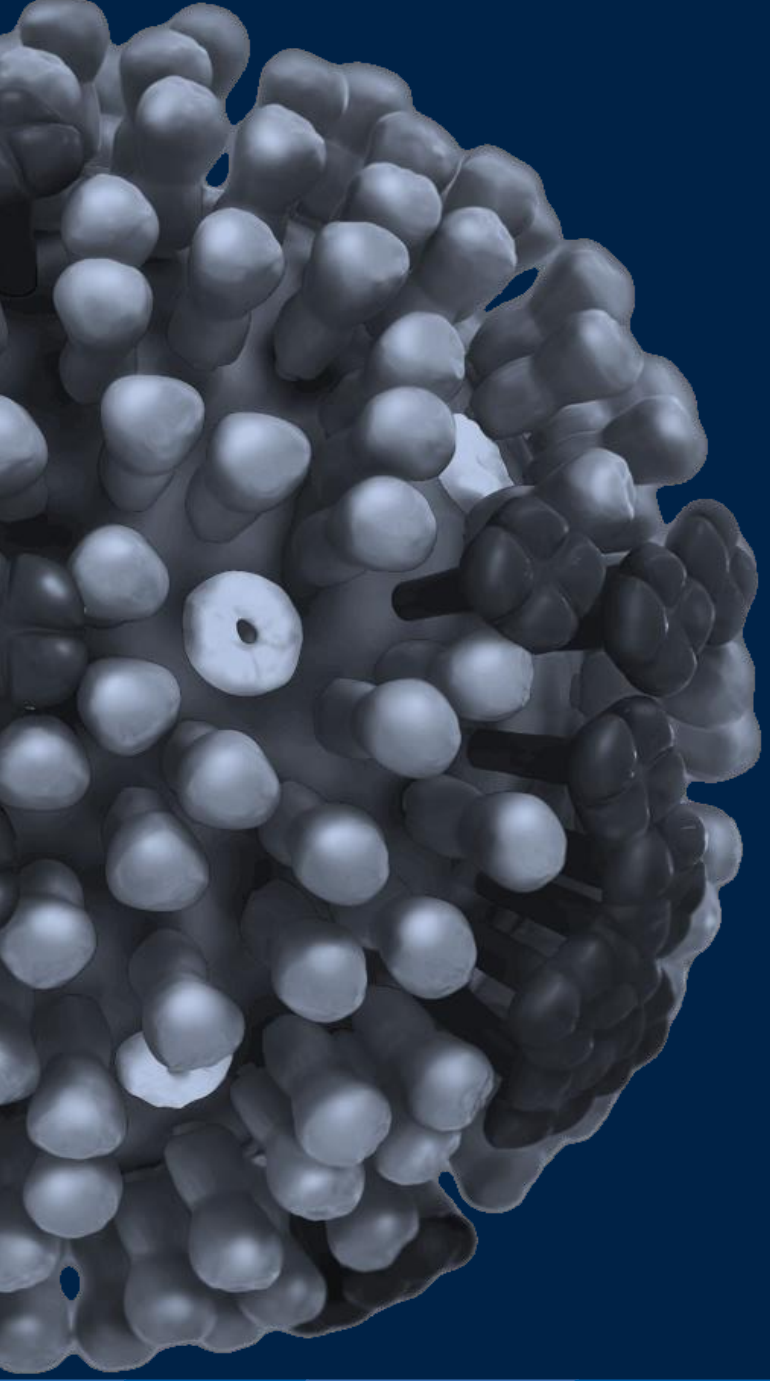

Pandemic Influenza: Past and Future Vaccine and Preparedness Challenges

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Centers for Disease Control and Prevention

Canadian Immunization Conference
December 4, 2018
Ontario, Canada

Disclosure Statement

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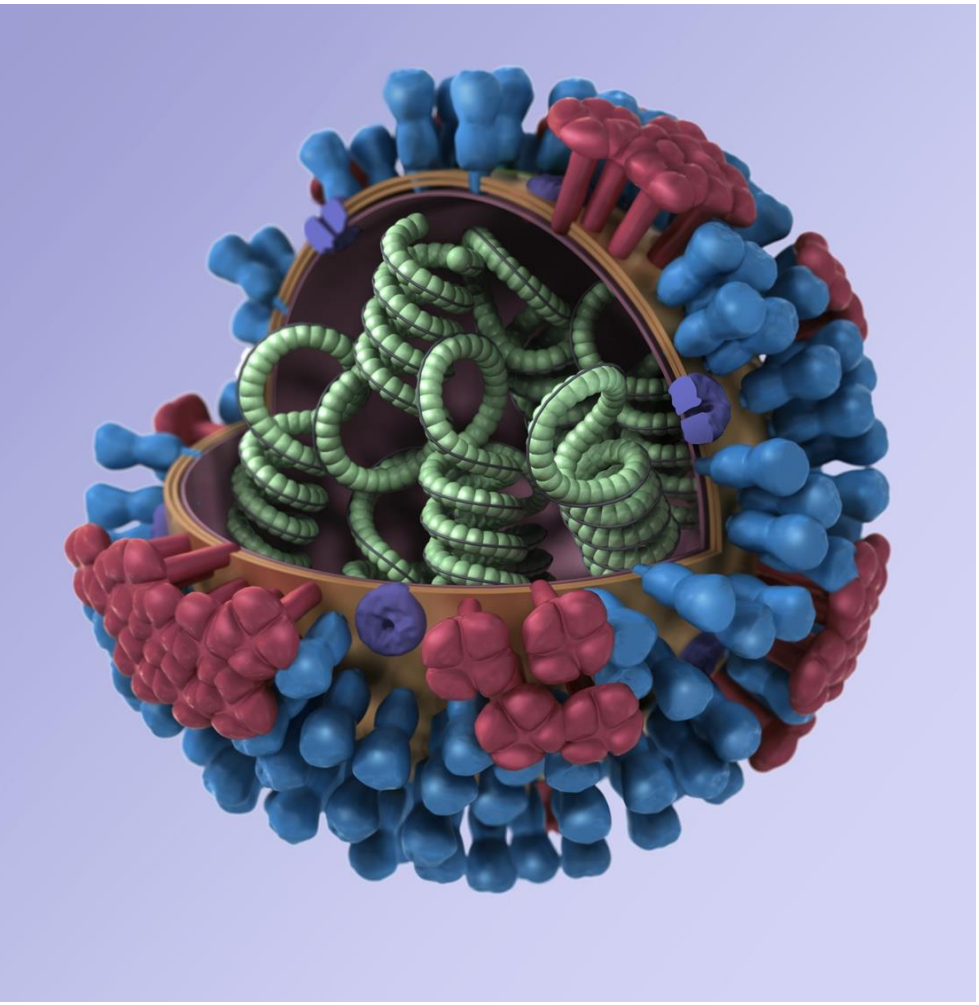
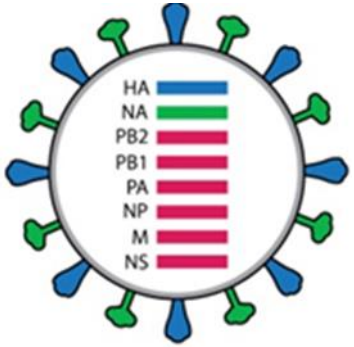
Influenza Virus Primer: Evolution Through Point Mutation and Gene Reassortment

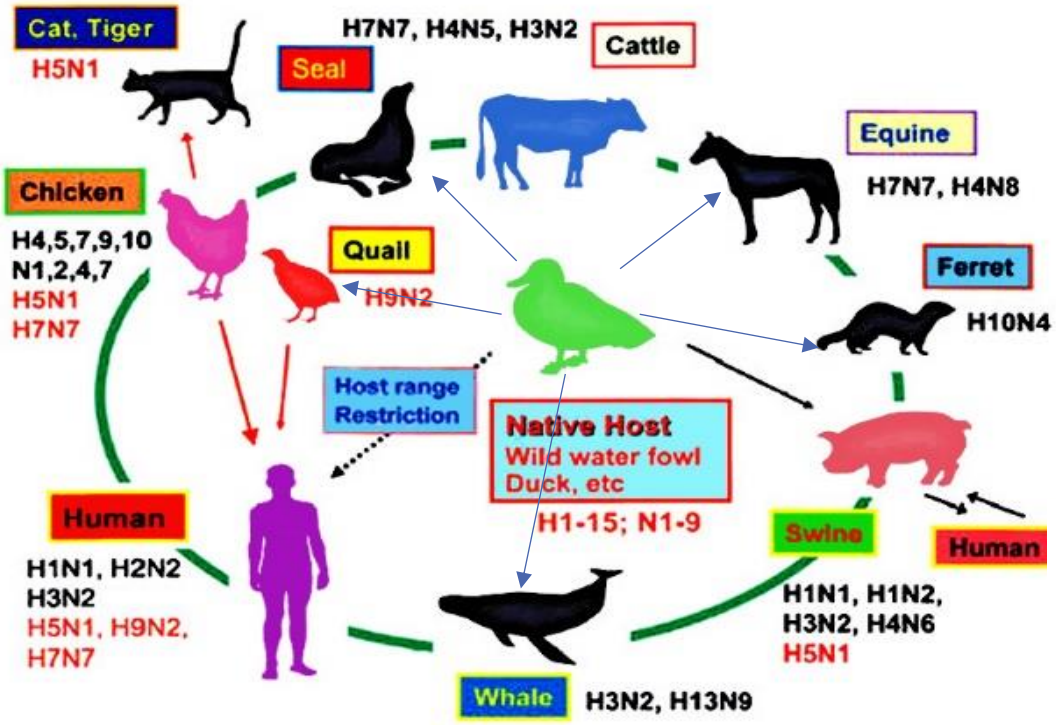


- 18 subtypes of hemagglutinin (HA) and 11 of neuraminidase (NA) with constant mutation of all 8 gene segments along with gene shuffling among viruses

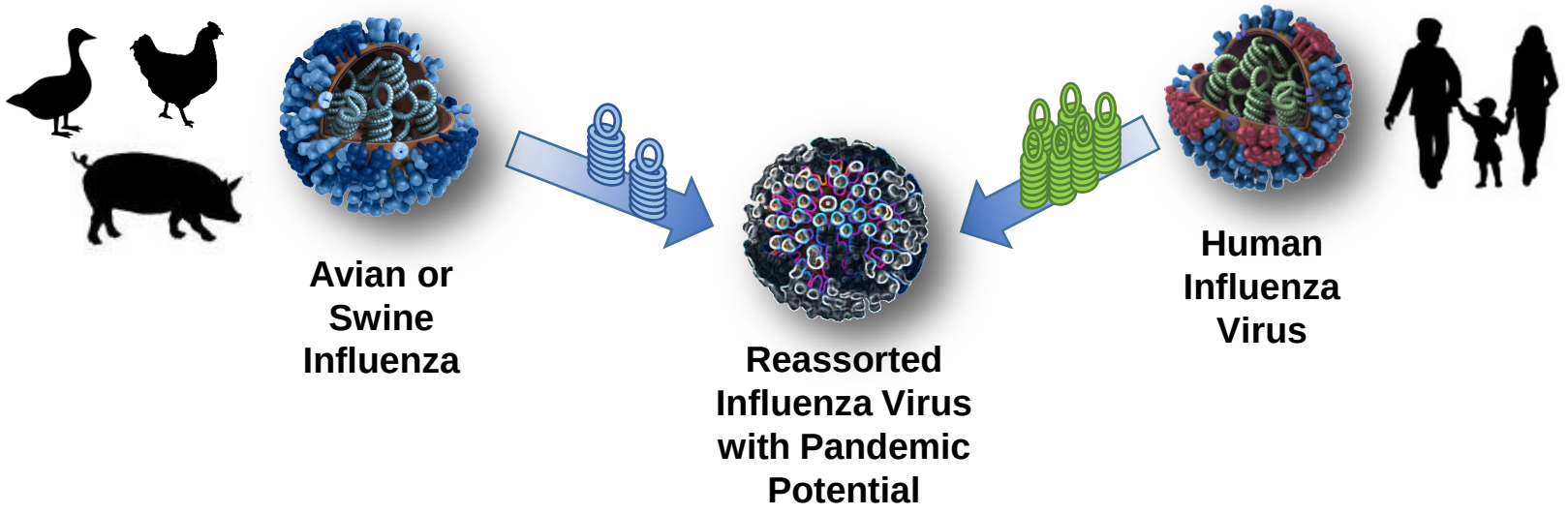


- Constant, unpredictable evolution of influenza virus genes necessitates rapid development and manufacture of and seasonal and pandemic vaccines

Where do Pandemic Viruses Come From: It's a Flu Zoo Out There!



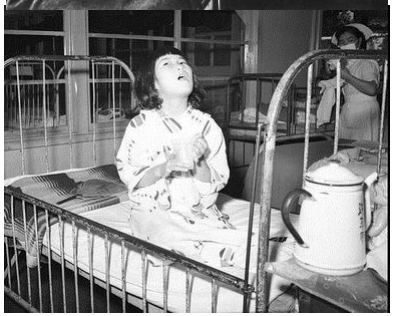
How Do Pandemic Influenza Viruses Arise?



