Update on Effectiveness of Live-Attenuated Versus Inactivated Influenza Vaccines in Children and Adolescents Aged 2–18 Years – US Flu VE Network

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Objectives

- Compare LAIV and IIV vaccine effectiveness (VE) among children and adolescents during 3 influenza seasons: 2011-12, 2012-13, and 2013-14

- Summarize other data from observational studies evaluating LAIV and IIV among children in 2013-14
Methods: US Flu VE Network

Enrollees: Outpatients aged ≥6 months with acute respiratory illness with cough ≤7 days duration

Methods: Prospective case-control study (test-negative design)

- All enrolled outpatients tested for influenza by RT-PCR
  - **Cases**: Outpatients with confirmed influenza
  - **Controls**: Outpatients without influenza (PCR-negative)

- Vaccination status: confirmed by medical record or registry
  - Includes only fully vaccinated per ACIP recommendations ≥14 days before illness onset

- **Analysis**: VE = (1 – adjusted OR) x 100%
  - Adjusted for: age, sex, site, days from illness onset to enrollment, high-risk health status, calendar time (2-week intervals), race/ethnicity and parental-rated general health
Analysis Methods

- **Inclusion Criteria**
  - 2–18 years of age
  - Received only one type of vaccine within season (LAIV or IIV)

- **VE of LAIV: LAIV vs no vaccine**
  - Excludes subjects 2–18 y who received IIV for that season

- **VE of IIV: IIV vs no vaccine**
  - Excludes subjects 2–18 y who received LAIV for that season

- **Relative effectiveness of LAIV to IIV: LAIV vs IIV**
  - Excludes unvaccinated subjects 2–18 y for that season
Distribution of influenza virus type/subtypes among influenza-positive cases in US Flu VE Network, past 3 influenza seasons

*Ohmit et al. CID 2013
Vaccine effectiveness (VE)

Live-attenuated influenza vaccine (LAIV)
LAIV effectiveness against medically-attended influenza among 2–18 yr olds, US Flu VE Network

<table>
<thead>
<tr>
<th>Year</th>
<th>Total, Flu +</th>
<th>LAIV, Flu +</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011-12</td>
<td>332</td>
<td>12</td>
</tr>
<tr>
<td>2012-13</td>
<td>738</td>
<td>61</td>
</tr>
<tr>
<td>2013-14</td>
<td>224</td>
<td>34</td>
</tr>
</tbody>
</table>

Adjusted Vaccine Effectiveness (%)
LAIV effectiveness against medically-attended influenza, by season and age category

<table>
<thead>
<tr>
<th></th>
<th>2011-12</th>
<th>2012-13</th>
<th>2013-14</th>
</tr>
</thead>
<tbody>
<tr>
<td>2–8 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total, Flu +</td>
<td>168</td>
<td>391</td>
<td>127</td>
</tr>
<tr>
<td>LAIV, Flu +</td>
<td>6</td>
<td>35</td>
<td>22</td>
</tr>
<tr>
<td>9–18 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total, Flu +</td>
<td>100</td>
<td>347</td>
<td>99</td>
</tr>
<tr>
<td>LAIV, Flu +</td>
<td>6</td>
<td>26</td>
<td>12</td>
</tr>
</tbody>
</table>
Vaccine effectiveness (VE)
Inactivated influenza vaccines (IIV)
IIV effectiveness against medically-attended influenza among 2–18 yr olds, US Flu VE Network

Adjusted Vaccine Effectiveness (%)

<table>
<thead>
<tr>
<th>Year</th>
<th>Total, Flu +</th>
<th>IIV, Flu +</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011-12</td>
<td>267</td>
<td>47</td>
</tr>
<tr>
<td>2012-13</td>
<td>878</td>
<td>201</td>
</tr>
<tr>
<td>2013-14</td>
<td>227</td>
<td>37</td>
</tr>
</tbody>
</table>
IIV effectiveness against medically-attended influenza, by season and age category

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total, Flu +</td>
<td>155</td>
<td>466</td>
<td>124</td>
<td>112</td>
<td>412</td>
<td>103</td>
</tr>
<tr>
<td>IIV, Flu +</td>
<td>29</td>
<td>110</td>
<td>21</td>
<td>18</td>
<td>91</td>
<td>16</td>
</tr>
</tbody>
</table>
LAIV and IIV vaccine effectiveness by influenza type/subtype
LAIV and IIV vaccine effectiveness among 2-18 yrs over 3 seasons, by influenza type/subtype

<table>
<thead>
<tr>
<th>Influenza type/subtype</th>
<th>LAIV</th>
<th>IIV</th>
<th>LAIV</th>
<th>IIV</th>
<th>LAIV</th>
<th>IIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1N1pdm09</td>
<td>8</td>
<td>63</td>
<td>30</td>
<td>39</td>
<td>55</td>
<td>59</td>
</tr>
<tr>
<td>H3N2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total, Flu +: 184 188 493 596 472 544
Vaccinated, Flu +: 24 28 48 151 33 105
LAIV and IIV vaccine effectiveness among 2-8 yrs over 3 seasons, by influenza type/subtype

