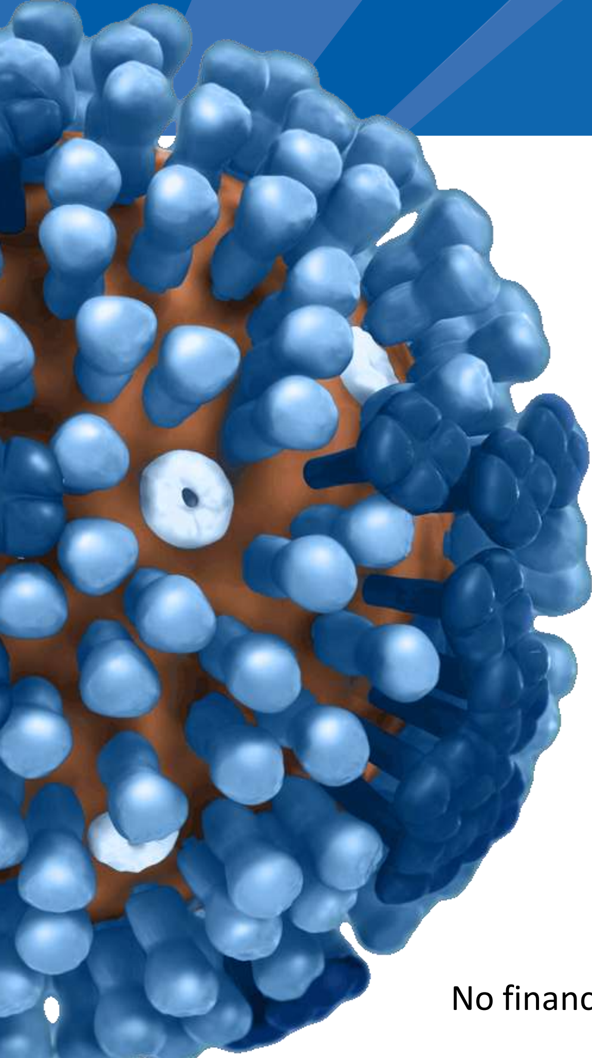

Improving on Influenza Vaccines: Managing the Challenges of Vaccine Mismatch

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National Center for Immunization and Respiratory Diseases

Centers for Disease Control and Prevention

August 28, 2016

No financial relationships with commercial interests to disclose.

- Where we were
- Where we are
- Where we are going

Where we were… where we are

On Arrival at Camp
Cabin has 25 Campers

Where we were… where we are

On Arrival at Camp
Cabin has 25 Campers

Where we were… where we are

On Arrival at Camp
Cabin has 25 Campers

One Week Later
Cabin has 11 Campers

Where we were… where we are

On Arrival at Camp
Cabin has 25 Campers

One Week Later
Cabin has 11 Campers

Where we were… where we are

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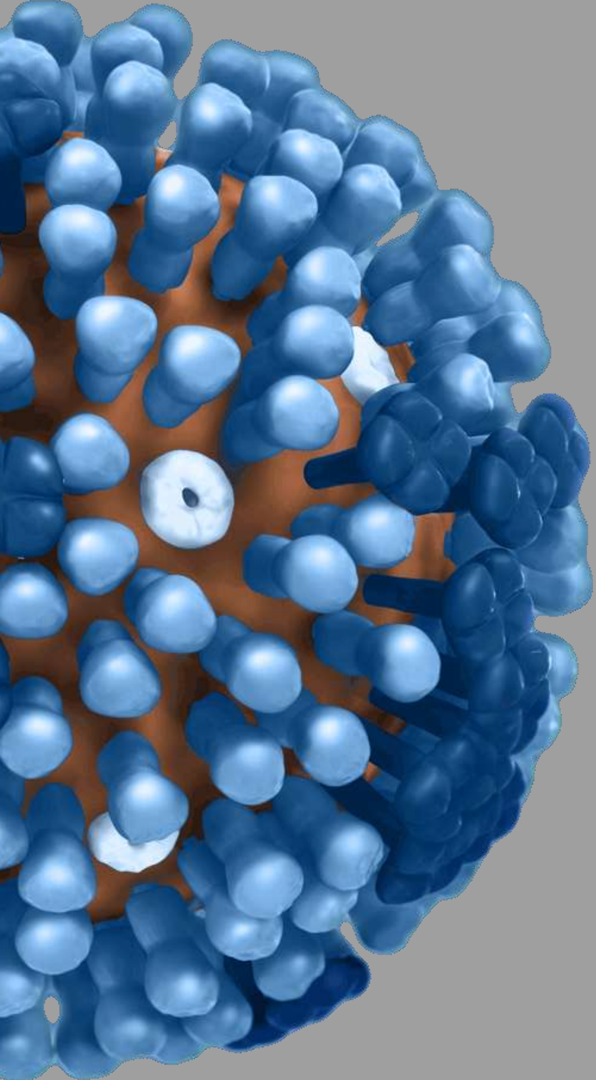
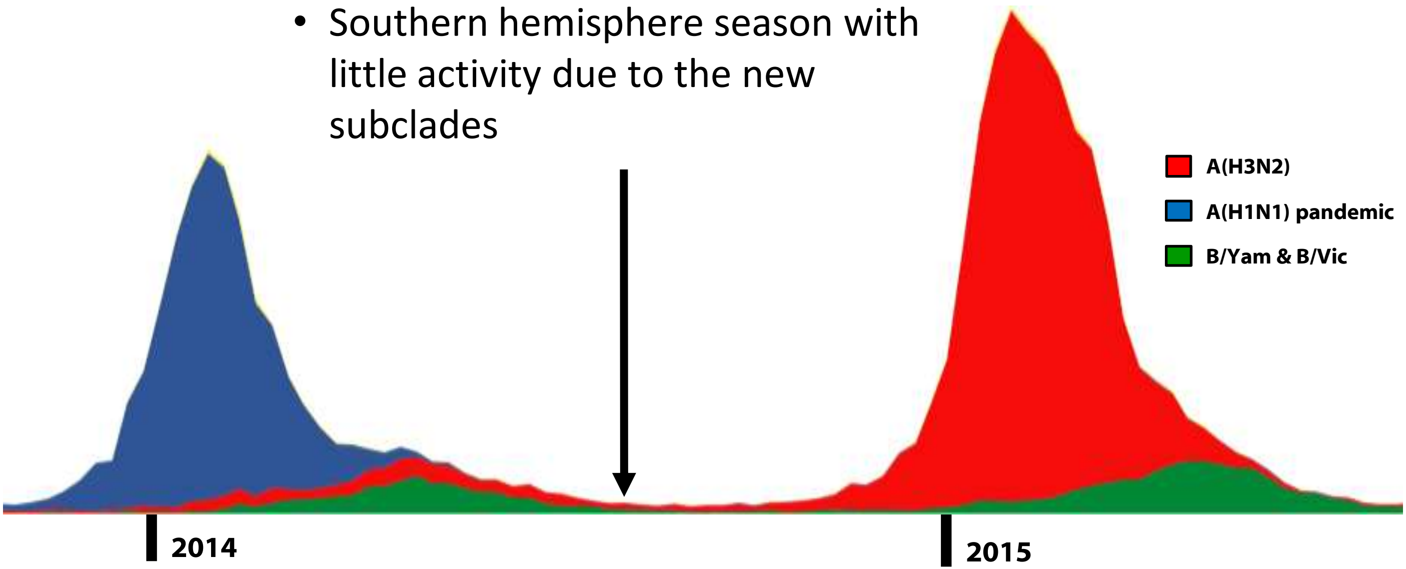


The 2014-15 Season

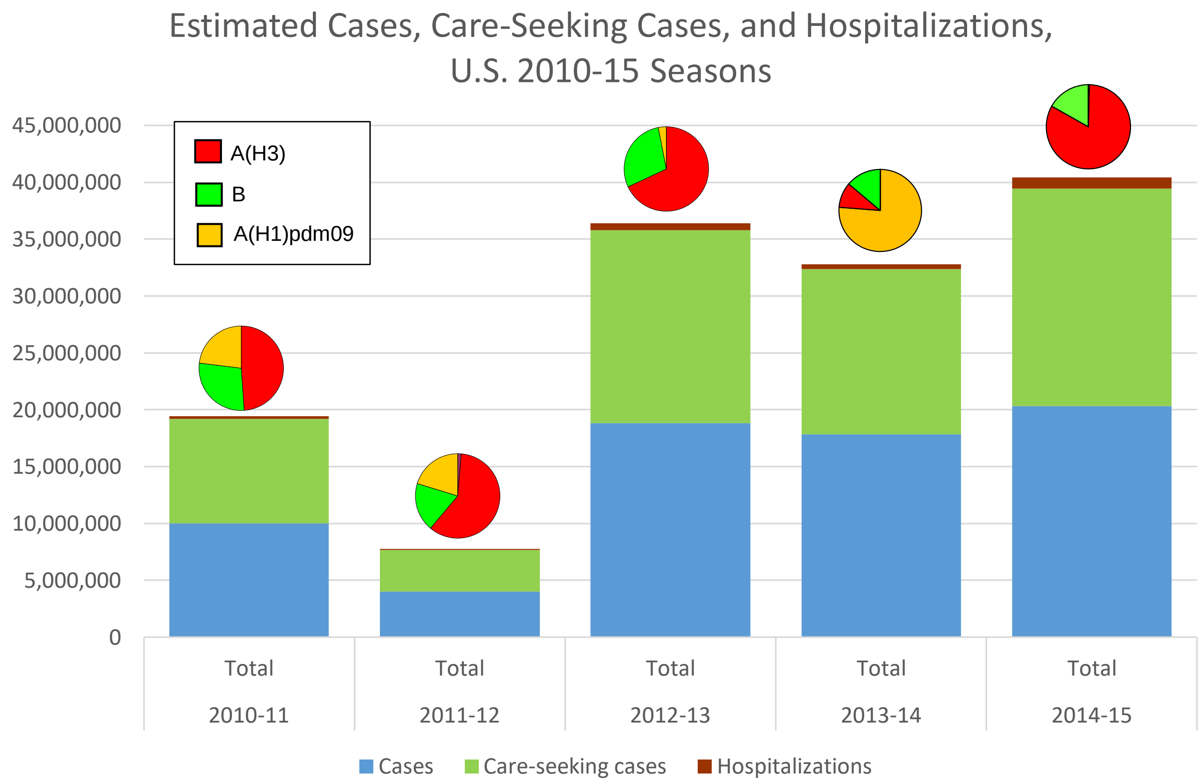
2014-15 Influenza Season – U.S.

- New H3N2 subclades 3C.2a & 3C.3a begin increasing in U.S.
- Southern hemisphere season with little activity due to the new subclades



CDC. US Influenza Virologic Surveillance. www.cdc.gov/flu/weekly/overview.htm

Annual Influenza Impact Varies by Predominant Virus



Reed et al. PLOS One 10(3):e0118369

http://www.cdc.gov/flu/about/disease/2014-15.htm

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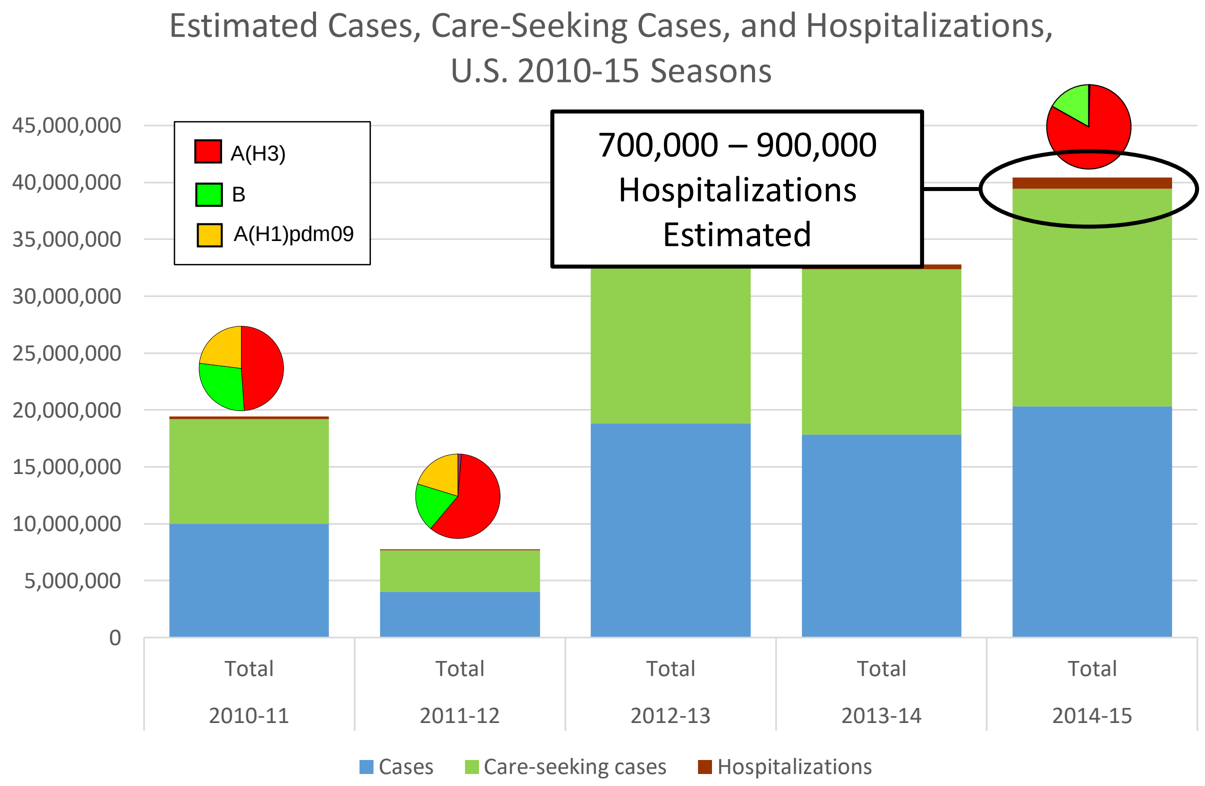
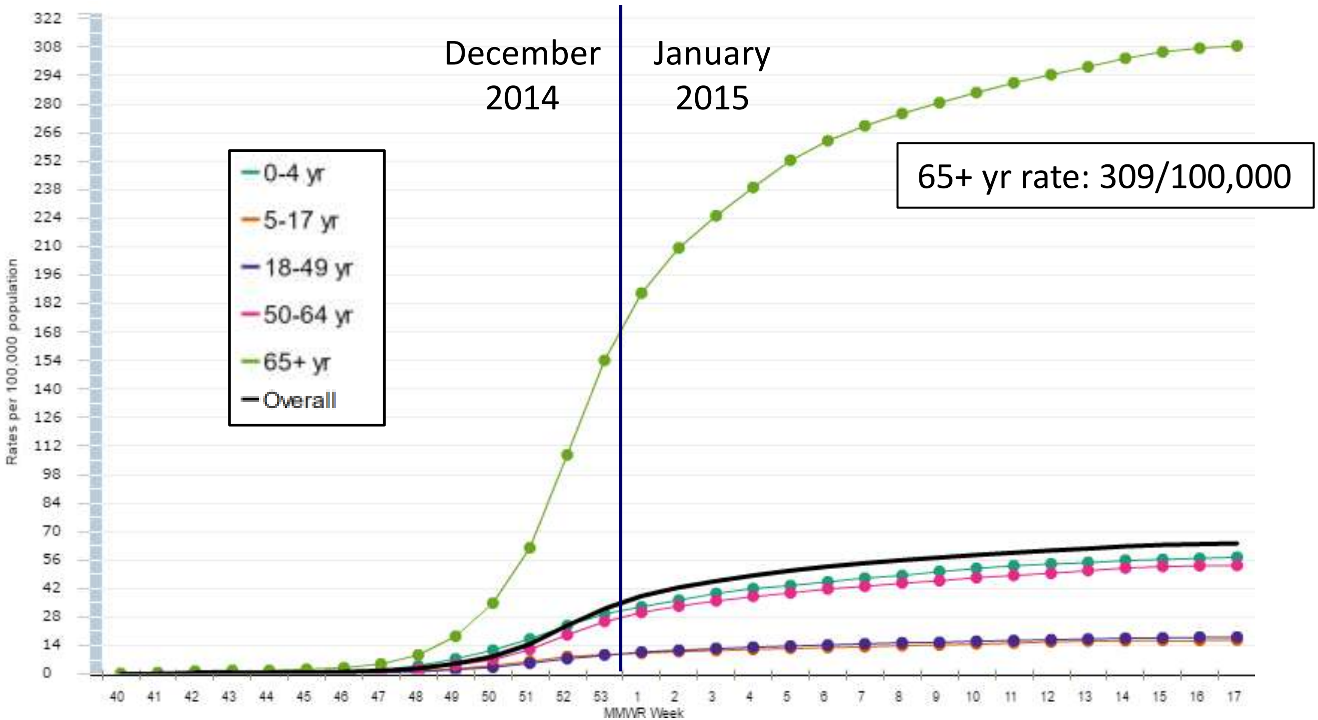


