Influenza Vaccines for Healthy Children aged 2 through 8 Years—Review of Comparative Studies of Live Attenuated Influenza Vaccine (LAIV) and Inactivated Influenza Vaccine (IIV)

METHODS

Background: An adaptation of Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methods [1] was used to evaluate relative benefits and harms of live attenuated influenza vaccine (LAIV) and inactivated influenza vaccine (IIV) for healthy children aged 2 through 8 years. As of the 2013-14 influenza season, the Advisory Committee on Immunization Practices (ACIP) recommendations stated that healthy children in this age group may receive either vaccine, with no preferential recommendation for one over the other. Outcome values and evidence of benefits and harms were reviewed in accordance with GRADE methods as adopted by the ACIP [1]. The primary policy question was "**Should LAIV be recommended preferentially over IIV for healthy children aged 2 through 8 years**?"

While several individual studies noted greater relative efficacy of LAIV relative to TIV among children [2-4], most studies conducted among adults have generally noted either similar efficacy or greater relative efficacy of IIV [5-11]. Because it is unclear at what age the greater relative efficacy of LAIV begins to decline, and given considerations to the feasibility of implementation of a potential change in program, this assessment focused on younger children. The rationale for the selected age range included the following considerations: 1) LAIV is not licensed in the U.S. for children under 2 years of age [12], and 2) 8 years is the current upper age limit for consideration of whether a child needs one or two doses of influenza vaccine [13], and was selected for programmatic consistency.

Identification and valuation of outcome measures: Efficacy and safety outcomes were discussed within the ACIP Influenza Work Group. Outcomes valued as "critical" or "important" [1] to policy decisions are summarized in Table 1. One initially selected outcome, "medically attended wheezing", was replaced with "medically significant wheezing" after literature review revealed data were available for this similar outcome. Three initially selected safety outcomes "febrile seizure", "immediate hypersensitivity/anaphylaxis", and "Guillain-Barré syndrome" were noted to be sufficiently rare that it would not be possible to draw meaningful comparisons between the two vaccines. As a proxy outcome intended to enumerate very rare but severe events, these outcomes were replaced with "any related serious adverse event (SAE)". Two additional outcomes, "respiratory symptoms" and "other neurologic outcomes" were not sufficiently specific to permit data collection.

Evidence retrieval: Prior to literature retrieval, study inclusion/exclusion criteria were defined. Included studies pertained to healthy children (i.e., did not specifically seek to enroll children with medical conditions conferring higher risk of complications due to influenza), evaluated

vaccines that were U.S.-licensed or were similar to U.S.-licensed products, and included both LAIV and IIV arms (so as to permit comparison within the same population and influenza season). Excluded studies included those assessing vaccines dissimilar from U.S.-licensed products (e.g., virosomal, whole-virus, and adjuvanted vaccines and Russian-manufactured LAIV), those exclusively of monovalent influenza A(H1N1)pdm 2009 vaccines, those for which inactivated vaccine antigen content was characterized in units other than micrograms of hemagglutinin (HA), those for which all participants were outside the indicated age range for either vaccine, and those for which outcomes were based upon ICD-9 codes (without clinical or laboratory evaluation). For efficacy outcomes, a total of five randomized trials [2-4, 14, 15] and six observational studies [16-21] were identified. Among the five randomized trials, three were excluded from the analysis: one in which not all influenza cases were laboratory confirmed [14], one of children 1 through 15 years of age for which age-stratified data were not available [15], and one of children 6 through 17 years of age for which-age stratified data were not available and for which having a diagnosis of asthma was an inclusion criterion [3]. Among the six observational studies, one study of children 5 through 18 years of age for which age stratified data were not available for the outcome of interest was excluded [21]. The efficacy assessment thus included two randomized trials [2, 4] and five observational studies [16-20]. For safety outcomes, observational studies were not included in GRADE analyses because of concerns that differences in the health status of the populations receiving LAIV and IIV might affect safety endpoints. Of the 5 randomized trials identified during the efficacy outcome search, 2 included safety outcomes in the appropriate age group [2, 4].

