Table 2a. TIV vaccination of children aged 6 months – 2 years

Is inactivated influenza vaccine versus placebo or control vaccine effective to prevent influenza infection in children aged 6 months to 2 years of age?				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting rating		2 RCT[1, 2]	4
	Factors decreasing confidence	Limitation in study design	None serious[3]	0
		Inconsistency	None serious[4]	0
		Indirectness	None serious[5]	0
		Imprecision	Serious[6]	-1
		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
	Final numerical rating of quality of evidence			**3**
Summary of Findings	**Statement on quality of evidence**			Our confidence in the estimate of effect of inactivated influenza vaccine in children aged 6 months to 2 years of age is moderate.
	Conclusion			In children aged 6 months to 2 years of age, inactivated influenza vaccine is **not significantly more efficacious than placebo** in preventing influenza incidence (risk ratio 0.55; 95% CI: 0.18 to 1.69). The relative efficacy of different influenza vaccine types against PCR-confirmed influenza infection (for matched strains): No significant difference between TIV versus control vaccine (2%; 95% CI: -129 to 58). Adjuvanted TIV is significantly more efficacious than both, control (75% (95% CI: 20 to 92)) and than TIV (75%; 95% CI: 25 to 91)).[8]

NOTES

[1] 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 or provided information on children aged 6 months to 2 years of age. Two RCTs (Hoberman et al. 2003, Vesikari et al. 2011) provided results on inactivated influenza vaccine efficacy in children in this age-group.

Hoberman et al. 2003 conducted an RCT of children aged 6 to 2 years of age. The 793 children enrolled received either two doses of inactivated influenza vaccine or placebo and outcomes measured were episodes of culture proven influenza (others were, e.g. episodes of acute otitis media). Efficacy analysis was done separately for two years/cohorts, but Jeffries et al. (2008) pooled the obtained estimates, which were used for evidence assessment and summarized in the conclusion section.

The RCT by Vesikari et al. 2011 was not included in the Cochrane review, due to its late publication date. In this trial, 4707 children aged 6 months to less than 6 years of age, stratified by age-groups, were enrolled and underwent randomization. 1941 children were vaccinated with MF59-adjuvanted trivalent influenza vaccine (ATIV), 1773 with TIV. Both intervention groups were compared to 993 control vaccine recipients (for children aged 6 months to less than 1 year of age, the control vaccine was meningococcal C

conjugate vaccine). Efficacy of ATIV, TIV, and control/non-influenza vaccine against confirmed influenza was assessed over two seasons (2007-08, 2008-09). Results for children aged 6 months to 2 years of age and efficacy against matched strains is used for evidence assessment.

[2] Another meta-analysis (Manzoli et al. 2007) was identified that provided age- and vaccine specific results but only univariately (e.g. estimate for age group below 2 years is not stratified by vaccine used (LAIV or TIV) and/or by comparison group used (placebo, control vaccine, or no intervention)). From this analysis, efficacy against laboratory-confirmed influenza indicated no significant reduction in children below 2 years of age (pooled risk ratio from two studies: 0.55; 95% CI: 0.18 to 1.69). However, it is not clear on which two studies this result is based on and if the intervention was LAIV or TIV.
One relevant observational study by Katayose et al. (2011) identified has assessed 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 of age over six seasons (matched and unmatched, depending on season). TIV was significantly effective against influenza A associated clinic visits (80% in children aged 6 months to below 1 year and 63% in those aged 1 to below 2 years; $p<0.01$). Total efficacy (study reported "efficacy" although "effectiveness" might be more appropriate in the context) from 6 months of age to below 6 years was 52% (95% CI: 47 to 56 %). The efficacy of TIV against influenza A associated hospitalization ranged between 69% (6 months to below 1 year old, $p <0.05$) to 80% (1 to below 2 years old, $p<0.01$). Total efficacy from 6 months of age to below 6 years was 71% (95% CI: 59 to 80 %). Given the type of study, systematic bias is very likely since immunized children can differ in certain aspects from those not being immunized. This observational study was not included for grading.

[3] There was adequate randomization and allocation concealment. Loss to follow-up was described.

[4] Heterogeneity may have affected studies on vaccine effectiveness (resulting from different follow-up times and different ILI case-definitions), which are not used for evidence grading. Although heterogeneity was an issue in the year-specific results presented by Hoberman et al. (2003), the finding of efficacy of TIV was consistent in message across the two RCTs used for grading and confirmed by the additional meta-analysis by Manzoli et al. (2007). There was no heterogeneity in the second RCT (Vesikari et al. 2011).

[5] 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. Additionally, efficacy against all strains (matched and unmatched) was similar (see note 9).

[6] Study sizes were small and confidence intervals relatively wide.

[7] Hoberman et al. (2003) provided year-specific estimates of vaccine efficacy against culture-confirmed influenza and concluded that in 1999 to 2000 the efficacy was 66% and in 2000 to 2001 it was -7%. However, influenza attack rates differed in each year (influenza in the placebo groups was 15.9% and 3.3% , respectively). The estimate used in the conclusion section is based on appropriate pooling done in the Cochrane review (Jefferson et al. 2008).
Jefferson et al. (2008) also pooled results from several cohort studies and found evidence to be in line with that shown from RCTs: up to 2 years of age, there was no difference between placebo and inactivated vaccine in preventing influenza (risk ratio 0.63; 95% CI: 0.27 to 1.47). There were no data available for children aged below 2 years from cohort studies on the effectiveness of inactivated vaccines.

[8] The efficacy against all strains in 6 months to 2 years old children was not significant for TIV versus control (11%; 95% CI: -89 to 58). Similar to the results on matched strains, ATIV was more efficacious than both, TIV and control vaccine resulting in a relative efficacy of 73% (95% CI: 29 to 90) and 77% (95% CI: 37 to 92), respectively (Vesikari et al. 2011).

References

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