Reed et al. PLOS One 10(3):e0118369

http://www.cdc.gov/flu/about/disease/2014-15.htm

Hospitalization Impact – 2014-15

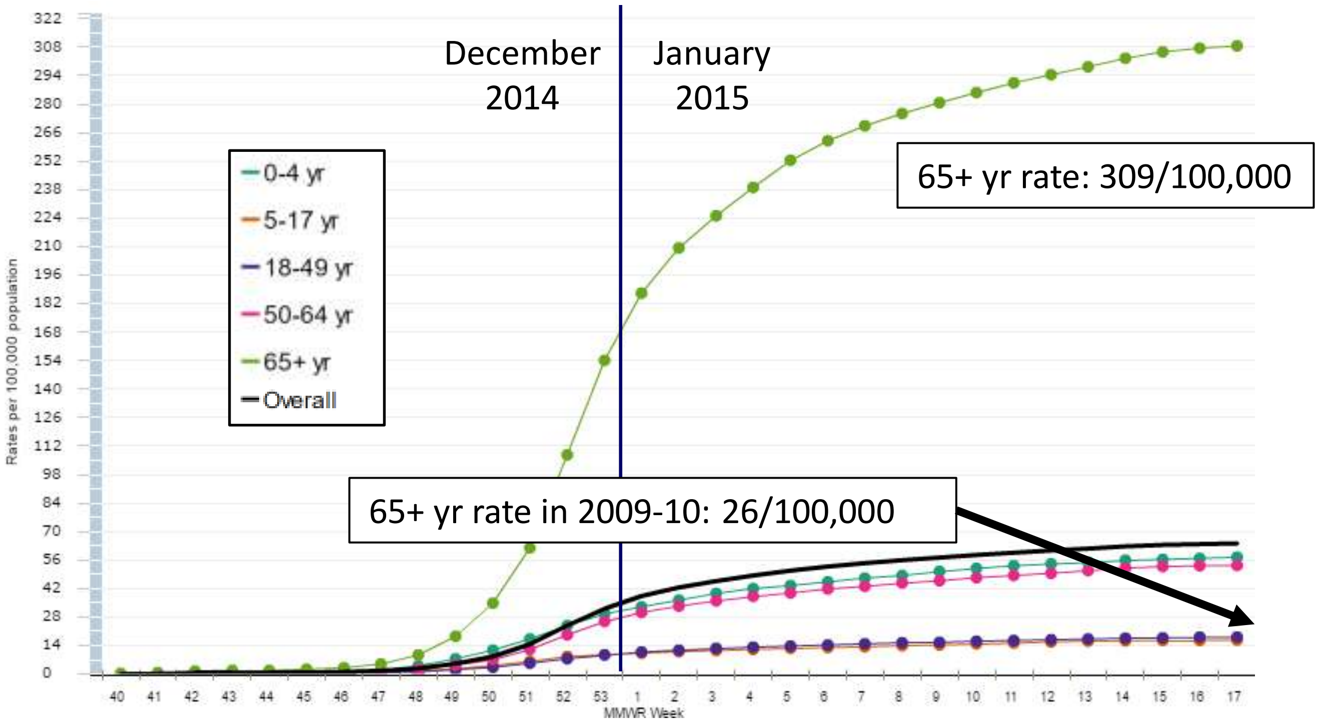
Cumulative Rate per 100,000 for Laboratory-Confirmed Influenza Hospitalizations in 65+, U.S. 2009-16



CDC. FluSurv-NET FluView Interactive. http://gis.cdc.gov/GRASP/Fluview/FluHospRates.html

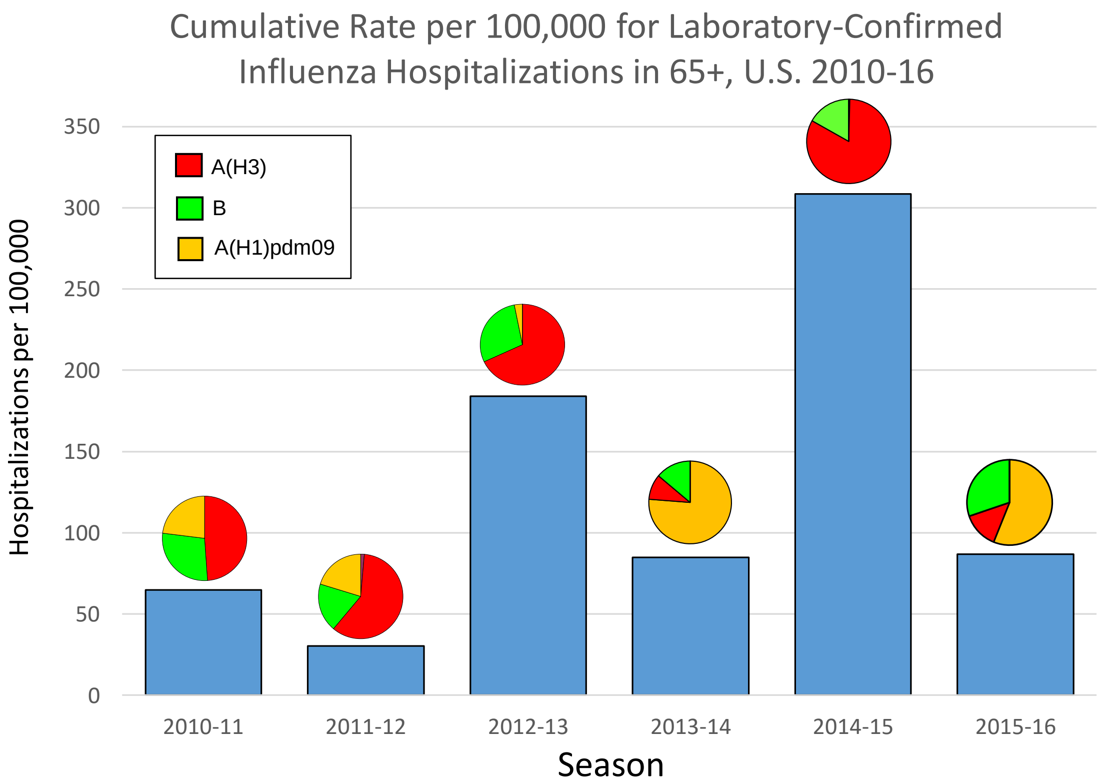
Hospitalization Impact – 2014-15

Cumulative Rate per 100,000 for Laboratory-Confirmed Influenza Hospitalizations in 65+, U.S. 2009-16

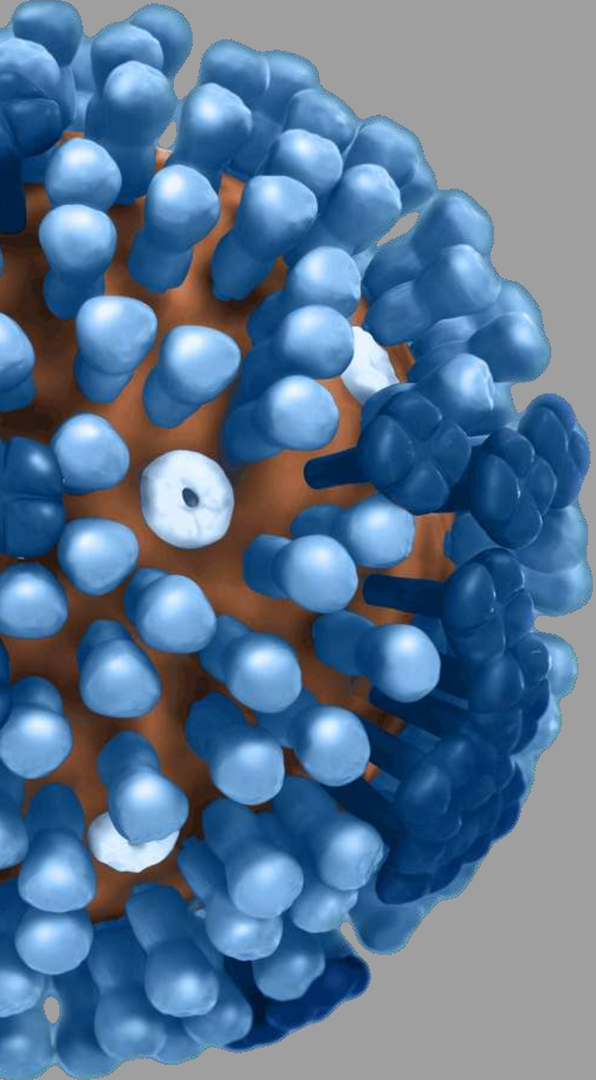


CDC. FluSurv-NET FluView Interactive. http://gis.cdc.gov/GRASP/Fluview/FluHospRates.html

Significant Impact of 2014-15 on 65+ year olds



CDC. FluSurv-NET FluView Interactive. http://gis.cdc.gov/GRASP/Fluview/FluHospRates.html



Vaccine Effectiveness and Mismatch

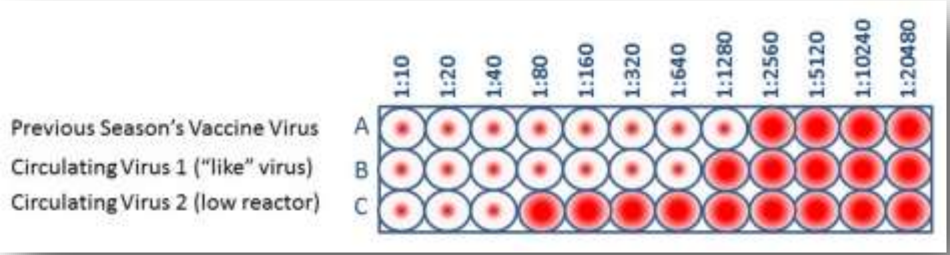
Mismatch

- "The degree of similarity or difference between the circulating viruses and the viruses in the vaccines is often referred to as 'vaccine match' or 'vaccine mismatch'."[1]
- "A vaccine mismatch occurs when viruses circulating among people during a given influenza season have acquired genetic and antigenic changes relative to the viruses used to make the vaccine for that season. Vaccine effectiveness would be expected to be lower when the match is less than optimal. Nevertheless, during the time of a vaccine mismatch, vaccines may still give some protection to vaccinees."[2]

1. WHO. Vaccine effectiveness Q and A. http://www.who.int/influenza/vaccines/virus/recommendations/201502_qanda_vaccineeffectiveness.pdf
2. WHO. Preferred Product Characteristics for Next Generation Influenza Vaccines. 2016 Draft document.

Antigenic Characterization

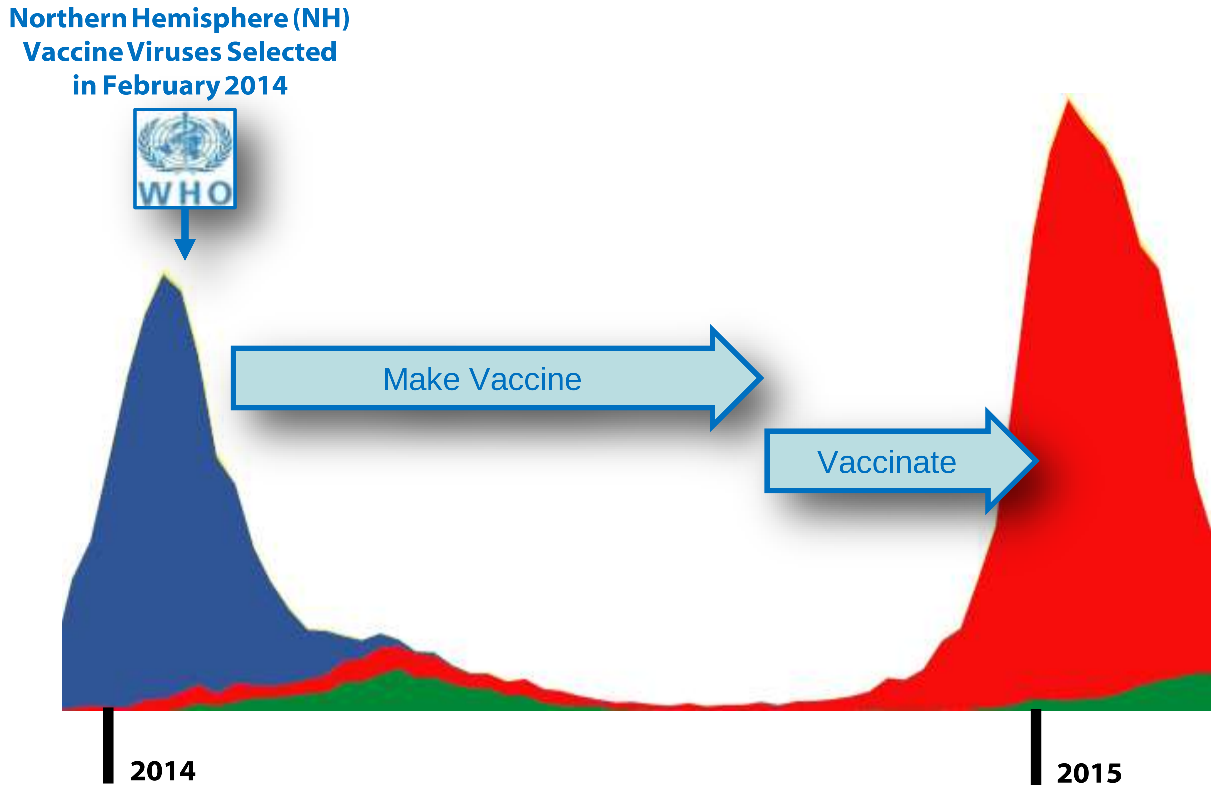
- The HI test assesses the degree of antigenic similarity between circulating and reference viruses using a scale based on greater dilutions of antibodies.
- In general:
  - "vaccine-like": Within four-fold dilution
  - "low reactor": Greater than four-fold dilution



CDC. Antigenic Characterization. http://www.cdc.gov/flu/professionals/laboratory/antigenic.htm

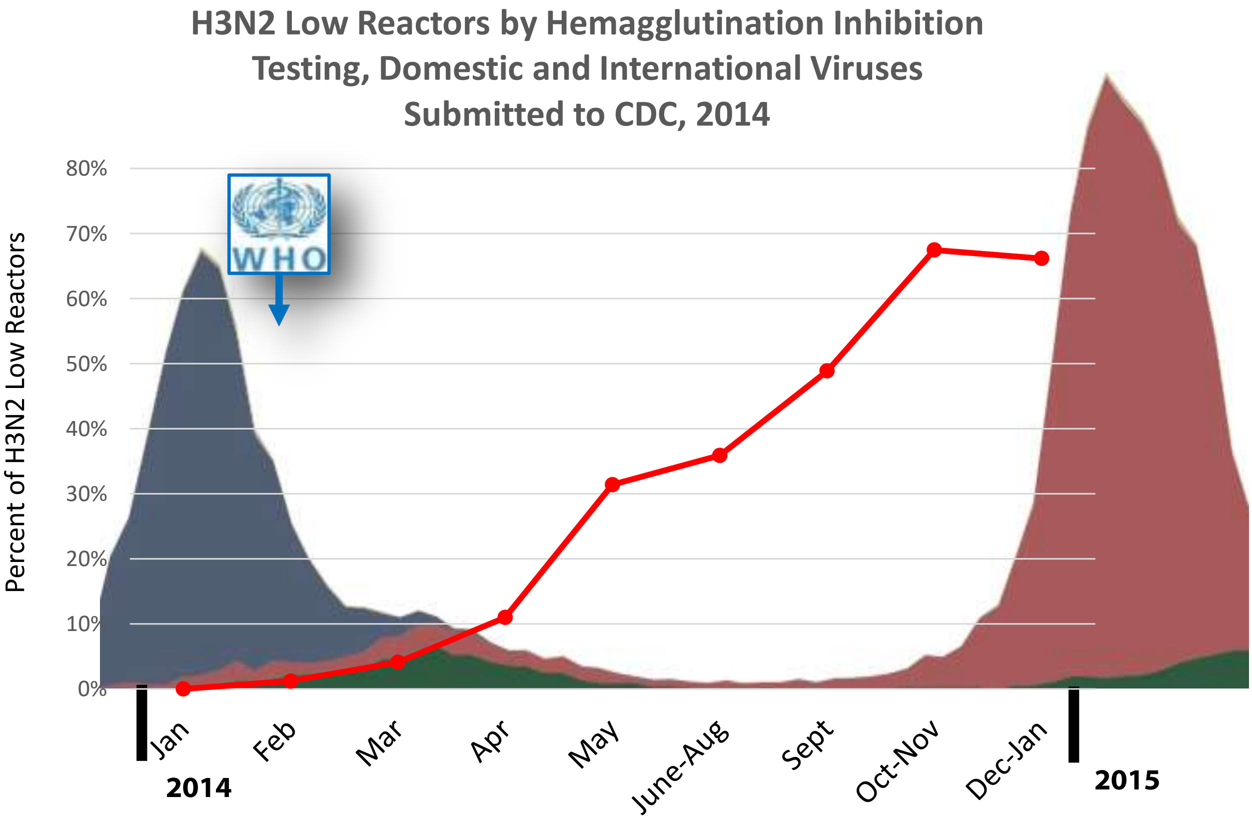
Influenza A/H3N2 Characterization - 2014

Domestic and International Viruses Submitted to CDC



CDC. Unpublished data. H3N2 hemagglutination inhibition test results by date of testing.
CDC. U.S. Influenza Virologic Surveillance. FluView Interactive. www.cdc.gov/flu

Influenza A/H3N2 Characterization - 2014



CDC. Unpublished data. H3N2 hemagglutination inhibition test results by date of testing. LR=low reactor (≥8-fold down to reference virus representing vaccine).
CDC. U.S. Influenza Virologic Surveillance. FluView Interactive. www.cdc.gov/flu

