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Title: **Routine antenatal anti-D prophylaxis for RhD-negative women (review)**

Produced by The University of Sheffield, School of Health and Related Research (ScHARR)

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Contributions 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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1. DEFINITION OF TERMS AND LIST OF ABBREVIATIONS

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader.

DEFINITION OF TERMS

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 foetal 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 foetalis	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 HDN.
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	Death of a foetus before 20 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 owing to the accumulation of excess lymph fluid
Oesophoria	A muscle condition in which, when both eyes are open, each 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 which is either congenital (as in HDN) or is 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
Secundigravida	Woman who is pregnant for the second time
Sensitisation (primary immunisation)	Development in the mother of a template for producing antibodies against foetal 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 foetomaternal haemorrhage which leads to primary or secondary sensitisation
Silent sensitisation	Sensitisation which does not result in the production of detectable anti-D antibodies
Stillbirth	Foetus born dead after 20 weeks' gestation

LIST OF ABBREVIATIONS

AADP	antenatal anti-D prophylaxis
BNF	British National Formulary
CP	cerebral palsy
DI	donor insemination
FMH	foeto-maternal haemorrhage
HDN	haemolytic disease of the newborn
Ig	Immunoglobulin
ITP	immune thrombocytopenic purpura
IU	international unit
IUT	intrauterine blood transffusion
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
PODCI	Pediatric Outcomes Data Collection Instrument
QALY	Quality-adjusted life year
RAADP	routine antenatal anti-D prophylaxis
RhD	Rhesus D
TPH	transplacental haemorrhage

2. EXECUTIVE SUMMARY

2.1 Background

Human blood is classified according to two main systems: the ABO system, and the Rh system. The Rh system refers to a protein called RhD antigen. People who have this antigen on their red blood cells are said to be RhD-positive, while those who do not are said to be RhD-negative. If the mother is RhD-negative and the foetus RhD-positive, the mother may react to foetal 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 foetus, but may result in Haemolytic Disease of the Newborn (HDN) during a second RhD-positive pregnancy. In its mildest form, the infant has sensitized 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.

2.2 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 NICE appraisal, and to assess the current clinical and cost-effectiveness of RAADP for RhD-negative women.

2.3 Methods

Searches of systematic reviews, randomised controlled trials and non-randomised controlled studies relating to the clinical or cost-effectiveness of RAADP were conducted in ten bibliographic databases. Additional searches were also carried out around the outcomes of HDN and the costs and quality of life associated with the outcomes. The health economic model developed for the 2002 NICE appraisal of RAADP was modified to assess the cost-effectiveness of different regimens of RAADP.

2.4 Results

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 or cost effectiveness from the previous assessment report. Therefore, within the clinical effectiveness review eight studies were

identified which compared RAADP with no prophylaxis, and 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 *et al*. 1999 and Mayne *et al*. The pooled results of these two studies suggest that 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 identified studies suggest that RAADP is associated with minimal adverse events.

Of the nine studies identified within the cost-effectiveness review, only the study by Vick *et al*., and Chilcott *et al*. 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 quality-adjusted life year (QALY) gained of RAADP given to primigravidae versus no RAADP is between £5,000 and £12,000, and for RAADP given to multigravidae rather than primigravidae is between £17,000 and £32,000 depending on the RAADP regimen (excluding WinRho). The one-dose regimen of 1500 IU 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 having the biggest impact upon the results. The cost-effectiveness of RAADP improves slightly for ethnic minorities in England and Wales.

2.5 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 BNF drug prices but, since 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 which 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 take into account the quality of life of the parents as a result of the loss of a child or of 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. In addition, since the actual price paid by hospitals for anti-D varies, the cost-effectiveness in practice may be better than that presented here.

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 four possible reasons for continuing cases of sensitisation which require consideration:

- failure to recognise potential sensitising events in pregnancy as such, and to treat them appropriately;
- failure to assess the extent of foeto-maternal haemorrhage (FMH) adequately;
- failure to comply with postpartum prophylaxis guidelines
- refusal of RAADP by the mother.

The key uncertainties associated with the assessment of RAADP are:

- Efficacy of different dosing regimens of routine anti-D;
- Quality of life of children and their parents suffering from HDN (including parents of stillborn children);
- Incidence rate of outcomes as a result of HDN;
- Costs associated with HDN in terms of management of sensitisation and outcomes over a patient's lifetime.

2.6 Conclusions

All of the evidence indicates that RAADP reduces the incidence of senstitisation 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 to 2.5 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 to £3 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 foetus.

3 BACKGROUND

3.1. Description of health problem

Human blood is classified according to two main systems: the ABO system, and the Rh system. The Rh system refers to a protein called RhD antigen. People who have this antigen on their red blood cells are said to be RhD-positive, while those who do not are said to be RhD-negative. Both ABO and Rh blood types are inherited characteristics, and therefore a foetus may inherit from its father a blood type which differs from that of its mother.

Haemolytic disease of the newborn (HDN) is a haemolytic anaemia which affects the foetus or neonate. It results from the transplacental passage of antibodies created by the mother and directed against foetal 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.

3.1.1 Aetiology, pathology and prognosis

3.1.1.1 Aetiology of HDN

During pregnancy and childbirth, a small quantity of foetal blood may enter the mother's circulation. Such transfer of foetal blood is termed a foetomaternal 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. Approximately 3% of women have detectable foetal blood cells in their circulation during the first trimester. 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 foetal red cells.[1]

Foetomaternal haemorrhage does not normally cause any adverse effects. However, if the mother is RhD-negative and the foetus RhD-positive, the mother may react to the foetal blood cells in her circulation by developing a template for producing anti-D antibodies,[2] 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.[3] Although some RhD-positive women produce anti-D following a sensitising event in pregnancy, this is extremely rare.[4]

Primary immunisation may lead to the the production of antibodies which are detectable after four 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,[5] stimulating the production within one to two weeks of anti-D antibodies. These maternal antibodies cross the placenta into the foetal 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, foetal 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 foetus's blood type, the volume of foetal blood entering the mother's circulation, and the mother's immune response.[6] It has been shown that, when RhD-negative volunteers are given repeated injections of D-positive cells, some are sensitised quickly and develop high levels of anti-D antibodies, while others only produce moderate amounts of antibody after repeated injections, and 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.[7] Such women may be sensitised after a relatively small TPH or an abortion (spontaneous or therapeutic).[8] 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.[7] The risk of sensitisation is increased when the mother and foetus have the same ABO blood group.[9] In the absence of antenatal and postpartum anti-D prophylaxis, the risk of sensitisation following a single ABO-compatible RhD pregnancy is about 16%,[8] but it is only 2% if the mother and foetus are ABO-incompatible.[10] As approximately 80% of pregnancies are ABO-compatible,[11] 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 study[12] 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 where the mother has already been sensitised as a result of a prior 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.

Prior to 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, it was detectable between 34 and 40 weeks gestation. At 6 months post-delivery, 4-9% of such women had detectable anti-D,[9] as did 1-2% of RhD-negative women who had borne a RhD-positive ABO-incompatible infant.[13] However, the 'true' rate of sensitisation is greater than that identified by the presence of anti-D at, or six months after, delivery: 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.[14] Prior to 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.[9]

Passive immunisation with anti-D immunoglobulin can prevent sensitisation, although the precise mechanism by which it does so is not known.[9] However, once a woman has developed anti-D antibodies, she cannot be desensitised.

3.1.1.2 Pathology and prognosis of HDN

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 which 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, causes 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.[9]

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 foetal blood sampling, which enabled the identification of foetal 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.[15] While overall survival in foetuses undergoing IUT is around 86 to 90%,[16,17] it is lower in those with hydrops, which is indicative of severe haemolytic disease: survival in foetuses with severe hydrops who receive IUT may be as low as 55% while in those with mild hydrops it may be as high as 98%.[16]

The most comprehensive recent data on the outcome of pregnancies in RhD-sensitised women derive from a study of all such pregnancies in Northern Ireland from September 1994 to February 1997. There were 124 pregnancies, including 4 sets of twins and one set of quadruplets, a total of 130 foetuses in all. Although there were eleven deaths (8.5%) from various causes, over 90% of infants survived the neonatal period[18] (see Table 1 below).

Table 1: Outcomes of pregnancies in RhD-sensitised women in Northern Ireland, September 1994-February 1997[18]

Outcome	**Number (%)**
Termination for foetal 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)

More recent data on the outcome of pregnancies 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 fifteen with RhD immunisation.[19] Twenty of the 23 foetuses (87%) were live-born. Four (17%) had hydrops: three of these were stillborn (two died before it was possible to perform IUT, while in the third death was not related to IUT), and the fourth survived.

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 study noted above. This found that, at two years of age, five of the 78 babies affected by HDN (6%) had minor developmental problems (eg myopia, squint, or delay in language and fine motor skills) while two (3%) had major permanent neurodevelopmental problems.[18]

The only studies which have reported long-term outcomes in foetuses who required IUT for HDN (primarily associated with RhD incompatibility) relate to children treated in the 1980s and 1990s (see Table 2). They indicate that, at that time, about 15% of foetuses receiving IUT died in utero; neonatal deaths reduced total survival to about 80%. Survival was higher in the less severely affected foetuses: in the German study, only 7/11 (64%) of those who had developed hydrops before the first transfusion survived, compared with 28/32 (88%) of those without hydrops.[20] 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.[21] By comparison, a more recent study[22] included 254 foetuses treated with 740 intravascular intrauterine transfusions at a single centre in the Netherlands between 1988 and 2001; in 85% of the pregnancies (217/254), foetal anaemia was due to maternal RhD alloimmunisation. Overall survival was higher, at 89% (225/254); there were 19 foetal deaths (7%) and 10 neonatal deaths (4%). Seven of the foetal 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.

Table 2: Outcomes of intravascular IUT

Study	**Doyle *et al.*[21]**	**Harper *et al.*[23]**	**Grab *et al.*[20]**	**Hudon *et al.*[24]**	**Janssens et al[25]**
Date of IUT	1984-1990	1985-95	1986-1991	1986-1992	1987-1993
Location	Australia	USA	Germany	USA	Netherlands
No of foetuses receiving IUT	52	18	43	49	92
Reason for IUT	Severe erythroblastosis (no. 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 (no. associated with anti-D antibodies not stated)
Mean no. of transfusions per foetus	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, median (days) (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 to 6 years)
No. with moderate or severe neurological impairment (other than hearing impairment) at follow-up	2[a]/38 (5%)	2[b]/16 (13%)	0	1[c]/22 (5%)	3[d]/69 (4%)

Study	Doyle *et al.*[21]	Harper *et al.*[23]	Grab *et al.*[20]	Hudon *et al.*[24]	Janssens et al[25]
No. with mild neurological impairment (other than hearing impairment) at follow-up	1[e]/38 (3%)	5[f]/16 (31%)	2[g]/30 (7%)	0	2[h]/69 (3%)
No. with motor delay requiring physiotherapy	No data	No data	No data	No data	17%
No. with speech delay requiring speech therapy	No data	No data	No data	No data	13%
No. with hearing tested	38	16	No data	21 (53% of survivors) tested before initial hospital discharge	58 (84%) screened at 9 months
No. of those tested with permanently impaired hearing	0	2[i]/16 (13%)	No data	2[j]/21 (10%)	3/58 (5%)

a One had severe developmental delay and multiple minor motor seizures, another had cerebral palsy with double hemiplegia

b One had static encephalopathy and cerebral palsy; one (the child of a mother who abused alcohol and illicit drugs) had mild mental retardation

c Right spastic hemiplegia diagnosed at 2.5 years, with normal development apart from walking difficulties. As only 11/40 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's syndrome, and in the other to Menkes' disease) which did not seem to be related to HDN.

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, at the age of 4 had only fine motor and speech delay).

e Mental developmental index of 72

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

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

h Minor neurological dysfunction leading to motor and speech delay

i One child had bilateral profound sensorineural hearing loss following kernicterus; one had unilateral mild conductive hearing loss

j One infant had mild peripheral sensitivity loss, the other had severe bilateral deafness (this child was not available for follow-up and so it was not possible to assess any other possible disabilities)

The studies followed up survivors for different lengths of time, and subjected them to different tests; follow-up ranged from 100% to 95% (see Table 2). Three studies screened for hearing disability: the Dutch study screened 58 infants (84% of survivors) at 9 months and found non-transient hearing loss in 3 (5%).[25] One US study screened 16 children (100% of survivors) at a mean age of ten years, and found that two (13%) had hearing loss (one had bilateral profound sensorineural hearing loss, and the other unilateral mild conductive hearing loss).[23] The other US study screened 21 infants (53% of survivors) before initial hospital discharge and found that two (10%) had permanent hearing deficit (in one case, severe bilateral deafness), a rate which was noted to be probably five to ten times higher than among infants not affected by HDN.[24]

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 study compared outcomes in IUT survivors with those in both a high-risk group of very premature and/or very low birth weight infants and a healthy control group. In the high-risk group, 18% of children who survived to the age of two 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. 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 in either the high-risk group or the healthy control group.[25] A small US study 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 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).[23] In the other US study, 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 geographic distances.[24]

Thus, the introduction of ultrasonographically-guided IUT has improved the ability to treat severely anaemic foetuses earlier in gestation, but has thereby increased the chances of survival of more severely affected foetuses with the potential for poor neurodevelopmental outcome.[24] Around 10-12% of foetuses affected by HDN will require IUT,[26] and a relatively high proportion of IUT survivors may suffer neurodevelopmental problems such as cerebral palsy, deafness and motor and speech delay which will

require specialist input and, in some cases, special education; others will suffer some degree of developmental delay requiring physiotherapy or speech therapy.

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

Ethnic groups vary in terms of the proportion of the population which 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 Africans, while virtually no Chinese are RhD-negative.[9] 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 that population which is RhD-negative is smaller than in the white UK population: 5.5% of blood donors in Vellore, south India, have been found to be RhD-negative,[27] 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).[28]

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, then 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 (see Table 3).

Table 3: Probability of RhD-negative woman having RhD-positive partner by chance (assuming both partners from ethnic groups with 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%

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.

3.1.3 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 populations[29] - approximately 1% of all neonates in England and Wales. Only a very small minority of cases of HDN occurred in first pregnancies, but one in a hundred second pregnancies, and a higher proportion of subsequent pregnancies, were affected.

Currently, only about 500 foetuses a year in England and Wales develop HDN,[30] approximately one in every 1,298 live and still births - less than a 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 1,000 total births in 1963 to 2.6 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.[31] Over the same period, advances in neonatal care were such that perinatal survival in infants with Rh HDN rose from 86.2% in 1963 to 97.4% in 1988.[31]

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.[32] 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%.[9] However, as these figures will not include women sensitised during their final pregnancy, the true figures will be higher.[33] Nearly half of the 1.5% known to have been sensitised (0.7% overall) seem to have been sensitised as a result of FMHs during the first pregnancy, a similar number as a result of FMHs during the second pregnancy, and the remainder (approximately 0.2% overall) as a result of failure to provide sufficient postpartum anti-D to cover a large FMH at the first delivery.[9]

In 1953, 310 deaths in England and Wales were attributed to RhD HDN - one in every 2,180 births.[9] An audit found that registered deaths and stillbirths attributed to Rh 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, which occurred mainly between 1977 and 1983, 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; the number of deaths in which the mother was sensitised during the first pregnancy, or despite having been given anti-D following one or more previous pregnancies (ie failure of prophylaxis), remained constant.[34] By 1989, the number of registered deaths and stillbirths had fallen to 10, 1.5 per 100,000 live births[35] - one 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 foetal 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. The major cause of underreporting was the exclusion from the certification data of both therapeutic and spontaneous abortions.[36,37] 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,[38] the Scottish data suggest that the true number of foetal 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 one year of life due to RhD alloimmunisation, in a population of approximately 5 million; this is consistent with an overall figure of around 30 for England and Wales (personal communication from S Wood; 2001).

CESDI notifications for England, Wales and Northern Ireland indicate that, for the period 1994-1999, an average of 18 foetal and infant deaths a year in England, Wales and Northern Ireland were due to RhD incompatibility (M Macintosh, personal communication, 2001). To these must be added any foetal losses which occur before 20 weeks' gestation. The Scottish data suggest that 20% (4/20) of all foetal 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 which 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, neonatal and postneonatal deaths.

Table 4: Foetal and infant death attributed to RhD incompatibility

Gestational age	Scotland 1987-1991[36] n (%)	UK excluding Scotland 1994-1999 (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)
Post-neonatal death	1 (5)	3 (3)
Total	20 (100)	109 (100)

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

3.1.4 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 well-being, then the direct impact of HDN on the health of the infant, and finally its indirect impact on the well-being of the family.

3.1.4.1 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 foetuses 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, personal communication, 2007).

3.1.4.2 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.[39,22]

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*.[24] and Janssens *et al*.[25] cited in section 3.1.1 above indicate that the most common permanent disabilities in this group are cerebral palsy (CP) and deafness; minor developmental problems include speech and motor delay such as require physiotherapy and speech therapy.

Cerebral palsy has substantial implications for both health (including reduced life expectancy) and quality of life (for a summary of quality of life in children and adolescents with CP, see Table 5). The impact of CP 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,[40] the presence of communication barriers, and the wide range of impairments found in people with CP.[41] However, it is important when possible to obtain the perspective of the children and adolescents with CP themselves because those who are capable of self-reporting consistently rate their quality of physical and psychosocial health more highly than do their parents.[42] Even so, in a recent study of Californian children and adolescents with CP (age 5-18 years), Varni *et al.* found that those who were able to self-report using the 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.[42]

A US study by Pirpiris *et al.* also found that both functional and psychosocial wellbeing in children with mild to moderate CP were lower than in non-affected peers; however, there was no correlation between physical function and psychosocial wellbeing, and children with mild CP had lower self- and parentally-reported psychosocial wellbeing than would be predicted by their functional disability.[43] By contrast, a

European study of 8-12-year-old children with CP 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 two years previously in all domains except the school environment (where the quality of life of those with CP was better) and physical wellbeing (which could not be formally compared because a slightly modified version of this domain of the questionnaire had been used with the children with CP). However, 54% of the children with CP 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.[44]

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 children. Thus, in a Canadian study, young adults (age 19-23) with CP who were capable of responding to a survey anticipated less success in future relationships, post-secondary education, employment and independent living than did matched controls, although adolescents (age 13-15) with CP did not differ from controls in their future expectations.[45]

Table 5: Summary of quality of life in children and adolescents with CP

Study	Country	Population	Tool	Findings
Dickinson *et al.* 2007[44]	Europe	Children with CP (age 8-12) 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 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 *et al.* 2006[43]	USA	Children with mild to moderate CP (mean age 10), 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 *et al.* 2005[42]	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

A US study[46] evaluated parentally-reported pain frequency in 198 children (mean age 10 years 7 months) with moderate to severe CP. 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 CP are exacerbated in adult life. Mobility may become more limited, and this is often accompanied by an increase in spasticity and pain.[47] In a US study of adults with CP with no more than mild cognitive impairment, 67% reported pain of more than three months' duration which was generally experienced on a daily basis.[48] Similarly, a Norwegian survey found that 28% of people with CP without intellectual disability reported daily pain for a year or more, compared with 15% in the general population.[49] An Italian study found that, although 29/70 (41%) adults with CP had walked independently (ie 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.[50]

Despite advances in education, technology, home support and environmental access for people with disability,[51] recent studies indicate that many people with CP 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 CP 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. Only 16% had paid employment other than sheltered labour; 41% attended a day activity centre for the disabled.[47] In a US study of *non-institutionalised* adults with CP 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. 53% were competitively employed (57% of those with moderate and 35% of those with severe physical disability); 7% were in semi-competitive employment, 18% in sheltered employment, and only 16% had never been involved in an organised work situation. However, 50% had speech deficits which severely compromised verbal communication, and by the age of 25 approximately 75% had stopped walking by choice because of the fatigue and inefficiency involved.[51] Neither of these studies may be fully representative of people with CP: the Dutch study obtained responses from only 46% (80/173) of young adults who met the study inclusion criteria,[47] while the US study population was limited to non-institutionalised adults, and was self-selected through contacts with the local United Cerebral Palsy Affiliate.[51]

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.[52] 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 study, 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.[53] Such problems persist in later life. In Belgium, a national health survey of people aged 15 and older found that people with a hearing disability of any kind reported poorer physical and mental health than those with normal hearing.[54]

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

Research has shown that the experience of losing a child is by far the most painful grief experience.[55] 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 foetal loss. Although several studies have considered the impact on parents of stillbirth and neonatal death, none has been found which specifically studies the impact of foetal 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 two years. Fathers experience similar levels of grief, anxiety and depression, although they generally display less active grief than mothers. Some parents suffer prolonged symptoms which 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.[56,57,58]

Some studies, including two prospective studies,[59,60,61] have suggested that grief following stillbirth or foetal 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 study found that, at two months post-termination, women who had terminated wanted pregnancies for foetal 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.[62] A second US study also found that the termination of a wanted pregnancy because of foetal 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.[63] 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 which follows a loss is intense, and will last for months to years. For some parents, this attachment happens very early in the pregnancy.[57]

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, personal communication, 2001).

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

To its parents, any infant or foetus who dies is an irreplaceable individual. However, most parents affected by miscarriage, stillbirth, neonatal 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 foetus 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, 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, there is still a 50% probability that a given pregnancy will be affected. As the severity with which the foetus 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 (DI) with RhD-negative sperm, but it is not known how many affected couples in the UK are offered, or accept, this option. Moreover, DI in itself may not be devoid of long-term psychological consequences. A review found that, although DI 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 DI.[64] One study of 60 couples who had children conceived both naturally and by DI found that the men were significantly closer to their children by DI than to their 'other' children.[65] However, another study found that parents who used DI 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.[66] Clearly, the psychological issues for fathers would differ if DI were used because of RhD incompatibility rather than male infertility; we are not aware of any studies of its use specifically because of RhD incompatibility.

3.1.4.4 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 study, 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.[67] This conflicts with the findings of a Canadian study, that adolescents and young adults with CP, 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 CP 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 CP, 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 CP. Parental future expectations were lower for adolescents and young adults with CP than for those without.[45]

An Australian study identified that the parents of children with mild to severe CP 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 CP, but the emotional impact was the same regardless of whether the child had mild or severe CP.[68] A US study also found that parents of children with mild to severe CP suffered greater emotional worry/concern and limitations in time available for their personal needs than a normative sample.[69] A Canadian study found that the primary caregivers of children with CP (in 95% of cases a parent, primarily the mother) reported significantly more physical and psychological illhealth than the general population of caregivers; they also had lower incomes, despite the absence of any important differences in education between the two samples.[70] A Turkish study found that quality of life in mothers who looked after children with CP 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 than in the mothers of less badly affected children.[71] More generally, an Australian study 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.[72]

Families with children with intellectual disabilities are significantly more disadvantaged on all indicators of socio-economic position than families with children without such disabilities.[73] A British study suggests that differences in socio-economic 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 the mothers of the disabled children.[74] The economic impact on the family of the presence of a disabled child extends beyond childhood: in the US, the prospective Wisconsin study found that, by the age of 53, the parents of adult children with developmental disabilities had significantly lower income and savings than comparison parents.[75]

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, and 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),[76] as would be the case with deafness caused by HDN.

