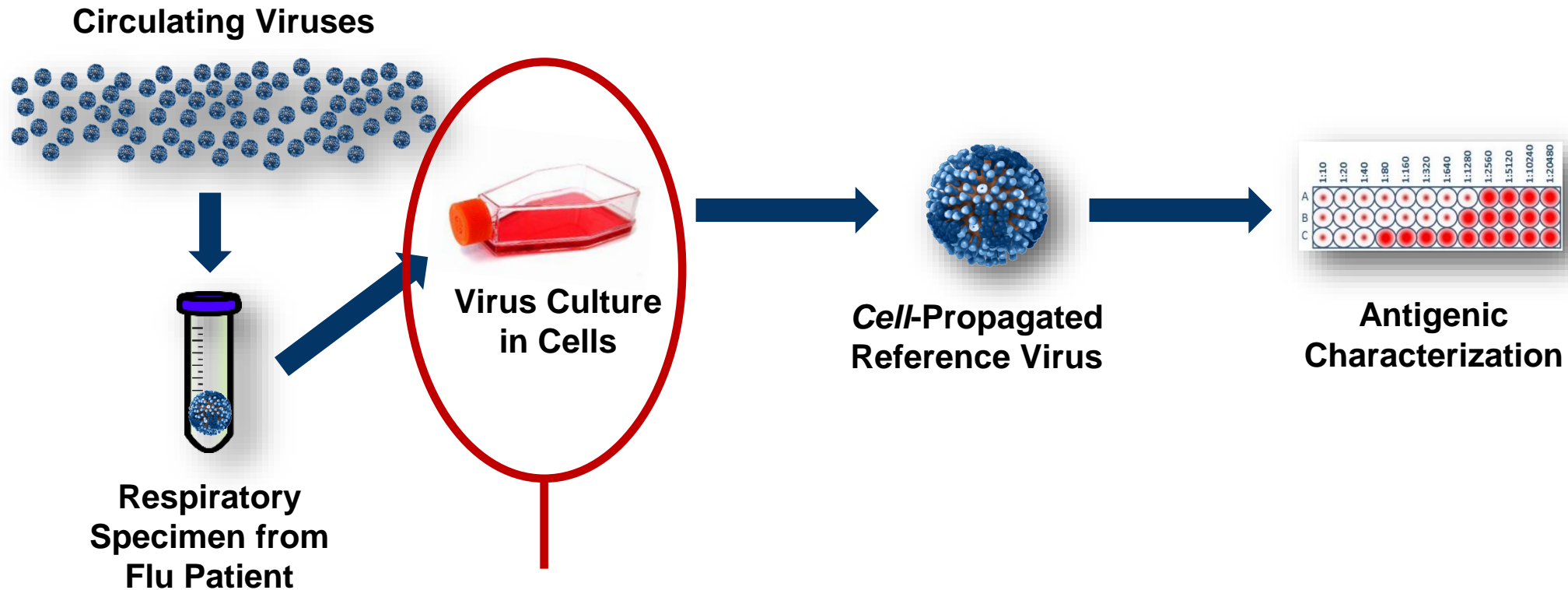


- 97% of circulating H3N2 viruses are similar to the cell-propagated H3N2 reference viruses representing the virus used in the vaccine this season in the U.S.

