Review of Effectiveness of Live Attenuated Influenza Vaccine

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Influenza Division, CDC
Advisory Committee on Immunization Practices

February 21, 2018
Outline

- Background
- Combined individual patient-level analysis of LAIV effectiveness
  - U.S. data
- Systematic review and meta analysis of published literature on LAIV effectiveness
  - U.S. and non-U.S. data
- Work Group considerations
- Proposed recommendation
Background
LAIIV Recommendations Summary, 2003-2016

- 2003: LAIV3 licensed for 5 through 49 years; in 2007, for 2 through 49 years
  - Recommended for healthy non-pregnant persons; no preference
- 2012: LAIV4 licensed; replaced LAIV3 for 2013-14 season
  - Recommended for healthy non-pregnant persons; no preference
- 2014: Preferential recommendation for healthy 2- through 8-year olds
  - Basis: pre-2009 pandemic data showing superiority of LAIV3 to IIV
- February 2015: Preferential recommendation removed following poor effectiveness of LAIV4 against H1N1pdm09 among 2- through 17-year-olds during 2013-14 season
  - No statistically significant effectiveness, whereas IIV was effective
LAIV Recommendations Summary, 2003-2016 (cont’d)

- June 2015: No better performance than IIV against H3N2 in 2014-15
  - Poor VE for LAIV4 and IIV during a drifted H3N2-predominant season
  - LAIV3 superior to IIV for drifted H3N2 viruses in pre-pandemic study

- 2015-16 season: LAIV4 H1N1pdm09-like virus changed to A/Bolivia/559/2013/H1N1pdm09 for 2015-16
  - Studies revealed poor fitness of previous LAIV4 H1N1pdm09-like vaccine virus, A/California/7/2009/H1N1pdm09

- June 2016: Poor effectiveness of LAIV4 against H1N1pdm09 for 2015-16
  - LAIV4 not recommended in the United States for 2016-17 and 2017-18
LAIV and IIIV vaccine effectiveness ages 2–17 years, by influenza type/subtype, 2015-16

U.S. Flu VE Network
2015-16 U.S. Season
Presented at ACIP, June 2016
MedImmune ICICLE Study

2015-16 U.S. Season

Presented at ACIP, June 2016

ICICLE: 2015-16 Adjusted Estimates of Effectiveness

- Results similar for 1) those fully vaccinated, 2) excluding those negative for any respiratory virus, and 3) excluding those with high-risk conditions

VE adjusted on site, age group, visit date, outpatient visits in past 6 months, health insurance, and sex
CI's truncated at -20 to enable graphical display

- Primary concern: effectiveness against H1N1pdm09 in 2013-14, 2015-16
- Point estimates of LAIV4 effectiveness against H1N1pdm09 varied in U.S.
- Higher point estimates in studies conducted outside the U.S.
  - e.g., Canada, United Kingdom, Germany, Finland (which have continued to use LAIV)
- Sources of variability not completely understood; possibilities include
  - Differences in use of trivalent as compared with quadrivalent LAIV
  - Small sample size and imprecision of estimates in most individual studies
    • Particularly when stratifying by vaccine types and influenza types/subtypes
  - Differences in prevalence of prior vaccination among children in different countries and populations
Review of LAIV Effectiveness data, 2010-11 through 2016-17

- Combined individual patient-level analysis of U.S. studies (US-IPD)
  - 5 studies and three seasons with LAIV4 (2013-14 through 2015-16)
  - Greater power for age group analyses
  - More precise estimates through pooling of data across multiple studies
  - Evaluation of effect of prior vaccination

- Systematic review and meta-analysis (SR/MA)
  - U.S. and non-U.S. studies from 2010-11 season forward
  - Evaluation of quality of individual studies (risk of bias; problems related to small sample size)
  - Summary VE results and exploration of heterogeneity
Combined US Individual Patient Level Analysis (US-IDP)

