GRADE evidence for inactivated Vero cell culture-derived JE vaccine (JE-VC; Ixiaro) in children

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CDC

JE vaccine for U.S. children traveling to endemic areas

- In 2009, JE-VC licensed for use in adults in U.S., Europe, and Australia
- ACIP then approved current recommendations for use of JE vaccines
  - JE-VC in adults ≥17 years of age
  - Inactivated mouse brain-derived JE vaccine (JE-MB) for adults and children ≥1 year of age
- JE-MB no longer produced and no JE vaccine available for U.S. children for past 2 years
- In May 2013, JE-VC licensed for use in children ≥2 months of age

Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) steps

- Develop policy question
- Identified and ranked importance of outcomes
- Searched and reviewed of published and unpublished data
- Summarized evidence for critical outcomes
- Evaluated quality of evidence for outcomes
- Assessed values related to options and outcomes
- Reviewed health economic data
- Considerations for formulating recommendations
- ACIP recommendations and GRADE category

Policy question

- Should JE-VC be recommended for use in children 2 months through 16 years of age at increased risk of travel-related exposure to JE virus?
  - Population: Children 2 months through 16 years of age traveling to JE-endemic areas
  - Intervention: JE-VC administered as a 2-dose primary series
  - Current option: No JE vaccine recommended and available for use in children

GRADE evaluation steps

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Outcome measure ranking and inclusion for use of JE-VC in children

	Importance	Include in evidence profile	Data available
Benefits			
Vaccine efficacy to prevent JE	Critical	Yes	No
Seroprotection at 1 month	Critical	Yes	Yes
Seroprotection at 6 months	Critical	Yes	Yes
Harms			
Serious adverse events	Critical	Yes	Yes
Systemic adverse events	Critical	Yes	Yes
Injection site reaction	Important	No	--
Interference with other vaccines	Important	No	--

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Evidence retrieval

- Performed a systemic search and review of published literature
  - Identified 12 studies that reported primary data relevant to the critical outcome measures in children (n=1) or adults (n=11)
- Reviewed unpublished data
  - Two clinical trials of JE-VC in children
  - VAERS reports for JE-VC administered from May 2009–April 2012 to adults in the United States or U.S. military personnel
  - Two clinical trials (one in children, one in adults) of a similar inactivated Vero cell culture-derived JE vaccine (JEEV) from India

GRADE evaluation steps

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Seroprotection at 1 month after a primary series of JE-VC or comparator JE vaccine in children

Sites	Type	Age group	$PRNT_{50}$ titer ≥10	
			JE-VC	Other JE vaccine
India	RCT	1–2 yr	42/44 (95%)	10/11 (91%)
Philippines	Obs*	2 mo–17 yr	478/483 (99%)	--
US/Eur/Aus	Obs	2 mo–17 yr	51/51 (100%)	--

*RCT with no comparative immunogenicity data

CDC

Seroprotection at 1 month after a primary series of JE-VC or comparator JE vaccine in adults

			$PRNT_{50}$ titer ≥10			
Sites	Type	Age group	JE-VC		Other JE vaccine	
US/Eur	RCT	≥18 yr	352/361	(98%)	347/364	(95%)
US	RCT	18–49 yr	21/22	(95%)	14/19	(74%)
India	RCT	18–49 yr	53/54	(98%)	107/108	(99%)
Eur	Obs*	≥18 yr	110/113	(97%)	--	
Eur	Obs*	≥18 yr	126/127	(99%)	--	
US	Obs	≥18 yr	88/92	(96%)	--	
Eur	Obs	≥18 yr	30/31	(97%)	13/15	(87%)

*RCT with no comparative immunogenicity data

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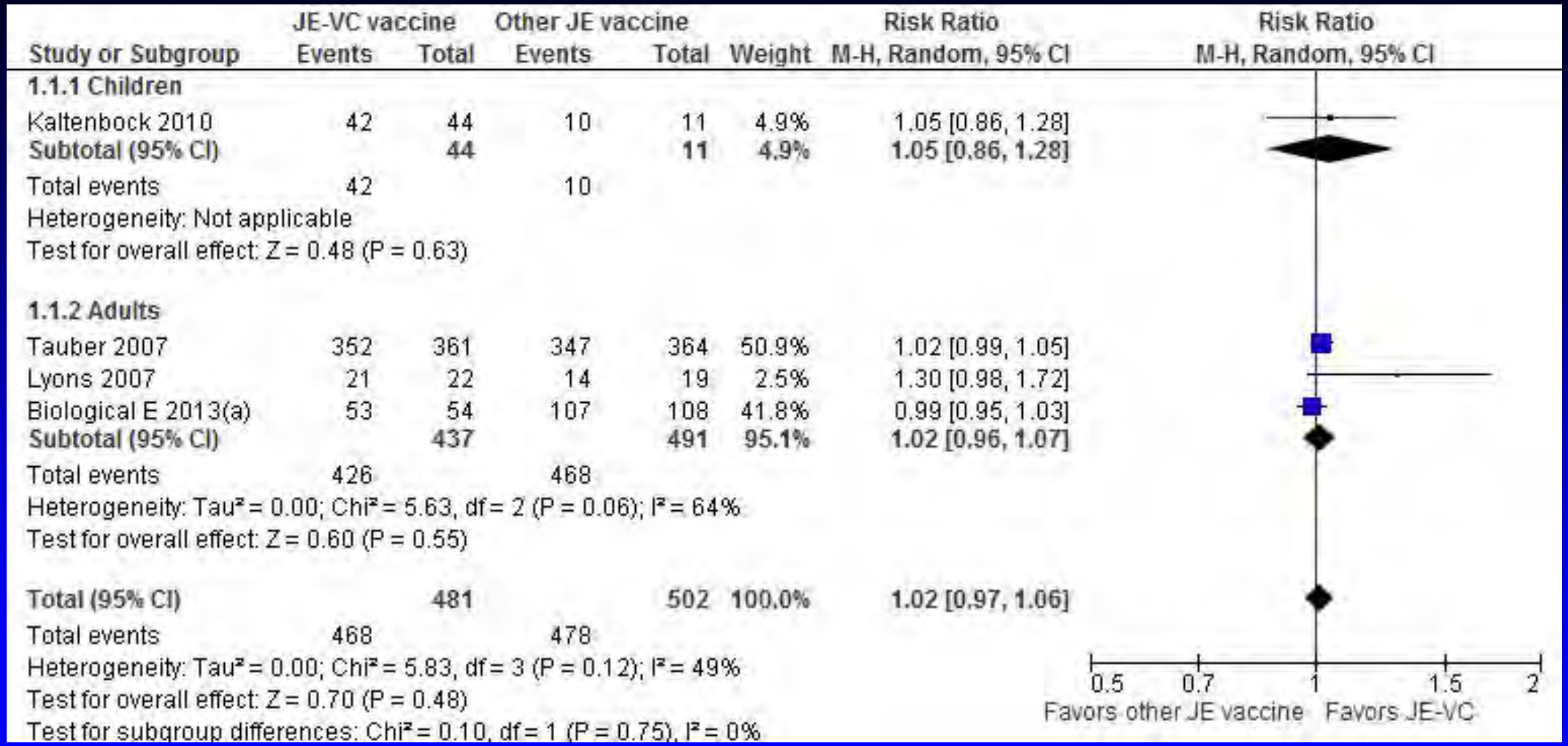
Seroprotection at 1 month after a primary series of JE-VC or comparator JE vaccine in RCTs in children and adults



