DoD Influenza Surveillance and Mid-Season Vaccine Effectiveness

Armed Forces Health Surveillance Branch (AFHSB)
Naval Health Research Center (NHRC)
United States Air Force School of Aerospace Medicine (USAFSAM)
DoD Global Influenza Network Partners

Presentation to the Vaccines and Related Biological Products Advisory Committee (VRBPAC) – 4 March 2016

CAPT Michael Cooper, PhD**

**Representing the DoD CONUS and OCONUS lab-based influenza surveillance activities
The views expressed in this presentation are those of the author and do not necessarily reflect the official policy or position of the Department of Defense or the U.S. Government.
PURPOSE: Provide a concise update to the VRBPAC on DoD influenza surveillance activities, 2015-2016

1. Program Description
2. Strain Circulation
3. Molecular Analyses
4. Vaccine Effectiveness
Breadth of DoD Influenza Surveillance

- **Global Virus Surveillance**
  - Approximately 400 locations in over 30 countries
    - Military; Local government/academic
  - Extensive characterization capabilities within the DoD
    - Culture, HAI, PCR (battery), Sequencing, Serology (HI, MN)
  - Rapid sharing of results with CDC and/or regional WHO reference centers
    - ~30,000 samples collected and analyzed in fiscal year 2015
    - ~500 sequences submitted to GenBank in fiscal year 2015

- **Comprehensive Epidemiology and Analysis Capabilities**
  - 1.4 Million Active Duty records (health care utilization, immunizations, deployment, reportable diseases, etc)
    - Medical Surveillance Monthly Reports, Ad-hoc requests, Studies/analyses, Routine reports/summaries
    - Weekly influenza reports
    - Vaccine safety and effectiveness studies
GEIS-Supported Influenza Surveillance Footprint

In 2015:
--Over 30 countries
--Over 400 sites
United States Military Recruits
Number and Proportion of Specimens Positive for Influenza by Subtype
Week 40, 2014 - Week 5, 2016

Source: NHRC
Ft Benning Georgia, Ft Jackson, SC, Ft Leonard Wood (Missouri), Naval Recruit Training Center, Great Lakes (Illinois), Lackland AFB (Texas), Marine Corps Recruit Depos, Paris Island (SC) and San Diego, Coast Guard Training Center, Cape May NJ
Army = 10 wks, Navy 8 weeks, Marines = 13 weeks, AF 8 weeks
North America
Number and Proportion of Specimens Positive for Influenza by Subtype
Week 40, 2014 - Week 6, 2016

Source: USAFSAM, NHRC
• Countries: USA, Mexico
Strain Circulation

Europe
Number and Proportion of Specimens Positive for Influenza by Subtype
Week 40, 2014 - Week 6, 2016

Source: LRMC/PHCR-Europe
• Countries: 7 countries, Belgium, Germany, Italy, Spain, Turkey, United Kingdom, Portugal
Egypt

Number and Proportion of Specimens Positive for Influenza by Subtype
Week 40, 2014 - Week 6, 2016

Source: NAMRU-3
Speaker Notes for Slide 12

- Country: Egypt
Speaker Notes for Slide 14

• Countries: Thailand, Cambodia, Bhutan, Nepal, the Philippines, South Korea, Japan
Summary of Circulating Strain Activity to date

• In North America and Europe, military members and dependents have experienced low flu activity so far; positive samples have been a mix of H3N2 and H1N1

• Globally, a mix of H3N2 and H1N1 has been detected in the DOD network; Egypt, so far, has experienced a relatively heavy season dominated by A/H1
Phylogenetic analysis
Distribution of Sequenced Influenza A/H1N1pdm09, A/H3N2, and B Specimens within the DoD, 2015 - 2016

196 Total Sequences

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USAMRU-K
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Belgium
Cambodia
Country 2
Egypt
Germany
Japan
Kenya
Peru
South Korea
Thailand
Turkey
United States

United States Air Force School of Aerospace Medicine
Public Health Epidemiology Laboratory
2510 5th Street, Wright-Patterson AFB OH 45433
• 196 sequences from 12 countries on 5 continents missing Australia and Antarctica
Vaccine effectiveness (VE)
VE Preview

