Live-Attenuated and Inactivated Influenza Vaccines for Young Children (GRADE)

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Advisory Committee on Immunization Practices
June 25, 2014

Acknowledgements

CDC

Karen Broder
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Brendan Flannery
Alicia Fry

Faruque Ahmed
Joseph Bresee
Ly Cloessner

CISA

Chip Walter
Buddy Creech
Kathy Edwards

USAF / DoD

Laurie DeMarcus
Katie Tastad
Shauna Zorich

Policy Question

- **Should live attenuated influenza vaccine (LAIV) be recommended preferentially over inactivated influenza vaccine (IIV) for healthy children 2 through 8 years of age?**

- **Rationale for selected age group:**
  - 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 programmatic consistency and simplicity)

- **GRADE assessment presented at February 2014 ACIP**
  - During discussion questions regarding use of LAIV for children with chronic medical conditions

EVIDENCE PROFILE
CHILDREN WITH ASTHMA/WHEEZING

Background

- **ACIP currently does not recommend use of LAIV for children with asthma or other chromic medical conditions conferring high risk of complications or severe illness due to influenza.**

- **2013-14 Package insert for LAIV:**
  - "Children younger than 5 years of age with recurrent wheezing and persons of any age with asthma may be at increased risk of wheezing following administration of FluMist Quadrivalent. FluMist Quadrivalent has not been studied in persons with severe asthma or active wheezing."
  - "The safety of FluMist Quadrivalent in individuals with underlying medical conditions that may predispose them to complications following wild-type influenza infection has not been established"

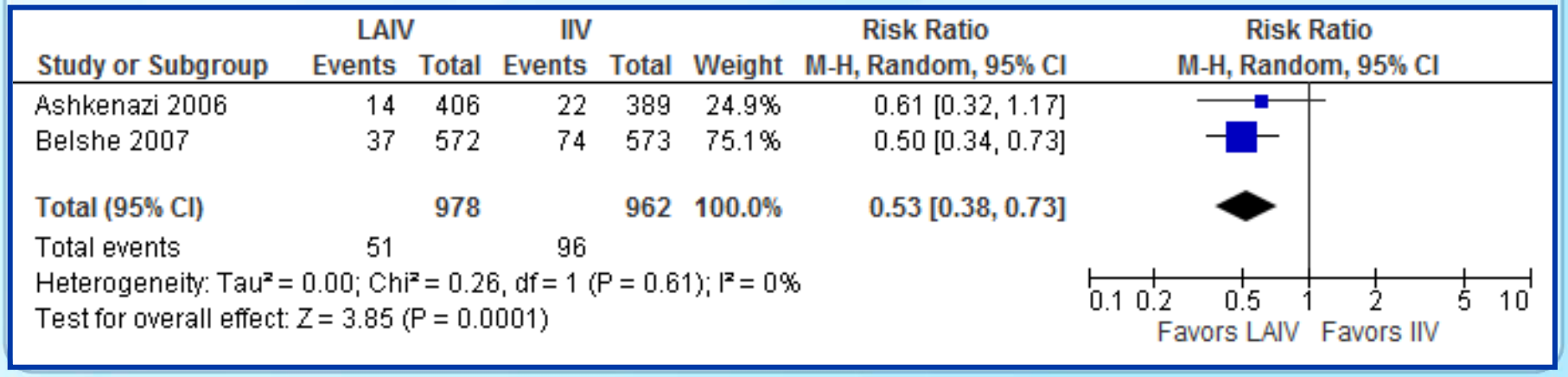
Comparative Studies of LAIV and IIV Including Children with Asthma/Wheezing