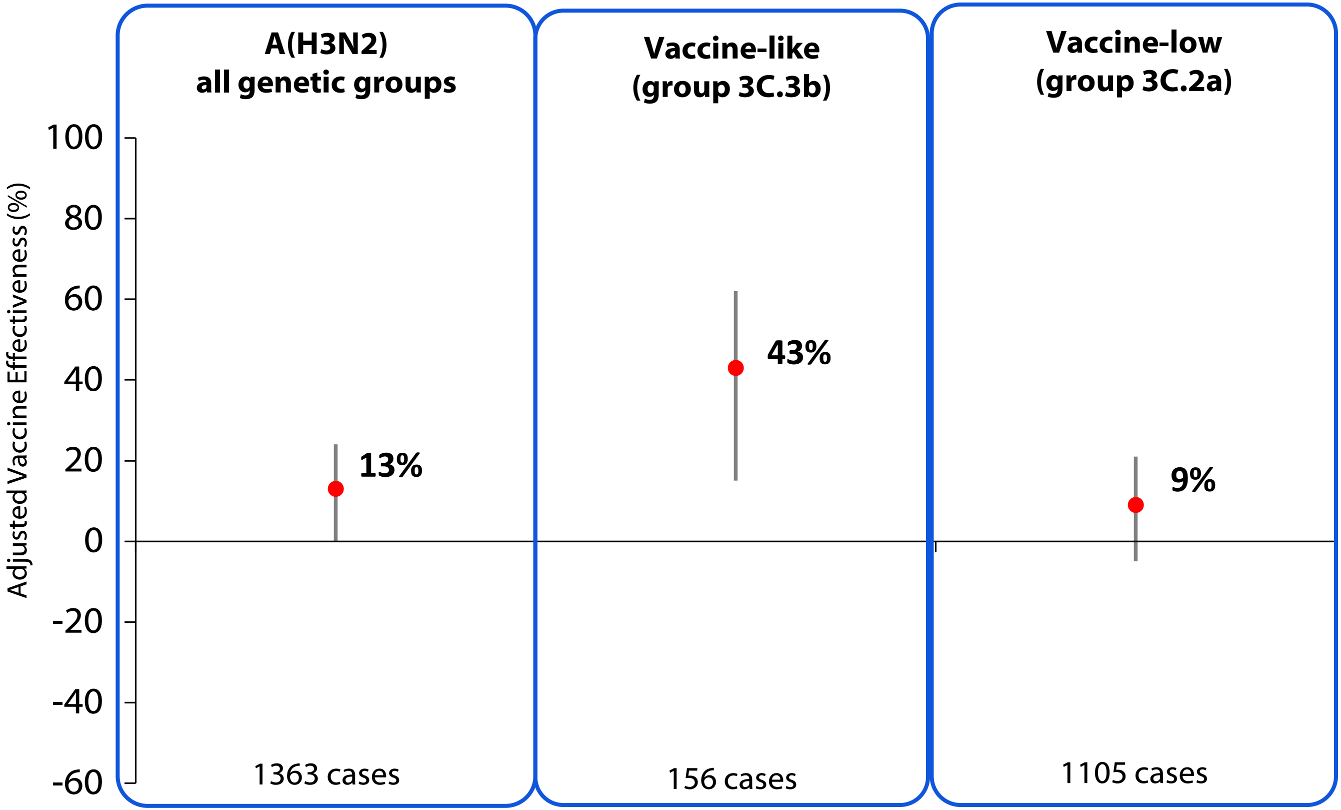
Vaccine Effectiveness, U.S. – 2014-15

Adjusted VE for Influenza Vaccination by Influenza A Subtype and B Virus Lineage, US Flu VE Network, 2014-15

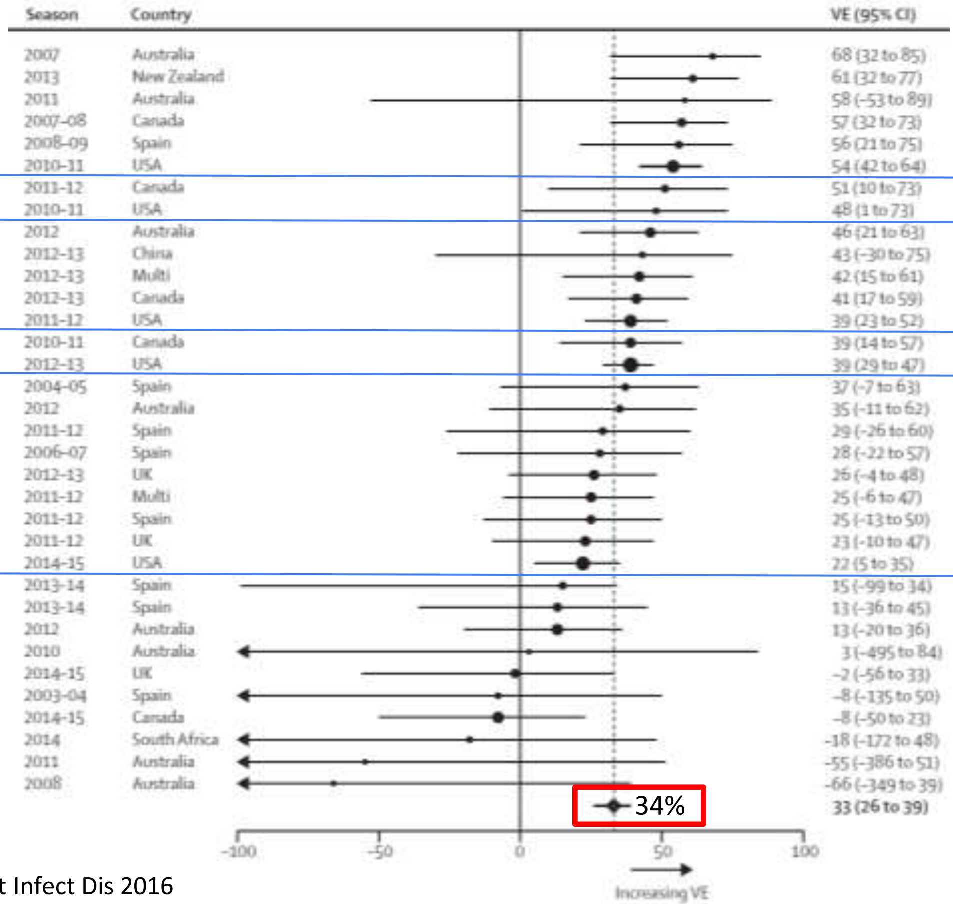
	Influenza-positive	% vaccinated	Influenza-negative	% vaccinated	Adjusted VE	(95% CI)
Influenza A (H3N2)						
All ages	941/1821	(52)	3866/7092	(55)	**13%**	(2 to 23)
Influenza B (Yamagata)						
All ages	125/340	(37)	3866/7092	(55)	**55%**	(43 to 65)
Influenza B (Victoria)						
All ages	12/47	(26)	3866/7092	(55)	**63%**	(26 to 81)

Adjusted VE for influenza vaccination by influenza A subtype and B virus lineage, US Flu VE Network, 2014-15

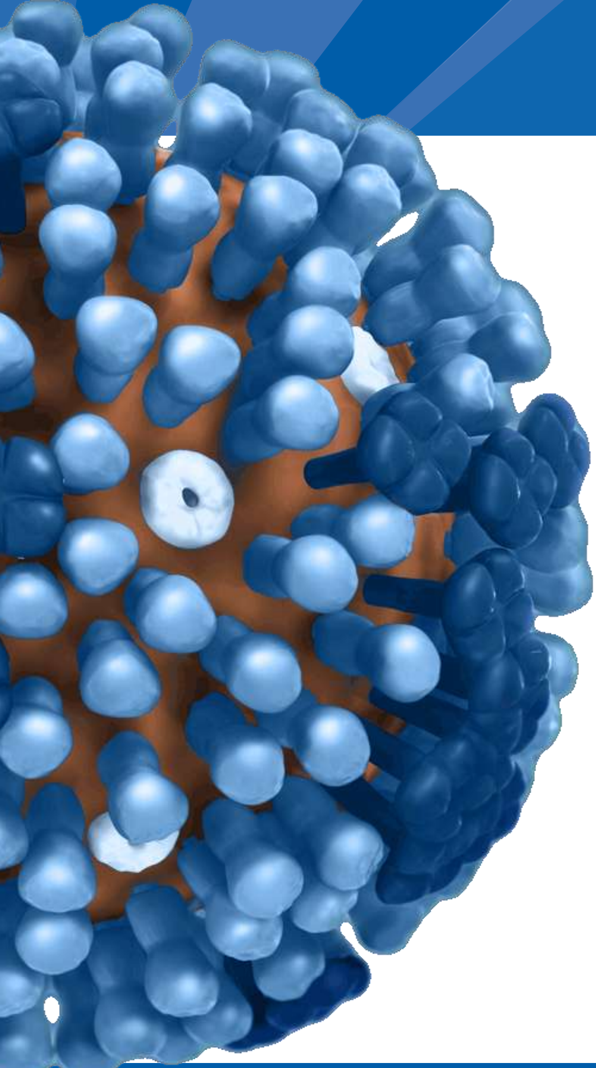
Subclade Specific VE 2014-15

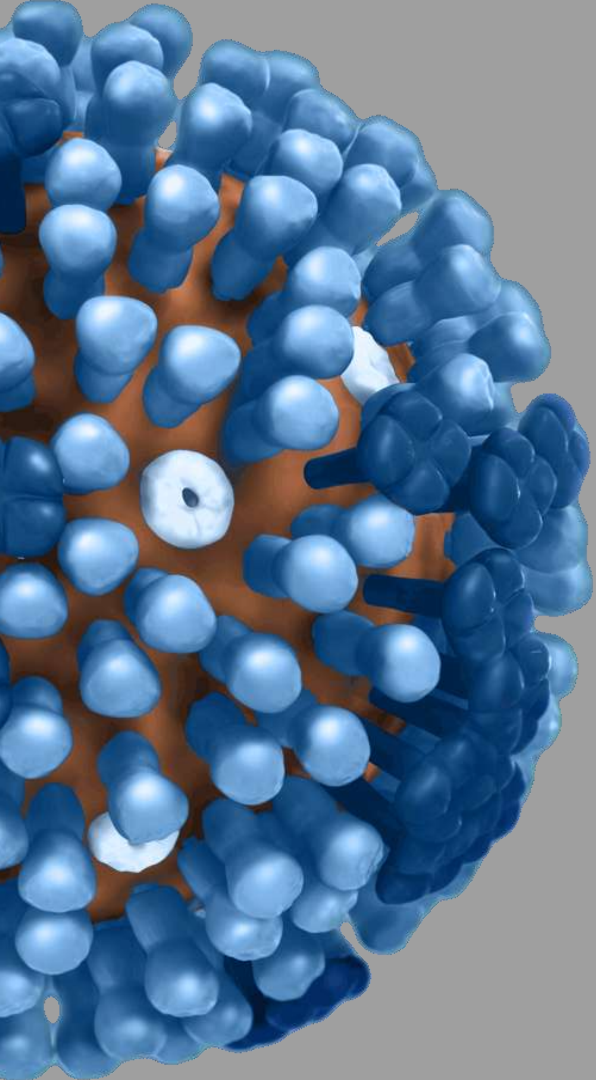


H3N2 Vaccine Effectiveness – 2004-2015



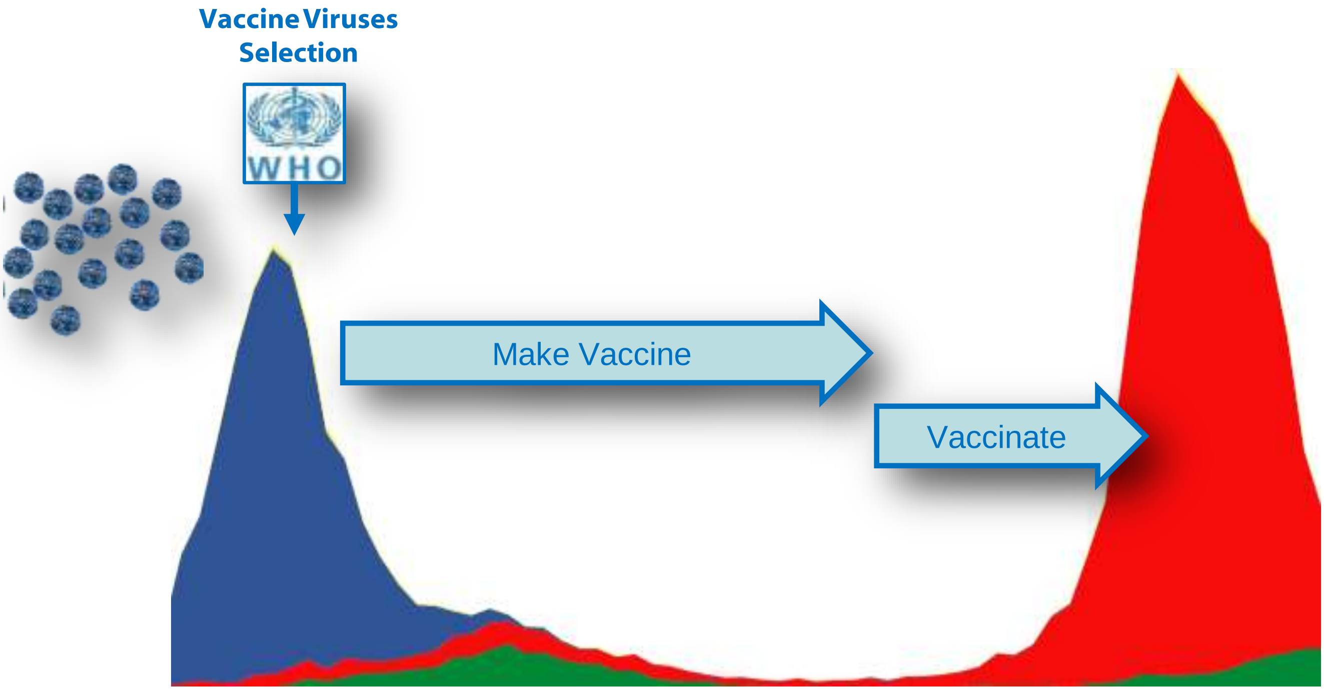
Belongia et al. Lancet Infect Dis 2016





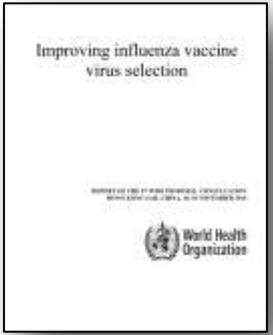
Improving Vaccine Virus Selection

Where can improvements occur?



WHO Consultation on Improving Influenza Vaccine

- 2014-15 season prompted focused efforts to improve virus selection
  - WHO Consultation on Improving Influenza Vaccine Virus Selection in Hong Kong – Nov 2015
    - Strengthen influenza surveillance
    - Improve virus characterization and candidate vaccine virus development
    - Address late emerging variants
    - Determine role of virus evolutionary analysis
    - Develop broadly protective, longer lasting vaccines
    - Address regulatory issues


Improving influenza vaccine virus selection

World Health Organization

WHO. Draft Report of the 4th WHO Informal Consultation on Improving Influenza Vaccine Virus Selection. Hong Kong SAR, China, 18-20 November 2015.

2014-15 Season Under Evaluation

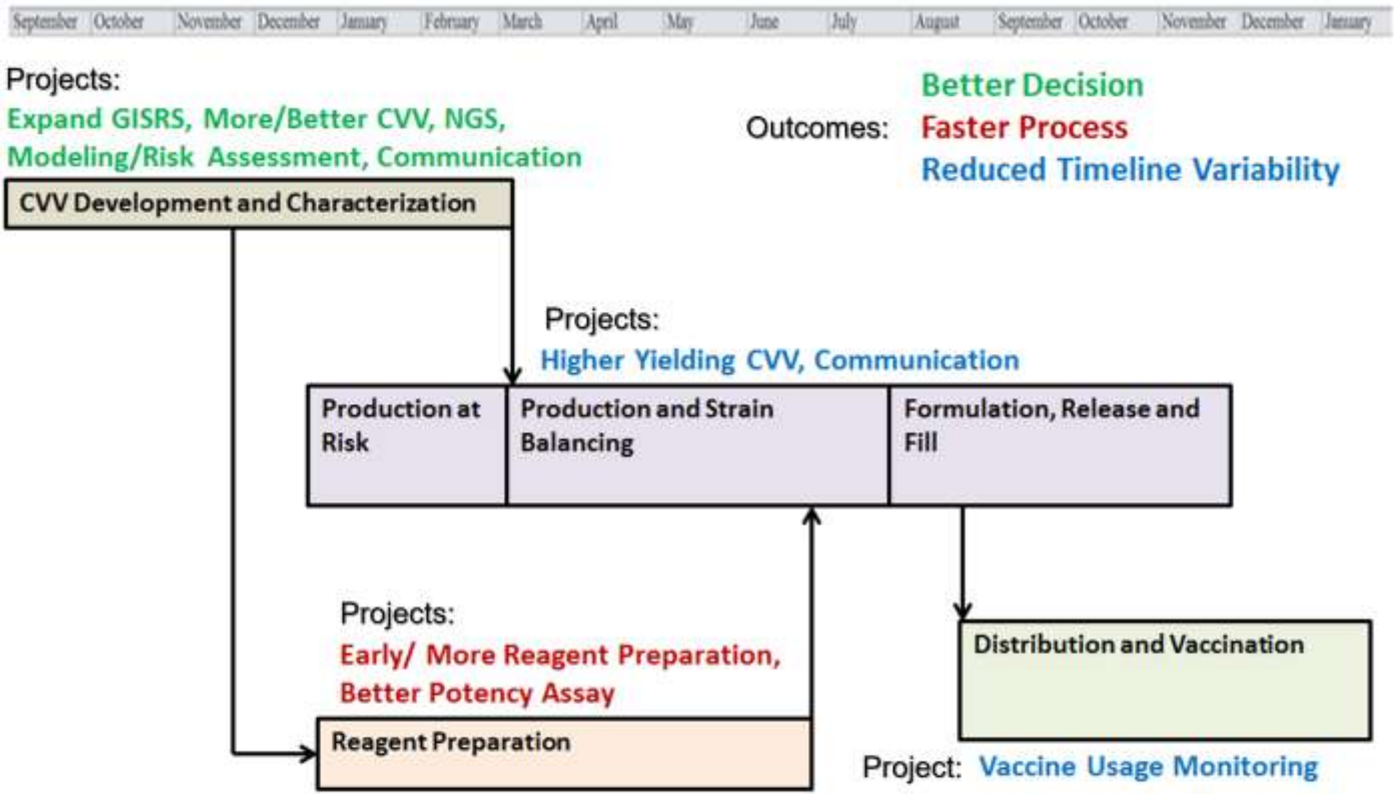
"U.S. Public Health Preparedness for Seasonal Influenza: Has the Response Improved?" – Oversight Committee

The Energy and Commerce Committee. U.S. Congress https://energycommerce.house.gov/hearings-and-votes/hearings/us-public-health-preparedness-seasonal-influenza-has-response-improved

New Vaccine Improvement Collaboration – SIVI

- Seasonal Influenza Vaccine Improvement (SIVI) Initiative
  - Collaboration of BARDA, FDA, NIH, and CDC
  - Response to U.S. Secretary of Health for mitigating mismatch
  - Seasonal improvements are pandemic preparedness
- Structured, five year mismatch mitigation plan to address:
  - Virus Characterization and CVV Development
  - Reagent Preparation
  - Production
  - Distribution and Vaccination

SIVI: Projects and Outcomes



Donabedian A, Katz J, Weir J, Spiro D, Bandremer A, Gerstner J. Improvement of seasonal influenza vaccine development, production and monitoring to mitigate vaccine mismatch (SIVI). Options Poster.

