LAIV vs. IIV Comparative Safety Studies in Children

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Evidence Review for Influenza Vaccine Safety in Children 2 through 8 Years of Age

Pediatric Influenza Vaccine Safety Evidence Review Group

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Disclosures for Potential Conflicts of Interest

- **Dr. Creech**
  - Clinical Investigator within 12 months (Novartis, Pfizer)
- **Dr. Edwards**
  - DSMB member IIV (Novartis)
- **Dr. Walter**
  - Prior clinical investigator IIV (Sanofi Pasteur, CSL)
  - Prior clinical investigator for LAIV (Medimmune)
  - DSMB member IIV (Novartis)
  - Consultant HAV project (Merck)
  - Clinical Investigator within 12 months (GSK, Merck, Pfizer)

Evidence Review for Influenza Vaccine Safety In Children 2 through 8 Years of Age

Objective

To evaluate the evidence for the safety of trivalent live, attenuated influenza vaccine, compared with trivalent inactivated, influenza vaccine in children aged 2 through 8 years using the ACIP Grading of Recommendations, Assessment, Development and Evaluation (GRADE) process

Safety Outcomes: ACIP Influenza Working Group Assessment

Safety Outcome	Importance
Immediate hypersensitivity / anaphylaxis	Critical
Febrile seizure	Critical
Medically-attending wheezing (MAW)	Critical
Guillain-Barre syndrome	Critical
Other neurologic outcomes	Important
Respiratory symptoms	Important

Final Safety Outcomes Selected for Review

Safety Outcome	Selected	Rationale
Anaphylaxis	No	Rare, limited information for review
Immediate hypersensitivity	No	Uncommon, limited information for review
Febrile seizure	No	Uncommon, limited information for review
Medically-attending wheezing (MAW)	**Keep**	**Common and clinically important**
Guillain-Barre syndrome	No	Rare, limited information for review
Fever	**Added**	**Common, medically important, comparable across studies, potential proxy for febrile seizure risk**
Serious adverse events (SAEs)	**Added**	**Important. Used in other reviews. Includes some rare and uncommon events**

Methods for Evidence Review

- Eight publications directly comparing LAIV to IIV3 selected for review
- Manuscripts reviewed by BC or CW using grading sheets
  - **Outcome definition, study design, season, ages of study population, and sample size**
  - **Limitations or potential for biases**
    - Randomized Trials- allocation concealment, blinding, loss to follow-up, failure to adhere to an intention to treat analysis, stopping early for benefit, failure to report an outcome
    - Observational Studies – Failure to apply and develop appropriate eligibility criteria, flawed measures for exposures or outcome, failure to control for confounding
  - **Indirectness:** population, intervention, or outcome differs from that of interest; vaccines are each compared with placebo, but not one another
- Assessments reviewed with Pediatric influenza vaccine safety evidence review group , CISA investigators, and ACIP Influenza WG

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Evaluations Comparing LAIV and IIV: Three Excluded From Safety Assessment

Author	Years	Population	Design	Study Groups	Safety Outcomes
Clover et al. JID, 1991	1986-1987	3-19 years	Double-blind, placebo controlled	(192) 1) IIV3 + nasal saline placebo 2) Saline placebo + bivalent LAIV	**Not described**
Neuzil et al. PIDJ, 2001	1985-1990	1-65 years (healthy) Reported on subjects <16 years	Randomized controlled trial	(791 received 1809 doses) 1) IIV (Year 1 bivalent no B Years 2-5 IIV3) + nasal placebo 2) Year 1 saline **Years 2-5 inactivated monovalent B** + LAIV (2 A strains) 3) Control :Year 1 saline Years 2-5 inactivated monovalent B + nasal placebo	**Only fever described**
Holloran et al. Vaccine, 2007	1998-2004 *2004	5-18 years (healthy – children with asthma received TIV)	Open-label, non randomized community based evaluation	1) IIV3 (548) 2) LAIV (1,706) 3) LAIV previously (983) 4) No vaccine 3166	**Not described**