Jessie Chung, MPH
Brendan Flannery PhD
# Included studies summary—Combined US-IPD analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Study Inclusion</th>
<th>Testing</th>
<th>Current Season vaccination status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza Clinical Investigation in Children (ICICLE), MedImmune</td>
<td>3521</td>
<td>ARI with fever &lt;5 days duration</td>
<td>RT-PCR</td>
<td>EMR, immunization registries</td>
</tr>
<tr>
<td>Influenza Incidence Surveillance Project (IISP), CDC</td>
<td>1102</td>
<td>ARI with fever and cough/sore throat ≤7 days duration</td>
<td>RT-PCR</td>
<td>EMR, immunization registries</td>
</tr>
<tr>
<td>LSU Health Sciences Center (LSU)</td>
<td>3822</td>
<td>Clinical laboratory testing for influenza</td>
<td>Rapid test; RVP of negatives</td>
<td>Immunization registry</td>
</tr>
<tr>
<td>US Air Force School of Aerospace Medicine dependents (USAFSAM), US DoD</td>
<td>1935</td>
<td>ARI with fever and cough/sore throat &lt;72 hours duration</td>
<td>Culture, RT-PCR</td>
<td>Immunization registry, parent report</td>
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<tr>
<td>Flu VE Network, CDC</td>
<td>6793</td>
<td>ARI with cough ≤7 days duration</td>
<td>RT-PCR</td>
<td>EMR, immunization registries</td>
</tr>
</tbody>
</table>
Adjusted VE of LAIV4 by influenza (sub)type and age group—Combined US-IPD analysis

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**Graph: Adjusted Vaccine Effectiveness (%)**

- **Any influenza (all 3 seasons)**
  - 2–17 years: 26, 19, 28, 34
  - 2–4 years: 20, 15, 36
  - 5–8 years: 66, 71, 66, 66

- **A/H1N1pdm09 (2013–14, 2015–16)**
  - 2–17 years: 5
  - 2–4 years: 7
  - 5–8 years: 12
  - 9–17 years: 8

- **A/H3N2 (2014–15)**
  - 2–17 years: 3

- **Influenza B (all 3 seasons)**
  - 2–17 years: 66
  - 2–4 years: 71
  - 5–8 years: 66
  - 9–17 years: 66

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**Legend:**
- Diamond shapes represent adjusted vaccine effectiveness (%) for different age groups.
- The bars indicate the range of adjusted vaccine effectiveness.
Relative Effectiveness Slides—Example of Format
<table>
<thead>
<tr>
<th>Influenza (sub)type/ Age group</th>
<th>Total</th>
<th>Influenza Positive N Vaccinated (%)</th>
<th>Influenza Negative N Vaccinated (%)</th>
<th>aOR (95% CI)</th>
</tr>
</thead>
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<tr>
<td>Any influenza (all 3 seasons)</td>
<td></td>
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<tr>
<td>A/H1N1pdm09 (2013-14 and 2015-16)</td>
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</tbody>
</table>

