Cost benefit of influenza vaccination in healthy, working adults: an economic analysis based on the results of a clinical trial of trivalent live attenuated influenza virus vaccine

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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
A trivalent, intranasal, live attenuated influenza virus vaccine (LAIV) was evaluated.

Type of intervention
Primary prevention (vaccination).

Economic study type
Cost-benefit analysis.

Study population
The study population comprised healthy working persons aged between 18 and 64 years. Individuals were eligible if they worked at least 30 hours per week outside of the home and had health insurance. People were excluded if they had a history of acute hypersensitivity to eggs or egg products, or had received the 1997-1998 inactivated influenza vaccine. Other exclusion criteria were self-reported pregnancy or unprotected risk for pregnancy within the last 3 months, and acute febrile illness or upper respiratory tract illness within 72 hours. The presence of any indications for routine vaccination with the inactivated vaccine was also considered as an exclusion criterion.

Setting
The setting was the community. The economic study was conducted in the USA.

Dates to which data relate
The effectiveness evidence and resource use data were gathered mainly from November 1997 to March 1998. Some evidence also came from studies published between 1993 and 1998. The price year was 1998.

Source of effectiveness data
The effectiveness evidence was derived from a single study and authors’ assumptions. Details of the study had been published elsewhere (Nichol et al 1999, see "Other Publications of Related Interest" below for bibliographic details).

Link between effectiveness and cost data
The costing was not conducted on the same sample of patients as that used in the effectiveness study.

Study sample
Power calculations were conducted in the preliminary phase of the study. These suggested that a sample of 4,200 persons would be required for a 90% power to detect statistically significant differences in the main outcome measure on the basis of some assumptions. The participants were recruited from 13 centres across the USA from 18 September
through 15 November 1997. Of an initial group of 4,891 persons screened, 330 (6.8%) were not eligible or did not consent to participation. Thus, the final study sample included 4,561 persons (93.2%), of which 3,041 were included in the vaccine group and 1,520 in the placebo group. The participants in the vaccine group had a mean age of 38.3 (+/- 10.2) years (age range: 18 - 65) and 1,664 were female. The participants in the placebo group had a mean age of 38.2 (+/- 10.0) years (age range: 18 - 65) and 825 were female. Each patient received up to $100 as a financial incentive.

**Study design**
This was a prospective, multi-centre (13 centres), double-blind placebo-controlled trial. The participants were allocated in a ratio of 2:1 to receive vaccine or placebo. Randomisation was performed using 6-unit blocks. Each participant was assigned to the next available sequential allocation number according to a predetermined, computer-generated randomisation schedule. Both the study participants and site personnel were blinded to the intervention assignment until all the outcome data had been gathered and analysed. The patients were followed during the influenza season (5 months) and contacted 7 and 28 days after vaccination (telephone interview). The patients completed symptom and illness cards, which were then returned to the site investigators. At the end of the study, data were available for 2,833 patients (93.2%) in the vaccine group and 1,420 patients (93.4%) in the placebo group. Thus, the loss to follow-up was comparable between the groups. Local laboratories were contacted to confirm data on influenza outbreak periods.

**Analysis of effectiveness**
The analysis of the clinical study was conducted on the basis of treatment completers only, as only patients whose follow-up data were available were included in the effectiveness study. Several health outcomes were estimated in the primary study, but only those relevant to the present economic evaluation will be reported:

- the number of days with health care provider visits among unvaccinated persons;
- the relative rate of health care provider visits because of illness among vaccinated persons versus unvaccinated persons;
- the number of days of work lost because of illness among unvaccinated persons;
- the relative rate of work lost because of illness among vaccinated versus unvaccinated persons;
- the number of days of reduced work effectiveness because of illness among unvaccinated persons; and
- the relative rate of reduced work effectiveness among vaccinated versus unvaccinated persons.

The study groups were shown to have been comparable at baseline in terms of demographic and educational characteristics.

**Effectiveness results**
The number of days with health care provider visits among unvaccinated persons (per 1,000 persons) was 338.9 (range: +/- 100).

The relative rate of health care provider visits because of illness among vaccinated persons versus unvaccinated persons was 0.87 (95% confidence interval, CI: 0.77 - 0.98).

The number of days of work lost because of illness among unvaccinated persons (per 1,000 persons) was 1,030 (range: 500 - 1,500).

The relative rate of work lost because of illness among vaccinated versus unvaccinated persons was 0.82 (95% CI: 0.74 - 0.91).

