

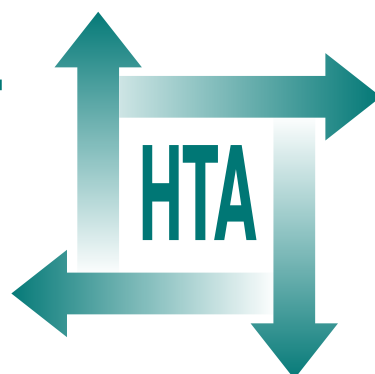
Routine antenatal anti-D prophylaxis for RhD-negative women: a systematic review and economic evaluation

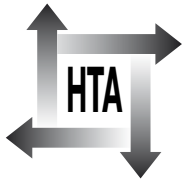
H Pilgrim, M Lloyd-Jones and A Rees



February 2009
DOI: 10.3310/hta13100

Health Technology Assessment
NIHR HTA Programme
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Routine antenatal anti-D prophylaxis for RhD-negative women: a systematic review and economic evaluation

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Declared competing interests of authors: none

Published February 2009

DOI: 10.3310/hta13100

This report should be referenced as follows:

Pilgrim H, Lloyd-Jones M, Rees A. Routine antenatal anti-D prophylaxis for RhD-negative women: a systematic review and economic evaluation. *Health Technol Assess* 2009; **13**(10).

Health Technology Assessment is indexed and abstracted in *Index Medicus/MEDLINE*, *Excerpta Medica/EMBASE*, *Science Citation Index Expanded (SciSearch®)* and *Current Contents®/Clinical Medicine*.

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The research reported in this issue of the journal was commissioned and funded by the HTA Programme on behalf of NICE as project number 07/05/01. The protocol was agreed in August 2007. The assessment report began editorial review in November 2007 and was accepted for publication in June 2008. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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ISSN 1366-5278

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Abstract

Routine antenatal anti-D prophylaxis for RhD-negative women: a systematic review and economic evaluation

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Objectives: To identify any evidence for advances in the use of routine antenatal anti-D prophylaxis (RAADP) since the 2002 National Institute for Health and Clinical Excellence (NICE) appraisal, and to assess the current clinical effectiveness and cost-effectiveness of RAADP for Rhesus D (RhD)-negative women.

Data sources: Main bibliographic databases were searched from inception to July 2007.

Review methods: Selected studies were assessed and data extracted using a standard template and quality assessment based on published criteria. Meta-analysis was used where appropriate, otherwise outcomes were tabulated and discussed within a descriptive synthesis. The health economic model developed for the 2002 NICE appraisal of RAADP was modified to assess the cost-effectiveness of different regimens of RAADP.

Results: The clinical effectiveness searches identified 670 potentially relevant articles. Of these, 12 papers were included in the review, relating to eight studies of clinical effectiveness. With one exception, no additional studies were identified in comparison with the previous assessment report, and some of the studies of clinical effectiveness included in the 2002 review had to be excluded because they did not use currently licensed doses. Therefore, eight studies comparing RAADP with no prophylaxis were identified in the clinical effectiveness review and nine (including the 2001 assessment report itself) in the cost-effectiveness review. The clinical efficacy studies were generally of poor quality and did not provide a basis for differentiating between regimens of RAADP. The best indication of the likely efficacy of a programme of RAADP comes from two non-randomised community-

based studies. The pooled results of these suggest that such a programme may reduce the sensitisation rate from 0.95% (95% CI 0.18–1.71) to 0.35% (95% CI 0.29–0.40). This gives an odds ratio for the risk of sensitisation of 0.37 (95% CI 0.21–0.65) and an absolute reduction in risk of sensitisation in RhD-negative mothers at risk (i.e. carrying a RhD-positive child) of 0.6%. The identified studies suggest that RAADP has minimal adverse effects. Of the nine studies in the cost-effectiveness review, only two described a model that could be applicable to the NHS. The economic model modified from the 2002 appraisal suggests that the cost per quality-adjusted life-year (QALY) gained of RAADP given to RhD-negative primigravidae versus no treatment is between £9000 and £15,000, and for RAADP given to all RhD-negative women rather than to RhD-negative primigravidae only is between £20,000 and £35,000 depending upon the regimen. The sensitivity analysis suggests that the results are reasonably robust to changes in the assumptions within the model.

Conclusions: RAADP reduces the incidence of sensitisation and hence of haemolytic disease of the newborn. The economic model suggests that RAADP given to all RhD-negative pregnant women is likely to be cost-effective at a threshold of around £30,000 per QALY gained. The total cost of providing RAADP to RhD-negative primigravidae in England and Wales is estimated to be around £1.8–£3.1 million per year, depending upon regimen, and to all RhD-negative pregnant women in England and Wales around £2–£3.5 million.



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Glossary and list of abbreviations

Glossary

Alloimmunisation Generally, production by an individual of antibodies against constituents of the tissues of another individual of the same species (for instance, following transfusion with blood from a member of a different blood group); in this case, production in a RhD-negative pregnant woman of antibodies against fetal RhD-positive red blood cells.

Ascites Accumulation of fluid in the peritoneal cavity.

Diplegia Cerebral palsy affecting corresponding parts on both sides of the body.

Erythroblastosis Another name for haemolytic disease of the newborn.

Haemolytic anaemia Anaemia caused by destruction of the red blood cells.

Hemiplegia Cerebral palsy affecting one side of the body.

Hydrops fetalis A complex syndrome involving profound anaemia with ascites, generalised oedema, gross enlargement of the liver and spleen, and heart failure. Hydrops forms the most severe manifestation of haemolytic disease of the newborn.

Hyperbilirubinaemia Abnormally high levels of the bile pigment bilirubin in the blood.

Kernicterus A form of brain damage caused by the deposition of bilirubin in brain tissues.

Miscarriage Spontaneous loss of a pregnancy before 24 weeks' gestation.

Multigravida Pregnant woman who has had one or more previous pregnancies.

Neonatal death Death of a live neonate in the first 28 days after birth.

Neonate Infant in the first 4 weeks of life.

Nullipara Woman who has never given birth to a child.

Oedema Swelling of any organ or tissue because of the accumulation of excess lymph fluid.

Oesophoria A muscle condition in which, when both eyes are open, each eye points accurately at the target but, if one eye is covered, it turns inwards.

Pathan Ethnic group living in southern Afghanistan and northern Pakistan.

Perinatal death Miscarriage, stillbirth or neonatal death.

Plasma The liquid part of the blood (about 60% by volume) in which the red and white blood cells and platelets float.

Prelingual deafness Deafness that is either congenital (as in haemolytic disease of the newborn) or otherwise acquired before the child has acquired speech and language.

Primigravida Woman who is pregnant for the first time.

Primipara Woman who has given birth to only one child.

Quadriplegia Cerebral palsy severely affecting all four limbs.

Secondary sensitisation (secondary immunisation) Stimulation of the production of detectable anti-D antibodies in a sensitised woman in response to a second sensitising event.

continued

Secundigravida Woman who is pregnant for the second time.

Sensitisation (primary immunisation)

Development in the mother of a template for producing antibodies against fetal RhD-positive red blood cells; in some cases, primary sensitisation also leads to the production of detectable anti-D antibodies.

Sensitising event Event causing a fetomaternal haemorrhage which leads to primary or secondary sensitisation.

Silent sensitisation Sensitisation that does not result in the production of detectable anti-D antibodies.

Stillbirth Fetus born dead after 20 weeks' gestation.

List of abbreviations

AADP antenatal anti-D prophylaxis

BNF *British National Formulary*

FMH fetomaternal haemorrhage

HDN haemolytic disease of the newborn

ICER incremental cost-effectiveness ratio

IU international unit

IUT intrauterine blood transfusion

LYG life-year gained

NICE National Institute for Health and Clinical Excellence

NNT number needed to treat

PedsQL 4.0 Pediatric Quality of Life Inventory version 4.0

QALY quality-adjusted life-year

RAADP routine antenatal anti-D prophylaxis

RCT randomised controlled trial

RhD Rhesus D

TPH transplacental haemorrhage

vCJD new variant Creutzfeldt–Jakob disease

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.



Executive summary

Background

Human blood is classified according to two main systems: the ABO system and the Rhesus (Rh) system. The Rh system consists of several related proteins, the most important of which is called the Rhesus D (RhD) antigen. People who have this antigen on their red blood cells are said to be RhD positive, whereas those who do not are said to be RhD negative. If the mother is RhD negative and the fetus RhD positive, the mother may react to fetal blood cells in her circulation by developing a template for producing anti-D antibodies, a process known as RhD sensitisation. Sensitisation is unlikely to affect the current fetus but may result in haemolytic disease of the newborn (HDN) during a second RhD-positive pregnancy. In its mildest form the infant has sensitised red cells, which are detectable only in laboratory tests; however, HDN may result in jaundice, anaemia, developmental problems or intrauterine death.

Routine antenatal anti-D prophylaxis (RAADP) can be given to RhD-negative women to prevent sensitisation and hence prevent HDN. A health technology appraisal of RAADP was carried out in 2002, which resulted in the national guidance that RAADP be offered to all non-sensitised pregnant women who are RhD negative. This assessment reviews the work carried out in the previous assessment report for the 2002 appraisal and considers additional RAADP regimens.

Objectives

The objective of this review is to consider whether there have been any advances in practice in the use of anti-D since the 2002 National Institute for Health and Clinical Excellence (NICE) appraisal, and to assess the current clinical effectiveness and cost-effectiveness of RAADP using D-Gam[®] (Bio Products Laboratory), Partobulin[®] (Baxter BioScience), Rhophylac[®] (CSL Behring) or WinRho[®] (Baxter BioScience) for RhD-negative women.

Methods

The scope of the assessment was to determine the clinical effectiveness and cost-effectiveness of any currently licensed regimen of RAADP in non-sensitised RhD-negative pregnant women, compared with either RAADP delivered using different dosing regimens or no RAADP. Relevant outcomes were a reduction in the incidence of sensitisation in RhD-negative women delivered of RhD-positive babies; a reduction in the incidence of HDN; survival of the child; disability of the child; health-related quality of life; and adverse effects of treatment.

Searches of systematic reviews, randomised controlled trials (RCTs) and non-RCTs relating to the clinical effectiveness or cost-effectiveness of RAADP were conducted in 10 bibliographic databases (MEDLINE, CINAHL, EMBASE, BIOSIS, Science Citation Index, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, NHS Health Technology Assessment database and NHS Economic Evaluations Database) from inception to July 2007. Additional searches were carried out around the outcomes of HDN and the costs and quality of life associated with the outcomes.

Inclusion criteria were as follows:

- Population: pregnant women who are RhD negative.
- Intervention: RAADP using either two doses of at least 500 IU at 28 and 34 weeks' gestation or a single dose of at least 1500 IU at 28 weeks' gestation, in either case followed, if the infant is RhD positive, by a further dose of anti-D given at, or within 72 hours of, delivery.
- Comparators: RAADP using different dosing regimens and/or methods of administration, or no RAADP.
- Outcomes: sensitisation (alloimmunisation) rates among RhD-negative women delivered of RhD-positive infants (the at-risk population); incidence of HDN; survival of the child;

disability of the child; health-related quality of life; or adverse effects of treatment.

- Study design: any of systematic reviews, RCTs or non-RCTs.

The exclusion criterion was studies considered methodologically unsound or not reporting results in the necessary detail.

Where appropriate, study results were combined in meta-analyses.

The health economic model developed for the 2002 NICE appraisal of RAADP was modified to assess the cost-effectiveness of different regimens of RAADP.

Results

The clinical effectiveness searches identified 670 potentially relevant articles. Of these, 12 papers were included in the review; they related to eight studies of clinical effectiveness.

With the exception of one RCT of the same anti-D preparation administered intravenously and intramuscularly, no additional studies were identified with regards to clinical effectiveness or cost-effectiveness from the previous assessment report, although some of the studies of clinical effectiveness included in the 2002 review were excluded because they did not use currently licensed doses of anti-D. Therefore, within the clinical effectiveness review eight studies were identified that compared licensed doses of RAADP with no prophylaxis; nine studies (including the 2001 assessment report itself) were identified within the cost-effectiveness review.

The clinical efficacy studies were generally of poor quality and do not provide a basis for differentiating between the regimens of RAADP. The best indication of the likely efficacy of a programme of RAADP in England and Wales comes from the two non-randomised community-based studies by MacKenzie and colleagues in 1999 and Mayne and colleagues in 1997. The pooled results of these two studies suggest that such a programme may reduce the sensitisation rate from 0.95% (95% CI 0.18–1.71) to 0.35% (95% CI 0.29–0.40). This gives an odds ratio for the risk of sensitisation of 0.37 (95% CI 0.21–0.65) and an absolute reduction in risk of sensitisation in RhD-negative mothers at risk (i.e. carrying a RhD-positive child) of 0.6%. The identified studies

suggest that RAADP is associated with minimal adverse events.

Of the nine studies identified within the cost-effectiveness review, only those by Vick and colleagues (1996) and Chilcott and colleagues (2003) describe a detailed modelling study that appears to be applicable to the UK NHS. Furthermore, no new mathematical models were provided within the manufacturers' submissions for the appraisal. The health economic model developed by the assessment group also incorporated two one-dose regimens as well as the two two-dose regimens included in the 2002 review. It suggests that the cost per quality-adjusted life-year (QALY) gained of RAADP given to RhD-negative primigravidae versus no RAADP is between £9000 and £15,000, and for RAADP given to all RhD-negative women rather than to RhD-negative primigravidae only is between £20,000 and £35,000 depending on the RAADP regimen (excluding WinRho). The one-dose regimen of 1500 IU of WinRho is estimated to have a cost per QALY gained above £60,000 for both indications. The sensitivity analysis suggests that the results are reasonably robust to changes in the assumptions within the model, the base-case sensitisation rate, the relative risk of sensitisation and the QALY valuation of a fetal loss having the biggest impact upon the results. The cost-effectiveness of RAADP improves slightly for ethnic minorities in England and Wales.

Discussion

Several arguments in addition to clinical effectiveness have been put forward to support the use of one or other regimen of RAADP; these relate to compliance, cost and safety. However, there is currently no published evidence comparing the different regimens of RAADP. The prices used in this assessment for anti-D itself are based upon *British National Formulary* drug prices but, as actual prices paid by hospitals vary according to supply and demand, the cost-effectiveness in practice may be better than that presented here. The formulation that is more expensive in terms of list price may in some cases be the cheaper drug because advantageous prices have been negotiated locally.

The health economic model does not explicitly take into account the quality of life of the parents as a result of the loss of a child or of having a disabled child because of the unquantifiable nature of these

measures. However, the implication of this is that the cost per QALY gained would be slightly lower than currently predicted.

Since the NICE guidance was issued in 2002, compliance rates with RAADP seem to have increased. However, although the implementation of a programme of RAADP should lead to a significant fall in the residual numbers of women becoming sensitised, some women continue to be affected. There are five possible reasons for continuing cases of sensitisation that require consideration:

- failure to recognise potential sensitising events in pregnancy as such and to treat them appropriately
- failure to assess the extent of fetomaternal haemorrhage (FMH) adequately
- failure to comply with postpartum prophylaxis guidelines
- refusal of RAADP by the mother
- failure to implement RAADP by some trusts, and incomplete adherence to advice (i.e. poor compliance with the second dose).

The key uncertainties associated with the assessment of RAADP are:

- the efficacy of different dosing regimens of routine anti-D prophylaxis
- the quality of life of children suffering from HDN and their parents (including parents of stillborn children)
- the incidence rate of outcomes as a result of HDN
- the costs associated with HDN in terms of the management of sensitisation and the

management of developmental problems over a patient's lifetime.

Conclusions

All of the evidence indicates that RAADP reduces the incidence of sensitisation and hence of HDN. The economic model suggests that RAADP given to all RhD-negative pregnant women is likely to be considered cost-effective at a threshold of around £30,000 per QALY gained. The total cost of providing RAADP to RhD-negative primigravidae in England and Wales is estimated to be around £1.8–£3.1 million per year, depending upon the regimen of RAADP used (excluding WinRho). This takes into account the cost of RAADP and its administration, the cost of the management of sensitisation, and the cost savings associated with avoiding HDN. The additional cost of providing RAADP to all RhD-negative pregnant women in England and Wales is estimated to be around £2–£3.5 million.

Further research is recommended to:

- compare the efficacy of the different RAADP regimens; issues relating to compliance and safety may also influence the efficacy of the different regimens of RAADP and hence further research would also be useful in these areas
- confirm or disprove the preliminary findings that protection against sensitisation provided by RAADP in primigravidae extends beyond the first pregnancy
- aim to improve non-invasive genotyping of the fetus.

Chapter 1

Background

This report updates the assessment of routine antenatal anti-D prophylaxis (RAADP) undertaken on behalf of the National Institute for Health and Clinical Excellence (NICE) by Chilcott and colleagues in 2001.¹ However, for ease of use it is intended to be a stand-alone document.

Description of health problem

Human blood is classified according to two main systems: the ABO system and the Rhesus (Rh) system. The Rh system consists of several related proteins, the most important of which is called the Rhesus D (RhD) antigen. People who have this antigen on their red blood cells are said to be RhD positive, whereas those who do not are said to be RhD negative. Both ABO and Rh blood types are inherited characteristics and therefore a fetus may inherit a blood type from its father which differs from that of its mother.

Haemolytic disease of the newborn (HDN) is a haemolytic anaemia that affects the fetus or neonate. It results from the transplacental passage of antibodies created by the mother and directed against fetal red cell antigens inherited from the father. Over 90% of all cases of clinically significant HDN affect RhD-positive infants born to RhD-negative mothers.

Aetiology, pathology and prognosis of haemolytic disease of the newborn

Aetiology

Modern laboratory methods have shown that fetal cells are present in the maternal circulation in all pregnancies from a very early stage. However, in some cases a quantity of fetal blood large enough to be detected by less sensitive methods such as the Kleihauer test enters the mother's circulation. Such a transfer of fetal blood is termed a fetomaternal haemorrhage (FMH) and is not uncommon. FMH occurs most frequently at delivery. However, it may also occur during events such as miscarriage or abortion, invasive tests and procedures during

pregnancy, or abdominal trauma; it also sometimes occurs in the absence of any observable risk. During the first trimester approximately 3% of women have enough fetal blood cells in their circulation to be detectable. This figure rises to 12% in the second trimester and 45% in the third trimester, until at delivery up to 50% of women delivering an ABO-compatible infant have detectable circulating fetal red cells.²

Fetomaternal haemorrhage does not normally cause any adverse effects. However, if the mother is RhD negative and the fetus RhD positive, the mother may react to the fetal blood cells in her circulation by developing a template for producing anti-D antibodies,³ a process known as RhD sensitisation or primary immunisation. Such women are said to be 'sensitised' and the event leading to sensitisation is known as the 'sensitising event'. The amount of blood required is small: most women who become sensitised do so as a result of an FMH of less than 0.1 ml.⁴ Although some RhD-positive women produce anti-D following a sensitising event in pregnancy, this is extremely rare.⁵

Primary immunisation may lead to the production of antibodies, which are detectable after 4 weeks. Alternatively, it may lead to sensitisation without visible antibodies. However, once such 'silent' sensitisation has occurred, secondary sensitisation may be produced by a much smaller FMH than that which caused the initial sensitisation,⁶ stimulating the production within 1–2 weeks of anti-D antibodies. These maternal antibodies cross the placenta into the fetal circulation and 'coat' or sensitise the infant's red cells, provoking their premature clearance from the circulation and resulting in anaemia and jaundice. In utero, fetal bilirubin crosses the placenta and is cleared by the maternal circulation, but after delivery its clearance is dependent on the immature neonatal liver, which allows unconjugated bilirubin to accumulate.

Not all RhD-negative pregnant women who are exposed to RhD-positive blood cells become sensitised. The risk of sensitisation is affected by a number of factors including the blood type of

the fetus, the volume of fetal blood entering the mother's circulation, and the mother's immune response.⁷ It has been shown that, when RhD-negative volunteers are given repeated injections of RhD-positive cells, some are sensitised quickly and develop high levels of anti-D antibodies, whereas others produce only moderate amounts of antibody; around 20% appear to be completely non-responsive. Similarly, in pregnancy, some women respond quickly, often in their first RhD-positive pregnancy; if they have a second RhD-positive pregnancy their antibody level rises rapidly and the infant may be severely affected.⁸ Such women may be sensitised after a relatively small transplacental haemorrhage (TPH) or an abortion (spontaneous or therapeutic).⁹ Mothers who develop antibodies in their third, fourth or later pregnancy have a much lower chance of losing the child. Thus, sensitisation is most likely in the earlier pregnancies, and women who reach their third or later RhD-positive pregnancy without developing antibodies appear to be less sensitive to the RhD antigen.⁸ The risk of sensitisation is increased when the mother and fetus have the same ABO blood group.¹⁰ In the absence of antenatal and postpartum anti-D prophylaxis, the risk of sensitisation following a single ABO-compatible RhD pregnancy is about 16%,⁹ but it is only 2% if the mother and fetus are ABO incompatible.¹¹ As approximately 80% of pregnancies are ABO compatible,¹² the overall risk of sensitisation, without prophylaxis, is approximately 13% of at-risk pregnancies.

In the absence of any programme of prophylaxis, most RhD-negative women who become sensitised do so following a small FMH at delivery of their first RhD-positive infant. Without RAADP, the majority of those primigravidae who are sensitised before delivery in the absence of an identifiable sensitising event appear to be sensitised in the third trimester. A New Zealand study¹³ found that 87% (14/16) of primigravidae who developed antibodies did so in the third trimester, compared with only 27% of multigravidae (7/26); these data suggest that many women who develop antibodies early in their second pregnancy have actually been sensitised late in the first pregnancy. Consequently, anti-D antibodies are not usually produced during the first RhD-positive pregnancy; the first RhD-positive infant will generally be affected by maternal antibodies only in the minority of cases in which the mother has already been sensitised as a result of a previous transfusion of RhD-positive red cells, a miscarriage or abortion, or a sensitising event earlier in the pregnancy, and then only following a subsequent FMH during the course

of that pregnancy. However, once the mother has been sensitised, her immune response will worsen with each successive RhD-positive pregnancy, and consequently each successive RhD-positive infant will be progressively more severely affected by HDN.

Before the introduction of prophylaxis, anti-D was found immediately after a first pregnancy in approximately 1% of untransfused RhD-negative women who delivered an ABO-compatible RhD-positive infant; in about half of these cases it was detectable between 34 and 40 weeks' gestation. At 6 months post-delivery, 4–9% of such women had detectable anti-D,¹⁰ as did 1–2% of RhD-negative women who had borne a RhD-positive ABO-incompatible infant.¹⁴ However, the 'true' rate of sensitisation is greater than that identified by the presence of anti-D at, or 6 months after, delivery, as a proportion of women who have been sensitised do not have detectable anti-D after their first RhD-positive pregnancy, but will give a secondary immune response when stimulated by a second sensitising event, usually during a later pregnancy. Thus, the appearance of anti-D before 28 weeks' gestation in a subsequent pregnancy is a strong indication of sensitisation in an earlier pregnancy.¹⁵ Before the introduction of routine antenatal and postpartum anti-D prophylaxis, approximately 17% of RhD-negative women were found to have detectable anti-D after their second RhD-positive ABO-compatible pregnancy; in most of these women, the initial sensitisation would have occurred during the first pregnancy.¹⁰

Passive immunisation with anti-D immunoglobulin can prevent sensitisation, although the precise mechanism by which it does so is not known.¹⁰ However, once a woman has developed anti-D antibodies she cannot be desensitised.

Pathology and prognosis

Survival and short-term outcomes

The severity of HDN varies according to certain properties of the antibody, its level in the maternal blood and the duration of exposure of the infant to that level of antibody. In its mildest form the infant has sensitised red cells that are detectable only in laboratory tests. More commonly, the infant has a mild degree of jaundice, which responds to phototherapy. More severe disease involves significant anaemia and progressive hyperbilirubinaemia. Certain neonatal brain structures, such as the thalamus and corpus striatum, are particularly sensitive to damage by unconjugated bilirubin. If severe jaundice is not treated by exchange transfusion the resulting

clinical condition, kernicterus, results in permanent brain damage and eventually death in 70% of affected infants. In the most severe form of HDN the in utero anaemia causes hydrops and intrauterine death.¹⁰

Although the chances of survival are related to the severity of the HDN, the management of potentially severely affected infants was eased by the introduction in the early 1980s of intrauterine fetal blood sampling, enabling the identification of fetal RhD type and haemoglobin level, not least because this facilitated direct intravascular intrauterine blood transfusion (IUT). Treatment thus became possible at a much earlier gestational age, and this reduced the incidence of death in utero from severe anaemia.¹⁶ Although overall survival in fetuses undergoing IUT is around 86–90%,^{17,18} it is lower in those with hydrops, which is indicative of severe haemolytic disease; survival in fetuses with severe hydrops who receive IUT may be as low as 55%, whereas in those with mild hydrops it may be as high as 98%.¹⁷

The most comprehensive recent data on the outcomes of pregnancies in RhD-sensitised women derive from a study of all such pregnancies in Northern Ireland from September 1994 to February 1997.¹⁹ The authors report that there were 124 pregnancies resulting in a total of 130 fetuses. Although there were 11 deaths (8.5%) from various causes, over 90% of infants survived the neonatal period (*Table 1*).

More recently, a study on the outcome of pregnancy in women with Rh sensitisation treated in a tertiary referral centre in Zagreb, Croatia, between January 1997 and January 2003 included two women with anti-Kell immunisation, six with combined RhD and C immunisation, and 15 with

RhD immunisation.²⁰ In total, 20 of the 23 fetuses (87%) were live-born. Four (17%) had hydrops; three of these were stillborn (two died before it was possible to perform IUT, whereas in the third death was not related to IUT) and the fourth survived.

Longer-term outcomes

Infants who survive HDN may suffer long-term neurodevelopmental problems caused either directly by the condition or indirectly by the prematurity associated with it. Several studies have reported on such problems. The most recent of these is the Northern Ireland study¹⁹ noted above. This found that, at 2 years of age, five of the 78 babies affected by HDN (6%) had minor developmental problems (e.g. myopia, squint or delay in language and fine motor skills) and two (3%) had major permanent neurodevelopmental problems.¹⁹

The only studies that have reported long-term outcomes in fetuses who required IUT for HDN (primarily associated with RhD incompatibility) relate to children treated in the 1980s and 1990s (*Table 2*). These studies indicate that, at this time, about 15% of fetuses receiving IUT died in utero; neonatal deaths reduced total survival to about 80%. Survival was higher in the less severely affected fetuses; in the German study²¹ only 7/11 (64%) of those who had developed hydrops before the first transfusion survived, compared with 28/32 (88%) of those without hydrops. Because early delivery was felt to pose fewer risks than additional transfusions, some of the recorded sensorineural disabilities may be associated with prematurity rather than specifically with IUT.²² By comparison, a more recent study²³ included 254 fetuses treated with 740 intravascular IUTs at a single centre in the Netherlands between 1988 and 2001; in 85% of the pregnancies (217/254) fetal anaemia was due to

TABLE 1 Outcomes of pregnancies in RhD-sensitised women in Northern Ireland, September 1994–February 1997¹⁹

Outcome	Number (%)
Termination for fetal abnormality	2 (2)
Miscarriage	5 (4)
Stillbirth of unknown cause	1 (1)
Stillbirth following IUT	2 (2)
Live-born affected babies (includes one neonatal death from severe hydrops)	76 (58)
Live-born unaffected babies	44 (34) (includes 17 RhD-negative pregnancies)
Total	130 (100)
IUT, intrauterine transfusion.	

TABLE 2 Outcomes of intravascular intrauterine transfusion

	Doyle et al. 1993 ²²	Harper et al. 2006 ²⁴	Grab et al. 1999 ²¹	Hudon et al. 1998 ²⁵	Janssens et al. 1997 ²⁶
Date of IUT	1984–90	1985–95	1986–91	1986–92	1987–93
Location	Australia	USA	Germany	USA	Netherlands
Number of fetuses receiving IUT	52	18	43	49	92
Reason for IUT	Severe erythroblastosis (number associated with anti-D antibodies not stated)	Hydrops (in most cases associated with anti-D either alone or in combination with other antibodies)	Severe erythroblastosis [40/43 (93%) associated with anti-D antibodies]	HDN [41/49 (84%) associated with anti-D antibodies]	Severe erythroblastosis (number associated with anti-D antibodies not stated)
Mean number of transfusions per fetus	Not stated. Median 4 per survivor (range 1–8)	Median 4.5 (range 1–7)	3.2	3.3	3.2
Intrauterine death	No data	2 (11%)	5 (12%) (4/5 before 28 weeks)	9 (18%) (mean gestational age 23.1 weeks)	15 (16%)
Number live-born	No data	16 (89%)	38 (88%)	40 (82%)	77 (84%)
Neonatal deaths	No data	0	3 (7%) (all preterm)	None reported	4 (4%)
Number surviving	38 (73%)	16 (89%)	35 (81%)	Apparently 40 (82%)	73 (79%)
Hospital stay (days), median (range)	No data	No data	No data	11 (3–101)	No data
Number of survivors followed up	38 (100% of survivors) at 2 years of age (corrected for prematurity)	16 (89%) for a mean of 10 years (range 4.5–12.9 years)	30 (86% of survivors) for up to 6 years	22 (55% of survivors) for a mean of 14.4 months; 11 (28% of survivors) for 36–62 months	69 (95% of survivors) for 0.5–6 years
Number with moderate or severe neurological impairment (other than hearing impairment) at follow-up	2/38 (5%) ^a	2/16 (13%) ^b	0	1/22 (5%) ^c	3/69 (4%) ^d
Number with mild neurological impairment (other than hearing impairment) at follow-up	1/38 (3%) ^e	5/16 (31%) ^f	2/30 (7%) ^g	0	2/69 (3%) ^h

	Doyle et al. 1993 ²²	Harper et al. 2006 ²⁴	Grab et al. 1999 ²¹	Hudon et al. 1998 ²⁵	Janssens et al. 1997 ⁶
Number with motor delay requiring physiotherapy	No data	No data	No data	No data	17%
Number with speech delay requiring speech therapy	No data	No data	No data	No data	13%
Number with hearing tested	38	16	No data	21 (53% of survivors) tested before initial hospital discharge	58 (84%) screened at 9 months
Number of those tested with permanently impaired hearing	0	2/16 (13%)	No data	2/21 (10%)	3/58 (5%)
<p>HDN, haemolytic disease of the newborn; IUT, intrauterine transfusion.</p> <p>a One had severe developmental delay and multiple minor motor seizures; another had cerebral palsy with double hemiplegia.</p> <p>b One had static encephalopathy and cerebral palsy; one (the child of a mother who abused alcohol and illicit drugs) had mild mental retardation.</p> <p>c Right spastic hemiplegia diagnosed at 2.5 years, with normal development apart from walking difficulties. As only 1/40 children were followed up for 62 months it is possible that others also suffered neurodevelopmental problems. Two infants who were not followed up had severe mental retardation (due in one case to Angelman syndrome and in the other to Menkes disease), which did not seem to be related to HDN.</p> <p>d Cerebral palsy: all three attended a special school for physically and mentally disabled children although their level of disability varied (one was physically disabled with an IQ of 40–50; one was physically disabled with speech delay; one, who initially had severe motor and speech delay, had only fine motor and speech delay at the age of 4 years).</p> <p>e Mental developmental index of 72.</p> <p>f One child had an articulation disturbance, two had affected gait, one had slight clumsiness of rapid alternating movements with mirror hand movements, and the fifth had oesophoria.</p> <p>g One infant had mild speech development delay at 24 months, after which he was lost to follow-up; the other had mild psychomotor disability at 12 months but subsequent evaluations, including a school performance test at age 6, were normal.</p> <p>h Minor neurological dysfunction leading to motor and speech delay.</p> <p>i One child had bilateral profound sensorineural hearing loss following kernicterus; one had unilateral mild conductive hearing loss.</p> <p>j One infant had mild peripheral sensitivity loss and the other had severe bilateral deafness (this child was not available for follow-up and so it was not possible to assess any other potential disabilities).</p>					

maternal RhD alloimmunisation. Overall survival was higher at 89% (225/254); there were 19 fetal deaths (7%) and 10 neonatal deaths (4%). Seven of the fetal deaths and five of the neonatal deaths were considered to be related to IUT, a rate of 1.6% per procedure. Longer-term outcomes were not reported.

The studies followed up survivors for different lengths of time and subjected them to different tests; follow-up ranged from 95% to 100% (see *Table 2*). Three studies screened for hearing disability: the Dutch study²⁶ screened 58 infants (84% of survivors) at 9 months and found non-transient hearing loss in three (5%); one US study screened 16 children (100% of survivors) at a mean age of 10 years and found that two (13%) had hearing loss (one had bilateral profound sensorineural hearing loss and the other unilateral mild conductive hearing loss);²⁴ the other US study screened 21 infants (53% of survivors) before initial hospital discharge and found that two (10%) had a permanent hearing deficit (in one case severe bilateral deafness), a rate that was noted to be probably five to ten times higher than that among infants not affected by HDN.²⁵

The studies also found that a number of IUT survivors suffered moderate or severe neurological impairment other than hearing loss – primarily cerebral palsy of varying degrees of severity. The Dutch study²⁶ compared outcomes in IUT survivors with those in both a high-risk group of very premature and/or very-low-birthweight infants and a healthy control group. In the high-risk group, 18% of children who survived to the age of 2 years had major or minor disabilities at that age, compared with 6% in the healthy control group and 10% (7/69) in the IUT survivors group. However, because of the very small numbers of IUT survivors there was no statistically significant difference between the proportion of affected children in that group and the proportion of affected children in either the high-risk group or the healthy control group. A small US study²⁴ used a battery of tests to compare IUT survivors with their unaffected siblings and found them to be within normal limits, compared with published norms and sibling controls, in terms of all physical, neurological and cognitive outcomes except for visual attention, for which the IUT survivors had significantly lower scores. However, because of the small sample size the investigators recognised the possibility of a type II error (failing to observe a difference when in fact there is one). In the other US study,²⁵ overall follow-up was very incomplete,

making it difficult to know how to interpret the information that the mean developmental scores of those who were assessed were within normal limits; the investigators admit that the children who did not return for evaluation may have been those at increased risk of severe neurodevelopmental compromise, although they felt that they were more likely to have been lost to follow-up as a result of geographical distances.

Thus, the introduction of ultrasonographically-guided IUT has improved the ability to treat severely anaemic fetuses earlier in gestation, but has thereby increased the chances of survival of more severely affected fetuses with the potential for poor neurodevelopmental outcomes.²⁵ Around 10–12% of fetuses affected by HDN will require IUT,²⁷ and a relatively high proportion of IUT survivors may suffer neurodevelopmental problems such as cerebral palsy, deafness and motor and speech delay that will require specialist input and, in some cases, special education; others will suffer some degree of developmental delay requiring physiotherapy or speech therapy.