Author	Season	Population	Design	Outcomes
Ashkenzi et al. PIDJ, 2006	2002-2003	6-71 months 2 RTIs in previous 12 mos.	Open-label, randomized	Medically documented wheezing Any Wheezing
Fleming et al. PIDJ, 2006	2002-2003	6-17 years clinical diagnosis of asthma plus ≥1 prescription for asthma medication within the past 12 months	Open-label, randomized	Medically attended wheezing Asthma exacerbation Asthma symptoms
Belshe et al. NEJM, 2007	2004-2005	6-59 months included children with mild or moderate asthma or wheezing history more than 42 days before enrollment.	Double-blind, placebo controlled	Medically significant Wheezing Any wheeze Hospitalization

Evidence Profile—LAIV vs. IIV—2-8-year-olds
Lab-confirmed Influenza
Children with Asthma and/or wheezing
(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	0.53 [0.38-0.73]	47 fewer per 1000 [27 fewer-62 fewer]	1 High

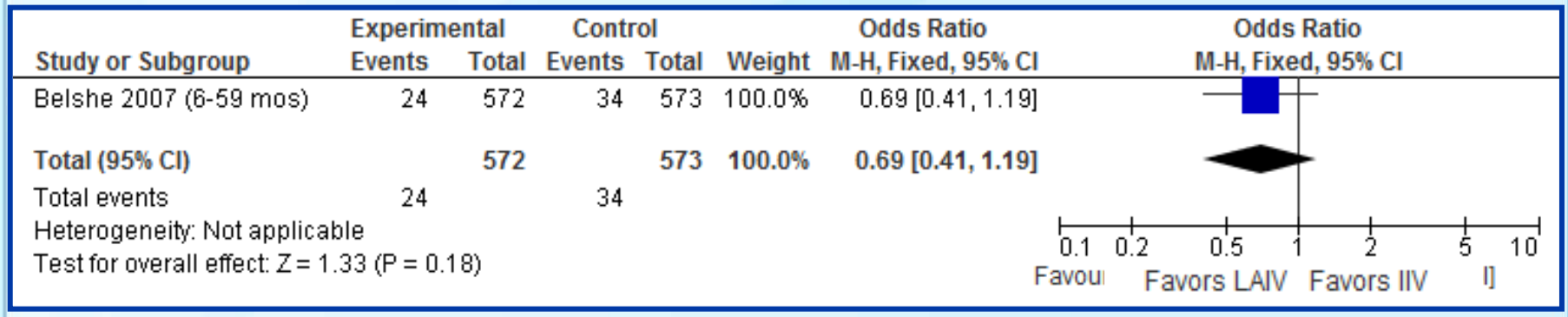
- Culture-confirmed influenza-associated with respiratory illness
- Any strain, without regard to match
- Data limited to children aged 24 through 59 months; children with asthma and/or history of wheezing (post hoc analysis, Ambrose et al, 2012)



Evidence Profile—LAIV vs. IIV—2-8-year-olds
Medically significant wheezing
Children with Asthma and/or wheezing
(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	Not Serious	Serious	0.69 [0.41-1.19]	18 fewer per 1000 [34 fewer-10 more]	2 (Moderate)

- Protocol-defined "medically significant wheezing"
- Data limited to children aged 24 through 59 months; children with asthma and/or history of wheezing (post hoc analysis, Ambrose et al, 2012)
- Follow-up 42 days.



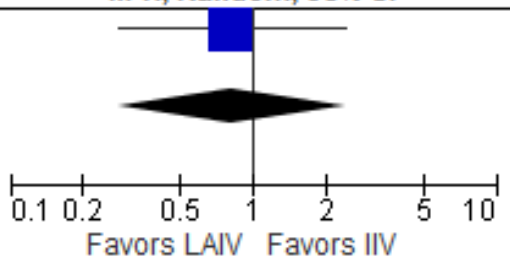
Evidence Profile—LAIV vs. IIV—2-8-year-olds
Medically significant wheezing
Children with Asthma and/or wheezing—no wheeze last 12 months (CRITICAL)

Studies (n)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Effect		Quality
					RR [95% CI]	Risk Difference with LAIV [95% CI]	
1	Not Serious	Not Serious	Not Serious	Serious	0.82 (0.28-2.40)	4 fewer per 1000 (17 fewer-34 more)	2 (Moderate)

- Protocol-defined "medically significant wheezing"
- Data limited to children aged 24 through 59 months; children with asthma and/or history of wheezing (post hoc analysis, Ambrose et al, 2012)
- Follow-up 42 days.

