Health benefits, risks, and cost-effectiveness of influenza vaccination of children

Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The authors compared two routine annual influenza vaccination programmes against a no-vaccination strategy for children in varying age and risk groups. The two vaccination programmes corresponded to the use of a live attenuated influenza vaccine (LAIV) and an inactivated vaccine. Inactivated vaccine was considered for all 10 sub-groups, whilst LAIV was only considered for children not at high risk.

Type of intervention
Primary prevention.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
The study population comprised children stratified into 10 sub-groups by age and risk status: 6 to 23 months, 24 to 35 months, 3 to 4 years, 5 to 11 years, 12 to 17 years, and high risk or not at high risk. Children were defined as being at high risk for influenza-related complications due to pre-existing medical conditions.

Setting
The study setting was the community. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness data were derived from studies and sources published between 1973 and 2005. The price year was 2003.

Source of effectiveness data
The effectiveness data were derived from published studies, supplemented by expert opinion where data were limited or unavailable.

Modelling
An analytic decision tree model, developed using TreeAge Pro 2004 software, was used to estimate the effect of influenza vaccination on the outcomes and costs among children. The authors used a time horizon of one year as most costs and consequences related to influenza occur during a single influenza season. However, they also included the costs and effects of long-term outcomes such as death, long-term sequelae of influenza-related hospitalisations or vaccine adverse events.

Outcomes assessed in the review
The outcomes assessed were:

the annual influenza illness attack rate;

the probability of otitis media for a child with medically attended influenza illness;

the probability of non-hospitalised pneumonia or other outpatient complication for a child with medically attended influenza illness;

the rate of hospitalisation for pneumonia or other respiratory conditions due to influenza;

the probability of long-term sequelae following influenza-related hospitalisation;

the probability of death during influenza-related hospitalisation;

the effectiveness of the vaccine in preventing influenza illness;

the probability of injection site reaction;

the probability of systemic reaction;

the probability of anaphylaxis;

the probability of Guillain-Barre syndrome; and

the quality of life associated with the health states of episode of influenza, otitis media, non-hospitalised complications, hospitalised complications, anaphylaxis and Guillain-Barre syndrome.

Study designs and other criteria for inclusion in the review
Not reported.

Sources searched to identify primary studies
Not reported.

Criteria used to ensure the validity of primary studies
Not reported.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
Approximately 11 primary studies were included in the review.

Methods of combining primary studies
Not reported.

Investigation of differences between primary studies
Not reported.
Results of the review
The annual influenza illness attack rate ranged from 0.157 in 6- to 23-month-old children to 0.06 in 12- to 17-year olds.

The probability of otitis media for a child with medically attended influenza illness ranged from 0.63 in 6- to 23-month-old children to 0.15 in 12- to 17-year olds.

The probability of non-hospitalised pneumonia or other outpatient complications for a child with medically attended influenza illness ranged from 0.2 in 6- to 23-month-old children to 0.08 in 12- to 17-year olds.

The rate of hospitalisation for pneumonia or other respiratory conditions due to influenza ranged from 28.3 per 10,000 in 6- to 23-month-old children to 3.1 in 5- to 17-year olds.

The probability of death during influenza-related hospitalisation was 0.00009.

The vaccine effectiveness in preventing influenza illness was 0.69 for the inactivated vaccine and 0.838 for the LAIV.

The probability of injection site reaction ranged from 0.008 in 6- to 23-month-old children to 0.00003 in 12- to 17-year olds.

The probability of systemic reaction ranged from 0.013 in 6-to 23-month-old children to 0.003 in 12- to 17-year olds.

The quality of life decrements associated with various health states were as follows:
0.005 for an episode of influenza;
0.042 for otitis media;
0.046 for non-hospitalised complications;
0.076 for hospitalised complications;
0.020 for anaphylaxis; and
0.141 for Guillain-Barre syndrome.

Methods used to derive estimates of effectiveness
The authors reported that, when data from the published literature were limited or unavailable, they were supplemented by expert opinion. However, no information about the experts or the methods used to elicit the experts' assumptions was provided. The authors used expert opinion to supplement data from the literature for the probability of otitis media and non-hospitalised pneumonia. Expert opinion was used exclusively to derive estimates for the probabilities of long-term sequelae, anaphylaxis and Guillain-Barre syndrome.

Estimates of effectiveness and key assumptions
The probability of long-term sequelae following influenza-related hospitalisation was 0.01 (range: 0.001 to 0.03).

The probability of anaphylaxis was 0.00000025 (range: 0 to 0.000001).

The probability of Guillain-Barre syndrome was 0.000001 (range: 0 to 0.00001).

Measure of benefits used in the economic analysis
The measure of benefits used were the influenza events averted, influenza hospitalisations averted, deaths averted and quality-adjusted life-years (QALYs) gained. The authors derived quality of life valuations from two studies in which adult respondents were asked to state the amount of time that they would be willing to give up from the end of their life
to prevent a specific temporary health state in a hypothetical child.