Antigenic Characterization of H3N2 Viruses is Increasingly Difficult

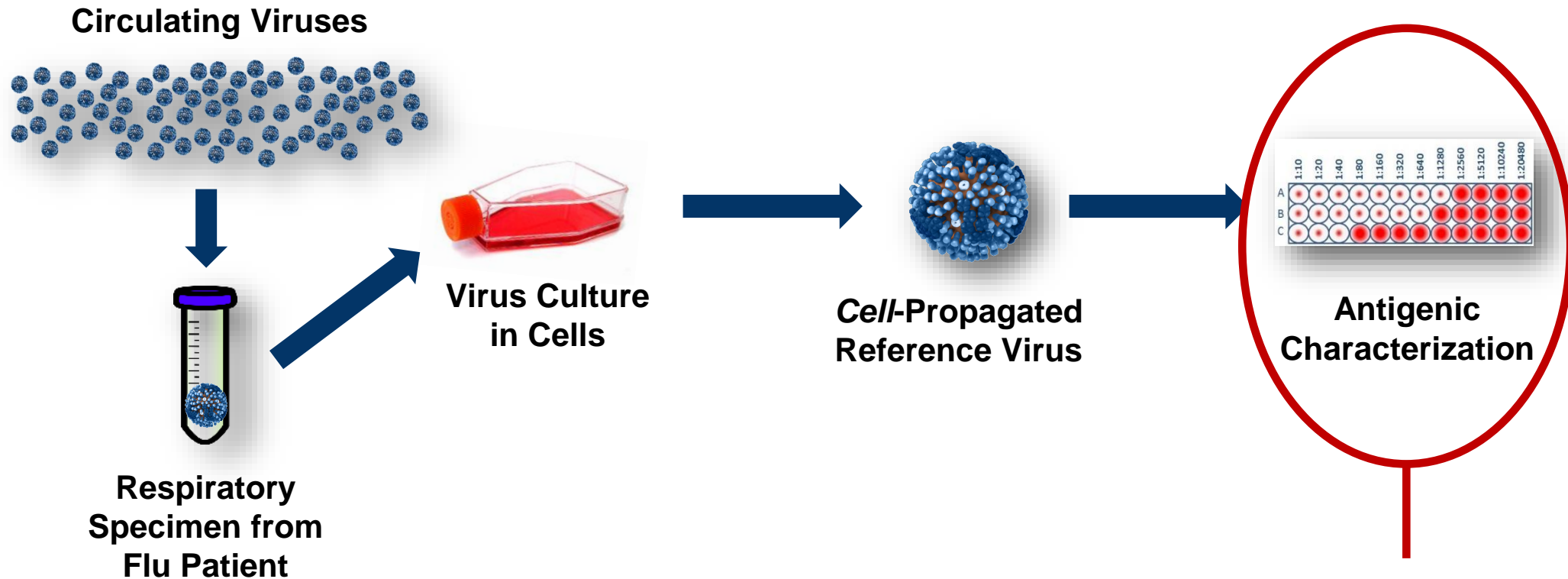


Antigenic Characterization of H3N2 Viruses is Increasingly Difficult



New methods required for propagating H3N2 viruses in cell culture

Antigenic Characterization of H3N2 Viruses is Increasingly Difficult



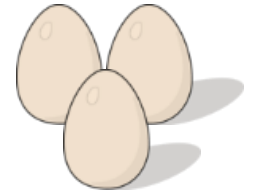
Recent H3N2 viruses require additional and new tests