Study or Subgroup	LAIV Events	LAIV Total	IIV Events	IIV Total	Weight	Risk Ratio M-H, Random, 95% CI
Belshe 2007 (6-59 mos)	6	313	7	298	100.0%	0.82 [0.28, 2.40]
Total (95% CI)		**313**		**298**	**100.0%**	**0.82 [0.28, 2.40]**
Total events	6		7			

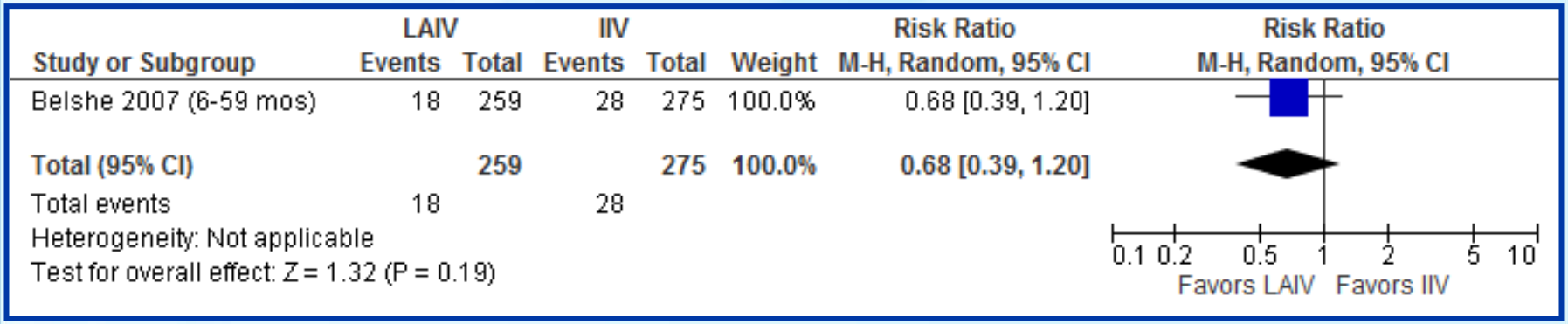
Heterogeneity: Not applicable
Test for overall effect: Z = 0.37 (P = 0.71)



Evidence Profile—LAIV vs. IIV—2-8-year-olds
Medically significant wheezing
Children with Asthma and/or wheezing—wheezed in last 12 months (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	Not Serious	Serious	0.68 [0.39-1.20]	33 fewer per 1000 [63 fewer-20 more)	2 (Moderate)

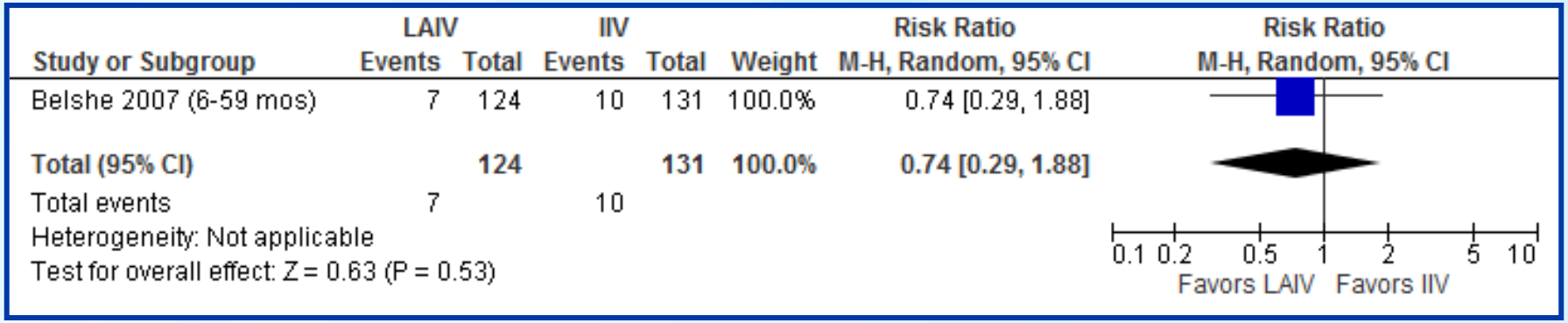
- Protocol-defined "medically significant wheezing"
- Data limited to children aged 24 through 59 months; children with asthma and/or history of wheezing (post hoc analysis, Ambrose et al, 2012)
- Follow-up 42 days.



