Influenza pandemic preparedness: current global strategy

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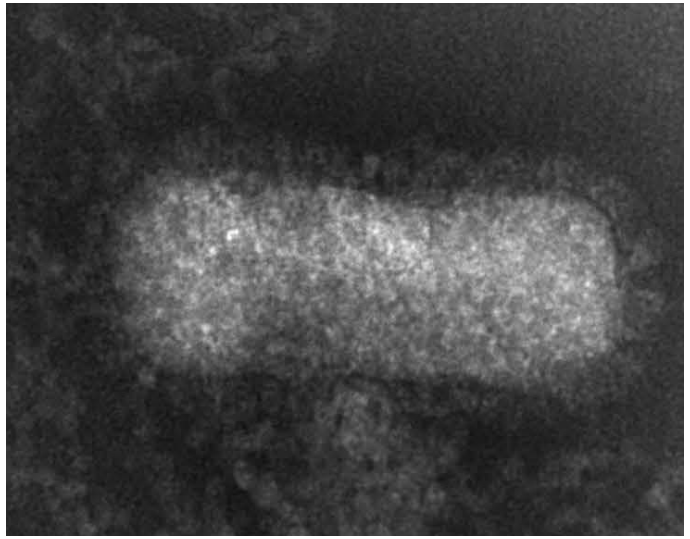
Influenza- a viral respiratory disease of global importance

- Influenza pandemic considered the greatest threat to global public health
- In 2018, the world observed the centenary start of the 1918 influenza pandemic
  - Resulted in > 50 million deaths (more than WWI)
  - Led to fundamental changes in public health and health care systems
- Impossible to predict when the next pandemic might occur, considered inevitable
- Increased economic globalization, mobility, urbanization, climate change
  - Next pandemic will spread further and faster

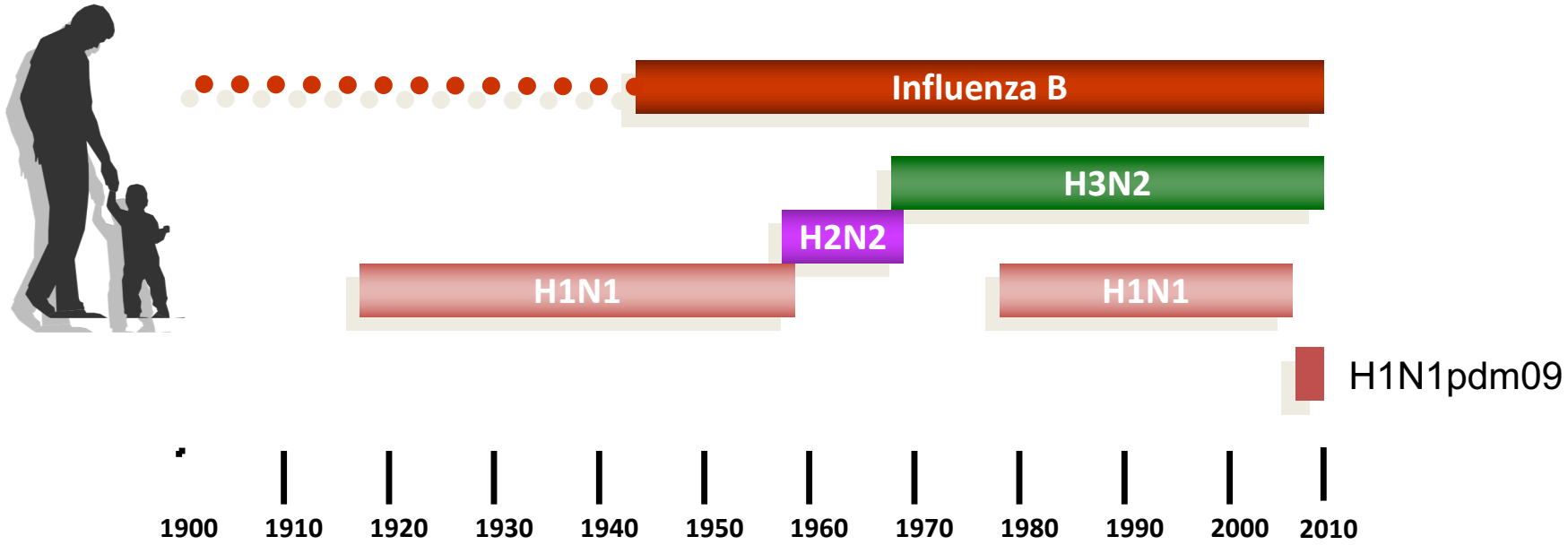


Influenza- a viral respiratory disease of global importance

WHO released in January 2019 a list of the top 10 major threats to global health- included another global influenza pandemic

> “The world will face another influenza pandemic. The only thing we don’t know is when it will hit and how severe it will be. Global defenses are only as effective as the weakest link in any country’s health emergency preparedness and response system," WHO said.

Influenza Pandemics



Influenza- a viral respiratory disease of global importance

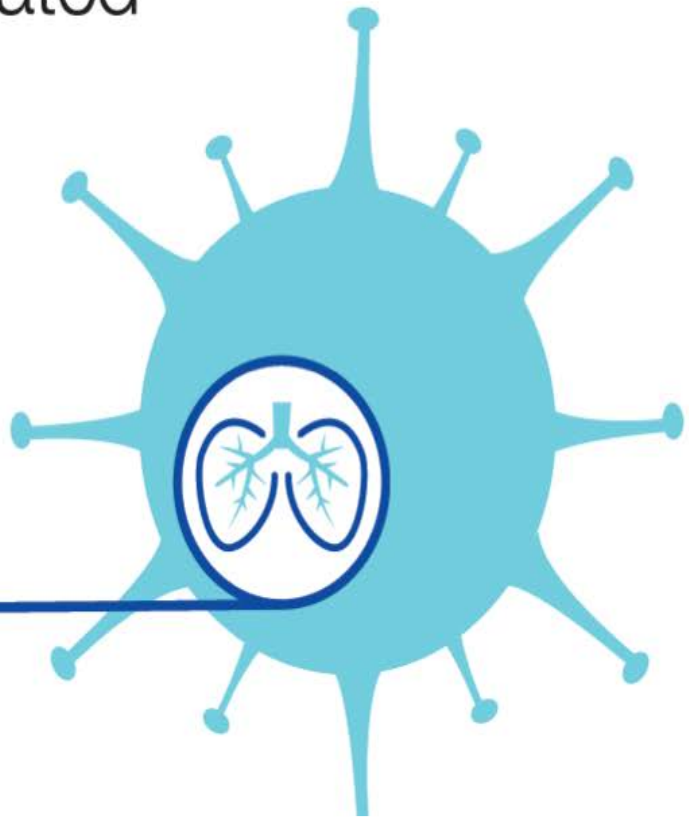
- Mortality and morbidity due to influenza is well-recognized during a pandemic, but is often underappreciated for ***seasonal influenza***
- ***Seasonal influenza*** viruses continuously evolve, annually cause severe disease, particularly among elderly, children, pregnant women, immunocompromised individuals
  - Estimated 1 billion cases of influenza worldwide each year
  - 3-5 million are severe cases

Luliano, A. D. *et al.* Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. *The Lancet* **391,** 1285–1300 (2018).

Seasonal Influenza Mortality Rates per Year

Annual seasonal influenza deaths likely higher than previously estimated

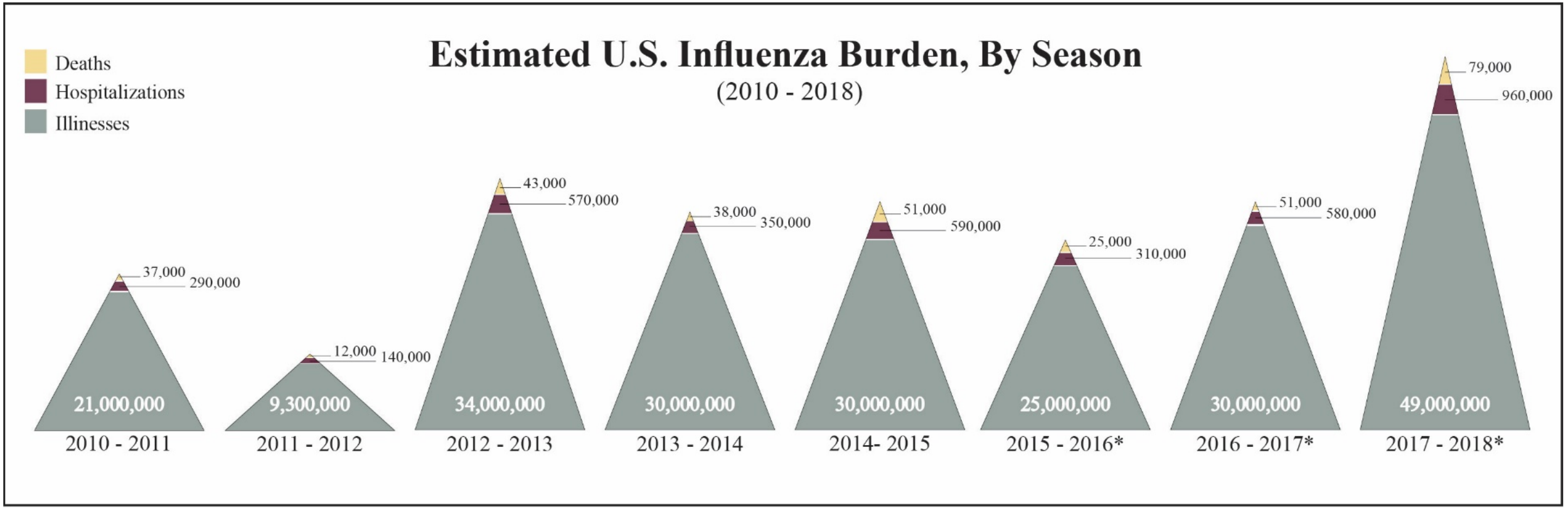
NEW ESTIMATE
290 000 – 650 000
(as of December 2017)
Influenza-related
RESPIRATORY DEATHS only



PREVIOUS ESTIMATE
250 000 - 500 000
(including respiratory and other deaths e.g. cardiovascular)

Luliano, A. D. *et al.* Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. *The Lancet* **391,** 1285–1300 (2018).

Estimated Influenza Disease Burden, by Season
United States, 2010-11 through 2017-18 Influenza Seasons



https://www.cdc.gov/flu/about/burden/index.html

U.S. Influenza Season 2018-2019

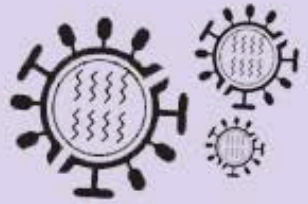
CDC estimates that, from **October 1, 2018,** through **April 13, 2019**, there have been:

36 million – 41.3 million
flu **illnesses**

16.7 million – 19.4 million
flu **medical visits**

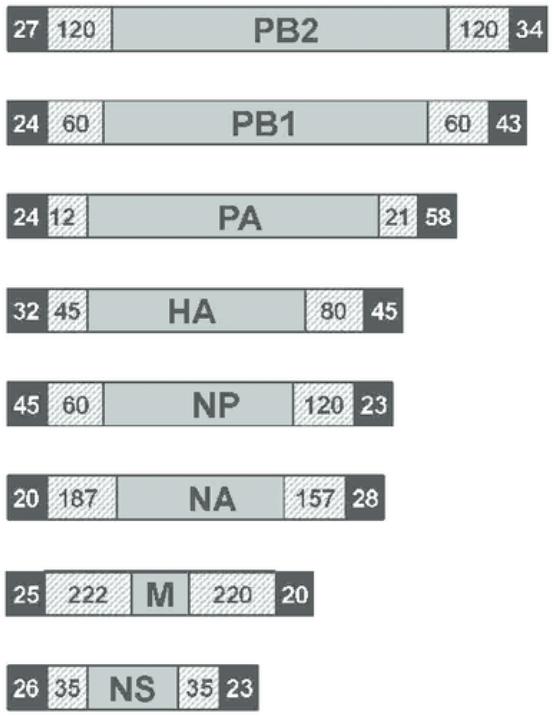
502,000 – 610,000
flu **hospitalizations**

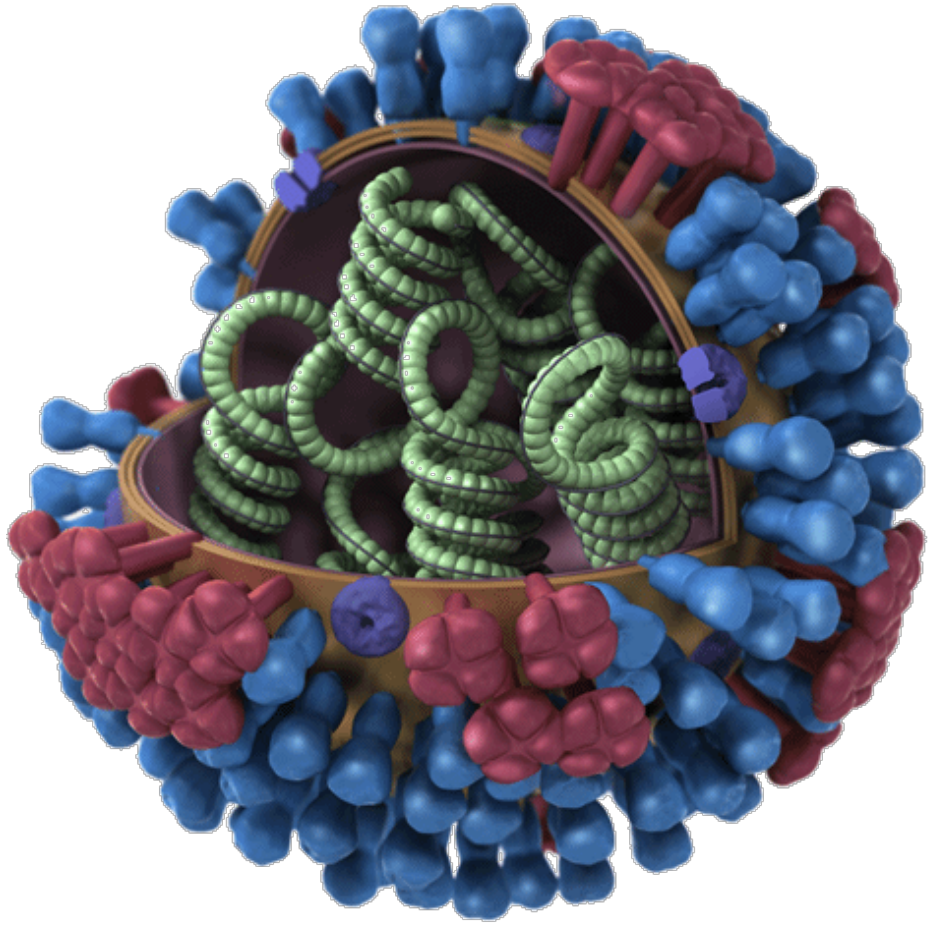
34,400 – 57,300
flu **deaths**

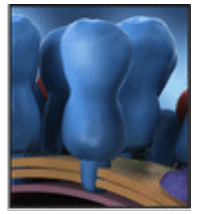


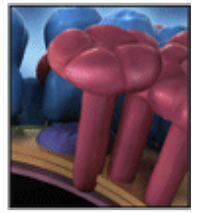
Influenza biology

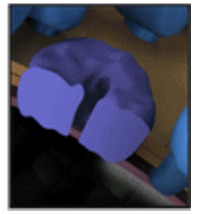
- Eight segmented negative-sense RNA genome
- Lacks proofreading mechanisms
- Allows continuous accumulation of mutations

