Table 7. Live attenuated influenza vaccine in children aged 2 to below 6 years of age

Is live attenuated influenza vaccine (LAIV) versus placebo or no intervention 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[1, 2]	4
	Factors decreasing confidence	Limitation in study design	Serious[3]	-1
		Inconsistency	Serious[4]	-1
		Indirectness	None serious	0
		Imprecision	None serious	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
	Final numerical rating of quality of evidence			**2**
Summary of Findings	**Statement on quality of evidence**			Our confidence in the estimate of effect of live attenuated influenza vaccine in children aged 2 to below 6 years of age is limited.
	Conclusion			In **children aged 2 to below 6 years of age**, live attenuated influenza vaccine is **significantly more efficacious than placebo or no intervention** in preventing influenza incidence (pooled risk ratio 0.15; 95% CI: 0.10 to 0.23) implying a 85% efficacy.[5]

NOTES

[1] Four RCTs (also included in the Cochrane review by Jefferson et al. 2008) provided age-sub-group specific results on LAIV efficacy in children aged 2 to below 6 years (Belshe et al. 1998, 2000, Clover et al. 1991, Vesikari et al. 2006). They were included in the grading process.

Belshe et al. (1998) conducted a multi-centre RCT enrolling 1602 children aged 15 months to below 6 years of age. Single and two dose regimes of cold-adapted trivalent influenza vaccine were compared with placebo (administered intranasally). The primary study outcome was culture-confirmed influenza in participants who became ill 28 days or more after dose one or immediately after dose two. In Belshe et al. 1998, the second year of the trial by Belshe et al. 1998 is described and included 1358 children aged 26 to 85 months from the first year. The primary outcome was culture-confirmed influenza, with symptoms of infection appearing 28 days or more after vaccination

The Clover et al. (1991) study was conducted in the second year of the RCT described in Gruber et al. 1990 and in addition to 70% of the initial study population that participated in year one, additional children aged 3 to 18 years were recruited. Of those, 58 children received live vaccine, 54 the inactivated vaccine and 82 placebo. The primary outcome measure was influenza infection, determined by positive viral culture or a post-season rise in antibodies in an individual who was ill within 10 days of a household contact who had a positive viral culture.

Vesikari et al. (2006, two seasons) conducted a RCT on efficacy and safety of intranasal CAIV-T and followed-up 1616 children aged 6 to 35 months in day care centers. 951 received the vaccine and 665

placebo and results were presented age-group specific. Evidence for children aged 24 to 35 months was included in the grading and the main outcome was culture-confirmed influenza.
The RCT by Tam et al. (2007) was excluded from the Cochrane review by Jefferson et al. 2008 due to very high risk of bias that derives from inconsistencies in reporting of denominators. Groups at year two showed differing sequence allocation to CAIV-T and placebo. The RCT enrolled 3174 children aged 1 year to 3 years and allocated either to CAIV (1900) or to placebo (1274). The main outcome was culture-confirmed influenza and efficacy of CAIV-T versus placebo was 72.9% (95% CI: 62.8 to 80.5%) against antigenically similar influenza subtypes and 70.1% (95% CI 60.9 to 77.3%) against any strain. The results were not included in the grading due to different age-group and limitations.
Safety was assessed in the trials by Vesikari et al. (2006) and Tam et al. (2007). Vesikari et al. 2006 showed no statistically significant differences in serious harms between treatment groups during the second period. Six lower respiratory tract illnesses were reported, all among CAIVT. Out of them, two cases of pneumonia were judged to be possibly, probably, or definitely related to study vaccination. Two CAIV-T recipients and two placebo recipients had adverse events. Tam et al. 2007 reported that runny nose/nasal congestion after dose two and three and use of fever medication after dose three were reported significantly more frequently in CAIV-T recipients.
Safety outcomes of Belshe et al. (1998 and 2000) are summarized in Piedra et al. 2002.