Epidemiology – demographic factors (age, sex, ethnicity, income, regional variation)

Ethnic groups vary in terms of the proportion of the population that is RhD negative and thus at risk of sensitisation. Approximately 16% of the white UK population is RhD negative compared with about 5% of West African people, whereas virtually no Chinese people are RhD negative.¹⁰ No data have been identified relating specifically to people of Asian subcontinent origin living in Britain, but data from various parts of that subcontinent suggest that the proportion of this population that is RhD negative is smaller than the proportion of the white UK population that is RhD negative; for example 5.5% of blood donors in Vellore, south India, have been found to be RhD negative,²⁸ as have 9% of young men reporting for army recruitment in Pakistan (ranging from 7.7% of Pathans to 10.9% of those of Kashmiri origin).²⁹

The incidence of HDN is clearly influenced by the prevalence of RhD-negative people in the population. Thus, if the prevalence of RhD negativity within a given ethnic group is low, there will be fewer women at risk of sensitisation. However, assuming that women draw their partners from their own ethnic group, each RhD-negative woman in an ethnic group with a low prevalence of RhD negativity has a higher risk of having an RhD-

positive partner than does an RhD-negative woman in an ethnic group with a higher prevalence of RhD negativity (*Table 3*).

The incidence of HDN is not influenced by parental age or socioeconomic status, except inasmuch as these factors affect family size; as noted above, once a RhD-negative woman has been sensitised, her successive RhD-positive pregnancies will be more severely affected, and therefore the impact of HDN will be greater in families in which the mothers undergo more pregnancies.

No data have been identified regarding regional variation in the distribution of HDN in England and Wales, but any such variation is likely to be due primarily to the distribution of people of different ethnic origins.

Incidence of haemolytic disease of the newborn

Before the introduction of anti-D prophylaxis, HDN due to RhD incompatibility affected about one in 20 children born to RhD-negative women in Caucasian populations³⁰ – approximately 1% of all neonates in England and Wales. Only a very small minority of cases of HDN occurred in first pregnancies, but 1 in 100 second pregnancies, and a higher proportion of subsequent pregnancies, were affected.

Currently, only about 500 fetuses a year in England and Wales develop HDN,³¹ approximately 1 in every 1298 live and stillbirths, less than one-tenth of the earlier figure. Although this change is largely due to the introduction of anti-D prophylaxis, it also reflects changes in family size. It has been estimated that 69% (95% CI 61–76%) of the observed reduction in maternal sensitisation rates in Manitoba (from 9.6 per 1000 total births in 1963 to 2.6 per 1000 total births in 1988) was due to the introduction of anti-D prophylaxis and 24% (95% CI 1–42%) to changes in family structure: in 1988, 40% of all births were first births, compared

with only 25% in 1963.³² Over the same period, advances in neonatal care were such that perinatal survival in infants with RhD HDN rose from 86.2% in 1963 to 97.4% in 1988.³²

In the UK, standard postpartum anti-D prophylaxis was introduced in 1969. Prophylaxis was extended in 1976 to include abortions and spontaneous miscarriages, and in 1981 to include a number of potential sensitising events.³³ Following the introduction of postpartum anti-D prophylaxis the proportion of RhD-negative women found by routine antenatal testing to have demonstrable anti-D within 6 months of the delivery of their first RhD-positive ABO-compatible pregnancy fell from 4–9% to 0.1–0.5%, and the proportion with demonstrable anti-D by the end of their second RhD-positive ABO-compatible pregnancy fell from 17% to around 1.5%.¹⁰ However, as these figures will not include women sensitised during their final pregnancy, the true figures will be higher.³⁴ Nearly half of the 1.5% known to have been sensitised (0.7% overall) seem to have been sensitised as a result of FMH during the first pregnancy, a similar number have been sensitised as a result of FMH during the second pregnancy, and the remainder (approximately 0.2% overall) have been sensitised as a result of failure to provide sufficient postpartum anti-D to cover a large FMH at the first delivery.¹⁰

In 1953, 310 deaths in England and Wales were attributed to RhD HDN – 1 in every 2180 births.¹⁰ An audit found that registered deaths and stillbirths attributed to RhD HDN in England and Wales between 1977 and 1987 fell by more than 70% over that period, from 106 (18.4 per 100,000 births) in 1977 to 27 (3.9 per 100,000 births) in 1987. This fall occurred mainly between 1977 and 1983 and was due to a large reduction in the number of cases in which the mother was believed to have been sensitised by a pregnancy following which she was not given anti-D prophylaxis; there was no change in the

TABLE 3 Probability of a RhD-negative woman having a RhD-positive partner by chance (assuming both partners are from ethnic groups with the same prevalence of RhD negativity)

Prevalence of RhD negativity within population	Probability of RhD-negative woman having RhD-positive partner by chance
1%	99%
5%	95%
9%	91%
16%	84%

number of deaths following sensitisation of the mother during the first pregnancy or after having been given anti-D following one or more previous pregnancies (i.e. failure of prophylaxis).³⁵ By 1989 the number of registered deaths and stillbirths had fallen to 10 (1.5 per 100,000 live births)³⁶ – 1 in approximately 66,500 live births or one-thirtieth of the 1950s figure. However, although these official figures clearly demonstrate the reduction in HDN mortality, they underestimate the true impact of the disease because they do not include fetal loss before 28 weeks. A retrospective review of births between 1987 and 1991 to mothers resident in Scotland found that five times as many deaths from RhD HDN were uncertified as were certified through the General Register Office. Of the 20 deaths identified, 11 occurred before 28 weeks' gestation, but only four before 20 weeks' gestation. The major cause of under-reporting was the exclusion from the certification data of both therapeutic and spontaneous abortions.^{37,38} Thus, although HDN was reported as the main or subsidiary cause of five stillbirths and one neonatal death (or 1 in approximately 108,200 total births) in England and Wales in 2005,³⁹ the Scottish data suggest that the true number of fetal and perinatal deaths in that year was likely to have been around 30 (1 in approximately 21,640 total births). In 2001 the Trent Confidential Enquiry into Stillbirths and Deaths in Infancy (CESDI) reported that in 1999 there were three deaths at between 20 weeks of pregnancy and 1 year of life as a result of RhD alloimmunisation in a population of approximately 5 million; this is consistent with an overall figure of around 30 for England and Wales (S Wood, 2001, personal communication).

CESDI notifications for England, Wales and Northern Ireland indicate that, for the period 1994–9, an average of 18 fetal and infant deaths a year in England, Wales and Northern Ireland

were due to RhD incompatibility (M Macintosh, 2001, personal communication). To these must be added any fetal losses that occur before 20 weeks' gestation. The Scottish data suggest that 20% (4/20) of all fetal and infant deaths due to RhD incompatibility occur before 20 weeks. This represents an additional 25% (4/16) in relation to the number of deaths that occurred from 20 weeks' gestation onwards. Consequently, on the basis of the CESDI figures for England, Wales and Northern Ireland, an average of five additional deaths a year can be estimated to occur before 20 weeks, leading to an average total of 23 deaths a year. As noted above, the CESDI figures are likely to under-report the incidence of deaths due to RhD incompatibility, and therefore this figure is compatible with the figure of 30 estimated earlier. The data summarised in *Table 4* indicate that the majority of deaths due to HDN occur after 24 weeks' gestation and thus are stillbirths and neonatal and postneonatal deaths.

Although a programme of RAADP cannot prevent every case of fetal loss, stillbirth, neonatal death or postnatal death attributable to RhD incompatibility, it can be expected to prevent a substantial majority of such cases.

Impact of health problem Significance for patients in terms of ill-health (burden of disease)

Any discussion of the impact of maternal sensitisation is complex, as the major burden of the condition relates to the direct impact on the health and well-being of children affected by HDN and the indirect impact which that has on their parents and any siblings. However, there are also some direct implications for maternal health and well-being. This section discusses, first, the direct impact of sensitisation on maternal health and

TABLE 4 Fetal and infant death attributed to RhD incompatibility

Gestational age	Scotland 1987–91, ³⁷ n (%)	UK excluding Scotland 1994–9 (CESDI data), n (%)
Under 20 weeks	4 (20)	No data
20–24 weeks	3 (15)	19 (17)
Stillbirth	7 (35)	51 (48)
Neonatal death	5 (25)	36 (33)
Postneonatal death	1 (5)	3 (3)
Total	20 (100)	109 (100)

CESDI, Confidential Enquiry into Stillbirths and Deaths in Infancy.

well-being; second, the direct impact of HDN on the health of the infant; and, third, the indirect impact of HDN on the well-being of the family.

Health and well-being of the mother

RhD sensitisation has a direct impact on maternal well-being as a result of the anxiety caused by the continuous monitoring of pregnancies in sensitised women, even if these pregnancies result in healthy babies.

There is a further implication for those sensitised women whose fetuses require IUT. More than 25% of these women develop additional antibodies apart from anti-D. As a consequence, should they require blood transfusions in future, it would be very difficult to find compatible blood for them (Professor M Contreras, 2007, personal communication).

Health of the affected child

HDN has both short- and long-term implications for affected infants. In the short term they may undergo a number of therapeutic procedures including IUT, exchange transfusion and phototherapy. These interventions are short-lived and their full impact on the infant's health and health-related quality of life is difficult to estimate. However, it should be noted that IUT is associated with an estimated death rate of approximately 2% per procedure.^{23,40}

In the longer term, with appropriate management, the majority of children affected by HDN achieve normal neurodevelopmental outcomes. However, those most severely affected do not achieve normal outcomes. The studies by Hudon *et al.*²⁵ and Janssens *et al.*²⁶ indicate that the most common permanent disabilities in this group are cerebral palsy and deafness; minor developmental problems include speech and motor delay, requiring physiotherapy and speech therapy.

Cerebral palsy has substantial implications for both health (including reduced life expectancy) and quality of life (*Table 5* provides a summary of quality of life in children and adolescents with cerebral palsy). The impact of cerebral palsy on quality of life in children is difficult to quantify because of the shortage of validated instruments for measuring quality of life in children, especially those with disabilities,⁴¹ the presence of communication barriers, and the wide range of impairments found in people with cerebral palsy.⁴² However, it is important when possible to obtain the perspective of the children and adolescents with cerebral palsy themselves because those who are capable of self-

reporting consistently rate their quality of physical and psychosocial health more highly than do their parents.⁴³ Even so, in a recent study of Californian children and adolescents with cerebral palsy (age 5–18 years), Varni *et al.*⁴³ found that those who were able to self-report using the Pediatric Quality of Life Inventory version 4.0 [PedsQL 4.0; 69/148 (47%)] reported considerably lower health-related quality of life than healthy children in terms of both physical and psychosocial well-being. Parental proxy reports attributed significantly higher physical and school functioning to children who were capable of self-report than to those who were not, but indicated no significant difference between the two groups in terms of emotional and social functioning. Self- and proxy reports indicated significantly lower physical and psychosocial functioning in children with quadriplegia than in those with hemiplegia and diplegia.⁴³

A US study by Pirpiris *et al.*⁴⁴ also found that both functional and psychosocial well-being in children with mild to moderate cerebral palsy were lower than in non-affected peers; however, there was no correlation between physical function and psychosocial well-being, and children with mild cerebral palsy had lower self- and parentally reported psychosocial well-being than would be predicted by their functional disability. By contrast, a European study⁴⁵ of 8- to 12-year-old children with cerebral palsy found that the quality of life of the 61% (500/818) who were able to self-report, as measured using the KIDSCREEN questionnaire, was similar to that of children of the same age in the general population who had been surveyed 2 years previously in all domains except for the school environment (where the quality of life of those with cerebral palsy was better) and physical well-being (which could not be formally compared because a slightly modified version of this domain of the questionnaire had been used with the children with cerebral palsy). However, 54% of the children with cerebral palsy reported pain during the previous week and this was significantly associated with poorer quality of life in relation to physical well-being, moods and emotions, autonomy, relationships with parents, self-perception and school environment. No information was presented regarding the quality of life of those children who were not able to self-report.

It is possible that the difference in results between the European and Californian studies may be due at least in part to the different age ranges involved: the Californian study included adolescents, who may have been less optimistic than younger

TABLE 5 Summary of quality of life in children and adolescents with cerebral palsy

Study	Country	Population	Tool	Findings
Dickinson <i>et al.</i> 2007 ⁴⁵	Europe	Children with CP (aged 8–12 years) capable of self-report	KIDSCREEN	Self-reported quality of life was similar to that of children of the same age in the general population surveyed 2 years previously in all domains except for the school environment (which was better in children with CP) and physical well-being (which was not comparable as a modified version of the questionnaire was used with children with CP)
Pirpiris <i>et al.</i> 2006 ⁴⁴	USA	Children with mild to moderate CP (mean age 10 years), mostly considered too young to self-report	PedsQL 4.0, PODCI	Parentally and self-reported functional and psychosocial well-being were lower than in non-affected peers
Varni <i>et al.</i> 2005 ⁴³	USA	Children and adolescents with CP (mean age 10 years) capable of self-report	PedsQL 4.0	Self-reported physical and psychosocial well-being were considerably lower than in healthy children

CP, cerebral palsy; PedsQL 4.0, Pediatric Quality of Life Inventory version 4.0; PODCI, Pediatric Outcomes Data Collection Instrument.

children. Thus, in a Canadian study,⁴⁶ young adults (aged 19–23) with cerebral palsy who were capable of responding to a survey anticipated less success in future relationships, post-secondary education, employment and independent living than did matched control subjects, although adolescents (aged 13–15) with cerebral palsy did not differ from control subjects in their future expectations.

A US study⁴⁷ evaluated parentally reported pain frequency in 198 children (mean age 10 years 7 months) with moderate to severe cerebral palsy. In total, 11% reported pain very often/almost every day. Pain was more prevalent with more severe impairment and was associated with missed school days and days in bed.

Many of the physical problems associated with cerebral palsy are exacerbated in adult life. Mobility may become more limited and this is often accompanied by an increase in spasticity and pain.⁴⁸ In a US study⁴⁹ of adults with cerebral palsy with no more than mild cognitive impairment, 67% reported pain of more than 3 months' duration, which was generally experienced on a daily basis. Similarly, a Norwegian survey⁵⁰ found that 28% of people with cerebral palsy without intellectual disability reported daily pain for 1 year or more, compared with 15% of the general population. An Italian study⁵¹ found that, although 29/70 (41%) adults with cerebral palsy had walked independently (i.e. without sticks or other aids) before the age of 18, only 16 (22%) currently did

so; the majority of those who had lost the ability to do so found this very frustrating.

Despite advances in education, technology, home support and environmental access for people with disability,⁵² recent studies indicate that many people with cerebral palsy are unable to achieve the same degree of independence as their peers. Thus, in 1996, although 75% of a Dutch cohort of young adults with cerebral palsy were mainly independent with respect to the activities of daily living, 24% required sheltered or institutional accommodation; 30% lived with their parents, compared with 20% of the general Dutch population of the same age; and only 12.5% lived with a partner, compared with 60% of the general Dutch population of the same age.⁴⁸ Only 16% had paid employment other than sheltered labour; 41% attended a day activity centre for the disabled.⁴⁸ In a US study⁵² of non-institutionalised adults with cerebral palsy aged from 19 to 74 years, most of whom had moderate to severe disabilities, 67% lived independently of parents or relatives, but almost half of these had an attendant. Approximately 25% had been married at some point in their lives. In total, 53% were competitively employed (57% of those with moderate and 35% of those with severe physical disability); 7% were in semicompetitive employment; 18% were in sheltered employment; and only 16% had never been involved in an organised work situation. However, 50% had speech deficits that severely compromised verbal communication, and by the age of 25

approximately 75% had stopped walking by choice because of the fatigue and inefficiency involved.⁵² Neither of these studies may be fully representative of people with cerebral palsy: the Dutch study obtained responses from only 46% (80/173) of young adults who met the study inclusion criteria,⁴⁸ whereas the US study population was limited to non-institutionalised adults and was self-selected through contacts with the local United Cerebral Palsy Affiliate.⁵²

Deafness also has substantial implications for quality of life. Even if they are provided with hearing aids and appropriate tuition and speech therapy at a young age, over 90% of prelingually deaf children are unlikely ever to develop good speech and good speech-reception skills.⁵³ They will therefore be excluded from many aspects of a largely hearing society and may suffer delayed social development and isolation. In an Australian cohort study⁵⁴ the parentally-reported psychosocial well-being of 7- to 8-year-old children with significant congenital hearing loss was significantly poorer than that of their hearing peers. Such problems persist in later life. In Belgium, a national health survey of people aged 15 years and older⁵⁵ found that those with a hearing disability of any kind reported poorer physical and mental health than those with normal hearing.

Parental and sibling well-being: psychological effects of fetal loss, stillbirth, neonatal death or postnatal death

Research has shown that the experience of losing a child is by far the most painful grief experience.⁵⁶ Contributory factors are likely to be the fact that such loss appears to go against the natural order and that, as both parents are equally affected, they are less able to support each other than they would be in the loss of a parent or sibling. Such factors are also likely to be relevant in relation to stillbirth and fetal loss. Although several studies have considered the impact on parents of stillbirth and neonatal death, none has been found that specifically studies the impact of fetal loss as a result of HDN.

Following perinatal death, mothers naturally experience sadness, anxiety, guilt and depressive symptoms. Although these feelings diminish in severity over the first year, it is normal for them to continue for up to 2 years. Fathers experience similar levels of grief, anxiety and depression, although they generally display less active grief than mothers. Some parents suffer prolonged symptoms that require psychological treatment, and 20% of both mothers and fathers suffer

post-traumatic stress disorder in the pregnancy following a stillbirth. Increases in parental discord and relationship break-up have also been identified following perinatal death. Older siblings may also suffer a severe sense of loss.⁵⁷⁻⁵⁹

Some studies, including two prospective studies,⁶⁰⁻⁶² have suggested that grief following stillbirth or fetal loss is related to length of gestation. However, other studies indicate that length of gestation is not necessarily a factor in the case of wanted pregnancies. A US study⁶³ found that, at 2 months post-termination, women who had terminated wanted pregnancies for fetal anomalies experienced grief as intense as those who had suffered spontaneous perinatal loss. Although the terminated pregnancies were of a younger gestational age (under 20 weeks) than the spontaneous losses, the grief responses were similar, being determined by the 'wantedness' of the pregnancy and not by gestational age.⁶³ A second US study⁶⁴ also found that the termination of a wanted pregnancy because of fetal anomalies was experienced as a perinatal death rather than as an elective abortion. The grief was independent of gestational age and it was felt that, in a wanted pregnancy, bonding started before conception.⁶⁴ Once parents perceive both the pregnancy and the baby as real, and begin to attach to their baby as their child, with a pet name and a personality, the grief that follows a loss is intense and will last for months to years. For some parents this attachment happens very early in the pregnancy.⁵⁸

No work has been undertaken on the valuation of parental grief following miscarriage, stillbirth or neonatal death, and it is considered that, for ethical reasons, such work would be impossible to undertake (M Jones-Lee, 2001, personal communication).

Parental and sibling well-being: ability to achieve intended family size

To its parents, any infant or fetus who dies is an irreplaceable individual. However, most parents affected by miscarriage, stillbirth, neonatal death or postneonatal death can hope to achieve their intended family size by a subsequent pregnancy. This may be considerably less easy when the infant or fetus has died as a result of RhD sensitisation, as that will affect all subsequent RhD-positive pregnancies in that mother. If the father is homozygous RhD positive (i.e. has two RhD-positive genes) then all future pregnancies will be affected and will require intensive monitoring and intervention, with the possibility of an unsuccessful outcome. If the father is heterozygous (i.e. has

one RhD-positive gene and one RhD-negative gene) there is still a 50% probability that a given pregnancy will be affected.⁶⁵ As the severity with which the fetus is affected increases with each RhD-positive pregnancy, a successful outcome becomes less likely with each successive pregnancy.

Although we are not aware of any published work in this field it seems likely that failure to achieve intended family size may be the cause of long-term psychiatric morbidity in the parents. It is theoretically possible for couples to complete their family using donor insemination with RhD-negative sperm, but it is not known how many affected couples in the UK are offered, or accept, this option. Moreover, donor insemination in itself may not be devoid of long-term psychological consequences. A review found that, although donor insemination parents generally appeared to be comparable to, or better than, natural parents in their interaction and emotional involvement with their children, some studies had identified an increase in emotional/behavioural problems in children conceived by donor insemination.⁶⁶ One study of 60 couples who had children conceived both naturally and by donor insemination found that the men were significantly closer to their children by donor insemination than to their 'other' children.⁶⁷ However, another study found that parents who used donor insemination because of infertility feared that, when they disclosed their status to the child, he/she would reject them and search for his/her genetic father; in addition, the majority of men in this study felt jealous of the donor.⁶⁸ Clearly, the psychological issues for fathers would differ if donor insemination were used because of RhD incompatibility rather than because of male infertility; we are not aware of any studies of its use specifically because of RhD incompatibility.

Parental and sibling well-being: effects of living with a disabled child

Living with a disabled child may affect parental and sibling well-being. In a German study⁶⁹ parents in families with children with mental and/or physical disabilities assessed the quality of life of all family members as significantly lower than did parents in families with children without disabilities. This conflicts with the findings of a Canadian study⁴⁶ in which adolescents and young adults with cerebral palsy and their mothers, fathers and siblings were broadly similar to control groups in their mean scores for family functioning, life satisfaction and perceived social support. However, the Canadian investigators note that their results may be affected by self-selection bias, in that families in which

care of the family member with cerebral palsy was particularly stressful and time-consuming may have chosen not to participate in the study; they also note that the control families were identified by the families of a person with cerebral palsy, who may have selected families with levels of functioning similar to their own. Fathers and siblings seemed to be more affected than mothers by the presence of a family member with cerebral palsy. Parental future expectations were lower for adolescents and young adults with cerebral palsy than for those without.⁴⁶

An Australian study⁷⁰ identified that the parents of children with mild to severe cerebral palsy experienced significantly more emotional worry/concern and limitations in time available for their personal needs as a result of their child's physical or psychosocial health than did the parents of unaffected children; moreover, their child's health had a significantly greater impact on family activities. As might be expected, the limitations in time, and the impact on family activities, were greater in parents of children with severe rather than mild cerebral palsy but the emotional impact was the same regardless of whether the child had mild or severe cerebral palsy.⁷⁰ A US study⁷¹ also found that parents of children with mild to severe cerebral palsy suffered greater emotional worry/concern and limitations in time available for their personal needs than a normative sample. A Canadian study⁷² found that the primary caregivers of children with cerebral palsy (in 95% of cases a parent, primarily the mother) reported significantly more physical and psychological ill-health than the general population of caregivers; they also had lower incomes, despite the absence of any important differences in education between the two samples.⁷² A Turkish study⁷³ found that quality of life in mothers who looked after children with cerebral palsy at home was significantly lower than that of mothers of children with minor health problems (fever, cough or diarrhoea) in all dimensions except physical functioning. Quality of life was significantly lower among the mothers of children with the least independent motor function compared with the mothers of less badly affected children.⁷³ More generally, an Australian study⁷⁴ found that the majority of mothers of children with a physical disability, intellectual disability or autism had significantly poorer mental health than local population norms.

Families with children with intellectual disabilities are significantly more disadvantaged on all indicators of socioeconomic position than families with children without such disabilities.⁷⁵ A British study⁷⁶ suggests that differences in socioeconomic

position, household composition and maternal characteristics (age, marital status and general health) between mothers of children with intellectual disabilities and mothers of 'typically developing' children account for the lower levels of happiness seen in the mothers of the disabled children. The economic impact on the family of the presence of a disabled child extends beyond childhood: in the US, the prospective Wisconsin study⁷⁷ found that, by the age of 53, the parents of adult children with developmental disabilities had significantly lower incomes and savings than comparison parents.

The presence of a child with prelingual deafness in a hearing family also has an impact on family members; however, some parents express marked anxiety about a child's deafness, others little or none. The impact on siblings varies depending on characteristics such as age, gender and birth order, family characteristics such as size and ethnicity, and parenting strategies; older hearing sisters are adversely affected because they frequently provide too much care for the deaf sibling, whereas older hearing brothers are less affected in this respect; all siblings are potentially equally affected by differential parental treatment of their deaf and hearing children. Sibling relationships are more difficult when the deaf child is younger than the hearing sibling(s),⁷⁸ as would be the case with deafness caused by HDN.

Significance for the NHS

In 2005, the most recent year for which figures are available, there were 645,835 live births and 3483 stillbirths in England and Wales.³⁹ As around 10% of all births in the UK are of RhD-positive infants delivered of RhD-negative women, each year in England and Wales approximately 65,000 live births and stillbirths will fall into this category. In the absence of RAADP around 1% of RhD-negative women who deliver a RhD-positive infant will become sensitised antenatally – approximately 650 women a year in England and Wales. Around 550 of these women are likely to have a subsequent pregnancy that will require close monitoring; approximately 415 of the fetuses are likely to develop RhD HDN and 31 of these are likely to suffer fetal death, stillbirth, neonatal death or postneonatal death. Some of the 550 sensitised women who undergo second pregnancies will go on to have further pregnancies and again a proportion of these will be affected. It seems likely that, when third and subsequent pregnancies in sensitised women are taken into account, there will be approximately 520 pregnancies a year in sensitised women in England and Wales.

Affected pregnancies must be monitored closely because the timing of IUT is a major part of optimal management; it should be delivered only in moderate to severe anaemia but before moderate to severe hydrops develops.⁷⁹ The obstetric input required to manage these cases is considerable, including:

- monitoring of the maternal serum antibody level at least monthly until 28 weeks' gestation and every 2 weeks thereafter⁸⁰
- consultant review, with Doppler scans, at a frequency determined by the level of risk: in many women this will be weekly, especially after 30 weeks (C Dhillon, 2008, personal communication)
- possible delivery at 34–36 weeks, with subsequent special care costs.

In utero transfusion may be required every 2–4 weeks and in severe cases the mother may also require infusions of immunoglobulin (N Davies, 2001, personal communication). The level of monitoring varies from case to case but the cost is clearly substantial.

In total, 10–12% of fetuses affected by HDN require IUT to correct anaemia,^{27,81} and its provision has led to a major reduction in the need for elective premature delivery (e.g. at 28 weeks). However, the benefit of avoiding elective premature delivery, and the resulting risks, has to be balanced against an estimated fetal loss from IUT of approximately 1–3%.⁴⁰ IUT requires a highly specialised unit with skilled personnel, equipment (particularly ultrasound) and access to specialised blood products.

Some neonates with HDN require postnatal exchange transfusions for rapidly rising serum concentrations of bilirubin that are not responsive to intensive phototherapy.³¹ Such infants present less frequently than in the past because neonatal jaundice and immediate anaemia are not major problems in newborns treated until near term with a successful IUT programme. However, because babies who have undergone IUT commonly develop anaemia between 2 and 6 weeks of age, they require monitoring and, if necessary, treatment with erythropoietin or top-up transfusions.^{2,82}

Two UK studies have identified outcomes (including resource use) in pregnancies in women with RhD antibodies. One study⁸³ collected data relating to all such women in the seven maternity units served by the Mersey and North Wales Blood

Centre, Liverpool, between December 1993 and November 1994, and the other study¹⁹ collected data relating to all such women in Northern Ireland between September 1994 and February 1997. A third, substantially smaller study²⁰ collected similar data in a tertiary care centre in Zagreb, Croatia. A very high proportion of infants in the Croatian study required IUT, intensive treatment unit (ITU) admission, exchange transfusions and/or phototherapy, presumably because the study included only severely affected pregnancies transferred to the tertiary care centre, whereas the two British studies presented data relating to all pregnancies in women with RhD antibodies. However, it is difficult to know how to interpret the noticeable difference between the two British studies in both the proportion of affected babies and the resource implications associated with their care (Table 6).

Resource utilisation data are also available from an audit of 70 pregnancies referred to the Liverpool

Women's Hospital for the management of RhD disease and 15 more pregnancies managed in consultation with colleagues in district general hospitals, over the 3.5 years before the introduction of RAADP. Between them these 85 pregnancies required:

- 292 visits to consultant specialists (mean of 3.4 per pregnancy)
- 102 scans (mean of 1.2 per pregnancy)
- 118 amniocenteses (mean of 1.4 per pregnancy)
- 86 intrauterine transfusions (mean of one per pregnancy)
- three emergency Caesarean sections for cord complications during the procedures in the third trimester.

One perinatal death and two deaths under 22 weeks were related to the procedures.⁸⁴

TABLE 6 Pregnancies in RhD-sensitised women: outcomes and resource use

	Mersey and North Wales, December 1993–November 1994,⁸³ n (%)	Northern Ireland, September 1994–February 1997,¹⁹ n (%)	Zagreb, Croatia, January 1997–January 2003,²⁰ n (%)
Number of pregnancies	100	124 (130 fetuses)	23
Termination for fetal abnormality	None reported	2 (2)	0
Miscarriage	4 (4)	5 (4)	0
Intrauterine death	2 (one following IUT)	0	3 (13)
Stillbirth of unknown cause	0	1 (1)	0
Stillbirth due to cardiac abnormality	1 (1)	0	0
Stillbirth following IUT	None reported	2 (2)	0
Live-born affected babies	34 (34)	76 (58) (includes one neonatal death from severe hydrops)	At least 17 (≥74)
Live-born unaffected babies	60 (60) (includes 38 RhD-negative pregnancies)	44 (34) (includes 17 RhD-negative pregnancies)	No more than 3 (≤13) (includes one RhD-negative pregnancy)
Total fetuses requiring IUT	4 (4) ^a (includes one intrauterine death)	Not reported	9 (39) (median number of transfusions 3, range 1–5)
Babies requiring admission to neonatal ITU	Not reported	59 (45) (mean length of stay 21.4 days)	6 (26) (median length of stay 6 days, range 3–8 days)
Babies requiring exchange or top-up transfusions	6 (6)	29 (22) (mean number of transfusions per baby 2.1)	14 (61) (median number of transfusions per baby 2, range 1–6)
Babies requiring phototherapy	8 (8)	55 (42) (mean length 5.1 days)	17 (74)

ITU, intensive treatment unit; IUT, intrauterine transfusion.
 a The three live-born babies who had IUT required 3–5 transfusions each.

Clinical experts suggest that practice has changed in recent years such that there are fewer invasive procedures such as amniocentesis but substantially more Doppler ultrasound scans per affected pregnancy. This has resulted in an increase in the number of antenatal outpatient visits but a marked reduction in the number of invasive procedures and the incidence of sensitisation and fetal loss associated with them.

If, as suggested earlier in this section, in the absence of RAADP there would be approximately 520 pregnancies a year in sensitised women in England and Wales then the implication of the study carried out in Northern Ireland¹⁹ is that, in addition to around 37 fetal or neonatal deaths, these pregnancies would result in approximately 21 children with minor developmental problems and eight with major permanent developmental problems. These children would require significant NHS and other resources. Although cerebral palsy varies widely in severity, treatment may be complex and long term, including therapy, special education, medication, orthopaedic surgery and the provision of appliances; in adulthood, special accommodation and employment may also be needed.^{70,71} Profound deafness is also associated with substantial costs. In the US the expected lifetime cost to society of a child with profound deafness of prelingual onset was estimated in the late 1990s to exceed US\$1 million because of the need for special education and because of reduced work productivity.⁸⁵ In the UK the mean societal cost of a year of life at 7–9 years of age at 2003 prices was estimated to be £14,093 for children with congenital bilateral permanent hearing impairment and £4207 for normally hearing children.⁸⁶

Current service provision

It is current national guidance that RAADP be offered to all non-sensitised pregnant women who are RhD negative. The clinician responsible for the prenatal care of a non-sensitised RhD-negative woman should enable her to make an informed choice about treatment taking into account circumstances under which such prophylaxis would not be necessary (for instance, if the woman has opted to be sterilised after the birth of her baby or is otherwise certain that she will not have another child after her current pregnancy, or if she is in a stable relationship with the father of the child and he is known or found to be RhD negative). Use of RAADP should not be affected by use of

prophylactic anti-D for a potential sensitising event earlier in the same pregnancy.⁸⁷

It is also current standard practice in the UK to give 500 IU of intramuscular anti-D immunoglobulin within 72 hours of delivery to all RhD-negative pregnant women who deliver RhD-positive infants and who are not already sensitised.⁸⁸ This dose will cover a TPH of at least 4 ml of fetal red cells (i.e. 99% of all TPHs).¹⁰ The size of any FMH is routinely estimated and further anti-D given if indicated. Any event during pregnancy with the potential to cause sensitisation should also prompt assessment of FMH and administration of anti-D within 72 hours. Such events include chorion villus sampling, (late) miscarriage, termination of pregnancy, amniocentesis, abdominal trauma, antepartum haemorrhage and external cephalic version.

There is some uncertainty about the current uptake of RAADP in England and Wales. It has not been universally adopted: in their submission,⁸⁹ the Royal College of Physicians and Royal College of Pathologists state that, in 2005, a survey of 328 UK maternity units found that only 75% were offering RAADP; of these, 81% were using the two-dose regimen. They also refer to a recent postal survey of 233 hospital transfusion laboratories which found that, of the 173 laboratories (75%) which responded, only 155 (90%) had fully implemented RAADP. There are no data on the level of uptake in terms of the number of RhD-negative pregnant women in those centres that have implemented RAADP who actually receive RAADP.⁹⁰

The Royal Colleges of Physicians and Pathologists also refer to anecdotal evidence that many centres are changing from a two-dose to a single-dose regimen, presumably for logistic reasons and perhaps also in the hope of increasing compliance.⁸⁹ The Bio Products Laboratory (BPL) submission⁹¹ indicates that 55% of hospitals that have implemented RAADP are currently using D-Gam 500 IU in a two-dose regimen, whereas Behring⁹² state that 71 centres in England and Wales are currently using a single 1500-IU dose of Rhophylac.

Description of technology under assessment

The technology under assessment is RAADP for non-sensitised pregnant women who are RhD negative. Prophylactic anti-D, whether antenatal or postpartum, can only suppress primary RhD

immunisation; it has no effect in women who have already developed anti-D, however weak,¹⁰ and therefore should not be given to such women.

The half-life of prophylactic anti-D is approximately 3 weeks; it can be detected by serological tests for several weeks, by the indirect antiglobulin test (IAT) for around 8 weeks, and by more sensitive techniques for up to 12 weeks (exceptionally, for several months).⁸⁰

RAADP may take the form of either two doses of at least 500 IU of anti-D immunoglobulin, the first at 28 weeks' and the second at 34 weeks' gestation, or a single dose of at least 1500 IU at 28 weeks (1500 IU of Rhophylac is sufficient anti-D to neutralise the sensitising potential of approximately 15 ml of RhD-positive red blood cells⁹³). In theory, if prophylactic anti-D has a half-life of up to 12 weeks, a two-dose regimen will provide greater protection in late pregnancy. The British Committee for Standards in Haematology supports the use of the two-dose regimen recommended in the previous NICE guidance and notes that more evidence is required to establish the comparative efficacy of a single dose of 1500 IU at 28 weeks.⁹⁴

RAADP is additional to any antenatal anti-D prophylaxis (AADP) offered in response to a potential sensitising event, and postpartum anti-D prophylaxis is still required within 72 hours of delivery if the infant is RhD positive.

