Clinical and economic impact of influenza vaccination on healthy children aged 2-5 years

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 study compared an inactivated, trivalent, virosome-formulated sub-unit influenza vaccine (Inflexal V; Berna Biotech, Berne, Switzerland) with no vaccination. The vaccine was administered intramuscularly in two doses (one at day 1 and one at day 31 +/- 3).

Type of intervention
Primary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised healthy children aged between 2 and 5 years who visited the outpatient clinic of the Institute of Paediatrics of the University of Milan for minor surgical problems. Excluded from the study were:

- children suffering from serious chronic diseases (e.g. chronic pulmonary diseases including asthma, cardiac or renal failure, or severe malnutrition, progressive neurological disease);
- children with a history of recurrent respiratory tract infections (e.g. more than three practitioner-attended respiratory tract infections in the preceding year);
- children with recurrent wheezing (e.g. minimum of four acute episodes of wheezing in the 12 months prior to enrolment);
- children suffering from Down's syndrome or other documented cytogenetic disorders;
- children suffering from a documented or suspected disease of the immune system;
- children under immunosuppressive therapy including systemic corticosteroids for a period longer than 14 days (i.e. a prednisone-equivalent dose of 2 mg/kg per day or a total of 20 mg/day for children above 10 kg);
- children receiving any blood products (i.e. immunoglobulin 6 months prior to the onset of the study until the ending of the study);
- children who were scheduled to receive any other investigational vaccine or agent during the period 1 month before enrolment until the end of the study;
- children who were previously vaccinated against influenza; and
- children with a documented history of hypersensitivity to egg or egg protein, or any other component of the vaccine.

It was ascertained that children included in the study were free from any febrile illness, or any other acute disease, for
at least 36 hours prior to vaccination. In addition, children or any other household member were free from any respiratory illness for at least 72 hours prior to vaccination and were free of wheezing for 2 weeks prior to vaccination. Finally, the children had not received any influenza treatment in the 2 weeks before participation in the study, or any antibiotic treatment for at least 72 hours prior to vaccination.

**Setting**
The setting was the outpatient clinic of the Institute of Paediatrics of the University of Milan. The economic study was carried out in Italy.

**Dates to which data relate**
The effectiveness data were collected during the 2002 to 2003 influenza season. It was reported that vaccination was implemented between 1 October 2002 and 10 November 2002. The cost data were derived from sources published between 1997 and 2004. The price year was not explicitly reported.

**Source of effectiveness data**
The effectiveness data were derived from a single study.

**Link between effectiveness and cost data**
It appears that the costing has been carried out prospectively on the same sample of patients as that used in the effectiveness study.

**Study sample**
It was not reported whether the sample size was determined in the planning phase of the study. In addition, power calculations were not performed retrospectively on the existing sample. Patients who visited the authors’ setting for minor surgical problems and fulfilled the inclusion criteria were enrolled in the study. Overall, 303 healthy children aged between 2 and 5 years were included in the study, of which 202 (54.5% male) received the influenza vaccine and 101 (52.5% male) did not. The mean age was 3.33 (± 1.31) years in the vaccine group and 3.16 (± 1.15) years in the unvaccinated group. It was reported that all participants completed the study.

**Study design**
The analysis was based on a single-centre, prospective, randomised single-blind study. The patients were randomised blind in a 2:1 ratio to receive the vaccine or not. Two investigators conducted the randomisation, but the method used was not reported. Three investigators, who were blind to the intervention, followed up patients during the influenza season. The parents or legal guardians of the children were not blind to the intervention. Individuals were followed up through bi-weekly telephone interviews and monthly medical visits until the end of seasonal influenza activity (20 April 2003). Follow-up was conducted using standardised questionnaires. No losses to follow-up were reported.

**Analysis of effectiveness**
It was not reported whether the analysis was conducted on an intention to treat basis. The primary health outcomes were:

- the number of upper and lower respiratory tract infections,
- the number of febrile respiratory illnesses,
- the number of hospitalisations,
- the number of antibiotic and antipyretic prescriptions, and
the number of school days missed.