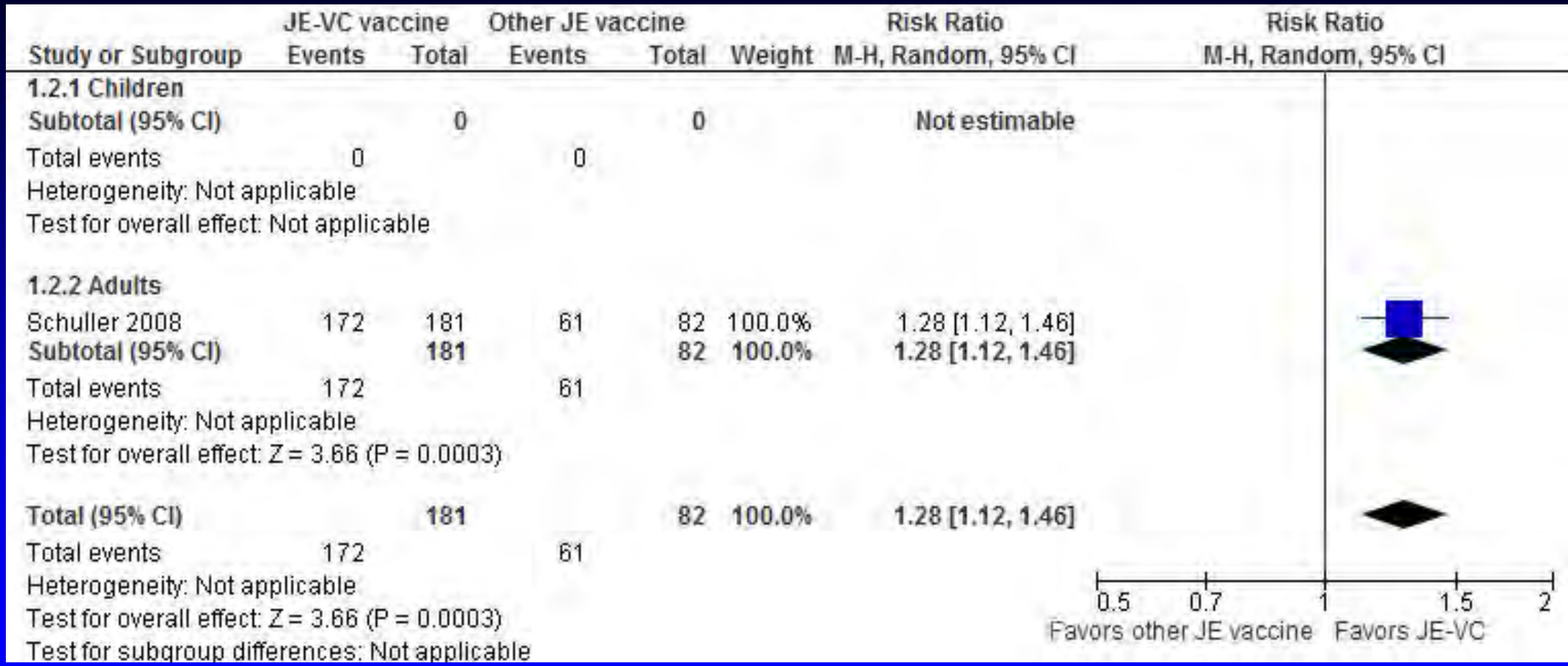
Study or Subgroup	JE-VC vaccine Events	Total	Other JE vaccine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Children						
Kaltenbock 2010	42	44	10	11	4.9%	1.05 [0.86, 1.28]
Subtotal (95% CI)		**44**		**11**	**4.9%**	**1.05 [0.86, 1.28]**
Total events	42		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.48 (P = 0.63)						
1.1.2 Adults						
Tauber 2007	352	361	347	364	50.9%	1.02 [0.99, 1.05]
Lyons 2007	21	22	14	19	2.5%	1.30 [0.98, 1.72]
Biological E 2013(a)	53	54	107	108	41.8%	0.99 [0.95, 1.03]
Subtotal (95% CI)		**437**		**491**	**95.1%**	**1.02 [0.96, 1.07]**
Total events	426		468			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.63$, df = 2 (P = 0.06); $I^2 = 64\%$						
Test for overall effect: Z = 0.60 (P = 0.55)						
Total (95% CI)		**481**		**502**	**100.0%**	**1.02 [0.97, 1.06]**
Total events	468		478			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.83$, df = 3 (P = 0.12); $I^2 = 49\%$						
Test for overall effect: Z = 0.70 (P = 0.48)						
Test for subgroup differences: $Chi^2 = 0.10$, df = 1 (P = 0.75), $I^2 = 0\%$						

Seroprotection at 5-6 months after a primary series of JE-VC or comparator JE vaccine in children or adults*

			$PRNT_{50}$ titer ≥10	
Sites	Type	Age group	JE-VC	Other JE vaccine
Philippines	Obs†	2 mo–17 yr	432/485 (89%)	--
US/Eur/Aus	Obs	2 mo–17 yr	18/18 (100%)	--
Eur	RCT	≥18 yr	172/181 (95%)	61/82 (74%)
Eur	Obs	≥18 yr	96/116 (83%)	--

*5 months after the 2-dose primary series in adults; 6 months after primary series in children.
†RCT with no comparative immunogenicity data.

Seroprotection at 5-6 months after primary series of JE-VC or comparator JE vaccine in RCTs in children and adults



Serious adverse events within 56 days after the first dose of JE-VC or control vaccine in children

Sites	Type	Age group	Serious adverse events	
			JE-VC	Control vaccine
India	RCT	1–2 yr	0/48 (0)	0/12 (0)
Philippines	RCT	2 mo–17 yr	6/1411 (<1%)*	5/458 (1%)
US/Eur/Aus	Obs	2 mo–17 yr	0/60 (0)	--

