Projected cost-effectiveness of rotavirus vaccination for children in Asia

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 rotavirus vaccination for children aged less than 5 years. The vaccination programme was based on two candidate rotavirus vaccines that might soon be licensed and available. Two doses of the vaccine were given at the age of 2 and 4 months.

Type of intervention
Primary prevention.

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

Study population
The study population comprised a hypothetical cohort of children.

Setting
The setting was primary care. The economic study was carried out in all countries in the Southeast Asian and Western Pacific regions of the World Health Organization (WHO), excluding Australia and New Zealand.

Dates to which data relate
The effectiveness data were derived from studies published from 1996 to 2005. The costs and resource use data came from studies published between 1998 and 2005. The price year was 2002.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of completed studies and authors' opinions.

Modelling
A decision model was constructed to assess the health care cost and disease burden associated with rotavirus diarrhoea, and the cost-effectiveness of vaccination in an annual birth cohort of children. The model projected the total health care costs associated with rotavirus disease-associated events in the Asian region. The estimated number of events and their associated costs provided a baseline estimate of the rotavirus disease burden in the absence of vaccination. Thus, the model estimated the number of rotavirus disease-associated events and costs that would occur in association with the introduction of a rotavirus vaccine. The children were followed until they were 5 years of age. The model was not presented graphically and few details of its structure were given. Asian countries were classified into three income groups according to 2004 World Bank criteria. Low-income counties were defined as having a 2003 per capita gross national income (GNI) of $765 or less, middle-income countries as having a 2003 GNI of $766 - $9,385, and high-income countries as having a GNI of $9,386 or more.
Outcomes assessed in the review
The outcomes estimated from the literature were:

the rates of death, hospitalisations, and outpatient visits associated with rotavirus disease;
vaccine efficacy;
rates of diphtheria-tetanus toxoids-pertussis vaccine (DPT) coverage;
the size of the annual birth cohort; and
disability weights.

Study designs and other criteria for inclusion in the review
It appears that the primary studies have been identified selectively rather than by a systematic review of the literature. Most of the clinical data came from Asian studies or publications by the United Nations Children's Fund (UNICEF). Information on the design and other characteristics of the primary studies was not 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 reported.

Number of primary studies included
Nineteen primary studies provided clinical data.

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

Investigation of differences between primary studies
Not stated.

Results of the review
The total birth cohort included 34,406,000 children in low-income countries, 27,393,000 in middle-income countries and 1,797,000 in high-income countries.

The cumulative rate of rotavirus disease-associated deaths per 1,000 live births was 3.7 in low-income countries, 1.7 in middle-income countries and 0.1 in high-income countries.

The cumulative rate of rotavirus disease-associated hospitalisations per 1,000 live births was 16.9 in low-income countries, 45.9 in middle-income countries and 41.5 in high-income countries.

The cumulative rate of rotavirus disease-associated outpatient visits per 1,000 live births was 202 in low-income countries, 218 in middle-income countries and 332 in high-income countries.
Vaccine efficacy against hospitalisations in the first year of life was 93%. Vaccine efficacy against outpatient visits was 78% in the first year of life and 75% after the first year of age.

The percentage of DPT coverage at 2 months of age (DPT-1) was 76% in low-income countries, 89% in middle-income countries and 96% in high-income countries.

The percentage of DPT coverage at 4 months of age (DPT-2) was 71% in low-income countries, 85% in middle-income countries and 96% in high-income countries.

Disability weights were not reported.

**Methods used to derive estimates of effectiveness**
The authors made some assumptions to derive clinical estimates that were not available from the literature.

**Estimates of effectiveness and key assumptions**
Vaccine efficacy against deaths and hospitalisations in the first year of life, as well as in subsequent years, was 93%. Rotavirus vaccine coverage at 2 and 4 months was the same as coverage for DPT-1 and DPT-2.