3.1.5 Significance for the NHS

In 2005, the most recent year for which figures are available, there were 645,835 live births and 3,483 stillbirths in England and Wales.[38] 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 which will require close monitoring: approximately 415 of the foetuses are likely to develop RhD HND, and 31 of these are likely to suffer foetal death, stillbirth, neonatal 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.[77] The obstetric input required to manage these cases is considerable, requiring:

- monitoring of maternal serum antibody level at least monthly until 28 weeks' gestation and every 2 weeks thereafter[78]
- consultant review, with ultrasound and Doppler scans, every 2 weeks

- cardiotocography
- 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 (Personal Communication from N Davies, 2001). The cost of this monitoring and treatment is clearly substantial.

10-12% of foetuses affected by HDN require IUT to correct anaemia,[79,26] 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 foetal loss from IUT of approximately 1-3%.[39] 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 which are not responsive to intensive phototherapy.[30] Such infants are fewer 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.[80,1]

Two UK studies have identified outcomes (including resource use) in pregnancies in women with RhD antibodies. One study 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,[81] and the other data relating to all such women in Northern Ireland between September 1994 and February 1997.[18] A third, substantially smaller, study collected similar data in a tertiary care centre in Zagreb, Croatia.[19] A very high proportion of infants in the Croatian study required IUT, ITU admission, exchange transfusions and/or phototherapy, and this is presumably due to the fact that the study only includes 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 (see Table 6).

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

	Number (%)		
	Mersey and North Wales, Dec 1993-Nov 1994[81] Number (%)	**Northern Ireland, Sept 1994-Feb 1997[18] Number (%)**	**Zagreb, Croatia, Jan 1997-Jan 2003[19] Number (%)**
Number of pregnancies	100	124 (130 foetuses)	23
Termination for foetal abnormality	None reported	2 (2)	0
Miscarriage	4 (4)	5 (4)	0
Intra-uterine death	2, 1 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 1 neonatal death from severe hydrops)	At least 17 (≥74)
Live-born unaffected babies	60 (60) (includes 38 RhD-negative)	44 (34) (includes 17 RhD-negative pregnancies)	No more than 3 (≤13) (includes 1 RhD-negative pregnancy)
Total foetuses requiring IUT	4 (4)[a] (includes 1 intra-uterine 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)
Babies requiring exchange or top-up tranfusions	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)

a the 3 live-born babies who had IUT required 3-5 transfusions each

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 managed in consultation with colleagues in DGHs, over the 3.5 years prior to 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 1 per pregnancy)

- 3 emergency Caesarian 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.[82]

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 Ireland[18] is that, in addition to around 37 foetal or neonatal deaths, these pregnancies would result in approximately 21 children with minor developmental problems and 8 with major permanent developmental problems. These children would require significant NHS and other resources. While CP 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.[68,69] Profound deafness is also associated with substantial costs. In the US, the expected lifetime cost to society for 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.[83] In the UK, the mean societal cost of a year of life at 7 to 9 years of age, at 2003 prices, was estimated to be £14,093 for children with congenital bilateral permanent hearing impairment, compared with £4,207 for normally-hearing children.[84]

3.2. Current service provision

It is current national guidance that routine antenatal anti-D prophylaxis 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.[85]

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.[86] This dose will cover a TPH of at least 4 ml of foetal red cells (i.e. 99% of all TPHs).[9] 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 the 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,[87] 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 about the level of uptake in terms of the number of RhD-negative pregnant women in those centres which have implemented RAADP who actually receive RAADP.[88]

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 hopes of increasing compliance.[87] The BPL submission indicates that 55% of hospitals which have implemented RAADP are currently using D-Gam 500 IU in a two-dose regimen,[89] while Behring state that 71 centres in England and Wales are currently using a single 1500 IU dose of Rhophylac.[90]

3.3. Description of technology under assessment

The technology under assessment is routine antenatal anti-D prophylaxis (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,[9] and therefore should not be given to such women.

RAADP may take the form of *either* two doses of at least 500 IU of anti-D immunoglobulin, the first at 28 and the second at 34 weeks' gestation, *or* a single dose of at least 1500 IU at 28 weeks (1500 IU being sufficient anti-D to effectively suppress the sensitising potential of approximately 17 mL of RhD-positive red blood cells[91]). The British Committee for Standards in Haematology recommends the use of the two-dose regimen, noting that more evidence is required to establish the comparative efficacy of a single dose of 1500 IU at 28 weeks.[92]

RAADP is additional to any antenatal anti-D prophylaxis 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.

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 foetus's RhD blood group would enable RAADP to be targeted to only those non-sensitised RhD-negative women pregnant with RhD-positive

infants. This approach has not been possible hitherto because identification of the foetus's blood group used to require a foetal blood sample which could only be 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,[93] in addition to an 0.5-1.0% risk of spontaneous abortion.[94] However, recent technological developments have made it possible to predict the foetal RhD genotype non-invasively by PCR using foetal DNA present in the mother's plasma.[93] In principle, this technology permits the screening of all non-sensitised RhD-negative pregnant women to enable antenatal prophylaxis to be targeted to only those carrying RhD-positive foetuses. However, to be feasible in practice, the test results must yield no false negatives (i.e. cases in which the foetus appears to be RhD negative but is actually RhD positive), and this level of accuracy does not yet appear to have been achieved.[94] (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 foetus will be given unnecessary prophylaxis.[94]) Moreover, targeted antenatal prophylaxis would only be possible if it were demonstrated that the test results were reliable when undertaken prior to 28 weeks' gestation. This has yet to be achieved. However, in their submission,[87] 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 where the foetus was confirmed to be RhD positive.[89]

It is likely that, in most cases, RAADP is administered by midwives based in the community and/or ante-natal clinic. Side effects (short-term discomfort at the injection site and, very rarely, anaphylaxis) are rare, and are not such as to 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 in order 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.[87]

3.3.1 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.[95] 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,[96,97] and we understand that this is now universal practice (Professor M Contreras, personal communication, 2007).

Historically, most RhD immunoglobulin products have been prepared using the Cohn cold ethanol fractionation method.[98] The yield of anti-D 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 can only be given intramuscularly, because it contains proteins which may cause adverse reactions if given intravenously, unless it has been specifically treated to remove those proteins. It also contains small but significant amounts of other plasma proteins, especially IgA and IgM, which may cause localised itching, swelling and discomfort and, very rarely, anaphylactic reactions.[99]

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 (6,000 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 made up prior to injection; it is therefore less convenient for healthcare personnel to use.[99] More recently, however, a multi-step chromatographic fractionation method has been developed which yields a liquid-stable anti-D (Rhophylac).[98]

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 foetus.[14] 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, though of course antenatal administration exposes the foetus as well as the mother to any such risk. These concerns are discussed in turn below.

3.3.1.1 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.[14]

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. Bio Products Laboratory 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.[89] Baxter reported in 2001 that anti-D was well tolerated: [redacted].[100] Baxter do not present more recent data, but state that their product's safety profile is unchanged.[101] 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.[90]

RAADP may potentially reduce the effectiveness of post-delivery rubella immunisation. It is known that, if women are immunised against rubella post-delivery, this immunisation is less effective if it is given following postpartum anti-D. It is possible that this effect would be greater if antenatal anti-D had been given. (Personal Communication from N Davies, 2001).

3.3.1.2 Concerns relating to exposure of the foetus to passive anti-D

Concerns have been expressed regarding the potential risks of RAADP to the foetus, who will not benefit directly from the intervention, which is intended to protect his or her future siblings.[102] It is theoretically possible that the transfer of passive anti-D from the mother could cause foetal 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 foetus, 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 sub-clinical and does not result in anaemia, jaundice or the need for phototherapy.[14,103]

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 babies' immune system, and may potentially also cause problems for RhD-negative baby girls in their

later reproductive lives.[102] 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.

3.3.1.3 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.[104] This method has been shown to produce non-infective immunoglobulin from plasma contaminated with hepatitis virus.[105]

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[106,105] and Ireland.[107] These outbreaks predated the identification of hepatitis C in 1989 and the introduction of screening of donations in 1991.[108] 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, though 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 not investigations into the much larger 1977 outbreak been undertaken in 1991 and 1994.[108] 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.[90] However, these measures may be of limited value against non-enveloped viruses such as hepatitis A and parvovirus B19.[109]

As with other human-derived blood products, the risk of new variant CJD (vCJD) transmission is unquantifiable.[110] Both the extent of vCJD infection in the population and its transmissibility by blood products are unknown.[8] The four cases of probable transfusion-associated vCJD identified in the UK in the last four 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.[111] Nonetheless, because of the long incubation period, it is not possible to conclude that there is no risk of vCJD infection.[112] 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 protein[90]). 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 300 kg.[98] 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 foetal 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 which occurred before the foetal genotype was known.

3.3.1.4 Summary of product characteristics

The product characteristics are briefly summarised in Table 7. Fuller details are presented below.

Table 7: Summary of product characteristics

Product name	**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 x 500 IU	2 x 1000-1650 IU	1 x 1500	1 x 1500
List price of RAADP	£54	£70	£46.50	£313.50
Current NHS price of RAADP	£39	[redacted]	Not known	Not known

(a) D-Gam

D-Gam is produced by the Bio Products Laboratory, a not-for-profit, government-owned plasma fractionation unit.[89] It is available in vials containing 250, 500, 1500, and 2500 IU human anti-D

immunoglobulin in the form of a solution ready for injection.[113] 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.[89]

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.[89]

The price listed in the BNF for 500 IU of non-proprietary anti-D is £27.00 per vial.[114] However, the current NHS price for 500 IU of D-Gam is said to be £19.50 per vial.[89]

(b) 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 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 erythrocyte concentrate.[115]

Partobulin SDF is produced from US plasma using a modified Cohn-Oncley fractionation process.[100] 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.[101] In addition, donors are selected by medical interview, and individual donations and plasma pools are screened for HbsAg and antibodies to HIV and HCV, while plasma pools are tested for genomic material of HCV.[115]

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.[115] 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.[115] In addition, as Partobulin SDF contains a small quantity of IgA, it may cause hypersensitivity reactions in IgA-deficient individuals.[115]

Partobulin SDF is supplied in prefilled syringes containing 1250 IU anti-D at a list price of £35;[114] [redacted]

(c) 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 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.[109]

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.[90] The measures taken are considered effective for HIV, and hepatitis B and C, but may be of limited value against non-enveloped viruses such as hepatitis A and parvovirus B19.[109] Although nanofiltration has been shown to contribute to the removal of abnormal prion protein,[90] the test prion was scrapie, not vCJD. Thus, the possibility of transmitting infective agents, including unknown or emerging viruses and other pathogens, cannot be totally excluded.[109]

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 (ADRs) relevant to its safety have been reported, one per 69,000 doses.[90] Although no details are provided, these ADRs, 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.[109] As Rhophylac may contain traces of IgA, it may cause hypersensitivity reactions in IgA-deficient individuals.[109]

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.[109]

Rhophylac is supplied in prefilled syringes containing 1500 IU anti-D immunoglobulin for intravenous or intramuscular injection,[109] at a list price of £46.50 per syringe.[114]

(d) 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 (ITP). 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.[101]

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, 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.[116]

In a small number of cases, administration of WinRho SDF has been accompanied by discomfort and swelling at the site of injection and 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.[91]

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. WinRho is supplied as a powder for reconstitution; the list price of a 1500 IU vial, with diluent, is £313.50.[114]

3.3.2 Identification of important sub-groups

As noted earlier, important sub-groups in relation to RAADP include

- women who will be sterilised after the birth;
- women who are certain they will have no more children;
- women who are in a stable relationship with the genetic father of their children and the father is known or found to be RhD-negative

as current guidance[85] notes that RAADP is not necessary under these circumstances. While it is desirable to avoid unnecessary blood product administration, it should be noted that the second and third groups are problematic. Some women who are certain they will have no more children do nonetheless go on to have more. In relation to the third group, the BCHS Guideline for blood grouping and antibody testing in pregnancy[78] 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.[117]

3.3.3 Current usage in the NHS

Implementation of the policy of RAADP appears to be fairly widespread. As noted in section 3.2 above, in 2005 a survey of 328 UK maternity units found that 75% were offering RAADP.[87] 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.[87]

While 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 which offered RAADP used the two-dose regimen.[87] The Bio Products Laboratory claims that 55% of hospitals which have implemented RAADP currently use D-Gam 500 at 28 and 34 weeks' gestation.[89] However, the more recent survey of hospital transfusion laboratories found that 53/173 (31%) were using the single 1500 IU dose at 28 weeks.[87] Whilst the survey did not collect data on compliance, a recent audit in two UK hospitals found 86.5% compliance with the two-dose regimen.[118]

MacKenzie *et al*. found that the proportion of women refusing at least one antenatal prophylaxis injection increased from 0.8% in the period 1992-1996 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.[119] A retrospective audit carried out in two UK hospitals in 2004[118] found much higher refusal rates. 10.6% of eligible women (22/207)

refused the first, 28 week, dose of a two-dose RAADP regimen, while 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 (see Table 8). Moreover, the first two reasons 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 that it therefore seems unlikely that they would have consented to a single-dose regimen.

Table 8: Reasons for declining RAADP[118]

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

3.3.4 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 per vial = £70.00
- Rhophylac: £46.50 per vial = £46.50
- WinRho SDF: £313.50 per vial = £313.50

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

4. DEFINITION OF THE DECISION PROBLEM

This review seeks to identify any evidence for advances in practice in RAADP since the 2002 appraisal conducted by the National Institute for Health and Clinical Excellence (NICE).[85] It assesses the current clinical and cost-effectiveness of RAADP for RhD-negative women.

4.1 Decision problem

The decision problem has been specified as follows:

Intervention

RAADP given by injection in any of the licensed regimens, ie:

- two doses of at least 500 IU 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),

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.

Population (including sub-groups)

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, due to the feasibility and ethical considerations of determining the genotype of the father, and to 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 Nursing[120] 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 in 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
- 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 haemolytic disease of the newborn (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
- Non-randomised controlled studies

4.2 Overall aims and objectives of assessment

The review has the following aims:

1. to evaluate the clinical effectiveness of anti-D for RhD-negative pregnant women, in any licensed regimen, in terms of reduction in the incidence of sensitisation (alloimmunisation) in RhD-negative women delivered of RhD-positive infants, reduction in the incidence of haemolytic disease of the newborn, survival of the child, disability of the child, and health-related quality of life of the child and parents (if relevant evidence is available)
2. to evaluate the adverse effect profile
3. to estimate the incremental cost effectiveness of different dosing regimens and different methods of administration of anti-D prophylaxis
4. to identify key areas for primary research
5. to estimate the possible overall cost in England and Wales.

5. ASSESSMENT OF CLINICAL EFFECTIVENESS

5.1 Methods for reviewing effectiveness

5.1.1 Identification of studies

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

a) *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. 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 website. In addition, the bibliographies of retrieved papers (including the previous review[121]) were scrutinised.

b) *Keyword strategies*

Sensitive keyword strategies using free-text and, where 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).

c) *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 2006.

A copy of the general search strategy may 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.

5.1.2 Inclusion and exclusion criteria

Inclusion criteria

Population: pregnant women who are RhD-negative

Intervention: routine antenatal anti-D prophylaxis using *either* 2 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.

Comparator:

- RAADP using different dosing regimens and/or methods of administration
- no RAADP

Outcomes:

- sensitisation (alloimmunisation) rates among RhD-negative women delivered of RhD-positive infants (the at-risk population)
- incidence of haemolytic disease of the newborn (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

Exclusion criteria: studies considered methodologically unsound, or not reporting results in the necessary detail.

5.1.3 Data abstraction strategy

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

5.1.4 Critical appraisal strategy

Published papers were assessed according to the accepted hierarchy of evidence, whereby meta-analyses of randomised controlled trials are taken to be the most authoritative forms of evidence, with uncontrolled observational studies the least authoritative. Because of the paucity of randomised controlled trials 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[122] (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.

5.1.5 Methods of data synthesis

The pre-specified outcomes outlined in section 5.1.1 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 group 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.

5.2 Results

5.2.1 Quantity and quality of research available

5.2.1.1 Quantity of research available

The original systematic review carried out on behalf of NICE[121] was not limited to specific licensed anti-D dosage regimens. It identified eleven studies which compared an intervention group receiving RAADP with a control group (for details, see Table 9). 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.*,[123] MacKenzie *et al.*,[124] Mayne *et al.*[125] and Tovey *et al.*,[126] which used two doses of 500 IU at 28 and 34 weeks;
- the study by Bowman *et al.*[127] which used two doses of 1500 IU at 28 and 34 weeks;
- the 1978 and 1987 studies by Bowman and Pollock[128,129] and the study by Trolle[130] which used a single dose of 1500 IU at 28 weeks.

An article by Thornton *et al*.[131] was also included as it presented follow-up data relating to the study by Tovey *et al*.,[126] studying the safety and efficacy of antenatal prophylaxis by examining obstetric data relating to women in that trial in their first and subsequent pregnancies.

Table 9: Characteristics of Studies Included in the Previous Review[121] (Studies Which Meet the Inclusion Criteria for the Current Review are Highlighted)

Study	Study type	Date and location of intervention	Date and location of control	Patient selection*	Specific product (production method) and route of administration	Dosage and administration schedule
Bowman *et al.* 1978[127]	Prospective study, historic/geographic controls	Dec 1968-Aug 1976 Winnipeg, Canada	Mar 1967-Dec 1974 Manitoba, Canada	Primigravidae	Rh_o[D] immune globulin (Cohn method), Connaught Laboratories, Toronto; IM[129]	2 x 1500 IU 28 & 34 weeks
Bowman & Pollock 1978[128]	Prospective study, historic controls	Mar 1976-June 1977 Manitoba, Canada	Mar 1967-Dec 1974 Manitoba, Canada	Primigravidae and unsensitised multigravidae	Rh_o[D] immune globulin (Cohn method), Connaught Laboratories, Toronto; IM	1500 IU 28 weeks
Bowman & Pollock 1987[129]	Retrospective study, historic controls	June 1977-Feb 1986 Manitoba, Canada	Mar 1967-Dec 1974 Manitoba, Canada	Primigravidae and unsensitised multigravidae	RhIG-IV (WinRho), Winnipeg Rh Institute (ion exchange); usually IM but could be IV	1500 IU 28 weeks
Hermann *et al.* 1984[132]	Prospective study, historic controls	Not stated Växjö, Sweden	1968-1977 Växjö, Sweden	Primigravidae and unsensitised multigravidae	Rhesonativ, KabiVitrum AB, Sweden; IM	1250 IU 32-34 weeks
Huchet *et al.* 1987[123]	Quasi-RCT	Jan 1983-June 1984 Paris	Jan 1983-June 1984 Paris	Primigravidae	Product not specified; IM	2 x 500 IU 28 & 34 weeks
Lee & Rawlinson 1995[133]	RCT	Not stated UK	Not stated UK	Primigravidae	Not specified	2 x 250 IU 28 & 34 weeks
MacKenzie *et al.* 1999[124]	Community intervention trial (controlled before-and-after study)	1990-1996 Oxfordshire	1990-1996 Northants	Primiparae	Not specified	2 x 500 IU 28 & 34 weeks
Mayne *et al.* 1997[125]	Retrospective before-and-after study	1993-1995 Southern Derbyshire	1988-1990 Southern Derbyshire	Primiparae	Not specified	2 x 500 IU 28 & 34 weeks

Study	Study type	Date and location of intervention	Date and location of control	Patient selection*	Specific product (production method) and route of administration	Dosage and administration schedule
Parsons *et al.* 1998[134]	Retrospective survey (geographical controls)	1988-1995 Nova Scotia	1988-1995 Scotland	Not stated	Not specified	1 dose 28 weeks
Tovey *et al.* 1983[126]	Prospective study, historic controls	1980-1981 Yorkshire	1978-1979 Yorkshire	Primigravidae	Not specified	2 x 500 IU 28 & 34 weeks
Trolle 1989[130]	Prospective study, historic controls	1980-1985 Kolding, Denmark	1972-1977 Kolding, Denmark	Primigravidae and unsensitised multigravidae	Not specified	1500 IU 28 weeks

* 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.

The update searches identified four additional papers which related to relevant studies of clinical effectiveness (for summary, see Table 10). Only one of these related to a study which was not included in our previous review. This was the relatively recent RCT by MacKenzie *et al*.[98] comparing intravenous with intramuscular Rhophylac. A conference abstract by MacKenzie *et al*.[135] related to MacKenzie *et al*.'s 1999 community intervention study;[124] it did not present any additional data. A further two papers by Bowman[99,13] 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.[129] As the clinical trial effectively takes the form of a case series compared with the control group reported in Bowman *et al*.'s 1978 study,[127] 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 1980[13] and by Bowman in 1982[99] have been considered as interim results in relation to the 1987 study.