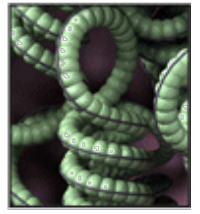





Hemagglutinin

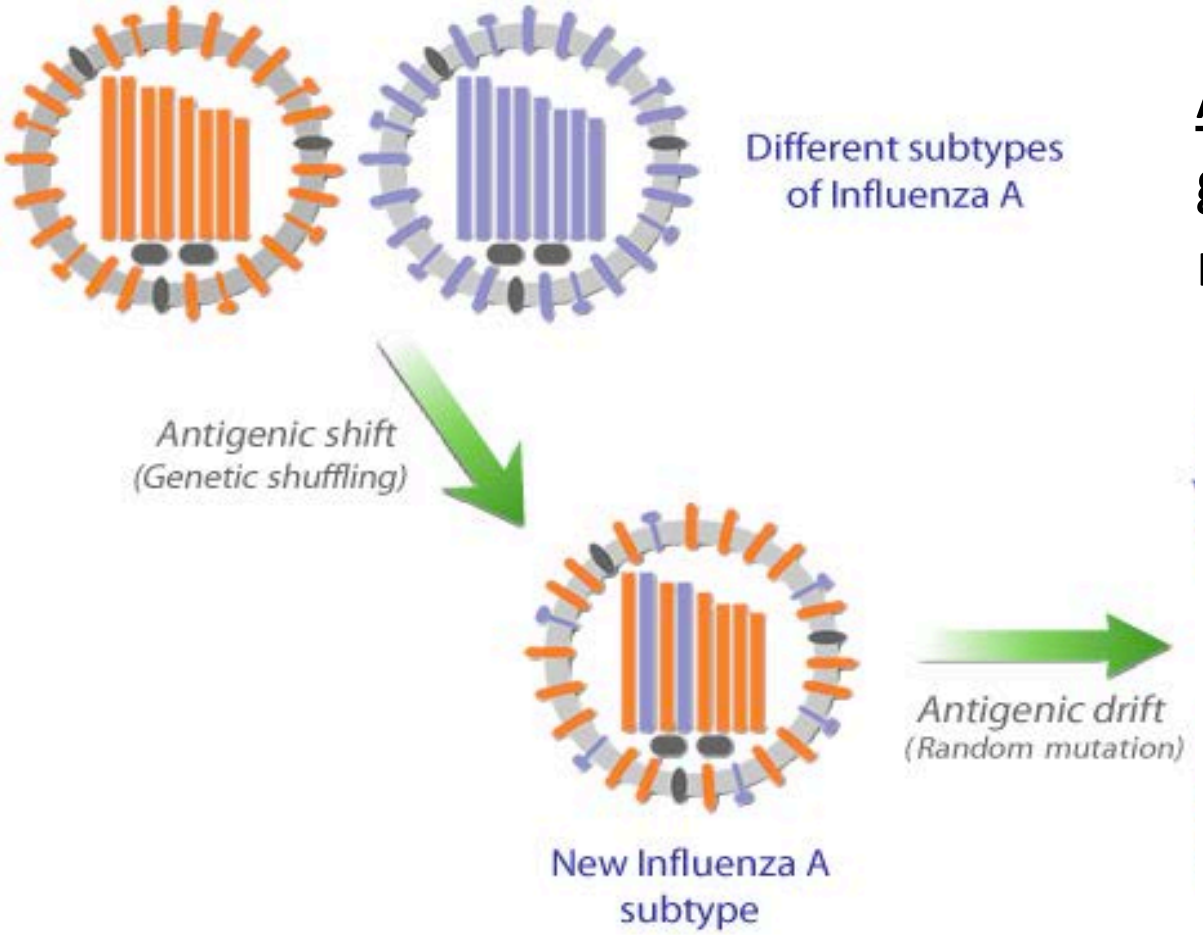

Neuraminidase


M2 Ion Channel


RNP

US CDC; public image

Continuing challenges in influenza



Antigenic Drift: variation in viral genome due to accumulation of mutations

Antigenic Shift: variation by re-assortment of genomes from two or more strains

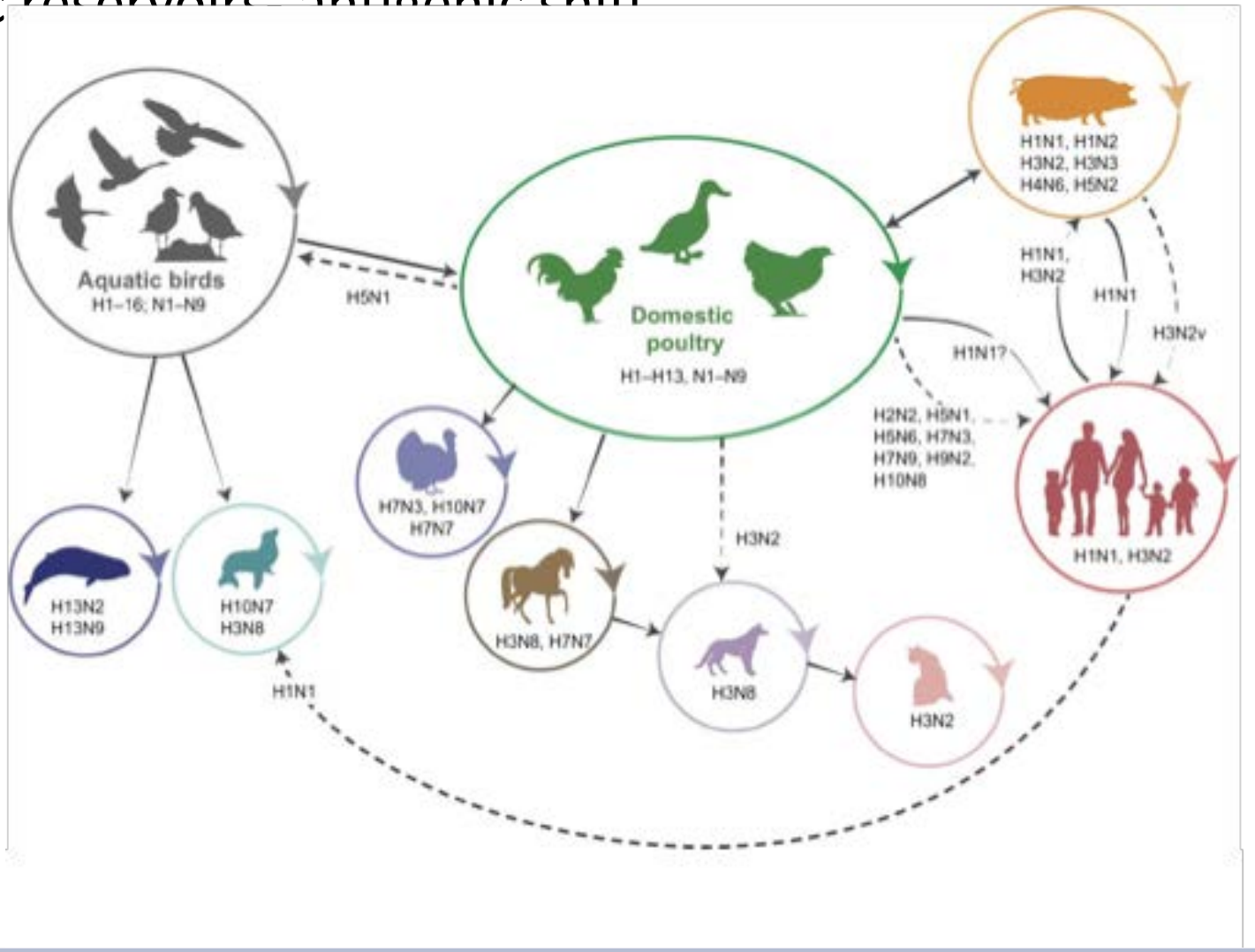
WHO; public image

Interspecies transmission of influenza A viruses

Aquatic birds and bats act as zoonotic reservoirs- antigenic shift

<u>Transmission requires adaptation:</u>

- Optimal temp. of virus replication
  - Decrease from 40°C (avian) to 37 °C (mammalian)
  - Site of replication changes from intestinal (avian) to respiratory (mammalian)
- Receptor specificity switches from α2,3 sialic acid to α2,6 sialic acid



Joseph, U., Su, Y. C. F., Vijaykrishna, D. and Smith, G. J. D. (2017), The ecology and adaptive evolution of influenza A interspecies transmission. Influenza and Other Respiratory Viruses 11, 74–84.

Full impact of influenza- SHIVERS New Zealand studies

Why New Zealand for an influenza study funded by NIAID?

- Excellent health infrastructure
- Mixed influenza vaccination histories (repeated and unvaccinated)
- High study retention rates

1) Dunedin Study (1972- current)

- 1972 birth cohort (n=1037)
- Interviews across years
  - At ages 3 -38 yrs
- 95% retention rate at age 38

2) Growing Up in NZ (2009- current)

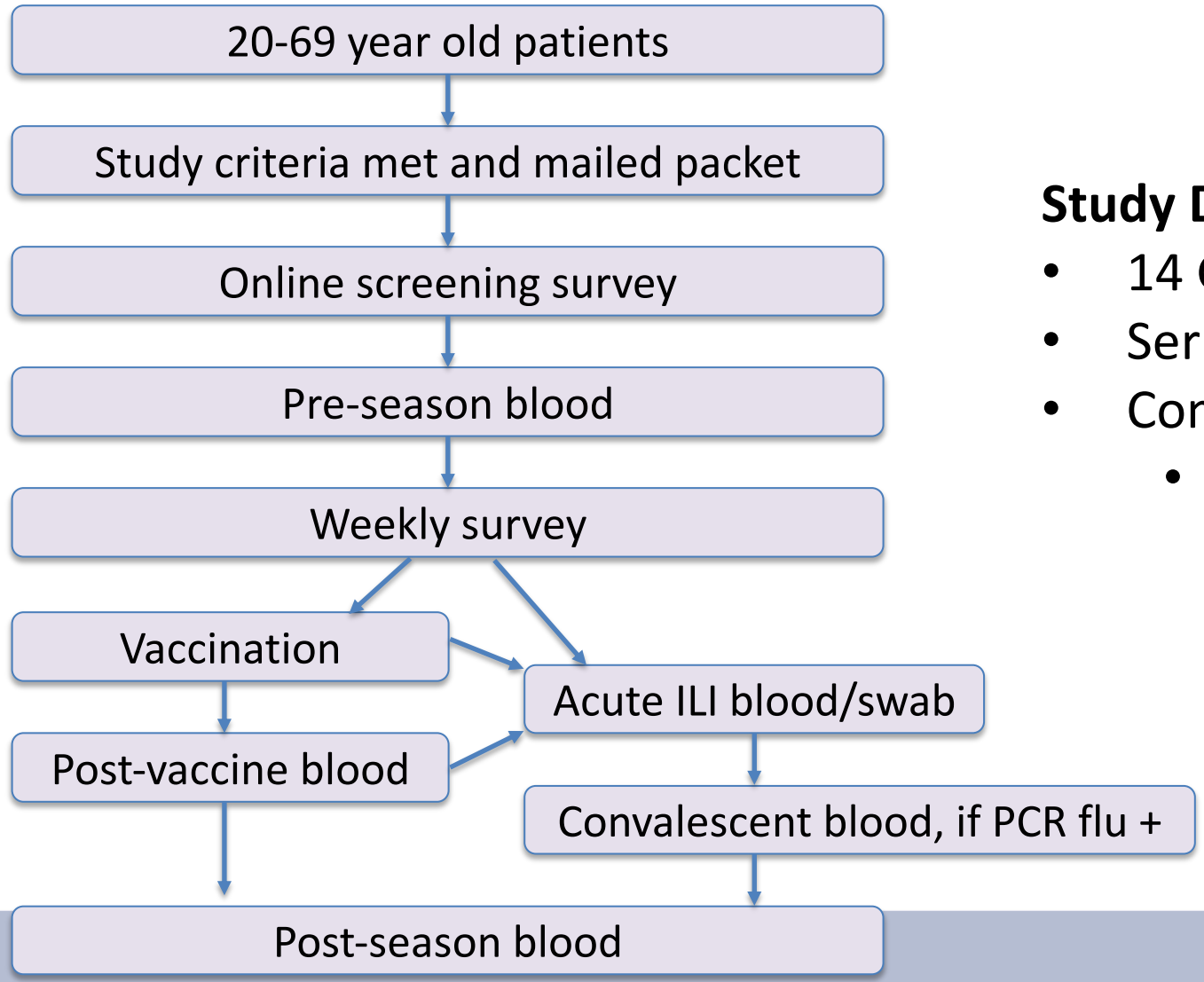
- 2009 birth cohort (n=6853)
- Interviews at 9 mos- 4.5 yrs
- 90% retention rate at 4.5 yrs

THE DUNEDIN STUDY
DUNEDIN MULTIDISCIPLINARY HEALTH AND DEVELOPMENT UNIT

Growing Up in New Zealand

Full impact of influenza- SHIVERS I study design

AIM: How many people were actually infected with influenza?

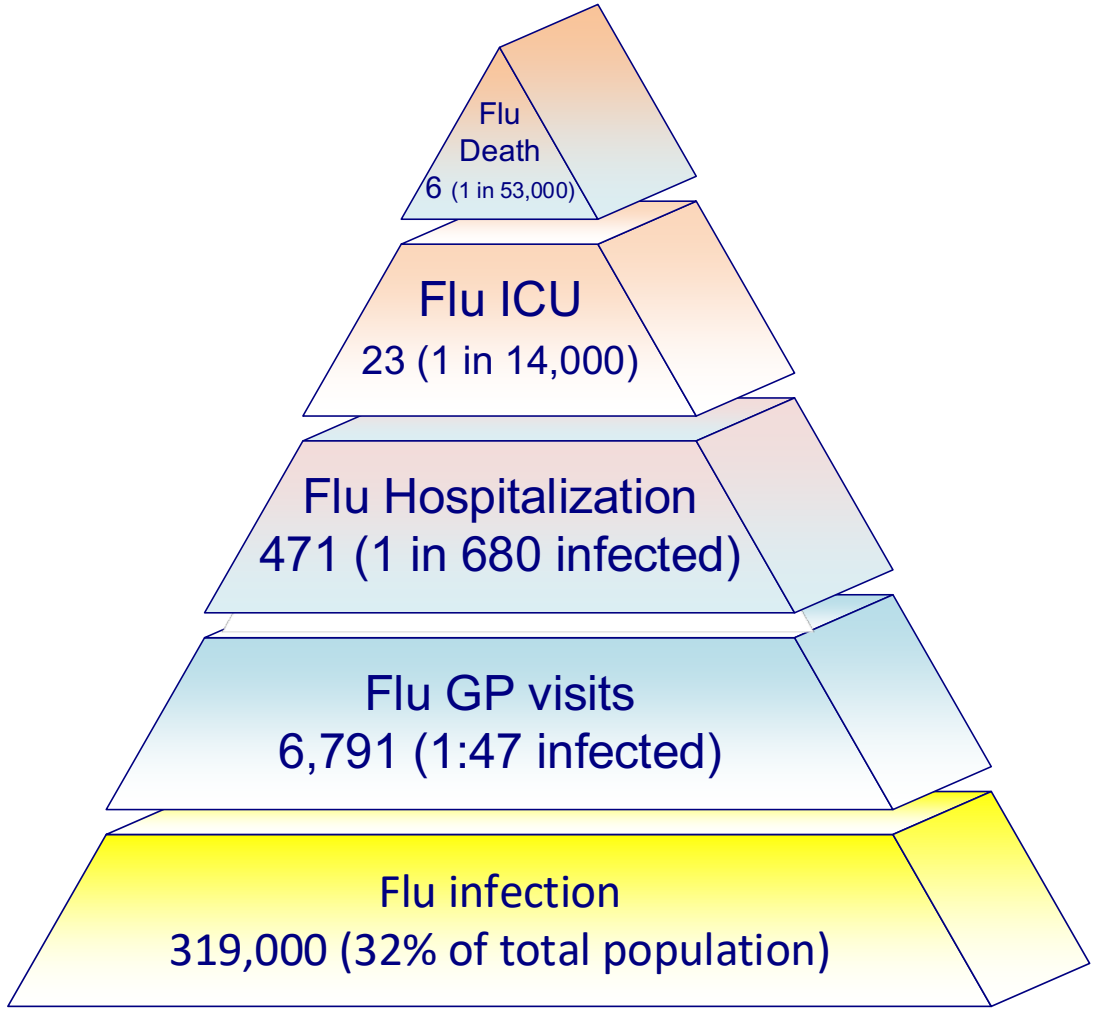


SHIVERS

Study Design:

- 14 GPs in Auckland
- Serum, PBMC, and respiratory swab
- Compensation
  - $30 mailed gift card after each collection

Full impact of influenza- SHIVERS I study findings



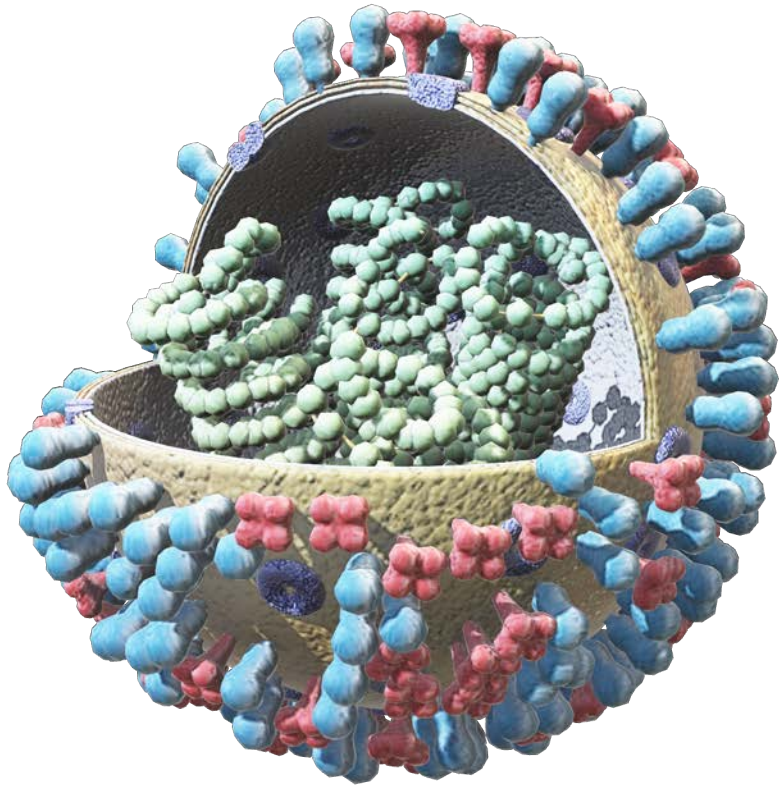
1,000,000 people over one season

SHIVERS

- 32% of population flu infected
- Of infected:
  - 24% developed influenza-like illness
  - 76% did not develop ILI

Question: who are most at-risk for developing ILI symptoms?