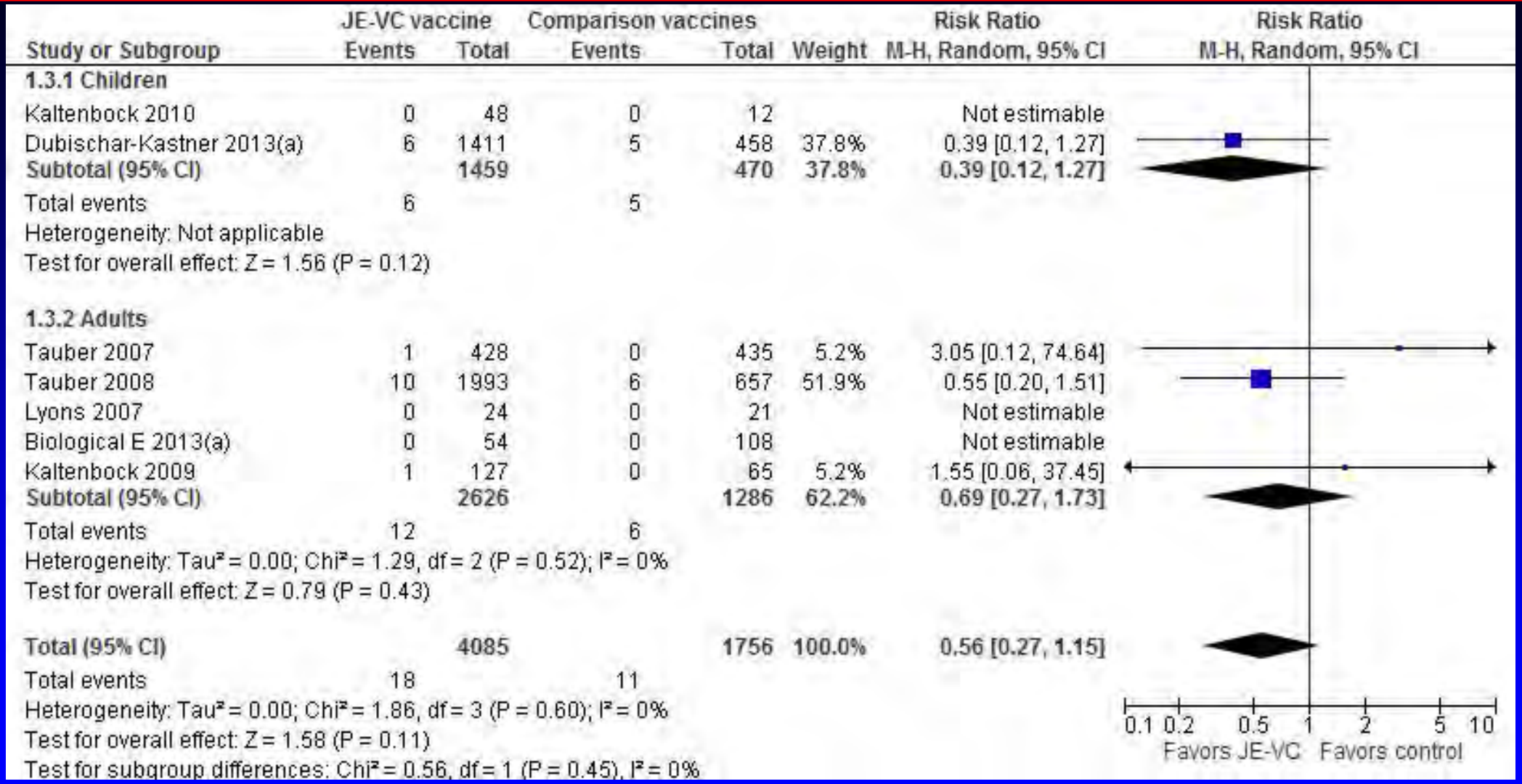
*Two febrile seizures (2 days after dose 2 and 20 days after dose 1), cellulitis (9 days after dose 2), gastroenteritis (12 days after dose 1), pneumonia (23 days after dose 2), dengue (24 days after dose 1)

Serious adverse events within 56 days after the first dose of JE-VC or control vaccine in adults

Sites	Type	Age group	Serious adverse events	
			JE-VC	Control vaccine
US/Eur	RCT	≥18 yr	1/428 (<1%)	0/435 (0)
US/Eur/Aus	RCT	≥18 yr	10/1993 (<1%)	6/657 (1%)
US	RCT	18–49 yr	0/24 (0)	0/21 (0)
India	RCT	18–49 yr	0/54 (0)	0/108 (0)
Eur	Obs	≥18 yr	1/127 (1)	0/65 (0)
Eur	Obs*	≥18 yr	0/125 (0)	--
US	Obs	≥18 yr	0/123 (0)	--

*RCT with no comparative safety data.

Serious adverse events within 56 days after the first dose of JE-VC or control vaccine in RCTs in children and adults

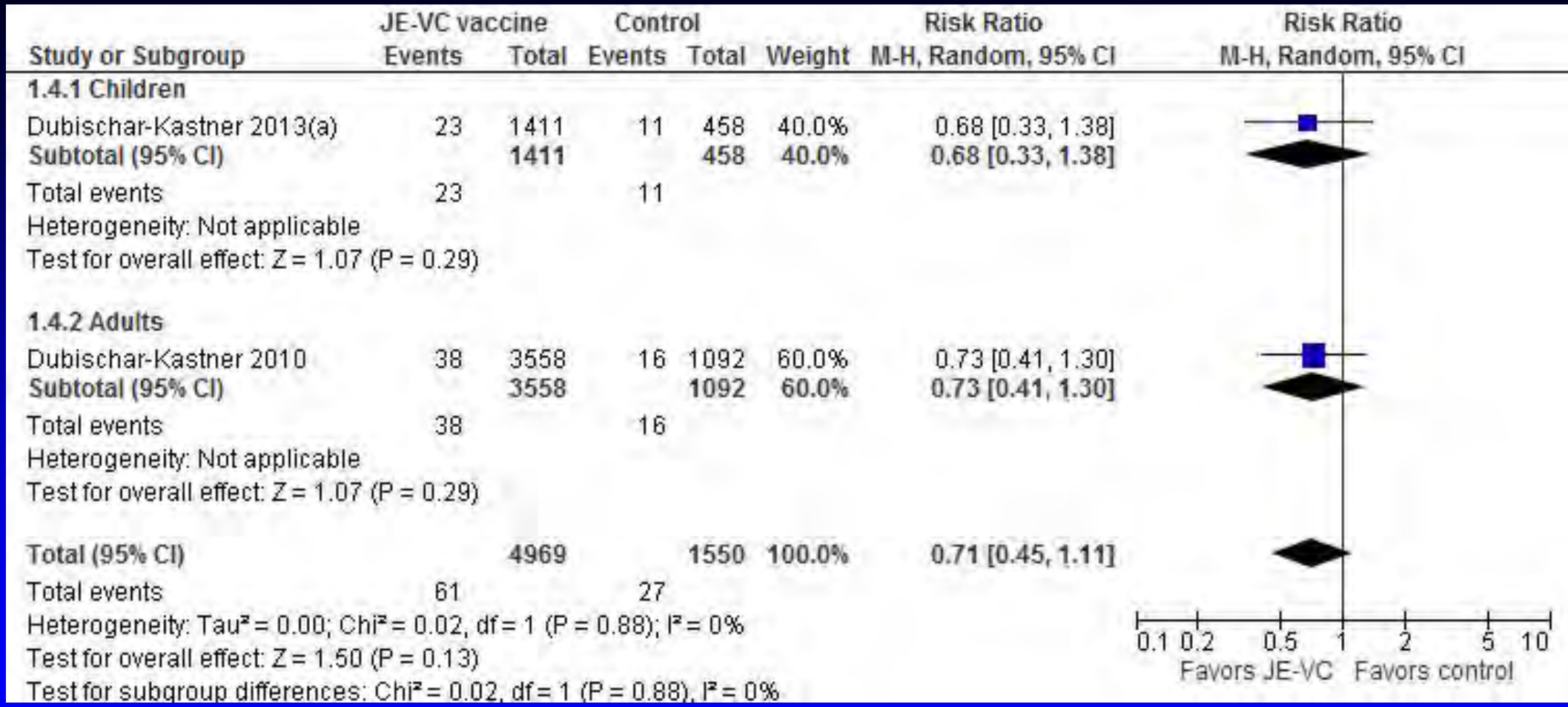


Serious adverse events at 6-7 months after the first dose of JE-VC or control vaccine in children and adults*

Sites	Type	Age group	Serious adverse events	
			JE-VC	Control vaccine
Philippines	RCT	2 mo–17 yr	23/1411 (2%)	11/458 (1%)
US/Eur/Aus	Obs	2 mo–17 yr	2/60 (3%)	--
US/Eur/Aus	RCT	≥18 yr	38/3558 (1%)	16/1092 (1%)

*6 months after the first dose in adults; 7 months after the first dose in children.