Improving Vaccine Virus Selection

Areas for Improvement

- Surveillance and Virus Collection
- Virus Characterization
- Candidate Vaccine Viruses (CVV)
- Vaccine Potency Assays
- Decision Making
- Communication and Coordination
- Distribution and Vaccination
- New Vaccines

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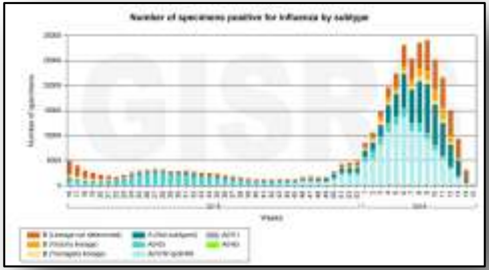
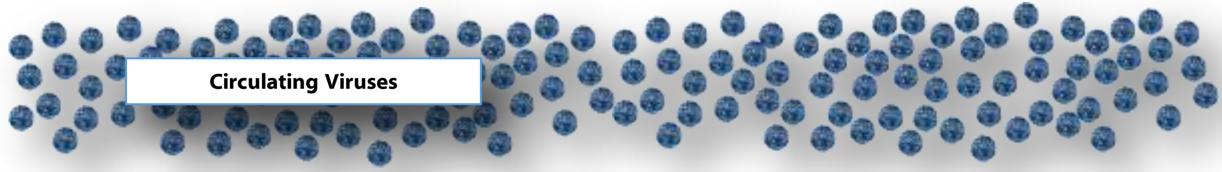
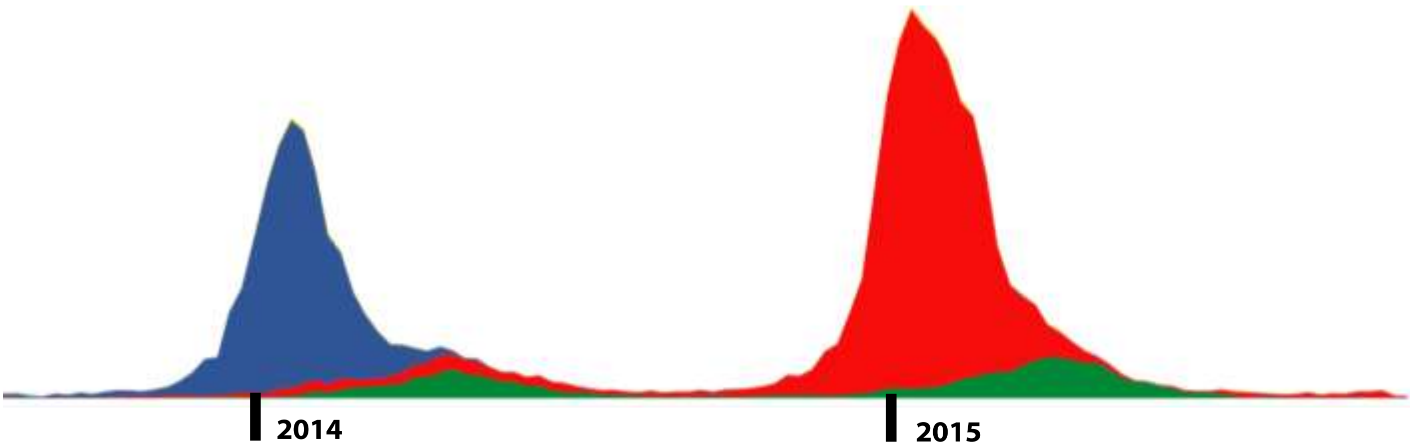
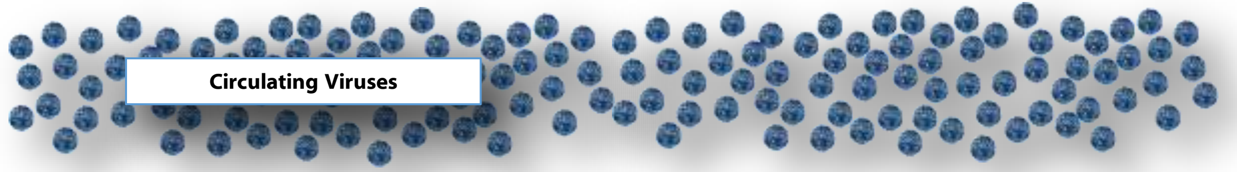
Surveillance and Virus Collection

- Expand Global Influenza Surveillance and Response System (GISRS)
  - Increase the number, timeliness, and representativeness of specimens submitted
  - Initiate a new round of capacity building cooperative agreements with new countries in strategic locations
  - Explore how best to implement “Right-Sizing” efforts for efficient collection of viruses

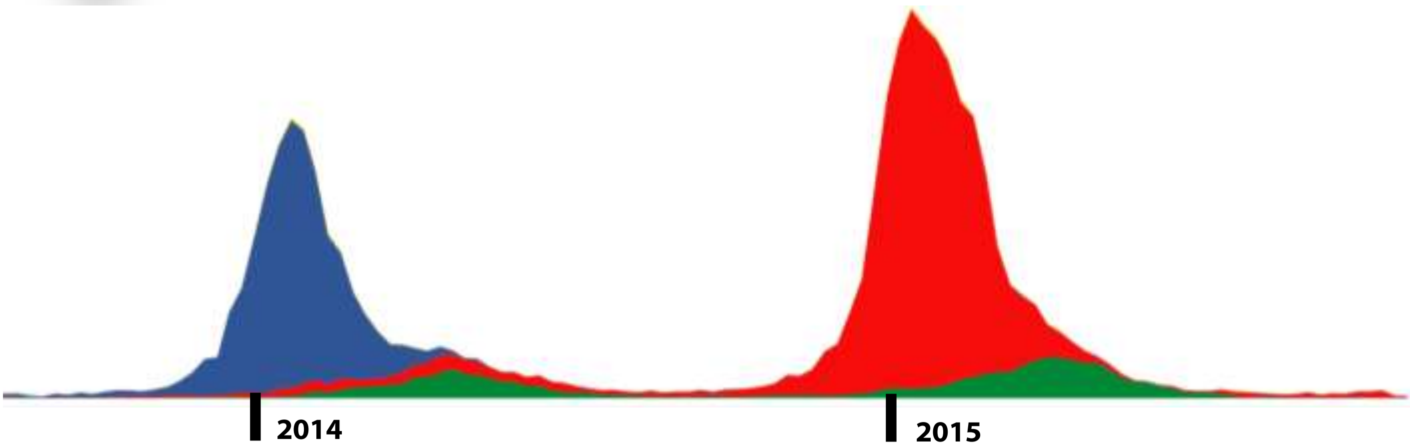


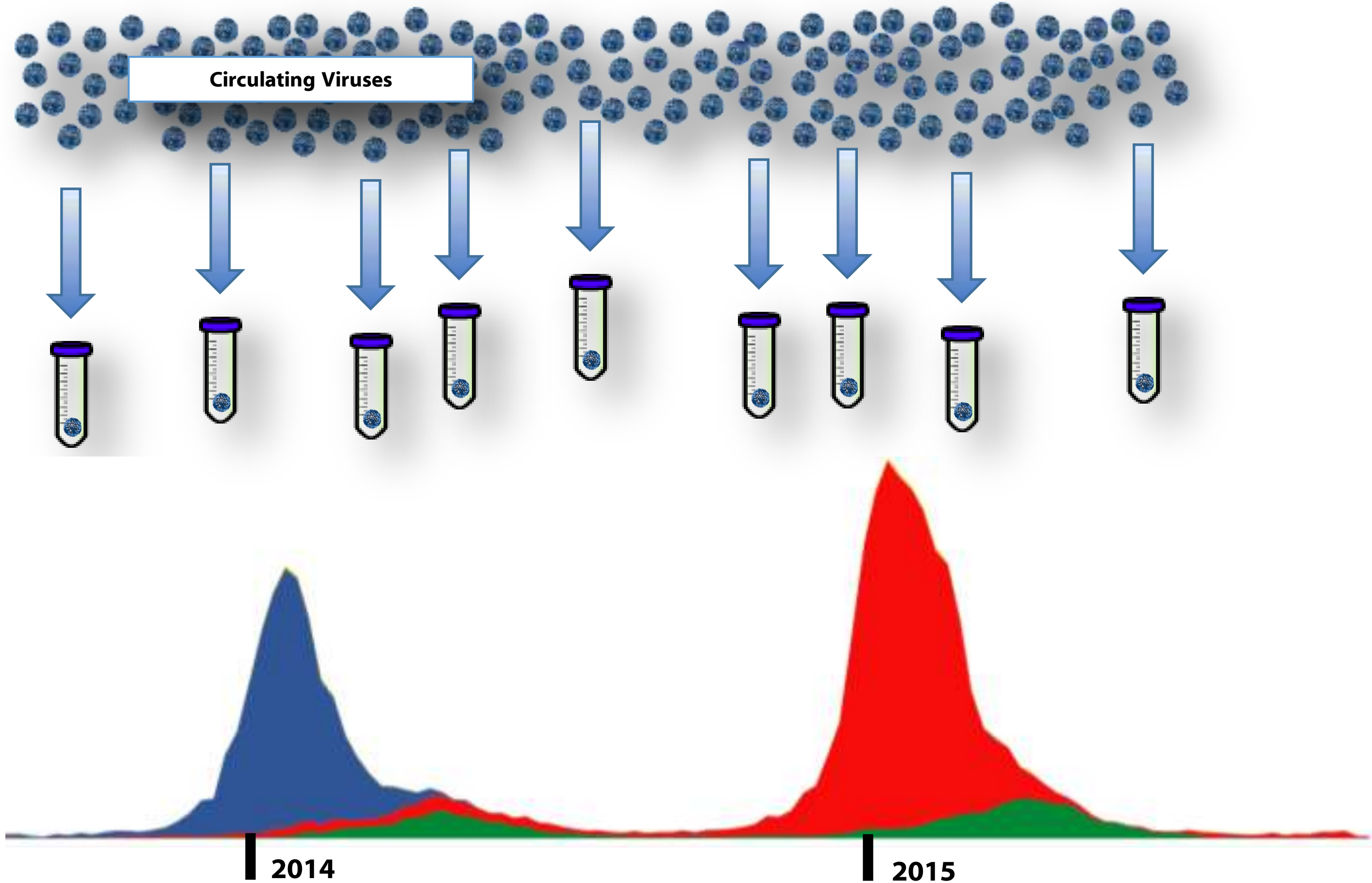

Circulating Viruses


2014
2015

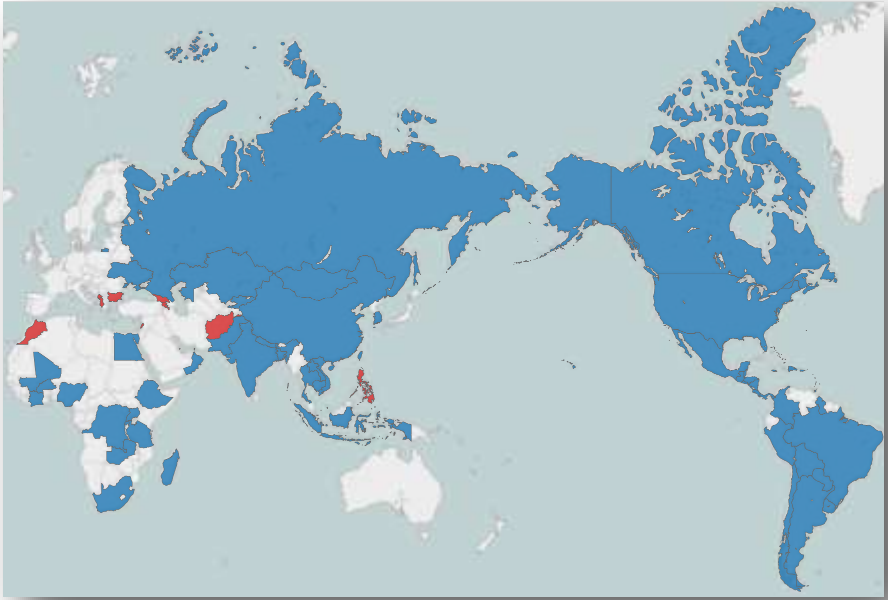


- Challenges with:
  - Representativeness
  - Timeliness
  - Original specimen vs grown virus




Circulating Viruses
2014
2015

Expanding GISRS: Specimen Submissions



- From July 2015 to August 2016:
  - Shipments to CDC increased from 38 to 81 countries (blue)
  - Specimens increased 50%; occurring more frequently with recent specimens
  - New countries added (red): Afghanistan, Albania, Armenia, Bulgaria, Georgia, Lebanon, Montenegro, Morocco and Philippines

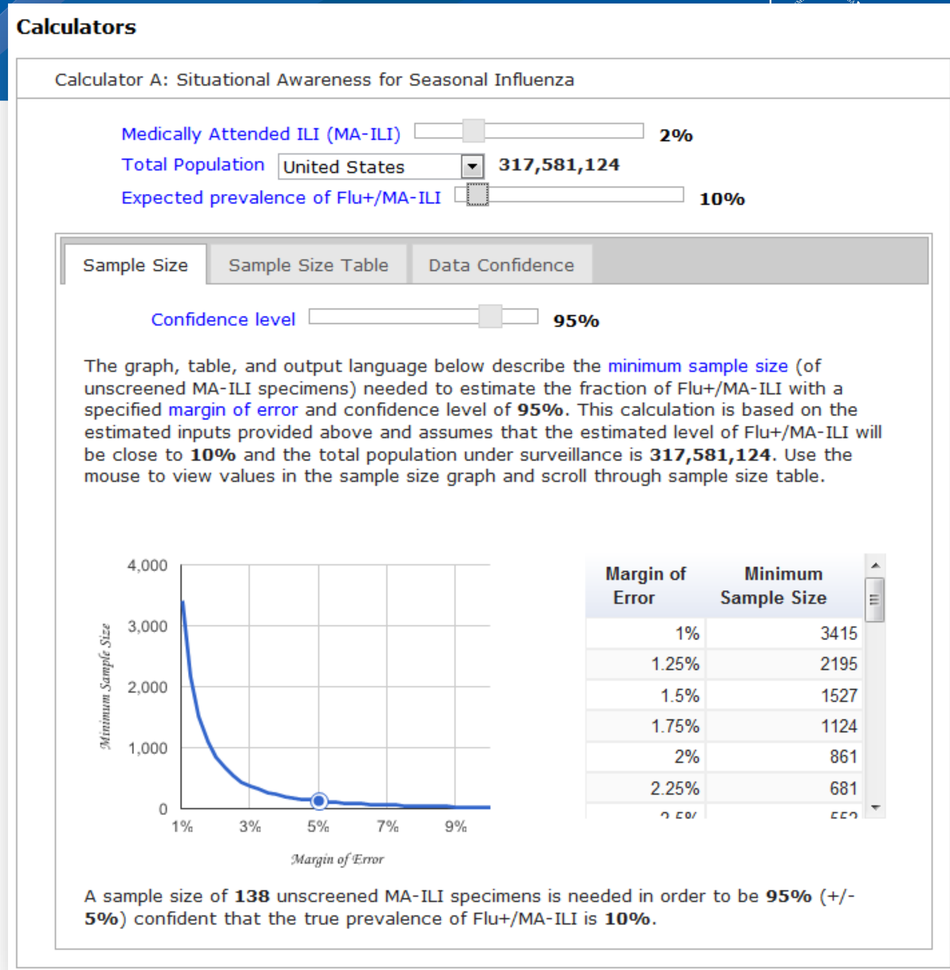
RightSizing

- Rightsize Calculators for U.S. virologic surveillance, possibly for international

