Review of Effectiveness of Live Attenuated Influenza Vaccine

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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

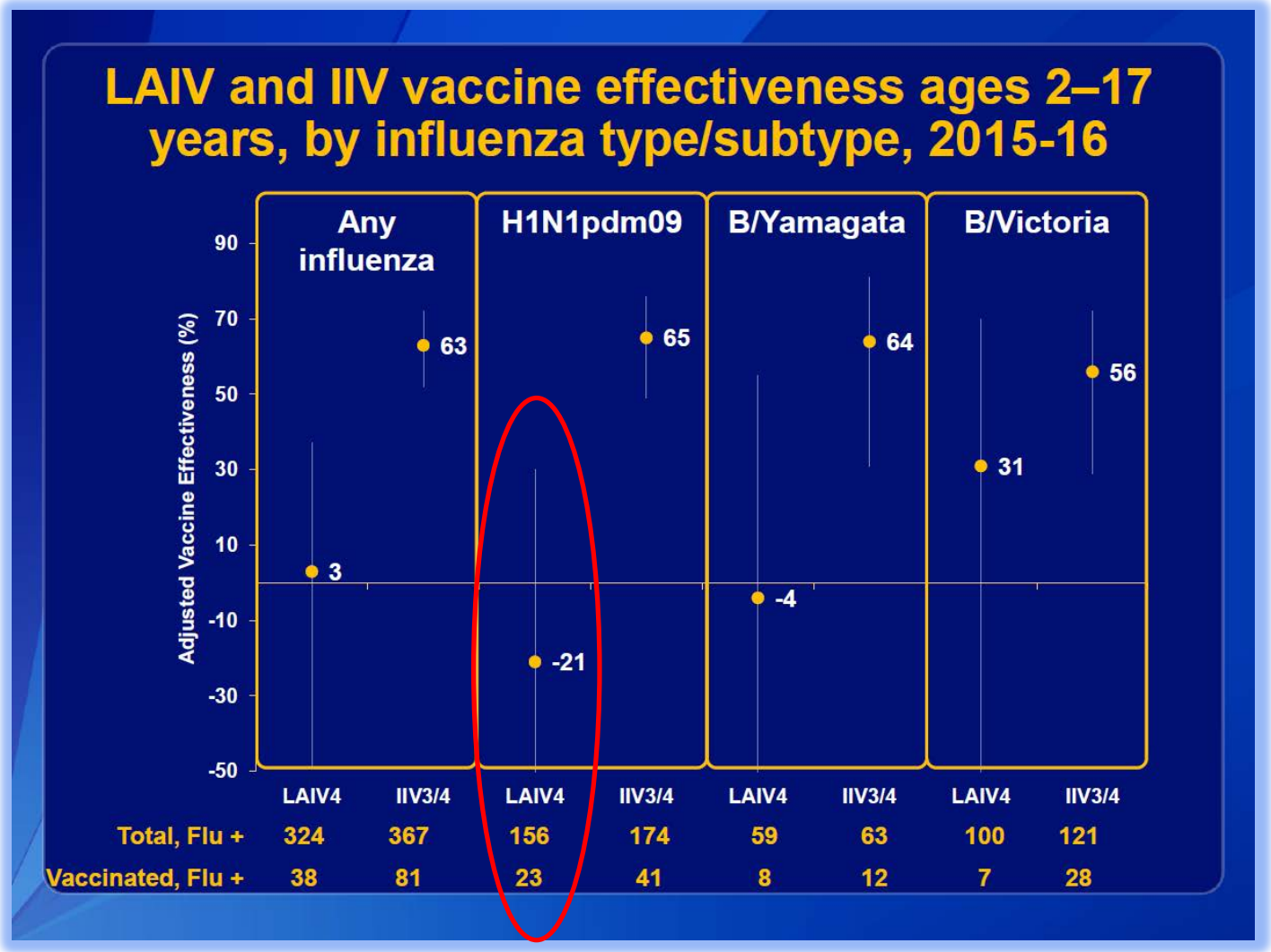
Background

LAIV 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

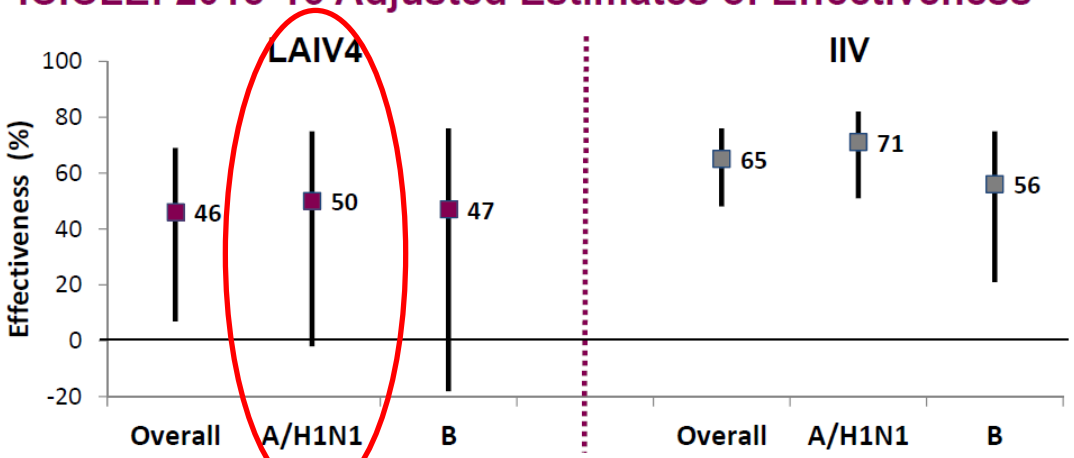


U.S. Flu VE Network

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

6

MedImmune ICICLE Study

2015-16 U.S. Season

Presented at ACIP, June 2016

Variability in LAIV Effectiveness Estimates—Observations From Data Presented in June, 2016

- 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)

Individual patient-level data meta-analysis of LAIV and IIV effectiveness among US children aged 2–17 years, 2013–14 through 2015–16 influenza seasons

