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

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Contents

Glossary 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. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

Isoimmunisation Production by an individual of antibodies against constituents of the tissues of another individual of the same species (e.g. following a transfusion of blood from a donor belonging to a different blood group).[1]

List of abbreviations

AADP	antenatal anti-D prophylaxis
BPL	Bio Products Laboratory
CCTR	Cochrane Controlled Trials Register
CDSR	Cochrane Database of Systematic Reviews
CEAC	cost-effectiveness acceptability curve
CESDI	Confidential Enquiry into Stillbirths and Deaths in Infancy
CI	confidence interval
CP	cerebral palsy
DI	donor insemination
GP	general practitioner
IgG	immunoglobulin G
IU	international unit
IUT	intrauterine transfusion
LYG	life-year gained
NHS CRD	NHS Centre for Reviews and Dissemination
NNT	number needed to treat
NRCT	non-randomised controlled trial
nvCJD	new variant Creutzfeldt-Jakob disease
QALY	quality-adjusted life-year
RCT	randomised controlled trial
RhD	rhesus D
TPH	transplacental haemorrhage

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

Executive summary

Background

Haemolytic disease of the newborn affects the fetus or neonate, and results from the transplacental passage of maternal allo-antibodies directed against fetal red cell antigens inherited from the father. Over 90% of all cases of clinically significant haemolytic disease of the newborn affect rhesus D (RhD)-positive infants born to RhD-negative mothers. The mothers usually make the anti-D antibody following a small feto-maternal haemorrhage at delivery of the first RhD-positive infant. This does not harm that infant, but successive RhD-positive infants are then progressively more affected by haemolytic disease of the newborn.

Prophylactic anti-D, whether antenatal or post-partum, can only suppress primary RhD immunisation; it has no effect in women who have already developed anti-D, however weak. Some women currently become sensitised prior to delivery of the first pregnancy. It is estimated that between 55% and 80% of these develop 'silent' sensitisation – i.e. sensitisation in the absence of any identifiable risk event such as should prompt the administration of anti-D. It is such cases which the proposed intervention seeks to prevent.

Approximately 16% of women in the UK are RhD-negative, and in about 10% of all pregnancies the mother is RhD-negative and the fetus RhD-positive. During these pregnancies, the mother is at risk of becoming sensitised by transplacental haemorrhage. The severity of haemolytic disease of the newborn varies. In its mildest form, it is detectable only in laboratory tests. More commonly, the infant has a mild degree of jaundice which responds to phototherapy. More severe disease can cause physical disabilities and mental retardation. In its most severe form, the *in utero* anaemia causes cardiac failure, hydrops and intrauterine death. Prior to the introduction of any immunoprophylaxis, the frequency of haemolytic disease of the newborn was one per 100 births in second pregnancies, and higher in subsequent pregnancies. In the mid 1950s in England and Wales, haemolytic disease of the newborn was responsible for one death in every 2180 births. Since that time, anti-D prophylaxis and advances in neonatal care have had a major impact, and the current figure approximates to one death in every 20,800 births.

In 1999, the most recent year for which figures are available, there were 621,872 total births in England and Wales. Around 10% of these would have been RhD-positive infants delivered of RhD-negative women.

Current provision of routine antenatal anti-D prophylaxis (AADP) across England and Wales is very patchy. It has been estimated that approximately 12% of hospitals are currently operating a policy of offering this intervention to pregnant RhD-negative women.

Description of proposed service

The proposed service evaluated in this report is the routine offering of AADP either to all pregnant women who are RhD-negative or to RhD-negative primigravidae only. The intramuscular anti-D immunoglobulin would be given as two doses at 28 and 34 weeks. It would supplement, rather than replace, current standard practice of routinely offering anti-D within 72 hours of delivery to all RhD-negative women delivered of RhD-positive infants who are not already sensitised, and also offering anti-D within 72 hours to all unsensitised RhD-negative pregnant women who undergo a potential sensitising event. Otherwise such women would not be protected against large bleeds in the antenatal period or around the time of delivery.

Objectives

The overall aim of the report was to evaluate the clinical effectiveness of AADP for pregnant women who are RhD-negative, and the comparative cost-effectiveness of:

- offering routine AADP to all pregnant women who are RhD-negative
- offering routine AADP only to primigravidae who are RhD-negative
- not offering routine AADP.

In each case, it was assumed that the current programme of offering anti-D antenatally to all

RhD-negative women who suffer a potential sensitising event, and post-partum to all RhD-negative women delivered of a RhD-positive infant, will continue.

Methods

A systematic review of the literature was performed to identify all studies that compared women receiving routine AADP with untreated controls or that evaluated the economic impact of routine AADP. A model-based economic evaluation of offering routine AADP to all pregnant women who are RhD-negative, and to RhD-negative primigravidae only, in addition to conventional AADP applicable to the NHS, was performed. This economic evaluation assessed the cost per fetal loss, stillbirth, neonatal or postneonatal death avoided, the cost per life-year gained (LYG) and the cost per quality-adjusted life-year (QALY) gained as a result of disabilities avoided.

Results

Number and quality of studies

Eleven studies met the inclusion criteria. They included seven non-randomised trials with historical or geographical controls, one randomised controlled trial (RCT), one quasi-RCT, one community intervention trial and one retrospective before-and-after study. A follow-up study to one of the non-randomised trials studied the safety and efficacy of antenatal prophylaxis by examining obstetric data relating to women in the trial in their first and subsequent pregnancies. Because of the paucity of RCT data (only one true RCT was found, and that used a dosage half that of the lowest dose currently considered appropriate), all these studies were retained for further consideration. However, most were methodologically poor.

Clinical effectiveness

In all studies, the proportion of women sensitised was lower in the intervention arm than in the control arm, although in some studies the difference was small and not statistically significant. Two doses of anti-D at 28 and 34 weeks' gestation appeared to be more effective than one dose at 34 weeks only. There appeared to be no significant difference between the effectiveness of two doses of 500 IU and two doses of 1500 IU. Although there was no evidence relating to the relative effectiveness of two doses of 1250 IU, it is unlikely that this will differ significantly from that of two doses of 1500 IU.

The best indication of the likely efficacy of a programme of routine AADP in England and Wales came from two non-randomised community-based studies. The pooled results of these studies suggested that such a programme may reduce the sensitisation rate from 0.95% to 0.35%. This gave an odds ratio for the risk of sensitisation of 0.37, and an absolute reduction in risk of sensitisation in RhD-negative mothers carrying a RhD-positive child of 0.6%. Although the number of such women needed to treat (NNT) to avoid one case of sensitisation was 166 (1/0.006), antenatally a RhD-negative woman will not know if she is carrying a RhD-positive child. Thus all RhD-negative pregnant women would require treatment, and not just the 60% who are carrying a RhD-positive child, making the overall NNT 278 (10/6 × 166).

It was estimated that currently 625 sensitisations of RhD-negative women per year lead to a total of at least 30 fetal deaths, stillbirths, neonatal and postneonatal deaths. Avoidance of sensitisation can thus be expected to avoid fetal/neonatal loss in 4.8% of cases. The NNT to avoid a fetal or neonatal loss in a subsequent pregnancy can therefore be estimated as approximately 5790.

Health economics

The drug costs of treating one pregnancy with two doses of 500 IU are £54.00, and with two doses of 1250 IU are £47.80, at NHS list prices. To this can be added an estimated cost of administration of £10.

The gross annual cost (including administration costs) of offering routine AADP to all RhD-negative pregnant women in England and Wales is estimated to be £6.1 million for the 2 × 1250 IU regimen, and £6.8 million for the 2 × 500 IU regimen. If cost savings from reductions in treating haemolytic disease of the newborn are considered, the total net cost to the NHS in England and Wales would be £5.7–6.4 million per year.

If routine AADP is only given to RhD-negative primiparae, the total gross cost of drugs would be approximately £2.4 million for the 2 × 500 IU regimen and £2.1 million for the 2 × 1250 IU regimen. The total cost of administration would be £450,000. The total net cost, including potential savings from reductions in haemolytic disease of the newborn, is estimated at approximately £2.3–2.6 million.

The cost per QALY gained from a policy of routine AADP given to primigravidae was calculated on the

basis of the published literature relating to the quality of life impact of minor developmental problems and long-term neurodevelopmental problems in low birth weight infants. In these terms, routine AADP is economically attractive from the perspective of disability prevention alone, irrespective of attitudes to parental grief and valuation of stillbirths, neonatal and postneonatal deaths. Routine AADP given to all pregnant women who are RhD-negative is economically attractive, using a maximum acceptable cost-effectiveness ratio of £30,000 per QALY, if the lost child, associated parental grief and subsequent high intervention pregnancy are valued at more than 9 QALYs.

In addition, routine AADP given to primigravidae has a cost per LYG that is very low in comparison to other interventions routinely funded by the NHS. The incremental cost per LYG of giving routine AADP to **all** pregnant women who are RhD-negative is not as low, but there is still a chance of approximately 90% of the incremental cost-effectiveness being better than £30,000 per LYG compared to a primigravidae-only policy.

Conclusions

The evidence suggests that routine AADP is effective in reducing the number of RhD-negative pregnant women who are sensitised during pregnancy. However, it cannot prevent all instances of sensitisation, some of which occur either despite or before appropriate administration of anti-D.

Some cases of sensitisation in the UK are due to failure to adhere to the existing guidelines for the administration of anti-D either post-partum or in response to potential sensitising events. It should therefore be possible to reduce sensitisation rates by stricter adherence to current guidelines, and it could be argued that this should be pursued before initiating guidelines for the routine offering of AADP to pregnant women who are RhD-negative.

Issues relating to implementation of a policy of routine AADP

If a programme of routine AADP were to be adopted, watertight mechanisms would need to be developed to ensure that prophylaxis is offered at the appropriate time to all women at risk of sensitisation, in order to avoid additional cases of sensitisation attributable to failure to provide prophylaxis when appropriate. As with other blood products, mechanisms would also be required to ensure that individual women could be linked with specific batches of anti-D.

The widespread administration of an intervention that would benefit only a few (unidentifiable) individuals is well established in medical practice, and would not present new ethical issues. However, it would be imperative that women were encouraged to make an informed choice, based on adequate information. The prime responsibility for ensuring that women understand the implications of the intervention, and consent to it, would rest with midwives. In many cases these midwives would be based in the community and/or antenatal clinic, and would currently have varying levels of involvement with the administration of postnatal anti-D. The introduction of routine AADP would therefore have significant education and training implications.

Recommendations for further research

Further research is required to:

- attempt to identify any characteristics which might identify the 10% of RhD-negative women who are at risk of sensitisation, so that antenatal prophylaxis may be targeted specifically at these women
- confirm or disprove the preliminary findings that protection against sensitisation provided by AADP in primigravidae extends beyond the first pregnancy.

Chapter 1
Introduction

Aim of the review

The overall aim of this review is to evaluate the clinical effectiveness of routine antenatal anti-D prophylaxis (AADP) for pregnant women who are rhesus D (RhD)-negative, and the comparative cost-effectiveness of:

- offering routine AADP to all pregnant women who are RhD-negative
- offering routine AADP only to primigravidae who are RhD-negative
- not offering routine AADP.

In each case, it is assumed that the current programme of offering anti-D antenatally to all RhD-negative women who suffer a potential sensitising event, and post-partum to all RhD-negative women delivered of a RhD-positive infant, will continue, as otherwise such women would not be protected against large bleeds in the antenatal period or around the time of delivery.

The overall impact of each policy on the NHS as a whole will be estimated.

As anti-D immunoglobulin G (IgG) is a pooled plasma-derived product, there are inevitably concerns regarding safety and availability. The possible risks, and ethical issues, associated with the widespread use of a plasma-derived product within this context are discussed.

Background

Description of underlying health problem

Aetiology

Haemolytic disease of the newborn is a haemolytic anaemia affecting the fetus or neonate and resulting from the transplacental passage of maternal allo-antibodies directed against fetal red cell antigens inherited from the father. Over 90% of all cases of clinically significant haemolytic disease of the newborn affect RhD-positive infants born to RhD-negative mothers. In the absence of any programme of prophylaxis, the mothers usually make the anti-D antibody following a small feto-maternal haemorrhage at delivery of the first RhD-positive infant. This does not harm that infant, but successive RhD-positive infants are then progressively more severely affected by haemolytic disease of the newborn. Maternal sensitisation can also result from the transfusion of RhD-positive red cells.

A proportion of women who do not have detectable anti-D after the index pregnancy are capable of giving a secondary immune response during a later pregnancy (i.e. they are 'sensibilised', rather than sensitised, by the index pregnancy). Thus the 'true' rate of isoimmunisation is greater than that identified by the presence of anti-D at delivery or at 6 months following delivery.[2]

Prophylactic anti-D, whether antenatal or post-partum, can only suppress primary RhD immunisation; it has no effect in women who have already developed anti-D, however weak.[3] Despite the current guidance regarding the use of anti-D both antenatally, in response to potential sensitising events during the pregnancy, and post-partum, some women become sensitised prior to delivery of the first pregnancy. These cases of sensitisation have been examined, and a proportion have been found to be due to failure to adhere to the existing UK guidelines[4] through lack of administration of (a) any anti-D, (b) enough anti-D or (c) timely anti-D when clearly indicated.[5–9] However, even after allowing for these failures to adhere to current guidance, there remains a significant number of women (estimated to be between 55%[10] and 80%[11] of those sensitised) who develop 'silent' sensitisation in the absence of any identifiable risk event such as should prompt the administration of anti-D. This silent sensitisation is presumably caused by transplacental haemorrhage (TPH). In the first two trimesters of pregnancy, TPHs are infrequent and small in volume. However, TPHs large enough to cause sensitisation are considerably more frequent in the third trimester.[3]

Epidemiology

Approximately 16% of women in the UK are RhD-negative,[3] and in about 10% of all pregnancies the mother is RhD-negative and the fetus RhD-positive. It is during these pregnancies that the mother is at risk of becoming sensitised by TPH. There is some

indication that the risk is highest when the mother and fetus have the same ABO blood group (about 80% of at-risk pregnancies).[3] Anti-D is found immediately after a first pregnancy in approximately 1% of untransfused RhD-negative women who deliver an ABO-compatible RhD-positive infant; in about half of these, it is detectable between 34 and 40 weeks of gestation. The incidence of detectable anti-D in these women rises to 4–9% at 6 months postdelivery.[3] However, because of the possibility of sensibilisation mentioned above, as many as 17% of women who have had a second RhD-positive ABO-compatible pregnancy have detectable anti-D: in most of these women, primary immunisation would have occurred during the first pregnancy.[3]

Prior to the introduction of any immunoprophylaxis, the frequency of RhD haemolytic disease of the newborn was one per 100 births in second pregnancies, and higher in subsequent pregnancies. In the mid 1950s in England and Wales, RhD haemolytic disease of the newborn was responsible for 310 deaths per year – one in 2180 births. Since that time, anti-D prophylaxis and advances in neonatal care have had a major impact. Standard post-partum anti-D prophylaxis was introduced in the UK in 1969. Prophylaxis was extended in 1976 to include abortions and spontaneous miscarriages, and in 1981 to include a number of potentially sensitising events.[10] By 1989 the death rate from haemolytic disease of the newborn due to anti-D was 1.5 per 100,000 live births,[12] or one in approximately 66,500 live births. However, all these figures are likely to underestimate fetal mortality as they do not include fetal loss before 28 weeks.

A retrospective review[13] of births to mothers resident in Scotland between 1987 and 1991 found that five times as many deaths from RhD haemolytic disease of the newborn were uncertified as were certified through the General Register Office. Of the 20 deaths identified, 11 occurred before 28 weeks of gestation, but only four before 20 weeks. The major cause of underreporting was the exclusion from the certification data of abortions (therapeutic or spontaneous).[13,14] In addition, the structure of the death/stillbirth certificate is such that deaths which occur during *in utero* treatment will be attributed to their primary cause (usually cord tamponade or haemorrhage), and RhD haemolytic disease of the newborn will be reported only as the secondary cause of death (Davies N, Consultant Obstetrician and Gynaecologist, Royal Hallamshire Hospital, Sheffield: personal communication, 2001). Thus, although RhD haemolytic disease of the newborn was reported as the main cause of five stillbirths and one neonatal death (or 1 in approximately 104,000 total births) in England and Wales in 1999,[15] the Scottish data suggest that the true number of fetal and perinatal deaths caused by RhD haemolytic disease in England and Wales in that year is likely to have been around 30. The Trent Confidential Enquiry into Stillbirths and Deaths in Infancy (CESDI) reported three deaths at between 20 weeks of pregnancy and 1 year of life due to RhD isoimmunisation in 1999, in a population of approximately 5 million; this is consistent with an overall figure of around 30 for England and Wales (Wood S, Regional CESDI Co-ordinator, Trent Region: personal communication, 2001).