Evidence assessment: Quality of available evidence was graded in terms of risk of bias, indirectness, imprecision, and inconsistency and was assessed as “High”, “Moderate”, “Low”, of “Very Low” for each outcome [1]. For randomized studies, when summarizing results for outcomes in which denominators reported individual participants, pooled weighted risk ratios were calculated using a random-effects model. For outcomes for which the denominator was expressed as person-time, risk ratios were calculated using the inverse variance method. For observational studies, odds ratios (ORs) were transformed by taking the natural logarithm and pooling log(OR)s and standard errors using the inverse variance method.

RESULTS

Assessment of Benefits and Harms

Table 1: Outcomes valued as "Critical" or "Important" to policymaking by the ACIP Influenza Work Group

Outcome	Importance	Data Available
Benefits (Efficacy)		
Laboratory-confirmed influenza	Critical	Yes
Influenza-associated mortality	Critical	No
Influenza-associated hospitalization	Critical	Yes
Medically attended acute respiratory illness	Critical	Yes
Influenza-like illness	Important	No
Influenza-associated acute otitis media	Important	Yes
Harms (Safety)		
Medically significant wheezing[1]	Critical	Yes
Immediate hypersensitivity/anaphylaxis[2]	Critical	No
Febrile seizure[2]	Critical	No
Guillain-Barre syndrome[2]	Critical	No
Respiratory symptoms[4]	Important	--
Other neurologic outcomes[4]	Important	--
Fever	Important	Yes
Any related SAE[3]	--	Yes

[1]Replaced medically attended wheezing.
[2]Rare events; insufficient frequency to permit comparison.
[3]Added as a means to potentially capture rare but serious events.
[4]Not sufficiently specific to permit assessment.

Table 2: Characteristics of included studies

Studies	Design	Number of participants	Age group evaluated	Efficacy/ Effectiveness	Safety
Ashkenazi, 2006 [2]	Randomized, open-label	2187	6 through 71 months[1] (1609 aged ≥2 years)	X	X
Belshe, 2007 [4]	Randomized, blinded, placebo-controlled	8352	6 through 59 months[1] (4166 aged ≥2 years)	X	X
Treanor, 2012 [16]	Observational, Test-negative case-control	49	2 through 8 years[2]	X	
Ohmit, 2013 [17]	Observational, Test-negative case-control	358	2 through 8 years[2]	X	
Fry, 2013 [18]	Observational, Test-negative case-control	559	2 through 8 years[2]	X	
Macintosh, 2013 [19]	Observational, Test-negative case-control	66	2 through 8 years[2]	X	
Eick-Cost, 2013 [20]	Observational, Test-negative case-control	195	2 through 8 years[2]	X	

[1]Data available for children aged 24 through 71 months for one outcome, laboratory-confirmed influenza, from a post-hoc meta-analysis of data from these two studies [22].
[2]Authors provided data specific to this age group

Table 3: LAIV vs. IIV for healthy children aged 2-8 years: Benefits—Randomized studies

Outcome (Studies, n) Value	Risk of Bias	Inconsistency	Indirectness	Imprecision	Outcome events		Effect		Quality
					With LAIV	With IIV	RR [95% CI]	Risk Difference per 1000 with LAIV	
Laboratory-confirmed influenza (2) Critical	Not serious[1]	Not serious	Not serious	Not serious	182/4966	398/4971	0.46 [0.39-0.54]	43 fewer [37-49 fewer]	1 High
Laboratory-confirmed influenza--24-71 month olds[2] (2) Critical	Not serious[1]	Not serious	Not serious	Not serious	117/2873	251/2902	0.47 [0.38-0.58]	46 fewer [36-54 fewer]	1 High
Influenza-associated hospitalization (1) Critical	Not serious[1]	Not serious	Serious[3]	Serious[4]	12/1048	11/1034	1.08 [0.48-2.43]	1 more [6 fewer-15 more]	3 Low
Influenza-associated acute otitis media (2) Important	Not serious[1]	Not serious	Not serious	Not serious	28/4964	60/4970	0.47 [0.30-0.73]	6 fewer [3-8 fewer]	1 High
Outcome (Studies, n) Value	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Outcome events**		**Effect**		Quality
					With LAIV[5]	**With IIV**	**Adj. OR [95% CI]**		
MAARI (1) Critical	Not serious[1]	Not serious	Serious	Not serious	878/72476	949/71337	0.91 [0.77-1.08]		2 Moderate

