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 2006; Bernstein PIDJ 2003; Belshe NEJM 1998; Belshe J Peds 2000; Gaglani et al, Arch Pediatr Adolesc Med 2004; Bracco Neto et al, PIDJ 2009 Clover JID 1991

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 States--Oregon	2-5
United States--Washington	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

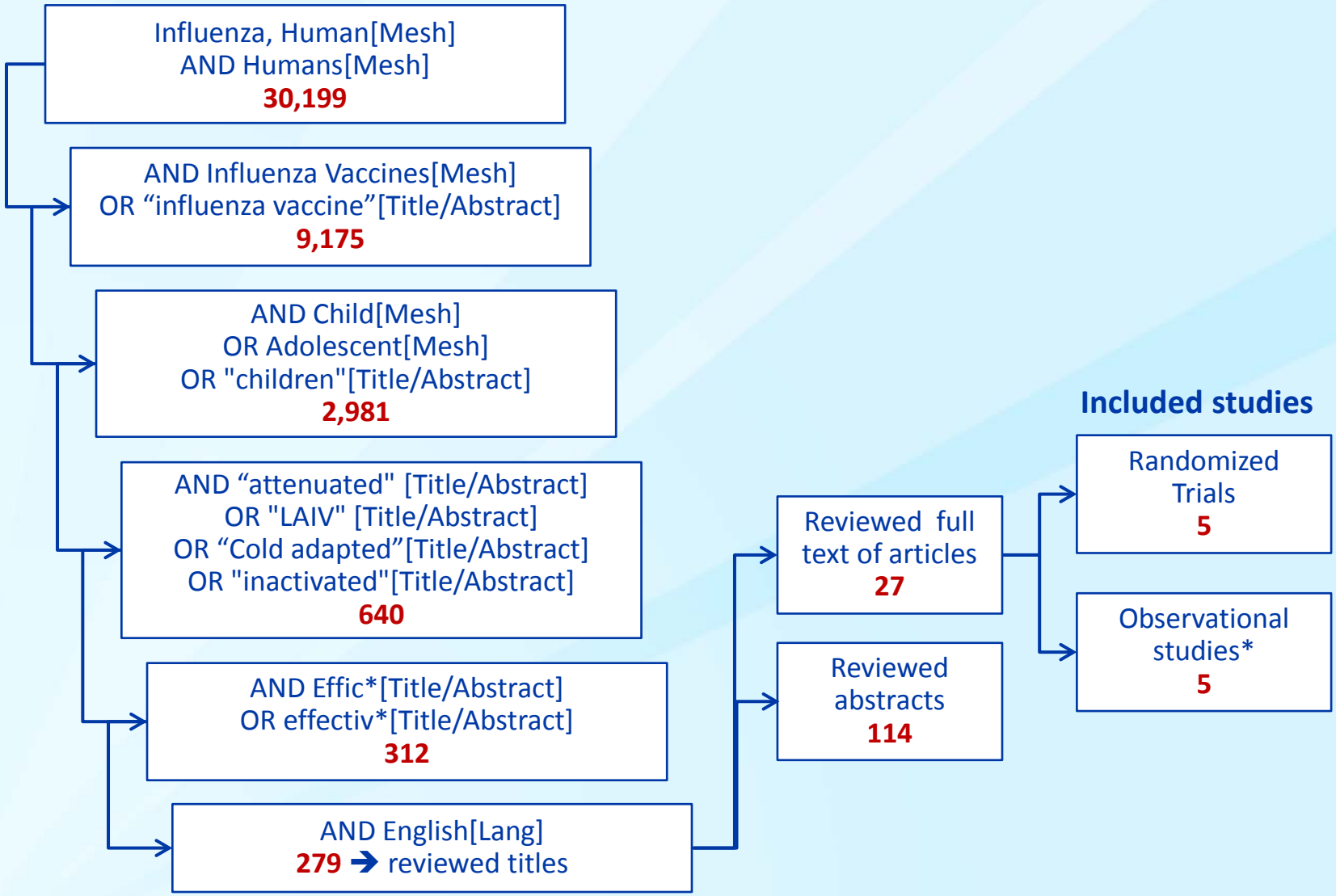
Efficacy Outcomes Selected by Influenza WG

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 Literature Search Flowchart (PubMed)