- Pandemic viruses arise from gene shuffling (genetic reassortment) between animal and human flu viruses with subsequent mutation and adaptation to replication in humans. Influenza pandemics occur when such novel viruses are transmitted among humans in an efficient and sustained manner.
- Four influenza pandemics in last 100 years
  - 1918, 1957, 1968 and 2009

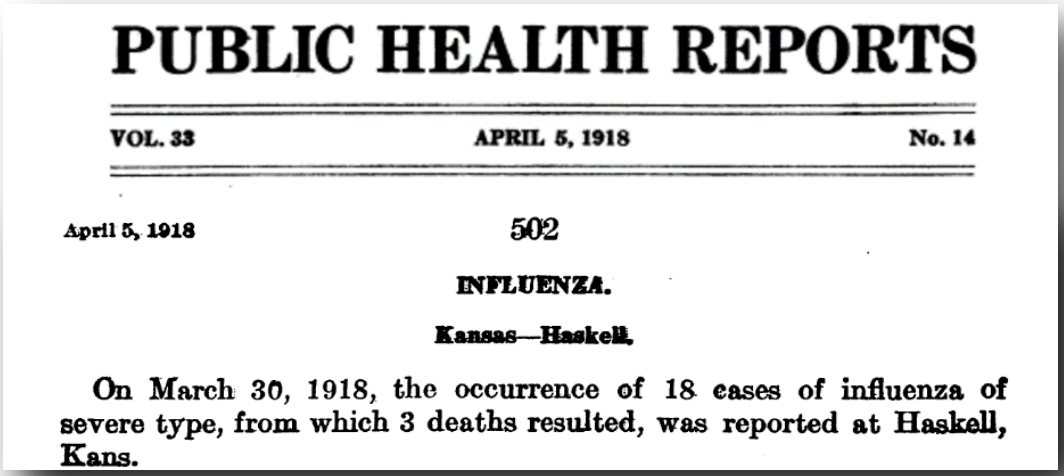
Impact of Pandemic Influenza

- **1918-19 Spanish Flu Pandemic (H1N1)**
  - ~ 650,000 deaths in the US
  - ~ 30-50,000 deaths in Canada
  - ~ 50 to 100 million global deaths
- **1957-58 Asian Flu Pandemic (H2N2)**
  - ~70,000 deaths in the US
  - ~ 2 M global deaths
- **1968-69 Hong Kong Flu Pandemic (H3N2)**
  - ~34,000 deaths in the US
  - ~ 1 M global deaths
- **2009 H1N1 Pandemic**
  - ~12,000 deaths in the US
  - ~280,000 global R&C deaths



1918 Influenza Pandemic

Pandemic Emergence in 1918



PUBLIC HEALTH REPORTS

VOL. 33 APRIL 5, 1918 No. 14

April 5, 1918 502

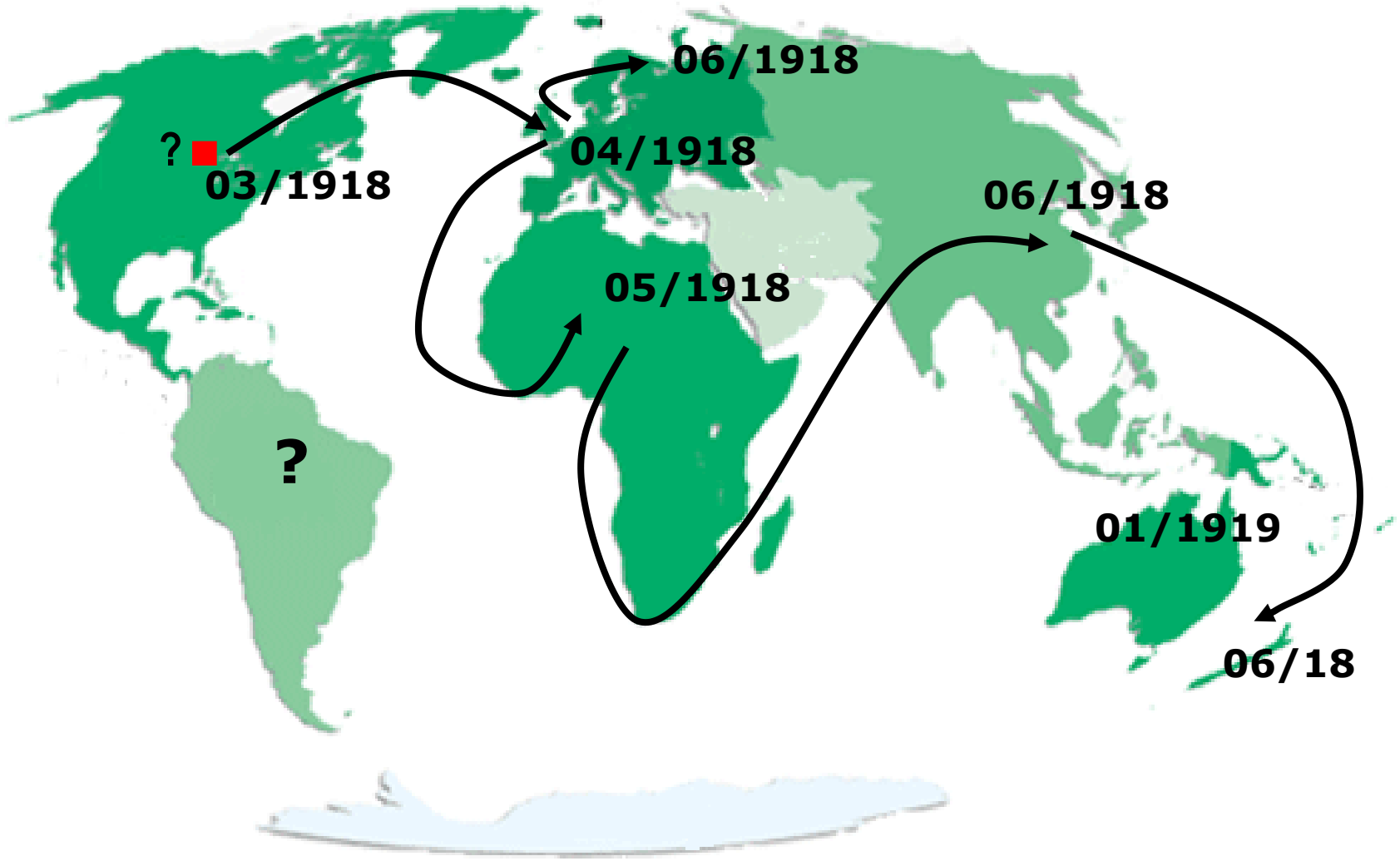
INFLUENZA.

Kansas—Haskell.

On March 30, 1918, the occurrence of 18 cases of influenza of severe type, from which 3 deaths resulted, was reported at Haskell, Kans.

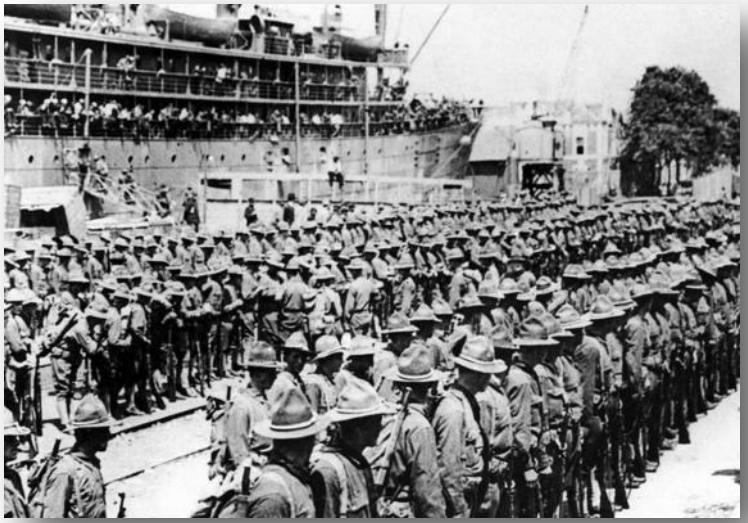
- Site of emergence not certain, purported in Haskell KS in U.S.
- 'Spanish Flu'
  - Not the source of the pandemic
  - Spain was a non-combatant in WWI and admitted having a big outbreak
  - Other countries stifled communications for national security reasons
- Context
  - WWI
  - Growing global industrialization and trade

Geographic spread: 1918-19



C.W. Potter, Textbook of Influenza, 1998

1918: Wartime Movement Aided Transmission

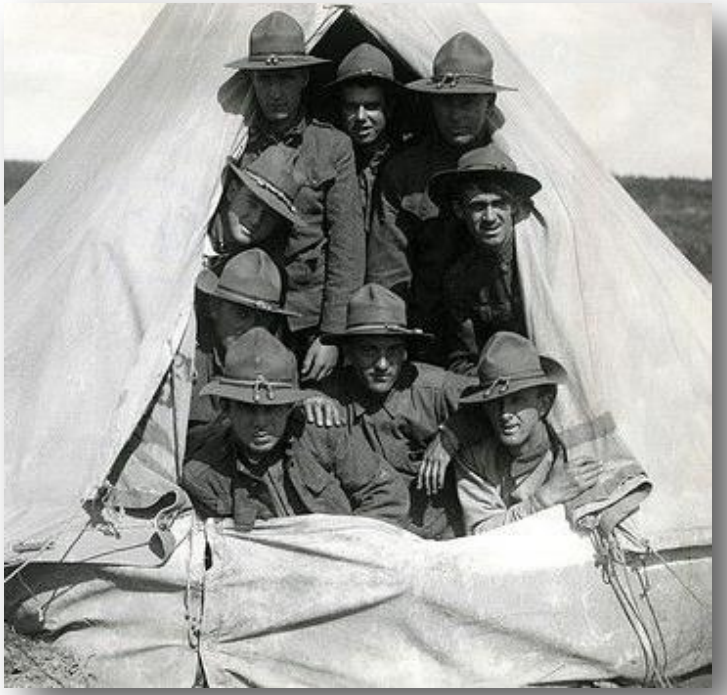


- Massive troop movement
  - Immunologically naïve young men, moved from isolated towns to training bases
  - By May 1918 hundreds of thousands of troops shipped across the Atlantic to Europe
  - 10,000 men shipped to France every day during summer 1918

- Unprecedented troop movement allowed infection to move from camp to camp
  - JAMA in Oct 1918 reported:
    - Measles
    - Chronic Bronchitis
    - Scarlet fever

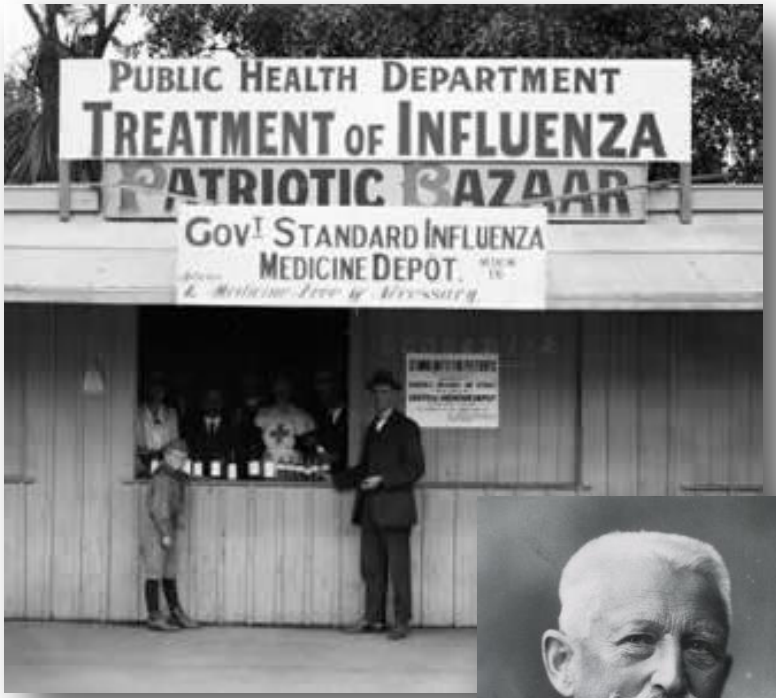
1918: Crowding Facilitated Transmission

- Industrialization and the war response added to urban overcrowding
- Soldiers lived in crowded camps and in terrible conditions during trench warfare
- Between September and November 1918, a second wave of influenza peaked in the Northern Hemisphere. This second wave was highly fatal and responsible for most of the deaths.
- >30% of doctors/nurses working for the military
  - Leaving a significant shortage of healthcare professionals and consequent deaths
- For example: Philadelphia was hit hard and reported more than 500 corpses awaited burial, some for more than a week.
- New York City reported a 40% decline in shipyard productivity due to flu illnesses



The Dawn of Modern Medicine

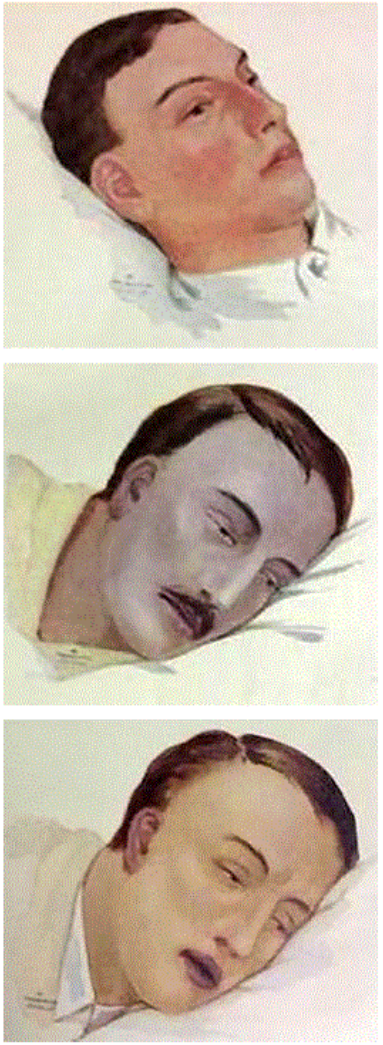
- Influenza viruses not yet discovered, no flu treatment or prevention, flu transmission poorly understood
  - Cause of influenza attributed in 1892 by Pfeiffer to be a bacillus – *Haemophilus influenza*
  - Controversy during 1918
  - Vaccines against Pfeiffer's bacillus used
- Few vaccines:
  - Typhoid, cholera, plague and rabies
- Only palliative therapies:
  - Aspirin, quinine, opium, ammonium, iodine, turpentine, beef tea



