Improving on Influenza Vaccines: Managing the Challenges of Vaccine Mismatch

Daniel B. Jernigan, MD MPH
Director, Influenza Division

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
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On Arrival at Camp
Cabin has 25 Campers

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Where we were... where we are

On Arrival at Camp Cabin has 25 Campers

One Week Later Cabin has 11 Campers
The 2014-15 Season
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

Estimated Cases, Care-Seeking Cases, and Hospitalizations, U.S. 2010-15 Seasons

- **A(H3)**
- **B**
- **A(H1)pdm09**

700,000 – 900,000 Hospitalizations Estimated

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

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

December 2014

January 2015

65+ yr rate: 309/100,000

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

65+ yr rate in 2009-10: 26/100,000

65+ yr rate: 309/100,000

Significant Impact of 2014-15 on 65+ year olds

Cumulative Rate per 100,000 for Laboratory-Confirmed Influenza Hospitalizations in 65+, U.S. 2010-16

Vaccine Effectiveness and 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

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
Influenza A/H3N2 Characterization - 2014
Domestic and International Viruses Submitted to CDC

Northern Hemisphere (NH)
Vaccine Viruses Selected in February 2014

Make Vaccine

Vaccinate

CDC. Unpublished data. H3N2 hemagglutination inhibition test results by date of testing.
Influenza A/H3N2 Characterization - 2014

H3N2 Low Reactors by Hemagglutination Inhibition Testing, Domestic and International Viruses
Submitted to CDC, 2014

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

<table>
<thead>
<tr>
<th></th>
<th>Influenza-positive</th>
<th>% vaccinated</th>
<th>Influenza-negative</th>
<th>% vaccinated</th>
<th>Adjusted VE</th>
<th>(95% CI)</th>
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<td>All ages</td>
<td>941/1821</td>
<td>(52)</td>
<td>3866/7092</td>
<td>(55)</td>
<td>13%</td>
<td>(2 to 23)</td>
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<td><strong>Influenza B (Yamagata)</strong></td>
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<tr>
<td>All ages</td>
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<td>(37)</td>
<td>3866/7092</td>
<td>(55)</td>
<td>55%</td>
<td>(43 to 65)</td>
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<tr>
<td><strong>Influenza B (Victoria)</strong></td>
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<tr>
<td>All ages</td>
<td>12/47</td>
<td>(26)</td>
<td>3866/7092</td>
<td>(55)</td>
<td>63%</td>
<td>(26 to 81)</td>
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</tbody>
</table>

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

A(H3N2) all genetic groups: 1363 cases, Adjusted Vaccine Effectiveness (%): 13%

Vaccine-like (group 3C.3b): 156 cases, Adjusted Vaccine Effectiveness (%): 43%

Vaccine-low (group 3C.2a): 1105 cases, Adjusted Vaccine Effectiveness (%): 9%
H3N2 Vaccine Effectiveness – 2004-2015

Improving Vaccine Virus Selection
Where can improvements occur?

Vaccine Viruses Selection

WHO

Make Vaccine

Vaccinate
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

2014-15 Season Under Evaluation

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

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

Calculators

**Calculator A: Situational Awareness for Seasonal influenza**

- **Medically Attended ILI (MA-ILI)**
- **Total Population**: United States, 317,581,124
- **Expected prevalence of Flu+/MA-ILI**

Sample Size | Sample Size Table | Data Confidence
---|---|---

Confidence level **95%**

The graph, table, and output language below describe the **minimum sample size** (of unscreened MA-ILI specimens) needed to estimate the fraction of Flu+/MA-ILI with a specified **margin of error** and confidence level of 95%. This calculation is based on the estimated inputs provided above and assumes that the estimated level of Flu+/MA-ILI will be close to 10% and the total population under surveillance is 317,581,124. Use the mouse to view values in the sample size graph and scroll through sample size table.

<table>
<thead>
<tr>
<th>Margin of Error</th>
<th>Minimum Sample Size</th>
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<tr>
<td>1%</td>
<td>3415</td>
</tr>
<tr>
<td>1.25%</td>
<td>2195</td>
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<tr>
<td>1.5%</td>
<td>1527</td>
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<tr>
<td>1.75%</td>
<td>1124</td>
</tr>
<tr>
<td>2%</td>
<td>861</td>
</tr>
<tr>
<td>2.25%</td>
<td>681</td>
</tr>
<tr>
<td>2.5%</td>
<td>555</td>
</tr>
</tbody>
</table>

A sample size of **138** unscreened MA-ILI specimens is needed in order to be 95% (+/- 5%) confident that the true prevalence of Flu+/MA-ILI is 10%.
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

- 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
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 for the 2016 southern hemisphere season, 24 Sept 2015.
Circulating Viruses
Changes in H3N2 Binding Properties

Increasing glycosylation on HA & decreasing avidity of H3N2 for \( \alpha 2,6 \) receptor
Increasing Glycosylation of H3N2 Hemagglutinin

H3N2 Hemagglutinin (HA1) From 1968

H3N2 Hemagglutinin (HA1) From 2015

Receptor Binding Site

Decreasing Glycan Binding for H3N2

Changes in H3N2 Hemagglutination Inhibition Testing

- Increasing glycosylation on HA & decreasing avidity of H3N2 for α2,6 receptor

**Hemagglutination Inhibition**
- Chicken RBCs
- Turkey RBCs
- Guinea Pig RBCs

**Cell-Propagated Virus**

Increasing glycosylation on HA & decreasing avidity of H3N2 for α2,6 receptor

Cell-Propagated Virus

Modified infectivity requires SIAT cells & increasing neuraminidase binding prompts use of oseltamivir

Guinea Pig RBCs

Turkey RBCs

Chicken RBCs

Hemagglutination Inhibition


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
When will antigenic testing on Michigan H3v's be available.
Thanks,
Dan.
When will antigenic testing on Michigan H3v’s be available.
Thanks,
Dan.
**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* → *Isolate and Propagate* → *Phenotypically Analyze*

2,000 per year
Whole Genome Next Generation Sequencing

Cloud Sequencing to Support Surveillance

Next Gen Sequencing at Public Health Labs

Sequencing As A Service

APHL Informatics Message Services (AIMS) Cloud

CDC Technical Staff Monitor:
1) Next Gen Quality
2) Specimen submissions
Cloud Sequencing to Support Surveillance

- Publicly Accessible Sequence Databases
- GISAID
- Genbank

Next Gen Sequencing at Public Health Labs

Sequencing As A Service

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Cloud Sequencing to Support Surveillance

Next Gen Sequencing at Public Health Labs

Sequencing As A Service

APHL Informatics Message Services (AIMS) Cloud

Publicly Accessible Sequence Databases
- GISAID
- Genbank

Mobile Sequencing for Outbreaks

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

Vaccine Viruses Selection

Make Vaccine

Vaccinate
Improving Vaccine Virus Selection

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

Vaccine Viruses Selection

WHO

Make Vaccine

Vaccinate
Thank You
Dan Jernigan, MD  MPH
DJernigan@cdc.gov

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<thead>
<tr>
<th>WHO</th>
<th>J Katz</th>
<th>J Bresee</th>
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<tr>
<td>BARDA</td>
<td>D Wentworth</td>
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