Evaluations Comparing LAIV and IIV: Five Included In Safety Assessment

Author	Years	Population	Design	Study Groups	Outcomes
Ashkenzi et al. PIDJ, 2006	2002-2003	6-71 months (recurrent respiratory tract infections)	Open-label, randomized	1) IIV3 (1,086) 2) CAIV-T[1.] (1,101)	**Fever** **MAW** **SAEs**
Fleming et al. PIDJ, 2006	2002-2003	6-17 years (asthma)	Open-label, randomized	1) IIV3 (1,115) 2) CAIV-T[1.] (1,114)	**Fever** **MAW** **SAEs**
Belshe et al. NEJM, 2007	2004-2005	6-59 months (included children with asthma or wheezing history)	Double-blind, placebo controlled	1) IIV3 + LAIV Placebo (4,173) 2) IIV3 Placebo + LAIV (4,179)	**Fever** **MAW** **SAEs**
Toback et al. Vaccine, 2013	2007-2010	24-59 months	Observational	1) IIV3 (27,937) 2) LAIV (28,226) 3) Unvaccinated (25,981)	**MAW** **SAEs**
Baxter et al. Vaccine 2012	2003-2008	5 -17 years	Observational	1) IIV3 (≈43,700) 2) LAIV (43,702) 3) Unvaccinated (53,336)	**MAW** **SAEs**

1. CAIV-T refers to LAIV

Fever as an Outcome: Measurements

Author	Fever Described	Measurement	Measurement Interval	Methods Description	Results Description
Ashkenazi	Yes	Axillary or rectal	11 days	≥ 37.5°C axillary ≥ 38°C rectal	≥ 37.5°C ≥ 38.6°C
Fleming	Yes	Oral	15 days	≥ 38°C oral	≥ 38°C ≥ 39.1°C ≥ 40.0°C
Belshe	Yes	Axillary, oral, or rectal	10 days[1.]	Not described	≥ 37.8°C ≥ 38.9°C

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1. Clarified from BLA

Temperature Elevations

Author		*Dose 1*			*Dose 2*		
Ashkenazi	Temp 11 days	CAIV-T[1.]/LAIV n=630-1067	TIV N=684-1050	p	CAIV-T[1.]/LAIV n=625-1029	TIV N=679-1012	p
	≥ 37.5°C	231 (23.5)	208 (21.4)	0.279	191 (19.8)	172 (18.5)	0.484
	≥ 38.6°C	49 (5.1)	62 (6.5)	0.204	53 (5.6)	47 (5.1)	0.682
Fleming	15 days	n=940-1086	N=936-1071				
	≥ 38°C	60 (6.3)	55 (5.8)	0.701	N/A	N/A	N/A
	≥ 39.1°C	7 (0.7)	10 (1.1)	0.477	N/A	N/A	N/A
	≥ 40.0°C	1 (0.1)	0 (0.0)	1.000	N/A	N/A	N/A
Belshe	Day 2	≈ 4179[2.]	≈ 4173[2.]				
	≥ 37.8°C	**5.4%**	**2.0%**	**<0.001**	†	†	†
	≥ 38.9°C	<1%	<1%		†	†	†

[1.] CAIV-T refers to LAIV
[2.] Loss to follow-up not described.
† Not reported in appendix as described in manuscript

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Grading the Evidence: Indirectness
Fever as an Outcome

Evaluation	Population differs from that of interest *Healthy (2-8 yrs.)*	Intervention differs from that of interest *(LAIV vs. IIV3)*	Outcome differs from that of interest *(Fever)*	Vaccines each compared with placebo but not one another
Ashkenazi	**Yes (some younger, RTI)**	No	No	No
Fleming	**Yes (some older, asthma)**	No	No	No
Belshe	**Yes (some younger, none aged 60-96 mos.)**	No	No	No

Grading the Evidence: Limitations / Potentials for Bias – Randomized Trials Fever as an Outcome

Evaluation	Allocation Concealment	Blinding	Loss to follow-up	Stopping early for benefit	Failure to report an outcome
Ashkenazi	Yes	**No**	**Yes**	No	No
Fleming	Yes	**No**	**Yes**	No	No
Belshe	Yes	Yes	**Yes**	No	No

Medically Attended Wheezing (MAW) as an Outcome

Author	Definition	Time Interval
Ashkenazi	Wheezing episodes observed by a medical practitioner	Day 11-41 after each dose
Fleming	Incidence of asthma exacerbation (acute wheezing illness associated with hospitalization, any unscheduled clinical visit, or any new prescription including rescue medication)	42 days after dose
Belshe	Presence of wheezing on a physical examination conducted by a health care provider, with a prescription for a daily bronchodilator; respiratory distress; or hypoxemia	42 day period after each dose
Toback / Baxter	Asthma and wheezing – asthma / reactive airway disease (RAD) encompassed individual diagnosis of asthma, cough variant asthma, and exercise-induced asthma; the term wheezing/shortness of breath (SOB) included the diagnosis of wheezing and dyspnea/SOB.	21 and 42 day periods after dose

