Disclosure: Session A2

In compliance with continuing education requirements, all presenters must disclose any financial or other associations with the manufacturers of commercial products, suppliers of commercial services, or commercial supporters as well as any use of unlabeled product(s) or product(s) under investigational use.

CDC, our planners, content experts, and their spouses/partners wish to disclose they have no financial interests or other relationships with the manufacturers of commercial products, suppliers of commercial services, or commercial supporters.

Planning committee discussed conflict of interest with each presenter to ensure there is no bias.

Content will not include any discussion of the unlabeled use of a product or a product under investigational use.

CDC did not accept commercial support for this continuing education activity.
Current Challenges

- Vaccine virus selection
  - Updated frequently
  - Three or four vaccine viruses
- A (H3N2)
- Annual vaccination
  - Monitor VE annually for all persons 6 months and older
  - Repeat vaccination
- Different vaccine types – which is best?
Vaccine virus selection - Influenza Vaccine Viruses Need to be Selected Six Months in Advance

Northern Hemisphere (NH) Vaccine Viruses Selected in February each year

- A(H3N2)
- A(H1N1)
- B/YamB/Vic

Make Vaccine

Vaccinate

January 2014 January 2015
Annual vaccination - Influenza Vaccine Effectiveness (VE) monitored every year with the US Flu VE Network

US Flu VE Network*

*Enrolls outpatients aged >6 months old with acute respiratory illness from 66 clinics.

Uses a test-negative case-control design where PCR positive flu = case and PCR negatives = control

<table>
<thead>
<tr>
<th>Season</th>
<th>VE against A/B influenza viruses (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-11</td>
<td>60% (53, 66)</td>
</tr>
<tr>
<td>2011-12</td>
<td>47% (36, 56)</td>
</tr>
<tr>
<td>2012-13</td>
<td>49% (43, 55)</td>
</tr>
<tr>
<td>2013-14</td>
<td>52% (44, 59)</td>
</tr>
<tr>
<td>2014-15</td>
<td>19% (10, 27)</td>
</tr>
<tr>
<td>2015-16</td>
<td>48% (41, 55)</td>
</tr>
<tr>
<td>2016-17</td>
<td>40% (32, 46)</td>
</tr>
</tbody>
</table>
Influenza A subtype specific VE estimates

VE against A/H1N1pdm09, all ages, US Flu VE Network

VE against influenza A (H3N2), all ages, US Flu VE Network
Variable influenza vaccine effectiveness by subtype: a systematic review and meta-analysis of test-negative design studies

Edward A Belongia, Melissa D Simpson, Jennifer PKing, Maria ESundaram, Nicholas S Kelley, Michael T Osterholm, Huong Q McLean

<table>
<thead>
<tr>
<th>Vaccine type</th>
<th>Pooled VE (%)</th>
<th>Pooled standard error</th>
<th>VE estimates (n)</th>
<th>p value for heterogeneity</th>
<th>( I^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type B</td>
<td>Seasonal</td>
<td>54% (46–61)</td>
<td>0.083</td>
<td>36</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>H3N2</td>
<td>Seasonal</td>
<td>33% (26–39)</td>
<td>0.050</td>
<td>34</td>
<td>0.005</td>
</tr>
<tr>
<td>H1N1pdm09</td>
<td>Seasonal</td>
<td>61% (57–65)</td>
<td>0.048</td>
<td>29</td>
<td>0.783</td>
</tr>
<tr>
<td>H1N1pdm09</td>
<td>Monovalent</td>
<td>73% (61–81)</td>
<td>0.188</td>
<td>10</td>
<td>0.217</td>
</tr>
<tr>
<td>H1N1 (pre-2009)</td>
<td>Seasonal</td>
<td>67% (29–85)</td>
<td>0.397</td>
<td>5</td>
<td>0.093</td>
</tr>
</tbody>
</table>

Data in parentheses are 95% CIs. VE = vaccine effectiveness.

