Economic evaluation of strategies for the control and management of influenza in Europe

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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
Six strategies for the control and management of influenza were examined. There were two vaccination strategies, two chemoprophylaxis strategies and two antiviral treatments:

- opportunistic vaccination (OppVacc) - vaccination was performed when a patient visited a general practitioner (GP) for another reason;
- comprehensive vaccination (CompVacc) - GPs have vaccination records and call and recall patients for vaccination;
- a 4-week (twice daily) chemoprophylaxis course (ChemoNI) using neuraminidase inhibitors (NIs) such as zanamivir or oseltamivir, which are active against both type A and type B influenza viruses;
- a 4-week (twice daily) chemoprophylaxis course (ChemoICI) using ion-channel inhibitors (ICIs) such as amantadine or rimantadine, which are active only against type A influenza viruses;
- early treatment (5 days, twice daily) with ICIs (TreatICI); and
- early treatment (5 days, twice daily) with NIs (TreatNI).

Type of intervention
Primary prevention and treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study referred to a hypothetical population of 10,000 elderly people aged 65 years and over in France and the UK, and aged 60 years and over in Germany.

Setting
The setting was primary care. The model parameters were derived using data from Germany, France, England, Wales and the USA.

Dates to which data relate
The effectiveness data were derived from studies published between 1994 and 2002. The dates relating to resource use were not reported. The price year was 2000.

Source of effectiveness data
The effectiveness evidence came from published studies, national unpublished studies and experts’ assumptions.
Modelling
A decision model was constructed, and reproduced graphically in the paper, to evaluate the cost-effectiveness of the six strategies for influenza in a typical influenza season in a population of 10,000 elderly.

Outcomes assessed in the review
Model parameters were derived from published studies. Those used as inputs to the model were duration of illness, current vaccination rate, excess GP consultation rate for ILI cases, antibiotic prescribing for ILI cases, current GP consultations within 2 days of symptoms, GP home visits, excess hospital admissions per 10,000 population (due to influenza and pneumonia, other respiratory illness, or congestive heart failure), average hospital length of stay, excess premature deaths per 10,000 elderly population, average age of ILI-related deaths, reductions in case rate, reductions in hospitalisation rate due to influenza and pneumonia, other respiratory illness, and congestive heart failure, reduction in mortality rate with vaccination, reduction in duration of illness, and reduction in antibiotic prescribing rate.

Study designs and other criteria for inclusion in the review
Not stated.

Sources searched to identify primary studies
Not stated.

Criteria used to ensure the validity of primary studies
Not stated.

Methods used to judge relevance and validity, and for extracting data
Not stated.

Number of primary studies included
The effectiveness evidence used in the model was derived from 19 primary studies.

Methods of combining primary studies
When an estimate was derived from more than one primary study or meta-analysis, it was not stated how the parameter estimates were derived.

Investigation of differences between primary studies
Not stated.

Results of the review
The current vaccination rate was 0.334 in England and Wales, 0.610 in France and 0.410 in Germany.

The excess GP consultation rate for ILI cases per 10,000 population was 53.7 in England and Wales, 307.9 in France and 115.5 in Germany.

Antibiotic prescribing for ILI cases was 57.4% in England and Wales, 59% in France and 36% in Germany.

Current GP consultations within 2 days of symptoms were 15.8% in England and Wales, 86% in France and 12.5% in Germany.
GP home visits were 38.6% in England and Wales, 50% in France, and 38.6% in Germany.

Excess hospital admissions for influenza and pneumonia, per 10,000 population, were 21.9% in England and Wales, 18.7% in France and 16.5% in Germany. The corresponding values for other respiratory illness were 83.4% (England and Wales), 71.3% (France) and 38.9% (Germany), and for congestive heart failure, 17.3% (England and Wales), 14.8% (France) and 9.4% (Germany).

The average length of hospital stay was 13.9 days in England and Wales, 8.8 days in France and 13.7 days in Germany.

Excess premature deaths per 10,000 elderly population were 15.6 in England and Wales, 16.3 in France and 10.3 in Germany.

