Influenza Vaccine
What are the Challenges?

Vaccinology 2018, Panama

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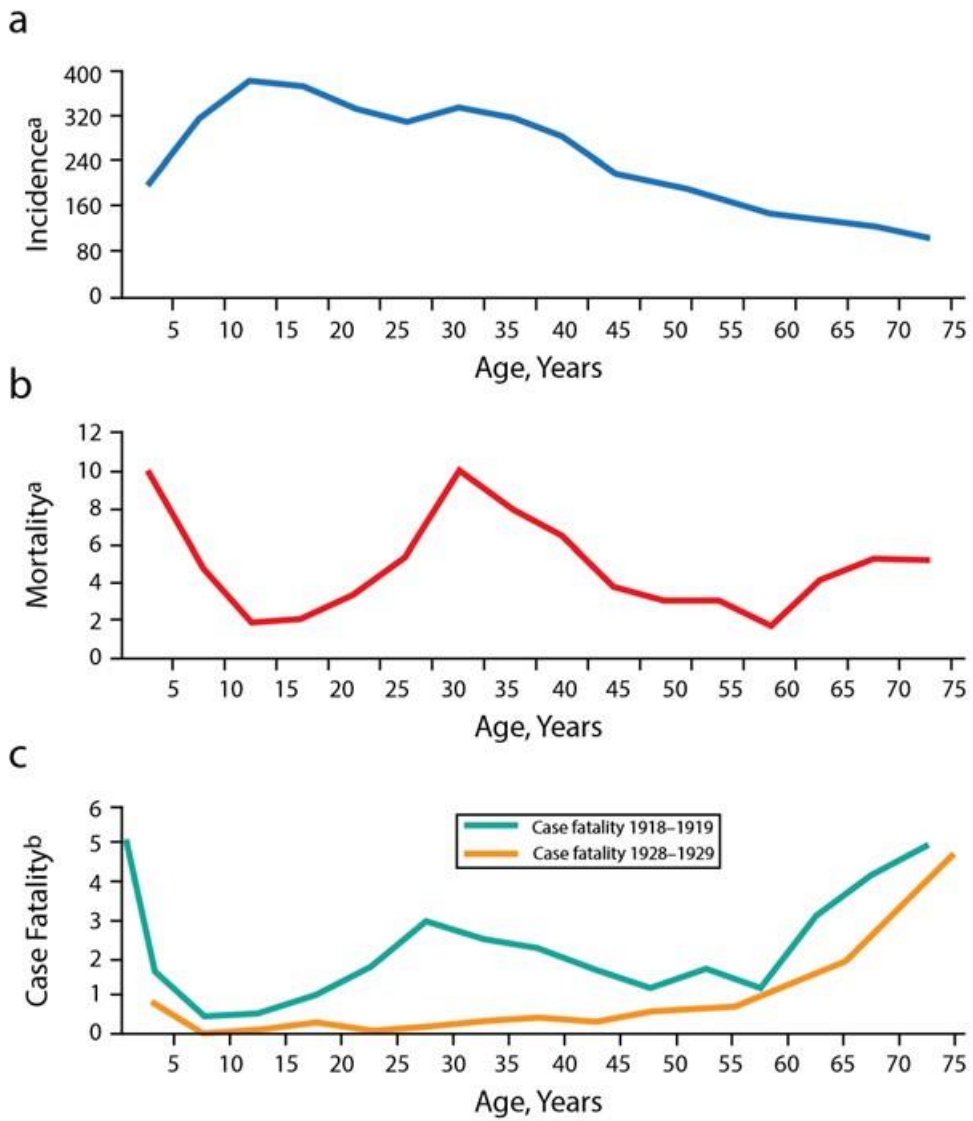
The 1918 -2018 Influenza Pandemic Anniversary

- 50-100 million deaths
- Unexpected clinical and epidemiological features
- Rapid global spread
- High mortality in young adults 20-40 yr
- Mortality associated with secondary bacterial pneumonia (staph, strep) more than influenza virus itself

Morens and Taubenberger, JPH 2018



Note. P&I = pneumonia and influenza. The bottom figure also compares typical U-shaped age-specific case fatality in 1928–1929 (bottom figure, amber line) with the unique 1918–1919 W-shaped curve of case fatality. A U-shaped curve of age-specific mortality is not shown but is similar in all respects to age-specific case-fatality curves.

[a]Per 1000 persons per age group.

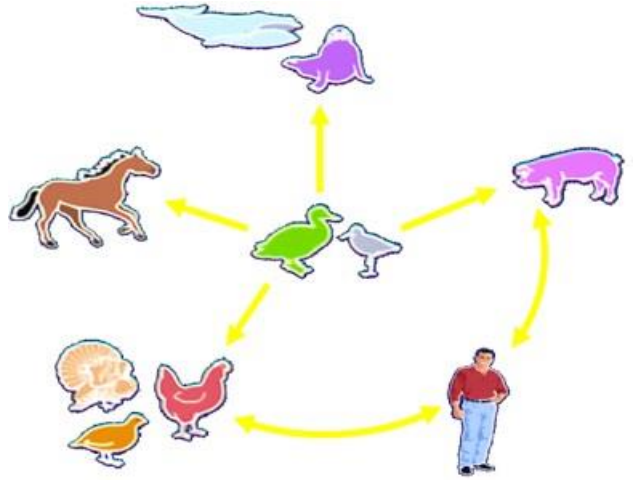
[b]Per 100 persons ill with pneumonia and influenza per age group.

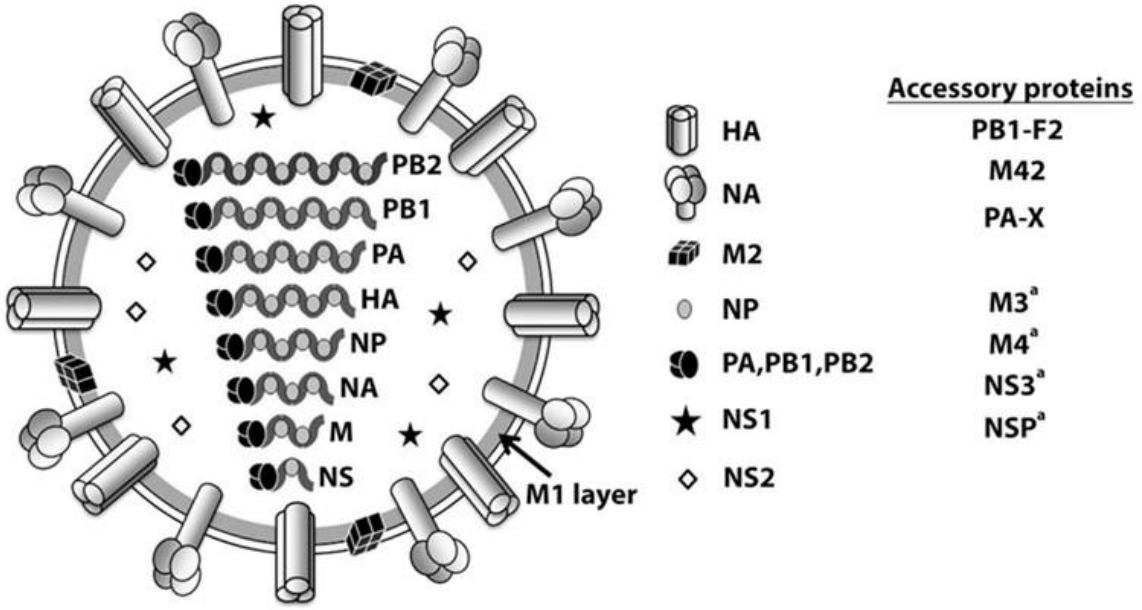
FIGURE 5—Age-Specific 1918–1919 Pandemic Influenza (a) Incidence, (b) Mortality, and (c) Case Fatality: United States