Table 2: Pooled VE by type and subtype in studies without age restriction

*Lancet Infect Dis 2016; 16: 942–51*
H3N2 Challenges

- Genetic diversity and rapid evolution

- H3N2 Viruses Evolve More Rapidly than Other Influenza Viruses
  - H3N2 has required twice the number of vaccine viruses changes than H1N1

- CDC surveillance shows several H3N2 genetic groups co-circulating this season

CDC collaboration with NextFlu. Neher, Bedford et al
https://nextflu.org/h3n2/ha/3y/
H3N2 Challenges

- Antigenic characterization of A(H3N2) viruses technically difficult
  - Eggs and H3N2 viruses
    - Egg propagation can change antigenicity or effect anti HA Ab binding
    - H3N2 viruses are difficult to propagate in eggs
      - Fewer vaccine candidates

Recent H3N2 viruses require additional and new tests
- Focus-reduction and microneutralization assays
- Developing “nano-neutralization” assay
**Repeat vaccination: Pooled data from 2004-2013, Marshfield Clinic**

<table>
<thead>
<tr>
<th>Vaccination History</th>
<th>Total</th>
<th>No. (%) cases</th>
<th>aVE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current season + frequent vaccinee</td>
<td>1103</td>
<td>248 (22)</td>
<td>24</td>
</tr>
<tr>
<td>Current season + infrequent vaccinee</td>
<td>531</td>
<td>102 (19)</td>
<td>35</td>
</tr>
<tr>
<td>Current season + nonvaccinee</td>
<td>119</td>
<td>15 (13)</td>
<td>65</td>
</tr>
<tr>
<td>No current season + frequent vaccinee</td>
<td>147</td>
<td>32 (22)</td>
<td>37</td>
</tr>
<tr>
<td>No current season + infrequent vaccinee</td>
<td>506</td>
<td>134 (26)</td>
<td>6</td>
</tr>
<tr>
<td>No current season + nonvaccinee</td>
<td>1052</td>
<td>318 (30)</td>
<td></td>
</tr>
</tbody>
</table>

* p = 0.01 comparing these two groups

McLean CID 2014
Repeat vaccination: Serologic effect

Post-vaccination antibodies may reach a plateau after vaccination. Cross-season “protection” from prior vaccination has been observed.
Do all vaccine types protect equally well?

<table>
<thead>
<tr>
<th>Vaccine type</th>
<th>Age (yrs)</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>High dose IIV3</td>
<td>65+</td>
<td>Egg seed, egg propagated (60ug)</td>
</tr>
<tr>
<td>MF59 adjuvanted IIV3</td>
<td>65+</td>
<td>Egg seed, egg propagated (15ug)</td>
</tr>
<tr>
<td>Flublok, quad</td>
<td>18+</td>
<td>Recombinant proteins (45ug)</td>
</tr>
<tr>
<td>Flucelvax, quad</td>
<td>4+</td>
<td>Egg seed, cell propagated 2017-18: H3 cell seed, cell propagated</td>
</tr>
<tr>
<td>Standard dose, IIV3</td>
<td></td>
<td>Egg seed, egg propagated</td>
</tr>
<tr>
<td>Standard dose, IIV4</td>
<td></td>
<td>Egg seed, egg propagated</td>
</tr>
<tr>
<td>Intradermal IIV4</td>
<td>18-64</td>
<td>Egg seed, egg propagated</td>
</tr>
</tbody>
</table>

https://www.cdc.gov/flu/protect/vaccine/vaccines.htm
Enhanced/ New vaccines

- 2011-12, 2012-13 (H3N2)
  • 24% relative effectiveness vs std dose

- 2014-15 (H3N2)
  • 33% relative effectiveness vs std dose
Which is best?

- What to do when there is no RCT?
  - Role for observational studies?

- What is the best comparison?
  - Most studies use standard dose egg–based vaccines as comparison vaccine

- How does one enhanced or new vaccine compare with other new vaccines?

- Are repeat vaccination effects different with newer vaccines?

- Are effects similar for all virus subtypes and lineages?
Can current annual vaccines be improved?

- Should we move away from the egg?
  - Seems likely to help for H3 but what about H1 and Bs
- Should we pay attention to NA concentration?
- Should enhanced vaccines be used more broadly?
  - HD – other high risk groups
  - Adjuvanted - children
- New egg-less enhanced vaccines?

