Effectiveness and cost-benefit of influenza vaccination of healthy working adults: a randomized controlled trial


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
Influenza vaccination of healthy working adults aged under 65.

Type of intervention
Primary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population was healthy working adults younger than 65 years of age. Persons eligible to participate were aged between 18 and 64 years, were full-time employees with no medical conditions for which influenza vaccine was recommended by the US Advisory Committee on Immunization Practices, and without contraindications to vaccination.

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

Dates to which data relate
Effectiveness and resource use data were taken from the period between 1997 and 1999. The price year was 1999.

Source of effectiveness data
The evidence for the final outcomes was based on a single study.

Link between effectiveness and cost data
Costing was conducted prospectively on the same patient sample as that used in the effectiveness analysis.

Study sample
Power calculations were used to determine the sample size: a sample size of 1,300 participants was calculated on the basis of an influenza attack rate of 5% among unvaccinated persons, vaccine efficacy of 60%, a confidence level of 95%, and 80% power. For each season, participants were randomly assigned to receive either trivalent inactivated influenza vaccine (n=595 in 1997-1998 with a median age of 44 years and n=587 in 1998-1999 with a median age of 44 years) or the placebo of a sterile saline injection (n=589 in 1997-1998 with a median age of 43 years and n=604 in 1998-1999 with a median age of 44 years).
Study design
The study was a double-blind, randomised, placebo-controlled trial, carried out in the community. The duration of follow-up was from November to March in each study year. For 1997-1998 95% (1,130/1,184) of participants had complete follow-up. In 1998-1999 99% (11,78/1,191) of participants had complete follow-up. 23% in each year had serologic testing. Randomisation was achieved using a random-numbers table. Participants in 1997-1998 were re-randomised if they participated in 1998-1999. Vaccine and saline were drawn up in identical syringes by one nurse and were administered by a different nurse who was blinded to participant randomisation. Blinding was maintained until data collection was complete. The study was conducted during 2 consecutive influenza seasons and the influenza period was defined based on virologic surveillance at the study site. Diagnostic testing was used to confirm influenza infection rates in a subset of participants. Participants were recruited through e-mail notices and study presentations at the worksite. The study also used e-mail as the primary means for data collection.

Analysis of effectiveness
The principle used in the analysis of effectiveness was both intention to treat and treatment completers. The primary clinical outcome measures were influenza-like illnesses (ILI) and associated physician visits and work absenteeism reported in biweekly questionnaires by all participants, and serologically confirmed influenza illness among 23% of participants in each year (n=275 in 1997-1998; n=278 in 1998-1999). Adverse effects of vaccination were also reported.

Clinical respiratory illness was defined in two ways:

ILI was defined as feverishness or a measured temperature of at least 37.7 degrees Centigrade (100 degrees Fahrenheit or more) plus cough or sore throat (CDC ILI surveillance definition); and

upper respiratory illness (URI) was defined as sore throat plus cough, feverishness, or a measured temperature of at least 37.7 degrees C (100 degrees F or more).

Outcome data for persons with no completed surveys from the influenza period (n=7 in 1997-1998 and n=9 in 1998-1999) were imputed using baseline demographic characteristics. The study groups appear to have been comparable in terms of their baseline characteristics.

Effectiveness results
In 1997-1998, when the vaccine virus differed from the predominant circulating viruses, vaccine efficacy against serologically confirmed influenza illness (2.2% in the vaccine group versus 4.4% in the placebo group) was 50% (p=0.33). Vaccination did not reduce ILI, physician visits, or lost workdays.

In 1998-1999, when the vaccine and the predominant circulating viruses were well matched, the vaccine efficacy was 86% (1% versus 10%, respectively, p=0.001). Vaccination reduced ILI, physician visits, and lost workdays by 34%, 42%, and 32%, respectively.

During both study periods only arm soreness (p<0.001 for both periods) and redness at the injection site (p<0.001 for both periods) were reported more often by vaccine recipients than by placebo recipients.

Clinical conclusions
In 1998-1999, when the vaccine and circulating influenza strains were well matched, vaccination clearly had health benefits. In that year, the vaccine efficacy against laboratory-confirmed influenza was 86% and there were statistically significant reductions in ILI, physician visits, and days lost from work among vaccine recipients. In the first year of the study, 1997-1998, when the vaccine and circulating strains were not well matched, the difference between the rates of ILI in the vaccine and placebo groups was not statistically significant.

Measure of benefits used in the economic analysis
No summary benefit measure was identified in the economic analysis, and only separate clinical outcomes were reported (see effectiveness results).