<p>| Influenza A and B 2-17 y LAIV | 1979  | 476 (24)                           | 1503 (76)                           | 1.48 (1.28, 1.7) |
| Influenza A and B 2-17 y IV | 4579  | 727 (16)                           | 3852 (84)                           |             |
| 2-4 y LAIV                   | 625   | 121 (19)                           | 504 (81)                            | 2 (1.5, 2.67)  |
| 2-4 y IV                     | 1950  | 199 (10)                           | 1751 (90)                           |             |
| 5-8 y LAIV                   | 727   | 196 (27)                           | 531 (73)                            | 1.39 (1.11, 1.74) |
| 5-8 y IV                     | 1216  | 252 (21)                           | 964 (79)                            |             |
| 9-17 y LAIV                  | 627   | 159 (25)                           | 469 (75)                            | 1.19 (0.92, 1.56) |
| 9-17 y IV                    | 1413  | 276 (20)                           | 1137 (81)                           |             |
| A/H1N1pdm09 2-17 y LAIV      | 868   | 140 (16)                           | 728 (84)                            | 2.66 (2.06, 3.44) |
| A/H1N1pdm09 2-17 y IV        | 2397  | 156 (7)                            | 2241 (94)                           |             |
| 2-4 y LAIV                   | 283   | 43 (15)                            | 240 (85)                            | 3.12 (1.62, 6.01) |
| 2-4 y IV                     | 1057  | 61 (6)                             | 996 (94)                            |             |
| 5-8 y LAIV                   | 331   | 67 (20)                            | 264 (80)                            | 2.79 (2.09, 3.71) |
| 5-8 y IV                     | 621   | 66 (9)                             | 565 (66)                            |             |
| 9-17 y LAIV                  | 254   | 30 (12)                            | 224 (88)                            | 2.19 (1.26, 3.81) |
| 9-17 y IV                    | 719   | 39 (5)                             | 680 (95)                            |             |</p>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2-17 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAIV</td>
<td>1009</td>
<td>234 (23)</td>
<td>775 (77)</td>
<td>1.3 (1.06 ,1.58)</td>
</tr>
<tr>
<td>IV</td>
<td>1922</td>
<td>311 (16)</td>
<td>1611 (64)</td>
<td></td>
</tr>
<tr>
<td>2-4 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAIV</td>
<td>320</td>
<td>56 (18)</td>
<td>264 (83)</td>
<td>1.99 (1.49,2.64)</td>
</tr>
<tr>
<td>IV</td>
<td>822</td>
<td>67 (8)</td>
<td>755 (92)</td>
<td></td>
</tr>
<tr>
<td>5-8 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAIV</td>
<td>353</td>
<td>86 (24)</td>
<td>287 (76)</td>
<td>1.16 (0.74,1.82)</td>
</tr>
<tr>
<td>IV</td>
<td>506</td>
<td>107 (21)</td>
<td>399 (70)</td>
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<tr>
<td>9-17 y</td>
<td></td>
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<tr>
<td>LAIV</td>
<td>336</td>
<td>92 (27)</td>
<td>244 (73)</td>
<td>1.15 (0.87,1.51)</td>
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<tr>
<td>IV</td>
<td>594</td>
<td>137 (23)</td>
<td>457 (77)</td>
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<tr>
<td><strong>Influenza B</strong></td>
<td></td>
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<td></td>
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<tr>
<td>2-17 y</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>LAIV</td>
<td>1561</td>
<td>58 (4)</td>
<td>1503 (96)</td>
<td>0.72 (0.46,1.13)</td>
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<tr>
<td>IV</td>
<td>4049</td>
<td>197 (5)</td>
<td>3852 (95)</td>
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</tr>
<tr>
<td>2-4 y</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>LAIV</td>
<td>511</td>
<td>7 (1)</td>
<td>504 (99)</td>
<td>0.56 (0.21,1.53)</td>
</tr>
<tr>
<td>IV</td>
<td>1798</td>
<td>47 (3)</td>
<td>1751 (97)</td>
<td></td>
</tr>
<tr>
<td>5-8 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAIV</td>
<td>556</td>
<td>25 (5)</td>
<td>531 (96)</td>
<td>0.68 (0.42,1.11)</td>
</tr>
<tr>
<td>IV</td>
<td>1030</td>
<td>75 (7)</td>
<td>964 (93)</td>
<td></td>
</tr>
<tr>
<td>9-17 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAIV</td>
<td>494</td>
<td>26 (5)</td>
<td>468 (95)</td>
<td>0.81 (0.38,1.72)</td>
</tr>
<tr>
<td>IV</td>
<td>1212</td>
<td>75 (6)</td>
<td>1137 (94)</td>
<td></td>
</tr>
</tbody>
</table>

A/H3N2 (2014-15)

Any Influenza B (all 3 seasons)
Contributors

**ICICLE:** Herve Caspard, Christopher Ambrose, Katherine Poehling, Timothy Peters, Edward Belongia, Blaise Congeni, Manjusha Gaglani, Marie Griffin, Stephanie Irving, Poornima Kavathekar, Huong McLean, Allison Naleway, Kathleen Ryan, H Keipp Talbot

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**LSU:** Rodolfo Begue

**USAFSAM:** Susan Federinko, Laurie DeMarcus

**USFLUVE:** Brendan Flannery, Alicia Fry, Arnold Monto, Emily Martin, Edward Belongia, Huong McLean, Manjusha Gaglani, Michael Jackson, Lisa Jackson, Richard Zimmerman, Mary Patricia Nowalk
Systematic Review and Meta-analysis (SR/MA)
Systematic Review and Meta-analysis of Studies Reporting LAIV Effectiveness, 2010-11 through 2016-17