**Measure of benefits used in the economic analysis**
The summary benefit measures used were deaths and disability-adjusted life-years (DALYs) averted. DALYs were estimated by combining life expectancy and disability weights obtained from the literature. However, no information on the disability weights was provided. An annual discount rate of 3% was applied. The number of hospitalisations and outpatient visits was also reported.

**Direct costs**
The analysis of the costs was performed from the perspective of the health care system. Only the direct costs of inpatient and outpatient hospital costs associated with disease and vaccine costs were included. The hospital costs included length of stay, diagnostic tests, medications and special services. The vaccine costs included the costs of administration and expected losses from waste. The administration costs included the costs of health care personnel, training, the cold chain, storage space and educating the public. The costs associated with adverse events were not considered because vaccine trials had shown that the vaccine was safe and adverse events, if any, would have been negligible. The unit costs were not presented separately from the quantities of resources used. The resource use data were derived from published studies, while the costs came mainly from population-based weighted average of the country-specific cost estimates. Since the price of the vaccine had not been established, it was set by the authors. Discounting was not relevant as the costs were incurred during short timeframe. The price year was 2002, and all costs were inflated to 2002 values using the purchasing power parity conversion factors and official exchange rates.

**Statistical analysis of costs**
The costs were treated deterministically in the base-case.

**Indirect Costs**
The indirect costs were not considered.

**Currency**
US dollars ($).

**Sensitivity analysis**
The cost-effectiveness analysis was carried out for several vaccine prices. A threshold analysis was performed to estimate vaccine prices that made the vaccination programme cost-neutral. In addition, one-way sensitivity analyses were carried out to assess the robustness of the model results to variations in several inputs. In particular, the incidence of rotavirus disease-associated death, hospitalisation, outpatient visits, vaccine efficacy, vaccine administration cost and hospitalisation cost. The authors mainly set the ranges of values used.

**Estimated benefits used in the economic analysis**

The estimated DALYs without and with vaccination were, respectively, 4,282,751 and 1,686,962 (difference 2,595,790) in low-income countries, 1,545,417 and 417,630 (difference 1,127,787) in middle-income countries, and 6,594 and 1,107 (difference 5,487) in high-income countries.

The estimated deaths without and with vaccination were, respectively, 125,582 and 49,431 (difference 76,151) in low-income countries, 45,198 and 12,181 (difference 33,017) in middle-income countries and 180 and 28 (difference 152) in high-income countries.

**Cost results**

The estimated medical costs (excluding vaccine costs) without and with vaccination were, respectively, $29,900,179 and $12,443,207 (difference $17,456,972) in low-income countries, $114,298,215 and $31,481,684 (difference $82,816,530) in middle-income countries, and $46,885,162 and $7,854,114 (difference $39,031,048) in high-income countries. Thus, the vaccination programme avoided hospitalisation and outpatient visit costs.

However, with the inclusion of vaccine costs, the vaccination strategy was generally more expensive than the no vaccination option for all countries. The exception was for high-income countries at vaccine prices of $10 or less per course.

**Synthesis of costs and benefits**

Incremental cost-utility and cost-effectiveness ratios were calculated to combine the costs and benefits of the alternative screening strategies.

At vaccine prices of between $2 and $60 per course, the incremental cost per DALY averted ranged from $19 to $638 in low-income countries, from $15 to $1,364 in middle-income countries, and from cost-saving to $15,428 in high-income countries. The incremental cost per death averted ranged from $664 to $21,764 in low-income countries, from $523 to $46,575 in middle-income countries, and from cost-saving to $557,498 in high-income countries.

The "medical break-even price", namely the vaccine price at which the cost of vaccination would be exactly offset by the medical cost-savings from prevented hospitalisations and outpatient visits, was also calculated. It $0.18 per course in low-income countries, 1.46 per course in middle-income countries and $15.20 per course in high-income countries.