Morens and Taubenberger, JPH 2018

Pandemic viruses

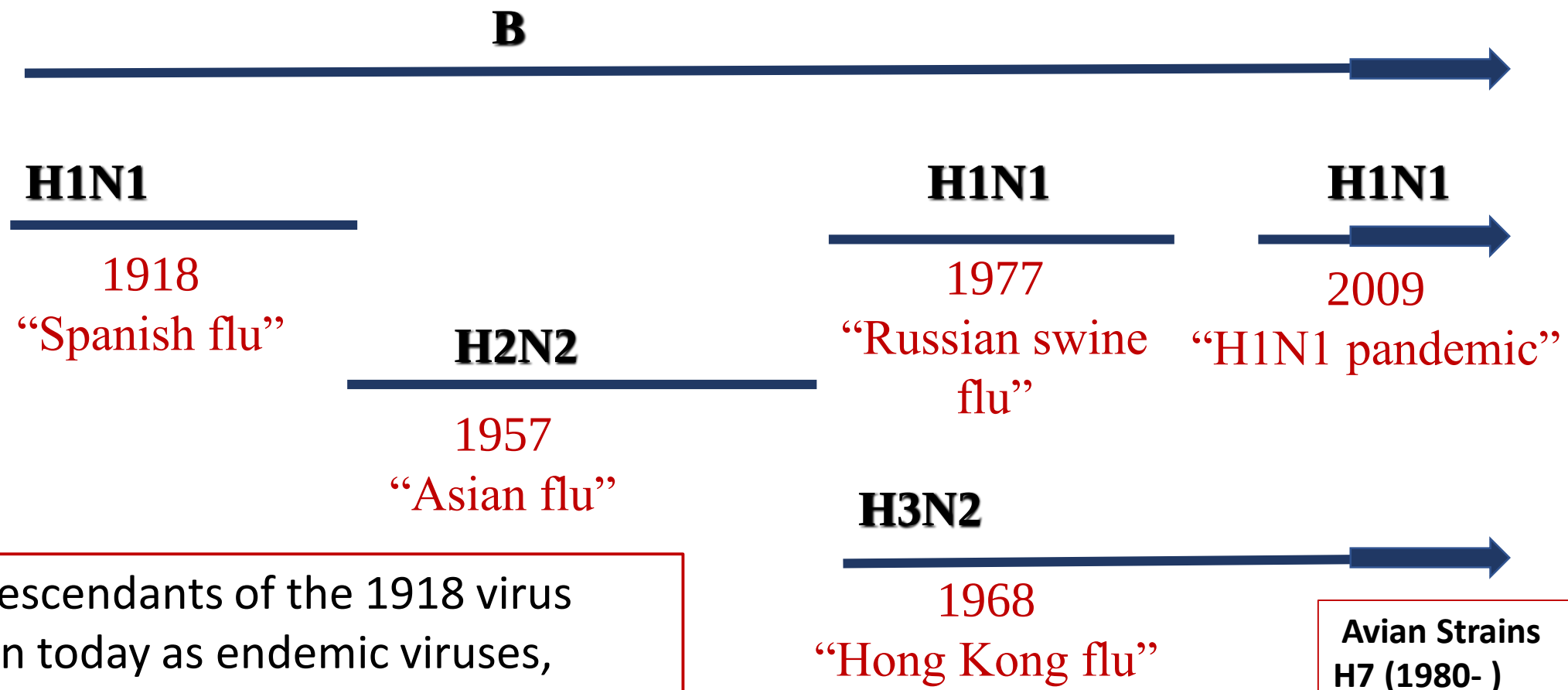
1. Direct or intermediate emergence of wild waterfowl viruses (1918 H1N1 virus)
2. Acquisition of gene segments via reassortment of novel HA subtypes (antigenic shift)
3. Complex evolutionary mechanisms (2009)





Morens and Taubenberger, JPH 2018

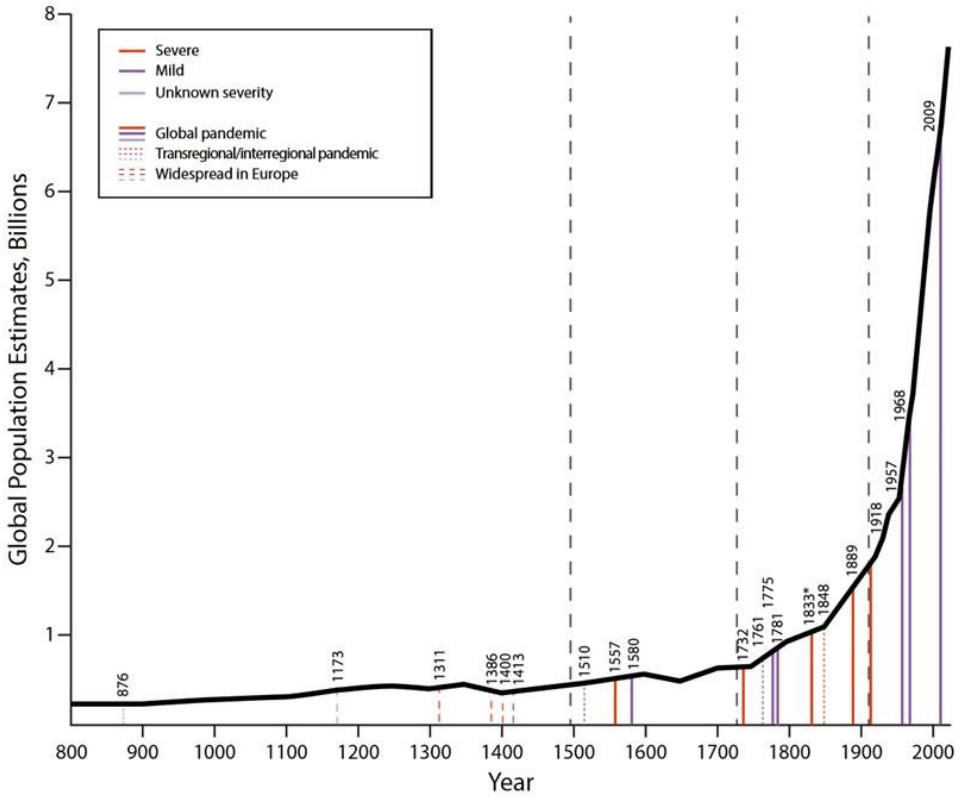
1918 Influenza Virus Strains and Pandemics of the 20th and 21st century



The descendants of the 1918 virus remain today as endemic viruses, causing significant mortality each year

Avian Strains
H7 (1980-)
H5N1 (1997-)
H9 (1999 -)

Where do we stand ?



Note. In the era before clipper ships and rapid intercontinental travel (i.e., before the mid-19th century), widespread pandemics were sometimes hemispheric rather than global.[2] Although human crowding and travel are associated with influenza spread and explosivity, the data do not suggest a clear role of human population size in the emergence of pandemics.