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Leslie Sokolow   Jessie Chung
Brendan Flannery  Ivo Foppa

February 21, 2018
Search Strategy

- MEDLINE, EMBASE, CINAHL, Scopus, ClinicalTrials.gov, Cochrane Register of Controlled Trials; indexed January 1, 2011-October 31, 2017
- English language
- 2010-11 through 2016-17 seasons
- Key terms:
  - influenza, influenza vaccine (or vaccination, shot, injection, spray, inoculation, mist), live attenuated influenza vaccine, LAIV, cold adapted influenza vaccine, CAIV, FluMist, case-control study, vaccine efficacy, vaccine effectiveness, relative vaccine efficacy, relative vaccine effectiveness
- Reference lists of reviewed to identify additional published studies.
- Titles/abstracts screened by ≥2 reviewers.
- Articles reviewed by ≥2 reviewers.
Study Inclusion Criteria

- Study designs:
  - Randomized controlled trials
  - Observational studies:
    - Test-negative case-control
    - Cohort
- Study population: Children 2 through 17 years of age
- Intervention: ≥1 dose of LAIV, administered intranasally
- Comparators: Unvaccinated, placebo, non-influenza vaccine, or intramuscular inactivated influenza vaccine
- Outcomes: Laboratory-confirmed (by PCR and/or culture) influenza outcomes (e.g., medically-attended outpatient influenza infection, influenza-associated hospitalizations)
Study Quality Assessment

• Randomized studies
  – Cochrane Risk of Bias Tool

• Observational Studies
  – ROBINS-I (Risk of Bias in Non-randomized Studies of Interventions; Cochrane Collaboration, Sterne JAC et al, BMJ 2016;355:i4919)
Literature Search Results

Two search periods

- January 2011—November 2016
- November 2016—October 2017

* VE reviews and meta-analyses; Analyses using same population as other abstracted studies; Interim and mid-season VE estimates; Outcome not of interest; Methodological issues; Participants outside age range of interest, Non-US LAIV products; Protocol descriptions and ClinicalTrials.gov entries with no published data

- Total = 1136
- Duplicate articles = 37
- Predated 2010-11 season = 105
- Not influenza = 297
- Non-human = 11
- Influenza but unrelated to vaccines = 82
- Influenza vaccines but unrelated to VE = 484
- VE but unrelated to LAIV = 29
- LAIV VE but unsuitable* = 71
- Non-English = 2
- Suitable = 18
Included Paper Characteristics

- 15 test-negative case-control studies (TNCC)
  - United States (9), United Kingdom (3), Canada (2), Germany (1)
- 1 prospective cohort study
  - United States (1)
- 2 cluster randomized trials
  - Canada (2)
- No individually randomized trials
- One retrospective cohort study from Finland did not meet testing modality criteria
  - included in sensitivity analysis for pooled H1N1pdm09 estimate
Study Quality—Observational Studies

- **ROBINS-I (16 papers)**
  - Low risk: 0
  - Moderate risk: 13
  - Serious risk: 3
  - Critical Risk: 0

- **Sparse data bias (45 estimates, LAIV vs. unvaccinated, 2-17 years)**
  - Low risk: 16
  - Moderate risk: 2
  - Serious risk: 21
  - Undetermined: 6

**Lack of adjustment for a potential confounding variable of interest**

Most commonly because events per variable (EPV) <10 (i.e., model adjusted for too many variables relative to number of influenza cases)
Odds of influenza A or B virus infection among children receiving LAIV compared to unvaccinated children, age 2-17 yr, by precision (n=15)