Pfeiffer

Signs and Symptoms of 1918 Pandemic

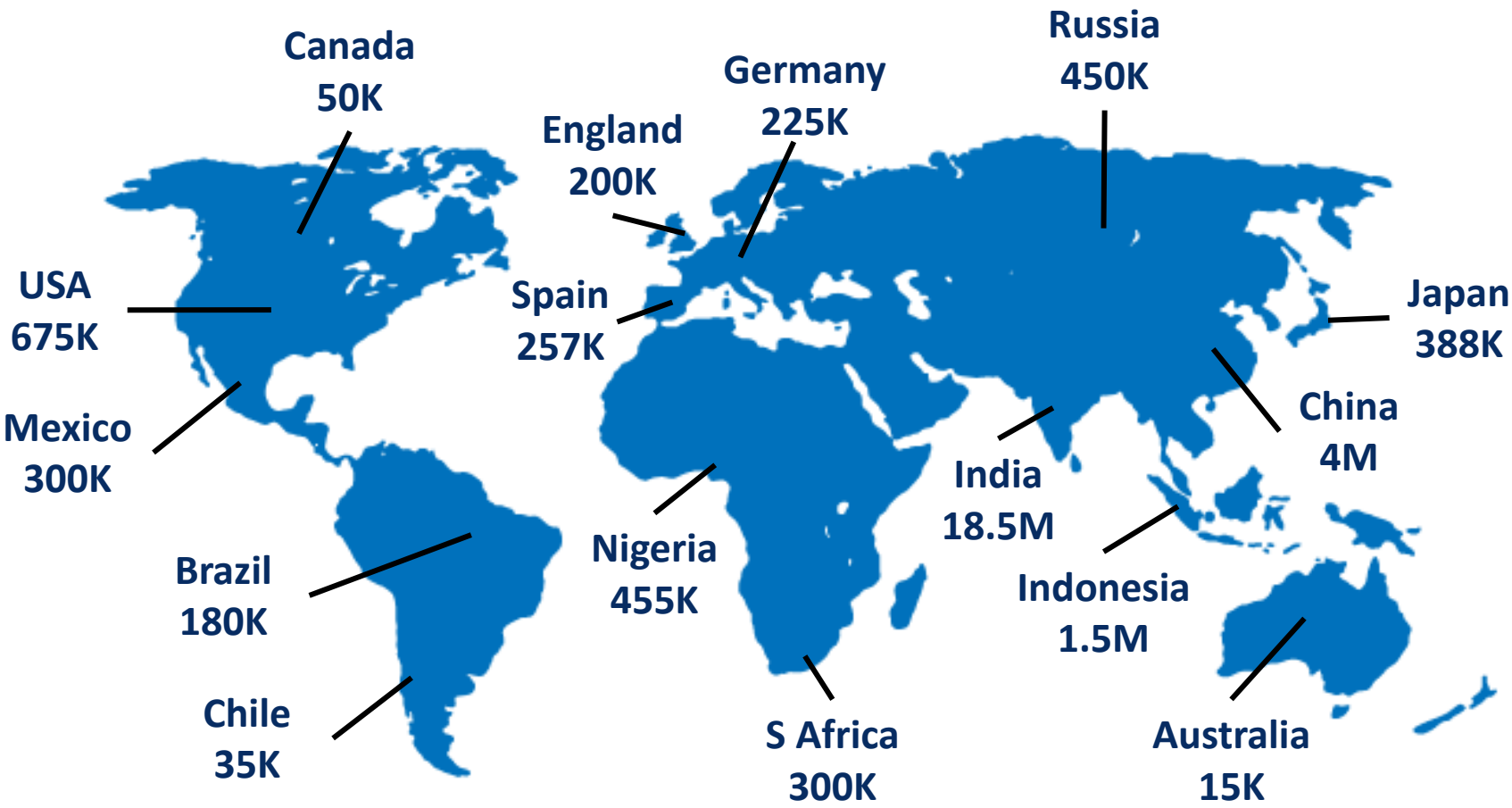
- Caused illness in about 30% of the population with classic flu symptoms in most people
- But very high rates of pneumonia in 10-20% of cases
- ‘Purple Death’ often in 24 hours
  - “They very rapidly develop the most vicious type of pneumonia that has ever been seen.”
  - “Cyanosis extending from their ears and spreading all over the face”
  - “It takes special trains to carry away the dead. For several days there were no coffins and the bodies piled up something fierce.”
  - “Bodies stacked in the morgue from floor to ceiling like cord wood.”



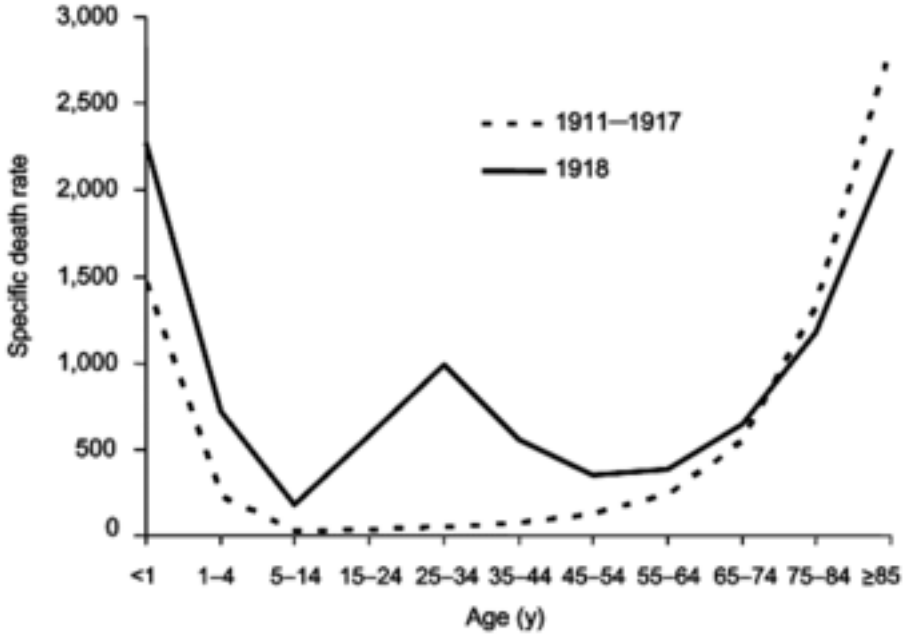
Figs. 1–3 Different stages of skin coloration as seen during the 1918 influenza pandemic characterized as "heliotrope" or deep blue cyanosis. Reproduced with permission from the Lancet archives.

Global Mortality From the 1918-1920 Pandemic

Estimated 50-100 Million Deaths



Age-specific Pneumonia and Influenza Mortality, 1911-1918



Taubenberger and Morens 2006

Social and Political Consequences of the 1918 Pandemic

- Slowed the delivery of Allied troops on the western front
- 43,000 deaths in U.S. Armed forces attributed to Spanish Flu”
- Contributed to failure of last German offensive in summer of 1918
  - Soldiers from all sides succumbbed to deadly ‘Spanish Flu’
- Reduced life expectancy due to high mortality in young healthy adults (by 12 years in US)
  - Economic consequences
  - Many children orphaned

- Alfred Cosby: “America’s Forgotten Pandemic, The Influenza of 1918
  www.historyplace.com/worldhistory/firstworldwar/index

1951
Johan Hultin at permafrost gravesite, Brevig Mission AK

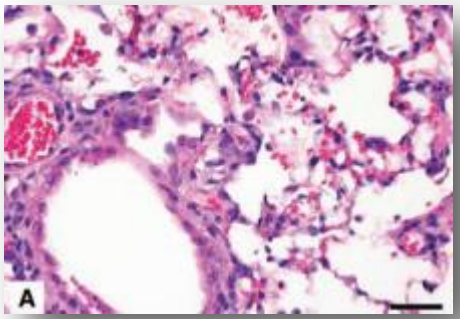
1951
Hultin unable to grow live 1918 virus in lab

1997
Hultin returns to gravesite for frozen lung tissue

Recent Chapter: Reconstructing The 1918 Influenza Virus

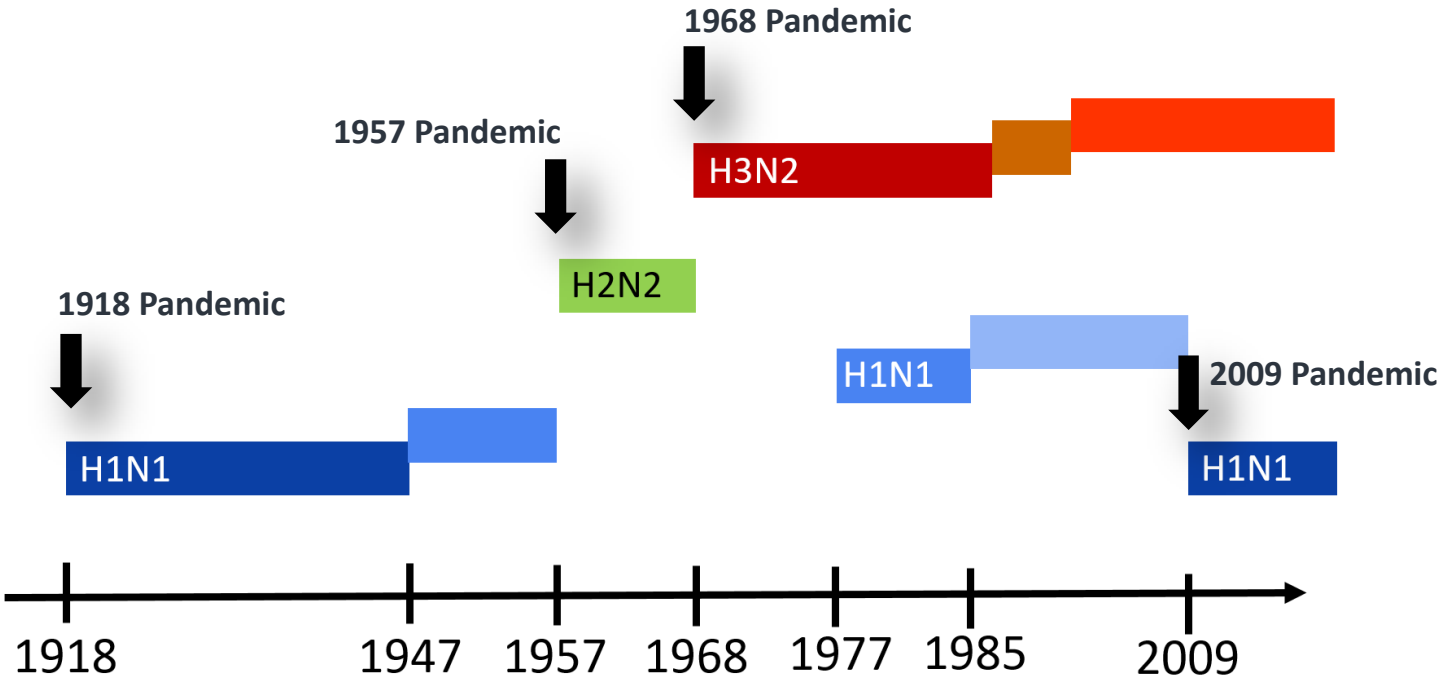
1997
Taubenberger at AFIP begins sequencing the 1918 virus genes

2004
Tumpey at CDC rescues 1918 virus in high containment lab



2005
CDC shows 1918 virus causes severe pneumonia in mice and identifies the genes responsible for high virulence

Human Seasonal Influenza A Viruses Since 1918



The Legacy of Past Pandemics: Annual Burden of Influenza

United States

Global

	United States	Global
Deaths	12,000 – 79,000	291,000 – 646,000
Severe Cases Hospitalizations	140,000 – 960,000	3M to 5M
Cases	9.2M – 49M	1.0 B

Influenza Vaccine Development: Key Historical Events

- 1933 - Landmark influenza A virus isolation work of W. Smith, C.H. Andrewes and P.P. Laidlaw, Mill Hill, U.K. *Lancet* 1933; 2: 66-68.
  - Demonstrated influenza was a "filterable agent"
  - Isolated virus in ferrets; immune serum neutralized virus
- 1934 - Confirmation of transmissibility of influenza virus by Thomas Francis, Jr., Rockefeller Institute, U.S.
  - Virus transmitted ferret-to-ferret-to-mouse; accidental transmission to a human
  - A/PR/8/34 isolated
- 1937 – First attempt to vaccinate humans against influenza. T Francis, TP Magill, *J. Exp Med* 1937; 65: 251-259.
  - Inactivated vaccine propagated in chick embryo cell culture
  - Equivocal results

Influenza Vaccine Development: Key Historical Events

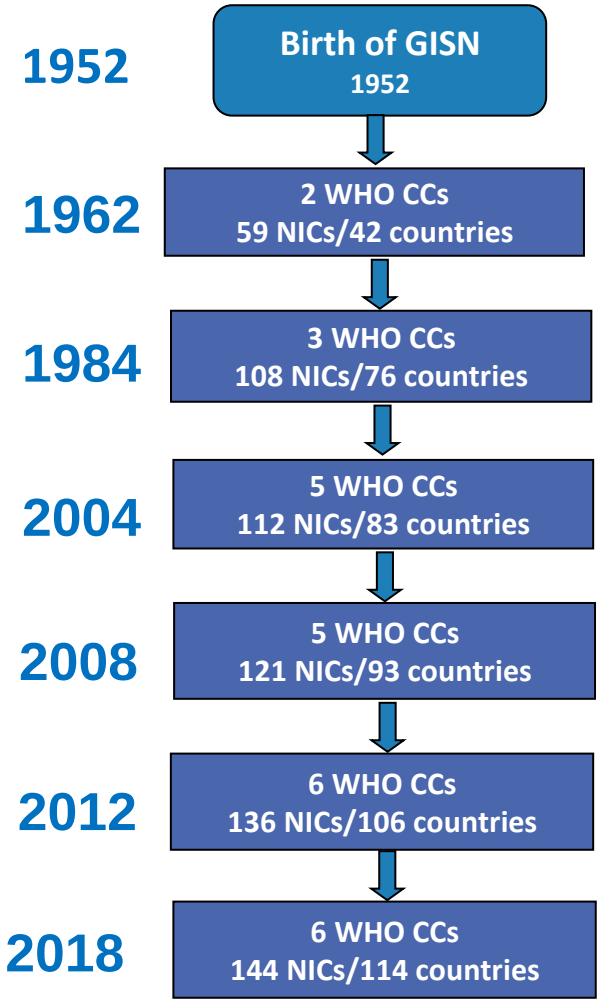
- 1940-43 – Dogma that influenza epidemics occurred every 2-3 years spurred vaccine trial planning during WW II
- June 1943 – Authorization for flu vaccine trial at universities and army posts
  - Vaccine with A/PR8/34, 1940 A virus and B/Lee, purified by centrifugation
  - Large fall epidemic
  - Vaccine efficacy was 69%
  - Best protection in those with highest serum Ab titers
  - Local and systemic adverse reactions acceptable with 0.2 mg antigen but higher doses increased reactions
- 1947 – Vaccine made with 1943 Weiss strain failed to protect vs. new variant clearly demonstrating antigenic drift results in vaccine failure
- During the 1960's zonal centrifugation and other advances improved vaccine purity and reduced reactogenicity
- Reactivity of whole virus vaccines in children recognized; began split virus and subunit vaccine production

Formation of the WHO's Global Influenza Surveillance Network

- 1947/8 – 3 years of discussion post-World War II resulted in establishment of the World Health Organization to serve as the health agency of the United Nations
- From WHO's inception, influenza surveillance viewed as essential as memories of the Great Influenza Pandemic of 1918 persisted
- 1947/8 – 'World Influenza Centre' established in London with Sir Christopher Andrews as first director

- 1948 to 1952 - National Influenza Centers (NIC) nominated by MoHs leading to formation of WHO's Global Influenza Surveillance and Response System
- WHO Collaborating Centers for human influenza established Atlanta in 1956, Melbourne in 1992, Tokyo in 1993, and Beijing in 2011; a Collaborating Center established in Memphis for animal influenza in 1975
- Four essential regulatory laboratories also contribute to vaccine strain selection

