Effectiveness of Live-Attenuated vs. Inactivated Influenza Vaccines for Healthy Children (GRADE)

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Background (1)

Healthy children aged 2 through 17 years may receive live attenuated influenza vaccine (LAIV) or inactivated influenza vaccine (IIV).

 Several studies indicate that LAIV may have advantages over IIV for children; particularly for younger children.

- Vaccine efficacy
- Onset of immune response
- Duration of immunity
- Heterotypic protection

Belshe NEJM 2007; Ashkenazi PIDJ 20 Belshe J Peds 2000; Gaglani et al, Arch Clover JID 1991

Ashkenazi PIDJ 2006; Bernstein PIDJ 2003; Gaglani et al, Arch Pediatr Adolesc Med 2004;

Belshe NEJM 1998; Bracco Neto et al, PIDJ 2009

Background (2)

□ ACIP currently expresses no preference for LAIV vs. IIV.

Recent recommendations expressing some degree of preference for LAIV for children:

Country	Age (years)
Canada	2-17
United Kingdom	2-17
Israel	2-17
Germany	2-6
United StatesOregon	2-5
United StatesWashington	2-7

Background (3)

 Preliminary GRADE efficacy assessment presented at October 2012 ACIP meeting

Safety assessment deferred

- Trivalent LAIV formulation (LAIV3) anticipated to be replaced with quadrivalent (LAIV4) in 2013-14;
- No post-marketing safety data was yet available for LAIV4

Objective for today's presentations

 Describe GRADE assessments for safety and efficacy of LAIV vs. IIV for healthy children

Policy Question

Should LAIV be recommended preferentially over IIV for healthy children?

- Ages 2-8
- Ages 9-18

Rationale for selected age categories

- LAIV not licensed for children under 2 years of age
- 8 years is upper limit of age range for consideration of 1 vs. 2 doses (selected for simplicity of recommendations)

Study Inclusion/Exclusion Criteria

Included:

- Data pertaining to healthy children, primarily
 - 1 study of children with asthma reviewed
- Vaccines licensed in US or similar to US licensed vaccines
- Studies including LAIV and IIV arms
- Literature in English

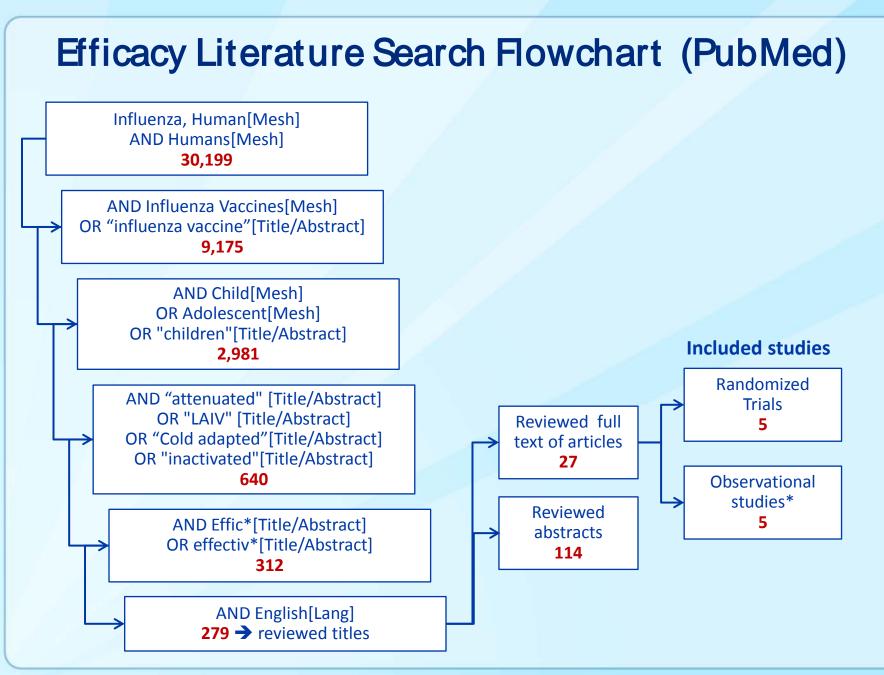
Excluded:

- Data for adjuvanted, whole virus, or virosomal vaccines
- LAIV produced using different seed strains from US products
- Studies in which all participants outside of indicated age range
- Outcomes based on ICD-9 codes only

Efficacy Outcomes Selected by Influenza WG

Outcome	Importance
Laboratory-confirmed influenza*	Critical
Mortality**	Critical
Hospitalization**	Critical
MAARI	Critical
Influenza-like illness	Important
Acute otitis media**	Important