When the original assessment of RAADP was undertaken on behalf of NICE by Chilcott *et al.* in 2001,¹ only two products were licensed for use in the UK. These products, manufactured by BPL and Baxter Healthcare, were both two-dose regimens. Since then two additional products have been licensed for UK use; these products, manufactured by CSL Behring and Baxter BioScience, are both single-dose regimens (for details see Summary of product characteristics). This updated assessment has been prompted by the availability of these single-dose products, as well as by the wish to reflect potential changes in the management of sensitised pregnancies, rather than by any significant change in the evidence base relating to the efficacy of RAADP.

As noted above, it is current national guidance that RAADP be offered to all non-sensitised pregnant women who are RhD negative. Prenatal identification of the fetus's RhD blood group would enable RAADP to be targeted only to those non-sensitised RhD-negative women pregnant

with RhD-positive infants. This approach has not previously been possible because identification of the blood group of the fetus used to require a sample of fetal cells, obtained using invasive procedures (amniocentesis or chorion villus biopsy), which themselves carry the risk of FMH and consequent sensitisation or, in women who have already undergone silent sensitisation, boosting of the maternal immune response,⁹⁵ in addition to an 0.5–1.0% risk of spontaneous abortion.⁹⁶ However, recent technological developments have made it possible to predict the fetal RhD genotype non-invasively by polymerase chain reaction (PCR) using fetal DNA present in the mother's plasma.⁹⁵ In principle, this technology permits the screening of all non-sensitised RhD-negative pregnant women to enable antenatal prophylaxis to be targeted only to those carrying RhD-positive fetuses. However, to be feasible in practice the test results must yield no false negatives (i.e. cases in which the fetus appears to be RhD negative but is actually RhD positive), and this level of accuracy does not yet appear to have been achieved.⁹⁶ (The existence of false positives is less important, as it simply means that, as in current practice, a RhD-negative woman carrying a RhD-negative fetus will be given unnecessary prophylaxis.⁹⁶) Moreover, targeted antenatal prophylaxis would only be possible if it was demonstrated that the test was reliable when undertaken before 28 weeks' gestation. This has yet to be achieved. However, in their submission,⁸⁹ the Royal College of Physicians and Royal College of Pathologists anticipate that a test which has 99% accuracy at 15+ weeks' gestation will become routinely available within 12–24 months, that the costs of implementation will not be prohibitive, and that the advantages in terms of the reduced use of anti-D (for potential sensitising events as well as for RAADP) will be significant. However, were such a test to be routinely used it would still be necessary to use anti-D in compliance with the current guidelines either in the absence of test results or if the results were equivocal, as well as in cases in which the fetus is confirmed to be RhD positive.⁹¹

In most cases it is likely that RAADP is administered by midwives based in the community and/or antenatal clinic. Side effects (short-term discomfort at the injection site and, very rarely, anaphylaxis) are rare and do not necessitate monitoring of recipients other than by extending the clinical audit process to include RAADP. However, as with other blood products, scrupulous record keeping is essential to be able to link individual women with specific batches of anti-D. This is important both because of the

risk of infection transmission and because of the importance of traceability for the interpretation of blood tests if a blood transfusion is needed at a later date.⁸⁹

Summary of intervention

Anti-D immunoglobulin is a blood product extracted from human plasma obtained from blood donors with high-titre circulating anti-D antibodies.⁹⁷ Originally these donors were RhD-negative women sensitised through pregnancy, and men and women immunised through transfusion; their antibody titres were then regularly boosted by the injection of RhD-positive red blood cells. However, as the demand for anti-D rose following the introduction of antenatal prophylaxis it became necessary in both the USA and Australia to deliberately immunise RhD-negative donors specifically for the purpose of obtaining anti-D immunoglobulin,^{98,99} and we understand that this is now universal practice (Professor M Contreras, 2007, personal communication).

Historically, most RhD immunoglobulin products have been prepared using the Cohn cold ethanol fractionation method.¹⁰⁰ The yield of anti-D immunoglobulin G (IgG) obtained using this method is low – only 50–60% of the anti-D present in the original plasma. Anti-D prepared by this method contains proteins that may cause adverse reactions if given intravenously and so it can only be given intramuscularly, unless it has been specifically treated to remove these proteins. It also contains small but significant amounts of other plasma proteins, especially immunoglobulin A (IgA) and immunoglobulin M (IgM), which may cause localised itching, swelling and discomfort and, very rarely, anaphylactic reactions.¹⁰¹

Anti-D can also be prepared using ion-exchange chromatography. This method retains over 90% of the anti-D present in the original plasma. Anti-D prepared in this way contains no demonstrable non-IgG protein and may therefore be given either intramuscularly or intravenously; if given intravenously it is more effective weight for weight than anti-D produced by the Cohn method given intramuscularly. However, care is needed when administering large quantities (in response to a massive TPH or an inadvertent RhD-incompatible blood transfusion) as intravenous delivery of the amount recommended for intramuscular use under such circumstances (6000 IU every 12 hours until the total required dose is given) may cause an unpleasant, and possibly hazardous, transfusion reaction. Anti-D prepared using the original ion-

exchange chromatography methods is unstable in solution and must be prepared before injection; it is therefore less convenient for health-care personnel to use.¹⁰¹ More recently, however, a multistep chromatographic fractionation method has been developed that yields a liquid-stable anti-D (Rhophylac).¹⁰⁰

There are two main concerns relating specifically to the safety of antenatal anti-D: the risk of enhanced anti-D immunisation of the mother ('augmentation') and the effect of passive anti-D on the fetus.¹⁵ In addition, there are theoretical concerns relating to the possibility of transmission of viral or prion diseases; these apply equally to postnatal administration of anti-D, although of course antenatal administration exposes the fetus as well as the mother to any such risk. These concerns are discussed in turn in the following sections.

Concerns relating to exposure of the pregnant woman to passive anti-D

In theory, the presence of low levels of passive anti-D in the maternal circulation following RAADP could result in the enhancement of a primary immune response to RhD-positive red blood cells following FMH. However, this has not been observed in clinical trials.¹⁵

There is also the possibility of short-term adverse events such as allergic or anaphylactic responses. Such adverse events are rare. None of the studies reviewed here reported occurrences of such short-term adverse events, and the manufacturers' submissions report very few. BPL state that, between October 1999 and March 2005, they issued over 700,000 vials of anti-D and received 15 reports of related adverse events, five of which were classed as serious. These included one probable and one possible anaphylactic reaction and one case with tongue swelling.⁹¹ Baxter reported in 2001 that anti-D was well tolerated – over 2.9 million doses of its product were given worldwide between January 1990 and July 2000 and only 11 reports of adverse reactions were received by Baxter. Two of these were classified as serious but both occurred long after the administration of anti-D and so were thought not to be related. Only two of the adverse reactions were thought to be possibly related to treatment – one of a visual field defect and palpitations, the other of hot flushes.¹⁰² Baxter do not present more recent data but state that their product's safety profile is unchanged.¹⁰³ Behring note that, between its initial launch in 1996 and the end of 2006, 2.07 million doses of Rhophylac were distributed worldwide and only

30 suspected adverse drug reactions relevant to its safety were reported, one per 69,000 doses.⁹²

Concerns relating to exposure of the fetus to passive anti-D

Concerns have been expressed regarding the potential risks of RAADP to the fetus, who will not benefit directly from the intervention, which is intended to protect his or her future siblings.¹⁰⁴ It is theoretically possible that the transfer of passive anti-D from the mother could cause fetal anaemia. However, there is no evidence that anti-D given to the mother during pregnancy is harmful to the infant, and the dosage used appears to be insufficient to cause observable haemolysis or anaemia in the fetus, even when repeated large doses are given. Although a minority (< 10%) of infants will be found to have laboratory evidence of red cell sensitisation, this is subclinical and does not result in anaemia, jaundice or the need for phototherapy.^{15,105}

There is some uncertainty about the possibility of longer-term adverse effects arising from exposure to anti-D. Concern has been expressed that exposing babies to anti-D in utero may have an effect on the immune system and may potentially also cause problems for RhD-negative baby girls in their later reproductive lives.¹⁰⁴ However, many babies who were exposed to anti-D in utero have now grown to adulthood and no evidence has been published to suggest any cause for concern.

Concerns relating to the possible transfer of viral or prion infection

Because the only source of therapeutic IgG is human plasma there are safety concerns related to the possible transfer of viral or prion infection. These vary according to the different manufacturing methods used.

Overall, immunoglobulins prepared by the Cohn cold ethanol fractionation method have an excellent safety record, which predates the introduction of specific virology testing of donors and viral inactivation of the end product.¹⁰⁶ This method has been shown to produce non-infective immunoglobulin from plasma contaminated with hepatitis virus.¹⁰⁷

By contrast, contaminated anti-D prepared by ion-exchange chromatography and used for intravenous postpartum prophylaxis was responsible for outbreaks of hepatitis C in the late 1970s in Germany^{107,108} and Ireland.¹⁰⁹ These outbreaks predated the identification of hepatitis C in 1989 and the introduction of screening of

donations in 1991.¹¹⁰ In Ireland, subsequent screening of all women exposed to anti-D manufactured by the Irish Blood Transfusion Service Board between 1970 and 1994 found that, although infection with hepatitis C was primarily associated with exposure to anti-D in 1977, it was also associated, although to a much lesser extent, with exposure between 1991 and 1994; again, the anti-D was an intravenous preparation manufactured by column chromatography. The investigators noted that this second, small-scale outbreak would probably not have been identified had investigations into the much larger 1977 outbreak not been undertaken in 1991 and 1994.¹¹⁰ Anti-D prepared by ion-exchange chromatography currently undergoes several processes to minimise the risk of virus transmission; these include virus inactivation by solvent-detergent treatment and nanofiltration.⁹² However, these measures may be of limited value against non-enveloped viruses such as hepatitis A and parvovirus B19.¹¹¹

As with other human-derived blood products, the risk of new variant Creutzfeldt–Jakob disease (vCJD) transmission is unquantifiable.¹¹² Both the extent of vCJD infection in the population and its transmissibility by blood products are unknown.⁹ The four cases of probable transfusion-associated vCJD identified in the UK in the last 4 years all involved donations of non-leucodepleted red blood cells transfused between 1996 and 1999, and no cases of vCJD have been associated with fractionated plasma products.¹¹³ Nonetheless, because of the long incubation period it is not possible to conclude that there is no risk of vCJD infection.¹¹⁴ Steps currently taken to inactivate viruses are unlikely to affect prion infectivity (although the manufacturer claims that the nanofiltration processes used in the production of Rhophylac contribute to the removal of abnormal prion protein⁹²). Moreover, as plasma is pooled to produce batches of immunoglobulin, many recipients will be exposed to plasma from an individual donor: in the routine manufacture of Rhophylac the pool size is 3001.⁹³ Therefore, as a precautionary measure, to minimise the theoretical risk of transmission of vCJD from blood products, all anti-D used in the UK is manufactured from US plasma, as bovine spongiform encephalopathy and vCJD have not been reported in the US.

Despite these measures, because anti-D is a human plasma-based product there is, naturally, public concern over its safety, and all staff should both receive, and give potential recipients, suitable evidence-based information about the product. Around one-third of RhD-negative women who

have children are likely only ever to have RhD-negative children. Therefore, if the introduction of targeted RAADP became possible as a result of advances in non-invasive fetal genotyping, the proportion of childbearing RhD-negative women with a lifetime exposure to anti-D IgG could in theory be reduced from 100% (assuming 100% compliance with blanket RAADP) to 75%. However, in reality the reduction would be slightly less than 25% as some women would require ad hoc prophylaxis for potential sensitising events that occurred before the fetal genotype was known.

Summary of product characteristics

The product characteristics are briefly summarised in *Table 7*. Fuller details are presented in the following sections. It should be noted that the previous study¹ reviewed the clinical effectiveness of any regimen of RAADP and the cost-effectiveness of RAADP using products manufactured by BPL and Baxter Healthcare; these are similar, but not necessarily identical, to D-Gam and Partobulin SDF respectively. The manufacturers have submitted updated data in relation to these products. The cost-effectiveness of Rhophylac and WinRho was not assessed in the previous review.

D-Gam

D-Gam is produced by BPL, a not-for-profit, government-owned plasma fractionation unit.⁹¹ It is available in vials containing 250, 500, 1500 and 2500 IU of human anti-D immunoglobulin in the form of a solution ready for injection.¹¹⁵ The 500-IU dose is licensed for RAADP in non-sensitised RhD-negative women at 28 and 34 weeks' gestation, for routine postpartum prophylaxis following delivery of a RhD-positive baby, and for potentially sensitising events during the second

half of pregnancy. The 250-IU dose is licensed to treat potentially sensitising events up to 20 weeks' gestation, and the 1500- and 2500-IU doses are licensed to provide larger doses to treat a large FMH.⁹¹

D-Gam is produced by fractionation. It is therefore suitable for intramuscular use only. Because of the possible risk of vCJD transmission, since 1999 only US plasma has been used in its manufacture. In July 2001 a solvent-detergent step was incorporated into the fractionation process as a safeguard against the transmission of lipid-enveloped viruses. The BPL's submission emphasises that there have been no previous substantiated reports of virus transmission involving BPL anti-D and that, internationally, there is no evidence of virus transmission with intramuscularly administered immunoglobulins.⁹¹

The price listed in the *British National Formulary*¹¹⁶ (BNF) for 500 IU of non-proprietary anti-D is £27.00 per vial. However, the current NHS price for 500 IU of D-Gam is said to be £19.50 per vial.⁹¹

Partobulin SDF

Partobulin SDF is produced by Baxter BioScience. It is licensed for the prevention of RhD immunisation in RhD-negative women in pregnancy or at delivery of a RhD-positive baby; in abortion/threatened abortion, ectopic pregnancy or hydatidiform mole; or when undergoing TPH resulting from antepartum haemorrhage, amniocentesis, chorionic biopsy, obstetric manipulative procedure or abdominal trauma. It is also licensed for the treatment of RhD-negative people following incompatible transfusions of RhD-positive blood or erythrocyte concentrate.¹¹⁷

TABLE 7 Summary of product characteristics

	D-Gam	Partobulin SDF	Rhophylac	WinRho SDF
Manufacturer	Bio Products Laboratory	Baxter BioScience	CSL Behring	Baxter BioScience
Method of production	Fractionation	Modified fractionation	Chromatographic adsorption	Anion-exchange column chromatography
Administration route	Intramuscular	Intramuscular	Intramuscular or intravenous	Intramuscular or intravenous
Licensed RAADP regimen	2 × 500 IU	2 × 1000–1650 IU	1 × 1500	1 × 1500
List price of RAADP	£54	£70	£46.50	£313.50
Current NHS price of RAADP	£39	£38–42	Not known	Not known

Partobulin SDF is produced from US plasma using a modified Cohn–Oneley fractionation process.¹⁰² To reduce the risk of disease transmission the manufacturing process includes solvent–detergent treatment to ensure the inactivation of lipid-enveloped viruses such as hepatitis B, hepatitis C and HIV, and nanofiltration to minimise the risk from non-enveloped viruses such as hepatitis A and parvovirus B19.¹⁰³ In addition, donors are selected by medical interview and individual donations and plasma pools are screened for hepatitis B surface antigen (HbsAg) and antibodies to HIV and hepatitis C virus and plasma pools are tested for genomic material of hepatitis C virus.¹¹⁷

Because it is produced by fractionation, Partobulin SDF is suitable for intramuscular use only. The recommended dose for routine antenatal prophylaxis is two doses of 1000–1650 IU, given slowly by deep intramuscular injection, at 28 and 34 weeks' gestation. If hypersensitivity reactions occur during administration the injection should be stopped immediately. Patients should be observed for at least 20 minutes after administration.¹¹⁷ True hypersensitivity reactions are said to be rare, but patients may suffer allergic-type responses such as hives, generalised urticaria, tightness of the chest, wheezing, hypotension and other allergic or anaphylactic reactions. Patients may also experience local pain or tenderness at the injection site.¹¹⁷ In addition, as Partobulin SDF contains a small quantity of IgA it may cause hypersensitivity reactions in IgA-deficient individuals.¹¹⁷

Partobulin SDF is supplied in prefilled syringes containing 1250 IU of anti-D at a list price of £35;¹¹⁶ however, the contract prices are said to be between £19 and £21 per syringe, depending on the volumes contracted for.¹⁰³

Rhophylac

Rhophylac is produced by CSL Behring Ltd. It is licensed for the prevention of RhD immunisation in RhD-negative women in pregnancy or at delivery of a RhD-positive baby; in abortion/threatened abortion, ectopic pregnancy or hydatidiform mole; or when undergoing transplacental haemorrhage resulting from antepartum haemorrhage, amniocentesis, chorionic biopsy, obstetric manipulative procedure or abdominal trauma. It is also licensed for the treatment of RhD-negative people following incompatible transfusions of RhD-positive blood or other products containing red blood cells.¹¹¹

Rhophylac is manufactured from pooled human plasma obtained from hyperimmunised donors,

using a combination of different chromatographic adsorption stages. The risk of transmitting viral infections is minimised by careful donor selection, screening of individual donations and plasma pools for specific markers of infection, and virus inactivation or elimination by the chromatographic purification process and by solvent–detergent treatment and nanofiltration.⁹² The measures taken are considered effective for HIV and hepatitis B and C viruses but may be of limited value against non-enveloped viruses such as hepatitis A and parvovirus B19.¹¹¹ Although nanofiltration has been shown to contribute to the removal of abnormal prion protein⁹² the test prion was scrapie and not vCJD. Thus, the possibility of transmitting infective agents, including unknown or emerging viruses and other pathogens, cannot be totally excluded.¹¹¹

The safety and tolerability of Rhophylac has been evaluated in six clinical studies. In these studies 931 doses of Rhophylac were administered to 628 individuals, 447 (71%) of whom were pregnant women. Drug-related adverse events were rare and mild; they included pain or itching at the injection site and headaches. No anaphylactic or severe allergic reactions were reported. As noted earlier, 2.07 million doses of Rhophylac have been distributed worldwide between its first launch in Switzerland in 1996 and the end of 2006, and only 30 adverse drug reactions relevant to its safety have been reported, one per 69,000 doses.⁹² Although no details are provided, these adverse drug reactions, together with the evidence from clinical studies, presumably underlie the product leaflet statement that patients may suffer fever, malaise, headache, cutaneous reactions and chills, and that there have been rare reports of nausea, vomiting, hypotension, tachycardia and allergic or anaphylactic reactions.¹¹¹ As Rhophylac may contain traces of IgA it may cause hypersensitivity reactions in IgA-deficient individuals.¹¹¹

The dose of Rhophylac recommended for routine antenatal prophylaxis is one dose of 1500 IU given by intravenous or intramuscular injection at, according to the manufacturer, 28–30 weeks' gestation. If symptoms of allergic or anaphylactic-type reactions occur during administration the injection should be stopped immediately. Patients should be observed for at least 20 minutes after administration.¹¹¹

Rhophylac is supplied in prefilled syringes containing 1500 IU of anti-D immunoglobulin for intravenous or intramuscular injection¹¹¹ at a list price of £46.50 per syringe.¹¹⁶

WinRho SDF

WinRho SDF is produced by Baxter BioScience. Although it is licensed for routine antenatal prophylaxis, in the UK it is marketed and used solely for the treatment of immune thrombocytopenic purpura. The manufacturer therefore notes that it is priced specifically for this market and should not be routinely used for RAADP, although it could be so used if there were supply problems.¹⁰³

WinRho SDF is prepared from pooled human plasma using an anion-exchange column chromatography method. The risk of transmission of viruses, including HIV and hepatitis B and C viruses, is reduced by the use of filtration to remove lipid-enveloped and non-enveloped viruses, and solvent-detergent treatment to inactivate lipid-enveloped viruses. However, the possibility of disease transmission, including the transmission of unknown infectious agents, cannot be wholly excluded.¹¹⁸

In a small number of cases, administration of WinRho SDF has been accompanied by discomfort and swelling at the site of injection and a slight elevation in temperature. As with all plasma derivatives there is a very small chance of an idiosyncratic or anaphylactic reaction to WinRho SDF in individuals who are hypersensitive to blood products.¹¹⁹

When used for routine antenatal prophylaxis the recommended dose of WinRho SDF is one dose of 1500 IU given intramuscularly or intravenously at 28 weeks' gestation. In the UK, WinRho is supplied as a powder for reconstitution; the list price of a 1500-IU vial with diluent is £313.50.¹¹⁶

Identification of important subgroups

As noted earlier, important subgroups in relation to RAADP include women who will be sterilised after the birth, women who are certain that they will have no more children and women who are in a stable relationship with the genetic father of their children, with the father known or found to be RhD negative – current guidance⁸⁷ notes that RAADP is not necessary under these circumstances. Although it is desirable to avoid unnecessary blood product administration it should be noted that all three groups are problematic. Some women who are sterilised after childbirth later become pregnant through in vitro fertilisation. Some women who are certain that they will have no more children do nonetheless go on to have more. In relation to the

third group, the British Committee for Standards in Haematology (BCSH) guideline for blood grouping and antibody testing in pregnancy⁷⁹ draws attention to the complexities of paternal testing and the potential for misidentification of the father; the Canadian guidelines caution that a partner's RhD status should not be tested unless the pregnant woman both volunteers and confirms in private that he is the biological father.¹²⁰

Current usage in the NHS

Implementation of the policy of RAADP appears to be fairly widespread. As noted in the previous section on current service provision, in 2005 a survey of 328 UK maternity units found that 75% were offering RAADP.⁸⁹ In total, 173/233 (75%) UK hospital transfusion laboratories responded to a recent postal survey carried out on behalf of the Royal College of Pathologists; of these, 155/173 (90%) had fully implemented RAADP.⁸⁹

Although the precise RAADP regimen used by the different centres varies, the single-dose regimen appears to be gaining popularity. In 2005, 81% of the UK maternity units that offered RAADP used the two-dose regimen.⁸⁹ BPL claims that 55% of hospitals that have implemented RAADP currently use D-Gam 500 at 28 and 34 weeks' gestation.⁹¹ However, the more recent survey of hospital transfusion laboratories found that 53/173 (31%) were using the single 1500-IU dose at 28 weeks.⁸⁹ Although the survey did not collect data on compliance, a recent audit in two UK hospitals found 86.5% compliance with the two-dose regimen.¹²¹

MacKenzie *et al.*¹²² found that the proportion of women refusing at least one antenatal prophylaxis injection increased from 0.8% in the period 1992–6 to 3.5% by 1997–2003. They attribute this to concerns about the possible transmission of infection by blood products and suggest that these concerns may have been exacerbated when the preparation originally used for RhD prophylaxis was withdrawn because of concerns relating to vCJD transmission.¹²² A retrospective audit carried out in two UK hospitals in 2004¹²¹ found much higher refusal rates: 10.6% of eligible women (22/207) refused the first 28-week dose of a two-dose RAADP regimen and 13.5% (28/207) refused the second dose; none of the women who declined the first dose at 28 weeks' gestation received the second dose at 34 weeks. However, very few women were documented as declining RAADP because of concerns about infection transmission (*Table 8*). Moreover, the first two reasons given in

TABLE 8 Reasons for declining routine antenatal anti-D prophylaxis¹²¹

Reason for declining	Number of women declining		
	First dose	Second dose	Overall
Partner RhD negative	6	8	8
Last planned pregnancy	3	5	5
Fear of infection	1	1	1
No reason documented	12	14	14
Total	22	28	28

Table 8 relate to circumstances in which RAADP is not indicated. Although higher compliance may perhaps be achieved with a single-dose than with a two-dose regimen it should be noted that the majority of women who declined the two-dose regimen declined at the first dose and it therefore seems unlikely that they would have consented to a single-dose regimen.

Anticipated costs associated with intervention

The anticipated costs associated with RAADP are the cost of anti-D itself plus the cost of

administration. The list prices of the different types of anti-D are:

- D-Gam: £27.00 per vial = £54.00
- Partobulin SDF: £35.00 per vial = £70.00
- Rhophylac: £46.50 per vial = £46.50
- WinRho SDF: £313.50 per vial = £313.50.

RAADP administration costs are minimal if anti-D can be provided during routine antenatal appointments. Resource implications for the management of adverse events associated with anti-D are extremely small.

Chapter 2

Definition of the decision problem

This review seeks to identify any evidence for advances in practice in RAADP since the 2002 appraisal conducted by NICE.⁸⁷ It assesses the current clinical effectiveness and cost-effectiveness of RAADP for RhD-negative women.

Decision problem

The decision problem has been specified as follows.

Intervention

RAADP given by injection in any of the licensed regimens, in line with current NICE guidance, which recommends that RAADP be offered to all non-sensitised pregnant women who are RhD negative regardless of whether they have already been offered prophylactic anti-D following a sensitising event earlier in the pregnancy:

- two doses of at least 500IU at 28 and 34 weeks' gestation (D-Gam)
- two doses of 1000–1650 IU at 28 and 34 weeks' gestation (Partobulin)
- one dose of 1500 IU at 28 weeks' gestation (Rhophylac)
- one dose of 1500 IU at 28 weeks' gestation (WinRho).

Population (including subgroups)

The population includes all non-sensitised primigravidae and multigravidae pregnant women who are RhD negative. Ethnic minorities within England and Wales are considered within a subgroup analysis.

It should be noted that, because of the feasibility and ethical considerations of determining the genotype of the father, and the lack of certainty associated with whether a woman will have more children, an evaluation of these subgroups has not been carried out as stated in the assessment protocol. For example, the Royal College of Nursing¹²³ states that the current guidance 'presents some practical difficulties for midwives' in that 'in addition to the sensitivities of discussing paternity, there are difficulties associated with an

institution assuming that the father is indeed RhD-negative as reported without having this confirmed by internal testing. Routine testing of the partners of RhD-negative women would have logistical, administrative and financial implications.'

Relevant comparators

RAADP delivered using different dosing regimens and different methods and no RAADP.

Outcomes

- Reduction in the incidence of sensitisation (alloimmunisation) in RhD-negative women delivered of RhD-positive infants (the at-risk population).
- Reduction in incidence of HDN.
- Survival of the child.
- Disability of the child.
- Health-related quality of life.
- Adverse effects of treatment.

Study types

- Systematic reviews.
- Randomised controlled trials (RCTs).
- Non-randomised controlled studies.

Overall aims and objectives of assessment

The review has the following aims:

- to evaluate the clinical effectiveness of anti-D for RhD-negative pregnant women, in any licensed regimen, in terms of a reduction in the incidence of sensitisation (alloimmunisation) in RhD-negative women delivered of RhD-positive infants, a reduction in the incidence of HDN, survival of the child, disability of the child, and health-related quality of life of the child and parents (if relevant evidence is available)
- to evaluate the adverse effect profile
- to estimate the incremental cost-effectiveness of different dosing regimens and different

methods of administration of anti-D
prophylaxis

- to identify key areas for primary research
- to estimate the possible overall cost in England and Wales.

Chapter 3

Assessment of clinical effectiveness

Methods for reviewing effectiveness

Identification of studies

The aim of the search strategy was to provide as comprehensive a retrieval as possible of trials relating to antenatal anti-D prophylaxis (AADP) for RhD-negative women.

Sources searched

Keyword and thesauri searches were undertaken in MEDLINE, CINAHL, EMBASE, BIOSIS, Science Citation Index, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, NHS Health Technology Assessment database and NHS Economic Evaluations Database from inception to July 2007. Websites containing registers of trials and ongoing research were also searched. These included the National Research Register and the MetaRegister of the Current Controlled Trials websites. In addition, the bibliographies of retrieved papers (including the previous review¹) were scrutinised. No specific searches were carried out to identify conference abstracts, other than those identified by the searches detailed above.

Keyword strategies

Sensitive keyword strategies using free text and, when available, thesaurus terms were developed to search the electronic databases. Synonyms relating to the intervention (e.g. Rh-Hr Blood-Group System, Rho(D) Immune Globulin, Rh Isoimmunisation and anti-D prophylaxis) were combined with synonyms relating to the patient population (e.g. pregnancy, pregnancy complications, pregnancy trimesters, prenatal care, postnatal care).

Search restrictions

A methodological filter aimed at identifying controlled clinical trials (including before and after studies) was used in the searches of MEDLINE, EMBASE and CINAHL. Further filters were used to identify papers relating to cost/s and systematic reviews. Language restrictions were not used on any database, and no date restrictions were applied. All searches were undertaken between May and August 2007.

A copy of the general search strategy can be found in Appendix 1.

Specific systematic searches for adverse event data were not undertaken, and the clinical review therefore includes only adverse event data reported by the included studies.

Inclusion and exclusion criteria

Inclusion criteria were as follows:

- Population: pregnant women who are RhD negative.
- Intervention: RAADP using either two doses of at least 500 IU at 28 and 34 weeks' gestation or a single dose of at least 1500 IU at 28 weeks' gestation, in either case followed by a further dose of anti-D given at, or within 72 hours of, delivery if the infant is RhD positive.
- Comparator: RAADP using different dosing regimens and/or methods of administration and no RAADP.
- Outcomes: sensitisation (alloimmunisation) rates among RhD-negative women delivered of RhD-positive infants (the at-risk population); incidence of HDN; survival of the child; disability of the child; health-related quality of life; adverse effects of treatment.
- Study design: any of systematic reviews, randomised controlled trials, non-randomised controlled trials.

The exclusion criterion was studies considered methodologically unsound or not reporting results in the necessary detail.

Study selection was undertaken by one researcher. Any studies that gave rise to uncertainty were reviewed by a second researcher and any disagreements resolved by discussion. Publication bias was not investigated.

Data abstraction strategy

Data were abstracted by one researcher using a standardised data extraction form. Any studies that gave rise to uncertainty were reviewed by a second researcher and any disagreements resolved by

discussion. Missing data were sought from authors when possible.

Critical appraisal strategy

Published papers were assessed according to the accepted hierarchy of evidence, whereby meta-analyses of RCTs are taken to be the most authoritative forms of evidence, with uncontrolled observational studies the least authoritative. Because of the paucity of RCTs in this area, data from non-randomised studies were also used. The quality of randomised studies was assessed using quality criteria based on those proposed by the NHS Centre for Reviews and Dissemination (CRD)¹²⁴ (see Appendix 2). However, the CRD quality criteria for observational studies were of very limited relevance to the specific non-randomised studies included in this review, and their quality was therefore judged primarily on the basis of two key factors: the comparability of the intervention and control groups, and the use of intention to treat analysis.

Methods of data synthesis

The prespecified outcomes outlined in the section on inclusion and exclusion criteria have been tabulated and discussed within a descriptive synthesis. Where appropriate, meta-analysis has been used to synthesise data. The meta-analyses were conducted using binary logistic regression with a fixed-effects model, using Minitab statistical software. The study and treatment groups were used as the variables for the model. The outcome of the regression analysis was an odds ratio for the treatment arm versus the control arm. Because of the low event probability the odds ratio was assumed to be a good approximation to the relative risk of sensitisation in the cohort who received RAADP, compared with the relative risk of sensitisation in patients who received conventional management. The Minitab software was also used to calculate a *p*-value for statistical heterogeneity. No subgroup analyses were undertaken.

Results

Quantity and quality of research available

Quantity of research available

The original systematic review carried out on behalf of NICE¹ was not limited to specific licensed anti-D dosage regimens. It identified 11 studies comparing an intervention group receiving RAADP with a control group (see Table 9 for

details). However, only eight of these studies met the inclusion criteria for the current review by stating that they used one of the currently licensed regimens. These were:

- the studies by Huchet *et al.*,¹²⁵ MacKenzie *et al.*,¹²⁶ Mayne *et al.*¹²⁷ and Tovey *et al.*,¹²⁸ which used two doses of 500 IU at 28 and 34 weeks' gestation
- the study by Bowman *et al.*,¹²⁹ which used two doses of 1500 IU at 28 and 34 weeks' gestation
- the 1978¹³⁰ and 1987¹³¹ studies by Bowman and Pollock and the study by Trolle,¹³² which used a single dose of 1500 IU at 28 weeks' gestation.

An article by Thornton *et al.*¹³³ was also included as it presented follow-up data relating to the study by Tovey *et al.*,¹²⁸ studying the safety and efficacy of antenatal prophylaxis by examining obstetric data relating to women in that trial in their first and subsequent pregnancies. There was agreement between the first and second reviewers in relation to study selection and validity.

The updated searches identified four additional papers that related to relevant studies of clinical effectiveness (see Table 10 for summary). Only one of these related to a study that was not included in our previous review. This was the relatively recent RCT by MacKenzie *et al.*¹⁰⁰ comparing intravenous with intramuscular Rhophylac. A conference abstract by MacKenzie *et al.*¹³⁷ related to the 1999 community intervention study by MacKenzie *et al.*;¹²⁶ it did not present any additional data. A further two papers by Bowman^{14,101} related to a clinical trial of WinRho whose results were combined with those of the subsequent service programme of RAADP with WinRho in Bowman and Pollock's 1987 analysis of failures of intravenous anti-D.¹³¹ As the clinical trial effectively takes the form of a case series compared with the control group reported in the 1978 study of Bowman *et al.*¹²⁹ there seems no reason to differentiate between the trial and the service programme components of the 1987 study, and therefore the results reported by Bowman *et al.* in 1980¹⁴ and by Bowman in 1982¹⁰¹ have been considered as interim results in relation to the 1987 study.

