



## Effective Public Health Practice Project Summary Statement

October 2006

This is a summary statement written to condense the work of the authors of a systematic review. The reference for the full review is below. The intent of this summary is to provide an overview of the findings and implications of the full review. For more information on individual studies included in the review, please see the review itself.

**Reference for Review:** Smith, S., Demicheli, V., Di Pietrantonj, C., Harnden, A.R., Jefferson, T., Matheson, N.J., et al. (2006). **Vaccines for preventing influenza in healthy children.** *The Cochrane Database of Systematic Reviews 2006, Issue 1.* Art. No.: CD004879.pub2. DOI:10.1002/14651858.CD004879.pub2.

### Issue

Influenza is the most common vaccine-preventable disease among children in Canada (Wootton et al., 2006); it is associated with serious illness and even death. Children 14 years and under represented 19.6% of the 10,006 influenza cases reported in Canada during the 2004-2005 influenza season (Xie et al., 2006), although this age group makes up only 17.6% of the Canadian population. These statistics mean that 0.03% of children aged 0-14 reported a case of influenza that season. In 2004-2005, 391 children aged 0-16, 46.1% of whom were healthy, were hospitalized for influenza. Among healthy children hospitalized for influenza, 96.7% were either not vaccinated at all or not vaccinated properly. Influenza is associated with significant morbidity and possible complications in healthy children, in addition to societal costs relating to health care and work absence for parents (National Advisory Committee on Immunization [NACI], 2006).

Currently, there are no recommendations for influenza vaccinations for healthy children in Ontario's Mandatory Health Programs and Services Guidelines (Ontario Ministry of Health and Long-Term Care [MOHLTC], 1997), although the province is in its sixth year of the Universal Influenza Immunization Program. This program makes the influenza vaccine available at no charge to anyone aged six months or older who lives, works or goes to school in Ontario (MOHLTC, 2006). In 2004, the National Advisory Committee on Immunization also recommended that children between the ages of 6 and 23 months receive the influenza vaccination, regardless of whether conditions that placed them at high risk were present (NACI, 2004). The NACI recognizes that the number of randomized trials that have examined children aged 6-23 months is limited and strongly encourages more research into the many unanswered questions relating to influenza vaccination for this age group (NACI, 2006). In the meantime, the NACI recommends that children 6-23 months of age be vaccinated due an increased risk of influenza-associated hospitalization when compared to healthy children of the same age.

The meta-analysis summarized here may provide evidence to inform public health policies regarding influenza vaccination.

## Review Content Summary

This systematic review with meta-analysis addressed the efficacy, effectiveness and safety of vaccines used to prevent influenza among healthy children. Evidence was available from 51 studies. Fourteen randomized controlled trials (RCT) and eleven comparative cohort studies reported on vaccine efficacy (defined by the reviewers as the prevention of confirmed influenza) or effectiveness (defined as the prevention of any influenza-like illness). The remaining studies provided data on the safety of the vaccines. There is good evidence (based on a meta-analysis of data from eight placebo-controlled randomized trials with a total of 19,044 participants) that live or inactivated vaccines reduce the number of cases of confirmed influenza and prevent influenza-like illness in children. There was insufficient evidence to reach conclusions about the use of influenza vaccines in children younger than two.

## Comments on this Review's Methodology

In addition to contacting experts in order to identify relevant published and unpublished trials, the reviewers searched biomedical databases to find comparative studies. Eligibility criteria were clearly defined. Two reviewers independently assessed all included studies for quality, using different criteria for randomized trials (unit of randomization, generation of allocation sequence, allocation concealment, blinding and follow-up) and non-experimental studies (sample selection, comparability of groups and ascertainment of outcome).

In general, appropriate methods were used to pool data across studies and to measure heterogeneity, but in some of the pooled analyses, some trials were counted more than once. If children from one study were revaccinated in a second study, for example, they were counted each time, which could introduce bias. Studies were grouped for analysis according to their design (randomized trial, comparative cohort study or case-control study). Given the large number of randomized trials that provided evidence on the outcomes of interest, it is not clear why the reviewers also included data from non-experimental studies. Heterogeneity statistics were significant for many of the pooled analyses even when the analysis was restricted to a specific age range and study results were consistent in direction.

No meta-analysis was completed for vaccine safety because of a high level of heterogeneity in the presentation of safety outcomes for live and inactivated vaccines. The short-term safety outcomes for both live attenuated and inactivated vaccine were presented in table format for the 32 studies that met the inclusion criteria and examined vaccine safety.

## Evidence and Implications for Practice & Policy

*Evidence points ARE NOT weighted or ranked according to strength.*

What's the evidence?	Implications for practice and policy:
<p><b>Vaccine efficacy in children <math>\leq</math> age 16</b></p> <ul style="list-style-type: none"> <li>&gt; There is evidence from meta-analysis that both live attenuated vaccines and inactivated vaccines prevent influenza.</li> <li>&gt; Pooled data from four RCTs (N=3,098) showed that live attenuated vaccines had an overall efficacy (prevention of confirmed influenza) of 79% (relative risk [RR], 0.21; 95% confidence interval [CI],</li> </ul>	<ul style="list-style-type: none"> <li>&gt; Both vaccines have proven to be efficacious in preventing influenza and have some effectiveness in preventing influenza-like illness in children 16 and under. It is not surprising that the vaccine effectiveness was lower than the vaccine efficacy, as the vaccine was not designed to prevent influenza-like illness.</li> </ul>