• To this point, the flu season has been relatively mild in most regions covered by the DoD influenza surveillance network

• Overall, the number of cases available for these VE analyses was down by over 90% from the previous year
VE Preview

• Mid-year estimates provided by:
  – US Air Force School of Aerospace Medicine (USAFSAM),
  – Naval Health Research Center (NHRC)
  – AFHSB, Epidemiology and Analysis

• Case-Control studies, logistic regression used to estimate VE
  – Two studies used control-test negative method
  – Epidemiology and Analysis used Health Controls
  – No analyses by flu subtype do to small number of cases
  – Each influenza infection was confirmed by PCR or viral culture
Testing Criteria for ILI

- Fever ≥100.5°F (38°Celsius) AND
- Cough and/or Sore Throat (<72 hours duration)

Specimens should be collected within 72 hours of onset symptoms.
• If there is an increase in ILI patients, sites are to continue submitting up to 10 specimens per week, giving priority to the sickest or hospitalized patients.
USAFSAM Case-Control Analyses
United States Air Force School of Aerospace Medicine (USAFSAM) Case-Control Analyses

- Adjusted Estimates of Vaccine Effectiveness
  - Population: DoD healthcare beneficiaries (excluding AD)
  - Analyses by beneficiary group (children, adults) and vaccine type (overall, IIV, LAIV)
  - Test negative controls were used
  - Models adjusted for age, gender, and region
  - Cases and controls were matched on week of illness
  - Cases = 119; Controls = 294
  - 15% of cases and 37% of controls vaccinated
  - 53% of all cases were A/H1N1
  - 9% of all cases were A/H3N2
  - 38% of all cases were Flu B
• NOTES:

• Cases are confirmed via PCR/Culture/FilmArray

• Controls are those who tested negative for influenza

• A person is considered vaccinated if he/she received the vaccine at least 14 days prior to the medical encounter
– Of those vaccinated:
  • 26% were vaccinated with LAIV
  • 74% were vaccinated with IIV

• Impacts sub-analyses
• No analyses by “Flu type”
• Limited analyses by “Vaccine Type”
Cases and Controls by Age Group (USAFSAM)

Age Groups

- <18: 49.6% Cases, 61.9% Controls
- 18-49: 24.4% Cases, 24.1% Controls
- 50+: 26.0% Cases, 13.9% Controls
• Adjusted Estimates of Vaccine Effectiveness
  – The overall estimate for VE for “All Beneficiaries” (Adults and Children combined) was statistically significant and protective
  – VE estimate for “All Beneficiaries” (Adults and Children combined) vaccinated with IIV was statistically significant and protective
• NOTES:

• Cases are confirmed via PCR/Culture/FilmArray

• Controls are those who tested negative for influenza

• A person is considered vaccinated if he/she received the vaccine at least 14 days prior to the medical encounter
### USAFSAM Mid-season 2015-2016 Influenza (VE) Estimates

<table>
<thead>
<tr>
<th>Beneficiary Status</th>
<th>Vaccine Type</th>
<th>Cases n (%)</th>
<th>Controls N (%)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
<th>VE Adjusted** (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Children (&lt;18)</strong></td>
<td>Vaccinated</td>
<td>10 (17)</td>
<td>59 (41)</td>
<td>0.27 (0.13, 0.59)</td>
<td>0.25 (0.11, 0.56)</td>
<td>75 (43, 89)a</td>
</tr>
<tr>
<td></td>
<td>Unvaccinated</td>
<td>49 (83)</td>
<td>69 (59)</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td><strong>Adult (18+)</strong></td>
<td>Vaccinated</td>
<td>8 (13)</td>
<td>39 (29)</td>
<td>0.41 (0.18, 0.93)</td>
<td>0.36 (0.15, 0.84)</td>
<td>64 (16, 85)</td>
</tr>
<tr>
<td></td>
<td>Unvaccinated</td>
<td>52 (87)</td>
<td>96 (71)</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td><strong>All Beneficiaries (Excluding AD)</strong></td>
<td>Vaccinated (Both)</td>
<td>18 (15)</td>
<td>109 (37)</td>
<td>0.30 (0.17, 0.53)</td>
<td>0.29 (0.16, 0.52)</td>
<td>71 (48, 84)</td>
</tr>
<tr>
<td></td>
<td>LAIV</td>
<td>9 (8)</td>
<td>26 (11)</td>
<td>0.75 (0.33, 1.68)</td>
<td>1.00 (0.42, 2.34)</td>
<td>0 (-134, 58)</td>
</tr>
<tr>
<td></td>
<td>IIV</td>
<td>9 (8)</td>
<td>90 (32)</td>
<td>0.19 (0.09, 0.39)</td>
<td>0.17 (0.08, 0.36)</td>
<td>83 (64, 92)</td>
</tr>
<tr>
<td></td>
<td>Unvaccinated</td>
<td>101 (85)</td>
<td>185 (63)</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
</tbody>
</table>