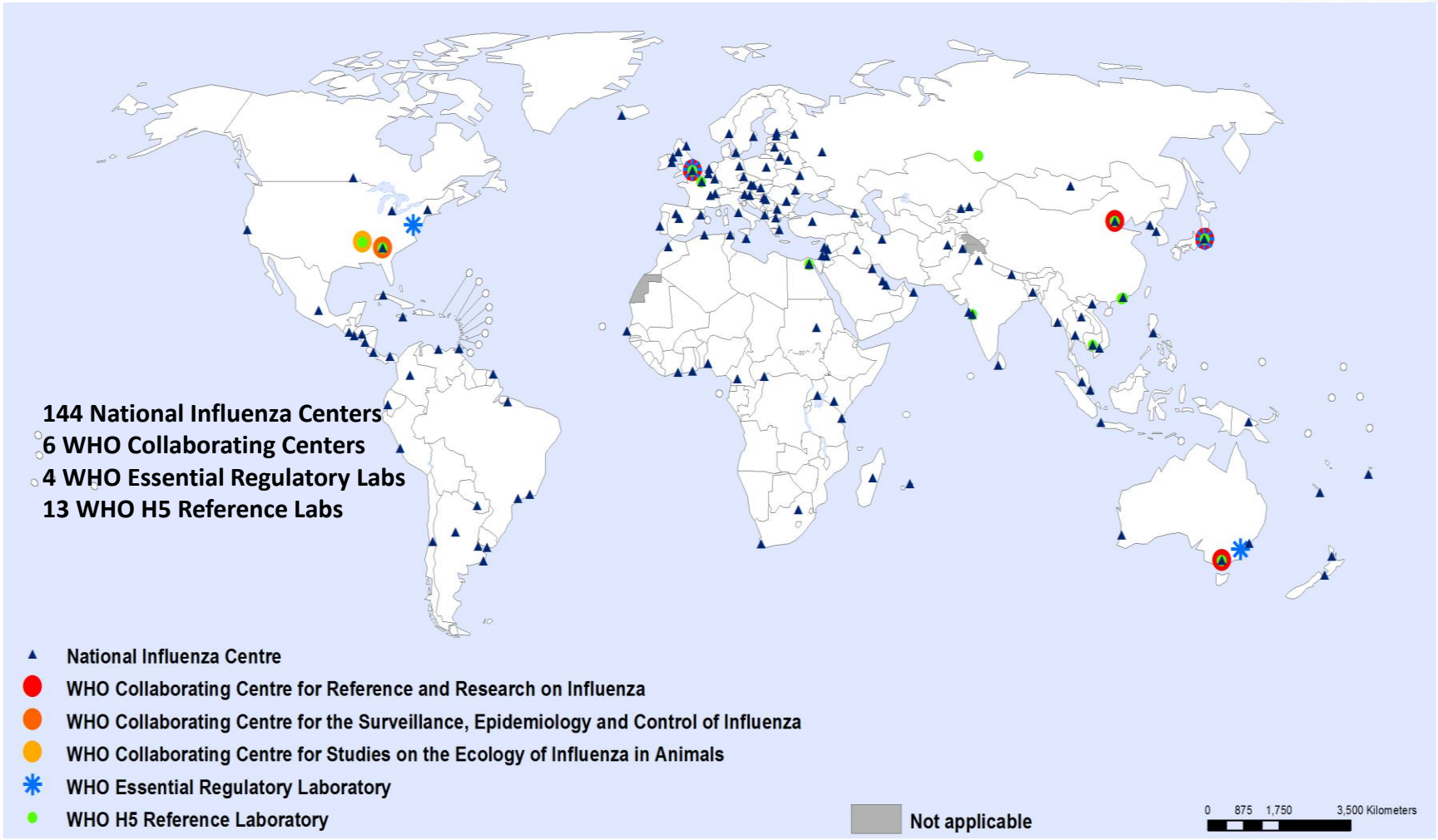
Growth of the Global Influenza Surveillance and Response System (GISRS)



- **Virus monitoring and risk assessment**
- Integration of epidemiologic and virologic data
- Laboratory diagnostics
- Lab and epi capacity building
- Communications and networking
- **Vaccine virus selection**
- Regular interactions with industry
- **Serves as a model international surveillance and response system with a strong ethos of collaboration and cooperation**

Expansion of GISRS

World Health Organization



2,000,000 specimens/yr tested in GISRS

> 20,000 viruses/yr shared with WHO CCs

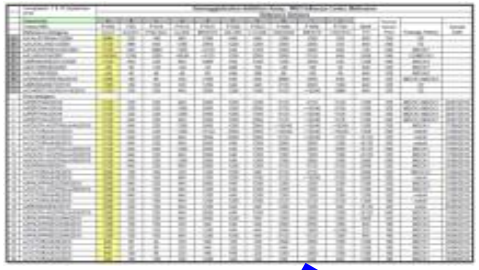
~ 10,000 viruses/yr characterized by CCs

Challenges in Prevention with Influenza Vaccines

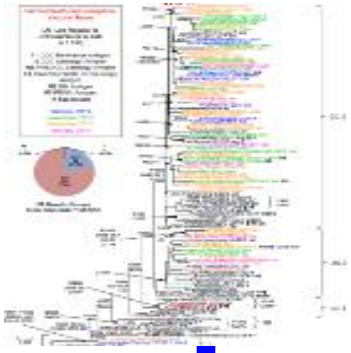
- Influenza vaccine targets are the set of rapidly changing seasonal viruses & pandemic viruses which emerge unpredictably
- "Variant-specific" immunity acquired after vaccination and infection with reduced protection vs. new antigenic variants; broadening cross-protection remains a challenge
- It's always a race against time to detect new influenza variants AND develop and produce vaccines prior to widespread disease
- Production of seasonal and pandemic influenza vaccines is a high-risk, high-stress endeavor for manufacturers
- The holy grail of a universal vaccine is elusive, but a variety of novel approaches are being vigorously explored

Data → Vaccine Virus Decision

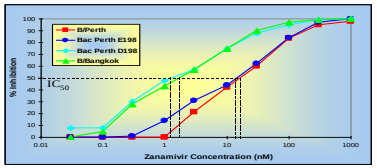
Comparative titres by haemagglutination inhibition assays



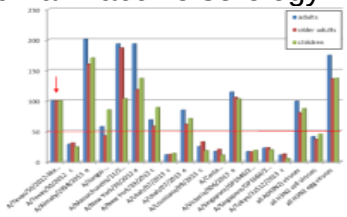
Sequence data
- mainly HA & NA
- Some others e.g. M



Antiviral drug resistance
- Oseltamivir
- Zanamivir
- Other compounds



Human vaccine serology



Other information

Growth in eggs & cells

Vaccine virus selection

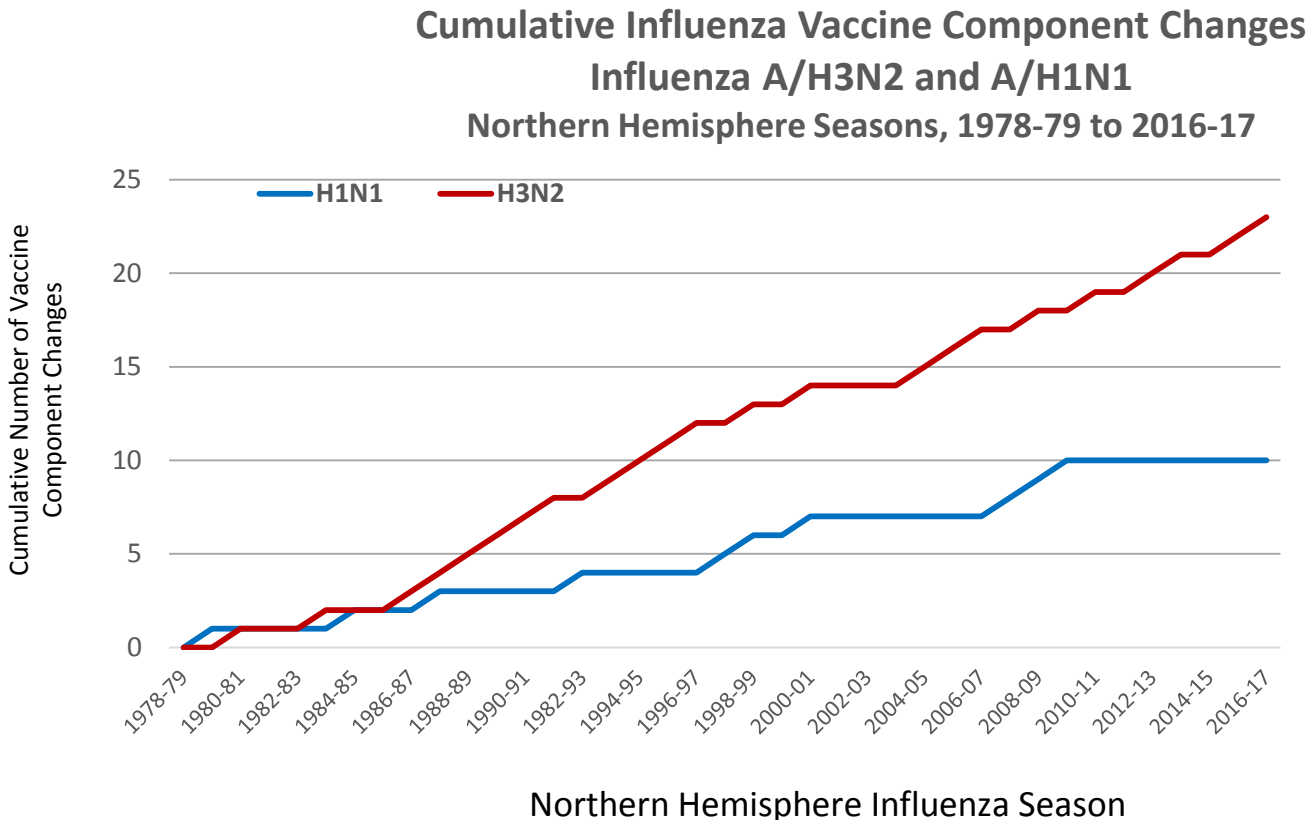
Other data:
- Epi data, Plaque reduction, Virus neuts, Structural data, VE, virus clade predictive modelling

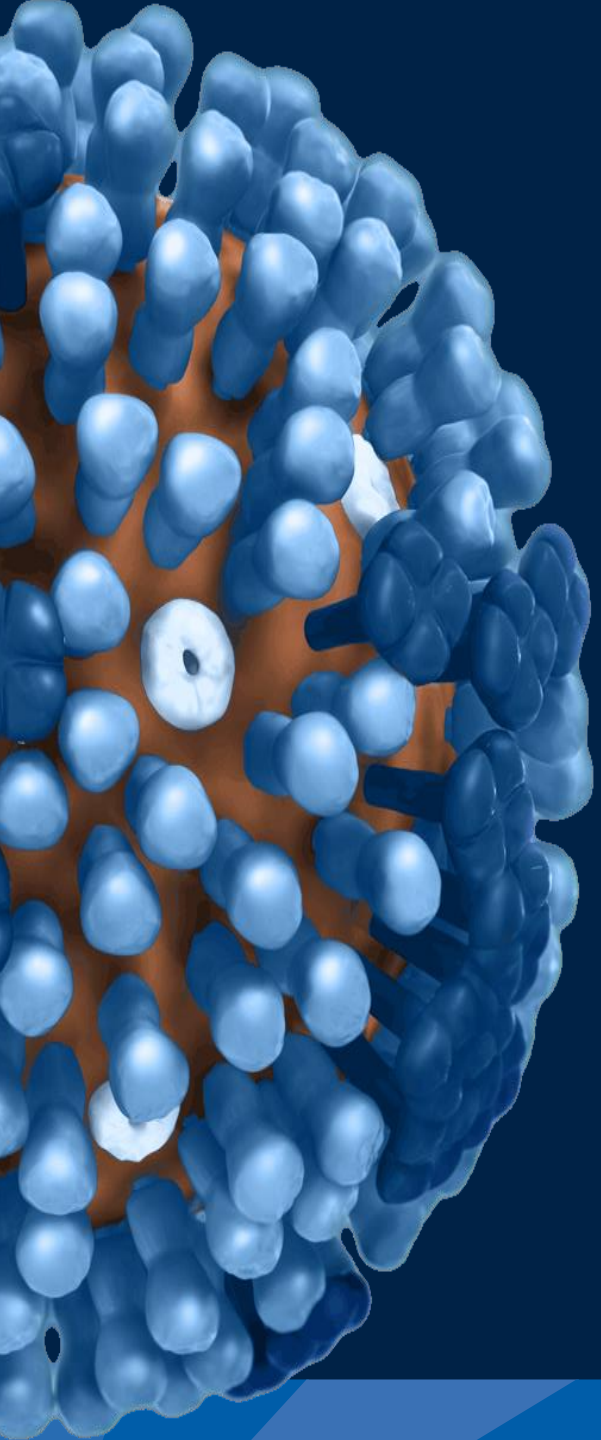
Revised from Ian Barr slide

When Should Vaccine Viruses Be Updated?

- Have new antigenic variants been detected? YES
  - Hemagglutination-inhibition assays and neutralization assays
- Do the antigenic variants have molecular changes in the HA/NA that are associated with the observed antigenic changes? YES
  - Sequencing HA and NA genes to look for “signature” amino acid changes
  - Look at nature and position of the HA aa changes
- Are the new antigenic variants associated with localized outbreaks epidemics ? YES
  - **Trend analysis** - monitor global spread of new variant
- Are current vaccines able to induce high levels of antibody to new variant viruses? NO
  - Panels of serum from vaccinated children, adults and older adults to determine if antibody levels are significantly lower to variant viruses
- Are there suitable egg-propagated high growth reassortants available for vaccine production? YES
  - It takes many attempts to produce a suitable H3N2 candidate vaccine virus
- What are interim vaccine effectiveness studies telling us?

