Varicella vaccination in Italy: an economic evaluation of different scenarios
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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 study examined three routine vaccination programmes against varicella (chickenpox) zoster virus (VZV).

Routine vaccination of toddlers (strategy B) was a mass vaccination programme for children aged 1 - 2 years old (i.e. 12 - 36 months).

Routine vaccination plus catch-up for 6-year old children (strategy B1) was a mass vaccination programme for children aged 1 - 2 years, with catch-up for 6-year-old children during the first 5 years of vaccine marketing.

Routine vaccination plus catch-up during the first year (strategy B2) was a mass vaccination programme for children aged 1 - 2 years, with catch-up for children aged 2 - 11 years for the first year of vaccine marketing.

All vaccination strategies were based on the Oka/Merk VZV live vaccine.

Type of intervention
Primary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of healthy children aged 1 - 2 years old.

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

Dates to which data relate
The effectiveness data were derived from studies published between 1994 and 2002. Most of the resource use data and costs were also obtained from studies published between 1994 and 2002. The price year was 2002.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of completed studies.

Modelling
An epidemiological dynamic model that had been developed for the USA was used to assess the impact of routine VZV vaccination in Italy. The model simulated the changes in the number and age distribution of chickenpox cases in a population as a result of vaccination. A population divided into 100 cohorts of identical size at birth was considered. A graphical representation of the model was presented in the paper. Individuals moved across health states according to
probabilities of transition that depended on time and age of individuals. Herd immunity was taken into account. Three vaccination results were considered:

- protection against the disease;
- impartial protection with a risk of developing an attenuated version of the disease called breakthrough chickenpox; and
- primary failure with an unchanged risk of contracting chickenpox.

The waning of immunity over time and boosting phenomena affecting individuals protected by the vaccine were also taken into account. However, the impact of VZV vaccination on herpes zoster (shingles) was not considered. The timeframe of the model was 50 years and the cycle length was 1 year. The three levels of vaccination coverage considered were a high-coverage scenario (vaccination in each generation with 90% of children having not contracted chickenpox at the age of vaccination), a medium-coverage scenario (70%), and a low-coverage scenario (45%).

Outcomes assessed in the review
The outcomes estimated from the literature were:

- patient demographics;
- the rate of varicella infection without vaccination according to age;
- the distribution of patient age at vaccination;
- the vaccine efficacy;
- the varicella hospitalisation and fatality rates according to age; and
- the medications, hospitalisations and deaths associated with breakthrough varicella.

Study designs and other criteria for inclusion in the review
It was unclear whether a systematic review of the literature was undertaken to identify the primary studies. The primary studies might have been identified selectively. Vaccine efficacy was taken from clinical trials on the Oka/Merk VZV vaccine. Age-specific chickenpox fatality rates came from a meta-analysis. Few other details of the study designs were given.

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
Twelve primary studies provided clinical data.

Methods of combining primary studies
The method used to combine the primary estimates was not stated. Each study appears to have been used as the source of a discrete series of clinical data.

Investigation of differences between primary studies
Not reported.

Results of the review
The annual birth cohort included 540,000 individuals.

The mortality rates were age-specific and were not reported.

The rates of varicella infection in the absence of vaccination varied according to patient age:
0.099 for age 0 - 4 years,
0.162 for age 5 - 9 years,
0.097 for age 10 - 14 years,
0.075 for age 15 - 24 years,
0.096 for age 25 - 44 years, and
0.064 for over 45 years.

In terms of chickenpox characteristics, the duration of the latent period was 14 days and the duration of the infectious period was 7 days. The mean duration of protection through maternal antibodies was 180 days.

The distribution of patient age at time of varicella vaccination was 80% for 12 - 24 months and 20% for 24 - 36 months.

With respect to vaccine efficacy:
the proportion of individuals for whom vaccination led to a seroconversion was 99%;
the proportion of individuals seroconverted and protected by vaccination was 97%;
the relative propensity of partly susceptible vaccinees to contract the virus was 73% (range: 50 - 73);
the relative infectiousness of vaccinees developing breakthrough chickenpox was 50% (range: 20 - 100);
the proportion of protected vaccinated persons immunised after re-exposure to the virus was 91% (range: 91 - 100); and
the rate at which protected vaccinees become partly susceptible to develop chickenpox was 3.1% (range: 2.1 - 5.0).