Notes:
- OR=odds ratio; VE=vaccine effectiveness; LAIV=live, attenuated influenza vaccine; IIV=inactivated influenza vaccine
- Subjects were considered vaccinated if the vaccine was received at least 14 days prior to specimen collection date
- Controls were matched to cases by week.
- **Overall adjusted VE was calculated using conditional multivariable logistic regression with adjustment for age, gender, and region**
- a The ‘Children’ overall analysis was only adjusted for gender and region.
See back up Slide 5 for characteristics of cases and controls.
NHRC Case-Control Analyses
Naval Health Research Center (NHRC)

- Adjusted Estimates of Vaccine Effectiveness
  - Population: Civilians only
    - DoD dependents Southern California and Illinois outpatient clinics
    - Civilians at outpatient clinics near US-Mexico border (CDC and CA State collaboration)
  - Adjusted for: age, study population (military dependents VS US-Mexico border civilians) and month of illness
  - Cases: n=106; confirmed by RT-PCR or viral culture
  - Controls: n=267; test-negative
  - Vaccination Rates: cases 20%, controls 38%
    - 58% of cases were A/H3N2; 25% were flu B; 15% were A/H1N1
    - Approximately 90% of vaccinated cases and controls were vaccinated with IIV
Cases and Controls by Age Group (NHRC)

- **0-17**: 77.0% Cases, 73.0% Controls
- **18-64**: 20.0% Cases, 25.0% Controls
- **65+**: 3.0% Cases, 2.0% Controls

Age Groups

Percentage Vaccinated
Adjusted Estimates of Vaccine Effectiveness

- Overall, adjusted VE was moderately protective and statistically significant
- For children, VE was moderately protective and statistically significant
- Adjusted VE for H3N2 infection specifically was moderately protective and statistically significant
• 365 ILI cases enrolled between DEC 21 2015 and FEB 11 2016
  – Lab-confirmed influenza by CDC RT-PCR assay
  – VE = 1 – Odds ratio

<table>
<thead>
<tr>
<th>Overall and A/H3N2 Vaccine Effectiveness Estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>Overall</td>
</tr>
<tr>
<td>A/H3</td>
</tr>
<tr>
<td>Children (0-17 H3,only)</td>
</tr>
</tbody>
</table>
AFHSB
Epidemiology and Analysis
Case-Control Analyses
• Matched Case Health-Control Study of VE
  – Population: Active component service members
    • Army, Navy, Air Force, Marines
    • CONUS and OCONUS
  – Lab-confirmed flu cases (n=183)
    • Rapid, RT-PCR, or culture
  – Health Controls (n=652)
    • Medical encounter for injuries or mental health conditions with no ILIs reported at encounter
    • No medical encounters for influenza during season
    • Matched to cases by sex, age, date of encounter (+/- 3 days), and location
  – Models adjusted for 5-yr vaccination status (Y/N)
  – Overall and vaccine-type VE calculated
– 84% of cases were vaccinated; 87% of controls
– 90% of cases had prior flu vaccine in previous 5 years
– Of those vaccinated:
  • 41% LAIV
  • 59% IIV
– Overall Adjusted VE of 24% (not statistically significant)
– Adjusted VE of 16% for those who received IIV (not statistically significant)
– Adjusted VE of 39% for those who received LAIV (not statistically significant)
## AFHSB Mid-Season 2015-2016 VE Estimates
### Active Component