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

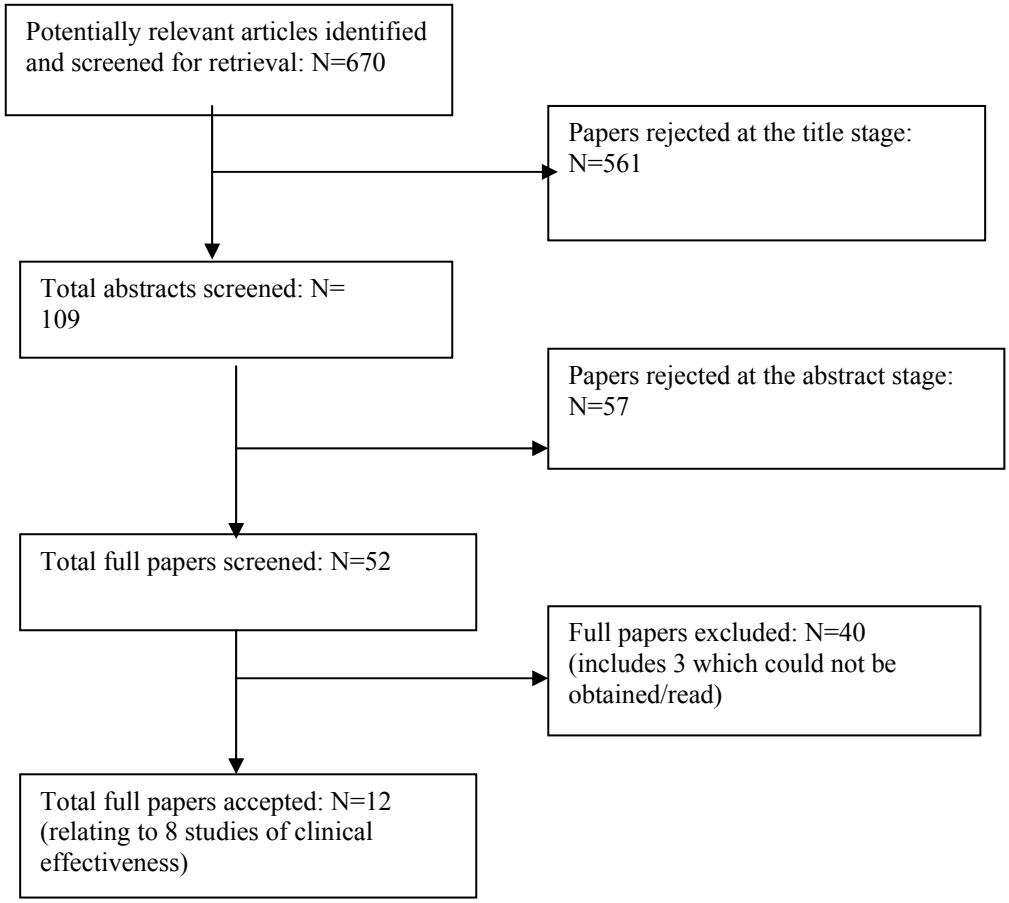
Paper	Status
MacKenzie *et al*. 2004[98]	Included as new independent study
MacKenzie *et al*. 1998[135]	Included as relating to a previously included study (MacKenzie *et al*. 1999[124])
Bowman 1982[99,13]	Included as relating to a previously included study (Bowman & Pollock 1987[129])
Bowman[99,13]. 1980[13]	Included as relating to a previously included study (Bowman & Pollock 1987[129])

It was not possible to read an additional, potentially relevant study by Eklund and Nevanlinna,[136] 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 by Potron *et al*.,[137] 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,[138] and understand that the principal investigator is now deceased.

A population study by Koelewijn *et al*.[139] 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.

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

Figure 1: Assessment of clinical effectiveness: Summary of study selection and exclusion



The update searches did not identify Bowman and Pollock's 1978 study,[128] which was identified by the searches for our earlier review;[121] this brought the total number of included studies to nine. A summary of the 1977 McMaster Conference on the prevention of RhD immunisation[140] 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; it appears to represent an interim analysis from the study published in 1984 by Hermann *et al.*,[132] included in our previous review,[121] which used a dose of 1250 IU. A study of alloimmunisation following RAADP in north east Scotland[141] was subsequently drawn to 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.[91] This used intravenous anti-D (implicitly WinRho SDF) according to three regimens,

- 1 x 600 IU (at 28 weeks)
- 1 x 1200 IU (at 28 weeks)
- 2 x 1200 IU (at 28 and 34 weeks),

only one of which (2 x 1200 IU) is currently licensed. 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 six 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 which was not included in our earlier review. This was the RCT by MacKenzie *et al*.[98]

5.2.1.2 Quality of included research:

Overall, the quality of included research was not high. We identified only one true RCT, that by MacKenzie *et al*.[98] 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 x 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 in order 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*.[123] 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*.[124]
- a retrospective before-and-after study by Mayne *et al*.[125]
- five non-randomised studies with historical or geographical controls (Bowman *et al*.,[127] Bowman and Pollock 1978[128] and 1987,[129] Tovey *et al*.,[126] and Trolle[130]).

Many of these studies are 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 (Bowman *et al.*,[127] Huchet *et al.*,[123] MacKenzie *et al.* 1999,[124] Mayne *et al.*,[125] and Tovey *et al.*[126]) recruited their intervention group from primigravidae. Four of these studies (Bowman *et al.*,[127] MacKenzie *et al.* 1999,[124] Mayne *et al.*,[125] and Tovey *et al.*[126]) recorded data relating to those women in subsequent pregnancies. Bowman *et al.*, MacKenzie *et al.* and Mayne *et al.* did this in order to assess the prevalence of sensitisation arising from the first pregnancy, and only the study by Tovey *et al.*[126,131] 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,[128,129] MacKenzie *et al.*, 2004[98] and Trolle[130] recruited both primigravidae and unsensitised multigravidae. In MacKenzie *et al.* 2004,[98] 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 section 5.2.2.1 below, 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.* compared RAADP using the same anti-D preparation (Rhophylac) administered intravenously and intramuscularly. The remaining studies compared RAADP with no RAADP; none used placebo. Four studies (Huchet *et al.*,[123] MacKenzie *et al.* 1999,[124] Mayne *et al.*,[125] and Tovey *et al.*[126]) used 500 IU at 28 and 34 weeks gestation, one (Bowman et al[127]) used 1500 IU at 28 and 24 weeks, and four (Bowman and Pollock 1978[128] and 1987,[129] MacKenzie *et al.* 2004,[98] and Trolle[130]) used a single dose of 1500 IU at 28 weeks.

It was originally stated that studies would only be included in the review 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,[129] which used WinRho, and the 2004 study by MacKenzie *et al.*,[98] which used Rhophylac. In their 1978 studies, Bowman *et al.*[127] and Bowman and Pollock[128] 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 Bowman and Pollock 1978[128] 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.*[98]
- the quasi-RCT by Huchet *et al.*[123]
- the community intervention trial by MacKenzie *et al.*[124]

The 1978 study by Bowman *et al.*[127] 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 (personal communication from JM Bowman, 2001). As pre-intervention 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 which antedate the intervention group by several years are likely to underestimate the true incidence of alloimmunisation in the control group,

and therefore to underestimate the degree of protection provided by AADP.[14] However, the community intervention trial by MacKenzie *et al*.[124] used a retrospective analysis of prospectively collected data to demonstrate the baseline comparability, in terms of rates of alloimmunisation, of the two communities compared in the prospective study. 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 historic 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, Trolle[130] 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 foetal 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 section 3.1.1 above). However, only two of the included studies - the 1999 study by MacKenzie *et al*.,[124] and the study by Mayne *et al*.[125] - 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.

Table 11: Characteristics of included studies

Study	Study type	Study quality	ITT analysis	Date and location of intervention	Date and location of control	Patient selection*	No. of RhD-women in intervention group delivered of RhD+ infants	Specific product (production method) and route of administration	Dosage and administra-tion schedule	Source of funding
Bowman *et al.* 1978[127]	Prospective study, historic/ geographic controls	Poor	No	Dec 1968-Aug 1976 Winnipeg, Canada	Mar 1967-Dec 1974 Manitoba, Canada	Primigravidae	1,357	Rh_o[D] immune globulin (Cohn method), Connaught Laboratories, Toronto; IM[129]	2 x 1500 IU 28 & 34 weeks	National Health & Medical Research Council of Canada
Bowman & Pollock 1978[128]	Prospective study, historic controls	Fair	No	Mar 1976-June 1977 Manitoba, Canada	Mar 1967-Dec 1974 Manitoba, Canada	Primigravidae and unsensitised multigravidae	1,804	Rh_o[D] immune globulin (Cohn method), Connaught Laboratories, Toronto; IM	1500 IU 28 weeks	Not stated
Bowman & Pollock 1987[129]	Retrospective study, historic controls	Poor	No	June 1977-Feb 1986 Manitoba, Canada	Mar 1967-Dec 1974 Manitoba, Canada	Primigravidae and unsensitised multigravidae	9,303	RhIG-IV (WinRho), Winnipeg Rh Institute (ion exchange); u sually IM but could be IV	1500 IU 28 weeks	Not stated
Huchet *et al.* 1987[123]	Quasi-RCT	Good	Yes	Jan 1983-June 1984 Paris	Jan 1983-June 1984 Paris	Primiparae (not all of whom were primigravidae)	599	Product not specified; IM	2 x 500 IU 28 & 34 weeks	Not stated
MacKenzie *et al.* 1999[124]	Community intervention trial (controlled before-and-after study)	Good	Yes	1990-1996 Oxfordshire	1990-1996 Northants	Primiparae	3,320	Product and route of administration not specified	2 x 500 IU 28 & 34 weeks	Bio Products Laboratories

Study	Study type	Study quality	ITT analysis	Date and location of intervention	Date and location of control	Patient selection*	No. of RhD-women in intervention group delivered of RhD+ infants	Specific product (production method) and route of administration	Dosage and administra-tion schedule	
MacKenzie *et al.* 2004[98]	Open-label RCT; results presented as uncontrolled study	Poor	No	Date not specified UK and US	IM controls contemporary with IV intervention. No untreated controls UK & US	Unselected (primigravidae 28.5%)	270 (figure includes those receiving IV and IM Rhophylac)	Rhophylac IV vs IM	1 x 1500 IU 28 weeks	Chiltern International
Mayne *et al.* 1997[125]	Retrospective before-and-after study	Fair	Yes	1993-1995 Southern Derbyshire	1988-1990 Southern Derbyshire	Primiparae	1,425	Product and route of administration not specified	2 x 500 IU 28 & 34 weeks	Bio Products Laboratories
Tovey *et al.* 1983[126]	Prospective study, historic controls	Fair	Yes	1980-1981 Yorkshire	1978-1979 Yorkshire	Primigravidae	1,238	Product and route of administration not specified	2 x 500 IU 28 & 34 weeks	Not stated
Trolle 1989[130]	Prospective study, historic controls	Poor	No	1980-1985 Kolding, Denmark	1972-1977 Kolding, Denmark	Primigravidae and unsensitised multigravidae	346	Product and route of administration not specified	1500 IU 28 weeks	Not stated

* 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.

5.2.2 Assessment of effectiveness

5.2.2.1 Critical review and synthesis of information

As noted in section 5.2.1.2, 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*. 1999,[124] and Mayne *et al*.,[125] took this as their primary endpoint; 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 which did not take it as their primary endpoint, the studies by Bowman *et al*.[127] and Tovey *et al*.,[126] 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 (see Table 12).

As noted in section 5.2.1 above, MacKenzie *et al*. 1999[124] 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*.[125] 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 three 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 present 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*. 1999 [124] and Mayne *et al*.,[125] which present sensitisation rates during the subsequent pregnancy, the figures in Table 13 are likely to underestimate the true prevalence of sensitisation at six months because the extent of overlap between women with demonstrable antibodies at delivery and at follow-up is not clear. Moreover, all 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 account of 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.

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 *et al.* 1978[127]	Prospective study, historic/geographic controls	2 x 1500 IU (28 and 34 weeks) (initially at 34 weeks only)	343	0	0.0 (0.0 to 0.0)	No data		
MacKenzie *et al.* 1999[124]	Community intervention trial	2 x 500 IU (28 and 34 weeks)	3,320	12	0.4 (0.2 to 0.6)	3,146	26	0.8 (0.5 to 1.1)
Mayne *et al.* 1997[125]	Before and after study	2 x 500 IU (28 and 34 weeks)	1,425	4	0.3 (0.0 to 0.6)	1,426	16	1.1 (0.6 to 1.7)
Tovey *et al.* 1983[126]	Prospective study, historic controls	2 x 500 IU (28 and 34 weeks)	325	2	0.6 (-0.2 to 1.5)	582	11[a]	1.9 (0.8 to 3.0)

Key:

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[127]	Prospective study, historic/ geographic controls	2 x 1500 IU (28 and 34 weeks) (initially at 34 weeks only)	Primigravidae	1,357[a]	1	0.1 (-0.1 to 0.3)	2,768	45	1.6 (1.2 to 2.1)
Bowman & Pollock 1978[128]	Prospective study, historic controls	1 x 1500 IU (28 weeks)	Unselected	1,804	5	0.3 (0.0 to 0.5)	3,533	62	1.8 (1.3 to 2.2)
Bowman & Pollock 1987[129]	Retrospective study, historic controls	1 x 1500 IU (28 weeks)	Unselected	9,303	25	0.3 (0.2 to 0.4)	3,533	62	1.8 (1.3 to 2.2)
Trolle 1989[130]	Prospective study, historic controls	1 x 1500 IU (28 weeks)	Unselected	346	0	0.0 (0.0 to 0.0)	354	6	1.7 (0.4 to 3.0)
MacKenzie *et al.* 2004[98]	Open-label RCT; results presented as uncontrolled study	1 x 1500 IU (28 weeks)	Unselected	248 (per protocol population)	0	0.0 (0.0 to 0.0)	-	-	-
Huchet *et al.* 1987[123]	Quasi-RCT	2 x 500 IU (28 and 34 weeks)	Primiparae	461	0	0.0 (0.0 to 0.0)	454	4	0.9 (0.0 to 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 to 2.1)

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)
MacKenzie *et al.* 1999[124]	Community intervention trial	2 x 500 IU (28 and 34 weeks)	Primiparae	3,320	12	0.4 (0.2 to 0.6)	3,146	26	0.8 (0.5 to 1.1)
Mayne *et al.* 1997[125]	Before and after study	2 x 500 IU (28 and 34 weeks)	Primiparae	1,425	4	0.3 (0.0 to 0.6)	1,426	16	1.1 (0.6 to 1.7)
Tovey *et al.* 1983[126]	Prospective study, historic controls	2 x 500 IU (28 and 34 weeks)	1st pregnancy	1238	4[b]	0.3 (0.0 to 0.6)	2,000	19[b]	1.0 (0.5 to 1.4)
			2nd pregnancy	604[b]	1[b]	0.2 (-0.2 to 0.5)	582	9[b]	1.5 (0.5 to 2.5)
			All pregnancies	2037[b]	6*	0.3 (0.1 to 0.5)	2721[b]	32[b]	1.2 (0.8 to 1.6)

Key:

RCT = randomised controlled trial
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
a 153 received only one dose, at 28 or 34 weeks
b Data from Thornton *et al.* 1989[131]

Comparability of results

The studies vary in the results which they present. Six studies – the study by Bowman *et al.*,[127] the two studies by Bowman and Pollock,[128,129] and the studies by Huchet *et al.*,[123] Tovey *et al.*,[126] and Trolle[130] - report in effect the aggregated results of treating individual women. Although Bowman and Pollock 1978[128] 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, Trolle[130] screened women for antibodies prior to inclusion, and gave no indication of the numbers who were excluded from the study on this basis.

Studies which only include data relating to women known both to have received the intervention, *and* to have received it prior to 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 which 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*. 1999[124] and Mayne *et al.*[125] MacKenzie *et al.*[124] 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.*[125] 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, since only the before-and-after studies included a number of untreated women in the intervention group. Moreover, as 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.*[98] found no difference in efficacy or safety between Rhophylac administered intravenously and 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.

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[127]	Prospective study, historic/ geographic controls	2 x 1500 IU (28 and 34 weeks) (initially at 34 weeks only)	Primigravidae	1,357[b]	1	0.1 (-0.1 to 0.3)	2,768	45	1.6 (1.2 to 2.1)
Bowman & Pollock 1978[128]	Prospective study, historic controls	1 x 1500 IU (28 weeks)	Unselected	1,806	11	0.6 (0.3 to 1.0)	3,533	62	1.8 (1.3 to 2.2)
Bowman & Pollock 1987[129]	Retrospective study, historic controls	1 x 1500 IU (28 weeks)	Unselected	9,295	30	0.3 (0.2 to 0.4)	3,533	62	1.8 (1.3 to 2.2)
Trolle 1989[130]	Prospective study, historic controls	1 x 1500 IU (28 weeks)	Unselected	346	0	0.0 (0.0 to 0.0)	354	6	1.7 (0.4 to 3.0)
Huchet *et al.* 1987[123]	Quasi-RCT	2 x 500 IU (28 and 34 weeks)	Primiparae	461	0	0.0 (0.0 to 0.0)	454	4	0.9 (0.0 to 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 to 2.1)
MacKenzie *et al.* 1999[124]	Community intervention trial	2 x 500 IU (28 and 34 weeks)	Primiparae	3,320	12	0.4 (0.2 to 0.6)	3,146	26	0.8 (0.5 to 1.1)

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)
Mayne *et al.* 1997[125]	Before and after study	2 x 500 IU (28 and 34 weeks)	Primiparae	1,425	4	0.3 (0.0 to 0.6)	1,426	16	1.1 (0.6 to 1.7)
Tovey *et al.* 1983[126]	Prospective study, historic controls	2 x 500 IU (28 and 34 weeks)	1st pregnancy	1238	4[c]	0.3 (0.0 to 0.6)	2,000	19[c]	1.0 (0.5 to 1.4)
			2nd pregnancy	604[c]	1[c]	0.2 (-0.2 to 0.5)	582	9[c]	1.5 (0.5 to 2.5)
			All pregnancies	2037[c]	6[c]	0.3 (0.1 to 0.5)	2721[c]	32[c]	1.2 (0.8 to 1.6)

Key:

NRCT = non randomised controlled trial
RCT = randomised controlled trial
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
a Information on numbers excluded from published analyses not available for Huchet or Trolle
b 153 received only one dose, at 28 or 34 weeks
c Data from Thornton *et al.* 1989[131]

Table 15: Women sensitised in intervention groups

Study	No of sensitised women in intervention group[a]	Comments
Bowman *et al.* 1978[127]	1	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
	Unspecified number	In the first six months of the study, an unspecified number of women were sensitised before 34 weeks; these were not included in the analysis
Bowman & Pollock 1978[128]	5	2 women were sensitised before 28 weeks; 1 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 2 more multigravidae may either have undergone silent sensitisation in a previous pregnancy or may represent failures of prophylaxis
	6	In addition, 2 primigravidae appeared to have been sensitised prior to what they stated was their first pregnancy; 3 multigravidae appeared to have undergone silent sensitisation by an earlier pregnancy, and 1 had received an RhD-positive blood transfusion: these were all excluded from the analysis
Bowman & Pollock 1987[129]	25	13 failures of prophylaxis 4 women in whom sensitisation could be due either to failure of prophylaxis or to failure to treat following a previous abortion or delivery 5 women sensitised by 28 weeks in current pregnancy 3 women sensitised by 28 weeks who possibly underwent silent sensitisation in an earlier pregnancy
	5	In addition, 5 women who appeared to have undergone silent sensitisation in a previous pregnancy were excluded from the analysis
Huchet *et al.* 1987[123]	1	Apparently a failure of prophylaxis - the woman in question had received anti-D during a previous pregnancy which was terminated for therapeutic reasons

Study	No of sensitised women in intervention group[a]	Comments
MacKenzie *et al.* 1999[124]	12	6 women were delivered of their first pregnancy outside Oxfordshire: 4 certainly, and 2 possibly, did not receive antenatal prophylaxis during that first pregnancy 1 woman had undergone a potential sensitising event at 18 weeks for which anti-D may not have been given 1 woman, who delivered at 37 weeks, had undergone a large foeto-maternal haemorrhage probably at 35 weeks. Routine prophylaxis had been given at 29 and 35 weeks 4 women had received prophylaxis at 28 and 34 weeks and did not appear to have suffered an incident likely to provoke a foeto-maternal haemorrhage
Mayne *et al.* 1997[125]	4	3 women had previously delivered in places where routine antenatal prophylaxis was unlikely 1 had not received prophylaxis during her first pregnancy despite the existence of a programme of RAADP
Tovey *et al.* 1983[126]	5	All seem due to failures of prophylaxis, though 2 women sensitised during their first pregnancy had low but persisting levels of antibodies which might possibly be rare "naturally occurring" anti-D
Trolle 1989[130]	0 Unspecified number	 An unspecified number of women who had been sensitised by 28 weeks were excluded from the study

a Where two figures are provided, the upper figure is the number of sensitised women included in the authors' analyses, and the lower figure the number of sensitised women excluded from those analyses

The studies were broadly comparable in terms of the percentage of women in their 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*. 1999[124] 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 1980-86 to 0.8% in 1990-96.

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*.[124] and Mayne *et al*.[125] 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 which used a dosage regimen of 500 IU at 28 weeks and 34 weeks and reported results for primigravidae - Huchet *et al*.,[123] MacKenzie *et al*. 1999,[124] Mayne *et al*.,[125] and Tovey *et al*.[126]

Group 2 the three studies which used a dosage regimen of 1,500 IU at 28 weeks - the two studies by Bowman and Pollock,[128,129] and that by Trolle.[130] These studies included both primigravidae and multigravidae.

Group 3 the two community-based UK studies which used a dosage regimen of 500 IU at 28 weeks and 34 weeks and reported results for primigravidae - MacKenzie *et al*. 1994,[124] and Mayne *et al*.[125]

The Group 3 studies were deemed to be the most representative for the cost-effectiveness analysis.

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 (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 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 Pollock[129] used the same control arm results as the 1978 study by the same authors.[128] In order to prevent double-counting, which would have a significant effect on the overall results due to 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.

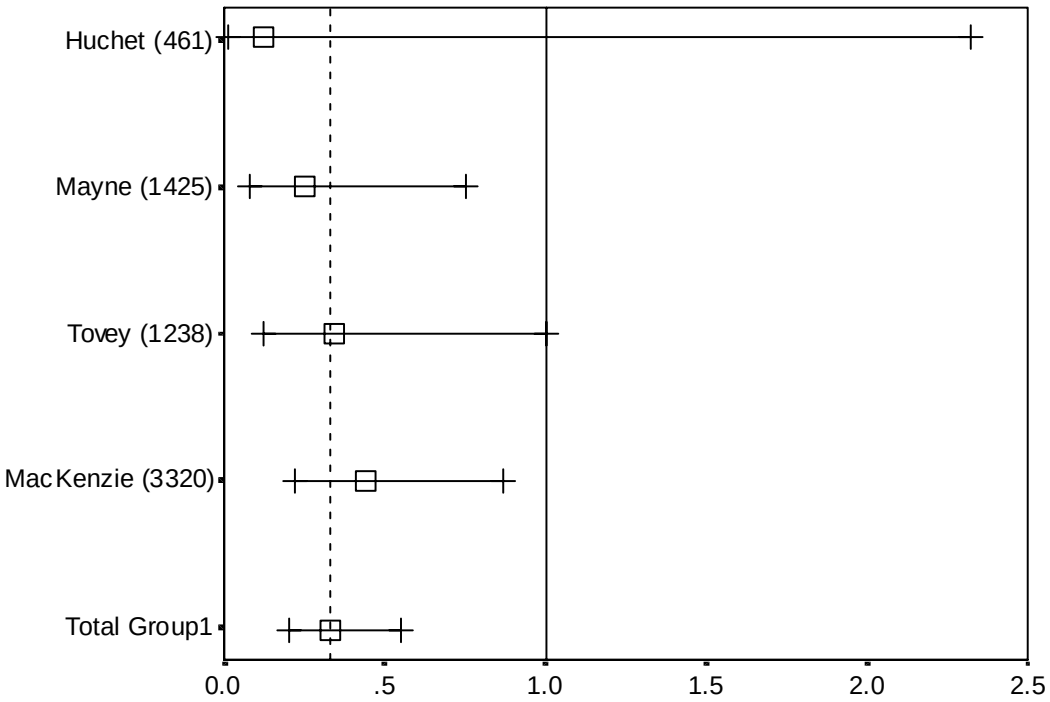
The results of the meta-analyses are shown in Table 16 and in Figures 2, 3 and 4 below.

