Cost-effectiveness of conjugate meningococcal vaccination strategies in the United States

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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
Three vaccination strategies based on a quadrivalent meningococcal conjugate polysaccharide A/C/Y/W-135 vaccine (MCV-4) were examined. These were infant vaccination, toddler vaccination and adolescent vaccination. The infant strategy consisted of a 3-dose regimen given at 2, 4 and 6 months of age. The toddler strategy consisted of a single dose given at 1 year of age. The adolescent strategy consisted of a single dose given at 11 years of age.

Type of intervention
Primary prevention (vaccination).

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

Study population
The study population comprised three hypothetical cohorts of children and adolescents. The study population depended on each immunisation programme.

Setting
The setting was primary care and the community.

Dates to which data relate
The effectiveness data and some resource use data were derived from studies published between 1983 and 2004. The costs were estimated from published sources and then expressed in 2003 values.

Source of effectiveness data
The effectiveness evidence came from a synthesis of published studies and some opinions.

Modelling
A decision model was constructed to assess the costs and benefits of the three vaccination strategies, compared with no immunisation, in hypothetical cohorts of 1,000,000 children and adolescents. The time horizon of the model was 22 years. This was chosen to reflect the impact of vaccination through two phases of life during which rates of disease have historically peaked: early childhood and late adolescence/early adulthood. Children and adolescents in the no vaccination strategy (or those not vaccinated in the vaccination strategies) could develop meningococcal disease. The model allowed for three primary outcomes of meningococcal disease, specifically, survival without sequelae, survival with long-term sequelae, and death. Long-term sequelae were divided into five categories. The categories were skin scarring, single amputation, multiple amputations, hearing loss, and significant neurologic disability. Patients vaccinated could incur moderate or severe adverse events. The decision model was presented graphically.
Outcomes assessed in the review
The outcomes estimated from the literature were:
  
  the disease incidence rates,
  
  the all-cause mortality rates and expected survival, 
  
  the probabilities of sequelae, 
  
  the risk of adverse events with vaccination, 
  
  quality of life (estimated using health-utility indices, HUIs), and 
  
  vaccine efficacy and coverage.

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. These studies may therefore have been identified selectively. Some data came from the Active Bacterial Core Surveillance database, which aggregates a population ranging from 12 million in 1993 to 34 million in 2002. Mortality data and population size were estimated from census sources. Other data came from published studies, the details of which were not provided.

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
The clinical data used to populate the decision model were derived from 25 primary studies.

Methods of combining primary studies
A narrative approach appears to have been used to combine the primary estimates in the decision model.

Investigation of differences between primary studies
Not reported.

Results of the review
The disease incidence rates were represented graphically.

The mortality data were not reported.

The percentage of survivors with skin scarring was 7.6% (range: 0 to 19), single amputation 1.9% (range: 0.5 to 10), multiple amputations 1.2% (range: 0.02 to 6), hearing loss 6.4% (range: 2 to 20), and significant neurologic disability 2.1% (range: 0.02 to 11).
The HUIs 1.0 (range: 0.8 to 1.0) for skin scarring, 0.710 (range: 0.31 to 0.8) for single amputation, 0.613 (range: 0.31 to 0.71) for multiple amputations, 0.723 (range: 0.64 to 0.82) for hearing loss, and 0.060 (range: 0 to 0.39) for significant neurologic disability.

Vaccine efficacy was 91.5% (range: 65 to 98) for infant vaccination, 92% (range: 65 to 98) for toddler vaccination, and 93% (range: 78 to 98) for adolescent vaccination.

Vaccination coverage was 77% (range: 34 to 90) for infants aged 5 to 11 months, 93% (range: 81 to 96) for infants aged 1 year or older, 91% (range: 54 to 98) for toddlers, and 71% (range: 16 to 95) for adolescents.

The risks of moderate and severe adverse events with vaccination were 0.0003 and 0.000002, respectively.

Methods used to derive estimates of effectiveness
The authors made some assumptions that were used in the decision model.