The number of days of reduced work effectiveness because of illness among unvaccinated persons (per 1,000 persons) was 1,502.5 (range: 1,000 - 2,000).
The relative rate of reduced work effectiveness among vaccinated versus unvaccinated persons was 0.82 (95% CI: 0.74 - 0.91).

**Clinical conclusions**

The effectiveness analysis showed that LAIV was effective in reducing the number of days of illness and the days of work lost in comparison with placebo.

**Modelling**

The authors stated that a model was used to estimate the net costs (savings) of the vaccination programme relative to the non-vaccination option, which actually referred to the estimation of the combined health benefits and costs. This calculation was carried out using probability values obtained from the literature and the single study.

**Measure of benefits used in the economic analysis**

Although not clearly stated in the paper, the summary measure of health benefit used for the economic evaluation appears to have been the lost time (i.e. due to vaccination, side effects, lost work and reduced productivity) associated with the vaccination programme when compared to placebo. Some of the categories of lost time were directly obtained from the effectiveness analysis; however, some of the components of the lost time were derived from a literature review and from some authors' assumptions (i.e. the reduction in work loss, days of work but at reduced effectiveness, and days with health care provider visits due to vaccination in comparison with no vaccination). Since this was a cost-benefit analysis, the human capital approach was used to assign monetary values to the time lost. The following outcomes were also assessed as average values per patient, and used for the estimation of the lost time: work lost for vaccination, the number of days of work lost due to side effects, and the productivity level during days of reduced work effectiveness. For the estimation of lost time it was assumed that the likelihood of missing work for vaccination was 0.5 (range: 0.2 - 0.8) and the number of health care provider visits due to side effects (per 1,000 persons) was 5 (range: 0-10).

**Direct costs**

Discounting was not relevant because the costs were incurred during 5 months. The unit costs were analysed separately from the quantities of resources used. The health services included in the economic analysis were vaccination and its administration, and potential side effects (medical care costs, including provider visits, tests and medications). Costs saved due to vaccination, such as medical care costs avoided, were considered when calculating the net costs of the vaccination programme. A Monte Carlo simulation was performed in order to estimate the mean case break-even costs per patient associated with the vaccine and its administration.

The cost/resource boundary adopted for the analysis of the direct costs was that of the health service provider. Resource use was estimated using data collected alongside the clinical trial that was used to derive the bulk of the effectiveness evidence and authors' assumptions. Unit costs of provider services were estimated from the National Center for Health Statistics in the USA, Healthcare Consultants of America, and the Drug Topics Red Book. All the costs were reported in 1998 values using the appropriate component of the Consumer Price Index.

**Statistical analysis of costs**

Statistical tests were not conducted on the costs or resources. However, each category of cost was assigned a probabilistic distribution. Ranges of the costs were reported.

**Indirect Costs**

The indirect costs, (such as lost work time for vaccination and its side effects, and the costs avoided because of the prevention of work loss and impaired productivity with the vaccination programme) were included in the analysis as a societal perspective was adopted. Discounting was not relevant because of the short time horizon of the analysis. The unit costs were reported separately from the quantities of resources used. The price year was likely to have been 1998.
These indirect costs were considered as the summary measure of health benefit in the economic evaluation. Therefore, for further information, the reader is referred to the "Measure of Benefit used in the Economic Analysis" section above.

Currency
US dollars ($).

Sensitivity analysis
To investigate the robustness of the estimated costs, univariate and multivariate sensitivity analyses were conducted on almost all probability values and cost estimates used in the study. The ranges used were based on data derived from the literature or from authors' assumptions. The authors focused the analysis of uncertainty on those values derived from assumptions or published studies. Monte Carlo simulations were conducted by simultaneously varying all variables used in the model across the pre-assigned probability distributions. Two thousand iterations were run for each simulation.

Estimated benefits used in the economic analysis
The reduction in the number of workdays at reduced effectiveness was 26.9 per 100 persons (5th - 95th percentiles: 17.2 - 36.1).

The reduction in the number of days with health care provider visits was 4.4 per 100 persons (5th - 95th percentiles: 1.6 - 7.0).

The work lost for vaccination was 0.5 hours (range: 0.25 - 0.75).

The number of days of work lost due to side effects (per 1,000 persons) was 10 (range: 0 - 20).

The productivity level during days of reduced work effectiveness was 50% (range: 20 - 100).