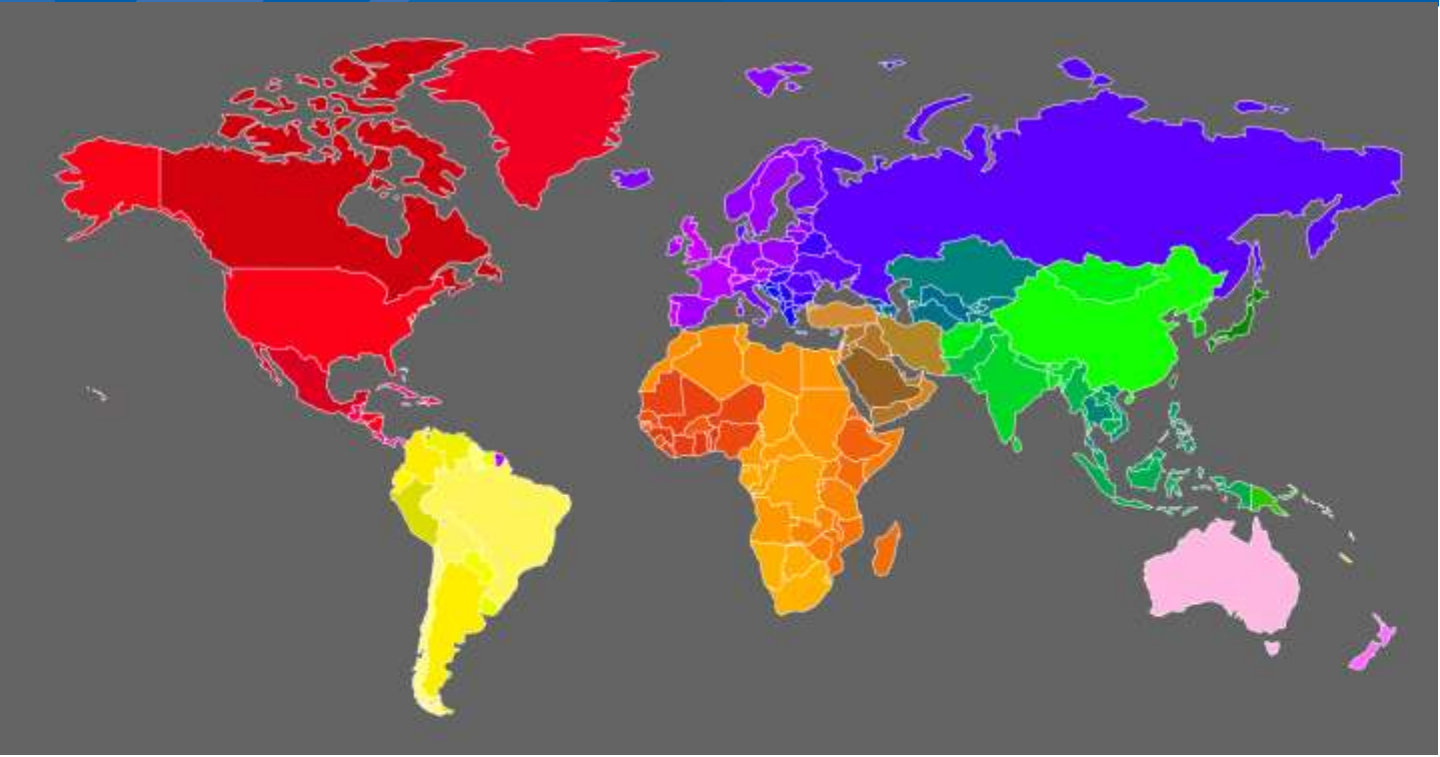
- Assists state health departments determine best number to collect for:

✓ Situational Awareness
✓ Novel Influenza Detection
✓ Antiviral resistance
✓ Vaccine strain selection

- If used globally:
  - Total number needed per year = 16,992
  - 2,832 per region per year
  - 1,416 per month worldwide



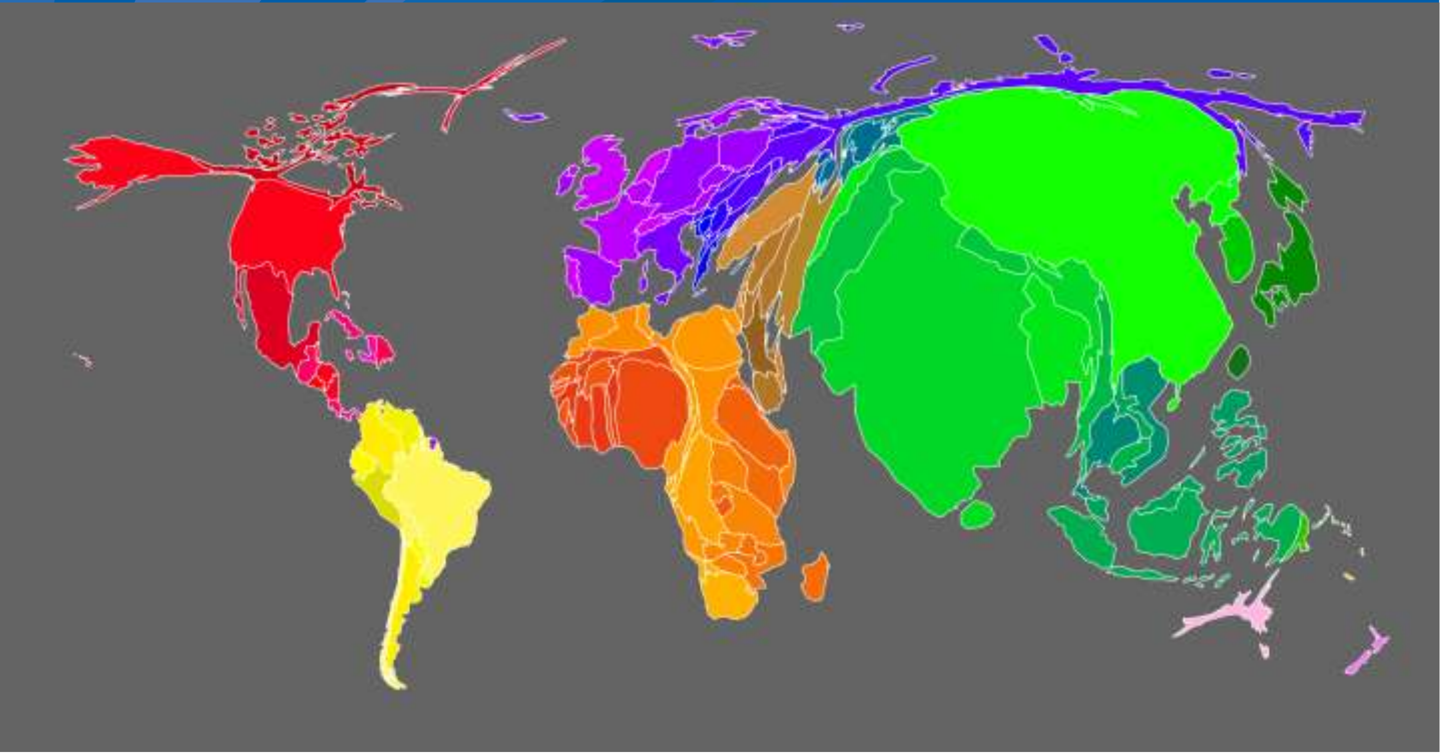
RightSizing: Representativeness of Specimens



Cartogram of Physical Geography

http://metrocosm.com/

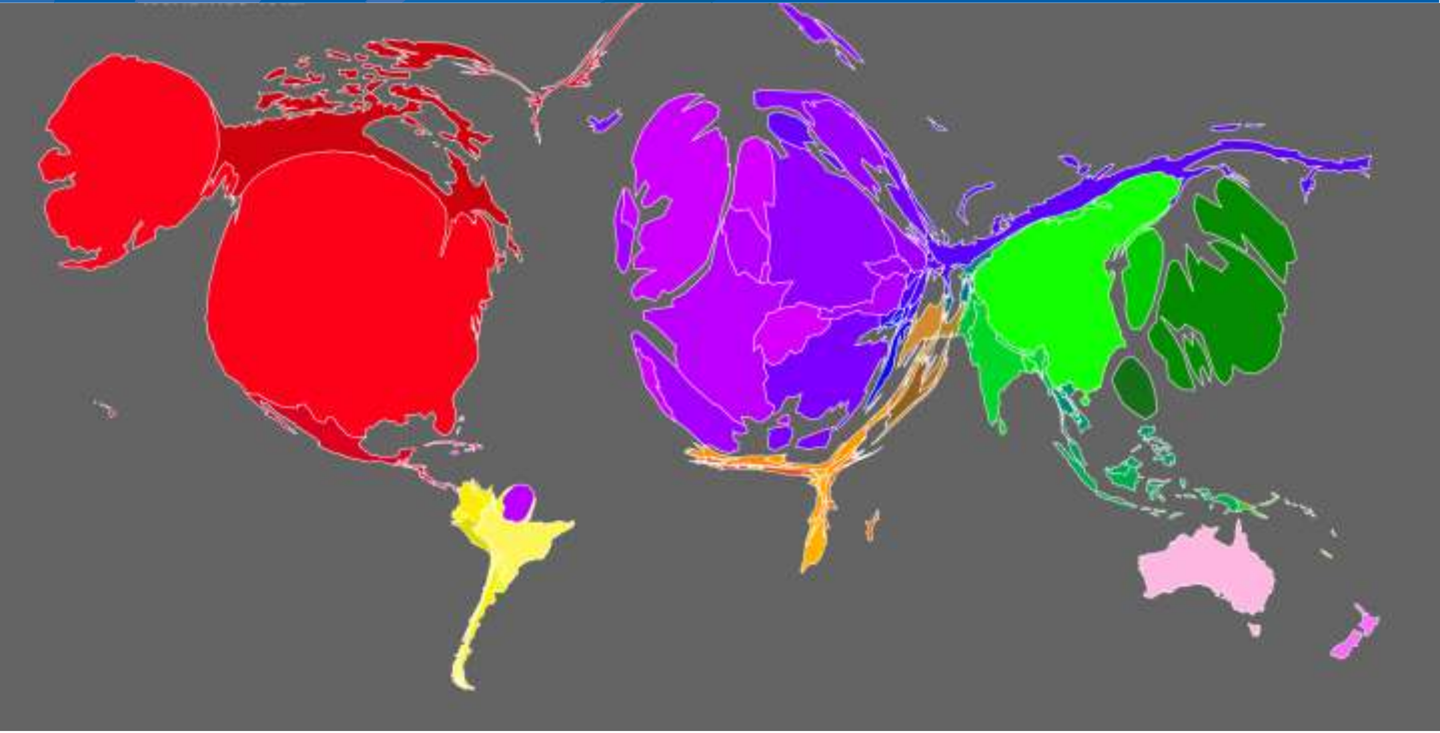
RightSizing: Representativeness of Specimens



Cartogram of Population

http://metrocosm.com/

RightSizing: Representativeness of Specimens



Cartogram of Wealth

http://metrocosm.com/

RightSizing: Representativeness of Specimens

Cartogram of Specimen Submission to CDC

Sam Shepard CDC. Unpublished data.

Improving Vaccine Virus Selection

Areas for Improvement

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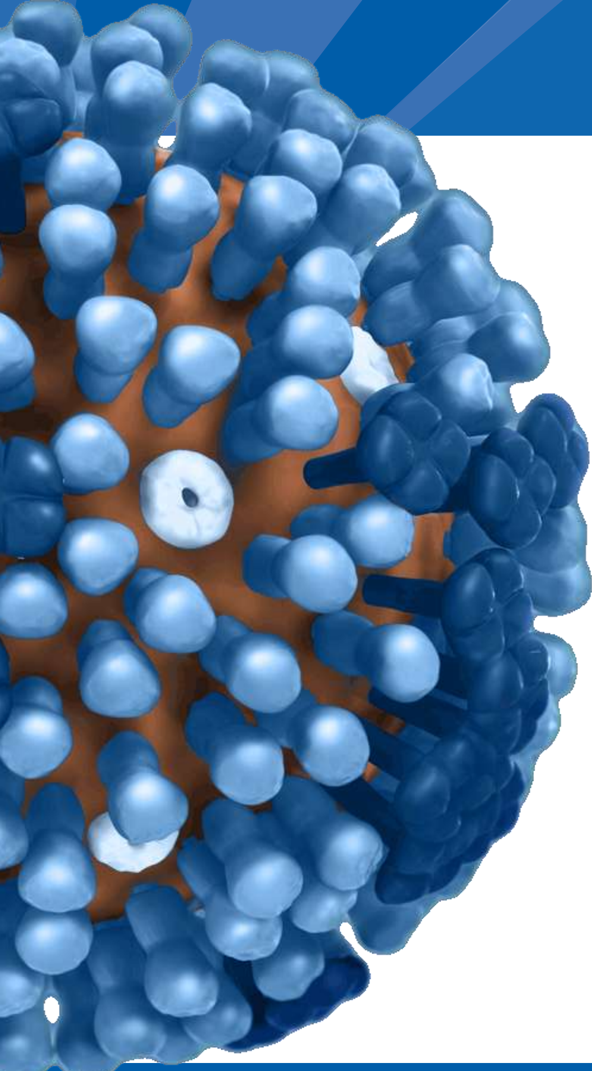
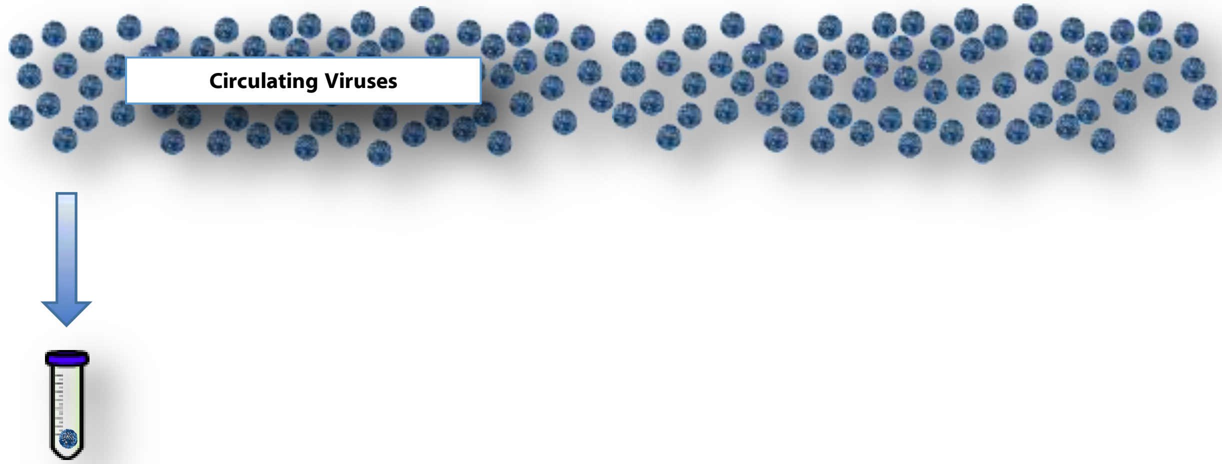
- Vaccine Potency Assays
- Decision Making and Forecasting
- Communication and Coordination
- Distribution and Vaccination
- New Vaccines

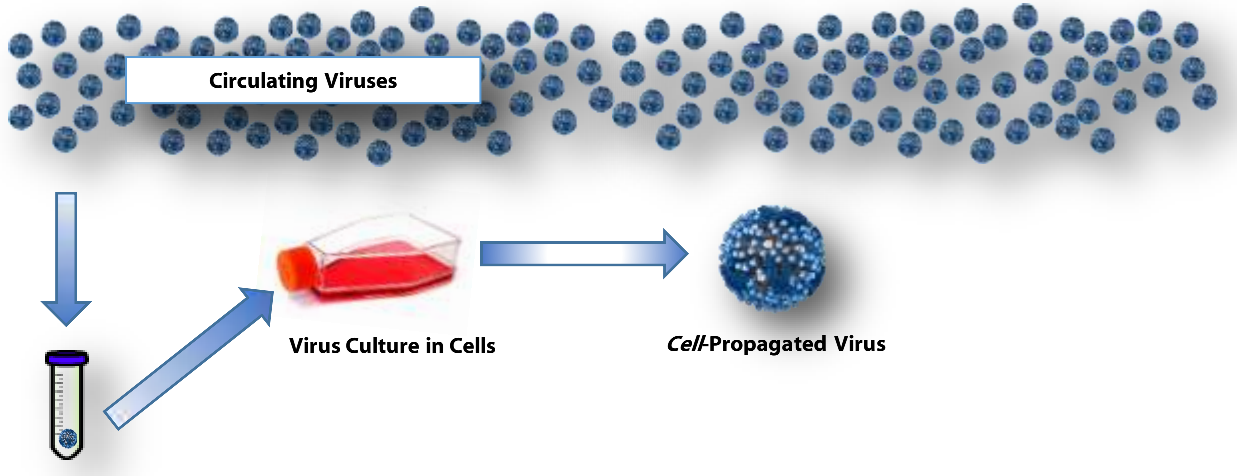
H3N2 Viruses are Increasingly More Challenging

- Over the last 40 years, H3N2 vaccine virus composition changes have occurred more frequently than for H1N1 or B components
- Antigenic characterization of H3N2 viruses remains technically difficult
  - Requires modification of testing processes
  - Requires alternative assays and approaches due to low hemagglutination activity
- Recent H3N2 viruses have had important antigenic changes during egg propagation

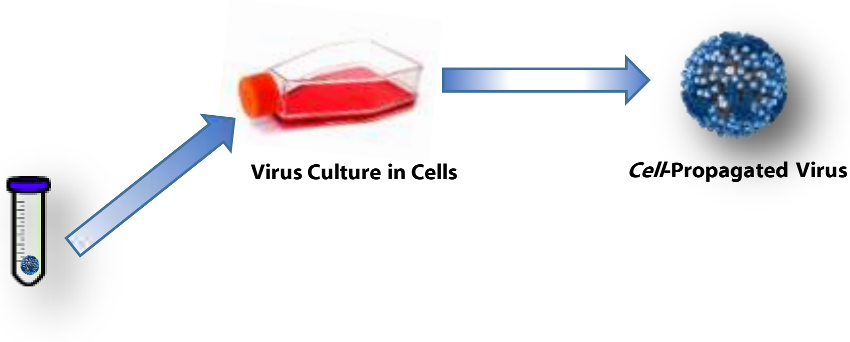
Conclusions from WHO information meeting on influenza vaccine composition fro the 2016 southern hemisphere season, 24 Sept 2015.