Estimates of effectiveness and key assumptions
A constant annual incidence rate with no variation in serogroup distribution was assumed.

The meningococcal disease occurred only once.

Vaccine-induced protection was assumed for the timeframe of the analysis.

To account for the presumed waning of vaccine-induced immunity, the protective efficacy dropped by 25%, 10 years after vaccination, and then remained constant at this level for the remainder of the model time horizon.

Measure of benefits used in the economic analysis
Four summary benefit measures were used in the analysis. These were the cases prevented, deaths avoided, life-years saved and quality-adjusted life-years (QALYs). Life-years gained and QALYs were discounted at an annual rate of 3%. The utility weights were estimated using data derived from the literature.

Direct costs
The analysis of the costs was carried out from a societal perspective. It included the direct costs associated with disease, which comprised management of an acute event (medical resources and public health response to an isolated case of meningococcal disease), lifetime sequelae, vaccine acquisition and treatment of vaccine-associated adverse events, and vaccination campaign. A detailed breakdown of the cost items was not provided, and the unit costs were not presented separately for all items. Details of the cost calculations were reported in an appendix. Resource use was based on authors’ assumptions and some published data. The costs came from multiple sources, including published studies and the Centers for Disease Control and Prevention. Discounting was relevant as the costs were incurred over a long timeframe. The price year was 2003.

Statistical analysis of costs
Probabilistic distributions were assigned to the costs, but no statistical analyses were performed.

Indirect Costs
The indirect costs (i.e. productivity losses associated with meningococcal disease) were included in the analysis as a societal perspective was adopted. Productivity losses differed by meningococcal disease sequelae. For example, the cost of productivity losses was equated to the sum of lifetime labour market earnings and household production losses for death. For survivors with multiple amputations, losses were equated to the sum of 30% of lifetime labour market earnings. The costs were estimated using age- and gender-specific wages. As in the analysis of the direct costs, 2003 prices were used and an annual discount rate of 3% was applied.
Currency
US dollars ($).

Sensitivity analysis
Univariate sensitivity analyses were performed to assess the robustness of the estimated costs and benefits to variations in key inputs, such as disease incidence, mortality data, rates of long-term sequelae, utility values, vaccine efficacy, vaccination coverage, acute meningococcal disease costs, lifetime costs of meningococcal disease sequelae, and vaccination costs. The ranges of values used were derived from the literature. The sensitivity of some assumptions about the length of vaccine protection was also investigated. Best- and worst-case scenarios were also considered and threshold analyses were performed in these scenarios. A Monte Carlo simulation was performed in which several model inputs were assigned a probabilistic distribution and were varied simultaneously.

Estimated benefits used in the economic analysis
For the adolescent strategy compared with no vaccination, 270 cases were prevented, 36 deaths were avoided, 1,798 life-years were gained, and 1,805 QALYs were gained.

For the infant strategy compared with no vaccination, 385 cases were prevented, 33 deaths were avoided, 1,620 life-years were gained, and 3,429 QALYs were gained.

Cost results
In comparison with no vaccination, the adolescent vaccination would save $68 million in terms of societal disease costs ($18 million in terms of direct disease costs). Thus, societal costs would be reduced by 46%. Routine toddler vaccination would reduce societal costs by 35%, while infant vaccination would reduce costs by 40%.

The adolescent vaccination programme would cost an extra $227 million at a vaccine price of $82.50. Therefore, the net societal cost of the adolescent vaccination programme would be $159 million (or $210 millions when only the direct costs were included).

The net costs would be $239 million for the toddler programme and $854 million for the infant programme.

The benefit-to-cost ratio (BC) was also calculated. This was equal to the economic benefits of avoiding disease through vaccination divided by the vaccination-programme costs. The societal BC was 0.27 (only direct costs: 0.08) with adolescent vaccination, 0.22 (only direct costs: 0.07) with toddler vaccination, and 0.08 (only direct costs: 0.03) with infant vaccination.

