The cost-effectiveness of influenza vaccination for people aged 50 to 64 years: an international model

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
The study examined two alternative influenza vaccination policies for persons aged 50 to 64 years. The current strategy was coverage only for people at high risk of complications. The proposed strategy was coverage for all individuals in this age group.

Type of intervention
Primary prevention (vaccination).

Economic study type
Cost-utility analysis.

Study population
The study population depended on the vaccination strategy. High-risk individuals were those with chronic conditions associated with an increased risk of complication of influenza-like illness (ILI). These conditions included chronic respiratory disease, chronic heart disease (excluding uncomplicated controlled hypertension), chronic renal disease, diabetes, and immunosuppression due to treatment or disease. All other individuals aged 50 to 59 (Germany, Brazil) or 50 to 64 (Italy, France) were considered at low-risk for ILI.

Setting
The setting was primary care. The economic study was carried out in Brazil, France, Germany and Italy.

Dates to which data relate
The clinical and economic data were derived from sources published between 1980 and 2006. The price year was 2003.

Source of effectiveness data
The clinical and epidemiological data used in the decision model were:

- the incidence of ILI,
- the rates of ILI-related consultations and hospitalisations,
- the death rates,
- vaccine efficacy,
- life expectancy,
- the population size,
the vaccination coverage rates, and

the probability of seeking medical attention given ILI symptoms.

**Modelling**
A probabilistic analytic decision model was constructed. The structure of the decision tree was represented graphically. The model was conservatively based on ILI rather than confirmed influenza. Individuals could or could not be vaccinated and faced different probabilities of remaining healthy or contracting ILI in the winter influenza season. Influenza complications (requiring or not requiring hospitalisation) were then modelled in terms of increased costs and reduction in quality of life. The model was based on the annual risk of influenza and the associated costs, but the benefits were modelled over a lifetime time horizon. A detailed description of possible pathways and relative transitions was given.

**Sources searched to identify primary studies**
The clinical data came from several sources, including published studies, national databases, general statistics (e.g. Organisation for Economic Co-operation and Development, Eurostat) and epidemiological surveillance websites. The authors also made some assumptions. Both country-specific and non country-specific sources were used on the basis of type of clinical data required. For example, the reduction in the number of ILI cases because of vaccination (vaccine efficacy) was taken from a systematic Cochrane review involving 10 clinical trials. Antiviral efficacy was also taken from systematic reviews of clinical trials. Country-specific data were instead taken from large national databases or surveys. In particular, the underlying prevalence of influenza was obtained from the INSERM network in France, while data for the other three countries were adjusted by age and historical distributions.

**Methods used to judge relevance and validity, and for extracting data**
It was not stated whether a systematic review of the literature was undertaken to identify the primary sources. However, the authors provided a clear justification of the clinical sources chosen, usually characterised by high internal validity for non country-specific data (e.g. systematic reviews of clinical trials) or recent large surveys or databases for country-specific data (e.g. vaccination coverage or influenza prevalence). The use of the INSERM network for influenza prevalence provides conservative estimates compared with clinical trial data.

**Measure of benefits used in the economic analysis**
The model outputs were averted ILI cases, hospital admissions and death, life-years (LYs) and quality-adjusted life-years (QALYs). QALYs were used as the summary benefit measure that was combined with the costs. The utility weights used to adjust survival and to calculate the QALYs were derived from the Health Survey for England in 1996 and based on the EuroQol 5-D questionnaire. The LYs and QALYs were discounted at an annual rate of 3%.

**Direct costs**
The analysis of the direct costs was performed from the perspective of the third-party payer. It included the costs of vaccination (such as vaccine acquisition and administration), primary care for ILI patients (general practitioner visits, prescription drugs, diagnostic tests, and possible referrals to a specialist in case of complication), and hospitalisation because of pneumonia, other respiratory complications, or cardiovascular complications. Patient co-payments were not considered when the third-party payer perspective was used, but were included when a societal perspective was adopted. The unit costs and the quantities of resources used were presented separately for all items. Resource use and cost data were derived from national sources and country-specific tariffs. Fee schedules and hospital costs were used for all countries. For example, Brazilian costs came from Tabelas de Procedimentos dos Sistemas de Informacoes Ambulatorial e Hospitalar do Sistema Unico de Saude (SIA and SIH/SUS) in 2004 and from the 2002 National Household Survey. Detailed sources were reported for all items. Discounting was not relevant as the costs were incurred during 1 year. The price year was 2003.
Statistical analysis of costs
Probabilistic distributions were assigned to the costs and quantities in the sensitivity analysis.