The average age of ILI-related deaths was 80.9 years in England and Wales, 80.9 years in France and 83.5 years in Germany.

The duration of illness was 8.3 in all countries.

The reduction in the case rate was 0.53 with vaccination, 0.55 with NIs and 0.35 with ICIs.

The reduction in the hospitalisation rate with vaccination was 0.39 for influenza and pneumonia, 0.32 for other respiratory illness and 0.27 for congestive heart failure.

The reduction in the mortality rate with vaccination was 0.50.

With NIs and ICIs, the reduction in the duration of illness was 1.20 days (NI) and 1.0 days (ICI), while the reduction in antibiotic prescribing rate was 0.24 with both early treatments.

**Methods used to derive estimates of effectiveness**
The authors made a number of assumptions on the basis of experts’ opinions and data observed in the literature.

**Estimates of effectiveness and key assumptions**
The assumptions made in the analysis were as follows:

10% of the unprotected population should develop symptoms of ILI during a typical influenza season;

the rate of after-hours GP consultations was 1%;

the years of potential life lost were 3.5;

the weekly non-compliance rate with both chemoprophylaxis strategies was 0.05;

GP consultations within 2 days of symptoms were 50%;

patients taking chemoprophylaxis did so following the same distribution of an influenza season;

chemoprophylaxis coverage rates were the same as with OppVacc;

most individuals would obtain their prescriptions for chemoprophylaxis during GP consultations for other medical reasons, although few patients may consult GPs specifically for the purpose of obtaining their prescriptions;

non-compliant patients and those not prescribed chemoprophylaxis would develop ILI at the same rate as that which would occur in the absence of an influenza control strategy;

antiviral medications would be dispensed on an intention to treat basis;
GP consultation rates were 0.46 with vaccination, 0.48 with ChemoNI, and 0.30 with ChemoICI; and NIs (oseltamivir) and ICIs (rimantadine) caused no side effects.

Other assumptions in reductions in hospitalisation rates were also reported.

**Measure of benefits used in the economic analysis**
The benefit measure common to all six interventions was the number of morbidity days averted (MDA) per 10,000 population. The life-years gained (LYG) per 10,000 population were calculated for the vaccination and chemoprophylaxis strategies. Cases, deaths, and hospitalisations averted were also reported. The lifetime benefits were discounted at a rate of 5% in Germany and France, and at 1.5% in England and Wales.

**Direct costs**
Discounting was not relevant since the costs were incurred in one year. The unit costs were reported, but details on resource use were only given for some items. The health service costs included in the economic evaluation were for GP consultations, after-hours visits, home visits, antibiotic course, hospitalisation, vaccine, vaccine administration, comprehensive vaccine programme administration, NI and ICI chemoprophylaxis, and NI and ICI treatment. The cost/resource boundary adopted in the study was that of the health care financer in each country. The costs were estimated using actual data derived from national sources, where possible, such as diagnosis-related groups. Some conservative assumptions were made to estimate resource consumption. The price year was 2000.

**Statistical analysis of costs**
The costs were treated deterministically in the base-case.

**Indirect Costs**
The indirect costs were not included.

**Currency**
Euros.

**Sensitivity analysis**
One-way sensitivity analyses were conducted on the key parameters used in the decision model. These included prices of the interventions, discount rates, years of potential life lost, ILI attack rate, number of GP consultations, vaccine prices, efficacy of vaccination on those who do not seek medical advice for ILI, coverage rates for OppVacc and chemoprophylaxis strategies, probability of being prescribed early antiviral therapy, and so on. All the assumptions were investigated in the sensitivity analysis in order to estimate the robustness of the estimated cost-effectiveness ratios. For England and Wales, an alternative scenario was represented for a major epidemic season. This was based on the authors' assumptions and published data, with changes in the clinical ILI attack rate in an unvaccinated population, the excess GP consultation rate, the excess hospital admissions and the excess premature death. For all interventions, the prices were altered by 50%.