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>Cases n (%)</th>
<th>Controls n (%)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)*</th>
<th>Vaccine Effectiveness (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>154 (84)</td>
<td>566 (87)</td>
<td>0.73 (0.42, 1.26)</td>
<td>0.76 (0.44, 1.32)</td>
<td>24 (-32, 56)</td>
</tr>
<tr>
<td>LAIV</td>
<td>56 (31)</td>
<td>237 (36)</td>
<td>0.58 (0.31, 1.07)</td>
<td>0.61 (0.33, 1.13)</td>
<td>39 (-13, 67)</td>
</tr>
<tr>
<td>IIV</td>
<td>96 (52)</td>
<td>326 (50)</td>
<td>0.81 (0.47, 1.41)</td>
<td>0.84 (0.48, 1.47)</td>
<td>16 (-47, 52)</td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>29 (16)</td>
<td>86 (13)</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
</tbody>
</table>

OR = Odds Ratio; IIV = inactivated influenza vaccine; LAIV = live, attenuated influenza vaccine; *Adjusted for vaccination status in 5 years prior

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AFHSB Mid-Season 2015-2016 VE Estimates
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<td>Ref</td>
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<td>Ref</td>
</tr>
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OR = Odds Ratio; IIV = inactivated influenza vaccine; LAIV = live, attenuated influenza vaccine; *Adjusted for vaccination status in 5 years prior
## AFHSB Mid-Season 2015-2016 VE by Type/Subtype

<table>
<thead>
<tr>
<th>Type</th>
<th>Vaccine Type</th>
<th>Cases n (%)</th>
<th>Controls n (%)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)*</th>
<th>Vaccine Effectiveness (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Any</td>
<td>125 (84)</td>
<td>464 (89)</td>
<td>0.56 (0.30, 1.05)</td>
<td>0.60 (0.31, 1.13)</td>
<td>40 (-13, 69)</td>
</tr>
<tr>
<td></td>
<td>LAIV</td>
<td>49 (33)</td>
<td>196 (38)</td>
<td>0.49 (0.25, 0.98)</td>
<td>0.52 (0.26, 1.05)</td>
<td>48 (-5, 74)</td>
</tr>
<tr>
<td></td>
<td>IIV</td>
<td>75 (51)</td>
<td>265 (51)</td>
<td>0.61 (0.33, 1.13)</td>
<td>0.65 (0.34, 1.22)</td>
<td>35 (-22, 66)</td>
</tr>
<tr>
<td></td>
<td>Unvaccinated</td>
<td>23 (16)</td>
<td>56 (11)</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
</tbody>
</table>

OR = Odds Ratio; IIV = inactivated influenza vaccine; LAIV = live, attenuated influenza vaccine; *Adjusted for vaccination status in 5 years prior.
Regarding USAFSAM and NHRC VE analyses:

- overall VE, (all flu and vaccination types combined) was statistically significant and moderately protective
- VE for IIV specifically, was statistically significant and moderately to highly protective
- The USAFSAM and NHRC analyses indicate that the IIV prevented between 64 and 83% of medically attended influenza cases

Regarding AHFSB’s VE analyses

None of these findings were statistically significant
Discussion

Limitations

– Subjects were sick enough to seek medical attention, can’t comment on vaccine impact for less severe cases
– Due to the relatively small numbers of cases, VE by flu subtypes or vaccine type couldn’t be estimated
– For the USAFSAM and NHRC analyses, over 80% of vaccinated cases and controls were vaccinated with IIV;
  • couldn’t compare VE by type of vaccine
  • numbers were too small to adequately evaluate LAIV
Limitations

– Regarding AFHSB’s analyses: Active Duty mil pop is highly immunized, (over 90%) this could have a negative impact on VE (potential method issues and biological effects such as attenuated immune response with repeated exposures)
– The military population is younger and healthier; cannot comment on vaccine impact in older, high-risk pops
– Small number of cases
Acknowledgement

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Additional Slides
Influenza Subtypes Mid-season 15-16 Beneficiaries (Excluding AD) USAFSAM Data