Indirect Costs
When the analysis was carried out from a societal perspective, the costs of sick leave were added to the costs considered from the viewpoint of the third-party payer. Productivity losses were based on data derived from each country using official sources. As in the analysis of the direct costs, the price year was 2003 and no discounting was performed.

Currency
Euros (EUR) for France, Germany and Italy, and Brazil reais (BRL). The authors stated that the mean nominal exchange rate in 2003 was BRL 3.07 per US dollar and BRL 3.52 per euro.

Sensitivity analysis
A deterministic sensitivity analysis was carried out to assess the robustness of the cost-utility ratios to variations in key model inputs. Alternative utility weights were derived from the Canadian National Population Health Survey in 1996. Other alternative values were also derived from the literature. A Monte Carlo simulation was carried out in which all model inputs were assigned probabilistic distributions; these were reported clearly. The simulation generated 95% credible intervals (CIs).

Estimated benefits used in the economic analysis
Using the assumed rates of population coverage, the expected QALYs with the current and the proposed vaccination programmes respectively were:

41,006,895 and 41,009,449 (incremental mean QALYs 2,554; 95% CI: 593 to 6,011) in Brazil;

128,999,864 and 129,005,243 (incremental mean QALYs 5,379; 95% CI: 1,182 to 12,801) in France;

131,175,999 and 131,177,634 (incremental mean QALYs 1,636; 95% CI: 310 to 3,805) in Germany; and

131,333,729 and 131,336,541 (incremental mean QALYs 2,812; 95% CI: 598 to 6,691) in Italy.

The proposed policy would avert approximately 80,000 cases of ILI per year in Brazil, 116,000 cases in France, 54,000 cases in Germany and 96,000 in Italy. This would translate into approximately 210 (Brazil), 440 (France), 120 (Germany) and 230 (Italy) deaths avoided annually in these four countries, respectively.

Cost results
From the perspective of the third-party payer using the assumed rates of population coverage, the expected costs (in millions) with the current and the proposed vaccination programmes respectively were:

BRL 6.50 and BRL 16.91 (incremental mean cost BRL 10.41; 95% CI: 9.06 to 11.27) in Brazil;

EUR 90.61 and EUR 161.37 (incremental mean cost EUR 70.8; 95% CI: 44.86 to 92.21) in France;

EUR 79.20 and EUR 125.93 (incremental mean cost EUR 46.73; 95% CI: 37.20 to 55.35) in Germany; and

EUR 95.96 and EUR 139.98 (incremental mean cost EUR 44.02; 95% CI: 26.83 to 58.69) in Italy.

From a societal perspective, the expected costs (in millions) with the current and the proposed vaccination programmes respectively were:

BRL 56.38 and BRL 65.33 (incremental mean cost BRL 7.17; 95% CI: -8.23 to 21.71) in Brazil;
EUR 369.07 and EUR 412.04 (incremental mean cost EUR 22.31; 95% CI: -22.31 to 91.04) in France; EUR 389.18 and EUR 374.26 (incremental mean cost -14.93; 95% CI: -45.45 to 5.96) in Germany; and EUR 333.92 and EUR 332.13 (incremental mean cost -EUR 1.79; 95% CI: -37.36 to 25.10) in Italy.

Synthesis of costs and benefits
Incremental cost-utility ratios were calculated in order to combine the costs and QALYs of the alternative strategies.

From the perspective of the third-party payer, the incremental cost per QALY gained with the proposed vaccination strategy was BRL 4,075 in Brazil, EUR 13,156 in France, EUR 31,387 in Germany and EUR 15,652 in Italy.