Prognosis

The severity of haemolytic disease of the newborn seen in the infant varies according to certain properties of the antibody, its level and the duration of exposure of the infant to that level. In affected pregnancies, therefore, close monitoring is required of both the maternal antibody level (every 2 weeks from 20 weeks) and the state of the fetus (using ultrasound, amniocentesis and periumbilical blood sampling, if indicated). The maternal antibody 'coats' or sensitises the infant's red cells, provoking their premature clearance from the circulation and resulting in anaemia and jaundice. *In utero*, fetal bilirubin crosses the placenta and is cleared by the maternal circulation. After delivery, however, clearance is dependent on the immature neonatal liver, and unconjugated bilirubin accumulates.

In the mildest form of haemolytic disease of the newborn, the sensitised red cells are detectable only in laboratory tests. However, 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 (e.g. the thalamus and corpus striatum) are particularly sensitive to damage by unconjugated bilirubin. The resulting clinical condition – kernicterus – has severe manifestations with physical disabilities and often mental retardation. In its most severe form, the *in utero* anaemia causes cardiac failure, hydrops and intrauterine death.

The benefits of close monitoring of bilirubin levels and the ability of exchange transfusion to correct both anaemia and hyperbilirubinaemia should

make kernicterus a thing of the past. The introduction of intrauterine fetal blood sampling in the early 1980s, and the ability to establish fetal RhD type and haemoglobin level, has eased the management of potentially severely affected infants, not least by facilitating direct intravascular intrauterine transfusion (IUT). This has led to a major reduction in the need for elective premature delivery (e.g. at 28 weeks) and the resulting risks. However, the benefit of avoiding elective premature delivery has to be balanced against an estimated fetal loss from IUT of approximately 1–3%.[16] In addition, IUT requires a highly specialised unit with skilled personnel, equipment (particularly ultrasound) and access to specialised blood products. Of the total of affected fetuses, 10–12% require IUT to correct anaemia.[17,18]

Time profile of fetal loss and infant death due to RhD haemolytic disease

There are two sources of UK data relating to the time profile of fetal loss and infant death attributable to RhD incompatibility: CESDI notifications for England, Wales and Northern Ireland, and a retrospective review of births to women in Scotland between 1987 and 1991 which sought to identify all cases of fetal loss from RhD incompatibility.[13] CESDI has provided the most recent available unpublished data, from 1994–99 inclusive, but stated that these are likely to be underestimates (Mackintosh M, Director, CESDI Secretariat: personal communication, 2002); moreover, they do not include fetal losses before 20 weeks of gestation. Data from the two sources are shown in *Table 1*.

A fetus is not viable before 20 weeks of gestation. Although there are a few reports of survival between 20 and 24 weeks, 24 weeks is generally accepted as the lower limit of viability, and is the upper limit at which termination of pregnancy is allowed. Loss of a fetus at 24 weeks or over is legally defined as stillbirth.

On average, in England, Wales and Northern Ireland, around three fetuses a year are reported to CESDI as being lost between 20 and 24 weeks as a result of RhD incompatibility, and around nine stillbirths a year are reported as being due to RhD incompatibility (see *Table 1*).

RhD incompatibility also causes neonatal and postneonatal deaths. On average, in England, Wales and Northern Ireland, six neonatal deaths and up to two postneonatal deaths a year are reported to CESDI as being due to RhD incompatibility (see *Table 1*).

The data summarised in *Table 1* indicate that the majority of deaths due to haemolytic disease occur after 24 weeks, and are thus stillbirths, neonatal and postneonatal deaths.

The CESDI data indicate that an average of 18 fetal and infant deaths a year in England, Wales and Northern Ireland are due to RhD incompatibility, in addition to any fetal losses which occur before 20 weeks of gestation. The Scottish data suggest that 20% (4/20) of all fetal and infant deaths due to RhD incompatibility occur before 20 weeks of gestation. This represents an additional 25% (4/16) in relation to those deaths which occurred from 20 weeks' gestation onwards. As a result, 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 attributable to RhD incompatibility, and therefore this figure is compatible with the figure of 30 estimated earlier. Although, as the evidence summarised in the full report indicates, the introduction of a programme of routine antenatal prophylaxis cannot prevent every case of fetal loss, stillbirth, neonatal or postneonatal death attributable to RhD

TABLE 1 *Fetal and infant death attributed to RhD incompatibility*

Gestational age	Scotland 1987–1991[13] *n* (%)	UK excluding Scotland 1994–1999 (unpublished CESDI data) *n* (%)
Under 20 weeks	4 (20)	No data
20–24 weeks	3 (15)	19 (17)
Stillbirth	7 (35)	51 (48)
Neonatal death	5 (25)	36 (33)
Postneonatal death	1 (5)	3 (3)
Total	**20 (100)**	**109 (100)**

incompatibility, it can be expected to prevent a substantial majority of such cases.

Psychological effects of stillbirth or fetal loss

Research has shown that the experience of losing a child is by far the most painful grief experience.[19] 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 case of the loss of a parent or sibling. Such factors are also likely to be relevant in relation to stillbirth and fetal loss.

Several studies have considered the impact on parents of stillbirth and neonatal death, but none has been found that specifically studies the impact of fetal loss as a result of RhD haemolytic disease, or that measures grief at any point later than 18 months after the bereavement.

A number of studies suggest that grief following stillbirth or fetal loss is related to length of gestation; these include two prospective studies, one Australian,[20,21] and one Dutch.[22] 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 2 months post-termination, women who had terminated wanted pregnancies for fetal anomalies experienced grief as intense as those who had suffered spontaneous perinatal loss. Although the terminated pregnancies were of a younger gestational age (under 20 weeks) than the spontaneous losses, the grief responses were similar, being determined by the 'wantedness' of the pregnancy and not by gestational age.[23] A second US study also found that the termination of a wanted pregnancy because of fetal anomalies was experienced as a perinatal death rather than as an elective abortion. The grief was independent of gestational age, and it was felt that in a wanted pregnancy bonding started before conception.[24]

No work has been undertaken on the valuation of parental grief following miscarriage, stillbirth or neonatal death, and it is considered that such work would be impossible to undertake for ethical reasons (Jones-Lee M, Department of Economics, University of Newcastle-upon-Tyne: personal communication, 2002).

Ability to achieve intended family size

To its parents, any fetus or infant 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 lost fetus or infant has died as a result of RhD sensitisation, as this will affect all subsequent RhD-positive pregnancies in that mother. If the father is homozygous RhD-positive, then all 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 fetus is affected increases with each RhD-positive pregnancy, a successful outcome becomes less likely with each successive pregnancy.

Although we are not aware of any published work in this field, it seems likely that failure to achieve intended family size may be the cause of long-term psychiatric morbidity in the parents. It is theoretically possible for couples to complete their family using donor insemination (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 is not 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.[25] 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.[26] 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 the men felt jealous of the donor.[27]

Outcome of pregnancies affected by RhD incompatibility – surviving offspring

Not all pregnancies affected by RhD incompatibility end in fetal or neonatal death. The most recent data on the outcome of pregnancies in RhD-sensitised women derive from a study of the outcome of all such pregnancies in Northern Ireland from October 1994 to February 1997. This study found that over 90% of these pregnancies resulted in infants who survived the neonatal period (see *Table 2*).[28]

The chances of survival are related to the severity of the RhD haemolytic disease. Fetuses that are relatively severely affected are treated using IUT.

TABLE 2 *Outcomes of pregnancies in RhD-sensitised women in Northern Ireland, October 1994–February 1997*[28]

Outcome	Number (%)
Miscarriage	5 (4)
Stillbirth	3 (2)
Neonatal death	1 (1)
Affected babies	78 (63)
Unaffected babies	37 (30)
Total	**124 (100)**

Overall survival in such cases has been found to be around 86–90%.[29,30] Hydrops is indicative of severe haemolytic disease and is associated with poorer outcomes, although survival in fetuses with mild hydrops who receive IUT may be as high as 98%, in those with severe hydrops it may be as low as 55%.[29]

Infants who survive RhD haemolytic disease of the newborn may suffer long-term neuro-developmental problems; these may be caused either directly by that disease or indirectly by the prematurity associated with it. Several studies were found which reported on such problems. The most recent of these is the Northern Ireland study noted above.[28] This found that, at 2 years of age, five of the 78 surviving babies affected by RhD haemolytic disease of the newborn (6%) had minor developmental problems and two (3%) had major permanent neuro-developmental problems.

A US study[31] of children who had received IUT between 1986 and 1992 for haemolytic disease, which was in the majority of cases due to RhD incompatibility, found that two out of 21 babies whose hearing was tested before discharge had permanent hearing deficit (in one case severe bilateral deafness) – a rate probably five to ten times higher than that among infants not affected by haemolytic disease of the newborn. In addition, right spastic hemiplegia was diagnosed in one of the 40 live-born children in the study at 2.5 years; she had developed normally except for walking difficulties. As only 11 of the 40 children were followed up to 62 months, it is possible that others also suffered neuro-developmental problems.

Follow-up was considerably more complete in a Dutch study of 92 fetuses treated between May 1987 and January 1993 with IUT for severe haemolytic disease.[32] Seventy-seven of the 92 fetuses (84%) were born alive, but one died in the neonatal period and three in the first week of life, making overall survival 79%. Sixty-nine of the 73 survivors were followed up, and seven (10%) were found to have disabilities. Five children (7%) had disturbed development: three had cerebral palsy (CP), while two had minor neurological dysfunction leading to motor and speech delay. The children with CP differed in the severity of their disabilities: one was physically disabled and had an IQ of 40–50, one was physically disabled with speech delay, and one had fine motor and speech delay; all three attended a special school for physically and mentally disabled children. The remaining 64 had no neurological abnormalities, and had normal developmental outcomes, although six children had slightly delayed development in relation to language understanding, speech, or fine or gross motor development. The relative level of achievement tended to improve with increasing age. Thus, although 17% had been treated by a physiotherapist and 13% by a speech therapist because of motor or speech delay in early childhood, some of these children had improved their skills and could be categorised as normal.

Comparison was made with 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,[33] as did 6% in the healthy control group.[32] Because of the very small numbers in the group with haemolytic disease of the newborn, 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.

The introduction of ultrasonographically guided IUT has improved the ability to treat severely anaemic fetuses earlier in gestation, and has thus increased the chances of survival of more severely affected fetuses with the potential for poor neuro-developmental outcome.[31] It thus seems likely that up to 10% of surviving children will suffer neuro-developmental problems such as CP, deafness and motor and speech delay which will require specialist input and, in some cases, special education, while others will suffer some degree of developmental delay requiring physiotherapy or speech therapy.

Significance in terms of ill-health

In 1999, the most recent year for which figures are available, there were 621,872 live births and

3305 stillbirths in England and Wales.[34] As around 10% of all births in the UK are of RhD-positive infants delivered of RhD-negative women, approximately 62,500 such births a year can be expected in England and Wales.

Assuming that 1% of RhD-negative women who deliver a RhD-positive infant become sensitised antenatally (see chapter 2, page 25), approximately 625 women a year will become sensitised in England and Wales. Around 530 of these women are likely to have a subsequent pregnancy, which will have to be closely monitored, and in which haemolytic disease of the newborn may occur. Of the 530 second pregnancies, approximately 400 fetuses are likely to develop RhD haemolytic disease and 30 of these are likely to suffer fetal death, stillbirth, or neonatal or postneonatal death. Some of the 530 sensitised women who undergo second pregnancies will go on to have further pregnancies, and again a proportion of these will be affected. The obstetric input required to manage these cases is considerable, as the following would be required:

- measurement of maternal serum antibody level every 2–4 weeks
- 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 IgG (Davies N, Consultant Obstetrician and Gynaecologist, Royal Hallamshire Hospital, Sheffield: personal communication, 2001). The cost of this monitoring and treatment is clearly substantial.

If, as seems likely when third and subsequent pregnancies in sensitised women are taken into account, there will be approximately 500 affected pregnancies a year in England and Wales, then the implication of the study carried out in Northern Ireland[28] is that, in addition to around 35 fetal or neonatal deaths, these pregnancies will result in approximately 30 children with minor developmental problems and 15 with major permanent developmental problems. Other studies cited above[31,32] indicate that the most common permanent disabilities in this group are CP and deafness. Minor developmental problems include speech and motor delay such as require physiotherapy and speech therapy.[32]

Both CP and deafness have substantial implications in terms of health and social costs. A multicentre study carried out in the USA found that children who were classified on the basis of mobility as having moderate to severe CP had multiple health-related problems; they had lower scores than the general population on most of the factors in the Child Health Questionnaire quality of life measure.[35]

Many of the 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.[36] A US study recruited adults with CP with no more than mild cognitive impairment from clinics and treatment facilities for people with developmental disabilities: this found that 67% reported pain of more than 3 months' duration which was generally experienced on a daily basis.[37] In addition, many people with CP are unable to achieve the same degree of independence as their peers. Thus, in a Dutch cohort of young adults with CP, although 75% were mainly independent with respect to the activities of daily living, 24% required sheltered or institutional accommo-dation, and 30% lived with their parents, compared with 20% of the general Dutch population of the same age. 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, and 41% attended a day activity centre for the disabled.[33]

Profound deafness is also associated with substantial costs – in the USA, the expected lifetime cost to society for a child with profound deafness of prelingual onset has been estimated to exceed US$1 million, largely because of the need for special education and because of reduced work productivity.[38]

Current service provision

In the UK, current standard practice is to give 500 IU of intramuscular anti-D IgG within 72 hours of delivery to all RhD-negative women who deliver RhD-positive infants and who are not already sensitised.[4] This dose will cover a TPH of at least 4 ml of fetal red cells (i.e. 99% of all TPHs).[3] The size of any feto-maternal bleed is routinely estimated and a further anti-D dose given if indicated. Any event during pregnancy with the potential to cause sensitisation should also prompt assessment of the feto-maternal bleed 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 (a manual method for inverting a baby in the uterus from the outside).

Currently, take-up of routine AADP is very patchy, with clusters of hospitals in some areas having identical policies. Anti-D suppliers estimate that overall approximately 12% of hospitals are currently using this intervention (Shephard J, product manager, Antibody Therapy, Baxter plc: personal communication, 2001).

Currently, the annual cost in England and Wales of providing 500 IU of anti-D for all RhD-negative women delivered of RhD-positive infants is approximately £1.7 million. This does not include the cost of either administration or additional anti-D required by such women if they have a larger feto-maternal bleed at delivery, nor does it include the cost of anti-D administered to those RhD-negative women who undergo a potential sensitising event during pregnancy.

Description of proposed new intervention

The current UK standard practice of providing prophylactic anti-D is unable to prevent silent sensitisation. It is therefore proposed that routine AADP be provided either to all pregnant women who are RhD-negative or to RhD-negative primigravidae only. The anti-D would be given as two doses at 28 and 34 weeks. It would supplement, rather than replace, current standard practice.

It is likely that the intervention would be administered by midwives, and this is in keeping with the increasing emphasis being placed on midwives as the primary carers of pregnant women. The prime responsibility for ensuring that women understand the implications of the intervention, and consent to it, would therefore rest with the midwives. It should be noted that in many cases these midwives will be based in the community and/or antenatal clinic; the latter group may currently have varying levels of involvement with postnatal anti-D administration. Any move to change practice to routinely offering AADP would thus have significant education and training implications.

Further, there may be an implication for general practitioners (GPs). The prescribing of the anti-D for those women who have most or all of their antenatal care in community settings would probably fall to the woman's GP. Thus GPs would have to be educated with regard to the practice of AADP and the prescription of the drug, and the costs of the anti-D would have to be added to primary care prescribing budgets. The storage of anti-D would have to be considered within the context of community settings since anti-D, as a blood product, requires appropriate storage facilities.