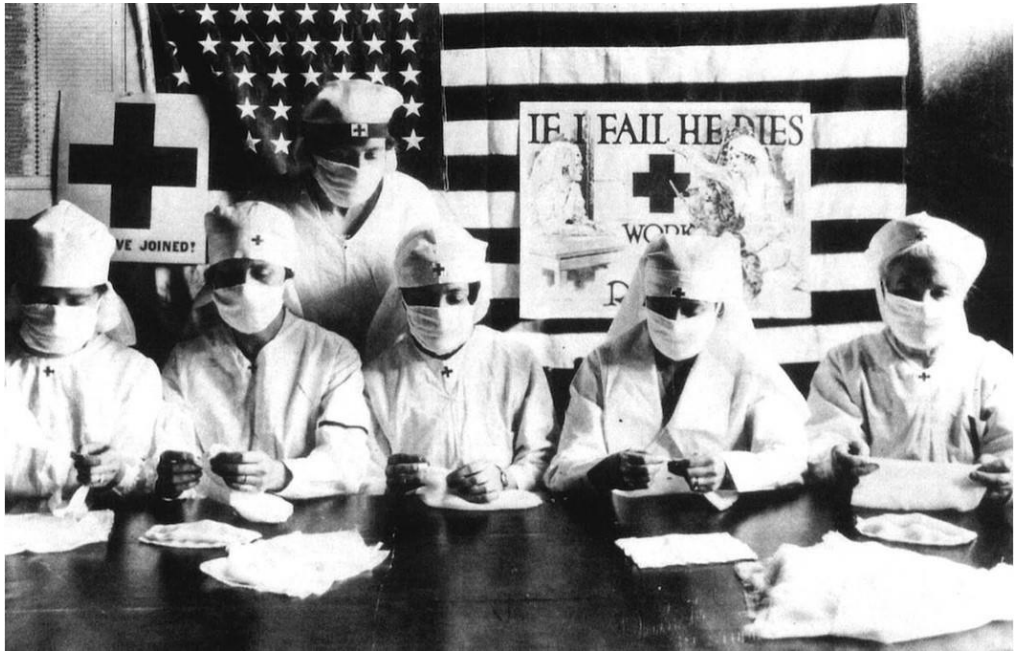
FIGURE 3—Severe and Mild Pandemics of Presumed Influenza Between 876 and 2018, as a Function of Global Population and Geographic Extent

Morens and Taubenberger, JPH 2018

- We **do not** currently **have tools to predict or prevent** the emergence of influenza pandemics
- **Partial protection** has been observed in every pandemic in individuals previously exposed to similar H1 or N1 of the 1918 virus or its descendants
- In experimental studies, contemporary waterfowl H1 gene segments confer the same degree of **pathogenicity** as the 1918 pandemic H1
- If the **population immunity to H1** ever drops significantly, an H1 pandemic as deadly as that of 1918 might result
- **Maintaining population immunity to H1 may be important for pandemic prevention**

Where do we go from here ?

- Better **surveillance** can improve understanding of avian viral circulation and evolution, but is unlikely to identify pre-pandemic viruses.
- **Time to produce effective vaccines** against novel strains still does not allow rapid intervention
- We do have better understanding of the utility of **standard public health approaches** in limiting and slowing pandemics (isolation, school closures, etc), which can help reduce spread and mortality while vaccine is available
- We have **antivirals and antibiotics**
- **Early diagnosis and treatment** can be life saving – given rapid progression - including early identification of viral/bacterial infection (**improved diagnostics**)
- We have **vaccines for influenza** (moderately effective) and **pneumococcus** (highly effective), still need **staph aureus** vaccines (**need improved vaccines**)



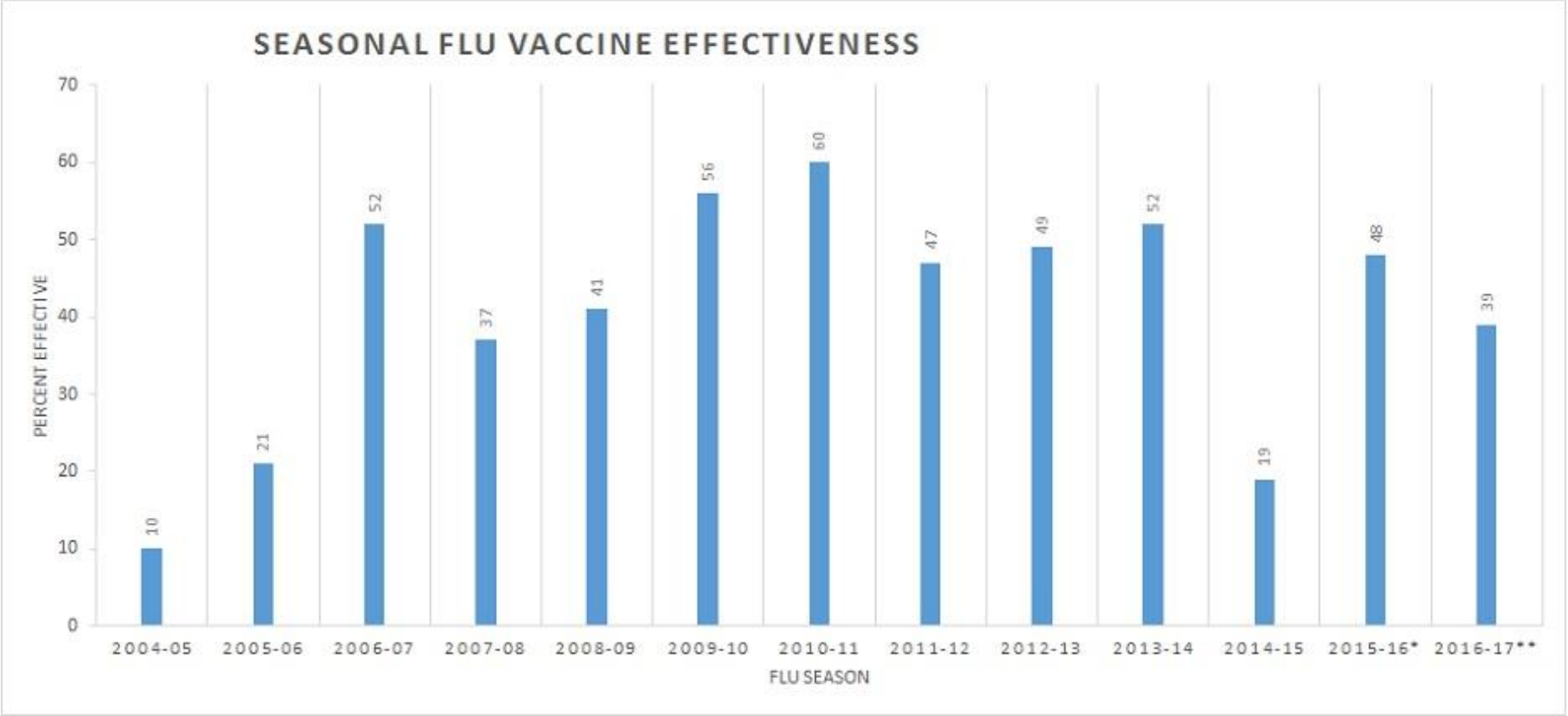
In 1918 the single variable most associated with influenza survival was good nursing care

Morens and Taubenberger, JPH 2018

Effectiveness of Seasonal Flu Vaccines 2004-2017 Flu Seasons

Factors affecting Flu Vaccine Effectiveness:

- Match of vaccine and circulating strain
- Health status
- Age
- Time of vaccination in relation to season
- Other?

