Evaluating rotavirus vaccination in England and Wales. Part II: The potential cost-effectiveness of vaccination

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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
Two rotavirus vaccines, RotaTeq and Rotarix, were examined in this study of infant vaccination. RotaTeq was administered at 2, 3 and 4 months of age, whereas Rotarix was administered at 2 and 4 months of age.

Type of intervention
Primary prevention.

Economic study type
Cost-utility analysis.

Study population
The modelled population comprised infants to whom a vaccine was administered at birth, according to manufacturers' recommendations and the childhood immunisation schedule in the UK. The birth cohort was the mid-year estimate for the 2003 England and Wales population under one year of age from the Office of National Statistics (ONS).

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

Dates to which data relate
The prevalence of rotavirus genotypes in the UK population was estimated from samples drawn from the period January to June 2006. Other effectiveness data used to populate the model came from studies and national sources published between 2001 and 2006. The price year was 2004.

Source of effectiveness data
Health care outcomes attributed to rotavirus that were considered in the model included the annual rates of the following:

- inpatient admissions;
- nosocomial infections;
- admissions to accident and emergency (A&E);
- general practitioner (GP) consultations; and
- calls to NHS Direct.

Mortality rates in the general population were used to calculate life expectancy, while the number of deaths attributable...
to rotavirus was independently estimated. Vaccine efficacy was incorporated in terms of impact on the outcomes for rotavirus (as listed above). For RotaTeq, the per-protocol reduction in all cases of gastroenteritis of any severity was reported, and this was used as the reduction in calls to NHS Direct and GP consultations due to rotavirus. The reduction in hospitalisations and emergency visits was taken as the clinical efficacy against episodes of rotavirus A&E consultations, hospitalisations, nosocomial infections and deaths. For Rotarix, the per-protocol clinical efficacy against cases of severe gastroenteritis was used. Vaccine efficacy was adjusted for the genotype distribution in the UK, resulting in a sample distribution for vaccine efficacy. Vaccine coverage rates were estimated for the infant cohort.

**Modelling**

A probabilistic cohort model was developed to evaluate the costs and outcomes associated with vaccination. The model followed children over the first 5 years of life and used data from various sources, including clinical trials of the new vaccines. Ages were stratified by 1-month age bands in the first year and by 1-year age bands thereafter. The size of the cohort was not reported.

**Sources searched to identify primary studies**

Data were drawn from published national data, such as the Hospital Episode Statistics and the ONS, as well as being obtained directly from a sample of London hospitals, from the Royal College of General Practitioners and from NHS Direct. The proportions of health care outcomes attributable to rotavirus in particular were mainly determined by seasonal trend data on gastrointestinal pathogens from the Health Protection Agency, presented in an accompanying publication (Harris et al. 2007, see ‘Other Publications of Related Interest’ below for bibliographic details). Vaccine efficacy data were estimated from one published Phase III trial per vaccine, although different case definitions were used in the two studies and so the efficacy data were not directly comparable. Genotype distribution was estimated from 315 samples from patients with rotavirus gastroenteritis obtained from surveillance centres around the UK (unpublished data). Vaccine coverage was estimated on the basis of coverage data for another mandatory infant vaccine.

**Methods used to judge relevance and validity, and for extracting data**

The authors did not discuss the methods used to obtain and select the data, although further information about the burden of rotavirus in the UK was presented in the accompanying publication (Harris et al. 2007). All model inputs and associated distributions were presented in the publication.

**Measure of benefits used in the economic analysis**

The summary measure of benefits was the number of quality-adjusted life-years (QALYs) saved in both patients and in two carers per patient as a result of the immunisation programme. The benefits were discounted at a rate of 3.5% a year for the first 30 years and 3.0% a year thereafter. Data were obtained from a Canadian study in which carers valued their children's daily QALY loss using the HUI-2 questionnaire and valued their own daily QALY loss using the EQ-5D questionnaire, over a period of 2 weeks. It was also stated that health-related quality of life scores were obtained from the UK general population, but this statement was not clarified. It does not appear that QALYs lost have been derived from the efficacy parameters in the model, as they were reported in the model inputs table as an independent variable per episode of rotavirus, with an associated distribution. Hospitalisations and episodes prevented, as well as deaths prevented, were also used in the economic analysis.