Serious adverse events within 6-7 months after JE-VC or control vaccine in RCTs in children and adults



Study or Subgroup	JE-VC vaccine Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Children						
Dubischar-Kastner 2013(a)	23	1411	11	458	40.0%	0.68 [0.33, 1.38]
Subtotal (95% CI)		**1411**		**458**	**40.0%**	**0.68 [0.33, 1.38]**
Total events	23		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.07 (P = 0.29)						
1.4.2 Adults						
Dubischar-Kastner 2010	38	3558	16	1092	60.0%	0.73 [0.41, 1.30]
Subtotal (95% CI)		**3558**		**1092**	**60.0%**	**0.73 [0.41, 1.30]**
Total events	38		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.07 (P = 0.29)						
Total (95% CI)		**4969**		**1550**	**100.0%**	**0.71 [0.45, 1.11]**
Total events	61		27			
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%						
Test for overall effect: Z = 1.50 (P = 0.13)						
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.88), I² = 0%						

Serious adverse events reported through post-marketing surveillance following receipt of JE-VC in adults

Sites	Reporting period	Doses distributed	Serious adverse events	
			No.	Rate per 100,000
US/Eur/Aus	Apr 2009–Mar 2010	246,687*	4	1.6
US	May 2009–Apr 2012	275,848*	9	3.3

*85,583 doses distributed in the United States from May 2009–March 2010 are included in both studies.

Fever within 7 days after a dose of JE-VC or control vaccine in children or adults

Sites	Type	Age group	Fever*	
			JE-VC	Control vaccine
India	RCT	1–2 yr	1/48 (2%)	1/12 (8%)
Philippines	RCT	2 mo–17 yr	136/1411 (10%)	52/458 (11%)
US/Eur/Aus	Obs	2 mo–17 yr	4/60 (7%)	--
US/Eur/Aus	RCT	≥18 yr	64/1993 (3%)	20/657 (3%)
US	RCT	18–49 yr	5/24 (21%)	1/21 (5%)
US	Obs	≥18 yr	6/123 (5%)	--

*Definition varies by study ranging from ≥37.6C to ≥38.0C.

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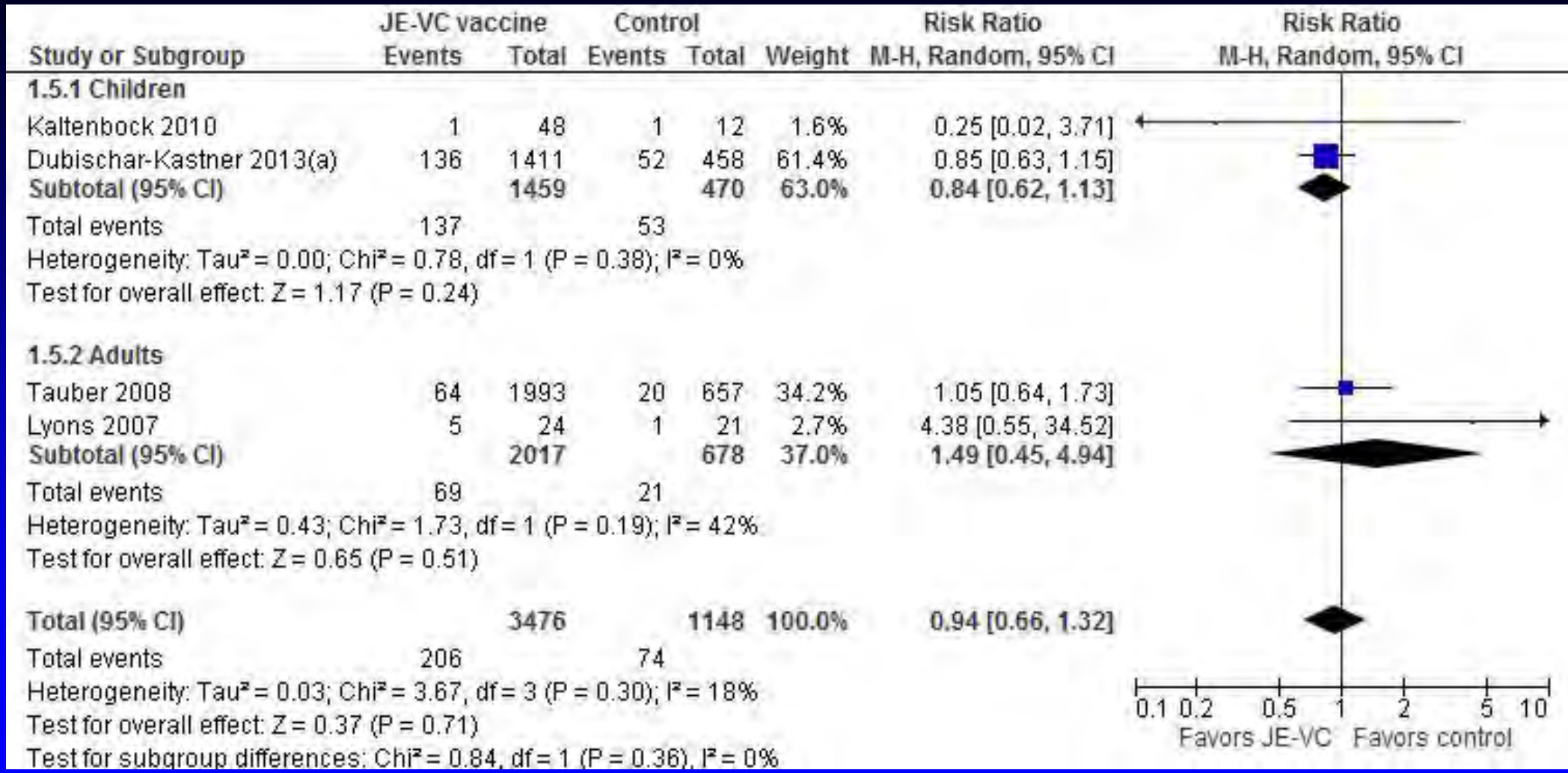
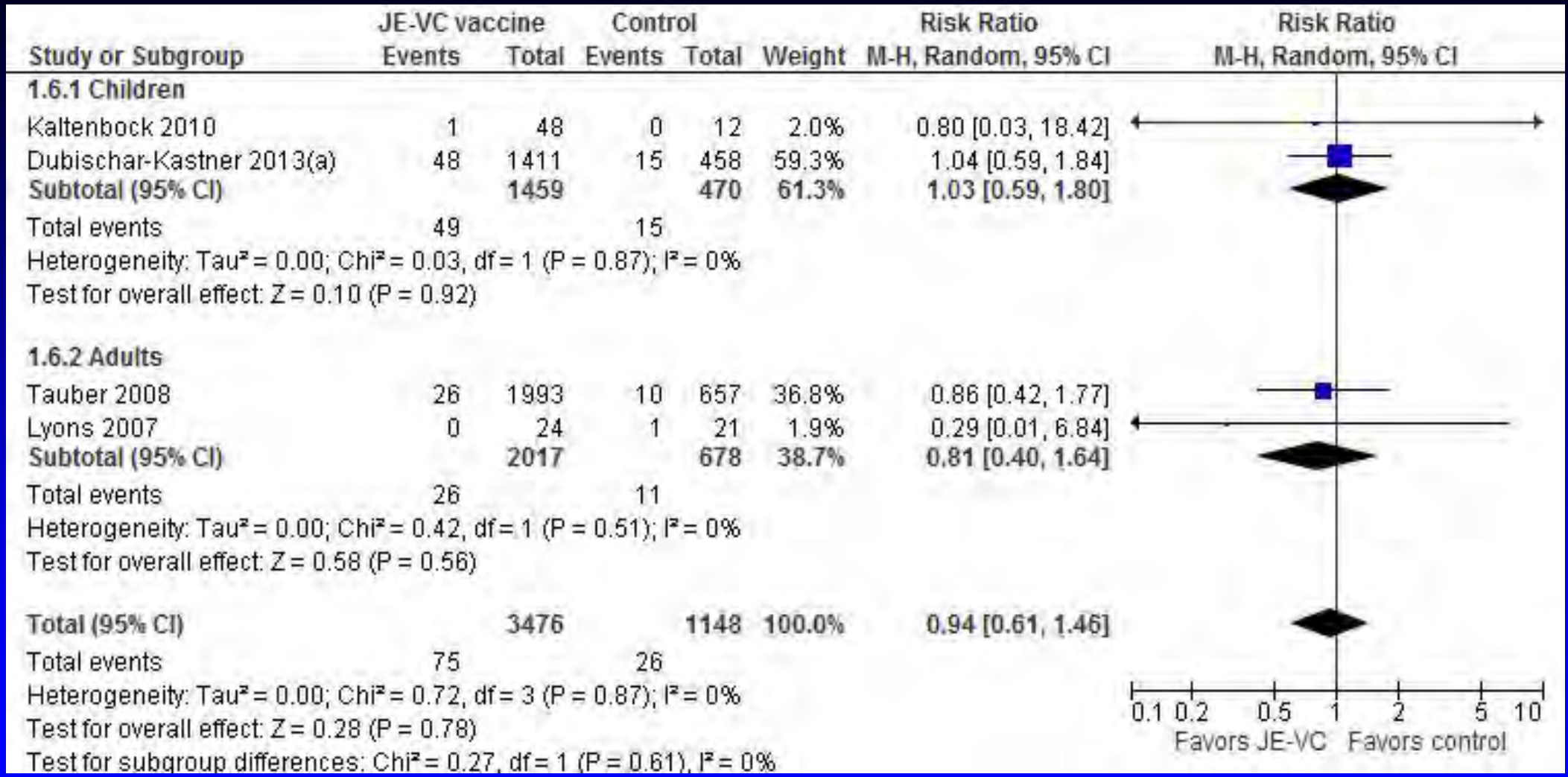
Fever within 7days after JE-VC or control vaccine in RCTs in children and adults