**Direct costs**
The direct costs included in the analysis were those to the health care system and the parents. The health care costs included were physician visits, prescription drugs, diagnostic tests and hospitalisations. Costs of physician visits, hospitalisations and vaccination-related events were calculated from a large database that reported payments for health insurance companies in the mid-Atlantic states of the USA. The vaccination costs covered vaccine dose, administration and medical attention for vaccine adverse events. The costs to the parents included over-the-counter medications and the time costs associated with taking children to additional outpatient visits. Discounting was not relevant, as the costs were incurred during a 1-year period, and was appropriately not reported. The study reported the total costs. Costs were adjusted to 2003 dollars using the medical cost component of the Consumer Price Index.

**Statistical analysis of costs**
The study reported the total costs together with 95% confidence intervals (CIs). CIs were derived by bootstrapping.

**Indirect Costs**
The indirect costs were not included.

**Currency**
US dollars ($).

**Sensitivity analysis**
A series of one-way sensitivity analyses were conducted on all variables by altering each variable within a range of plausible values. To evaluate the effects of parameter uncertainty, a probabilistic sensitivity analysis was conducted in which each variable was assigned a distribution of possible values (beta for probabilities and log-normal for costs). The model then randomly picked a different value for each variable from the associated distribution. The model was run 10,000 times for each age-risk and vaccine combination, providing mean values plus 2.5% and 97.5% bootstrapped percentiles.

**Estimated benefits used in the economic analysis**
The total QALYs gained per 1,000 children administered with the inactivated influenza vaccine in the non high-risk group were:

- 3.0 (95% CI: 0.4 to 9.0) for those aged 6 to 23 months;
- 2.4 (95% CI: 0.3 to 7.3) for those aged 2 years;
- 1.7 (95% CI: 0.2 to 5.2) for those aged 3 to 4 years;
- 0.6 (95% CI: 0.1 to 1.7) for those aged 5 to 11 years; and
- 0.4 (95% CI: 0 to 1.1) for those aged 12 to 17 years.

The total QALYs gained per 1,000 children administered with the inactivated influenza vaccine in the high-risk group were:

- 7.2 (95% CI: 0.8 to 23.2) for those aged 6 to 23 months;
- 5.4 (95% CI: 0.6 to 17.2) for those aged 2 years;
4.0 (95% CI: 0.4 to 13.1) for those aged 3 to 4 years;  
1.6 (95% CI: 0.2 to 5.6) for those aged 5 to 11 years; and  
1.3 (95% CI: 0.1 to 4.5) for those aged 12 to 17 years.  
The total QALYs gained per 1,000 children administered with the LAIV in the non high-risk group were:  
3.7 (95% CI: 0.5 to 10.5) for those aged 6 to 23 months;  
2.9 (95% CI: 0.4 to 8.5) for those aged 2 years;  
2.1 (95% CI: 0.3 to 6.1) for those aged 3 to 4 years;  
0.7 (95% CI: 0.1 to 1.9) for those aged 5 to 11 years; and  
0.5 (95% CI: 0.1 to 1.3) for those aged 12 to 17 years.

Cost results  
The net costs (cost of vaccination minus savings from disease averted) of giving the inactivated influenza vaccine to non high-risk children were:  
$37,000 (95% CI: -119,000 to 98,000) for those aged 6 to 23 months;  
$43,000 (95% CI: -40,000 to 83,000) for those aged 2 years;  
$47,000 (95% CI: 2,000 to 78,000) for those aged 3 to 4 years;  
$44,000 (95% CI: 21,000 to 68,000) for those aged 5 to 11 years; and  
$44,000 (95% CI: 22,000 to 68,000) for those aged 12 to 17 years.  
The net costs of giving the inactivated influenza vaccine to high-risk children were:  
-$74,000 (95% CI: -552,000 to 83,000) for those aged 6 to 23 months;  
-$22,000 (95% CI: -292,000 to 72,000) for those aged 2 years;  
$2,000 (95% CI: -212,000 to 70,000) for those aged 3 to 4 years;  
$12,000 (95% CI: -125,000 to 59,000) for those aged 5 to 11 years; and  
$13,000 (95% CI: -120,000 to 59,000) for those aged 12 to 17 years.  
The net costs of giving the LAIV to non high-risk children were:  
$32,000 (95% CI: -155,000 to 99,000) for those aged 6 to 23 months;  
$42,000 (95% CI: -59,000 to 85,000) for those aged 2 years;  
$50,000 (95% CI: -3,000 to 83,000) for those aged 3 to 4 years;  
$48,000 (95% CI: 22,000 to 73,000) for those aged 5 to 11 years; and  
$49,000 (95% CI: 23,000 to 73,000) for those aged 12 to 17 years.
Synthesis of costs and benefits

The costs and benefits were combined using cost-effectiveness (i.e. extra costs per influenza episode averted, per hospitalisation averted, and per death averted) and using cost-utility incremental ratios (i.e. extra cost per QALY gained).

For children not at high risk, the incremental cost-utility ratio (2.5% and 97.5% percentiles) of using the inactivated influenza vaccine over non-vaccination was:

- $12,000 (cost-savings to 208,000) for children aged 6 to 23 months;
- $18,000 (cost-savings to 217,000) for those aged 2 years;
- $28,000 (1,000 to 290,000) for those aged 3 to 4 years;
- $79,000 (15,000 to 682,000) for those aged 5 to 11 years; and
- $119,000 (24,000 to 1,040,000) for those aged 12 to 17 years.