It was not possible to read an additional, potentially relevant study by Eklund and Nevanlinna,¹³⁸ as it was published in Finnish and had no English abstract. However, as it was published in 1971 it seems highly likely that it dealt with postpartum rather than antenatal prophylaxis. Similarly, it was not possible to obtain a potentially relevant paper

TABLE 9 Characteristics of studies included in the previous review¹

Study	Study type	Date and location of intervention	Date and location of control	Patient selection ^a	Specific product (production method) and route of administration	Dosage and administration schedule
^b Bowman <i>et al.</i> 1978 ¹²⁹	Prospective study, historical/geographical controls	December 1968–August 1976, Winnipeg, Canada	March 1967–December 1974, Manitoba, Canada	Primigravidae	Rh ₀ (D) immune globulin (Cohn method), Connaught Laboratories, Toronto; i.m. ¹³¹	2 × 1500 IU, 28 and 34 weeks
^b Bowman and Pollock 1978 ¹³⁰	Prospective study, historical controls	March 1976–June 1977, Manitoba, Canada	March 1967–December 1974, Manitoba, Canada	Primigravidae and unsensitised multigravidae	Rh ₀ (D) immune globulin (Cohn method), Connaught Laboratories, Toronto; i.m.	1500 IU, 28 weeks
^b Bowman and Pollock 1987 ¹³¹	Retrospective study, historical controls	June 1977–February 1986, Manitoba, Canada	March 1967–December 1974, Manitoba, Canada	Primigravidae and unsensitised multigravidae	Rh(G-IV (WinRh)) (ion exchange), Winnipeg Rh Institute; usually i.m. but could be i.v.	1500 IU, 28 weeks
Hermann <i>et al.</i> 1984 ¹³⁴	Prospective study, historical controls	Not stated, Växjö, Sweden	1968–77, Växjö, Sweden	Primigravidae and unsensitised multigravidae	Rhesonativ, KabiVitrum AB, Sweden; i.m.	1250 IU, 32–34 weeks
^b Huchet <i>et al.</i> 1987 ¹²⁵	Quasi-RCT	January 1983–June 1984, Paris	January 1983–June 1984, Paris	Primigravidae	Product not specified; i.m.	2 × 500 IU, 28 and 34 weeks
Lee and Rawlinson 1995 ¹³⁵	RCT	Not stated, UK	Not stated, UK	Primigravidae	Not specified	2 × 250 IU, 28 and 34 weeks
^b Mackenzie <i>et al.</i> 1999 ¹²⁶	Community intervention trial (controlled before-and-after study)	1990–6, Oxfordshire	1990–6, Northants	Primiparae	Not specified	2 × 500 IU, 28 and 34 weeks
^b Mayne <i>et al.</i> 1997 ¹²⁷	Retrospective before-and-after study	1993–5, southern Derbyshire	1988–90, southern Derbyshire	Primiparae	Not specified	2 × 500 IU, 28 and 34 weeks
Parsons <i>et al.</i> 1998 ¹³⁶	Retrospective survey, geographical controls	1988–95, Nova Scotia	1988–95, Scotland	Not stated	Not specified	One dose, 28 weeks
^b Tovey <i>et al.</i> 1983 ¹²⁸	Prospective study, historical controls	1980–1, Yorkshire	1978–9, Yorkshire	Primigravidae	Not specified	2 × 500 IU, 28 and 34 weeks
^b Trolle 1989 ¹³²	Prospective study, historical controls	1980–5, Kolding, Denmark	1972–7, Kolding, Denmark	Primigravidae and unsensitised multigravidae	Not specified	1500 IU, 28 weeks

i.m., intramuscularly; i.v., intravenously; RCT, randomised controlled trial.

a In describing participants as primigravidae or primiparae, the wording used by the original authors has been followed. Because women may not always reveal details of previous pregnancies, information on parity is likely to be the more reliable.

b Studies that meet the inclusion criteria for the current review.

TABLE 10 Additional papers relating to relevant studies of clinical effectiveness identified by the update searches

Paper	Status
MacKenzie <i>et al.</i> 2004 ¹⁰⁰	Included as a new independent study
MacKenzie <i>et al.</i> 1998 ¹³⁷	Included as relating to a previously included study (MacKenzie <i>et al.</i> 1999 ¹²⁵)
Bowman <i>et al.</i> 1980 ¹⁴	Included as relating to a previously included study (Bowman and Pollock 1987 ¹³¹)
Bowman 1982 ¹⁰¹	Included as relating to a previously included study (Bowman and Pollock 1987 ¹³¹)

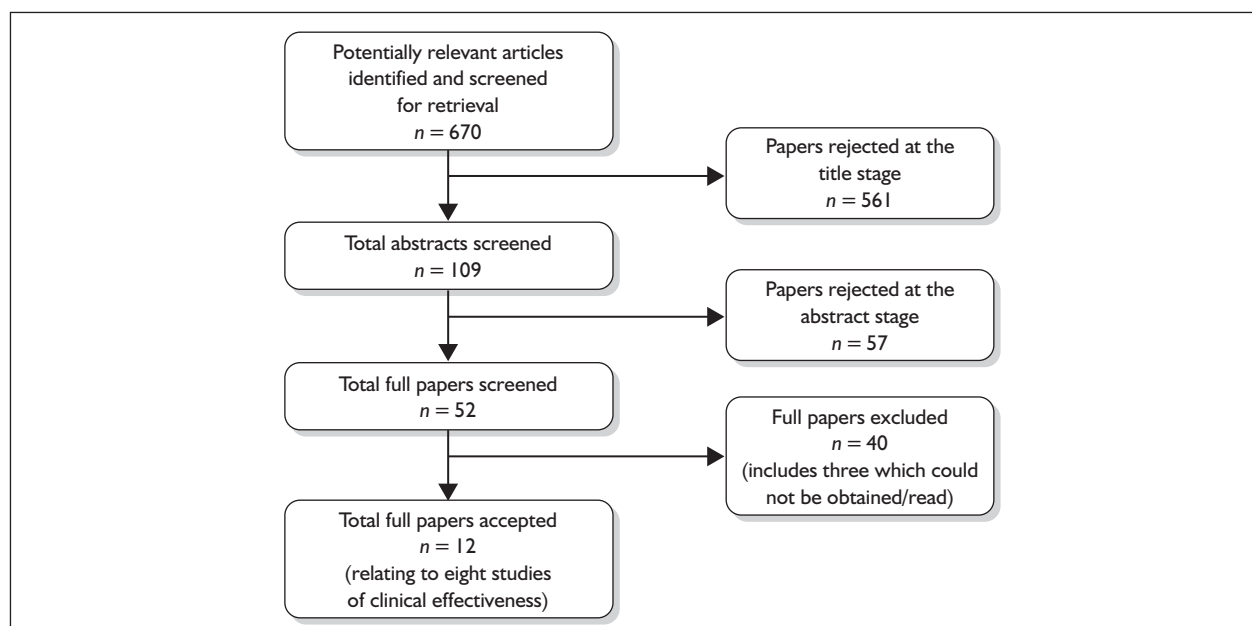
by Potron *et al.*,¹³⁹ but because this was published in 1973 it seems likely that it too would have dealt with postpartum rather than antenatal prophylaxis. Finally, we were unable to find any further information regarding a proposed multicentre trial of monoclonal anti-D,¹⁴⁰ and understand that the principal investigator is now deceased.

A population study by Koelewijn¹⁴¹ of the effect of the introduction of RAADP in the Netherlands did not meet our inclusion criteria as it used a single dose of only 1000 IU of anti-D at 30 weeks' gestation.

Thus, the electronic literature searches identified 670 potentially relevant references, 12 of which referred to eight relevant studies of clinical effectiveness. Only one reference related to a study that had not been included in our earlier review (*Figure 1*). For details of excluded studies, including those included in the previous review, see Appendix 3.

The updated searches did not identify the 1978 study of Bowman and Pollock,¹³⁰ which was identified by the searches for our earlier review;¹ this brought the total number of included studies to nine. A summary of the 1977 McMaster Conference on the prevention of RhD immunisation¹⁴² was identified from a citation. This included brief summaries of the results of three unpublished studies of RAADP. Two of these studies, the Australian and Hamilton studies, did not meet our inclusion criteria because, although both were said to use a two-dose regimen, the actual dose was not specified. These studies do not appear to have been published elsewhere and attempts to obtain fuller reports from the investigators have been unsuccessful. The third, Swedish study was excluded because it used a single unspecified dose at 34 weeks' gestation; it appears to represent an interim analysis of the study published in 1984 by Hermann *et al.*,¹³⁴ included in our previous review,¹ which used a dose of 1250 IU. A study of alloimmunisation following RAADP in north-east Scotland¹⁴³ was subsequently drawn to

FIGURE 1 Assessment of clinical effectiveness: summary of study selection and exclusion.



our attention; this could not be included because it identified sensitised women as a proportion of all RhD-negative women who had received RAADP and was therefore not comparable with the included studies, which identified them as a proportion of only those RhD-negative women who had subsequently been delivered of RhD-positive infants.

An additional study, described by Baxter Healthcare as pivotal, appeared to have been completed by 1993 but was still unpublished in 2005.¹¹⁹ This used intravenous anti-D (WinRho SD) according to three regimens, only one of which (2×1200 IU) is currently licensed:

- 1×600 IU (at 28 weeks)
- 1×1200 IU (at 28 weeks)
- 2×1200 IU (at 28 and 34 weeks).

There appears to have been no untreated control group, although reference is made to the expected level of sensitisation. Follow-up was very poor: of 806 RhD-negative women delivered of an RhD-positive infant, only 325 (40%) were tested 6 months after delivery for evidence of sensitisation. For these reasons this study was not felt to meet our inclusion criteria.

In summary, we identified only one relevant study that was not included in our earlier review. This was the RCT by MacKenzie *et al.*¹⁰⁰

Quality of included research

Overall, the quality of included research was not high. We identified only one true RCT, that by MacKenzie *et al.*¹⁰⁰ This used a computer-generated randomisation schedule but did not state how treatment allocation was concealed. The randomised comparison was between the same dose of Rhophylac (1×1500 IU) given intravenously and intramuscularly. However, the study was not powered to demonstrate a difference in efficacy between these two administration routes as the sample size had been calculated to test the null hypothesis that Rhophylac was inferior to currently marketed anti-D products in terms of the number of sensitisations. In other words, the sample size had been calculated not to compare one of the two randomised groups with the other but to compare the pooled results of the two randomised groups with the pooled results of the earlier studies, whose populations differed from the study population chronologically and in most cases also geographically.

A quasi-RCT by Huchet *et al.*¹²⁵ used year of birth to allocate participants to treatment groups (those born in odd years forming the intervention group and those in even years the control group); it compared two 500-IU doses of anti-D with no treatment.

Because of the shortage of RCTs comparing a currently licensed dose of anti-D with no treatment, all relevant non-randomised studies were retained for further consideration. They are:

- a community intervention trial (controlled before-and-after study) by MacKenzie *et al.*¹²⁶
- a retrospective before-and-after study by Mayne *et al.*¹²⁷
- five non-randomised studies with historical or geographical controls.^{128–132}

Many of these studies were poorly designed. The greatest concerns relate to the comparability of the intervention and control groups: although the larger non-randomised studies are probably large enough to ensure comparability in terms of potential confounding factors such as ABO blood group distribution and maternal age, the use in a number of studies of non-contemporary or geographically distant controls raises the issue of possible differences in clinical care other than the use of RAADP (see further below). The use of intention to treat analysis is also important in assessing the impact of a programme of RAADP. The lack of blinding is less problematic given the objective nature of the main outcome measure (the presence/absence of anti-D). *Table 11* contains a summary of study quality based on the comparability of the control groups and the use of intention to treat analysis; more detailed comments on study quality are presented in Appendix 4.

The studies vary in terms of their patient selection criteria and dosage regimens. Five studies^{125–129} recruited their intervention group from primigravidae. Four of these studies^{126–129} recorded data relating to these women in subsequent pregnancies. Bowman *et al.*,¹²⁹ MacKenzie *et al.*¹²⁶ and Mayne *et al.*¹²⁷ did this to assess the prevalence of sensitisation arising from the first pregnancy; only the study by Tovey *et al.*^{128,133} also provided data relating to the incidence of sensitisation resulting from subsequent RhD-positive pregnancies in which RAADP was not provided.

The studies by Bowman and Pollock,^{130,131} MacKenzie *et al.*¹⁰⁰ and Trolle¹³² recruited both

TABLE 11 Characteristics of included studies

Study	Study type	Study quality	ITT analysis	Date and location of intervention	Date and location of control
Bowman <i>et al.</i> 1978 ¹²⁹	Prospective study, historical/geographical controls	Poor	No	December 1968–August 1976, Winnipeg, Canada	March 1967–December 1974, Manitoba, Canada
Bowman and Pollock 1978 ¹³⁰	Prospective study, historical controls	Fair	No	March 1976–June 1977, Manitoba, Canada	March 1967–December 1974, Manitoba, Canada
Bowman and Pollock 1987 ¹³¹	Retrospective study, historical controls	Poor	No	June 1977–February 1986, Manitoba, Canada	March 1967–December 1974, Manitoba, Canada
Huchet <i>et al.</i> 1987 ¹²⁵	Quasi-RCT	Good	Yes	January 1983–June 1984, Paris	January 1983–June 1984, Paris
MacKenzie <i>et al.</i> 1999 ¹²⁶	Community intervention trial (controlled before-and-after study)	Good	Yes	1990–6, Oxfordshire	1990–6, Northants
MacKenzie <i>et al.</i> 2004 ¹⁰⁰	Open-label RCT; results presented as uncontrolled study	Poor	No	Date not specified, UK and US	i.m. controls contemporary with i.v. intervention; no untreated controls, UK and US
Mayne <i>et al.</i> 1997 ¹²⁷	Retrospective before-and-after study	Fair	Yes	1993–5, southern Derbyshire	1988–90, southern Derbyshire
Tovey <i>et al.</i> 1983 ¹²⁸	Prospective study, historical controls	Fair	Yes	1980–1, Yorkshire	1978–9, Yorkshire
Trolle 1989 ¹³²	Prospective study, historical controls	Poor	No	1980–5, Kolding, Denmark	1972–7, Kolding, Denmark

i.m., intramuscularly; ITT, intention to treat; i.v., intravenously; RCT, randomised controlled trial.

a In describing participants as primigravidae or primiparae the wording used by the original authors has been followed. Because women may not always reveal details of previous pregnancies, information on parity is likely to be the more reliable.

primigravidae and unsensitised multigravidae. In MacKenzie *et al.*¹⁰⁰ almost three-quarters (71.5%) of the participants had been pregnant before and, of these, 81.9% had received anti-D in a previous pregnancy; as noted in the later section on critical review and synthesis of information, this may offer some degree of protection in subsequent pregnancies and may therefore have affected the study results.

As noted above, the 2004 study by MacKenzie *et al.*¹⁰⁰ compared RAADP using the same anti-D preparation (Rhopylac) administered intravenously and intramuscularly. The remaining studies compared RAADP with no RAADP; none used placebo. Four studies^{125–128} used 500 IU at 28 and 34 weeks' gestation, one¹²⁹ used 1500 IU at 28 and 24 weeks, and four^{100,130–132} used a single dose of 1500 IU at 28 weeks.

Patient selection ^a	Number of RhD– women in intervention group delivered of RhD+ infant	Specific product (production method) and route of administration	Dosage and administration schedule	Source of funding
Primigravidae	1357	Rh ₀ (D) immune globulin (Cohn method), Connaught Laboratories, Toronto; i.m. ¹³¹	2×1500IU, 28 and 34 weeks	National Health and Medical Research Council of Canada
Primigravidae and unsensitised multigravidae	1804	Rh ₀ (D) immune globulin (Cohn method), Connaught Laboratories, Toronto; i.m.	1500IU, 28 weeks	Not stated
Primigravidae and unsensitised multigravidae	9303	RhIG-IV (WinRho) (ion exchange), Winnipeg Rh Institute; usually i.m. but could be i.v.	1500IU, 28 weeks	Not stated
Primiparae (not all of whom were primigravidae)	599	Product not specified; i.m.	2×500 IU, 28 and 34 weeks	Not stated
Primiparae	3320	Product and route of administration not specified	2×500 IU, 28 and 34 weeks	Bio Products Laboratories
Unselected (primigravidae 28.5%)	270 (figure includes those receiving i.v. and i.m. Rhophylac)	Rhophylac i.v. vs i.m.	1×1500IU, 28 weeks	Chiltern International
Primiparae	1425	Product and route of administration not specified	2×500IU, 28 and 34 weeks	Bio Products Laboratories
Primigravidae	1238	Product and route of administration not specified	2×500IU, 28 and 34 weeks	Not stated
Primigravidae and unsensitised multigravidae	346	Product and route of administration not specified	1500IU, 28 weeks	Not stated

It was originally stated that studies would be included in the review only if they used the specific licensed interventions, as follows:

- D-Gam 500 IU or Partobulin SDF 1000–1650 IU given intramuscularly at weeks 28 and 34 of pregnancy
- Rhophylac 1500 IU given as a single dose intramuscularly or intravenously at week 28 of pregnancy

- WinRho SDF 1500 IU given as a single dose intramuscularly or intravenously at week 28 of pregnancy.

However, only two studies met this criterion: the 1987 study by Bowman and Pollock,¹³¹ which used WinRho, and the 2004 study by MacKenzie *et al.*,¹⁰⁰ which used Rhophylac. In their 1978 studies, Bowman *et al.*¹²⁹ and Bowman and Pollock¹³⁰ used anti-D prepared by the Connaught laboratories

using the Cohn method. The remaining studies did not specify what product was used, and some did not even state the route of administration (see *Table 11*). Consequently, the review has not been limited to studies which stated that they used one of the specific varieties of anti-D listed above.

All of the included studies with the exception of that by Bowman and Pollock in 1978¹³⁰ stated that women in both the intervention and control groups who were delivered of RhD-positive infants received postpartum anti-D. It seems highly likely that this was also the case in that study.

Only three of the included studies had contemporary controls: the RCT by MacKenzie *et al.*,¹⁰⁰ the quasi-RCT by Huchet *et al.*¹²⁵ and the community intervention trial by MacKenzie *et al.*¹²⁶ The 1978 study by Bowman *et al.*¹²⁹ purported to be a community intervention trial with contemporary controls. However, it in fact combined the results for a contemporary control group with the results for a geographically contiguous group of women during an overlapping but not identical time period (JM Bowman, 2001, personal communication). As preintervention data were not provided for the two groups it is not clear to what extent they were actually comparable. Because the intervention group was a city population and the control group was derived in the main from a largely rural population, they may have differed in relation to key variables such as rates of Caesarean section and other invasive procedures. They certainly differed in that the intervention group included only women who for all of their pregnancies were treated in accordance with the trial protocol, whereas the reported control group included women who had had previous pregnancies. Although these pregnancies appeared not to have resulted in alloimmunisation, they may in some cases have resulted in silent sensitisation, thus potentially elevating the alloimmunisation rate in the control group and exaggerating the effectiveness of RAADP.

It has been suggested that, because the antiglobulin tests formerly used to identify maternal anti-D are less sensitive than more recent assays, studies using controls that antedate the intervention group by several years are likely to underestimate the true incidence of alloimmunisation in the control group and therefore the degree of protection provided by AADP.¹⁵ However, the community intervention trial by MacKenzie *et al.*¹²⁶ used a retrospective analysis of prospectively collected data to demonstrate the baseline comparability of the two communities compared in the prospective study in terms of

rates of alloimmunisation. It also demonstrated that the rate of sensitisation in the control group fell substantially over time, although the reduction was not as great as in the intervention group. This change over time in the control group is presumably due to changes in obstetric practice, possibly including a more comprehensive use of anti-D following potential sensitising events; it suggests that studies which use historical controls may overestimate, rather than underestimate, the degree of protection provided by RAADP when compared with current good practice.

Although most TPHs large enough to cause sensitisation occur in the last trimester, some women become sensitised before the 28th week. However, Trolle¹³² excluded women who were sensitised between the first antibody screen test in the first trimester and the 28th week from the intervention group but apparently not from the control group. Moreover, in this study, 38.8% of women in the control group had received more than 1 µl of fetal blood, compared with only 7.9% in the intervention group ($p < 0.001$). The study results are therefore likely to be biased in favour of the intervention.

The studies also vary in terms of the time at which they collected data on sensitisation. The true rate of sensitisation is greater than that identified by the presence of anti-D at, or 6 months following, delivery (see Chapter 1, Aetiology, pathology and prognosis). However, only two of the included studies – the 1999 study by MacKenzie *et al.*¹²⁶ and the study by Mayne *et al.*¹²⁷ – provided data on the number of women found to be sensitised during a subsequent pregnancy. Moreover, these data also underestimate the true rate of sensitisation because, although they include women in whom silent sensitisation did not become identifiable until a subsequent pregnancy, they exclude those women who did not undergo a subsequent pregnancy.

Assessment of effectiveness

Critical review and synthesis of information

As noted earlier (see Quality of included research), the studies reviewed here vary in terms of the administration schedule and doses of anti-D, and the primary outcome measures used, as well as in their choice of study design and use of intention to treat analysis. The clinically important outcome measure in relation to RAADP is the number of RhD-negative women delivered of a RhD-positive baby who are found to be sensitised during a subsequent RhD-positive pregnancy, although this

will underestimate the total number of sensitised women as it will not take into account those who do not go on to become pregnant again. Only two studies, those by MacKenzie *et al.*¹²⁶ and Mayne *et al.*,¹²⁷ took this as their primary end point; both were community-based studies and therefore their results included women who in fact did not receive RAADP in their first pregnancy. However, two studies that did not take it as their primary end point, the studies by Bowman *et al.*¹²⁹ and Tovey *et al.*,¹²⁸ also included information on the number of RhD-negative women delivered of RhD-positive infants in either the intervention or the control group who were found to be sensitised during a subsequent RhD-positive pregnancy (Table 12).

As noted in the previous section on quantity and quality of research available, MacKenzie *et al.*¹²⁶ found a fall over time in the number of women in the control group who were found to be sensitised during a subsequent RhD-positive pregnancy. This change, which was not statistically significant, may have been due to the growth of good practice in the delivery of anti-D, both postpartum and antenatally, in response to potential sensitising events, and this may also have affected the intervention group; it was stated that it was not due to the use of antenatal prophylaxis in some women in the control group. Thus, Mayne *et al.*¹²⁷ noted that the introduction of a programme of RAADP was associated with an increase in requests for anti-D following vaginal bleeding or antepartum haemorrhage: they conjectured that this was due to heightened awareness of anti-D among midwives and community doctors, and that it may therefore have contributed to reducing the overall sensitisation rate in women receiving RAADP.

Other outcome measures used in the studies are sensitisation during pregnancy or within 3 days of delivery, and sensitisation at postnatal follow-up. Data relating to sensitisation at these different dates are tabulated in Appendix 5. As these figures differ, an attempt is made in Table 13 to estimate the total number of sensitised women in each study. As none of the included studies presents the total number of women found to be sensitised at either delivery or 6-month follow-up, with the exception of the studies by MacKenzie *et al.*¹²⁶ and Mayne *et al.*,¹²⁷ which present sensitisation rates during the subsequent pregnancy, the figures in Table 13 are likely to underestimate the true prevalence of sensitisation at 6 months because the extent of overlap between women with demonstrable antibodies at delivery and at follow-up is not clear. Moreover, all of the studies are likely to underestimate the numbers of women who would

be found to be sensitised were they to become pregnant again, either because they did not measure that outcome and thus did not take into account the phenomenon of silent sensitisation or because, in the case of the studies by MacKenzie and Mayne, they could not identify those women who were sensitised but did not become pregnant again.

Comparability of results

The studies vary in the results that they present. Six studies – the study by Bowman *et al.*,¹²⁹ the two studies by Bowman and Pollock^{130,131} and the studies by Huchet *et al.*,¹²⁵ Tovey *et al.*¹²⁸ and Trolle¹³² – report in effect the aggregated results of treating individual women. Although Bowman and Pollock¹³⁰ set out to describe the results of providing RAADP on a Canadian province-wide basis, they in fact only present the results for those women who actually received RAADP (stated to be only 89% of those at risk). In addition, as noted above, Trolle¹³² screened women for antibodies before inclusion and gave no indication of the numbers who were excluded from the study on this basis.

Studies that only include data relating to women known both to have received the intervention and to have received it before sensitisation will provide an indication of the clinical effectiveness of RAADP but will overestimate its efficacy in non-trial conditions. Efficacy can only be indicated by community studies that demonstrate the likely reduction in sensitisation rates achievable in practice by offering the intervention in a geographical area and including all women in that area in an intention-to-treat analysis. Only two studies were of this nature, those by MacKenzie *et al.*¹²⁶ and Mayne *et al.*¹²⁷ MacKenzie *et al.*¹²⁶ gave prophylaxis to all non-sensitised pregnant RhD-negative nulliparae, and reported the results in terms of the number of those women found to be sensitised in their second continuing pregnancy. Mayne *et al.*¹²⁷ gave prophylaxis to primigravidae and women with no living children, but presented the results for *all* women ‘at risk’ (i.e. all RhD-negative women delivered of RhD-positive babies having a subsequent pregnancy), thus indicating the overall efficacy of the programme, which in its second and subsequent years was said to reach most RhD-negative primiparae in the area.

It would therefore not be surprising if the results obtained by before-and-after studies differed from those of the other studies, as only the before-and-after studies included a number of untreated women in the intervention group. Moreover, as

TABLE 12 Summary of trial results: women found to be sensitised in a subsequent pregnancy as a result of a previous pregnancy, by total anti-D dose

Study	Study design	Dosage	Anti-D prophylaxis group			Control group		
			n	r	% Sensitised (95% CI)	n	r	% Sensitised (95% CI)
Bowman <i>et al.</i> 1978 ¹²⁹	Prospective study, historical/geographical controls	2 × 1500 IU (28 and 34 weeks) (initially at 34 weeks only)	343	0	0.0 (0.0–0.0)	No data		
MacKenzie <i>et al.</i> 1999 ¹²⁶	Community intervention trial	2 × 500 IU (28 and 34 weeks)	3320	12	0.4 (0.2–0.6)	3146	26	0.8 (0.5–1.1)
Mayne <i>et al.</i> 1997 ¹²⁷	Before-and-after study	2 × 500 IU (28 and 34 weeks)	1425	4	0.3 (0.0–0.6)	1426	16	1.1 (0.6–1.7)
Tovey <i>et al.</i> 1983 ¹²⁸	Prospective study, historical controls	2 × 500 IU (28 and 34 weeks)	325	2	0.6 (–0.2 to 1.5)	582	11 ^a	1.9 (0.8–3.0)

CI, confidence interval; n, number of RhD-negative women in the trial group undergoing subsequent pregnancy following a RhD-positive pregnancy; r, number of sensitised RhD-negative women in the trial group.

^a For comparability with other studies this figure excludes 11 women who developed antibodies in a previous pregnancy but were retained in the study.

TABLE 13 Summary of trial results: overall percentage of women sensitised, including silent sensitisation (authors' figures), by total anti-D dose

Study	Study design	Dosage	Patient Selection	Anti-D prophylaxis group				Control group			
				n	r	% Sensitised, including silent sensitisation (95% CI)	n	r	% Sensitised, including silent sensitisation (95% CI)		
Bowman et al. 1978 ¹²⁹	Prospective study, historical/geographical controls	2 × 1500 IU (28 and 34 weeks) (initially at 34 weeks only)	Primigravidae	1357 ^a	1	0.1 (-0.1 to 0.3)	2768	45	1.6 (1.2–2.1)		
Bowman and Pollock 1978 ¹³⁰	Prospective study, historical controls	1 × 1500 IU (28 weeks)	Unselected	1804	5	0.3 (0.0–0.5)	3533	62	1.8 (1.3–2.2)		
Bowman and Pollock 1987 ¹³¹	Retrospective study, historical controls	1 × 1500 IU (28 weeks)	Unselected	9303	25	0.3 (0.2–0.4)	3533	62	1.8 (1.3–2.2)		
Trolle 1989 ¹³²	Prospective study, historical controls	1 × 1500 IU (28 weeks)	Unselected	346	0	0.0 (0.0–0.0)	354	6	1.7 (0.4–3.0)		
MacKenzie et al. 2004 ¹⁰⁰	Open-label RCT; results presented as uncontrolled study	1 × 1500 IU (28 weeks)	Unselected	248 (per protocol population)	0	0.0 (0.0–0.0)	–	–	–		

continued

TABLE 13 Summary of trial results: overall percentage of women sensitised, including silent sensitisation (authors' figures), by total anti-D dose (continued)

Study	Study design	Dosage	Patient Selection	Anti-D prophylaxis group			Control group		
				n	r	% Sensitised, including silent sensitisation (95% CI)	n	r	% Sensitised, including silent sensitisation (95% CI)
Huchet <i>et al.</i> 1987 ¹²⁵	Quasi-RCT	2 × 500 IU (28 and 34 weeks)	Primiparae	461	0	0.0 (0.0–0.0)	454	4	0.9 (0.0–1.7)
			Multiparae	138	1	0.7 (–0.7 to 2.1)	136	3	2.2 (–0.3 to 4.7)
			Unselected	599	1	0.2 (–0.2 to 0.5)	590	7	1.2 (0.3–2.1)
MacKenzie <i>et al.</i> 1999 ¹²⁶	Community intervention trial	2 × 500 IU (28 and 34 weeks)	Primiparae	3320	12	0.4 (0.2–0.6)	3146	26	0.8 (0.5–1.1)
Mayne <i>et al.</i> 1997 ¹²⁷	Before-and-after study	2 × 500 IU (28 and 34 weeks)	Primiparae	1425	4	0.3 (0.0–0.6)	1426	16	1.1 (0.6–1.7)
Tovey <i>et al.</i> 1983 ¹²⁸	Prospective study, historical controls	2 × 500 IU (28 and 34 weeks)	First pregnancy	1238	4 ^b	0.3 (0.0–0.6)	2000	19 ^b	1.0 (0.5–1.4)
			Second pregnancy	604 ^b	1 ^b	0.2 (–0.2 to 0.5)	582	9 ^b	1.5 (0.5–2.5)
			Third pregnancies	2037 ^b	6 ^b	0.3 (0.1–0.5)	2721 ^b	32 ^b	1.2 (0.8–1.6)

CI, confidence interval; n, number of RhD-negative women in the trial group delivered of RhD-positive babies; r, number of sensitised RhD-negative women in the trial group; RCT, randomised controlled trial.

a 153 received only one dose, at 28 or 34 weeks.

b Data from Thornton *et al.*¹³³

noted above, they report the effect of a policy of RAADP in primigravidae on sensitisation in subsequent pregnancies, and the number of women found to be sensitised at this point could theoretically also include women sensitised early in their second rather than in their first pregnancy.

Finally, there were some discrepancies between the studies in terms of the inclusion or exclusion from the reported results of cases of apparent sensitisation in women who received RAADP. For comparability with the before-and-after studies, *Table 14* displays the overall numbers of sensitised women including, where possible, any stated to have been excluded from the authors' analyses. *Table 15* provides details of the numbers of women excluded from the authors' analyses, and the reasons for this, together with further information relating to the women sensitised despite being in the intervention groups, i.e. potential failures of protection.

The 2004 study by MacKenzie *et al.*¹⁰⁰ found no difference in efficacy or safety between Rhophylac administered intravenously and Rhophylac administered intramuscularly. However, this does not prove that there was no difference, as the study was not powered to identify such a difference, even though this was the randomised comparison.

The studies were broadly comparable in terms of the percentage of women in the control groups who were sensitised: this ranged from 1.2–1.8% in unselected groups, 0.8–1.6% in primiparae and 1.4–2.2% in multiparae (see *Table 14*). MacKenzie *et al.*¹²⁶ found an unexpected, and statistically non-significant, reduction in the number of cases observed in the control arm between the two study periods, from 1.3% in 1980–6 to 0.8% in 1990–6.

In all studies the proportion of women who were sensitised was lower in the intervention arm than in the control arm. However, the difference between sensitisation rates in the intervention and control arms varied between studies. As might be expected, this difference was particularly small, at 0.4–0.7%, in the before-and-after studies by MacKenzie *et al.*¹²⁶ and Mayne *et al.*¹²⁷ as their intention to treat analyses will have included women who had not received RAADP.

Meta-analysis of clinical effectiveness

In our earlier review we conducted meta-analysis on three groups of studies using the overall results presented in *Table 14*, which include, where possible, women excluded from the authors' analyses:

- Group 1: the four studies that used a dosage regimen of 500 IU at 28 weeks and 34 weeks and reported results for primigravidae – Huchet *et al.*,¹²⁵ MacKenzie *et al.*,¹²⁶ Mayne *et al.*¹²⁷ and Tovey *et al.*¹²⁸
- Group 2: the three studies that used a dosage regimen of 1500 IU at 28 weeks – the two studies by Bowman and Pollock^{130,131} and that by Trolle.¹³² These studies included both primigravidae and multigravidae.
- Group 3: the two community-based UK studies that used a dosage regimen of 500 IU at 28 weeks and 34 weeks and reported results for primigravidae – MacKenzie *et al.*¹²⁶ and Mayne *et al.*¹²⁷

As the current systematic review identified no additional studies comparing RAADP with no treatment, we present the results of these meta-analyses again here. On the basis of face validity, visual examination of the absolute trial results, individual odds ratios within trials and results of the meta-analyses (*Table 16*), the trials show a remarkable consistency in results, even between dosage regimens. Consequently, the results of the meta-analysis of group 3 trials are deemed to give a representative reflection of the actual effectiveness of RAADP and these figures are used in the economic evaluation.

Sensitisation rates for the conventional management groups were calculated by applying to each study the average of the sensitisation event probabilities estimated in the logistic regression model. Within group 2, the 1987 study by Bowman and Pollock¹³¹ used the same control arm results as the 1978 study by the same authors.¹³⁰ To prevent double counting, which would have a significant effect on the overall results because of the size of the studies, the two studies were combined into a three-arm study within the meta-analysis, consisting of two treatment arms and one control arm.

The results of the meta-analyses are shown in *Table 16* and *Figures 2–4*.