- 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

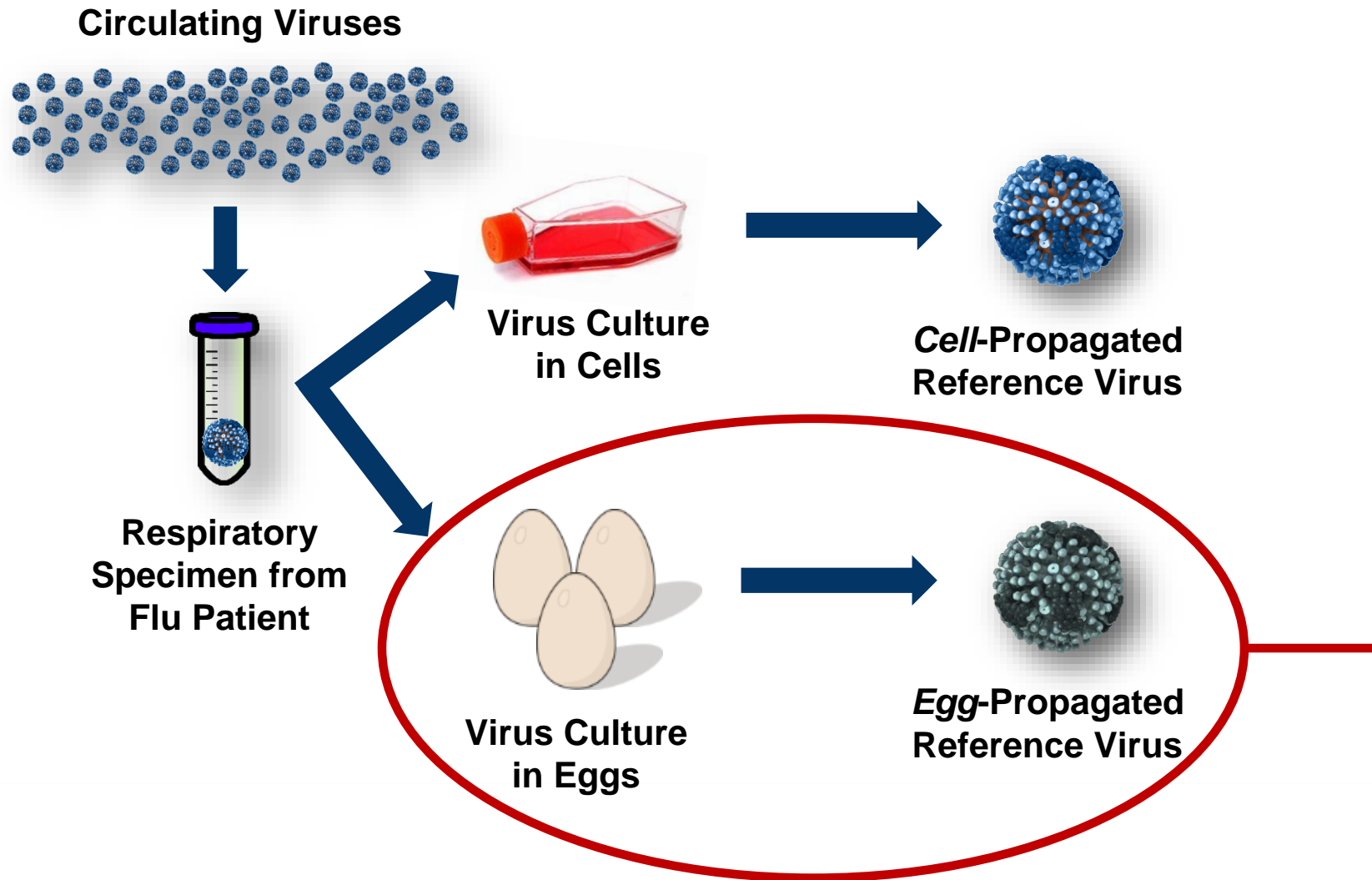


➤ Influenza Vaccines Made Without Eggs

- 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

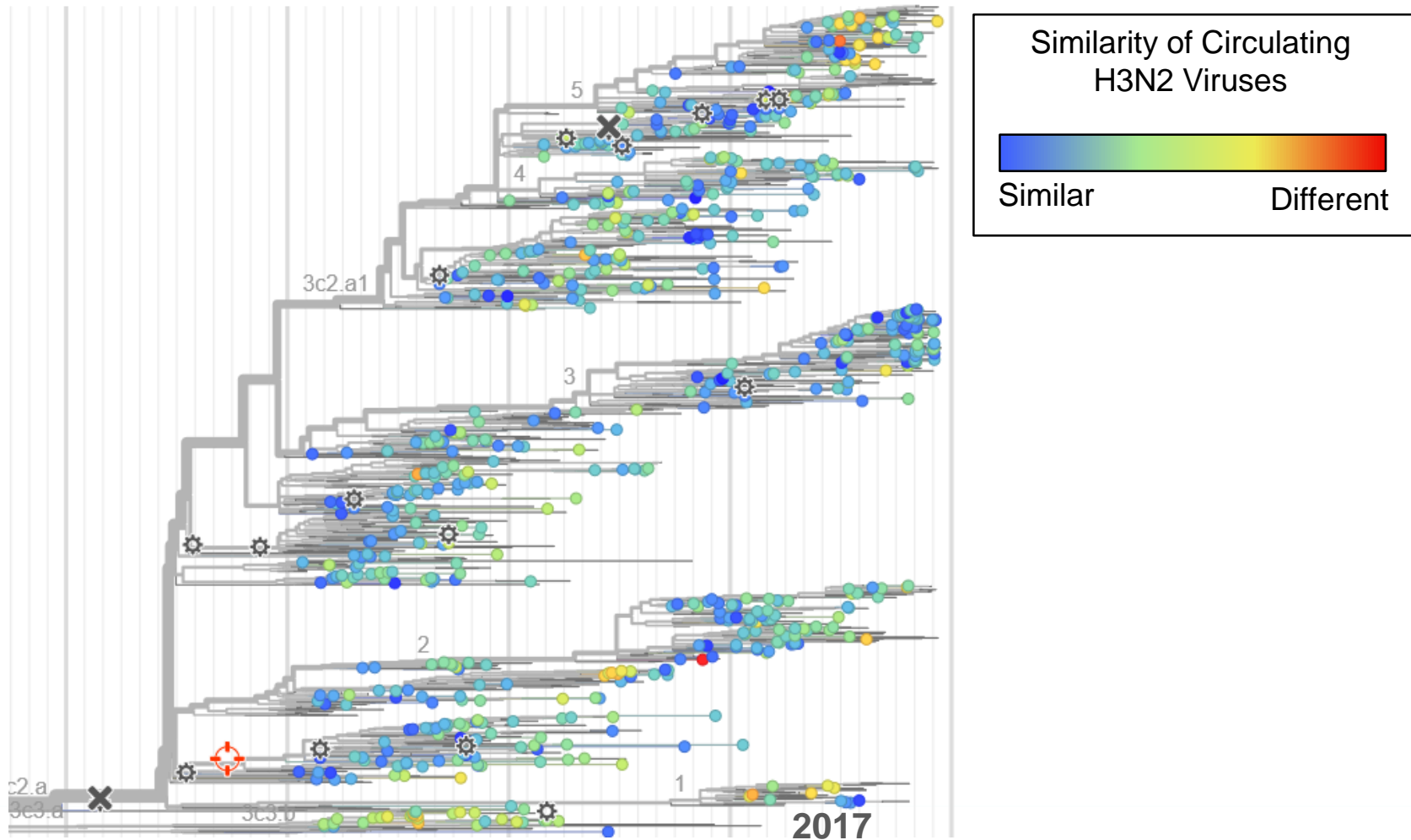


H3N2 Virus Growth in Eggs Is Increasingly Challenging



