

Table 2b. TIV in children aged 2 to 6 years

Is inactivated influenza vaccine versus placebo or no intervention or non-influenza vaccine effective to prevent influenza infection in children aged 2 to below 6 years?				
		Rating	Adjustment to rating	
Quality Assessment	No of studies/starting rating		4 RCT <sup>1,2</sup>	4
	Factors decreasing confidence	Limitation in study design	Serious <sup>3</sup>	-1
		Inconsistency	None serious <sup>4</sup>	0
		Indirectness	Serious <sup>5</sup>	-1
		Imprecision	None serious <sup>6</sup>	0
		Publication bias	None serious	0
	Factors increasing confidence	Strength of association/ large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic /mitigated bias and confounding	Not applicable	0
	<b>Final numerical rating of quality of evidence</b>			<b>2</b>
Summary of Findings	<b>Statement on quality of evidence</b>		Our confidence in the estimate of effect of inactivated influenza vaccine in children aged 2 to below 6 years of age is limited.	
	<b>Conclusion</b>		In <b>children aged 2 to below 6 years</b> , inactivated influenza vaccine is <b>not significantly more efficacious than placebo or no intervention</b> in preventing influenza (pooled risk ratio 0.61; 95% CI: 0.34 to 1.08) <sup>7</sup> but pooled estimates that include <b>all age-groups below 6 years</b> revealed <b>significantly higher efficacy of the vaccine compared to placebo and no intervention</b> (pooled risk ratio: 0.41; 95% CI: 0.29 to 0.59, efficacy of 59%; 95% CI: 41-71). <sup>8</sup> Pooled estimates also showed effectiveness against ILI in children aged 2 to below 6 years (pooled risk ratio of 0.39; 95% CI: 0.21 to 0.69). <sup>9</sup> In children aged 3 to below 6 years, <b>inactivated influenza vaccine (TIV) is significantly more efficacious than non-influenza vaccine in preventing PCR-confirmed influenza infection</b> (for matched strains) (48%; 95% CI: 8 to 71). <sup>10</sup>	

**NOTES**

<sup>1</sup>The vast majority of trials identified by a Cochrane review (Jeffries et al. 2008) did not break down their efficacy and effectiveness assessment into age-groups. Two of the RCTs included into the grading process provided age-sub-group specific results on inactivated influenza vaccine efficacy in children aged 2 to below 6 years (Gruber et al. 1990 and second year analysis of the same RCT by Clover et al. 1991, inactivated vaccine versus placebo). In addition to these two RCTs that assessed efficacy, one other was included reporting on the effectiveness of the vaccine in preventing ILI in 344 children aged 1 to below 6 years (Colombo et al 2001, inactivated vaccine versus no intervention) and a fourth RCT was included evaluating the efficacy of adjuvanted TIV (ATIV), TIV, and control vaccine against confirmed influenza in 4707 children aged 6 to 72 months of age, stratified by age-group (Vesikari et al. 2011).

The RCT by Gruber et al. enrolled 189 children aged 3 to 18 years and presented data in three age-groups (3 to 5 years, 6 to 9 years, 10 to 18 years). Follow-up was carried out for 6 months post-vaccination. Safety outcomes were also assessed up to 14 days post-vaccination and local reactions were reported from 20% of vaccine recipients and 19% of controls. Clover et al. (1991) carried out analysis on the second year of the RCT described by Gruber et al. (1990). The study population consisted of 166 adults and 225 children (new enrollments). 157 adults and 202 children completed the study. Children received live vaccine, inactivated vaccine or placebo.

Colombo et al. 2001 also recorded safety data and stated that two children experienced fever and malaise after vaccination and two erythema at the injection site. There was no placebo data. Overall, no meta-analysis on safety issues was carried out due to heterogeneity in the presentation of outcomes in the studies.

The RCT by Vesikari et al. 2011 was not included in the Cochrane review, due to its late publication date but used for grading. In this trial, 4707 children aged 6 to less than 6 years of age, stratified by age-groups, were enrolled and underwent randomization. 1941 children were vaccinated with MF59-adjuvant trivalent influenza vaccine (ATIV), 1773 with TIV. Both intervention groups were compared to 993 control vaccine recipients (tickborne encephalitis vaccine for children aged 1 year to less than 6 years of age). Results for children aged 3 years to less than 6 years of age and efficacy against matched strains is used for evidence assessment.

<sup>2</sup>Two other meta-analysis identified did present results on children in the relevant age-category. Manzoli et al. 2007 provided age- and vaccine specific results but only univariate (e.g. no estimate for age group 2 to 6 years by vaccine type and/or by comparison group used in studies (placebo, control vaccine, or no intervention). From this analysis, the efficacy against laboratory-confirmed influenza in children below 6 years indicates a significant reduction in laboratory-confirmed influenza with an efficacy of 61% (pooled risk ratio from nine studies: 0.39; 95% CI: 0.19 to 0.80). It is not clear on which studies this result is based on and if the intervention was LAIV or TIV.