Medically Attended Wheezing (MAW)

Author	*Dose 1*	*Dose 2*
	Percent Difference CAIV-T / LAIV[1.] – TIV (90% CI)	Percent Difference CAIV-T / LAIV[1.] – TIV (90% CI)
Ashkenazi	0.7% (-0.6 - 2.1)	0.0 % (-1.6 - 1.6)
Fleming	0.1% (-2.4 - 2.2)	N/A
	Adjusted Rate Difference LAIV-TIV (95% CI)	Adjusted Rate Difference LAIV-TIV (95% CI)
Belshe Previously unvaccinated[2, 3]	**Total 0.77% (.12 - 1.46)** **< 24 mo. 1.18% (.13 - 2.29)** 24-59 mo. 0.30% (-0.46-.1.09)	Total 0.20% (-.56 - .97) < 24 mo. 1.15% (-0.04-2.38) 24-59 mo. -0.85% (-1.83-0.05)
	Hazard Ratio (95%CI) Comparing LAIV to IIV3	Hazard Ratio (95%CI) Comparing LAIV to IIV3
Baxter	**5-8 years 0.38 (0.30, 0.47)** **9-17 years 0.35 (0.28, 0.44)**	**5- 8 years 0.46 (0.21, 0.97)**
	Any Dose	
Toback	**24-59 months 0.41 (0.36, 0.7)**	

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1. CAIV-T refers to LAIV
2. Note groups include children < 24 months of age
3. Increase seen mostly in weeks 2-4 after vaccination

Grading the Evidence: Indirectness MAW as an Outcome

Evaluation	Population differs from that of interest *Healthy (2-8 yrs.)*	Intervention differs from that of interest *(LAIV vs. IIV3)*	Outcome differs from that of interest *(MAW)*	Vaccines each compared with placebo but not one another
Ashkenazi	**Yes (some younger, RTI)**	No	**Yes (Omits first 10 days)**	No
Fleming	**Yes (some older, asthma)**	No	No	No
Belshe	**Yes (none aged 60-96 mos.)**	No	No	No
Tobeck	**Yes (none aged 60-96 mos.)**	No	No	No
Baxter	**Yes (none aged 24-59 mos.)**	No	No	No

Grading the Evidence: Limitations / Potentials for Bias – Randomized Trials MAW as an Outcome

Evaluation	Allocation Concealment	Blinding	Loss to follow-up	Stopping early for benefit	Failure to report an outcome
Ashkenazi	Yes	**No**	**Yes**	No	No
Fleming	Yes	**No**	**Yes**	No	No
Belshe	Yes	Yes	**Yes**	No	No

Grading the Evidence: Limitations / Potentials for Bias – Observational Study MAW as an Outcome

Evaluation	Failure to develop or apply appropriate eligibility criteria	Flawed measurement of exposure or outcome	Failure to control for confounding
Toback	No	No	**Yes**
Baxter	No	No	**Yes**

Serious Adverse Events (SAEs) as an Outcome

Author	Definition	Time Interval	Relatedness
Ashkenazi	Not clearly described (included hospitalizations)	Enrollment through completion of the study	Possibly (per investigator)
Fleming	Events considered life-threatening; or resulting in death, hospitalization or prolongation of hospitalization, persistent or significant disability or incapacity, cancer, or in congenital anomaly or birth defect. Also included other medical events which in medical judgment, jeopardized the patient or subject and required medical or surgical intervention to prevent an outcome listed above.	Through influenza surveillance period	Probably (per investigator)
Belshe	Events considered life-threatening; or resulting in death, hospitalization or prolonged hospitalization, significant disability or incapacity, or another important medical event requiring intervention to prevent one of these outcomes	Dose 1 through influenza surveillance period	Potentially (per investigator)
Toback	Not clearly described	0-42 days post vaccination	Possibly (per investigator)
Baxter	In a similar manner to previous LAIV studies	0-42 days post vaccination	Determined per investigator

Serious Adverse Events (SAEs)

