Is influenza vaccination cost effective for healthy people between ages 65 and 74 years: a randomised controlled trial
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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
Influenza vaccination for healthy people aged 65 to 74 years was examined. Each dose of influenza vaccine (0.5 mL, inactivated split virion) contained 15 microg of A/Beijing/262/95 (H1N1), 15 microg of A/Sydney/5/97 (H3N2) and 15 microg of B/Beijing/184/93. All patients were additionally vaccinated with the 23-valent-pneumococcal polysaccharide vaccine, unless it had been administered in the past 10 years.

Type of intervention
Primary prevention.

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

Study population
The study population comprised community-dwelling people between the ages of 65 and 74 years, who were without any of the chronic illnesses for which influenza vaccination was recommended.

Setting
The setting was primary care. The economic study was carried out in the UK.

Dates to which data relate
The effectiveness and resource use data were gathered from September or October 1999 to March 2000. The price year was not explicitly reported, but some of the costs were derived from 2001 sources.

Source of effectiveness data
The effectiveness evidence was derived from a single study and authors’ assumptions.

Link between effectiveness and cost data
The costing was carried out prospectively on the same sample of patients as that used in the effectiveness study.

Study sample
Power calculations were performed in the preliminary phase of the study on the basis of an assumed seasonal attack rate of influenza of 15%. These suggested that a total of 2,135 patients would achieve an 80% power to detect a true 5% difference between the groups. The participants were identified by general practitioners (GPs) or their practice nurses, and were contacted during September or October 1999. Of the 9,727 individuals initially identified, 3,852 were not eligible (had co-morbid conditions), 4,578 decline to participate, and 568 were excluded for other reasons. Thus, the
The study sample comprised 729 individuals, of which 552 individuals (51.8% men) received the influenza vaccination and 177 (57.6% men) received placebo. The participants had a median age of 68.9 years (interquartile range, IQR: 4.4 years) in the vaccine group and 69.1 years (IQR: 5.2 years) in the placebo group.

**Study design**

This was a prospective, single-blind, randomised, placebo-controlled clinical trial that was carried out at 20 GP surgeries in Liverpool. The participants were given a numbered, sealed, opaque envelope containing a card revealing a letter A, B, C or D. Each participant received either influenza vaccine or placebo (0.5 mL physiological saline) in a ratio 3:1 and was unaware of which intervention he or she had received. Before each vaccination session, the project statistician used a list of computer-generated numbers to produce a blocked, random allocation sequence of letters stratified by GP practice and assigned one letter to placebo. The team member who administered the vaccine was aware of which participants received placebo. The length of follow-up was unclear, but the trial ran for one year. No patient was lost to the follow-up assessment.

**Analysis of effectiveness**

The analysis of the clinical study appears to have been conducted on an intention to treat basis. The primary outcome measure was occurrence of influenza, as recorded by a GP diagnosis of pneumonia or influenza-like illness (ILI). ILI was defined as an illness of sudden onset with features of cough, feverishness, prostration, myalgia and widespread aches and pains.

The secondary outcome measures were:

- self-reported ILI,
- GP consultations for any respiratory symptom,
- GP-prescribed antibiotics for any respiratory symptom,
- hospitalisations for any respiratory illness, and
- deaths.

The study groups were comparable at baseline in terms of clinical and demographic characteristics.

**Effectiveness results**

The proportion of individuals with a GP diagnosis of ILI was 0.9% with vaccine and 1.1% with placebo (relative risk, RR=0.8, 95% confidence interval, CI: 0.16 - 4.1).

The proportion of individuals with a GP diagnosis of pneumonia was 0 in both groups.

The rate of GP consultations for any respiratory symptom was 8% (vaccine group) versus 9.6% (placebo group) (RR 0.83, 95% CI: 0.49 - 1.42).

The rate of GP-prescribed antibiotics for any respiratory symptom was 6.9% (vaccine group) versus 5.1% (placebo group) (RR 1.35, 95% CI: 0.67 - 2.74).

No hospitalisations for any respiratory illness were observed.

The rate of deaths was 0.5% (vaccine group) versus 0.6% (placebo group) (RR 0.96, 95% CI: 0.1 - 9.19).

No statistically significant difference between the groups was observed in any of the outcome measures.