* Associated with respiratory illness; without regard to vaccine match
** Associated with influenza



Efficacy Papers/Studies Identified: Randomized Trials

						Outc	omes		
Design	Paper	Ages	Season	LCI	Hosp	Death	MAARI	ILI	AOM
Open label	Ashkenazi 2006	6-71 mo, with recurrent RTI	2002-03	X	Х		Х	Х	Х
Open-label	Fleming 2006	6-17 yrs, with asthma*	2002-03	х	Х		Х		
	Belshe 2007	6-59 mo	2004-05	Х					Х
Double-blind, placebo controlled	Neuzil 2001	1-15 yrs*	1985-86 through 1989-90	X		 		 	
	Clover 1991	3-19 yrs*	1986-87	×				 	

*Included both age groups of interest; (2-8 and 9-18); data of interest not stratified.

Efficacy Papers/Studies Identified: Observational Studies

						Out	comes		
Design	Paper	Ages	Season	LCI	Hosp	Death	MAARI	ILI	AOM
	Treanor, 2012	≥6 mo	2010-11	Х	 			· 	
Test-	Ohmit, 2013	≥6 mo	2011-12	X	 				
negative, case-	MacIntosh, 2013	2-18 yrs	2011-12	Х					
control	Eick-Cost, 2013	2-18 yrs	2012-13	X	 			 	l L
	Fry, 2013	≥6 mo	2012-13	X			r	r — — I	

Differences in Criteria for Testing for Influenza

Study	Criteria for swabbing
	 <u>One or more of the following</u>: Fever, shortness of breath, pulmonary congestion, pneumonia, ear infection, wheezing, or
Ashkenazi 2006	 <u>Two or more of the following</u>: Runny nose, nasal congestion, sore throat, cough, muscle aches, chills, headache, irritability, decreased activity, vomiting, or
	Clinical discretion
	 <u>One or more of the following</u>: Fever, pulmonary congestion, pneumonia or ear infection, or
Fleming 2006	• <u>Two or more of the following</u> : Shortness of breath, runny nose or nasal congestion, sore throat, cough, muscle ache, chills, headache, irritability, decreased activity, vomiting, increase in wheezing, increased use of medication to treat wheezing, or
	Clinical discretion
Belshe 2007	Symptoms suggestive of influenza
Neuzil 2001	 Fever of abrupt onset with >1: chills, headache, malaise, myalgia, cough, pharyngitis, or other upper respiratory complaints
Clover 1991	Respiratory illness

Data Contributing to Each Outcome

Efficacy Outcomes	Importance	Studies 2-18 years (n)	Studies 2-8 years (n)	Studies 9-18 years (n)
Lab-confirmed influenza*	Critical	10	7	5
Mortality**	Critical	0	0	0
Hospitalization**	Critical	2	1	0
MAARI	Critical	2	1	0
Influenza-like illness	Important	1	1	0
Acute otitis media**	Important	2	2	0

* Associated with respiratory illness; without regard to vaccine match
** Associated with influenza

EVIDENCE PROFILE 2—8 YEARS

Evidence Profile—LAIV vs. IIV—2-8-year-olds Lab-confirmed Influenza—Randomized Studies (CRITICAL)

Studies	Risk of					Effect		
(n)	Bias	Inconsistency	Indirectness	Imprecision	RR [95% Cl]	Risk Difference with LAIV [95% CI]	Quality	
2	Not serious	Not Serious	Not Serious	Not Serious	0.46 [0.39 – 0.54]	43 fewer per 1000 [37 – 49 fewer]	1 (High)	

	LAI\	/	IIV			Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	
Ashkenazi 2006 (6-71	M) 29	1050	60	1035	15.4%	0.48 [0.31, 0.74]	_ _	
Belshe 2007 (6-59	M) 153	3916	338	3936	84.6%	0.45 [0.38, 0.55]		
Total (95% CI)		4966		4971	100.0%	0.46 [0.39, 0.54]	•	
Total events	182		398					
Heterogeneity: Tau ² = 0.00; Chi ² = 0.04, df = 1 (P = 0.85)					5); I ^z = 09	6		10
Test for overall effect:	Z = 8.95 ((P < 0.0	0001)				Favors LAIV Favors IIV	10

Evidence Profile—LAIV vs. IIV—2-8-year-olds Lab-confirmed Influenza—Randomized Studies (CRITICAL)

Studioo	Dick of					Effect		
Studies (n)	Risk of Bias	Inconsistency	Indirectness	Imprecision	RR [95% Cl]	Risk Difference with LAIV [95% CI]	Quality	
2	Not serious	Not Serious	Not Serious	Not Serious	0.47 [0.38 – 0.58]	46 fewer per 1000 [36 – 54 fewer]	1 (High)	