In addition, influenza-like morbidity and vaccine effectiveness for the household contacts were also used as outcomes. Such outcomes included the number of influenza-like illnesses, medical visits for influenza-like illness, hospitalisations, antibiotic and antipyretic prescriptions, loss of parental work days and missed days of siblings. Vaccine effectiveness for the study population was defined as 1 minus the attack rate (i.e. the rate of illness divided by the total population) among the vaccinated children divided by the attack rate among the controls. Similarly, vaccine effectiveness for household contacts was defined as 1 minus the attack rate among the household contacts of vaccinated children divided by the attack rate among the household contacts of controls. Adverse events due to vaccination were also accounted for. It was reported that the two patient groups were comparable at baseline in terms of their demographic characteristics.

**Effectiveness results**

For the study population, the mean number (+/- standard deviation, SD) of upper respiratory tract infections was 1.66 (+/- 0.62) in the vaccinated group versus 2.47 (+/- 0.43) in the unvaccinated group. The difference was statistically significant, (p<0.001). The mean number (+/- SD) of lower respiratory tract infections was 0.32 (+/- 0.88) in the vaccinated group versus 0.41 (+/- 1.32) in the unvaccinated group. The difference was statistically significant, (p=0.004). Vaccine effectiveness was 33% for upper respiratory tract infections and 22% for lower respiratory tract infections.

The number of febrile respiratory illnesses was 2.47 (+/- 1.49) in the vaccinated group and 3.32 (+/- 2.74) in the unvaccinated group, (p<0.0001). Vaccine effectiveness was 26%.

The number of hospitalisations did not differ significantly between the two groups, (p=0.417).

The number of antibiotic prescriptions was 1.36 (+/- 1.28) in the vaccinated group and 1.98 (+/- 1.59) in the unvaccinated group, (p<0.0001). Vaccine effectiveness was 32%.

The number of antipyretic prescriptions was 4.70 (+/- 2.03) in the vaccinated group and 6.59 (+/- 2.37) in the unvaccinated group, (p<0.001). Vaccine effectiveness was 29%.

The number of school days missed was 4.61 (+/- 6.23) in the vaccinated group and 8.84 (+/- 12.50) in the unvaccinated group, (p<0.001). Vaccine effectiveness was 48%.

For household contacts of influenza vaccinated and unvaccinated children, the differences were statistically significant between the two groups for the number of influenza-like illnesses, (p=0.0005), the number of medical visits for influenza-like illness, (p=0.002), and the number of antibiotic and antipyretic prescriptions, (p<0.0001).

Loss of parental work was 1.91 (+/- 1.43) days in the vaccinated group and 2.93 (+/- 2.31) days in the unvaccinated group, (p=0.001). Vaccine effectiveness was 35%.

Lost days from work were 3.22 (+/- 1.86) for mothers of vaccinated children and 4.78 (+/- 2.34) for mothers of unvaccinated children, (p=0.001).

Lost days from work were 0.56 (+/- 0.46) for fathers of vaccinated children and 0.98 (+/- 1.22) for fathers of unvaccinated groups, (p=0.0001).

Missed school days were 1.43 (+/- 2.61) for siblings of vaccinated children and 2.93 (+/- 4.10) for siblings of unvaccinated children, (p<0.0001).

It was reported that the severity and duration of adverse events due to vaccination were limited. Therefore, discontinuation of the vaccination programme was not required. The statistical results were reported in full, but were too numerous to be reported in this abstract.

**Clinical conclusions**
The authors reported that influenza vaccination of healthy children aged between 2 and 5 years reduces influenza-like illness, not only in the vaccinated children themselves but also in their unvaccinated household contacts, during the influenza season.

Measure of benefits used in the economic analysis
The authors did not derive a measure of benefit in the economic analysis. In effect, a cost-consequences analysis was performed.