ABBREVIATIONS: adj. OR, adjusted odds ratio; CI, confidence interval; MAARI, Medically attended acute respiratory illness.

[1] One trial was open-label [2].

[2] Meta-analysis including these two trials contained data restricted to those children aged 2 years and older.

[3] Hospitalizations were for influenza-like respiratory illness that prompted culture, rather than laboratory-confirmed influenza

[4] Wide confidence interval; includes 1.0 and exceeds 0.75 in lower bound and 1.25 in upper bound.

[5] Denominator was surveillance-days

Table 4: LAIV vs. IIV for healthy children aged 2-8 years: Benefits—Observational studies

Outcome (Studies, n) Value	Risk of Bias	Inconsistency	Indirectness	Imprecision	Outcome events		Effect	Quality
					With LAIV	With IIV	Adj. OR [95% CI]	
Laboratory-confirmed influenza[1] (5) Critical	Not serious	Not serious	Not serious	Serious[2]	83/288	257/939	0.74 [0.50-1.08]	4 [Very Low]

[1]Authors provided data for subgroup of children aged 2 through 8 years.
[2]Wide confidence interval includes 1.0 and exceeds 0.75 in lower bound.

Table 5: LAIV vs. IIV for healthy children aged 2-8 years: Harms—Randomized studies

Outcome (Studies, n) Value	Risk of Bias	Inconsistency	Indirectness	Imprecision	Outcome events		Effect		Quality
					With LAIV	With IIV	RR [95% CI]	Risk Difference per 1000 with LAIV	
Medically significant wheezing, 42 days--Following dose 1, vaccine-naïve[1] (1) Critical	Not serious	Not serious	Not serious	Serious[2]	19/1521	14/1520	1.36 [0.68-2.69]	3 more [3 fewer-16 more]	2 Moderate
Medically significant wheezing, 42 days--Following dose 1, previously vaccinated[1] (1) Critical	Not serious	Not serious	Not serious	Serious[2]	12/666	14/678	0.87 [0.41-1.87]	3 fewer [12 fewer-18 more]	2 Moderate
Medically significant wheezing, 42 days—Following dose 2, not previously vaccinated[1] (1) Critical	Not serious	Not serious	Not serious	Serious[3]	16/1424	28/1439	0.58 [0.31-1.06]	8 fewer [13 fewer-1 more]	2 Moderate
Fever, days 0-10-- ≥38.6°C or ≥38.9°C[4] (2) Critical	Not Serious[5]	Not serious	Not serious	Serious[3]	189/5095	211/5068	0.89 [0.73-1.08]	5 fewer [11 fewer-3 more]	2 Moderate
Any related serious adverse event (SAE) (2) (Not valued)	Not Serious[5]	Not serious	Not serious	Serious[2]	8/5280	9/5289	0.90 [0.34-2.37]	0 fewer [1 fewer-2 more]	2 Moderate

[1]Data limited to children aged 24 through 59 months.
[2]Wide confidence interval; includes 1.0 and exceeds 0.75 in lower bound and 1.25 in upper bound.
[3]Wide confidence interval; includes 1.0 and exceeds 0.75 in lower bound.
[4]Fever reported differently in the two studies.
[5]One trial was open-label.

Table 6: Evidence summary.