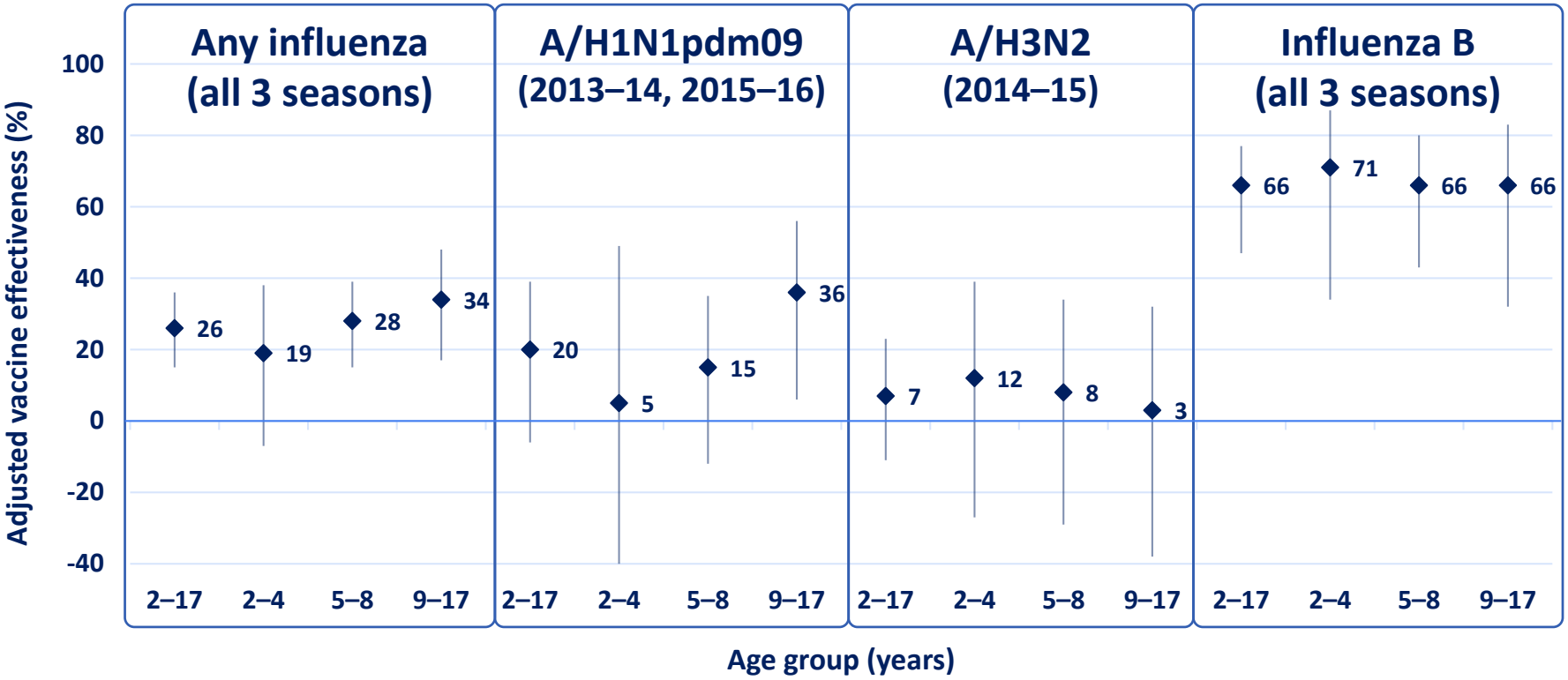
Jessie Chung, MPH

Brendan Flannery PhD

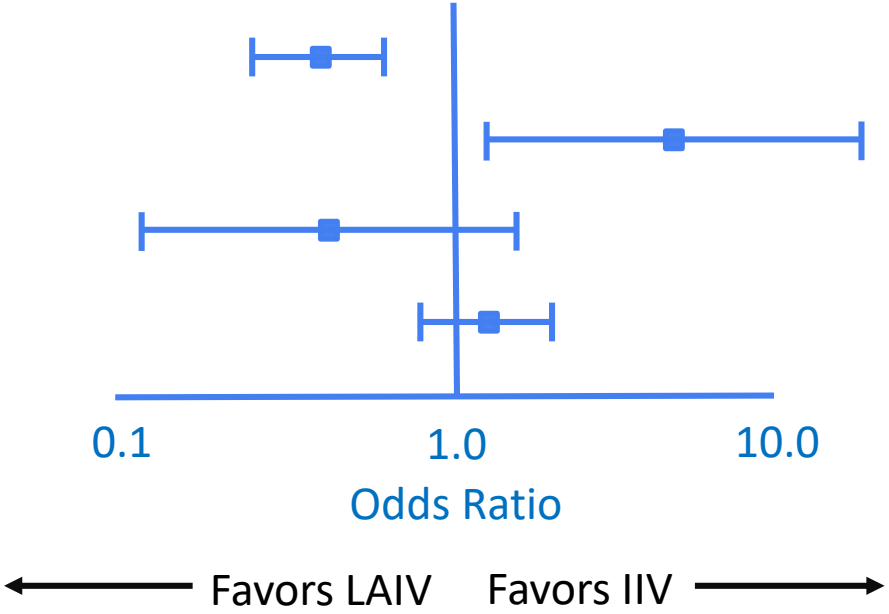
Included studies summary—Combined US-IPD analysis

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

Adjusted VE of LAIV4 by influenza (sub)type and age group—Combined US-IPD analysis



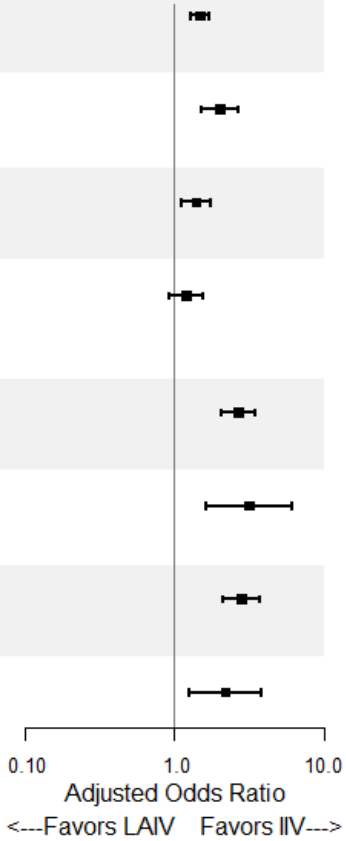
Relative Effectiveness Slides—Example of Format



Any influenza (all 3 seasons)

A/H1N1pdm09 (2013-14 and 2015-16)

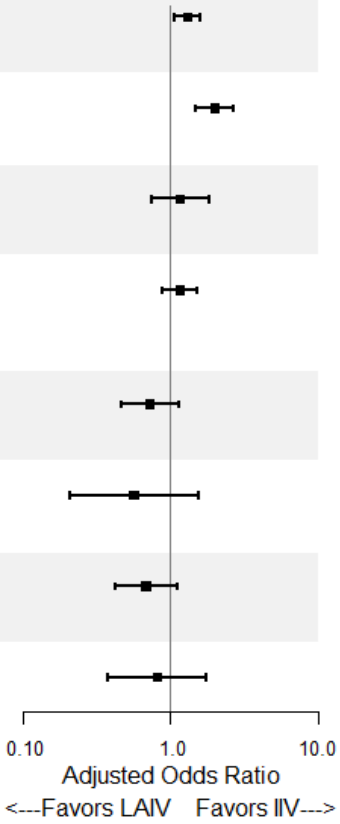
Influenza (sub)type/ Age group	Total	Influenza Positive N Vaccinated (%)	Influenza Negative N Vaccinated (%)	aOR (95% CI)
Influenza A and B				
2-17 y				
LAIV	1979	476 (24)	1503 (76)	1.48 (1.28 ,1.7)
IIV	4579	727 (16)	3852 (84)	
2-4 y				
LAIV	625	121 (19)	504 (81)	2 (1.5 ,2.67)
IIV	1950	199 (10)	1751 (90)	
5-8 y				
LAIV	727	196 (27)	531 (73)	1.39 (1.11 ,1.74)
IIV	1216	252 (21)	964 (79)	
9-17 y				
LAIV	627	159 (25)	468 (75)	1.19 (0.92 ,1.56)
IIV	1413	276 (20)	1137 (81)	
A/H1N1pdm09				
2-17 y				
LAIV	868	140 (16)	728 (84)	2.66 (2.06 ,3.44)
IIV	2397	156 (7)	2241 (94)	
2-4 y				
LAIV	283	43 (15)	240 (85)	3.12 (1.62 ,6.01)
IIV	1057	61 (6)	996 (94)	
5-8 y				
LAIV	331	67 (20)	264 (80)	2.79 (2.09 ,3.71)
IIV	621	56 (9)	565 (68)	
9-17 y				
LAIV	254	30 (12)	224 (88)	2.19 (1.26 ,3.81)
IIV	719	39 (5)	680 (95)	