**Estimated benefits used in the economic analysis**
In comparison with no intervention, the total number of total MDA (and MDA excluding deaths) was:

- in England and Wales, 5,474 (1,677) with OppVacc, 10,654 (3,264) with CompVacc, 1,897 (591) with ChemoNI, 1,207 (376) with ChemoICI, 10 (10) with TreatNI, and 8 (8) with TreatICI;
- in France, 8,225 (2,871) with OppVacc, 10,113 (3,530) with CompVacc, 2,842 (1,001) with ChemoNI, 1,808 (637)
with ChemoICI, 187 (187) with TreatNI, and 156 (156) with TreatICI; and

in Germany, 4,795 (1,943) with OppVacc, 7,602 (3,080) with CompVacc, 1,658 (677) with ChemoNI, 1,055 (431) with ChemoICI, 27 (27) with TreatNI, and 23 (23) with TreatICI.

The LYG were:

in England and Wales, 10.4 with OppVacc, 20.2 with CompVacc, 3.6 with ChemoNI, and 2.3 with ChemoICI;

in France, 14.7 with OppVacc, 18 with CompVacc, 5.0 with ChemoNI, and 3.2 with ChemoICI; and

in Germany, 7.8 with OppVacc, 12.4 with CompVacc, 2.7 with ChemoNI, and 1.7 with ChemoICI.

Cost results
The total direct costs of the strategy and the medical care costs averted (in euros) per 10,000 population were:

in England and Wales, 38,984 and 52,745 with OppVacc, 96,550 and 102,647 with CompVacc, 729,299 and 21,656 with ChemoNI, 96,662 and 13,781 with ChemoICI, 5,306 and -190 with TreatNI, and 3,270 and -190 with TreatICI;

in France, 73,651 and 56,809 with OppVacc, 122,055 and 69,847 with CompVacc, 791,843 and 22,478 with ChemoNI, 146,837 and 14,304 with ChemoICI, 15,474 and 7,813 with TreatNI, and 10,843 and 3,362 with TreatICI;

in Germany, 52,407 and 29,334 with OppVacc, 116,319 and 46,506 with CompVacc, 704,763 and 11,541 with ChemoNI, 99,637 and 3,362 with ChemoICI, 13,512 and 3,362 with TreatNI, and 10,843 and 3,362 with TreatICI.

Thus, the benefit-to-cost ratio, defined as the ratio between the medical costs averted and the direct costs of the strategy, was:

in England and Wales, 1.35 with OppVacc, 1.06 with CompVacc, 0.03 with ChemoNI, 0.14 with ChemoICI, -0.04 with TreatNI, and -0.06 with TreatICI;

in France, 0.77 with OppVacc, 0.57 with CompVacc, 0.03 with ChemoNI, 0.50 with TreatNI, and 0.85 with TreatICI; and

in Germany, 0.56 with OppVacc, 0.40 with CompVacc, 0.07 with ChemoNI, 0.25 with TreatNI, and 0.31 with TreatICI.

Synthesis of costs and benefits
An incremental cost-effectiveness analysis was conducted to combine the costs and benefits of the strategies for influenza in comparison with no intervention.

The incremental cost (in euros) per MDA total (and MDA excluding deaths) was:

in England and Wales, -2.5 (-8.2) with OppVacc, -0.6 (-1.9) with CompVacc, 373.1 (1,197.7) with ChemoNI, 68.7 (220.4) with ChemoICI, 568.3 (568.3) with TreatNI, and 429.3 (429.3) with TreatICI;

in France, 2 (5.9) with OppVacc, 5.2 (14.8) with CompVacc, 270.7 (768.9) with ChemoNI, 73.3 (208.1) with ChemoICI, 41 (41) with TreatNI, and 8.8 (8.8) with TreatICI; and

in Germany, 4.8 (11.9) with OppVacc, 9.2 (22.7) with CompVacc, 418.2 (1,024.7) with ChemoNI, 87.5 (214.4) with ChemoICI, 371.1 (371.1) with TreatNI, and 328.3 (328.3) with TreatICI.