- **H1N1pdm09**
  - LAIV: 10
  - IIV: 62

- **H3N2**
  - LAIV: 47
  - IIV: 35

- **B**
  - LAIV: 68
  - IIV: 56

Total, Flu +:
- LAIV: 111
- IIV: 112
- H1N1pdm09: 265
- H3N2: 321
- B: 249
- IIV: 290

Vaccinated, Flu +:
- LAIV: 17
- IIV: 18
- H1N1pdm09: 27
- H3N2: 83
- B: 17
- IIV: 58
Relative effectiveness of LAIV to IIV
Relative effectiveness of LAIV to IIV against medically-attended influenza

Adjusted OR (95% CI)
Relative effectiveness of LAIV to IIV, aged 2-18 yrs over past 3 influenza seasons, US Flu VE Network

<table>
<thead>
<tr>
<th>Influenza Season</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011-12</td>
<td>0.83</td>
</tr>
<tr>
<td>2012-13</td>
<td>1.03</td>
</tr>
<tr>
<td>2013-14</td>
<td>3</td>
</tr>
</tbody>
</table>

Favors LAIV  | Favors IIV
Relative effectiveness of LAIV to IIV during past 3 influenza seasons, by age group

<table>
<thead>
<tr>
<th>Influenza Season</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011-12</td>
<td>0.54</td>
</tr>
<tr>
<td>2012-13</td>
<td>0.74</td>
</tr>
<tr>
<td>2013-14</td>
<td>5.17</td>
</tr>
</tbody>
</table>

2–8 years

- 2011-12: 1.02
- 2012-13: 1.16
- 2013-14: 1.61

9–18 years

- 2011-12: 1.02
- 2012-13: 1.16
- 2013-14: 1.61
Limitations

- **Single season vs. H1N1 vaccine virus?**
  - Limited circulation of H1N1pdm09 in US Flu VE Network from 2010-2013

- **Ability to measure VE among children by vaccine type (LAIV vs IIV) depends on vaccine uptake and requires large sample size**
  - Limited ability to control for potential confounding variables
Summary: US Flu VE Network

- During 2011-12 and 2012-13, relative effectiveness favored LAIV versus IIV in young children but was not significant.
- During 2013-14, relative effectiveness favored IIV versus LAIV in young children.
- H1N1pdm09 was predominant virus for the first time during 2013-14.
  - Subtype analysis is consistent with low VE for LAIV against H1N1pdm09.
  - Cannot rule out specific issue related to 2013-14, e.g. study enrollees or design, unmeasured confounding, or vaccine issue.
Review of additional data from 2013-14 season on LAIV and IIV effectiveness in children and adolescents
LAIV Effectiveness Study
Preliminary Results from 2013-2014

October 20, 2014
Chris Ambrose, M.D.
Vice President, US Medical Affairs
Summary of MedImmune Study Findings

◆ MedImmune study results are similar to CDC results
  – High LAIV effectiveness for influenza B
  – No significant effectiveness for A/H1N1 overall

◆ Significant differences in effectiveness observed by vaccine lot shipping time

◆ No clear explanation at present; comprehensive investigations into potential explanations are ongoing

◆ Differences by lot might be explained by H1N1 strain potency loss
  – A/California LAIV more susceptible to thermal degradation due to unique HA stalk sequence\(^1\)
  – Sequence not present in seasonal influenza LAIV strains

MedImmune Study of LAIV effectiveness

- Community-dwelling children 2-17 years of age
  - Vanderbilt/Tennessee (Marie Griffin)
  - Wake Forest/North Carolina (Katherine Poehling)
  - Scott and White/Texas (Manjusha Gaglani)
  - Marshfield Clinic/Wisconsin (Edward Belongia)

- Similar study design to CDC study

- Enrolled 1082 children; 1033 available for analysis
MedImmune Study:
Adjusted Estimates of Absolute Effectiveness
MedImmune Study:
Adjusted LAIV H1N1 Effectiveness by Shipment Group

-49
83

-100 -80 -60 -40 -20 0 20 40 60 80 100

Effectiveness (%)

Shipped Weeks 4-9  Earlier or Later Shipment

➢ Not explained by any other study covariates
Influenza Vaccine Effectiveness: Air Force Children, 2013-2014 Influenza Season

Angelia Cost, PhD, ScM
Senior Managing Epidemiologist
Epidemiology & Analysis
Armed Forces Health Surveillance Center
Angelia.a.cost.ctr@mail.mil
Methods

• Time Period:
  – Vaccinations: 01AUG2013 - 31MAY2014
  – Outcomes: 01SEP2013 - 31MAY2014

• Population: Air Force dependents 2-17 years of age
  – Only service with database of dependent immunizations

• Case / Test-negative control design
  – Lab-confirmed influenza cases (PCR, culture, or rapid)
  – Test negative controls (PCR or culture only; rapid negative test excluded)

• Considered vaccinated if vaccine received at least 14 days prior to lab test
Summary of Findings

• Moderate VE found for any vaccine type and IIV for all age groups (not statistically significant among 9-17 year olds)