Table 16: Results of the meta-analysis

	Group 1 **2 x 500 IU Primigravidae**	**Group 2** **1 x 1500 IU**	**Group 3** **Mayne & MacKenzie 1999**
Test for heterogeneity (p-value)	0.812	0.940	0.976
Odds ratio of sensitisation with antenatal prophylaxis	0.33 (0.20 ; 0.55)	0.20 (0.13 ; 0.29)	0.37 (0.21; 0.65)
Sensitisation rate of control group	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	0.30% (0.22% ; 0.38%)	0.34% (0.28% ; 0.40%)	0.35% (0.29% ; 0.40%)

Figure 2: Group 1: 2 x 500 IU in RhD-negative primigravidae

Note: Number of women in intervention group in brackets

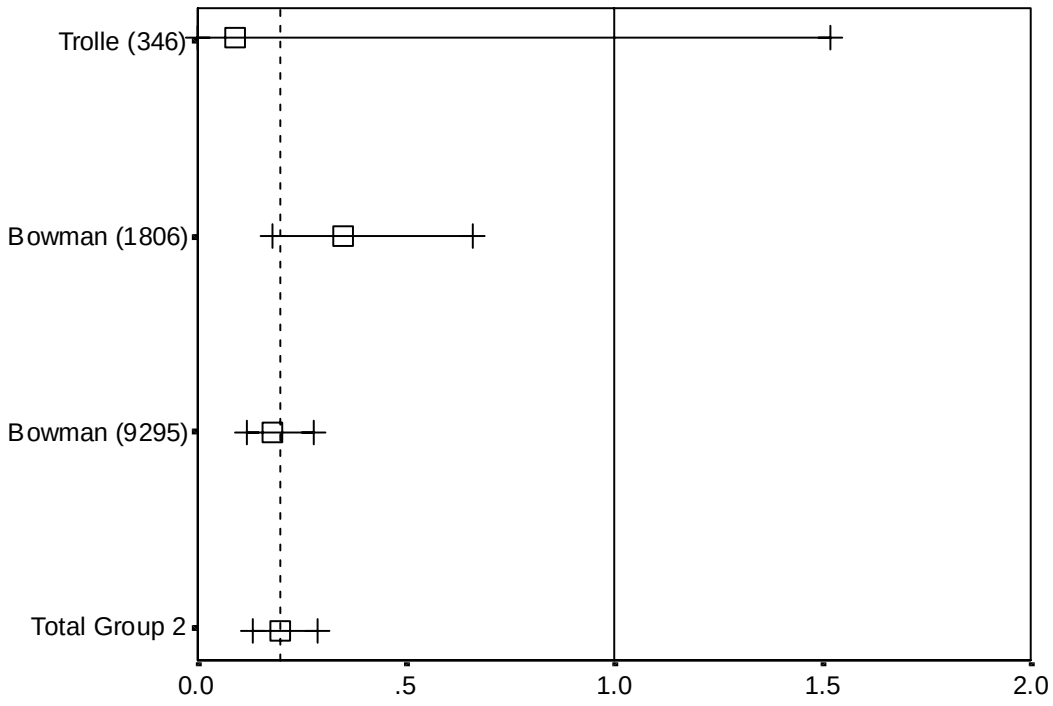


Odds Ratio = 0.330

95% confidence intervals = (0.20 ; 0.55)

Figure 3: Group 2: 1 x 1500 IU in unselected RhD-negative women

Note: Number of women in intervention group in brackets

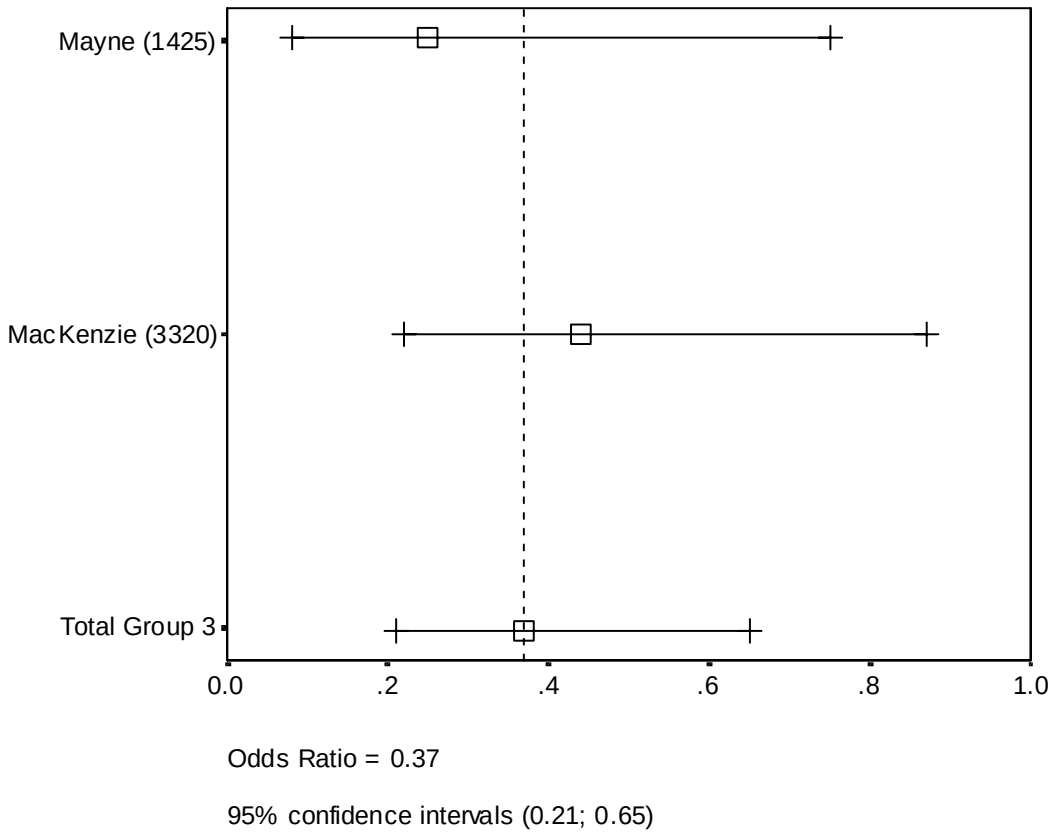


Odds Ratio = 0.20

95% confidence interval = (0.13 ; 0.29)

Figure 4: Group 3: 2 x 500 IU in RhD-negative primigravidae

Note: Number of women in intervention group in brackets



Comparison of dosage regimens

Pooling the data from those studies which 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 which used two doses of 1500 IU at 28 and 34 weeks reported a rate of 0.1%.[127] Although this suggests that, as one might expect, two doses of 1500 IU are more effective than one, there are no trials which directly compare the 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.[14] Pooling the data from those studies which 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 2 x 500 IU studies than in all the other studies, the point estimate of the odds ratio for

one dose of 1500 IU at 28 weeks is lower (i.e. more effective), at 0.20, 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*.,[124] examined the extent to which comprehensive prophylaxis was achieved. This found that, of a sample of eligible women delivered in the John Radcliffe Hospital, Oxford, during 1992-1996, 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.[119] 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*. provided information on the clinical outcomes of 17 subsequent RhD-positive pregnancies in the 62 sensitised women in the study's control group.[127] Seven of the 17 infants (41%) required treatment related to HDN (see Table 17).

Table 17: Clinical outcomes of RhD-positive pregnancies in sensitised women[127]

Outcome	No of pregnancies (%)
Foetal and exchange transfusion required	2 (12%)
Exchange transfusion and early delivery required	3 (18%)
Phototherapy required	2 (12%)
Direct Coombs' positive[a] – treatment not required	5 (29%)
Direct Coombs' 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.

In the study by Tovey *et al*.,[126] anti-D antibodies were identified during their first pregnancy in 18 women in the control group: 14 of their infants (78%) were mildly affected, and two (11%) were moderately affected, requiring exchange transfusion, while 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%) moderately affected, and one severely (requiring six exchange transfusions).

Thornton *et al*.[131] 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.*,[126] and reports on the same cohorts of women. Thornton *et al*. found that only one woman who had received RAADP in her first pregnancy produced anti-D antibodies in her second pregnancy, none in the third and only one in the fourth (see 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 18: Anti-D antibody detected in first and subsequent pregnancies of RhD-negative women delivered of an RhD-positive infant (RAADDP given to the treatment group in the first pregnancy only)[131]

First pregnancy		**Second pregnancy**		**Third pregnancy**		**Fourth pregnancy**	
Treatment group (n=1,234)	Control group (n=1,881)	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 -	3 (2.5%)	1 (3.1%)	1 (5.5%)

More recently, a retrospective longitudinal observational study carried out by MacKenzie *et al*.[142] compared the rate of RhD sensitisations 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 whereby 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.* provided data relating to pre-term 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 difference was observed

either in terms of these outcomes, or in terms of maternal hypertension and proteinuria in the first, second and third pregnancies.[131]

ABO compatibility

As noted in section 3.1.1 above, in approximately 20% of pregnancies in RhD-negative women the mother and foetus have different ABO blood groups. Sensitisation is less common where mother and baby are ABO-incompatible. This is demonstrated by information from the control group of the study by Bowman *et al*.[127] (see Table 19).

Table 19: ABO compatibility and incidence of sensitisation in RhD-negative women not treated with RAADP[127]

ABO compatibility	n	r	% Sensitised (95% CI)
Primigravidae	2,768	45	1.6 (1.2 to 2.1)
Compatible	2,257	44	1.9 (1.4 to 2.5)
Incompatible	511	1	0.2 (-0.2 to 0.6)
Multigravidae	765	17	2.2 (1.2 to 3.3)
Compatible	602	14	2.3 (1.4 to 3.5)
Incompatible	163	3	1.8 (-0.2 to 3.9)

Key :

n = number of deliveries of RhD-positive babies to RhD-negative women
r = number of sensitised RhD-negative women

Summary of clinical effectiveness

In the eight studies which compared RAADP with no prophylaxis, RAADP was given to, or available for, RhD-negative women undergoing a total of around 19,719 pregnancies which resulted in RhD-positive babies. 65 of these pregnancies (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 which resulted in RhD-positive babies: 136 of these pregnancies (1.2%) resulted in sensitisation.

The largest study, Bowman and Pollock 1987,[129] 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 1967-1974.

Overall, it would appear that, of the 65 pregnancies in the intervention groups which 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 where, in the absence of any recognised sensitising event, sensitisation preceded the administration of prophylaxis, or where 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 which resulted in sensitisation despite antenatal prophylaxis would appear to be as low as 29/19,719 (0.15% - 95% CI 0.1 to 0.2%). This figure would rise to a maximum of 48/19,719 (0.24% - 95% CI 0.2 to 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*. 1999[124] and Mayne *et al*.[125] 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 foetal genotyping, a RhD-negative woman will not know if she is carrying a RhD-positive child, and in fact only 60% of them will be, making the overall NNT 10/6 x 166 = 278.

Further, a woman will only benefit clinically *if* she has a 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 haemolytic disease of the newborn in *that* infant which constitutes the clinical benefit.

In section 3.1.5, 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 foetal or neonatal losses per year. Avoidance of sensitisation can be expected to avoid foetal 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 number needed to treat to avoid a foetal or neonatal loss in a subsequent pregnancy is therefore 278/0.048 = 5,790.

5.2.2.2 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*. 2004 reported a few cases of mild pain, soreness or itching at the injection site following administration of Rhophylac.[98] Bowman *et al.* reported mild adverse reactions (marked flushing and mild chest discomfort which disappeared within 30 seconds without the use of medication) in two out of 3,733 women given WinRho either antenatally or postpartum; they both received WinRho from a lot containing unacceptable levels of moisture and aggregated IgG.[13]

MacKenzie *et al*.'s 2004 study[98] was unique in screening for blood group alloantibodies and viral markers both before RAADP and six 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 HAV antibodies, three for CMV and one for anti-HBc; 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 HAV followed immunisation for international travel. Moreover, as the investigators acknowledge, the Committee for Proprietary Medicinal Products' note for guidance on the clinical investigation of human anti-D immunoglobulin for intravenous and/or intramuscular use[143] 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 while 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, though not necessarily as part of RAADP.[87] 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 foetus 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.* 1999[124] and by Mayne *et al*.[125] These are community-based studies with high external validity, as they demonstrate the effectiveness of RAADP in real life rather than under trial conditions, in the UK, 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 four 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.

Prior to 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 1991[144] 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.[145] A questionnaire survey published in 1994 found that many Accident and Emergency 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.[146] 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.[147] In an audit of singleton pregnancies delivered in nine hospitals within a hundred-mile radius of Manchester between 1st August 1994 and 31st 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%.[148] In 1998, an audit of 3,274 RhD-negative women in Northern Ireland found that anti-D was given after only 44% (117/264) of potentially sensitising events which occurred before, and 58% (184/319) of those which 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.[149]

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 1994,[147] and in 98% of cases (1820/1852) in Northern Ireland in 1998.[149]

It should be noted that the above studies were all carried out in the 1990s. While 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 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 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 blood-borne infections; this is minimised by the safeguards built into the modern manufacturing process.

One-dose versus two-dose regimen

No head-to-head studies have been undertaken which 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) will clearly not provide protection against an FMH at 28 weeks, and may be insufficient to provide protection against an FMH at 39 weeks.[120] Neither regimen would provide adequate protection against an undetected FMH of >10 ml occurring between approximately 34 and 40 weeks' gestation.[2] Indeed, Bowman observed that, in some failures of RAADP, the interval between the single dose at 28 weeks and delivery was over 13-5/7 weeks, and therefore recommended a second dose 12 weeks after the first for women who had not delivered by that date.[3]

Turner et al (2007)[150] have carried out a meta-analysis around the clinical effectiveness studies identified within our earlier systematic review.[121] 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 in Section 5.2.2.1 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 is not viable in the time available. However, this work could be used 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.[87] In their 2006 study of compliance with RAADP, MacKenzie *et al.*[119] found that, in 1997-2003, 13% of women did not receive the second dose of a two-dose regimen, while 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 study has found that the majority of women who declined the two-dose regimen declined at the first dose,[118] 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 offers 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.[120]

Cost: the single-dose regimen is cheaper than the two-dose regimen even though it uses more anti-D (1500 vs 1000 IU): at the prices quoted by the manufacturer, the single-dose regimen using Partobulin SDF is approximately half the cost of the two-dose regimen using D-Gam (see section 3.3.1.4 above). A single-dose regimen would also offering savings in laboratory and midwife administration time.[88]

Safety: none of the manufacturers can supply both the 1500 IU dose needed for the single-dose regimen and the 500 IU dose which 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.[87]

Intravenous versus intramuscular administration

As noted earlier, the ion exchange chromatography method produces anti-D which 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 made up prior to injection,[99] but more recently a liquid-stable version (Rhophylac) has been developed.[98] 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.[10] Moreover, intravenous administration causes less discomfort for the recipient,[10] but is less convenient for antenatal prophylaxis in the community setting.[98]

The ion exchange chromatography method is also more efficient, retaining over 90% of the anti-D present in the original plasma,[98] compared with only 50-60% using the Cohn method.[99]

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,[10] although this is not reflected in the licensed doses. However, as noted in section 3.3.1.3 above, on the only occasions when anti-D is known to have transmitted viral infection, it was anti-D prepared by ion-exchange chromatography which was implicated. While 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 and parvovirus B19.[109]

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 which minimise the volume of plasma required. These include:

- the use of a two-dose 500 IU regimen, as this uses two-thirds 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 which is not without risk to the donor.[151]

Tovey and Taverner have argued that, if the provision of RAADP in every pregnancy is difficult to achieve because of either the 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.[7]

Targeted prophylaxis

As noted in section 3.3 above, non-invasive foetal 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 which is sufficiently accurate at an early enough gestational date may become available in the next few years.

Even though non-invasive foetal genotyping cannot currently be used to target RAADP, it has other potential benefits. The BCHS Guideline for blood grouping and antibody testing in pregnancy[78] 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 foetus's genotype will affect the management of a pregnancy in a sensitised RhD-negative woman: if the foetus 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 foetus is anaemic.[93]

6. ASSESSMENT OF COST-EFFECTIVENESS

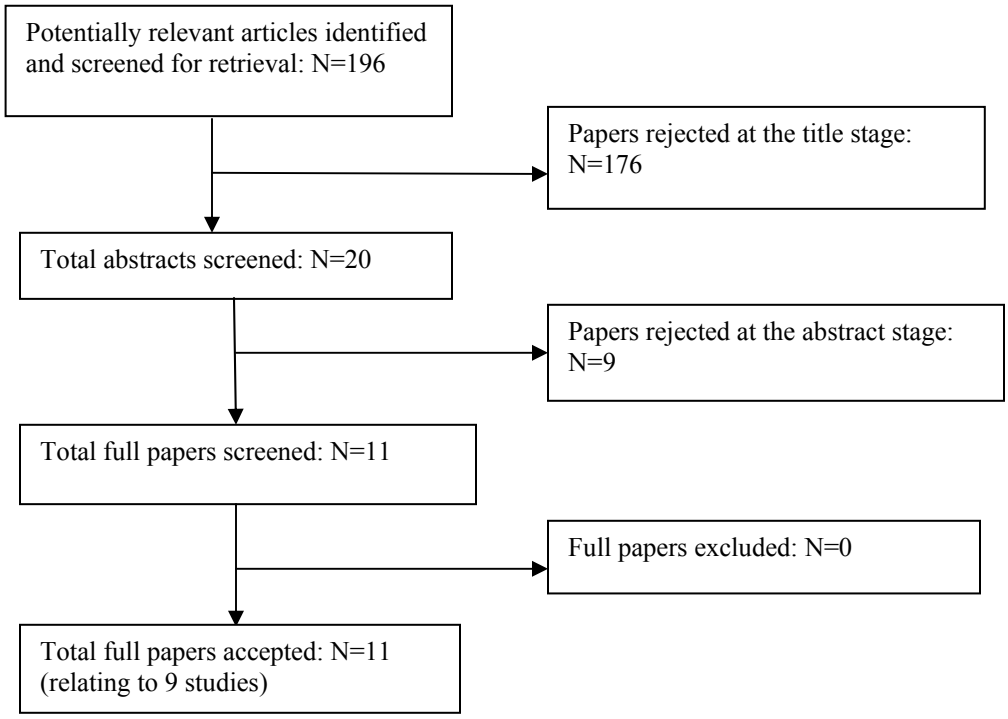
The cost-effectiveness of providing RAADP to RhD-negative women has been evaluated from a UK NHS perspective. The comparators assessed against a base case of no RAADP, for both primigravidae and multigravidae, are:

- 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).

6.1 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 (Section 5.1.1); the only variation from this being the study design criteria defined as economic evaluations. Eleven papers (9 different studies) were identified by the systematic searches (see Figure 5); eight of these studies were included in the RAADP assessment report for NICE in 2001.[152] These were the studies by Adams *et al.*,[153] Baskett and Parsons,[154] Lim *et al.*,[155] Mackenzie *et al.*,[124] Selinger,[156] Torrance and Zipursky,[157] Tovey *et al.*,[126] and Vick *et al.* (1995),[158] (1996).[159] Two of these studies (Mackenzie *et al.*[124] and Tovey *et al.*[126]) 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.[121]

Figure 5: Assessment of cost effectiveness: Summary of study selection and exclusion



Owing to the variability between the studies, a quality assessment has not formally been carried out. However, the following section of this report presents an overview of the nine included economic evaluations. The description of eight of these studies presented here has been taken from the previous anti-D Health Technology Assessment by Chilcott *et al.* carried out in 2001[121] 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.*,[158,159] and Chilcott *et al.*[121] describe a detailed modelling evaluation that appears to be applicable to the UK NHS. The economic evaluations included in the review cover a range of RAADP regimens, as summarised in Table 20.

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

Economic evaluation	Primi- (P) or Multi-gravidae (M)	2x500 IU at 28 & 34 wks	2x1250 IU at 28 & 34 wks	1x1500 IU at 28 wks	1x1250 IU at 28 wks	Unknown dose at 28 wks	Unknown dose and timing
Lim *et al.*[155]	M					√	
Tovey *et al.*[160]	P	√					
Adams *et al.*[153]	P			√			
Torrance *et al.*[157]	P & M						√
Baskett *et al.*[154]	M					√	
Vick *et al.*[158,159]	P & M	√	√		√		
Selinger *et al.*[156]	P	√					
Mackenzie *et al.*[124]	P	√					
Chilcott *et al.*[121,161]	P & M	√	√				

Lim *et al.*, 1982. Reduction of Rh0(D) Sensitisation: A Cost-effective Analysis[155]

Lim and colleagues[155] 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 3,995 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 $8,450.96. 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.

Tovey *et al.*, 1983. The Yorkshire Antenatal Anti-D Immunoglobulin Trial in Primigravidae[126]

Tovey and colleagues[126] compare a group of primigravidae receiving 500 IU antenatal anti-D prophylaxis at 28 and 34 weeks pregnancy with historic controls. The main outcome measure is cost per immunisation avoided. The extra cost in anti-D immunoglobulin was approximately

£1,600 for each woman sensitised. As little economic information is provided, more detail cannot be reported here.

Adams *et al.*, 1984. Cost implications of routine antenatal administration of Rh immune globulin[153]

The evaluation put forward by Adams and colleagues[153] estimates the benefits, risks and costs of a programme of RAADP to RhD-negative primiparae in the US, using decision analytic modelling. The comparators within the model are:

- routine antepartum and postpartum administration of 1500 IU 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 haemolytic disease of the newborn;
- 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=$28,571
	Black=$22,222
	Asian=$11,429.

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

Torrance GW and Zipursky A, 1984. Cost-effectiveness of Antepartum Prevention of Rh Immunisation[157]

This economic evaluation 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=$2,700
	Cost per case of Rh-disease prevented=$3,700
	Cost per life saved=$29,500
	Cost per life-year (LY) saved=$1,500
Cost-utility	Cost per QALY gained=$1,500.

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.

Baskett TF *et al.*, 1990. Prevention of Rh(D) alloimmunisation: a cost-benefit analysis[154]

Baskett and colleagues[154] 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 $3,986 while the cost per case prevented is calculated to be $1,495.

Vick *et al.*, 1995, 1996. The Cost-effectiveness of Antenatal Anti-D Prophylaxis[158,159]

Vick *et al.*, 1995,1996[158,159] describe a model to calculate the incremental cost per RhD-alloimmunisation prevented and the incremental cost per RhD haemolytic disease of the newborn foetal loss prevented for six different AADP programmes. The evaluation uses 'real-world' data obtained from blood transfusion centres, hospitals and haematology laboratories in Scotland in order to assess the incremental cost-effectiveness. The results calculated from the model are presented in Table 21.