[2] Three other meta-analysis identified did present results on children but did not stratify in a way that the age-group of interest for grading is represented appropriately. However, results point to similar directions as presented in the conclusion section.
The meta-analysis by Negri et al. (2005) included 13 RCTs with age of subjects ranging from 1 to 18 years. Efficacy estimates are presented as vaccine-type specific but not further stratified into sub-age-groups. The pooled estimate (1 to 18 years) found for LAIV against culture-confirmed (6 studies) and serologically confirmed influenza (5 studies) was 80% (95% CI: 53 to 91) and 54% (95% CI: 20 to 74), 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 being included into grading.
Rhorer et al. (2009) included studies on children aged 6 to 17 years in their meta-analysis. LAIV showed efficacy of 77 to 87% against antigenically similar culture-confirmed influenza compared to placebo. There was no evidence of difference by sub-age-groups regarding the efficacy.
Another meta-analysis (Manzoli et al. 2007) provided age- and vaccine- specific results but only univariate (e.g. estimate for the intervention vaccine is not stratified by age-group). From this analysis, live aerosol vaccine appears to be efficacious against lab.-confirmed influenza (risk ratio pooled estimates 0.28; 95% CI: 0.13 to 0.62). However, it is not clear on which studies this result is based, what type of control group was used and/or how this may have impacted on the result.

[3] The RCTs documented loss to follow-up but initial randomization of the Clover et al. study that was based on Gruber et al. (1990), not fully described randomization, and allocation concealment is unclear. There were major differences between the groups studied described in the discussion section of Gruber et al. 1990, which may allude to serious problems with randomization that could have affected the outcome of the Clover et al. 1991 trial. Additionally, in Gruber et al. (1990) and subsequently Clover et al. (1991), outcomes were reported selectively.
Belshe et al. 1998 and 2000 and Vesikari et al. 2006 had adequate randomization and allocation concealement but in Vesikari et al. 2006, there were high dropout rates which also differed by placebo and intervention group. A limited or delayed availability of the vaccine as well as inconclusive reporting may have impacted the trial results and methodological quality of Vesikari et al. 2006.

[4] Heterogeneity was high between the trials used for evidence-grading.

[5] Pooled estimate from Jefferson et al. (2008), based on the four RCTs (Belshe et al. 1998, 2000, Clover et al. 1991, Vesikari et al. 2006) for age-group 2 to below 6 years.

References

Belshe, R.B., et al., *Efficacy of vaccination with live attenuated, cold-adapted, trivalent,intranasal influenza virus vaccine against a variant (A/Sydney) not contained in the vaccine.* The Journal of Pediatrics, 2000. **136**:168-75.

Belshe, R.B., et al., *The efficacy of live attenuated, cold-adapted, trivalent, intranasal influenzavirus vaccine in children.* The New England Journal of Medicine, 1998. **338**:1405-12

Clover, R.D., et al., *Comparison of heterotypic protection against influenza A/Taiwan/86 (H1N1) by attenuated and inactivated vaccines to A/Chile/83-like viruses.* The Journal of Infectious Diseases, 1991. **163**:300-4.

Gruber, W.C., et al., *Evaluation of live attenuated influenza vaccines in children 6-18 months of age: safety, immunogenicity, and efficacy. National Institute of Allergy and Infectious Diseases, Vaccine and Treatment Evaluation Program and the Wyeth-Ayerstca Influenza Vaccine Investigators Group.* The Journal of Infectious Diseases, 1996. **173**:1313-9.

Jefferson, T., et al., Vaccines for preventing influenza in healthy children. Cochrane Database of Systematic Reviews, 2008(2): p. CD004879.

Manzoli, L. et al., *The efficacy of influenza vaccine for healthy children. A meta-analysis evaluationg potential sources of variation in efficacy estimates including study quality.* Pediatric Infectious Diseases Journal 2007. 26: 97-106

Negri, E., et al., *Influenza vaccine in healthy children: a meta-analysis.* Vaccine, 2005. **23**:2851-61.

Rhorer, J, et al.; *Efficacy of live attenuated influenza vaccine in children: A meta-analysis of nine randomized clinical trials.* Vaccine 2009. **27**: 1101-10.

Vesikari, T., et al., *Safety, efficacy, and effectiveness of cold-adapted influenza vaccine-trivalent against community-acquired, culture-confirmed influenza in young children attending day care.* Pediatrics, 2006. **118**:2298-312.

Tam, J.S., et al., *Efficacy and safety of a live attenuated, cold-adapted influenza vaccine, trivalent against culture-confirmed influenza in young children in Asia.* The Pediatric Infectious Disease Journal, 2007. **26**:619-28.