To meet the suggested standard of cost per DALY less than the per capita GNI, the maximum vaccine price for the 2-dose vaccine would be $43.18 per course for low-income countries, $100.50 per course for middle-income countries and $77.98 per course for high-income countries in Asia.

The sensitivity analysis showed that the variables that affected the medical cost per child were the rate of rotavirus disease-associated hospitalisations and the cost of hospitalisation more than the rate of outpatient visits. For example, a 25% change in the hospitalisation rate or the hospitalisation cost estimate led to a 15 to 21% change in the average medical cost per child. A 25% change in the rate of outpatient visits only resulted in a 4 to 10% change in the medical cost per child.

Other interesting results were as follows. If the hospitalisation rate increased by 25% in high-income countries, the cost per DALY averted would have been $7,016 instead of $8,541 at a vaccine price of $40 per course. That same 25% increase in the hospitalisation rate in low-income countries would affect the cost-utility ratio only slightly (from $105/DALY to $104/DALY). Similarly, a 50% increase in vaccine administration costs resulted in an 11% increase in the cost-utility ratio for the high-income group, but only a 2% increase in the cost-utility ratio for the low-income
In general, for high-income countries, the cost-utility ratios were greatly influenced by the efficacy of vaccine against hospitalisation, the rate and cost of hospitalisation, and the cost of vaccine administration. Cost-utility ratios in low-income countries were mostly affected by estimates of mortality. Finally, for middle-income countries that may have increased treatment costs and high mortality rates, all parameters may have a substantial effect on the medical cost per child or the cost-utility ratios.

Authors' conclusions
Universal vaccination with an effective rotavirus vaccine reduced the rotavirus disease burden and the associated health care costs in Asia. Therefore, the rotavirus vaccine has the potential to be cost-effective, although decision-makers should assess the relative cost-effectiveness of the rotavirus vaccination strategy in comparison with other strategies for improving the health of children.

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

Validity of estimate of measure of effectiveness
The effectiveness data were estimated from published studies. It was not stated whether a systematic review of the literature was undertaken to identify the primary studies, which appear to have been included selectively. Most of the evidence came from international sources (WHO or UNICEF). Limited information on the studies used to estimate clinical inputs was provided. Further, the authors made some assumptions because of the lack of published evidence or because of the uncertainty in some data. The issue of variability in the data was addressed in the sensitivity analysis.

Validity of estimate of measure of benefit
DALYs and deaths were the most appropriate benefit measures because they capture the impact of the intervention on both quality of life and survival, which are the most relevant dimensions of care. Details on the approach used to derive disutility weights were reported. DALYs are commonly used to assess the change in the health burden in developing countries. Further, the use of DALY enables comparisons with the benefits of other health care interventions. Discounting was applied, as recommended by economic evaluation guidelines.

Validity of estimate of costs
The perspective adopted in the study was explicitly stated and the categories of costs included in the analysis were consistent with this perspective. A breakdown of the costs was not provided since most of the costs were presented as macro-categories. This limits the possibility of replicating the results of the analysis in other settings. The unit costs were not provided separately from the quantities of resources used. No statistical analyses of the costs were carried out. The sources of economic data were reported for each group of costs. The impact of alternative cost estimates was investigated in the sensitivity analysis. The price year was reported, which makes reflation exercises in other settings possible.

Other issues
The authors did not make extensive comparisons of 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, several sensitivity analyses were carried out, which, to some extent, enhance the external validity of the study. The authors noted that some categories of costs and some benefits associated with the vaccination option were not included in the model, owing to the lack of published data. For example, the benefits of vaccination for unvaccinated children were not taken into consideration. Also, lost productivity of caretakers and the cost of transportation were not included. The study referred to children in Asian countries and this was reflected in the conclusions of the analysis.
Implications of the study
The study results suggested that decision-makers should consider not only the economic savings associated with a rotavirus vaccination programme, but also the value of preventing mortality and morbidity associated with rotavirus diarrhoea, particularly in low-income countries where the disease burden is great.

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