Rash within 7 days after a dose of JE-VC or control vaccine in children or adults

Sites	Type	Age group	Rash	
			JE-VC	Control vaccine
India	RCT	1–2 yr	1/48 (2%)	0/12 (0)
Philippines	RCT	2 mo–17 yr	48/1411 (3%)	15/458 (3%)
US/Eur/Aus	Obs	2 mo–17 yr	2/60 (3%)	--
US/Eur/Aus	RCT	≥18 yr	26/1993 (1%)	10/657 (2%)
US	RCT	18–49 yr	0/24 (0)	1/21 (5%)
US	Obs	≥18 yr	2/123 (2%)	--

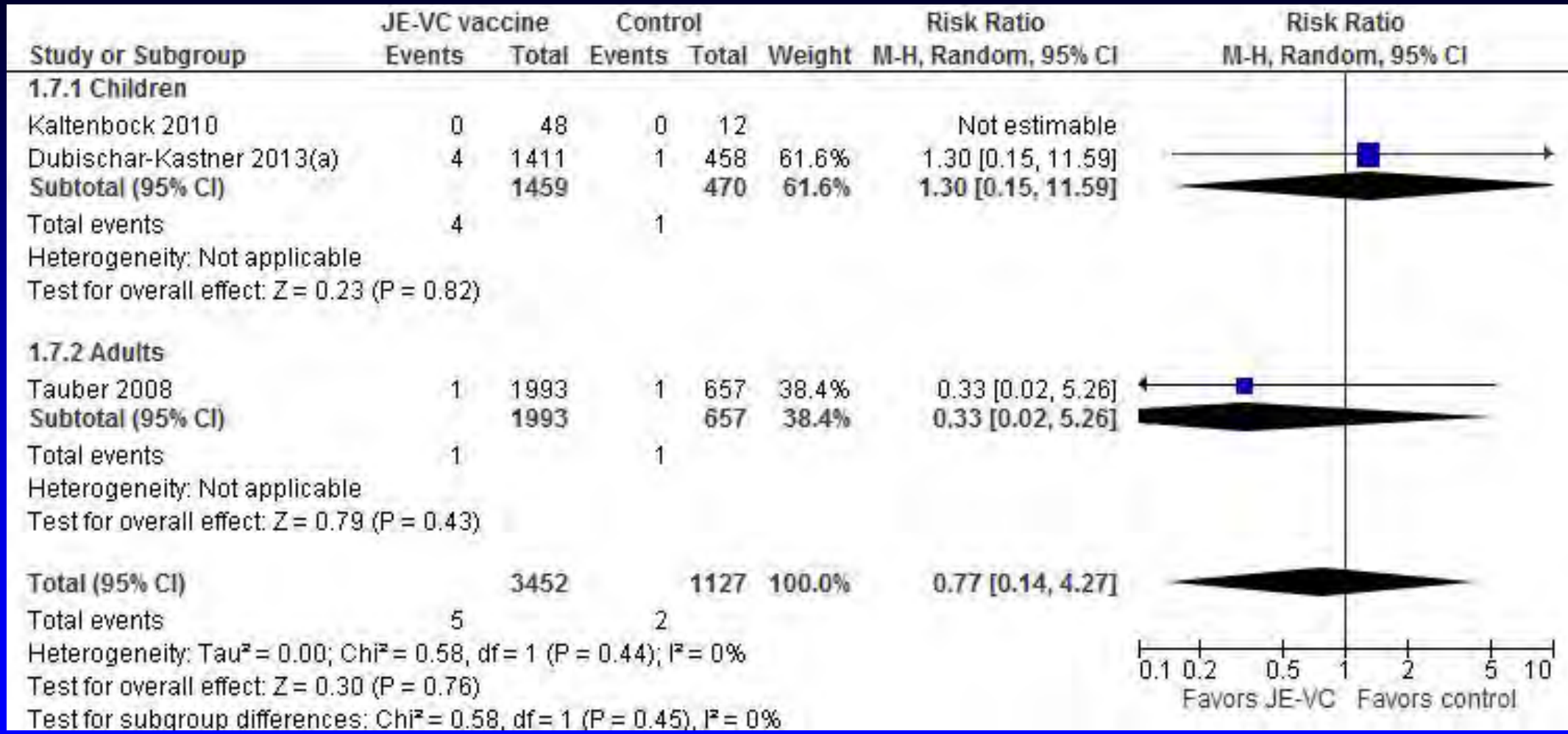
Rash within 7days after JE-VC or control vaccine in RCTs in children and adults



Hypersensitivity or urticaria within 56 days after the first dose of JE-VC or control vaccine in children or adults

Sites	Type	Age group	Hypersensitivity or urticaria	
			JE-VC	Control vaccine
India	RCT	1–2 yr	0/48 (0)	0/12 (0)
Philippines	RCT	2 mo–17 yr	4/1411 (<1%)	1/458 (<1%)
US/Eur/Aus	Obs	2 mo–17 yr	0/60 (0)	--
US/Eur/Aus	RCT	≥18 yr	1/1993 (<1%)	1/657 (<1%)
US	Obs	≥18 yr	0/123 (0)	--

Hypersensitivity or urticaria in 56 days after the first dose of JE-VC or control vaccine in RCTs in children and adults



Neurologic adverse events within 56 days after the first dose of JE-VC or control vaccine in children or adults

Sites	Type	Age group	Neurologic adverse events*	
			JE-VC	Control vaccine
India	RCT	1–2 yr	0/48 (0)	0/12 (0)
Philippines	RCT	2 mo–17 yr	5/1411 (<1%)	3/458 (<1%)
US/Eur/Aus	Obs	2 mo–17 yr	0/60 (0)	--
US/Eur/Aus	RCT	≥18 yr	26/1993 (1)	8/657 (1%)
US	Obs	≥18 yr	0/123 (0)	--

*Excludes headache; no cases of meningitis, encephalitis, acute disseminated encephalomyelitis, or Guillain Barré syndrome were reported.