**Direct costs**
Costs were not discounted due to the short time frame of the cost analysis. Quantities were reported separately from the costs. A cost breakdown was reported separately. The cost analysis covered the costs of vaccination and ILI, including, physician visits, physician visit co-payments, prescriptions, prescription co-payments, over-the-counter drugs, and hospitalisation. The cost per person was calculated by multiplying the cost per category by the number of events per ILI by the number of ILIs per person. For reasons of confidentiality, the study was not able to obtain actual costs related to physician visits. A large health insurance database of persons aged 18 to 84 years was used to obtain the median insurance payments for International Classification of Diseases, Ninth Revision (ICD-9) coded visits and related prescriptions. These were in 1996 prices. The study participants reported information on respiratory illnesses and related physician visits, medications, and hospitalisations twice monthly. All costs were adjusted to 1999 prices. The costs of the adverse effects of vaccination were not incorporated in the cost analysis since no additional labour or medical costs were reported in this study.

**Statistical analysis of costs**
No statistical analysis was performed on cost outcomes, but statistical analysis was conducted on some of the resource use data.

**Indirect Costs**
Costs were not discounted due to the short time frame of the cost analysis. Quantities were reported separately from the costs. A cost breakdown was reported separately. The indirect cost analysis covered the costs of time lost from work. The study participants reported information on respiratory illnesses and related lost workdays. The time lost from work for vaccination was incorporated in the total cost of vaccination. The perspective adopted in the indirect cost analysis was that of society. For reasons of confidentiality, the study was not able to obtain actual costs related to the salaries of each study participant. The estimated average cost for a lost workday was based on the hourly rate for wages plus benefits for civilian workers in goods-producing industries in large US companies in 1999.

**Currency**
US dollars ($).

**Sensitivity analysis**
A set of one-way sensitivity analyses was performed on labour costs, time lost from work for vaccination, and ILI attack rates. The changes were based on the 1998-99 values.

**Estimated benefits used in the economic analysis**
The effectiveness results are reported above.

**Cost results**
In 1997-1998 period, the mean total (societal) cost per person was $124.21 in the vaccination group versus $58.62 in the placebo group, a net difference of $65.59 per person. The corresponding values in the 1998-1999 season were $51.43 and $40.26: a net societal cost of $11.17 per person.

**Synthesis of costs and benefits**
Costs and benefits were not combined.
Authors' conclusions
Influenza vaccination of healthy working adults younger than 65 years can reduce the rates of ILI, lost workdays, and physician visits during years when the vaccine and circulating viruses are similar, but vaccination may not provide overall economic benefits in most years.

CRD COMMENTARY - Selection of comparators
The strategy of no vaccination (the use of placebo) was explicitly regarded as the comparator. This was appropriate and allowed the active value of the vaccination strategy to be evaluated.

Validity of estimate of measure of effectiveness
The internal validity of the effectiveness results is likely to be high owing to the randomised nature of the study design, and the power calculations that were performed to justify the sample size. Furthermore, the study groups were comparable in terms of baseline characteristics. The study sample also appears to have been representative of the study population.

Validity of estimate of measure of benefit
No summary benefit measure was identified in the economic study, and as a result, the study was a cost-consequences analysis, although the cost-consequences approach was appropriate for the study hypothesis. A summary health benefit measure (composite measure or otherwise) could have been used in the building of a cost-effectiveness measure (ie, cost per case averted). It was acknowledged that the study did not consider the potential benefits of reducing transmission of influenza to co-workers and household members, or the potential benefit of intangibles, such as avoiding the discomforts and inconveniences associated with influenza illness. In this sense the benefits of the vaccination programme may have been underestimated.

Validity of estimate of costs
Positive features of the cost analysis, likely to have enhanced its validity, were that the resource use profile was reported, details of the methods of cost estimation were given, the price year and perspectives adopted in the study were specified and statistical analyses were performed on some resource use data. The effects of alternative procedures on indirect costs were addressed and sensitivity analyses were performed to address the robustness of the cost results. However, the cost analysis was not based on true costs (due to the issue of confidentiality), some bias may have been introduced to the resource use profile from self-reporting bias, and no statistical analysis was performed on cost outcomes.

Other issues
The authors’ conclusions may not to be fully justified given the conflicting outcomes of the two influenza seasons. Future studies may wish to investigate the impact of this type of vaccination programme using a synthesised cost-effectiveness measure where feasible. The issue of generalisability to other settings or countries was addressed in the authors’ comments by noting that the cost estimates applied to this study population may not be generalisable to other populations, particularly those with lower incomes or those that lack health care access. It was further mentioned that the study population differed from the Minnesota vaccination study by age, sex, income level, and other variables. The authors also noted that the study was not able to maintain blinding with regard to vaccine status given that arm soreness and redness at the injection site are associated with vaccination against influenza and participants were informed about potential adverse effects as part of the consent process. However, this was perceived not to have affected the illness rate and related costs as they were comparable with those seen in studies using similar case definitions. The authors discussed how far the study sample is representative of the study population.

Implications of the study
Regardless of the cost-benefit of influenza vaccination in healthy adults, some working adults may choose to be vaccinated to reduce their risk of being infected with influenza. However, the results of this study could be used to help
set societal priorities when vaccine is in short supply.

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