Routine antenatal anti-D prophylaxis for RhD-negative women: a systematic review and economic evaluation
Pilgrim H, Lloyd-Jones M, Rees A

CRD summary
This review assessed the effectiveness of routine antenatal anti-D prophylaxis for Rhesus D negative women compared with no prophylaxis. They concluded that all the evidence suggested that prophylaxis reduced the incidence of sensitisation and therefore haemolytic disease of the newborn, while being associated with minimal adverse events. Overall, the authors' conclusions are appropriate and likely to be reliable.

Authors' objectives
To assess the clinical effectiveness of routine antenatal anti-D prophylaxis for Rhesus D negative women. The authors also investigated the cost-effectiveness of this intervention and whether there had been any advances in its use in the UK National Health Service since 2002 (see report for further details of these aspects).

Searching
MEDLINE, CINAHL, EMBASE, BIOSIS Previews, Cochrane Central Register of Controlled Trial (CENTRAL), Science Citation Index, Cochrane Database of Systematic Reviews, DARE, NHS EED, and NHS Health Technology Assessment databases were searched up to July 2007. Search terms were provided. There were no language restrictions. In addition, several websites containing registers of trials and ongoing research were searched, along with the bibliographies of retrieved papers.

Study selection
Studies assessing the effectiveness of routine antenatal anti-D prophylaxis in pregnant women who are Rhesus D negative were included. To be eligible the dose used had to be either two doses of at least 500 international units (IU) of anti-D immunoglobulin at 28 and 34 weeks' gestation, or a single dose of at least 1,500 IU at 28 weeks gestation followed, in either case, by a further dose at delivery of a Rhesus D positive baby or within 72 hours. Eligible comparators were no prophylaxis or comparisons of different doses, or methods of administration. Randomised and non-randomised controlled trials were eligible provided they were methodologically sound.

The key outcome of interest was the sensitisation rate for Rhesus D negative women who delivered a Rhesus D positive infant. Other outcomes of interest were incidence of haemolytic disease of the newborn, child survival and disability, health-related quality of life, and adverse effects of treatment.

The included studies, which were community-based, varied in whether they included unsensitised women who had had a previous pregnancy, as well as women pregnant for the first time. They also varied in the time at which they collected sensitisation data.

Study selection was undertaken by one researcher; studies where there was uncertainty about eligibility were assessed by a second researcher. Disagreements resolved through discussion.

Assessment of study quality
Studies were assessed based on criteria from CRD Report 4, including methods of randomisation, allocation concealment, baseline comparability, blinding, proportion of withdrawals and whether an intention-to-treat analysis (ITT) was included. Studies were then classified as being of good, fair or poor quality.

The authors did not state how many researchers undertook the quality assessment.

Data extraction
Data were extracted from each study on the number of women sensitised in the intervention and comparison group; the
percentage sensitised with 95% confidence interval (CI) were calculated, as well as the odds ratio (OR). Data on the clinical outcomes of Rhesus D positive pregnancies in sensitised women and number of adverse events were also extracted. Authors were contacted for missing data, where possible.

Data were extracted by one researcher using a standardised extraction form; any studies that gave rise to uncertainty were reviewed by a second researcher. Disagreements were resolved by discussion.

**Methods of synthesis**
A narrative synthesis was undertaken with accompanying tabulation of the data. A meta-analysis using binary logistic regression with a fixed-effects model was also undertaken.

The studies were pooled in three groups: studies using a two dose regimen that included only women pregnant for the first time (Group 1); studies using a single dose regimen that included women pregnant for the first time and women with one or more previous pregnancies (Group 2); and community based UK studies using a two dose regimen that included only women pregnant for the first time (Group 3), which was a subgroup of Group 1.

Statistical heterogeneity was assessed using p-value.

**Results of the review**
Nine studies were included: one RCT (although only uncontrolled data available); one quasi-RCT; five non-randomised studies with historical or geographical controls; and two community based studies (one was a controlled before-and-after study and one a retrospective before-and-after study). Two studies were rated as good quality, three as fair and four as poor. From the studies comparing routine antenatal anti-D prophylaxis to no prophylaxis, there were 30,768 pregnancies resulting in Rhesus D positive babies. There was a sensitisation in 65 intervention group pregnancies and 136 in the control group.

The authors identified two community-based interventions as providing the best estimate of likely efficacy, due to their study design. Based on the pooling of these studies, the pooled sensitisation rate in women pregnant for the first time was 0.95% (95% CI 0.18 to 1.71) in the antenatal prophylaxis group compared with 0.35% (95% CI 0.29 to 0.40) for the control group. The odds ratio for risk of sensitisation was 0.37 (95% CI 0.21 to 0.65) and the absolute risk reduction for sensitisation was 0.6%.

There was also a reduced risk with prophylaxis in women pregnant for the first time based on the pooling of all studies using a two dose regimen (OR 0.33, 95% CI 0.20 to 0.55; four studies) and pooling of single dose studies (OR 0.20, 95% CI 0.13 to 0.29; three studies). There was no statistically significant heterogeneity.

There were minimal adverse events.

**Cost information**
The cost per quality-adjusted life-year (QALY) gained by routine antenatal anti-D prophylaxis for Rhesus D negative women during first pregnancy compared to no prophylaxis was between £9,000 and £15,000; prophylaxis for all women Rhesus D negative women was estimated as £20,000 to £35,000 per QALY.

Sensitivity analysis suggested that the results were robust; base-case sensitisation rate and the odds ratio for the sensitisation rate associated with routine antenatal anti-D prophylaxis had the greatest impact on the incremental cost-effectiveness ratio.

Data were also reported for cost per life year gained, cost per foetal loss avoided, and cost per sensitisation avoided.

**Authors’ conclusions**
All the evidence suggested that routine antenatal anti-D prophylaxis for Rhesus D negative women reduced the incidence of sensitisation and therefore haemolytic disease of the newborn, while being associated with minimal...
adverse events.

**CRD commentary**
This review had clearly stated inclusion criteria and searched several sources for studies, including some sources of unpublished studies. There were no language restrictions in the search strategy, although the authors were unable to translate two studies to assess eligibility for inclusion. The method of reducing error and bias in study selection and data extraction may have had some limitations in detecting errors, as only papers where the first researcher had uncertainty were checked by the second researcher.

Study quality was assessed and discussed in detail in the narrative synthesis, with consideration given to how this may have influenced the direction of the results. The key relevant study details were provided and the statistical pooling seemed appropriate.

Overall, the authors’ conclusions are appropriate and likely to be reliable.

**Implications of the review for practice and research**

**Practice:** The authors did not make recommendations for practice.

**Research:** The authors stated that further research is required to: compare the efficacy of different prophylaxis regimens including compliance and safety; to investigate whether protection from sensitisation provided in first pregnancy by routine antenatal anti-D prophylaxis extends beyond that pregnancy; and to improve non-invasive genotyping of the foetus.

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**MeSH**
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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.