• Data from both studies restricted to children aged ≥24 m on ths (m eta-analysis by Ambrose et al, Vaccine 2012)

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Ashkenazi 2006 (24-7	71M) 23	790	46	819	18.8%	0.52 [0.32, 0.85]	_
Belshe 2007 (24-5	59M <mark>)</mark> 94	2083	205	2083	81.2%	0.46 [0.36, 0.58]	
Total (95% CI)		2873		2902	100.0%	0.47 [0.38, 0.58]	•
Total events	117		251				
Heterogeneity: Tau² =	= 0.00; Chi ^z	= 0.19,	df = 1 (P	= 0.66)); I² = 0%		
Test for overall effect:	Z = 6.96 (P	P < 0.00	001)				Favors LAIV Favors IIV

Evidence Profile—LAIV vs. IIV—2-8-year-olds Lab-confirmed Influenza--Observational Studies (CRITICAL)

Studies (n)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Effect Adj. OR [95% Cl]	Quality
5	Not Serious	Not Serious	Not Serious	Serious	0.74 [0.50 –1.08]	4 (Very Low)

• Downgraded for imprecision (width of confidence interval)

Chudu an Carbonna	In a foot de Deffert	0.5	10/_:_b4	Odds Ratio	Odds Ratio
Study or Subgroup	log[Odds Ratio]	SE	vveight	IV, Random, 95% Cl	IV, Random, 95% CI
Eick-Cost 2013	-0.2286	0.4401	20.2%	0.80 [0.34, 1.89]	
Fry 2013	-0.4372	0.2606	57.6%	0.65 [0.39, 1.08]	
MacIntosh 2013 (2-	•8Yall) 0.4457	0.6601	9.0%	1.56 [0.43, 5.69]	
Ohmit 2013	-0.5536	0.5825	11.5%	0.57 [0.18, 1.80]	
Treanor 2012a	0.955	1.5433	1.6%	2.60 [0.13, 53.51]	
Total (95% CI)			100.0%	0.74 [0.50, 1.08]	•
Heterogeneity: Tau ² = Test for overall effect:			= 0.66); I ^z	² = 0%	0.1 0.2 0.5 1 2 5 10 Favors LAIV Favors IIV

Evidence Profile—LAIV vs. IIV—2-8-year-olds Hospitalization—Randomized Studies (CRITICAL)

Qudi	udioo	Risk of Bias						
	Studies (n)		Inconsistency	Indirectness	Imprecision	RR [95% Cl]	Risk Difference with LAIV [95% CI]	Quality
	1	Not Serious	Not Serious	Serious	Serious	1.08 [0.48 – 2.43]	1 fewer per 1000 [6 fewer – 15 more]	3 (Low)

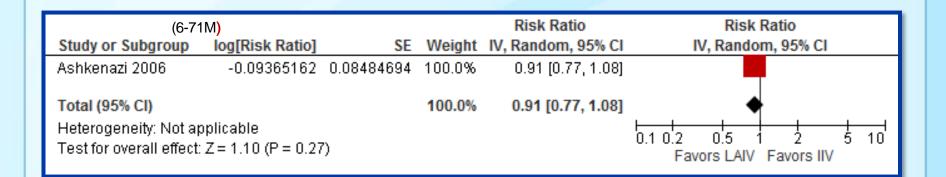
- Hospitalizations associated with 'current illness.'
- Downgraded for indirectness (hospitalizations for influenza-like illness rather than influenza).
- Downgraded for imprecision (width of confidence interval)

	LAI	/	IIV			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Ashkenazi 2006 (6-71	M) 12	1048	11	1034	100.0%	1.08 [0.48, 2.43]	
Total (95% CI)		1048		1034	100.0%	1.08 [0.48, 2.43]	
Total events	12		11				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z=0.18 ((P = 0.8	6)				Favors LAIV Favors IIV

Evidence Profile—LAIV vs. IIV—2-8-year-olds MAARI—Randomized Studies (CRITICAL)

Studies (n)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Effect RR [95% CI]	Quality
1	Not Serious	Not Serious	Serious	Not Serious	0.91 [0.77 – 1.08]	2 (Moderate)

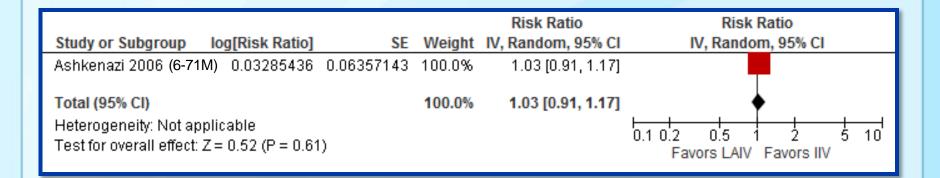
• Downgraded for indirectness (illnesses not necessarily related to influenza).