<b>What's the evidence?</b>	<b>Implications for practice and policy:</b>
<p>0.08 to 0.52).</p> <ul style="list-style-type: none"> <li>&gt; The live vaccine's ability to protect against influenza was significant for the age groups 'Under 6 years' and 'Over 6 years'.</li> <li>&gt; When data from seven RCTs were pooled (N=1,628), the efficacy for inactivated vaccines was lower (59%), but still statistically significant (RR, 0.41; 95% CI, 0.29 to 0.59)</li> <li>&gt; The efficacy of the inactivated vaccine remained significant for the age group 'Over 6 years', but not for the under 6 age group.</li> <li>&gt; There were insufficient data to determine the efficacy of either type of vaccine for children under 2.</li> </ul>	<ul style="list-style-type: none"> <li>&gt; There is still a lack of data on the subject of vaccine efficacy and effectiveness for children under the age of 2 years. Given the national recommendations for influenza vaccinations in children ages 6 to 23 months, regardless of their level of risk, this lack of information may be a cause for concern. In order to ensure the use of an evidence-based approach to public health recommendations, it may be prudent to require solid research evidence on which to base policy on these issues.</li> <li>&gt; It must also be noted that five of the 15 randomized clinical trials were translated from Russian, two were from Europe, and the other seven were from the US. Some caution should therefore be exercised when generalizing these results to Canada.</li> </ul>
<p><b><i>Vaccine effectiveness in children <math>\leq</math> age 16</i></b></p> <ul style="list-style-type: none"> <li>&gt; There is evidence from meta-analysis that both live attenuated vaccines and inactivated vaccines are effective for preventing influenza-like illness, overall (RR, 0.67 for live attenuated vaccines and 0.64 for inactivated vaccines), in children under 6 and in those over 6.</li> </ul>	
<p><b><i>Vaccine safety</i></b></p> <ul style="list-style-type: none"> <li>&gt; The evidence on safety available from the systematic review is not presented in a format that can easily be translated into practice.</li> <li>&gt; Although the reviewers listed the number of patients who experienced various adverse effects (including temperature and local reactions) in each of the individual studies, they did not present any narrative or quantitative synthesis of this information or conclusions about the risks associated with influenza vaccination in children.</li> <li>&gt; There is little evidence on safety available for children under 2 years of age.</li> </ul>	<ul style="list-style-type: none"> <li>&gt; In a study completed by Humiston et al. (2005), 70% of parents stated that the safety of the influenza vaccine for children 6-23 months of age was their most important concern when deciding whether or not to vaccinate their child.</li> <li>&gt; Ideally, vaccine safety should be tested with randomized clinical trials (or other methodologically sound cohort studies with an appropriate comparison group) among healthy and high risk children ages 6-23 months.</li> </ul> <p>Until such research is available, the risk of adverse effects of the vaccine should be weighted against the risk of acquiring influenza and subsequent severity of illness when determining vaccination policies for children 6-23 months old.</p>

What's the evidence?	Implications for practice and policy:
<p><b>Other outcomes</b></p> <ul style="list-style-type: none"> <li>&gt; One RCT showed that influenza vaccines (both live and inactivated) were significantly more effective than placebo in reducing school absences (n=187).</li> <li>&gt; Neither influenza vaccine was found to prevent secondary cases, lower respiratory disease, hospitalization or consequences of otitis media.</li> <li>&gt; When one-dose live-attenuated vaccines were compared indirectly to two-dose vaccines, the latter appeared to be more efficacious, although no trials did a head-to-head comparison. The efficacy of the two-dose vaccine was based on one study only.</li> <li>&gt; The review's authors stated that they could find no convincing evidence in the literature showing that influenza vaccine can reduce mortality, hospital admissions, serious complications and community transmission of influenza.</li> </ul>	<ul style="list-style-type: none"> <li>&gt; The results listed here should be interpreted cautiously, since they are based on a small number of total participants in only one or two studies.</li> <li>&gt; More research needs to be completed before any firm conclusions on these topics can be drawn.</li> </ul>
<p><b>General Implications:</b> Both live attenuated and inactivated influenza vaccines have been shown to be efficacious in preventing influenza in children 16 and under. However, there is limited RCT evidence regarding the safety of either type of vaccine for children 6 to 23 months of age. This evidence may be used to implement or revise public health policy and/or programs (such as the Universal Influenza Immunization Program).</p>	

**Cost Benefit or Cost-Effectiveness Information:** Not included in the review.

#### References Used to Outline Issue

Ontario Ministry of Health and Long-Term Care. (1997). Mandatory Health Programs and Services Guidelines. Retrieved October 23, 2006 from:

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Ontario Ministry of Health and Long-Term Care. (2006). Universal Influenza Immunization Program. Retrieved October 23, 2006 from:

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- Xie, L., Squires, S.G., Macey, J.F., Aziz, S., Winchester, B, Zheng, H. & Tam T.W.S. (2006). Influenza in Canada, 2004-2005 season. *Canadian Communicable Disease Report=Relevé des maladies transmissibles au Canada*, 32 (6), 57-74.

#### **Additional Reference Cited in the Evidence Table**

- Humiston, S.G., Lerner, E.B., Hepworth E., Blythe T., & Goepf, J.G. (2005). Parent opinions about universal influenza vaccination for infants and toddlers. *Archives of Pediatric and Adolescent Medicine*, 159 (2), 108-12.

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