Evidence Profile—LAIV vs. IIV—2-8-year-olds
Medically significant wheezing
Children with an Asthma Diagnosis (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	Not Serious	Serious	0.74 [0.29-1.88]	20 fewer per 1000 [54 fewer-67 more]	2 (Moderate)

- Protocol-defined "medically significant wheezing"
- Data limited to children aged 24 through 59 months; children with asthma and/or history of wheezing (post hoc analysis, Ambrose et al, 2012)
- Follow-up 42 days.



Studies Involving Other Chronic Conditions

HR Condition	Study	Seasons	Subjects	N	Outcomes
Cancer	Carr 2011	2008-09 1 season	Children 2–21Y	28 LAIV / 27 TIV	**SAFETY** (SAEs): (a) 11Y old LAIV required hospitalization for fever, cough, rhinorrhea, myalgia, mild hypertension and positive Flu A test (b) 2Y old TIV developed afebrile seizure-like activity within 30 minute of TIV injection.
Cystic fibrosis	Gruber 1994	1989-1992 3 seasons	Children 6M–23Y	44 LAIV / 42 TIV subject years	**SAFETY**: fever = no difference **EFFICACY**: LCI = 6 LAIV and 3 TIV
	King 1987	1984-85 1 season	Children & young adults	27 LAIV, then MIV 1 week later	**SAFETY**: Reactions such as fever at Day 3 and Day 6 post-vaccination. Results not analyzed statistically.
HIV	Levin 2008	2004-05 1 season	Children 5–17Y	122 LAIV / 121 TIV	**SAFETY**: SAEs based on dairy cards, phone calls & scheduled study visits on different days for each arm. "Pulmonary signs" included asthma & wheezing ≤28 days = no difference between arms.

Limitations

- Studies not powered to detect differences in wheezing/asthma outcomes among the subgroup of children with history of these conditions (wide confidence intervals).
- Data do not clearly indicate degree of asthma severity for which LAIV benefits outweigh risks.
- Relatively long follow up time (42 days)
- Few comparative data for other chronic medical conditions
- Proposed language changes for the upcoming season focus primarily on healthy children