First Plant-Based Seasonal Flu Vaccine Candidate Reaches Final Clinical Stage

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Medicago
Thank You

afry@cdc.gov

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Text-Illness Monitoring during an Influenza A(H3N2)v Virus Outbreak at Agricultural Fairs in Michigan, 2016

Matthew Biggerstaff, ScD, MPH
Research Epidemiologist
Epidemiology and Prevention Branch, Influenza Division
CDC

2018 National Immunization Conference
May 15, 2018

Special thanks to Becky Schicker

Findings are draft and not for distribution
Novel Influenza Virus

- Subtype of influenza A virus that is different from currently circulating influenza viruses among humans
  - Includes H5, H7, H9
- H1 and H3 subtypes also considered novel if from a non-human species or a genetic reassortment between animal and human viruses
- Novel flu in the US is usually from persons exposed to swine
  - Called variant influenza
- Pandemic threat
Monitoring for Novel Influenza

- Nationally notifiable
- Work with states to monitor for novel flu infection
- Active or passive monitoring may be recommended
  - Avian influenza responders
  - May involve daily phone calls
  - Minnesota monitored 459 responders for 10 days in 2014/15 avian outbreak

CDC/Christine Pearson
How to Reach People in the United States

- <50% of US households have landlines

- Mobile ownership very high
  - 95% owned a cell phone
  - 77% own a smartphone

- Previous success with text-based monitoring
  - Research studies
  - Monitoring for avian influenza in Australia
Developed Text-Illness Monitoring (TIM)

- Designed for active monitoring of novel influenza
- Uses two-way Short Message Service (SMS) to monitor for symptoms of influenza
- Piloted among department of health staff in Colorado, Idaho, Texas, Michigan, Pennsylvania, and North Carolina
- Never previously deployed in an outbreak
Methods
First Michigan cases of influenza variant detected at Muskegon County Fair

A pig curiously pokes its snout out of its pen at the 2016 Muskegon County Fair in Fruitport, Mich. (Erin Lefevre | MLive.com) (Erin Lefevre)

By Malachi Barrett | mbarret1@mlive.com on August 05, 2016 at 4:23 PM, updated August 06, 2016 at 9:05 AM
Recruitment

- Selected 9 fairs
- Youth-agricultural club coordinators sent emails to all swine exhibitor families asking them to enroll
- Attended exhibitor meetings and/or distributed flyers
- Each fair assigned a unique code to text into system for enrollment (e.g. BARN, FARM, DERBY)

Text “DERBY” to ###### to enroll
Overview of Text-Illness Monitoring (TIM) Methods

Thank you! If anyone starts to have symptoms, please contact your health department or text ‘phone’ to this number.

Response of “Yes”

We’re sorry to hear someone is ill. Your health department will contact you to learn more. Seek care immediately for serious illness.

Response of “No”

None

No answer by 6PM EST

Thank you! If anyone starts to have symptoms, please contact your health department or text ‘phone’ to this number.

You have not responded to today’s check in. Do any fair attendees within your household have any symptoms? Reply yes or no.

If Yes or No
The following users have answered in the affirmative

###-###-#### on 8/17/2016 at 2:44.20 PM: YES
Follow-up and Testing

- All county health departments agreed to monitoring platform
- Provided guidance for follow-up and testing
- Handle suspect cases per their novel influenza A case protocol
Enrollment

9 Fairs
1052 Exhibitors
87 Families Enrolled
392 People in Active Surveillance
Respondent Retention

Fair Day 3

Number of Respondents

During Fair | Post Fair

Day 1 | Day 2 | Day 3 | Final Day | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 8 | Day 9 | Day 10
Alerts and Illnesses

- Actively Monitored: 392
- Illness Alerts: 22
- Sought Care: 5
- Tested: 2
- Positive Case: 2
13 illness alerts did not seek care

2: Health dept could not reach
1: Medical director instructed against
1: Declined due to cost
1: Declined b/c thought another diagnosis more likely
8: Declined; unknown reason
Epidemic Curve of Influenza A(H3N2)v Cases by Date of Symptom Onset—Michigan, 2016

Date of Symptom Onset

No. of Cases

Traditional Detection Method  TIM

17%
Conclusions
Conclusions

- Successfully deployed a newly developed text-based illness monitoring system during an ongoing outbreak of influenza A(H3N2)v virus infections
- Detected 2 of the 12 cases
- Few participants with reports of illness were tested
- Future applications of TIM system could benefit from enhanced enrollment techniques and adapted protocols to make follow-up and testing more logistically feasible
- TIM is an available tool for persons investigating outbreaks of influenza
  - Enhanced online platform for illness alerts
Acknowledgments

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Michigan Association of Fairs and Exhibitions

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