A/H3N2 (2014-15)

Any Influenza B (all 3 seasons)

Influenza (sub)type/ Age group	Total	Influenza Positive N Vaccinated (%)	Influenza Negative N Vaccinated (%)	aOR (95% CI)
Influenza A/H3N2				
2-17 y				
LAIV	1009	234 (23)	775 (77)	1.3 (1.06 ,1.58)
IIV	1922	311 (16)	1611 (84)	
2-4 y				
LAIV	320	56 (18)	264 (83)	1.99 (1.49 ,2.64)
IIV	822	67 (8)	755 (92)	
5-8 y				
LAIV	353	86 (24)	267 (76)	1.16 (0.74 ,1.82)
IIV	506	107 (21)	399 (79)	
9-17 y				
LAIV	336	92 (27)	244 (73)	1.15 (0.87 ,1.51)
IIV	594	137 (23)	457 (77)	
Influenza B				
2-17 y				
LAIV	1561	58 (4)	1503 (96)	0.72 (0.46 ,1.13)
IIV	4049	197 (5)	3852 (95)	
2-4 y				
LAIV	511	7 (1)	504 (99)	0.56 (0.21 ,1.53)
IIV	1798	47 (3)	1751 (97)	
5-8 y				
LAIV	556	25 (5)	531 (96)	0.68 (0.42 ,1.11)
IIV	1039	75 (7)	964 (93)	
9-17 y				
LAIV	494	26 (5)	468 (95)	0.81 (0.38 ,1.72)
IIV	1212	75 (6)	1137 (94)	



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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)

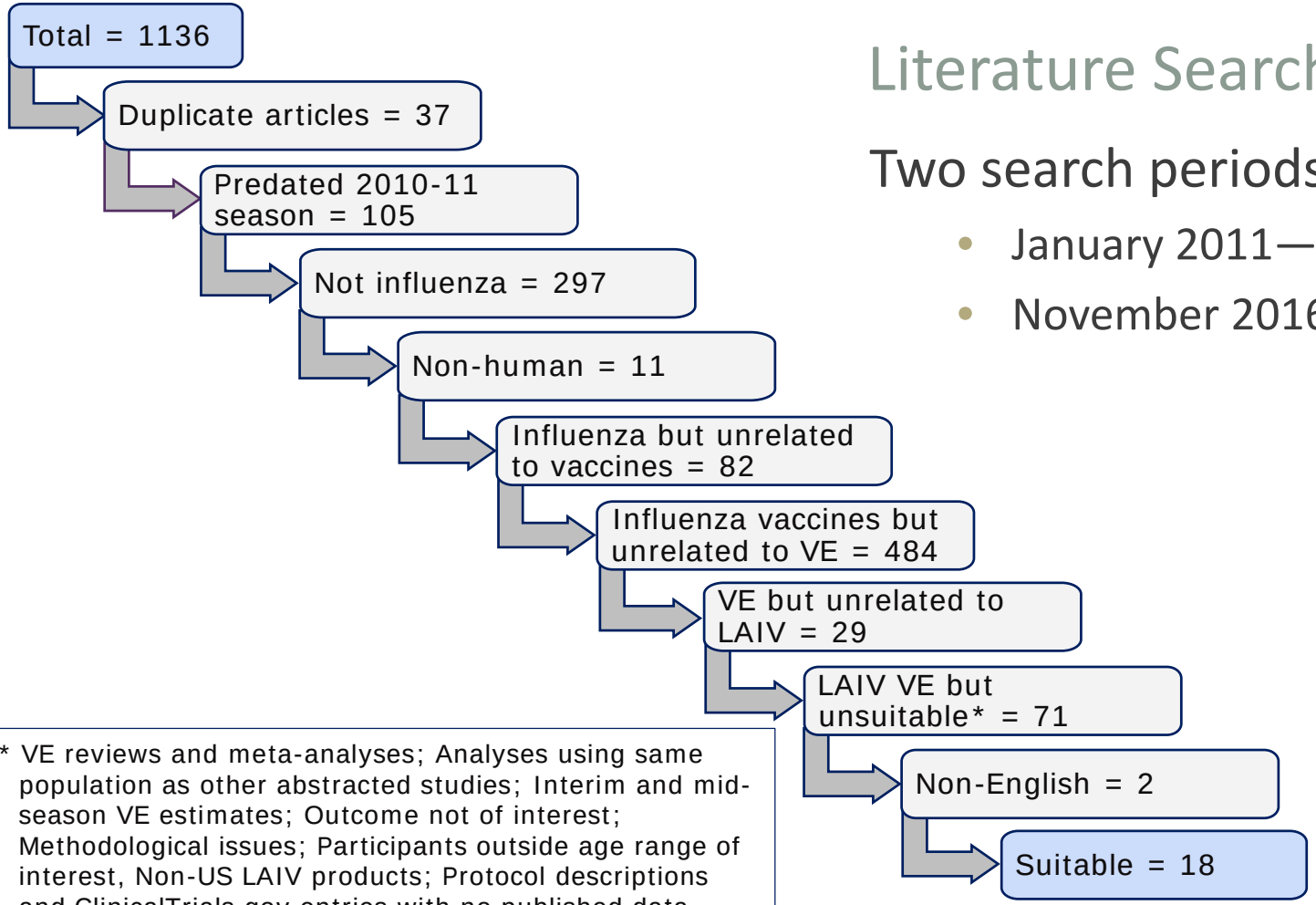
Study Quality Assessment

- 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)
  - Sparse Data Bias (Adapted from Greenland S, et al, BMJ. 2016 Apr 27;352:i1981)

