

**Table 4a TIV in patients with asthma**

Is inactivated influenza vaccine versus placebo effective to prevent influenza-related asthma exacerbations in patients with asthma?				
		Rating	Adjustment to rating	
Quality Assessment	No of studies/starting rating		1 RCT <sup>1,2</sup>	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious <sup>3</sup>	0
		Indirectness	Serious <sup>4</sup>	-1
		Imprecision	Serious <sup>5</sup>	-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
	<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 patients with asthma is limited.	
	<b>Conclusion</b>		In <b>children with asthma</b> , influenza vaccine did <b>not significantly reduce influenza related asthma exacerbations</b> compared to placebo (risk difference of 0.01; 95% CI: -0.02 to 0.04). <sup>6</sup> Duration and severity of exacerbations were not significantly different between vaccine and placebo group. <sup>7</sup>  There was no significant increase in patients with asthma exacerbations following influenza vaccination (risk difference of 0.00; 95% CI: -0.02 to 0.02). <sup>8</sup>	

**NOTES**

<sup>1</sup> There was one RCT (Bueving et al. 2003) that assessed the protective effects/benefits of influenza vaccine in 696 children aged 6 to 18 years. 347 children were vaccinated with inactivated influenza vaccine and 349 with placebo. The primary outcome measure was the number of asthma exacerbations associated with virologically proven influenza. The RCT also evaluated differences of the duration of influenza related asthma exacerbations as well as severity of influenza related asthma exacerbations, symptom scores during influenza positive weeks, the proportion of patients with minimum important difference in symptom scores during influenza-positive weeks, and the mean difference of FEV-1 during influenza- positive weeks. This trial was part of a Cochrane review conducted by Cates et al. 2008 that focused on the efficacy of influenza vaccination with stable asthma. Data were pooled and estimates for outcomes were stratified by harms and benefits. The main outcome measures for both, harms and benefits were asthma exacerbations, hospital admissions, pneumonia, asthma symptom scores and other secondary outcomes. There were several issues related to the late and early outcome measures among the studies found in this meta-analysis, and very few studies looked for late outcomes in order to assess efficacy of the vaccine.

Among the studies that assessed harms of inactivated influenza vaccination in asthmatic patients were the trials by Castro et al. 2001 and by Nicholson et al. 1998. Both reported on differences regarding

asthma exacerbations (see note 8). Other secondary outcomes related to harms and references to studies reporting these outcomes numerically or descriptive are provided in Cates et al. 2008.

<sup>2</sup> LAIV vaccines were mainly assessed in regard to harms and there was no trial on benefits such as decrease in asthma exacerbations following vaccination included in the Cochrane review by Cates et al. 2008). Harms of LAIV in asthmatic patients were studied in RCTs by Atmar et al. 1989 and Redding et al. 2002. Atmar et al. 1989 included 17 asthmatic adults out of which 11 received LAIV and 6 placebo and there were no significant differences in hospital-admissions for asthma exacerbations, fall in mean FEV-1, and number of patients with exacerbation. Similarly, Redding et al. that conducted a trial among 48 children aged 9 to 17 years and found no significant difference for asthma exacerbations and no significant change in % of predicted FEV-1.

Another RCT (Fleming et al. 2006) included 2229 asthmatic children aged 6 to 17 years and compared recipients of a single dose of LAIV to those receiving a single dose of TIV. The outcome measure was culture-confirmed influenza and it was found that there were 35% fewer cases of influenza caused by matched strains among LAIV recipients versus TIV recipients with an incidence rate ratio LAIV/TIV of 0.68 (95% CI: 0.48 to 0.97). The pooled estimate for differences in incidence of asthma exacerbations between LAIV and TIV recipients over the total study period was not significant (Cates et al. 2008). However, there was a significant increase among LAIV-immunized children versus TIV in terms of reporting runny nose or nasal congestion in the 15 days after vaccination (OR 1.78; 95% CI: 1.5 to 2.11), and the increase was also significant in those reporting rhinitis as an adverse event.

<sup>3</sup> Overall, there is heterogeneity across the available studies due to a wide diversity of patients, settings and types of influenza vaccine studied. This is a reason why only one RCT qualified for being included into the grading process, for which no serious heterogeneity exists.

<sup>4</sup> Indirectness is related to the fact that many other respiratory viruses can cause asthma exacerbations. The trial used for grading (Bueving et al. 2003) assured that exacerbations following an ILI are regarded as being due to influenza only if laboratory-confirmed. However, this evidence used for grading is in children only, which introduces a serious level of indirectness.

<sup>5</sup> Small number of observed events and CIs indicate effects in both directions.

<sup>6</sup> The risk difference estimate relates to confirmed influenza only and the estimate is based on the calculation in the meta-analysis (Cates et al. 2008), that included published and unpublished data related to the Bueving et al. 2003 trial (see references). When all exacerbations (influenza virus confirmed and unconfirmed exacerbations) were considered, the risk difference was -0.04 (95% CI: -0.09 to 0.00) (Cates et al. 2008).

<sup>7</sup> Mean difference (days) for duration of influenza related asthma exacerbations was -2 (95% CI: -4.84 to 0.84) and mean difference (symptom score) for severity of influenza related asthma exacerbations was -1.70 (95% CI: -3.49 to 0.09) (Cates et al. 2008). A significant difference was only found for the symptom score during influenza positive weeks (0.60; 95% CI: 0.12 to 1.08) (Cates et al. 2008).

<sup>8</sup> Pooled and adjusted risk difference estimate from Cates et al. 2008, based on two studies (Castro et al. 2001, Nicholson et al. 1998) that assessed harms of inactivated influenza vaccination in asthmatic patients (see note 1) such as increases in asthma exacerbations.

## References

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