Once the woman's informed consent had been gained, and the anti-D obtained, the actual administration of anti-D in itself would be comparatively straightforward, involving only two intramuscular injections. Side-effects are rare, including short-term discomfort at the injection site and, very rarely, anaphylaxis. There would thus be no need for additional monitoring during the remainder of the pregnancy of women who have received AADP, other than by extending the clinical audit process to include AADP. Also, as with administration of other blood products, scrupulous record-keeping would be essential in order to be able to link individual women with specific batches of anti-D.

Summary of product characteristics

Bio Products Laboratory anti-D immunoglobulin

Bio Products Laboratory (BPL) human anti-D immunoglobulin is licensed for the prevention of antenatal sensitisation in RhD-negative women. The licensed dose for routine antenatal prophylaxis is 500 IU given intramuscularly at 28 and 34 weeks of gestation.[39]

Baxter Healthcare

Baxter anti-D (Rh_0) immunoglobulin, BP Immuno is licensed for the prevention of RhD sensitisation. It is prepared from pooled human venous plasma, using only plasma units which are non-reactive in tests for hepatitis B surface antigen and antibodies to human immunodeficiency virus 1 and 2 (HIV1 and HIV2) and hepatitis C virus. The licensed dose for routine antenatal prophylaxis is 1250 IU given intramuscularly at 28 and 34 weeks' gestation. It is supplied in preloaded syringes.[40]

Chapter 2

Clinical effectiveness

Methods for reviewing effectiveness

Identification of studies

The search strategy used aimed to identify all studies which compared outcomes in RhD-negative women without anti-D antibodies who were given anti-D prophylaxis at 28 weeks or more of pregnancy, and their infants, with control women and their infants. Search strategies included sensitive quality filters to limit results to clinical trials, reviews, guidelines, quality of life studies or economics studies. Date and language restrictions were not used. Searches of the following economic databases were undertaken: MEDLINE (from 1966), EMBASE (from 1980), Best Evidence, Biological Abstracts (from 1985), CINAHL (from 1982), Health Management Information Consortium (HMIC), Science Citation Index (from 1981), Cochrane Database of Systematic Reviews (CDSR), Cochrane Controlled Trials Register (CCTR), the NHS Centre for Reviews and Dissemination (CRD) databases (Database of Abstracts and Reviews of Effectiveness (DARE), NHS Economic Evaluations Database (NHS EED) and HTA) and the Office of Health Economics (OHE) Database (HEED). A search of the last 4 months of PubMED was undertaken on 30 November 2000 to identify recent studies not yet indexed on MEDLINE, and the MEDLINE search was updated in September 2001.

In addition to searches of electronic bibliographic databases, further sources were consulted to identify current research and grey literature. The National Research Register (NRR), MRC (Medical Research Council) Clinical Trials Register, Current Research in Britain (CRIB) and Current Research Worldwide (CRW) databases were searched. The publication lists and current research registers of HTA and guideline-producing agencies and funding and regulatory bodies were also consulted.

The MEDLINE search strategy may be found in appendix 1. Keyword strategies for all other databases are available from the authors.

Inclusion and exclusion criteria

Inclusion criteria

- subjects – pregnant women who are RhD-negative
- intervention – routine antenatal anti-D administration
- comparator – no treatment
- outcome measures – any of:
  - sensitisation rates among women at risk (i.e. RhD-negative women delivered of RhD-positive infants)
  - adverse effects
  - cost
- methodology – any of:
  - systematic reviews
  - randomised controlled trials
  - non-randomised controlled trials
  - economic evaluations.

Exclusion criteria

Studies considered methodologically unsound, or not reporting results in the necessary detail, or not using appropriate dosage regimes were excluded from the meta-analyses but were retained for discussion. Thus no relevant studies were wholly excluded from the review.

Quality assessment strategy

The quality of both randomised and observational studies was assessed using the quality criteria proposed by the NHS CRD.[41] This proved to be a poor means of discriminating between the studies relevant to this review, which used a number of different study designs. Only the question 'were the groups similar at baseline in terms of prognostic factors?' appeared to discriminate meaningfully between studies, and they have therefore been awarded a quality score of good, fair or poor on the basis of this criterion alone. The majority of studies were poor by this standard: only three[42–44] merit classification as good and two[45,46] as fair. Moreover, one of the studies rated as good did not use a licensed dose of anti-D, and was terminated prematurely because the dose was found to be too low.[44] The aspects of all studies which relate to quality have been discussed in more detail both in appendix 2 and in the relevant sections of the report.

Blinding of the quality assessors to author, institution or journal was not considered necessary.[47,48]

Data extraction strategy

Data were extracted by one researcher, and checked by another, using customised data

extraction forms; any disagreements were resolved by discussion.

Where available, the following data will be reviewed:

- number of RhD-negative women found to be sensitised in a subsequent pregnancy as a result of a previous RhD-positive pregnancy
- number of RhD-negative women found to be sensitised during the current pregnancy or within three days of delivery
- number of RhD-negative women found to be sensitised at postnatal follow-up
- total number of RhD-negative women sensitised or sensibilised.

In clinical terms, the most important outcome measure is the number of RhD-negative women delivered of a RhD-positive baby who are found to be sensitised during a subsequent pregnancy. However, not all studies reported this data, thus necessitating the use of data relating to the other outcome measures.

Meta-analysis was undertaken, using MINITAB™ statistical software (Minitab inc., USA; <http://www.minitab.com>) on three groups of studies that were comparable in design and dose of anti-D.

Results

Quantity and quality of research available

Number and type of studies identified

The electronic literature searches identified 599 potentially relevant articles. Of these, eleven articles related to ten trials of the clinical effectiveness of routine AADP which made a comparison with a control group (see *Figure 1*). These studies included six non-randomised trials with historical or geographical controls,[45,49–53] one randomised controlled trial (RCT),[44] one quasi-RCT,[42] one community intervention trial (controlled before-and-after study)[43] and one retrospective before-and-after study.[46] A follow-up study[54] to one of the non-randomised trials[45] studied the safety and efficacy of antenatal prophylaxis by examining obstetric data relating to women in the trial in the first and subsequent pregnancies.

An additional retrospective study was found subsequent to the literature searching; this was published in abstract form only.[55]

The electronic searches identified eight articles relating to seven studies that related to the cost or cost-effectiveness of AADP;[43,45,56–61] two of these[43,45] were also studies of clinical effectiveness, and are listed as such above.[43,45] An additional occasional paper[62] was also identified.

Only one quasi-RCT was found that used a dosage that is currently considered appropriate;[42] the only true RCT that was found used a lower dose.[44] The non-randomised studies have therefore been retained for further consideration. Many of these studies were poorly designed. The greatest concerns arise in relation to the comparability of the intervention and control groups: although the larger unrandomised studies were probably large enough to ensure comparability in terms of ABO distribution and maternal age, the use of non-contemporary or geographically distant controls is an issue in a number of studies (see further below). The lack of blinding is less problematic given the objective nature of the main outcome measure (the presence/absence of anti-D). For further details of studies, see *Table 3* and appendix 2.

The studies varied in terms of their patient selection criteria and dosage regimes.

Six studies[42–46,49] recruited the intervention group from primigravidae. Four of these studies[43,45,46,49] also recorded data relating to those women in subsequent pregnancies. In three cases this was done in order to assess the prevalence of sensitisation arising from the first pregnancy, and in only one study[45,54] were data also provided relating to the incidence of sensitisation resulting from subsequent RhD-positive pregnancies in which AADP was not provided.

Four studies[50–53] certainly, and a fifth study[55] probably, recruited both primigravidae and unsensitised multigravidae.

All studies compared routine AADP with no routine AADP; none used placebo. The dose of anti-D used varied six-fold between studies, from two doses of 1500 IU to two doses of 250 IU. The two dosage regimes most commonly used were 500 IU at 28 and 34 weeks' gestation, or a single dose of 1500 IU at 28 weeks. The studies fell into five groups in terms of dose and administration schedule:

- 2 × 1500 IU (28 and 34 weeks)[49]
- 1 × 1500 IU (28 weeks)[50–52]
- 1 × 1250 IU (34 weeks)[53]

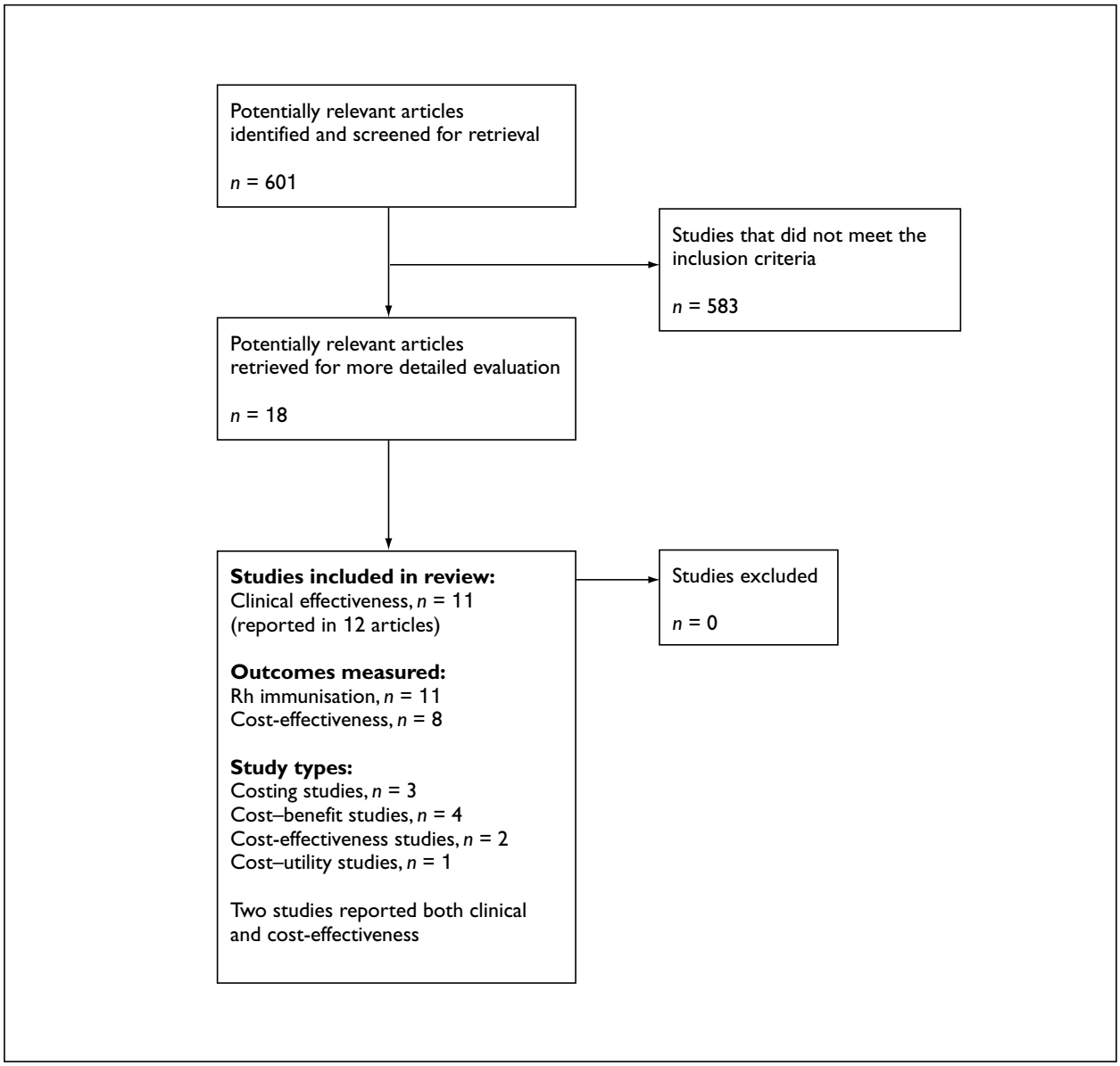

FIGURE 1 *Summary of study selection and exclusion*

- 2 × 500 IU (28 and 34 weeks)[42,43,45,46]
- 2 × 250 IU (28 and 34 weeks).[44]

The eleventh study provided prophylaxis at 28 weeks only;[55] whilst this is not stated, it is most probable that this used the standard Canadian dose of 1500 IU.

Four studies stated that the anti-D was given intramuscularly,[42,45,50,53] and one that it was usually given intravenously although it could be given intramuscularly.[51] The remainder did not state what route was used. In nine studies, women in both the intervention and control groups who were delivered of RhD-positive infants were said to have received post-partum anti-D; in two studies,[50,55] this was not explicitly stated.

Only five studies had contemporary controls – the randomised[44] and quasi-randomised[42] trials, a community intervention trial,[43] a comparative study,[49] and a retrospective study.[55] 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 isoimmunisation in the control group and thus also to underestimate the degree of protection provided by the intervention.[2] However, in the community intervention trial (controlled before-and-after study) referred to above,[43] a retrospective analysis of prospectively collected data was used to demonstrate the comparability at baseline, in terms of rates of iso-

TABLE 3 *Characteristics of included studies of clinical effectiveness*

Study	Study type	Date and location of intervention	Date and location of controls	Patient selection	Dosage used	Source of funding
Bowman *et al.*, 1978[49]	Prospective study, historic/geographic controls	Dec 1968–Aug 1976 Winnipeg, Canada	Mar 1967–Dec 1974 Manitoba, Canada	Primigravidae	2 x 1500 IU 28 and 34 weeks	National Health and Medical Research Council of Canada
Bowman and Pollock, 1978[50]	Prospective study, historic controls	Mar 1976–Jun 1977 Manitoba, Canada	Mar 1967–Dec 1974 Manitoba, Canada	Primigravidae and unsensitised multigravidae	1500 IU 28 weeks	Not stated
Bowman and Pollock, 1987[51]	Retrospective study, historic controls	Jun 1977–Feb 1986 Manitoba, Canada	Mar 1967–Dec 1974 Manitoba, Canada	Primigravidae and unsensitised multigravidae	1500 IU 28 weeks	Not stated
Trolle, 1989[52]	Prospective study, historic controls	1980–1985 Kolding, Denmark	1972–1977 Kolding, Denmark	Primigravidae and unsensitised multigravidae	1500 IU 28 weeks	Not stated
Parsons *et al.*, 1998[55]	Retrospective survey, geographical controls	1988–1995 Nova Scotia, Canada	1988–1995 Scotland, UK	Not stated	Not stated	Not stated
Hermann *et al.*, 1984[53]	Prospective study, historic controls	Not stated Växjö, Sweden	1968–1977 Växjö, Sweden	Primigravidae and unsensitised multigravidae	1250 IU 34 weeks	Not stated
Tovey *et al.*, 1983[45]	Prospective study, historic controls	1980–1981 Yorkshire, UK	1978–1979 Yorkshire, UK	Primigravidae	2 x 500 IU 28 and 34 weeks	Not stated
Huchet *et al.*, 1987[42]	Quasi-RCT	Jan 1983–Jun 1984 Paris, France	Jan 1983–Jun 1984 Paris, France	Primigravidae	2 x 500 IU 28 and 34 weeks	Not stated
Mayne *et al.*, 1997[46]	Retrospective survey (before-and-after)	1993–1995 Southern Derbyshire, UK	1988–1990 Southern Derbyshire, UK	Primiparae	2 x 500 IU 28 and 34 weeks	Bio Products Laboratory
MacKenzie *et al.*, 1999[43]	Community intervention trial	1990–1996 Oxfordshire, UK	1990–1996 Northants, UK	Primiparae	2 x 500 IU 28 and 34 weeks	Bio Products Laboratory
Lee and Rawlinson, 1995[44]	RCT	Not stated UK	Not stated UK	Primigravidae	2 x 250 IU 28 and 34 weeks	Not stated

immunisation, of the two communities compared in the prospective study. It also showed that the rate of isoimmunisation in the control group fell substantially over time, although not to the same extent as in the intervention group. The change over time seen in the control group was 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 routine antenatal anti-D when compared with current good practice.

One study which purported to be a community intervention trial with contemporary controls[49] combined the results for that control group with those of a geographically contiguous group of women during an overlapping but not identical time period (Bowman JM, 231 Handsart Boulevard, Winnipeg, MB, Canada: personal communi-

cation, 2001). As pre-intervention data were not provided for the two groups, it is not clear to what extent they were in fact comparable. As the intervention group was a city population while 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. In addition, the two groups 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 had apparently not resulted in isoimmunisation, they may in some cases have resulted in sensibilisation (see page 1).