1) Elderly (≥65 yrs and older)
2) Children (≤5 yrs and younger)
3) Immunocompromised persons
4) Chronic health conditions
    1) Obesity
5) Native Americans/ Native Alaskans
6) Pregnant women



Children (under 18 years)

Burden of Influenza in children US estimates

CDC published data over a **six-season range** (2010- 2016)

Age group	Symptomatic community illness	Outpatient medical visits	Hospitalizations	Excess deaths	
				Pneumonia & influenza[a]	Respiratory & circulatory[b]
Overall	9 200 000–35 600 000	4 200 000–16 700 000	139 000–708 000	4000–20 000	12 000–56 000
<5 y	900 000–3 800 000	600 000–2 500 000	6000–26 000	60–300	100–700
5–17 y	1 900 000–6 900 000	1 000 000–3 600 000	5000–19 000	50–300	100–600

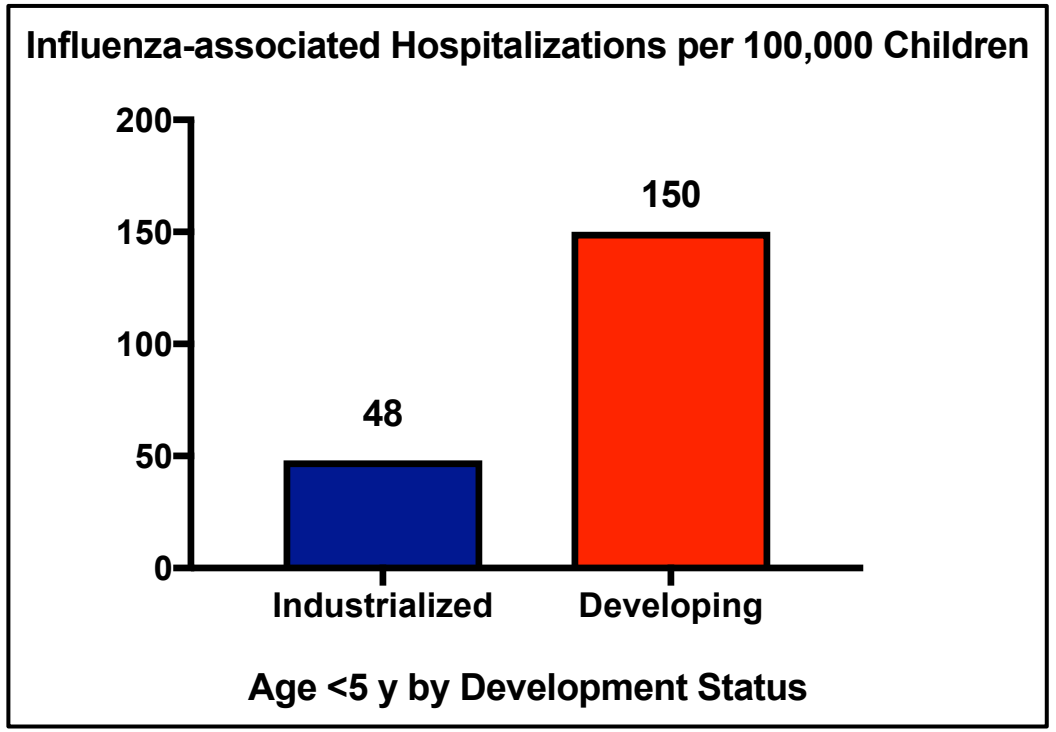
[a] Pneumonia and influenza deaths are only a subset of the total deaths associated with influenza that occur each year, which may be 2 to 4 times higher when other complications are also considered.

Rolfes MA, et al. Annual estimates of the burden of seasonal influenza in the United States: A tool for strengthening influenza surveillance and preparedness. Influenza Other Respi Viruses. 2018; 12:132– 137

Estimated Global Burden of Influenza in Children

- Global Influenza-associated hospitalizations:
  - ~10% of children <18 yr
  - ~374,000 of children <1 yrs
  - ~870,000 of children <5 yrs

- 9,000-100,000 influenza-related deaths in children <5 yrs



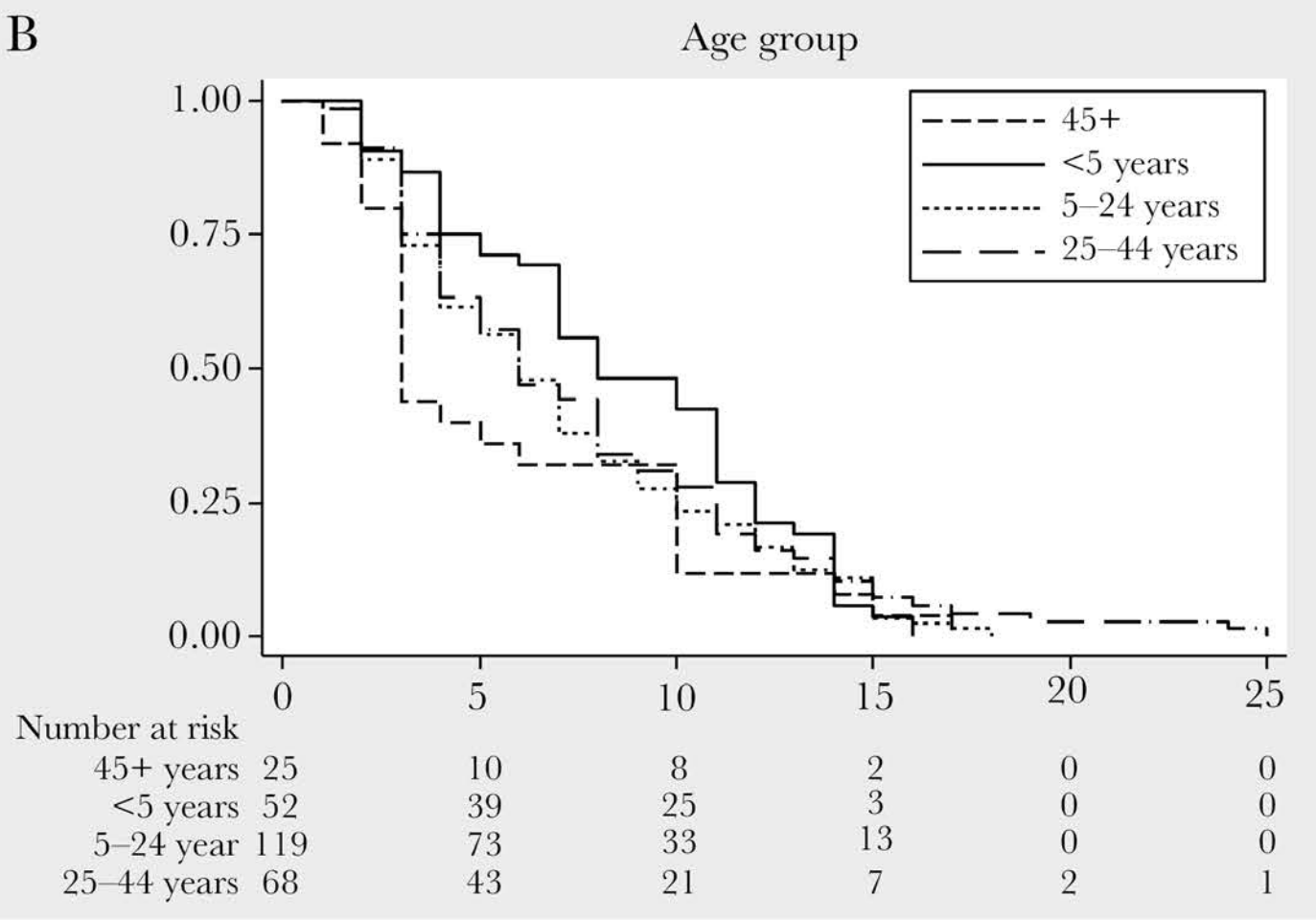
- Highest burden of severity in low-middle income countries
  - Influenza-associated outcomes in developing countries:
    - Hospitalizations 3-fold higher
    - Mortality 17-fold higher

Luliano, A. D. *et al.* Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. *The Lancet* **391,** 1285–1300 (2018).

Lafond KE, et al. (2016) Global Role and Burden of Influenza in Pediatric Respiratory Hospitalizations, 1982–2012: A Systematic Analysis. PLOS Medicine 13(3): e1001977.

Children Shed Influenza Virus longer than Adults

Influenza shedding in prospective cohort of children and adults in South Africa, 2012-2014



Kaplan-Meyer plots showing the probability of RT-PCR-positive Influenza virus result by day after shedding onset by age group

Claire von Mollendorf, et.al. Influenza Viral Shedding in a Prospective Cohort of HIV-Infected and Uninfected Children and Adults in 2 Provinces of South Africa, 2012–2014, *The Journal of Infectious Diseases*, Volume 218, Issue 8, 15 October 2018, Pages 1228–1237

Vaccination of Children Provide Community Immunity

49 Hutterite (Canada) colonies randomized

25 colonies randomized to receive influenza vaccine (1773 retained)

24 colonies randomized to receive hepatitis A vaccine (1500 retained)

Vaccine delivered to 36 month to 15 year old's only

Followed adults for influenza infection during season

Loeb et al JAMA 2010

Vaccination of Children Provide Community Immunity

Table 2. Protective Effectiveness on Nonrecipients of Immunizing Children and Adolescents With Influenza Vaccine

Study Group	Nonrecipients in Vaccine Colony: Influenza (n = 1271)	Nonrecipients in Vaccine Colony: Hepatitis (n = 1055)	Protective Effectiveness of Influenza Vaccine (95% CI), %	*P* Value
Influenza detected by PCR, No. (%)	39 (3.1)	80 (7.6)		
Person-day of follow-up, No. (%)	182 866	151 902		
No. of cases/10 000 person-days	2.13	5.27	Simple, 61 (8-83)[a]	.03
			Adjusted, 61 (8-83)[b]	.03

Summary: vaccinating just children resulted in 61% protective effectiveness

Loeb et al JAMA 2010

Immunocompromised Population

Respiratory infections in children with cancer

- Healthy children
  - infection typically limited to upper respiratory tract (URTIs)
- *Immunocompromised hosts*
  - are vulnerable to severe infections, including lower respiratory tract infections (LRTIs)
  - URTI ⟶ LRTIs 30-50% of patients
- Adverse outcomes more likely in immunocompromised persons due to defects in innate adaptive immunity:
  - Progression to pneumonia
  - Respiratory failure
  - Increased mortality rates

Hijano, Diego R et al. “Respiratory Viral Infections in Patients With Cancer or Undergoing Hematopoietic Cell Transplant.” *Frontiers in microbiology* vol. 9 3097. 12 Dec. 2018

Community respiratory viruses (CRVs)

Community respiratory viruses- main cause of hospitalization (unlike opportunistic infections, atypical or uncommon organisms)

- Difficult to determine which virus causes most infection
  - Dependent on seasonal outbreaks (RSV and influenza)
  - Geographic location
  - LMI versus HMI countries
- On average, most common viruses: RSV, influenza, parainfluenza
- Most common co-infections with two or more viruses include RSV and influenza

Hijano, Diego R et al. “Respiratory Viral Infections in Patients With Cancer or Undergoing Hematopoietic Cell Transplant.” *Frontiers in microbiology* vol. 9 3097. 12 Dec. 2018

Challenge of viral respiratory infections in children with cancer

- Clinical presentation in immunocompromised versus healthy children
  - Higher incidence of co-infections
  - Atypical symptoms such as rash, diarrhea
  - Asymptomatic viral shedding
  - Prolonged viral shedding
  - Sudden severe respiratory distress

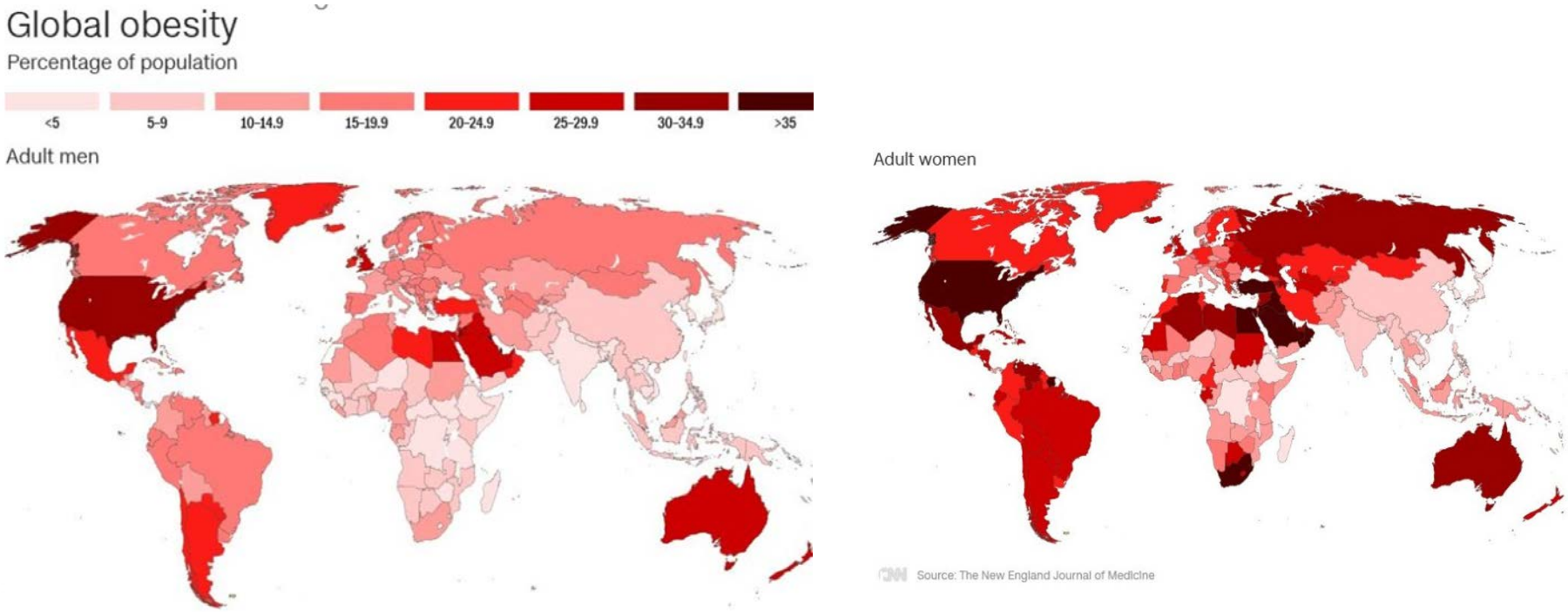
- Atypical clinical manifestations can result in *delayed* or *lack* of diagnosis

- Current focus is to determine specific risk factors for URTI to LRTI; goal to identify patients who would benefit from interventions

- Clinical scores have been developed in adults but has not been validated in children

Obese Population

Obesity and Influenza



OBESITY =
Chronic, low-level inflammation

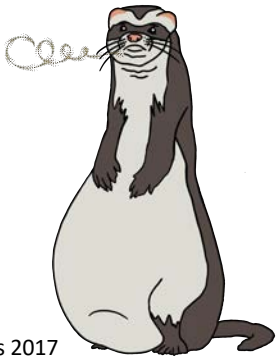
IMMUNOCOMPROMISED STATE

Obesity and Influenza- what do we know?