The chickenpox hospitalisation rates were 2.6% (range: 0 - 5.5) for age under 1 year, 0.3% (range: 0.2 - 0.3) for 1 - 17 years, and 1.5% (range: 1 - 1.8) for over 18 years.

The chickenpox fatality rates were:
4.8/100 000 (range: 1.5 - 8.2) for age under 1 year,
0.7/100,000 (range: 0.3 - 1.2) for 1 - 4 years,
0.8/100,000 (range: 0.4 - 1.3) for 5 - 9 years.
1.1/100,000 (range: 0.1 - 2.1) for 10 - 14 years,
5.5/100,000 (range: 1.0 - 10.0) for 15 - 19 years,
3.3/100,000 (range: 2.5 - 4.3) for 20 - 44 years,
11.8/100,000 (range: 6.8 - 18.0) for 45 - 64 years, and
78.6/100,000 (range: 57.2 - 99.8) for over 65 years.

The rate of medical consultations, prescribed and over-the-counter drugs, and additional examinations associated with breakthrough chickenpox was 100%.

The rate of hospitalisation associated with breakthrough chickenpox was 1% (range: 0 - 5).

The rate of death associated with breakthrough chickenpox was 1% (range: 0 - 1).

Measure of benefits used in the economic analysis

Four main model outputs were reported. Specifically, natural chickenpox cases, breakthrough chickenpox cases, hospitalisations and deaths. However, none of these was combined with the costs. In effect, a cost-consequences analysis appears to have been carried out.

Direct costs

The analysis of the direct costs was undertaken from the perspective of the health care system. It included the costs associated with varicella vaccination (vaccine, administration and the treatment of adverse events) and chickenpox treatment (medical consultations, pharmaceutical prescriptions, additional examinations, hospitalisations and over-the-counter drugs). The unit costs were not presented separately from the quantities of resources used for all items. Resource use was derived from published studies and experts' opinions, while the costs were mainly estimated from Italian sources. There was extensive information on the sources used to derive costs and the assumptions made to derive some resource use data. The price year was 2002. Discounting was relevant given the long timeframe of the analysis, and an annual discount rate of 3% was applied.

Statistical analysis of costs

The costs were treated deterministically.

Indirect Costs

The indirect costs (i.e. productivity losses due to chickenpox) were included, which was appropriate as a societal perspective was also adopted. The resource use data were derived from a study carried out in France, while the costs came from average, Italian annual employee wages. The unit costs were presented separately from the quantities of resources used. The price year was 2002. Discounting was relevant given the long timeframe of the analysis, and an annual discount rate of 3% was applied.

Currency

Euros (EUR). The costs were estimated in Italian liras and then converted into Euros.

Sensitivity analysis

Probabilistic sensitivity analyses were carried out to assess the impact of variations in model inputs on the total costs for all parameters except vaccine efficacy. Uniform distributions were used. Best- and worst-case scenarios were considered for different levels of vaccine efficacy.
Estimated benefits used in the economic analysis
Using a high coverage rate (90%) over a 50-year time frame, the number of natural chickenpox cases was:

537,097 with no vaccination,

96,611 with strategy B (82% reduction compared with no vaccination),

64,193 with strategy B1 (34% reduction compared with B), and

53,087 with strategy B2 (45% reduction compared with B).

The cases of breakthrough chickenpox were 0 with no vaccination, 43,429 with strategy B, 50,258 with strategy B1, and 52,520 with strategy B2.

The number of hospitalisations was:

3,112 with no vaccination,

998 with strategy B (68% reduction),

729 with strategy B1 (27% reduction compared with B), and

629 with strategy B2 (37% reduction compared with B).

The number of deaths was 10 with no vaccination, 4 with strategies B and B1, and 3 with strategy B2.

Using lower coverage rates (70% or 45%), the reduction of natural chickenpox cases ranged from 41 to 64% for strategy B compared with no vaccination, from 12 to 19% for strategy B1 compared with strategy B, and from 15 to 25% for strategy B2 compared with strategy B. The reduction in hospitalisations ranged from 25 to 45% for strategy B compared with no vaccination, from 9 to 15% for strategy B1 compared with strategy B, and from 15 to 21% for strategy B2 compared with strategy B. The reduction in deaths ranged from 18 to 34% for strategy B compared with no vaccination, from 5 to 7% for strategy B1 compared with strategy B, and from 9 to 10% for strategy B2 compared with strategy B.

Cost results
In the high-coverage scenario (90%), the total societal costs (in millions) were EUR 3,155 with no vaccination, EUR 1,896 with strategy B, EUR 1,681 with strategy B1, and EUR 1,613 with strategy B2.