EVIDENCE PROFILE
HEALTHY CHILDREN AGED 2—8 YEARS

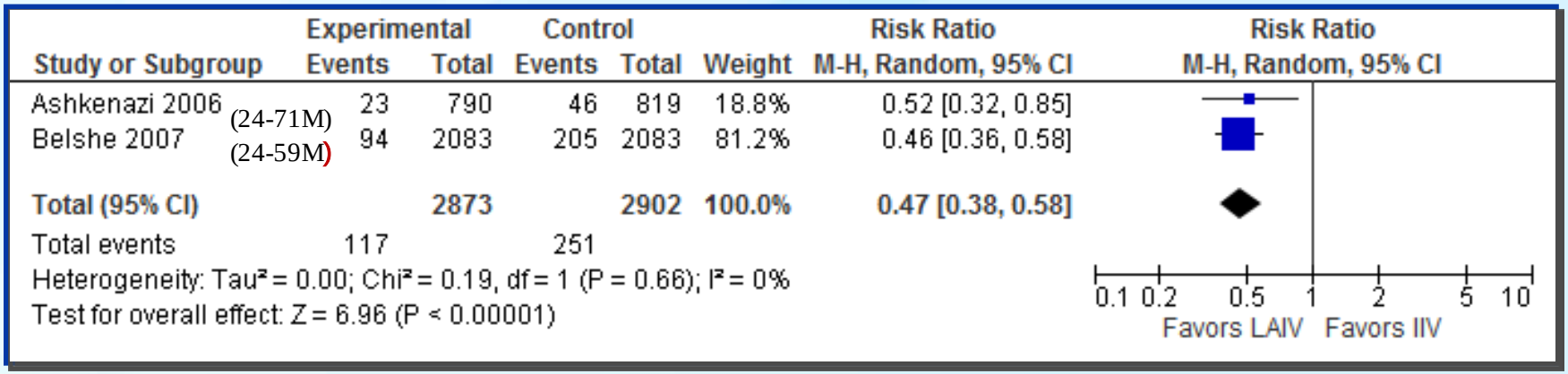
Outcomes

Benefits	Value	Include?	Data?
Lab-confirmed influenza	Critical	Yes	Yes
Influenza-associated mortality	Critical	Yes	No
Influenza-associated hospitalization	Critical	Yes	Yes
MAARI	Critical	Yes	Yes
ILI	Important	Yes	Yes
Influenza-associated acute otitis media	Important	Yes	Yes
Harms	**Value**	**Include?**	**Data?**
Medically-attended wheezing	Critical	Yes	Yes
Medically-significant wheezing	Critical	Yes	Yes
Immediate hypersensitivity/anaphylaxis	Critical	Yes	No
Febrile seizure[2]	Critical	Yes	No
Guillain-Barre syndrome	Critical	Yes	No
Respiratory symptoms	Important	No	--
Other neurologic outcomes	Important	No	--
Fever	Important	Yes	Yes
Any related SAE[3]	--	Yes	Yes

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

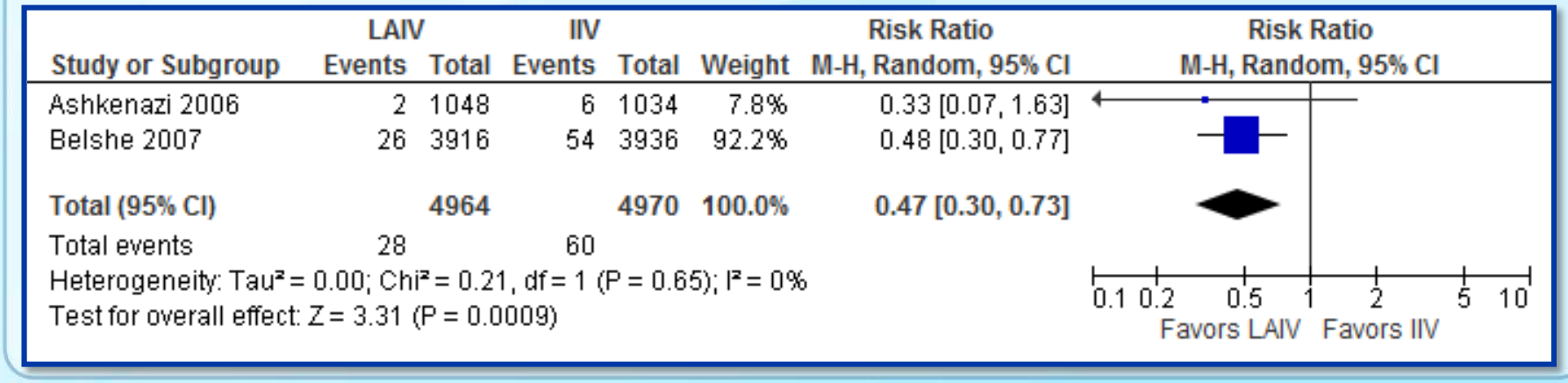
Studies (n)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Effect		Quality
					RR [95% CI]	Risk Difference with LAIV [95% CI]	
2	Not serious	Not Serious	Not Serious	Not Serious	0.47 [0.38 – 0.58]	46 fewer per 1000 [36 – 54 fewer]	1 (High)