1) Increased morbidity
2) Decreased survival
3) Increased susceptibility to influenza infection (MLD_{50})
4) Increased lung injury
5) Decreased wound repair (Ki67) and *increased basement membrane exposure*
6) Increased morbidity secondary bacterial infections independent of time or strain
7) Virus – higher titers, shed longer, changes faster
8) Poor vaccine efficacy

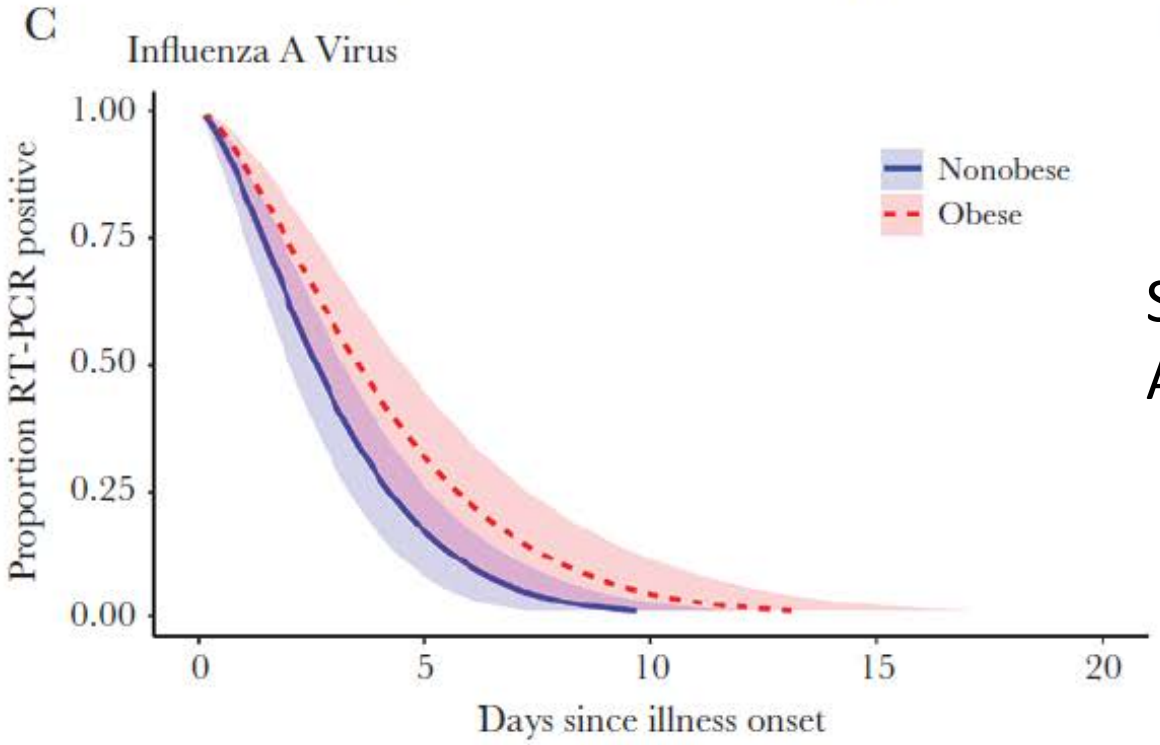
Obesity and Influenza

↑ hospitalizations
↑ ICU duration
↑ mortality



Karlsson et al mBio 2016; mBio 2017
Sheridan et al Int J Obesity 2011
Neidich et al Int J Obesity 2017
O'Brien et al JID 2012
Karlsson et al mBio 2017; Sci Reports 2017
Schultz-Cherry JID 2018
Meliopoulos et al J Virol 2019
Honce and Schultz-Cherry Front Immunol 2019; J Travel Med 2019

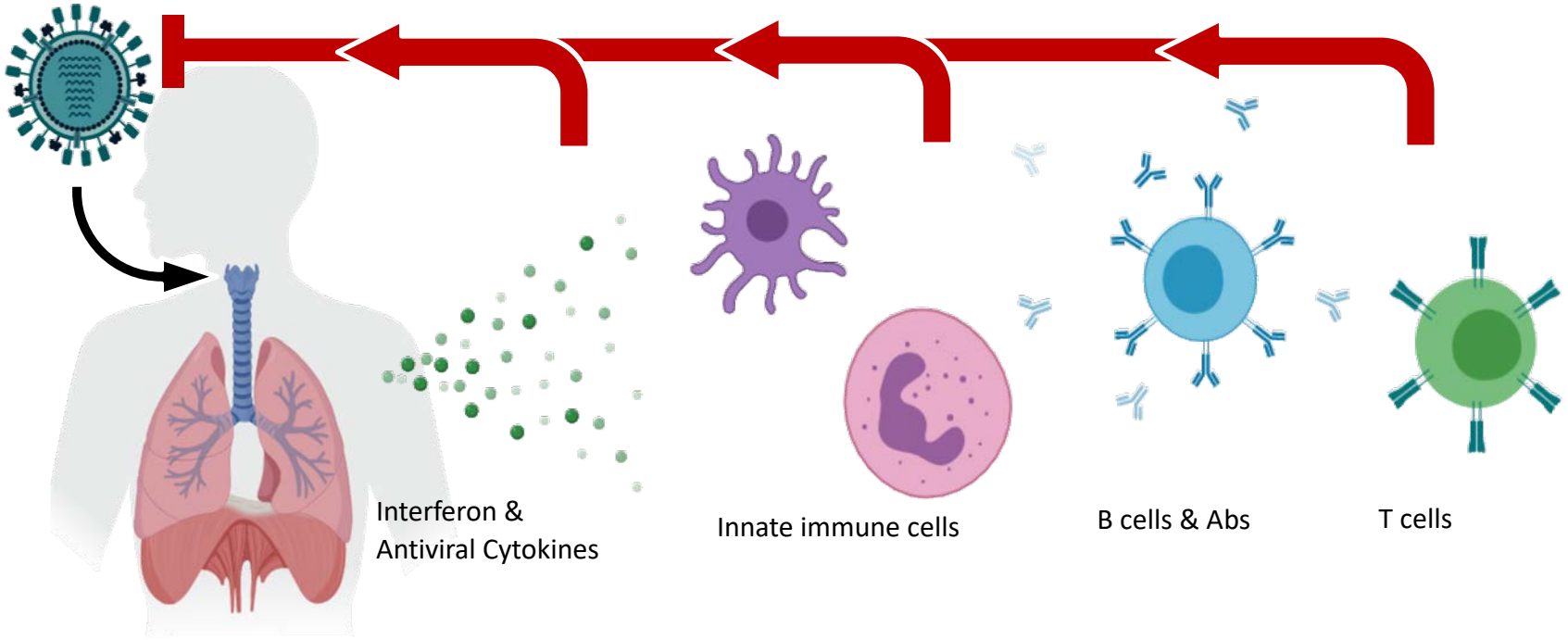
Obese Adults Shed more IAV for Longer



Symptomatic obese adults: **shed 42% longer**
Asymptomatic obese adults: **shed 104% longer**

Why?

Poor epithelial responses = impact on all downstream immune responses



NOT specific to influenza infection or vaccines

Flu is BAD!

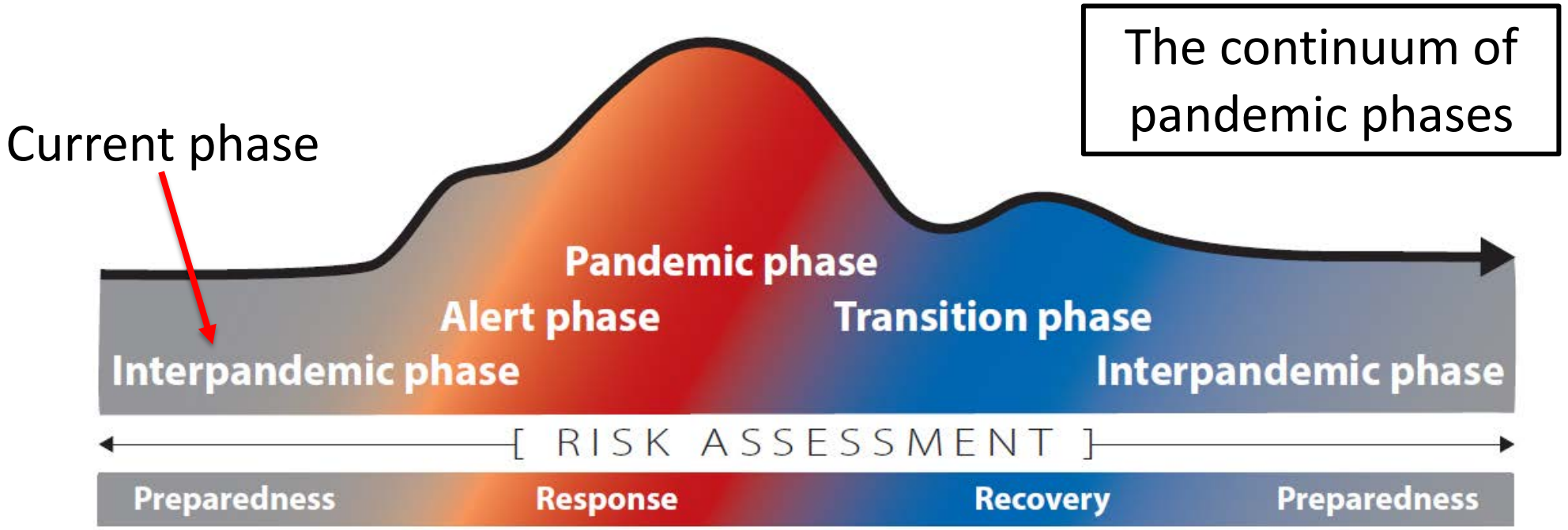
What are we doing to combat influenza?

Global Influenza Strategy

- After 2009 H1N1 pandemic, the Review Committee on the Functioning of the International Health Regulations (IHR) concluded,
  - *“the world is ill-prepared to respond to a severe influenza pandemic or to any similarly global, sustained, and threatening public health emergency”*

- Resulted in a movement to strengthen pandemic preparedness and health security

Adoption of the Pandemic Influenza Preparedness (PIP) Framework



ALERT PHASE: New subtype has been identified in humans; increased vigilance and risk assessment at local, national, global levels

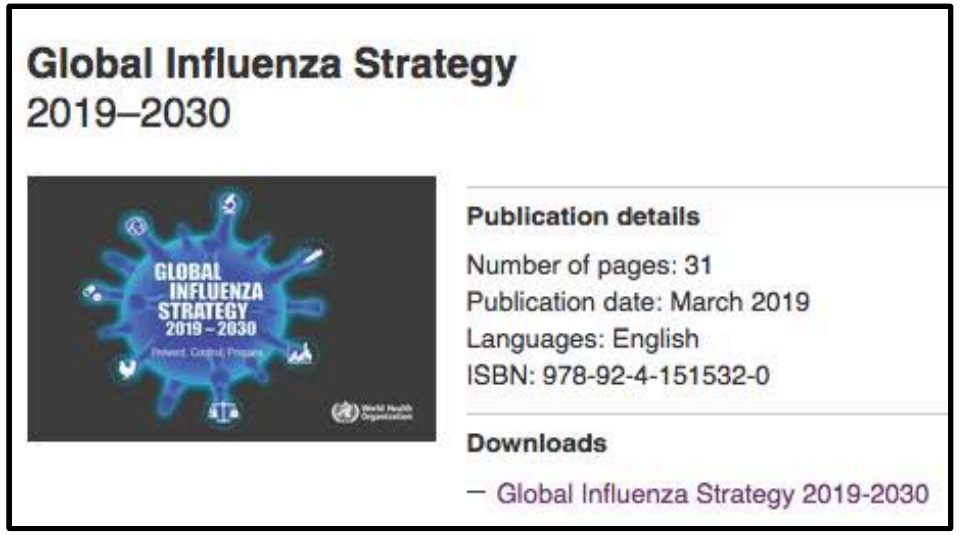
PANDEMIC PHASE: New subtype has spread globally; based on virological, epidemiological, clinical data; WHO-Director General declaration; decision to move from seasonal vaccine production to pandemic vaccine production

TRANSITION PHASE: De-escalation of global actions; response activities moved to national level

Pandemic Influenza Risk Management: A WHO guide to inform and harmonize national and international pandemic preparedness and response (2017)

WHO Global Influenza Strategy 2019-2030

Areas of focus for 2030:



1) **Better global tools:** a focused, consensus-driven plan:
   - greater research
   - innovation
   - availability of new and improved tools for the prevention, detection, control and treatment of influenza

2) **Stronger country capacities: evidence-based influenza programs in** every country that is:
   - optimized to fit the country's needs
   - contributes to national and global preparedness

WHO Global Influenza Strategy 2019-2030

Four Strategic Objectives:

1) **Promote research and innovation to address unmet public health needs**

    a) Improved and novel diagnostics, vaccine, and treatments against influenza
    b) Implementation of influenza prevention and control programs
    c) Better understanding of virus characteristics and host factors that drive the impact of influenza

WHO Global Influenza Strategy 2019-2030

Four Strategic Objectives:

2) Strengthen global influenza surveillance, monitoring and data utilization

a) Enhance, integrate and expand virological and disease surveillance
b) Build a strong evidence base for understanding the impact and burden of influenza
c) Develop effective influenza communication strategies across multiple sectors and between stakeholders

WHO Global Influenza Strategy 2019-2030

Four Strategic Objectives:

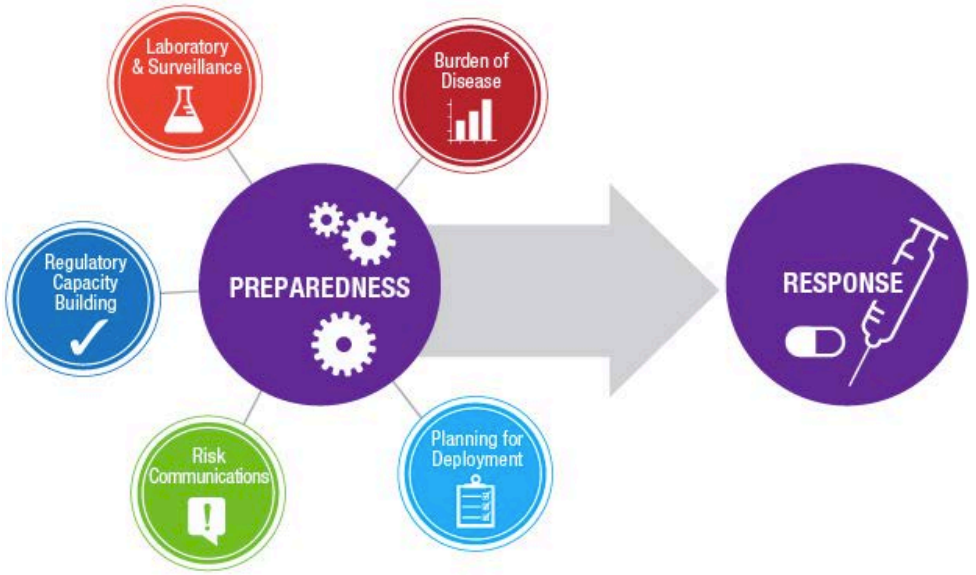
3) **Expand seasonal influenza prevention and control policies and programs to protect the vulnerable**
   a) Integrate nonpharmaceutical interventions (NPIs) into prevention and control programs
   b) Reduce transmission and disease severity through evidence-based immunization policies and programs
   c) Design and implement evidence-based treatment policies and programs to reduce morbidity and mortality