Efficacy Papers/Studies Identified: Randomized Trials

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

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

Efficacy Papers/Studies Identified: Observational Studies

				Outcomes					
Design	**Paper**	**Ages**	**Season**	**LCI**	**Hosp**	**Death**	**MAARI**	**ILI**	**AOM**
Test-negative, case-control	Treanor, 2012	≥6 mo	2010-11	X					
	Ohmit, 2013	≥6 mo	2011-12	X					
	MacIntosh, 2013	2-18 yrs	2011-12	X					
	Eick-Cost, 2013	2-18 yrs	2012-13	X					
	Fry, 2013	≥6 mo	2012-13	X					

Differences in Criteria for Testing for Influenza

Study	Criteria for swabbing
Ashkenazi 2006	• One or more of the following: Fever, shortness of breath, pulmonary congestion, pneumonia, ear infection, wheezing, **or** • Two or more of the following: Runny nose, nasal congestion, sore throat, cough, muscle aches, chills, headache, irritability, decreased activity, vomiting, **or** • Clinical discretion
Fleming 2006	• One or more of the following: Fever, pulmonary congestion, pneumonia or ear infection, **or** • Two or more of the following: 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

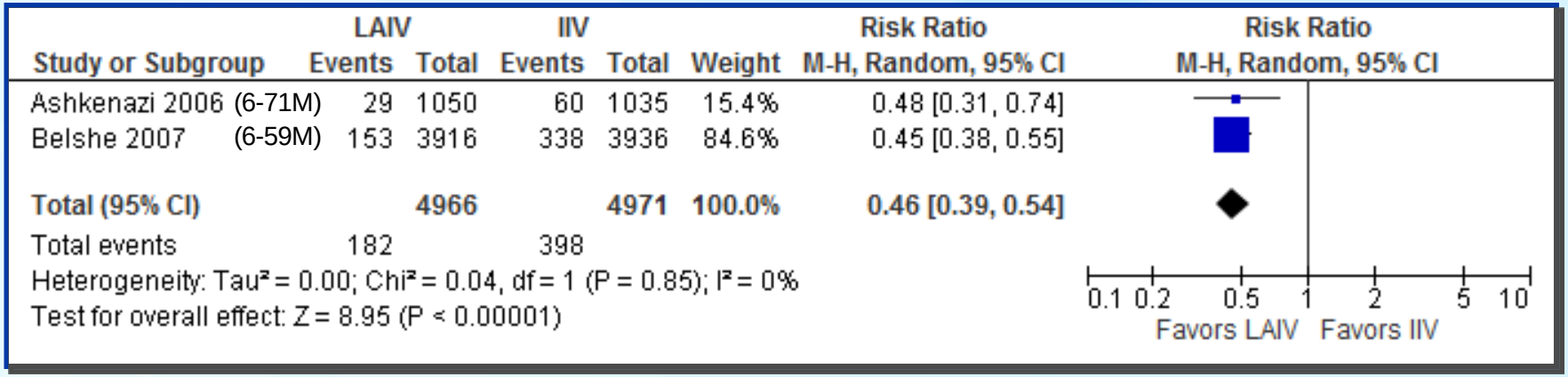
* Associated with respiratory illness; without regard to vaccine match

** Associated with influenza

EVIDENCE PROFILE
2—8 YEARS

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

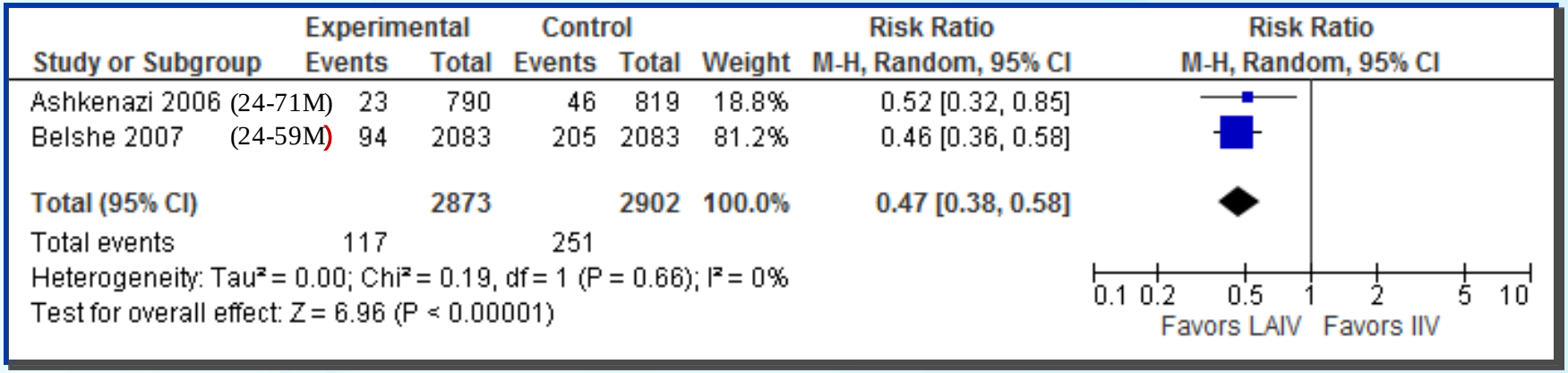
Studies (n)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Effect		Quality
					RR [95% CI]	Risk Difference with LAIV [95% CI]	
2	Not serious	Not Serious	Not Serious	Not Serious	0.46 [0.39 – 0.54]	43 fewer per 1000 [37 – 49 fewer]	1 (High)