Comparison of dosage regimens

Pooling the data from those studies that used one dose of 1500 IU at 28 weeks (group 2) produced a point estimate for sensitisation in the RAADP group of 0.34%. In comparison, the study by Bowman *et al.*,¹²⁹ which used two doses of 1500 IU at 28 and 34 weeks, reported a rate of 0.1%. Although this suggests that, as one might expect, two doses of 1500 IU are more effective than one,

TABLE 14 Summary of trial results: comparison with no treatment: overall percentage of women sensitised, including silent sensitisation, by total anti-D dose, including, where possible, women excluded from published analyses for various reasons^a (see Table 16)

Study	Study design	Dosage	Patient selection	Anti-D prophylaxis group			Control group		
				n	r	% Sensitised, including silent sensitisation (95% CI)	n	r	% sensitised, including silent sensitisation (95% CI)
Bowman et al. 1978 ¹²⁹	Prospective study, historical/geographical controls	2 x 1500 IU (28 and 34 weeks) (initially at 34 weeks only)	Primigravidae	1357 ^b	1	0.1 (-0.1 to 0.3)	2768	45	1.6 (1.2-2.1)
Bowman and Pollock 1978 ¹³⁰	Prospective study, historical controls	1 x 1500 IU (28 weeks)	Unselected	1806	11	0.6 (0.3-1.0)	3533	62	1.8 (1.3-2.2)
Bowman and Pollock 1987 ¹³¹	Retrospective study, historical controls	1 x 1500 IU (28 weeks)	Unselected	9295	30	0.3 (0.2-0.4)	3533	62	1.8 (1.3-2.2)
Trolle 1989 ¹³²	Prospective study, historical controls	1 x 1500 IU (28 weeks)	Unselected	346	0	0.0 (0.0-0.0)	354	6	1.7 (0.4-3.0)
Huchet et al. 1987 ¹²⁵	Quasi-RCT	2 x 500 IU (28 and 34 weeks)	Primiparae	461	0	0.0 (0.0-0.0)	454	4	0.9 (0.0-1.7)
			Multiparae	138	1	0.7 (-0.7 to 2.1)	136	3	2.2 (-0.3-4.7)
			Unselected	599	1	0.2 (-0.2 to 0.5)	590	7	1.2 (0.3-2.1)
MacKenzie et al. 1999 ¹²⁶	Community intervention trial	2 x 500 IU (28 and 34 weeks)	Primiparae	3320	12	0.4 (0.2-0.6)	3146	26	0.8 (0.5-1.1)
Mayne et al. 1997 ¹²⁷	Before-and-after study	2 x 500 IU (28 and 34 weeks)	Primiparae	1425	4	0.3 (0.0-0.6)	1426	16	1.1 (0.6-1.7)
Tovey et al. 1983 ¹²⁸	Prospective study, historical controls	2 x 500 IU (28 and 34 weeks)	First pregnancy	1238	4 ^c	0.3 (0.0-0.6)	2000	19 ^c	1.0 (0.5-1.4)
			Second pregnancy	604 ^c	1 ^c	0.2 (-0.2 to 0.5)	582	9 ^c	1.5 (0.5-2.5)
			All pregnancies	2037 ^c	6 ^c	0.3 (0.1-0.5)	2721 ^c	32 ^c	1.2 (0.8-1.6)

CI, confidence interval; n, number of RhD-negative women in the trial group delivered of RhD-positive babies; r, number of sensitised RhD-negative women in the trial group; RCT, randomised controlled trial.

a Information on numbers excluded from published analyses not available for Huchet and Trolle studies.

b 153 received only one dose, at 28 or 34 weeks.

c Data from Thornton et al.¹³³

TABLE 15 Women sensitised in intervention groups

Study	Number of sensitised women in intervention group ^a	Comments
Bowman <i>et al.</i> 1978 ¹²⁹	1, unspecified number	Considered by the investigators probably to be a case of passive RhD antibody persisting at 6 months after delivery; as the woman was lost to follow-up at 9 months it was not possible to establish whether it still existed at that point. In the first 6 months of the study an unspecified number of women were sensitised before 34 weeks; these were not included in the analysis
Bowman and Pollock 1978 ¹³⁰	5, 6	Two women were sensitised before 28 weeks; one multigravida may have undergone silent sensitisation as a result of an earlier abortion when no anti-D was given or may have been sensitised before receiving prophylaxis at 29 weeks in the current pregnancy; and two more multigravidae may either have undergone silent sensitisation in a previous pregnancy or may represent failures of prophylaxis. In addition, two primigravidae appeared to have been sensitised before what they stated was their first pregnancy; three multigravidae appeared to have undergone silent sensitisation by an earlier pregnancy; and one had received an RhD-positive blood transfusion: these were all excluded from the analysis
Bowman and Pollock 1987 ¹³¹	25, 5	13 failures of prophylaxis; four women in whom sensitisation could be due either to failure of prophylaxis or to failure to treat following a previous abortion or delivery; five women sensitised by 28 weeks in current pregnancy; and three women sensitised by 28 weeks who possibly underwent silent sensitisation in an earlier pregnancy. In addition, five women who appeared to have undergone silent sensitisation in a previous pregnancy were excluded from the analysis
Huchet <i>et al.</i> 1987 ¹²⁵	1	Apparently a failure of prophylaxis – the woman in question had received anti-D during a previous pregnancy, which was terminated for therapeutic reasons
MacKenzie <i>et al.</i> 1999 ¹²⁶	12	Six women were delivered of their first pregnancy outside Oxfordshire: four certainly and two possibly did not receive antenatal prophylaxis during that first pregnancy; one woman had undergone a potential sensitising event at 18 weeks for which anti-D may not have been given; one woman, who delivered at 37 weeks, had undergone a large fetomaternal haemorrhage, probably at 35 weeks (routine prophylaxis had been given at 29 and 35 weeks); and four women had received prophylaxis at 28 and 34 weeks and did not appear to have suffered an incident likely to provoke a fetomaternal haemorrhage
Mayne <i>et al.</i> 1997 ¹²⁷	4	Three women had previously delivered in places where routine antenatal prophylaxis was unlikely; one had not received prophylaxis during her first pregnancy despite the existence of a programme of RAADP
Tovey <i>et al.</i> 1983 ¹²⁸	5	All seem due to failures of prophylaxis, although two women sensitised during their first pregnancy had low but persisting levels of antibodies, which might possibly be rare 'naturally occurring' anti-D
Trolle 1989 ¹³²	0, unspecified number	An unspecified number of women who had been sensitised by 28 weeks were excluded from the study

a When two figures are provided, the first figure is the number of sensitised women included in the authors' analyses and the second figure is the number of sensitised women excluded from these analyses.

TABLE 16 Results of the meta-analysis

	Group 1	Group 2	Group 3
Test for heterogeneity (p-value)	0.812	0.940	0.976
Odds ratio of sensitisation with antenatal prophylaxis (95% CI)	0.33 (0.20–0.55)	0.20 (0.13–0.29)	0.37 (0.21–0.65)
Sensitisation rate of control group (95% CI)	0.89% (0.21–1.56%)	1.60% (0.37–2.83%)	0.95% (0.18%–1.71%)
Sensitisation rate of antenatal prophylaxis group using meta-analysis (95% CI)	0.30% (0.22–0.38%)	0.34% (0.28–0.40%)	0.35% (0.29–0.40%)

CI, confidence interval.

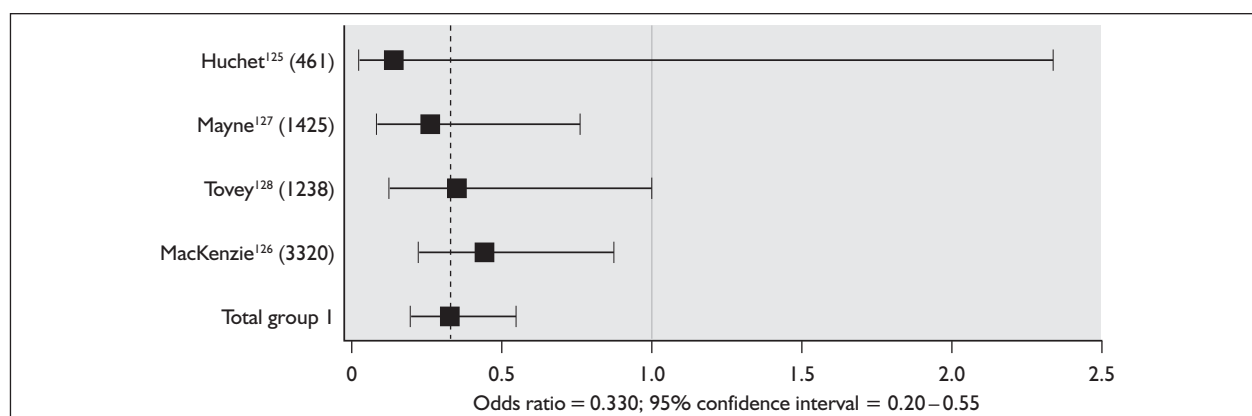


FIGURE 2 Group 1: 2 x 500IU in RhD-negative primigravidae. Note: number of women in intervention group in brackets.

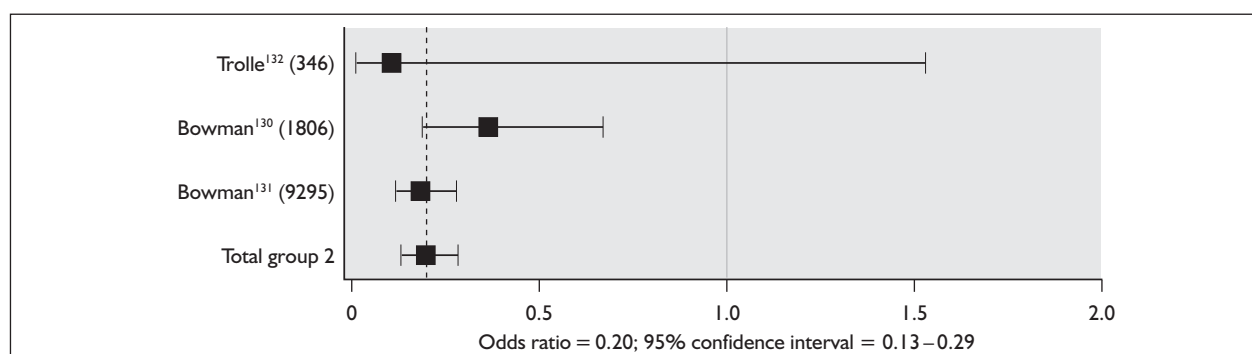


FIGURE 3 Group 2: 1 x 1500IU in unselected RhD-negative women. Note: number of women in intervention group in brackets.

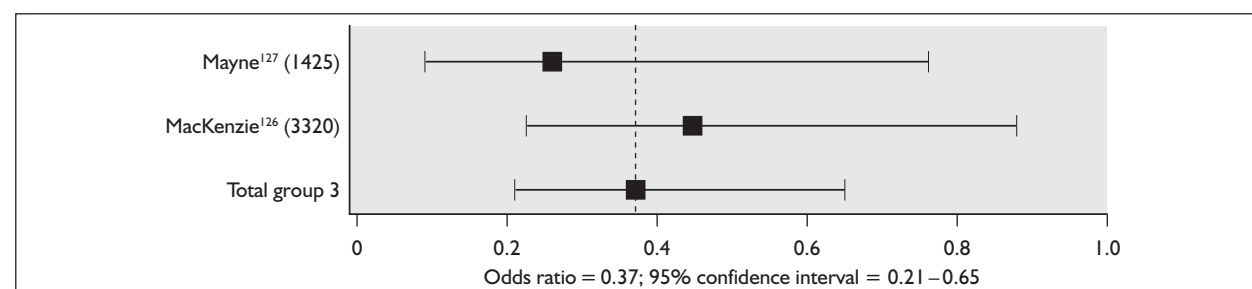


FIGURE 4 Group 3: 2 x 500IU in RhD-negative primigravidae. Note: number of women in intervention group in brackets.

there are no trials that directly compare these two regimens.

In theory, two doses of 500 IU at 28 and 34 weeks should also be more effective than a single dose of 1500 IU at 28 weeks, as they would result in a slightly higher residual anti-D at term.¹⁵ Pooling the data from those studies that used two doses of 500 IU at 28 and 34 weeks yields a point estimate for sensitisation in the RAADP group of 0.30%, marginally lower than that for a single dose of 1500 IU (0.34%). However, because the sensitisation rate in the control groups was lower in the studies using two doses of 500 IU than in all of the other studies, the point estimate of the odds ratio for one dose of 1500 IU at 28 weeks is lower (0.20; i.e. more effective) than that for two doses of 500 IU (0.33). For both the odds ratios and the point estimates of the sensitisation rates the 95% confidence intervals of the estimates overlap, implying that the differences are not statistically significant.

Compliance

Only one of the included studies, the 1999 study by MacKenzie *et al.*,¹²⁶ examined the extent to which comprehensive prophylaxis was achieved. This study found that, of a sample of eligible women delivered in the John Radcliffe Hospital, Oxford, during 1992–6, only 89% received the first dose of a two-dose regimen, only 76% received both doses and only 29% received both doses at the correct gestation. This audit was later extended to include the years 1997–2003.¹²² During the latter period 90% of women received the first dose and 79% both doses. Although these modest improvements were not statistically significant, in the later period the timing of both injections had improved significantly. Despite this improvement in compliance there was estimated to be no reduction in the sensitisation rate among women who had delivered their first baby in the Oxford district and

who would have been eligible for RAADP during that pregnancy.

Longer-term outcomes

Bowman *et al.*¹²⁹ provided information on the clinical outcomes of 17 subsequent RhD-positive pregnancies in the 62 sensitised women in the study's control group. Seven of the 17 infants (41%) required treatment related to HDN (*Table 17*).

In the study by Tovey *et al.*¹²⁸ anti-D antibodies were identified during their first pregnancy in 18 women in the control group: 14 of their infants (78%) were mildly affected, two (11%) were moderately affected, requiring exchange transfusion, one died for reasons other than RhD HDN and one was RhD negative. Between them these 18 women, and one other woman in the control group in whom the antibody had been detected before her first pregnancy, went on to have 11 further pregnancies: five (45%) of these infants were mildly affected, two (18%) were moderately affected and one was severely affected (requiring six exchange transfusions).

Thornton *et al.*¹³³ studied the effect of RAADP given only in the first pregnancy on sensitisation rates in subsequent pregnancies. This was a follow-up to the study by Tovey *et al.*¹²⁸ and reports on the same cohorts of women. Thornton *et al.*¹³³ found that only one woman who had received RAADP in her first pregnancy produced anti-D antibodies in her second pregnancy, none produced anti-D antibodies in the third pregnancy and only one produced anti-D antibodies in the fourth pregnancy (*Table 18*). Overall, sensitisation occurred in six women in the treatment group and in 32 women in the control group. No explanation was proposed as to why prophylaxis provided in the first pregnancy should appear to confer benefits in subsequent pregnancies.

TABLE 17 Clinical outcomes of RhD-positive pregnancies in sensitised women¹²⁹

Outcome	Number of pregnancies (%)
Fetal and exchange transfusion required	2 (12%)
Exchange transfusion and early delivery required	3 (18%)
Phototherapy required	2 (12%)
Direct Coombs' test positive ^a – treatment not required	5 (29%)
Direct Coombs' test negative – unaffected	5 (29%)

^a The Coombs' test measures the presence of antibodies on the surface of red blood cells. It may be measured directly in the infant or indirectly in the mother.

TABLE 18 Anti-D antibody detected in first and subsequent pregnancies of RhD-negative women delivered of an RhD-positive infant (RAADP given to the treatment group in the first pregnancy only)¹³³

First pregnancy		Second pregnancy		Third pregnancy		Fourth pregnancy	
Treatment group (n = 1234)	Control group (n = 1881)	Treatment group (n = 604)	Control group (n = 582)	Treatment group (n = 167)	Control group (n = 121)	Treatment group (n = 32)	Control group (n = 18)
4 (0.32%)	19 (1%)	1 (0.17%)	9 (1.5%)	0 (0%)	3 (2.5%)	1 (3.1%)	1 (5.5%)

More recently, a retrospective longitudinal observational study carried out by MacKenzie *et al.*¹⁴⁴ compared the rate of RhD sensitisation following the implementation of a policy of restricted prophylaxis, in which RAADP was offered to all non-sensitised RhD-negative pregnant women with no living children booked for confinement in the Oxford Health District, with that predicted by mathematical modelling following a policy of universal prophylaxis, in which RAADP would be offered to all RhD-negative pregnant women irrespective of parity. This study also found that the policy of restricted prophylaxis provided continuing protection in subsequent pregnancies.

Thornton *et al.*¹³³ provided data relating to preterm deliveries, birth weights and perinatal deaths in both the first and second pregnancy, and abortions in the second pregnancy, in RhD-negative women who, following RAADP in their first pregnancy, had delivered a RhD-positive baby in that first pregnancy. These data were compared with those relating to untreated RhD-negative women who gave birth to RhD-positive babies in their first pregnancy and to RhD-positive mothers who were comparable except for the RhD status. No significant differences were observed either in terms of these outcomes or in terms of maternal hypertension and proteinuria in the first, second and third pregnancies.¹³³

ABO compatibility

As noted in Chapter 1 (see Aetiology, pathology and prognosis), in approximately 20% of pregnancies in RhD-negative women the mother and fetus have different ABO blood groups. Sensitisation is less common when mother and baby are ABO incompatible. This is demonstrated by information from the control group of the study by Bowman *et al.*¹²⁹ (Table 19).

Summary of clinical effectiveness

In the eight studies that compared RAADP with no prophylaxis, RAADP was given to, or available for, RhD-negative women undergoing a total of around 19,719 pregnancies that resulted in RhD-positive babies. Of these pregnancies, 65 (0.33%) resulted in sensitisation. The control groups for these studies (six groups in all, as all three studies by Bowman used the same control population) included a total of 11,049 pregnancies in women at risk of RhD sensitisation that resulted in RhD-positive babies: 136 of these pregnancies (1.2%) resulted in sensitisation.

The largest study, by Bowman and Pollock,¹³¹ accounts for nearly half of the total number of pregnancies in which RAADP was given or available. However, its design is relatively weak, comparing women who received RAADP between 1977 and 1986 with controls from the same geographical area during the period 1967–74.

TABLE 19 ABO compatibility and incidence of sensitisation in RhD-negative women not treated with routine antenatal anti-D prophylaxis¹²⁹

ABO compatibility	n	r	% Sensitised (95% CI)
Primigravidae	2768	45	1.6 (1.2–2.1)
Compatible	2257	44	1.9 (1.4–2.5)
Incompatible	511	1	0.2 (–0.2 to 0.6)
Multigravidae	765	17	2.2 (1.2–3.3)
Compatible	602	14	2.3 (1.4–3.5)
Incompatible	163	3	1.8 (–0.2 to 3.9)

CI, confidence interval; n, number of deliveries of RhD-positive babies to RhD-negative women; r, number of sensitised RhD-negative women.

Overall, it would appear that of the 65 pregnancies in the intervention groups that were reported to have resulted in sensitisation (including silent sensitisation):

- 29 represented possible or probable failures of treatment (i.e. cases in which sensitisation occurred despite appropriate administration of anti-D)
- at least 19 represented probable or possible logistic failures (i.e. instances in which, in the absence of any recognised sensitising event, sensitisation preceded the administration of prophylaxis or in which prophylaxis was not administered despite the existence of a policy of antenatal prophylaxis)
- 12 were sensitised as a result of a previous delivery in a place where routine antenatal prophylaxis was either certainly or probably not provided.

Overall, therefore, the number of eligible pregnancies that resulted in sensitisation despite antenatal prophylaxis would appear to be as low as 29/19,719 (0.15%; 95% CI 0.1–0.2%). This figure would rise to a maximum of 48/19,719 (0.24%; 95% CI 0.2–1.3%) with the inclusion of logistic failures of prophylaxis – women sensitised either before the date at which the first dose of antenatal prophylaxis would have been administered or following failure to administer either routine prophylaxis or prophylaxis following a potential sensitising event.

The best indication of the likely efficacy of a programme of routine AADP in England and Wales comes from the two non-randomised community-based studies by MacKenzie *et al.*¹²⁶ and Mayne *et al.*¹²⁷ The pooled results of these two studies suggest that, compared with no RAADP, such a programme may reduce the sensitisation rate from 0.95% to 0.35%. This gives an odds ratio for the risk of sensitisation of 0.37, and an absolute reduction in risk of sensitisation in RhD-negative mothers at risk (i.e. carrying a RhD-positive child) of 0.6%. The number of such women needed to treat (NNT) to avoid one case of sensitisation is $1/0.006$, which is 166. However, in the absence of a programme of non-invasive fetal genotyping a RhD-negative woman will not know if she is carrying a RhD-positive child; in fact, only 60% of them will be, making the overall $NNT = 10/6 \times 166 = 278$.

Further, a woman will only benefit clinically if she has an RhD-positive infant and she would have been sensitised and she goes on to have a further infant who is also RhD positive. It is the avoidance

of HDN in that infant which constitutes the clinical benefit.

In Chapter 1 (see Significance for the NHS) we estimated that currently, were there no programme of RAADP, approximately 650 RhD-negative women a year would be sensitised antenatally and that subsequent pregnancies in these women would lead to around 31 fetal or neonatal losses per year. Avoidance of sensitisation can be expected to avoid fetal loss in 4.8% of cases (this takes into account the fact that women who become immunised during a first pregnancy may be ‘high responders’ who produce a vigorous response to a small FMH). An estimate of the overall NNT to avoid a fetal or neonatal loss in a subsequent pregnancy is therefore $278/0.048 = 5790$.

Adverse events

No serious adverse events related to the administration of RAADP were reported by any of the studies included in the review of clinical effectiveness. MacKenzie *et al.*¹⁰⁰ reported a few cases of mild pain, soreness or itching at the injection site following administration of Rhophylac. Bowman *et al.*¹⁰⁰ reported mild adverse reactions (marked flushing and mild chest discomfort that disappeared within 30 seconds without the use of medication) in two out of 3733 women given WinRho either antenatally or postpartum; they both received WinRho from a lot containing unacceptable levels of moisture and aggregated IgG.

The study by MacKenzie *et al.*¹⁰⁰ was unique in screening for blood group alloantibodies and viral markers both before RAADP and 6 months after the last administration of anti-D. Anti-C was identified in the sera of three women who had received intravenous Rhophylac. In terms of viral markers two women seroconverted for hepatitis A virus antibodies, three for cytomegalovirus and one for anti-HBc (hepatitis B core antigen); for these women the route of Rhophylac administration was not specified but the investigators considered it unlikely that any of the observed seroconversions were related to Rhophylac; one of the seroconversions for hepatitis A virus followed immunisation for international travel. Moreover, as the investigators acknowledge, the note for guidance from the Committee for Proprietary Medicinal Products¹⁴⁵ on the clinical investigation of human anti-D immunoglobulin for intravenous and/or intramuscular use states that, because of the effectiveness of procedures to control potential viral contamination, ‘it is no longer considered appropriate to use clinical trials to investigate viral

safety with regard to enveloped viruses', and that, although these procedures may be of limited value against non-enveloped viruses such as hepatitis A and parvovirus B19, 'the safety of the products with respect to non-enveloped viruses cannot currently be adequately evaluated in clinical studies'.

In 2006, 77 adverse events relating to the administration of anti-D for all indications were reported to the SHOT (Serious Hazards of Transfusion) Committee. All involved lack of communication and poor documentation. The nature of the majority of these incidents is not specified. However, it was stated that 13 women with immune anti-D received treatment with anti-D immunoglobulin, although not necessarily as part of RAADP.⁸⁹ This is a particular cause for concern because it implies a failure to identify a pregnant woman as sensitised, which can in turn lead to failure to monitor immune antibodies during pregnancy, with the risk of adverse outcomes if the fetus is affected by HDN.

Discussion

All of the evidence indicates that RAADP reduces the incidence of sensitisation. In assessing the impact of a programme of RAADP the most relevant studies are those by MacKenzie *et al.*¹²⁶ and Mayne *et al.*¹²⁷ These are community-based studies with high external validity as they demonstrate the effectiveness of RAADP in real life in the UK rather than under trial conditions and as measured by the most clinically relevant outcome measure, the number of women found to be sensitised in a subsequent pregnancy. Meta-analysis of the data from these studies indicates that the introduction of such a programme is associated with a fall of 0.6% (from 0.95% to 0.35%) in the number of women found in a subsequent pregnancy to be sensitised, an odds ratio of 0.37 (95% CI 0.21–0.65).

However, although the implementation of a programme of RAADP should lead to a significant fall in the residual numbers of women becoming sensitised, some women continue to become sensitised. There are five possible reasons for continuing cases of sensitisation:

- failure to recognise potential sensitising events in pregnancy as such and to treat them appropriately
- failure to assess the extent of FMH adequately
- failure to comply with postpartum prophylaxis guidelines

- refusal of RAADP by the mother
- failure to implement RAADP by some trusts and incomplete adherence to advice (i.e. poor compliance with the second dose).

Before the introduction of RAADP there was not universal adherence to UK guidelines, particularly with respect to administration of anti-D following potentially sensitising events in pregnancy. An audit of anti-D sensitisation carried out in Yorkshire between 1988 and 1991¹⁴⁶ found that the guidelines were followed fully in only 52% (30/58) of possible sensitising events for which full data were available. In Scotland an audit found that, in 1992, anti-D was given in only 70% (195/280) of recorded antenatal events which should have resulted in its administration.¹⁴⁷ A questionnaire survey published in 1994 found that many A&E departments in England and Wales were not adequately prepared for treating with anti-D women bleeding in early pregnancy and were not following the guidelines so to do.¹⁴⁸ A retrospective study of 922 RhD-negative women delivered in Merseyside in 1994 found that, in 39% (158/396) of potentially sensitising events, the guideline recommendations were not recorded as having been followed.¹⁴⁹ In an audit of singleton pregnancies delivered in nine hospitals within a hundred-mile radius of Manchester between 1 August 1994 and 31 July 1995, anti-D was recorded as being administered after 79% (478/602) of potentially sensitising events overall, but administration rates in the individual hospitals ranged from 58% to 96%.¹⁵⁰ In 1998 an audit of 3274 RhD-negative women in Northern Ireland found that anti-D was given after only 44% (117/264) of potentially sensitising events that occurred before, and 58% (184/319) of those that occurred after, 20 weeks' gestation. However, in some cases this was because the women themselves had not sought advice from maternity care staff within 72 hours of the event.¹⁵¹

The evidence suggests closer adherence to the guidelines for postpartum administration. Appropriate postnatal prophylaxis was given in 95% of cases (497/520) in Merseyside in 1994¹⁴⁹ and in 98% of cases (1820/1852) in Northern Ireland in 1998.¹⁵¹

It should be noted that the above studies were all carried out in the 1990s. Although more recent evidence has not been found it is possible that compliance with guidance relating to the administration of anti-D following potentially sensitising events in pregnancy may have improved

following the introduction of RAADP and the consequent raising of awareness of the importance of antenatal prophylaxis. Probably only a minority of the current cases of sensitisation are attributable to failure to comply with current established UK guidelines relating to either postpartum prophylaxis or prophylaxis in response to potential sensitising events. Nevertheless, these observations inevitably raise the question of whether sensitisation rates cannot be further reduced by stricter adherence to these guidelines rather than by offering RAADP to all RhD-negative pregnant women who are not already sensitised.

There is no evidence to suggest that RAADP is associated with adverse effects of any consequence for either mother or child other than the possibility of transmission of bloodborne infections; this is minimised by the safeguards built into the modern manufacturing process.

One-dose versus two-dose regimens

No head-to-head studies have been undertaken that compare a one-dose with a two-dose regimen of RAADP, and the studies reviewed above do not provide any evidence to suggest that two 500-IU doses of anti-D at 28 and 34 weeks are more or less effective than a single dose of 1500 IU at 28 weeks. However, the Royal College of Nursing has expressed concern that a single dose given at 30 weeks (as is possible under the licensed indication for Rhophylac) may not provide protection against an FMH occurring at 28 or 39 weeks.¹²³ Although it is obvious that anti-D given at 30 weeks cannot provide protection against an FMH at 28 weeks, the argument that it may also be insufficient to provide protection at 39 weeks relates to the half-life of prophylactic anti-D, as discussed in Chapter 1 (see Description of technology under assessment). There is some support for the suggestion that a single dose may be inadequate, at least if given at 28 rather than 30 weeks. Bowman⁴ observed that, in some failures of RAADP, the interval between a single dose at 28 weeks and delivery was over 13 weeks and 5 days and therefore recommended a second dose 12 weeks after the first for women who had not delivered by that date. Moreover, neither regimen would provide adequate protection against an undetected FMH of > 10 ml occurring between approximately 34 and 40 weeks' gestation.³

Turner *et al.*¹⁵² have carried out a meta-analysis around the clinical effectiveness studies identified within our earlier systematic review.¹²³ This paper

uses Bayesian methods to weight the clinical efficacy studies according to the amount of internal and external bias associated with each of them. The result of this meta-analysis is similar to that described by the meta-analysis carried out earlier in this chapter (see Critical review and synthesis of information) of the two clinical efficacy studies with the least external bias, which helps to validate this result.

This bias modelling paper could also in theory be used to assess the difference in efficacy between the one-dose and two-dose regimens. This would require elicitation of bias using the opinion of clinical experts and unfortunately this is not viable in the time available. However, this work could be carried out in the future as an additional analysis around any differences in efficacy of the two dosing regimens.

Several other arguments in addition to clinical effectiveness have been put forward to support the use of one or other regimen. These arguments, which relate to compliance, cost, and safety, are summarised briefly below.

Compliance

It has been suggested that compliance would be higher with a single-dose regimen.⁸⁹ In their 2006 study of compliance with RAADP, MacKenzie *et al.*¹²² found that, in 1997–2003, 13% of women did not receive the second dose of a two-dose regimen, whereas in 23% there was an inappropriately long interval between the two doses; they argue that a single-dose strategy would eliminate these problems. However, a recent study¹²¹ has found that the majority of women who declined the two-dose regimen declined at the first dose and it therefore seems unlikely that the use of a single-dose regimen would have a significant impact on maternal consent rates. Moreover, as noted by the Royal College of Nursing, the single-dose regimen only allows one opportunity to offer RAADP, whereas with the two-dose regimen, if the first dose is not administered, there is at least an opportunity to reduce the level of risk somewhat with the 34-week dose.¹²³

Cost

The single-dose regimen using Rhophylac is cheaper than the two-dose regimen using D-Gam even though it uses more anti-D (1500 versus 1000 IU) (see Chapter 1, Summary of product characteristics). A single-dose regimen would also offer savings in laboratory and midwife administration time.⁹⁰

Safety

None of the manufacturers can supply both the 1500-IU dose needed for the single-dose regimen and the 500-IU dose that is suitable for treating most sensitising events. Adoption of the single-dose regimen would therefore mean either exposing women to more than one manufacturer's product, in conflict with the BCHS guidelines that batch exposure should be limited to limit donor exposure, or using higher doses than necessary to treat potential sensitising events.⁸⁹

Intravenous versus intramuscular administration

As noted earlier, the ion-exchange chromatography method produces anti-D that may be given either intramuscularly or intravenously, whereas anti-D produced by the Cohn cold ethanol fractionation method can only be given intramuscularly. There are various arguments for and against the intravenous and intramuscular administration of anti-D. Anti-D prepared using the original ion-exchange chromatography method had the disadvantage of being unstable in solution and therefore needing to be reconstituted before injection,¹⁰¹ but more recently a liquid-stable version (Rhophylac) has been developed.¹⁰⁰ Anti-D produced by ion-exchange chromatography is said to be purer than that produced by the cold ethanol method and is therefore less likely to produce a reaction in the recipient.¹⁰⁰ Moreover, intravenous administration causes less discomfort for the recipient¹⁰⁰ but is less convenient for antenatal prophylaxis in the community setting.¹⁰⁰

The ion-exchange chromatography method is also more efficient, retaining over 90% of the anti-D present in the original plasma¹⁰⁰ compared with only 50–60% using the Cohn method.¹⁰¹ Moreover, if given intravenously, anti-D prepared by the ion-exchange chromatography method is more effective weight for weight than anti-D produced by the Cohn method given intramuscularly, making it in theory possible to use a smaller dose,¹⁰¹ although this is not reflected in the licensed doses. However, as noted in Chapter 1 (see Concerns relating to the possible transfer of viral or prion infection), on the only occasions when anti-D is known to have transmitted viral infection it was anti-D prepared by ion-exchange chromatography that was implicated. Although the cold ethanol fractionation process used to produce the intramuscular product has intrinsic virucidal benefits, additional procedures have subsequently been introduced to the chromatography method to protect against

future cases of viral transmission. However, these additional procedures may be of limited value against non-enveloped viruses such as hepatitis A virus and parvovirus B19.¹¹¹

Availability of donor plasma

Problems have been encountered in the past in relation to the availability of anti-D. If such problems are likely to be encountered in the future then an argument can be made for those strategies that minimise the volume of plasma required. These include:

- the use of a two-dose 500-IU regimen, as this uses two-thirds of the quantity of anti-D used by the single-dose regimen and there is no evidence that it is not equally effective
- the use of the ion-exchange chromatography method of preparation, as this retains 30–40% more anti-D than the Cohn method.

Indeed, it can be argued that plasma-sparing strategies should be preferred regardless of any anticipated problems relating to supplies of donor plasma because of ethical concerns relating to the issue of harm to the plasma donors. In most donors an adequate antibody titre is obtained or maintained only by regular injection of RhD-positive red cells, a procedure that is not without risk to the donor.¹⁵³

Tovey and Taverner⁸ have argued that, if the provision of RAADP in every pregnancy is difficult to achieve because of either the cost or the availability of sufficient anti-D, the cheaper alternative of giving RAADP to all RhD-negative primigravidae, and to RhD-negative secundigravidae whose first baby was RhD-negative, would ensure that most RhD-negative mothers receive anti-D during their first RhD-positive pregnancy and should enable all RhD-negative mothers to have at least three live children.

Targeted prophylaxis

As noted in Chapter 1 (see Description of technology under assessment), non-invasive fetal genotyping has not yet been demonstrated to be sufficiently accurate to enable its use to target provision of RAADP to only those non-sensitised RhD-negative women pregnant with RhD-positive infants. However, a test that is sufficiently accurate at an early enough gestational date may become available in the next few years.

Even though non-invasive fetal genotyping cannot currently be used to target RAADP it has other potential benefits. The BCSH guideline for blood grouping and antibody testing in pregnancy⁸⁰ suggests that its use is clinically relevant when the mother has high antibody levels and/or a history of HDN and the father is heterozygous for RhD, because knowledge of the genotype of the fetus will affect the management of a pregnancy in a sensitised RhD-negative woman: if the fetus is predicted to be RhD positive, invasive procedures, which carry an inherent risk of boosting maternal anti-D levels, may then be avoided until Doppler monitoring indicates that the fetus is anaemic.⁹⁵

Results in context of other reviews

Only one systematic review of RAADP was identified other than that updated in this report. This was the Cochrane review by Crowther and Middleton.¹⁵⁴ As Cochrane reviews include only RCTs and quasi-RCTs, this review included only two studies: that by Huchet *et al.*,¹²⁵ which met our inclusion criteria, and that by Lee and Rawlinson,¹³⁵ which was excluded from the current review because it used an unlicensed regimen (two doses each of 250 IU). Crowther and Middleton¹⁵⁴ found that RAADP reduced the incidence of sensitisation compared with no RAADP.

Chapter 4

Assessment of cost-effectiveness

The cost-effectiveness of providing RAADP to RhD-negative women has been evaluated from a UK NHS perspective. The comparators assessed against a base case of no RAADP, for both primigravidae and multigravidae, are:

- 500IU at 28 and 34 weeks' gestation (D-Gam)
- 1250IU at 28 and 34 weeks' gestation (Partobulin)
- 1500IU at 28 weeks' gestation (Rhophylac)
- 1500IU at 28 weeks' gestation (WinRho).

Systematic review of existing cost-effectiveness evidence

A systematic review of economic evaluations was carried out using the search criteria and databases set out within the clinical effectiveness section (see Chapter 3, Identification of studies); the only variation from this was that the study design was defined as economic evaluations. A total of 11 papers (nine different studies) were identified by the systematic searches (*Figure 5*); eight of these studies were included in the RAADP assessment report for NICE in 2001,¹⁵⁵ later published as a NICE Health Technology Assessment report.¹ These were the studies by Adams *et al.*,¹⁵⁶ Baskett and Parsons,¹⁵⁷ Lim *et al.*,¹⁵⁸ Mackenzie *et al.*,¹²⁶

Selinger,¹⁵⁹ Torrance and Zipursky,¹⁶⁰ Tovey *et al.*¹²⁸ and Vick *et al.*^{161,162} Two of these studies^{126,128} were also included as studies of clinical effectiveness. Only one additional economic evaluation was identified by the updated searches. This was the previous RAADP NICE Health Technology Assessment by Chilcott *et al.* carried out in 2001.¹

Because of the variability between the studies a quality assessment has not formally been carried out. However, the following sections of this report present an overview of the nine included economic evaluations. The description of eight of the studies presented here has been taken from the previous anti-D Health Technology Assessment by Chilcott *et al.* carried out in 2001¹ for the NICE appraisal of RAADP. Of the nine studies included in the review, five evaluations used UK costs, but only the studies by Vick *et al.*^{161,162} and Chilcott *et al.*¹ describe a detailed modelling evaluation that appears to be applicable to the UK NHS. Four of the studies are over 20 years old and an additional three of the studies are over 10 years old; hence, caution should be taken if comparing these results with those of the model presented here. The economic evaluations included in the review cover a range of RAADP regimens, as summarised in *Table 20*.