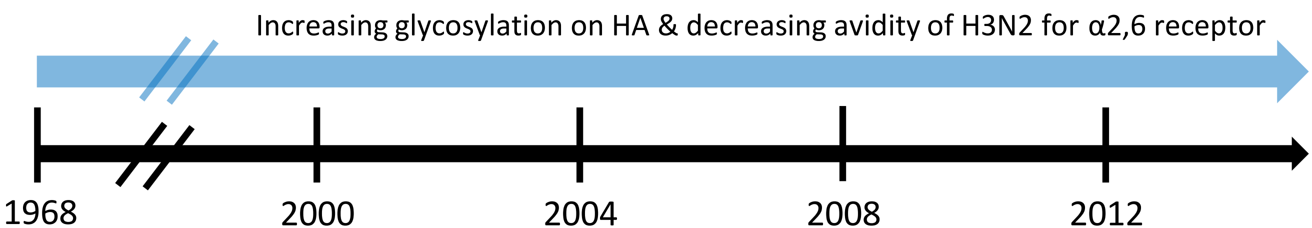



Circulating Viruses


Circulating Viruses
Virus Culture in Cells
Cell-Propagated Virus

Changes in H3N2 Binding Properties

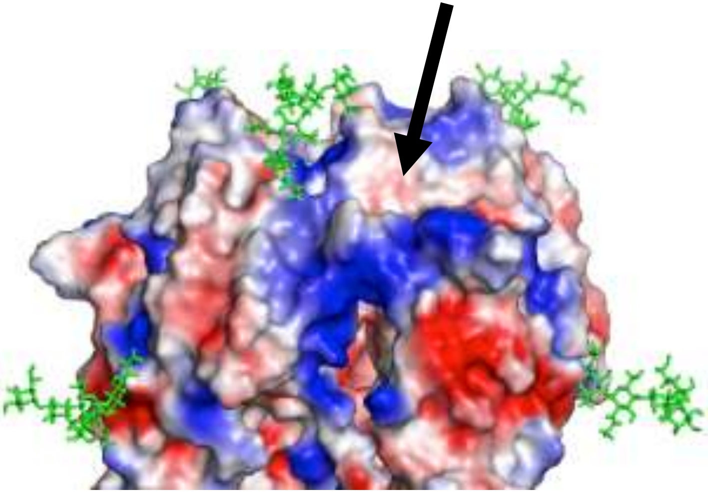




Yang et al. Virology 2015;477:18-31; Lin et al. PNAS 2012;109(52):21474-21479; Gulati et al. PLOS 2013;8(6):e66325.

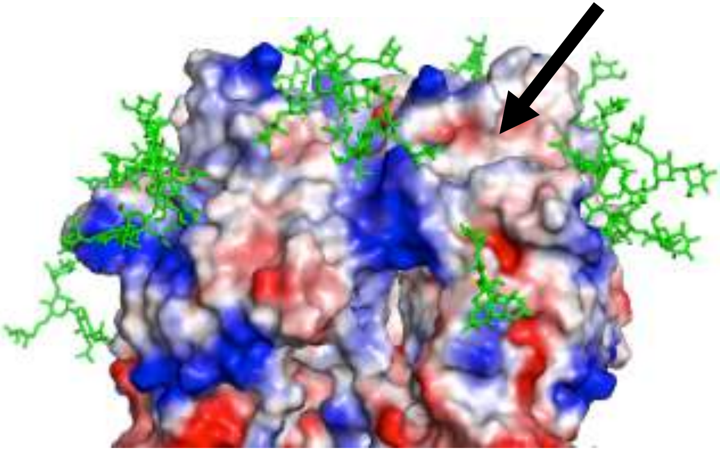
Increasing Glycosylation of H3N2 Hemagglutinin

Receptor
Binding Site



H3N2 Hemagglutinin (HA1)
From 1968

Receptor
Binding Site

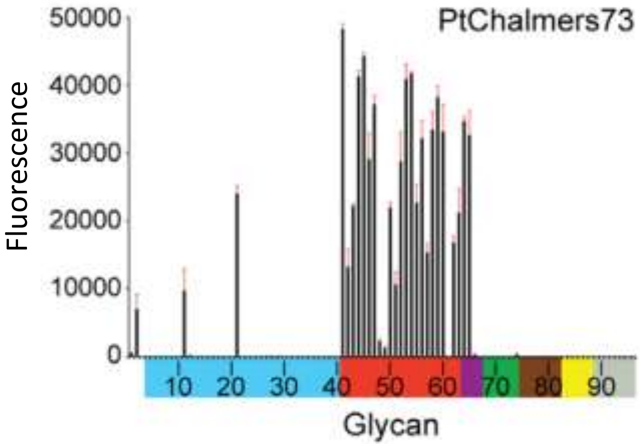


H3N2 Hemagglutinin (HA1)
From 2015

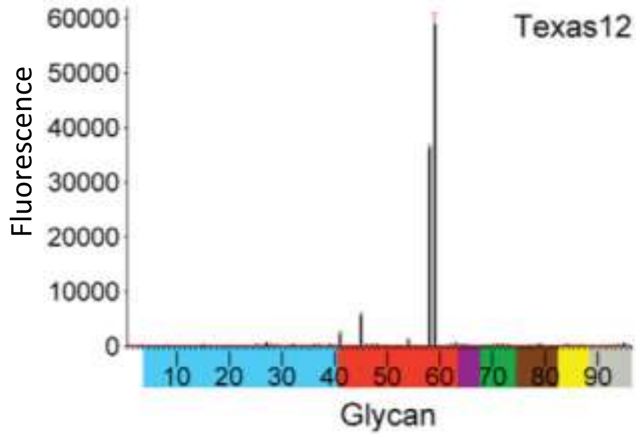
Stevens J. CDC unpublished data, 2016. Red: Negative Charge, Blue: Positive Charge; Green Biantennaries: glycosylatino of carbohydrates

Decreasing Glycan Binding for H3N2

Glycan Binding of H3N2 from 1973



Glycan Binding of H3N2 from 2012



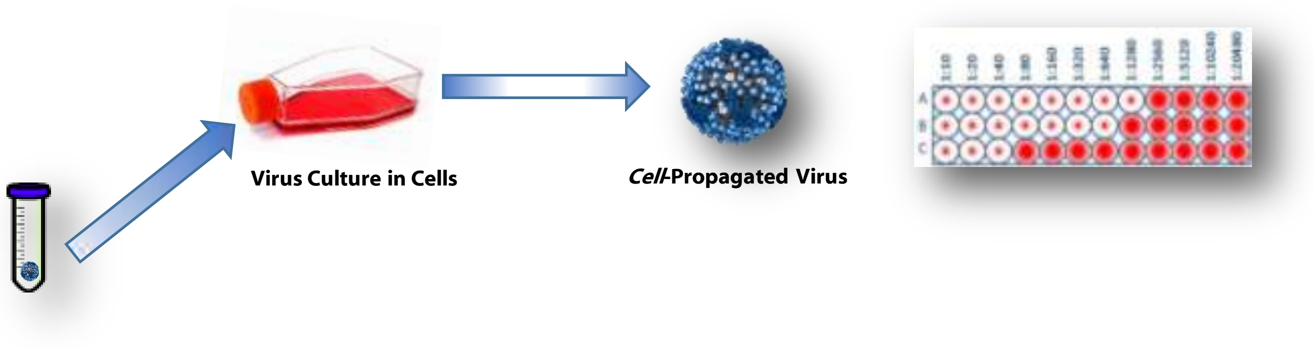
α2-3 avian-type sialic acid receptors

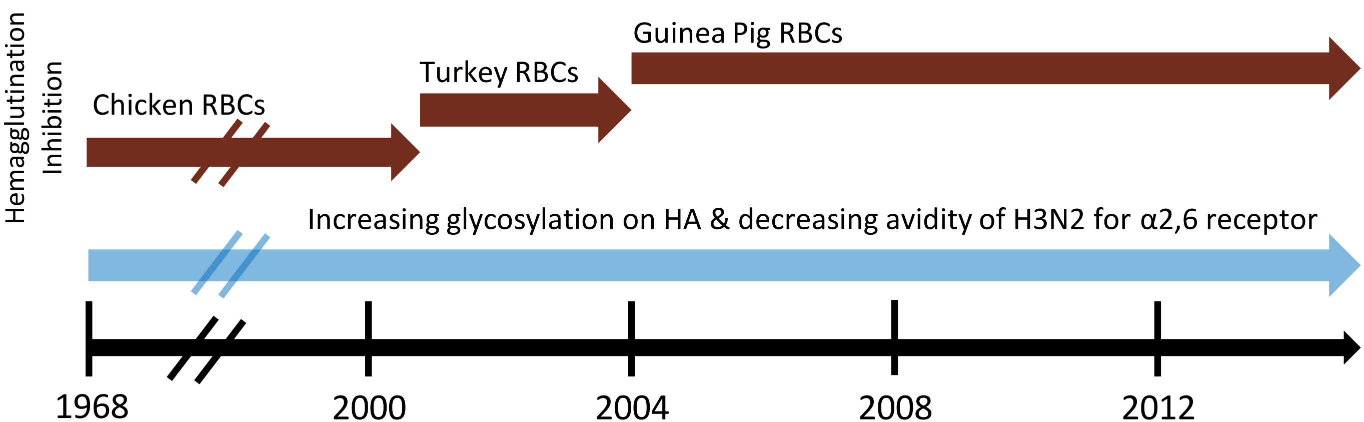
α2-6 human-type sialic acid receptors

α2-6/α2-3 mixed sialic acid receptors

Yang et al. Virology 2015;477:18-31.

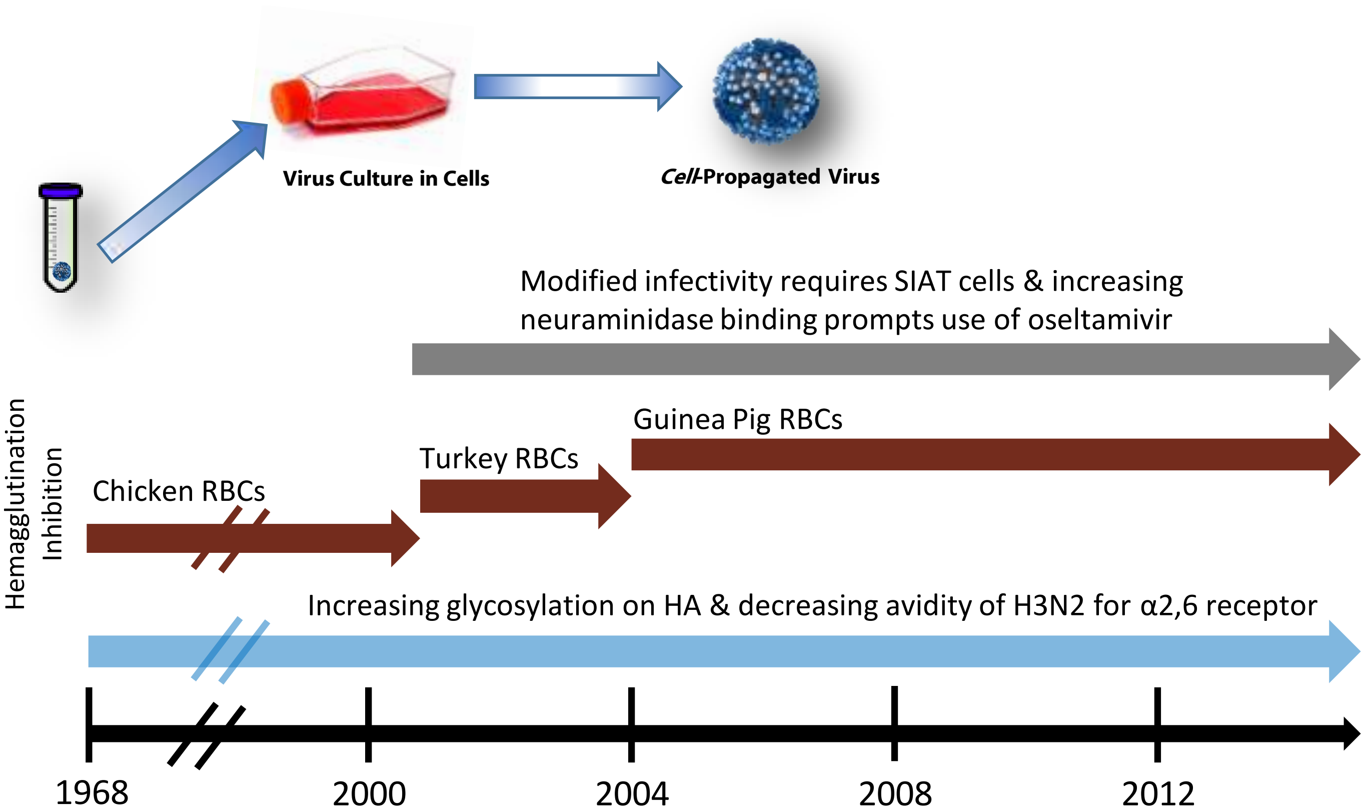
Changes in H3N2 Hemagglutination Inhibition Testing





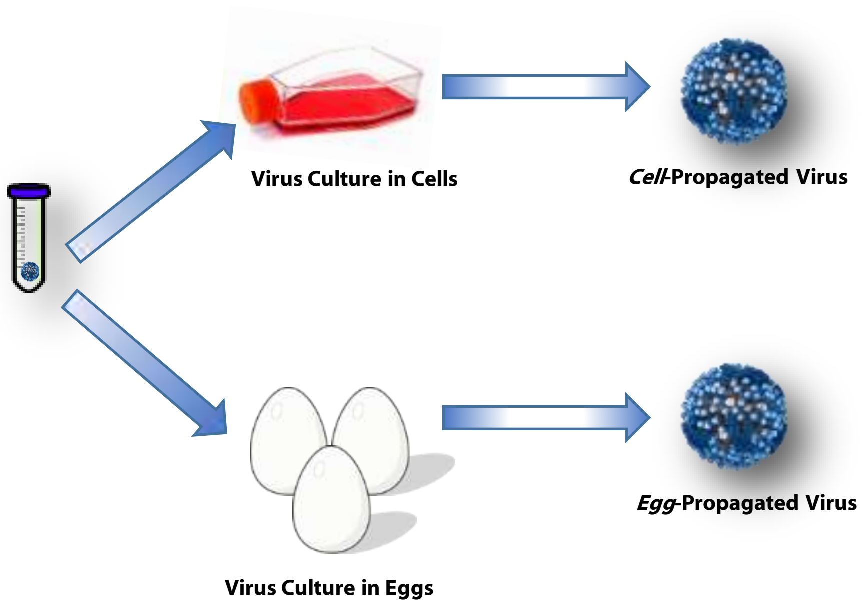
Yang et al. Virology 2015;477:18-31;   Lin et al. PNAS 2012;109(52):21474-21479;   Gulati et al. PLOS 2013;8(6):e66325.

Neuraminidase Binding and Variable Infectivity

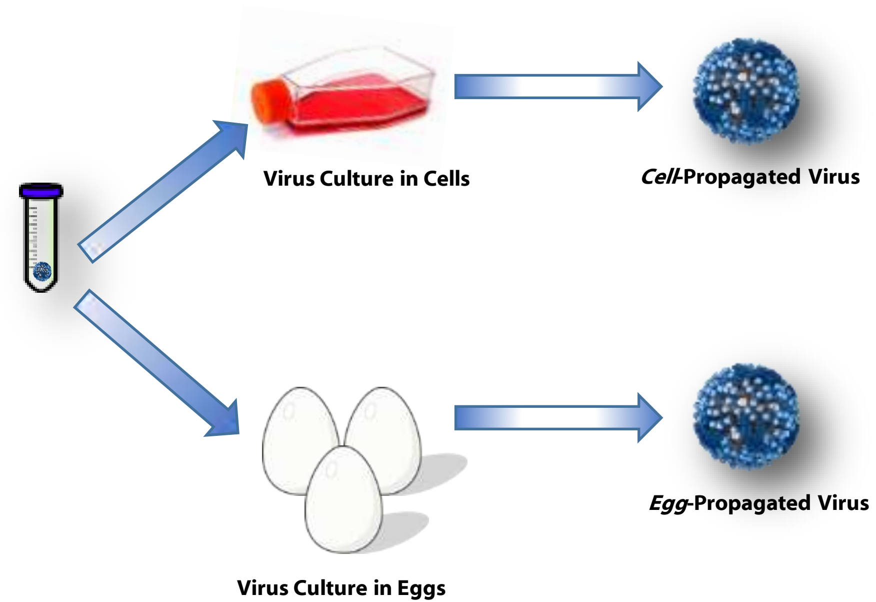


Yang et al. Virology 2015;477:18-31; Lin et al. PNAS 2012;109(52):21474-21479; Gulati et al. PLOS 2013;8(6):e66325.

Most Influenza Vaccine Manufacturing is Egg-Based



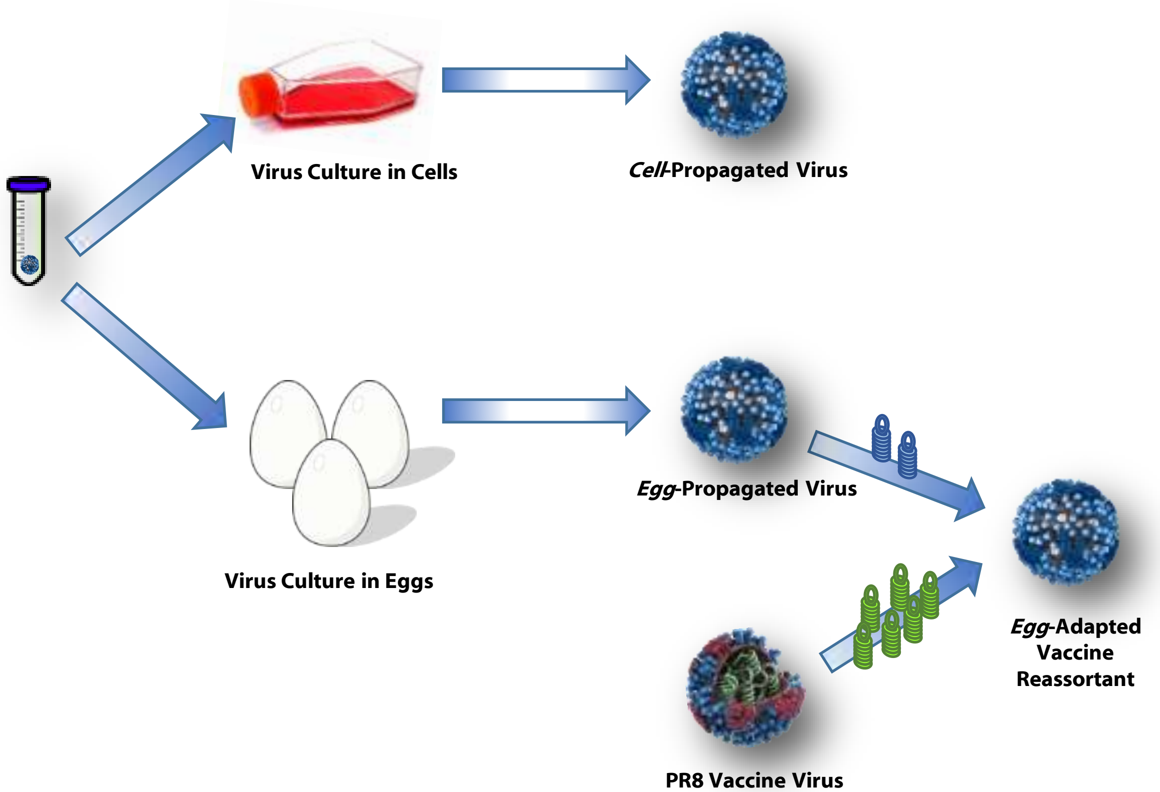
Propagation in Eggs Can Present Challenges



- **Poor Propagation**: H3N2 viruses have been difficult to grow in eggs.
- **Egg Propagation Can Change Antigenicity**: H3N2 3C.2a viruses encode a glycosylation motif at 158-160 in HA1. This glycosylation motif is lost on egg-adaptation and in a proportion of cell-propagated viruses.

