Vaccination versus treatment of influenza in working adults: a cost-effectiveness analysis
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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
Four strategies for the management of influenza were compared:

- annual vaccination;
- empirical amantadine antiviral therapy for patients presenting with influenza-like symptoms;
- rapid testing for patients presenting with influenza-like symptoms, followed by oseltamivir antiviral therapy if the results are positive; and
- no intervention.

Type of intervention
Primary prevention and treatment.

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

Study population
The study population comprised a hypothetical cohort of healthy working adults aged younger than 50 years.

Setting
The setting was occupational health services and primary care. The economic evaluation was conducted in the USA.

Dates to which data relate
The effectiveness and resource use data were gathered from sources published between 1969 and 2002. The cost data were taken from published and electronic sources relating to 1999 to 2002, and were adjusted to 2001 prices.

Source of effectiveness data
The estimates for the final outcomes were derived from a synthesis of published studies and authors’ assumptions.

Modelling
A decision model was used to estimate the benefits and costs of the alternative patient management strategies for a time horizon of 1 year. A Markov process with a cycle length of 1 week was used, during which patients either remained in a healthy state or contracted an influenza-like illness (ILI) caused by influenza A, influenza B or other viruses. All patients were in the healthy state at the start of the influenza season. Patients with ILI who visited a doctor could be prescribed empirical therapy or undergo a rapid test for influenza, or not receive an intervention. Patients with influenza could develop complications that required antibiotics, emergency department visits or hospitalisation. At the end of the
season, all patients returned to the healthy state and the process was repeated for the next season.

The model made the following assumptions:

- the decision to vaccinate or use antiviral therapy was made at the start of the influenza season;
- vaccination was provided in a low-cost setting, such as an employee health service, and antiviral treatment was prescribed in a doctor's office;
- antiviral therapy was only initiated if the patient presented within 48 hours of symptom onset, and influenza infections in the previous week comprised at least 10% of ILI cases;
- the choice of antiviral medication was made when the patients presented to the doctor; and
- after recovering from influenza, patients were immune to that strain of the virus for the rest of the season.

Outcomes assessed in the review
The following parameters were used in the model and were expressed the probability of an event occurring, unless otherwise stated:

- the development of ILI;
- influenza, given ILI;
- influenza B, given influenza;
- complication of influenza requiring antibiotics;
- hospitalisation, given influenza;
- vaccination, efficacy against matched strain;
- vaccination, minor side effects;
- vaccination, Guillain-Barre syndrome side effects;
- the sensitivity and specificity of the influenza rapid test;
- reductions in illness duration with amantadine antiviral therapy and oseltamivir antiviral therapy;
- the efficacy of amantadine and of oseltamivir against complications requiring antibiotics; and
- the side effects of amantadine and oseltamivir.

Study designs and other criteria for inclusion in the review
The outcomes were derived from published clinical trials of influenza vaccine and antiviral drugs, incorporating 10 years of surveillance data from the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) reports of the week-by-week incidence of ILI; the authors confirmed influenza infections by type from 1993 through 2002. The efficacy and side effects of antiviral drugs were taken from randomised placebo-controlled trials of average-risk individuals with naturally occurring infection.

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
The review comprised 24 studies.

Methods of combining primary studies
The methods used to combine the data were not reported. For some parameters, only one source was cited. For each model parameter, a base-case value and a range for use in the sensitivity analysis were presented.

Investigation of differences between primary studies
Not reported.

Results of the review
The following values, expressed as probabilities unless otherwise stated, were used in the model:

- the development of ILI, 0.02 (range: 0.005 - 0.03);
- influenza, given ILI, varies by week and year (range: 0 - 0.31);
- influenza B, given influenza, varies by week and year (range: 0 - 1);
- complication of influenza requiring antibiotics, 0.10 (range: 0.05 - 0.17);
- hospitalisation, given influenza, 0.004 (range: 0.001 - 0.007);
- vaccination, efficacy against matched strain, 0.72 (range: 0.54 - 0.83);
- vaccination, minor side effects, 0.64 (range: 0.10 - 0.70);
- vaccination, Guillain-Barre syndrome side effects, 1 x10^-6 (range: 1 x10^-5 - 1 x10^-7);
- sensitivity of the influenza rapid test 0.65 (range: 0.50 - 0.78) and specificity 0.99 (range: 0.95 - 1.00);
- amantadine antiviral therapy shortens illness duration by 24 hours (range: 17.5 - 31.0);
- oseltamivir antiviral therapy shortens illness duration by 24 hours (range: 24 - 72);
- efficacy of amantadine against complications requiring antibiotics, 0;
- efficacy of oseltamivir against complications requiring antibiotics, 0.53 (range: 0.08 - 0.76);
- side effects of amantadine, 0.09 (range: 0 - 0.26); and
- side effects of oseltamivir, 0.10 (range: 0.075 - 0.11).