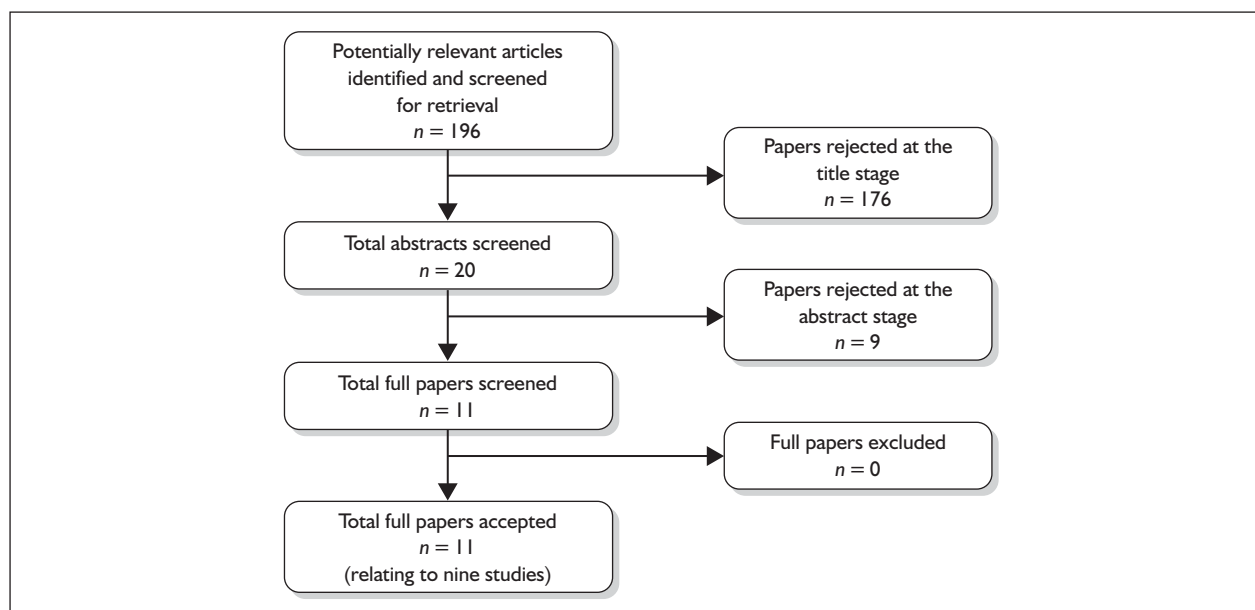


FIGURE 5 Assessment of cost-effectiveness: summary of study selection and exclusion.

TABLE 20 Dose and timing of anti-D assessed within the identified economic evaluations

Economic evaluation	Primi- (P) or multigravidae (M)	2 × 500 IU at 28 and 34 weeks	2 × 1250 IU at 28 and 34 weeks	1 × 1500 IU at 28 weeks	1 × 1250 IU at 28 weeks	Unknown dose at 28 weeks	Unknown dose at 28 weeks and timing
Lim <i>et al.</i> ¹⁵⁸	M					✓	
Tovey <i>et al.</i> ¹⁶³	P	✓					
Adams <i>et al.</i> ¹⁵⁶	P			✓			
Torrance <i>et al.</i> ¹⁶⁰	P and M						✓
Baskett <i>et al.</i> ¹⁵⁷	M	✓				✓	
Vick <i>et al.</i> ^{161,162}	P and M	✓	✓		✓		
Selinger <i>et al.</i> ¹⁵⁹	P	✓					
Mackenzie <i>et al.</i> ¹²⁶	P	✓					
Chilcott <i>et al.</i> ^{1,164}	P and M	✓	✓				

Reduction of Rh_o(D) sensitisation: a cost-effective analysis

Lim and colleagues¹⁵⁸ put forward both a cost-effectiveness and a cost-benefit analysis of RAADP at 28 weeks' gestation, although the details reported are very limited. The study is the first American study on the incidence of gestational sensitisation, using patient data collected from hospitals in the Los Angeles area between 1976 and 1978. Data from 3995 deliveries are used in the analysis. The actual methods used for calculating cost-effectiveness and cost-benefit are not well detailed. The cost of preventing one sensitisation using anti-D administered at 28 weeks (unspecified amount) was estimated to be US\$8450.96. The authors believe that lifesaving benefit will be realised from more liberal usage of anti-D. It should be noted that savings arising from preventing sensitisation and savings in newborn intensive care unit costs, which have been included in other evaluations, are not included in this analysis.

The Yorkshire antenatal anti-D immunoglobulin trial in primigravidae

Tovey and colleagues¹²⁸ compare a group of primigravidae receiving 500 IU of AADP at 28 and 34 weeks' pregnancy with historical controls. The main outcome measure is cost per immunisation avoided. The extra cost in anti-D immunoglobulin was approximately £1600 for each woman sensitised. As little economic information is provided, more detail cannot be reported here.

Cost implications of routine antenatal administration of Rh immune globulin

The evaluation put forward by Adams and colleagues¹⁵⁶ estimates the benefits, risks and costs using decision analytic modelling of a programme of RAADP administered to RhD-negative primiparae in the US. The comparators within the model are:

- routine antepartum and postpartum administration of 1500 IU of anti-D IgG for RhD-negative primiparae at 28 weeks' gestation
- postpartum administration.

The model enables the number of women experiencing each outcome to be estimated. These outcomes are:

- the number of births with mild or moderate/severe RhD HDN
- the number of women without second pregnancies
- the number of women with unaffected pregnancies.

The model also has the ability to assess the impact of alternative strategies on morbidity, mortality and medical care cost. The primary outcome for the model is cost per case avoided, and the results are presented by ethnic group, as follows:

- cost per case avoided: white = US\$28,571, black = US\$22,222, Asian = US\$11,429.

The authors claim to present a conservative analysis by overestimating the risks of the antepartum programme and underestimating benefits.

Cost-effectiveness of antepartum prevention of Rh immunisation

The economic evaluation by Torrance and Zipursky¹⁶⁰ assesses both the cost-effectiveness and the cost-utility of an RAADP prevention programme in Ontario, Canada. The purpose of the study is to assess whether a programme of RAADP is not only cost-effective but also sufficiently cost-effective to warrant its use.

The key economic results of the study are summarised below:

- cost-effectiveness: cost per immunisation prevented = US\$2700; cost per case of Rh disease prevented = US\$3700; cost per life saved = US\$29,500, cost per life-year saved = US\$1500
- cost-utility: cost per quality-life adjusted life-year (QALY) gained = US\$1500.

The authors conclude that RAADP treatment of all RhD-negative pregnant women is sufficiently cost-effective to warrant its use. Treating primiparae is found to be more favourable than treating multiparae. It is recognised that the results are specific to Ontario only and are therefore not generalisable worldwide.

Prevention of Rh(D) alloimmunisation: a cost-benefit analysis

Baskett and colleagues¹⁵⁷ report a cost-benefit analysis of the prevention and treatment of RhD

alloimmunisation in Nova Scotia, Canada. This economic evaluation uses patient data collected from the Rh Programme of Nova Scotia between 1982 and 1986. The evaluation weighs the costs of additional medical procedures and hospital days associated with the complications resulting from RhD alloimmunisation against the costs associated with one dose of anti-D IgG at 28 weeks (unspecified amount) and its administration. The effectiveness of the conventional treatment comparator is based upon previously published studies of a historical population from a different country, which brings into question the validity of this study. The study reports the total additional costs associated with subsequent complications. The author suggests that 80.1% of the additional health-care expenses were incurred because of the need for neonatal intensive care. The headline result of the study is that an RhD alloimmunisation prevention programme is cost-effective. Based on 1986 prices the cost per case treated is calculated to be US\$3986 while the cost per case prevented is calculated to be US\$1495.

Cost-effectiveness of antenatal anti-D prophylaxis

Vick *et al.*^{161,162} describe a model to calculate the incremental cost per RhD alloimmunisation prevented and the incremental cost per RhD HDN fetal loss prevented for six different AADP programmes. The evaluation uses ‘real world’ data obtained from blood transfusion centres, hospitals and haematology laboratories in Scotland to assess the incremental cost-effectiveness. The results calculated from the model are presented in *Table 21*.

This is the only model for which extensive detail of the methods and sensitivity analysis are provided.

The economic outcomes are robust although there is some concern about the inclusion of cost savings arising in the current (i.e. treated) pregnancy, the clinical justification for which is unclear. A cost per QALY outcome is not assessed because of the difficulties involved in assigning quality of life gains appropriately. A policy of RAADP for RhD-negative primigravidae has a better cost-effectiveness ratio than a policy of RAADP for all RhD-negative pregnant women. When comparing dose protocols the 1×1250 IU dosage regimen is more effective and less costly than the 2×1250 IU programme. It should be noted that, although in this analysis cost savings are estimated to arise in the current pregnancy, this is not in fact the case. The net costs of the programme may therefore be underestimated.

Building on success: antenatal prophylaxis. The pharmacoeconomics of antenatal prophylaxis

Selinger¹⁵⁹ reports a cost-benefit evaluation of two doses of 500 IU of antenatal prophylaxis at 28 and 34 weeks of pregnancy versus perinatal care for the treatment of RhD disease. Resource and effectiveness data relate to the Oxford Regional Health Authority, and evaluation takes the form of annual costs. Selinger calculates that, within this setting, the antenatal prophylaxis programme would have a cost advantage of £48,700 (37%) per year over perinatal care (£132,000–£83,300). However, he suggests that this may be an overestimate and that, as a result of other resource and cost factors that have not been captured within the evaluation, the true cost advantage of antenatal prophylaxis may be approximately 30%. This, however, assumes that all RhD HDN is eradicated.

TABLE 21 Summary of economic results from Vick *et al.*¹⁶²

	Dose regimen		
	1 × 1250 IU	2 × 500 IU	2 × 1250 IU
Incremental cost per RhD alloimmunisation prevented			
Primigravidae vs no routine AADP	–£1172	–£197	£1464
All women vs primigravidae	£2915	£4908	£8272
Incremental cost per Rh HDN loss prevented			
Primigravidae vs no routine AADP	–£17,136	–£2,845	–£21,268
All women vs primigravidae	£42,346	£71,308	£120,174

AADP, antenatal anti-D prophylaxis; HDN, haemolytic disease of the newborn.

The author suggests the need for further high-quality trials.

Routine antenatal Rhesus D immunoglobulin prophylaxis: the results of a prospective 10-year study

MacKenzie *et al.*¹²⁶ assess the clinical and financial impact of 500 IU of RAADP for RhD-negative nulliparae at 28 and 34 weeks' gestation. The evaluation uses empirical resource and cost data to evaluate the cost savings associated with implementing antenatal prophylaxis. The study reports the reductions in resource requirements that might be achieved as a consequence of implementing the programme across England and Wales. It is estimated that the savings from reduced antenatal and postnatal management as a result of such a programme would be £3,431,000. It is suggested that this may be a conservative estimate as 16% of the study population had previous pregnancies outside the study district and probably had not received RAADP. The uptake of the programme of routine antenatal prophylaxis appears to be promising. However, the costs of the programme are estimated at £2,135,000 for nulliparae only, and double that – i.e. more than the estimated savings – for all RhD-negative pregnant women.

A review of the clinical effectiveness and cost-effectiveness of routine anti-D prophylaxis for pregnant women who are Rhesus negative

This assessment report, produced by Chilcott *et al.*¹ for NICE in 2001 for the 2002 RAADP appraisal,⁸⁷ evaluates the use of two regimens of RAADP against no routine anti-D:

- two doses of 500 IU at 28 and 34 weeks' gestation
- two doses of 1250 IU at 28 and 34 weeks' gestation.

The evaluation suggested that there was insufficient evidence to indicate a difference in efficacy between the dosing regimens and hence the difference between economic outcomes is dependent only on price differences between the indications.

The model evaluates the cost-effectiveness of RAADP for primigravidae and multigravidae in terms of the following outcomes:

- cost per fetal loss, stillbirth, neonatal death or postneonatal death avoided
- cost per life-year gained (LYG)
- number of disabilities avoided
- cost per QALY gained as a result of disabilities avoided.

The cost per LYG and cost per QALY gained for primigravidae versus no RAADP were estimated to be around £5000 and £11,000–£13,000, respectively, whereas the incremental LYG and incremental QALY gained for primigravidae and multigravidae versus primigravidae were estimated at around £15,000 and £46,000–£52,000 respectively. Because of the limited evidence concerning the impact of fetal loss and parental grief in terms of health-related quality of life, a threshold analysis was undertaken around this parameter. The threshold analysis suggested that, to obtain a cost-effectiveness ratio below £30,000 per QALY for anti-D given to primigravidae and multigravidae, the lost child, associated parental grief and subsequent high intervention pregnancy would need to be valued at more than nine QALYs.

Independent economic assessment

There were no new health economic models provided within the manufacturers' submissions for this assessment report. The independent economic model that was developed in 2001 for the NICE RAADP appraisal⁸⁷ has been modified to incorporate recent additional evidence identified for this review. This review reassesses the use of 500 IU and 1250 IU of anti-D at 28 and 34 weeks' gestation and, in addition, evaluates the use of a single dose of 1500 IU of anti-D at 28 weeks' gestation. Although coverage of RAADP is currently approximately 90%,⁸⁹ these regimens are evaluated against no RAADP to enable the assessment of all interventions against the same comparator and to enable a reassessment of the cost-effectiveness of RAADP against no RAADP. Within this assessment, in an attempt to improve upon the cost per QALY analysis, we have also revisited the assumptions around valuation of fetal loss and quality of life of those who suffer from developmental problems. Population parameters, costs and current statistics such as average life expectancy and the probability associated with having subsequent children have also been updated within this assessment.

Methods

Modelling methodology and scope

The model simulates the experience of a hypothetical cohort of women to whom national fertility rates are assumed to apply. The experience of this cohort over time is assumed to match the experience of a mixed population of primigravidae and multigravidae during any one year. The model follows a NHS perspective and all costs and utilities are discounted at a rate of 3.5% each year.

The interventions for both primigravidae and multigravidae are:

- 500 IU at 28 and 34 weeks' gestation (D-Gam)
- 1250 IU at 28 and 34 weeks' gestation (Partobulin)
- 1500 IU at 28 weeks' gestation (Rhophylac)
- 1500 IU at 28 weeks' gestation (WinRho).

It should be noted that, although WinRho is licensed for use as RAADP, the manufacturers state that it is marketed and used solely for the clotting disorder immune thrombocytopenic purpura and hence is priced specifically for that market.¹⁰³ Interventions are compared against each other and against a policy of no RAADP.

The outcomes of interest within the model are:

- cost per sensitisation avoided
- cost per affected pregnancy avoided
- cost per fetal loss avoided (where fetal loss includes stillbirths and neonatal and postnatal deaths)
- cost per LYG
- cost per QALY gained.

Efficacy of RAADP

The systematic review of clinical effectiveness presented in Chapter 3 did not identify any evidence to suggest a difference in efficacy between the different regimens of RAADP. On the basis of face validity, visual examination of the absolute trial results, individual odds ratios within trials and results of the meta-analyses (shown in *Table 16*), the trials show a remarkable consistency in results, even between dosage regimens. Consequently, the results of the meta-analysis of group 3 trials (see Chapter 3, Critical review and synthesis of information) are deemed to give a representative reflection of the actual effectiveness of RAADP, and these figures are used in the economic evaluation. Therefore, within the economic model the base-case sensitisation rate is assumed to be 0.95% and the odds ratio for each of the regimens of RAADP is assumed to

be 0.37. Thus, any differences in the economic results between the different RAADP regimens are dependent on price only. However, an economic model is required to evaluate the cost-effectiveness of RAADP given to RhD-negative women in comparison with no RAADP and to compare the cost-effectiveness of RAADP for all RhD-negative women versus RhD-negative primigravidae.

A cohort of 104,000 women is modelled to represent the number of RhD-negative women in England and Wales based on a birth rate of 12.1 per 1000 women per year¹⁶⁵ and assuming that 16% of the population is RhD negative.¹⁰ Of these women, 45,041 are RhD-negative primigravidae, based on the probability of having a second, third and fourth pregnancy (conditional on having the previous pregnancy) being 85%, 40% and 35% respectively.¹⁶⁵ Of the primigravidae, 61% will have a RhD-positive baby and, therefore, their pregnancy will be at risk. This proportion is based on the zygosity of the father, and its derivation is described in the next section. This results in 27,430 pregnancies at risk. In the case described the mothers are given RAADP for all pregnancies and, therefore, 0.35% will become sensitised based on the meta-analysis described in Chapter 3 (see Critical review and synthesis of information). This results in an estimated 97 sensitisations. Of these women, 85% are expected to go on to have a second pregnancy,¹⁶⁵ and around 70% of these second pregnancies will be RhD positive and with an affected fetus. The increase in the proportion of RhD-positive fetuses during the second pregnancy is based upon the fact that, once a couple have had one RhD-positive baby, they are more likely to have another one (see the next section for method of calculation). This results in 58 cases of HDN in the next pregnancy.

This cycle is then repeated. The number of non-sensitised RhD-negative women entering a second pregnancy is the original number of non-sensitised women minus the prevalent number of women sensitised during earlier pregnancies multiplied by 85%, the percentage of women having a second pregnancy. This results in 38,285 non-sensitised RhD-negative women entering a second pregnancy. Of these, 70% (25,392 pregnancies) will have a RhD-positive baby and, therefore, their pregnancy will be at risk. As RAADP is given, 0.35% of these will become sensitised for the first time (90 sensitisations). The number entering a third pregnancy equals the number sensitised for the first time in the second pregnancy plus the number sensitised in the first pregnancy who continued

on to a second pregnancy multiplied by 40%, the percentage of women having a third pregnancy given that they have had a second pregnancy. Of these fetuses, 70% will be RhD positive and, therefore, will be affected. This results in 48 cases of HDN in the next pregnancy.

This process is then repeated again, with the percentage of women entering a fourth pregnancy given that they have had a third pregnancy reduced to 35%.

This method of calculation has been used for all scenarios, and so in the case in which AADP is not administered, the sensitisation rate is 0.95% instead of 0.35%. When prophylaxis is given only to primigravidae, only the first 45,041 pregnancies are given antenatal prophylaxis and, therefore, the risk of sensitisation in second and subsequent pregnancies returns to 0.95%. Based on the above assumptions and parameter values the clinical outcomes for the base-case population of England and Wales for no RAADP, RAADP for RhD-negative primigravidae and RAADP for all RhD-negative women are as shown in *Table 22*.

Proportion of RhD-positive babies born to RhD-negative women

The proportion of RhD-positive babies born to RhD-negative women is dependent upon the zygosity of the father. If the father is homozygous (i.e. he has two RhD-positive genes) all of his children will be RhD positive, but if he is heterozygous (i.e. he has one RhD-positive gene and one RhD-negative gene) his children will have a 50% chance of being RhD negative.⁶⁵ Therefore the model assumes:

$$\begin{aligned} \% \text{ of RhD-positive babies born to RhD-} \\ \text{negative women} = \% \text{ of RhD-positive men} - (\% \\ \text{of RhD-positive men} \times \% \text{ of heterozygous} \\ \text{men} \times \text{probability that a heterozygous man will} \\ \text{produce a RhD-positive baby}) \end{aligned}$$

Assuming that the probability of a father in the general population being RhD positive is 84%,¹⁰ based on the above, the probability of a RhD-negative woman having a RhD-positive baby is 61%. This closely matches published estimates.^{156,162} However, following one RhD-positive baby, a woman may be more likely to have another RhD-positive baby because of the genetic make-up of the father. This probability is dependent upon the baby having the same father in consecutive pregnancies and is therefore highly uncertain. It is calculated as shown in *Table 23*.

These calculations are based on the assumption that there is the same probability of a baby having the same father as for the previous pregnancy, independent of size of family. As shown in *Table 23* the probability that the baby will be RhD positive in subsequent pregnancies is reasonably robust to changes in the proportion of babies with the same father in that pregnancy, with a standard error of 4%.

HDN outcomes

To assess the implications of HDN, a literature search was undertaken to identify the possible outcomes associated with HDN and their impacts upon costs and health-related quality of life. The largest study identified around the outcomes associated with HDN is a study by Craig *et al.*¹⁹ based on all pregnant women in Northern Ireland from September 1994 to February 1997. This study is described in further detail in Chapter 1 (see Aetiology, pathology and prognosis). Because of the small proportion of babies affected by HDN, large studies of RhD-negative women have very few occurrences of the disease. Therefore, although this study was based on all pregnant women in Northern Ireland over a 3-year period, there were three fetal losses and two babies born with major developmental problems and five born with minor developmental problems as a result of HDN. Thus, based on this study, for an at-risk fetus the probability of fetal loss is around 4%, the probability of minor developmental problems (including myopia, squint, delays in language development) is around 6%, and the probability of major developmental problems (including severe permanent neurodevelopmental delay such as cerebral palsy) is around 3%. However, given the small number of HDN-related events, these estimates are subject to considerable uncertainty.

Within the model a fetal loss is associated with a loss of 79 life-years and 70 QALYs. This is based on the theory that a fetus that has not been affected by HDN is likely to have lived to average life expectancy and hence this has been modelled in the same way as for other diseases that would end life prematurely. After discounting, this equates to 28 life-years and 24 QALYs lost. A separate parameter has not been included for any reduction in the quality of life of the parent(s). However, a threshold analysis has been carried out to assess the impact of different views on the QALY loss associated with a fetal loss. This parameter includes both the life-years lost by the fetus and the QALYs lost by the parent(s). These have not been assessed distinctly because of the different weightings people would place upon the value of each.

TABLE 22 Expected number of affected pregnancies in England and Wales

	Pregnancy number	Number of RhD-negative pregnancies	Number having RhD-positive baby who have not been sensitised previously	Number sensitised in current pregnancy	Number sensitised from previous pregnancy who go on to have another baby	Prevalent number of sensitised women during each pregnancy	Number of affected (RhD-positive) fetuses following sensitisation
No RAADP	First	45,041	27,430	261	0	261	0
	Second	38,285	25,295	240	221	462	155
	Third	15,314	10,123	96	185	281	129
	Subsequent	5360	3520	33	98	132	69
	Total	104,000	66,368	630	505	1135	353
RAADP given to RhD-negative primigravidae	First	45,041	27,430	97	0	97	0
	Second	38,285	25,392	241	82	324	58
	Third	15,314	10,165	97	129	226	91
	Subsequent	5360	3534	34	79	113	55
	Total	104,000	66,522	468	291	759	204
RAADP given to all RhD-negative women	First	45,041	27,430	97	0	97	0
	Second	38,285	25,392	90	82	172	58
	Third	15,314	10,208	36	69	105	48
	Subsequent	5360	3566	13	37	49	26
	Total	104,000	66,596	235	188	424	132

TABLE 23 Probability of RhD-positive baby following delivery of a RhD-positive baby

Parameter	Mean value	SE ^a	Source/calculation
Births within marriage	369,997	–	Office for National Statistics ¹⁶⁶
Percentage of births of same father within marriage	100%	–	Assumption
Births outside of marriage	269,724	–	Office for National Statistics ¹⁶⁶
Percentage of births of same father outside marriage	50%	15%	Assumption
Percentage of babies with same father in next pregnancy	79%	5%	Calculated from rows above: $(a/a+c) \times b + (c/a+c) \times d$
Probability that baby will be RhD positive in first pregnancy/in subsequent pregnancies given different father	61%	4%	Calculated as described above
Probability that baby will be RhD positive given same father	73%	4%	Calculated using formula above
Probability that baby will be RhD positive in second, third and fourth pregnancies	70%	4%	Calculated based on weighted probability of the fetus being RhD positive given the same or different father

SE, standard error.
a All distributions are normal unless otherwise stated.

Within the model the quality of life of a child with minor developmental problems is based on a study that assessed the health utility of low-birthweight babies,¹⁶⁶ given the limited data around children with myopia, squint and language delay. The control group of this study has been used to represent the health utility of babies who are not affected by HDN. Therefore health utility scores of 0.85 and 0.88 were used to represent children with minor developmental problems and children and adults with no developmental problems respectively. Children with myopia and squint are typically provided with glasses to correct the problem; the cost of an eye test is around £16¹⁶⁷ and the cost of glasses is around £84¹⁶⁸ (average of published prices), meaning that the annual cost is estimated to be around £100 per patient. Teachers and carers of children with language delay are likely to require education by language and speech therapists as to how they may help such children to progress with their language development more rapidly; however, the annual societal cost for these children is extremely variable. Moreover, the proportion of children affected by each of myopia, squint and language delay associated with HDN is highly uncertain. Therefore, the model assumes that the annual cost for children with minor developmental problems is £100 based on the myopia/squint estimates. At age 16 these costs are no longer paid by the NHS and the quality of life

implications of the minor developmental problems are assumed to become negligible.

To value the health-related quality of life and costs associated with major developmental problems the model uses data from cerebral palsy studies, as this is likely to be one of the major developmental problems associated with HDN. The health utility score associated with major developmental problems is assumed to be 0.42 based on a study of young adults with a range in severity of cerebral palsy who self-assessed their own quality of life.¹⁶⁹ The cost associated with this group is based on a study by Beecham *et al.*¹⁷⁰ This study calculates the additional cost of a person with cerebral palsy in comparison with a non-disabled child in the UK. The costs incurred to the NHS and Personal Social Services (PSS) taken from this study include inpatient hospital stays, outpatient appointments, A&E attendances, community health services (including chiropody, orthotist, occupational therapy, physiotherapy, speech therapy, psychiatry, psychology, counselling and contact with doctors and surgeons) and primary care services (including general practitioner, opticians and dentist). The annual cost is therefore assumed to be £458 on average, although the confidence intervals associated with this cost are wide and skewed because of the large variation in severity of major developmental problems and the treatment costs

associated with them. The life expectancy of people with major developmental problems is assumed to be between 40 and 79, based on an extrapolation of data from a paper by Hemming *et al.*,¹⁷¹ which presents an assessment of the life expectancy of people with cerebral palsy in the UK. The upper bound is such that the life expectancy of a person with a major developmental problem will not be greater than the life expectancy of a person without a developmental problem within the model.

It should be noted that the parameters associated with the outcomes of HDN are subject to considerable uncertainty because of limitations in the evidence base. The impact of this uncertainty on the cost-effectiveness of RAADP has been explored within the sensitivity analysis.

Cost of routine antenatal anti-D prophylaxis

The cost of anti-D was taken from the BNF.¹¹⁶ At current prices the cost is between £27 and £313.50 per vial depending upon manufacturer and dosage; however, the cost paid by hospitals may be lower than these listed prices. The cost of 500 IU of D-Gam is reported by the manufacturer of this product to be £19.50 per vial.⁹¹ Similarly, the NHS price quoted for Partobulin by the manufacturer is between £19 and £21. Therefore, the cost of anti-D and its administration has been tested within a threshold analysis. It should be noted that, because the current market price in the anti-D field varies with supply and demand and could easily change, the formulation that is more expensive in terms of list price may in some cases be less expensive because of local price negotiations. Therefore, comparisons between the cost-effectiveness of the anti-D regimens should be interpreted with caution.

Cost of management of sensitisation

The cost of the management of sensitisations is taken from a range of sources including Selinger,¹⁵⁹ Craig *et al.*,¹⁵⁹ Kumar and Regan,³¹ Greenough *et al.*¹⁷² and expert opinion (Dr D Peebles, 2007, personal communication). NHS reference costs from 2005–6¹⁷³ are applied to the interventions required as shown in *Table 24*. The total average cost per person is estimated to be £2885. However, this is a complex condition and hence many factors including differences in severity will affect the cost of treatment. Further, some may require repeat Doppler scans or transfusions given inconclusive results and some additional costs not included here may be incurred for mothers 'rooming in' (i.e. staying at the hospital but without requiring

treatment). Because of the uncertainty associated with this parameter a wide standard error of £700 has been applied, which ensures that all estimates are greater than £0.

Model parameters and assumptions

The parameters used within the model as described above are outlined in *Table 25*. Costs refer to 2007 prices.

Within the model the following assumptions have also been made:

- there will be approximately the same proportion of primigravidae and multigravidae every year
- sensitisations do not affect the first RhD-positive child
- anti-D used within one pregnancy has no effect in reducing sensitisations during the next pregnancy
- the proportion of RhD-negative people is based on the Caucasian population given that this group makes up over 90% of the population of England and Wales;¹⁶⁵ the cost-effectiveness of RAADP for ethnic minorities is tested in a subgroup analysis
- the proportion of homozygous males is the same regardless of ethnic minority
- fetal loss of the newborn results in 79 life-years lost (average life expectancy) and 70 QALYs lost, which equates to 28 discounted life-years lost and 24 discounted QALYs lost.

Subgroup analysis

Because the proportion of RhD-negative people varies with ethnic race, a subgroup analysis has been carried out to assess the implications for cost-effectiveness of using RAADP amongst some of the ethnic minorities in England and Wales. The parameters used within this analysis are taken from Contreras¹⁰ and Ali *et al.*²⁹ and are shown in *Table 26*.

This subgroup analysis assumes that 55% of fathers are heterozygous irrespective of ethnicity.

Sensitivity analysis

One-way sensitivity analysis has been undertaken to identify key determinants of cost-effectiveness. Probabilistic sensitivity analysis has been undertaken to explore the impact of joint uncertainty in all model parameters upon the cost-effectiveness results. The confidence intervals used to describe the uncertainty in the parameters

TABLE 24 Cost of management of sensitisation

Intervention	Percentage of sensitised mothers/babies requiring intervention	Average number required per person	Average days per treatment	Unit cost of intervention	Total cost	Listed NHS reference costs used for the unit costs
Blood tests, bilirubin, monitoring, etc.	100%	6	1	£93	£558	Antenatal outpatients – other high-risk expectant mother follow-up visit
Doppler scanning	90%	4	1	£83	£299	Doppler ultrasound
In utero transfusion	5%	3	1	£93	£14	Antenatal outpatients – other high-risk expectant mother follow-up visit
Phototherapy	71%	1	3	£724	£1542	Neonates with one minor diagnosis – non-elective
Exchange transfusion	5%	2	1	£724	£72	Neonates with one minor diagnosis – non-elective
Neonatal follow-up visits	10%	2	1	£724	£145	Neonates with one minor diagnosis – elective
Neonatal intensive care unit	5%	1	5	£1020	£255	Neonatal intensive care unit – level 1
Total					£2885	

Sources: Selinger,¹⁵⁹ Craig *et al.*,¹⁹ Kumar and Regan,³¹ Greenough *et al.*¹⁷² and expert opinion (Dr D Peebles, 2007, personal communication).

TABLE 25 Model parameters

Parameter	Mean value	SE ^a	Source
Discount rate for utilities	3.5%	–	Recommended by NICE
Discount rate for costs	3.5%	–	Recommended by NICE
Number of women requiring treatment	104,000	–	Office for National Statistics ¹⁶⁵
Average woman's life expectancy (years)	79	–	Office for National Statistics ¹⁶⁵
Crude birth rate: all births per 1000 population	12.1	–	Office for National Statistics ¹⁶⁵
Sensitisation rate without RAADP	0.95%	0.39%	Based on meta-analysis (see Chapter 3, Assessment of effectiveness)
Relative risk of sensitisation with RAADP (all regimens)	0.37	Log norm (–1.23 to 0.69)	Based on meta-analysis (see Chapter 3, Assessment of effectiveness)
Cost of RAADP per vial			
500 IU at 28 and 34 weeks (D-Gam)	£27.00	–	<i>British National Formulary</i> ¹¹⁶
1250 IU at 28 and 34 weeks (Partobulin)	£35.00	–	
1500 IU at 28 weeks (Rhophylac)	£46.50	–	
1500 IU at 28 weeks (WinRho)	£313.50	–	
Percentage of RhD-negative people	16% ^b	–	Romen and Pernoll 2003 ⁶⁵
Percentage of fathers who are heterozygous	55%	10%	Romen and Pernoll 2003 ⁶⁵
Percentage of RhD+ babies in RhD– women (first baby)	61%	4%	Assumption based on Romen and Pernoll 2003 ⁶⁵ (see Table 23 for details).
Percentage of RhD+ babies in RhD– women (second, third and fourth babies)	70%	4%	
Percentage of first pregnancies proceeding to next pregnancy	85%	–	Office for National Statistics ¹⁶⁵
Percentage of second pregnancies proceeding to next pregnancy	40%	–	Office for National Statistics ¹⁶⁵
Percentage of third pregnancies proceeding to next pregnancy	35%	–	Office for National Statistics ¹⁶⁵
Fetal loss rate per woman at risk	4%	1%	Craig <i>et al.</i> 2000 ¹⁹
Percentage of babies affected by HDN with minor developmental problems	6%	2%	Craig <i>et al.</i> 2000 ¹⁹
Duration of minor developmental problems (years)	16	5	Based on the fact that the NHS stops paying for children's treatment at age 16
Percentage of babies affected by HDN with major permanent developmental problems	3%	1%	Craig <i>et al.</i> 2000 ¹⁹
Life expectancy of person with major developmental problems	60	Uniform (40–79)	Assumption based on Hemming <i>et al.</i> 2005 ¹⁷¹
QoL for person with no developmental problems	0.88	0.02	Saigal <i>et al.</i> 2006 ¹⁶⁶
QoL for minor developmental problems	0.85	0.02	Saigal <i>et al.</i> 2006 ¹⁶⁶
QoL for major developmental problems	0.42	0.03	Rosenbaum <i>et al.</i> 2007 ¹⁶⁹
Cost of anti-D administration per dose	£5	£2	Submission to NICE from the Association of Radical Midwives, 2001

continued

TABLE 25 Model parameters (continued)

Parameter	Mean value	SE ^a	Source
Cost of management of a sensitised woman	£2885	£700	Based on Selinger 1997, ¹⁵⁹ Kumar and Regan ³¹ and Greenough <i>et al.</i> ¹⁷² and NHS reference costs 2005–6 ¹⁷³
Cost of minor developmental problems per year	£100	£35	Assumption based on treatment of myopia/squint ^{167,168}
Cost of major developmental problems per year	£458	Gamma (5.84, 0.76)	Beecham <i>et al.</i> 2001 ¹⁷⁰ (uplifted to 2006 prices)

HDN, haemolytic disease of the newborn; QoL, quality of life; SE, standard error.
a All distributions are normal unless otherwise stated.
b Assessed in subgroup analysis.