Author	All SAE		Vaccine Related SAE		Deaths
	CAIV-T / LAIV[1.]	TIV	CAIV-T / LAIV[1.]	TIV	
Ashkenazi	5.8% 104 in 64 subjects	4.7% 76 in 51 subjects	0.2% 2	0.4% 4	0
Fleming	1.8% (Respiratory 0.9%)	1.7% (Respiratory 0.9%)	3 Pneumonia / asthma attack (d. 2) Pansinusitis (d. 93) Painful gland behind ear (d. 43)	1 Hyperglycemia with nausea (3 hours)	NR
Belshe	3.3% 136 /4179 Hospitalizations[2] All 3.1% **6-11 mos. 6.1%** 12-23 mos. 3.2% 24-59 mos. 2.1%	3.1% 128/4173 Hospitalizations[2] All 2.9% **6-11 mos. 2.6%** 12-23 mos. 3.5% 24-59 mos. 2.5%	6 Bronchiolitis N=2 Asthma exacerbation Wheezing AGE Reactive airway disease	5 Pneumonia Wheezing Febrile convulsion Febrile convulsion and pneumonia Viral gastroenteritis	2 (1 each group) FB aspiration House fire

1. CAIV-T refers to LAIV
2. Clarified from BLA

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Serious Adverse Events (SAEs)

Author	All SAE		Vaccine Related SAE		Deaths
	LAIV	TIV	LAIV	TIV	
Toback	0.91 per 1000[1.] person-months	1.14 per 1000[1.] person-months	2 RML infiltrate, fever, RSV Intussusception and viral infection	Not noted or described	None in children receiving LAIV
Baxter	<u>5- 8 years</u> *Dose 1.* 0.56 per 1000 person-months *Dose 2.* 0.47 per 1000 person- months <u>9-17 years</u> 1.08 per 1000 person-months	Noted not to be different	2 Dystonic tongue posturing 3 days post vaccination Bell's Palsy 2 days post vaccination	Not noted or described	LAIV (n=3) Auto accident Choking House fire TIV (n=1) Unvaccinated (n=1)

[1.] Unvaccinated 0.62 per1000 person-months

Grading the Evidence: Indirectness
SAE as an Outcome

Evaluation	Population differs from that of interest *Healthy (2-8 yrs.)*	Intervention differs from that of interest *(LAIV vs. IIV3)*	Outcome differs from that of interest *(SAE)*	Vaccines each compared with placebo but not one another
Ashkenazi	**Yes (some younger, RTI)**	No	No	No
Fleming	**Yes (some older, asthma)**	No	No	No
Belshe	**Yes (some younger, none aged 60-96 mos.)**	No	No	No
Toback	**Yes (none aged 60-96 mos.)**	No	No	No
Baxter	**Yes (none aged 24-59 mos.)**	No	No	No

Grading the Evidence: Limitations / Potentials for Bias – Randomized Trials SAE as an Outcome

Evaluation	Allocation Concealment	Blinding	Loss to follow-up	Stopping early for benefit	Failure to report an outcome
Ashkenazi	Yes	**No**	**Yes**	No	No
Fleming	Yes	**No**	**Yes**	No	No
Belshe	Yes	Yes	**Yes**	No	No

Grading the Evidence: Limitations / Potentials for Bias – Observational Study
SAE as an Outcome

Evaluation	Failure to develop / apply appropriate eligibility criteria	Flawed measurement of exposure or outcome	Failure to control for confounding
Toback	No	**Possible (All SAEs diagnosed in hospital setting)**	**Yes**
Baxter	No	No	**Yes**

Evidence Review for Influenza Vaccine Safety In Children 2 through 8 Years of Age: Limitations

- Few studies directly comparing LAIV and IIV
- Some studies did not assess outcomes of interest
- Definitions for outcomes of interest not standardized
- Follow-up intervals vary across studies
- Confounding in observational studies
- Finding observed for fever and MAW pertained to only one study during a single season
- Difficult to judge risk of serious rare AEs from trials
- Difficult to distinguish if a temporal association between influenza vaccine and an adverse event is coincidental or causal
- Review limited to trivalent influenza vaccines giving according to current indications

Evidence Review for Influenza Vaccine Safety In Children 2 through 8 Years of Age: Summary of Review of 8 Articles for Selected Outcomes

- When given according to current indications there is no evidence for an increased risk of SAE or MAW after LAIV vs. TIV in this age group
- Evidence for transient increased risk of mild fever after LAIV vs. TIV during one influenza season