Cost-effectiveness of a vaccine to prevent herpes zoster and postherpetic neuralgia in older adults

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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
The authors studied a live attenuated varicella-zoster virus (VZV) vaccine to determine whether it would reduce the incidence and severity of herpes-zoster and its sequelae.

Type of intervention
Primary prevention.

Economic study type
Cost-utility analysis.

Study population
The target study population comprised older adults (aged 60 years or older) who were immunocompetent and had a history of VZV infection. The representative person started without herpes zoster but faced some risk of experiencing the virus.

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

Dates to which data relate
The effectiveness data related to studies published between 1965 and 2005. The resource and unit cost data were taken from published studies and national report sources published between 2000 and 2006. The price year was 2006.

Source of effectiveness data
The effectiveness data were derived from a review and synthesis of published studies, supplemented with some authors' and experts' opinion-based assumptions when required.

Modelling
The authors used a state transition Markov model to describe the health states that each individual would pass through. The model was created using Microsoft Office Excel 2003 and Microsoft Visual Basic 6.3 software. The aim of the model was to "compare the clinical and cost effects of VZV vaccination with those of no vaccination" in the target population. The health states explored were no herpes zoster, herpes zoster for 1 to 6 months, post-herpetic neuralgia (PHN) and no further sequelae.

Outcomes assessed in the review
The authors explored the following outcomes for input into their Markov model:
the incidence of herpes zoster per 1,000 person-years over 3 years, broken down by age group (60 to 64, 65 to 69, 70 to 74, 75 to 79, 80 to 84, 85 to 89, and 90+);

the burden-of-illness scores for cases of herpes zoster;

the probability of persistent PHN at 182 days after onset;

the duration of persistent PHN from the start of the episode;

the risk of zoster-related death per 10,000 persons (reported by age group); and

the probability of a vaccine injection site reaction.

**Study designs and other criteria for inclusion in the review**
The authors looked for studies of original data that provided descriptive statistics relevant to the following questions.

What is the duration of PHN?

What is the duration of vaccine efficacy?

What is the lost work productivity due to an episode of acute zoster?

The authors gave a complete report of their search, including the search terms used, and discussed the papers identified in an appendix to their paper.

**Sources searched to identify primary studies**
PubMed was searched for literature published in the English language between 1966 and March 2006.

**Criteria used to ensure the validity of primary studies**
The majority of the data for the study were taken from the Shingles Prevention Study, "one of the largest (40,000 subjects) randomised, controlled trials conducted in the past decade". The authors used supplementary data when this trial was unable to provide relevant data. For instance, since the follow-up in this study was limited to 3.1 years, other data sources were used to inform the assumption made about the duration of vaccine efficacy.

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

**Number of primary studies included**
Nine primary studies were included, although many more papers were reviewed for inclusion. For instance, 56 studies were found on the duration of PHN, 26 studies on the duration of vaccine efficacy, and 101 studies on lost work productivity.

**Methods of combining primary studies**
The authors used a single study to inform a single parameter estimate. They did not combine the primary estimates.

**Investigation of differences between primary studies**
The authors carried out an extensive investigation of differences between the studies and reported this in their appendix. Differences between the studies were used to inform ranges for the sensitivity analyses.
Results of the review
Point estimates and ranges for the incidence of herpes zoster per 1,000 person-years when vaccinated were reported in full for all age groups.

Point estimates and ranges for the incidences of herpes zoster per 1,000 person-years when not vaccinated were reported in full for all age groups.

The burden-of-illness scores for cases of herpes zoster were 147.1 (126.0 to 168.2) for vaccinated individuals and 177.7 (157.9 to 197.4) for non-vaccinated individuals.

The probability of persistent PHN at 182 days after onset was 2.9 (1.3 to 5.4) for vaccinated individuals and 5.1 (3.6 to 7.1) for non-vaccinated individuals.

The duration of persistent PHN from the start of the episode was 8 months (0 to 18) for vaccinated individuals and 8 months (0 to 18) for non-vaccinated individuals.

The risk of zoster-related death per 10,000 persons was:
- 0 (0 to 0) for age 60 to 64 years;
- 0.25 (0 to 0.5) for age 65 to 69 years;
- 0.75 (0.5 to 1.0) for age 70 to 74 years;
- 2.5 (0 to 4) for age 75 to 79 years;
- 9.5 (0 to 15) for age 80 to 84 years; and
- 28 (0 to 38) for ages 90+ years.

These risks were the same whether or not an individual was vaccinated.

The probability of a vaccine injection site reaction was 31.7% (28.3 to 32.6) for vaccinated individuals.

Methods used to derive estimates of effectiveness
The authors made some assumptions that were supported, where possible, by the best available evidence in terms of published literature and expert opinion.

Estimates of effectiveness and key assumptions
The duration of vaccine injection side reactions was assumed to be 2 days (0 to 5).

The duration of vaccine efficacy was assumed to be 30 years (3 to 30).

Measure of benefits used in the economic analysis
The summary measure of health benefit was the quality-adjusted life-years (QALYs). The utilities were taken from a published paper (Coplan et al. 2004, see 'Other Publications of Related Interest' below for bibliographic details) that referred to the Shingles Prevention Study. This source estimated utilities using the EuroQol visual analogue scale scores. The utility was 0.860 for no herpes zoster and 0.594 for patients with PHN. QALYs were estimated by multiplying the utilities by the mean discounted duration spent in each health state. The benefits were discounted at a rate of 3%.