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

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

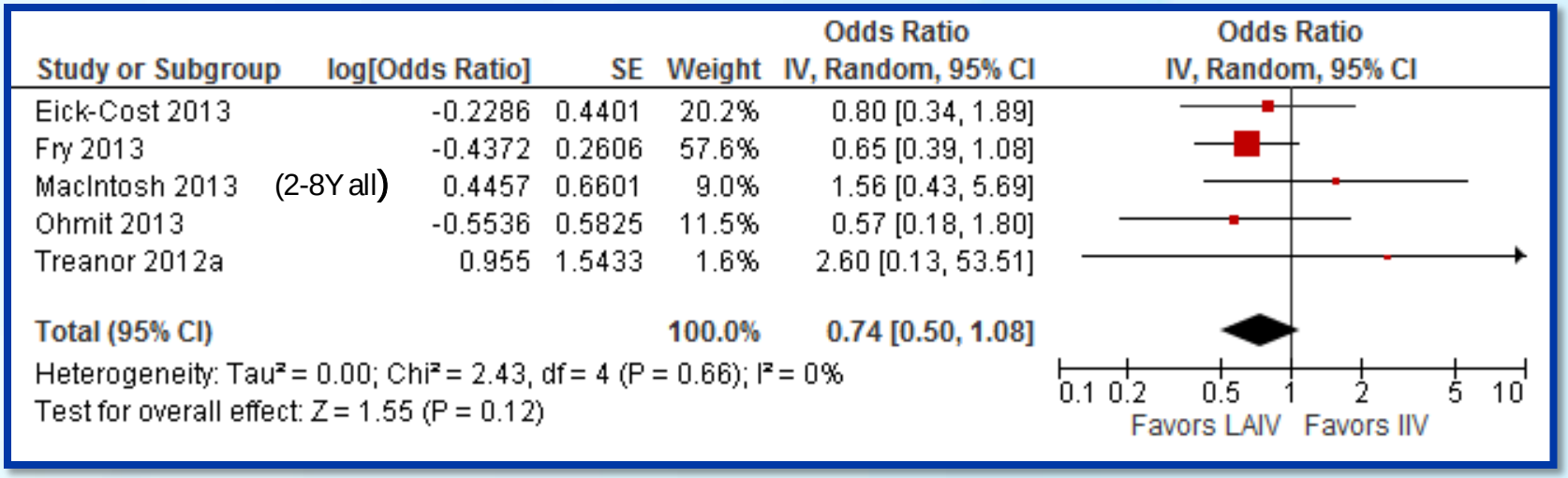
- Data from both studies restricted to children aged ≥24 months (meta-analysis by Ambrose et al, Vaccine 2012)



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

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

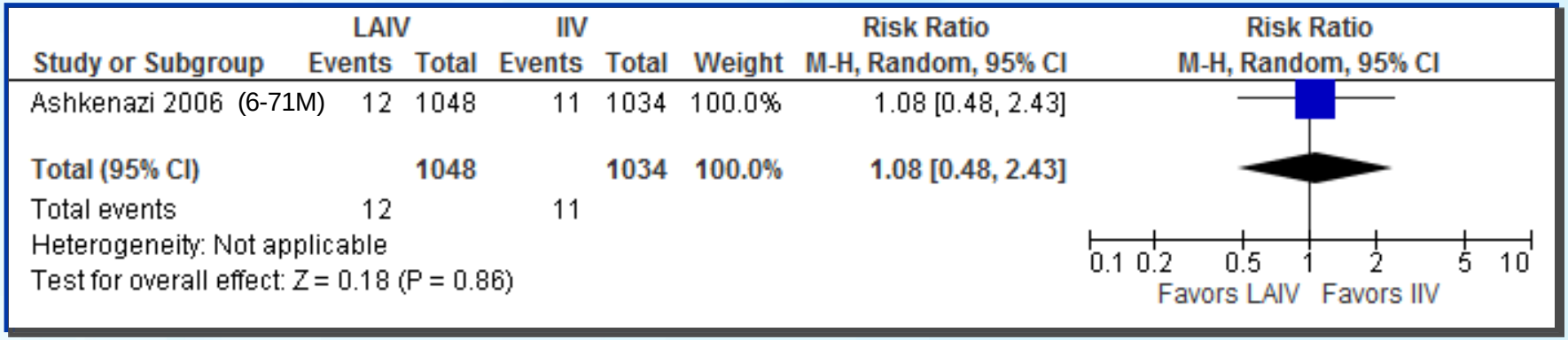
- Downgraded for imprecision (width of confidence interval)