Recent H3N2 High Growth Reassortants are Challenging

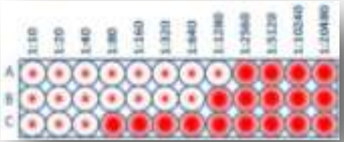
Fewer egg-propagated candidate vaccine viruses leads to fewer egg-adapted vaccine reassortants



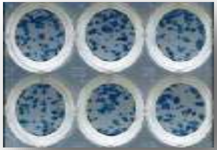
Improving Virus Characterization

Better Assays

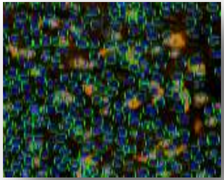
- Improving hemagglutination inhibition (HI) assays
  - Automation of HI Testing
  - Develop a “synthetic” antigenic assay
- Improving neutralization assays
  - Focus Reduction Assay (FRA) per Crick
  - Nanoneutralization Assay (CellInsight CX-5)
- Increase use of sera from vaccinated humans to characterize circulating viruses



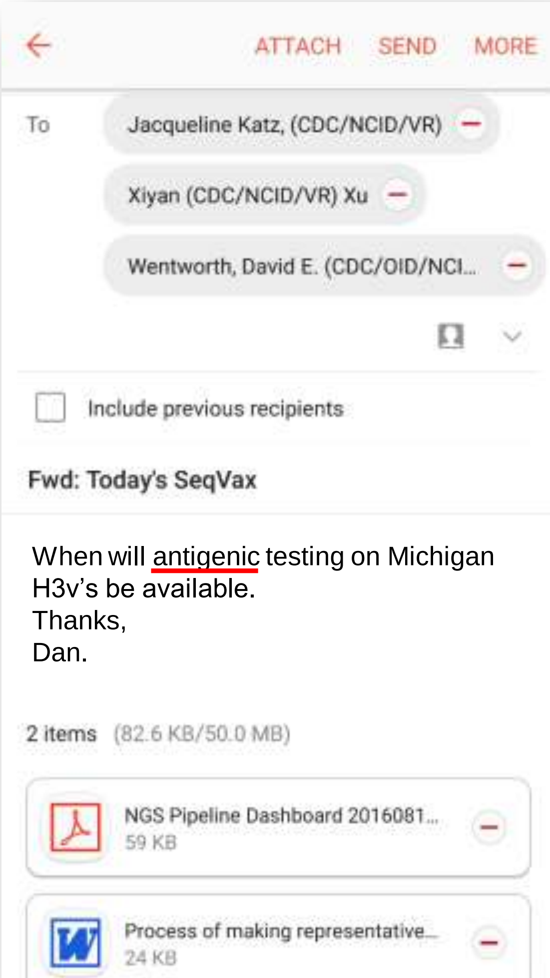
Hemagglutination Inhibition



Focus Reduction Assay



Nanoneutralization



ATTACH SEND MORE

To Jacqueline Katz, (CDC/NCID/VR)

Xiyan (CDC/NCID/VR) Xu

Wentworth, David E. (CDC/OID/NCI...

Include previous recipients

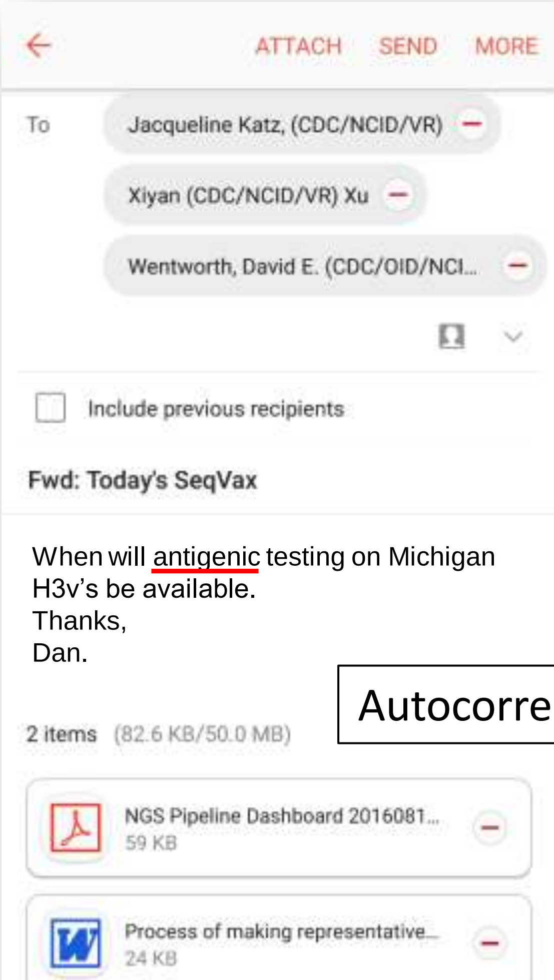
Fwd: Today's SeqVax

When will antigenic testing on Michigan H3v's be available.
Thanks,
Dan.

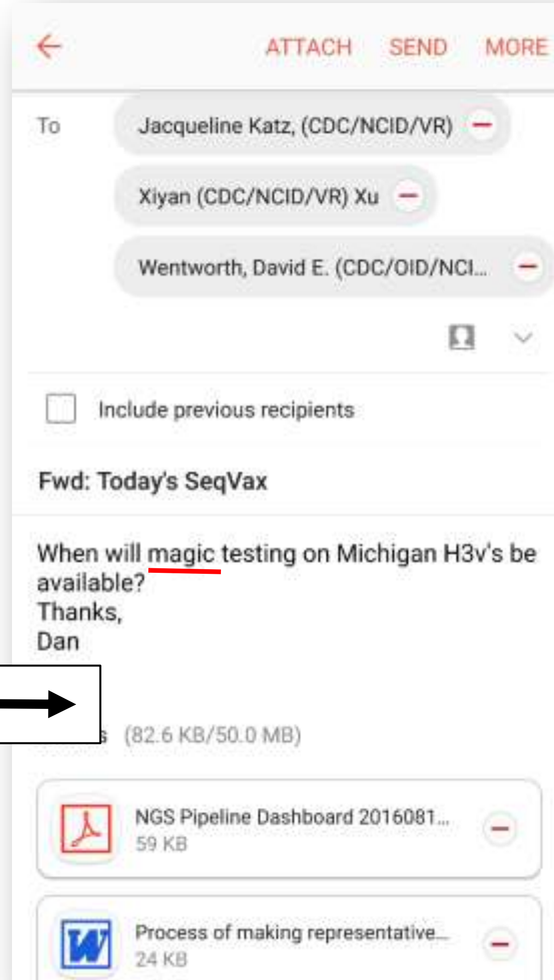
2 items (82.6 KB/50.0 MB)

NGS Pipeline Dashboard 2016081...
59 KB

Process of making representative...
24 KB

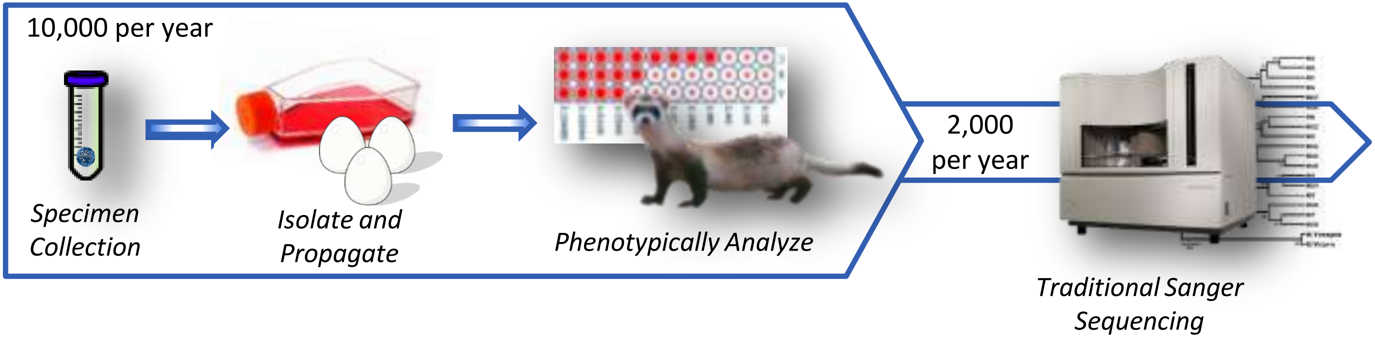


Autocorrect?



Sequence First Initiative

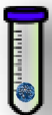
Old



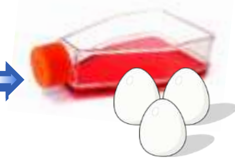
Sequence First Initiative

Old

10,000 per year



Specimen Collection



Isolate and Propagate

Phenotypically Analyze

2,000 per year

Traditional Sanger Sequencing

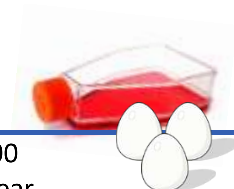
New

10,000 per year

Specimen Collection

Next Generation Whole Genome Sequencing

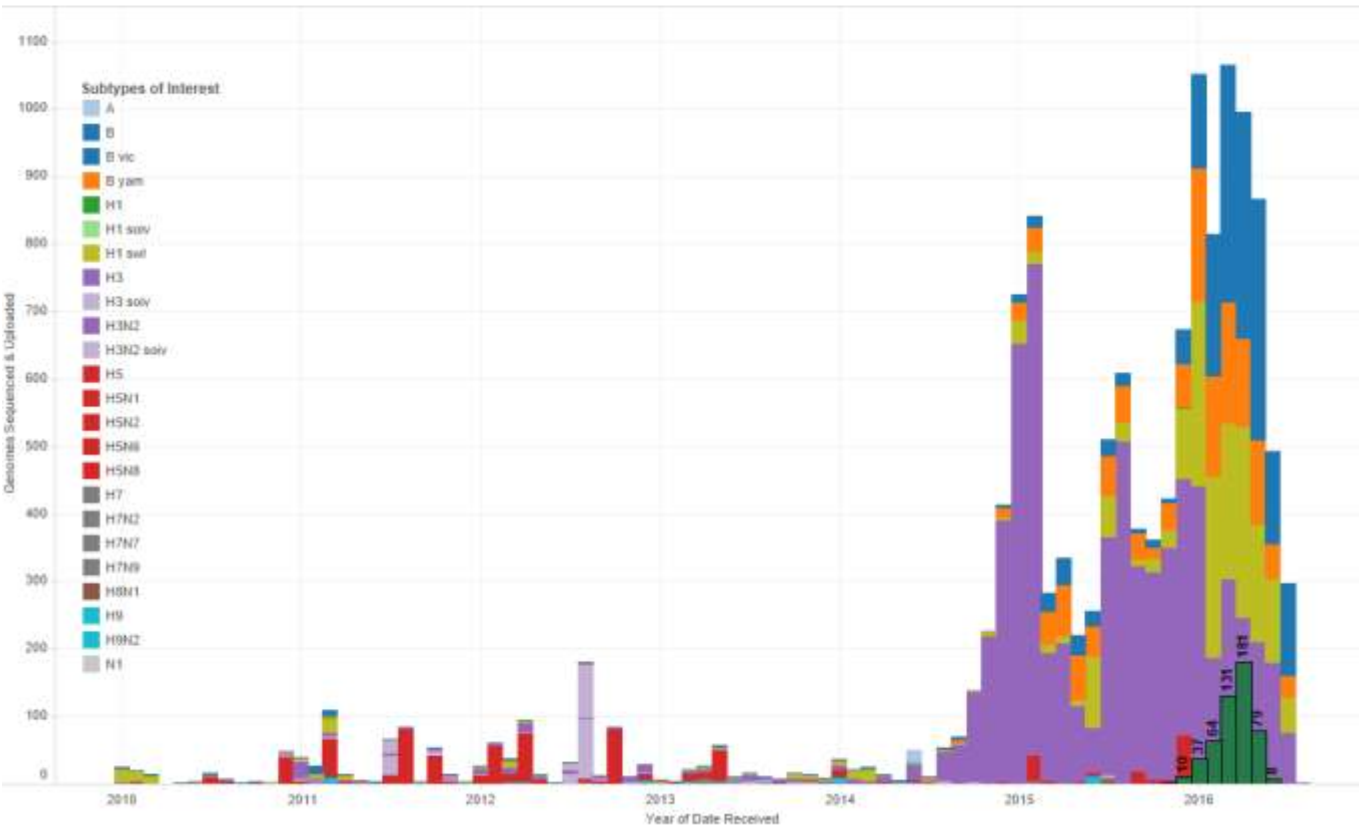
2,000 per year



Isolate and Propagate

Phenotypically Analyze

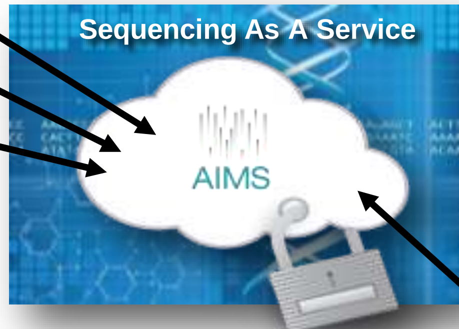
Whole Genome Next Generation Sequencing



Barnes, Neuhaus, Wentworth, et al. CDC unpublished data. 2016.

Cloud Sequencing to Support Surveillance

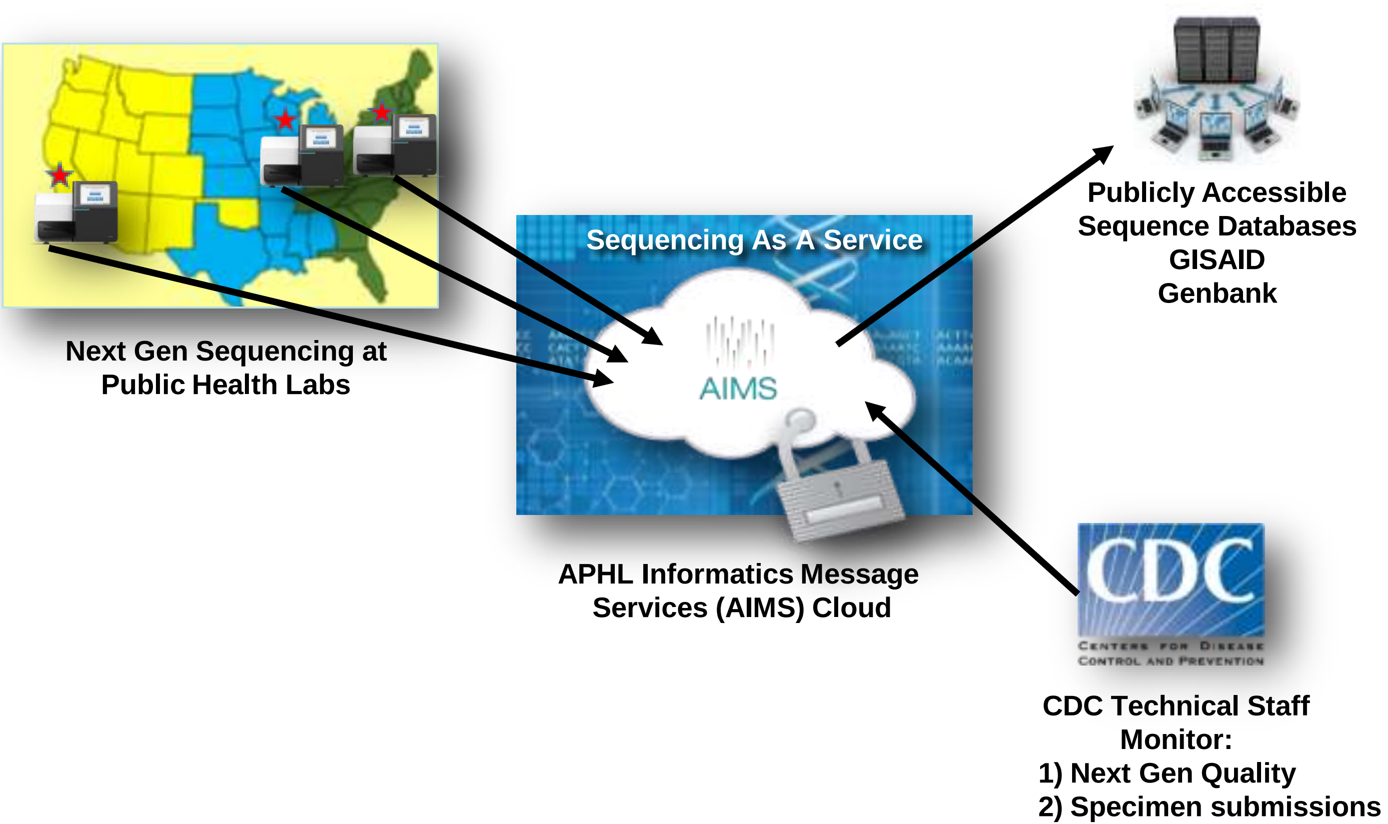
Next Gen Sequencing at
Public Health Labs



