Reassessing the cost-effectiveness of meningococcal serogroup C conjugate (MCC) vaccines using a transmission dynamic model

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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
Alternative meningococcal serogroup C conjugate (MCC) vaccination strategies were evaluated. Six different "introductory" strategies that combined routine and catch-up vaccination at different ages, and three possible future strategies (given that vaccination is already implemented in England and Wales) were compared with no vaccination.

The introductory strategies were:
- routine vaccination at 2, 3 and 4 months and no group targeted for catch-up vaccination (strategy 1);
- routine vaccination at 12 months and no group targeted for catch-up vaccination (strategy 2);
- routine vaccination at 2, 3 and 4 months and under-18 year-olds targeted for catch-up vaccination (strategy 3);
- routine vaccination at 2, 3 and 4 months and under-25 year-olds targeted for catch-up vaccination (strategy 4);
- routine vaccination at 12 months and under-18 year-olds targeted for catch-up vaccination (strategy 5); and
- routine vaccination at 12 months and 12 years and no group targeted for catch-up vaccination (strategy 6).

The future strategies included:
- adding a booster dose at 12 years of age, 12 years after the start of the campaign (strategy 7);
- switching from the 2-, 3-, 4-month routine schedule to 1 dose at 12 months (strategy 8), or 5 (strategy 8a) or 10 (strategy 8b) years after the start of the campaign; and
- switching from the 2-, 3-, 4-month routine schedule to 1 dose at 12 months and 1 dose at 12 years (strategy 9), or 5 (strategy 9a) or 10 (strategy 9b) years after the start of the campaign.

The paper also had a strong methodological objective and compared two "modelling technologies": a static model accounting for direct effects of vaccination, and a dynamic model that also considered herd immunity or indirect effects.

Type of intervention
Primary prevention.

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

Study population
The target population comprised 75 cohorts of individuals aged from 0 to 74 years, which reflected the England and...
Wales age-structure.

**Setting**
The setting was the community and primary care. The economic study was carried out in London, UK.

**Dates to which data relate**
The effectiveness evidence came from economic evaluation studies from 2002 to 2005 which were the forerunners of this study. These included references with a detailed description of the model (Trotter et al. 2002 and 2005, see 'Other Publications of Related Interest' below for bibliographic details). The dates for resource use were explained in more detail in one of these papers (Trotter et al. 20020, and dates reported were from the year 2000. The price year was 2000.

**Source of effectiveness data**
The effectiveness data were derived from a review or synthesis of published studies.

**Modelling**
An age-structured transmission model was used. This was described in full elsewhere (Trotter et al. 2005). Briefly, vaccination confers not only direct protection against disease but also some protection against carriage acquisition and can, therefore, generate herd immunity. The probability of infection is modelled as a function of the number of MCC carriers in the population and the age-specific mixing patterns. It varies after the introduction of vaccination and depends on the ages and proportions of vaccinated individuals. For each simulation, the model was run for 100 years, and the costs and benefits of routine vaccination were considered for 75 birth cohorts. Though the follow-up for cohorts born after year 25 of the vaccination programme was incomplete, this had negligible effects on the estimated results. Nine mutually exclusive compartments were modelled for each age strata as a combination of being unvaccinated, being vaccinated routinely, or having received catch-up immunisation, and being susceptible, carriers of MCC or carriers of other meningococcal strains or Neisseria lactamica.

**Outcomes assessed in the review**
The parameters included in the model were:

- carriage and disease data;
- age-specific forces of infection (that in the case of MCC varies according to MCC carriers in the population and age-specific contact rates);
- recovery from carriage;
- vaccine coverage rates and variable effectiveness by age;
- vaccine protection against carriage;
- proportions of MCC survivors with sequelae and their quality of life reduction; and
- rates of adverse events following vaccination.

**Study designs and other criteria for inclusion in the review**
These data were not described in the present paper (see Trotter et al. 2005).

**Sources searched to identify primary studies**
Not stated (see Trotter et al. 2005).

**Criteria used to ensure the validity of primary studies**
Not stated (see Trotter et al. 2005).

**Methods used to judge relevance and validity, and for extracting data**
Not stated (see Trotter et al. 2005).

**Number of primary studies included**
The authors cited five primary references in addition to their earlier paper (Trotter et al. 2005) where the model was described in detail.