<table>
<thead>
<tr>
<th>Source</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zimmerman 2016 (2014-15)</td>
<td>0.88 [0.68; 1.14]</td>
</tr>
<tr>
<td>McLean 2015 (2012-13)</td>
<td>0.51 [0.36; 0.72]</td>
</tr>
<tr>
<td>McLean 2017 (2014-15)</td>
<td>0.50 [0.34; 0.73]</td>
</tr>
<tr>
<td>Jackson 2017 (2015-16)</td>
<td>0.95 [0.61; 1.47]</td>
</tr>
<tr>
<td>Gagliani 2016 (2013-14)</td>
<td>0.98 [0.63; 1.53]</td>
</tr>
<tr>
<td>Caspard 2016 (2013-14)</td>
<td>0.68 [0.41; 1.13]</td>
</tr>
<tr>
<td>Poehling 2017 (2015-16)</td>
<td>0.54 [0.31; 0.94]</td>
</tr>
<tr>
<td>Pebody 2016 (2015-16)</td>
<td>0.42 [0.24; 0.75]</td>
</tr>
<tr>
<td>Chung 2017 (2010-11)</td>
<td>0.43 [0.24; 0.76]</td>
</tr>
<tr>
<td>Ohmit 2014* (2011-12)</td>
<td>0.44 [0.25; 0.79]</td>
</tr>
<tr>
<td>Pebody 2015* (2014-15)</td>
<td>0.62 [0.35; 1.10]</td>
</tr>
<tr>
<td>Pebody 2017* (2016-17)</td>
<td>0.34 [0.17; 0.70]</td>
</tr>
<tr>
<td>Skowronskei 2017* (2015-16)</td>
<td>0.26 [0.10; 0.65]</td>
</tr>
<tr>
<td>Helmeke 2015 (2012-13)</td>
<td>0.16 [0.05; 0.53]</td>
</tr>
<tr>
<td>Skowronskei 2015* (2013-14)</td>
<td>0.17 [0.04; 0.75]</td>
</tr>
</tbody>
</table>

Pooled VE LAIV vs. unvaccinated: 45% (32 to 56)

Heterogeneity: $\chi^2 = 36.18$ (P < .01), $I^2 = 61\%$

Ordered by precision

*Crude estimate
Odds of influenza \( A(H1N1)pdm09 \) virus infection among children receiving LAIV compared to unvaccinated children, age 2-17 yr, by precision (n=10)

Pooled VE LAIV vs. unvaccinated 25% (6 to 40)

<table>
<thead>
<tr>
<th>Source</th>
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</tr>
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<tbody>
<tr>
<td>Caspard 2016 (2013-14)</td>
<td>0.87 [0.59; 1.27]</td>
</tr>
<tr>
<td>Gaglani 2016 (2013-14)</td>
<td>0.88 [0.52; 1.48]</td>
</tr>
<tr>
<td>Jackson 2017 (2015-16)</td>
<td>1.19 [0.67; 2.12]</td>
</tr>
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<td>Pebody 2016 (2015-16)</td>
<td>0.58 [0.32; 1.09]</td>
</tr>
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<td>Poehling 2017 (2015-16)</td>
<td>0.50 [0.25; 1.01]</td>
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<td>0.85 [0.35; 2.08]</td>
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<td>0.49 [0.17; 1.37]</td>
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<td>0.61 [0.13; 2.81]</td>
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<tr>
<td>Skowronski 2015 * (2013-14)</td>
<td>0.14 [0.02; 1.10]</td>
</tr>
</tbody>
</table>

Heterogeneity: \( \chi^2 = 10.96 \) (\( P = .28 \)), \( I^2 = 18\% \)

Ordered by descending precision of estimate
*Crude estimate
Odds of influenza A(H1N1)pdm09 virus infection among children receiving LAIV compared to unvaccinated children, age 2-17 yr, by location (n=10)

**Pooled VE**
LAIV vs. unvaccinated
US: 17% (-6 to 35)
Non-US: 48% (15 to 68)
Odds of influenza $A(H1N1)pdm09$ virus infection among children receiving LAIV compared to unvaccinated children, age 2-17 yr, by LAIV formulation (n=10)

Pooled VE:
LAIV vs. unvaccinated:
LAIV4: 24% (2 to 41)
LAIV3: 38% (-32 to 71)
Sensitivity Analysis: Inclusion of Nohynek 2016 influenza A estimate†

Odds of influenza A(H1N1)pdm09 virus infection among children receiving LAIV compared to unvaccinated children, age 2-17 yr

Without Nohynek 2016

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Heterogeneity: $\chi^2_8 = 10.96$ (P = .28), $I^2 = 18\%$

Ordered by season
*Crude estimate

Pooled VE excluding Nohynek et al
LAIV vs. unvaccinated:
25% (6 to 40)

