Cost-effectiveness analysis of pneumococcal conjugate vaccination in England and Wales
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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
Universal infant vaccination with the seven-valent pneumococcal conjugate vaccine (PCV; three doses) was examined.

Type of intervention
Primary prevention.

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

Study population
The study population comprised a hypothetical cohort of healthy infants.

Setting
The setting was primary care. The economic study was carried out in England and Wales.

Dates to which data relate
The clinical data and some resource use data were derived from studies published between 1996 and 2002. Resource use data were also taken from a database covering April 1995 to March 1998. The price year was 2002.

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

Modelling
The authors stated that a model was constructed to estimate the costs and life expectancy of a cohort of vaccinated or unvaccinated individuals from birth to death. Other details of the model were not reported.

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

- the annual incidences of pneumococcal-related diseases, hospitalisations and general practitioner (GP) consultations;
- the case-fatality ratio and length of stay due to pneumococcal (Pnc) septicaemia, Pnc meningitis and pneumonia;
- the vaccine efficacy;

- the outcomes from a meningitis episode (proportions of children with severe bilateral hearing loss, other sensorineural hearing loss, conductive hearing loss, or seizures); and
the reductions in the quality of life due to bacteraemia, meningitis (bilateral hearing loss or other hearing loss), pneumonia, or otitis media (OM).

Study designs and other criteria for inclusion in the review
A systematic review of the literature was not undertaken to identify the primary studies. The efficacy of the vaccine was derived from a clinical trial and life expectancy came from life tables. Much of the other data came from epidemiological databases, such as the CDSC/RSIL for incidence rates, Hospital Episode Statistics for hospitalisation data, and the Royal College of General Practitioners for GP consultations. However, no information on the sources used to derive quality of life losses was provided.

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
Fourteen primary studies provided clinical data.

Methods of combining primary studies
Each study provided a series of estimates that were not directly combined with data derived from other studies.

Investigation of differences between primary studies
Not stated.

Results of the review
All data were age-specific and were reported for age classes of 5-year age bands, with the exception of data for those under 1 year of age, which were grouped in one age category.

For example, the incidence rate per 100,000 populations per year of Pnc bacteraemia was 27.3 for age <1 year, 10.6 for age 1-4, 1.9 for age 5-9, 0.7 for age 10-14, 1.2 for age 15-19, 1.8 for age 20-24, 3.1 for age 25-44, 6.5 for age 45-64, 18.7 for age 65-74, and 42.5 for age >75.

Overall, the annual incidence rate was 8.4 per 100,000 for Pnc bacteraemia and 0.6 per 100,000 for Pnc meningitis.

The annual hospitalisation rate per 100,000 was 102.7 for pneumonia with positive film and 30.5 for acute OM.

The annual GP consultation rate per 100,000 was 266 with pneumonia and 3,612 with acute OM.

The overall case-fatality ratio was 22% due to Pnc septicaemia, 12% due to Pnc meningitis, and 29% due to pneumonia (all increased with age).

The length of stay was 11.5 days due to Pnc septicaemia, 16.9 days due to Pnc meningitis, and 8.1 days due to pneumonia.
Vaccine efficacy was 63 - 87% against invasive pneumococcal disease in the first 5 years of life, 17.7% (95% confidence interval, CI: 4.8 - 28.9) against all-cause clinical pneumonia with a positive film, and 7% (95% CI: -5 - 17) against any confirmed OM.

The rate of severe bilateral hearing loss was 14%, the rate of other sensorineural hearing loss was 16%, the rate of conductive hearing loss was 19%, and the rate of seizures was 16%.

The reductions in quality of life were as follows:

- bacteraemia, 0.0079;
- meningitis, 0.0232;
- bilateral hearing loss in the first year, 0.460;
- bilateral hearing loss in subsequent years, 0.200;
- other hearing loss (all subsequent years, 0.100;
- outpatient pneumonia, 0.004;
- inpatient pneumonia, 0.006; and
- OM, 0.005.

**Measure of benefits used in the economic analysis**
The summary benefit measures were life-years in the cost-effectiveness analysis and quality-adjusted life-years (QALYs) in the cost-utility analysis. The benefits were discounted at an annual rate of 1.5%. Quality of life adjustments were derived from the literature. Other benefits measures were the total number of death for vaccinated and unvaccinated individuals, the burden of invasive pneumococcal disease, all-cause pneumonia and OM. These were also reported as model outputs.

**Direct costs**
The cost analysis was carried out from the perspective of the NHS. The health services included in the economic evaluation were the vaccine (dose and administration) and the treatment of Pnc diseases (including inpatient stay and diagnostic tests). A detailed breakdown of the cost items was provided, as well as information on the unit costs and quantities of resources used. Resource use was estimated from published sources. The price of the vaccine was derived from the British National Formulary, assuming a volume-based discount and making an additional allowance for the cost of a nurse consultation for administration of the schedule. Other costs came from standard NHS sources, such as PSSRU and reference prices from the Department of Health. Costs that were incurred after the first year were discounted at an annual rate of 3.5%. The price year was 2002.

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

**Indirect Costs**
The indirect costs were not included in the economic evaluation.

**Currency**
UK pounds sterling (£). The average exchange rate for 2001-2004 was 1 = 1.55 US dollars and 1 = 1.54 Euros.
Sensitivity analysis
A univariate sensitivity analysis was performed to examine the robustness of the cost-effectiveness and cost-utility ratios. Each clinical and economic parameter was varied within its given range.