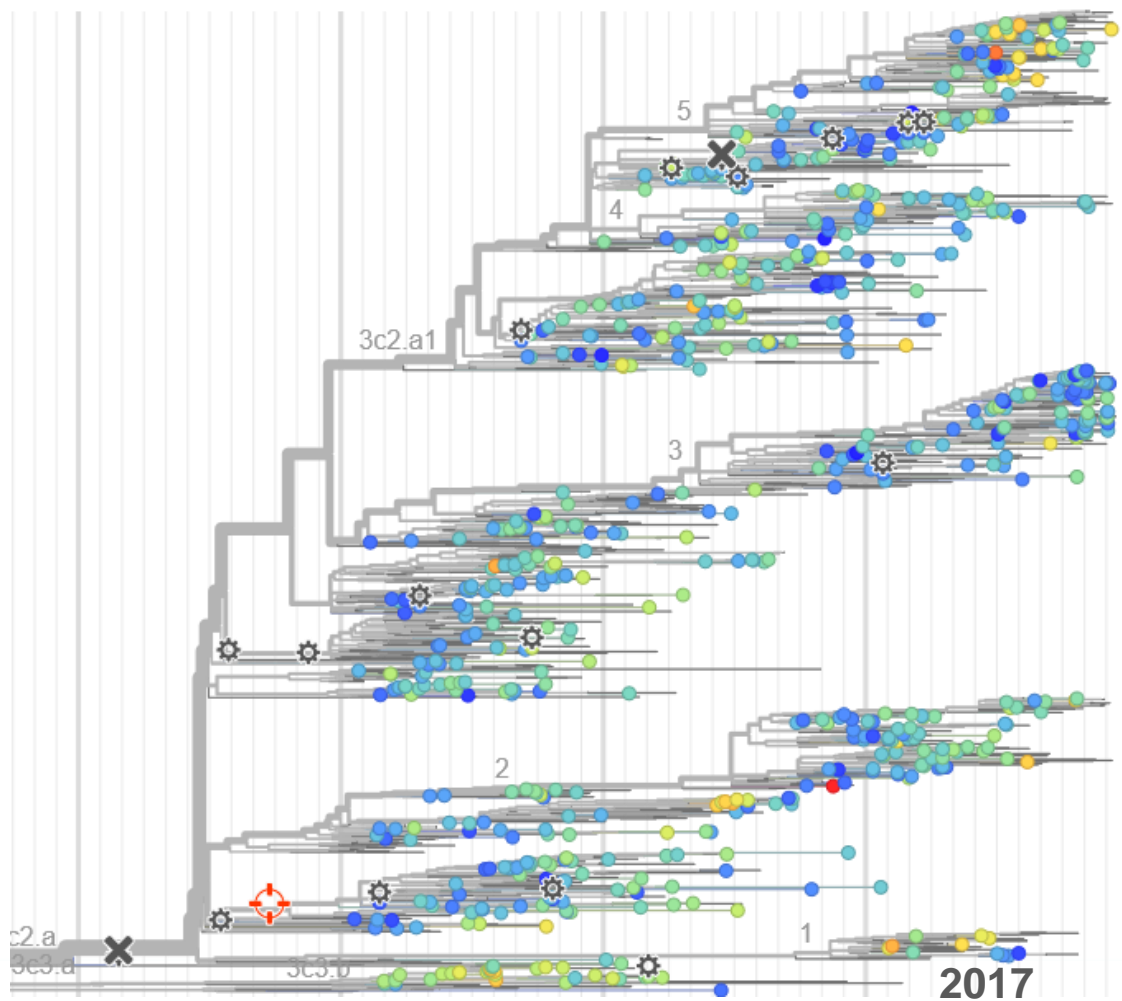
- **Poor Propagation:** H3N2 viruses are difficult to propagate in eggs.
- **Egg Propagation Can Change Antigenicity:** Contemporary H3N2 (3C.2a) viruses acquire changes on the hemagglutinin protein upon propagation in eggs and this can impact the antigenic properties.