TABLE 26 Effect of ethnicity upon RhD genotype

Ethnicity	Proportion RhD negative	Source
Caucasian	16%	Contreras ¹⁰
Asian	9%	Ali <i>et al.</i> ²⁹
West African	5%	Contreras ¹⁰
Chinese	1%	Contreras ¹⁰

within the probabilistic sensitivity analysis are the same as those used within the one-way sensitivity analysis. The uncertainty around the parameters is described using the normal distribution unless otherwise stated. The parameters assessed within the one-way sensitivity analysis are as follows:

- Odds ratio for sensitisation rate of anti-D – The efficacy of RAADP is assumed to vary between 0.21 and 0.65 based on the meta-analysis of the clinical studies (see Chapter 3, Assessment of effectiveness).
- Base-case sensitisation rate – The base-case sensitisation rate is assumed to vary between 0.18% and 1.71% based on the meta-analysis of the clinical studies (see Chapter 3, Assessment of effectiveness).
- Proportion of heterozygous males – This parameter will affect the proportion of RhD-positive babies born to RhD-negative mothers and hence it is important to assess whether it is a key determinant of cost-effectiveness. Evidence identified suggests that this parameter lies between 55% and 60%; however, a wider confidence interval of 35% and 75% has been used because of the limited evidence available in this area.
- Fetal loss rate per woman at risk – The fetal loss rate is varied using a normal distribution with confidence intervals of 2% and 6%. This range ensures that all estimates are greater than 0%.
- Yearly cost of major developmental problems; life expectancy for people with major developmental problems, quality of life of people with major developmental problems – There is limited evidence around the outcomes of HDN and their costs and consequences. Therefore, the major parameters impacting upon these outcomes are assessed within the one-way sensitivity analysis using the standard errors presented within the studies used for each of these parameters.
- Cost of management of sensitisation – The mid-estimate for this parameter is £2885 per sensitisation; however, previous estimates have been lower and it is anticipated that this cost will vary considerably in practice. Therefore, a sensitivity analysis has been carried out using a wide standard error of £700, which ensures that all estimates fall above £0.
- Percentage of births outside marriage with the same father – This parameter affects the proportion of RhD-positive babies in second, third and fourth pregnancies. There is no evidence around the proportion of babies having the same father (and mother) as the previous baby; therefore, a mid-estimate of 50% is assumed to be reasonable. This parameter requires a large standard error to

account for the large amount of uncertainty associated with it; therefore, upper and lower confidence intervals are assumed to be 26% and 74% based on a standard error of 12%. This standard error allows all estimates to fall between 0% and 100%.

The parameters associated with minor developmental problems have not been assessed within the one-way sensitivity analysis as they are expected to have a similar but smaller impact on the results as the parameters associated with major developmental problems. As discussed earlier in this chapter a threshold analysis around the valuation of a fetal loss and around the cost of anti-D has also been carried out (see HND outcomes and Cost of RAADP respectively).

Results

Results of the deterministic analysis

The incremental cost-effectiveness outcomes associated with RAADP for RhD-negative primigravidae and for all RhD-negative women are shown in *Tables 27* and *28* respectively.

The model results show that WinRho RAADP would not be considered cost-effective in comparison with the other regimens of RAADP. Excluding WinRho, for all other regimens of RAADP given to RhD-negative primigravidae versus no RAADP, the cost per sensitisation avoided and the cost per affected pregnancy avoided are estimated to be between £11,000 and £21,000. The cost per fetal loss avoided is estimated to be between £300,000 and £515,000. These high estimates are due to the low proportion of fetal losses occurring as a result of HDN within a group of pregnant RhD-negative women.

RAADP given to all RhD-negative women is expected to decrease the number of sensitisations, the number of affected pregnancies and the number of fetal losses, but it is also expected to increase costs. Therefore, giving RAADP to RhD-negative primigravidae and multigravidae compared with giving RAADP to RhD-negative primigravidae only results in a cost per sensitisation avoided of between £8000 and £15,000 and a cost per affected pregnancy avoided of between £28,000 and £48,000 for all regimens of RAADP excluding WinRho. The cost per fetal loss avoided is estimated to be between £697,000 and £1.2 million.

Giving RAADP to RhD-negative primigravidae compared with no RAADP results in a cost per

LYG of between £7000 and £12,000 for all RAADP regimens excluding WinRho. For RAADP given to RhD-negative primigravidae and multigravidae versus RhD-negative primigravidae only, the cost per LYG is estimated to be between £17,000 and £29,000. The cost per QALY gained as a result of RAADP given to RhD-negative primigravidae versus no RAADP is between £9000 and £15,000 for all RAADP regimens apart from the one-dose regimen of 1500 IU of WinRho, which has a cost per QALY gained of around £67,000. For RhD-negative primigravidae and multigravidae compared with primigravidae only, the cost per QALY gained as a result of RAADP is between £20,000 and £35,000 for all anti-D products, again with the exception of 1500 IU of WinRho, which has a cost per QALY gained of around £156,000. As described previously, any comparisons between the different regimens of RAADP should be considered with caution given the variability in actual prices paid by hospitals for anti-D.

Results of the subgroup analysis

Ethnic minorities in England and Wales are less likely to be RhD negative and hence the absolute number of women requiring routine anti-D is expected to be smaller for these subgroups; however, the impact per person is expected to increase if we assume that the father is of the same ethnicity. For example, considering Asian, West African and Chinese people, the model predicts that, although the proportionate number of sensitisations, affected pregnancies and fetal losses will be lower in these ethnic minorities than in the Caucasian population, the cost per sensitisation, cost per affected pregnancy and cost per fetal loss will also be lower. Consequently, the cost-effectiveness ratio is estimated to be slightly better for ethnic minorities. Because the efficacy of each of the RAADP regimens is assumed to be the same within the model, the impact of changes in the proportion of people who are RhD negative is expected to have the same relative impact across the different regimens. Therefore, these results are presented in terms of a 500-IU dose of anti-D (D-Gam) at 28 and 34 weeks' gestation (*Table 29*).

Results of the one-way sensitivity analysis

Several key uncertain parameters within the model (see Sensitivity analysis) have been explored within a one-way sensitivity analysis to assess the robustness of the model. Because the only difference modelled between the RAADP regimens is the price of the drug, each of the model parameters would be expected to have a similar impact upon the cost-effectiveness ratio independent of the RAADP regimen of anti-D.

TABLE 27 Incremental cost-effectiveness outcomes associated with RAADP for RhD-negative primigravidae versus no RAADP

Anti-D dose	Total additional cost	Number of sensitisations avoided	Number of affected pregnancies avoided	Number of fetal losses avoided	LYG	QALYs gained	Cost per sensitisation avoided	Cost per affected pregnancy avoided	Cost per fetal loss avoided	Cost per LYG	Cost per QALY gained
Baseline value ^a	£1,796,546	630	353	14	2,878,648	2,533,240					
2 × 500 IU (D-Gam)	£2,360,604	162	150	6	250	207	£14,561	£15,783	£394,580	£9457	£11,384
2 × 1250 IU (Partobulin)	£3,081,262	162	150	6	250	207	£19,006	£20,602	£515,040	£12,344	£14,859
1 × 1500 IU (Rhophylac)	£1,797,590	162	150	6	250	207	£11,088	£12,019	£300,471	£7201	£8669
1 × 1500 IU (WinRho)	£13,823,575	162	150	6	250	207	£85,267	£92,426	£2,310,641	£55,378	£66,661

LYG, life-year gained; QALY, quality-adjusted life-year.
^a The baseline values are the absolute totals.

TABLE 28 Incremental cost-effectiveness outcomes associated with RAADP for all RhD-negative women versus primigravidae

Anti-D dose	Total cost	Number of sensitisations avoided	Number of affected pregnancies avoided	Number of fetal losses avoided	LYG gained	QALYs gained	Cost per sensitisation avoided	Cost per affected pregnancy avoided	Cost per fetal loss avoided	Cost per LYG	Cost per QALY gained
2 × 500 IU (D-Gam)	£2,645,120	233	72	3	120	100	£11,358	£36,679	£916,982	£21,977	£26,455
2 × 1250 IU (Partobulin)	£3,457,346	233	72	3	120	100	£14,846	£47,942	£1,198,556	£28,725	£34,578
1 × 1500 IU (Rhophylac)	£2,010,568	233	72	3	120	100	£8634	£27,880	£697,002	£16,705	£20,108
1 × 1500 IU (WinRho)	£15,564,594	233	72	3	120	100	£66,836	£215,831	£5,395,767	£129,317	£155,666

LYG, life-year gained; QALY, quality-adjusted life-year.

TABLE 29 Incremental cost-effectiveness results for different ethnicities

Ethnicity (% RhD negative) ^a	Total additional cost	Number of sensitisations avoided	Number of affected pregnancies avoided	Number of fetal losses avoided	LYG	QALYs gained	Cost per sensitisation avoided	Cost per affected pregnancy avoided	Cost per fetal loss avoided	Cost per LYG	Cost per QALY gained
Baseline Caucasian (16%)	£1,796,546	630	353	14.1	2,878,648	2,533,240					
RhD-negative Caucasian primigravidae	£2,360,604	162	150	6	250	207	£14,561	£15,783	£394,580	£9457	£11,384
All RhD-negative Caucasian women	£2,645,120	233	72	3	120	100	£11,358	£36,679	£916,982	£21,977	£26,455
Baseline Asian (9%)	£1,073,357	375	216	8.64	1,619,211	1,424,923					
RhD-negative Asian primigravidae	£1,302,875	99	93	4	154	128	£13,188	£14,080	£352,012	£8436	£10,155
All RhD-negative Asian women	£1,473,105	136	43	2	72	60	£10,797	£34,316	£857,902	£20,561	£24,750
Baseline West African (5%)	£615,566	215	125	5.0	899,553	791,617					
RhD-negative West African primigravidae	£715,875	57	54	2	90	75	£12,494	£13,226	£330,651	£7925	£9539
All RhD-negative West African women	£814,149	77	25	1	41	34	£10,525	£33,158	£828,949	£19,867	£23,915
Baseline Chinese (1%)	£126,868	44	26	1.0	179,909	158,322					
RhD-negative Chinese primigravidae	£141,583	12	11	0	19	16	£11,856	£12,445	£311,116	£7456	£8976
All RhD-negative Chinese women	£162,045	16	5	0	8	7	£10,284	£32,119	£802,986	£19,245	£23,166

LYG, life-year gained; QALY, quality-adjusted life-year.
 a The baseline values are the absolute totals.

Therefore, these results are presented in *Table 30* in terms of a 500-IU dose of anti-D (D-Gam) at 28 and 34 weeks' gestation to avoid unnecessary repetition.

The one-way sensitivity analysis suggests that changing many of the model assumptions has only a small impact upon the incremental cost-effectiveness ratio (ICER). The parameters that have the greatest impact upon the ICER are the base-case sensitisation rate and the odds ratio for the sensitisation rate associated with RAADP. If the base-case sensitisation rate was lower than predicted, anti-D would have a lower absolute effect and hence the cost per QALY gained would increase. At a base-case sensitisation rate of 0.18% (the lower 95% confidence interval), the cost per QALY gained for providing RAADP to all RhD-negative pregnant women is estimated to be around £162,000. At a base-case sensitisation rate of 0.95%, increasing the odds ratio for the sensitisation of RAADP in comparison with no RAADP to its upper 95% confidence interval of 0.65 gives a cost per QALY gained of around £50,000 for RAADP given to all RhD-negative women.

Decreasing the fetal loss rate as a result of HDN from 4% to 2% would increase the cost per QALY gained by around £8000 to £34,000. Decreasing the impact of HDN in any way will increase the ICER to some extent as RAADP will then have less of an impact in terms of efficacy. However, different assumptions around the quality of life and cost of people with major developmental problems do not affect the ICER substantially, increasing it by around £1000 and £3000 respectively. Similarly, different assumptions around the costs of anti-D administration and the management of sensitisation do not have a big impact upon the ICER.

Threshold analysis of the valuation of a fetal loss

Because the valuation of a fetal loss is subjective, according to how the individual may value the QALYs lost associated with the fetus and the QALYs lost by the parent(s), a threshold analysis has been carried out to investigate the impact of different valuations associated with fetal loss. The results are presented in *Table 31*.

These results show that RAADP given to RhD-negative primigravidae compared with no RAADP would be considered cost-effective at a threshold of £30,000 per QALY gained if a fetal loss is assumed to be worth 10, 14 and 6 QALYs lost for

D-Gam, Partobulin and Rhophylac respectively. Similarly, RAADP given to all RhD-negative women compared with RhD-negative primigravidae only would be considered cost-effective at a threshold of £30,000 per QALY gained if a fetal loss is assumed to be worth 20, 30 and 13 QALYs lost for D-Gam, Partobulin and Rhophylac respectively. These QALY losses are a combination of both the parental QALYs lost and those QALYs lost as a result of the death of the fetus itself. As a lifetime lost with a life expectancy of 79 years is equal to 24 QALYs after discounting, Partobulin would be considered cost-effective for all RhD-negative women compared with RhD-negative primigravidae at a threshold of £30,000 per QALY gained if the loss of a fetus was assumed to be equal to the loss of a life with average lifetime expectancy and six QALYs lost by the parent(s).

Threshold analysis of the cost of anti-D

Because the listed price of anti-D in the BNF¹¹⁶ may be different from the actual cost of the drug, a threshold analysis has been carried out. This analysis evaluates the estimated price of anti-D in order for it to be cost-effective at a range of thresholds. The results are presented in *Figure 6* below.

This shows that, at a cost per QALY gained of £30,000, RAADP given to all RhD-negative women compared with RAADP given to primigravidae only would be considered cost-effective at a cost of £76. However, because the results presented here include an administration cost of £5 per dose, a two-dose regimen of RAADP would be considered cost-effective at a cost of £33 per dose [$(£33 \times 2) + £10 = £76$] whereas, at this threshold, a one-dose regimen would be considered cost-effective at a cost of £71 per dose ($£71 + £5 = £76$).

Results of the probabilistic sensitivity analysis

The results of the probabilistic sensitivity analysis for RAADP given to primigravidae versus no RAADP and RAADP given to primigravidae and multigravidae versus primigravidae only in terms of LYG and QALYs gained are shown in *Tables 32* and *33* respectively.

The results of the probabilistic sensitivity analysis closely match those of the deterministic analysis. Any slight difference in the efficacy of each of the RAADP regimens is due to the stochastic nature of the analysis. After taking into account the uncertainty associated with the model parameters, each of the RAADP regimens with the exception of WinRho has an ICER that is between £9000

TABLE 30 Results of the one-way sensitivity analysis

Parameter	Parameter value	Cost per QALY gained	
		Primigravidae	Multigravidae
Base case		£11,384	£26,455
Odds ratio for sensitisation rate of RAADP	Base case	0.37	
	LB	0.21	£8551
	UB	0.65	£22,571
Base-case sensitisation rate	Base case	0.95%	
	LB	0.18%	£70,452
	UB	1.71%	£5255
Proportion of heterozygous males	Base case	55%	
	LB	35%	£8497
	UB	75%	£15,817
Fetal loss rate per woman at risk	Base case	4%	
	LB	2%	£17,378
	UB	6%	£8466
Cost of anti-D administration per dose	Base case	£5	
	LB	£1	£9646
	UB	£9	£13,121
Cost of management of sensitisation	Base case	£2885	
	LB	£1513	£12,458
	UB	£4257	£10,310
Rate of major developmental problems	Base case	3%	
	LB	1%	£14,180
	UB	5%	£9469
Yearly cost of major developmental problems	Base case	£458	
	LB	£78	£11,559
	UB	£1532	£10,886
Life expectancy for people with major developmental problems	Base case	60	
	LB	40	£11,077
	UB	79	£11,556
QoL of people with major developmental problems	Base case	0.42	
	LB	0.36	£11,029
	UB	0.48	£11,762
Percentage of births outside marriage with same father	Base case	50%	
	LB	26%	£11,193
	UB	74%	£11,581

LB, lower bound; QALY, quality-adjusted life-year; QoL, quality of life; RAADP, routine antenatal anti-D prophylaxis; UB, upper bound.

and £15,000 per QALY gained for RAADP given to RhD-negative primigravidae versus no RAADP, and between £20,000 and £34,000 per QALY gained for RAADP given to primigravidae and multigravidae compared with primigravidae only.

WinRho has a cost per QALY gained of around £66,000 for RAADP given to primigravidae versus no RAADP and around £155,000 for RAADP given to all RhD-negative women versus RhD-negative primigravidae only.

TABLE 31 Implied quality-adjusted life-year differential per fetal loss avoided

		Threshold						
		£20K	£25K	£30K	£35K	£40K	£45K	£50K
RAADP given to RhD-negative primigravidae versus no RAADP	D-Gam	17	13	10	8	6	5	4
	Partobulin	24	18	14	12	9	8	7
	Rhophylac	12	8	6	5	3	3	2
RAADP given to all RhD-negative women versus primigravidae	D-Gam	36	26	20	16	13	10	8
	Partobulin	50	38	30	24	20	16	14
	Rhophylac	25	18	13	10	7	5	4

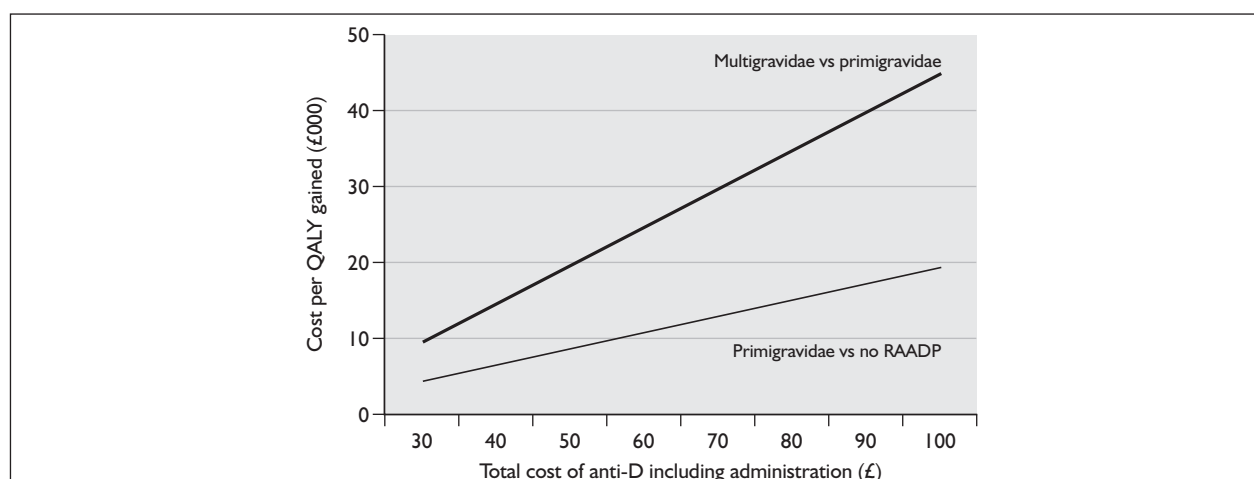


FIGURE 6 Cost per quality-adjusted life-year (QALY) gained based on cost of anti-D and its administration per person.

TABLE 32 Results of probabilistic sensitivity analysis – RAADP given to RhD-negative primigravidae versus no RAADP

Anti-D regimen	Total additional cost	LYG	QALYs gained	Cost per LYG	Cost per QALY gained
Base case: no RAADP ^a	£1,788,704	2,878,650	2,532,262		
D-Gam: 2×500IU	£2,361,850	250	208	£9434	£11,347
Partobulin: 2×1250IU	£3,082,766	251	208	£12,305	£14,821
Rhophylac: 1×1500IU	£1,798,655	250	208	£7184	£8634
WinRho: 1×1500IU	£13,825,342	250	208	£55,281	£66,446

LYG, life-years gained; QALY, quality-adjusted life-year.
 a The baseline values are the absolute totals.

TABLE 33 Results of probabilistic sensitivity analysis – RAADP given to all RhD-negative women versus primigravidae only

Anti-D regimen	Total additional cost	LYG	QALYs gained	Cost per LYG	Cost per QALY gained
D-Gam: 2 × 500 IU	£2,645,112	121	101	£21,871	£26,306
Partobulin: 2 × 1250 IU	£3,457,481	121	100	£28,633	£34,409
Rhophylac: 1 × 1500 IU	£2,010,281	121	101	£16,610	£19,977
WinRho: 1 × 1500 IU	£15,564,912	121	101	£128,746	£154,758

LYG, life-years gained; QALY, quality-adjusted life-year.

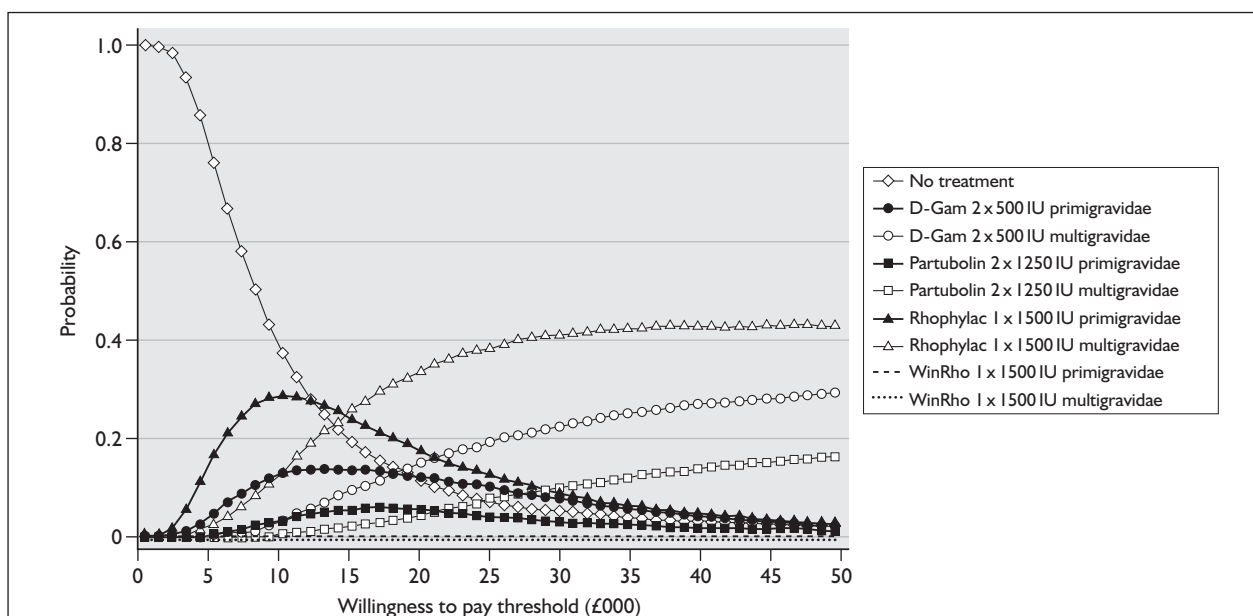
**FIGURE 7** Cost-effectiveness acceptability curves (CEACs).

Figure 7 presents cost-effectiveness acceptability curves for each of the regimens of RAADP versus no RAADP and each other. These curves describe the probability that each of the regimens of RAADP and no RAADP have a cost per QALY ratio that is better than a given willingness to pay threshold (λ).

Figure 7 suggests that, at a threshold of £30,000 per QALY gained, it is more likely to be cost-effective to give RAADP to all RhD-negative pregnant women than to not provide RAADP or to provide RAADP to primigravidae only. Because the model assumes that the efficacy of the different anti-D regimens is the same, the cheaper regimens of anti-D are estimated to be more cost-effective. Therefore, based on the BNF drug prices,¹¹⁶ one dose of 1500 IU of Rhophylac at 28 weeks' gestation is most likely to be cost-effective (around 40% probability) followed by two doses of 500 IU of D-Gam (around 25% probability) and two doses of 1250 IU of Partobulin (around 10% probability)

at 28 and 34 weeks' gestation. The comparison of cost-effectiveness between these three RAADP regimens should be interpreted with caution because of the variability in actual prices paid by hospitals for anti-D. The probability that any of the regimens of RAADP (excluding WinRho) given to all RhD-negative pregnant women is cost-effective at a threshold of £30,000 compared with RAADP given to RhD-negative primigravidae or providing no RAADP is around 70%. One dose of 1500 IU of WinRho is not likely to be considered cost-effective at any threshold because it is substantially more expensive and because of the availability of its comparators.

Discussion

Generalisability of the results

Assuming that there are approximately the same number of primigravidae and multigravidae births each year the results may be considered

representative of Caucasian people within England and Wales. For ethnic minorities within England and Wales, RAADP is expected to be more cost-effective although required less often because of the lower proportion of RhD-negative genotypes in these subgroups. This impact can be seen within the subgroup analysis presented earlier in this chapter (see Results of the deterministic analysis).

The economic model is fairly robust to changes in parameter values. The three key parameters affecting the ICER are:

- the base-case sensitisation rate
- the odds ratio associated with the sensitisation rate with RAADP
- the assumption around the valuation of a fetal loss.

The ICER does not increase by more than £15,000 per QALY for all other parameters assessed within the one-way sensitivity analysis.

The base-case results presented suggest a lower cost per QALY gained as a result of a programme of RAADP than was suggested within the previous RAADP NICE Health Technology Assessment report.¹ Within this assessment report a greater degree of benefit is assumed as a result of the avoidance of sensitisations, as the number of life-years lost associated with a fetal loss is assumed to be equal to average life expectancy. Also, the parameters around developmental problems and the cost of management of sensitisations have been substantially revised. The cost of RAADP itself has increased in comparison with the original assessment and additional comparators of one dose of 1500 IU of anti-D were also considered within this assessment. Finally, population parameters have been revised and average life expectancy has increased by 5 years.

It is important to note that the cost per QALY comparing the different regimens of RAADP presented is driven by the costs of the drugs, as efficacy is assumed to be the same for all dosing regimens of anti-D. There is an argument to suggest that the two-dose regimen could be more effective than the one-dose regimen because of the half-life of anti-D; however, there is no published evidence around this. The cost of anti-D is based on BNF drug prices,¹¹⁶ but as actual prices paid by hospitals vary according to supply and demand, the cost-effectiveness in practice may be better than that presented here. Furthermore, the actual price paid for the different regimens of RAADP may vary, and the formulation that is

more expensive in terms of list price may in some cases be the cheaper drug because advantageous prices have been negotiated locally. It should be noted that, although WinRho is licensed for use as RAADP, the manufacturers state that it is marketed and used solely for the clotting disorder immune thrombocytopenic purpura, and hence is priced specifically for that indication.¹⁰³ The manufacturers suggest that WinRho should not routinely be considered for RhD-negative pregnant women but that, if there were disruptions to the supply of the other three available products, WinRho SDF could provide an alternative to supplement anti-D supplies.¹⁰³

The assessment of RAADP given to all RhD-negative women versus RhD-negative primigravidae is dependent on the assumption that anti-D given in the first pregnancy will not have an impact upon the sensitisation rate of the subsequent pregnancies. There is some evidence to suggest that anti-D given in the first pregnancy may decrease the probability of a sensitisation occurring within subsequent pregnancies¹³³ and hence providing RAADP to RhD-negative primigravidae would be more cost-effective than predicted here. Further research is required in this area.

Finally, there is a small probability that sensitisations may occur in the first pregnancy and hence the first RhD-positive baby may be affected by HDN. Because anti-D should be given to women who have potential sensitising events, we have assumed that this would not be the case. If sensitisations were to occur within the first pregnancy, the absolute number of sensitisations would increase from those estimated within the model, but the relative impact on the cost-effectiveness of anti-D would remain approximately the same.

Quality of life of the parents

The model does not explicitly take into account the quality of life of the parents as a result of the loss of a child, or of being responsible for a disabled child, because of difficulties in the empirical measurement of these quantities. Research suggests that, although quality of life is likely to decrease substantially in the year after the loss of a child, in subsequent years the parents' quality of life is likely to increase to a similar level as before the loss.¹⁷⁴ In general, published evidence suggests that the quality of life of parents of disabled children is lower than that of parents of non-disabled children, but this is also difficult to quantify and is likely to vary considerably. There is also likely to be anxiety caused by continuous monitoring of those

pregnancies in which the mother is sensitised, which is likely to temporarily reduce the mother's quality of life. The implications of a reduction in parental quality of life following sensitisation or HDN is that the cost per QALY gained would be slightly lower than currently predicted.

Compliance and one versus two doses

Within the model it has been assumed that compliance with RAADP for the one-dose or the two-dose regimen would be 100%. Current evidence suggests that only around 90% of women eligible for RAADP receive the drug,⁸⁹ potentially leading to more sensitisations than estimated by the model. If there was a difference in compliance between the one-dose and two-dose regimens this could affect the cost-effectiveness ratio. Compliance may be greater with the one-dose regimen than with the two-dose regimen for logistical reasons; conversely, the one-dose regimen offers only one opportunity to provide RAADP.¹²³ There are currently no published studies comparing compliance between the two regimens but if it was substantially better for one of the routine anti-D regimens then it would improve the overall efficacy of that regimen and hence provide better outcomes.

The analysis also assumes that RAADP can be provided within routine antenatal appointments. Some patients may require additional appointments for the administration of RAADP and some hospitals may have separate clinics for anti-D administration, which will lead to greater costs. If anti-D is not offered during routine appointments this may also have an impact on compliance and hence an effect upon the effectiveness of the drug.

Fetal genotyping

It is now possible to test the genotype of the fetus using non-invasive methods. It should be noted that fetal genotyping would affect not only RAADP but also anti-D given for other indications and hence it is beyond the scope of this assessment.

However, a brief exploratory analysis of the new technology is presented here.

Because just under two-thirds of babies born to RhD-negative mothers are RhD positive, fetal genotyping could save around one-third of RhD-negative women having to be given anti-D. However, if the sensitivity of the fetal genotyping test is not 100% (i.e. each fetus who is RhD positive is detected) then the number of sensitisations is likely to increase. The sensitivity of the fetal genotyping test is currently estimated to be around 99%¹⁷⁵ and hence would need to improve if the proportion of sensitisations is to remain the same.

Fetal genotyping may be associated with an improvement in efficacy in terms of the reduction in the mother's anxiety about the anti-D administrations and the reduction in exposure to different blood products. However, as discussed in Chapter 1 (see Summary of intervention), adverse effects associated with this exposure are extremely rare. Therefore, the efficacy of RAADP using fetal genotyping is unlikely to improve, meaning that for it to be considered cost-effective the cost would need to be less than that of current treatment.

Based on our model, the cost of fetal genotyping compared with the cost of anti-D can be denoted by the formula:

$$\text{anti-D cost} \geq 0.61(\text{anti-D cost}) + \text{cost of fetal genotyping}$$

This simplifies to:

$$0.39(\text{anti-D cost}) \geq \text{cost of fetal genotyping}$$

The cost of RAADP and its administration lies between £51.50 and £319.50 (assuming a £5 administration cost for each dose of anti-D). Therefore, for fetal genotyping to reduce costs associated with RAADP it would need to be priced below that shown in *Table 34*, including administration.

TABLE 34 Cost of fetal genotyping

Anti-D	Cost of anti-D	Cost of fetal genotyping
D-Gam	£64	£24.96
Partobulin	£80	£31.20
Rhophylac	£51.50	£20.09
WinRho	£319.50	£124.22

Current estimates suggest that fetal genotyping is likely to cost around £40 per person.¹⁷⁵ This suggests that fetal screening is likely to be more costly than providing all RhD-negative pregnant women with routine anti-D, except in the case of WinRho. It should be noted that this analysis does not allow for price reductions in anti-D and hence the cost of fetal genotyping may need to be lower

than that estimated here. Furthermore, if the test was not 100% specific the cost of the test would need to be lower still to allow for the additional anti-D given to those women who were carrying an RhD-negative fetus. Therefore, research into fetal genotyping should aim to improve sensitivity and reduce the cost of the test.

Chapter 5

Assessment of factors relevant to the NHS and other parties

Routine anti-D is currently estimated to be used in around 90% of hospitals⁸⁹ and hence the implications for current service provision of recommending RAADP are small. Anti-D can usually be provided during routine antenatal appointments and hence the burden on services not currently providing anti-D is expected to be minimal. The costs associated with providing no RAADP (management of sensitisations, lifetime costs of developmental problems) are estimated to be around £1.8 million throughout England and Wales. The additional costs of supplying RAADP

to RhD-negative primigravidae and to all RhD-negative women in England and Wales each year are shown in *Tables 35* and *36* respectively.

The use of RAADP for RhD-negative primigravidae is estimated in total to cost the NHS an additional £1.8–£3.1 million per year (excluding WinRho) compared with no RAADP according to the RAADP regimen. Giving RAADP to RhD-negative multigravidae in addition to RhD-negative primigravidae increases the costs by a further £2–£3.5 million per year (excluding WinRho).

TABLE 35 Total additional cost to the NHS per year of RAADP given to RhD-negative primigravidae compared with no RAADP provision

Anti-D regimen	Cost of anti-D	Cost of administration	Cost savings associated with HDN ^a	Total cost
2 × 500 IU (D-Gam)	£2,432,222	£450,411	£522,029	£2,360,604
2 × 1250 IU (Partobulin)	£3,152,880	£450,411	£522,029	£3,081,262
1 × 1500 IU (Rhophylac)	£2,094,413	£225,206	£522,029	£1,797,590
1 × 1500 IU (WinRho)	£14,120,398	£225,206	£522,029	£13,823,575

HDN, haemolytic disease of the newborn.
 a Savings associated with the cost of the management of sensitisation and with the cost to society of people with developmental problems.

TABLE 36 Total additional cost to the NHS per year of RAADP given to all RhD-negative women compared with RhD-negative primigravidae

Anti-D regimen	Cost of anti-D	Cost of administration	Cost savings associated with HDN ^a	Total cost
2 × 500 IU (D-Gam)	£2,741,264	£507,641	£603,785	£2,645,120
2 × 1250 IU (Partobulin)	£3,553,490	£507,641	£603,785	£3,457,346
1 × 1500 IU (Rhophylac)	£2,360,533	£253,821	£603,785	£2,010,568
1 × 1500 IU (WinRho)	£15,914,558	£253,821	£603,785	£15,564,594

HDN, haemolytic disease of the newborn.
 a Savings associated with the cost of the management of sensitisation and with the cost to society of people with developmental problems.

Chapter 6

Discussion

Statement of principal findings

All of the evidence indicates that RAADP reduces the incidence of sensitisation. In assessing the impact of the introduction of a programme of RAADP the most relevant studies are those by MacKenzie *et al.*¹²⁶ and Mayne *et al.*¹²⁷ Meta-analysis of the data from these studies indicates that the introduction of such a programme is associated with a fall of 0.6% (from 0.95% to 0.35%) in the number of women found in a subsequent pregnancy to be sensitised, an odds ratio of 0.37 (95% CI 0.21–0.65). These are community-based studies with high external validity as they demonstrate the effectiveness of RAADP in real life in the UK rather than under trial conditions and as measured by the most clinically relevant outcome measure, the number of women found to be sensitised in a subsequent pregnancy.

