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
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

- H3N2
- H1N1
- H2N2
- H3N2
- Influenza B
- H1N1
- H1N1
- H1N1pdm09

Timeline:
- 1900
- 1910
- 1920
- 1930
- 1940
- 1950
- 1960
- 1970
- 1980
- 1990
- 2000
- 2010
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

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)

Estimated U.S. Influenza Burden, By Season
(2010 - 2018)

- Deaths
- Hospitalizations
- Illnesses

2010 - 2011: 21,000,000
2011 - 2012: 9,300,000
2012 - 2013: 140,000
2013 - 2014: 34,000,000
2014 - 2015: 38,000
2015 - 2016*: 30,000,000
2016 - 2017*: 51,000
2017 - 2018*: 960,000

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

https://www.cdc.gov/flu/about/burden/index.html
CDC estimates that, from **October 1, 2018**, through **April 13, 2019**, there have been:

- **36 million – 41.3 million** flu illnesses
- **502,000 – 610,000** flu hospitalizations
- **16.7 million – 19.4 million** flu medical visits
- **34,400 – 57,300** flu deaths
Influenza biology

- Eight segmented negative-sense RNA genome
- Lacks proofreading mechanisms
- Allows continuous accumulation of mutations
Continuing challenges in influenza

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

Antigenic Shift: variation by re-asserstment of genomes from two or more strains
Interspecies transmission of influenza A viruses

Aquatic birds and bats act as zoonotic reservoirs - antigenic shift

Transmission requires adaptation:

• 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 $\alpha 2,3$ sialic acid to $\alpha 2,6$ sialic acid

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
AIM: How many people were actually infected with influenza?

20-69 year old patients

Study criteria met and mailed packet

Online screening survey

Pre-season blood

Weekly survey

Vaccination

Acute ILI blood/swab

Post-vaccine blood

Convalescent blood, if PCR flu +

Post-season blood

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

- 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)

<table>
<thead>
<tr>
<th>Age group</th>
<th>Symptomatic community illness</th>
<th>Outpatient medical visits</th>
<th>Hospitalizations</th>
<th>Excess deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>9 200 000–35 600 000</td>
<td>4 200 000–16 700 000</td>
<td>139 000–708 000</td>
<td>4000–20 000</td>
</tr>
<tr>
<td>&lt;5 y</td>
<td>900 000–3 800 000</td>
<td>600 000–2 500 000</td>
<td>6000–26 000</td>
<td>60–300</td>
</tr>
<tr>
<td>5–17 y</td>
<td>1 900 000–6 900 000</td>
<td>1 000 000–3 600 000</td>
<td>5000–19 000</td>
<td>50–300</td>
</tr>
</tbody>
</table>

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\(^a\) 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.

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


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

Vaccination of Children Provide Community Immunity

49 Hutterite (Canada) colonies randomized

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

25 colonies randomized to receive influenza vaccine (1773 retained)

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

Followed adults for influenza infection during season

Loeb et al JAMA 2010
Summary: vaccinating just children resulted in 61% protective effectiveness
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

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

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
GLOBAL OBESITY

Percentage of population

Adult men

Adult women

Source: The New England Journal of Medicine

CHILDHOOD OBESITY

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

O’Brien et al JID 2012
Karlsson et al mBio 2016; mBio 2017
Schultz-Cherry JID 2018
Sheridan et al Int J Obesity 2011
Meliopoulos et al J Virol 2019
Neidich et al Int J Obesity 2017
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

Interferon & Antiviral Cytokines

Innate immune cells

B cells & Abs

T cells

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

Current phase

**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

The continuum of pandemic phases

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

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


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
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

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

Impact

Likelihood

A(H5N6)

2017 A(H7N9)

A(H7N9)

A(H9N2)

A(H1N1) TRIG
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)
In 2017, WHO published Pandemic Influenza Severity Assessment (PISA)

Initial assessment (when data is sparse) of potential influenza pandemic severity:

<table>
<thead>
<tr>
<th>Transmissibility of the virus</th>
<th>Seriousness of Disease</th>
<th>Population Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Virologic characterization</td>
<td>• Virologic characterization</td>
<td>• None</td>
</tr>
<tr>
<td>• Animal transmission studies</td>
<td>• Animal morbidity studies</td>
<td></td>
</tr>
<tr>
<td>• Underlying population immunity</td>
<td>• Underlying population immunity</td>
<td></td>
</tr>
<tr>
<td>• Secondary attack rate in closed settings</td>
<td>• Inferences about risk of mortality and hospitalization from early case reports and outbreaks</td>
<td></td>
</tr>
<tr>
<td>(e.g. households, schools)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Early estimates of $R_0$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Compared to seasonal epidemics:

- **A**: Similar transmission and severity
- **B**: Transmission greater
- **C**: Transmission is similar, severity is greater
- **D**: Transmission and severity greater

# CDC Systematic Framework for Refined Assessment

## Transmissibility

<table>
<thead>
<tr>
<th>Parameter no. and Description</th>
<th>Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1</strong> Symptomatic attack rate, community, %</td>
<td>1</td>
</tr>
<tr>
<td>≤10</td>
<td>11-15</td>
</tr>
<tr>
<td><strong>2</strong> Symptomatic attack rate, school, %</td>
<td>≤20</td>
</tr>
<tr>
<td><strong>3</strong> Symptomatic attack rate, workplace, %</td>
<td>≤10</td>
</tr>
<tr>
<td><strong>4</strong> Household secondary attack rate, symptomatic, %</td>
<td>≤5</td>
</tr>
<tr>
<td><strong>5</strong> R0; basic reproductive no.</td>
<td>≤1.1</td>
</tr>
<tr>
<td><strong>6</strong> Peak % outpatient visits for ILI</td>
<td>1-3</td>
</tr>
</tbody>
</table>

## Clinical Severity

<table>
<thead>
<tr>
<th>Parameter no. and Description</th>
<th>Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1</strong> Case-fatality ratio, %</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td><strong>2</strong> Case-hospitalization ratio, %</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td><strong>3</strong> Ratio, deaths: hospitalization, %</td>
<td>≤3</td>
</tr>
</tbody>
</table>

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Scaled measure of clinical severity

Low Severity

Moderate Severity

High Severity

Very High Severity

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
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
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
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
In 2007, St. Jude is designated one of five CEIRS Centers funded by the NIH.
Nine advisors to WHO
Process driven by manufacturing limitations

WHO Consultation for Northern Hemisphere (February)

WHO Consultation for Southern Hemisphere (September)

Number of specimens

NH season

SH season

SH vaccine released

NH vaccine released

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
Number of specimens processed by GISRS

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

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

Low represented titers ≥ 8-fold low to vaccine strain
A(H3N2) low reactors in HI assays by WHO CCs

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

Low represented titers ≥ 8-fold low to vaccine strain
Many viruses are developed, many fail

<table>
<thead>
<tr>
<th><strong>A(H1N1):</strong> A/California/07/09-like</th>
<th><strong>A(H3N2):</strong> A/Hong Kong/4801/14-like</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/Brisbane/10/10</td>
<td>A/Hong Kong/7127/14</td>
</tr>
<tr>
<td>A/Bolivia/559/13</td>
<td>A/New Caledonia/71/14</td>
</tr>
<tr>
<td>A/South Africa/3626/13</td>
<td>A/Norway/2178/14</td>
</tr>
<tr>
<td>A/New Caledonia/58/14</td>
<td>A/Montana/28/15</td>
</tr>
<tr>
<td>A/Florida/62/14</td>
<td>A/South Australia/09/15</td>
</tr>
<tr>
<td>A/Minnesota/32/15</td>
<td>A/Brisbane/47/15 &amp; /82/15</td>
</tr>
<tr>
<td>A/Slovenia/2903/15</td>
<td></td>
</tr>
<tr>
<td>A/St. Petersburg/61/15</td>
<td></td>
</tr>
<tr>
<td>A/Michigan/45/15 (6B.1)</td>
<td></td>
</tr>
<tr>
<td>A/Iowa/53/16 (6B.2)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>**B Victoria: ** B/Brisbane/60/08-like</th>
<th><strong>B Yamagata:</strong> B/Phuket/3073/13-like</th>
</tr>
</thead>
<tbody>
<tr>
<td>B/Texas/2/13</td>
<td>B/Brisbane/9/14</td>
</tr>
<tr>
<td>B/Indiana/25/15</td>
<td>B/Utah/09/14</td>
</tr>
<tr>
<td>B/Brisbane/46/15</td>
<td>B/Maryland/12/15</td>
</tr>
<tr>
<td></td>
<td>B/California/12/15</td>
</tr>
</tbody>
</table>
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 with HA sequence available

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

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2-del = 121
3-del = 85
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
Thank you

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