Focus	Outcome (Importance)	Design (n)	Findings (difference between LAIV and IIV)	Evidence Quality by Outcome	Overall Evidence Quality
Benefits	Laboratory-confirmed influenza CRITICAL	RCT (2)	Lower risk with LAIV	1 (High)	2 (Moderate)[1]
		OBS (5)	No difference	4 (Very low)	
	Influenza-associated hospitalization CRITICAL	RCT (1)	No difference	3 (Low)	
	Medically attended acute respiratory illness CRITICAL	RCT (1)	No difference	2 (Moderate)	
	Acute otitis media IMPORTANT	RCT (2)	Lower risk with LAIV	1 (High)	
Harms	Medically significant wheezing CRITICAL	RCT (1)	No difference	2 (Moderate)	2 (Moderate)
	Fever IMPORTANT	RCT (2)	No difference	1 (High)	
	Any related severe adverse event IMPORTANT	RCT (2)	No difference	2 (Moderate)	

[1]For Benefits, quality is taken to be "moderate" rather than "low" because available hospitalization data was downgraded for indirectness (respiratory illness-associated hospitalizations rather than influenza-associated hospitalizations), and because data were available for two other critical outcomes.

Cost considerations:

A formal cost analysis was not performed. Such analysis would be complex given the current spectrum of available influenza vaccine products available in the United States, and their widely variable costs. As of 2013-14, LAIV is available in the U.S. only as a quadrivalent vaccine, while IIV is available in both quadrivalent and trivalent formulations of highly differing cost. A cost effectiveness model compared LAIV3 and IIV3 for younger children and estimated a cost savings of USD$45.80 for each child vaccinated with LAIV as compared with IIV [23]. It is unclear how applicable such an analysis is at present, given the recent availability of quadrivalent vaccines. Private sector process listed in the 2014-15 Vaccines for Children (VFC) price list for trivalent IIVs range from $7.65 to $14.81/dose; those for quadrivalent IIV from $14.90 to $21.09/dose. The most highly priced quadrivalent IIV4 is similar in cost to LAIV at $22.70 per dose (available at: http://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/index.html**).**

Table 7: Considerations for Formulating Recommendations

Key factor	Comments
Evidence type for benefits and harms	• Overall evidence quality 2 (MODERATE) for efficacy and safety. • Evidence lacking for some critical outcomes, such as influenza-associated mortality, febrile seizure, Guillain-Barré syndrome, immediate hypersensitivity • Available studies not powered to detect rare but serious events
Balance between benefits and harms	• Benefits outweigh harms • Modestly better efficacy of LAIV (~46 fewer cases of laboratory-confirmed influenza per 1000) • No significant differences in rates of wheezing or fever
Value	• ACIP Influenza Work Group placed high value on prevention of laboratory-confirmed influenza
Cost-effectiveness	• Uncertainty regarding cost benefit given current available range of vaccines

LIMITATIONS

- All data reviewed pertain to trivalent influenza vaccines. As of the 2013-14 season, all LAIV available in the United States is quadrivalent, and IIV is available in both trivalent and quadrivalent formulations. Quadrivalent vaccines met criteria for immunogenic non-inferiority compared to trivalent vaccines prior to licensure, and pre-licensure studies demonstrated similar safety profiles.
- It is as yet unknown whether greater relative efficacy is sustained with repeated vaccination/increasing age. Comparative studies of LAIV and IIV in adults generally have noted either that the two vaccines are similar in efficacy, or that IIV is somewhat more effective. The age or degree of previous seasonal vaccine exposure at which relative benefits of LAIV decline, or are no longer apparent, is not known. Available RCT data include children under 2 years of age; data excluding these children was only available for one outcome (laboratory-confirmed influenza). Moreover, available RCT data does not include children over 71 months of age. While the age or degree of previous seasonal vaccine exposure at which relative benefits of LAIV begins to decline is unknown, one additional comparative RCT of older children (aged 6 through 17 years) with asthma has also noted greater relative efficacy of LAIV [3].

Given these limitations, ongoing evaluation of the relative efficacy of current formulations of LAIV and IIV will be important.

SUMMARY

Benefits outweigh harms. High value was placed on the prevention of laboratory-confirmed influenza. The Work Group recommended that when LAIV is available, it should be used for children aged 2 through 8 years (Category A).

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