Although most TPHs large enough to cause sensitisation occur in the last trimester, some women become isoimmunised before the 28th week. The studies reviewed in this report varied in their handling of such cases. One study excluded women sensitised by the 28th week from both the intervention and the control group.[44] In another study, women who were isoimmunised between the first antibody screen test in the first trimester and the 28th week were excluded from the intervention group but apparently not from the control group.[52] In addition, in this study 38.8% of women in the control group had received more than 1 µl of fetal blood, compared with only 7.9% in the intervention group ($p < 0.001$). In a third study,[53] women who were isoimmunised between the first antibody screen test in the first trimester and the 32nd–34th week were excluded from the intervention group; it is not clear whether the control group was similarly screened at 32–34 weeks.

Although the true rate of isoimmunisation is greater than that identified by the presence of anti-D at, or 6 months following, delivery (see page 1), only four studies provided data on the number of women found to be sensitised during a subsequent pregnancy.[43,46,49,53]

Number and type of studies included

Eleven studies have been included in this report, despite variations in design, patient selection criteria, dosage, and choice of outcome measure.

Number and type of studies excluded, with reasons for specific exclusions

No apparently relevant studies have been entirely excluded from the report. However, as indicated earlier in this chapter (see 'Number and type of studies identified', page 10), the differences between the studies were such that direct comparisons between them were not always possible, and not all data from all the studies have been used.

Tabulation of quality of studies, characteristics of studies and evidence rating

A brief summary of the characteristics of the 11 studies is included in *Table 3*. Fuller details are presented in appendix 2. In describing participants as primigravidae or primiparae, the wording used by the original authors has been followed. It is recognised that, because women may not always reveal details of previous pregnancies, information on parity is likely to be the more reliable.

Tabulation of results

Outcome measures

As noted earlier in this chapter, the studies reviewed here varied in the doses and the administration schedule of anti-D, and in 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 routine antenatal anti-D 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. Only two studies had this as their primary end-point[43,46] and, as these were both community-based studies, their results could and did include women who in fact did **not** receive AADP in the first pregnancy.

Three other studies 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[49,53,45] (see *Table 4*). In another study, it was not clear at what point sensitisation was measured.[55]

It is noticeable that, in the British studies, the number of RhD-negative women delivered of RhD-positive infants in the control group who were found to be sensitised during a subsequent RhD-positive pregnancy fell over time. This has been assumed to be due to the growth of good practice in the delivery of anti-D both post-partum and antenatally, in response to potential sensitising events. However, in one study it was noted that the introduction of an AADP programme was associated with an increase in requests for anti-D following vaginal bleeding or antepartum haemorrhage; this was conjectured to be due to heightened awareness among midwives and community doctors, and

TABLE 4 *Summary of trial results: women found to be sensitised in a subsequent pregnancy as a result of a previous pregnancy*

Study	Study design	Dosage	Anti-D prophylaxis group					Control group				
			n	*r*	% sensitised	Upper 95% CI	Lower 95% CI	*n*	*r*	% sensitised	Upper 95% CI	Lower 95% CI
Bowman *et al.*, 1978[49]	NRCT	2 x 1500 IU (28 and 34 weeks) (initially at 34 weeks only)	343	0	0.0	0.0	0.0	No data				
Hermann *et al.*, 1984[53]	NRCT	1 x 1250 IU (34 weeks)	39	0	0.0	0.0	0.0	No data				
Tovey *et al.*, 1983[45]	NRCT	2 x 500 IU (28 and 34 weeks)	325	No data				582	11	1.9	3.0	0.8
Mayne *et al.*, 1997[46]	Before and after	2 x 500 IU (28 and 34 weeks)	1425	4	0.3	0.6	0.0	1426	16	1.1	1.7	0.6
MacKenzie *et al.*, 1999[43]	NRCT	2 x 500 IU (28 and 34 weeks)	3320	12	0.4	0.6	0.2	3146	26	0.8	1.1	0.5

n = number of RhD-negative women in the trial group undergoing subsequent pregnancy with a RhD-positive infant
r = number of sensitised RhD-negative women in the trial group

may have contributed to reducing the overall sensitisation rate in the intervention group.[46]

Other outcome measures used in the studies were sensitisation during pregnancy or within 3 days of delivery, and sensitisation at postnatal follow-up. Data relating to sensitisation at these different dates are tabulated in *Tables 5* and *6*. As these figures differ, an attempt has been made in *Table 7* to estimate the total number of women in each study who had been sensitised or sensibilised. However, only one study stated the total number of women found to be sensitised at either delivery or 6-month follow-up.[44] In the remaining studies, with the exception of the studies by Mayne and co-workers[46] and MacKenzie and co-workers[43] noted above, the figures in *Table 7* may therefore be lower than the true prevalence of sensitisation at 6 months as the extent of over-lap between the women with demonstrable antibodies at delivery and at follow-up is not clear. These studies are likely have underestimated the numbers of women who would be found to be sensitised were they to become pregnant again.

Presentation of results

The studies also varied in the results which they presented. Eight[42,44,45,49–53] reported, in effect, the aggregated results of treating individual women. Although one of these[50] set out to describe the results of providing antenatal prophylaxis on a Canadian province-wide basis, it in fact only presented the results for those women who received this prophylaxis, and these were stated to be only 89% of those at risk. In addition, as noted above, some studies screened women for antibodies prior to inclusion, and gave no indication of the numbers who were excluded from the study on this basis.[44,52,53]

Studies which only include data relating to women known to have received the intervention, and to have received it prior to sensitisation, will provide an indication of the clinical effectiveness of routine AADP, 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 three of the 11 studies were of this nature.[43,46,55] In one case,[46] although prophylaxis was given only to primigravidae and to those with no living children (presumably as a measure to increase cost-effectiveness as they are the most likely to have further pregnancies), the results were presented for all women 'at risk' (i.e. RhD-negative, having a second or subsequent pregnancy), thus indicating the overall efficacy of the programme. This programme was said to reach most RhD-negative primiparae in the area. In the second study, it was not specified whether prophylaxis was given to all women or only to primigravidae but, in the absence of any statement to the contrary, and as results appear to be have been presented for all women, it seems most likely that it was given to unselected women.[55] In the third study,[43] prophylaxis was given to all non-sensitised pregnant RhD-negative nulliparae, and the results were reported in terms of numbers of women found to be sensitised in their next pregnancy.

It is not surprising that the results obtained by these community intervention studies differ from the others, since they will have included in their intervention group a number of untreated women while the other studies will not have done so. Two of the community intervention studies[43,46] also reported the effect of a policy of AADP in primigravidae on the numbers of women found to be sensitised in subsequent pregnancies, but in both studies these numbers could theoretically also include women sensitised early in their second as well as in their first pregnancy. It is not clear at what point the third study[55] identified the number of women sensitised.

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 prophylactic anti-D. Thus one study stated that two women in the intervention group who had weak antibodies 8 months after delivery had been isoimmunised, although no antibodies could be detected at 14 and 20 months respectively after delivery; one woman in the control group had comparably weak antibodies at 8 months.[53] Another study excluded such cases from the analysis on the grounds that, rather than representing isoimmunisation, they resulted from the prophylaxis.[49] One study excluded from analysis women in the intervention group who were sensitised before receiving prophylaxis,[53] whereas some other studies[50,51] included such women as logistic failures of prophylaxis. For comparability with the community studies, when studies state the number of sensitised women who have been excluded from the authors' analyses, these have been included in the overall figures of numbers of women sensitised displayed in *Table 8*. *Table 9* provides details of the numbers of women excluded from the authors' analyses,

TABLE 5 *Summary of trial results: women sensitised during pregnancy or within 3 days of delivery*

Study	Study design	Dosage	Patient selection	Anti-D prophylaxis group					Control group				
				n	*r*	% sensitised	Upper 95% CI	Lower 95% CI	*n*	*r*	% sensitised	Upper 95% CI	Lower 95% CI
Bowman *et al.*, 1978[49]	NRCT	2 x 1500 IU (28 and 34 weeks; initially at 34 weeks only)	Primigravidae	1357	1	0.1	0.3	0.0	2768	45	1.6	2.1	1.2
Bowman and Pollock, 1978[50]	NRCT	1 x 1500 IU (28 weeks)	Unselected	1804	5	0.3	0.5	0.0	3533	62	1.8	2.2	1.3
Bowman and Pollock, 1987[51]	NRCT	1 x 1500 IU (28 weeks)	Unselected	9303	18	0.2	0.3	0.1	3533	62	1.8	2.2	1.3
Trolle, 1989[52]	NRCT	1 x 1500 IU (28 weeks)	Unselected	346	No data				354	No data			
Parsons *et al.*, 1998[55]	NRCT	? 1500 IU (28 weeks)	Unselected	9684	No data				No data				
Hermann *et al.*, 1984[53]	NRCT	1 x 1250 IU (34 weeks)	Primigravidae	236	0	0.0	0.0	0.0	286	3	1.7	3.3	0.2
			Multigravidae	332	0	0.0	0.0	0.0	359	7	1.4	2.6	0.2
			Unselected	568	0	0.0	0.0	0.0	645	10	1.6	2.5	0.6
Tovey *et al.*, 1983[45]	NRCT	2 x 500 IU (28 and 34 weeks)	Primigravidae	1238	2	0.2	0.4	0.0	2000	18	0.9	1.3	0.5
			Multigravidae	325	2	0.6	1.5	0.0	582	11*	1.9	3.1	0.8
			Unselected	1563	4	0.3	0.6	0.0	2582	29	1.1	1.5	0.7
Huchet *et al.*, 1987[42]	RCT	2 x 500 IU (28 and 34 weeks)	Primigravidae	461	0	0.0	0.0	0.0	454	4	0.9	1.7	0.0
			Multigravidae	138	1	0.7	2.1	0.0	136	2	1.5	3.5	0.0
			Unselected	599	1	0.2	0.5	0.0	590	6	1.0	1.8	0.2
Mayne *et al.*, 1997[46]	Before and after	2 x 500 IU (28 and 34 weeks)	Primiparae	No data					No data				
MacKenzie *et al.*, 1999[43]	NRCT	2 x 500 IU (28 and 34 weeks)	Primiparae	No data					No data				
Lee and Rawlinson, 1995[44]	RCT	2 x 250 IU (28 and 34 weeks)	Primigravidae	513	4	0.8	1.5	0.0	595	7	1.2	2.0	0.3

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

TABLE 6 *Summary of trial results: women sensitised at postnatal follow-up*

Study	Study design	Dosage	Patient selection	Anti-D prophylaxis group					Control group				
				n	*r*	% sensitised	Upper 95% CI	Lower 95% CI	*n*	*r*	% sensitised	Upper 95% CI	Lower 95% CI
Bowman *et al.*, 1978[49]	NRCT	2 x 1500 IU (28 and 34 weeks; initially at 34 weeks only)	Primigravidae	1004	1	0.1	0.3	0.0	2768*	45	1.6	2.1	1.2
Bowman and Pollock, 1978[50]	NRCT	1 x 1500 IU (28 weeks)	Unselected	807	No data				3533*	50	1.4	1.8	1.0
Bowman and Pollock, 1987[51]	NRCT	1 x 1500 IU (28 weeks)	Unselected	9303*	25	0.3	0.4	0.2	3533*	50	1.4	1.8	1.0
Trolle, 1989[52]	NRCT	1 x 1500 IU (28 weeks)	Unselected	291	0	0.0	0.0	0.0	322	6	1.9	3.3	0.4
Parsons *et al.*, 1998[55]	NRCT	1500 IU (assumed) (28 weeks)	Not stated	9684	No data				No data				
Hermann *et al.*, 1984[53]	NRCT	1 x 1250 IU (34 weeks)	Primigravidae	236*	1	0.4	1.3	0.0	286*	5	1.7	3.3	0.2
			Multigravidae	332*	1	0.3	1.0	0.0	359*	5	1.4	2.6	0.2
			Unselected	568*	2	0.4	0.9	0.0	645*	10	1.6	2.5	0.6
Tovey *et al.*, 1983[45]	NRCT	2 x 500 IU (28 and 34 weeks)	Primigravidae	1059	2	0.2			No data	No data			
			Multigravidae	No data	No data	0.5							
			Unselected			0.0							
Huchet *et al.*, 1987[42]	RCT	2 x 500 IU (28 and 34 weeks)	Primigravidae	362	0	0.0	0.0	0.0	360	4	1.1	2.2	0.0
			Multigravidae	110	1	0.9	2.7	0.0	108	3	2.8	5.9	0.0
			Unselected	472	1	0.2	0.6	0.0	468	7	1.5	2.6	0.4
Mayne *et al.*, 1997[46]	Before and after	2 x 500 IU (28 and 34 weeks)	Primiparae	No data					No data				
MacKenzie *et al.*, 1999[43]	NRCT	2 x 500 IU (28 and 34 weeks)	Primiparae	No data					No data				
Lee and Rawlinson, 1995[44]	RCT	2 X 250 IU (28 and 34 weeks)	Primigravidae	361	3	0.8	1.8	0.0	405	7	1.7	3.0	0.5

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

TABLE 7 *Summary of trial results: overall percentage of women sensitised or sensibilised (authors' figures)*

Study	Study design	Dosage	Patient selection	Anti-D prophylaxis group					Control group				
				n	*r*	% sensitised or sensibilised	Upper 95% CI	Lower 95% CI	*n*	*r*	% sensitised or sensibilised	Upper 95% CI	Lower 95% CI
Bowman *et al.*, 1978[49]	NRCT	2 x 1500 IU (28 and 34 weeks; initially at 34 weeks only)	Primigravidae	1357*	1	0.1	0.3	0.0	2768	45	1.6	2.1	1.2
Bowman and Pollock, 1978[50]	NRCT	1 x 1500 IU (28 weeks)	Unselected	1804	5	0.3	0.5	0.0	3533	62	1.8	2.2	1.3
Bowman and Pollock, 1987[51]	NRCT	1 x 1500 IU (28 weeks)	Unselected	9303	25	0.3	0.4	0.2	3533	62	1.8	2.2	1.3
Trolle, 1989[52]	NRCT	1 x 1500 IU (28 weeks)	Unselected	346	0	0.0	0.0	0.0	354	6	1.7	3.0	0.4
Parsons *et al.*, 1998[55]	NRCT	1500 IU (assumed) (28 weeks)	Not stated	9684	72	0.7	0.9	0.6	No data	No data	0.8		
Hermann *et al.*, 1984[53]	NRCT	1 x 1250 IU (34 weeks)	Primigravidae	236	1	0.4	1.3	0.0	286	5	1.7	3.3	0.2
			Multigravidae	332	1	0.3	1.0	0.0	359	7	1.4	2.6	0.2
			Unselected	568	2	0.4	0.9	0.0	645	12	1.9	2.9	0.8
Tovey *et al.*, 1983[45]	NRCT	2 x 500 IU (28 and 34 weeks)	1st pregnancy	1238	4†	0.3	0.6	0.0	2000	19†	1.0	1.4	0.5
			2nd pregnancy	604†	1†	0.2	0.5	0.0	582	9†‡	1.5	2.5	0.5
			All pregnancies	2037†	6†	0.3	0.5	0.1	2721†	32†	1.2	1.6	0.8
Huchet *et al.*, 1987[42]	RCT	2 x 500 IU (28 and 34 weeks)	Primiparae	461	0	0.0	0.0	0.0	454	4	0.9	1.7	0.0
			Multiparae	138	1	0.7	2.1	0.0	136	3	2.2	4.7	0.0
			Unselected	599	1	0.2	0.5	0.0	590	7	1.2	2.1	0.3
Mayne *et al.*, 1997[46]	Before and after	2 x 500 IU (28 and 34 weeks)	Primiparae	1425	4	0.3	0.6	0.0	1426	16	1.1	1.7	0.6
MacKenzie *et al.*, 1999[43]	NRCT	2 x 500 IU (28 and 34 weeks)	Primiparae	3320	12	0.4	0.6	0.2	3146	26	0.8	1.1	0.5
Lee and Rawlinson, 1995[44]	RCT	2 x 250 IU (28 and 34 weeks)	Primigravidae	513	5	1.0	1.8	0.1	595	9	1.5	2.5	0.5

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*

* *153 received only one dose, at 28 or 34 weeks*
† *Data from Thornton* et al., *1989*[54]
‡ *For comparability with other studies, this figure excludes those women who developed antibodies in a previous pregnancy but were retained in the study*

