The economics of routine antenatal anti-D prophylaxis for pregnant women who are rhesus negative

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 use of routine antenatal anti-D prophylaxis in the prevention of haemolytic disease in the newborn was examined. Two different target populations were considered, all pregnant women who were rhesus (RhD)-negative and women who were RhD-negative primigravidae only. The two different prophylactic treatments considered were Bio Products Laboratory (BPL) anti-D immunoglobulin(Ig)G (2 x 500 IU) and Baxter anti-D IgG (2 x 1,250 IU). These differed only in their price.

Type of intervention
Primary prevention.

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

Study population
The study population comprised a hypothetical cohort of pregnant women who were RhD negative.

Setting
The setting was secondary care and a hospital. The economic study was carried out in the UK.

Dates to which data relate
The effectiveness data were derived from studies published between 1997 and 2003. Some costs and resource use data were derived from sources published in 1991, 1997 and 2001. The price year was 2001.

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

Modelling
No standard decision model was used, but a description of the treatment pathway was provided.

Outcomes assessed in the review
The outcomes estimated from the literature were:
the fertility rates, birth statistics and population trends (all required to determine the population requiring routine antenatal prophylaxis);
the efficacy of routine antenatal anti-D prophylaxis (impact of offering routine antenatal anti-D prophylaxis to women who were RhD-negative on sensitisation rates); and

the utility values associated with minor and major developmental problems as a result of haemolytic disease.

**Study designs and other criteria for inclusion in the review**

In general, a systematic review of the literature was not carried out and the primary studies were identified selectively. Only the efficacy of routine antenatal anti-D prophylaxis was estimated from a systematic review that identified two main studies (an observational study and a community trial). Fertility rates, birth statistics and population trends came from official statistics.

**Sources searched to identify primary studies**

Not stated.

**Criteria used to ensure the validity of primary studies**

The authors stated that the sources used to derive the primary estimates were considered robust.

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

Not stated.

**Number of primary studies included**

The primary estimates were derived from 6 primary studies.

**Methods of combining primary studies**

Not stated.

**Investigation of differences between primary studies**

Not stated.

**Results of the review**

The crude birth rate per 1,000 population was 12.5.

The population estimate for England and Wales was 52,700,000. Thus, there were 658,750 births per year.

Approximately 16% of women in the UK were RhD-negative, and in about 10% of all pregnancies the mother was RhD-negative and the foetus RhD-positive. Therefore, there were approximately 105,000 pregnancies in RhD-negative women, of which approximately 65,000 pregnancies would be at risk.

The risk of sensitisation with conventional management was 0.95%, but treatment with routine antenatal anti-D prophylaxis in addition to conventional management could reduce the risk to 0.35% (odds ratio 0.37).

The utility values associated with minor and major developmental problems as a result of haemolytic disease were, respectively, 0.8 (applied for the first 10 years of life) and 0.4 (applied for the full duration of life expectancy).

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

The benefit measures used were:
the number of sensitisations avoided,
the number of affected foetuses avoided,
the number of foetuses lost avoided,
the total life-years gained, and
the total quality-adjusted life-years (QALYs) gained.

The number of infants with minor and major developmental disabilities was also reported as a model output. Discounting was applied to the benefit measures at an annual rate of 1.5%.

**Direct costs**
Discounting was relevant because of the long time horizon of the study and an annual rate of 6% was applied. The unit costs were presented separately from the quantities of resources used for only a few items, as most of the costs were given as macro-categories. The health services included in the economic evaluation were anti-D IgG treatments (Baxter or BPL), drug administration (time and materials), and the management of a sensitised pregnancy (including amniocentesis, possible intrauterine transfusion, blood sampling, phototherapy, and exchange transfer, hospital stay for the infant, and neonatal follow-up visits). The cost/resource boundary of the NHS was adopted in the study. The costs and resource use were estimated from manufacturer’ prices, data from the Association of Radical Midwives, and a published study. All the costs were presented in 2001 values using the Health Service Inflation indices.

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

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

**Currency**
UK pounds sterling (§).

**Sensitivity analysis**
The authors stated that a sensitivity analysis was carried out to deal with the issue of uncertainty in some estimates. However, the results of the deterministic analysis were not reported. A Monte Carlo probabilistic sensitivity analysis was also performed to examine uncertainty in the cost per life-year gained. The results were presented using a cost-effectiveness acceptability curve.

**Estimated benefits used in the economic analysis**
The number of sensitisations avoided, compared with conventional management alone, was 155.04 with routine antenatal anti-D prophylaxis offered to RhD-negative primigravidae only and 211.60 with routine antenatal anti-D prophylaxis offered to all RhD-negative pregnant women.

The numbers of affected foetuses avoided were 169.99 (RhD-negative primigravidae only) and 77.52 (all RhD-negative pregnant women), while the numbers of foetuses lost avoided were 11.52 and 5.25, respectively.

The total life-years gained were 11.52 (RhD-negative primigravidae only) and 5.25 (all RhD-negative pregnant women), while the total QALYs gained were 145 and 66, respectively.
Cost results
When BPL prophylaxis was used, the net costs associated with routine antenatal anti-D prophylaxis offered to RhD-negative primigravidae only or all RhD-negative pregnant women, compared with conventional management, were 2,590,829 and 3,738,579, respectively. The corresponding costs with Baxter prophylaxis were 2,314,922 and 3,365,039, respectively.