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

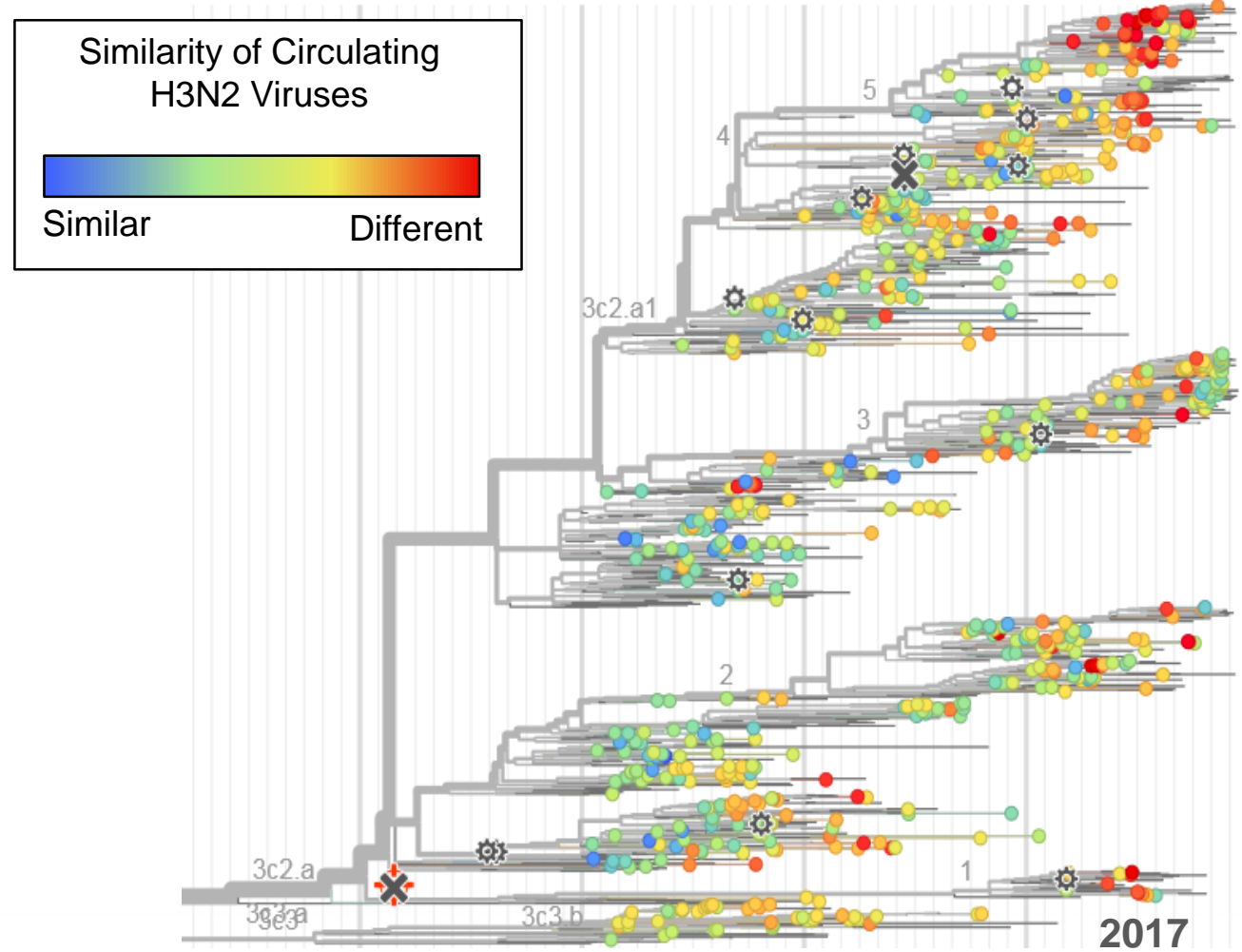


Cell-Propagated H3N2 Reference Virus

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

Influenza Vaccination

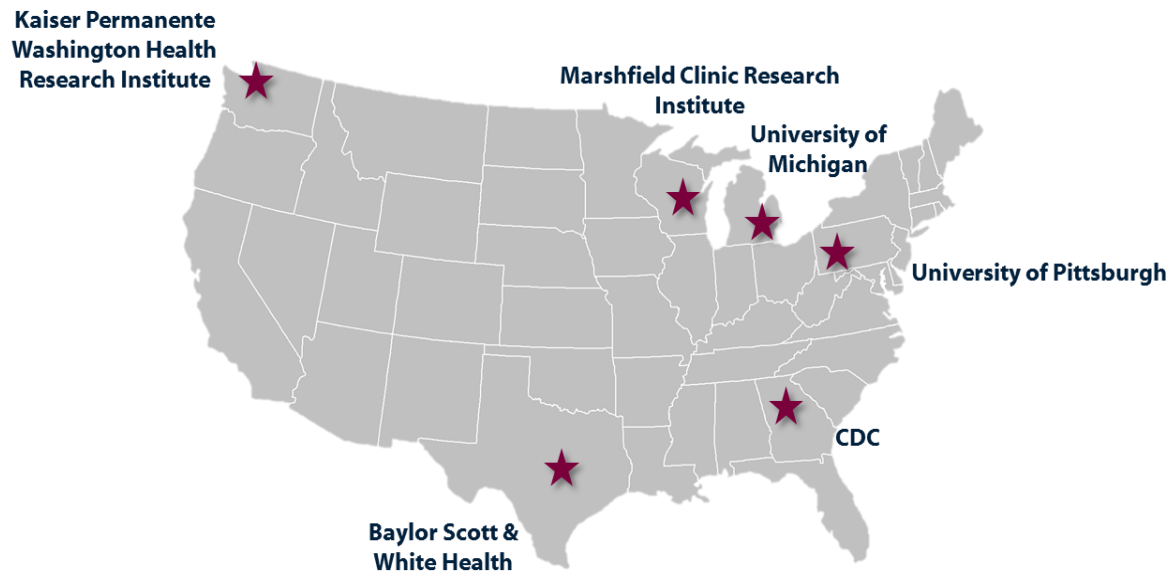
- Influenza vaccination is recommended for all persons aged 6 months and older *each year*
- The 2017-18 influenza vaccine contains a similar H3N2 virus as last season, only the H1N1 virus was updated

2017-18 Influenza vaccine composition:

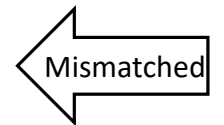
- A/Michigan/45/2015 (H1N1)pdm09-like virus (updated);
 - A/Hong Kong/4801/2014 (H3N2)-like virus (same)
 - B/Brisbane/60/2008-like virus (same)
- B/Phuket/3073/2013-like virus (same, only in quadravalent)