TABLE 8 *Summary of trial results: overall percentage of women sensitised or sensibilised including, where possible, women excluded from published analyses for various reasons*[*] *(see* Table 10*)*

Study	Study design	Dosage	Patient selection	Anti-D prophylaxis group					Control group				
				n	*r*	% sensitised or sensibilised	Upper 95% CI	Lower 95% CI	*n*	*r*	% sensitised or sensibilised	Upper 95% CI	Lower 95% CI
Bowman *et al.*, 1978[49]	NRCT	2 x 1500 IU (28 and 34 weeks) (initially at 34 weeks only)	Primigravidae	1357[†]	1	0.1	0.3	0.0	2768 (includes multi-gravidae)	45	1.6	2.1	1.2
Bowman & Pollock, 1978[50]	NRCT	1 x 1500 IU (28 weeks)	Unselected	1806	11	0.6	1.0	0.3	3533	62	1.8	2.2	1.3
Bowman & Pollock, 1987[51]	NRCT	1 x 1500 IU (28 weeks)	Unselected	9295	30	0.3	0.4	0.2	3533	62	1.8	2.2	1.3
Trolle, 1989[52]	NRCT	1 x 1500 IU (28 weeks)	Unselected	346	0	0.0	0.0	0.0	354	6	1.7	3.0	0.4
Parsons *et al.*, 1998[55]	NRCT	1500 IU (assumed) (28 weeks)	Not stated	9684	72	0.7	0.9	0.6	No data	No data	0.8		
Hermann *et al.*, 1984[53]	NRCT	1 x 1250 IU (34 weeks)	Primigravidae	236	4	1.7	3.3	0.0	286	5	1.7	3.3	0.2
			Multigravidae	332	1	0.3	1.0	0.0	359	7	1.4	2.6	0.2
			Unselected	568	5	0.9	1.6	0.1	645	12	1.9	2.9	0.8
Tovey *et al.*, 1983[45]	NRCT	2 x 500 IU (28 and 34 weeks)	1st pregnancy	1238	4[‡]	0.3	0.6	0.0	2000	19[‡]	1.0	1.4	0.5
			2nd pregnancy	604[‡]	1[‡]	0.2	0.5	0.0	582	9[‡,§]	1.5	2.5	0.5
			All pregnancies	2037[‡]	6[‡]	0.3	0.5	0.1	2721[‡]	32[‡]	1.2	1.6	0.8
Huchet *et al.*, 1987[42]	RCT	2 x 500 IU (28 and 34 weeks)	Primiparae	461	0	0.0	0.0	0.0	454	4	0.9	1.7	0.0
			Multiparae	138	1	0.7	2.1	0.0	136	3	2.2	4.7	0.0
			Unselected	599	1	0.2	0.5	0.0	590	7	1.2	2.1	0.3
Mayne *et al.*, 1997[46]	Before and after	2 x 500 IU (28 and 34 weeks)	Primiparae	1425	4	0.3	0.6	0.0	1426	16	1.1	1.7	0.6
MacKenzie *et al.*, 1999[43]	NRCT	2 x 500 IU (28 and 34 weeks)	Primiparae	3320	12	0.4	0.6	0.2	3146	26	0.8	1.1	0.5
Lee & Rawlinson, 1995[44]	RCT	2 x 250 IU (28 and 34 weeks)	Primigravidae	513	5	1.0	1.8	0.1	595	9	1.5	2.5	0.5

[*] *This information is not available for Trolle, 1989,*[52] *Huchet,* et al., *1987*[42] *and Lee and Rawlinson, 1995*[44]

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*

[†] *153 received only one dose, at 28 or 34 weeks*
[‡] *Data from Thornton* et al., *1989*[54]
[§] *For comparability with other studies, this figure excludes those women who developed antibodies in a previous pregnancy but were retained in the study*

TABLE 9 *Women sensitised in intervention groups*

Study	Number of women in intervention group sensitised or sensibilised (included and excluded from authors' analyses)	Comments
Bowman *et al.*, 1978[49]	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 6 months of the study, an unspecified number of women became isoimmunised before 34 weeks; these were not included in the authors' analysis
Bowman and Pollock, 1978[50]	5	Two women were sensitised before 28 weeks; one multigravida may have been sensibilised as a result of an earlier abortion when no anti-D was given or may have been sensitised before receiving prophylaxis at 29 weeks in the current pregnancy, and two more multigravidae may either have been sensibilised in a previous pregnancy or may represent failures of prophylaxis
	6	In addition, two primigravidae appeared to have been sensitised prior to what they stated was their first pregnancy; three multigravidae appeared to have been sensibilised by an earlier pregnancy, and one had received a RhD-positive blood transfusion: these were all excluded from the authors' analysis
Bowman and Pollock, 1987[51]	25	13 failures of prophylaxis 4 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 sensitised by 28 weeks – possibly sensibilised in an earlier pregnancy
	5	In addition, five women who appeared to have been sensibilised in a previous pregnancy were excluded from the authors' analysis
Trolle, 1989[52]	0	No women included in the author's analysis were sensitised
	Unspecified number	An unspecified number of women who had been sensitised by 28 weeks were excluded from the study
Parsons *et al.*, 1998[55]	72	2 were sensitised before the protocol was established 2 refused prophylaxis 1 data incomplete 26 sensitised by 28 weeks 14 developed antibodies despite antenatal prophylaxis 9 developed antibodies despite post-partum prophylaxis 18 presumably failed to receive prophylaxis at the appropriate time (7 at 28 weeks, 1 post-partum, 9 post-abortion and 1 post-amniocentesis)
Hermann *et al.*, 1984[53]	2	One primigravida and one multigravida had weak antibodies 8 months after delivery which had disappeared by 14 and 20 months respectively after delivery
	3	In addition, three primiparae were sensitised before receiving prophylaxis: they were excluded from the authors' analysis
Tovey *et al.*, 1983[45]	5	All seem due to failures of prophylaxis, though two women sensitised during their first pregnancy had low but persisting levels of antibodies which might possibly be rare 'naturally occurring' anti-D

continued

***TABLE 9* contd** *Women sensitised in intervention groups*

Study	Number of women in intervention group sensitised or sensibilised (included and excluded from authors' analyses)	Comments
Huchet *et al.*, 1987[42]	1	Apparently a failure of prophylaxis – the woman in question had received anti-D during a previous pregnancy which was terminated for therapeutic reasons
Mayne *et al.*, 1997[46]	4	Three women had previously delivered in places where routine antenatal prophylaxis was unlikely One had not received prophylaxis during her first pregnancy despite the existence of a programme of routine antenatal prophylaxis
MacKenzie *et al.*, 1999[43]	12	Six women were delivered of their first pregnancy outside Oxfordshire: four certainly, and two possibly, did not receive antenatal prophylaxis during that pregnancy One woman had undergone a potential sensitising event at 18 weeks for which anti-D may not have been given One woman, who delivered at 37 weeks, had undergone a large feto-maternal haemorrhage probably at 35 weeks. Routine prophylaxis had been given at 29 and 35 weeks Four women had received prophylaxis at 28 and 34 weeks and did not appear to have suffered an incident likely to provoke a feto-maternal haemorrhage
Lee and Rawlinson, 1995[44]	5	In one case, sensitisation was attributed to a potentially sensitising event for which anti-D was not given Four cases appeared to be failures of prophylaxis Participants were recruited specifically from women free of anti-D (other than passive) at 28 weeks; the number of women who failed to meet this criterion is not stated

and the reasons for this, together with information relating to the other sensitised women.

The studies were broadly comparable in terms of the percentage of isoimmunised women in their control groups: this ranged from 1.2–1.9% in unselected groups, 0.8–1.7% in primiparae and 1.4–1.9% in multiparae. In one study,[43] there was a 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. This reduction, although not statistically significant, was unexpected and unexplained; it was stated that it was not due to the use of antenatal prophylaxis in some women.

In all studies, the proportion of women sensitised was lower in the intervention arm than in the control arm. However, the difference varied between studies. In some instances this could be attributed to either the dose or the schedule used. In two studies, the investigators found 34 weeks to be too late for routine prophylaxis. In one of these, three out of four primiparae who were sensitised already had antibodies by 34 weeks, leading the authors to conclude that immunisation at 28 weeks might have been more effective.[53] Another study, which initially gave 1500 IU at 34 weeks only, introduced an additional dose at 28 weeks because of evidence that some women were becoming isoimmunised before 34 weeks.[49] A third study (published in abstract only),[55] in which the proportion of women sensitised in the intervention group barely differed from that in the control group, offered no explanation for this. However, as it used geographical controls, the possibility cannot be excluded that the results reflect different obstetric practices in the two countries.

Meta-analysis of clinical effectiveness

Meta-analysis was conducted on three groups of studies:

- Group 1 includes the results of the four studies[42,43,45,46] (one randomised, three non-randomised) that used a dosage regime of 500 IU at 28 weeks and 34 weeks and that reported results for primigravidae.

- Group 2 includes the results of the three studies[50–52] (none of them randomised) that used a dosage regime of 1500 IU at 28 weeks. These studies included both primigravidae and multigravidae.
- Group 3 includes the results of the two community-based UK studies[43,46] that used a dosage regime of 500 IU at 28 weeks and 34 weeks and reported results for primigravidae. These are deemed to be the most representative for the cost-effectiveness analysis.

Meta-analysis was conducted using MINITAB™ statistical software. Binary logistic regression was conducted using a fixed effects model. This used the study and treatment groups as the variables for the model. The outcome of the regression analysis was an odds ratio for the treatment arm versus the control arm. Due to the low event probability, the odds ratio was assumed to be a good approximation of the relative risk of sensitisation in the cohort that received AADP, compared with the relative risk of sensitisation in patients who received conventional management.

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 10*), the trials showed a remarkable consistency in results, even between dosage regimes. Consequently, the results of the meta-analysis of group 3 trials[43,46] were deemed to give a representative reflection of the actual effectiveness of AADP, and these figures were used in the economic evaluation.

Sensitisation rates for the conventional management groups were calculated using the average of the sensitisation event probabilities estimated in the logistic regression model, and applying these to each study. Within group 2, the study by Bowman and Pollock (1987)[51] used the same control arm results as their study of 1978.[50] 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-analysis are shown in *Table 10*; the results of the meta-analysis for study groups 1, 2 and 3 are shown in *Figures 2, 3* and *4*, respectively.

Comparison of dosage regimens

The point estimate for sensitisation in the routine AADP group, obtained by pooling the data from those studies which explicitly stated that they used one dose of 1500 IU at 28 weeks,[50–52] is 0.34%. In comparison, the single study that used two doses of 1500 IU at 28 and 34 weeks[49] reported a rate of 0.1%. Although this suggests that, as one might expect, a single dose of 1500 IU is less effective than two, there are no trials that directly compare the two regimes. One study suggested that one dose (presumably of 1500 IU) at 28 weeks offers virtually no protection;[55] as this study only reported the sensitisation rate (not the numbers of patients) for the control group, its results cannot be included in the pooled data. Moreover, their inclusion would not necessarily be appropriate since, as noted above, this study had a relatively weak design, comparing intervention and control groups taken from different continents.

In theory, two doses of 500 IU at 28 and 34 weeks should 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.[2] The

TABLE 10 *Results of the meta-analyses*

	Group 1,[42,43,45,46] 2 x 500 IU primagravidae	**Group 2,[50–52] 1 x 1500 IU unselected**	**Group 3,[43,46] 2 x 500 IU primagravidae**
Test for heterogeneity (*p* value)	0.812	0.940	0.976
Odds ratio of sensitisation with antenatal prophylaxis (95% CI)	0.33 (0.20 to 0.55)	0.20 (0.13 to 0.29)	0.37 (0.21 to 0.65)
Sensitisation rate of control group (%) (95% CI)	0.89 (0.21 to 1.56)	1.60 (0.37 to 2.83)	0.95 (0.18 to 1.71)
Sensitisation rate of antenatal prophylaxis group using meta-analysis (%) (95% CI)	0.30 (0.22 to 0.38)	0.34 (0.28 to 0.40)	0.35 (0.29 to 0.40)

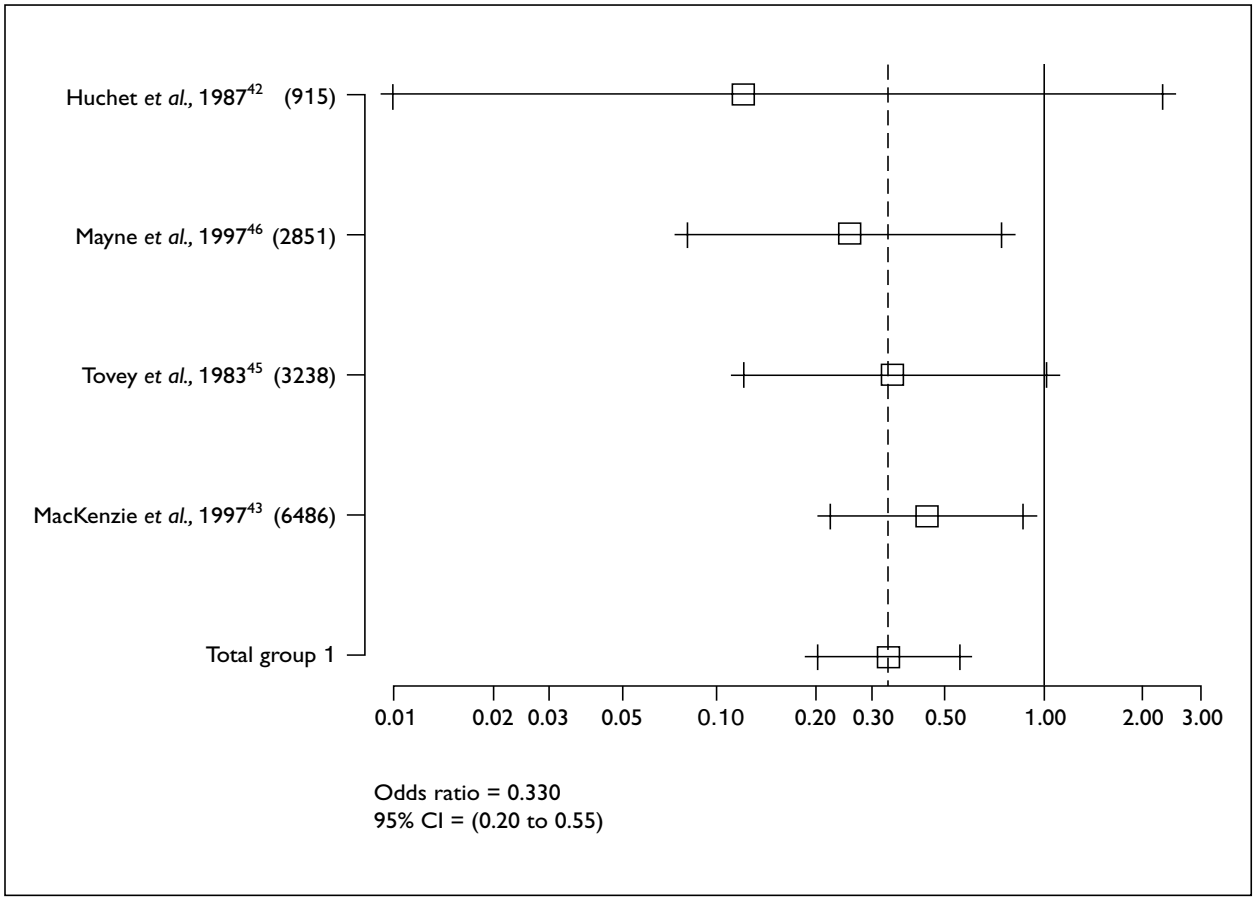

FIGURE 2 *Group 1: 2 x 500 IU in RhD-negative primigravidae (trial population is given in brackets)*

