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

Lisa Grohskopf, Sonja Olsen, Leslie Sokolow

Advisory Committee on Immunization Practices February 26, 2014



Overview

- □ Three outcomes
 - Fever
 - Medically-attended wheezing
 - Serious adverse events (SAEs)
- Safety analyses focus upon younger children
- Observational studies excluded
 - Differences in health status of underlying populations may affect interpretation of safety outcomes

EVIDENCE PROFILE 2—8 YEARS

Studies	Risk of					Effect		
(n)			Indirectness Imprecision		RR[95% CI]	Risk Difference with LAIV [95% Cl]	Quality	
1	Not Serious	Not Serious	Not Serious	Serious	1.11 [0.67 – 1.85]	1 more per 1000 [4 fewer – 11 more]	2 (Moderate)	

- Protocol-defined "medically significant wheezing"
- Follow-up 42 days.
- Data limited to children aged 24 through 59 months.
- Following dose 1; without regard to previous vaccination.

	LAI\	/	IIV			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Belshe 2007 (6-59 mos)	31	2187	28	2198	100.0%	1.11 [0.67, 1.85]	_
Total (95% CI)		2187		2198	100.0%	1.11 [0.67, 1.85]	*
Total events Heterogeneity: Not applical Test for overall effect: Z = 0.		.68)	28				0.1 0.2 0.5 1 2 5 10 Favors LAIV Favors IIV

Studies	Risk of					Effect		
(n)	Inconsistency		Indirectness Imprecision		RR[95% CI]	Risk Difference with LAIV [95% Cl]	Quality	
1	Not Serious	Not Serious	Not Serious	Serious	1.36 [0.68 – 2.69]	3 more per 1000 [3 fewer – 16 more]	2 (Moderate)	

- Protocol-defined "medically significant wheezing"
- Follow-up 42 days.
- Data limited to children aged 24 through 59 months.
- Following dose 1; NOT previously vaccinated.

	LAI\	/	IIV			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Belshe 2007 (6-59 mos)	19	1521	14	1520	100.0%	1.36 [0.68, 2.69]	_
Total (95% CI)		1521		1520	100.0%	1.36 [0.68, 2.69]	*
Total events Heterogeneity: Not applical Test for overall effect: Z = 0		.38)	14				0.1 0.2 0.5 1 2 5 10 Favors LAIV Favors IIV

Studies	Risk of					Effect		
(n)	Bias Inconsistency		Indirectness Imprecision		RR[95% CI]	Risk Difference with LAIV [95% Cl]	Quality	
1	Not Serious	Not Serious	Not Serious	Serious	0.87 [0.41 – 1.87]	3 fewer per 1000 [12 fewer–18 more]	2 (Moderate)	

- Protocol-defined "medically significant wheezing"
- Follow-up 42 days.
- Data limited to children aged 24 through 59 months.
- Following dose 1; previously vaccinated.

	LAI\	/	IIV			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Belshe 2007 (6-59 mos)	12	666	14	678	100.0%	0.87 [0.41, 1.87]	_
Total (95% CI)		666		678	100.0%	0.87 [0.41, 1.87]	*
Total events Heterogeneity: Not applical Test for overall effect: Z = 0		.73)	14				0.1 0.2 0.5 1 2 5 10 Favors LAIV Favors IIV

Studies	Risk of					Effect		
(n)			Indirectness Imprecision		RR[95% CI]	Risk Difference with LAIV [95% Cl]	Quality	
1	Not Serious	Not Serious	Not Serious	Serious	0.58 [0.31 – 1.06]	8 fewer per 1000 [13 fewer – 1 more]	2 (Moderate)	

- Protocol-defined "medically significant wheezing"
- Follow-up 42 days.
- Data limited to children aged 24 through 59 months.
- Following dose 2; NOT previously vaccinated.