Although some instances of sensitisation are inevitable, others can be avoided (namely those attributable to failure to provide prophylaxis when appropriate despite the existence of a policy of RAADP). However, the avoidance of such cases will require careful adherence to guidelines. Further, a woman will only benefit clinically if she has an RhD-positive infant and she would have been sensitised and she goes on to have a further infant who is also RhD positive. It is the avoidance of HDN in that infant which constitutes the clinical benefit of RAADP.

No head-to-head studies have been undertaken that compare a one-dose with a two-dose regimen of RAADP, and the studies reviewed above do not provide any evidence to suggest that two 500-IU or 1250-IU doses of anti-D at 28 and 34 weeks' gestation are more or less effective than a single dose of 1500 IU of anti-D at 28–30 weeks' gestation. However, the Royal College of Nursing has expressed concern that a single dose given at 30 weeks (as is possible under the licensed indication for Rhophylac) will clearly not provide protection against an FMH at 28 weeks and may be insufficient to provide protection against an FMH at 39 weeks.¹²³ Several other arguments in addition to clinical effectiveness have been put forward to

support the use of one or other regimen; these relate to compliance and safety. However, there is no published evidence that demonstrates any such differences. It could also be argued that the regimen that uses least anti-D, and places least demand on plasma donors, has an advantage.

There is no evidence to suggest that RAADP is associated with adverse effects of any consequence for either mother or child other than the possibility of transmission of bloodborne infections; this risk is minimised by the safeguards built into the modern manufacturing process.

The economic analysis of RAADP is based on the model developed for the 2002 NICE RAADP appraisal.⁸⁸ However, as well as considering the cost-effectiveness of the two-dose regimens, D-Gam and Partobulin, this assessment also evaluates the use of the one-dose regimens, Rhophylac and WinRho. Of the nine studies identified within the cost-effectiveness review, only those by Vick *et al.*^{161,162} and Chilcott *et al.*^{1,164} describe a detailed modelling study that appears to be applicable to the UK NHS. Furthermore, no new mathematical models were provided within the manufacturers' submissions for the appraisal. The health economic model developed by the assessment group suggests that the cost per QALY gained of RAADP given to RhD-negative primigravidae versus no RAADP is between £9000 and £15,000, and of RAADP given to all RhD-negative women rather than RhD-negative primigravidae only is between £20,000 and £35,000, depending on the RAADP regimen (excluding WinRho). However, as the actual prices paid by hospitals vary, the cost-effectiveness in practice may be better than that presented here. The one-dose regimen of 1500 IU of WinRho is estimated to have a cost per QALY gained above £60,000. The cost-effectiveness of RAADP improves slightly for ethnic minorities in England and Wales.

Strengths and limitations of the assessment

This assessment report reviews the work carried out for the NICE RAADP appraisal from 2002,⁸⁷ despite further research being recommended

within the original report, no additional evidence was identified to be used within the analysis in terms of either clinical effectiveness or cost-effectiveness. Therefore, both the clinical effectiveness and cost-effectiveness are based largely on data taken from the 1990s. However, the clinical effectiveness of anti-D is based on two large community-based UK studies with high external validity. There is no comparative evidence available regarding the efficacy of different RAADP regimens, and therefore the economic comparison of the different regimens is dependent on price only. However, the model of cost-effectiveness is reasonably robust to changes in the parameter values and, hence, at a threshold of £35,000 it is likely that D-Gam, Partobulin and Rhophylac RAADP given to all RhD-negative pregnant women will be cost-effective.

Uncertainties

The key uncertainties associated with the assessment of RAADP are:

- the efficacy of different dosing regimens of RAADP
- the quality of life of children suffering from HDN and of their parents (including parents of stillborn children)
- the incidence rate of outcomes as a result of HDN
- the costs associated with HDN in terms of the management of sensitisation and the management of people with developmental problems over their lifetime.

Other relevant factors

Problems have been encountered in the past in relation to the availability of anti-D. If such problems are likely to be encountered in the future then an argument can be made for those strategies that minimise the volume of plasma required. These include:

- the use of a two-dose 500-IU D-Gam regimen, as this uses two-thirds of the quantity of anti-D used by the single-dose regimen

- the use of the ion-exchange chromatography method of preparation, as this retains 30–40% more anti-D than the Cohn method.

Since the NICE guidance was issued in 2002, rates of compliance with RAADP seem to have increased.⁸⁹ However, although the implementation of a programme of RAADP should lead to a significant fall in the residual numbers of women affected, some women continue to become sensitised despite the existence of such a programme. There are five possible reasons for continuing cases of sensitisation:

- the failure to recognise potential sensitising events in pregnancy as such and to treat them appropriately
- the failure to assess the extent of FMH adequately
- the failure to comply with postpartum prophylaxis guidelines
- the refusal of RAADP by the mother
- the failure to implement RAADP by some trusts and incomplete adherence to advice (i.e. poor compliance with the second dose).

Consideration of these issues is required.

The Royal College of Nursing¹²³ suggests that Section 1.2 of the NICE Technology Appraisal No. 41⁸⁷ presents some practical difficulties for midwives as 'in addition to the sensitivities of discussing paternity, there are difficulties associated with an institution assuming that the father is indeed RhD-negative as reported without having this confirmed by internal testing'. Other practical concerns have been raised with regards to the certainty with which a woman may know that she is not going to have another child. These issues were not considered in a subgroup analysis as planned because of their feasibility in practice.

Finally, non-invasive fetal genotyping has not yet been demonstrated to be sufficiently accurate to enable its use to target provision of RAADP only to those non-sensitised RhD-negative women pregnant with RhD-positive infants. However, a test that is sufficiently accurate at an early enough gestational date may become available in the next few years.

Chapter 7

Conclusions

All of the evidence indicates that RAADP reduces the incidence of sensitisation and hence HDN. Furthermore, anti-D is associated with minimal adverse events. The economic model suggests that, at a threshold of £35,000 per QALY gained, RAADP given to all RhD-negative pregnant women is likely to be considered cost-effective compared with RAADP given to RhD-negative primigravidae or not offering RAADP. The total cost of providing RAADP to RhD-negative primigravidae in England and Wales is estimated to be around £1.8–£3.1 million per year depending upon the regimen of RAADP used (excluding WinRho). This takes into account the cost of RAADP and its administration, the cost of the management of sensitisation and the cost savings associated with avoiding HDN. The additional cost of providing RAADP to all RhD-negative pregnant women in England and Wales is estimated to be around £2–£3.5 million.

Further research is required to:

- compare the efficacy of the different RAADP regimens; issues relating to compliance and

safety may also influence the efficacy of the different regimens of RAADP and hence further research would also be useful in these areas

- confirm or disprove the preliminary findings that protection against sensitisation provided by RAADP in primigravidae extends beyond the first pregnancy
- aim to improve non-invasive genotyping of the fetus.

It is recognised that it would be unrealistic to seek to compare the efficacy of the different RAADP regimens by means of an RCT as each regimen is considered to be equally effective in practice and therefore the size of any trial powered to demonstrate a difference would be wholly unfeasible. However, the relative efficacy of the different regimens, and the impact of the potentially varying levels of compliance with them, could be assessed using large-scale audits of residual sensitisations.



Acknowledgements

Thanks are due to the following clinical experts: Ms Julie Wray, Lecturer in Midwifery; Dr Hora Soltani, Senior Lecturer in Midwifery; and Dr Therese Callaghan, Consultant Haematologist. We would also like to thank the following advisors: Professor Dame Marcela Contreras, Professor of Transfusion Medicine; Professor Stan Urbaniak, Professor of Transfusion Medicine; and Rumona Dickson, Claire McLeod and Angela Boland from the Liverpool Reviews and Implementation Group. Thanks also to Andrea Shippam, Project Administrator, ScHARR, for her help in the retrieval of papers and in preparing and formatting the report. Finally, thanks to Jim Chilcott for providing advice around the original NICE Health Technology Assessment of routine antenatal anti-D. Jim Chilcott and Eva Kaltenthaler are guarantors.

About ScHARR

The School of Health and Related Research (ScHARR) is one of the four Schools that comprise the Faculty of Medicine at the University of Sheffield. ScHARR brings together a wide range of medical- and health-related disciplines including public health, general practice, mental health, epidemiology, health economics, management sciences, medical statistics, operational research and information science. It includes the Sheffield unit of the Trent RDSU, which is funded by NIHR

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Contribution of authors

H Pilgrim was the review lead and undertook the cost-effectiveness review. M Lloyd-Jones undertook the clinical effectiveness review. A Rees conducted the literature searches.



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Appendix I

Literature search strategies

General search strategy for anti-D/pregnancy

1 Rh-Hr Blood-Group System/
2 “Rho(D) Immune Globulin”/
3 Rh Isoimmunisation/
4 anti-d prophylaxis.tw.
5 or/1-4
6 exp pregnancy/

7 exp pregnancy complications/
8 exp pregnancy trimesters/
9 pregnan\$.tw.
10 prenatal care/
11 postnatal care/
12 or/6-11
13 5 and 12

Appendix 2

Quality assessment

Quality assessment criteria for experimental studies (based on the criteria proposed by the NHS Centre for Reviews and Dissemination¹²⁴)

Was the method used to assign participants to the treatment groups really random? (Adequate methods: computer-generated random numbers, random number tables; inadequate methods: alternation, case record numbers, birth dates, days of the week)	
What method of assignment was used?	
Was the treatment allocation adequately concealed? (Adequate methods: centralised or pharmacy-controlled randomisation, serially numbered identical containers, on-site computer-based system with randomisation sequence that is not readable until allocation, other robust methods to prevent foreknowledge by clinicians or patients; inadequate methods: alternation, case record numbers, birth dates, days of the week, open random number lists, serially numbered envelopes, even if opaque)	
What method was used to conceal treatment allocation?	
Was the number of participants who were randomised stated?	
Were details of baseline comparability presented?	
Was baseline comparability achieved?	
Were the eligibility criteria for study entry specified?	
Were any co-interventions identified that may influence the outcomes for each group?	
Were the outcome assessors blinded to the treatment allocation?	
Were the care providers blinded to the treatment allocation?	
Were the participants who received the intervention blinded to the treatment allocation?	
Was the success of the blinding procedure assessed?	
Were at least 80% of the participants originally included in the randomised process followed up in the final analysis?	
Were the reasons for withdrawal stated?	
Was an intention to treat analysis included?	
Y, item addressed; N, no; ?, not enough information or not clear; NA, not applicable.	

Appendix 3

Table of excluded studies with rationale

TABLE 37 Studies identified by the electronic searches and other searches and excluded at the full paper stage, for reasons not immediately apparent from the full text

Study	Reason for exclusion
Australian study ¹⁴²	Anti-D dose not specified
Eklund and Nevanlinna 1971 ¹³⁸	In Finnish, no English abstract; from publication date seems highly likely that it dealt with postpartum rather than antenatal prophylaxis
Hamilton study ¹⁴²	Anti-D dose not specified
Hermann <i>et al.</i> 1984 ¹³⁴	Wrong anti-D regimen (single dose of 1250 IU at 32–34 weeks)
Koelewijn 2003 ¹⁴¹	Wrong anti-D regimen (single dose of 1000 IU at 30 weeks)
Lee and Rawlinson 1995 ¹³⁵	Wrong anti-D regimen (two doses of 250 IU at 28 and 34 weeks)
Parsons <i>et al.</i> 1998 ¹³⁶	Anti-D dose not specified
Potron <i>et al.</i> 1973 ¹³⁹	Could not be obtained by library; from publication date seems highly likely that it dealt with postpartum rather than antenatal prophylaxis
Swedish study ¹⁴²	Wrong anti-D regimen (unspecified dose at 34 weeks); appears to be the same study as that by Hermann <i>et al.</i> ¹³⁴ above
Unpublished study cited by Baxter Healthcare ¹¹⁹	Only one of three arms received a licensed anti-D regimen; there appeared to be no untreated control group; follow-up was very poor
Urbaniak <i>et al.</i> 2006 ¹⁴³	Identified sensitised women only as a proportion of all RhD-negative women who had received RAADP, not specifically those who had subsequently been delivered of RhD-positive infants; its results were therefore not comparable with those of the other included studies

TABLE 38 Studies referred to in the manufacturers' submissions that did not meet the study inclusion criteria

Manufacturer/study	Reason for exclusion
Baxter BioScience	
Hermann <i>et al.</i> 1984 ¹³⁴	Unlicensed dose (1 x 1250 IU)
Lee and Rawlinson 1995 ¹³⁵	Unlicensed dose (2 x 250 IU)
Thornton <i>et al.</i> 1989 ¹³³	Included in this report as a follow-up to the study by Tovey <i>et al.</i> 1983 ¹²⁸ and not as a separate study, as inappropriately carried out by Baxter BioScience
BPL	
None	
CSL Behring	
Bichler <i>et al.</i> 2003 ¹⁷⁶	Pharmacokinetic study; no relevant outcomes
Kennedy <i>et al.</i> 1998 ¹⁷⁷	Pharmacokinetic study; no relevant outcomes
Witter <i>et al.</i> 1990 ¹⁷⁸	Pharmacokinetic study; no relevant outcomes

Appendix 4

Characteristics of included studies

Bowman et al. 1978¹²⁹

Method: As described, this was a community intervention trial in which, between December 1968 and August 1976, antenatal anti-D was given to all RhD-negative primigravidae delivered in two Winnipeg hospitals but not to those delivered at the other three hospitals in the city; by January 1972 enough untreated women had been accumulated to act as control subjects and antenatal prophylaxis was offered to all RhD-negative women whose delivery was to take place in Winnipeg hospitals. However, data from the trial control arm of primigravidae delivered in the three Winnipeg hospitals were combined with data related to RhD-negative primigravidae with no history of blood transfusion or abortion, and multigravidae with no previous evidence of RhD alloimmunisation who had been given immunoglobulin after all previous RhD-positive abortions and deliveries, in Manitoba between 1 March 1967 and 15 December 1974; these appear to have been all such women who gave birth to RhD-positive babies in Manitoba during this period (clarification from Bowman, personal communication).

Participants: RhD-negative primigravidae to be delivered in Winnipeg hospitals. Women who entered the trial as primigravidae re-entered the trial in all subsequent pregnancies.

Interventions: Approximately 1500 IU of intramuscular anti-D at 34 weeks; from May 1969 a second dose was added at 28 weeks. Women in both the intervention and control groups delivered of RhD-positive babies received 1500 IU of anti-D postpartum.

Outcomes: Incidence of immunisation during pregnancy and within 3 days of delivery; incidence of immunisation at 6–9 months following delivery.

Notes: The groups for which data are provided are dissimilar at baseline in that the intervention group included only women who, for all of their pregnancies, were treated in accordance with the trial protocol, whereas the 'control' group included women who had had previous pregnancies.

Although these had not resulted in identifiable sensitisation, it is possible that multigravidae in the control group developed RhD alloimmunisation because of 'sensibilisation' resulting from inadequate treatment related to previous pregnancies. Only 74% of the intervention group were screened at 6–9 months after delivery; it is not clear whether, in the reported control group, only those women who had been found to be immunised during pregnancy or within 3 days of delivery were screened at 6–9 months.

The authors state that in May 1969 a dose of anti-D was introduced at 28 weeks because of evidence that some women were becoming alloimmunised before 34 weeks. No information is given regarding these women, who presumably belonged to the intervention group.

Quality: Poor.

Bowman and Pollock 1978¹³⁰

Method: Comparison with historical controls (those RhD-negative primigravidae with no history of blood transfusion or abortion, and multigravidae with no previous evidence of RhD alloimmunisation who had been given immunoglobulin after all previous RhD-positive abortions and deliveries, in Manitoba between 1 March 1967 and 15 December 1974, whose data were reported in Bowman *et al.*¹²⁹)

Participants: All pregnant RhD-negative women in Manitoba with RhD-positive husbands and without evidence of RhD alloimmunisation in their current pregnancy. These fell into two categories:

- group 1: primigravidae, plus multigravidae who had received RhD immunoglobulin antenatally and postnatally in all previous RhD-positive pregnancies and after all previous abortions
- group 2: multigravidae who had received RhD immunoglobulin only postnatally or not at all after previous RhD-positive pregnancies and abortions.

Only 89% of those women at risk received antenatal prophylaxis and had their results included in the analysis. In addition, two women who had become alloimmunised before what they stated was their first pregnancy were excluded from the analysis as they could not be considered failures of antenatal prophylaxis.

Interventions: 1500 IU of intramuscular anti-D as close to 28 weeks' gestation as possible.

Outcomes: Incidence of immunisation during pregnancy and within 3 days of delivery; incidence of immunisation at 6–9 months following delivery.

Notes: Only 45% of the intervention group were screened at 6–9 months after delivery; it is not clear whether, in the reported control group, only those women who had been found to be immunised during pregnancy or within 3 days of delivery were screened at 6–9 months. It is possible that multigravidae in both the intervention and control groups developed RhD alloimmunisation not because of a failure of antenatal prophylaxis but because of 'sensibilisation' resulting from inadequate treatment after previous pregnancies.

Quality: Fair.

Bowman and Pollock 1987¹³¹

Method: Retrospective comparison with historical controls (those RhD-negative primigravidae with no history of blood transfusion or abortion, and multigravidae with no previous evidence of RhD alloimmunisation who had been given immunoglobulin after all previous RhD-positive abortions and deliveries, in Manitoba between 1 March 1967 and 15 December 1974, whose data were reported in Bowman *et al.*¹²⁹). Although Urbaniak¹⁵ claims that this study includes all of the cases reported in Bowman's earlier trials, this does not seem possible given the reported dates of the experiences recorded in this study.

This study is said to combine the results of a clinical trial of WinRho, reported briefly elsewhere,^{14,101} with the results of the subsequent service programme. In this trial pregnant women were initially given 120 µg (600 IU) of WinRho intravenously at 28 weeks but, after it was realised that RhD antibody could seldom be demonstrated for more than 6 weeks after that injection, the protocol was soon modified by the addition of a second 120-µg dose at 34 weeks.¹⁴ By 30 September 1980, 2792 women had received AADP with WinRho as part of this clinical trial. By that date,

1992 women had delivered RhD-positive babies; none of the 870 who were only tested at delivery showed signs of sensitisation and only one of the 1122 who were tested both at delivery and 4–6 months later showed evidence of sensitisation.¹⁴ Because of the success of the trial, WinRho was licensed for clinical use in Canada in June 1980 and was used thereafter in the Manitoba programme of RAADP.¹⁰¹ However, as the clinical trial is effectively a case series, which makes reference to control group data from the 1978 study of Bowman *et al.*,¹²⁹ there seems no reason to differentiate between the trial and the service programme components of the study.

Participants: RhD-negative women delivered of RhD-positive babies in Manitoba between June 1977 and February 1986.

Interventions: 1500 IU of intramuscular anti-D at 28 weeks' gestation. Women in both the intervention and control groups delivered of RhD-positive babies received postnatal anti-D.

Outcomes: Incidence of immunisation during pregnancy and within 3 days of delivery.

Notes: The authors' comparison is with the primigravidae only in the 'control' group reported in Bowman *et al.*¹²⁹ It is not clear why their comparison was not with the unselected group. The 6-week and 6-month post-delivery blood samples were not universally available and so it was not possible to determine directly the total number of women RhD immunised by 6 months after delivery.

Quality: Poor.

Huchet *et al.* 1987¹²⁵

Method: Quasi-randomised trial; intention to treat analysis.

Participants: RhD-negative primiparae without anti-D antibodies attending antenatal clinics at 23 maternity units in the Paris region.

Interventions: 500 IU of intramuscular anti-D at 28 and 34 weeks (in practice this was administered between weeks 26 and 29 and weeks 32 and 36). All RhD-negative women in the intervention and control groups delivered of RhD-positive babies received 500 IU of intravenous postpartum anti-D.

Outcomes: Incidence of immunisation during pregnancy; incidence of immunisation at delivery;

incidence of immunisation at 2–12 months following delivery; number of infants with serious HDN or requiring exchange transfusion; passage of fetal red blood cells during pregnancy; cost-effectiveness of treatment.

Notes: Allocation to treatment groups was by year of birth (those born in even years formed the control group and those born in odd years the intervention group). Results from the postnatal check-up were available for only 79% of the mothers in either the control group or the intervention group who were delivered of an RhD-positive baby.

Quality: Good.

MacKenzie et al. 1999¹²⁶

Method: Community intervention trial with historical and contemporary controls:

- a retrospective analysis of the rate of alloimmunisation in RhD-negative women delivered of their first child between 1 January 1980 and 31 December 1986 in Oxfordshire or Northants who underwent a second continuing pregnancy; data on sensitised women were derived from a prospectively maintained serology laboratory register and verified from individual case records, and the at-risk population was calculated using hospital statistics for total annual births to nulliparae and women delivering their second baby and assuming a 16% prevalence of RhD negativity
- a prospective study of the rates of alloimmunisation in RhD-negative women undergoing a second continuing pregnancy with an expected date of delivery between 1 January 1990 and 31 December 1996 in two similar populations; in one of these populations (Oxfordshire) routine antenatal prophylaxis had been offered since April 1986 to all RhD-negative women with no living children booked for confinement in the county, whereas in the other population (Northants) it had not.

An intention to treat analysis was used.

The update of RAADP in Oxfordshire was assessed by an audit of the clinical records of every fifth RhD-negative women who had delivered her first baby in the John Radcliffe Hospital, Oxford, from 1987 to 1996.

Participants: Non-sensitised RhD-negative pregnant nulliparae.

Interventions: 500 IU of routine anti-D offered at 28 and 34 weeks' gestation to RhD-negative nulliparae booked for confinement in Oxfordshire but not to those booked for confinement in Northants. In Oxfordshire, standard prophylaxis was offered to all RhD-negative women postpartum, but in Northants it was offered only to those delivered of a RhD-positive baby.

Outcomes: Prevalence of sensitisation during the second continuing pregnancy; success in providing prophylaxis to eligible women; changes in serology laboratory activity; cost of, and potential savings from, the prophylaxis programme.

Notes: The sensitisation rate for 1980–6 was compared with that for 1990–6 because the mean national interval between first and second delivery was 2.4 years and, therefore, women who delivered their first baby in 1987, the first full year of the study, would on average deliver their next baby during 1990.

This study illustrates the dangers inherent in the use of historical controls. A noticeable reduction in the incidence of sensitisation observed in Northants between the two study periods, although not statistically significant, was unexpected and unexplained. It could not be attributed to the use of antenatal prophylaxis. However, the study used the historical data to demonstrate that the two geographically contiguous populations were comparable in their rates of alloimmunisation before the introduction of the anti-D programme.

Quality: Good.

MacKenzie et al. 2004¹⁰⁰

Method: Allegedly an RCT (multicentre, open-label, using a computer-generated randomisation scheme) it is in fact a one-arm study in relation to its primary efficacy outcome and is underpowered in relation to its secondary efficacy outcome (which is a randomised comparison).

Participants: RhD-negative women aged ≥ 18 years with no evidence of Rh(D) sensitisation and with known Rh(D)-positive partners, within 14 days before the 28th week of gestation, who had not previously received anti-D during the current pregnancy and who had not received blood or any other bloodborne products during the 6 months before enrolment. In total, 71.5% of participants had been pregnant before and 81.9% had received anti-D in a previous pregnancy.

Interventions: 1500 IU of Rhophylac (a new chromatographically produced Rh immunoglobulin) at 28 weeks' gestation, with another dose within 72 hours of delivery of a RhD-positive child and additional doses as required to treat potential sensitising events or excessive FMHs. One group received all doses of Rhophylac intravenously and the other received all doses intramuscularly; there was no control group receiving a standard anti-D preparation. Women in either group who delivered within 21 days of RAADP did not receive a postpartum dose unless there was evidence of an excessive FMH. Treatment with anti-D other than Rhophylac constituted a protocol violation.

Outcomes: Incidence of RhD immunisation, assessed 6–11.5 months after delivery and, if positive, retested 3 months later, in mothers who had delivered a RhD-positive baby; relative incidence of RhD immunisations in those receiving intramuscular and intravenous anti-D; routine laboratory safety parameters at 1 week after administration of RAADP (compared with blood taken at the screening visit); viral markers, etc., approximately 6 months after the last administration of anti-D (compared with blood taken shortly before the antenatal injection).

Notes: All safety evaluations were conducted on the intention to treat population (i.e. all women who received at least one dose of Rhophylac); efficacy evaluations were conducted on the per protocol population (i.e. all women from the intention to treat population who had delivered an RhD-positive child and who complied with the study's inclusion/exclusion criteria). In total, 95% of the per protocol population were available for follow-up.

The primary efficacy outcome in this study is the incidence of RhD immunisation in women in the combined intramuscular and intravenous groups delivered of an RhD-positive child. The sample size was calculated to test the null hypothesis that Rhophylac was inferior to currently marketed anti-D products in immunisation frequency. Although this raises the expectation that participants will be randomised to one of the current anti-D products as well as to Rhophylac, in fact reference is made to a rate of seroconversion in women treated ante- and postnatally reported in earlier studies of approximately 0.1–0.3%. Thus, for the primary efficacy outcome, the comparison is made not with contemporary randomised control subjects but with populations who are separated

from the study population in time and, in many of the reported studies, also in geographical location. In relation to this primary outcome, therefore, this is a one-armed study with no randomised comparator group; this is recognised by the investigators who claim that it is acceptable given the existence of other scientific data.

The investigators note that the Committee for Proprietary Medicinal Products' most recent note for guidance on the clinical investigation of human anti-D immunoglobulin¹⁴⁵ states that clinical trials are not a suitable method for investigating safety in relation to the transmission of either enveloped or non-enveloped viruses.

Quality: Poor.

Mayne et al. 1997¹²⁷

Method: Retrospective before-and-after study, comparing data from years when the antenatal anti-D programme was fully operational with data from before its introduction; intention to treat analysis.

Participants: All pregnant RhD-negative primiparae in southern Derbyshire.

Interventions: 500 IU of anti-D given intramuscularly at 28 and 34 weeks' gestation, plus postpartum anti-D for all women (in the intervention and control groups) delivered of RhD-positive babies.

Outcomes: Number of women sensitised in each group; requests for anti-D after bleeding from the vagina or antepartum haemorrhage.

Notes: The number of requests for anti-D following bleeding increased following the introduction of the anti-D programme. This may have been due to heightened awareness among midwives and community doctors, and may have contributed to reducing the overall sensitisation rate in the intervention group.

Quality: Fair.

Tovey et al. 1983,¹²⁸ Thornton et al. 1989¹³³

Method: Prospective study with historical controls; intention to treat analysis.

Participants: Non-sensitised RhD-negative primigravidae in Yorkshire who gave birth to RhD-

positive infants in 1980–1; controls were 2000 non-sensitised RhD-negative primigravidae in Yorkshire who gave birth to RhD-positive infants in 1978–9.

Interventions: 500 IU of anti-D at 28 and 34 weeks, plus 500 IU of postpartum anti-D for all women (in both the intervention and control groups) delivered of RhD-positive babies.

Outcomes: Incidence of immunisation at delivery; incidence of immunisation at 9–12 months following delivery; prevalence of immunisation in a subsequent pregnancy; pre-eclampsia and proteinuria; gestation at delivery; birthweight; fetal survival at 1 month.

Notes: In total, 85% of the intervention group were screened 6 months after their first delivery. No information is given regarding the proportion receiving such screening after subsequent deliveries or the proportion of women in the control group who were screened. Although historical controls were used they were close in time to the intervention group.

Only 69% of women in the intervention group and 71% in the control group who had had at least one further pregnancy were followed up clinically; however, these were considered to be representative of the full groups.

Quality: Fair.

Trolle 1989¹³²

Method: Prospective study with historical controls; intention to treat analysis.

Participants: All pregnant RhD-negative women in Kolding who did not show any sign of immunisation at the first antibody screen test, performed in the first trimester, and again at 28 weeks (control subjects were all RhD-negative

women having RhD-positive babies in Kolding in the years 1972–7).

Interventions: 1500 IU of anti-D at 28 weeks' gestation; women in both the intervention and control groups who were delivered of RhD-positive babies were given 1000 IU of anti-D the day after delivery if the fetomaternal transfusion was estimated to be less than 15 nl of blood.

Outcomes: Incidence of immunisation 10 months after delivery or in next pregnancy; amount of fetal blood in maternal circulation after delivery.

Notes: The control group was said to be comparable to the study group in all respects with regard to the number of first pregnancies and factors known to provoke fetomaternal transfusion (e.g. instrument-assisted deliveries, Caesarean section and stimulation of labour). However, 38.8% of women in the control group had received more than 1 µl of fetal blood, compared with only 7.9% in the intervention group ($p < 0.001$). Moreover, only the intervention group underwent antenatal antibody screening in the 28th week, as a result of which, although the control group may include women who were alloimmunised before the 28th week, the intervention group does not. In total, 91% of the control group but only 84% of the intervention group were screened for antibodies. Moreover, although the reporting is unclear, it appears that women in the control group were screened either at 10 months or in the next pregnancy, whereas all women in the intervention group were screened at 10 months, although some women may have undergone silent sensitisation that would only become apparent during a subsequent RhD-positive pregnancy. For all of these reasons, alloimmunisation is more likely to be found in the control group.

Quality: Poor.

Appendix 5

Data abstraction tables

TABLE 39 Summary of trial results: women sensitised during pregnancy or within 3 days of delivery, by total anti-D dose

Study	Study design	Dosage	Patient selection	Anti-D prophylaxis group			Control group		
				n	r	% Sensitised (95% CI)	n	r	% Sensitised
Bowman <i>et al.</i> 1978 ¹²⁹	Prospective study, historical/geographical controls	2 × 1500 IU (28 and 34 weeks) (initially at 34 weeks only)	Primigravidae	1357	1	0.1 (-0.1 to 0.3)	2768	45	1.6 (1.2-2.1)
Bowman and Pollock 1978 ¹³⁰	Prospective study, historical controls	1 × 1500 IU (28 weeks)	Unselected	1804	5	0.3 (0.0-0.5)	3533	62	1.8 (1.3-2.2)
Bowman and Pollock 1987 ¹³¹	Retrospective study, historical controls	1 × 1500 IU (28 weeks)	Unselected	9303	18	0.2 (0.1-0.3)	3533	62	1.8 (1.3-2.2)
Trolle 1989 ¹³²	Prospective study, historical controls	1 × 1500 IU (28 weeks)	Unselected	346	No data	No data	354	No data	No data
Huchet <i>et al.</i> 1987 ¹²⁵	Quasi-RCT	2 × 500 IU (28 and 34 weeks)	Primigravidae	461	0	0.0 (0.0-0.0)	454	4	0.9 (0.0-1.7)
			Multigravidae	138	1	0.7 (-0.7 to 2.0)	136	2	1.5 (-0.6 to 3.5)
			Unselected	599	1	0.2 (-0.2 to 0.5)	590	6	1.0 (0.2-1.8)
MacKenzie <i>et al.</i> 1999 ¹²⁶	Community intervention trial	2 × 500 IU (28 and 34 weeks)	Primiparae	3320	No data	No data	3146	No data	No data
Mayne <i>et al.</i> 1997 ¹²⁷	Before-and-after study	2 × 500 IU (28 and 34 weeks)	Primiparae	1425	No data	No data	1426	No data	No data
Tovey <i>et al.</i> 1983 ¹²⁸	Prospective study, historical controls	2 × 500 IU (28 and 34 weeks)	Primigravidae	1238	2	0.2 (-0.1 to 0.4)	2000	18	0.9 (0.5-1.3)
			Multigravidae	325	2	0.6 (-0.2 to 1.5)	582	11 ^a	1.9 (0.8-3.1)
			Unselected	1563	4	0.3 (0.0-0.6)	2582	29	1.1 (0.7-1.5)

CI, confidence interval; n, number of deliveries of RhD-positive babies to RhD-negative women in the trial group; r, number of sensitised RhD-negative women in the trial group; RCT, randomised controlled trial.

a For comparability with other studies this figure excludes 11 women who developed antibodies in a previous pregnancy but were retained in the study.

TABLE 40 Summary of trial results: women sensitised at postnatal follow-up, by total anti-D dose

Study	Study design	Dosage	Patient selection	Anti-D prophylaxis group			Control group		
				n	r	% Sensitised (95% CI)	n	r	% Sensitised (95% CI)
Bowman et al. 1978 ²⁹	Prospective study, historical/geographical controls	2 × 1500 IU (28 and 34 weeks) (initially at 34 weeks only)	Primigravidae	1004	1	0.1 (-0.1 to 0.3)	2768 ^a	45	1.6 (1.2-2.1)
Bowman and Pollock 1978 ³⁰	Prospective study, historical controls	1 × 1500 IU (28 weeks)	Unselected	807	No data		3533 ^a	50	1.4 (1.0-1.8)
Bowman and Pollock 1987 ³¹	Retrospective study, historical controls	1 × 1500 IU (28 weeks)	Unselected	9303 ^a	25	0.3 (0.2-0.4)	3533 ^a	50	1.4 (1.0-1.8)
Trolle 1989 ³²	Prospective study, historical controls	1 × 1500 IU (28 weeks)	Unselected	291	0	0.0 (0.0-0.0)	322 ^b	6	1.9 (0.4-3.3)
MacKenzie et al. 2004 ¹⁰⁰	Open-label RCT; results presented as uncontrolled study	1 × 1500 IU (28 weeks)	Unselected	248 (per protocol population)	0	0.0 (0.0-0.0)	-	-	-
Huchet et al. 1987 ¹²⁵	Quasi-RCT	2 × 500 IU (28 and 34 weeks)	Primigravidae	362	0	0.0 (0.0-0.0)	360	4	1.1 (0.0-2.2)
			Multigravidae	110	1	0.9 (-0.9 to 2.7)	108	3	2.8 (-0.3 to 5.9)
			Unselected	472	1	0.2 (-0.2 to 0.6)	468	7	1.5 (0.4-2.6)
MacKenzie et al. 1999 ¹²⁶	Community intervention trial	2 × 500 IU (28 and 34 weeks)	Primiparae	3320	No data		3146	No data	
Mayne et al. 1997 ¹²⁷	Before-and-after study	2 × 500 IU (28 and 34 weeks)	Primiparae	1425	No data		1426	No data	
Tovey et al. 1983 ¹²⁸	Prospective study, historical controls	2 × 500 IU (28 and 34 weeks)	Primigravidae	1059	2	0.2 (-0.1 to 0.5)	No data	No data	
			Multigravidae	No data	No data		No data	No data	
			Unselected	No data	No data		No data	No data	

CI, confidence interval; n, number of RhD-negative women in the trial group delivered of RhD-positive babies and screened postnatally; r, number of sensitised RhD-negative women in the trial group; RCT, randomised controlled trial.

a It is not clear how many women in the group were screened postnatally; the denominator is therefore the total number in the group.

b Women screened at 10 months or during their next pregnancy.



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We look forward to hearing from you.