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

US Flu VE Network*

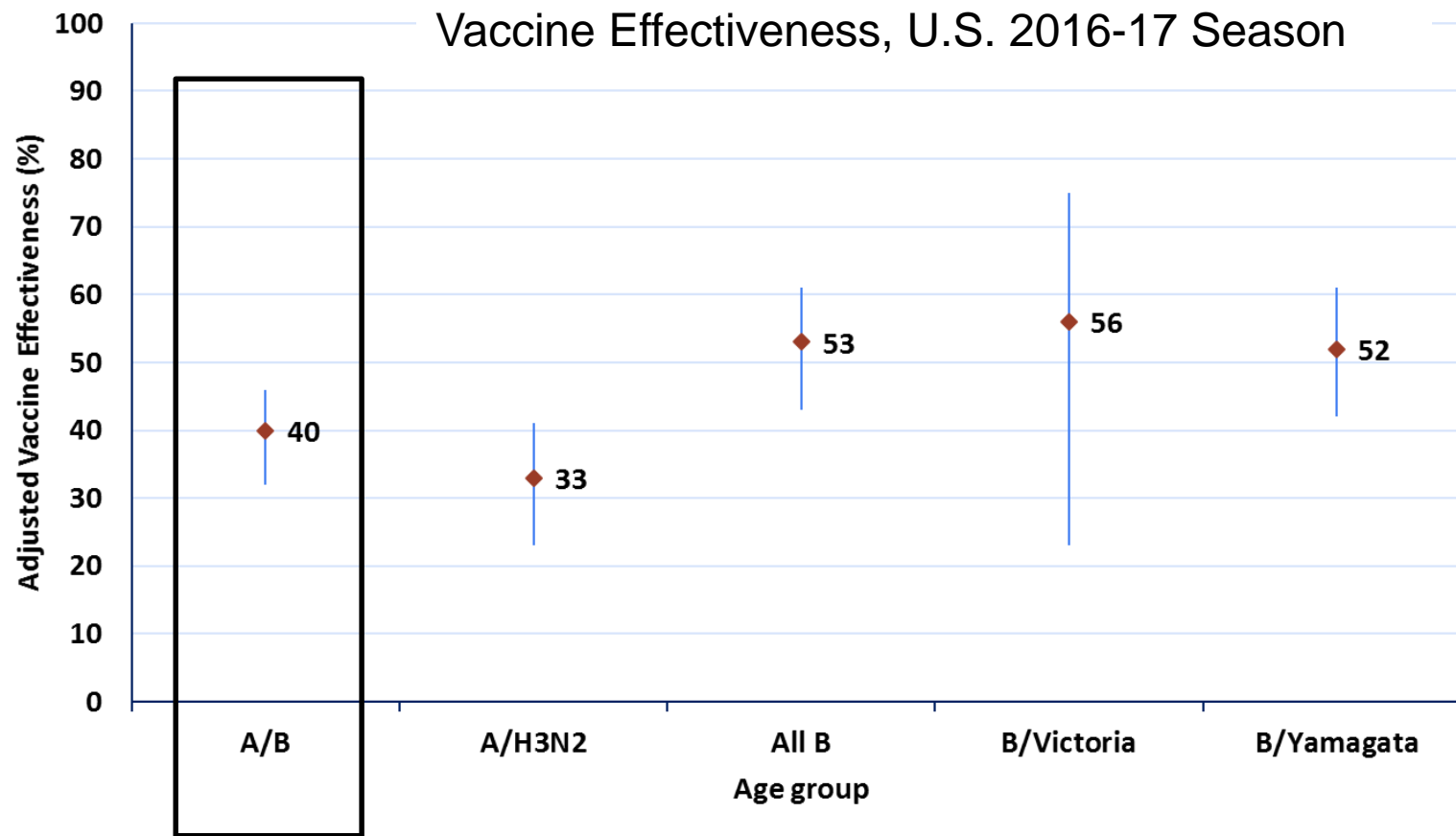


Season	VE against A/B influenza viruses (95% CI)
2010-11	60% (53, 66)
2011-12	47% (36,56)
2012-13	49% (43, 55)
2013-14	52% (44,59)
2014-15	19% (10,27)