**Direct costs**

The authors measured health care provider costs, including rotavirus-related deaths, hospital inpatient admissions, nosocomial infections, A&E attendances, GP consultations and calls to NHS Direct. As with the benefits, the costs were discounted at a rate of 3.5% a year for the first 30 years and 3.0% a year thereafter. The cost to the NHS of administering either vaccine was unknown as they were not publicly available at the time of the study. The cost was therefore estimated from catalogue prices of the drugs and assumptions about nurse time and the administration schedule. Costs were drawn from published sources and the proportion attributed to rotavirus was estimated using data on non-specific gastrointestinal illnesses in children from the General Practice Research Database (GPRD). The costs were inflated to 2004 prices with a health index.
Statistical analysis of costs
The costs were treated deterministically in the base-case. Both the costs and quantities were assigned distributions, which were sampled in sensitivity analysis to produce confidence ellipses around the cost-effectiveness estimates (see next section).

Indirect Costs
The authors estimated economic costs by estimating the value of caregivers' work loss prevented by reducing the number of rotavirus episodes, although these were not included in the base-case. Children were assumed to suffer no productivity loss, not being employed. Data were drawn from a published study and inflated to 2004 levels with a general index.

Currency
UK sterling (€).

Sensitivity analysis
Point estimates of parameters were used in the base-case. Each parameter was independently varied over the 95% confidence interval of the range of values in its distribution (univariate analysis). Multivariate sensitivity analysis was performed using Monte Carlo sampling. A total of 100,000 sample points for parameter values were sampled over their joint distribution using the Latin hypercube method. In the base-case, it was assumed that the vaccine was fully effective from the first dose, and there was no decrease in protection over time. In the sensitivity analysis, figures for the decrease in RotaTeq vaccine efficacy between the first and second rotavirus season were used as the maximum possible annual decrease due to waning protection. The efficacy of partial doses was altered such that they were assumed to give no protection. The costs were varied within 20% of the base-case values in the sensitivity analysis. The ranges and distributions for all parameters were tabulated.

Estimated benefits used in the economic analysis
The total discounted QALYs lost were estimated to be 759 without vaccination (made up of 696 in nonfatal QALYs and 64 life-years lost from death), 240 with RotaTeq vaccination (made up of 231 in nonfatal QALYs and 9 life-years lost from death), and 166 with Rotarix vaccination (made up of 152 in nonfatal QALYs and 14 life-years lost from death).

Cost results
The total costs in the base-case (direct medical costs only) were estimated to be 12,217,619 without vaccination, 53,744,222 with RotaTeq vaccination, and 48,358,797 with Rotarix vaccination.

Synthesis of costs and benefits
Incremental cost-utility ratios were calculated. RotaTeq and Rotarix were associated with costs per QALY gained of 79,905 and 60,928, respectively.

The cost per hospitalisation prevented was 3,803 for RotaTeq and 3,647 for Rotarix.

The cost per episode prevented was 525 for RotaTeq and 391 for Rotarix.

The cost per life saved was 15,634,105 for RotaTeq and 14,992,022 for Rotarix.

When including the economic value of work lost by caregivers, the cost-utility ratios improved to 74,000 for RotaTeq and 54,500 for Rotarix.
Univariate and multivariate sensitivity analyses indicated that, at the prices in the study (RotaTeq cost 25 per dose and Rotarix cost 35 per dose), an immunisation programme was unlikely to be cost-effective for any realistic value of the key parameters. A price of 10 per dose for RotaTeq and 19 per dose for Rotarix would be required to bring the cost-utility ratio to 30,000 per QALY gained. The model was most sensitive to the QALYs lost by caregivers per episode, the cost of the vaccine and, for RotaTeq only, vaccine efficacy against non-hospitalised cases.

Authors' conclusions
Routine immunisation could reduce the short-term morbidity burden due to rotavirus, but was unlikely to be cost-effective unless vaccines were competitively priced.