Methods used to derive estimates of effectiveness
Parameter values were also based on the authors’ estimates and assumptions.

**Estimates of effectiveness and key assumptions**
The authors assumed that no patients died of influenza.

As vaccine efficacy varies from year to year, depending on how well the vaccine matches the circulating strains, the authors calculated vaccine efficacy for each simulated year by multiplying 0.72 by the percentage of circulating viruses that matched the vaccine strain in that year.

**Measure of benefits used in the economic analysis**
The measures of benefit used were the number of days of illness avoided, and the numbers of quality-adjusted days and quality-adjusted life-years (QALYs) saved. The results from published studies that employed the Quality of Well-Being Index were used to value health-related quality of life. Some utility values were also derived from authors’ estimates.

**Direct costs**
Only the direct costs of medical care were included in the analysis. The unit costs included were for vaccination (including vaccine and administration costs), a course of amantadine, a course of oseltamivir, antibiotics for influenza complications, a rapid test for influenza, a doctor's visit of moderate complexity, an emergency department visit, hospitalisation for influenza, and Guillain-Barre syndrome. The quantities and the costs were not reported separately. The direct cost data were obtained from seven published and electronic sources relating to 1999 to 2002, except for the cost for the rapid test, which was obtained from an unreferenced "list price". The cost data were adjusted to a 2001 price year using the medical care component of the Consumer Price Index. Discounting was not applied, which was correct since the time horizon of the analysis was 1 year.

**Statistical analysis of costs**
No statistical analysis of the costs was reported.

**Indirect Costs**
Lost productivity due to illness was included in the analysis. Lost earnings for a day of work were reported. Weekend days did not contribute to indirect costs from work loss but were included as quality-adjusted days. Lost earnings per day were calculated from the average hourly cost of compensation for all civilian workers, obtained electronically from the US Bureau of Labor Statistics, and reported for the first quarter of 2001. Only productivity losses of patients, not their caregivers, were included. Discounting was not applied, which was correct since the time horizon was 1 year.

**Currency**
US dollars ($).

**Sensitivity analysis**
Sensitivity analyses were undertaken to investigate variability in the data. One-way and multi-way sensitivity analyses were conducted on all effectiveness variables and on the cost of vaccine, vaccine administration, rapid test for influenza, hospitalisation for influenza, and lost earnings for a days work. The ad hoc review provided the range over which the variables were tested. In addition, a Monte Carlo analysis of 1,000 repetitions was used to determine the probability that each intervention was reasonably cost-effective. Normal distributions were used for variables with values greater than 1, and logit distributions for values between 0 and 1.

**Estimated benefits used in the economic analysis**
The incremental number of illness days avoided by amantadine therapy compared with no intervention was 0.006.
The incremental number of illness days avoided by rapid test and oseltamivir compared with amantadine was 0.018.

The incremental number of illness days avoided by annual vaccination compared with amantadine was 0.124.

The incremental number of quality-adjusted days gained by amantadine therapy compared with no intervention was 0.0102.

The incremental number of quality-adjusted days gained by rapid test and oseltamivir compared with amantadine was 0.0002.

The incremental number of quality-adjusted days gained by annual vaccination compared with amantadine was 0.0409.

The duration of benefits was limited to 1 year. The side effects of vaccination and antiviral drugs were included in the analysis.

Cost results
The cost per person per year was $234 for amantadine therapy, $236 for no intervention, $237 for rapid test and oseltamivir, and $239 for annual vaccination.

The incremental cost of no intervention compared with amantadine therapy was $2.31.

The incremental cost of rapid test and oseltamivir compared with amantadine therapy was $2.51.

The incremental cost of annual vaccination compared with amantadine therapy was $4.64.

The duration of costs was limited to 1 year. Only the cost of treatment for the vaccination side effect of Guillain-Barre syndrome was included. All other adverse effects were assumed to be of minor cost and were not included in the analysis.

Synthesis of costs and benefits
The costs and benefits were combined by calculating the incremental cost-effectiveness ratio of each management strategy. This was expressed as the cost per day of illness avoided and the cost per quality-adjusted day gained.

The least expensive strategy varied from year to year, but over the 10-year period amantadine therapy was the overall least costly strategy. The no intervention strategy was dominated by amantadine therapy (i.e. it was more costly and less effective). Extended dominance of the rapid test and oseltamivir strategy was observed. Compared with amantadine therapy, the annual vaccination strategy cost $37 per day of illness avoided and $113 per quality-adjusted day gained ($41,000 per QALY saved).