For self-reported measures:
the proportion of individuals with at least one or more episodes of self-reported ILI was 4.6% (vaccine group) versus 8.9% (placebo group) (RR 0.51, 95% CI: 0.28 - 0.96; p=0.034);

the proportion of individuals with at least one or more episodes of self-reported ILI involving a GP consultation was 1.7% (vaccine group) versus 2.4% (placebo group) (RR 0.72, 95% CI: 0.23 - 2.32); and

the proportion of individuals who self-reported ILI not requiring a doctor consultation, but involving the use of over-the-counter medication was 2.1% (vaccine group) versus 4.2% (placebo group) (RR 0.50, 95% CI: 0.2 - 1.28).

Clinical conclusions
The effectiveness analysis showed that, compared with placebo, influenza vaccination did not reduce the GP diagnosis of influenza, or the number of consultations, prescriptions or hospitalisations. However, a lower rate of self-reported ILI was observed.

Modelling
A modelling approach was used to extrapolate the clinical and economic outcomes of the trial to the population of 65- to 74-year-olds in England. The authors used population estimates and made some assumptions to carry out both a cost-effectiveness analysis and a cost-utility analysis.

Methods used to derive estimates of effectiveness
The authors made several assumptions in order to extrapolate the clinical results obtained in the trial to the whole population in England. Some assumptions were based on published population statistics, or on the trial results, and then manipulated.

Estimates of effectiveness and key assumptions
The population of persons aged 65 to 74 years in England was 4,090,000, of which approximately 2,045,000 were healthy (assuming that around 50% suffer from chronic illness).

Twenty per cent of healthy 65- to 74-year-olds would actively seek influenza vaccination without any promotional campaign.

The hospitalisation rate for the target group would be 0.32% per year.

The relevant mortality rate for hospitalised cases would be 0.01% per year.

It was estimated that 6.0% of the group would suffer an episode of ILI with 60% vaccination coverage, compared with 7.65% with only 20% coverage. This would result in 33,800 fewer episodes of influenza (a relative reduction of 21.6%).

The expected incidence of respiratory symptoms suggestive of ILI leading to a reduction in GP consultation rate from 9.6% to 8.0% would result in 13,400 fewer consultations.

Acute hospital episodes were estimated to reduce by 442 because of increased vaccination coverage.

Increased vaccination would lead to 3,208 fewer hospital bed-days being required.

The scenario in which vaccination increased from 20 to 60% resulted in only 14 fewer deaths across the whole of England in a year (from 196 to 182).

Patients suffering from premature death from influenza could expect a further 8 years of life at a utility value of 80%.
Measure of benefits used in the economic analysis
The summary benefit measures used were the number of GP consultations and the number of self-reported ILI episodes. Both were derived directly from the clinical trial.

In the model, the benefit measures were GP consultations avoided, hospital admissions avoided, deaths avoided, life-years gained (LYG) and quality-adjusted life-years (QALYs) gained.

LYG and utility values were based on authors' assumptions. It was not stated whether discounting was applied to life expectancy.

Direct costs
Discounting was not relevant because of the short timeframe of the analysis (one year). The unit costs were presented separately from the quantities of resources used. The health services included in the economic evaluation were vaccine and its administration, over-the-counter medications, GP consultations and GP prescriptions of antibiotics. The treatment of side effects was not considered since no adverse events were observed. The perspectives of the National Health Service (NHS) and the patient were adopted. Resource use was estimated using patient-level data derived from the clinical trial. The costs were based on assumptions or typical NHS sources. The price year was not explicitly reported, although some costs were estimated from 2001 sources. The modelling approach considered vaccination costs, over-the-counter medications, GP consultations and prescriptions, and hospitalisations. Vaccination costs included vaccine promotion expenses and were estimated from the Department of Health.

Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
The indirect costs were not included in the economic evaluation because, owing to the age of the participants, they were not relevant.

Currency
UK pounds sterling (£).

Sensitivity analysis
Univariate sensitivity analyses were carried out in the modelling approach to examine the impact of variations in model inputs on the cost-effectiveness and cost-utility ratios. The parameters varied were target coverage, hospital admission risk, mortality risk, efficacy of vaccine, incidence rate, zero programme promotional costs, the cost per hospital episode and life expectancy. The authors appear to have set the ranges of values used.

Estimated benefits used in the economic analysis
The number of GP consultations and the number of self-reported ILI episodes are given in the 'Effectiveness Results' section. The other estimated benefits were not reported.

Cost results
Based on the results of the trial, the total NHS costs were 954.38 in the placebo group (n=177) and 4,547.88 in the vaccine group (n=552). Thus, the cost per person was 5.39 in the placebo group and 8.24 in the vaccine group (difference 2.85).

The total costs estimated using the modelling approach were not reported.
Synthesis of costs and benefits
An incremental cost-effectiveness ratio was calculated to combine the costs and benefits of vaccination over placebo.