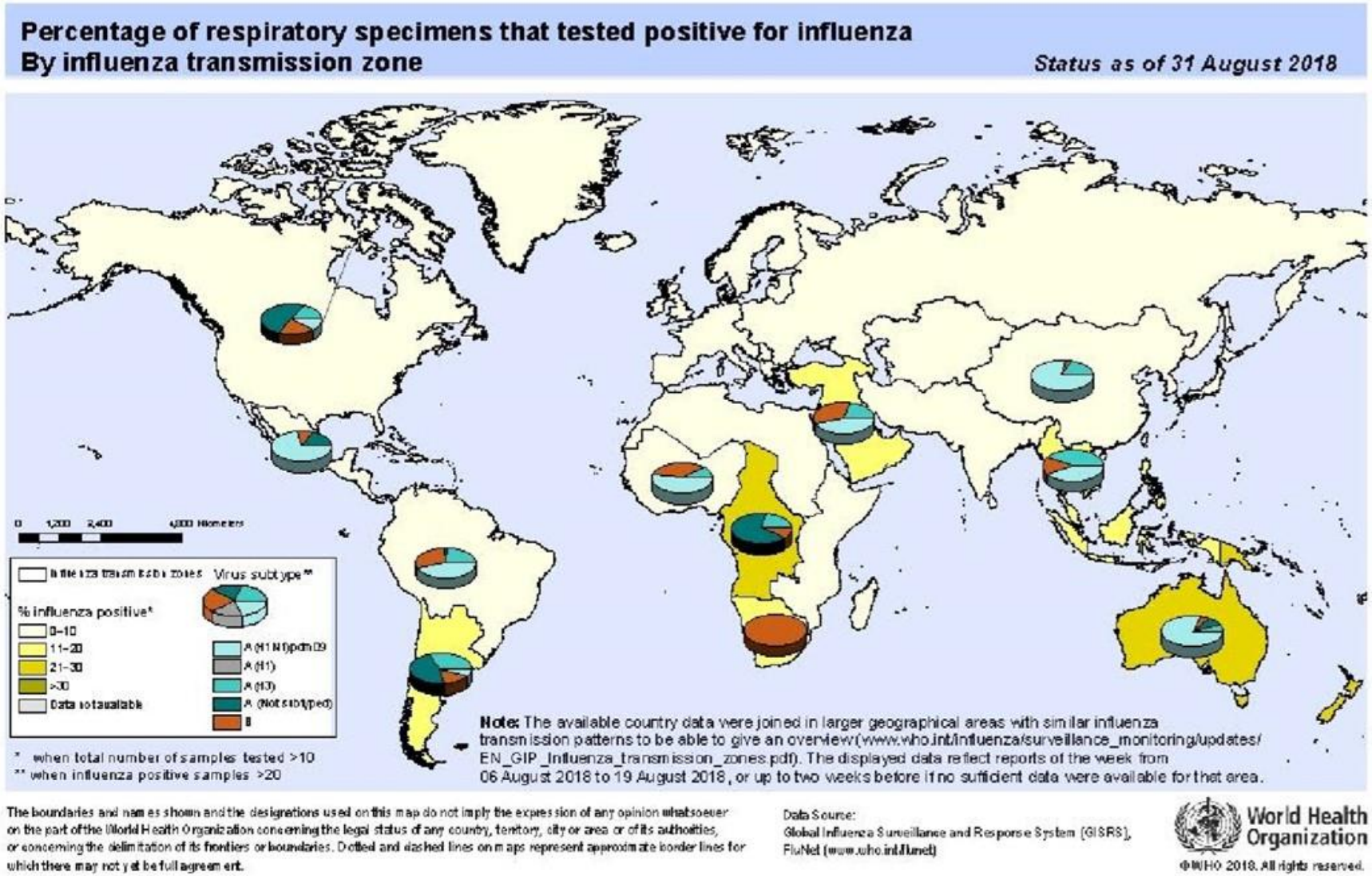


Influenza Vaccination Protects against Severe Influenza and Death

- **PICU Hospitalization**
  - 44 cases, 172 PICU controls, 93 community controls among children 6 mo-17 yrs, in 21 PICUs in US, 2010-2012 (PALISI)
  - Vaccinated children were **74%** (95% CI 19-91%) **or 82%** (95% CI 23-96%) **less likely to be admitted to PICU for influenza** vs. PICU or community controls
  - 1 dose only (when 2 needed), was NOT protective
- **Death**
  - 359 influenza associated deaths among children 6 mo to 17 years
  - 26% received flu vaccine vs. 48% in comparative survey cohort
  - **Overall VE against death: 65%** (95% CI 54%-74%)
  - **Children with high-risk conditions VE: 51%** (95% CI 31%-67%)
  - **Children without high risk conditions VE: 65%** (95% CI 47% to 78%)

Ferdinands et al. J Infect Dis 2014; Flannery et al. Pediatrics 2017

Influenza in 2018

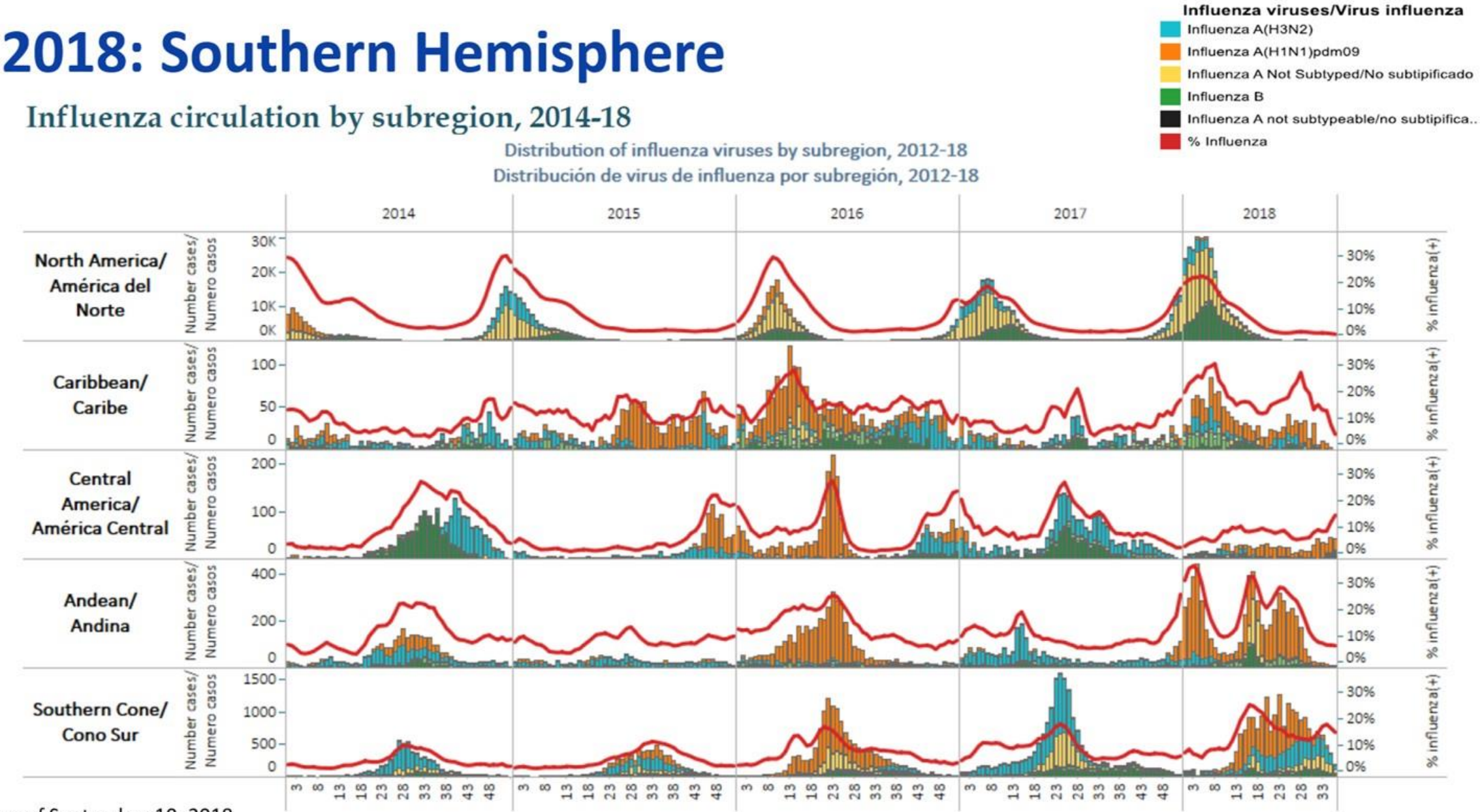


Data Source:
Global Influenza Surveillance and Response System (GISRS),
FluNet (www.who.int/flunet)