**Methods of combining primary studies**
A narrative method was used to combine the primary studies.

**Investigation of differences between primary studies**
Not reported.

**Results of the review**
Most of the parameters were not reported in detail, thus the reader is referred to Trotter et al. 2005 or other references from the study. The parameters reported were a 67% vaccine protection against carriage, a 7% proportion of survivors with sequelae which have a health-related quality of life reduction of 0.282, and a 34.5/100,000 rate of adverse events of vaccination.

**Methods used to derive estimates of effectiveness**
Some authors' assumptions were used. These were mostly based on published references.

**Estimates of effectiveness and key assumptions**
The authors assumed that vaccination conferred an average of 15 months' protection for children vaccinated in infancy and 10 years' protection for children vaccinated in the catch-up campaign. Protection obtained from routine vaccination at 12 months (rather than at 2, 3 or 4 months) was assumed to last 5 years. Individuals who responded were assumed to have complete protection against serogroup C disease and some degree of protection against the acquisition of serogroup C carriage. As several parameters were unknown, the authors limited their possible parameter set by comparing the cases predicted by the model with the observed cases of disease in the UK between 1998 to 1999 and 2003 to 2004. Hence, they assumed that the duration of serogroup C carriage was 3 months and that an assortative mixing pattern was most appropriate.

**Measure of benefits used in the economic analysis**
The main outcome measures were the life-years (LYs) and quality-adjusted life-years (QALYs). A reference was given when stating the QALY figures used, but no details of this study were reported (DeWals et al. 2002, see ‘Other Publications of Related Interest’ below for bibliographic details). Discounting was carried out at a rate of 3% for the base-case.

**Direct costs**
The perspective adopted was that of the UK National Health Service. The quantities and the costs were derived using...
modelling. The cost categories included covered hospitalisations, outpatient care and care of mild and severe sequelae as well as adverse events, outbreak control and vaccination (including wastage, cost per dose, delivery payments and advertising campaign). The sources of the data were well-referenced national institutions. The price year was 2000.

**Statistical analysis of costs**
The costs were treated deterministically and no statistical tests were carried out.

**Indirect Costs**
No indirect costs were included.

**Currency**
UK pounds sterling (£). The conversion rate to US dollars ($) was 1 = $1.70.

**Sensitivity analysis**
The results with and without herd immunity were compared. The discount rate was varied between 0 and 6% and the vaccine cost between 8 and 18 per dose, with base-case parameters assumed otherwise. As disease incidence and case-fatality ratios had been shown to have a significant impact in the static model (Trotter et al. 2002) and the general result was not expected to change with the dynamic model, this was not tested further. The method used to select the ranges was not reported. The models were tested to see how well they would fit the previous epidemiological situation.

**Estimated benefits used in the economic analysis**
The base-case dynamic model fitted real epidemiological data better than the direct effect model, as indirect protection plays a major role in reducing the number of cases of serogroup C disease for a considerable period of time.

The results for the MCC strategy adopted in England and Wales (routine infant immunisation at 2, 3 and 4 months with a catch-up campaign for those under 25; strategy 4) were compared with the two models. These showed that the indirect benefits were about three times as great as the direct benefits (76,238 versus 22,284 LYS, or 90,969 versus 27,136 QALYs). The indirect benefits from a routine-only programme (strategy 1) were substantial (roughly the same number of LYS and QALYs are prevented by herd immunity as by direct protection) but were proportionately less than the strategy with a campaign, which provides greater indirect protection than the routine programme.

The absolute discounted LYS were 52,057 for strategy 2, 97,554 for strategy 5, 21,105 for strategy 1, 97,432 for strategy 3, 98,522 for strategy 4 and 87,683 for strategy 6.

**Cost results**
The total costs (in ascending order) were:

- strategy 2, 230,135,394;
- strategy 5, 322,798,870;
- strategy 1, 805,463,666;
- strategy 3, 848,893,603;
- strategy 4, 882,207,631; and
- strategy 6, 954,376,670.

The discount rate used was 3%.
Synthesis of costs and benefits
The incremental cost per LY gained for non-dominated strategies was 4,421 for strategy 2, 2,037 for strategy 5 and 577,699 for strategy 4. The remaining strategies were dominated.

For strategies that included catch-up vaccination, the incremental cost per LY gained was 38,164 for strategy 1, 569 for strategy 3 and 30,573 for strategy 4.