For children at high risk, the incremental cost-utility ratio (2.5% and 97.5% percentiles) of using the inactivated influenza vaccine over non-vaccination was:

- cost-savings per QALY gained (cost-savings to 85,000) for children aged 6 to 23 months;
- cost-savings (cost-savings to 100,000) for those aged 2 years;
- $1,000 (cost-savings to 130,000) for those aged 3 to 4 years;
- $7,000 (cost-savings to 260,000) for those aged 5 to 11 years; and
- $10,000 (cost-savings to 367,000) for those aged 12 to 17 years.

For children not at high risk, the incremental cost-utility ratio (2.5% and 97.5% percentiles) of using the LAIV over non-vaccination was:

- $9,000 (cost-savings to 167,000) for children aged 6 to 23 months old;
- $15,000 (cost-savings to 180,000) for those aged 2 years;
- $25,000 (cost-savings to 236,000) for those aged 3 to 4 years;
- $72,000 (14,000 to 592,000) for those aged 5 to 11 years; and
- $109,000 (22,000 to 888,000) for those aged 12 to 17 years.

The results of the probabilistic sensitivity analyses showed that the probability that the cost-effectiveness of the inactivated vaccine would be <= $30,000 ranged from 51 to 89% for all children aged 6 to 23 months and 2 years. For children of any age and not at high risk, the probability that the inactivated vaccine would be cost-saving was less than 10%. For children aged 5 or older and not at high risk, the probability that the LAIV, compared with no vaccination, was cost-effective at the $30,000 per QALY threshold ranged from 5 to 13%.

The results of the one-way sensitivity analysis showed that cost-effectiveness ratios were most sensitive to changes in the influenza illness attack rate, hospitalisation rates, vaccination costs and vaccine effectiveness.

Authors' conclusions

Routine annual influenza vaccination using an inactivated vaccine for children aged 2 years or older who were not at high risk was likely to result in health benefits, but the cost-effectiveness ratios were likely to be less favourable than
for younger children and children of any age with a high-risk condition. The authors also concluded that cost-effectiveness among children decreased with age, although risk status was more important than age when determining the economic impact of annual influenza vaccination.

CRD COMMENTARY - Selection of comparators
A justification was given for using no vaccination as the comparator: the American Academy of Pediatrics did not recommend influenza vaccination for children older than 39 months. You should decide if this intervention represents current practice in your own settings.

Validity of estimate of measure of effectiveness
The authors did not report if a systematic review of the literature was undertaken to identify all relevant research and minimise biases. Although the authors provided supplementary information on the studies included in the review in the form of free online supplementary appendices, the methods used to derive data from the literature and from the expert panel were not reported. For example, the authors did not report the sources used to identify published studies, the composition of the expert panel, or how expert opinions were elicited. However, the authors appropriately varied all assumptions and estimates from the literature in extensive sensitivity analyses, which clearly enhance the validity of the results.

Validity of estimate of measure of benefit
The estimation of benefits was modelled using a decision analytic model, which was appropriate for the study question. Further, the benefits were reported using four different outcomes (influenza episodes averted, hospitalisations averted, deaths averted and QALYs gained). This enhances the comparability of the results with respect to both similar interventions/patient domains and other health care programmes.

Validity of estimate of costs
Although the authors did not report the perspective used in the economic analysis, the perspectives of the health care system and parents appear to have been included. From these perspectives, no major cost category appears to have been omitted from the analysis and all relevant costs appear to have been included. The costs and the quantities were not reported separately, which will limit the generalisability of the authors' conclusions. The costs were appropriately derived from published sources. Appropriate sensitivity analyses of the costs were undertaken. Discounting was unnecessary, as all the costs were incurred during one year, and was therefore not performed. All costs were inflated to a base price year by use of the Consumer Price Index. However, it would have been more appropriate if inflation exercises had been undertaken using the medical component of the Consumer Price Index as, in general, health care prices rise faster than those of the general economy. The price year was reported, which will facilitate any possible future inflation exercises.

Other issues
The authors reported that prior studies evaluating the cost-effectiveness of vaccination had been overly optimistic about its effectiveness as they assumed very high influenza attack rates and low vaccination costs. Further, the authors reported that their study was the first to compare the LAIV with the inactivated vaccine. The issue of generalisability to other setting was partly addressed in the sensitivity analysis. The authors do not appear to have reported their results selectively and their conclusions reflected the wide scope of the analysis.

The authors reported a number of limitations to their study. First, the model was conservative and did not include outcomes such as a reduced probability of immunised patients with influenza suffering from otitis media. Second, the model did not include the benefits of herd immunisation. Finally, the time trade-off methods used included loss of quality of life for both children and parents.

Implications of the study
The authors recommended future work to assess the impact of herd immunity on the cost-effectiveness of expanding influenza vaccine recommendations.

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**Other publications of related interest**
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