WHO Global Influenza Strategy 2019-2030

<u>Four Strategic Objectives:</u>

4) **Strengthen pandemic preparedness and response for influenza to make the world safer**
    a) Strengthen national, regional and global planning to enable timely and effective pandemic readiness

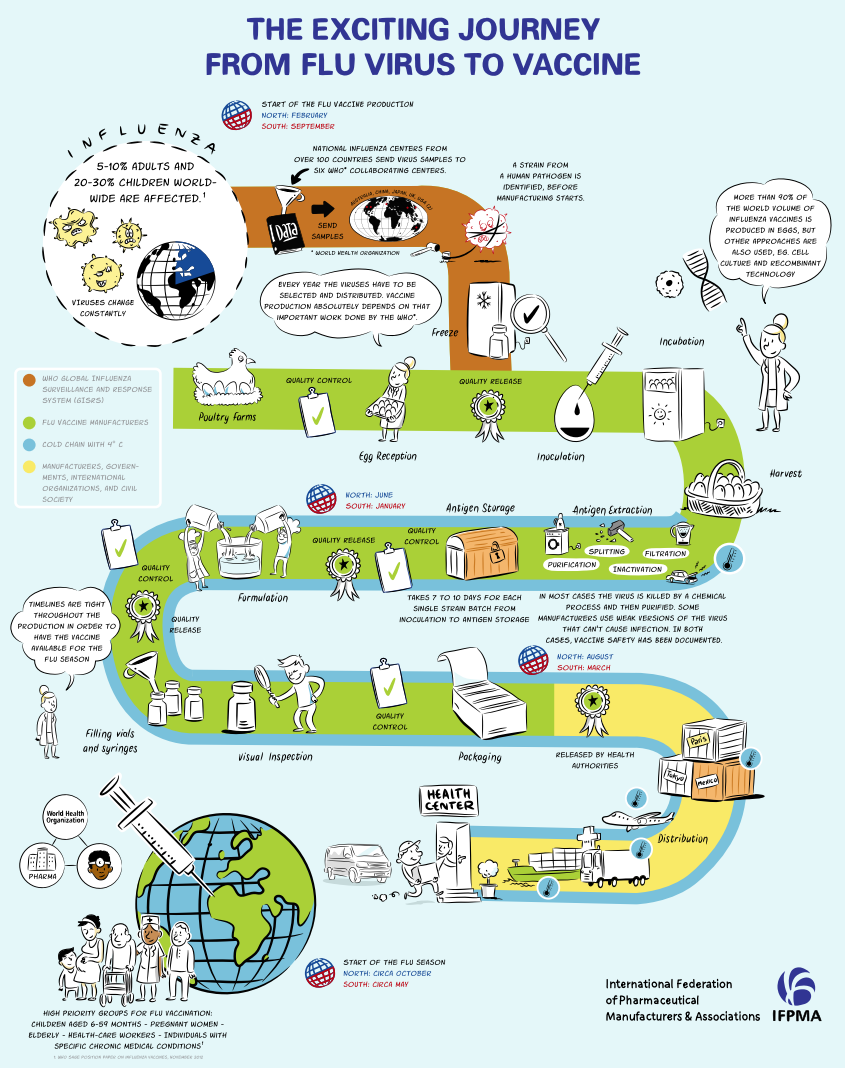
WHO Global Influenza Strategy 2019-2030



Pandemic readiness tools and areas of focus:

1) Global Action Plan for Influenza Vaccines (GAP)
2) Tool for Influenza Pandemic Risk Assessment (TIPRA)
3) Pandemic Influenza Severity Assessment (PISA)
4) Non-pharmaceutical public health measures (NPIs)
5) Expansion of the Global Influenza Surveillance and Response System (GISRS)

Expansion of vaccine use and production in LMICs- GAP

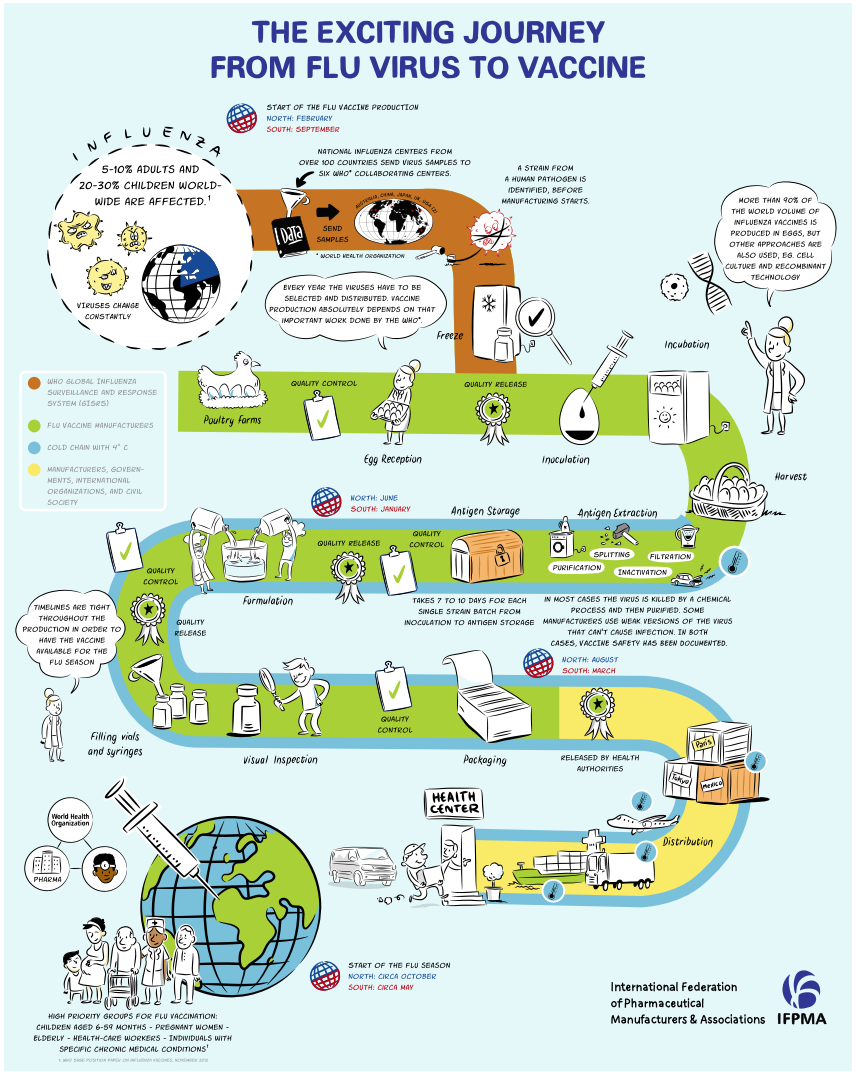


- Only 32% of LMICs have influenza vaccine programs
- Most common cited reasons for lack of vaccine policies:
-
  - Lack of influenza disease burden estimates
  - Lack of awareness about influenza disease among stakeholders
  - Uncertain impact of vaccines on important public health outcomes
  - Technical challenges providing vaccination services

Ortiz, J. R. & Neuzil, K. M. Influenza Immunization in Low- and Middle-Income Countries: Preparing for Next-Generation Influenza Vaccines. *J. Infect. Dis.* **219,** S97–S106 (2019).

World Health Organization. Vaccines against influenza WHO position paper. *Wkly Epidemiol Rec.* 87, 461–76 (2012).

Expansion of vaccine use and production- GAP



- Vaccine production:
  - 2006- 500 million doses
  - 2016- 6.4 billion doses
  - Still short of the estimated 10 billion doses needed during a pandemic
- WHO has provided funding and oversite for 14 vaccine manufacturers in developing countries
  - Ex) Brazil, Iran, India, Egypt, Kazakhstan, Thailand
- Six of the countries have licensed locally produced vaccines
- Maintaining this capacity requires a thriving seasonal influenza vaccine market

Ortiz, J. R. & Neuzil, K. M. Influenza Immunization in Low- and Middle-Income Countries: Preparing for Next-Generation Influenza Vaccines. *J. Infect. Dis.* **219,** S97–S106 (2019).

World Health Organization. Vaccines against influenza WHO position paper. *Wkly Epidemiol Rec.* 87, 461–76 (2012).

WHO Tool for Influenza Pandemic Risk Assessment (TIPRA)

- In 2016, WHO released TIPRA:
  - provides a standardized and transparent approach to support the risk assessment of influenza viruses with pandemic potential
  - Modelled after CDC Influenza Risk Assessment Tool (IRAT)

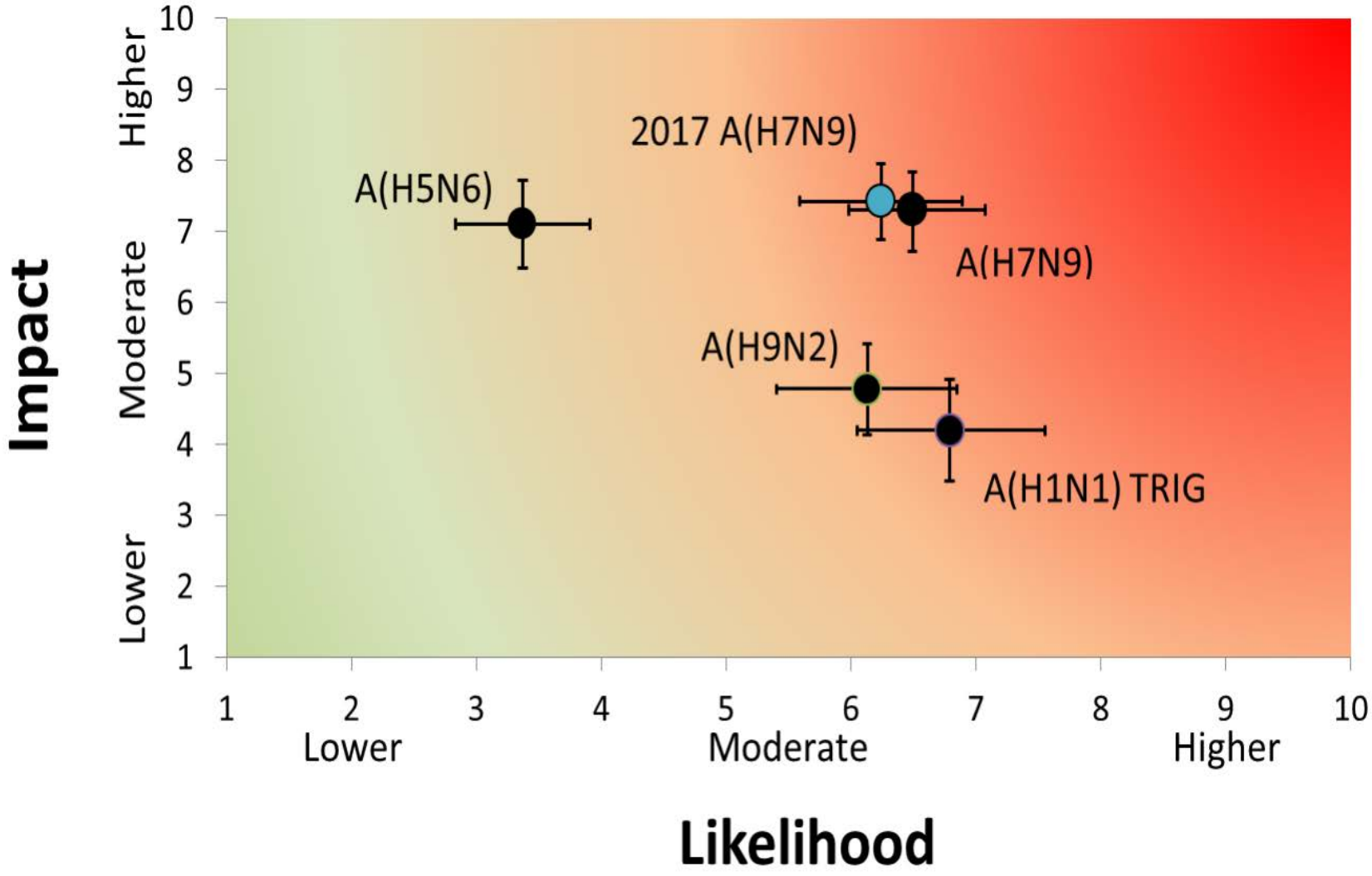
- Technical experts (surveillance network, academics, public health officials) score virus attributes known as risk elements

Properties of the Virus	Attributes in the Human Population	Virus Ecology and Epidemiology in non-human hosts
1) Receptor binding properties 2) Genomic characteristics 3) Transmission in animal models 4) Susceptibility to antiviral treatment	5) Human infection 6) Disease severity 7) Population immunity	8) Geographic distribution in animals 9) Infection in animals

TIPRA Triggers for Use

- Human infection with a non-season or animal influenza virus
- Increased detection of a virus with reduced antiviral susceptibility
- Cluster of human cases:
  - potential human-to-human transmission of virus
  - infections beyond blood-related family members
- Changes in epidemiological trends associated with the virus:
  - number of cases detected
  - disease severity
  - mortality ratio
  - geographic dispersion

TIPRA Outcomes



Determining Pandemic Influenza Severity in Real-time

- Historically, assessment of influenza pandemic effects characterized by using estimate of the overall case-fatality ratio (CFR)

- Multiple challenges using CFR alone:
  - Deaths may occur weeks after illness begins
  - Subject to reporting bias
  - Single overall CFR does not account for potential varying effects on high-risk population subgroups
  - Does not address societal effects (e.g. absenteeism, demand on health care services)

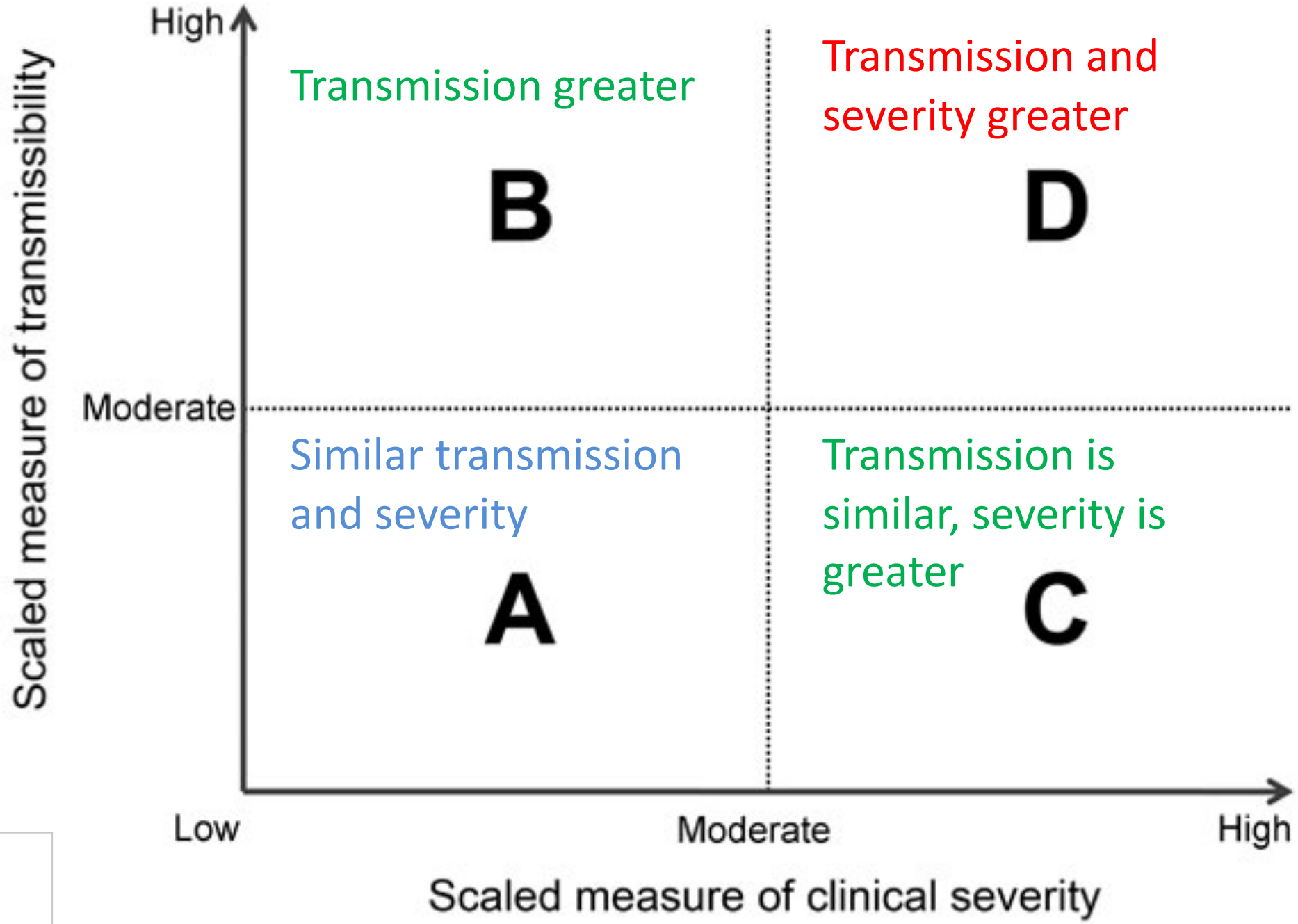
Systematic Framework for Assessing Potential Pandemics