Direct costs
The direct costs used in the analysis covered vaccination, medical examinations of children included in the study and related household members, and the treatment of influenza-like illness for children and their households (including the cost of hospitalisation, antibiotics and antipyretics). The cost of vaccination included the vaccine, personnel, preparation, administration and surplus accounted as a flat rate, adverse effects necessitating pharmacological treatment, and the absence from work of household members for the purpose of vaccine administration.

The costs and the quantities of resources used were reported separately. The quantities were derived from the effectiveness study, while all unit costs were derived from official published sources. However, although the cost data related to different price years, no appropriate adjustments for inflation were conducted and the price year was not reported. Discounting was not relevant as the costs were incurred during less than 2 years.

Statistical analysis of costs
It was reported that all data were analysed using SAS Windows version 12. The cost data were reported as mean values +/- SD. The authors conducted an extensive statistical analysis on all data and a p-value of less than 0.05 was assumed to be statistical significant for all tests. Parametric data were analysed using analysis of variance (PROC GLM and LSD) in terms of treatment. The Kruskal-Wallis test was used for data not normally distributed or non-parametric data. Categorical data were analysed using contingency tables with the chi-squared or Fisher's test.

Indirect Costs
The indirect costs included in the analysis were for productivity losses due to absence from work of household members for influenza-like illness in their children and themselves. The indirect costs were evaluated according to the net productivity loss tables per capita, which came from official published sources. Discounting was not relevant as the costs were incurred during less than 2 years. The price year was not explicitly reported.

Currency
Euros (EUR).

Sensitivity analysis
No sensitivity analysis was carried out.

Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

Cost results
The total costs were reported per patient.

The mean (+/- SD) total costs (including indirect costs) were EUR 451.04 (+/- 493.40) in the vaccinated group and EUR 582.47 (+/- 506.31) in the unvaccinated group.
It was reported that the intervention resulted in savings of EUR 131.43 (+/- 540.03) per vaccinated child.

**Synthesis of costs and benefits**
The costs and benefits were not combined.

**Authors' conclusions**
"Influenza vaccination of healthy children aged 2 to 5 years substantially reduces influenza-like illness and related costs in the children themselves and their families."

**CRD COMMENTARY - Selection of comparators**
The authors compared an influenza vaccination programme in healthy children aged 2 to 5 years versus no vaccination. This allowed the active value of the intervention to be evaluated. You should decide if this represents a widely used technology in your own setting.

**Validity of estimate of measure of effectiveness**
The analysis was based on a prospective randomised single-blind trial, which appears to have been appropriate given the study question. The study sample was representative of the study population and the patient groups were shown to be comparable at analysis. Randomisation and blinding were reported, suggesting that the internal validity of the study is likely to be good. In addition, appropriate statistical analyses were undertaken to account for potential biases and confounding factors. However, power calculations were not reported, thus, it was not possible to ascertain whether the results obtained were due to the intervention or to chance.

**Validity of estimate of measure of benefit**
The authors did not derive a summary measure of benefit. In effect, a cost-consequences analysis was performed.

**Validity of estimate of costs**
The authors reported that the study had been conducted from a societal perspective. It appears that all the relevant categories of costs have been included in the analysis. The costs and the quantities were reported separately, which would enable the analysis to be easily reworked for other settings. The costs were derived from official published sources, while the quantities of resources used were derived from actual data (i.e. patients' records). No sensitivity analysis on the costs or quantities was conducted to assess the robustness of the estimates used, which may limit the interpretation of the study findings. The costs were derived from sources referring to different price years. However no appropriate adjustments for inflation were conducted and the price year was not reported. Discounting was not necessary since the costs were all incurred during less than 2 years.

**Other issues**
The authors compared their findings with those from other studies, and found them generally to be in agreement. Differences found in comparison with one study were attributed to differences in sample sizes. The issue of generalisability of the results to other settings was not addressed. The authors do not appear to have presented their results selectively. The study enrolled healthy children aged between 2 and 5 years and this was reflected in the authors' conclusions. The authors did not report any further limitations to their study.

**Implications of the study**
The authors did not make explicit recommendations for changes in policy or practice. However, they called for a larger study with longer time horizon, which will include multiple seasons, to derive more robust estimates.
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