Evidence Profile—LAIV vs. IIV—2-8-year-olds Influenza-Like IIIness—Randomized Studies (IMPORTANT)

Studies (n)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Effect RR [95% CI]	Quality
1	Not Serious	Not Serious	Serious	Not Serious	1.03 [0.91 – 1.17]	2 (Moderate)

• Downgraded for indirectness (illnesses not necessarily related to influenza).



Evidence Profile—LAIV vs. IIV—2-8-year-olds Otitis Media—Randomized Studies (IMPORTANT)

Qudioo	Risk of				[
Studies (n)	Bias	Inconsistency	Indirectness	Imprecision	RR [95% Cl]	Risk Diff. with LAIV [95% CI]	Quality	
2	Not Serious	Not Serious	Not Serious	Not Serious	0.47 [0.30-0.73]	6 fewer per 1000 [3-8 fewer]	1 (High)	

	LAI	/	IIV			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Ashkenazi 2006 (6-7	1M) 2	1048	6	1034	7.8%	0.33 [0.07, 1.63]	← • <u>–</u> –
Belshe 2007 (6-5	9M) 26	3916	54	3936	92.2%	0.48 [0.30, 0.77]	
Total (95% CI)		4964		4970	100.0%	0.47 [0.30, 0.73]	•
Total events	28		60				
Heterogeneity: Tau ² = 0.00; Chi ² = 0.21, df = 1 (P = 0.6				P = 0.6	5); I² = 0%	b	0.1 0.2 0.5 1 2 5 10
Test for overall effect:	Z = 3.31	(P = 0.0	1009)				Favors LAIV Favors IIV

EVIDENCE PROFILE 9—18 YEARS

Evidence Profile—LAIV vs. IIV—9-18-year-olds Lab-confirmed Influenza--Observational Studies (CRITICAL)

Studies (n)	s Risk of Bias Inconsistency		Indirectness	Imprecision	Effect Adj. OR [95% Cl]	Quality
5	Not serious	Not Serious	Not Serious	Serious	1.14 [0.76 – 1.71]	4 (Very Low)

• Downgraded for imprecision (width of confidence interval)

				Odds Ratio	Odds Ratio
Study or Subgroup log	g[Odds Ratio]	SE	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Eick-Cost 2013	0.1555	0.3962	27.2%	1.17 [0.54, 2.54]	
Fry 2013	0.1865	0.3389	37.2%	1.21 [0.62, 2.34]	
MacIntosh 2013 (9-18Y	all) -0.1411	0.6243	11.0%	0.87 [0.26, 2.95]	
Ohmit 2013		0.5998	11.9%	1.16 [0.36, 3.77]	
Treanor 2012a	0.1558	0.5766	12.8%	1.17 [0.38, 3.62]	
Total (95% CI)			100.0%	1.14 [0.76, 1.71]	◆
Heterogeneity: Tau ² = 0.0 Test for overall effect: Z =	0.1 0.2 0.5 1 2 5 10 Favors LAIV Favors IIV				

Other Considerations (1)

Harmonization with AAP recommendations

□ LAIV supply

Safety of quadrivalent vaccines

Other Considerations (2)

Comparative U.S. price/dose

2014-15 private sector costs (per VFC information)

Vaccine product	Price/dose		
LAIV	LAIV4:	\$22.70	
IV (w ith indication for ≪8 years)	IIV3:	\$7.65 - \$14.81	
III (W IIII III III III III III III III	IIV4:	\$14.90 - \$21.09	

Summary—Efficacy Outcomes

2-8 year olds	Study Design (n)	Findings	Quality
Lab confirmed influenza (Critical)	RCT (2)	Decreased risk with LAIV	1 (High)
	Obs (5)	No Difference	4 (Very Low)
Hospitalization (Critical)	RCT(1)	No difference	3 (Low)
MAARI (Critical)	RCT(1)	No difference	2 (Moderate)
Influenza-like illness (Important)	RCT(1)	No difference	2 (Moderate)
Otitis media (Important)	RCT (2)	Decreased risk with LAIV	1 (High)
9-18 year olds	Study Design (n)	Findings	Quality
Lab confirmed influenza (Critical)	Obs (5)	No difference	4 (Very Low)

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Thank You!

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