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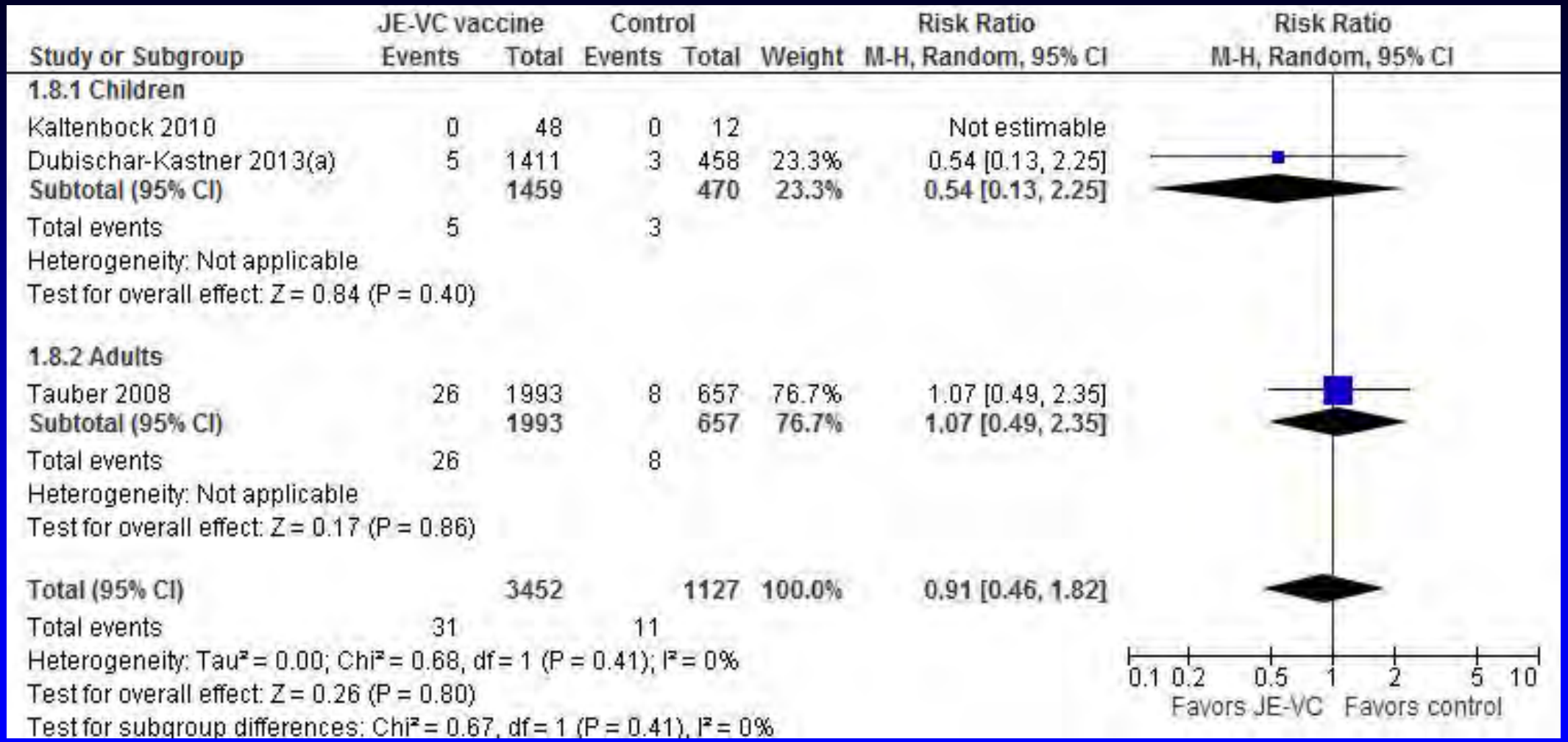
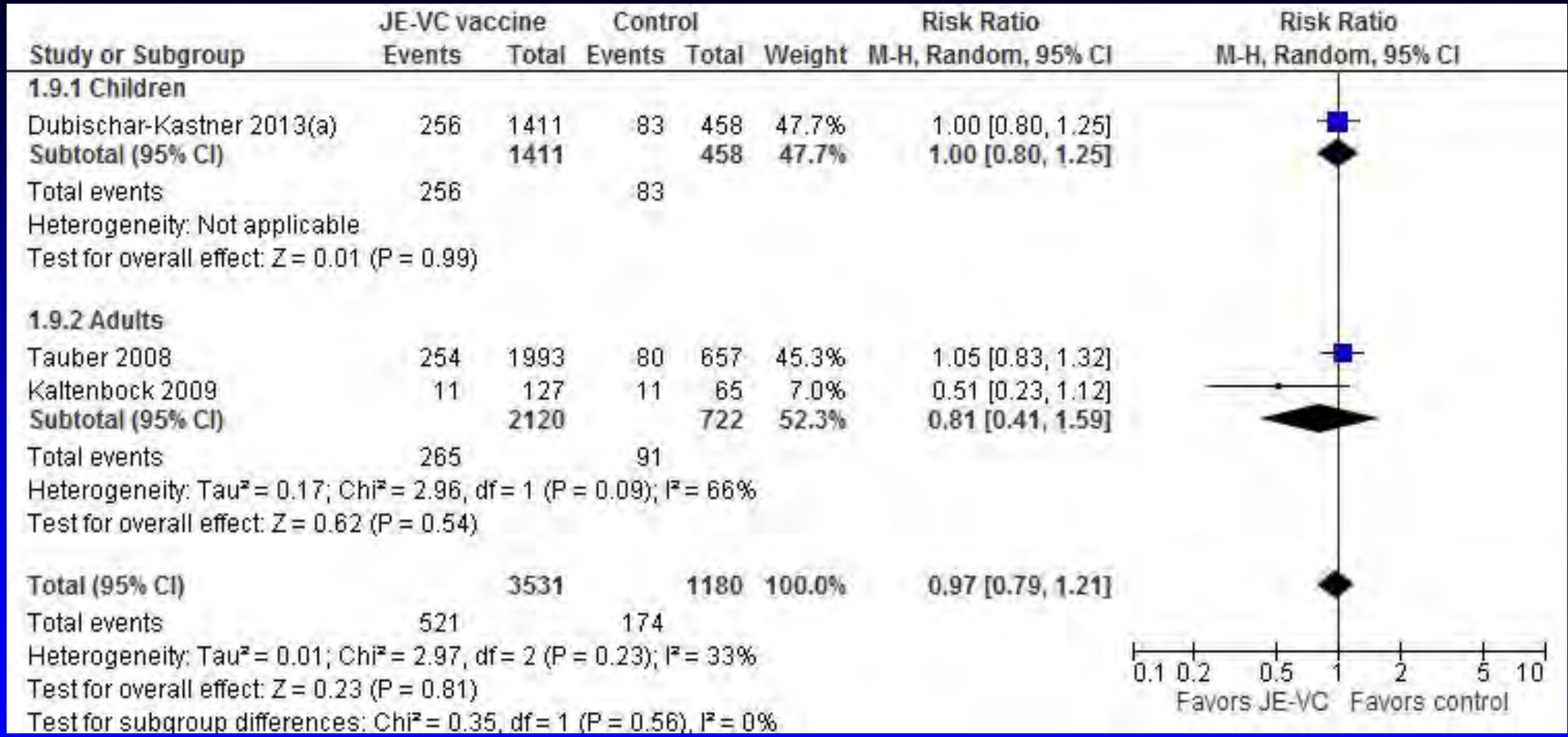
Neurologic adverse events in 56 days after the first dose of JE-VC or control vaccine in RCTs in children and adults