With Nohynek 2016

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<tr>
<td>Ohmit 2016* (2013-14)</td>
<td>0.23 [0.05; 1.04]</td>
</tr>
<tr>
<td>Jackson 2017 (2015-16)</td>
<td>1.19 [0.67; 2.12]</td>
</tr>
<tr>
<td>Pebody 2016 (2015-16)</td>
<td>0.56 [0.32; 1.09]</td>
</tr>
<tr>
<td>Poehling 2017 (2015-16)</td>
<td>0.50 [0.25; 1.01]</td>
</tr>
<tr>
<td>Nohynek 2016 (2015-16)</td>
<td>0.49 [0.17; 1.37]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2_8 = 13.51$ (P = .20), $I^2 = 26\%$

Ordered by season
*Crude estimate

Pooled VE including Nohynek et al
LAIV vs. unvaccinated:
31% (13 to 46)

†Estimate for Influenza A, presumed predominantly H1N1pdm09; study population includes only 2-year-olds
Odds of influenza A(H1N1)pdm09 virus infection among children receiving LAIV compared to children receiving IIV (relative effectiveness), age 2-17 yr (n=4)

Source | OR (95% CI)
--- | ---
Chung 2017 (2010-11) n = 522 | 5.53 [1.35; 22.71]
Chung 2017 (2013-14) n = 613 | 2.65 [1.34; 5.26]
Poehling 2017 (2015-16) n = 389 | 1.71 [0.78; 3.74]
Skowronski 2017 * (2015-16) n = 47 | 3.75 [0.65; 21.74]

Heterogeneity: $\chi^2 = 2.35 (P = .50)$, $I^2 = 0$

Ordered by season

*Crude estimate

Favors LAIV Favors IIV
Odds of influenza B virus infection among children receiving LAIV compared to children receiving IIV (relative effectiveness), age 2-17 yr (n=5)

<table>
<thead>
<tr>
<th>Source</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chung 2017 (2010-11), n = 548</td>
<td>0.46 [0.15; 1.41]</td>
</tr>
<tr>
<td>Chung 2017 (2012-13), n = 694</td>
<td>0.93 [0.55; 1.57]</td>
</tr>
<tr>
<td>McLean 2017 (2014-15), n = NA</td>
<td>0.18 [0.06; 0.54]</td>
</tr>
<tr>
<td>Poehling 2017 (2015-16), n = 380</td>
<td>1.20 [0.51; 2.84]</td>
</tr>
<tr>
<td>Skowronski 2017* (2015-16), n = 53</td>
<td>0.27 [0.05; 1.40]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 10.22 (P = .04), I^2 = 61$

Ordered by season

*Crude estimate

Favors LAIV  Favors IIV
Odds of influenza A(H3N2) virus infection among children receiving LAIV compared to children receiving IIV (relative effectiveness), age 2-17 yr (n=4)

Source | OR (95% CI)
-------|----------------
Chung 2017 (2010-11), n = 534 | 1.89 [0.68; 5.24]
Chung 2017 (2011-12), n = 640 | 0.73 [0.30; 1.77]
Chung 2017 (2012-13), n = 694 | 0.77 [0.44; 1.33]
Mclean 2017 (2014-15), n = NA | 1.17 [0.73; 1.87]

Heterogeneity: $\chi^2 = 3.28$ ($P = .35$), $I^2 = 9\%$

Ordered by season

$\leftarrow$ Favors LAIV  Favors IIV $\rightarrow$
Summary points—US-IPD and SR/MA

- **LAIV vs. no vaccine for influenza A(H1N1)pdm09:**
  - Significant effectiveness for 9-17 yrs in US-IPD
  - In SR/MA, significant effectiveness only in non-US studies
    - More imprecise estimates/higher risk of bias for 3/4 of these
  - No studies with effectiveness estimates for LAIV containing A/Slovenia

- **LAIV vs. IIV for influenza A(H1N1)pdm09:**
  - IIV better for all age groups in US-IPD
  - IIV better in SR/MA

- **LAIV vs. IIV for influenza B:** Point estimate favors LAIV for both analyses, but not significantly different

- **LAIV vs. IIV for A(H3N2):** IIV better for 2-4 yrs in US-IPD; no significant difference in other age groups or in SR/MA
Limitations

For these analyses:
- B lineages not analyzed separately

LAIV4 is compared against a variety of different products (all IIVs)
- In general do not know relative proportions of IIV3 and IIV4
- Many different IIV formulations

In general:
- No US VE data available for LAIV4 since 2015-16
- VE for current LAIV4 formulation against H1N1pdm09 unknown
What is new since 2016? What is still not known?