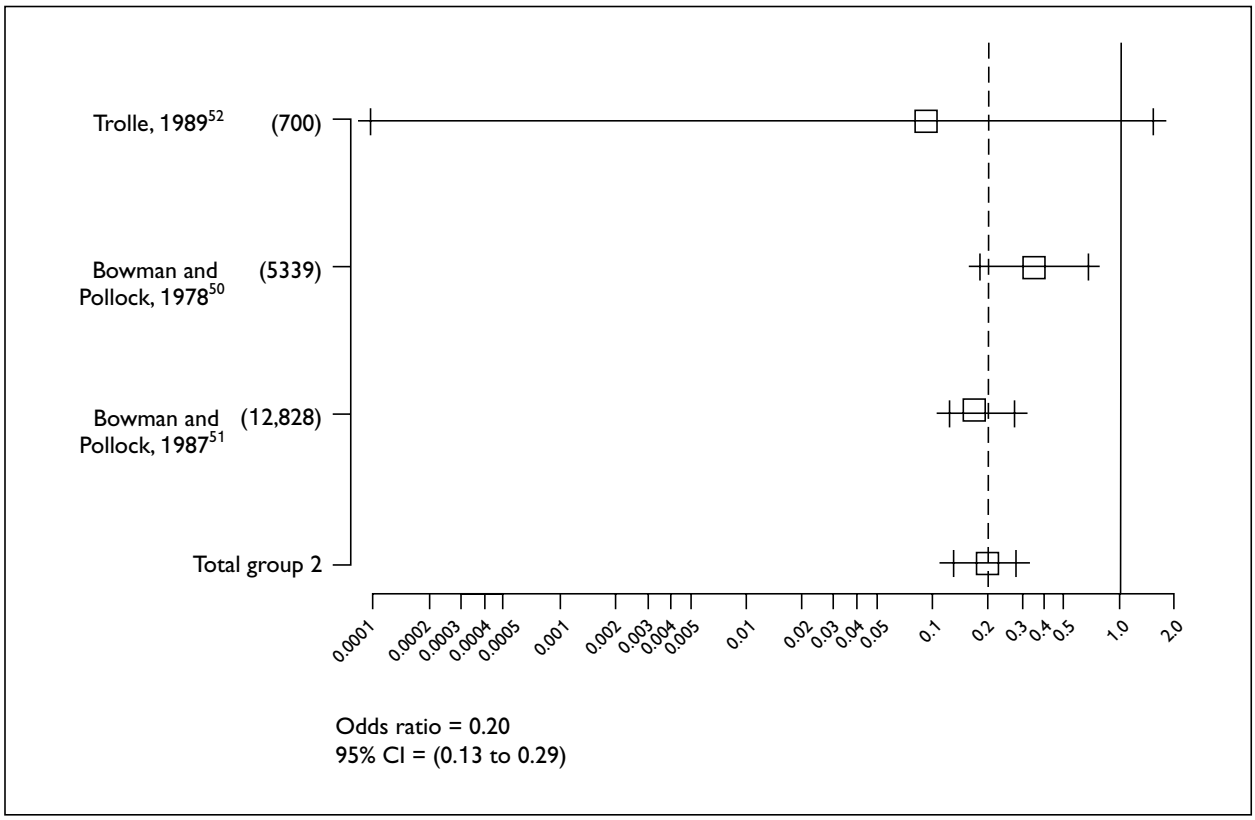

FIGURE 3 *Group 2: 1 x 1500 IU in unselected RhD-negative women (trial population is given in brackets)*

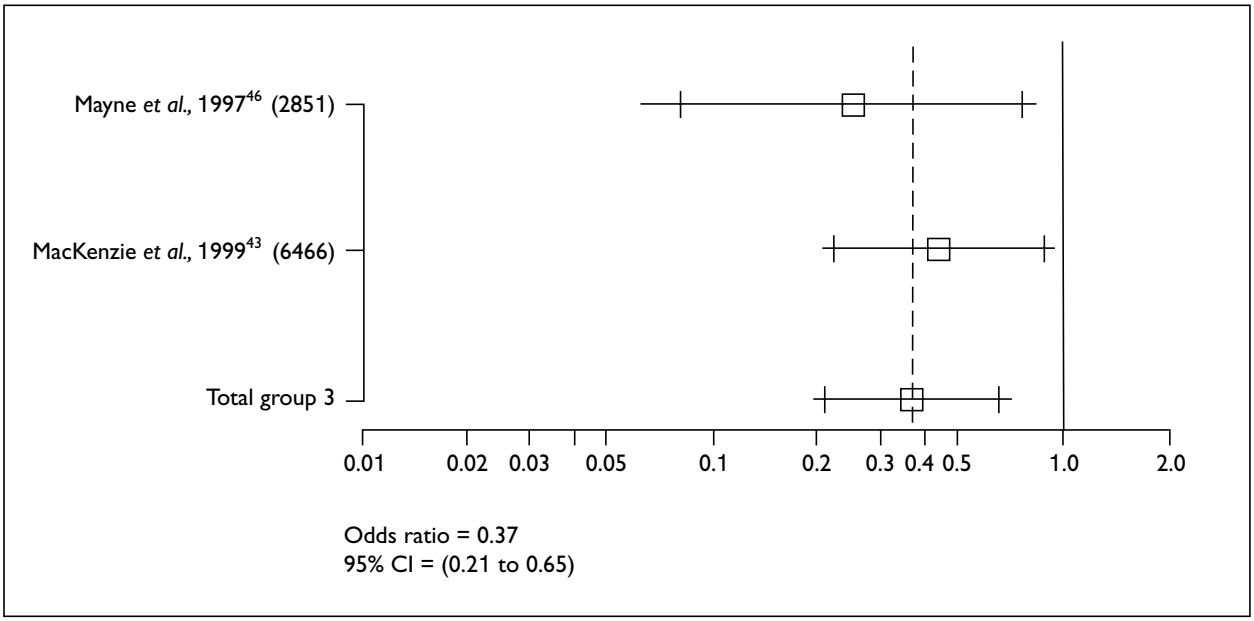

FIGURE 4 *Group 3: 2 x 500 IU in RhD-negative primigravidae (trial population is given in brackets:)*

point estimate for sensitisation in the AADP group obtained by pooling the data from those studies[42,43,45,46] which used two doses of 500 IU at 28 and 34 weeks is 0.30%, which is slightly lower than that for a single dose of 1500 IU (0.34%).[50–52] However, because the sensitisation rate in the control groups was lower in the 2 × 500 IU studies than in all but one[55] of 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 (CIs) of the estimates overlap, implying that the differences are not statistically significant.

Two doses of 250 IU did not significantly reduce the incidence of isoimmunisation.[44]

Failures of protection

Only one study examined the extent to which comprehensive prophylaxis was achieved. This found that, of a sample of eligible women delivered in the John Radcliffe Hospital during 1992–96, only 89% received the first dose of anti-D, only 76% received both doses, and only 29% received both doses at the correct gestation.[43] Another study found that, of 72 women sensitised in a community with a policy of single-dose prophylaxis at 28 weeks, seven failed to receive prophylaxis at 28 weeks; a further two women refused prophylaxis.[55]

Further information on women sensitised despite being in the intervention groups is provided in *Table 9*.

Longer-term outcomes

One study provided information on the clinical outcomes of 17 subsequent RhD-positive pregnancies in 62 sensitised women in the study's control group[49] (see *Table 11*).

TABLE 11 *Clinical outcomes of RhD-positive pregnancies in sensitised women[49]*

Outcome	Number of pregnancies
Fetal and exchange transfusion required	2
Exchange transfusion and early delivery required	3
Phototherapy required	2
Direct Coombs'-positive* – treatment not required	5
Direct Coombs'-negative* – unaffected	5

* *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*

One report[54] looked at the outcome of subsequent pregnancies in women who received AADP in the first pregnancy, but not in subsequent pregnancies. This was a follow-up to the study by Tovey and colleagues,[45] and reported on the same cohorts of women. This follow-up study found that, even though antenatal prophylaxis was given in only the first pregnancy, only one woman from the intervention group produced anti-D antibody in her second pregnancy, none in the third and only one in the fourth (see *Table 12*). Overall, sensi-

TABLE 12 *Anti-D antibody detected in first and subsequent pregnancies of RhD-negative women delivered of a RhD-positive infant (AADP given to the treatment group in the first pregnancy only)*[54]

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

tisation occurred in six women in the treatment group and in 32 women in the control group. No explanation was given as to why anti-D should give protection for more than one pregnancy.

ABO compatibility

In approximately 20% of pregnancies in RhD-negative women, the mother and fetus have different ABO blood groups. Sensitisation is less common where mother and baby are ABO-incompatible. Two of the studies reviewed here provided information relating the incidence of sensitisation to whether the mother and fetus were ABO-compatible or incompatible, though only one of these provided information for the intervention group. As might be expected, sensitisation was less common in cases of ABO incompatibility (see *Table 13*).

Summary of clinical effectiveness

In the eleven studies, AADP was given to, or available for, a total of 29,288 RhD-negative women who then bore 30,917 RhD-positive babies. Of these women, 147 (0.5%) became sensitised. The control groups in ten of the eleven studies comprised a total of 12,153 women who were at risk of RhD sensitisation; these women gave birth to 12,871 babies, and 167 women (1.4%) became sensitised. In the eleventh study,[55] 0.8% of a control group of unspecified size became sensitised.

The two largest studies[51,55] account for nearly two-thirds of the total number of intervention patients in the literature, but the design of both studies was relatively weak. The first compared women who received AADP between 1977 and 1986 with controls from the same geographical area during the period 1967–74. The second (reported as an abstract only) compared women who gave birth from 1988–95 in an area (Nova Scotia, Canada) in which routine AADP was provided with those who gave birth in the same period in another geographical area (Scotland, UK) in which routine AADP was not provided.

Overall, it would appear that, of the 147 women in the intervention groups who were reported to have been sensitised or sensibilised:

- 51 represented possible or probable failures of treatment (i.e. cases in which sensitisation occurred despite appropriate administration of anti-D)
- more than 51 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)
- 27 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 women who were sensitised or sensibilised because of possible or probable failures of antenatal prophylaxis would appear to be as low as 51/29,288 (0.17%; 95% CI, 0.1 to 0.2%). This figure would rise to a minimum of 102/29,288 (0.35%; 95% CI, 0.3 to 0.4%) 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.[46,43] 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 number of such women needed to treat (NNT) to avoid one case of sensitisation is 1/0.006, which

TABLE 13 *ABO compatibility and incidence of sensitisation*

Study	Anti-D prophylaxis group						Control group					
	ABO compatibility	***n***	***r***	**% sensitised**	**Upper 95% CI**	**Lower 95% CI**	**ABO compatibility**	***n***	***r***	**% sensitised**	**Upper 95% CI**	**Lower 95% CI**
Bowman *et al.*, 1978[49]	***Primagravidae***	***1357***		No data			***Primigravidae***	***2768***	***45***	***1.6***	***2.1***	***1.2***
	Compatible	1042		No data			Compatible	2257	44	1.9	2.5	1.4
	Incompatible	315		No data			Incompatible	511	1	0.2	0.6	0.0
							Multigravidae	***765***	***17***	***2.2***	***3.3***	***1.2***
							Compatible	602	14	2.3	3.5	1.4
							Incompatible	163	3	1.8	3.9	0.0
Hermann *et al.*, 1984[53]	***Primigravidae***	***236***	***1***	***0.4***	***1.3***	***0.0***	***Primigravidae***	***286***	***5***	***1.7***	***3.3***	***0.2***
	Compatible	192	1	0.5	1.5	0.0	Compatible	244	4	1.6	3.2	0.0
	Incompatible	44	0	0.0	0.0	0.0	Incompatible	42	1	2.3	7.0	0.0
	Multigravidae	***293***	***1***	***0.3***	***1.0***	***0.0***	***Multigravidae***	***359***	***5***	***1.4***	***2.6***	***0.2***
	Compatible	241	1	0.4	1.2	0.0	Compatible	287	5	1.7	3.3	0.2
	Incompatible	52	0	0.0	0.0	0.0	Incompatible	72	0	0.0	0.0	0.0

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*

is 166, but because antenatally a RhD-negative woman will not know if she is carrying a RhD-positive child – in fact only 60% of them will be – the overall NNT is $10/6 \times 166 = 278$.

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.

We estimate that currently (see chapter 1, 'Significance in terms of ill-health', page 5) 625 sensitisations per year of RhD-negative women lead to at least 30 fetal or neonatal losses per year. Avoidance of sensitisation can thus be expected to avoid fetal loss in 4.8% of cases (this takes into account the fact that women who become immunised during a first pregnancy may be 'high responders' who produce a vigorous response to a small feto-maternal haemorrhage). An estimate of the overall NNT to avoid a fetal or neonatal loss in a subsequent pregnancy is therefore $278/0.048 = 5790$.

Adverse effects of intervention

Concerns relating to the safety of antenatal anti-D

There are two main concerns relating specifically to the safety of antenatal anti-D: the risk of enhanced anti-D immunisation ('augmentation') and the effect of passive anti-D on the fetus.[2] 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 also exposes the infant to any such risk.

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 could result in the enhancement of a primary immune response to RhD-positive red blood cells, but this has not been observed in trials.[2]

There is also the possibility of short-term adverse events such as allergic responses. None of the studies reviewed here reported occurrences of such short-term adverse events. In its submission to this review,[39] BPL stated that anti-D is well tolerated. Between April 1994 and September 1999 they issued over 660,000 vials of anti-D, and received only three reports of adverse events possibly or probably related to anti-D. One of those reports related to an anaphylactic reaction. Baxter similarly report that anti-D is well tolerated. Between 1990 and 2000, 2.9 million doses of the Baxter product were given worldwide, and a total of only 11 reports of adverse reactions were received by Baxter. Although two of these were classified as serious, both occurred long after the administration of anti-D, and so were thought not to be related. Only two of the adverse reactions were thought to be possibly related to treatment – one a visual field defect and palpitations, the other hot flushes.[40]

In addition, it is possible that AADP may 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 post-partum anti-D. It is possible that this effect would be greater if antenatal anti-D had been given (Davies N, Consultant Obstetrician and Gynaecologist, Royal Hallamshire Hospital, Sheffield: personal communication, 2001).

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

Transfer of passive anti-D from the mother could cause fetal anaemia. However, there is no evidence that anti-D given to the mother during pregnancy is harmful to the infant, and it would appear that the dosage used is insufficient to cause observable haemolysis or anaemia in the fetus, even when repeated large doses are given. A minority (< 10%) of infants will be found to have laboratory evidence of red cell sensitisation but this is subclinical and does not result in anaemia, jaundice or the need for phototherapy.[2]

Only one of the studies reviewed in this report provided data relating to longer-term outcomes, in terms of preterm deliveries, birth weights and perinatal deaths in both the first and second pregnancy, and abortions in the second pregnancy, in RhD-negative women who, following antenatal prophylaxis in their first pregnancy, had delivered a RhD-positive baby in that first pregnancy. No significant difference in terms of these outcomes was observed between the intervention and control groups of untreated RhD-negative women who gave birth to a RhD-positive baby in their first pregnancy, and RhD-positive mothers who were comparable except for their RhD status, in terms of these outcomes, or in terms of maternal hypertension and proteinuria in the first, second and third pregnancies.[54]

There is some uncertainty about the possibility of longer-term adverse effects arising from exposure to anti-D. The Association of Radical Midwives, in its submission, expresses concern about the possible effect of exposing babies to anti-D *in utero*, suggesting that this 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.[63] Two of the peer reviewers of an earlier draft of this report have discounted this possibility: even though many such babies have now grown to adulthood, no evidence has been published to suggest any cause for concern.

Concerns relating to the possible transfer of viral or prion infection

There are also safety concerns related to the transfer of viral infection. The only source of therapeutic IgG is human plasma. In the past, hepatitis C has been transmitted through the use of anti-D,[64] but this was from a batch prepared using a method that has now been abandoned.[65] Both the Baxter[40] and the BPL[39] submissions stress the viral safety of their products: this is based both on sourcing plasma from donors who are screened for known viruses, and on viral inactivation through cold ethanol fractionation and solvent/detergent treatment as part of the manufacturing process. Overall, intramuscular immunoglobulins, which include anti-D, have an excellent safety record which extends from before the introduction of specific virology testing of donors and viral inactivation of the end product.[66] Monoclonal anti-D is under development, but remains several years away from routine use; it may prove to be less effective than polyclonal anti-D (Davies N, Consultant Obstetrician and Gynaecologist, Royal Hallamshire Hospital, Sheffield: personal communication, 2001).