- In 2017, WHO published Pandemic Influenza Severity Assessment (PISA)
- Initial assessment (when data is sparse) of potential influenza pandemic severity:

Transmissibility of the virus	Seriousness of Disease	Population Impact
• Virologic characterization • Animal transmission studies • Underlying population immunity • Secondary attack rate in closed settings (e.g. households, schools) • Early estimates of R_0	• Virologic characterization • Animal morbidity studies • Underlying population immunity • Inferences about risk of mortality and hospitalization from early case reports and outbreaks	• None

Reed C, et al. Novel Framework for Assessing Epidemiologic Effects of Influenza Epidemics and Pandemics. Emerg Infect Dis. 2013;19(1):85-91. https://dx.doi.org/10.3201/eid1901.120124

Compared to seasonal epidemics:

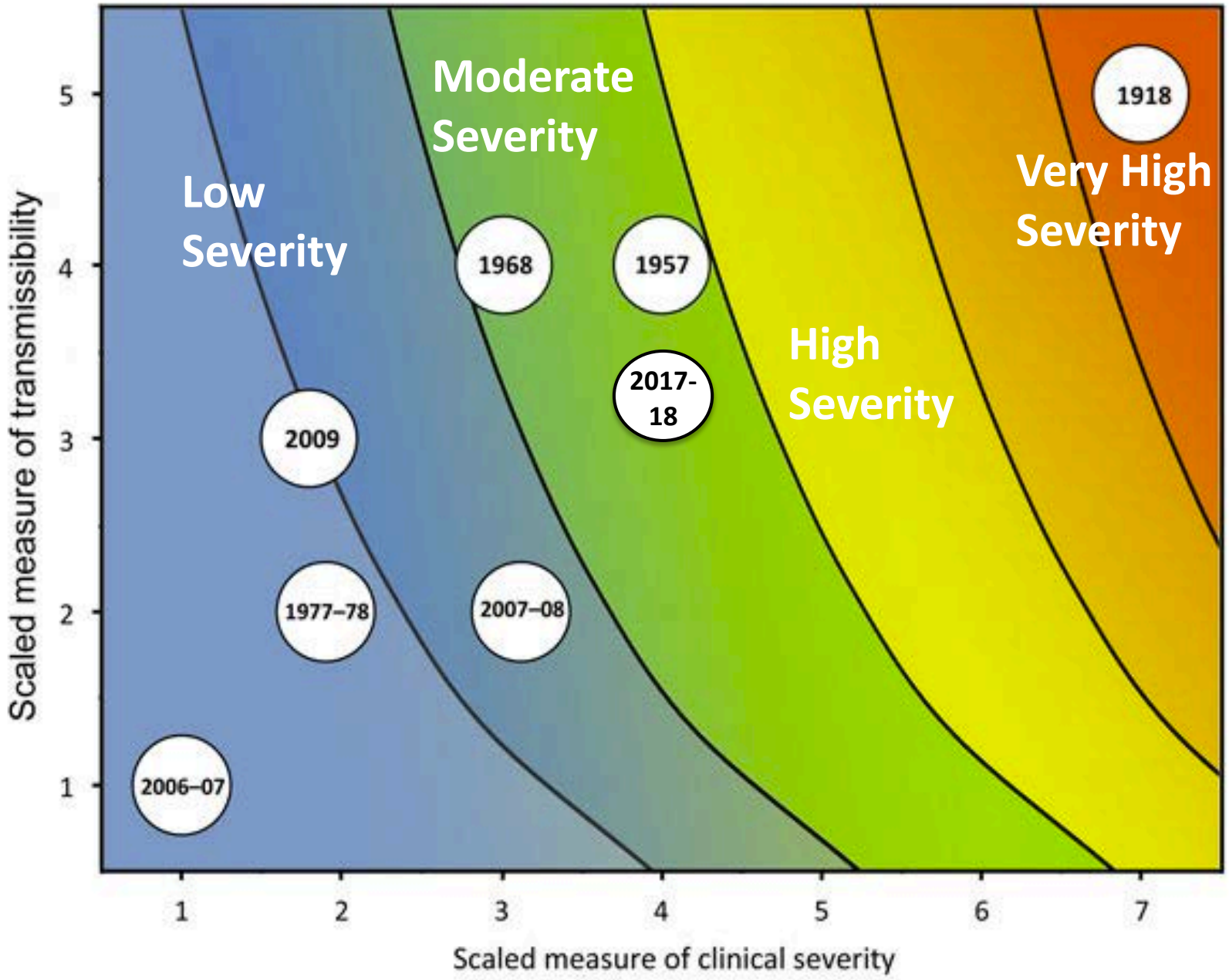


Reed C, et al. Novel Framework for Assessing Epidemiologic Effects of Influenza Epidemics and Pandemics. Emerg Infect Dis. 2013;19(1):85-91. https://dx.doi.org/10.3201/eid1901.120124

CDC Systematic Framework for ***Refined*** Assessment

Parameter no. and Description		Scale 1	2	3	4	5	6	7
Transmissibility								
1	Symptomatic attack rate, community, %	≤10	11-15	16-20	21-24	≥25		
2	Symptomatic attack rate, school, %	≤20	21-25	26-30	31-35	≥36		
3	Symptomatic attack rate, workplace, %	≤10	11-15	16-20	21-24	≥25		
4	Household secondary attack rate, symptomatic, %	≤5	6-10	11-15	16-20	≥21		
5	R0; basic reproductive no.	≤1.1	1.2-1.3	1.4-1.5	1.6-1.7	≥1.8		
6	Peak % outpatient visits for ILI	1-3	4-6	7-9	10-12	≥13		
Clinical Severity								
1	Case-fatality ratio, %	<0.02	0.02-0.05	0.05-0.1	0.1-0.25	0.25-0.5	0.5-1	>1
2	Case-hospitalization ratio, %	<0.5	0.5-0.8	0.8-1.5	1.5-3	3-5	5.7	>7
3	Ratio, deaths: hospitalization, %	≤3	4-6	7-9	10-12	13-15	16-18	>18

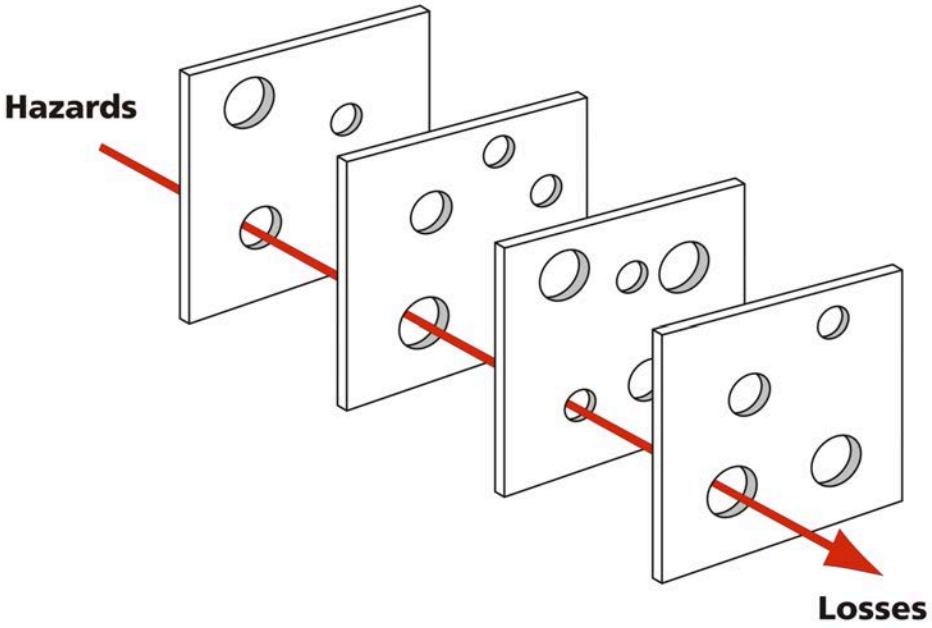
Reed C, et al. Novel Framework for Assessing Epidemiologic Effects of Influenza Epidemics and Pandemics. Emerg Infect Dis. 2013;19(1):85-91. https://dx.doi.org/10.3201/eid1901.120124



Reed C, et al. Novel Framework for Assessing Epidemiologic Effects of Influenza Epidemics and Pandemics. Emerg Infect Dis. 2013;19(1):85-91. https://dx.doi.org/10.3201/eid1901.120124

Mitigating the next Influenza Pandemic

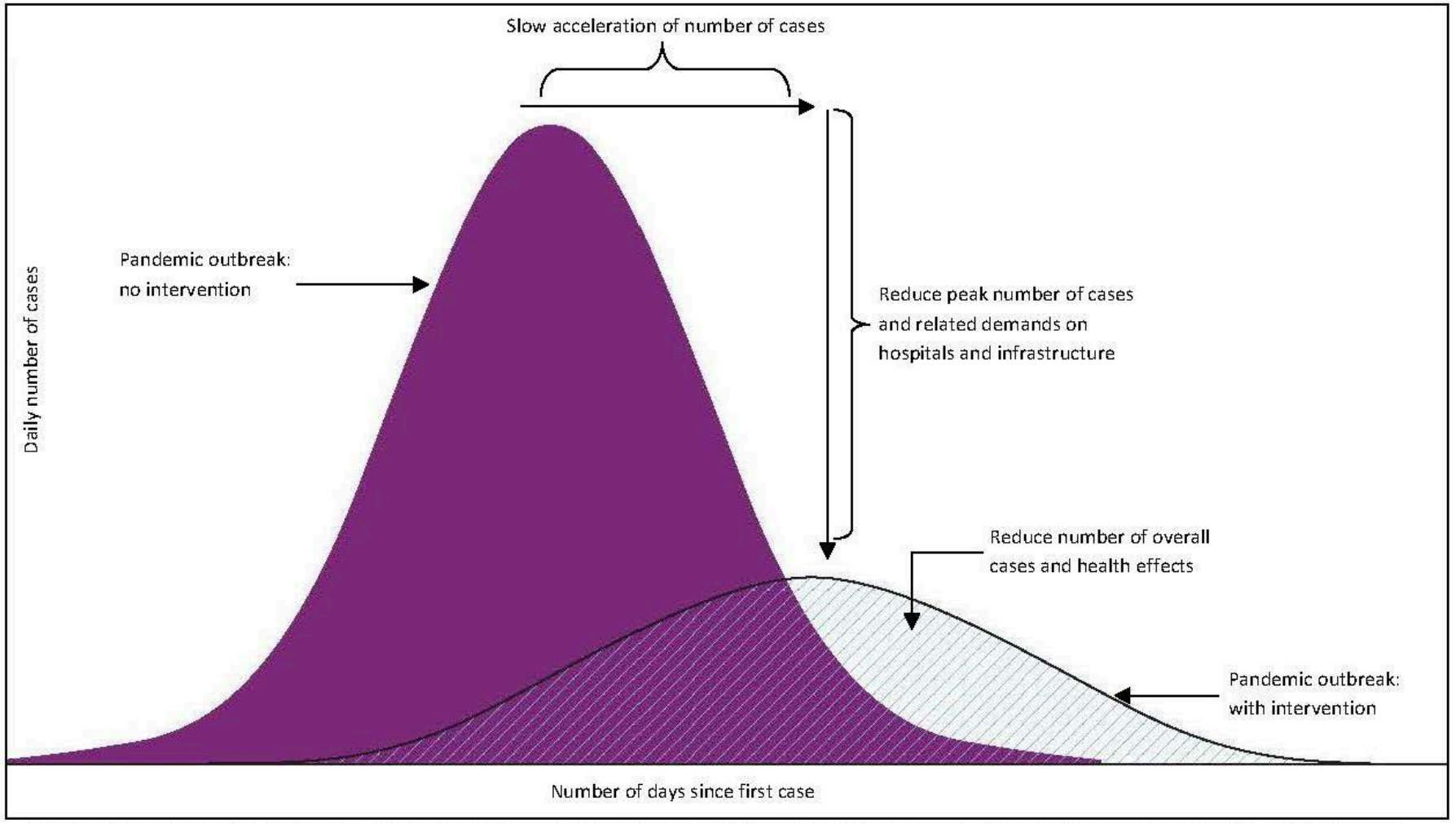
- Vaccine but not available immediately
- Antivirals but mainly available in resource-rich countries
- Pandemic mitigation in the early months will mostly rely on *non-pharmaceutical public health measures (NPIs):*
  - Personal measures, including face masks and hand washing
  - Workplace and school closures
  - Isolation of sick, quarantine of exposed persons
  - Travel restrictions



Potential Impact of NPIs on an Influenza Pandemic

Community mitigation measures may:

1) Slow spread of infections
2) Delay peak of infections
3) Reduce size of peak
4) Reduce spreading infections over time



Public health measures: Canadian Pandemic Influenza Preparedness: Planning Guidance for the Health Sector

GISRS

Global Influenza Surveillance and Response System (GISRS)- est. 1952 by WHO

1) Global mechanism of surveillance, preparedness and response for seasonal, pandemic, and zoonotic influenza
2) Global platform for monitoring influenza epidemiology and disease
3) Global alert for novel influenza viruses and respiratory pathogens

- 115 WHO Member States
- Conducts:
  - antigenic and sequence analysis
  - population susceptibility based on antibody levels in human sera

WHO Global Influenza Surveillance and Response System

20 December 2017

- National Influenza Centre
- WHO Collaborating Centre for Reference and Research on Influenza
- WHO Collaborating Centre for the Surveillance, Epidemiology and Control of Influenza
- WHO Collaborating Centre for Studies on the Ecology of Influenza in Animals
- WHO Essential Regulatory Laboratory
- WHO H5 Reference Laboratory

Not applicable

0 875 1,750 3,500 Kilometers

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: Global Influenza Surveillance and Response System (GISRS), WHO
Map Production: Global Influenza Programme
World Health Organization