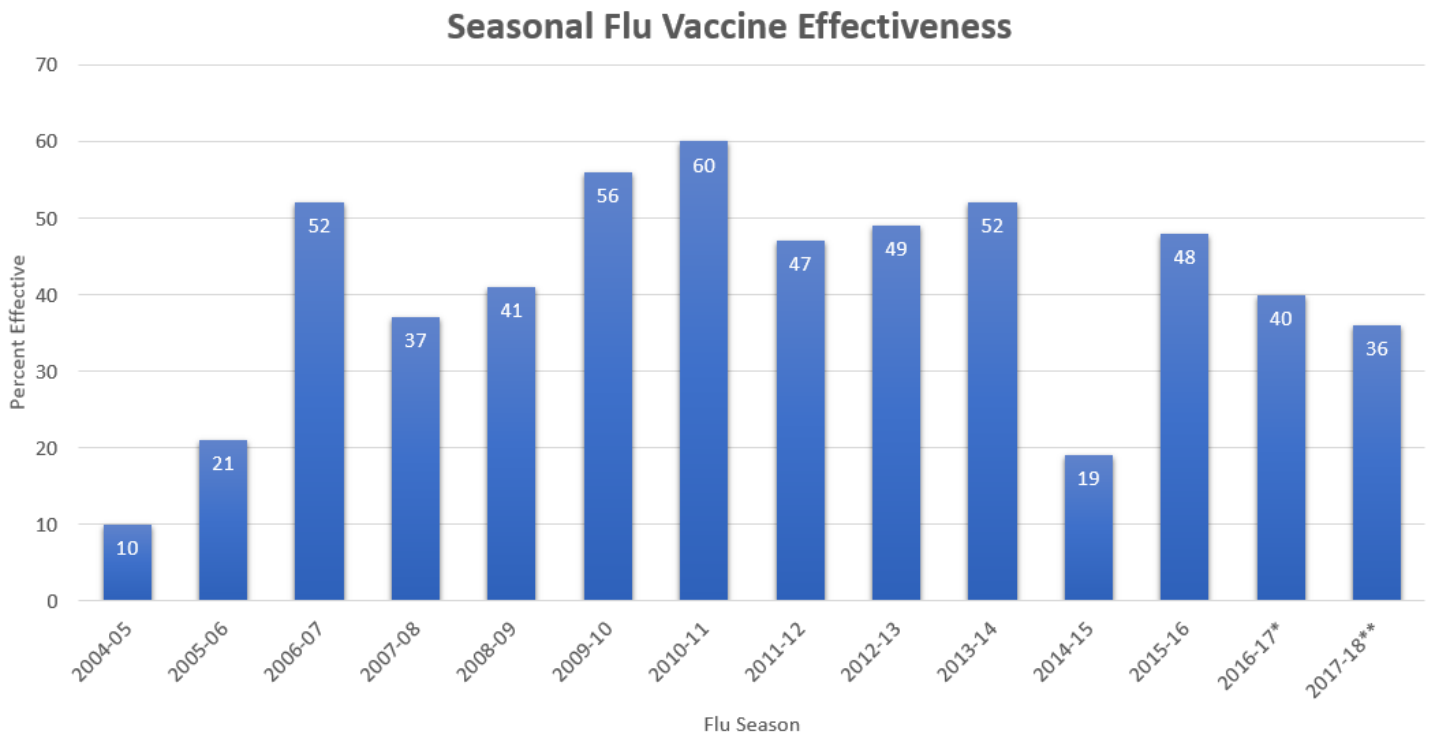
Highest Number of WHO Recommended Vaccine Changes: H3N2





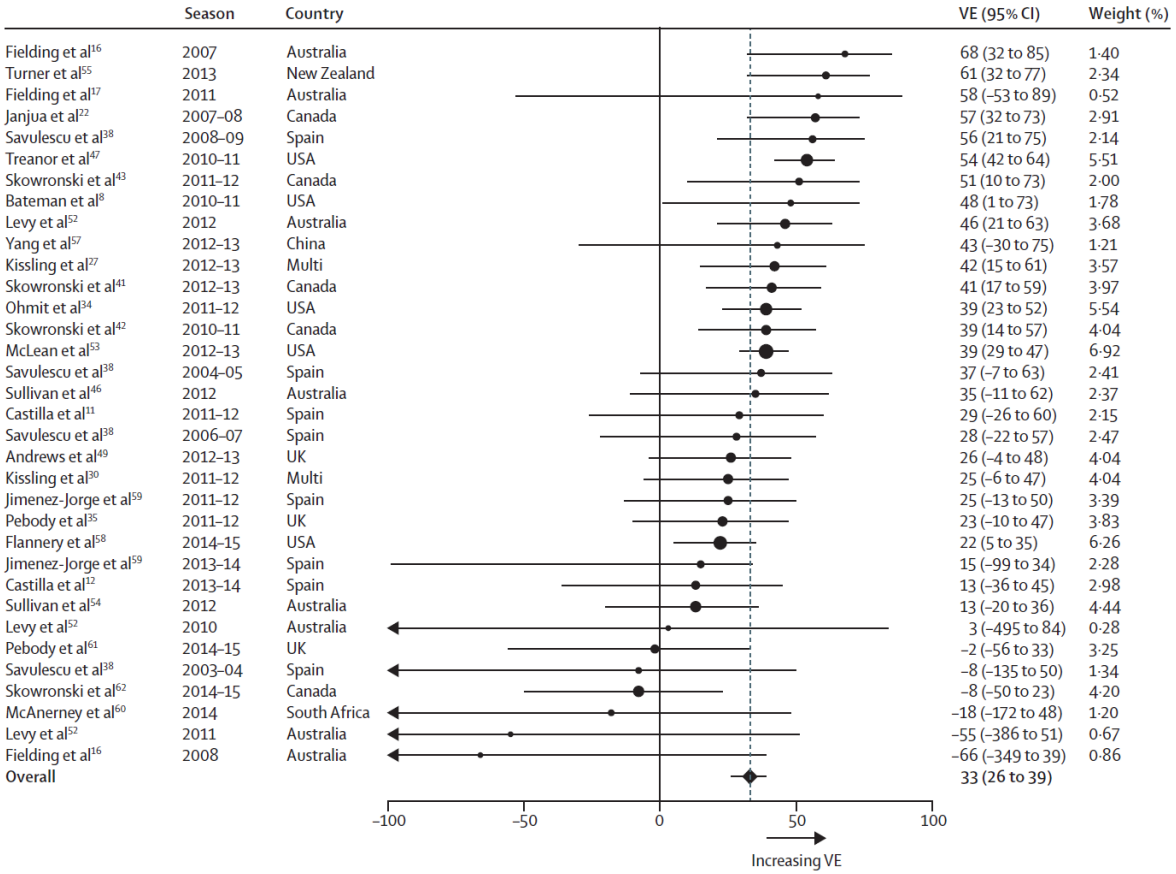
Vaccine Effectiveness

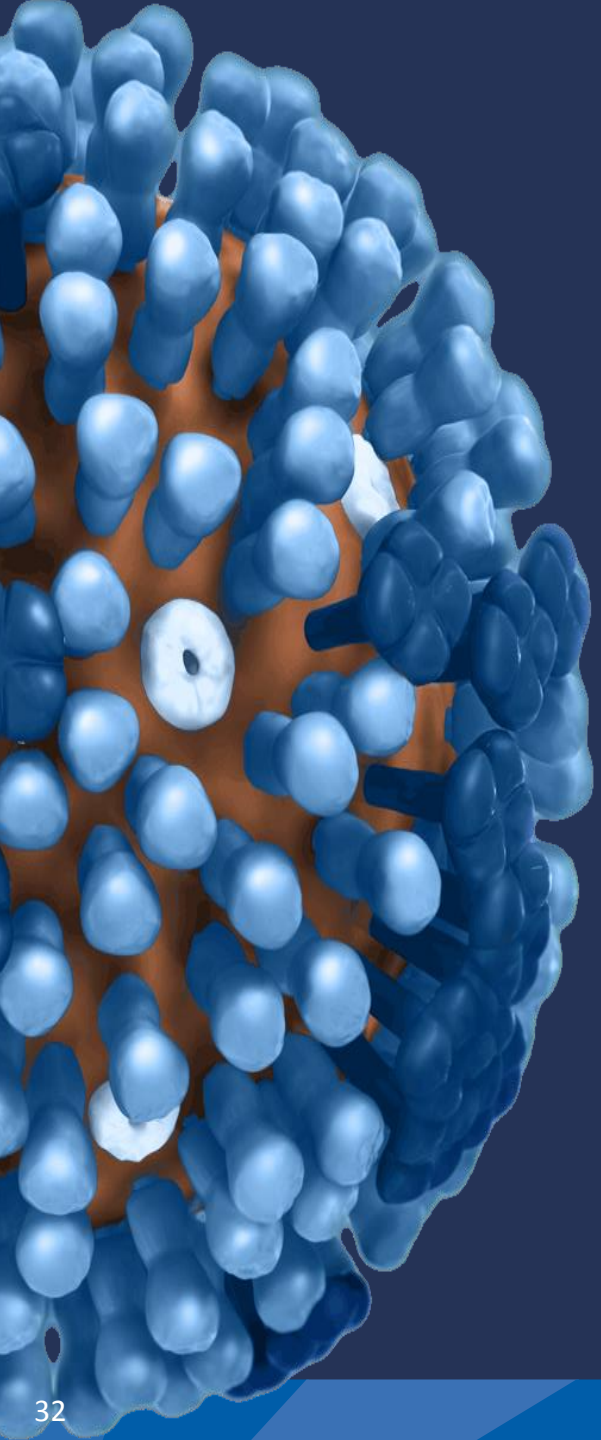
Influenza Vaccine Effectiveness at Preventing Outpatient Visits for Lab-Confirmed Influenza Varies By Season: U.S. Data



H3N2 Vaccine Component Has Lower Effectiveness Than Others

- Meta-analysis of observational VE studies conducted in ambulatory care settings, 2004-2015
  - B = 54%
  - A(H1N1) pdm09 = 61%
  - A(H3N2) = 33%





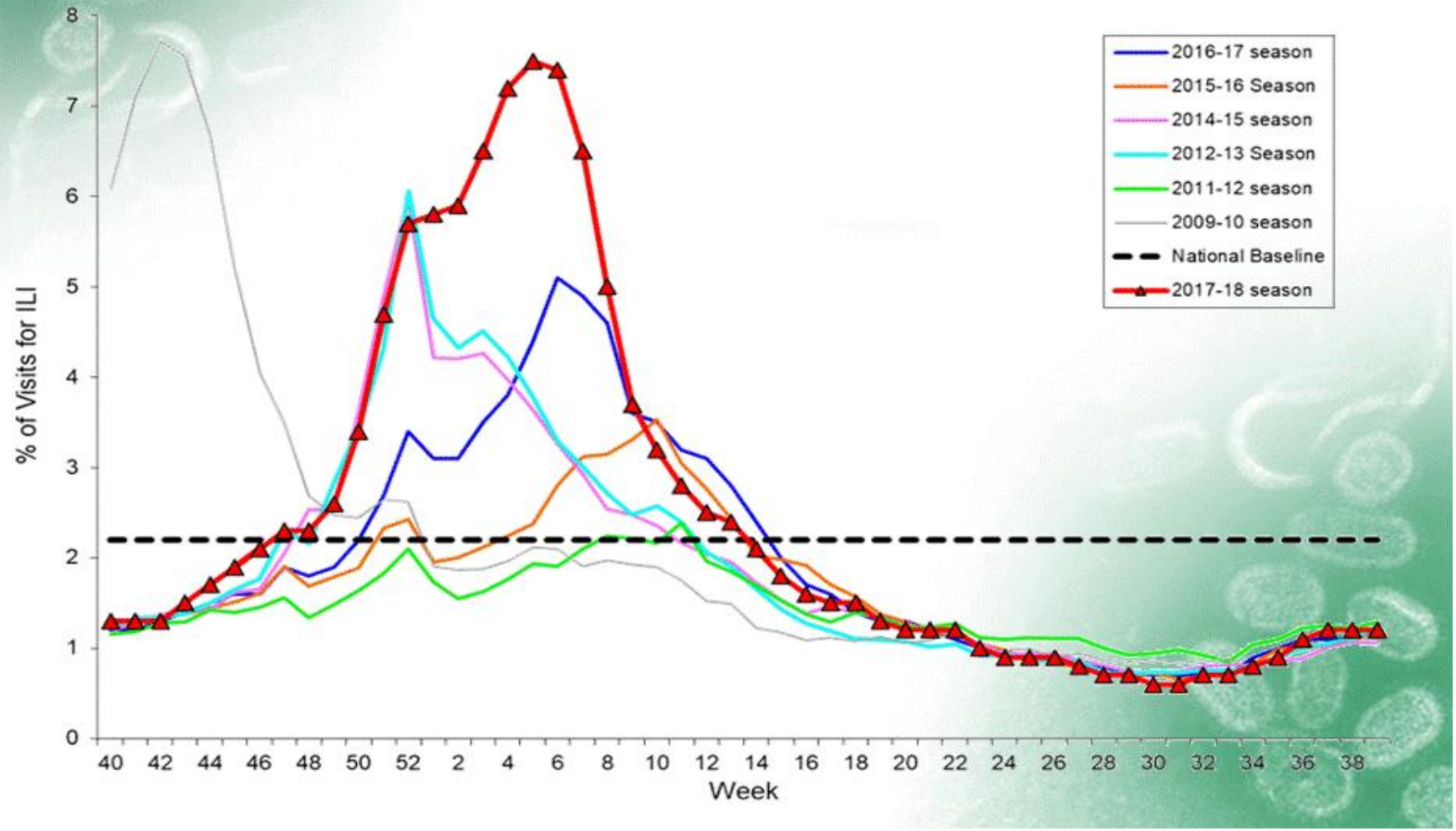
Challenges of H3N2

Impact of 2017-18 Season in the U.S.