The meta-analysis by Negri et al. (2005) included 13 RCTs and age ranged from 1 to 18 years. Efficacy estimates are presented as vaccine-type specific but not further stratified into sub-age-groups. The pooled estimate (6 studies, 1 to 18 years) found for the inactivated vaccine against culture-confirmed and serologically confirmed influenza was 65% (95% CI: 45 to 77) and 63% (95% CI: 43 to 76), respectively. A significant heterogeneity between studies involved in this meta-analysis was reported and only English paper published after 1990 were included. Given the broad age-group, evidence was not appropriate for inclusion into grading.

Observational studies were identified assessing the impacts on influenza vaccine for this age-group. Maeda et al. (2002) focused on children aged 2 to under 6 years and concluded that influenza vaccine is effective in preventing laboratory-confirmed influenza with a risk ratio of 0.34 (95% CI: 0.13 to 0.89). Katayose et al. (2011) assessed several indirect effects of two doses of TIV on prevention of rapid-diagnostic-test-confirmed influenza associated clinic visits and hospitalization in approximately 15,000 children aged 6 months to 5 years over six seasons (matched and unmatched, depending on season). TIV was significantly effective against influenza A associated clinic visits (35% in children aged 5 to below 6 years,  $p < 0.01$ ; 57% in children aged 2 to below 3 years,  $p < 0.01$ ). The efficacy (study reported "efficacy" although "effectiveness" might be more appropriate in the context) of TIV against influenza A associated hospitalization was not significant in the age-group 5 years to below 6 years but significant for the 3 to below 5 year age-groups. Total efficacy from 6 months of age to below 6 years was 71% (95% CI: 59 to 80) for influenza-associated hospitalization. Given the type of study, systematic bias is very likely since immunized children can differ in certain aspects from those not being immunized and the study is not included for grading.

<sup>3</sup>The RCTs documented loss to follow-up but Gruber et al. (1990) did not fully describe randomization and allocation procedure and also in Clover et al. (1991), allocation concealment is unclear. Particularly differences between the groups studied and described in the discussion section (Gruber et al. 1990) may allude to serious problems with randomization that could have affected the outcome. Additionally, in Gruber et al. (1990) and subsequently Clover et al. (1991), outcomes were reported selectively and it is

also not clear how many subjects received placebo intranasally or intramuscularly, which may impact safety outcomes. The trial by Colombo et al. (2001) which provided information on effectiveness against ILI only, had adequate randomization and allocation was concealed adequately. There was adequate randomization and allocation concealment in Vesikari et al. (2011).

<sup>4</sup> Heterogeneity may have affected the outcome of the RCTs on vaccine effectiveness (resulting from ILI case-definitions used). Heterogeneity was not present in Gruber et al. and Clover et al. and heterogeneity was incorporated in the pooled overall estimates.

<sup>5</sup> Vesikari et al. 2011 stated that, since the results of their study were principally from year 2, when vaccine-like H3N2 viruses were predominated, the vaccine efficacy presented is an H3N2-specific observation. Therefore, conclusion on the efficacy of ATIV or TIV against H1N1 and B viruses could not be reached. For evidence grading, results on the matched vaccine are used. In Clover et al. 1991, the circulating strain of influenza was A/Taiwan/86 (H1N1), which was not included in either vaccine assessed.

<sup>6</sup> Study sizes were rather small leading to small number of observed events. Confidence intervals are relatively wide.

<sup>7</sup> Pooled estimate from Jefferson et al. (2008), based on the two RCTs (Clover et al. 1991, Gruber et al. 1990) for age-group 2 to below 6 years.

<sup>8</sup> Pooled estimate from Jefferson et al. (2008), based on four RCTs (Clover et al. 1991, Gruber et al. 1990, Hoberman et al. 2003, Beutner et al. 1979) including age-groups 1 to below 6 years. Overall result in this section is supported by observational studies and other evidence which was not included in the grading due to indirect outcome measures and methodological limitations (see note 2).

<sup>9</sup> Pooled estimate from Jefferson et al. (2008), based on three RCTs (Clover et al. 1991, Gruber et al. 1990, Colombo et al. 2001) for age-group 2 to below 6 years. The pooled estimate from all RCTs independent of child age-group was a rate ratio of 0.64 (95% C: 0.54 to 0.76) implying a significant reduction in ILI achieved by inactivated influenza vaccine.

<sup>10</sup> The relative efficacy of ATIV versus control against PCR-confirmed influenza (matched strains) was 96% (95% CI: 81 to 99) in the age group of 3 years to below 6 years and the relative efficacy of ATIV versus TIV was 91% (95% CI: 63 to 98) (Vesikari et al. 2011).

## References

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