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

Included Paper Characteristics

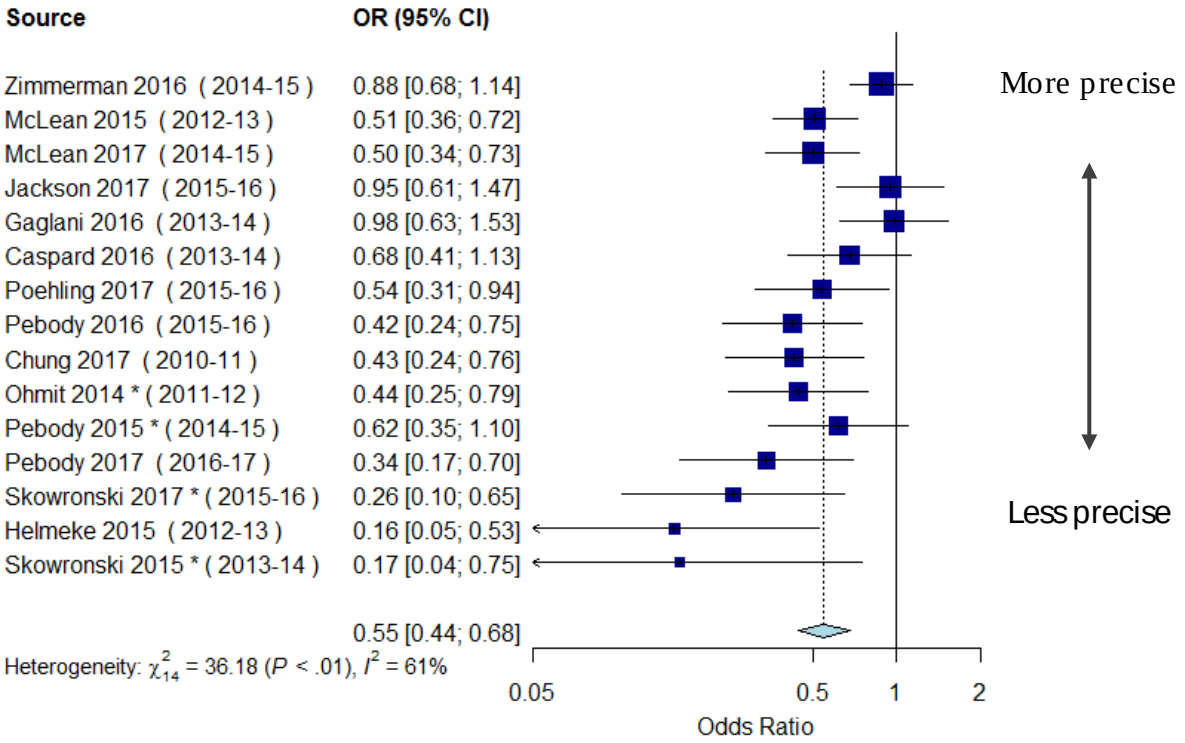
- 15 test-negative case-control studies (TNCC)
  - United States (9), United Kingdom (3), Canada (2), Germany (1)
- 1 prospective cohort study
  - United States (1)
- 2 cluster randomized trials
  - Canada (2)
- No individually randomized trials
- One retrospective cohort study from Finland did not meet 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 → Lack of adjustment for a potential confounding variable of interest
  - Critical Risk 0
- Sparse data bias (45 estimates, LAIV vs. unvaccinated, 2-17 years)
  - Low risk 16
  - Moderate risk 2
  - Serious risk 21 → Most commonly because events per variable (EPV) <10 (i.e., model adjusted for too many variables relative to number of influenza cases)
  - Undetermined 6

Odds of influenza A or B virus infection among children receiving LAIV compared to unvaccinated children, age 2-17 yr, by precision (n=15)