FLUVIEW

A Weekly Influenza Surveillance Report Prepared by the Influenza Division

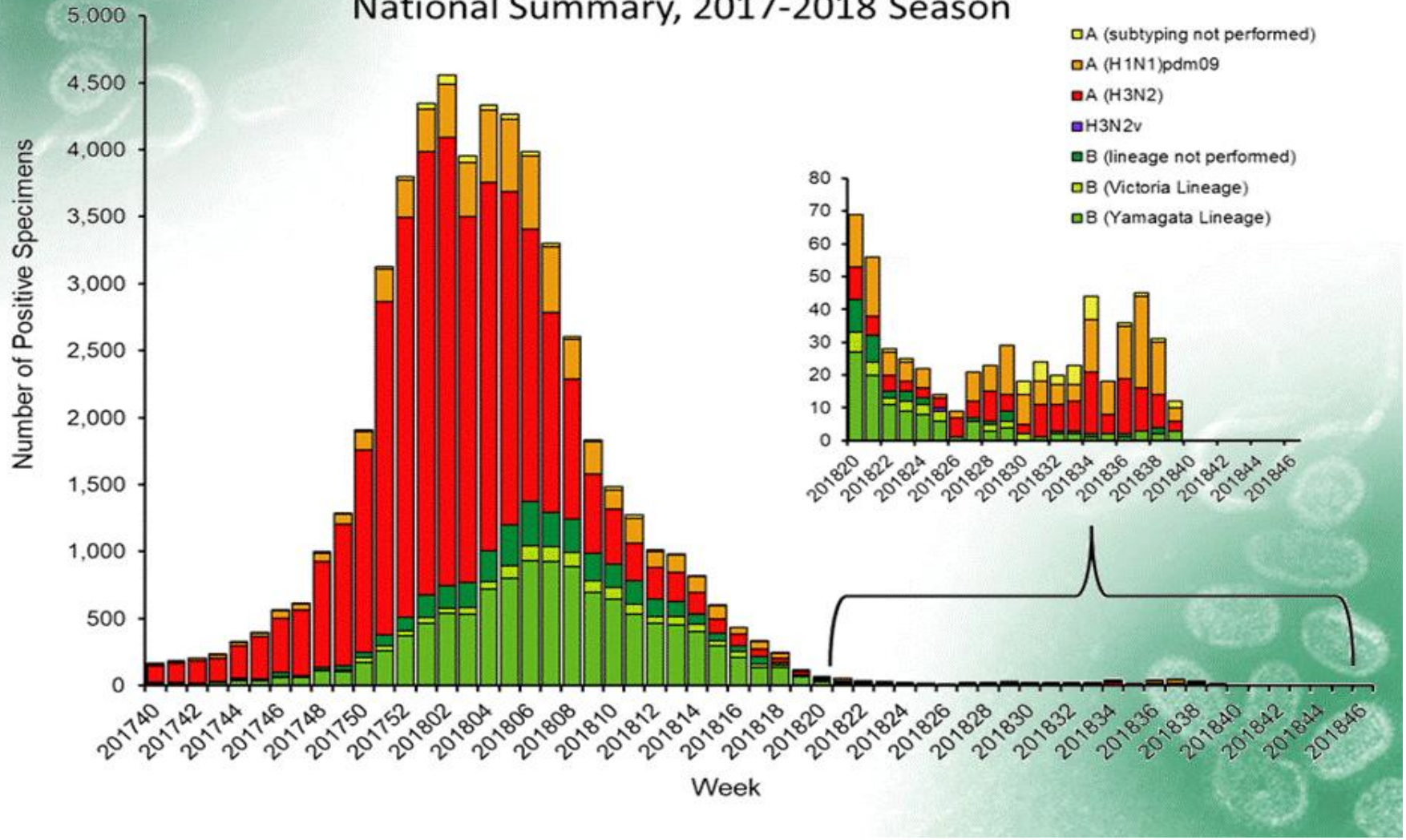
Percentage of Visits for Influenza-like Illness (ILI) Reported by the U.S. Outpatient Influenza-like Illness Surveillance Network (ILINet), Weekly National Summary, 2017-2018 and Selected Previous Seasons



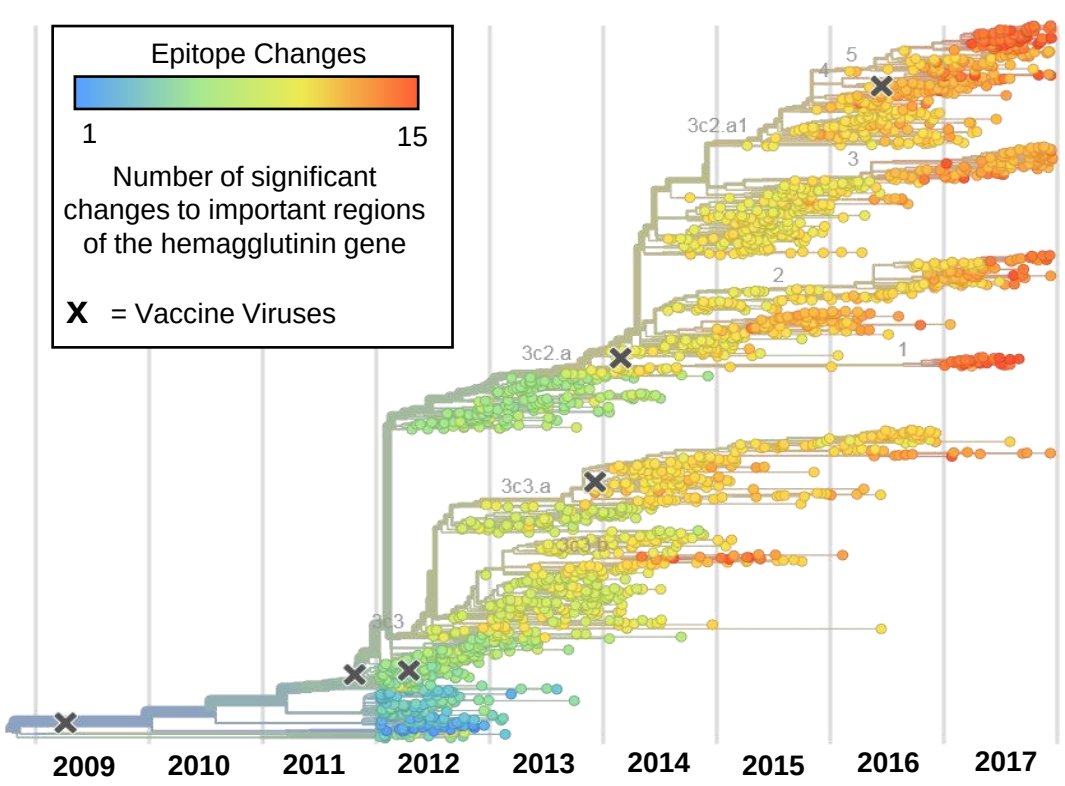
FLUVIEW

A Weekly Influenza Surveillance Report Prepared by the Influenza Division

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



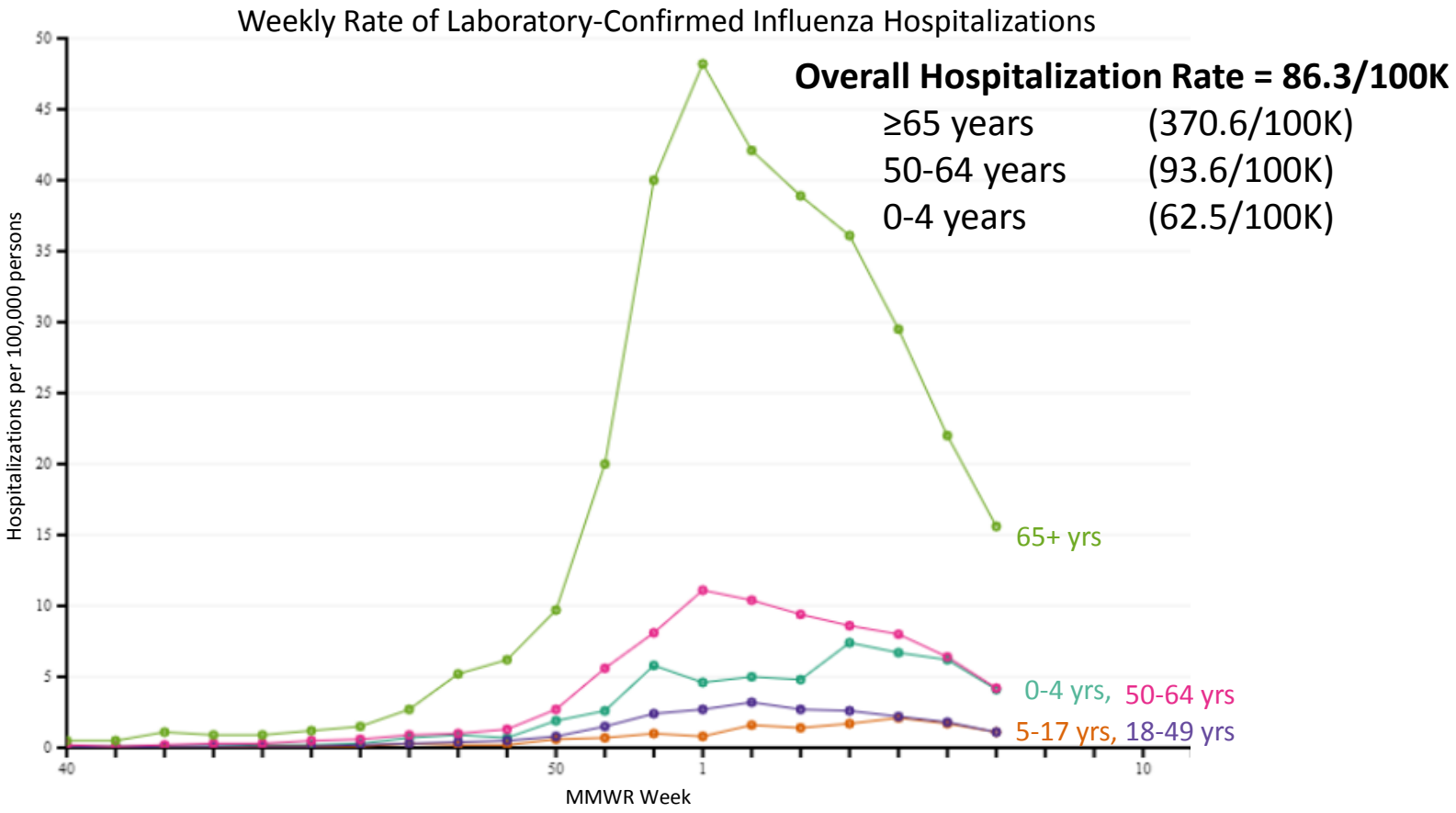
Genetically Distinct H3N2 Clades Currently Circulating



Most common in Australia 2017

Most common in Canada and U.S. 2017-18 season

Hospitalizations Highest Since Surveillance Started

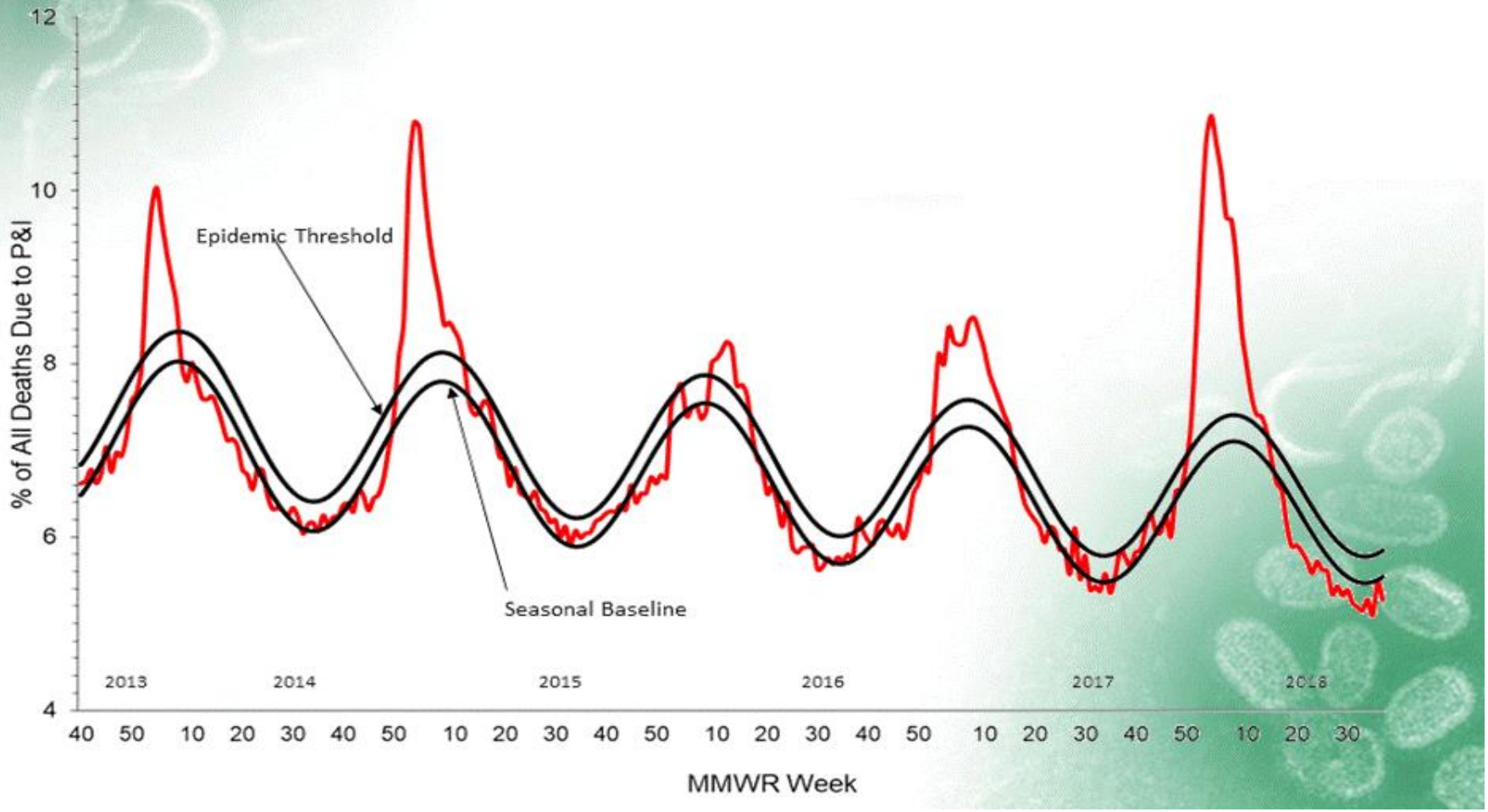


FLUVIEW

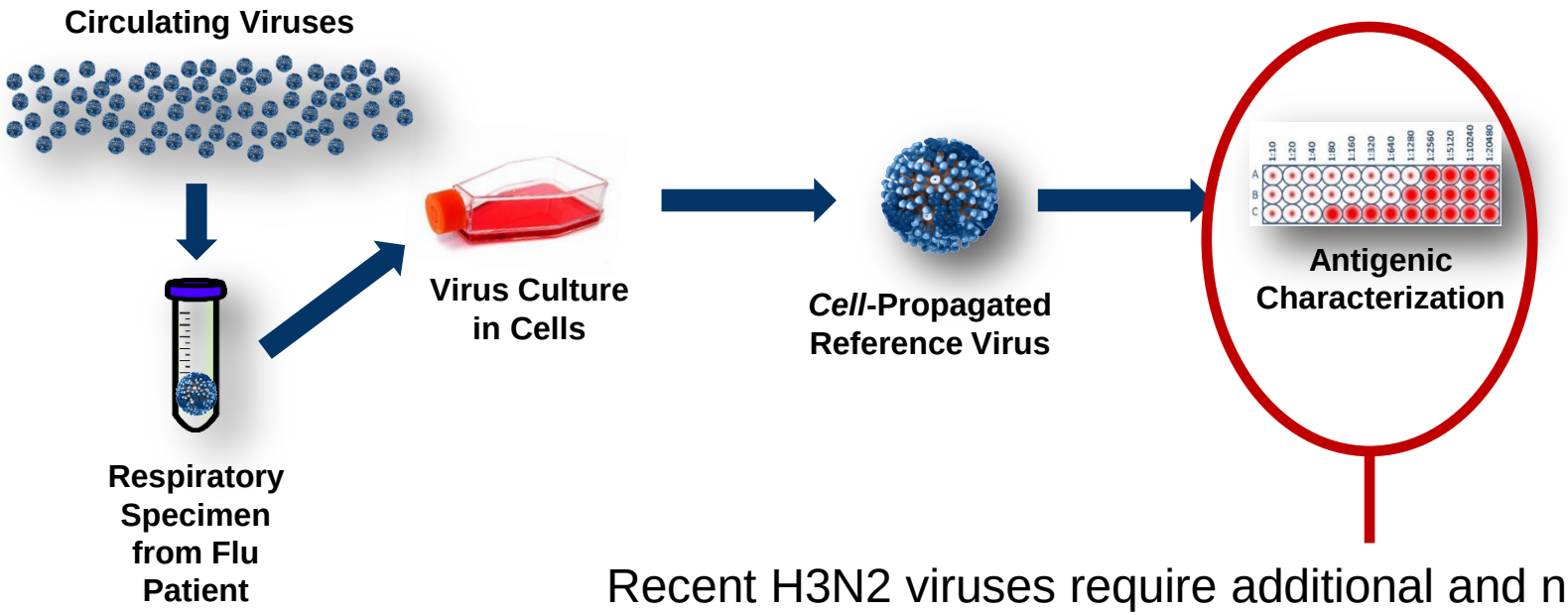
A Weekly Influenza Surveillance Report Prepared by the Influenza Division