The model was most sensitive to lower vaccination costs, higher annual probabilities of influenza and higher number of workdays lost. In these instances, vaccination was cost-saving in comparison with all other strategies.

The Monte Carlo simulation showed that annual vaccination was always the most effective strategy, as well as being the least expensive strategy 18% of the time. Amantadine therapy was the least expensive the rest of the time. Annual vaccination cost less than $100 per quality-adjusted day gained for 40% of the time, and less than $300 per quality-adjusted day gained for 77% of the time. Rapid testing followed by oseltamivir was more cost-effective than the other two strategies for less than 4% of the time.

Authors' conclusions
Vaccination for healthy working adults is reasonably economic and in some cases is cost-saving, but amantadine antiviral therapy is consistently cost-saving. Although influenza vaccination benefits healthy adults, the cost-effectiveness of vaccination depends on the interaction of worksite variables (e.g. vaccination cost and average number of sick days) and influenza season-specific determinants (e.g. incidence of influenza and vaccine efficacy in a given
CRD COMMENTARY - Selection of comparators
A justification was given for the comparators used. They represented current practice alternatives in the authors' setting. You should decide if these are representative of management strategies for influenza in your own setting.

Validity of estimate of measure of effectiveness
A systematic review of the literature was not undertaken. Although this is common practice with models, it does not always ensure that the best available data are used in the model. Data from the studies were used to define the baseline values and the range of values used in the sensitivity analysis. The authors discussed the impact of differences between the primary studies and the results that these studies reported. However, the authors did not describe whether they considered these differences when estimating the effectiveness. Vaccine efficacy for each simulated year was based on authors' estimates, and these were explored in the sensitivity analysis. Given the lack of detail provided on the methods used to derive the model inputs, it was difficult to comment on their quality.

Validity of estimate of measure of benefit
The measures of benefit used were the number of days of illness avoided and the number of quality-adjusted days and QALY saved. The results from published studies that employed the Quality of Well-Being Index were used to value health-related quality of life for people with influenza. Technically, this instrument does not produce utilities, although they have been reported as such. The authors acknowledged imprecision of this estimate of utility and tested the full range, from 0 to 1, in the sensitivity analysis. Utility values for side effects of antiviral drugs and vaccine (excluding Guillain-Barre Syndrome) were based on authors' estimates and were explored in the sensitivity analysis. The estimation of benefits was modelled. The instrument used to derive the measure of health benefit, a decision analysis model, was appropriate.

Validity of estimate of costs
The authors explicitly stated the perspective of the study. As such, it appears that all the relevant categories of costs have been included in this analysis. The costs were reported separately from other model parameters, and the source of the cost data was given for each item. An adjustment to a single price year was made. This enhances the reproducibility of the study results in other settings. The costs of side effects to vaccination (other than Guillain-Barre Syndrome) were omitted from the analysis, as the authors assumed they were minor. This could have resulted in an overestimation of the benefits of vaccination, as illustrated by the occurrence in 1976 of post vaccination rates of Guillain-Barre Syndrome which were 10 times higher than usual. Similarly, the costs of side effects to antiviral drug therapies were not included in the analysis and could have led to an underestimation of the benefits of vaccination. No statistical tests were conducted on the costs. The cost of the vaccine and its administration, the rapid test, hospitalisation for influenza and lost work days were varied in the sensitivity analysis. The effect of the cost of drugs, doctor and emergency department visits, and Guillain-Barre Syndrome were not explored. Discounting was not relevant since the costs were incurred during less than 2 years.

Other issues
The authors made appropriate comparisons of their findings with those from other studies, and discussed possible reasons for discordant results. They did not directly address the issue of the generalisability of the results to other settings. However, the extensive sensitivity analysis explored the effect of several factors, which increases the generalisability of the results. The authors do not appear to have reported their results selectively and their conclusions reflected the scope of the analysis. The authors reported three limitations of their study. First, by not including a pandemic year, the benefits of vaccination might have been underestimated. Second, in ignoring the effect of herd immunity the benefits might have been underestimated again. Finally, in assuming that vaccination side effects would be mild, the authors risked overestimating the benefits of vaccination.
Implications of the study
Influenza vaccination benefits healthy adults but is not always cost-effective. Consequently, individuals, health plans and employers must decide whether to vaccinate on the basis of their particular circumstances. As an alternative, amantadine antiviral therapy reduces both days of illness and costs in comparison with no intervention. The authors stated that the interaction of worksite-specific and influenza season-specific variables means that further randomised clinical trials cannot answer the question of whether it is cost-effective to vaccinate healthy working adults against influenza.

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