- LAIV4 contains new H1N1pdm09-like virus (A/Slovenia) since 2017-18 (used in UK, Finland, Canada)
  - H3N2-predominant season thus far; no H1N1pdm09 VE estimates
- Recent shedding/immunogenicity data for new H1N1pdm09-like virus encouraging
  - Effectiveness of this formulation against H1N1pdm9 not known
  - Likely to remain unknown until next H1N1-predominant season (assuming adequate uptake)
  - Cannot predict when this will occur
Variability in VE estimates

- VE varies with many factors e.g.:
  - Host factors (age, health status)
  - Influenza type/subtype
  - Different seasons

- Many influenza vaccines licensed in the US (13, including LAIV)
  - Estimates of effectiveness of individual products may vary even within a given vaccine category (e.g., among different IIVs)
  - However, in many instances comparative data for different individual products are not available
  - Recommendations for other individual influenza vaccines not generally based upon comparative effectiveness data
    - Given other sources of variability in VE, might not be possible to demonstrate differences in all populations
Conclusions

- Since 2013-14, a plausible root cause of poor effectiveness of LAIV4 against H1N1pdm09 identified
- Encouraging shedding and immunogenicity evidence that problem may be addressed with new H1N1pdm09 virus
  - Caveat: whether this problem is solved will not be known until there is an effectiveness estimate against H1N1pdm09
- New LAIV vaccine virus selection processes to be applied going forward
- Combined analyses indicate LAIV4 effective compared with no vaccination against all influenza and influenza B among 2-17 year olds
  - IIV better vs. H1N1pdm09; against all influenza in some age groups
  - No clear difference in performance of LAIV vs. IIV for H3N2
  - Decision to recommend (or not) individual influenza vaccines not generally based upon effectiveness comparisons to other products
Problem, Benefits/Harms, Values, Acceptability, and Implementation
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Problem:

- Influenza is an important cause of morbidity and mortality in children.
  - Pediatric deaths ranging from 37 (2011-12) to 171 (2012-13) each non-pandemic season since 2004-05;
  - 358 deaths during 2009 pandemic period.
  - Also important cause of hospitalizations—data from *FluView Interactive*:

<table>
<thead>
<tr>
<th>Season</th>
<th>0-4 years</th>
<th>5-17 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-14</td>
<td>47.3</td>
<td>9.4</td>
</tr>
<tr>
<td>2014-15</td>
<td>57.3</td>
<td>16.6</td>
</tr>
<tr>
<td>2015-16</td>
<td>42.5</td>
<td>9.7</td>
</tr>
<tr>
<td>2016-17</td>
<td>40.8</td>
<td>15.5</td>
</tr>
</tbody>
</table>
Benefits vs. Harms:

- Benefit of the current formulation of LAIV4 against H1N1pdm09-like viruses is currently not known (no effectiveness data yet)
- Data suggest good effectiveness of LAIV4 against influenza B viruses
- Data suggest LAIV4 is comparable to IIV against H3N2
- No new safety concerns raised for LAIV4 at the time that the recommendation for its use was removed
- Potential for harm if new formulation of LAIV4 is not effective
Values: How does the target population view the balance of the benefits and risks?