Pneumonia and Influenza Mortality from the National Center for Health Statistics Mortality Surveillance System

Data through the week ending September 15, 2018, as of October 4, 2018



Antigenic Characterization of H3N2 Viruses is Increasingly Difficult

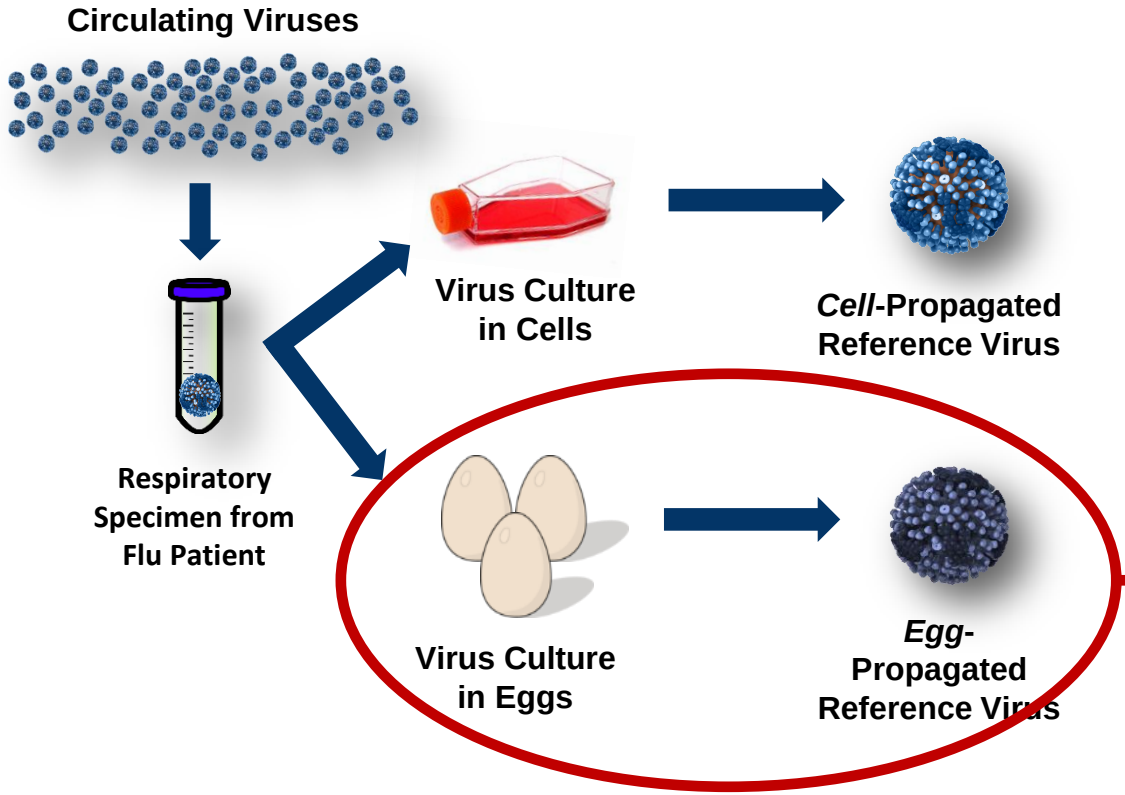


Recent H3N2 viruses require additional and new tests

- Focus-reduction and microneutralization assays
- Developed new “nano-neutralization” assay

H3N2 Virus Growth in Eggs Is Increasingly Challenging

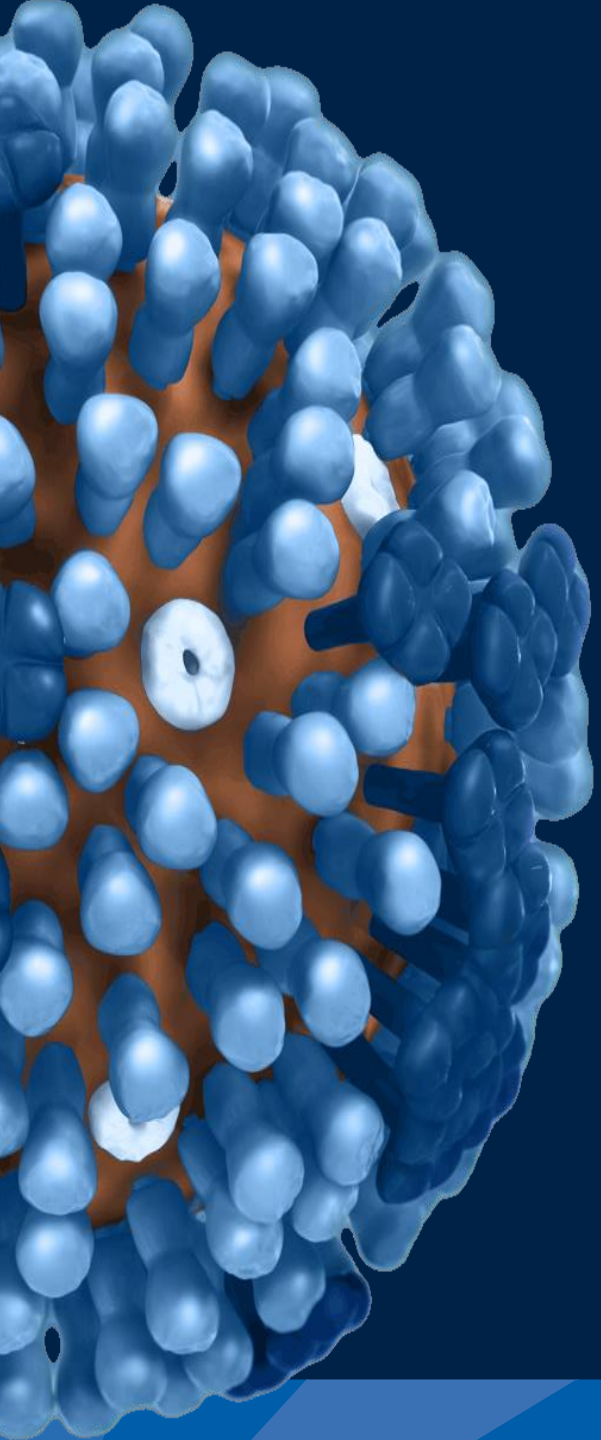
80-85% of Vaccines Manufactured in Eggs



Poor egg-propagation with H3N2 requires virus to adapt, impacting antigenic properties

H3N2 Summary

- During the past 50 years, H3N2 caused more severe influenza seasons than H1N1 and B viruses
- During the past 10 years, H3N2 VE has been lower than for other vaccine components during the past 10 years
- H3N2 viruses have become exquisitely adapted to binding to glycan receptors in the human respiratory tract, limiting development of optimal vaccine viruses for egg-based manufacturing
  - Egg-propagation results mutations in the HA during replication leading to vaccine viruses with lower antigenic similarity to circulating strains which likely contributes to low VE
- Studies are needed to better understand the role of immunological imprinting, repeat vaccination, virus adaptation and other factors that may contribute to both the continued significant impact of H3N2 viruses and reduced VE



Benefits and Burden Averted

Vaccination Benefits

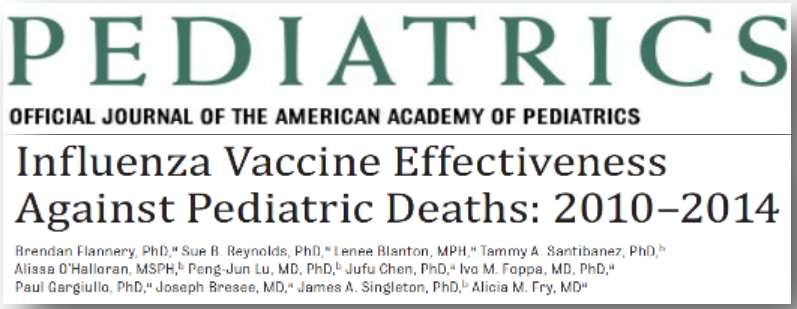
- Prevents influenza illness
- Reduces risk of flu-associated hospitalization in children and older adults
- Important preventive tool for people with chronic conditions
- Protects women during and after pregnancy, and also protects the baby several months after birth
- Reduces a child's risk of dying from influenza

Influenza Vaccine Effectiveness in Preventing Severe Disease in Children

- VE against hospitalization in children[1]
  - **52-79%** reduction in risk of influenza-associated hospitalization (multiple countries, multiple seasons for inactivated and LAIV vaccines)
- VE against critical illness in children (U.S. 2010-2012)
  - **74%** reduction in risk of life-threatening influenza requiring PICU admission

Blyth Eurosurveillance 2016; Cowling Vaccine 2014; Buchan PLOS ONE 2017; Sugaya Vaccine 2018; Pebody Eurosurveillance 2017; Cowling Influenza Other Resp Viruses 2017; 2) Ferdinands J Infect Dis 2014

Vaccine Effectiveness for Preventing Death in Children


PEDIATRICS

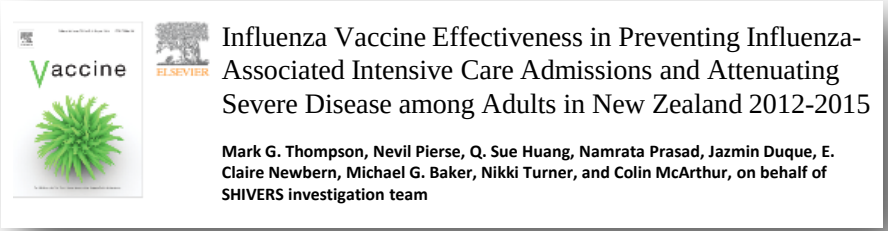
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Influenza Vaccine Effectiveness Against Pediatric Deaths: 2010–2014

Brendan Flannery, PhD,[a] Sue B. Reynolds, PhD,[a] Lenee Blanton, MPH,[a] Tammy A. Santibanez, PhD,[b] Alissa O'Halloran, MSPH,[b] Peng-Jun Lu, MD, PhD,[b] Jufu Chen, PhD,[a] Ivo M. Foppa, MD, PhD,[a] Paul Gargiullo, PhD,[a] Joseph Bresee, MD,[a] James A. Singleton, PhD,[b] Alicia M. Fry, MD[a]

- VE against death in children ***with*** high-risk conditions
  - 51% (31%-67%)
- VE against death in children ***without*** high-risk conditions
  - 65% (47%-78%)

Vaccine Reduces Severe Illness in Adults



- Reduced the risk of non-ICU hospitalization for flu by 32%
- Reduced risk of ICU admission by 82%

- Reduced in-hospital death 52-79%
- Reduced ICU admissions 37%

the **benefits** of **flu vaccination** 2016-2017

The estimated number of flu **illnesses prevented** by flu vaccination during the 2016-2017 season:

5.3 million,

about the population of the Atlanta metropolitan area.

The estimated number of flu **medical visits prevented** by vaccination during the 2016-2017 season:

2.6 million,

or more than the number of students in all K-12 schools in Florida.

The estimated number of flu **hospitalizations prevented** by vaccination during the 2016-2017 season:

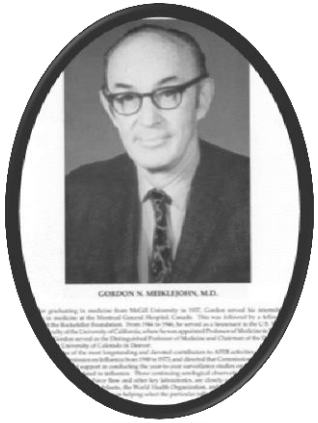
85,000,

or more than the number of hospital beds in California and Oregon.

DATA: Influenza Division program impact report 2016-2017, https://www.cdc.gov/flu/about/disease/2016-17.htm.

Are We Ready For The Next Severe Influenza Pandemic?