Direct costs
The costs were estimated from a societal perspective over the lifetime of the patient and were taken from a number of
published sources. The analysis focused on physician visits, antivirals for the treatment of herpes zoster, and hospitalisation-related costs. Average wholesale prices and retail prices from online retailers were used to estimate the unit costs of antivirals. Reimbursement for hospitalisation was taken from the Medicare Provider Analysis and Review. The quantities were determined through the Markov model and the length of time spent in each health state. The cost of the vaccine was based on a published study and was varied to represent different possible prices. The costs were discounted at a rate of 3%. The price year was 2006. The unit costs were reported separately from the quantities.

**Statistical analysis of costs**
The costs were treated deterministically.

**Indirect Costs**
In accordance with the societal perspective, the authors measured indirect costs in relation to the effects on economic productivity. The costs of lost labour participation were informed by the US Department of Labour Bureau of Statistics. The estimate took the rate of labour participation from older persons into consideration.

**Currency**
US dollars ($).

**Sensitivity analysis**
Extensive one-way sensitivity analyses were carried out. The authors varied each input in the model using ranges informed by their review of the literature. A probabilistic sensitivity analysis was used to estimate the probability that the cost-effectiveness ratio was less than $50,000 and $100,000. This was achieved through assigning variables a distribution based on values in the literature and expert opinion.

**Estimated benefits used in the economic analysis**
At the base-case of 69 years of age, the number of QALYs was 9.9111 without the vaccine and 9.9095 with the vaccine (difference of 0.0016 or 0.6 days) over the lifetime of the patient.

**Cost results**
At the base-case of 69 years of age, the direct medical care costs of a zoster episode were $61 with the vaccine and $98 without the vaccine (difference -$37).

At the base-case of 69 years of age, the costs of lost work productivity were $29 with the vaccine and $49 without the vaccine (difference -$20).

Although the authors showed that about $1.3 billion might be saved at a vaccine cost of $50, through the reduction of herpes zoster cases, they found few circumstances in which widespread vaccination would lead to cost-savings.

**Synthesis of costs and benefits**
Vaccination was shown to be more cost-effective with a longer duration of efficacy. The cost-effectiveness ratio was shown to remain less than $100,000 per QALY gained for every scenario in which the vaccine cost was less than $100, regardless of the duration of efficacy.

**Authors’ conclusions**
Vaccination would reduce the mean incidence of acute zoster and postherpetic neuralgia (PHN) in a cohort of persons aged 60 years or older. "Vaccination would be more cost-effective if it were targeted to populations that are at higher risk for herpes zoster."
CRD COMMENTARY - Selection of comparators
The authors compared vaccination against herpes zoster with no vaccination. These comparators are exhaustive and would be applicable within any settings. However, settings may differ in the extent of vaccination coverage and readers should consider their own setting and the objectives of vaccination.

Validity of estimate of measure of effectiveness
The authors undertook a systematic review of the literature. They stated clearly the outcomes they sought, the sources searched, study designs and criteria informing the search, and the key search terms. The authors reviewed key papers identified in an appendix. The authors explicitly discussed the quality of their data, noting that they obtained much of their evidence from one of the largest randomised controlled trials in the past decade. A sensitivity analysis was used to explore the impact of differences between the primary studies.

Validity of estimate of measure of benefit
The authors used a published study to provide utilities. They combined these utilities with the duration of time spent in any given health state in the Markov model to define QALYs. This measure provides an estimate of benefit that is widely comparable with other health care technologies.

Validity of estimate of costs
The costs were estimated from a societal perspective. All the costs relevant to this perspective appear to have been included in the analysis. Notably, the authors accounted for the vaccination costs, the costs of an episode of herpes zoster, and the indirect costs to society from lost productivity. A sensitivity analysis was used to explore potential variation in the data and the required cost of a vaccine to ensure cost-effectiveness. The analysis was reported in great detail with the unit costs being reported separately. The reporting of the discount rate and price year provides transparency in the analysis.

Other issues
The authors were able to draw comparisons between their own work and that of other authors, noting in particular that their own estimates of cost-effectiveness were higher than some already published. The authors were able to approximate these different outcomes by altering their own quality of life inputs and by lowering the mean age of the individuals vaccinated. The issue of generalisability was not explicitly addressed, although it was improved greatly by the extensive sensitivity analyses and the use of randomised controlled trial with over 40,000 participants as the primary data source. The authors presented and discussed their results thoroughly. The probabilistic sensitivity analyses enable the reader to gain a thorough understanding of the influence of uncertainty and the key cost and effectiveness drivers. Several limitations were reported. These centred on limited evidence on utility, the uncertainty of the vaccination beyond 3 years, and the actual costs of a vaccination programme.

Implications of the study
The authors did not make any recommendations for policy or practice. They did, however, show how the study could shape future research agenda through further work on developing an epidemiological model, ascertaining the longer run effects of vaccination, and conducting larger quality of life studies.

Source of funding
None stated.

Bibliographic details
Other publications of related interest
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Indexing Status
Subject indexing assigned by NLM

MeSH
Age Factors; Aged; Aged, 80 and over; Computer Simulation; Cost of Illness; Cost-Benefit Analysis; Decision Theory; Female; Herpes Zoster /epidemiology /immunology /prevention & control; Herpesvirus 3, Human /immunology; Herpesvirus Vaccines /economics /therapeutic use; Humans; Immunocompetence; Incidence; Male; Markov Chains; Middle Aged; Neuralgia, Postherpetic /epidemiology /immunology /prevention & control; Quality-Adjusted Life Years; Sensitivity and Specificity

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