2015-16	48% (41, 55)
2016-17	40% (32, 46)

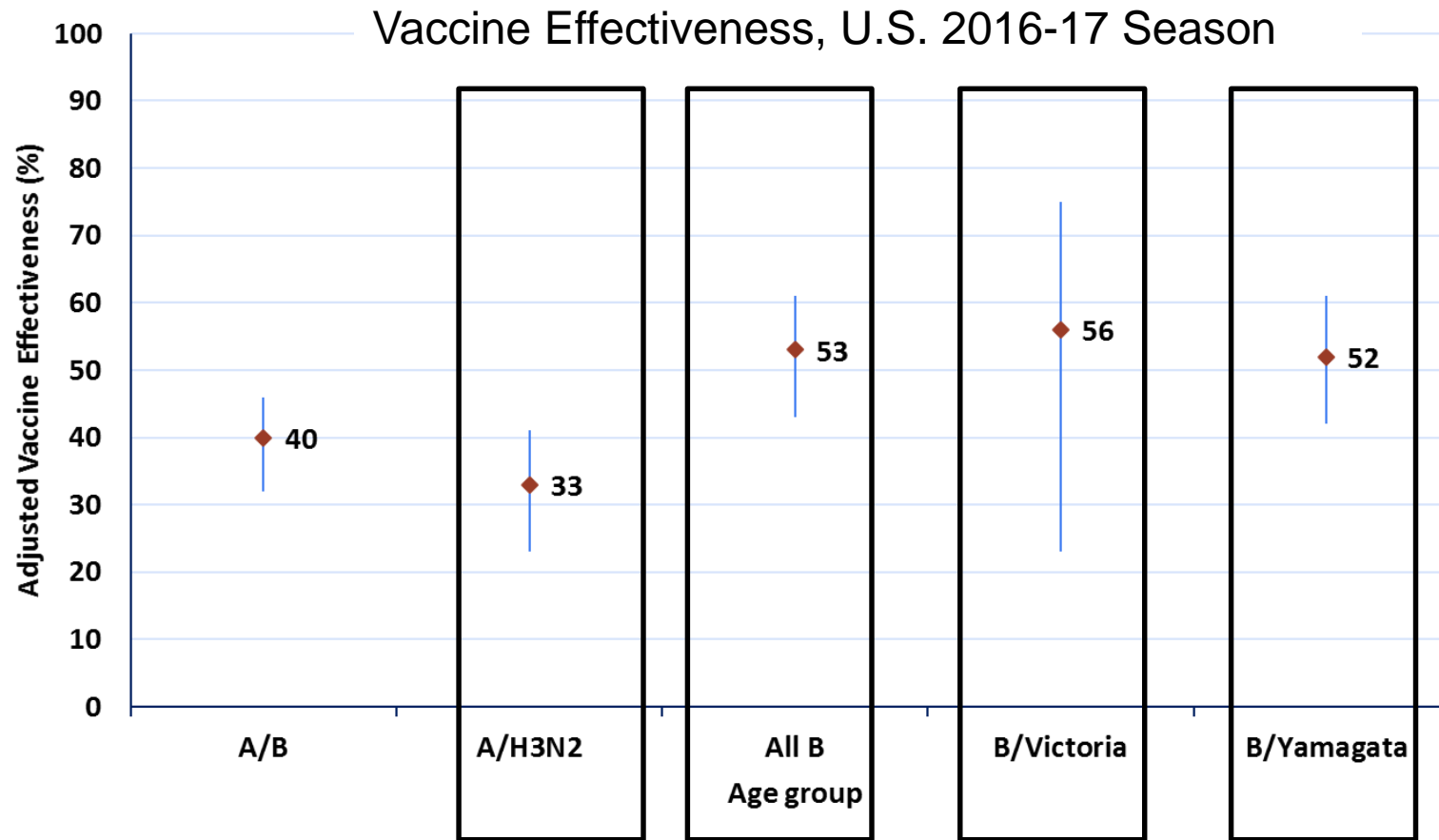


*Enrolls outpatients aged ≥ 6 months old with acute respiratory illness from 66 clinics. Uses a test-negative case-control design where PCR positive flu = case and PCR negatives = control