World Health Organization

2018: Southern Hemisphere

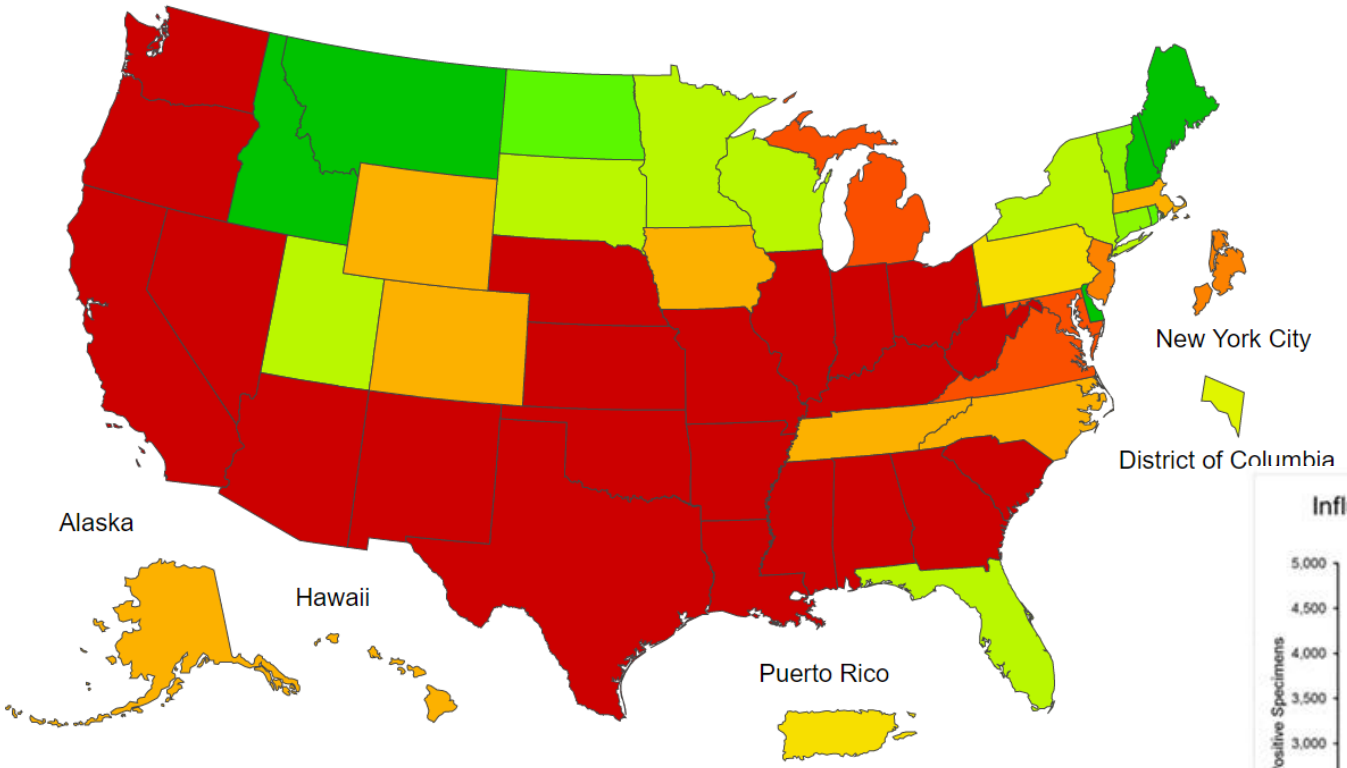
Influenza circulation by subregion, 2014-18



Data as of September 10, 2018

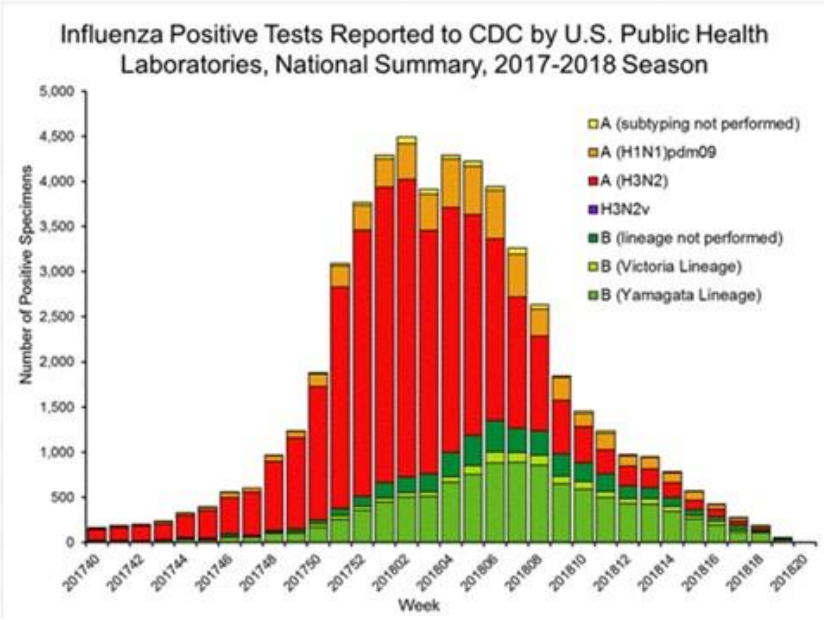
https://www.paho.org/hq/index.php?option=com_content&view=article&id=3352:influenza-situation-report&Itemid=2469&lang=pt