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



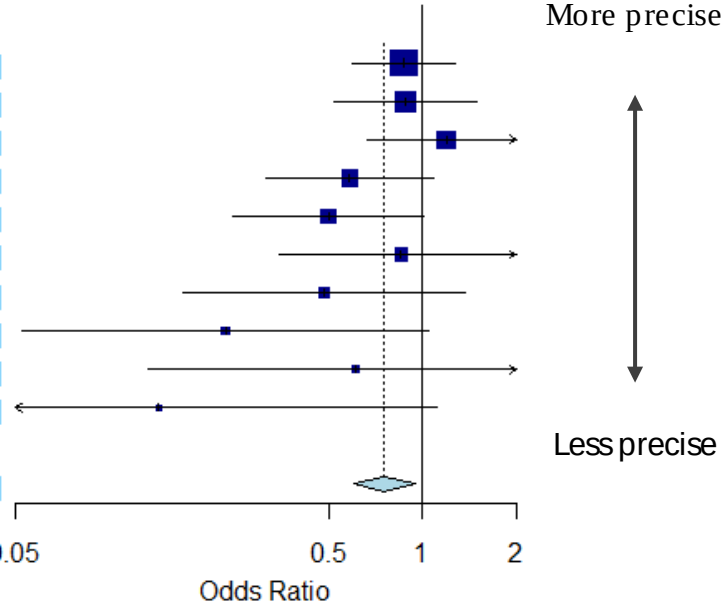
Ordered by precision
*Crude estimate

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)

Source	OR (95% CI)
Caspard 2016 (2013-14)	0.87 [0.59; 1.27]
Gaglani 2016 (2013-14)	0.88 [0.52; 1.48]
Jackson 2017 (2015-16)	1.19 [0.67; 2.12]
Pebody 2016 (2015-16)	0.58 [0.32; 1.09]
Poehling 2017 (2015-16)	0.50 [0.25; 1.01]
Chung 2017 (2010-11)	0.85 [0.35; 2.08]
Skowronski 2017 * (2015-16)	0.49 [0.17; 1.37]
Ohmit 2016 * (2013-14)	0.23 [0.05; 1.04]
Helmeke 2015 (2012-13)	0.61 [0.13; 2.81]
Skowronski 2015 * (2013-14)	0.14 [0.02; 1.10]
	0.75 [0.60; 0.94]

Heterogeneity: $\chi^2_9 = 10.96$ ($P = .28$), $I^2 = 18\%$

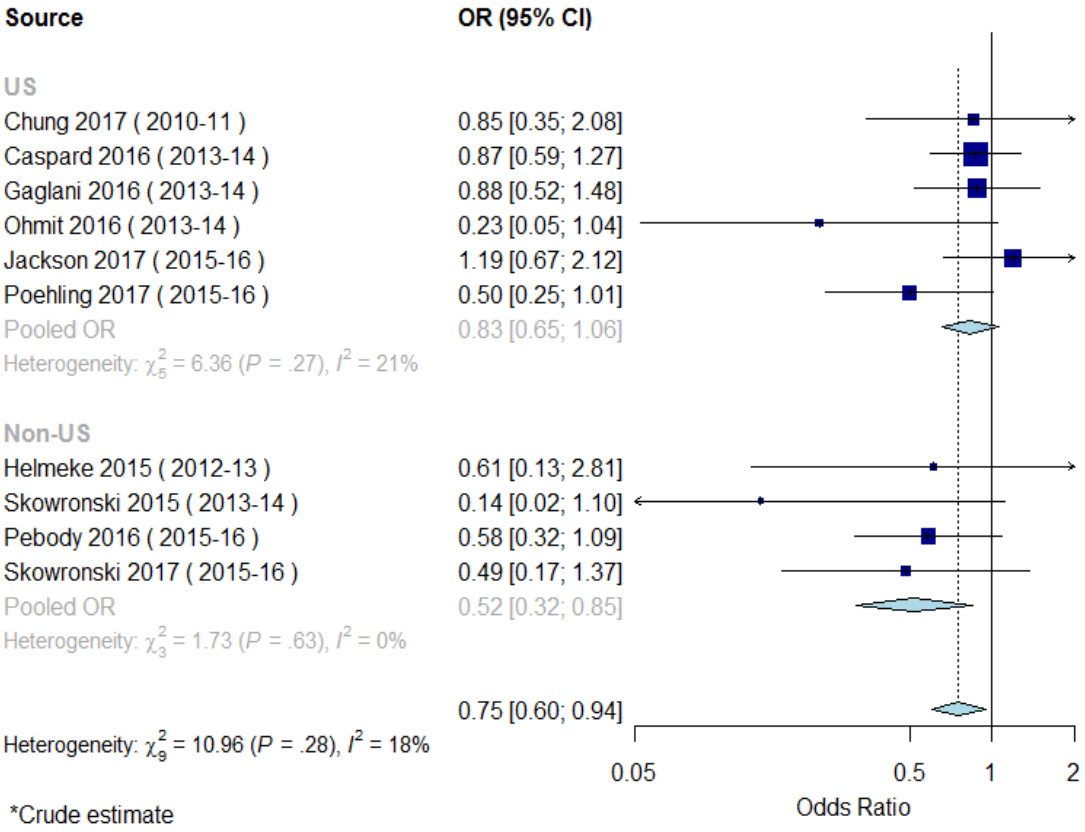


Ordered by descending precision of estimate

*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)