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 ≥ 14 days (*recommended for all ages*)
- Inhaled zanamivir (Relenza®)
 - Approved for treatment age ≥ 7 years
- Intravenous peramivir (Rapivab®)
 - Approved for treatment age ≥ 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 ≥ 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

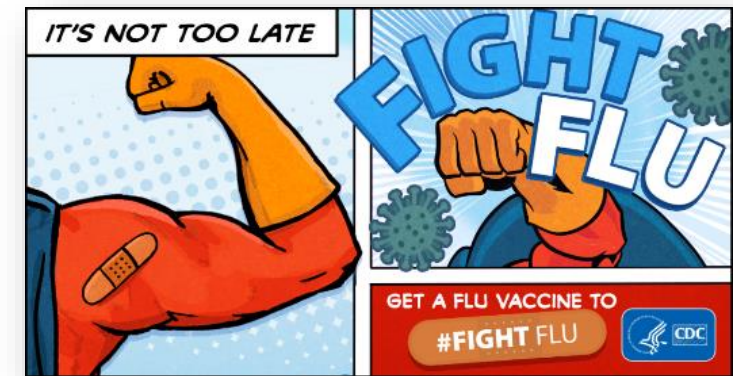
- **There is adequate national supply to meet the high demands from this season**
- **Spot shortages have been reported in areas with high influenza activity**
 - We are working with manufacturers to address existing gaps
 - CDC has a webpage on antiviral drug supply with manufacturer information for inquires 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**

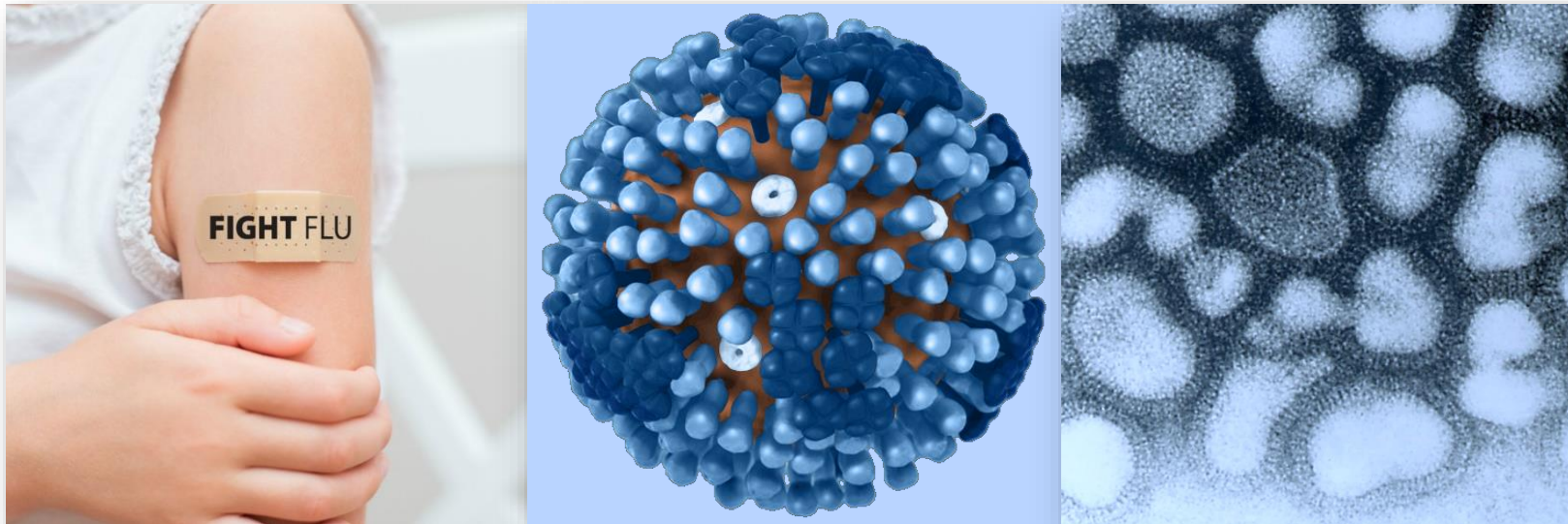
Conclusions

- 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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