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

Studies (n)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Effect		Quality
					RR [95% CI]	Risk Difference with LAIV [95% CI]	
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)

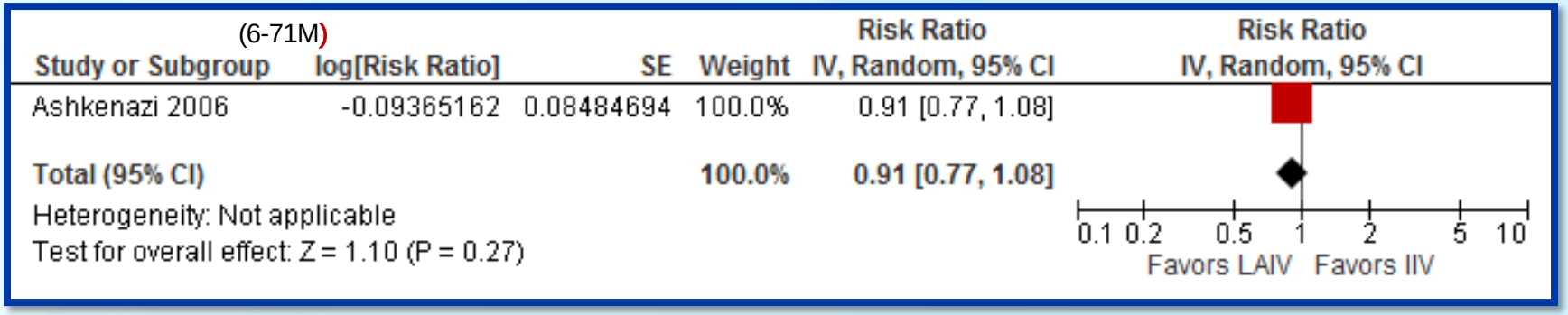


Evidence Profile—LAIV vs. IIV—2-8-year-olds MAARI—Randomized Studies (CRITICAL)

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).

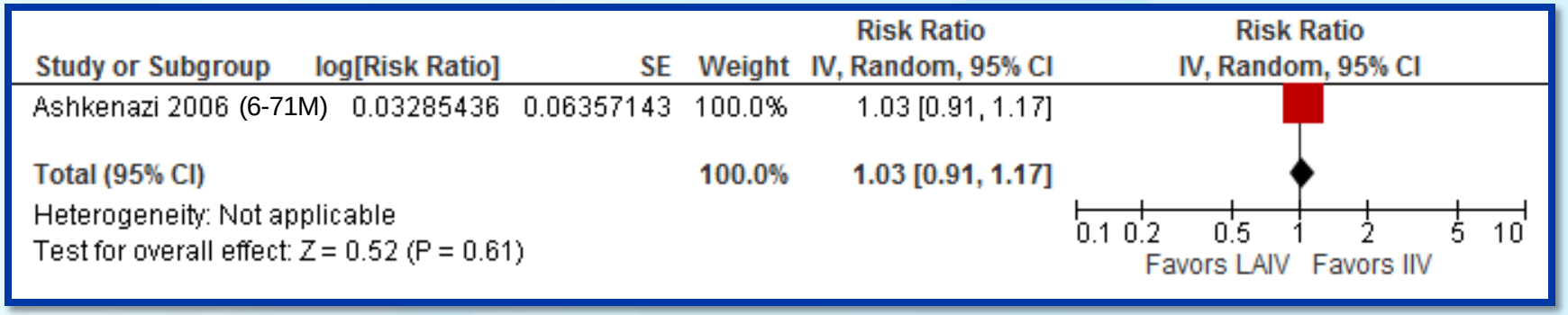
(6-71M)