Table 21: Summary of economic results from Vick *et al.*[159]

Dose regimen	1x1250 IU	2x500 IU	2x1250 IU
Incremental cost per Rh D-alloimmunisation prevented			
Primigravidae vs no routine AADP	-£1,172	-£197	£1,464
All women vs primigravidae	£2,915	£4,908	£8,272
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

This is the only model to provide extensive detail of its methods and sensitivity analysis. The economic outcomes are robust, though 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 Quality-Adjusted Life Year (QALY) outcome is not assessed owing to 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 1x1250 IU dosage regimen is more effective and less costly than the 2x1250 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.

Selinger M, 1997. Building on success: Antenatal prophylaxis. The pharmacoeconomics of antenatal prophylaxis[156]

Selinger[156] reports a cost-benefit evaluation of two doses of 500 IU 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 HND is eradicated. The author suggests the need for further high-quality trials.

Mackenzie *et al.*, 1999. Routine Antenatal Rhesus D Immunoglobulin Prophylaxis: The Results of a Prospective 10 Year Study[124]

MacKenzie *et al.*[124] assess the clinical and financial impact of 500 IU RAADP for RhD-negative nulliparae at 28 and 34 weeks pregnancy. 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 which 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 since 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.

Chilcott *et al.*, 2003,[121] 2004.[161] 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 for NICE in 2001 for the 2002 RAADP appraisal evaluates the use of two regimens of routine antenatal anti-D prophylaxis against no routine anti-D:

- 2 doses of 500 IU at 28 and 34 weeks;
- 2 doses of 1250 IU at 28 and 34 weeks.

The evaluation suggested that there was insufficient evidence to indicate a difference in efficacy between each of 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 foetal loss, stillbirth, neonatal 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, while the incremental LYG and incremental QALY gained for multigravidae versus primigravidae were estimated at around £15,000 and £46,000-£52,000 respectively. Due to the limited evidence concerning the impact of foetal 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, in order to obtain a cost-effectiveness ratio below £30,000 per QALY for multigravidae, the lost child, associated parental grief and subsequent high intervention pregnancy would need to be valued at more than 9 QALYs.

6.2 Independent economic assessment

There were no new health economic models provided within the manufacturers' submissions for this assessment report. The independent economic model which was developed in 2001 for the NICE RAADP appraisal[85] has been modified to incorporate recent additional evidence identified for this review. This review re-assesses the use of 500 IU and 1250 IU anti-D at weeks 28 and 34 gestation, and evaluates the use of a single dose of 1500 IU anti-D at 28 weeks in addition. Although coverage of RAADP is currently approximately 90%,[87] these regimens are evaluated against no RAADP to enable the assessment of all interventions against the same comparator, and to enable a re-assessment of the cost-effectiveness of RAADP against no RAADP. Within this assessment, in order to attempt to improve upon the cost per QALY analysis, we have also revisited the assumptions around valuation of foetal 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.

6.2.1 Methods

6.2.1.1 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, whilst WinRho is licensed for use as a 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.[101] Interventions are compared against each other and against a policy of no routine antenatal anti-D.

The outcomes of interest within the model are:

- cost per sensitisation avoided;
- cost per affected pregnancy avoided;
- cost per foetal loss avoided[a];
- cost per LYG;
- cost per QALY gained.

6.2.1.2 Efficacy of RAADP

The systematic review of clinical effectiveness presented in Chapter 5 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, Section 5.2.2), the trials show a remarkable consistency in results, even between dosage regimens. Consequently, the results of the meta-analysis of Group 3 trials (See page 79, Section 5.2.2.1) are deemed to give a

[a] Where foetal loss includes stillbirths, neonatal and postneonatal deaths

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 in order to evaluate the cost-effectiveness of RAADP in comparison to no RAADP and to compare the cost-effectiveness of RAADP in multigravidae versus 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 year[162] and assuming that 16% of the population is RhD-negative.[9]

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.[162] 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 Section 6.2.1.2.1 below. 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 Section 5.2.2.1. This results in an estimated 97 sensitisations. Of these women, 85% are expected to go on to have a second pregnancy,[162] and around 70% of these second pregnancies will be RhD-positive and with an affected foetus. The increase in the proportion of RhD-positive foetuses 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 Section 6.2.1.2.1 below 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 foetuses, 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 and continues exactly as described, but the percentage of women entering a fourth pregnancy given that they have had a third pregnancy reduces to 35%.

This method of calculation has been used for all scenarios, so in the case where antenatal anti-D prophylaxis is not administered, the sensitisation rate increases to 0.95%, instead of 0.35%. Where 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 primigravidae and multigravidae are as shown in Tables 22 and 23 respectively.

Table 22: Effectiveness of RAADP for primigravidae in England and Wales

Pregnancy No.	No. of Rh-negative pregnancies	No. having Rh-positive baby who have not been sensitised previously	No. sensitised in current pregnancy	No. sensitised from previous pregnancy that go on to have another baby	Prevalent no. of sensitised women during each pregnancy	No. of affected (RhD pos) foetuses following sensitisation
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	5,360	3,534	34	79	113	55
TOTAL	**104,000**	**66,522**	**468**	**291**	**759**	**204**

Table 23: Effectiveness of RAADP for multigravidae in England and Wales

Pregnancy No.	No. of Rh-negative pregnancies	No. having Rh-positive baby who have not been sensitised previously	No. sensitised in current pregnancy	No. sensitised from previous pregnancy that go on to have another baby	Prevalent no. of sensitised women during each pregnancy	No. of affected (RhD pos) foetuses following sensitisation
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	5,360	3,566	13	37	49	26
TOTAL	**104,000**	**66,596**	**235**	**188**	**424**	**132**

6.2.1.2.1 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.[163] Therefore the model assumes:

% of RhD-positive babies born to RhD-negative women
= % of RhD-positive men − (% of RhD-positive men × % of heterozygous men ×
probability that a heterozygous man will produce a RhD-positive baby)

Assuming that the probability of a father in the general population being RhD-positive is 84%,[9] based on the above, the probability of a RhD-negative woman having a RhD-positive baby is 61%. This closely matches published estimates.[159,153] 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 24 below.

Table 24: Probability of RhD-positive baby following delivery of a RhD-positive baby

Parameter	Mean value	S.E.[b]	Source/ calculation
(a) Births within marriage	369,997	-	Office for National Statistics[162]
(b) % of births of same father within marriage	100%	-	Assumption
(c) Births outside of marriage	269724	-	Office for National Statistics[162]
(d) % of births of same father outside marriage	50%	15%	Assumption
% of babies with same father in next pregnancy	79%	5%	Calculated from rows above: (a/a+c)×b + (c/a+c)×d
Probability that baby will be RhD-positive in 1st 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 2nd, 3rd & 4th pregnancies	70%	4%	Calculated based on weighted probability of the foetus being RhD-positive given the same or different father

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 24, 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%.

6.2.1.3 HDN outcomes

In order to assess the implications of HDN, a literature search was undertaken to identify the possible outcomes associated with HDN and their associated 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.*[18] based on all pregnant women in Northern Ireland from September 1994 to February 1997. This study is described in further detail in Section 3.1.1. Owing to the small proportion of babies affected by HDN, large studies of RhD-negative women have very few occurrences of the disease. Therefore, whilst this study was based on all pregnant women in Northern Ireland over a three year period, there were only three foetal 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 foetus the probability of foetal loss is around 4%, the probability of minor developmental problems (including myopia, squint, delays in

[b] Note: S.E = Standard Error. All distributions are normal unless otherwise stated.

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, the quality of life of a child with minor developmental problems is based on a study which assessed the health utility of low birth weight babies,[164] 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; where the cost of an eye test is around £16[165] and the cost of glasses is around £84[166] (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 educating by language and speech therapists as to how they may help the child 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.

In order to value the health-related quality of life and costs associated with major developmental problems, the model uses data from cerebral palsy studies, since 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.[167] The cost associated with this group is based on a study by Beecham *et al*. This study calculates the additional cost to society of a person with cerebral palsy in comparison to a non-disabled child in the UK.[168] This cost includes accommodation and living expenses, education, hospital services, community care services, primary care services and social care services. The annual cost is therefore assumed to be £7319 on average, although the confidence intervals associated with this cost are wide owing to 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*. which presents an assessment of the life expectancy of people with cerebral palsy in the UK.[169] 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 owing to limitations in the evidence base. The impact of this uncertainty on the cost-effectiveness of RAADP has been explored within the sensitivity analysis.

6.2.1.4 Cost of RAADP

The cost of anti-D was taken from the British National Formalary (BNF);[114] 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 D-Gam is reported to be £19.50 per vial by the manufacturer of this product.[89] [redacted]. 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 which is more expensive in terms of list price may in some cases be less expensive owing to local price negotiations. Therefore, comparisons between the cost-effectiveness of the anti-D regimens should be interpreted with caution.

6.2.1.5 Cost of management of sensitisation

The cost of the management of sensitisations is taken from a range of sources including Selinger *et al.,*[156] Craig *et al.*,[18] Kumar *et al*.,[30] Greenough *et al*.[170] and expert opinion (Personal Communication with Dr D.Peebles 2007). NHS reference costs from 2005-06[171] are applied to the interventions required as shown in Table 25. 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).

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

Table 25: Cost of Management of Sensitisation

Intervention	% of sensitised mothers/ babies requiring interven-tion	Average no. required per person	Average days per treatment	Unit cost of interven-tion	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 mothers 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 mothers follow up visit
Phototherapy	71%	1	3	£724	£1,542	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	£1,020	£255	Neonatal Intensive Care Unit - Level 1
Total					**£2,885**	

Source: Selinger *et al.,*[156] Craig *et al.*,[18] Kumar *et al*.,[30] Greenough *et al*.[170] and expert opinion (Personal Communication with Dr D.Peebles 2007).

6.2.1.6 Model parameters and assumptions

The parameters used within the model as described above are outlined in Table 26.

Table 26: Model parameters

Parameter	Mean value	S.E.[c]	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[162]
Average woman's life expectancy (yrs)	79	-	Office for National Statistics[162]
Crude birth rate: all births per 1,000 pop.	12.1	-	Office for National Statistics[162]
Sensitisation rate without routine anti-D	0.95%	0.39%	Based on meta-analysis (Section 5.2.2)
Relative risk of sensitisation with RAADP (all regimens)	0.37	Log norm (-1.23, 0.69)	Based on meta-analysis (Section 5.2.2)
Cost of routine anti-D per vial 500 IU at 28 and 34 weeks (D-Gam) 1250 IU at 28 and 34 weeks (Partobulin) 1500 IU at 28 weeks (Rhophylac) 1500 IU at 28 weeks (WinRho)	 £27.00 £35.00 £46.50 £313.50	 - - - -	BNF[114]
% of RhD-negative people	16%[d]	-	Romen *et al.* (2003)[163]
% of fathers who are heterozygous	55%	10%	Romen *et al.* (2003)[163]
% of RhD+ babies in RhD- women (1st baby)	61%	4%	Assumption based on Romen *et al.* (2003).[163] See Table 24 for details.
% of RhD+ babies in RhD- women (2nd, 3rd and 4th babies)	70%	4%	
% of 1st preg proceeding to next pregnancy	85%	-	Office for National Statistics[162]
% of 2nd preg proceeding to next pregnancy	40%	-	Office for National Statistics[162]
% of 3rd preg proceeding to next pregnancy	35%	-	Office for National Statistics[162]
Foetal loss rate per woman at risk	4%	1%	Craig *et al* (2000)[18]
% of babies affected by HDN with minor developmental problems	6%	2%	Craig et al (2000)[18]
Duration of minor developmental problems (years)	16	5	Based on the fact that the NHS stops paying for children's treatment at age 16.
% of babies affected by HDN with major permanent developmental problems	3%	1%	Craig et al (20000)[18]

[c] Note: S.E = Standard Error. All distributions are normal unless otherwise stated
[d] Assessed in subgroup analysis

Parameter	Mean value	S.E.[e]	Source
Life expectancy of person with major developmental problems	60	Uni form (40,79)	Assumption based on Hemming et al (2005)[169]
QoL for person with no developmental problems	0.88	0.02	Saigal et al (2006)[164]
QoL for minor developmental problems	0.85	0.02	Saigal et al (2006)[164]
QoL for major developmental problems	0.42	0.03	Rosenbaum (2007)[167]
Cost of anti-D administration per dose	£5	£2	Submission to NICE from the Association of Radical Midwives, 2001
Cost of management of a sensitised woman	£2885	£700	Based on Selinger *et al*. (1997)[156] & Kumar *et al*.[30] & Greenough *et al*.[170] & NHS reference costs 2005-06[171]
Cost of minor developmental problems per year	£100	£35	Assumption based on treatment of myopia/ squint[166, 165]
Cost of major developmental problems per year	£7271	Log norm (8.71, 0.61)	Beecham et al (2001)[168] (uplifted to 2006 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.[162] 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.
- Foetal loss of the newborn results in 79 life years lost (average life expectancy) and 69.5 QALYs lost. This is based on the theory that if the foetus had not been affected by HDN they are likely to have lived to the average life expectancy, modelled in the same way as other diseases which would end life prematurely.

[e] Note: S.E = Standard Error. All distributions are normal unless otherwise stated

6.2.1.7 Subgroup analysis

Because the proportion of RhD-negative people varies with ethnic race, a subgroup analysis has been carried out to assess the implications of using RAADP amongst some of the ethnic minorities in England and Wales upon cost-effectiveness. The parameters used within this analysis are taken from Contreras *et al.*[9] and Ali *et al.*[28] which are shown in Table 27.

Table 27: Effect of ethnicity upon RhD genotype

Ethnicity	Proportion RhD-negative	Source
Caucasian	16%	Contreras *et al.*[9]
Asian	9%	Ali *et al.*[28]
West African	5%	Contreras *et al.*[9]
Chinese	1%	Contreras *et al.*[9]

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

6.2.1.8 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 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 section 5.2.2).
- *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 section 5.2.2).
- *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-effectivness. 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.
- *Foetal loss rate per woman at risk*: The foetal 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%.
- *Life years lost as a result of a foetal loss*: Within the model it has been assumed that foetal loss is associated with 79 life years lost (average life expectancy). However, different views around the valuation of a life have been considered by assessing the effect of a fetal loss being equivalent to 40 and 10 life years lost.

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 to the parameters around major developmental problems. As discussed in Section 6.2.1.4 above, a threshold analysis around the cost of anti-D has also been carried out.

6.2.2 Results

6.2.2.1 Results of the deterministic analysis

The incremental cost-effectiveness outcomes associated with RAADP for primigravidae and multigravidae are shown in Table 28 and Table 29 respectively.

Table 28: Incremental cost-effectiveness outcomes associated with RAADP for primigravidae compared with no RAADP

Anti-D dose	Total cost	No. of sensitisations avoided	No. of affected pregnancies avoided	No. of foetuses lost	LYG	QALYs gained	Cost per sensitis-ation avoided	Cost per affected pregnancy avoided	Cost per foetal loss avoided	Cost per LYG	Cost per QALY gained
Basecase value	£3,305,385	630	353	14.1	2878648	2533240					
2x500 IU (D-Gam)	£1,701,409	162	150	6.0	250	207	£10,495	£11,376	£284,394	£6,816	£8,205
2x1250 IU (Partobulin)	£2,422,067	162	150	6.0	250	207	£14,940	£16,194	£404,854	£9,703	£11,680
1x1500 IU (Rhopylac)	£1,138,395	162	150	6.0	250	207	£7,022	£7,611	£190,285	£4,560	£5,490
1x1500 IU (WinRho)	£13,164,380	162	150	6.0	250	207	£81,201	£88,018	£2,200,455	£52,737	£63,483

Table 29: Incremental cost-effectiveness outcomes associated with RAADP for multigravidae compared with primigravidae

Anti-D dose	Total cost	No. of sensitisations avoided	No. of affected pregnancies avoided	No. of foetuses lost	LYG	QALYs gained	Cost per sensitis-ation avoided	Cost per affected pregnancy avoided	Cost per foetal loss avoided	Cost per LYG	Cost per QALY gained
2x500 IU (D-Gam)	£2,357,910	233	72	2.9	120	100	£10,125	£32,697	£817,415	£19,591	£23,582
2x1250 IU (Partobulin)	£3,170,136	233	72	2.9	120	100	£13,613	£43,960	£1,098,989	£26,339	£31,706
1x1500 IU (Rhopylac)	£1,723,358	233	72	2.9	120	100	£7,400	£23,897	£597,435	£14,318	£17,236
1x1500 IU (WinRho)	£15,277,384	233	72	2.9	120	100	£65,602	£211,848	£5,296,200	£126,931	£152,794

For RAADP given to RhD-negative primigravidae versus no RAADP, the cost per sensitisation avoided and the cost per pregnancy avoided are estimated to be around £81,000 and £88,000 respectively for WinRho RAADP, and between £7,000 and £16,000 for all other regimens of RAADP. The cost per foetal loss avoided is estimated to be around £2 million for WinRho RAADP and between £190,000 and £405,000 for all other regimens of RAADP. These high estimates are due to the low proportion of foetal losses occurring as a result of HDN within a group of pregnant RhD-negative women.

RAADP given to RhD-negative multigravidae is expected to decrease the number of sensitisations, the number of affected pregnancies and the number of foetal losses, but is also expected to increase costs. Therefore, giving WinRho RAADP to multigravidae compared to primigravidae results in a cost per sensitisation avoided of around £66,000 and a cost per affected pregnancy avoided of around £212,000. For all other regimens of RAADP, the cost per sensitation avoided is estimated to be between £7,000 and £14,000 and the cost per affected pregnancy avoided is estimated to be between £24,000 and £44,000. The cost per foetal loss avoided is estimated to be around £5 million for WinRho RAADP and between £597, 000 and £1 million for all other RAADP regimens.

Giving RAADP to RhD-negative primigravidae compared with no RAADP results in a cost per LYG of around £53,000 for WinRho RAADP and between £4,000 and £10,000 for all other RAADP regimens. For RAADP given to multigravidae versus primigravidae, the cost per LYG is estimated to be around £127,000 for WinRho and between £14,000 and £27,000 for all other anti-D regimens. The cost per QALY gained as a result of RAADP given to primigravidae versus no RAADP is between £4,000 and £8,000 for all RAADP regimens apart from the one-dose regimen of 1500 IU WinRho, which has a cost per QALY gained of around £39,000. For multigravidae, in comparison to primigravidae, the cost per QALY gained as a result of routine anti-D is between £12,000 and £23,000 for all anti-D products, again with the exception of 1500 IU WinRho, which has a cost per QALY gained of around £93,000. 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.

6.2.2.2 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, whilst the proportionate number of sensitisations, affected pregnancies and foetal losses will be lower in these ethnic minorities than in the Caucasian population, the cost per sensitisation, cost per affected pregnancy and cost per foetal 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 to the proportion of people that 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 weeks 28 and 34 gestation in Table 30.

Table 30: Incremental cost-effectiveness results for different ethnicities

Ethnicity (% RhD-negative)	Total cost	No. of sensitisa-tions avoided	No. of affected pregnancies avoided	No. of foetuses lost	LYG	QALYs gained	Cost per sensitisa-tion avoided	Cost per affected pregnancy avoided	Cost per foetal loss avoided	Cost per LYG	Cost per QALY gained
Basecase Caucasian (16%)	£3,305,385	630	353	14.1	2878648	2533240					
Primigravidae	£1,701,409	162	150	6.0	250	207	£10,495	£11,376	£284,394	£6,816	£8,205
Multigravidae	£2,357,910	233	72	2.9	120	100	£10,125	£32,697	£817,415	£19,591	£23,582
Basecase Asian (9%)	£1,996,141	375	216	8.6	1619211	1424923					
Primigravidae	£895,052	99	93	3.7	154	128	£9,060	£9,673	£241,826	£5,796	£6,977
Multigravidae	£1,302,127	136	43	1.7	72	60	£9,544	£30,333	£758,328	£18,174	£21,878
Basecase West African (5%)	£1,151,822	215	125	5.0	899553	791617					
Primigravidae	£477,317	57	54	2.2	90	75	£8,331	£8,819	£220,465	£5,284	£6,360
Multigravidae	£716,351	77	25	1.0	41	34	£9,261	£29,175	£729,373	£17,480	£21,042
Basecase Chinese (1%)	£238,851	44	26	1.0	179909	158322					
Primigravidae	£91,440	12	11	0.5	19	16	£7,657	£8,037	£200,930	£4,816	£5,797
Multigravidae	£141,950	16	5	0.2	8	7	£9,008	£28,136	£703,409	£16,858	£20,293

6.2.2.3 Results of the one-way sensitivity analysis

Several key uncertain parameters within the model (discussed in section 6.2.1.8) 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. Therefore, these results are presented in Table 31 in terms of a 500 IU dose of anti-D (D-Gam) at weeks 28 and 34 gestation in order to avoid unnecessary repetition.