	LAI	/	IIV			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Belshe 2007 (6-59 mos)	16	1424	28	1439	100.0%	0.58 [0.31, 1.06]	-
Total (95% CI)		1424		1439	100.0%	0.58 [0.31, 1.06]	◆
Total events Heterogeneity: Not applical Test for overall effect: Z = 1		.08)	28				0.1 0.2 0.5 1 2 5 10 Favors LAIV Favors IIV

Evidence Profile—LAIV vs. IIV—2-8-year-olds Fever, ≥38.6°C or ≥38.9°C—Randomized Studies (IMPORTANT)

Studies	Pick of	Risk of ,						
(n)	Bias Inconsistency		Indirectness Imprecision		RR[95% CI]	Risk Difference with LAIV [95% CI]	Quality	
2	Not Serious	Not Serious	Not Serious	Serious	0.89 [0.73 – 1.08]	5 fewer per 1000 [11 fewer – 3 more]	2 (Moderate)	

- Follow-up days 0-10.
- Following dose 1.
- Data for Belshe et al. from sBLA.
- Temperature thresholds differed slightly between studies: 38.6°C (Ashkenazi) vs. 38.9°C (Belshe).

	LAIV	IIV			Risk Ratio	Risk Ratio
Study or Subgroup	Events Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Ashkenazi 2006 (6-71 mos)	49 961	62	954	28.0%	0.78 [0.55, 1.13]	
Belshe 2007 (6-59 mos)	140 4134	149	4114	72.0%	0.94 [0.75, 1.17]	#
Total (95% CI)	5095		5068	100.0%	0.89 [0.73, 1.08]	•
Total events	189	211				
Heterogeneity: Tau² = 0.00; Ch	i²= 0.64, df= 1	(P = 0.42)	$ \mathbf{r} = 0$	%		0.1 0.2 0.5 1 2 5 10
Test for overall effect: Z = 1.18	(P = 0.24)					Favors LAIV Favors IIV

Evidence Profile—LAIV vs. IIV—2-8-year-olds Related SAEs

Studies	Risk of					Effect		
(n)	Bias	Inconsistency	Indirectness	Imprecision	RR[95% Cl]	Risk Difference with LAIV [95% Cl]	Quality	
2	Not Serious	Not Serious	Not Serious	Serious	0.90 [0.34 – 2.37]	0 fewer per 1000 [1 fewer – 2 more]	2 (Moderate)	

	1.007		115.7			Di-I- D-4i-	Diele Detie
	LAIV		IIV			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Ashkenazi 2006 (6-71 mos)	2	1101	4	1086	32.9%	0.49 [0.09, 2.69]	-
Belshe 2007 (6-59 mos)	6	4179	5	4173	67.1%	1.20 [0.37, 3.92]	
Total (95% CI)		5280		5259	100.0%	0.90 [0.34, 2.37]	
Total events	8		9				
Heterogeneity: Tau² = 0.00; Ch	$ni^2 = 0.71, 0$	df = 1 ((P = 0.40)	$); I^{2} = 0^{4}$	%		0.1 0.2 0.5 1 2 5 10
Test for overall effect: Z = 0.22	(P = 0.82)	ı					Favors LAIV Favors IIV
							FAVOIS LAIV FAVOIS IIV

Evidence Summary: Safety

2-8 year olds	Study Design (n)	Findings	Quality
Medically attended wheezing (Critical)	RCT(1)	No difference	2 (Moderate)
Fever (Important)	RCT(2)	No Difference	2 (Moderate)
Related SAE	RCT(2)	No difference	2 (Moderate)

Limitations

- Definitions of outcomes of interest not standardized across studies.
- Studies not adequately powered to detect differences in rare but serious outcomes (e.g., Guillain-Barré; anaphylaxis).
- All data pertain to trivalent vaccines (LAIV3 and IIV3).

Acknowledgements

The Clinical Immunization Safety Assessment (CISA) Project

CISA Evidence
Review Group

Emmanuel (Chip) Walter Buddy Creech

Kathy Edwards

Pediatric Fever and Influenza Vaccine Study

Melissa Stockwell

Philip LaRussa

Kathleen Jakob

FDA

Chris Jankosky

Jane Woo

CDC/ISO

Karen Broder

Maria Cano

Frank DeStefano

Eric Weintraub

Penina Haber

Beth Hibbs

Paige Lewis

Pedro Moro

Oidda Museru

Dave Sharma

Tom Shimabukuro

CDC/ID

Joseph Bresee

David Shay

CDC/NCIRD

Faruque Ahmed

Thank You!

For more information please contact Centers for Disease Control and Prevention

1600 Clifton Road NE, Atlanta, GA 30333

Telephone, 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348

E-mail:cdcinfo@cdc.gov Web:www.cdc.gov