The incremental cost (in euros) per LYG was:

in England and Wales, -1,324 (dominant) with OppVacc, -301 (dominant) with CompVacc, 197,919 with ChemoNI.
and 36,427 with ChemoICI.

in France, 1,149 with OppVacc, 2,897 with CompVacc, 152,629 with ChemoNI, and 41,316 with ChemoICI; and
in Germany, 2,954 with OppVacc, 5,638 with CompVacc, 258,068 with ChemoNI, and 53,991 with ChemoICI.

The sensitivity analyses showed that the vaccination strategies were most sensitive to vaccine price and attack rate for
clinically symptomatic ILI;

chemoprophylaxis programmes were sensitive to the timing of the programme, price of antiviral, antiviral dose, and
years of potential life lost;

early treatment strategies were sensitive to GP consultation rates, and the percentage of those consultations occurring
within 2 days after developing clinical symptoms.

Country-specific results were reported. In the special scenario for England and Wales, both the opportunistic and
comprehensive vaccination strategies were cost-saving. The prophylaxis strategies were the most next cost-effective
strategies.

Authors’ conclusions
Both vaccination strategies were the most cost-effective in all three countries, while the chemoprophylaxis strategies
were the most expensive. The cost-effectiveness of antiviral treatments was close to that of vaccination only in France.

CRD COMMENTARY - Selection of comparators
The authors stated that, at the time of study, some of the strategies for influenza had yet to be approved for general use
in the three study countries. For example, no comprehensive vaccination was being implemented in any of the
countries.

Validity of estimate of measure of effectiveness
The analysis of effectiveness used data derived from published studies. Although a formal review of the literature was
not undertaken, the authors appear to have referred to studies considered as relevant in each country. A significant
exception noted by the authors was that estimates of vaccination effectiveness were derived from populations in the
USA. Study designs and details of the primary studies were not reported. All the effectiveness data were entered into
the decision model, but the authors did not state whether they took into account differences across the primary studies.
A number of assumptions were also used to construct the decision model and derive some outcome measures. Most of
the assumptions and some of the model inputs were investigated in the sensitivity analyses. The authors acknowledged
that some of their effectiveness estimates were derived from studies that analysed the US population.

Validity of estimate of measure of benefit
The main benefit measure used in the economic analysis was the number of MDA per 10,000 population, which was
selected because it was common to all six interventions. However, the LYG per 10,000 population with both
vaccination strategies and chemoprophylaxis strategies were used. The use of LYG permits the benefit of the study
strategies to be compared with the benefits of other interventions funded in the health care system. Appropriate
discounting was performed and country-specific discount rates were used.

Validity of estimate of costs
The perspective adopted in the study was explicitly reported, and it appears that all the relevant categories of costs have
been included in the economic analysis. The authors stated that the indirect costs were excluded from the analysis since
they were not relevant to the perspective adopted. The unit costs and sources of data were reported for each country.
The authors made some assumptions to estimate resource use. The price year was reported, thus facilitating reflation
exercises in other settings. The costs were treated deterministically in the base-case and estimations were specific to the
study settings, but several sensitivity analyses were conducted. The cost-effectiveness of the vaccination strategies was most sensitive to vaccination prices. The authors also noted that resource consumption might be subject to large variations across countries.

**Other issues**
The authors did not compare their findings with those from other studies. They also did not explicitly address the issue of the generalisability of the study results to other settings. However, extensive sensitivity analyses were conducted and the results were reported in detail. Thus, the reproducibility of the study results in other contexts appears to be high. The study referred to the general population of elderly patients and this was reflected in the conclusions of the analysis. The authors discussed some limitations of their analysis. These were mainly related to the use of data not strictly derived from the three countries examined in the study. The authors did not compare the incremental cost-effectiveness ratio of each strategy to the next most effective strategy after eliminating options that were dominated. This is necessary for proper economic comparisons between the strategies. The results were reported in full.

**Implications of the study**
The study suggests that both comprehensive and opportunistic vaccination strategies should be implemented for the management of influenza in the elderly in France, Germany, and England and Wales. The authors noted that vaccination may provide some protection against variant strains of the influenza virus the next year and may be administered over a period prior to the influenza season. Finally, antiviral treatments, although similarly expensive, did not reduce hospitalisations and deaths associated with influenza.

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