The exclusion of indirect herd immunity effects had a large impact on the average cost-effectiveness ratios for all strategies. Only strategies 2 and 4 had a cost-effectiveness ratio of less than 30,000 per LY saved compared with the no vaccination scenario. In the incremental analysis, the additional cost per additional LY gained for the under 18 catch-up campaign (strategy 5 versus strategy 2) was much higher (9 times) than when herd immunity was included. Strategies 1, 3 and 4 were dominated.

With future implementation strategies, the incidence of serogroup C disease is predicted to fall to very low levels, which will not rise because of persistent herd immunity. Strategy 7, which adds an extra booster dose at 12 years of age, was found to be highly cost-ineffective (average of more than 1 million per LY saved). Strategies 8 and 9 both reduced the number of doses of vaccine given and improved the LY saved, thus dominating the current strategy. The incremental cost-effectiveness of strategy 9a compared with strategy 8a was more than 2 million per LY saved.

The analysis was sensitive to the discount rate (vaccination became less cost-effective as the discount rate increased) and to the cost of the vaccine (vaccination became more cost-effective as the price per vaccine dose fell). Nevertheless, the relative costs and benefits of the different strategies did not change.

Authors' conclusions
The inclusion of herd immunity improved the average cost-effectiveness ratio in all cases. In general, those strategies that offered 1 dose early in the second year of life dominated strategies that offered 3 doses in infancy. Catch-up vaccination up to the age of 18 years was also highly attractive as the prevalence of serogroup C carriage is highest in teenagers, and vaccinating this age group has the largest impact on transmission herd immunity.

CRD COMMENTARY - Selection of comparators
The authors explicitly justified their choice of the comparators. The authors included an extensive list of comparators, both for current possible immunisation strategies and for future policy-making in the UK compared with no vaccination.

Validity of estimate of measure of effectiveness
The key feature of the model was that it included vaccine direct protection against disease and some protection against carriage acquisition. The derivation of the effectiveness evidence was reported in another paper so it is not possible to comment on its validity here. The model was described in full elsewhere (Trotter et al. 2005).

Validity of estimate of measure of benefit
LYs gained and QALYs were reported to be the benefit measures. The comments in the 'Validity of estimate of measure of effectiveness' field also apply here.

Validity of estimate of costs
All relevant cost categories and items for the perspective adopted seem to have been considered. The unit costs and the quantities were reported separately. Resource use and costs came mainly from published sources (well-referenced national institutions), and the price year was stated. Further detail was presented by Trotter et al. (2005). A sensitivity analysis was conducted, mainly on vaccine dose costs.
Other issues
The authors made appropriate comparisons of their findings, mainly with the findings of the direct effect model. The generalisability of the study results was not directly explored. The authors reported some caveats of their study. First, the assumption of exponential decline of vaccination (which makes an appreciable fraction of children vaccinated at age 12 months still protected during teenage years). Second, they were ignorant of the actual distribution of waning protection. Third, there were uncertainties surrounding a number of other parameters (the use of historical rather than recent carriage data; the assumptions of age-specific mixing patterns). Finally, a simple (instead of a probabilistic) sensitivity analysis was performed. All of these might have influenced their findings.

Implications of the study
Models that do not include the indirect effects of vaccination will underestimate the impact of MCC vaccination, distort the relative cost-effectiveness of different components of the campaign (i.e. routine versus catch-up immunisation), and may lead to incorrect decision-making. Estimating the cost-effectiveness of vaccination programmes requires the use of an appropriate model, which will depend on the question being asked, the properties of the vaccine, and the current understanding of the epidemiology of the infection one is seeking to control.

Shifting the age at routine vaccination from 2, 3 and 4 months (3 doses) to 12 months (1 dose) resulted in a net gain in the total number of cases prevented with only a few extra cases occurring in children under 1 year of age. This programme dominated the current UK vaccination strategy and was the most cost-effective strategy. Further, if the UK were to switch its programme from 2, 3, 4 months to 12 months, then the model suggests that this should be done sooner rather than later. This may be considered by UK policy-makers in the future, especially if serogroup C disease incidence continues to decline as predicted and the immunisation schedule is revised to accommodate pneumococcal conjugate vaccination.

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Other publications of related interest
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