Pandemic Influenza Vaccines: Past

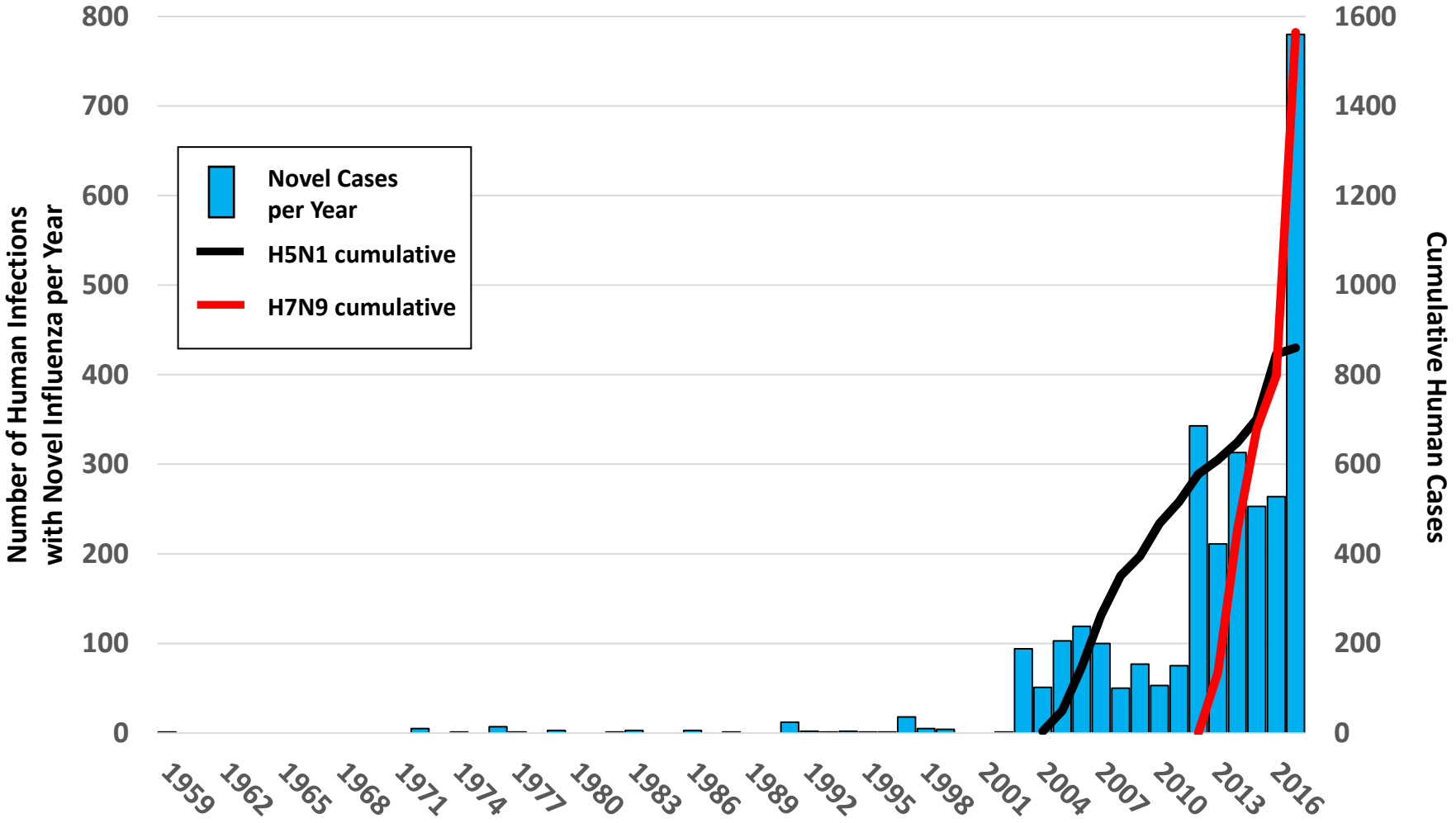


- 1957-58 Influenza Pandemic
  - First pandemic of “modern” virologic era
  - High degree of antigenic change/antigenic shift
  - Virus spread prior to winter season so vaccine was produced for fall wave of disease
  - Studies demonstrated vaccine was immunogenic with 60% vaccine efficacy
  - Vaccines available prior to November disease peak - little public interest and vaccine was wasted

Pandemic Influenza Vaccines: Past

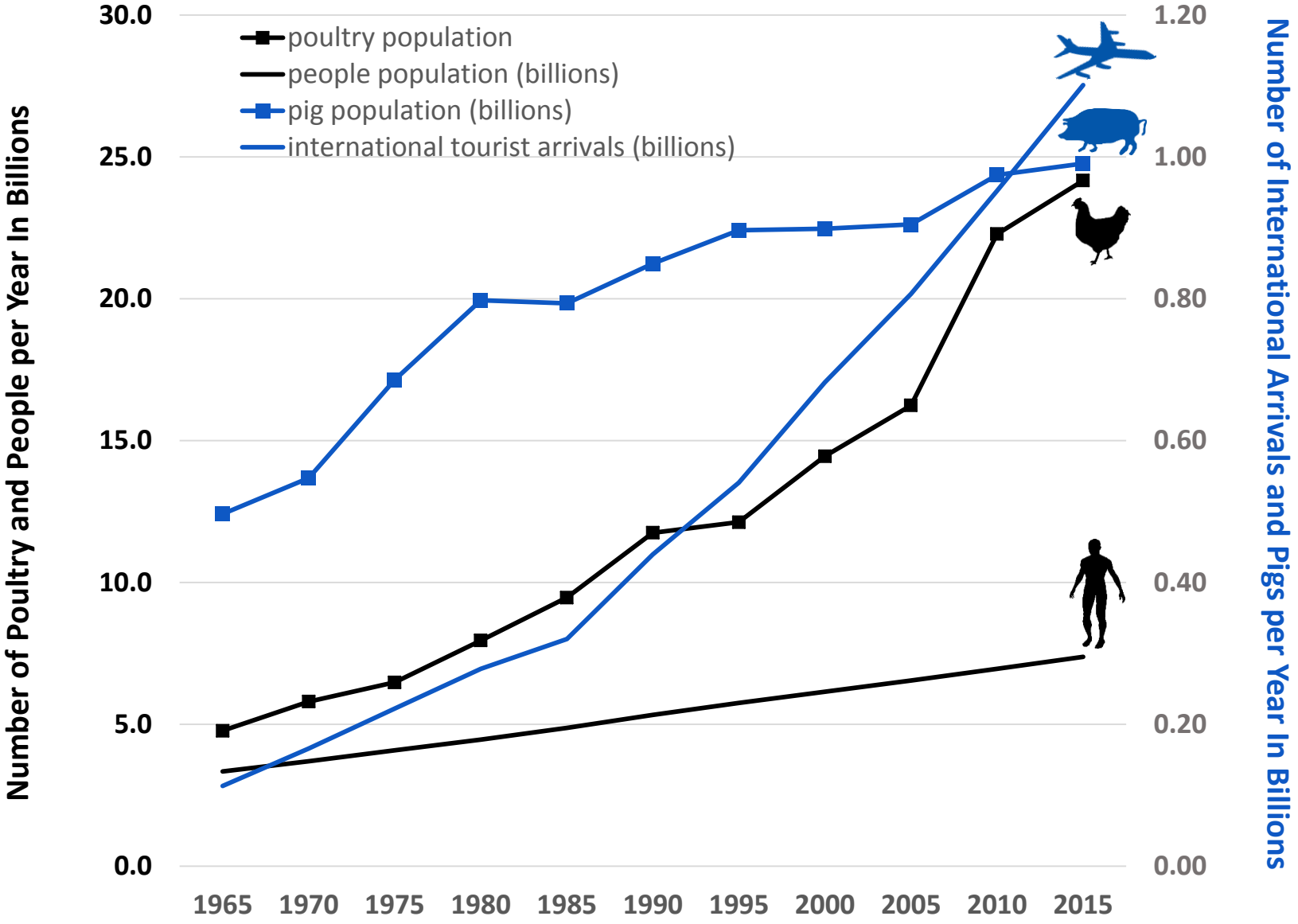
- For the 1968 and 2009 H1N1 pandemics
  - Vaccine production difficulties resulted in delays in availability of vaccine
  - Fall wave of disease peaked about 4 months after vaccine production began
  - Little vaccine available before each of these pandemic outbreaks
  - Vaccine availability/delivery described as ‘too late’

Increasing Number of Human Cases of Novel Influenza A Infection, 1959-2017



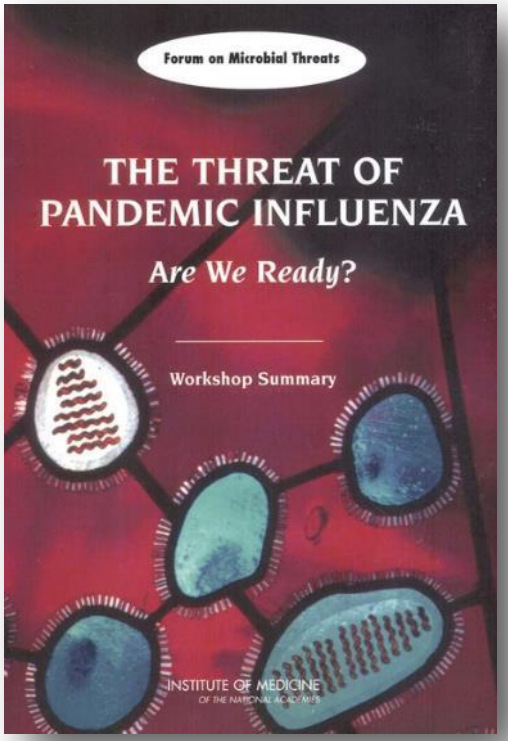
Freidl G, Meijer A, de Bruin E, et al. Euro Surveill. 2014 May 8;19(18); Cumulative cases of H5N1 and H7N9. WHO.
Graph includes avian H4, H5, H6, H7, H9. H10 & swine H1, H3 (not pH1N1).

Increasing Number of Poultry, Pigs, People and Passengers 1965-2015



Pandemic Readiness

- If 1918-like pandemic were to occur today, estimated 105-110 million deaths
  - Infection in 20-30% of global population
- Potential disruption of transportation and just in time supply chains
- Potential disruption of healthcare services
- Potential high economic costs
  - $181B-$570B estimated for moderate to severe influenza pandemic
  - SARS cost $30 billion in only 4 months



Surveillance and Diagnostic Readiness

- Strengths
  - WHO Global Influenza Surveillance and Response System (GISRS)
    - Year-round seasonal surveillance and novel flu detection
    - Significantly greater genomic sequencing of flu viruses and characterization by WHO CCs
  - Greatly improved flu assays for fast results
- Gaps
  - Limited flu testing and poor lab capacity in low income countries
  - 'Data Deserts' in parts of the globe on flu circulation and disease burden
  - Inadequate surveillance in poultry and swine
  - Specimen sharing is too slow and complicated

Development of Candidate Vaccine Viruses for Pandemic Preparedness, Coordinated by WHO

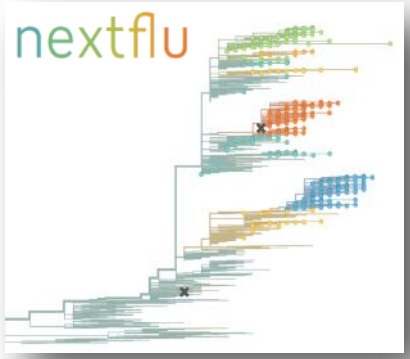
- Creation of a 'library' of pre-pandemic candidate vaccine viruses (CVVs) against known emerging pandemic threats including H5N1, H5N6, H5N8, H7N9, H9N2,H3N2v, H1N2v and H1N1v that originate in birds or pigs but have infected humans
  - Coordinated by WHO at twice annual vaccine composition meetings
  - Began in 2004 with re-emergence of H5N1 bird flu in Asia
  - 60 candidates developed by reverse genetics, lab safety tested and available
  - 13 more vaccine viruses in development

World Health Organization

- Build stockpiles of pre-pandemic vaccines and adjuvants
  - USG funded studies to determine CVV growth characteristics for production and immunogenicity and safety of vaccines in humans for a subset of the CVVs
  - Bulk quantities of some of these pre-pandemic vaccines have been stored
  - Caveat - very expensive to maintain and may become outdated

Vaccine Readiness

- Strengths
  - New vaccine technologies available
    - Synthetic biology for making vaccine viruses
    - Cell-grown vaccines
    - Recombinant protein vaccines
  - Improved virus gene sequencing and virologic forecasting
    - More rapid sharing of influenza gene sequences via GISAID's sharing mechanism
  - More global manufacturing capacity
    - WHO Global Action Plan
  - New programs for introducing vaccine for low and middle income countries
- Gaps
  - Vaccine production takes too long for effective pandemic response
  - Need more effective seasonal and pandemic vaccines as we work toward a truly "universal" influenza vaccine



GAP INFLUENZA VACCINES

PIVI THE TASK FORCE FOR GLOBAL HEALTH
PARTNERSHIP FOR INFLUENZA VACCINE INTRODUCTION

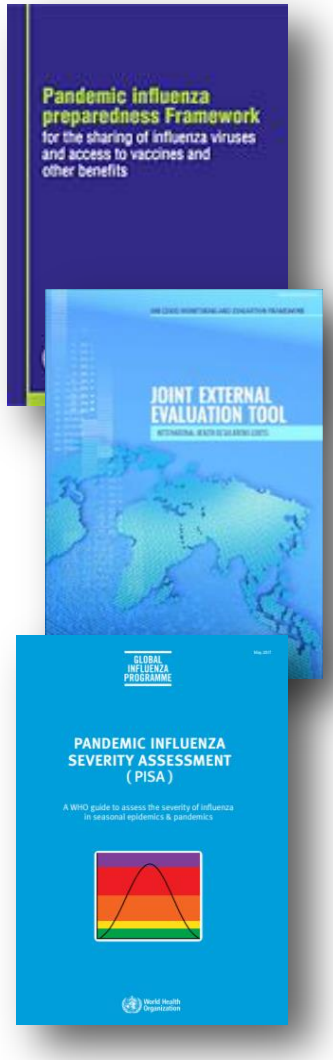
Therapeutic and Clinical Readiness

- Strengths
  - Antivirals
    - Increased availability of antivirals and new monoclonal antibody (mAb) therapies in pipeline
  - Clinical Care
    - After SARS/MERS/Ebola, new facilities built for treating patients with emerging infections with high fatalities

- Gaps
  - Need better performing antiviral treatments with:
    - Benefit in severe, hospitalized influenza infections
    - Greater availability and lower cost
  - Need reusable respiratory protective devices
  - Ventilatory and clinical support capacity is insufficient in most of globe for a severe pandemic

Preparedness Planning and Response

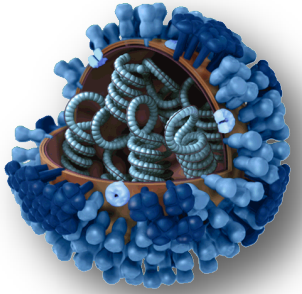
- Strengths
  - International Health Regulations since 2005 for greater awareness and response to pandemic threats
  - WHO Pandemic Influenza Preparedness (PIP) Framework
    - Support for improving surveillance and more equitable response during an influenza pandemic
    - 400 M vaccine doses anticipated for LMIC in next pandemic
  - Response Tools are Available
    - Pandemic Risk Assessments (IRAT and TIPRA)
    - Pandemic Severity Assessments (PISA)
    - Pandemic preparedness resources
- Gaps
  - Most countries lack robust pandemic plans and very few exercise response efforts
  - Only 1/3 of countries ready for response based on IHR review



Conclusions

- Seasonal influenza causes a significant burden each year, but the 1918 pandemic was exceptionally severe
  - A similar pandemic today could cause tremendous illness, death, and cost

- Number of emerging novel influenza viruses is increasing, necessitating ongoing laboratory surveillance and risk assessments



- Efforts to improve pandemic readiness and response are underway, however, many gaps remain

- Are we ready in 2018 for a severe influenza pandemic?
  - Better than we were before the 2009 pandemic, but not where we need to be
  - **Vaccine readiness has a long way to go**

Thanks to Dan Jernigan for slide updates.

Thanks to all in the Influenza Division, CDC for their work and dedication.

Thanks to the WHO Global Influenza Surveillance and Response System for 7 decades of work on influenza.

Thanks for your Attention!
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