Three alternative scenarios were also considered. In scenario 1, the incidence rates were inflated to take possible under ascertainment into account (high-incidence scenario). In scenario 2, the indirect effects on the reduction in Pnc disease were assumed (herd immunity effect scenario). Based on the literature it was assumed that the reduction in incidence of invasive pneumococcal disease was 32% in the age group 20-39 years, 8% in the age group 40-64, and 18% in individuals older than 65 years. In scenario 3, the potential effect of a complete substitution of vaccine types with non-vaccine ones on the cost-effectiveness of the programme was explored by reducing both the direct effect of the vaccine among vaccinated individuals and the indirect effect produced among unvaccinated individuals (serotype replacement scenario).

A multivariate sensitivity analysis was also performed using a Monte Carlo simulation (1,000 iterations).

In general, the ranges of values used were either set by the authors or derived from published studies.

Estimated benefits used in the economic analysis
The discounted (undiscounted) life-years gained (LYG) with vaccination were 629 (1,087).

The discounted (undiscounted) QALYs gained with vaccination were 1,188 (1,824).

The number of deaths was 19,346 in the unvaccinated cohort and 19,331 in the vaccinated cohort (difference 14).

Cost results
The vaccination programme had a net discounted cost to the health service of 71 million, i.e. the 75 million cost of vaccinating the cohort (56 for administration and 19 million for vaccine costs) was only partially offset by discounted medical care savings of 4m over their lifetime.

The number of hospitalisations was 77,492 in the unvaccinated cohort and 75,602 in the vaccinated cohort (difference 1,890).

The number of GP consultations was 1,952,942 in the unvaccinated cohort and 1,889,987 in the vaccinated cohort (difference 62,995).

Synthesis of costs and benefits
Incremental cost-effectiveness ratios and cost-utility ratios were calculated to combine the costs and benefits of vaccination over no vaccination.

The incremental cost per LYG was 113,231.

The incremental cost per QALY was 59,945.

The sensitivity analysis showed that the cost-effectiveness and cost-utility ratios were sensitive to variations in the incidence of invasive pneumococcal disease, the inclusion of herd immunity effects, and the cost of the vaccine. However, wide variations in the base-case parameters were required for vaccination to be cost-effective (at a cost per QALY threshold of 30,000).

Under the high-incidence scenario, the cost per LYG dropped to 48,257 and the cost per QALY gained to 23,800.

The cost per LYG and QALY gained decreased dramatically if indirect protection in older age groups from the introduction of infant vaccination were included (around 5,000 per QALY gained and per LYG). Also, the herd immunity with complete serotype replacement scenario was significantly more cost-effective than the base-case (around
25,000 per QALY gained or 30,000 per LYG). When different vaccine schedules were considered, the lowest cost per QALY gained was observed for a one-dose schedule at 1 year of age (31,021). The cost of the vaccine should be reduced to one third of the value of the base-case in order for it to be cost-effective given the threshold used.

The multivariate sensitivity analysis showed that, in the base-case, only 29% of the model simulations resulted in a cost per QALY gained of less than 30,000. When assuming a 5% reduction of Pnc disease incidence among unvaccinated individuals (herd immunity), 100% of the model simulations were below this level. Finally, when a less strong hypothesis was assumed for serotype replacement (i.e. the level of serotype replacement is uncertain and thus is assumed to vary between 0 and 1) and the level of herd immunity was fixed at 5%, then around 90% of the simulations were deemed to be cost-effective at an upper limit of 30,000 per LY/QALY gained.

Authors' conclusions
The universal vaccination of infants in England and Wales with pneumococcal conjugate vaccine (PCV) was not a cost-effective strategy. Ignoring potential herd-immunity effects, vaccination could only be cost-effective from the perspective of the National Health Service (NHS) with a substantial reduction in the cost of the vaccine. In scenarios where benefits from herd immunity were considered, vaccination approached cost-effectiveness.

CRD COMMENTARY - Selection of comparators
The selection of the comparator (no universal vaccination) was appropriate as it reflected the standard of care in the authors' context. You should decide whether this is a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came from published data. However, it was not stated whether a review of the literature had been undertaken to identify the primary studies. Much of the data came from UK statistics, while efficacy data were estimated from a clinical trial. No other details about the primary studies were given. The primary estimates were not combined since each study provided a series of values. All clinical parameters were extensively varied in the sensitivity analysis where alternative scenarios were considered.

Validity of estimate of measure of benefit
The use of life-years and QALYs as the summary benefit measures was appropriate as they reflected the impact of the interventions on both expected survival and quality of life. The utility weights came from the literature, but the source of such data was not clearly described. Discounting was applied as recommended in the UK. However, undiscounted results were also reported.

Validity of estimate of costs
The costs included were consistent with the perspective adopted in the study and the indirect costs were not included. Extensive information on the unit costs and quantities of resources used was provided, which enhances the possibility of replicating the results of the study in other settings. Typical NHS sources were used to assess the costs, while resource consumption reflected UK treatment patterns. The costs were treated deterministically in the base-case, but the cost estimates were varied in the sensitivity analysis. The price year was reported, which aids reflation exercises in other time periods.

Other issues
The authors did not make extensive comparisons of their findings with those from other studies, stating that their study was the first analysis to quantify the impact of indirect effects on the cost-effectiveness of pneumococcal conjugate vaccination. The issue of the external validity of the study results was implicitly addressed in the sensitivity analysis, where alternative scenarios for both costs and clinical parameters were considered. The results of the study were reported clearly. The authors stated that a modelling approach was used in the analysis, but no description of the model was provided.
Implications of the study
The study results did not support the implementation of a universal vaccination programme with PCV in infants in England and Wales.

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Other publications of related interest


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