2017-18 Influenza Season Week 52 ending Dec 30, 2017

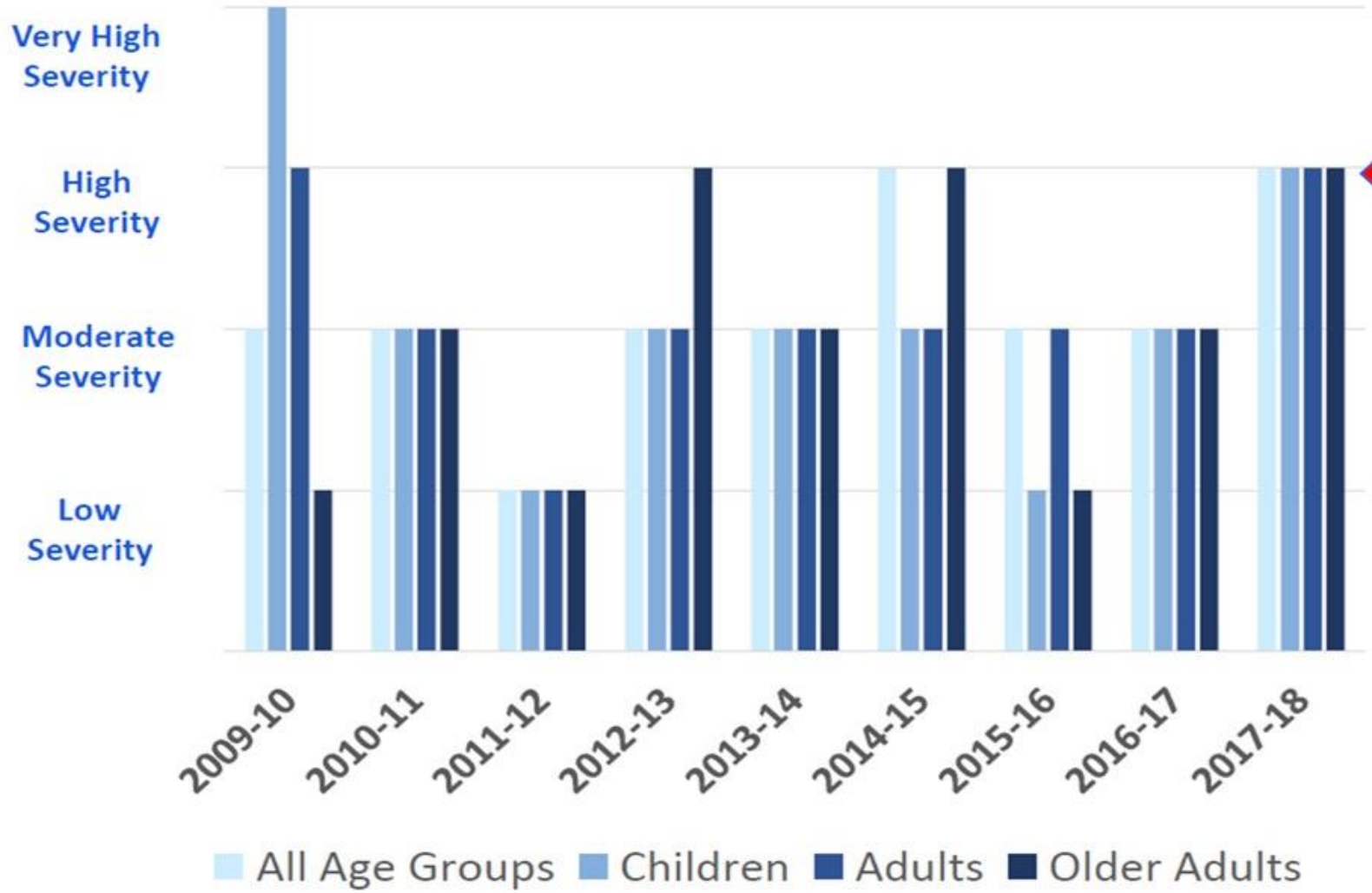


ILI Activity Level

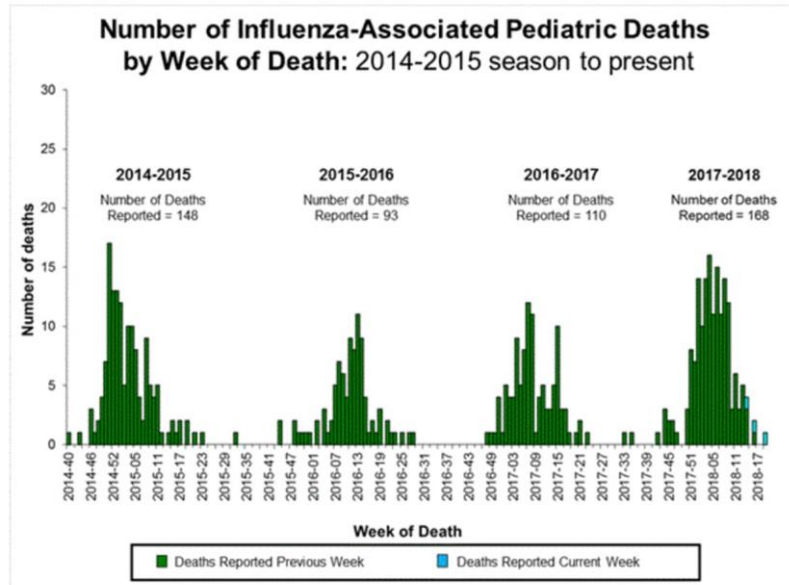
- High
- Moderate
- Low
- Minimal
- Insufficient Data



Season Severity Assessment – By Age Group and Season, 2009-10 through 2017-18



2017-18 was High Severity based on outpatient visits, hospitalizations, and deaths



Biggerstaff, et al Am J Epi 2018

2018-2019 Influenza Vaccine Recommendations

USA

<u>Everyone</u> starting at 6 months of age

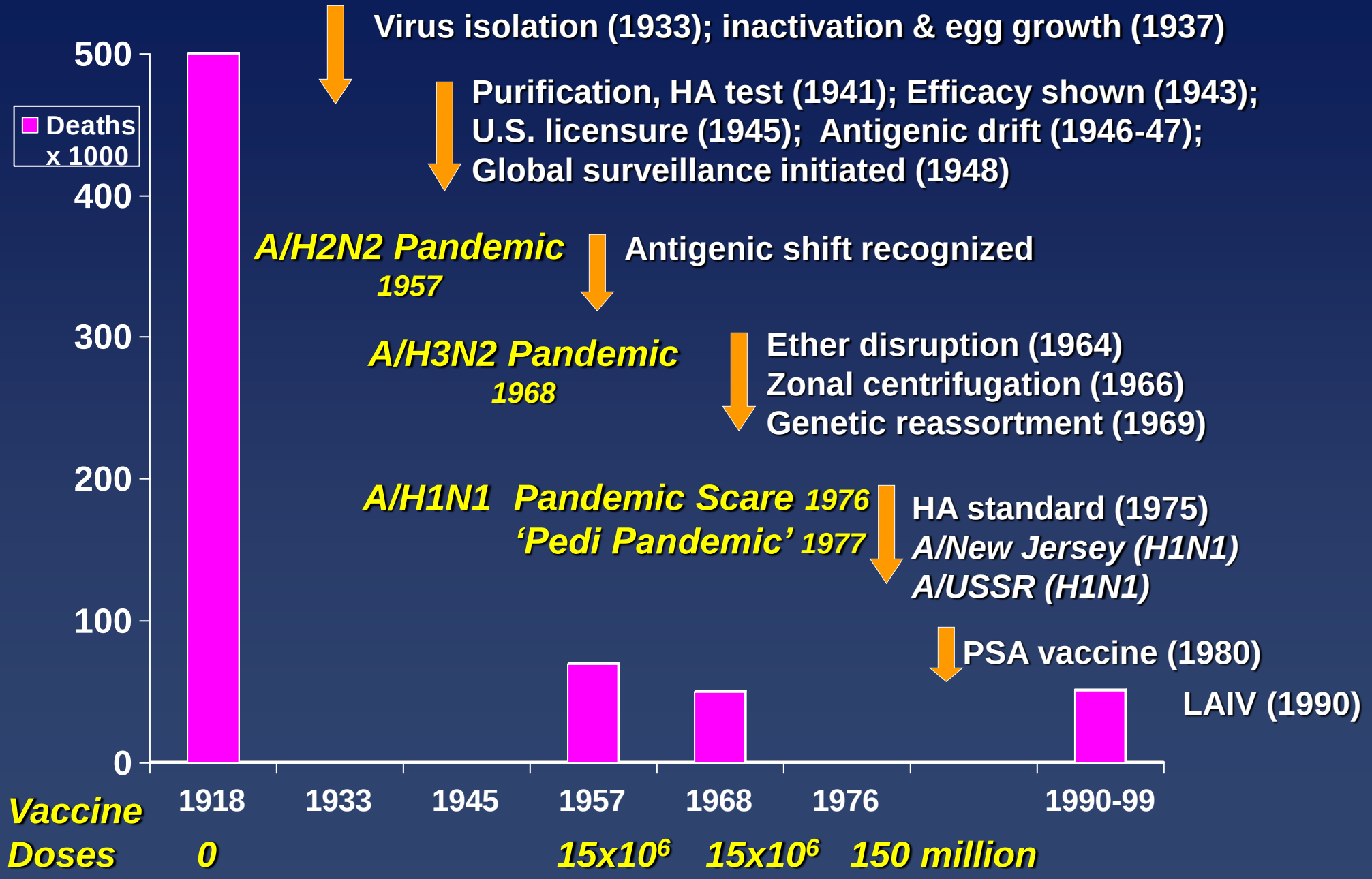
World

High Risk groups

The Challenges of Influenza

- Permanence of viruses in the environment and global circulation
- Ability of viruses to change requires annual vaccination (duration of protection limited by need to match strains)
- Short incubation period (1-4 days) limiting containment options
- Everyone is at risk – those at higher risk have lower vaccine performance
- Variable, moderate vaccine effectiveness to prevent infection, severe disease and mortality
- Need to better understand the basis and correlates of natural and vaccine-induced immunity, especially on the mucosal immune system
- Acceptance: Low recognition of influenza as a severe disease
- Cost-effectiveness, accessibility, production of sufficient number of doses

Influenza Vaccine Development in the 20th Century



Limitations of current vaccines and potential solutions

Limitation	Potential Solution
• Dependence on Egg-based production	• Cell-culture based production of virus • Recombinant Antigens • Synthetic Vaccines
• Limited efficacy in elderly and unprimed populations	• Increase immunogenicity and breadth of immune response
• Lack of cross reactivity	• “Universal” vaccine
• Limited worldwide availability	• Addition of adjuvants / dose sparing • Alternative administration routes • Increase heat stability and shelf life • Technology transfer production

Looi H Int Rev Immunol 2018

Next Generation Influenza Vaccines

WHO Statement (2016)

- Safe and well tolerated influenza vaccines that **prevent severe influenza illness, provide broad protection beyond single year***, and are suitable for programmatic use, are needed for low and middle income countries (LMICs).
- Vaccines with broad activity against influenza strains can substantially reduce the impact of annual influenza epidemics and pandemics

* Next Generation Vaccines

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WHO Preferred Product Characteristics

WHO Preferred Product Characteristics (PPCs) for next-generation influenza vaccines five and ten year strategic goals.