As with other human-derived blood products, the risk of new variant CJD (Creutzfeld-Jakob disease; nvCJD) transmission is unquantifiable.[67] There are no methods of screening for nvCJD, the extent of infection in the population is unknown, and the transmissibility by blood products is also unknown.[68] It is known from animal experiments that plasma is unlikely to be a source of high levels of infectivity, and that peripheral inoculation is a much less efficient route for transmitting infection than central (cerebral) inoculation or oral consumption. Furthermore, nvCJD infectivity has not been detected in plasma of affected patients.[69] However, steps currently taken to inactivate viruses are unlikely to affect prion infectivity, and the pooling of donors to produce batches of immunoglobulin greatly increases the numbers of recipients exposed to plasma from an individual donor (though most women will only receive three doses of anti-D per pregnancy, compared, for example, with the repeated administration of Factor VIII to a haemophiliac).

Nevertheless, as a precautionary measure, because of the theoretical risk of transmission of nvCJD from blood products, all anti-D in use in the UK is manufactured from US plasma, as bovine spongiform encephalopathy and nvCJD have not been reported in the USA.

Despite all these measures, as anti-D IgG is a human plasma-based product, there is, naturally, public concern over its safety. However, as the current practice is to give anti-D IgG routinely to all RhD-negative mothers who give birth to a RhD-positive infant, and to all RhD-negative pregnant women who undergo a potential sensitising event, all staff should already be both receiving and giving women suitable evidence-based information about the product. One-quarter of RhD-negative women who have children are likely only ever to have RhD-negative children. If none of these women ever received prophylaxis following a potential sensitising event, the introduction of a policy of routine antenatal prophylaxis would increase the proportion of women with a lifetime exposure to anti-D IgG by one-third (from 75% to 100% of all childbearing RhD-negative women), representing an increase of about 25,000 women per year over current exposure levels. In reality, because of the use of *ad hoc* antenatal prophylaxis, the number of women currently exposed to anti-D is somewhat higher than 75%, and the actual increase would therefore be less than a third. More significant, in purely numerical terms, is the increase in the number of fetuses exposed to anti-D *in utero*, which would rise from very low levels currently, to approximately 100,000 per year (all infants of RhD-negative mothers).

Alternative means to decrease sensitisation rates

Although we may conclude that routine antenatal anti-D administration is likely to lead to a significant fall in the residual numbers of women becoming sensitised, alternative strategies for reducing sensitisation rates should be considered.

There are three possible reasons for continuing cases of sensitisation:

- failure to recognise potential sensitising events in pregnancy as such, and to treat appropriately
- failure to assess the extent of feto-maternal haemorrhage adequately
- failure to comply with post-partum prophylaxis guidelines.

With respect to the first point, there is good evidence that current UK guidelines, particularly in relation to the administration of anti-D following potentially sensitising events in pregnancy, are not universally adhered to. In a retrospective study of 922 RhD-negative women delivered in Merseyside in 1994, the guideline recommendations were not recorded as being followed in 158 of 396 (39%) of potentially sensitising events.[7] In an audit of anti-D sensitisation in Yorkshire,[5] the guidelines were followed fully in only 30 out of 58 (52%) possible sensitising events for which full data were available. A further regional audit of 3684 RhD-negative women undertaken in Northern Ireland found that only 11 out of 44 (25%) who had amniocentesis received anti-D.[9]

There is also evidence that many Accident and Emergency departments are not adequately prepared for treating women who bleed in early pregnancy with anti-D, and are not following the guidelines so to do.[70] Fortunately, the evidence suggests that the guidelines for post-partum administration are more closely adhered to.[7,9]

Probably only a minority of the current residual cases of sensitisation are attributable to failure to comply with current established UK guidelines. Nevertheless, these observations inevitably raise the question of whether sensitisation rates cannot be further reduced by stricter adherence to current guidelines, and whether this should not be pursued before initiating guidelines for the routine offering of AADP to pregnant women who are RhD-negative.

Chapter 3

Economic analysis

Cost and benefit implications of adopting AADP

The aim of this section of the review is to evaluate the costs and cost-effectiveness relevant to the NHS of providing routine AADP for RhD-negative pregnant women. There are three possible treatment strategies:

- offering routine AADP to all pregnant women who are RhD-negative, in addition to conventional management
- offering routine AADP only to primigravidae who are RhD-negative, in addition to conventional management
- conventional management alone.

Conventional management is defined as:

- offering anti-D prophylaxis to all pregnant women who are RhD-negative within 72 hours of identified potentially sensitising events, such as abdominal trauma etc
- offering postnatal anti-D IgG within 72 hours of delivery to all RhD-negative women delivered of RhD-positive infants who are not already sensitised.

One treatment regimen is assessed here: this consists of two injections of either 500 IU or 1250 IU of anti-D IgG, one at 28 weeks and the second at 34 weeks. The costs and benefits of adding routine AADP to conventional management are evaluated against the comparator of conventional management alone. The evidence for clinical effectiveness reviewed in chapter 2 suggests that there is no statistically significant difference between a regimen of 2 × 1500 IU and one of 2 × 500 IU. It is thus assumed that there is no statistically significant difference in clinical effectiveness between the two licensed treatment regimens, and therefore the results of the meta-analysis are used to evaluate the cost-effectiveness of all dose regimens of AADP. As a result of this, the difference in cost-effectiveness between the licensed products is based entirely on the costs of the products themselves, as the costs of administering the treatment are the same whichever dose is used, and the sensitisation rates are assumed to be the same with either dose.

The economic analysis is based on:

- a review of previous economic evaluations (see 'Overview of previous economic evaluations', below)
- an economic evaluation of offering routine AADP to all pregnant women who are RhD-negative, and to RhD-negative primigravidae only, in addition to conventional AADP applicable to the NHS.

The economic evaluation assesses:

- the cost per fetal loss, stillbirth, neonatal or postneonatal death avoided (see section starting on page 34)
- the cost per life-year gained (LYG) (see section starting on page 34)
- the number of disabilities avoided (see section starting on page 38)
- the cost per quality-adjusted life-year (QALY) gained as a result of disabilities avoided (see section starting on page 38).

Overview of previous economic evaluations

A number of economic evaluations of antenatal RhD haemolytic disease prevention programmes have been conducted. The following section of this report presents an overview of the eight relevant economic evaluations. Of these, four evaluations used UK costs, but only the study by Vick and co-workers[57,58] describes a detailed modelling study that appears to be applicable to the UK NHS.

Baskett *et al.*, 1990. Prevention of Rh(D) isoimmunisation: a cost–benefit analysis[56]

Baskett and colleagues[56] report a cost–benefit analysis of the prevention and treatment of RhD isoimmunisation 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 isoimmunisation, against the costs

associated with anti-D IgG 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 calls 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 healthcare expenses were incurred because of the need for neonatal intensive care. The headline result of the study is that a RhD isoimmunisation prevention programme is cost-effective. Based on 1986 prices, the cost per case treated is calculated to be Can$3986 whereas the cost per case prevented is calculated to be Can$1495.

Selinger, 1996. Building on success: antenatal prophylaxis. The pharmaco-economics of antenatal prophylaxis[62]

Selinger[62] reports a cost–benefit evaluation of antenatal prophylaxis versus perinatal care for the treatment of RhD haemolytic disease. Resource and effectiveness data relate to the former 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% less expensive) 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 haemolytic disease of the newborn is eradicated. The author highlights 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[43]

MacKenzie and colleagues[43] assess the clinical and financial impact of routine AADP for RhD-negative nulliparae. The evaluation uses actual resource and cost data, as opposed to modelling techniques, 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 routine AADP. 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.

Vick *et al.*, 1995, 1996. An economic evaluation of antenatal anti-D prophylaxis in Scotland,[57] and cost-effectiveness of antenatal anti-D prophylaxis[58]

Vick and colleagues[57,58] describe a model to estimate the incremental cost per RhD-isoimmunisation prevented and the incremental cost per fetal loss from RhD haemolytic disease of the newborn prevented for six different AADP programmes. The evaluation uses 'real-world' data obtained from blood transfusion centres, hospitals and haematology laboratories in Scotland, UK in order to assess the incremental cost-effectiveness. The results calculated from the model are presented in *Table 14*.

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 this is unclear. A cost per QALY outcome is not assessed owing to the

TABLE 14 *Summary of economic results from Vick* et al., *1996*[58]

Dose regimen	1 x 1250 IU	2 x 500 IU	2 x 1250 IU
Incremental cost per RhD-isoimmunisation prevented (£)			
Primigravidae vs no routine AADP	–1,172	–197	1,464
All women vs primigravidae	2,915	4,908	8,272
Incremental cost per loss from RhD haemolytic disease prevented (£)			
Primigravidae vs no routine AADP	–17,136	–2,845	–21,268
All women vs primigravidae	42,346	71,308	120,174

difficulties involved in assigning quality of life gains appropriately. A policy of routine AADP for primigravidae has a better cost-effectiveness than a policy of routine AADP for all women. When comparing dose protocols, the 1 × 1250 IU dosage regimen is more effective and less costly than the 2 × 1250 IU programme.

This is clearly the most comprehensive economic evaluation conducted to date which is within the public domain. However, 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.

Lim *et al.*, 1982. Reduction of $Rh_0(D)$ sensitisation: a cost-effective analysis[59]

Lim and colleagues[59] put forward both a cost-effectiveness and a cost–benefit analysis, but the details reported are very limited. The study is the first American study on the incidence of gestational sensitisation, using patient data collected from hospitals in the Los Angeles area between 1976 and 1978. Data from 3995 deliveries are used in the analysis. The actual methods used for calculating cost-effectiveness and cost–benefit are not well detailed. The cost of preventing one sensitisation, using anti-D administered at 28 weeks, was estimated to be US$8451. 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[45]

Tovey and colleagues[45] compare a group of primigravidae receiving antenatal prophylaxis 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.

Torrance and Zipursky, 1984. Cost-effectiveness of antepartum prevention of Rh immunization[60]

This economic evaluation assesses both the cost-effectiveness and the cost-utility of an ante-partum prevention programme in Ontario, Canada. The purpose of the study is to assess whether a programme of antepartum prevention 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 = Can$2700
  - cost per case of Rh-disease prevented = Can$3700
  - cost per life saved = Can$29,500
  - cost per LYG = Can$1500
- cost–utility
  - cost per QALY gained = Can$1500.

The authors conclude that ante-partum treatment of all RhD-negative 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.

Adams *et al.*, 1984. Cost implications of routine antenatal administration of Rh immune globulin[61]

The evaluation put forward by Adams and colleagues[61] estimates the benefits, risks and costs of a programme of routine ante-partum administration of anti-D IgG to RhD-negative primiparae in the USA, using decision analytic modelling. The comparators within the model are:

- routine ante-partum and post-partum administration of anti-D IgG for RhD-negative primiparae
- post-partum 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 = US$28,571
- Black = US$22,222
- Asian = US$11,429.

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

Modelling the cost-effectiveness of routine AADP in RhD-negative women

This section of the report presents an economic evaluation of offering routine AADP to all pregnant women who are RhD-negative, and to RhD-negative primigravidae only, in addition to conventional AADP prophylaxis applicable to the NHS.

Costs used in economic evaluation

The costs incurred through providing AADP are the cost of the anti-D IgG and the cost of the administration of the treatment. The economic benefits of the programme are the direct savings due to the avoidance of the additional treatment costs which would have been incurred as a result of any subsequent pregnancy in a sensitised woman. The effects of future benefits gained and future costs incurred are discounted at 1.5% and 6%, respectively.

The cost of a single 500 IU vial of anti-D IgG is £27.00 (BPL); therefore, the cost of treating one pregnancy with the 500 IU dose regimen is £54.00. The cost of a single 1250 IU vial of anti-D IgG is £23.90; therefore the cost of treating one pregnancy with the 1250 IU dose regimen is £47.80. The Association of Radical Midwives estimates the cost of administration as around £3.50 per dose including the midwife's time and materials.[63] In some cases part of this cost may be incurred by GPs. This assessment uses an estimate of £10 for administering two doses per pregnancy. Administration is assumed to be carried out by a midwife during a normal antenatal visit.

Assuming that, of the total of approximately 625,000 births per annum in England and Wales, 16% are to RhD-negative women, the gross annual cost of offering routine AADP to around 100,000 women, using 2 × 500 IU, is estimated to be approximately £6,400,000.

Selinger[62] estimated the direct savings of prevention of sensitisation in 1996 to be £1,320 per affected pregnancy avoided (*Box 1*). This estimate includes the following costs:

- amniocentesis
- possible IUT
- blood sampling
- phototherapy and exchange transfer
- longer, more intensive hospital stay for the infant
- neonatal follow-up visits.

Due to increasing health service costs, this estimate has been uplifted to £1,442 by applying health service inflation indices from the Hospital and Community Health Service Cost Index (Brown F, Department of Health Public Expenditure Team: personal communication, 2001).

The savings per affected pregnancy avoided are likely to represent an underestimate as they do not take into account a longer hospital stay for the mother of the infant, the cost of a greater number of caesarean sections and inductions of labour, the possibility of problems in future pregnancies, and the cost of future care of premature and/or handicapped babies.

For all women in Great Britain, the median length of time between the birth of the first and second child is 36 months.[71] The intervals between subsequent pregnancies have been assumed to be of a similar magnitude. The value of the savings has been discounted at 6% for 3 years, and therefore the present value of the savings is estimated at £1,210.

The model of the cost-effectiveness of routine AADP

The assessment model allows the calculation of a number of economic outcomes, namely:

- cost per sensitisation avoided
- cost per case of RhD haemolytic disease of the newborn avoided
- cost per fetal loss avoided
- cost per LYG.

The measures of cost per fetal loss, stillbirth, neonatal or postneonatal death avoided and cost per LYG have been included as they enable a comparison of cost-effectiveness with other healthcare interventions. Incremental analysis was conducted by ranking the interventions in order of clinical effectiveness: this represents the cost-effectiveness between a treatment and its next best alternative.

BOX 1 Cost of treating 100 pregnancies in sensitised women (Selinger, 1997[62])		
Number of new cases with immunisation per year		***100***
• Number of cases requiring intensive antibody monitoring (A)		90
• Number of cases severe enough to require fetal assessment/treatment		10
• Number of cases undergoing serial fetal blood sampling (B)		5
• Number of cases undergoing serial intrauterine transfusion (C)		5
• Number of cases requiring neonatal care only (D)		10
NB: as these outcomes are not mutually exclusive, the total exceeds 100		
Cost of A (£)		
• 5 antenatal serology investigations + management in 90 cases		22,500
	Subtotal A	**22,500**
Cost of B (£)		
• 5 cases requiring 3 fetal blood sampling + 5 days high-dependency neonatal unit = 5 × [(3 × £500) + (5 × £800)]		27,500
• 5 cases requiring 2 neonatal follow-up visits = 5 × £100		500
	Subtotal B	**28,000**
Cost of C (£)		
• 5 cases requiring 3 intrauterine transfusions + 3 days intensive care neonatal unit + 5 days high-dependency neonatal unit = 5 × [(3 × £1200) + (3 × £1200) + (5 × £800)]		56,000
• 5 cases requiring 2 neonatal follow-up visits = 5 × £100		£500
	Subtotal C	**56,500**
Cost of D (£)		
• 10 cases requiring phototherapy/exchange transfer only = 10 × (3 × £800)		24,000
• 10 cases requiring 2 neonatal follow-up visits = 10 × £100		1,000
	Subtotal D	**25,000**
Cost per 100 RhD-negative pregnant women, sensitised in a previous pregnancy (£)		
• **Total A + B + C + D**		**132,000**

Table 15 shows the parameters used within the base-case analysis for the three treatment options. Because of the implied homogeneity between trial groups presented in the meta-analysis, it is assumed that anti-D has equal effectiveness when used in treating both primigravidae and all women. There is evidence that routine AADP in the first pregnancy only can give some long-term protection against sensitisation in subsequent pregnancies.[54] This evidence however is only suggestive and therefore has not been included in estimating the incremental cost of routine AADP in all pregnancies as opposed to primigravidae.

The model uses a hypothetical cohort of women to whom national fertility rates are assumed to apply. The treatment effects of the two AADP strategies (all pregnant women or primigravidae only) are modelled using this cohort. The model assumes that fertility patterns are constant, and therefore 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 fertility patterns of women who have completed their childbearing are derived from the most up-to-date data, that for women born in 1956.[64] The first, second, third and subsequent deliveries of 105,000 women within such a cohort are presented in *Table 16*.