Cost results
The estimated direct cost associated with the vaccination programme per person were: $0.61 due to side effects, (with the costs of vaccination and administration unknown), and the direct costs of medical care averted due to vaccination per person was $5.39.

The monetary values associated with the lost time related to the vaccination programme were: $4.58 and $1.47 due to vaccination and side effects, respectively, while those associated with the lost time due to work loss and reduced effectiveness avoided with vaccination were, respectively, $27.16 and $17.18.

Synthesis of costs and benefits
Estimated heath benefits and costs were combined by estimating the net costs (savings) associated with the vaccination programme as the cost of vaccination minus the costs averted due to vaccination (which actually included the monetary estimation associated with health benefits).

The estimated costs of vaccination per patient were $6.66 (costs of vaccine and administration being excluded as they were unknown), while the estimated average costs averted because of vaccination were $49.73. Thus, the mean break-even cost for vaccine and its administration was estimated to be $43.07 (5th - 95th percentiles: 25.72 - 58.92).

Results from the sensitivity analyses showed that the major cost drivers were hourly wage, productivity level when working at reduced effectiveness, and relative rate of work loss among vaccinated versus unvaccinated persons. The range of the 5th to 95th percentile for the break even cost for vaccination and its administration varied in the sensitivity analyses from $12.85 to $97.68.

Authors' conclusions
The implementation of an influenza vaccination programme proved to be beneficial in healthy working adults in terms of both health and economic implications.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparator was clear. The influenza vaccination was compared with placebo since the aim of the study was to estimate the active value of the vaccine. However, the authors discussed the potential choice of another vaccine, trivalent inactivated vaccine (TIV) and stated that the two vaccines presented similar efficacy and safety profiles. Thus, the results of the present study also applied to TIV.

Validity of estimate of measure of effectiveness
The analysis of effectiveness was based on data coming from a single study, details of which were published in a separate article. This was a randomised study that was conducted in several centres and was based on a double-blind design. Power calculations were conducted preliminarily and the baseline comparability of the study groups was shown. The basis of the analysis of the clinical study was treatment completers only, but the loss to follow-up was negligible and comparable between the two groups. The methods of patient selection and randomisation were described. These issues tend to enhance the internal validity of the study, the design of which was appropriate for the study question. Most of the effectiveness estimates were used as probability values in order to calculate the costs of the vaccination strategy.

Validity of estimate of measure of benefit
The summary measure of benefit used for the economic analysis (i.e. lost time averted with the vaccination programme) may have been appropriate, although it would not permit comparisons to be made with different health interventions, as it referred to a specific aspect of the health intervention under analysis. It was derived directly from the single study, from data selectively chosen from the literature, and from authors’ assumptions. The authors investigated the issue of uncertainty in the estimates used by conducting sensitivity analyses.

Validity of estimate of costs
The validity of the cost analysis was high because the authors provided many details about the economic study. The perspective adopted in the study was reported, as were data on resource use and the unit costs, which were analysed separately. A breakdown of the costs was given. The price year was reported, thus facilitating reflation exercises in other settings. The calculations required to estimate the costs were explicitly reported. Each category of cost was assigned a probabilistic distribution and used in the Monte Carlo simulation. The simulation was appropriately carried out to deal with the issue of uncertainty. The sources of data relating to the costs and resource use were reported.

Other issues
A more appropriate way of reporting the estimated health benefits and costs would have been by clearly identifying what the authors considered to be the health benefits associated with the intervention, on the one hand, and the costs incurred in implementing the vaccination programme on the other, when compared to placebo. It would also have been more useful had the authors combined the health benefits and costs as the net social benefit associated with the programme (i.e. the monetary value associated with the health benefits minus the total costs incurred in the vaccination programme, when compared to placebo), and not simply reported all these outcomes as if they were costs.

The authors compared their findings with those from other studies that evaluated the TIV among healthy working adults. The issue of the generalisability of the study results to other settings was not addressed, but several sensitivity analyses were conducted and the results of the study were presented under several assumptions. This enhanced the external validity of the analysis. The study referred to healthy working adults and this was reflected in the conclusions of the analysis. The authors highlighted some limitations of their study. These limitations focused on the cost analysis and the possibility that the cost-savings of vaccination were underestimated (some extended cost-savings were not included in the analysis).
Implications of the study
The study results suggested that LAIV might be beneficial to healthy working adults, who are usually not considered to be among those who may benefit the most from influenza vaccination. The authors noted that some caution is required when interpreting their results, owing to the uncertainty in some estimates used as probability values.

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