The costs from the health care system perspective (in millions) were EUR 820 with no vaccination, EUR 724 with strategy B, EUR 733 with strategy B1, and EUR 747 with strategy B2.

With lower coverage rates (70% and 45%), the total societal costs (in millions) ranged from EUR 2,492 to EUR 2,869 with strategy B, from EUR 2,314 to EUR 2,750 with strategy B1, and from EUR 2,238 to EUR 2,649 with strategy B2.

The costs from the health care system perspective (in millions) ranged from EUR 755 to EUR 786 with strategy B, from EUR 758 to EUR 790 with strategy B1, and from EUR 769 to EUR 800 with B2.

Each vaccination strategy was always cheaper than the no vaccination strategy. Vaccination costs were more than offset by savings in chickenpox treatment costs alone. Cost offsets were higher for all vaccination strategies as the coverage rate increased.

Strategies B1 and B2 were less costly than strategy B from the societal perspective, but relatively more expensive from the third-party payer perspective.

Cost-savings associated with strategy B compared with no vaccination and for strategies B1 and B2 compared with strategy B held in the probabilistic sensitivity analysis. Less certain results were obtained when a health care system
perspective was adopted, although in general the conclusions of the economic model were robust. However, compared with strategy B, a higher level of uncertainty was associated with the results of the two catch-up strategies (B1 and B2).

**Synthesis of costs and benefits**
The costs and benefits were not synthesised as a cost-consequences analysis appears to have been carried out.

**Authors' conclusions**
A routine varicella zoster virus (VZV) vaccination programme for children in Italy may be cost-effective, having a positive impact on both chickenpox-related costs and morbidity. The analysis suggested that achieving a high coverage rate is a key determinant of the benefit gained from vaccination. Catch-up programmes provide additional benefits to routine vaccination and are cost-saving from a societal perspective. However, their balance of costs is close to zero from a health care system perspective.

**CRD COMMENTARY - Selection of comparators**
The rationale for the selection of the comparators was clear. The choice of no vaccination as the basic comparator was appropriate and different catch-up strategies were also considered. You should decide whether this is a valid comparator in your own setting.

**Validity of estimate of measure of effectiveness**
The effectiveness evidence was estimated from published studies. It was not stated whether a systematic review of the literature was undertaken to identify primary studies, which might have been included selectively. Vaccine efficacy was derived from clinical trials a fact that should ensure the internal validity of the results. The authors stated that a conservative approach was used in selecting the measure of efficacy, which was lower than that estimated on the basis of clinical experts. Also, herd immunity was assumed to be lower than that used in other published studies. There was limited information on the other studies used to estimate clinical inputs. Similarly, the methods used to extract and then combine the primary estimates were not described. The issue of uncertainty around the model parameters was addressed using a probabilistic sensitivity analysis.

**Validity of estimate of measure of benefit**
No summary benefit measure was used in the analysis because a cost-consequences analysis was conducted. Please refer to the comments in the 'Validity of estimate of measure of effectiveness' field (above).

**Validity of estimate of costs**
The perspectives adopted in the cost analysis were appropriate. All the relevant categories of costs appear to have been included in the study. The unit costs and the quantities of resources used were presented separately for only a few items. This may reduce the possibility of replicating the results of the analysis in other settings. However, several details on the methods used to calculate costs (sources and assumptions) were provided, which enhances the robustness of the economic analysis. The costs were treated deterministically in the base-case, but extensive probabilistic sensitivity analyses were carried out. In general, the costs were specific to the study setting since traditional Italian sources were used. The price year was reported, which will simplify reflation exercises in other settings.

**Other issues**
The authors stated that their findings were consistent with other studies carried out in both Italy and other European countries. The issue of the generalisability of the study results to other settings was not explicitly addressed, but a probabilistic sensitivity analysis was undertaken to evaluate the robustness of the model results. The authors noted that local costs and treatment patterns represent key factors for establishing the cost-effectiveness of vaccination strategies. It was also pointed out that the model did not consider the impact of VZV vaccination on herpes zoster, owing to the debatable relationship between herpes zoster and chickenpox incidence.
Implications of the study
The study results supported the implementation of a routine VZV vaccination programme for children in Italy. There are additional benefits associated with a massive catch-up programme targeting children aged 2 - 11 years during the first year of vaccine marketing.

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Other publications of related interest


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