Medically attended adverse events within 56 days after the first dose of JE-VC or control vaccine in children or adults

Sites	Type	Age group	Medically attended adverse events	
			JE-VC	Control vaccine
Philippines	RCT	2 mo–17 yr	256/1411 (18%)	83/458 (18%)
US/Eur/Aus	Obs	2 mo–17 yr	3/60 (5%)	--
US/Eur/Aus	RCT	≥18 yr	254/1993 (13%)	80/657 (12%)
Eur	RCT	≥18 yr	11/127 (9%)	11/65 (17%)
US	Obs	≥18 yr	0/123 (0)	--

Medically attended adverse events in 56 days after first dose of JE-VC or control vaccine in RCTs in children and adults



Hypersensitivity reactions reported through post-marketing surveillance following receipt of JE-VC in adults

Sites	Reporting period	Doses distributed	Hypersensitivity	
			No.	Rate per 100,000
US/Eur/Aus	Apr 2009–Mar 2010	246,687	11*	4.5
US	May 2009–Apr 2012	275,848	13†	4.7

*Five reports of rash, and one report each of urticaria, glossodynia, oral hypoaesthesia, oropharyngeal spasm, pruritus, and swollen tongue.

†These 13 events occurred within 14 days after vaccination; seven after administration of JE-VC alone and six after concomitant administration of JE-VC with other vaccines.

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Neurologic adverse events reported through post-marketing surveillance following receipt of JE-VC in adults

			Neurologic adverse event	
Sites	Reporting period	Doses distributed	No.	Rate per 100,000
US	May 2009–Apr 2012	275,848	5*	1.8

*One report of encephalitis at 39 days after vaccination with JE-VC and four other vaccines, and four reports of seizures within 5 days after vaccination; three of the subjects with seizures had received other vaccines and for one there was no information available.

Seroprotection, serious adverse events, and systemic adverse events following receipt of JEEV in children

Outcome	JEEV*	JenceVac†
$PRNT_{50}$ titer ≥10 at 1 month	258/280 (92%)	140/142 (99%)
Serious adverse events within 56 days	1/304 (<1%)	1/152 (1%)
Systemic adverse events within 7 days		
Fever	34/304 (11%)	24/152 (16%)
Rash	4/304 (1%)	2/152 (1%)

*JEEV is manufactured by Biological E (India) with technology transfeerd from Intercell. JEEV and JE-VC use the same virus strain, adjuvant, and virus purification; however, no comparability studies have been completed and it cannot be assumed that the two final vaccine products are the same.

†Inactivated mouse brain-derived JE vaccine from Korea.

CDC

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Initial evidence type used for GRADE analysis

1 =	RCTs or overwhelming evidence from observational studies
2 =	RCTs with important limitations or exceptionally strong evidence from observational studies
3 =	Observational studies or RCTs with notable limitations
4 =	Clinical experience, observational studies with important limitations, or RCTs with several major limitations

Limitations and evidence type for benefits of JE-VC in children

	Seroprotection at 1 mo		Seroprotection at 6 mos	
Design (# studies)	RCT (4)	Obs (6)	RCT (1)	Obs (3)
Risk of bias	No serious	No serious	No serious	No serious
Inconsistency	No serious	No serious	No serious	No serious
Indirectness	Yes*	No serious	Yes*	No serious
Imprecision	No serious	No serious	No serious	No serious
Evidence type†	2	3	2	3

*Indirectness due to different population (majority of data are in adults).
†Other criteria considered that had no effect on evidence type included publication bias, strength of association, dose response, and residual confounding.

Limitations and evidence type for harms of JE-VC in children

	Serious adverse events		Systemic adverse events	
Design (# studies)	RCT (8)	Obs (5)	RCT (5)	Obs (4)
Risk of bias	Yes*	No serious	Yes*	No serious
Inconsistency	No serious	No serious	No serious	No serious
Indirectness	Yes†	Yes†	No serious	No serious
Imprecision	No serious	No serious	No serious	No serious
Evidence type‡	3	4	2	3

*Risk of bias due to inadequate blinding of study participants and personnel.
†Indirectness due to different population (majority of data are in adults).
‡Other criteria considered that had no effect on evidence type included publication bias, strength of association, dose response, and residual confounding.

Overall quality of evidence for JE-VC in children

Outcome	Design (# studies)	Evidence type*	Overall evidence
Seroprotection at 1 mo	RCT (4)	2	2
Seroprotection at 6 mos	RCT (1)	2	
Serious adverse events	RCT (8)	3	
Systemic adverse events	RCT (5)	2	

*Both RCTs and observational studies considered in body of evidence, but final evidence type based on RCT studies that provided the higher quality of evidence

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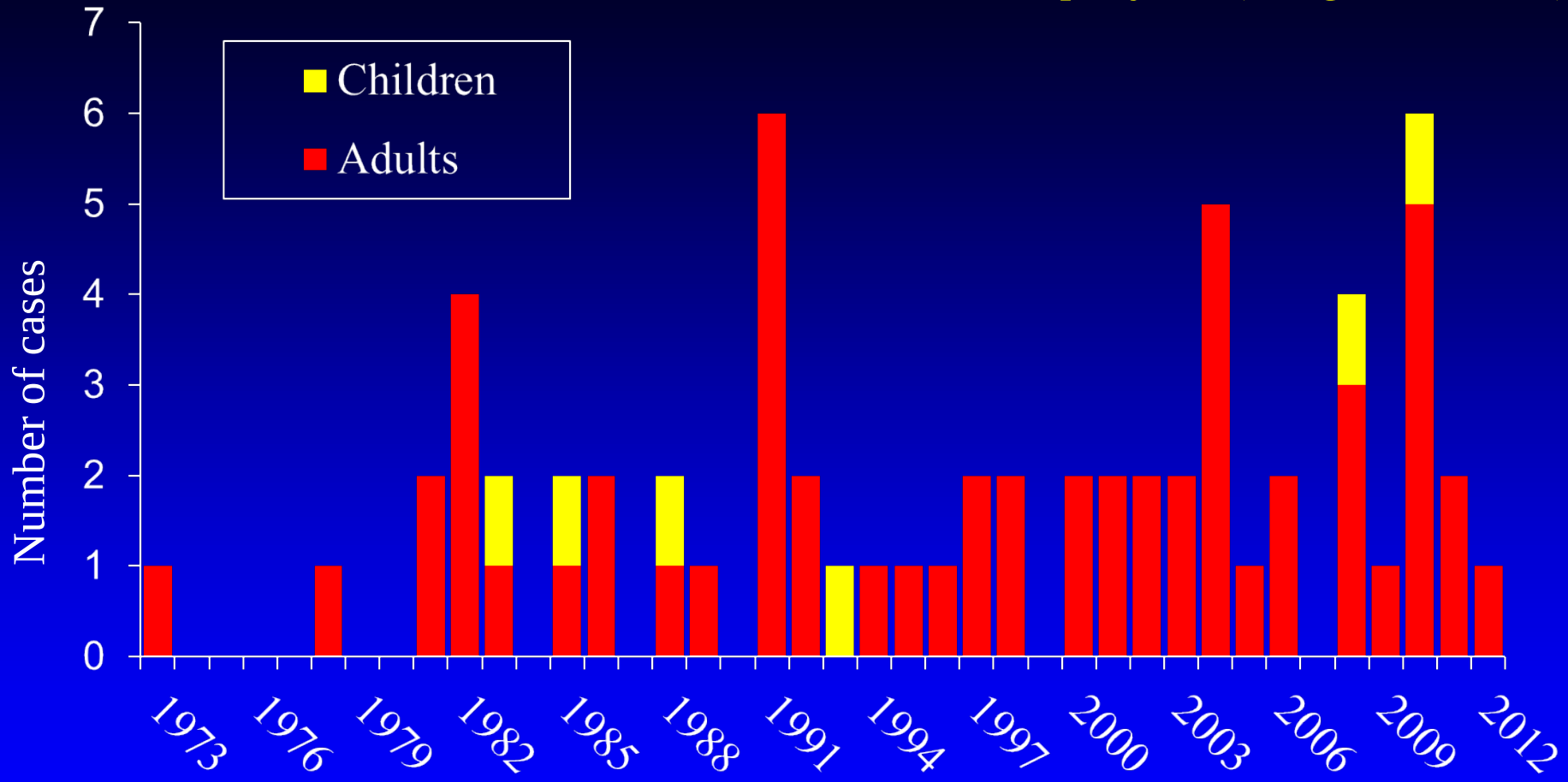
JE among travelers from non-endemic areas