• Low to negative, non-statistically significant VE for LAIV among all age groups

• Low LAIV VE may be related to predominance of A/H1 circulation this season
  – Subtype analysis overall and among 2-8 year olds revealed LAIV VE point estimates moderate for A/H3, but not for A/H1 (none were statistically significant)
Summary of observational data

- 3 US studies during 2013-14 season using test-negative design reported low VE for LAIV4
  - All 3 reported higher and significant VE for IIV among children/adolescents

- All 3 studies reported low VE (nonsignificant) for LAIV4 against H1N1pdm09 in 2013-14

- MedImmune post-licensure study reported significant VE for LAIV4 (similar to IIV) against influenza B-Yamagata, but not H1N1pdm09
Several studies suggested potential advantages of LAIV over IIV for children, including better vaccine efficacy and heterotypic protection.

Several countries (Canada, the United Kingdom, Israel, Germany) and two U.S. states (Washington, Oregon) previously expressed some degree of LAIV preference for young children.

In June 2014, ACIP recommended that LAIV should be used when available for healthy children aged 2 through 8 years, following GRADE assessment of data from 2 comparative RCTs.
LAIV vs. IIV—2-8-year-olds—Lab-confirmed Influenza—Randomized Studies

<table>
<thead>
<tr>
<th>Studies (n)</th>
<th>Risk of Bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Risk of Bias</th>
<th>Inconsistency</th>
<th>RR [95% CI]</th>
<th>Risk Difference with LAIV [95% CI]</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Not serious</td>
<td>Not Serious</td>
<td>Not Serious</td>
<td>Not Serious</td>
<td>0.46</td>
<td>[0.39 – 0.54]</td>
<td>43 fewer per 1000</td>
<td>[37 – 49 fewer]</td>
<td>⊕⊕⊕⊕ High</td>
</tr>
</tbody>
</table>

- **Influenza cases included all influenza types/subtypes**
  - All A(H1N1), A(H3N2), and B
  - Without regard to antigenic similarity to viruses in vaccine
Type/Subtype- and Match-specific Relative VE (1)

Belshe, 2007 (2004-05 season)

- Randomized, placebo-blinded comparative trial of LAIV and IIV

- All H1N1 antigenically matched vaccine (A/New Caledonia/20/1999)
  - Relative VE (LAIV vs. IIV): 89.2 (95%CI, 67.7—97.4)

- All H3N2 were antigenically mismatched (drifted)
  - Relative VE (LAIV vs. IIV): 79.2 (95%CI, 70.6—85.7)

- B viruses from both lineages (some matched vaccine, some not)
  - Relative VE (LAIV vs IIV, matched): 27.3 (95%CI, -4.8—49.9)
  - Relative VE (LAIV vs. IIV, mismatched): 6.3 (95%CI, -31.6—33.3)

Belshe et al, NEJM 367;7: 685-696
Type/Subtype- and Match-specific Relative VE (2)

Ashkenazi, 2006 (2002-03 season)

- Randomized, open-label comparative trial of LAIV and IIV

- Cases included
  - A(H1N1), A(H3N2) and B viruses regarded as antigenically similar to vaccine, and
  - Some H3N2 regarded as antigenically distinct from vaccine.

- Vaccine A(H1N1) was A/New Caledonia/20/1999

- Results specific to mismatched strains not reported

- Type/subtype-specific, without regard to match, relative (LAIV vs. IIV) VE
  - A(H1N1): 100 (95%CI, 56.0—100)
  - A(H3N2): -47.9 (95%CI, -236.5—32.6)
  - B: 68.9 (95%CI, 39.2—85.2)

Ashkenazi et al, PIDJ 2006;25:870-879
Summary--VE of LAIV Against A(H1N1)pdm09

- Comparative studies of LAIV and IIV were conducted prior to 2009 pandemic
  - No H1N1pdm09-specific efficacy data available from RCTs
  - Relatively little effectiveness data for monovalent LAIV

- 2013-14 was first H1N1-predominant influenza season since 2009 pandemic
  - First clear indication of suboptimal effectiveness of LAIV for H1N1pdm09

- Explanation for 2013-14 findings unknown
  - Differences by lot shipping time in MedImmune data under investigation
    - But, good VE for LAIV against Influenza B; similar findings in three different datasets
  - Current data are from observational studies; potential confounding
    - However, similar observations in three different datasets
Summary--VE of LAIV Against A(H1N1)pdm09

- LAIV H1N1pdm09 may be less stable than seasonal H1N1 LAIV viruses (Cotter et al, 2014)
  - Sequence in HA stalk confers higher susceptibility to thermal degradation
  - Potentially could affect stability and/or replicative fitness of the vaccine virus
    - Biologically plausible
    - Could be consistent with previous VE observed with seasonal H1N1 and 2013-14 observations of good effectiveness of LAIV against influenza B

- Looking forward
  - 2014-15 vaccine has already been produced—no changes anticipated this season
  - US Flu VE Network receiving resources to increase enrollment of children
  - Work Group will discuss additional data from these and other sources as it becomes available