Table 31: Results of one-way sensitivity analysis

Parameter (LB=Lower Bound, UB=Upper Bound)		Parameter value	Cost per QALY gained	
			Primigravidae	Multigravidae
Basecase			£8,205	£23,582
Odds ratio for sensitisation rate of RAADP	Base case	0.37		
	LB	0.21	£5,372	£16,963
	UB	0.65	£19,392	£49,724
Basecase sensitisation rate	Base case	0.95%		
	LB	0.18%	£67,274	£161,929
	UB	1.71%	£2,075	£9,217
Proportion of heterozygous males	Base case	55%		
	LB	35%	£5,319	£16,591
	UB	75%	£12,638	£34,407
Foetal loss rate per woman at risk	Base case	4%		
	LB	2%	£12,421	£35,918
	UB	6%	£6,152	£17,578
Cost of anti-D administration per dose	Base case	£5		
	LB	£1	£6,467	£19,521
	UB	£9	£9,942	£27,644
Cost of management of sensitisation	Base case	£2,885		
	LB	£1,513	£9,279	£26,343
	UB	£4,257	£7,131	£20,822
Rate of major developmental problems	Base case	3%		
	LB	1%	£12,876	£31,527
	UB	5%	£5,007	£18,143
Yearly cost of major developmental problems	Base case	£7,319		
	LB	£1,849	£10,739	£25,872
	UB	£20,402	£2,143	£18,105
Life exp. for people with major dvlpm. problems	Base case	60		
	LB	40	£8,406	£23,290
	UB	79	£8,091	£23,747
QoL of people with major devlpm. problems	Base case	0.42		
	LB	0.36	£7,949	£22,847
	UB	0.48	£8,477	£24,366
% of births outside marriage with same father	Base case	50%		
	LB	26%	£8,014	£22,790
	UB	74%	£8,402	£24,408
Life years lost as a result of foetal loss	Life expectancy	79		
	Altern.1	40	£9,489	£27,273
	Altern.2	10	£15,374	£44,189

The one-way sensitivity analysis suggests that changing many of the model assumptions results in only a small impact upon the incremental cost-effectiveness ratio (ICER). The parameters which have the greatest impact upon the ICER are the base case sensitisation rate, the odds ratio for the sensitisation rate associated with RAADP and the number of life years lost as a result of a foetal

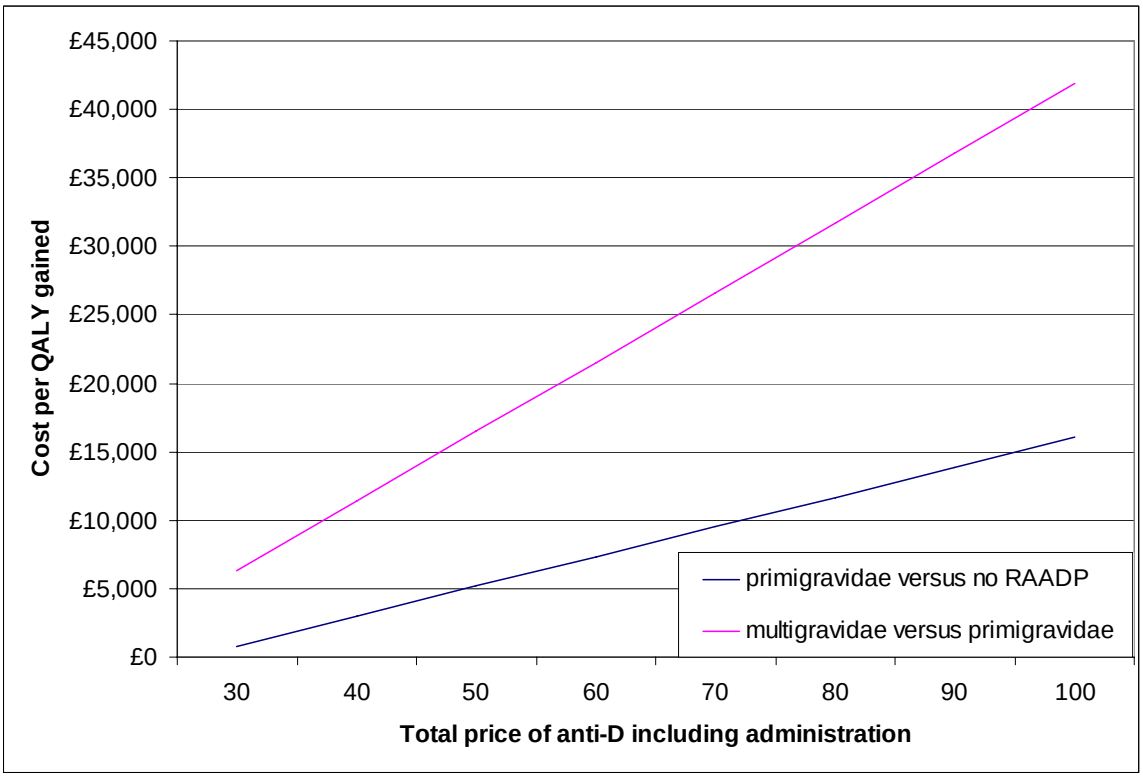
loss. If the base case sensitisation rate was lower than predicted, then anti-D would have a lower absolute effect and hence the cost per QALY gained would increase. At a base case sensitisation rate of 0.18 (the lower 95% confidence interval), the cost per QALY gained for providing RAADP to all RhD-negative 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 to no RAADP to its upper 95% confidence interval of 0.65 gives a cost per QALY gained of around £50,000 for RAADP in the multigravidae indication. Assuming that a foetus's life is valued at 10 life years (8.8 quality-adjusted life years) rather than a full life expectancy of 79 years, the cost per QALY for RAADP given to multigravidae increases to around £44,000.

Decreasing the foetal loss rate as a result of HDN from 4% to 2%, the cost per QALY gained would increase by around £8,000 to £34,000. Decreasing the impact of HDN in any way will increase the ICER to some extent since 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 £1,000 and £3,000 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.

6.2.2.4 Threshold analysis of the cost of anti-D

Because the listed price of anti-D in the BNF[114] may be different from the actual cost of the drug, a threshold analysis has been carried out. The results are presented in Figure 6 below.

Figure 6: Cost per QALY gained based on cost of anti-D and its administration



The results presented here include an administration cost of £5 per dose. Hence, at a cost per QALY gained of £30,000, a two-dose regimen of RAADP given to all RhD-negative pregnant women compared to primigravidae would be considered cost-effective at a cost of £33 per dose whereas, at this threshold, a one-dose regimen would be considered cost-effective at a cost of £71 per dose.

6.2.2.5 Results of the probabilistic sensitivity analysis

The results of the probabilistic sensitivity analysis for primigravidae versus no RAADP and multigravidae versus primigravidae are shown in Table 32 and 33 respectively.

Table 32: Results of probabilistic sensitivity analysis – RAADP given to primigravidae versus no RAADP

Anti-D regimen	Difference in costs	Difference in LYs	Difference in QALYs	Cost per LYG	Cost per QALY gained
Basecase: no RAADP	£3,283,355	£2,878,644	2532868		
D-Gam: 2x500 IU	£1,709,048	250	208	£6,829	£8,222
Partobulin:2x1250 IU	£2,425,795	250	209	£9,720	£11,596
Rhophylac: 1x1500 IU	£1,147,062	250	208	£4,583	£5,519
WinRho:1x1500 IU	£13,175,123	250	208	£52,754	£63,426

Table 33: Results of probabilistic sensitivity analysis – RAADP given to multigravidae versus primigravidae

Anti-D regimen	Difference in costs	Difference in LYs	Difference in QALYs	Cost per LYG	Cost per QALY gained
D-Gam: 2x500 IU	£2,361,215	121	100	£19,531	£23,516
Partobulin:2x1250 IU	£3,169,457	121	101	£26,091	£31,367
Rhophylac: 1x1500 IU	£1,726,640	121	100	£14,322	£17,199
WinRho:1x1500 IU	£15,282,616	121	100	£126,591	£152,194

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 £5,000 and £12,000 per QALY gained for RAADP given to RhD-negative primigravidae versus no RAADP, and between £17,000 and £32,000 per QALY gained for RAADP given to multigravidae compared to primigravidae. WinRho has a cost per QALY gained of around £63,000 for RAADP given to primigravidae versus no RAADP and around £152,000 for RAADP given to multigravidae versus primigravidae.

Figure 7 presents CEACs for each of the regimens of RAADP versus no RAADP and versus each other regimen. 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: Cost effectiveness acceptability curve (CEAC)

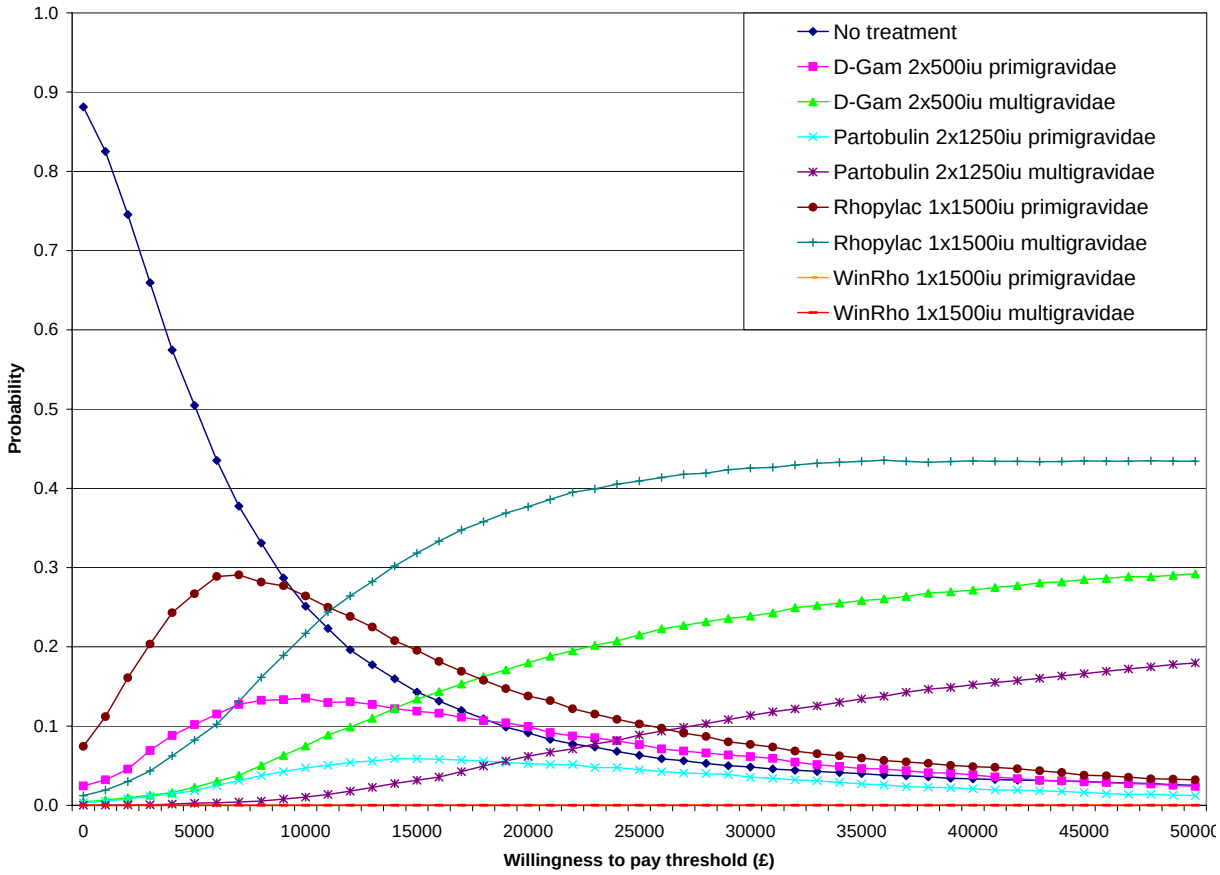


Figure 7 suggests that, at a threshold of £30,000 per QALY gained, it is more likely to be cost-effective to give RAADP to all RhD-negative pregnant women rather than to not provide RAADP or to provide RAADP to primigravidae only. Because the model assumes that the efficacy of the different anti-D regimens is the same, the cheaper regimens of anti-D are estimated to be more cost-effective. Therefore, based on the BNF drug prices,[114] one dose of 1500 IU Rhophylac at week 28 gestation is most likely to be cost-effective (around 40% probability) followed by two doses of 500 IU D-Gam (around 25% probability) and two doses of 1250 IU Partobulin at weeks 28 and 34 gestation (around 10% probability). The comparison of cost-effectiveness between these three RAADP regimens should be interpreted with caution owing to 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 to RAADP given to primigravidae or providing no RAADP is over 75%. One dose of 1500 IU WinRho is not likely to be considered cost-effective at any threshold, since it is substantially more expensive and given the availability of its comparators.

6.2.3 Discussion

6.2.3.1 Generalisability of the results

Assuming that there is 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, owing to the lower proportion of RhD-negative genotypes in these subgroups. This impact can be seen within the subgroup analysis presented in Section 6.2.2.1.

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

(1) The base case sensitisation rate;
(2) The odds ratio associated with the sensitisation rate with RAADP;
(3) The assumption around the valuation of a foetal loss.

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

The results presented suggest a better cost per QALY gained as a result of a programme of RAADP than was suggested within the previous RAADP NICE Health Technology Assessment report.[121] Within this assessment report, a greater degree of benefit is assumed as a result of the avoidance of sensitisations, since the number of life years lost associated with a foetal 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 the RAADP itself has increased in comparison to the original assessment and additional comparators of one dose of 1500 IU anti-D were also considered within this assessment. Finally, population parameters have been revised and average life expectancy has increased by five 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 drug since 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 owing to the half-life of anti-D; however, there is no published evidence around this. The prices used in this assessment for anti-D itself are based upon BNF drug prices[114] but, since 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 which 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, whilst WinRho is licensed for use as a 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.[101] 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, then WinRho SDF could provide an alternative to supplement anti-D supplies.[101]

The assessment of RAADP given to multigravidae versus 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 pregnancies,[131] 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.

6.2.3.2 Quality of life of the parents

The model does not 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, whilst 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.[172] 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 where the mother is sensitised, which is likely to temporarily reduce the mother's quality of life. The implications of a reduction in quality of life of the parents following sensitisation or HDN is that the cost per QALY gained would be slightly lower than currently predicted.

6.2.3.3 Compliance and one versus two doses

Within the model, it has been assumed that compliance using routine anti-D for the one-dose or two-dose regimen would be 100%. Current evidence suggests that only around 90% of women eligible for RAADP receive the drug,[87] potentially leading to more sensitisations than estimated by the model. If there were a difference in compliance between the one-dose or two-dose regimen, this could affect the cost-effectiveness ratio. Compliance may be greater with the one-dose regimen than the two-dose regimen for logistical reasons; however, conversely, the one-dose regimen only offers one opportunity to provide RAADP.[120] There are currently no published studies comparing compliance with 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 routine anti-D can be provided within routine antenatal appointments. However, a small sample of hospitals have provided information which suggests that hospitals using the one-dose regimen may need to provide additional appointments in order to provide RAADP to RhD-negative women, and hence this may incur additional cost. 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.

6.2.3.4 Foetal genotyping

It is now possible to test the genotype of the foetus using non-invasive methods. It should be noted that foetal genotyping would not just affect RAADP but also anti-D given in other indications and hence is beyond the scope of this assessment. However, a brief exploratory analysis around the new technology is presented here.

Since just under two thirds of babies born to RhD-negative mothers are RhD-positive, this would save around one third of RhD-negative women having to be given anti-D. However, using foetal genotyping, if the sensitivity of the test is not 100% (i.e. each foetus who is RhD-positive is

detected), then the number of sensitisations is likely to increase. The sensitivity of the foetal genotyping test is currently estimated to be around 99%[173] and hence would need to improve if the proportion of sensitisations is to remain the same.

Foetal 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 Section 3.2.1, adverse effects associated with this exposure are extremely rare. Therefore, the efficacy of RAADP using foetal genotyping is unlikely to improve substantially, meaning that as well as the test becoming 100% sensitive, the cost would need to be less than that of current treatment for the test to be considered desirable.

Based on our model, the cost of foetal genotyping in comparison to the cost of anti-D can be denoted by the formula:

$$\text{Anti-D cost} \geq 0.61\ (\text{Anti-D cost}) + \text{Cost of foetal genotyping}$$

This simplifies to:

$$0.39\ (\text{Anti-D cost}) \geq \text{Cost of foetal genotyping}$$

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

Table 34: Cost of foetal genotyping

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

Current estimates suggest that foetal genotyping is likely to cost around £40 per person.[173] This suggests that foetal screening is likely to be more costly than providing all RhD-negative pregnant women with routine anti-D, apart from when compared against WinRho. It should be noted that this analysis does not allow for price reductions in anti-D and hence the cost of foetal genotyping may need to be lower than 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 foetus. Therefore, research into foetal genotyping should aim to improve sensitivity and reduce the cost of the test.

7. ASSESSMENT OF FACTORS RELEVANT TO THE NHS AND OTHER PARTIES

Routine anti-D is currently estimated to be used in around 90% of hospitals,[87] and hence the implications for current service provision of recommending RAADP are small. Anti-D can be provided during routine antenatal appointments, and hence the burden on services not currently providing anti-D is expected to be minimal. A small sample of hospital data supplied by one of our advisors suggests that the one-dose regimen may be less likely to be supplied during routine antenatal visits, and hence may incur additional cost for administration. Assuming that this is not the case, the total cost of supplying RAADP to RhD-negative primigravidae and the additional cost of supplying RAADP to RhD-negative multigravidae in England and Wales each year is shown in Tables 35 and 36.

Table 35: Total cost of RAADP given to primigravidae to the NHS per year

Anti-D regimen	Cost of anti-D	Cost of administration	Cost savings associated with HDN[f]	Total cost
2x500 IU (D-Gam)	£2,432,222	£450,411	£1,181,236	£1,701,398
2x1250 IU (Partobulin)	£3,152,880	£450,411	£1,181,236	£2,422,056
1x1500 IU (Rhopylac)	£2,094,413	£225,206	£1,181,236	£1,138,383
1x1500 IU (WinRho)	£14,120,398	£225,206	£1,181,236	£13,164,369

Table 36: Total additional cost of RAADP given to multigravidae in comparison to primigravidae to the NHS per year

Anti-D regimen	Cost of anti-D	Cost of administration	Cost savings associated with HDN[6]	Total cost
2x500 IU (D-Gam)	£2,741,264	£507,641	£890,991	£2,357,914
2x1250 IU (Partobulin)	£3,553,490	£507,641	£890,991	£3,170,140
1x1500 IU (Rhopylac)	£2,360,533	£253,821	£890,991	£1,723,362
1x1500 IU (WinRho)	£15,914,558	£253,821	£890,991	£15,277,388

The costs associated with no RAADP (management of sensitisations, lifetime costs of developmental problems) are estimated to be around £3 million throughout England and Wales. The use of RAADP for primigravidae RhD-negative women is estimated in total to cost between an additional £1 million and £13 million according to the RAADP regimen. Giving RAADP to all RhD-negative pregnant women increases the costs by a further £2 - £15 million.

[f] Savings associated with the cost of the management of sensitisation and with the cost to society of people with developmental problems

8. DISCUSSION

8.1 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.* 1999[124] and by Mayne *et al*.[125] 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 rather than under trial conditions, in the UK, 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 a 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 haemolytic disease of the newborn in that infant which constitutes the clinical benefit of RAADP.

No head-to-head studies have been undertaken which 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 are more, or less, effective than a single dose of 1500 IU anti-D 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) will clearly not provide protection against an FMH at 28 weeks, and may be insufficient to provide protection against an FMH at 39 weeks.[120] 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 which demonstrates any such differences. It could also be argued that the regimen that uses least anti-D, and 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 blood-borne 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 RAADP NICE appraisal.[85] However, as well as considering the cost-effectiveness of the two-dose regimens, D-Gam and Partobulin RAADP, 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 the study by Vick *et al*., and Chilcott *et al*. 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 quality-adjusted life year (QALY) gained of RAADP given to RhD-negative primigravidae versus no RAADP is between £5,000 and £12,000, and for RAADP given to multigravidae rather than primigravidae is between £17,000 and £32,000 depending on the RAADP regimen (excluding WinRho). However, since 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 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.

8.2 Strengths and limitations of the assessment

This assessment report reviews the work carried out for the NICE RAADP appraisal from 2002 and, 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 and cost effectiveness is largely based 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 £30,000 it is likely that D-Gam, Partobulin and Rhophylac RAADP given to all RhD-negative pregnant women will be cost-effective.

8.3 Uncertainties

The key uncertainties associated with the assessment of RAADP are:

- Efficacy of different dosing regimens of routine anti-D;
- Quality of life of children suffering from HDN and their parents (including parents of stillborn children);
- Incidence rate of outcomes as a result of HDN;
- Costs associated with HDN in terms of management of sensitisation and outcomes over a patient's lifetime.

8.4 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 which minimise the volume of plasma required. These include:

- the use of a two-dose 500 IU D-Gam regimen, as this uses two-thirds 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.[87] 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 four 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.

Consideration of these issues is required.

The Royal College of Nursing[120] suggests that Section 1.2 of the NICE Technology Appraisal No. 41 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 made 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 due to their feasibility in practice.

Finally, non-invasive foetal 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 which is sufficiently accurate at an early enough gestational date may become available in the next few years.

9. CONCLUSIONS

All of the evidence indicates that RAADP reduces the incidence of senstitisation and hence HDN. Furthermore, anti-D is associated with minimal adverse events. The economic model suggests that at a threshold of £30,000 per QALY, RAADP given to all RhD-negative pregnant women is likely to be considered cost-effective in comparison to RAADP given to RhD-negative primigravidae or compared to not offering RAADP. The total cost of providing RAADP to RhD-negative primigravidae in England and Wales is estimated to be around £1 to 2.5 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 to £3 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 foetus.

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 two regimens, and the impact of the potentially varying levels of compliance with them, could be assessed using large-scale audits of residual sensitisations.

10. APPENDICES

Appendix 1: 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 Dissemination[122])

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 which 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 allocations?	
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 36: 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[140]	Anti-D dose not specified
Eklund & Nevanlinna 1971[136]	In Finnish, no English abstract; from publication date, seems highly likely that it dealt with postpartum rather than antenatal prophylaxis
Hamilton study[140]	Anti-D dose not specified
Hermann *et al.* 1984[132]	Wrong anti-D regimen (single dose of 1250 IU at 32-34 weeks)
Koelewijn *et al.* 2003[139]	Wrong anti-D regimen (single dose of 1000 IU at 30 weeks)
Lee & Rawlinson 1995[133]	Wrong anti-D regimen (two doses of 250 IU at 28 & 34 weeks)
Parsons *et al.* 1998[134]	Anti-D dose not specified
Potron *et al.* 1973[137]	Could not be obtained by library; from publication date, seems highly likely that it dealt with postpartum rather than antenatal prophylaxis
Swedish study[140]	Wrong anti-D regimen (unspecified dose at 34 weeks); appears to be the same study as that by Hermann et al listed above
Unpublished study cited by Baxter Healthcare[91]	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 *et al.* 2006[141]	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 37: Studies referred to in the manufacturers' submissions which did not meet the study inclusion criteria, with reasons

Manufacturer/study	Reason for exclusion
Baxter BioScience	
Hermann *et al.* 1984[132]	Unlicensed dose (1 x 1250 IU)
Lee & Rawlinson 1995[133]	Unlicensed dose (2 x 250 IU)
Thornton *et al.* 1989[131]	Included in this report as a follow-up to the study by Tovey *et al.* 1983[126] and not as a separate study, as inappropriately done by Baxter BioScience
BPL	
None	
CSL Behring	
Bichler *et al.* 2003[174]	Pharmacokinetic study; no relevant outcomes
Kennedy *et al.* 1998[175]	Pharmacokinetic study; no relevant outcomes
Witter *et al.* 1990[176]	Pharmacokinetic study; no relevant outcomes

APPENDIX 4 CHARACTERISTICS OF INCLUDED STUDIES

Study: Bowman *et al.* 1978[127]

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 controls, 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 prior evidence of RhD alloimmunisation who'd 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 the 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 intra-muscular 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 anti-D postpartum.

Outcomes: incidence of immunisation during pregnancy and within three 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 were screened at 6-9 months who had been found to be immunised during pregnancy or within three days of delivery.

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

Study: Bowman and Pollock 1978[128]

Method: comparison with historic controls (those RhD-negative primigravidae with no history of blood transfusion or abortion, and multigravidae with no prior evidence of RhD alloimmunisation who'd 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.* 1978)

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 prior to 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 intra-muscular anti-D as close to 28 weeks gestation as possible.