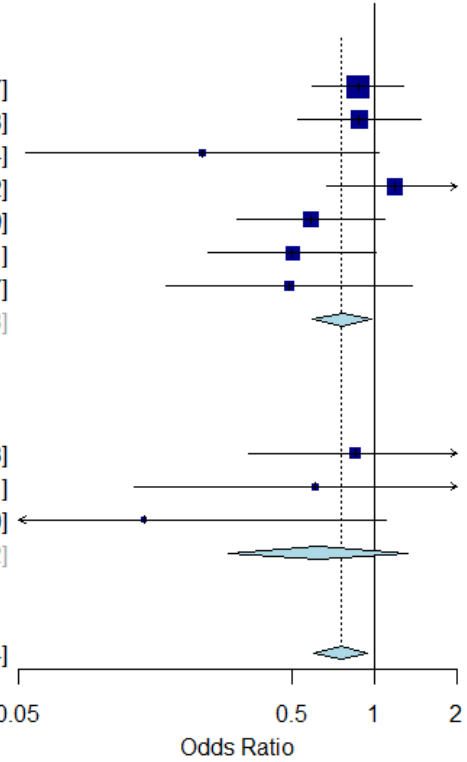


*Crude estimate

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)

Source	OR (95% CI)
Quadrivalent	
Caspard 2016 (2013-14)	0.87 [0.59; 1.27]
Gaglani 2016 (2013-14)	0.88 [0.52; 1.48]
Ohmit 2016 (2013-14)	0.23 [0.05; 1.04]
Jackson 2017 (2015-16)	1.19 [0.67; 2.12]
Pebody 2016 (2015-16)	0.58 [0.32; 1.09]
Poehling 2017 (2015-16)	0.50 [0.25; 1.01]
Skowronski 2017 (2015-16)	0.49 [0.17; 1.37]
Pooled OR	0.76 [0.59; 0.98]
Heterogeneity: $\chi^2_6 = 8.24$ ($P = .22$), $I^2 = 27\%$	
Trivalent	
Chung 2017 (2010-11)	0.85 [0.35; 2.08]
Helmeke 2015 (2012-13)	0.61 [0.13; 2.81]
Skowronski 2015 (2013-14)	0.14 [0.02; 1.10]
Pooled OR	0.62 [0.29; 1.32]
Heterogeneity: $\chi^2_2 = 2.45$ ($P = .29$), $I^2 = 18\%$	
	0.75 [0.60; 0.94]
Heterogeneity: $\chi^2_9 = 10.96$ ($P = .28$), $I^2 = 18\%$	

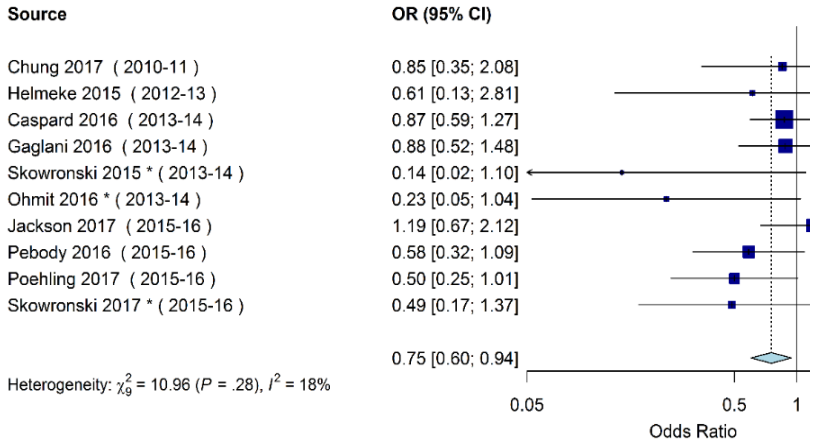


*Crude estimate

Sensitivity Analysis: Inclusion of *Nohynek 2016* influenza A estimate†

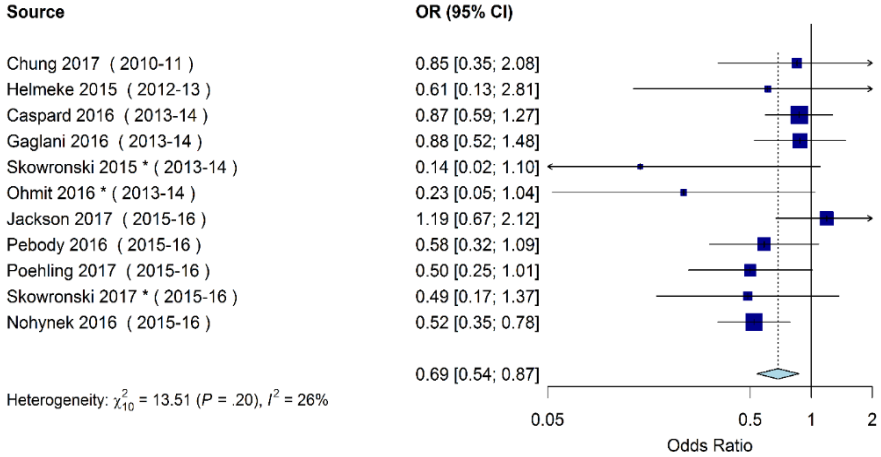
Odds of influenza A(H1N1)pdm09 virus infection among children receiving LAIV compared to unvaccinated children, age 2-17 yr