World Health Organization

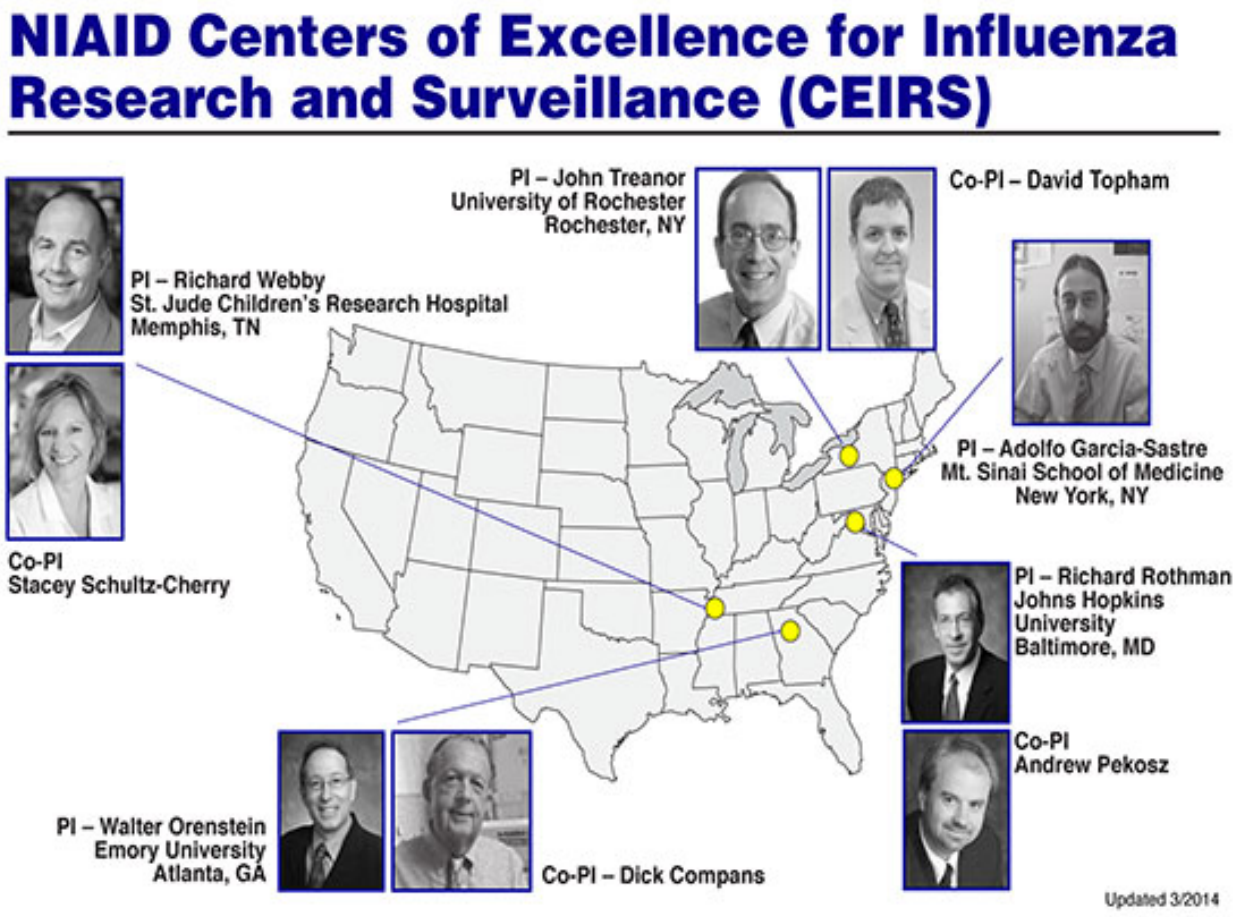
St. Jude as a WHO Collaborating Center

- Robert Webster, PhD joined St. Jude in 1968
  - Identified that human influenza viruses originate in avian species

- One of six WHO Collaborating Centers-
  1) Atlanta, US (CDC)
  2) St. Jude Children's Hospital, Memphis TN (est. 1976)
  3) Beijing, China
  4) London, UK
  5) Tokyo, Japan
  6) Melbourne, Australia

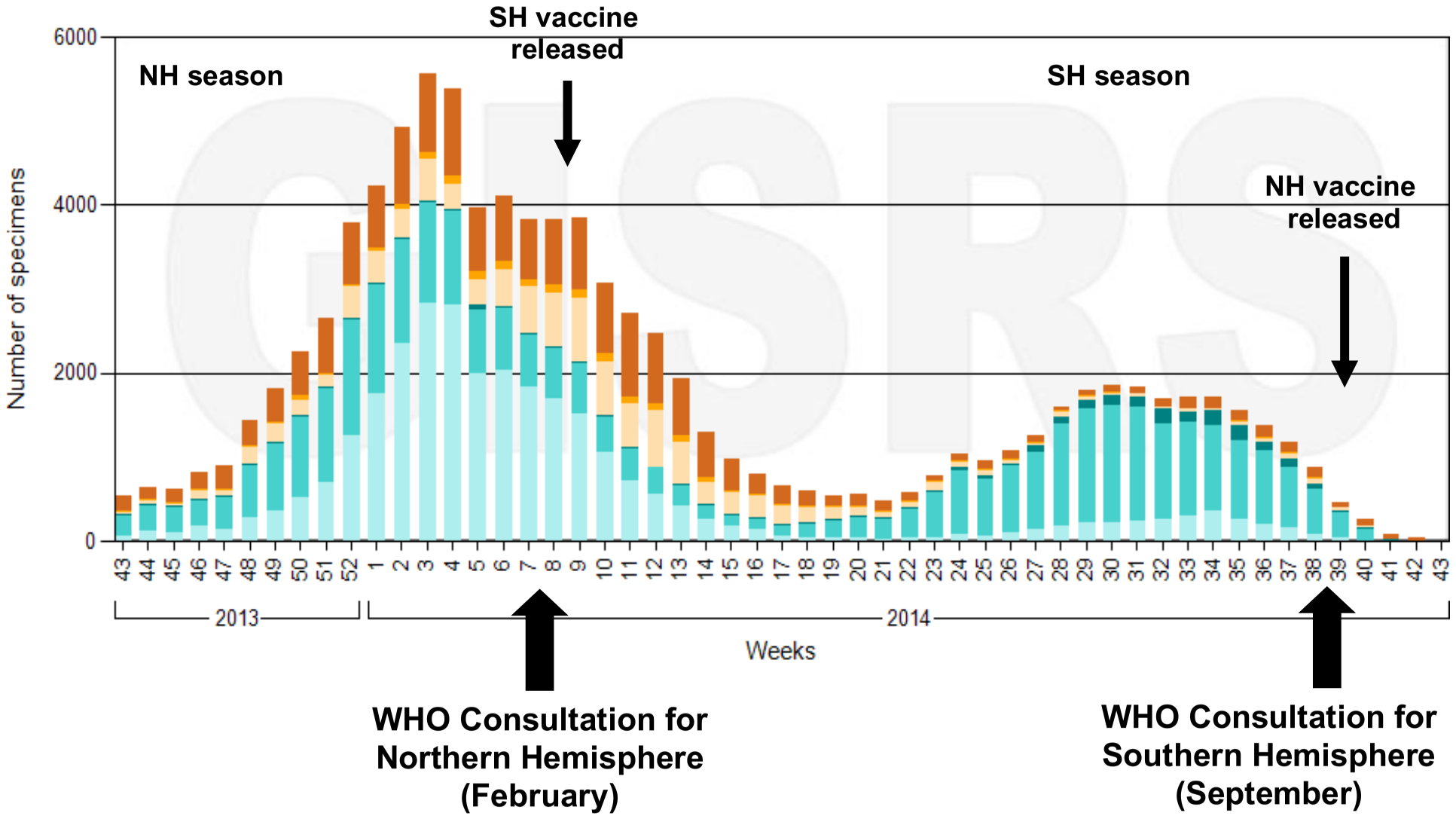
NIAID CEIRS Centers

In 2007, St. Jude is designated one of five CEIRS Centers funded by the NIH



Nine advisors to WHO

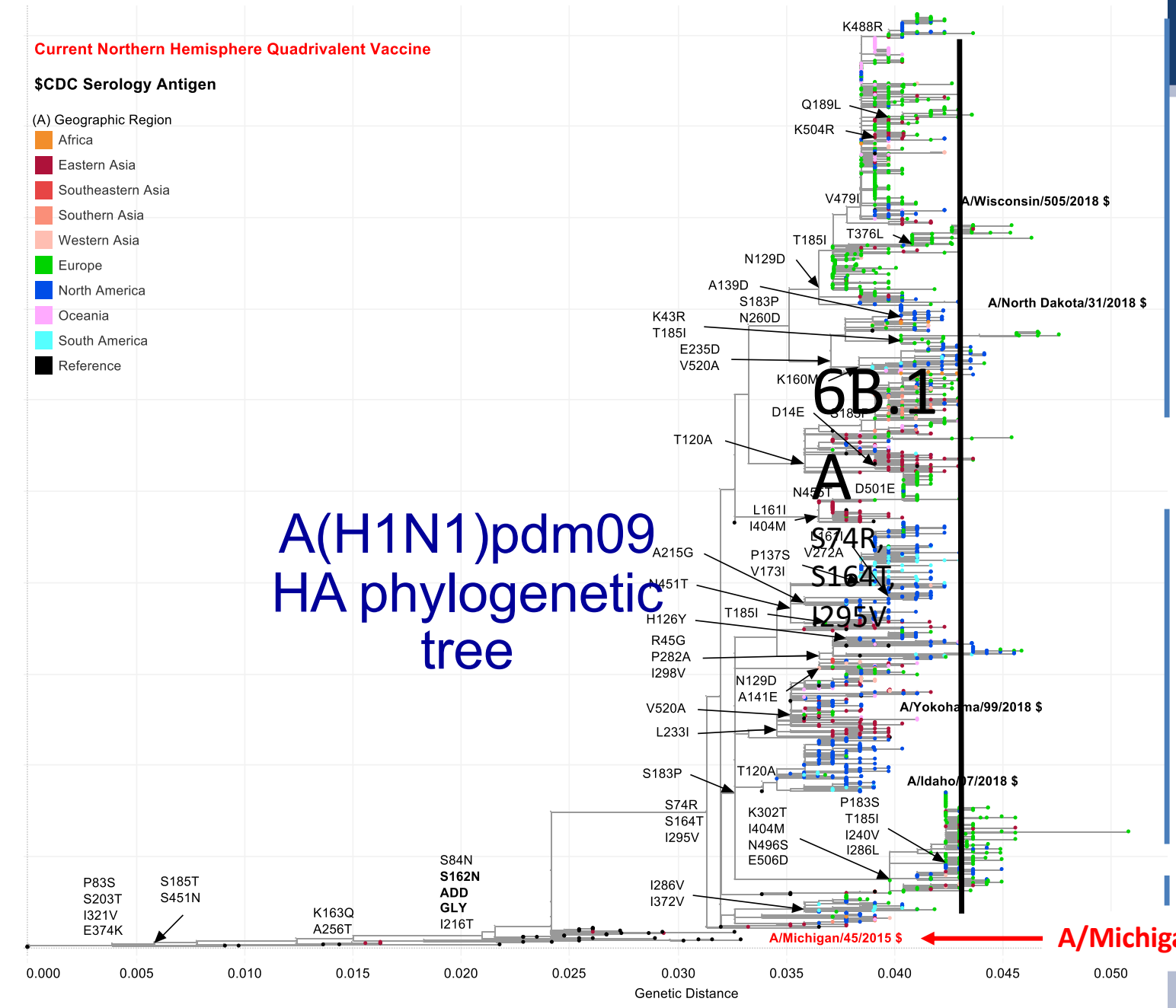
Process driven by manufacturing limitations



Question: are the latest field viruses similar to current vaccine stains or not?

Multiple data types used:

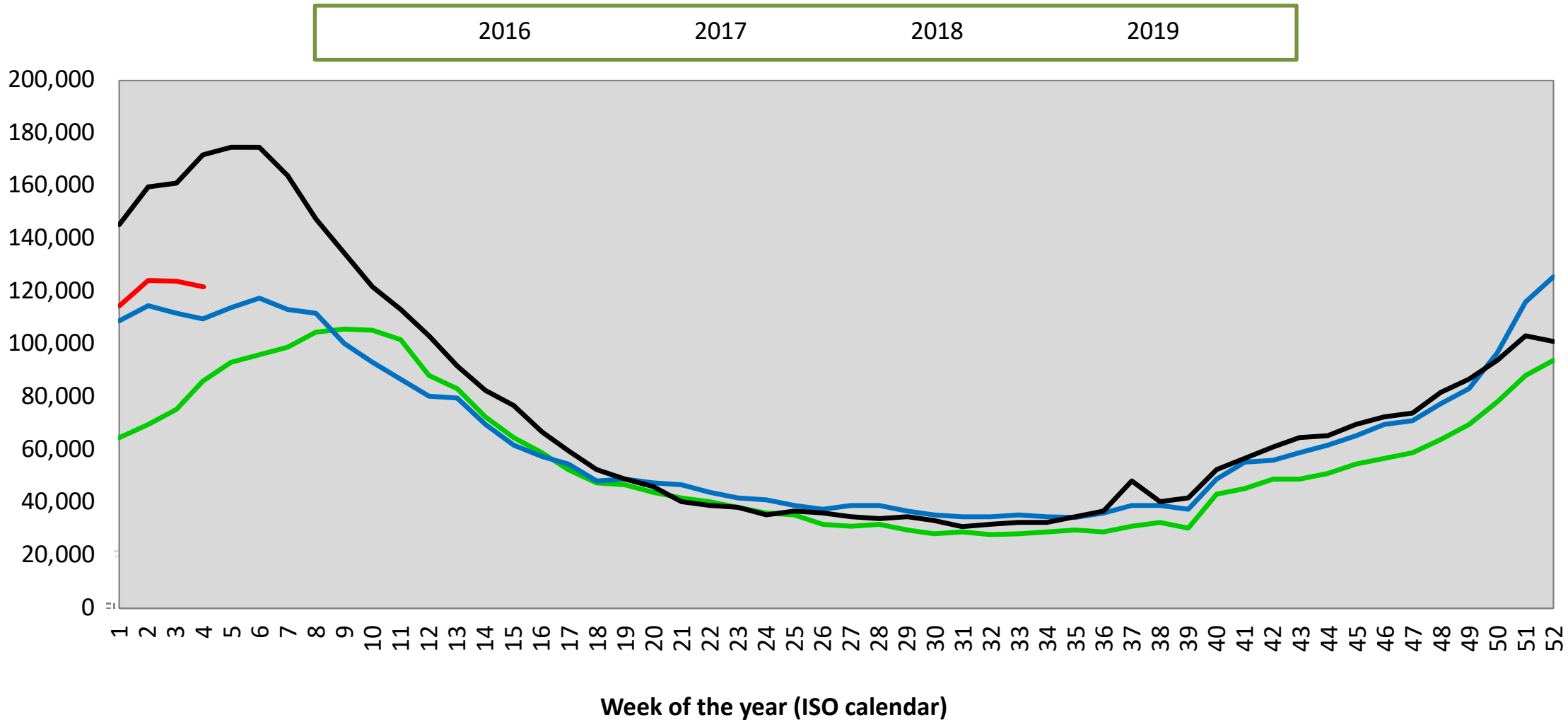
- Sequence data, much more available now
- Antigenic data -hemagglutination inhibition or microneutralization
- Human serology
- Predictive modeling (in its infancy)
- Vaccine effectiveness data



S183P

2017-2018 vaccine strain

Number of specimens processed by GISRS



Data source: FluNet, (www.who.int/flunet), Global Influenza Surveillance and Response System (14 September 2018)

Criteria for strain change

Widespread and increasing circulation of viruses showing:

(1) marked change in antigenic profile compared with previous vaccine strains (typically 4 to 8 fold reduction in HAI titers)

AND

(2) changes in sequence of HA protein, especially at known antibody- or receptor-binding sites

AND

(3) poor recognition by serum antibodies from people who received the previous vaccine

AND

(4) availability of suitable candidate vaccine strains isolated in eggs

Not all viruses are suitable for vaccine production

- Egg adaptive changes
- Stability of antigens
- Poor growth
- Not all viruses reassort successfully