- Some communications (published/unpublished letters) have expressed concern that lack of recommendation for LAIV may be detrimental in some settings (e.g., school-based clinics)
- Maintaining consumer confidence in influenza vaccines is important in the setting of low VE estimates overall
Acceptability: Risk of recommending LAIV without effectiveness data against H1N1 with the new strain

Work Group Perspectives: A plausible root cause of reduced effectiveness against H1N1pdm09 identified

- Some expressed view other factors (interference) may have contributed
- Varying viewpoints regarding promise of the shedding study data
  - Some viewed it as encouraging.
  - Others expressed concern about the size of the study and problems with using immunogenicity/shedding to gauge effectiveness of LAIV
- If issue not resolved, potentially more influenza cases.
- Understanding that influenza VE varies by season for all vaccines, and that initial licensure of some newer vaccines (e.g., some recent quadrivalents) has been based upon immunogenicity data
  - Risk similar to introduction of new influenza vaccine product
Acceptability: Risk that if LAIV is not recommended in the US during 2018-2019, it may not return to market

Work Group Perspectives: It is valued to have multiple types of influenza vaccine available

- LAIV remains a licensed product.
- Challenge of holding all manufacturers to the same standards for effectiveness of influenza vaccines
  - Effectiveness of LAIV has been examined each season
  - For most other individual influenza vaccines, recommendation is not based upon annual assessment of product-specific VE
Implementation: Has influenza vaccine coverage been impacted by not recommending LAIV?

- National vaccination coverage remained stable during the 2016-2017 influenza season
  - Local variation likely, reports of reduced coverage in areas with strong school-based programs that relied on LAIV

- National coverage did not increase, and was 2% lower in the 5-12 year-old age group
# Influenza Vaccination Coverage by Age Group, Children 6 months–17 years, NIS-Flu, United States, 2016–17 Season

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Unweighted Sample Size</th>
<th>%* ± 95% Cl†</th>
<th>Difference from the 2015–16 Season ± 95% Cl</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months–17 years</td>
<td>143,169</td>
<td>59.0 ± 0.7</td>
<td>-0.3 ± 1.1</td>
</tr>
<tr>
<td>6 months–4 years</td>
<td>44,094</td>
<td>70.0 ± 1.3</td>
<td>0.0 ± 1.9</td>
</tr>
<tr>
<td>6–23 months</td>
<td>16,374</td>
<td>76.3 ± 2.0</td>
<td>1.0 ± 2.6</td>
</tr>
<tr>
<td>2–4 years</td>
<td>27,720</td>
<td>66.2 ± 1.6</td>
<td>-0.6 ± 2.4</td>
</tr>
<tr>
<td>5–17 years</td>
<td>99,075</td>
<td>55.6 ± 0.8</td>
<td>-0.3 ± 1.2</td>
</tr>
<tr>
<td>5–12 years</td>
<td>63,130</td>
<td>59.9 ± 1.0</td>
<td>-1.9 ± 1.6‡</td>
</tr>
<tr>
<td>13–17 years</td>
<td>35,945</td>
<td>48.8 ± 1.3</td>
<td>2.0 ± 1.9‡</td>
</tr>
</tbody>
</table>

* Percentage vaccinated.
† Confidence interval half-widths.
‡ Statistically significant difference between the 2016–17 season and the 2015–16 season by t-test (P<0.05).
**Policy Question: Should LAIV be recommended for the 2018-19 season?**

<table>
<thead>
<tr>
<th>Factor</th>
<th>WG Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Problem</strong></td>
<td>• Influenza is an important source of morbidity and mortality among children.</td>
</tr>
</tbody>
</table>
| **Benefits and harms** | • Benefit of LAIV for H3N2 comparable to IIV.  
  • Data suggest good effectiveness for influenza B compared with no vaccine.  
  • Limited immunogenicity and shedding data suggest new H1N1pdm09 virus in LAIV4 may promote improved effectiveness (however, this is not yet known).  
  • No vaccine safety concerns at the time LAIV vaccine was not recommended by ACIP.  
  • Potential for harm if vaccine ineffective. |
| **Values**    | • Several papers and unpublished and published letters, indicate support for availability of a non-injectable formulation of influenza vaccine.       |
| **Acceptability** | • Varying levels of accepting risk of vaccine not being as effective against H1N1 and potential detriment to confidence in influenza vaccines.          |
| **Implementation** | • While national coverage appears not to have been impacted by lack of LAIV recommendation, LAIV is an important option for school-based clinics and may contribute to efforts to increase vaccination coverage. |
| **Summary**   | • There was not complete agreement on the WG.  
  • Most felt the issue should be discussed at ACIP.  
  • A recommendation would need to acknowledge lack of effectiveness data for current LAIV4 against H1N1pdm09 like viruses. |