Synthesis of costs and benefits
Incremental cost-effectiveness and cost-utility ratios were calculated to combine the costs and benefits of the two routine antenatal programmes with conventional management alone.

When BPL prophylaxis was used, the incremental costs per sensitisation avoided with routine antenatal anti-D prophylaxis offered to either RhD-negative primigravidae only or to all RhD-negative pregnant women, compared with conventional management, were 16,711 and 17,668, respectively. The corresponding values with Baxter prophylaxis were 14,931 and 15,903, respectively.

When BPL prophylaxis was used, the incremental costs per case of haemolytic disease of the newborn avoided were 15,241 and 48,225, respectively. The corresponding values with Baxter prophylaxis were 13,618 and 3,407 when Baxter was used.

When BPL prophylaxis was used, the incremental costs per foetal loss avoided (including stillbirths, neonatal and postnatal death) were 224,933 and 711,706, respectively. The corresponding values with Baxter prophylaxis were 200,979 and 640,595, respectively.

When BPL prophylaxis was used, the incremental costs per life-year gained were 5,053 and 15,988, respectively. The corresponding values with Baxter prophylaxis were 4,515 and 14,391, respectively.

When BPL prophylaxis was used, the incremental costs per QALY gained were 12,731 and 51,529, respectively. The corresponding values with Baxter prophylaxis were 10,821 and 45,861, respectively.

The cost-effectiveness acceptability curve showed that uncertainty in cost-effectiveness was low. In particular, the probability that the incremental cost per life-year gained with both routine antenatal prophylaxis strategies over conventional management was lower than 30,000 was 0.90 or higher. These results, however, did not include the valuation of foetal loss or the long-term impact of disabilities.

A threshold analysis was conducted within the cost-utility framework. This showed that if a lost child, associated parental grief, and subsequent high intervention pregnancies were valued at less than 9 QALYs, then the routine antenatal anti-D prophylaxis offered to all RhD-negative pregnant women was not considered economically attractive (assuming a threshold of 30,000 per QALY gained). Conversely, a valuation of greater than 9 QALYs would imply that the routine antenatal anti-D prophylaxis offered to all RhD-negative pregnant women would be attractive.

Authors' conclusions
Offering routine antenatal anti-D prophylaxis to rhesus (RhD)-negative primigravidae was a cost-effective strategy in comparison with other antenatal interventions routinely delivered and funded by the NHS. A routine antenatal anti-D prophylaxis offered to all pregnant women who were RhD-negative could be cost-effective, but only under specific conditions. More specifically, if the values of a lost child, associated parental grief, and subsequent high intervention pregnancies were more than 9 quality-adjusted life-years (QALYs).

CRD COMMENTARY - Selection of comparators
The rationale for the selection of the comparators was clear. The choice of conventional care as the basic comparator was appropriate since it reflects current patterns of care for the prevention of haemolytic disease of the newborn. The two programmes of routine antenatal care were delivered at some Trusts across UK, but their use was not widespread.
Validity of estimate of measure of effectiveness
The effectiveness evidence came from published studies, but a systematic review of the literature was not carried out. In fact, the primary studies appear to have been identified selectively. Some data came from UK statistics, while clinical information came from a published meta-analysis, which ensures the validity of the primary source. The source of the utility values was unclear. The issue of uncertainty in such estimates was investigated in a probabilistic sensitivity analysis.

Validity of estimate of measure of benefit
A number of benefit measures were used and were combined with the costs. Some measures were specific to the disease considered in the study, while other measures (e.g. life-years gained and QALYs) are comparable with the benefits of other health care interventions. Discounting was performed for expected survival, following UK recommendations. The authors noted the controversial use of some benefit measures in the economic evaluation of interventions affecting the rates of foetal losses and stillbirths.

Validity of estimate of costs
The authors reported explicitly the perspective adopted in the study. As such, all the categories of costs were included in the economic evaluation. The costs associated with the management of a sensitised pregnancy were derived from a published study, and a detailed breakdown of the cost items was not provided. This limits the possibility of replicating the study. The drug costs were estimated using two different manufacturers, but a small difference in the costs was observed. The authors noted that differences in local prices could exist, depending on local competitive price negotiations. The price year was reported, which aids reflation exercises in other settings. The cost estimates were specific to the study setting and were not varied in the sensitivity analysis.

Other issues
The authors did not compare their findings with those from other studies. They also did not address the issue of the generalisability of the study results to other settings. The authors stated that deterministic sensitivity analyses were carried out, but the methods and results of such analyses were not reported. The study referred to women who were RhD-negative and this was reflected in the authors' conclusions.

Implications of the study
The study results suggested that routine antenatal anti-D prophylaxis represents a cost-effective intervention for preventing haemolytic disease of the newborn in the pregnancies of women who are RhD-negative.

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Other publications of related interest
D prophylaxis for pregnant women who are Rhesus (RhD) negative. Health Technology Assessment 2003;7(4):1-72.


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