Without Nohynek 2016



Ordered by season
*Crude estimate

With Nohynek 2016



Ordered by season
*Crude estimate

Pooled VE <u>excluding</u> *Nohynek et al*
LAIV vs. unvaccinated:
25% (6 to 40)

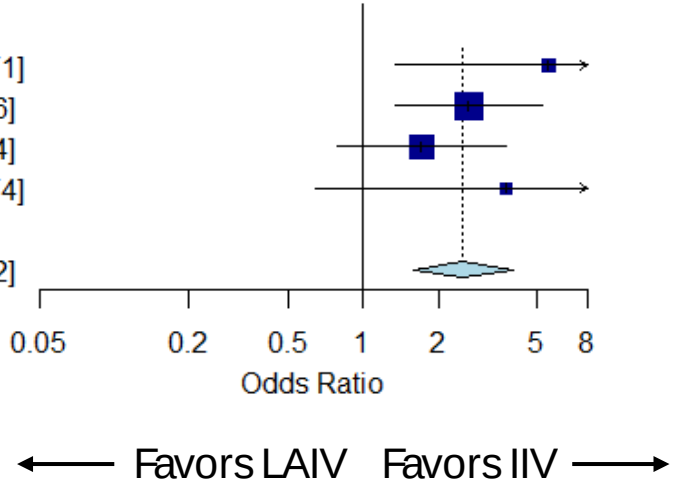
Pooled VE <u>including</u> *Nohynek et al*
LAIV vs. unvaccinated:
31% (13 to 46)

†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]
	2.52 [1.58; 4.02]

Heterogeneity: $\chi^2_3 = 2.35$ ($P = .50$), $I^2 = 0\%$



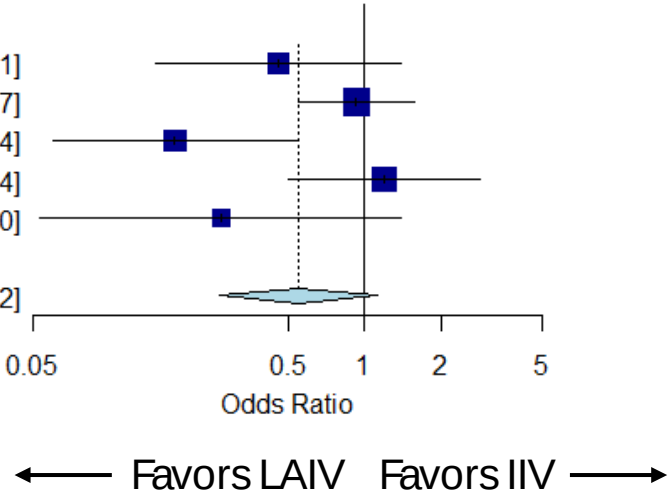
Ordered by season

*Crude estimate

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

Source	OR (95% CI)
Chung 2017 (2010-11), n = 548	0.46 [0.15; 1.41]
Chung 2017 (2012-13), n = 694	0.93 [0.55; 1.57]
McLean 2017 (2014-15), n = NA	0.18 [0.06; 0.54]
Poehling 2017 (2015-16), n = 380	1.20 [0.51; 2.84]
Skowronski 2017 * (2015-16), n = 53	0.27 [0.05; 1.40]
	0.55 [0.27; 1.12]

Heterogeneity: $\chi^2_4 = 10.22$ ($P = .04$), $I^2 = 61\%$



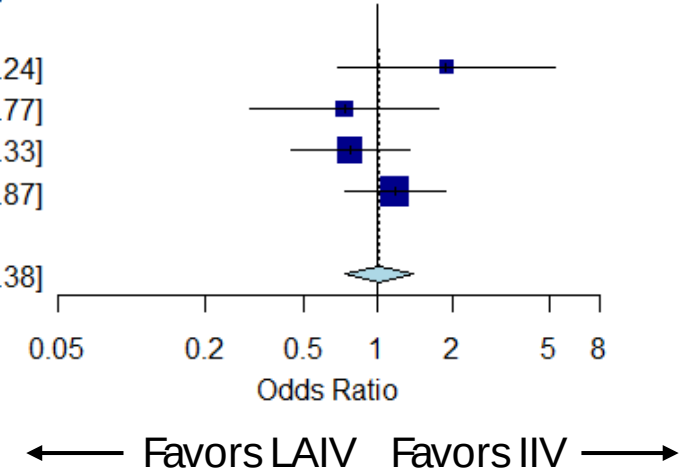
Ordered by season

*Crude estimate

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]
	1.01 [0.73; 1.38]

Heterogeneity: $\chi^2_3 = 3.28$ ($P = .35$), $I^2 = 9\%$



Ordered by season

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:*

	Hospitalizations/100,000 persons-years	
Season	**0-4 years**	**5-17 years**
2013-14	47.3	9.4
2014-15	57.3	16.6
2015-16	42.5	9.7
2016-17	40.8	15.5

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

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

* 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?

Factor	WG Interpretation
Problem	• Influenza is an important source of morbidity and mortality among children.
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.