- One study (Ashkenazi) was open-label
- 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
Otitis Media—Randomized Studies
(IMPORTANT)

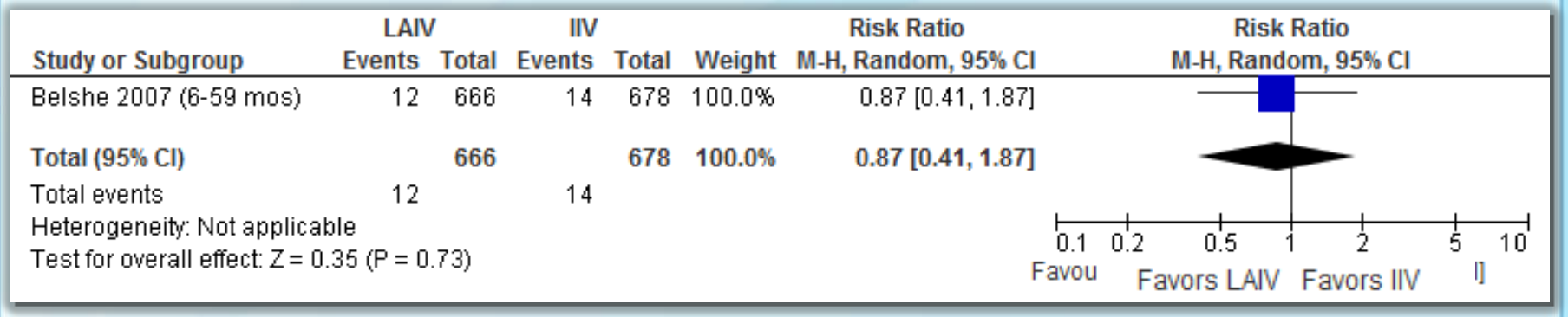
Studies (n)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Effect		Quality
					RR [95% CI]	Risk Diff. with LAIV [95% CI]	
2	Not Serious	Not Serious	Not Serious	Not Serious	0.47 [0.30 – 0.73]	6 fewer per 1000 [3 – 8 fewer]	1 (High)



Evidence Profile—LAIV vs. IIV—2-8-year-olds Medically-Significant Wheezing—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	Not Serious	Serious	0.87 [0.41 – 1.87]	3 fewer per 1000 [12 fewer–18 more]	2 (Moderate)

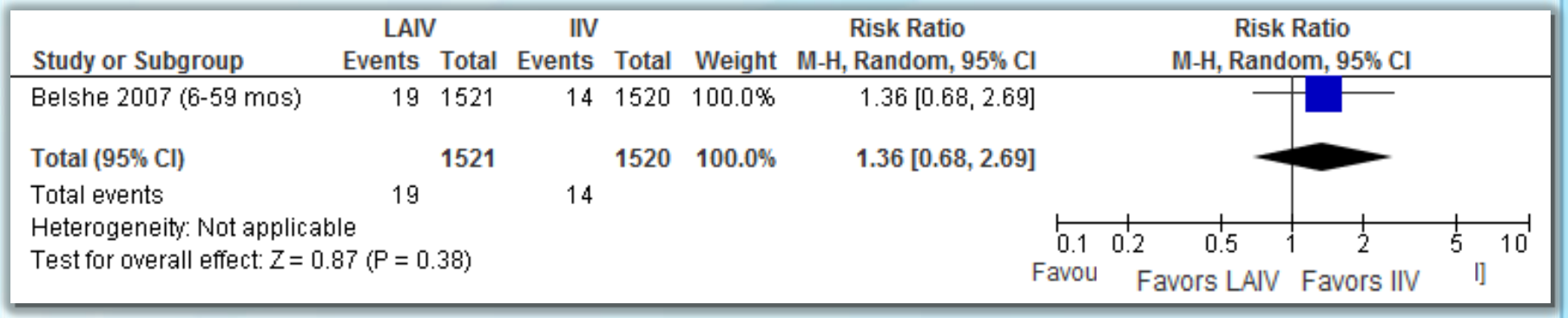
- Protocol-defined "medically significant wheezing"
- Follow-up 42 days.
- Data limited to children aged 24 through 59 months.
- Following dose 1; previously vaccinated.