Based on the trial results, the incremental cost per GP consultation avoided was 174 (from the NHS perspective), while the incremental cost per self-reported ILI episode avoided was 0.99 (from the patient's perspective).

In the modelling approach, the incremental NHS cost per GP consultation avoided was approximately 2,000.

The incremental NHS cost per hospital admission avoided was approximately 61,000.

The incremental NHS cost per death avoided was approximately 1,900,000.

The incremental NHS cost per LYG was approximately 244,000.

The incremental NHS cost per QALY gained was approximately 304,000.

The sensitivity analysis showed that under the most optimistic scenario (target uptake rates could be achieved with no additional expenditure on promoting vaccination) NHS costs would be reduced by about 85%. Thus, the cost-effectiveness and cost-utility ratios were reduced by the same proportion. However, even in the best scenario, the cost per LYG was approximately 40,000 and the cost per QALY gained was approximately 50,000.

In all other scenarios, the cost per LYG or per QALY was higher than 60,000 and in many cases higher than 300,000.

Authors' conclusions
Compared with unvaccinated people, the absolute risk of a serious influenza-like illness (ILI) resulting in hospitalisation or premature death was minimal in the vaccinated population of individuals aged 65 to 74 years. Further, the vaccination campaign led to increased expense to the National Health Service (NHS). Thus, influenza vaccination for healthy individuals aged 65 to 74 years was not a cost-effective strategy.

CRD COMMENTARY - Selection of comparators
The selection of the comparator (no vaccination) was appropriate because, at the time the trial was started, this represented usual care for healthy individuals aged 65 to 74 years. However, as the authors pointed out, in the year 2000 influenza vaccination became available and was reimbursed by the NHS for all individuals aged 65 years and older. You should decide whether this is a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came from a well-conducted clinical trial, which was appropriate for the study question. The internal validity of the study was enhanced by several features. For example, stratified randomisation, justification of the sample size (power calculations were performed), single-blind, intention to treat analysis of the clinical results, and baseline comparability of the study groups. In addition, extensive details on the process of selecting the participants were provided. The authors made a series of assumptions to extrapolate the clinical results to a larger population of individuals. Uncertainty around some key assumptions was investigated in the sensitivity analysis. Broad inclusion criteria were used and the study sample could have been representative of the patient population. However, the authors noted that the study was initially planned to last two years, but was carried out for one year only because of a change in vaccination policy. Thus, the study might have been underpowered to detect statistically significant differences between the study groups.

Validity of estimate of measure of benefit
The summary benefit measures were appropriate to examine the impact of the vaccination on patients' health. Both disease-specific and more generalisable measures were used. For example, the use of QALYs permits comparisons with the benefits of other health care interventions. However, the estimation of utility values was based on authors' assumptions and no justification was given for the value used. Also, no sensitivity analysis was performed around this
parameter. The cost-utility results should therefore be viewed with caution.

**Validity of estimate of costs**

A societal perspective was adopted in the cost analysis, which was appropriate for the study question. However, indirect costs were not relevant, owing to the non-working age of most individuals considered in the analysis, and were not included. A detailed breakdown of the cost items was provided, and details of the unit costs and quantities of resources used were given. This enhances the possibility of replicating the analysis in other settings. The source of the data was reported for each item. No statistical analyses of the costs were carried out, but some key cost estimates were varied in the modelling approach. The price year was unclear, which makes reflation exercises difficult.

**Other issues**

The authors reported some results from published studies and stated that caution is required when extrapolating previous results to UK, owing to differences in patient populations and settings. The issue of the generalisability of the study results to other settings was not addressed, although some sensitivity analyses were carried out. These enhanced the external validity of the study. The analysis referred to healthy individuals aged 65 to 74 years and this was reflected in the authors’ conclusions. In general, the extrapolation of trial results to healthy individuals aged 65 to 74 for all England represented a weakness of the study because of the numerous assumptions made by the authors. In addition, as the authors underlined, it is difficult to generalise influenza results of one season to other years because of the differences in attack rates among influenza seasons. In particular, the attack rate in the year considered in this study was quite low. Thus, the results of the analysis might have underestimated the potential benefit (averted cases of ILI) of the vaccine. Finally, the cost-utility analysis was not accurately described, as mentioned earlier.

**Implications of the study**

The study results suggested that influenza vaccination for healthy individuals aged 65 to 74 years was not cost-effective. The authors stressed that NHS resources may be best actively targeted at monitoring and improving vaccine uptake in the highest risk groups.

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**Bibliographic details**

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**Other publications of related interest**