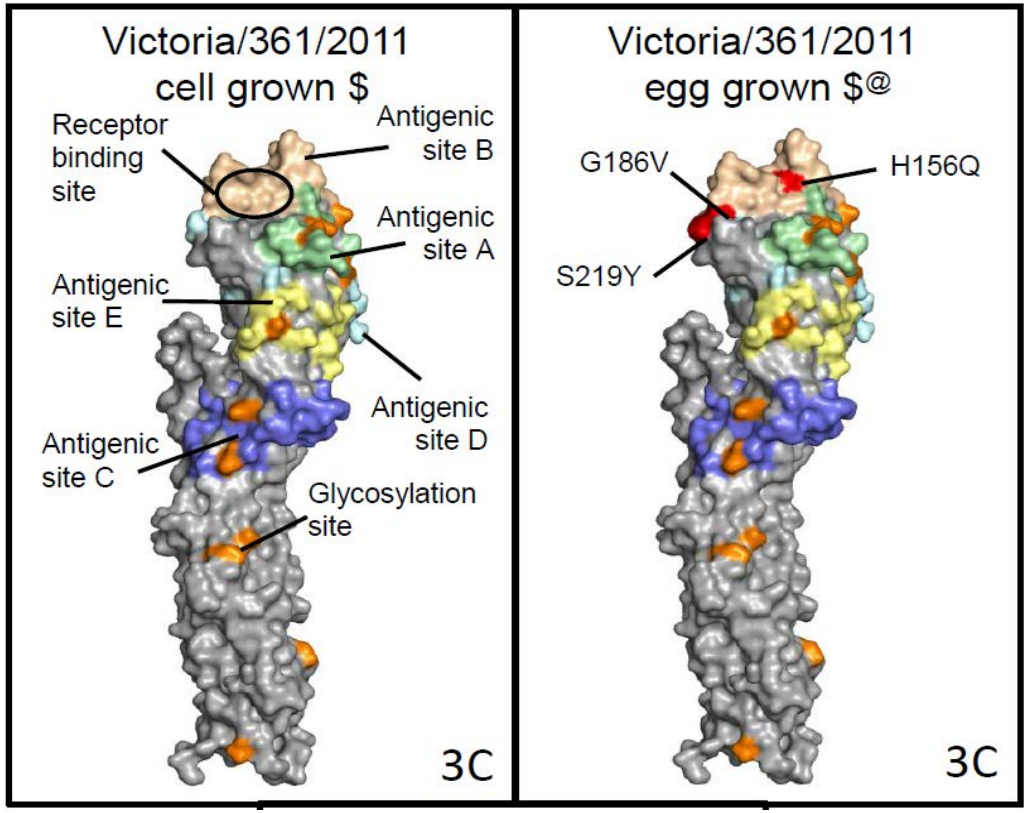


Image prepared by WHO CC at US CDC and presented at Information Meeting, WHO, Geneva, February 2013

A(H3N2) low reactors in **HI** assays by WHO CCs

WHO CC	A/Singapore/INFIMH-16-0019/2016-**Cell** (3C.2a1)	Low (≥ 8 fold)
CNIC	73 (84%)	14 (16%)
VIDRL	248 (98%)	5 (2%)
Total	549 (96%)	21 (4%)

Low represented titers ≥ 8-fold low to vaccine strain

A(H3N2) low reactors in **HI** assays by WHO CCs

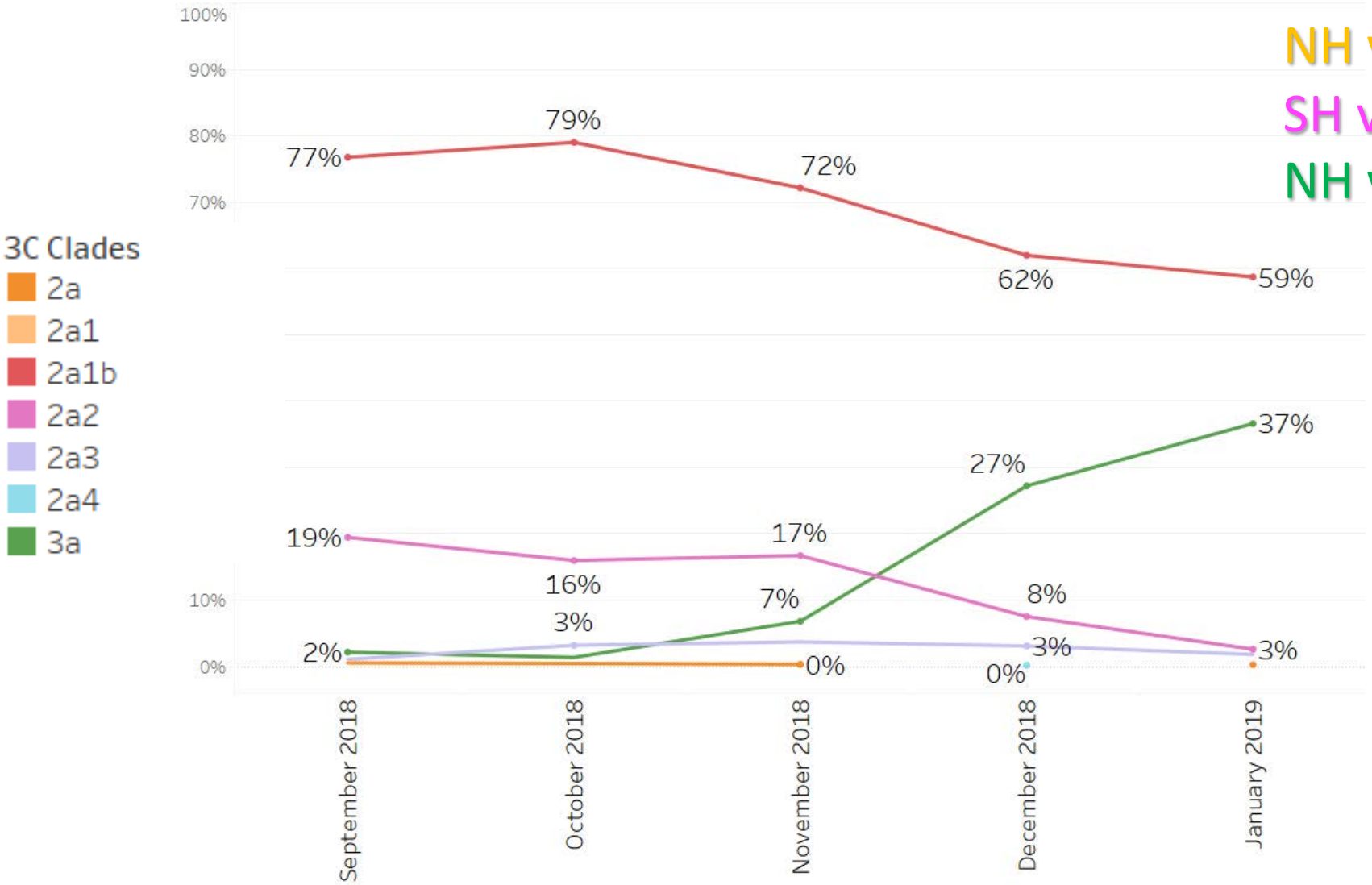
WHO CC	A/Singapore/INFIMH-16-0019/2016-**Egg** (3C.2a1)	Low (≥ 8 fold)
CDC	18 (11%)	140 (89%)
CNIC	78 (90%)	9 (10%)
CRICK	28 (52%)	26 (48%)
VIDRL	8 (3%)	245 (97%)
Total	132 (24%)	420 (76%)

Low represented titers ≥ 8-fold low to vaccine strain

Many viruses are developed, many fail

- **A(H1N1):** A/California/07/09-like
  - A/Brisbane/10/10
  - A/Bolivia/559/13
  - A/South Africa/3626/13
  - A/New Caledonia/58/14
  - A/Florida/62/14
  - A/Minnesota/32/15
  - A/Slovenia/2903/15
  - A/St. Petersburg/61/15
  - A/Michigan/45/15 (6B.1)
  - A/Iowa/53/16 (6B.2)
- **B Victoria:** B/Brisbane/60/08-like
  - B/Texas/2/13
  - B/Indiana/25/15
  - B/Brisbane/46/15
- **A(H3N2):** A/Hong Kong/4801/14-like
  - A/Hong Kong/7127/14
  - A/New Caledonia/71/14
  - A/Norway/2178/14
  - A/Montana/28/15
  - A/South Australia/09/15
  - A/Brisbane/47/15 & /82/15
- **B Yamagata:** B/Phuket/3073/13-like
  - B/Brisbane/9/14
  - B/Utah/09/14
  - B/Maryland/12/15
  - B/California/12/15

A(H3N2) 3C clade dynamics based on available HA sequences

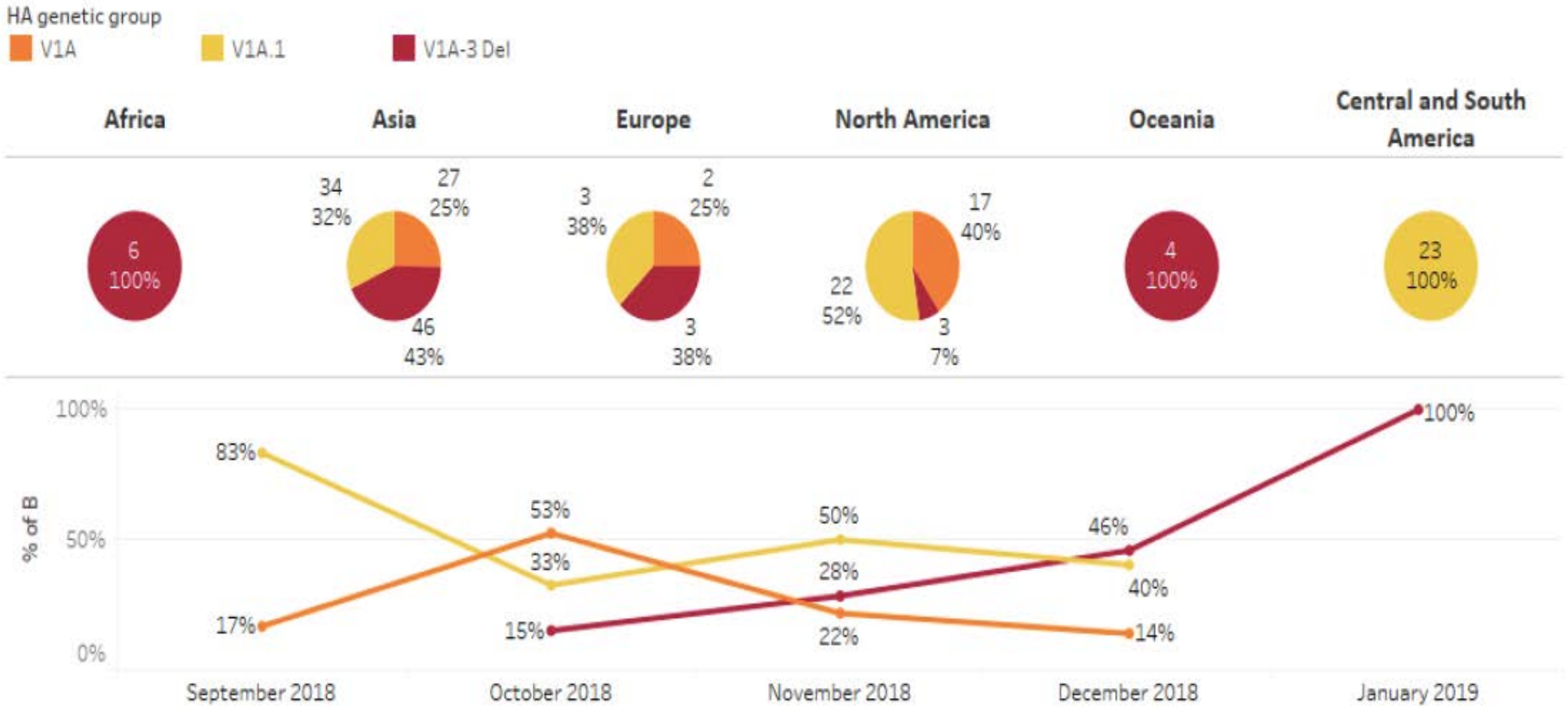


NH vaccine strain 2018-19: 2a1

SH vaccine strain 2019: 2a2

NH vaccine strain 2019-20: 3a

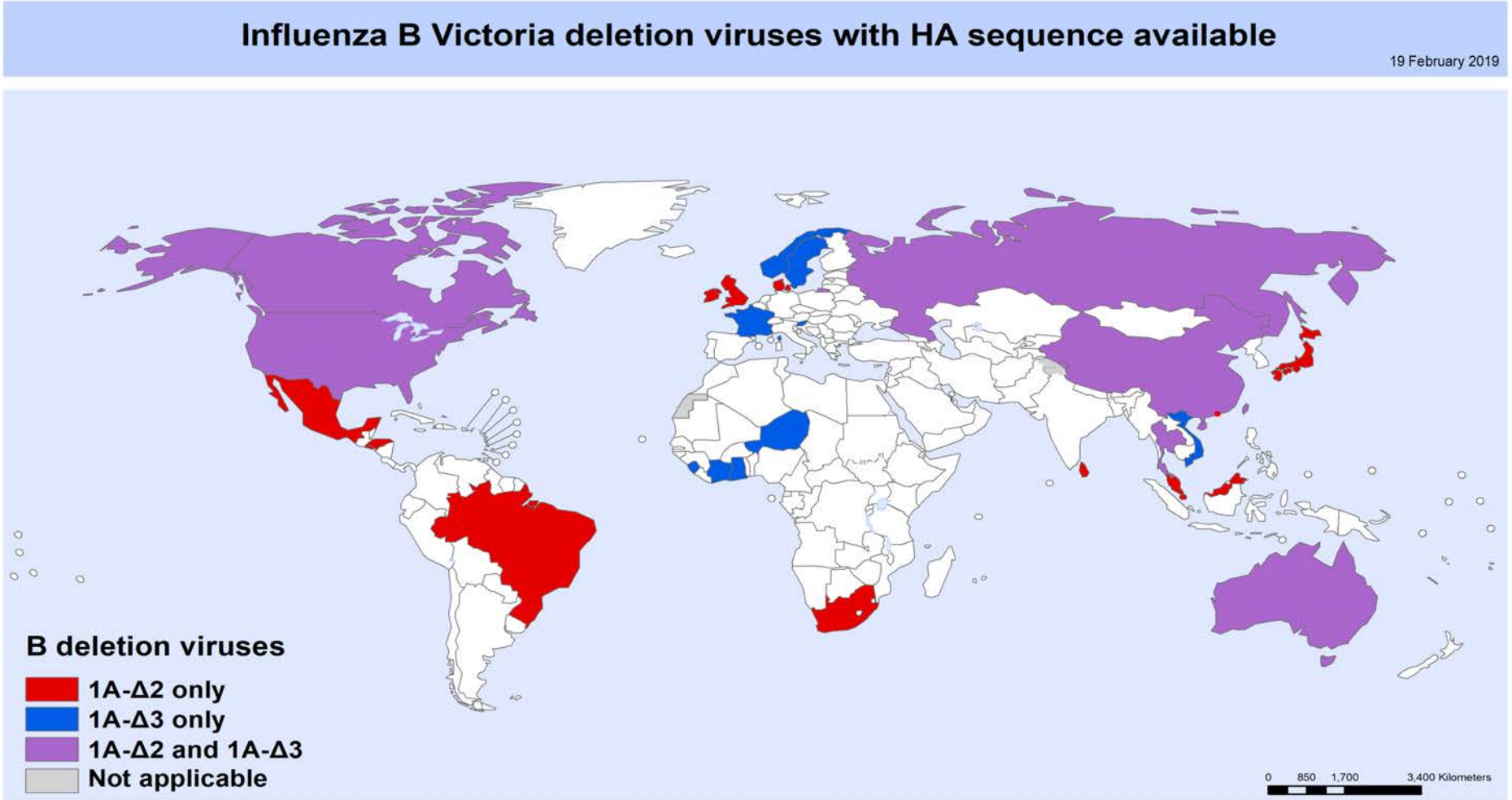
Global influenza B/Victoria lineage clades based on available HA sequences (WHOCC Atlanta)



Influenza B/Victoria deletion viruses

2-del = 121

3-del = 85



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Data Source: WHO CCs and NICs of GISRS, February 2019
Map Production: WHO GISRS Team
World Health Organization

World Health Organization

Vaccine composition recommendation

It is recommended vaccines for use in the 2019-2020 northern hemisphere influenza season contain the following:

Quadrivalent

- A/Brisbane/02/2018 (H1N1)pdm09-like virus;
- A/Kansas/14/2017 (H3N2)- like virus; (3a strain)
- B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage); and (2 deletion strain)
- B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage)

Trivalent

- Two A components as above
- B/Colorado/06/2017-like

Give It Your Best Shot

World Health Organization

CEIRS
NIAID Centers of Excellence for Influenza Research and Surveillance

Thank you

Richard Webby, PhD
Miguela Caniza, MD
Stacey-Schultz-Cherry, PhD
Sanja Trifkovic, PhD