Evidence Profile—LAIV vs. IIV—2-8-year-olds Medically-Significant Wheezing—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	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.



LAIV and IIV for Healthy 2 through 8 Year Olds: Evidence Table

Outcome	Risk of Bias	Inconsistency	Indirectness	Imprecision	Evidence Type	Overall Evidence Type
Lab Confirmed Influenza (Critical) 2 RCT 5 OBS	 Not serious Not serious	 Not serious Not serious	 Not serious Not serious	 Not serious Serious	 1 (High) 4 (V. Low)	2 (Mod.)
Hospitalization (Critical) 1 RCT	Not serious	Not serious	Serious	Serious	3 (Low)	
MAARI (Critical) 1 RCT	Not serious	Not serious	Serious	Not serious	2 (Mod.)	
ILI (Important) 1 RCT	Not serious	Not serious	Serious	Not serious	2 (Mod.)	
Otitis Media (Important) 2 RCT	Not serious	Not serious	Not serious	Not serious	1 (High)	
Medically Significant Wheezing (Critical) 1 RCT	Not serious	Not serious	Not serious	Serious	2 (Mod.)	2 (Mod.)
Fever (Important) 2 RCT	Not serious	Not serious	Not serious	Serious	2 (Mod.)	
Any Related SAE 2 RCT	Not serious	Not serious	Not serious	Serious	2 (Mod.)	

= lower risk with LAIV = no difference

Relative Costs of LAIV and IIV

- **Formal cost-effectiveness analysis not done**
  - Complex due to large number of influenza products of different presentations (trivalent vs quadrivalent, prefilled syringes vs vials)
- **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

- **2008 cost effectiveness model estimated savings of $45.80 per child with LAIV as compared with IIV**
  - Unclear applicability given current range of products, including quadrivalents

2014-15 Pediatric Influenza Vaccine Price List. Available at: http://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/index.html
Luce BR et al, Vaccine (2008),;26:2841-2848

Considerations For Formulating Recommendations

Key Factor	Comments
Evidence type for benefits and harms	• Overall evidence Type 2 (Moderate) for efficacy and safety. • Evidence lacking for some critical outcomes (influenza-related mortality, febrile seizure, Guillain-Barré syndrome, immediate hypersensitivity) • Studies not powered to detect rare but serious events
Balance between benefits and harms	• Benefits outweigh harms • Modestly better efficacy of LAIV (~47 fewer cases of Lab-confirmed influenza per 1000) • No significant differences in rates of wheezing, fever.
Value	• Influenza Work Group placed high value on prevention of lab-confirmed influenza
Cost-effectiveness	• Uncertainty regarding cost benefit given current available range of vaccines

Limitations

- Published studies used trivalent vaccines (LAIV3 and IIV3)
  - All LAIV now quadrivalent; IIV3 and IIV4 both available
- Unclear whether greater relative efficacy is sustained with repeated vaccination/increasing age
  - Studies in adults generally have noted similar efficacy, or slightly greater efficacy of IIV

Thank You!

For more information please contact Centers for Disease Control and Prevention

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