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Frequency</th>
<th>Percent</th>
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<tr>
<td>B</td>
<td>45</td>
<td>37.82</td>
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<tr>
<td>H1</td>
<td>63</td>
<td>52.94</td>
</tr>
<tr>
<td>H3</td>
<td>11</td>
<td>9.24</td>
</tr>
</tbody>
</table>
### Influenza Percent Positive by Week

**USAFSAM**

<table>
<thead>
<tr>
<th>MMWR_week</th>
<th>Case</th>
<th>Control</th>
<th>Total</th>
<th>% Positive</th>
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<tbody>
<tr>
<td>2015_42</td>
<td>1</td>
<td>3</td>
<td>4</td>
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<td>2015_45</td>
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<td>9</td>
<td>12</td>
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<td>2015_46</td>
<td>2</td>
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<td>2015_48</td>
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<td>33</td>
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<td>25.0</td>
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<td>50</td>
<td>70</td>
<td>28.6</td>
</tr>
<tr>
<td>2016_07</td>
<td>24</td>
<td>28</td>
<td>52</td>
<td>46.2</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>119</strong></td>
<td><strong>294</strong></td>
<td><strong>413</strong></td>
<td><strong>28.8</strong></td>
</tr>
<tr>
<td>Demographic</td>
<td>Cases (n= 119) No.(%)</td>
<td>Controls (294) No.(%)</td>
<td>p-Value</td>
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<tr>
<td>-----------------------------</td>
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<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>54 (45.37)</td>
<td>160 (54.42)</td>
<td>0.0958</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>65 (54.62)</td>
<td>134 (45.57)</td>
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<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50+</td>
<td>31 (26.05)</td>
<td>41 (13.94)</td>
<td>0.0094</td>
<td></td>
</tr>
<tr>
<td>18-49</td>
<td>29 (24.36)</td>
<td>71 (24.14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18</td>
<td>59 (49.57)</td>
<td>182 (61.90)</td>
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<tr>
<td>Beneficiary Category</td>
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<tr>
<td>Child</td>
<td>59 (49.57)</td>
<td>182 (61.90)</td>
<td>0.0183</td>
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</tr>
<tr>
<td>Adult</td>
<td>60 (50.41)</td>
<td>112 (38.09)</td>
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<td>Geographic Regiona</td>
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<tr>
<td>Northern Command</td>
<td>107 (89.91)</td>
<td>282 (95.91)</td>
<td>0.0182</td>
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<tr>
<td>Other Commands</td>
<td>12 (10.08)</td>
<td>12 (4.08)</td>
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<tr>
<td>Collection Periodb</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Quartile 1</td>
<td>13 (10.92)</td>
<td>41 (13.94)</td>
<td>0.4095</td>
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</tr>
<tr>
<td>Quartile 2</td>
<td>106 (89.07)</td>
<td>253 (86.05)</td>
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<td>Vaccination Statusc</td>
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</tr>
<tr>
<td>No</td>
<td>101 (84.87)</td>
<td>185 (62.92)</td>
<td>d</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>18 (15.12)</td>
<td>109 (37.07)</td>
<td>d</td>
<td></td>
</tr>
<tr>
<td>IIV</td>
<td>9 (7.563)</td>
<td>90 (30.61)</td>
<td>d</td>
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</tr>
<tr>
<td>LAIV</td>
<td>9 (7.563)</td>
<td>19 (6.462)</td>
<td>d</td>
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</tr>
</tbody>
</table>

Note: Northern Command (includes North America); Other Commands: PACOM = Pacific Command (Alaska, Guam, Japan, S. Korea; n=24) and CENTCOM = Central Command (Afghanistan, Kuwait); IIV = Inactivated Influenza Vaccine; LAIV = Live Attenuated Influenza Vaccine.

*a All countries are grouped regionally as defined areas of responsibility categorized by the U.S Department of Defense.

*b Specimen collection/enrollment began Week 40 (October 4, 2015) and continued through Week 7 (February 20, 2016). Collection period was split into two even quartiles for total number of cases and controls (Quartile 1 = Week 40-52; Quartile 2 = Week 52-7)

*c Both cases and controls were generally vaccinated before influenza activity began in the Northern Hemisphere.

*d Vaccination status is the exposure of interest.
Speaker Notes for Slide 54

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