When a societal perspective was adopted, the proposed vaccination policy was dominant (more effective and less expensive) than the current vaccination strategy in both Germany and Italy, while the incremental cost per QALY gained was BRL 2,805 in Brazil and EUR 7,989 in France.

The results of the analysis were mainly driven by the potential increase in vaccine uptake as a result of the proposed strategy. In particular, the greatest QALY gains are expected in France and Brazil where existing coverage levels are relatively low.

The deterministic sensitivity analysis showed that the results of the analysis were particularly sensitive to variations in attack rate, size of high-risk population, and death rates after consultation for ILI. For example, for all three European countries, the incremental cost per QALY gained fell below EUR 50,000 provided the attack rate exceeded 3%. The number of workdays lost to ILI had a moderate impact on the results when the societal perspective was adopted. Further, some variables had a country-specific influence. For example, in France, the vaccine administration setting was influential since the base-case assumption for the cost of vaccination reflected the current practice that physicians rather than nurses administer the vaccine. In Brazil, the cost of vaccine administration was substantially higher in the private sector, making the results sensitive to the setting.

Cost-effectiveness acceptability curves generated from the probabilistic sensitivity analysis suggested that, at a threshold of EUR 50,000 per QALY, the probabilities of the proposed policy being cost-effective would be 94% in France, 89% in Italy and 72% in Germany from the perspective of a third-party payer. The corresponding probabilities from the societal perspective would be 95% in France, 99% in Italy and 100% in Germany. In Brazil, when the threshold for a QALY was set at the level of the 2003 per capita gross domestic product (approximately EUR 2,500), the proposed policy would be cost-effective with a probability of 83% from the perspective of a third-party payer and 79% from a societal perspective.

Authors' conclusions
Extending routine influenza vaccination to people aged 50 years or older was very likely to be cost-effective in Brazil, France, Germany and Italy.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparators was clear in that the current policy was compared with the proposed vaccination strategy. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The clinical data came from published sources. No systematic search for data was reported. The parameters for the model were mainly derived using country-specific data. The sources of clinical evidence were reported for key items. No specific comment on the validity of these sources was made, but sources with high internal validity were used for general items such as vaccine efficacy or antiviral effectiveness while large databases or surveys were used for country-specific data. The authors performed an extensive sensitivity analysis on key clinical parameters.
Validity of estimate of measure of benefit
The use of QALYs as the summary benefit measure was appropriate as they capture the impact of the interventions on both quality of life and survival, which are two relevant dimensions of health. QALYs have the further advantage of being comparable with the benefits of other health care interventions. The sources and methods used to obtain the utility weights were provided. Other model outputs that might be of interest to health care professionals were also reported. Discounting was appropriately performed.

Validity of estimate of costs
The analysis of the costs was consistent with the two perspectives adopted in the analysis. It appears that all the relevant categories of costs have been included. The sources of the costs were reported for key economic items. A detailed breakdown of the cost items was given, and the resource quantities were presented separately from the unit costs. The costs were discounted at an annual rate of 3%, which would appear appropriate in this instance. The impact of variations in the discount rate was investigated. Probabilistic distributions were assigned to the costs and quantities, and cost estimates were varied in the deterministic sensitivity analysis. The reference year for the costs was reported, thus facilitating reflation exercises in other time periods.

Other issues
The authors did not make explicit comparisons of their findings with those from other studies, but stated that the current analysis confirmed the results of published economic evaluations that have established the cost-effectiveness of influenza vaccination. The issue of the generalisability of the study results to other settings was implicitly addressed in the sensitivity analysis, and the study was performed in four different countries with different disease incidence and uptake rates. The authors noted some limitations of their analysis, the most relevant being the lack of published data that were available in the form required for the decision model. However, the issue of uncertainty was extensively addressed in the sensitivity analysis. Another issue was the seasonal nature of influenza, which may limit the validity of the analysis for future patterns of disease.

Implications of the study
The study results support a policy of extending influenza vaccination to all individuals aged 50 to 64 years.

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Other publications of related interest
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Scuffham PA, West PA. Economic evaluation of strategies for the control and management of influenza in Europe.
Vaccine 2002;20:2562-78.


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