- For most travelers, the risk for JE is very low but it varies based on destination, duration, season, and activities
- >300 JE cases reported among U.S. military personnel during the Vietnam and Korean Wars
- From 1973-2012, 65 cases of travel-associated JE among people from non-endemic areas reported to CDC or in literature*
  - 6 (9%) cases in children <17 years of age

Travel-associated JE cases by year, 1973–2012 (N=65)*

Median 1 case per year (Range: 0-6 cases)



*Two cases occurred before 1993 but specific year not reported

CDC

Outcomes of travel-associated JE cases, 1973–2012

	All ages (N=65)	Adults (N=59)	Children (N=6)
Died	13 (20%)	11 (19%)	2 (33%)
Survived			
Sequelae	28 (43%)	25 (42%)	3 (50%)
No sequelae	15 (23%)	15 (25%)	0 (0%)
Unknown	9 (14%)	8 (14%)	1 (17%)

Itineraries for reported travel-associated JE cases, 1973-2012 (n=47)

Duration of travel			(N=47)
≥1 month			30 (64%)
2 – 4 weeks	}	"Short-term"	13 (27%)
1 – 2 weeks	}		4 (8%)

Rural exposure for short-term travelers	(N=17)
Extensive rural travel	4 (24%)
Short trips to rural areas	10 (59%)
Primarily coastal areas	3 (18%)
Urban areas only	0 (0%)

Country of citizenship for travel-associated JE cases, 1973–2012

	All ages (N=65)	Adults (N=59)	Children (N=6)
United States	19 (29%)	16 (27%)	3 (50%)
Sweden	7 (11%)	7 (12%)	--
Germany	6 (9%)	6 (10%)	--
Australia	4 (6%)	2 (3%)	2 (33%)
Italy	3 (5%)	3 (5%)	--
Norway	3 (5%)	3 (5%)	--
Netherlands	3 (5%)	3 (5%)	--
Other	20 (31%)	19 (32%)	1 (17%)

JE vaccine considerations for U.S. travelers

- Risk of JE disease for most travelers is very low
- Risk varies based on location, duration, season, activities
- JE is a severe disease with substantial morbidity & mortality
- There is no specific treatment
- Safe and effective vaccine is available
- Vaccine is expensive
- Does not prevent importation or spread of JE virus

Values considered by the workgroup

- High value placed on preventing this life-threatening disease
- Survey performed in the U.S. in 2001*
  - Parents and community members willing to pay median of $500 to reduce risk of bacterial meningitis from 21 to 6 per 100,000
  - Disease rates used in survey higher than risk for JE among travelers but support a willingness to pay to prevent serious outcome
- Workgroup also places high value on educating healthcare providers to:
  - Help counsel travelers about JE and JE vaccine
  - Inform decisions about JE vaccination based on traveler's itinerary

*Prosser. Pediatrics 2004;113:283

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Considering the costs of JE vaccine for travelers

- Using JE vaccine for children in endemic areas is cost-saving
- JE vaccine for all travelers to Asia would not be cost-effective
  - Large numbers of U.S. travelers to Asia (>5.5 million/year)
  - Overall low risk of disease (<1 case per million travelers)
  - High cost of JE-VC ($200-250/dose)
- For some travelers, even a low risk of serious adverse events due to the vaccine may be higher then the risk for disease
- Therefore, JE vaccine should be targeted to travelers who are at increased risk for disease based on their planned itinerary

CDC

No cost-effectiveness analysis for GRADE

- Number of U.S. children who travel to Asia and have an itinerary that puts them at increased risk for JE is likely very low
  - Travel vaccines are usually paid for by the travelers themselves
  - Not included in Vaccines for Children (VFC)
  - Not covered by most private insurance plans
- Workgroup decided not to perform a cost-effectiveness study of JE vaccine for U.S. children traveling to endemic areas

GRADE evaluation steps

- Develop policy question
- Identified and ranked outcomes to be evaluated
- Searched and reviewed published and unpublished data
- Summarized evidence for critical outcomes
- Evaluated quality of evidence for outcomes
- Assessed values related to options and outcomes
- Reviewed health economic data
- Considerations for formulating recommendations
- ACIP recommendations and GRADE category

Considerations for formulating recommendations

- JE-VC provides high levels of seroprotection in children following a 2-dose primary series
- Serious adverse events are uncommon and rates similar to those seen with comparison vaccines
- Systemic adverse events occur at rates similar to comparison vaccines
- High value placed on prevention of a serious disease with no treatment and substantial morbidity and mortality
- Low risk of disease, low risk of vaccine-related adverse events, and high vaccine cost warrant targeted vaccination of higher risk travelers

Workgroup conclusions and recommendations

- JE-VC is effective using seroprotection as the endpoint and safe in children aged 2 months through 16 years (Overall evidence type 2).
- Workgroup proposes to extend current ACIP recommendations for use of JE-VC to include children ≥2 months of age
- No other changes to the existing recommendations are proposed

GRADE evaluation steps

- Develop policy question
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Current ACIP recommendations (1 of 3)

"JE vaccine is recommended for travelers who plan to spend a month or longer in endemic areas during the JE virus transmission season. This includes long-term travelers, recurrent travelers, or expatriates who will be based in urban areas but are likely to visit endemic rural or agricultural areas during a high-risk period of JE virus transmission (Recommendation category A)."

Current ACIP recommendations (2 of 3)

"JE vaccine should be considered for short-term (<1 month) travelers to endemic areas during the JE virus transmission season if they plan to travel outside of an urban area and have an increased risk for JE virus exposure (e.g., spending substantial time outdoors in rural or agricultural areas, participating in extensive outdoor activities, staying in accommodations without air conditioning, screens, or bed nets). JE vaccine also should be considered for travelers to an area with an ongoing JE outbreak and travelers to endemic areas who are uncertain of specific destinations, activities, or duration of travel (Recommendation category B)."

Current ACIP recommendations (3 of 3)

"JE vaccine is not recommended for short-term travelers whose visit will be restricted to urban areas or times outside of a well-defined JE virus transmission season (Recommendation Category A)."

Next steps

- Questions and discussion
- Proposed vote on extending current ACIP recommendations for use of JE-VC to include children ≥2 months of age
- No VFC vote

ACIP JE Vaccine Workgroup members

ACIP members

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