Outcomes: incidence of immunisation during pregnancy and within three 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 were screened at 6-9 months who had been found to be immunised during pregnancy or within three days of delivery. It is possible that multigravidae in both the intervention and control group developed RhD alloimmunisation not because of a failure of antenatal prophylaxis but because of "sensibilisation" resulting from inadequate treatment after previous pregnancies

Quality: fair

Study: Bowman and Pollock 1987[129]

Method: retrospective comparison with historic controls (those RhD-negative primigravidae with no history of blood transfusion or abortion, and multigravidae with no prior evidence of RhD alloimmunisation who'd 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.* 1978). Although Urbaniak[14] claims that this study includes all 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, briefly reported elsewhere,[99,13] 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 six weeks after that injection, the protocol was soon modified by the addition of a second 120 μg dose at 34 weeks.[13] By 30th 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, only one of the 1122 who were tested both at delivery and 4-6 months later showed evidence of sensitisation.[13] 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.[99] However, as the clinical trial is effectively a case series, which makes reference to control group data from Bowman et al's 1978 study,[127] 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 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 three days of delivery.

Notes: the authors' comparison is with the primigravidae only in the "control" group reported in Bowman *et al.* 1978. It is not clear why their comparison was not with the unselected group. 6-week and 6-month post-delivery blood samples were not universally available, so it was not

possible to determine directly the total number of women RhD-immunised by 6 months after delivery.

Quality: poor

Study: Huchet *et al.* 1987[123]

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 intramuscular anti-D at 28 and 34 weeks (in practice this was administered between weeks 26-29 and 32-36). All RhD-negative in the intervention and control groups delivered of RhD-positive babies received 500 IU 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 haemolytic disease of the newborn or requiring exchange transfusion; passage of foetal 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 in odd years the intervention group). Results from the post-natal 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

Study: MacKenzie *et al.* 1999[124]

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 Jan 1980 and 31 Dec 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 Jan 1990 and 31 Dec 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, and in the other (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 1987-1996.

Participants: non-sensitised RhD-negative pregnant nulliparae.

Interventions: 500 IU 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 Northamptonshire. In Oxfordshire, standard prophylaxis was offered to all RhD-negative women postpartum, but in Northamptonshire 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 1980-86 was compared with that for 1990-96 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 historic controls. A noticeable reduction in the incidence of sensitisation observed in Northamptonshire 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 prior to the introduction of the anti-D programme.

Quality: good

Study: MacKenzie et al. 2004[98]

Method: allegedly an RCT (multi-centre, 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, with known Rh(D)-positive partners, within 14 days before 28th week of gestation, who had not previously received anti-D during the current pregnancy, and had not received blood or any other blood-borne products during the 6 months prior to enrolment. 71.5% of participants had been pregnant before, and 81.9% had received anti-D in a previous pregnancy

Interventions: 1500 IU 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 IM and IV 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 six 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 (ie all women who received at least one dose of Rhophylac). Efficacy evaluations were conducted on the per-protocol population, ie all women from the ITT population who had delivered an RhD-positive child and who complied with the study's inclusion/exclusion criteria. 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 IM and IV 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, controls, 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 is acceptable given the existence of other scientific data.

The investigators note that the Committee for Proprietary Medicine Products' most recent Note for Guidance on the Clinical Investigation of Human Anti-D immunoglobulin 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

Study: Mayne *et al.* 1997[125]

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 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

Study: Tovey *et al.* 1983,[126] Thornton *et al*. 1989[131]

Method: prospective study with historic controls; intention-to-treat analysis.

Participants: non-sensitised RhD-negative primigravidae in Yorkshire Region who gave birth to RhD-positive infants in 1980-1981; controls were 2000 non-sensitised RhD-negative primigravidae in Yorkshire who gave birth to RhD-positive infants in 1978-79.

Interventions: 500 IU anti-D at 28 and 34 weeks, plus 500 IU 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; birth weight; foetal survival at one month.

Notes: 85% of the intervention group were screened six 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 historic 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

Study: Trolle 1989[130]

Method: prospective study with historic 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 (controls were all RhD-negative women having RhD-positive babies in Kolding in the years 1972-1977)

Interventions: 1500 IU 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 anti-D the day after delivery if the foeto-maternal transfusion was estimated to be less than 15nl blood.

Outcomes: incidence of immunisation 10 months after delivery or in next pregnancy; amount of foetal 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 foeto-maternal 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 foetal 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. 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 which 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 38: 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 *et al.*1978[127]	Prospective study, historic/ geographic controls	2 x 1500 IU (28 and 34 weeks) (initially at 34 weeks only)	Primigravida e	1,357	1	0.1 (-0.1 to 0.3)	2,768	45	1.6 (1.2 to 2.1)
Bowman & Pollock 1978[128]	Prospective study, historic controls	1 x 1500 IU (28 weeks)	Unselected	1,804	5	0.3 (0.0 to 0.5)	3,533	62	1.8 (1.3 to 2.2)
Bowman & Pollock 1987[129]	Retrospective study, historic controls	1 x 1500 IU (28 weeks)	Unselected	9,303	18	0.2 (0.1 to 0.3)	3,533	62	1.8 (1.3 to 2.2)
Trolle 1989[130]	Prospective study, historic controls	1 x 1500 IU (28 weeks)	Unselected	346	No data		354	No data	
Huchet *et al.* 1987[123]	Quasi-RCT	2 x 500 IU (28 and 34 weeks)	Primigravida e Multigravida e Unselected	461 138 599	0 1 1	0.0 (0.0 to 0.0) 0.7 (-0.7 to 2.0) 0.2 (-0.2 to 0.5)	454 136 590	4 2 6	0.9 (0.0 to 1.7) 1.5 (-0.6 to 3.5) 1.0 (0.2 to 1.8)
MacKenzie *et al.*1999[124]	Community intervention trial	2 x 500 IU (28 and 34 weeks)	Primiparae	3,320	No data		3,146	No data	
Mayne *et al.* 1997[125]	Before and after study	2 x 500 IU (28 and 34 weeks)	Primiparae	1,425	No data		1,426	No data	

Tovey *et al.* 1983[126]	Prospective study, historic controls	2 x 500 IU (28 and 34 weeks)	Primigravidae	1,238	2	0.2 (-0.1 to 0.4)	2,000	18	0.9 (0.5 to 1.3)
				325	2	0.6 (-0.2 to 1.5)	582	11[a]	1.9 (0.8 to 3.1)
			Multigravidae	1,563	4	0.3 (0.0 to 0.6)	2,582	29	1.1 (0.7 to 1.5)
			Unselected						

Key:

RCT = randomised controlled trial
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
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 39: SUMMARY OF TRIAL RESULTS: WOMEN SENSITISED AT POSTNATAL FOLLOW-UP, BY TOTAL ANTI-D DOSE

Study	Study Design	Dosage	Patient Selection	Ant-D Prophylaxis Group			Control Group		
				n	r	% Sensitised (95% CI)	N	r	% Sensitised (95% CI)
Bowman *et al.* 1978[127]	Prospective study, historic/ geographic controls	2 x 1500 IU (28 and 34 weeks) (initially at 34 weeks only)	Primigravidae	1,004	1	0.1 (-0.1 to 0.3)	2,768[a]	45	1.6 (1.2 to 2.1)
Bowman & Pollock 1978[128]	Prospective study, historic controls	1 x 1500 IU (28 weeks)	Unselected	807	No data		3,533[a]	50	1.4 (1.0 to 1.8)
Bowman & Pollock 1987[129]	Retrospective study, historic controls	1 x 1500 IU (28 weeks)	Unselected	9,303[a]	25	0.3 (0.2 to 0.4)	3,533[a]	50	1.4 (1.0 to 1.8)
Trolle 1989[130]	Prospective study, historic controls	1 x 1500 IU (28 weeks)	Unselected	291	0	0.0 (0.0 to 0.0)	322[b]	6	1.9 (0.4 to 3.3)
MacKenzie *et al.* 2004[98]	Open-label RCT; results presented as uncontrolled study	1 x 1500 IU (28 weeks)	Unselected	248 (per protocol population)	0	0.0 (0.0 to 0.0)	-	-	-
Huchet *et al.* 1987[123]	Quasi-RCT	2 x 500 IU (28 and 34 weeks)	Primigravidae Multigravidae Unselected	362 110 472	0 1 1	0.0 (0.0 to 0.0) 0.9 (-0.9 to 2.7) 0.2 (-0.2 to 0.6)	360 108 468	4 3 7	1.1 (0.0 to 2.2) 2.8 (-0.3 to 5.9) 1.5 (0.4 to 2.6)
MacKenzie *et al.* 1999[124]	Community intervention	2 x 500 IU (28 and 34 weeks)	Primiparae	3,320	No data		3,146	No data	

	trial								
Mayne *et al.* 1997[125]	Before and after study	2 x 500 IU (28 and 34 weeks)	Primiparae	1,425	No data		1,426	No data	
Tovey *et al.* 1983[126]	Prospective study, historic controls	2 x 500 IU (28 and 34 weeks)	Primigravidae Multigravidae Unselected	1059 No data No data	2 No data No data	0.2 (-0.1 to 0.5)	No data	No data	

Key:

RCT = randomised controlled trial
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
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

11. REFERENCES

1. Stockman, J. A., III and de Alarcon, P. A. Overview of the state of the art of Rh disease: history, current clinical management, and recent progress. *Journal of Pediatric Hematology/Oncology* 2001; **23** 385-393.

2. MacKenzie, I. Antenatal anti-D prophylaxis: one dose or two? *British Journal of Midwifery* 2004; **12** 13-19.

3. Bowman, J. M. The prevention of Rh immunisation. *Transfusion Medicine Reviews* 1988; **2** 129-150.

4. Filbey, D., Berseus, O., and Carlberg, M. Occurrence of anti-D in RhD-positive mothers and the outcome of the newborns. *Acta Obstetricia et Gynecologica Scandinavica* 1996; **75.**

5. Selinger, M. Immunoprophylaxis for rhesus disease--expensive but worth it? *British Journal of Obstetrics & Gynaecology* 1991; **98** 509-512.

6. Harrod, K. S., Hanson, L., VandeVusse, L., and Heywood, P. Rh negative status and isoimmunisation update. A case-based approach to care. *Journal of Perinatal and Neonatal Nursing* 2003; **17** 166-178.

7. Tovey, L. A. and Taverner, J. M. A case for the antenatal administration of anti-D immunoglobulin to primigravidae. *Lancet* 18-4-1981; **1** 878-881.

8. Urbaniak, S. J. and Greiss, M. A. RhD haemolytic disease of the fetus and the newborn. *Blood Reviews* 2000; **14** 44-61.

9. Contreras, M. The prevention of RH haemolytic disease of the fetus and newborn - general background. *British Journal of Obstetrics & Gynaecology* 1998; **105** 7-10.

10. Bowman, J. Rh-immunoglobulin: Rh prophylaxis. *Baillieres Best Practice & Research in Clinical Haematology* 2006; **19** 27-34.

11. Bowman, J. M. Fetomaternal ABO incompatibility and erythroblastosis fetalis. *Vox Sanguinis* 1986; **50** 104-106.

12. Tuohy, J. F., Sangalli, M., and Kim, L. Red blood cell iso-immunisation in the Wellington area of New Zealand: the case for antenatal prophylaxis. *Australian & New Zealand Journal of Obstetrics & Gynaecology* 2004; **44** 458-459.

13. Bowman, J. M., Friesen, A. D., Pollock, J. M., and Taylor, W. E. WinRho: Rh immune globulin prepared by ion exchange for intravenous use. *Canadian Medical Association Journal* 6-12-1980; **123** 1121-1127.

14. Urbaniak, S. J. The scientific basis of antenatal prophylaxis. *British Journal of Obstetrics & Gynaecology* 1998; **105** 11-18.

15. Stewart, G., Day, R. E., Del Priore, C., Whittle, M. J., Turner, T. L., and Holland, B. M. Developmental outcome after intravascular intrauterine transfusion for rhesus haemolytic disease. *Archives of Disease in Childhood Fetal & Neonatal Edition* 1994; **70** F52-F53.

16. van Kamp, I. L., Klumper, F. J., Bakkum, R. S. L. A., Oepkes, D., Meerman, R. H., Scherjon, S. A., and et al The severity of immune fetal hydrops is predictive of fetal outcome after intrauterine treatment. *American Journal of Obstetrics & Gynecology* 2001; **185** 668-673.

17. Farina, A., Calderoni, P., Carinci, P., and Rizzo, N. Survival analysis of transfused fetuses affected by Rh-alloimmunisation. *Prenatal Diagnosis* 2000; **20** 881-885.

18. Craig, S., Morris, K., Tubman, T., and McClure, B. The fetal and neonatal outcomes of rhesus D antibody affected pregnancies in Northern Ireland. *Irish Medical Journal* 2000; **93** 17-18.

19. Matijevic, R., Grgic, O., Klobucar, A., and Miskovic, B. Diagnosis and management of Rh alloimmunisation. *Fetal Diagnosis & Therapy* 2005; **20** 393-401.

20. Grab, D., Paulus, W. E., Bommer, A., Buck, G., and Terinde, R. Treatment of fetal erythroblastosis by intravascular transfusions: outcome at 6 years. *Obstetrics & Gynecology* 1999; **93** 165-168.

21. Doyle, L. W., Kelly, E. A., Rickards, A. L., Ford, G. W., and Callanan, C. Sensorineural outcome at 2 years for survivors of erythroblastosis treated with fetal intravascular transfusions. *Obstetrics & Gynecology* 1993; **81** 931-935.

22. van Kamp, I. L., Klumper, F. J. C. M., Oepkes, D., Meerman, R. H., Scherjon, S. A., Vandenbussche, F. P. H. A., and Kanhai, H. H. H. Complications of intrauterine intravascular transfusion for fetal anemia due to maternal red-cell alloimmunisation. *American Journal of Obstetrics & Gynecology* 2005; **192** 171-177.

23. Harper, D. C., Swingle, H. M., Wiener, C. P., Bonthius, D. J., Aylward, G. P., and Widness, J. A. Long-term neurodevelopmental outcome and brain volume after treatment for hydrops fetalis by in utero intravascular transfusion. *American Journal of Obstetrics & Gynecology* 2006; **195** 192-200.

24. Hudon, L., Moise, K. J., Jr., Hegemier, S. E., Hill, R. M., Moise, A. A., Smith, E. O'B., and Carpenter, R. J. Long-term neurodevelopmental outcome after intrauterine transfusion for the treatment of fetal hemolytic disease. *American Journal of Obstetrics & Gynecology* 1998; **179** 858-863.

25. Janssens, H. M., de Haan, M. J., van, Kamp, I, Brand, R., Kanhai, H. H., and Veen, S. Outcome for children treated with fetal intravascular transfusions because of severe blood group antagonism. *Journal of Pediatrics* 1997; **131** 373-380.

26. Ouwehand, W. H., Goodyear, E., Camilleri-Ferrante, C., Burgess, C., and Rankin, A. Epidemiology of RhD haemolytic disease of the newborn in East Anglia. *British Journal of Obstetrics & Gynaecology* 1998; **105** 23-24.

27. Das, P. K., Nair, S. C., Harris, V. K., Rose, D., Mammen, J. J., Bose, Y. N., and Sudarsanam, A. Distribution of ABO and Rh-D blood groups among blood donors in a tertiary care centre in South India. *Tropical Doctor* 2001; **31** 47-48.

28. Ali, N., Anwar, M., Bhatti, F. A., Nadeem, M., Nadeem, A., and Ali, A. M. Frequency of ABO and Rh blood groups in major ethnic groups and casts of Pakistan. *Pakistan Journal of Medical Science* 2005; **21** 26-29.

29. Prevention of haemolytic diseases of the newborn due to anti-D. *British Medical Journal Clinical Research Ed* 28-2-1981; **. 282** 676-677.

30. Kumar, S. and Regan, F. Management of pregnancies with RhD alloimmunisation. *BMJ* 28-5-2005; **330** 1255-1258.

31. Joseph, K. S. and Kramer, M. S. The decline in Rh hemolytic disease: should Rh prophylaxis get all the credit? *American Journal of Public Health* 1998; **88** 209-215.

32. Robson, S. C., Lee, D., and Urbaniak S. Anti-D immunoglobulin in RhD prophylaxis. *British Journal of Obstetrics & Gynaecology* 1998; **105** 129-134.

33. Duguid, J. K. M. and Bromilow, I. M. What is the true rate of RhD isoimmunisation in the UK? *British Journal of Obstetrics & Gynaecology* 1998; **105** 33-33.

34. Clarke, C. A. Preventing rhesus babies: the Liverpool research and follow up. *Archives of Disease in Childhood* 1989; **64** 1734-1740.

35. Hussey, R. M. and Clarke, C. A. Deaths from Rh haemolytic disease in England and Wales in 1988 and 1989. *BMJ* 1991; **303** 445-446.

36. Whitfield, C. R., Raafat, A., and Urbaniak, S. J. Underreporting of mortality from RhD haemolytic disease in Scotland and its implications: retrospective review. *BMJ* 1997; **315** 1504-1505.

37. Murphy, K. W. and Whitfield, C. R. Rhesus disease in this decade. *Contemporary Reviews in Obstetrics & Gynaecology* 1994; **6** 61-67.

38. Mortality statistics. Childhood, infant and perinatal. Review of the Registrar General on deaths in England and Wales, 2005. 2007; **DH3 no. 38.**

39. Schumacher, B. and Moise, K. J. Fetal transfusion for red blood cell alloimmunisation in pregnancy. *Obstetrics and Gynecology* 1996; **88** 137-150.

40. Bjornson, K. F. and McLaughlin, J. F. The measurement of health-related quality of life (HRQL) in children with cerebral palsy. *European Journal of Neurology* 2001; **8** 183-193.

41. Livingston, M. H., Rosendbuam, P. L., Russell, D. J., and Palisano, R. J. Quality of life among adolescents with cerebral palsy: what does the literature tell us? *Developmental Medicine and Child Neurology* 2007; **49** 225-231.

42. Varni, J. W., Burwinkle, T. M., Sherman, S. A., Hanna, K., Berrin, S. J., Malcarne, v. L., and Chambers, H. G. Health-related quality of life in children and adolescents with cerebral palsy: hearing the voices of the children. *Developmental Medicine and Child Neurology* 2005; **47** 592-597.

43. Pirpiris, M., Gates, P. E., McCarthy, J. J., D'Astous, J., Tylkowksi, C., Sanders, J. O., Dorey, F. J., Ostendorff, S., Robles, G., Caron, C., and Otsuka, N. Y. Function and well-being in ambulatory children with cerebral palsy. *Journal of Pediatric Orthopedics* 2006; **26** 119-124.

44. Dickinson, H. O., Parkinson, K. N., Ravens-Sieberer, U., Schirripa, G., Thyen, U., Arnaud, C., Beckung, E., Fauconnier, J., McManus, V., Michelsen, S. I., Parkes, J., and Colver, A. F. Self-reported quality of life iof 8-12-year-old children with cerebral palsy: a cross-sectional European study. *Lancet* 2007; **369** 2171-2178.

45. Magill-Evans, J., Darrah, J., Pain, K., Adkins, R., and Kratchovil, M. Are families with adolescents and young adults with cerebral palsy the same as other families? *Developmental Medicine and Child Neurology* 2001; **43** 466-472.

46. Houlihan, C. M., O'Donnell, M., Conaway, M., and Stevenson, R. D. Bodily pain and health-related quality of life in children with cerebral palsy. *Developmental Medicine & Child Neurology* 2004; **46** 305-310.

47. van der Dussen, L., Nieuwstraten, W., Roebroeck, M., and Stam, H. J. Functional level of young adults with cerebral palsy. *Clinical Rehabilitation* 2001; **15** 84-91.

48. Schwartz, L., Engel, J. M., and Jensen, M. P. Pain in persons with cerebral palsy. *Archives of Physical Medicine and Rehabilitation* 1999; **80** 1243-1246.

49. Jahnsen, R., Villien, L., Aamodt, G., Stanghelle, J. K., and Holm, I. Musculoskeletal pain in adults with cerebral palsy compared with the general population. *Journal of Rehabilitation Medicine* 2004; **36** 78-84.

50. Bottos, M., Feliciangeli, A., Sciuto, L., Gericke, C., and Vianello, A. Functional status of adults with cerebral palsy and implications for treatment of children. *Developmental Medicine & Child Neurology* 2001; **43** 516-528.

51. Murphy, K. P., Molnar, G. E., and Lankasky, K. Employment and social issues in adults with cerebral palsy. *Archives of Physical Medicine and Rehabilitation* 2000; **81** 807-811.

52. Margolis, A. C. Implications of prelingual deafness. *Lancet* 2001; **358** 76-76.

53. Wake, M., Hughes, E. K., Collins, C. M., and Poulakis, Z. Parent-reported health-related quality of life in children with congenital hearing loss: a population study. *Ambulatory Pediatrics* 2004; **4** 411-417.

54. Van Oyen, H., Tafforeau, J., and Demarest, S. The impact of hearing disability on well-being and health. *Sozial- und Praventivmedizin* 2001; **46** 335-343.

55. Jacob, S. R. and Scandrett-Hibdon, S. Mothers grieving the death of a child. Case reports of maternal grief. *Nurse Practitioner* 1994; **19** 60-65.

56. Badenhorst, W. and Hughes, P. Psychological aspects of perinatal loss. *Best Practice & Research in Clinical Obstetrics & Gynaecology* 2007; **21** 249-259.

57. Hutti, M. H. Social and professional support needs of families after perinatal loss. *JOGNN - Journal of Obstetric, Gynecologic, & Neonatal Nursing* 2004; **34** 630-638.

58. Callister, L. C. Perinatal loss. A family perspective. *Journal of Perinatal and Neonatal Nursing* 2006; **20** 227-234.

59. Vance, J. C., Foster, W. J., Najman, J. M., Embelton, G., Thearle, M. J., and Hodgen, F. M. Early parental responses to sudden infant death, stillbirth or neonatal death. *Medical Journal of Australia* 1991; **155** 292-297.

60. Vance, J. C., Najman, J. M., Thearle, M. J., Embelton, G., Foster, W. J., and Boyle, F. M. Psychological changes in parents eight months after the loss of an infant from stillbirth, neonatal death, or sudden infant death syndrome - a longitudinal study. *Pediatrics* 1995; **96** 998-998.

61. Janssen, H. J. E. M., Cuisinier, M. C. J., de Graauw, K. P. H. M., and Hoogduin, K. A. L. A prospective study of risk factors predicting grief intensity following pregnancy loss. *Archives of General Psychiatry* 1997; **54** 56-61.

62. Zeanah, C. H., Dailey, J. V., Rosenblatt, M. J., and Saller, D. N. Do women grieve after terminating pregnancies because of fetal anomalies? A controlled investigation. *Obstetrics & Gynecology* 1993; **82** 270-275.

63. Kolker, A. and Burke, B. M. Grieving the wanted child: ramifications of abortion after prenatal diagnosis of abnormality. *Health Care for Women International* 1993; **14** 513-526.

64. Brewaeys, A. Review: parent-child relationships and child development in donor insemination families. *Human Reproduction Update* 2001; **7** 38-46.