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

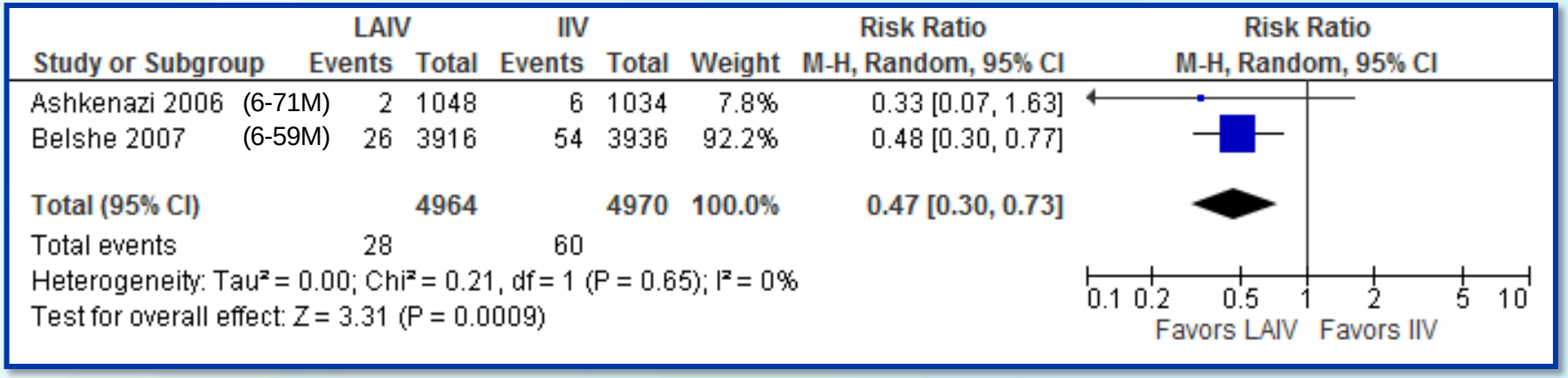
Studies (n)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Effect	Quality
					RR [95% CI]	
1	Not Serious	Not Serious	Serious	Not Serious	1.03 [0.91 – 1.17]	2 (Moderate)

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



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

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

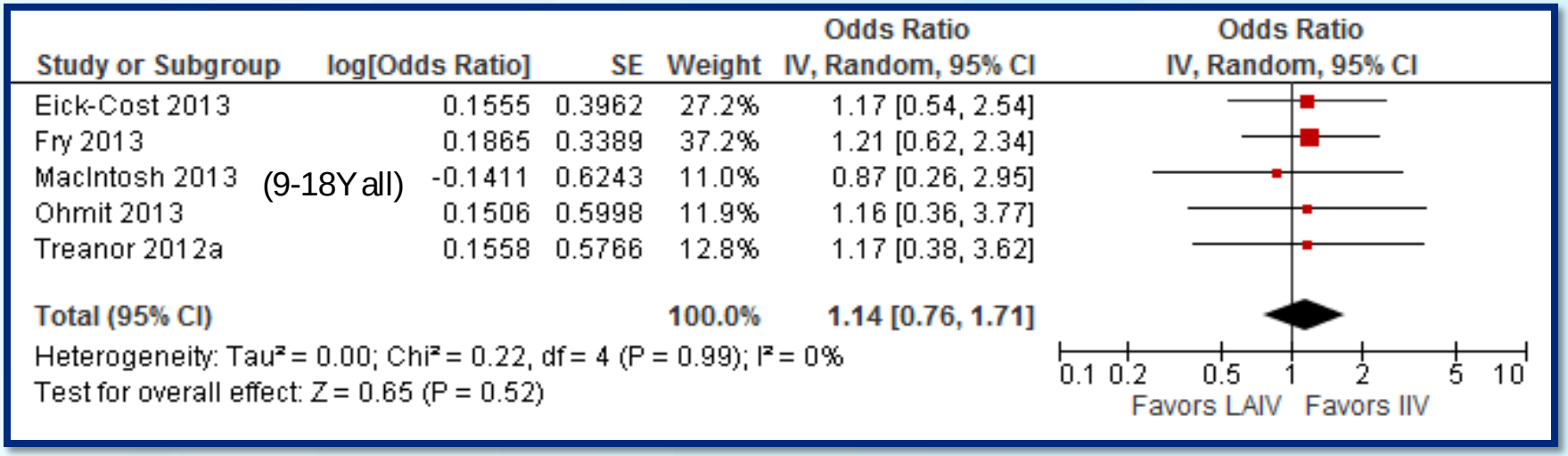


EVIDENCE PROFILE
9—18 YEARS

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

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

- Downgraded for imprecision (width of confidence interval)



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
IIV (with indication for ≤8 years)	IIV3: $7.65 –$14.81 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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