Synthesis of costs and benefits
Incremental cost-effectiveness ratios (ICERs) were calculated to combine the costs and benefits of each vaccination programme with a strategy of no intervention. When QALYs were combined with the costs, to avoid double counting, only the direct costs were included in the numerator of the ICER.

The median ICER was:

$633,000 per case prevented, $4,957,000 per death averted, $121,000 per life-year saved, and $138,000 per QALY saved with adolescent vaccination;

$629,000 per case prevented, $7,324,000 per death averted, $166,000 per life-year saved, and $105,000 per QALY saved with toddler vaccination; and

$1,923,000 per case prevented, $23,957,000 per death averted, $482,000 per life-year saved, and $271,000 per QALY saved with infant vaccination.
The sensitivity analysis showed that higher incidence rates improved the cost-effectiveness of all vaccination strategies. Changes in utility values did not alter the conclusions of the analysis. The cost-utility ratios were particularly sensitive to the rates of long-term sequelae. Changes in the assumptions about waning vaccine-induced immunity had a greater effect on the cost-effectiveness of toddler and infant strategies than on the cost-effectiveness of the adolescent vaccination programme.

The threshold analysis showed that the vaccine price at which the vaccination would be cost-neutral to society (cost-savings equal to disease costs) was $23 for the adolescent strategy, $18 for the toddler strategy, and less than $10 for the infant strategy. The cost per life-year gained with adolescent vaccination was $29,000 in the best-case scenario and $494,000 in the worst-case scenario. The results of the Monte Carlo simulations were not explicitly reported, but 5th and 95th percentiles for each ICER were provided.

Authors’ conclusions
The quadrivalent meningococcal conjugate polysaccharide A/C/Y/W-135 vaccine (MCV-4) reduced the burden of disease in vaccinated cohorts, but at a relatively high net societal cost in comparison with other recommended preventive programmes. The cost-effectiveness of toddler vaccination was essentially similar to adolescent vaccination, while infant vaccination was much less cost-effective.

CRD COMMENTARY - Selection of comparators
The authors compared each vaccination programme with the strategy of no vaccination, which was appropriate as it represented the current standard of care in several settings. The three vaccination options were clearly described. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence was derived from published sources. However, it was not stated whether a systematic review of the literature was undertaken, and the primary studies appear to have been identified selectively. Since limited information on the primary studies was reported, it was difficult to assess the validity of the primary sources. Further, the issue of the homogeneity of primary studies was not addressed. Some assumptions were also made, which might have introduced further uncertainty into the model. However, extensive sensitivity analyses were performed.

Validity of estimate of measure of benefit
The authors used both disease-specific and more generalisable benefit measures, which were appropriate for the study question. The use of QALYs was helpful, as they capture the impact of the interventions on the most relevant dimensions of health (i.e. quality of life and survival). The authors noted the uncertainty around utility values, and this issue was explicitly addressed in the sensitivity analysis. Discounting of the expected survival was applied, as recommended by US guidelines.

Validity of estimate of costs
The choice of a societal perspective for the analysis was appropriate as all the costs were included in the analysis. The costs included were consistent with the perspective adopted in the study. A detailed breakdown of the cost items was not provided as the costs were derived from a published study and information on both unit costs and resource consumption was not provided. This limits the possibility of replicating the cost analysis in other settings. However, some details of the cost calculation were reported. The price year was reported, which will facilitate reflation exercises in other settings. No statistical analyses of the costs were performed, but sensitivity analyses were carried out on key estimates. The source of the data was reported for all costs, whereas information on resource use was mainly based on authors’ opinions.

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, the use of sensitivity analyses enhances the external validity of the study. The authors pointed out that most of their assumptions were based on the UK experience, thus epidemiology and available conjugate vaccine might differ in comparison with the USA. Further, the potential benefits of a reduction in the number of outbreaks of meningococcal disease were not considered.

**Implications of the study**
The study results do not support the implementation of adolescent, toddler, or infant vaccination against meningococcal disease. The authors stated that catch-up vaccination of older adolescents not previously vaccinated has the potential for generating herd immunity, thus this strategy should be further evaluated.

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