Five year goal	By 2022, greater protection against vaccine-matched or drifted influenza strains than provided by currently prequalified non-adjuvanted non-replicating influenza vaccines, and protection against severe influenza for at least one year, will have been demonstrated for seasonal influenza vaccines that are suitable for high-risk groups in low- and middle-income countries
Ten year goal	By 2027, influenza vaccines that have the potential to provide protection against severe influenza A virus illness for at least five years, and are suitable for high-risk groups in low-and middle-income countries, will be in advanced clinical development

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How do we get there?

- **Development of universal influenza vaccines will be challenging and protracted**
- Development of **improved seasonal vaccines** may represent the lower hanging fruit in terms of regulatory acceptability, compared to the timelines for a truly universal vaccine.
- Develop **public health goals** and **guidance to establish improved performance** of such vaccines

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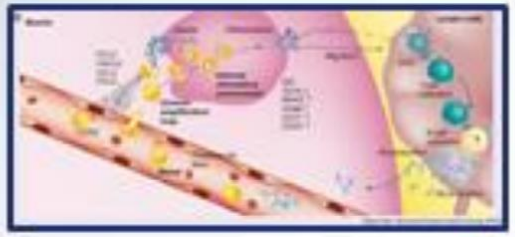
Potential to meet the 5-year goal with Existing vaccines

- Adjuvanted vaccines (e.g. MF59), high-dose, and live attenuated vaccines have the potential to induce broad and/or longer lasting protection
- Efforts to evaluate these vaccines in expanded age groups and populations should be prioritized

Potential to meet the 10-year goal with Novel vaccines

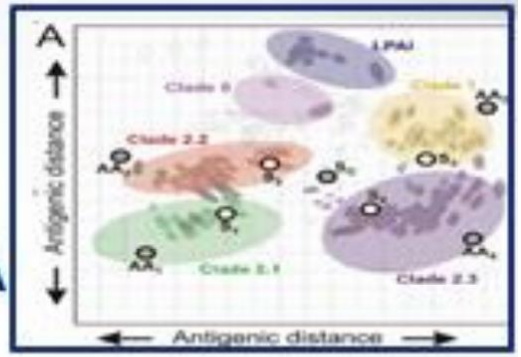
- Most currently licensed vaccine induce strain specific neutralizing serum antibodies to HA, which offer limited protection
- **Broadly protective vaccines result in humoral and cellular immune responses directed to conserved epitopes** shared by various influenza viruses, rather than immunodominant and variable epitopes that are affected by antigenic drift and shift.
- Innovative approaches include:
  - Rational antigen design
  - Novel approaches to antigen delivery
  - Adjuvants
  - Heterologous prime-boost regimens