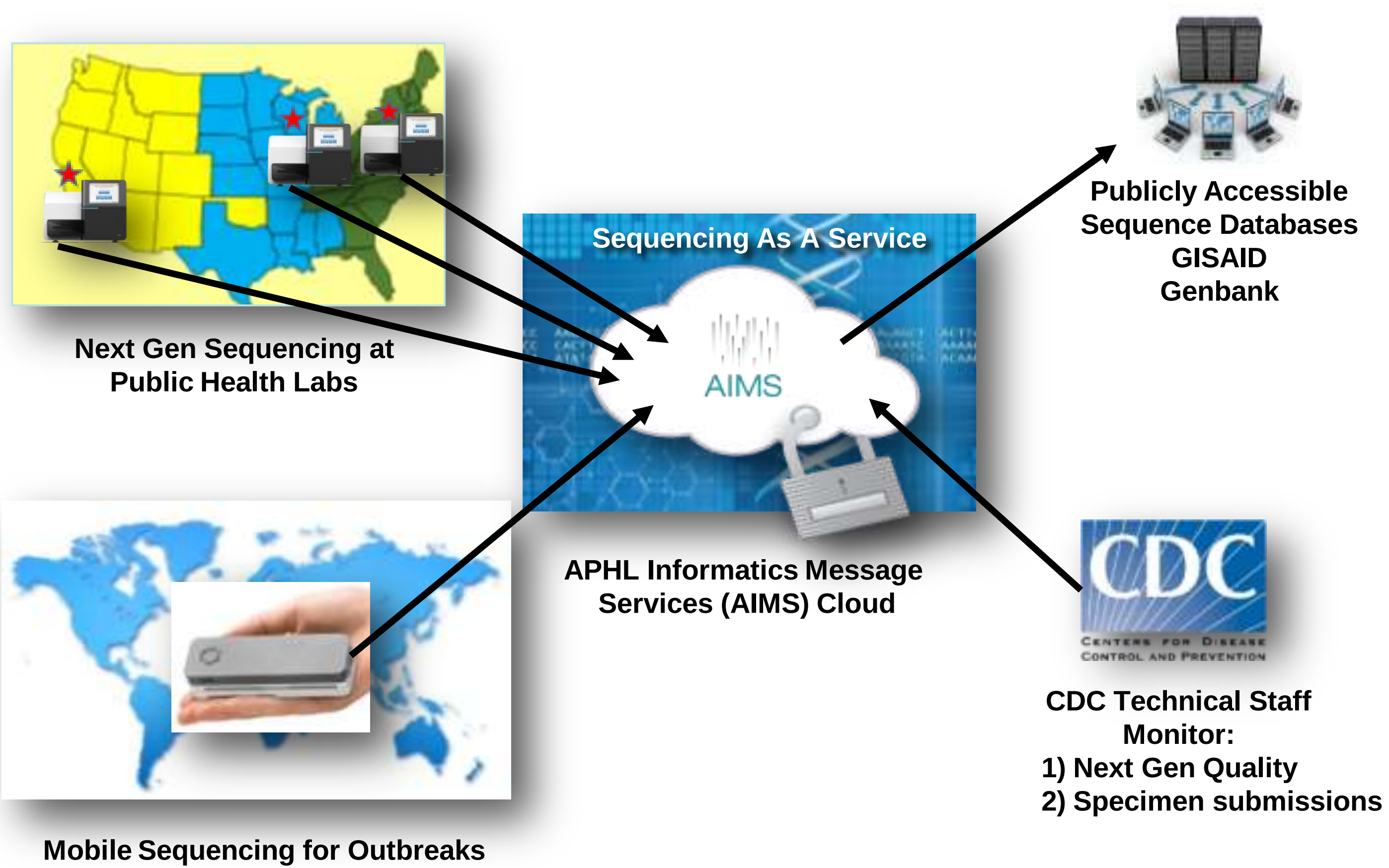
APHL Informatics Message
Services (AIMS) Cloud

CDC Technical Staff
Monitor:
1) Next Gen Quality
2) Specimen submissions

Cloud Sequencing to Support Surveillance



Cloud Sequencing to Support Surveillance

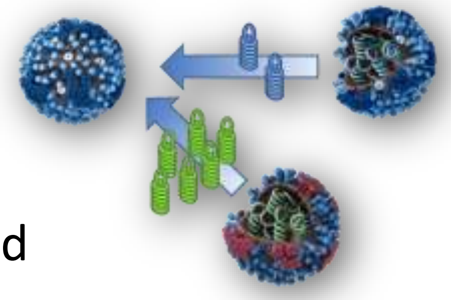


Improving Vaccine Virus Selection

Areas for Improvement

- Surveillance and Virus Collection
- Virus Characterization
- Candidate Vaccine Viruses (CVV)
- Vaccine Potency Assays
- Decision Making and Forecasting
- Communication and Coordination
- Distribution and Vaccination
- New Vaccines

Improving Vaccine Virus Selection
Candidate Vaccine Viruses



- Expand the number of reassorting laboratories
- Develop high-growth reassortant viruses to improve manufacturing yield
- Increase the number and timeliness of CVVs available as pairs of egg- and cell-adapted viruses
- Develop CVVs using synthetic biology for better growth in eggs
- Develop cell-grown CVVs for use in cell-based manufacturing

Improving Vaccine Virus Selection

Areas for Improvement

- Surveillance and Virus Collection
- Virus Characterization
- Candidate Vaccine Viruses (CVV)
- Vaccine Potency Assays
  - Begin potency assay reagent development early and prepare alternate reagent sets
  - support the development and licensure of new potency assay
- Decision Making
- Communication and Coordination
- New Vaccines

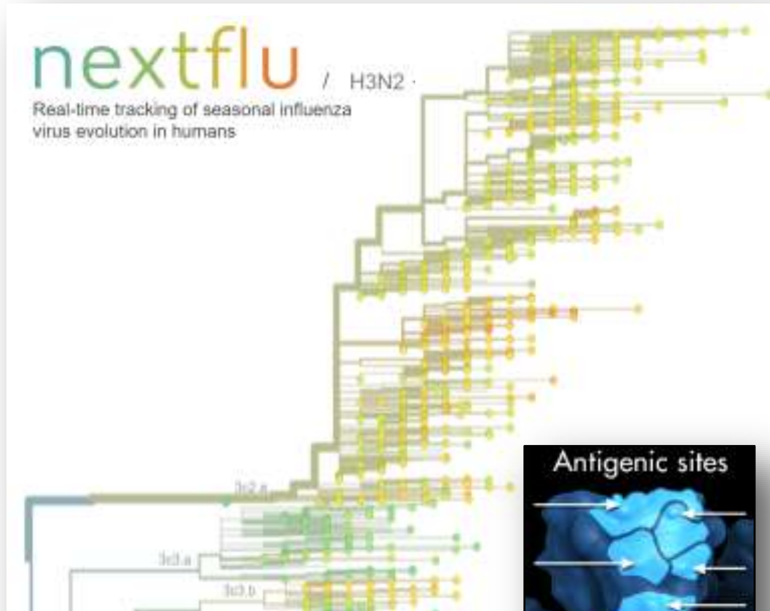
Improving Vaccine Virus Selection

Areas for Improvement

- Surveillance and Virus Collection
- Virus Characterization
- Candidate Vaccine Viruses (CVV)
- Vaccine Potency Assays
- Decision Making and Forecasting
- Communication and Coordination
- Distribution and Vaccination
- New Vaccines

Virus Evolution Forecasting

- CDC, WHO, and collaborators working to develop models to combine:
  - Whole genome, next-generation, sequencing data
  - Antigenic data describing host responses to flu virus proteins
  - Geotemporal and epidemiologic data from surveillance
- Recent meeting in NJ led to concrete next steps



http://www.nextflu.org/H3N2/1y/

Improving Vaccine Virus Selection

Areas for Improvement

- Surveillance and Virus Collection
- Virus Characterization
- Candidate Vaccine Viruses (CVV)
- Vaccine Potency Assays
- Decision Making and Forecasting
- Communication and Coordination
  - Increase communication between WHO CCs, ERLs, and manufacturers
  - Provide timely reports of WHO vaccine meetings
- Distribution and Vaccination
- New Vaccines

Improving Vaccine Virus Selection

Areas for Improvement

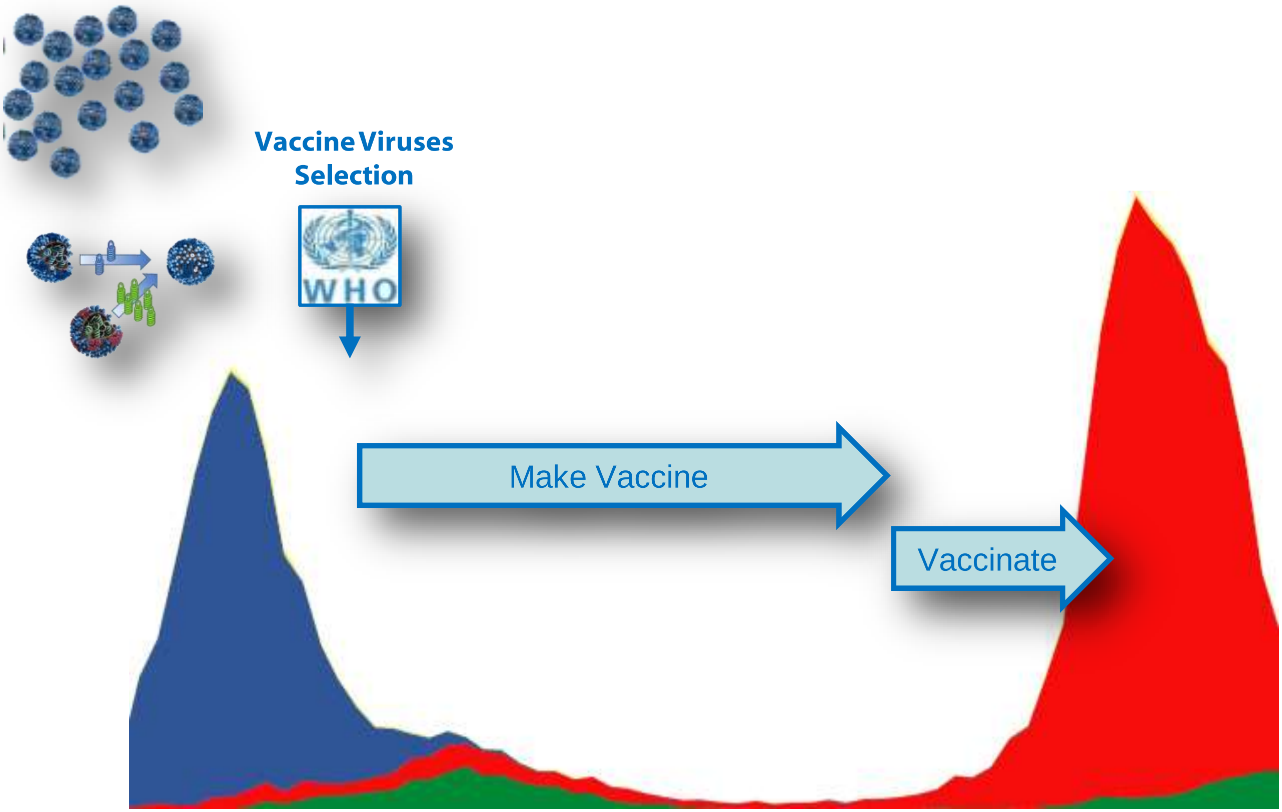
- Surveillance and Virus Collection
- Virus Characterization
- Candidate Vaccine Viruses (CVV)
- Vaccine Potency Assays
- Decision Making
- Communication and Coordination
- Distribution and Vaccination
  - Establish vaccine usage monitoring to improve vaccine tracking and uptake
- New Vaccines

Improving Vaccine Virus Selection

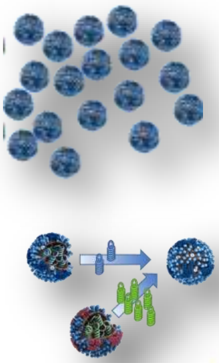
Areas for Improvement

- Surveillance and Virus Collection
- Virus Characterization
- Candidate Vaccine Viruses (CVV)
- Vaccine Potency Assays
- Decision Making
- Communication and Coordination
- Distribution and Vaccination
- New Vaccines
  - Development of more broadly protective and longer lasting vaccines

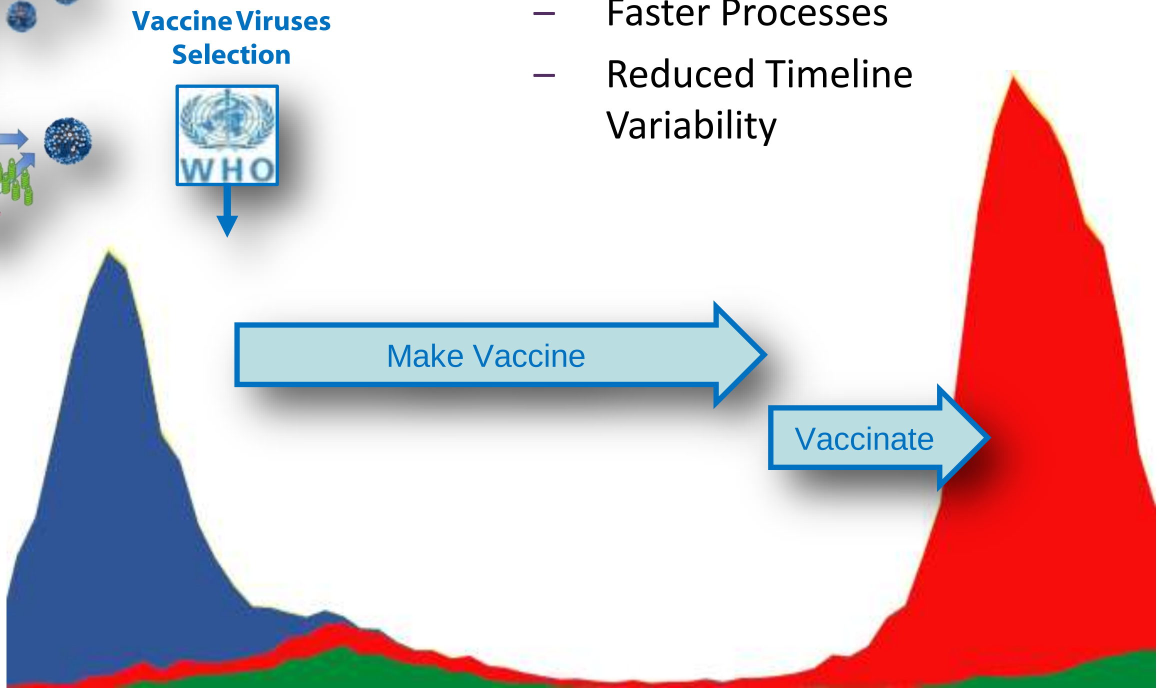
Improving Vaccine Virus Selection

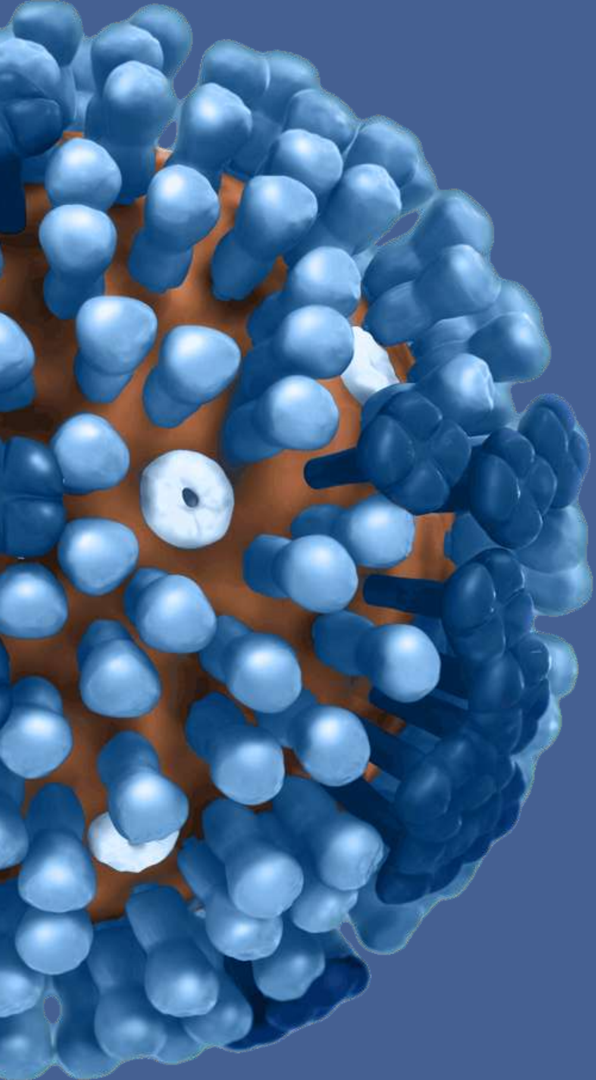


Improving Vaccine Virus Selection



- Goals
  - Better Decisions
  - Faster Processes
  - Reduced Timeline Variability





Thank You

Dan Jernigan, MD MPH
DJernigan@cdc.gov

WHO
BARDA
NIH
FDA

W Zhang
R Hatchett
R Bright
R Donis
A Donabedian
D Spiro
J Weir

J Katz
D Wentworth
T Tumpey
X Xu
J Barnes
B Garten
L Gubareva
T Davis
L Chen
S Lindstrom
M Levine
I York
T Maines
S Sambhara

J Bresee
S Olsen
A Fry
C Reed
L Brammer
B Flannery
M Biggerstaff
A Budd
B Neuhaus
E Eisenberg
S Shepard