CRD COMMENTARY - Selection of comparators
The comparator was no vaccination, which represented current practice in the UK at the time of publication. You should decide whether this represents current practice in your own setting.

Validity of estimate of measure of effectiveness
The parameters were derived from national statistics, published research, primary data supplied from clinical practice and Phase III randomised controlled trials. No details of the search methods or selection criteria were provided. The data sources were well described and, while data were combined without adjustment in the model, it would appear that no synthesis was employed. The quality of the data sources appears to have been high.

Validity of estimate of measure of benefit
It became apparent that the costs and QALYs were modelled independently, with no relationship between the variables or the data sources used. Other measures of benefit (hospitalisations, number of episodes and deaths) did appear to form part of the cost base. The primary benefit measure, QALYs lost, appears to have been estimated by summing losses for patients and two carers per episode. The estimates were taken from a Canadian study. The authors did not discuss why this study was considered an appropriate proxy for a UK population, or why two different questionnaires were used to value the patients' and carers' health-related quality of life in the study. In light of these issues, the appropriateness of this method in terms of deriving an accurate measure of health benefit is doubtful and should have been clearly disclosed and justified by the authors. As shown in the sensitivity analysis, the model is sensitive to this input and so careful interpretation of the base-case results is required. There is insufficient evidence that the base-case QALYs lost are accurate representations of reality in the UK, thus the base-case results cannot be relied upon for decision-making.

Validity of estimate of costs
The analysis of the costs was performed from the perspective of the NHS. It appears to have included all the relevant categories of cost. A top-down approach was used to estimate resource use and to value costs, and incidence (quantities) and costs were reported separately, with adequate reporting of sources. The costs (and benefits) were appropriately discounted. The authors evaluated uncertainty appropriately by sampling from parameter distributions jointly to produce confidence ellipses around the point estimates of cost-effectiveness. The price year was reported (2004).

Other issues
The authors made relevant comparisons of their findings with those from other studies. The study was designed for the UK NHS, which is also the perspective of NHS EED. The results were not presented selectively, although it was stated that assumptions were chosen to be favourable to the vaccines. The authors noted that vaccine efficacy should not be compared for the two interventions because case definitions used in the efficacy trials for each vaccine were different. This is not entirely consistent with the authors' approach of using a common model for both vaccines and applying these "different" efficacy values to the same model parameters. No comparison should be drawn between the two vaccines on the basis of this study.

The authors noted, as a limitation of their study, the fact that clinical trials of the vaccines were mainly conducted in the USA and in developing countries; the authors adjusted for genotype distribution of rotavirus in the UK, but other confounding factors cannot be ruled out. They also noted that the number of deaths due to rotavirus is important in the model, but reliable data were not available; they stated that their estimate was the best available (the reader is referred
Implications of the study
The authors suggested that episodes of rotavirus have little impact on the quality of life of patients and caregivers due to the shortness of the episodes and the fact that few deaths are attributable to rotavirus. The study implied that the price negotiated by the NHS for new vaccines should be one half or less of the expected launch prices if these products are to achieve cost-effectiveness in evaluation by the National Institute for Health and Clinical Excellence.

Source of funding
Funded by the Research and Development Directorate of the UK Department of Health.

Bibliographic details

PubMedID
17400341

DOI
10.1016/j.vaccine.2007.02.070

Other publications of related interest
Because readers are likely to encounter and assess individual publications, NHS EED abstracts reflect the original publication as it is written, as a stand-alone paper. Where NHS EED abstractors are able to identify positively that a publication is significantly linked to or informed by other publications, these will be referenced in the text of the abstract and their bibliographic details recorded here for information.


Indexing Status
Subject indexing assigned by NLM

MeSH
Cost-Benefit Analysis; Drug Costs; England /epidemiology; Humans; Infant; Models, Economic; Quality of Life; Rotavirus; Rotavirus Infections /economics /epidemiology /prevention & control; Rotavirus Vaccines /administration & dosage /economics; Sensitivity and Specificity; Vaccination /economics /methods; Vaccines, Attenuated /administration & dosage /economics; Wales /epidemiology

AccessionNumber
22007001118

Date bibliographic record published
31/12/2007

Date abstract record published
31/12/2007