65. Durna, E. M., Bebe, J., Leader, L. R., Steigrad, S. J., and Garrett, D. G. Donor insemination: effects on parents. *Medical Journal of Australia* 1995; **163** 248-251.

66. Baron, L., Blanco, L., Valzacchi, G. R., and Pasqualini, S. Oocyte donation (OD) and donor insemination (DI): a comparative psychological study of parents and children. *Fertility and Sterility* 1998; **70** 278S-278S.

67. Bode, H., Weidner, K., and Storck, M. 'Quality of life in families of children with disabilities'. *Developmental Medicine and Child Neurology* 2000; **42** 354-354.

68. Wake, M., Salmon, L., and Reddihough, D. Health status of Australian children with mild to severe cerebral palsy: cross-sectional survey using the Child Health Questionnaire. *Developmental Medicine and Child Neurology* 2003; **45** 194-199.

69. Vargus-Adams, J. Health-related quality of life in childhood cerebral palsy. *Archives of Physical Medicine and Rehabilitation* 2005; **86** 940-945.

70. Brehaut, J. C., Kohen, D. E., Raina, P., Walter, S. D., Russell, D. J., Swinton, M., O'Donnell, M., and Rosenbaum, P. The health of primary caregivers of children with cerebral palsy: how does it compare with that of other Canadian caregivers? *Pediatrics* 2004; **114** e182-e191.

71. Eker, L. and Tuzun, E. H. An evaluation of quality of life of mothers of children with cerebral palsy. *Disability & Rehabilitation* 2-12-2004; **26** 1354-1359.

72. McConnell, D. and Llewellyn, G. Health of mothers of school-age children with disabilities. *Australian & New Zealand Journal of Public Health* 2006; **30** 572-574.

73. Emerson, E. Mothers of children and adolescents with intellectual disability: social and economic situation, mental health status, and the self-assessed social and psychological impact of the child's difficulties. *Journal of Intellectual Disability Research* 2003; **47** 385-399.

74. Emerson, E., Hatton, C., Llewellyn, G., Blacker, J., and Graham, H. Socio-economic position, household composition, health status and indicators of the well-being of mothers of children with and without intellectual disabilities. *Journal of Intellectual Disability Research* 2006; **50** 862-873.

75. Parish, S. L., Seltzer, M. M., Greenberg, J. S., and Floyd, F. Economic implications of caregiving at midlife: comparing parents with and without children who have developmental disabilities. *Mental Retardation* 2004; **42** 413-426.

76. Bat-Chava, Y. and Martin, D. Sibling relationships of deaf children: the impact of child and family characteristics. *Rehabilitation Psychology* 2002; **47** 73-91.

77. Oepkes, D. and van Scheltema, P. A. Intrauterine fetal transfusions in the management of fetal anemia and fetal thrombocytopenia. *Seminars In Fetal & Neonatal Medicine* 2007; **12** 432-438.

78. British Committee for Standards in Haematology Guideline for blood grouping and antibody testing in pregnancy. *internet* 2006.

79. Ulm, B., Svolba, G., Ulm, M. R., Bernaschek, G., and Panzer, S. Male fetuses are particularly affected by maternal alloimmunisation to D. *Transfusion* 1999; **39** 169-173.

80. Murray, N. A. and Roberts, I. A. G. Haemolytic disease of the newborn. *Archives of Disease in Childhood Fetal & Neonatal Edition* 2007; **92** F83-F88.

81. Howard, H., Martlew, V., McFadyen, I., Clarke, C., Duguid, J., Bromilow, I., and Eggington, J. Consequences for fetus and neonate of maternal red cell allo-immunisation. *Archives of Disease in Childhood* 1998; **78** F62-F66.

82. Walkinshaw, S. Antenatal prophylaxis - proposing. *British Journal of Obstetrics & Gynaecology* 1998; **105** 25-25.

83. Mohr, P. E., Feldman, J. J., Dunbar, J. L., McConkey-Robbins, A., Niparko, J. K., Rittenhouse, R. K., and Skinner, M. W. The societal costs of severe to profound hearing

loss in the United States. *International Journal of Technology Assessment in Health Care* 2000; **16** 1120-1135.

84. Schroeder, L., Petrou, S., Kennedy, C., McCann, D., Law, C., Watkin, P. M., Worsfold, S., and Yuen, H. M. The economic costs of congenital bilateral permanent childhood hearing impairment. *Pediatrics* 2006; **117** 1101-1112.

85. National Institute for Clinical Excellence Guidance on the use of routine antenatal anti-D prophylaxis for RhD-negative women. 2002; **Technology Appraisal No. 41.**

86. Lee, D., Contreras, M., Entwistle, C. C., Forman, K. M., Fraser, I. D., Gascoigne, E. W., and et al Recommendations for the use of anti-D immunoglobulin. *Prescribers' Journal* 1991; **31** 145-145.

87. Royal College of Physicians and Royal College of Pathologists National Institute for Health and Clinical Excellence Review of Technology Appraisal Guidance - No. 41 Guidance on the use of routine antenatal anti-D prophylaxis for RhD-negative women. Submission on behalf of the Royal College of Physicians and the Royal College of Pathologists. 2007.

88. Nottingham City Primary Care Trust Health technology appraisal: pregnancy - routine anti-D prophylaxis for rhesus negative women (review of TA41). 2007.

89. Dash, C. H. Submission to NICE on the use of anti-D as routine antenatal prophylaxis (RANP) to aid updating technology appraisal guidance. 2007.

90. CSL Behring, UK Rhophylac(R) manufacturer's submission. Routine antenatal anti-D prophylaxis for Rh D-negative women. 2007.

91. Baxter Healthcare Corporation Rho(D) immune globulin intravenous (human). WinRho(R) SDF. *internet* 2005.

92. British Committee for Standards in Haematology Guidelines for the use of prophylactic anti-D immunoglobulin. 2006.

93. Finning, K. M. Prediction of fetal D status from maternal plasma: Introduction of a new noninvasive fetal RHD genotyping service. *Transfusion (Bethesda)* 2002; **42.**

94. Daniels, G., Finning, K., Martin, P., and Soothill, P. Fetal blood group genotyping from DNA from maternal plasma: an important advance in the management and prevention of haemolytic disease of the fetus and newborn. *Vox Sanguinis* 2004; **87** 225-232.

95. ACOG practice bulletin. Prevention of Rh D alloimmunisation. Number 4, May 1999 (replaces educational bulletin Number 147, October 1990). Clinical management guidelines for obstetrician-gynecologists. American College of Obstetrics and Gynecology. *International Journal of Gynecology & Obstetrics* 1999; **66** 63-70.

96. Smith, J. A. Issues in anti-D plasma procurement. *British Journal of Obstetrics & Gynaecology* 1998; **105** 32-32.

97. Schiff, P., Kelle, A. J., and Wylie, B. Meeting the demand for anti-D in Australia. *British Journal of Obstetrics & Gynaecology* 1998; **105** 32-32.

98. MacKenzie, I. Z., Bichler, J., Mason, G. C., Lunan, C. B., Stewart, P., Al-Azzawi, F., De, Bono M., Watson, N., and Andresen, I. Efficacy and safety of a new, chromatographically purified rhesus (D) immunoglobulin. *European Journal of Obstetrics, Gynecology, & Reproductive Biology* 1-12-2004; **117** 154-161.

99. Bowman, J. M. The advantages of intravenous Rh-immune globulin. *Clinical Obstetrics & Gynecology* 1982; **25** 341-347.

100. Baxter Healthcare Ltd The clinical and cost effectiveness of anti-D prophylaxis for rhesus negative women in pregnancy. Submission to the National Institute for Clinical Excellence. 2007.

101. Harrop, S. Letter from Baxter Healthcare Ltd to NICE. 2007.

102. Wickham, S. Routine antenatal anti-D - a review of the evidence. *internet* 2001.

103. Maayan-Metzger, A., Schwartz, T., Sulkes, J., and Merlob, P. Maternal anti-D prophylaxis during pregnancy does not cause neonatal haemolysis. *Archives of Disease in Childhood Fetal & Neonatal Edition* 2001; **84** F60-F62.

104. Tabor, E. The epidemiology of virus transmission by plasma derivatives: clinical studies verifying the lack of transmission of hepatitis B and C viruses and HIV type 1. *Transfusion* 1999; **39** 1160-1168.

105. Foster, P. R., McIntosh, R. V., and Welch, A. G. Hepatitis C infection from anti-D immunoglobulin. *Lancet* 1995;372-372.

106. Meisel, H., Reip, A., Faltus, B., Lu, M., Porst, H., Wiese, M., and et al Transmission of hepatitis C virus to children and husbands by women infected with contaminated anti-D immunoglobulin. *Lancet* 1995; **345** 1209-1211.

107. Power, J. P., Lawlor, E., Davidson, F., and et al Hepatitis C viraemia in recipients of Irish intravenous anti-D immunoglobulin. *Lancet* 1994; **343** 1166-1167.

108. Smith, D. B., Lawlor, E., Power, J., O'Riordan, J., McAllister, J., Lycett, C., Davidson, F., Pathirana, S., Garson, J. A., Tedder, R. S., Yap, P. L., and Simmonds, P. A second outbreak of hepatitis C virus infection from anti-D immunoglobulin in Ireland. *Vox Sanguinis* 1999; **76** 175-180.

109. CSL Behring UK Limited Rhophylac 300 (1500 IU). 2006.

110. Turner, M. L. and Ironside, J. W. New-variant Creutzfeld-Jakob disease: the risk of transmission by blood transfusion. *Blood Reviews* 1998; **12** 255-268.

111. Editorial Team Fourth case of transfusion-associated vCJD infection in the United Kingdom. *Euro Surveillance: Bulletin Europeen sur les Maladies Transmissibles = European Communicable Disease Bulletin* 2007; **12** E070118.4.

112. Burnouf, T. and Padilla, A. Current strategies to prevent transmission of prions by human plasma derivatives. *Transfusion Clinique et Biologique* 2006; **13** 320-328.

113. BPL (Bio Products Laboratory) D-GAM(R), human anti-D immunoglobulin. *internet* 2004.

114. British National Formulary. 2007; **53.**

115. Summary of product characteristics. 2003.

116. WinRho(R) SDF product monograph. 2007.

117. Fung Kee, Fung K., Eason, E., Crane, J., Armson, A., De La, Ronde S., Farine, D., Keenan-Lindsay, L., Leduc, L., Reid, G. J., Aerde, J. V., Wilson, R. D., Davies, G., Desilets, V. A., Summers, A., Wyatt, P., Young, D. C., and Maternal-Fetal Medicine Committee, Genetics Committee. Prevention of Rh alloimmunisation. *Journal of Obstetrics & Gynaecology Canada: JOGC* 2003; **25** 765-773.

118. Chaffe, B., Ford, J., and Bills, V. Routine antenatal anti-D prophylaxis and patient compliance with the two-dose regimen. *Transfusion Medicine* 2007; **17** 403.

119. MacKenzie, I. Z., Findlay, J., Thompson, K., and Roseman, F. Compliance with routine antenatal rhesus D prophylaxis and the impact on sensitisations: Observations over 14 years. *BJOG: An International Journal of Obstetrics & Gynaecology* 2006; **113** 839-843.

120. Royal College of Nursing National Institute for Health and Clinical Excellence. Health Technology Appraisal: Pregnancy - routine anti-D prophylaxis for rhesus negative women (review of TA41). Comments provided by Royal College of Nursing. 2007.

121. Chilcott J, Lloyd-Jones M, Wight J, Forman K, Wray J, Beverley C, and Tappenden P A review of the clinical effectiveness and cost effectiveness of routine anti-D prophylaxis for pregnant women who are rhesus (RhD) negative. *Health Technology Assessment* 2003; **7** 1-72.

122. Centre for Reviews and Dissemination Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews. 2001; **4 (2nd edition).**

123. Huchet, J., Dallemagne, S., Huchet, C., Brossard, Y., Larsen, M., and Parnet-Mathieu, F. Application anté-partum du traitement préventif d'immunisation rhésus D chez les femmes rhésus négatif. Evaluation parallèle des passages transplacentaires d'hématies foetales. Résultats d'une étude multicentrique menée en région parisienne [Ante-partum administration of preventive treatment of Rh-D immunisation in rhesus-negative women. Parallel evaluation of transplacental passage of fetal blood cells. Results of a multicenter study carried out in the Paris region]. [French]. *Journal de Gynecologie, Obstetrique et Biologie de la Reproduction* 1987; **16** 101-111.

124. MacKenzie, I. Z., Bowell, P., Gregory, H., Pratt, G., Guest, C., and Entwistle, C. C. Routine antenatal Rhesus D immunoglobulin prophylaxis: the results of a prospective 10 year study. *British Journal of Obstetrics & Gynaecology* 1999; **106** 492-497.

125. Mayne, S., Parker, J. H., Harden, T. A., Dodds, S. D., and Beale, J. A. Rate of RhD sensitisation before and after implementation of a community based antenatal prophylaxis programme. *BMJ* 1997; **315** 1588-1588.

126. Tovey, L. A., Townley, A., Stevenson, B. J., and Taverner, J. The Yorkshire antenatal anti-D immunoglobulin trial in primigravidae. *Lancet* 30-7-1983; **2** 244-246.

127. Bowman, J. M., Chown, B., Lewis, M., and Pollock, J. M. Rh isoimmunisation during pregnancy: antenatal prophylaxis. *Canadian Medical Association Journal* 18-3-1978; **118** 623-627.

128. Bowman, J. M. and Pollock, J. M. Antenatal prophylaxis of Rh isoimmunisation: 28-weeks'-gestation service program. *Canadian Medical Association Journal* 1978; **118** 627-630.

129. Bowman, J. M. and Pollock, J. M. Failures of intravenous Rh immune globulin prophylaxis: an analysis of the reasons for such failures. *Transfusion Medicine Reviews* 1987; **1** 101-112.

130. Trolle, B. Prenatal Rh-immune prophylaxis with 300 micrograms immune globulin anti-D in the 28th week of pregnancy. *Acta Obstetricia et Gynecologica Scandinavica* 1989; **68** 45-47.

131. Thornton, J. G., Page, C., Foote, G., Arthur, G. R., Tovey, L. A., and Scott, J. S. Efficacy and long term effects of antenatal prophylaxis with anti-D immunoglobulin. *BMJ* 24-6-1989; **298** 1671-1673.

132. Herman, M., Kjeilman, H., and Ljunggren, C. Antenatal prophylaxis of Rh immunisation with 250 mcg anti-D immunoglobulin. *Acta Obstetricia et Gynecologica Scandinavica* 1984;4-14.

133. Lee, D. and Rawlinson, V. I. Multicentre trial of antepartum low-dose anti-D immunoglobulin. *Transfusion Medicine* 1995; **5** 15-19.

134. Parsons, M. L., Van den Hoj, M. C., Armson, B. A., Coffey, J., Liston, R. M., Peddle, L. J., and Stinson, D. A. A comparison of the rate of RhD alloimmunisation between Nova Scotia and Scotland. *British Journal of Obstetrics & Gynaecology* 1998; **105** 39-39.

135. MacKenzie, I. Z., Bowell, P. J., Pratt, G., Gregory, H., Guest, C., and Entwistle, C. C. Routine antenatal anti-D prophylaxis: Results of a prospective 10-year study. *British Journal of Obstetrics & Gynaecology* 1998; **105** 25-25.

136. Eklund, J. and Nevanlinna, H. R. [Prevention of Rh immunisation in Finland. Results obtained in a two-year national anti-D programme]. [Finnish]. *Duodecim* 1971; **87** 861-866.

137. Potron, G., Quereux, C., and Freal, C. [Prevention of Rh disease by anti-D plasma. A 2-year study]. [French]. *Revue Francaise de Transfusion* 1973; **16** 11-31.

138. Weaver, J. A multicentre study to examine the potential effect of monolocal ant-D IgG on prevention of haemolytic disease of the new-born when given routinely to RhD negative pregnant women both antenatally and at delivery. 2000.

139. Koelewijn, J. M. Effect of a single gift of antenatal anti-D-prophylaxis with 1000 IU in week 30 on the incidence of rhesus-D-immunisation in the first trimester of next pregnancy. *Vox Sanguinis* 2003; **91** 17-17.

140. Davey, M. G. and Zipursky, A. McMaster Conference on prevention of Rh immunisation. *Vox Sanguinis* 1979; **36** 50-64.

141. Urbaniak, J., Greiss, A., Promwong, C., Witterick, R., and Burnett, J. Alloimmunisation in D negative women following routine antenatal anti-D immunoglobulin prophylaxis (RAADP) in the north east of Scotland: a five-year retrospective study. *Vox Sanguinis* 2006; **91** 136-137.

142. MacKenzie, I. Z., Roseman, F., Findlay, J., Thompson, K., and McPherson, K. Clinical validation of routine antenatal anti-D prophylaxis questions the modelling predictions adopted by NICE for rhesus D sensitisation rates: results of a longitudinal study. *European Journal of Obstetrics, Gynecology, & Reproductive Biology* 2007.

143. Committee for Proprietary Medicinal Products (CPMP) Note for guidance on the clinical investigation of human anti-D immunoglobulin for intravenous and/or intramuscular use. *internet* 2000.

144. McSweeney, E., Kirkham, J., Vinall, P., and Flanagan, P. An audit of anti-D sensitisation in Yorkshire. *British Journal of Obstetrics & Gynaecology* 1998; **105** 1091-1094.

145. Ghosh, S. and Murphy, W. G. Implementation of the rhesus prevention programme: A prospective study. *Scottish Medical Journal* 1994; **39** 147-149.

146. Gilling-Smith, C., Toozs-Hobson, P., Potts, D. J., Touquet, R., and Beard, R. W. Management of bleeding in early pregnancy in accident and emergency departments. *BMJ* 1994; **309** 574-575.

147. Howard, H., Martlew, V. J., McFadyen, I. R., and Clarke, C. A. Preventing Rhesus D haemolytic disease of the newborn by giving anti-D immunoglobulin: are the guidelines being adequately followed? *Journal of Obstetrics & Gynaecology* 1997; **104** 37-41.

148. Vause, S. and Maresh, M. Indicators of quality of antenatal care: a pilot study. *British Journal of Obstetrics & Gynaecology* 1999; **106** 197-205.

149. Vause, S., Wray, J., and Bailie, C. Management of women who are Rhesus D negative in Northern Ireland. *Journal of Obstetrics & Gynaecology* 2000; **20** 374-377.

150. Turner, R. M., Spiegelhalter, D. J., Smith, G. C. S., and Thompson, S. G. Bias modelling in evidence synthesis. 2007; (under review).

151. Tovey, G. H. Should anti-D immunoglobulin be given antenatally? *Lancet* 30-8-1980; **2** 466-468.

152. Chilcott, J. The clinical effectiveness and cost-effectiveness of routine anti-D prophylaxis for rhesus negative women in pregnancy. 2001.

153. Adams, M. M., Marks, J. S., and Koplan, J. P. Cost implications of routine antenatal administration of Rh immune globulin. *American Journal of Obstetrics & Gynecology* 15-7-1984; **149** 633-638.

154. Baskett, T. F. and Parsons, M. L. Prevention of Rh(D) alloimmunisation: a cost-benefit analysis. *CMAJ Canadian Medical Association Journal* 15-2-1990; **142** 337-339.

155. Lim, O. W., Fleisher, A. A., and Ziel, H. K. Reduction of Rh0(D) sensitisation: a cost-effective analysis. *Obstetrics & Gynecology* 1982; **59** 477-480.

156. Selinger, M. The pharmacoeconomics of antenatal prophylaxis. 1997;6-7.

157. Torrance, G. W. and Zipursky, A. Cost-effectiveness of antepartum prevention of Rh immunisation. *Clinics in Perinatology* 1984; **11** 267-281.

158. Vick, S., Cairns, J., Urbaniak, S., Whitfield, C., and Rafaat, A. An economic evaluation of antenatal anti-D prophylaxis in Scotland (Structured abstract). *None* 1995.

159. Vick, S., Cairns, J., Urbaniak, S., Whitfield, C., and Raafat, A. Cost-effectiveness of antenatal anti-D prophylaxis. *Health Economics* 1996; **5** 319-328.

160. Tovey, L. A. D. Antenatal anti-D immunoglobulin. *Lancet* 15-10-1983; **2** 918-918.

161. Chilcott, J., Tappenden, P., Lloyd Jones, M., Wight, J., Forman, K., Wray, J., and Beverley, C. The economics of routine antenatal anti-D prophylaxis for pregnant women who are rhesus negative. *BJOG: An International Journal of Obstetrics & Gynaecology* 2004; **111** 903-907.

162. Office for National Statistics. *Office for National Statistics* 2007.

163. Romen A and Pernoll M Late Pregnancy Complications. 2003; **9** 296-300.

164. Saigal, S., Stoskopf, B., Pinelli J, Streiner D, Hoult, L., Paneth, N., and Goddeeris J Self-perceived Health-Related Quality of Life of Former Extremely Low Birth Weight Infants at Young Adulthood. *Pediatrics* 2006; **118** 1140.

165. Curtis L and Netten A. Unit costs of health and social care. 2006.

166. Charges and optical voucher values. 22-3-2007.

167. Rosenbaum, P. L., Livingston, M. H., Palisano, R. J., Galuppi, B. E., and Russell, D. J. Quality of life and health-related quality of life of adolescents with cerebral palsy. *Developmental Medicine & Child Neurology* 2007; **49** 516-521.

168. Beecham, J., O'Neill, T., and Goodman, R. Supporting young adults with hemiplegia: services and costs (Provisional record). *Health and Social Care in the Community* 2001; **9** 51-59.

169. Hemming K, Hutton J, Colver A, and Platt, M. J. Regional variation in Survival of People With Cerebral Palsy in the United Kingdom. *Pediatrics* 2005; **116** 1383.

170. Greenough, A., Hartnoll G, Hambley H, and Richards J Treatment requirement of infants with rhesus isoimmunisation within a geographically defined area. *Archives of Disease in Childhood* 2002; **87** F202-F203.

171. NHS reference costs 2005-06. *Department of Health* 2006.

172. Oswald A and Powdthavee N Death and the Calculation of Hedonic Damages. 2007.

173. Ospienko L RhD NIPD in the UK. *RhD NIPD Implementation Workshop* 2007.

174. Bichler, J., Schondorfer, G., Pabst, G., and Andresen, I. Pharmacokinetics of anti-D IgG in pregnant RhD-negative women. *BJOG: An International Journal of Obstetrics & Gynaecology* 2003; **110** 39-45.

175. Kennedy, M. S., McNanie, J., and Waheed, A. Detection of anti-D following antepartum injections of Rh immune globulin. *Immunohematology* 1998; **14** 138-140.

176. Witter, F. R., Shirey, R. S., Nicol, S. L., and Ness, P. M. Postinjection kinetics of antepartum Rh immune globulin. *American Journal of Obstetrics & Gynecology* 1990; **163** 786.