Current Development Efforts



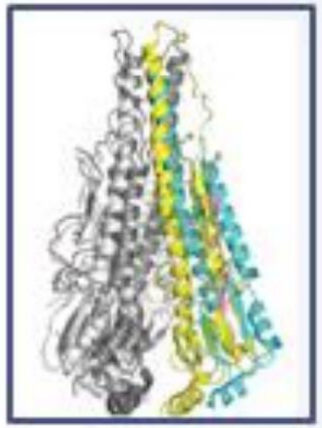
Adjuvants

Antigenically advanced HA vaccines

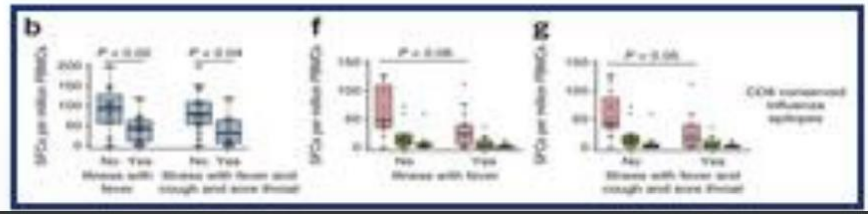


Mucosal delivery

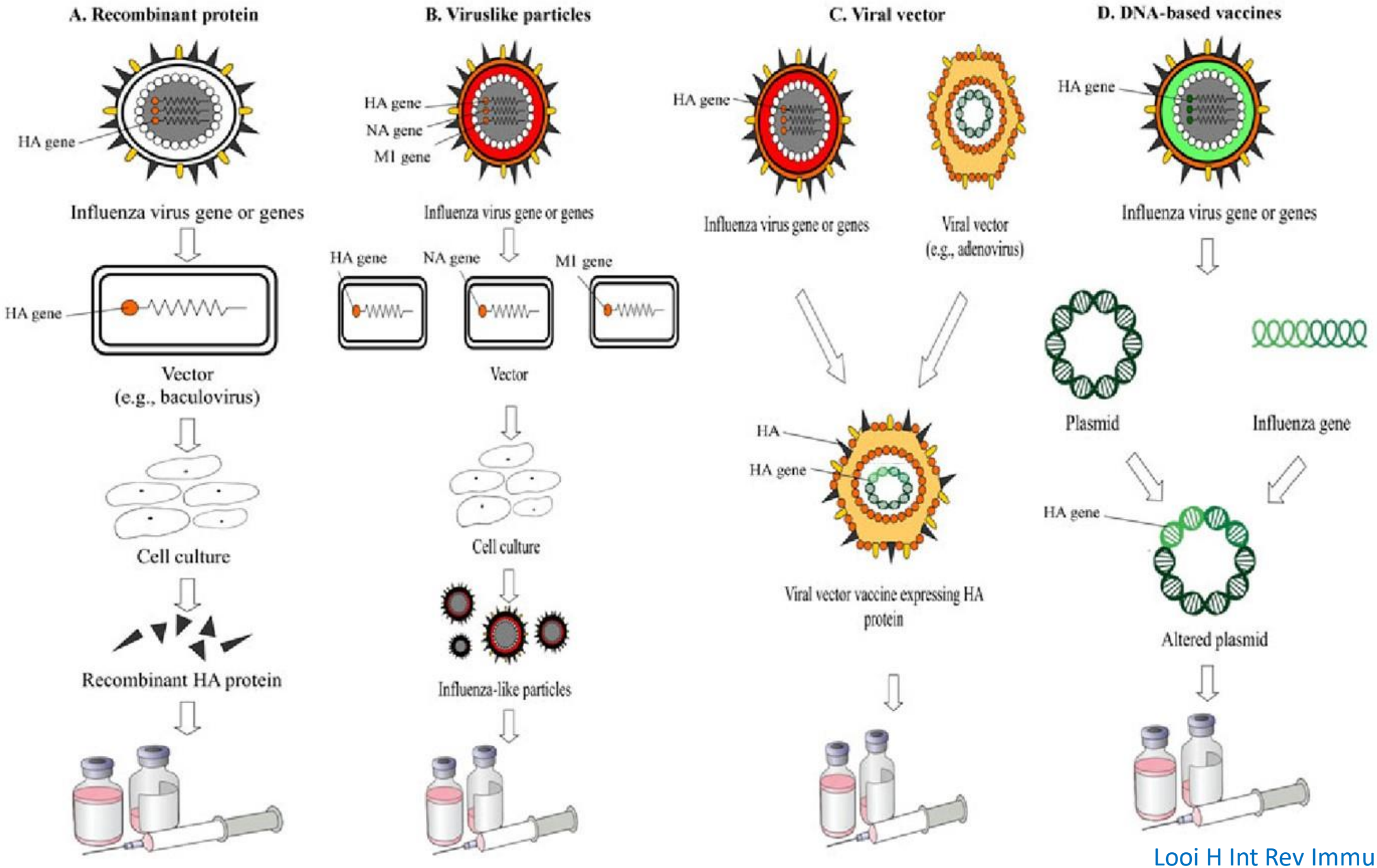
Targeting HA Stem



T-cells to conserved Ag



Source: WHO/BARDA_PDVAC17



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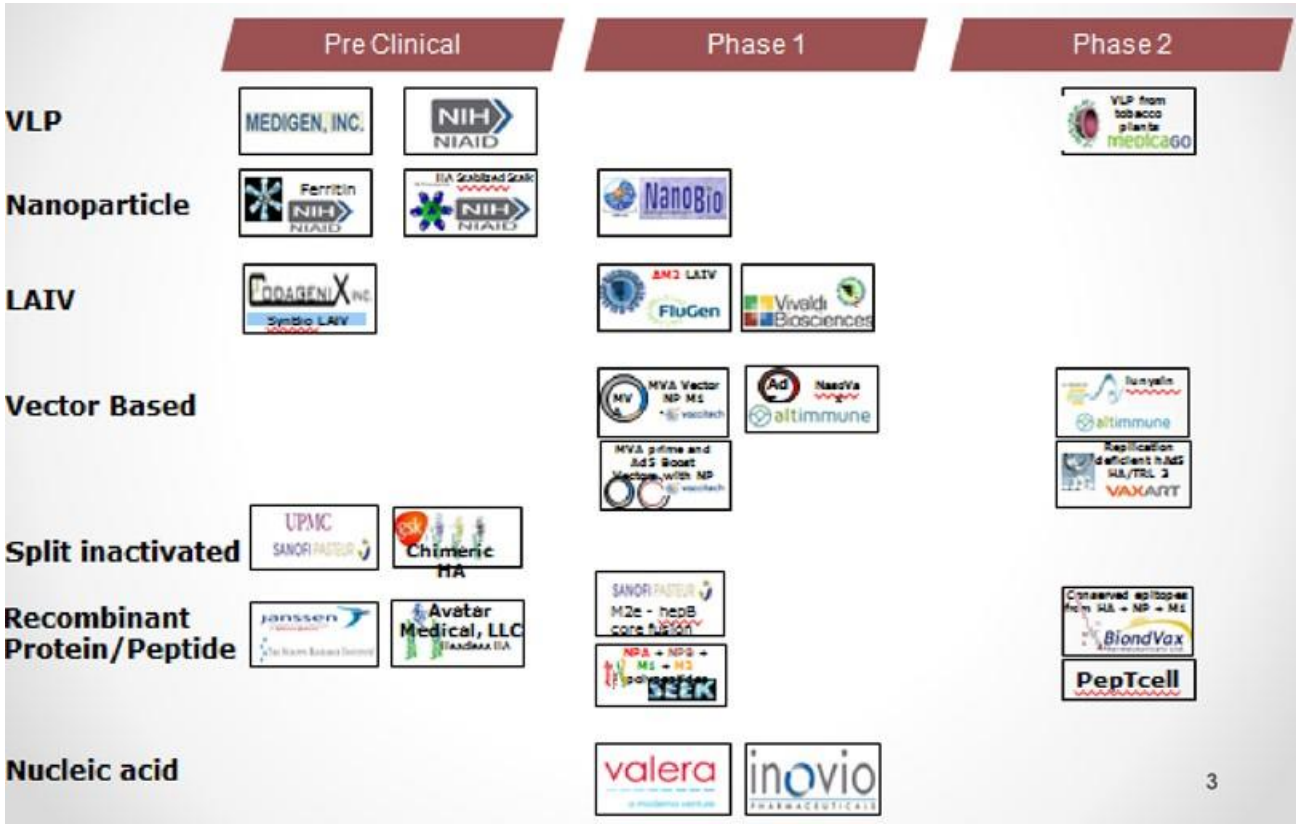
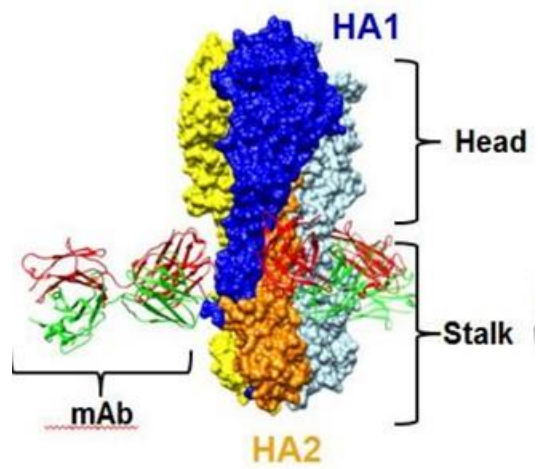
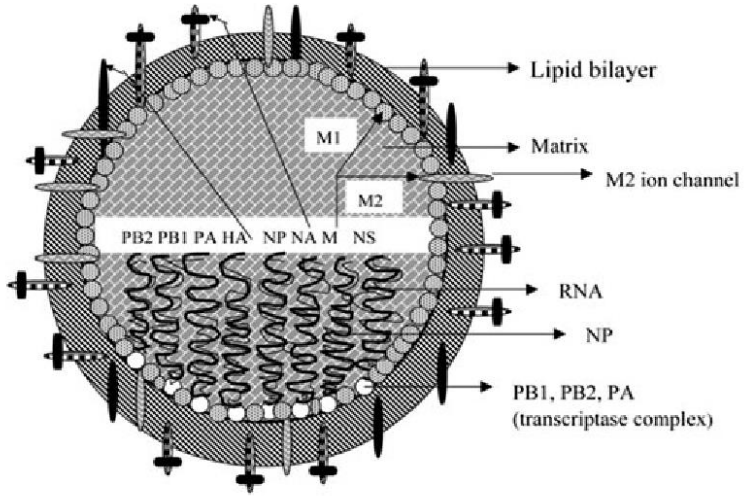
Landscape of broadly protective "universal" vaccines

- Several (~20) vaccine candidates in US and Europe
- Target antigens: M2e, HA-stalk region







Additional considerations

Immunologic and virologic assessments

- Evaluation in ‘new populations” such as children < 6 months
- Understanding of immune responses to influenza infection and vaccination in different target groups
- Understanding the impact of repeat vaccination

Assay Development and Standardization

- Development of new assays to detect antibodies to different viral target antigens, CMI assays and correlates of protection.

Additional Considerations

Correlates of Protection

- New vaccines will require biomarkers and new correlates of protection
- Regulatory guidelines will likely require efficacy studies for licensure

Human Challenge Studies

- Allow detailed analysis of human immune responses and identification of correlates of protection.
- Difficult to do and exclude children

Additional Considerations

Clinical Trials

- **Phase III studies** to demonstrate **not inferior efficacy** to current vaccines **and clinical benefit** from increased breadth of protection and/or increased duration of immunity
- Well powered (large) to demonstrate **superior prevention of any severity and severe influenza disease**
- Need to **establish the magnitude, quality and duration of immunity in unprimed children and primed individuals** of all ages, to understand the effect of previous exposures on protection, and discount the possibility of disease enhancement or rebound effects.
- **Longitudinal clinical trials** needed (2-5 years) to establish **surrogates of durable immunity (primary clinical endpoints: laboratory confirmed disease of various severit**
- **Post-licensure studies ies and assessment of circulating and similar or drifted strains)** to assess **protection and safety in neonates, pregnant women, and other special populations**
- **Post-marketing risk management plan** to monitor benefits and risks of influenza vaccines

The road is long – but our journey has begun

Source: Malik Masim@google