Complications due to sensitisation of the mother only occur in subsequent RhD-positive pregnancies. In order to achieve the annual equivalent of 105,000 pregnancies, a cohort of 44,501 RhD-negative primigravidae needs to be considered. This is calculated as shown in *Table 16*. The method of calculation when no antenatal prophylaxis is given is as follows:

The number of RhD-negative pregnancies treated in each pregnancy (i.e. first, second, third) is the number in the previous pregnancy multiplied by the percentage going on to a further pregnancy. Therefore, the total number of RhD-negative pregnancies treated is just the sum of these.

TABLE 15 *Baseline parameters for evaluation of cost-effectiveness*

Parameters	Value
Average life expectancy	74 years
Discounted life expectancy (using a 1.5% discount rate)	44.5 years
Sensitisation rate with no routine AADP	0.95%
Sensitisation rate with routine AADP	0.35%
Odds ratio	37%
Fetal loss rate* per woman at risk under current service provision	0.04%
Current service provision of routine AADP	12%
Cost of AADP	
2 x 500 IU	£54.00
2 x 1250 IU	£47.80
Cost of administration	£10
Economic savings per affected pregnancy avoided	£1442
Median interval between pregnancies	36 months

* *Including stillbirths, neonatal and postneonatal deaths*

A total of 44,501 non-sensitised RhD-negative women have a first pregnancy. Of these, 59%, will have a RhD-positive baby and, therefore, their pregnancy will be at risk. This results in 26,256 pregnancies being at risk. In the case described, the mothers are not given antenatal prophylaxis and, therefore, 0.95% will become sensitised. This results in 249 sensitisations. Of these women, 86% will go on to have a second pregnancy, of which 80% will be RhD-positive and with an affected fetus. This results in 171 cases of RhD haemolytic disease.

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 86%, the percentage of women having a second pregnancy. This results in 38,057 non-sensitised RhD-negative women entering a second pregnancy. Of these, 59% will have a RhD-positive baby and, therefore, their pregnancy will be at risk. This results in 22,454 pregnancies at risk. As no prophylaxis is given, 0.95% of these will become sensitised for the first time, i.e. 213 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 44%, the percentage of women having a third pregnancy. Of these fetuses, 80% will be RhD-positive and, therefore, will be affected. This results in 150 cases of RhD haemolytic disease.

This process is then repeated again and continues exactly as described, but the percentage of women entering a fourth and subsequent pregnancy reduces to 32%.

This method of calculation has been used for all scenarios, so in the case where antenatal prophylaxis is administered, the sensitisation rate reduces to 0.35% instead of 0.95%. For the primigravidae-only strategy, only the first 44,501 pregnancies are given antenatal prophylaxis and, therefore, the risk of sensitisation in second and subsequent pregnancies returns to 0.95%.

Cost-effectiveness of routine antenatal anti-D prophylaxis in primigravidae and all RhD-negative women

Table 16 presents the clinical outcomes from the base-case analysis for the population of England and Wales; these outcomes differ depending on whether treatment is given to all pregnant women who are RhD-negative, or to RhD-negative primigravidae only. In so far as population profiles are stable, the figures in *Table 16* represent estimates of annual outcomes under the different management policies. As the effectiveness of both dosage regimens is assumed to be the same, the only difference between economic outcomes will result from price differences.

Table 17 presents the cost-effectiveness outcomes associated with providing AADP for RhD-negative primigravidae and for all pregnant women who are RhD-negative, using the 2 × 500 IU IgG dosage regimen and the 2 × 1250 IU IgG dosage regimens.

From *Table 17*, it can be seen that, for both the 500 IU and the 1250 IU IgG dosage, it is markedly less expensive to treat RhD-negative primigravidae with AADP than to treat all pregnant women who are RhD-negative. This is largely due to the different number of women treated under each scenario. The differences between the net costs of 2 × 500 IU IgG and 2 × 1250 IU IgG are due only to the different prices.

The incremental cost per case of RhD haemolytic disease of the newborn prevented for the 2 × 500 IU IgG dose has a central estimate of £15,241 when treating primigravidae only, and £48,225 when all RhD-negative women are treated. The incremental cost per case of RhD

TABLE 16 *Effectiveness of routine AADP for the population of England and Wales*

Pregnancy	Rh-negative pregnancies	Non-sensitised Rh-negative pregnancies	Number at risk	Sensitised in current pregnancy	Sensitised from previous pregnancies	Number of fetuses affected	Number of fetuses lost	Pregnancies treated
Conventional management: no routine prophylaxis								
First	44,501	44,501	26,256	248.8	0.0	0.0	0.0	0
Second	38,271	38,057	22,454	212.8	214.0	171.2	11.6	0
Third	16,839	16,557	9,769	92.6	187.8	150.2	10.2	0
Subsequent	5,389	5,209	3,073	29.1	89.7	71.8	4.9	0
Total	**105,000**	**104,324**	**61,552**	**583.3**	**491.5**	**393.2**	**26.4**	**0**
Routine AADP: primigravidae only								
First	44,501	44,501	26,256	92.1	0.0	0.0	0.0	44,501
Second	38,271	38,192	22,533	213.6	79.2	63.3	4.3	0
Third	16,839	16,676	9,839	93.2	128.8	103.0	7.0	0
Subsequent	5,389	5,265	3,106	29.4	71.1	56.8	3.9	0
Total	**105,000**	**104,634**	**61,734**	**428.3**	**279.1**	**223.1**	**15.1**	**44,501**
Routine AADP: all RhD-negative pregnant women								
First	44,501	44,501	26,256	92.1	0.0	0.0	0.0	44,501
Second	38,271	38,192	22,533	79.0	79.2	63.3	4.3	38,192
Third	16,839	16,735	9,874	34.6	69.6	55.7	3.8	16,735
Subsequent	5,389	5,322	3,140	11.0	33.4	26.7	1.8	5,322
Total	**105,000**	**104,750**	**61,803**	**216.7**	**182.2**	**145.7**	**9.9**	**104,750**

TABLE 17 *Incremental cost-effectiveness of providing routine AADP for RhD-negative primigravidae and for all pregnant women who are RhD-negative*

	Incremental values: BPL		Incremental values: Baxter	
	Primigravidae only vs conventional	All RhD-negative pregnant women vs primigravidae only	Primigravidae only vs conventional	All RhD-negative pregnant women vs primigravidae only
Number of sensitisations avoided	155.04	211.60	155.04	211.60
Number of affected fetuses avoided	169.99	77.52	169.99	77.52
Number of fetuses lost* avoided	11.52	5.25	11.52	5.25
Total LYGs	512.73	223.83	512.73	223.83
Net cost (£)	2,590,829	3,738,579	2,314,922	3,365,039
Cost per sensitisation avoided (£)	16,711	17,668	14,931	15,903
Cost per case of rhesus disease avoided (£)	15,241	48,225	13,618	43,407
Cost per fetal loss* avoided (£)	224,933	711,706	200,979	640,595
Cost per LYG (£)	5,053	15,988	4,515	14,391

* *Including stillbirths, neonatal and postneonatal deaths*

haemolytic disease of the newborn prevented for the 2 × 1250 IU IgG dose has a central estimate of £13,618 when RhD-negative primigravidae only are treated, and £43,407 when all pregnant women who are RhD-negative are treated.

The treatment cost scenarios for primigravidae presented in *Table 17* are cost-effective in comparison with other treatments currently funded by the NHS. The incremental cost per LYG for the 2 × 500 IU IgG dose has a central estimate of £5,053 when primigravidae only are treated, and £15,988 when all pregnant women who are RhD-negative are treated. The cost per LYG for the 2 × 1250 IU IgG dose has a central estimate of £4515 when primigravidae only are treated, and the incremental cost-effectiveness of treating all pregnancies is £14,391.

Sensitivity analysis of cost-effectiveness of antenatal anti-D prophylaxis

In order to estimate uncertainty surrounding the model parameters, multivariate sensitivity analysis has been conducted to assess the range of cost-effectiveness. Sensitivity analysis has been conducted for each treatment strategy and at each dosage. The distribution of the sensitisation rate has been derived from the meta-analysis described in the previous chapter (see page 21) and is used for the treatment groups and control group, respectively. The mean, standard error and assumed distributions for those parameters varied within the analysis are presented in *Table 18*.

Incremental cost-effectiveness acceptability curves (CEACs) are presented in *Figure 5;* these demonstrate the uncertainty surrounding the incremental cost-effectiveness of AADP. The steep gradient of the curves suggests that uncertainty in these estimates of cost-effectiveness is low. It is also evident from the CEACs that treating only primigravidae has a higher probability of being cost-effective at specific thresholds than programmes whereby all pregnant women who are RhD-negative are treated. Furthermore, despite the differences in drug costs, the cost-effectiveness of each drug is similar for each management option.

Cost per QALY gained by the avoidance of disabilities associated with RhD haemolytic disease of the newborn

Due the difficulties in placing a value on parental grief and a fetal loss, stillbirth, neonatal or postnatal death avoided, this economic analysis focuses on estimating the cost per QALY gained by the avoidance of disabilities associated with RhD haemolytic disease of the newborn. The economics of routine AADP prophylaxis, ignoring the clinical benefits from stillbirths, neonatal or postnatal deaths avoided, and focusing purely on disabilities avoided, are presented in *Table 19*. The impact of different attitudes to grief etc is investigated through a health economic threshold analysis presented in *Table 20*.

The treatment policies considered are:

TABLE 18 *Parameters varied within the sensitivity analysis*

Parameter	Assumed distribution	Parameter 1	Parameter 2	Parameter 3
Risk of RhD-positive fetus in next pregnancy	Triangular	0.8	0.6	0.9
Fetal loss rate* per woman at risk	Normal	0.0004	0.0001	
Cost of administration per RhD-negative woman treated	Triangular	10	5	15
Total cost per pregnancy affected	Lognormal	7.18	0.3	
No treatment sensitisation	Lognormal	–4.6588	0.40442	
Relative risk of sensitisation with routine AADP	Lognormal	–0.9942	0.355	
Parameter key	**Distribution**	**Parameter 1**	**Parameter 2**	**Parameter 3**
	Normal	Mean	Standard error	Not applicable
	Lognormal	Mean	Standard error	Not applicable
	Triangular	Mean	Minimum	Maximum

* *Including stillbirths, neonatal and postneonatal deaths*

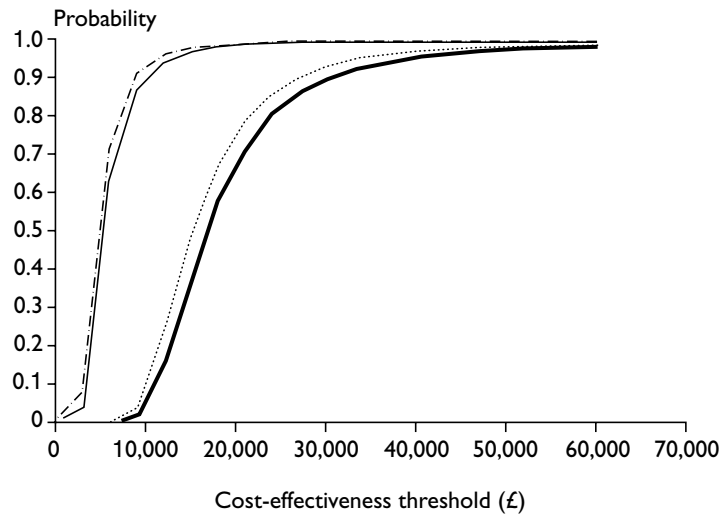

FIGURE 5 *Incremental CEAC for AADP in RhD-negative women. From the left: (1) Baxter routine AADP: 2 × 1250 IU, primagravidae only versus conventional management; (2) BPL routine AADP: 2 × 500 IU, primagravidae only versus conventional management; (3) Baxter routine AADP: 2 × 1250 IU, all RhD-negative women versus primagravidae only; (4) BPL routine AADP: 2 × 500 IU, all RhD-negative women versus primagravidae only*

TABLE 19 *Incremental analysis of disability outcomes and economics of routine AADP (includes no valuation of stillbirths and grief etc)*

Incremental avoided	Cost (£)	Number of children with minor developmental disabilities avoided	Number of children with major neuro-developmental disabilities avoided	QALYs gained	Cost per QALY (£)
BPL routine AADP: 2 x 500 IU: primigravidae only	1,839,694	9.5	4.8	145	12,731
BPL routine AADP: 2 x 500 IU: all RhD-negative pregnant women	3,396,018	4.3	2.2	66	51,529
Baxter routine AADP: 2 x 1250 IU: primigravidae only	1,563,787	9.5	4.8	145	10,821
Baxter routine AADP: 2 x 1250 IU: all RhD-negative pregnant women	3,022,478	4.3	2.2	66	45,861

TABLE 20 *Threshold analysis to identify the circumstances under which a policy of giving routine AADP to all RhD-negative pregnant women might be considered economically attractive compared to a primigravidae only policy*

Marginal cost (*M*)	£3,396,018				
Marginal QALYs gained (*Q*)	66				
Marginal cost per QALY (*M*/*Q*)	£51,529				
Threshold cost-effectiveness (*T*)	£20,000	£25,000	£30,000	£35,000	£40,000
Implied threshold QALY (*M*/*T*)	170	136	113	97	85
Implied QALY differential ($\delta Q = M/T - Q$)	104	70	47	31	19
Stillbirths avoided in the population (*S*)	5.3	5.3	5.3	5.3	5.3
Implied QALY differential per stillbirth avoided ($\delta Q/S$)	20	13	9	6	4

- conventional management (i.e. 12% routine AADP)
- BPL routine AADP: 2 × 500 IU: primigravidae only
- BPL routine AADP: 2 × 500 IU: all RhD-negative pregnant women
- Baxter routine AADP: 2 × 1250 IU: primigravidae only
- Baxter routine AADP: 2 × 1250 IU: all RhD-negative pregnant women.

The annual number of minor developmental problems and major long-term neurodevelopmental problems expected in the population of England and Wales under the different treatment policies is estimated from the results of the most recent study in this area, that is the Northern Ireland study,[28] applied to the outputs of the economic model previously described. These figures are presented in *Table 19*.

The quality of life impact of minor developmental problems and long-term neurodevelopmental problems is taken from published literature studying outcomes in low birth weight infants.[72,73] The quality of life in people with minor developmental problems is taken as a utility of 0.8, and this adjustment has been assumed to last for the first 10 years of life. The quality of life in people with long-term neurodevelopmental problems is estimated as a utility of 0.4 per year assumed for the full duration of life expectancy.

The lifetime cost of caring for a disabled child is enormous. A paper by Stevenson and co-workers[74] on the cost of care for disabled low birth weight infants to the age of 8 to 9 years quotes a figure of £6926 per disabled low birth weight child compared with £4027 for a non-disabled low birth weight child, with costs discounted and expressed in 1979 prices. This cost includes neonatal care, health service use, special education and institutional care. The paper continues, using the assumption that a non-disabled low birth weight child will impose no extra cost on the exchequer after age 9, and will receive mainstream education to age 18, to estimate a lifetime cost of disability to be £69,597 per disabled child. These costs have been revalorised to 2001 values using the Health Service Cost Index.

As can be seen from *Table 19*, a policy of giving routine AADP to primigravidae only is economically attractive from the perspective of disability prevention alone, irrespective of attitudes to parental grief and valuation of stillbirths, neonatal and postneonatal deaths.

Table 20 presents a threshold analysis for a policy of giving routine AADP to all RhD-negative women who are pregnant compared with a primigravidae-only policy option based upon the least cost-effective regimen (i.e. routine AADP with 2 × 500 IU).

The total marginal cost of the all-women policy over and above the primigravidae policy option is estimated to be approximately £3.4 million for England and Wales. To obtain a cost-effectiveness better than, say, £30,000 per QALY, it would be necessary to achieve a total of around 114 QALYs gained over the entire population. The marginal QALYs gained associated with reduced incidence of disabilities associated with RhD haemolytic disease is estimated at approximately 66 QALYs. This implies a shortfall of around 48 QALYs.

The policy of giving routine AADP to all RhD-negative pregnant women is associated with avoiding 5.3 stillbirths, neonatal or postnatal deaths each year compared with a primigravidae-only option. Thus, using a maximum acceptable cost-effectiveness ratio of £30,000 per QALY, if the lost child, associated parental grief and subsequent high intervention pregnancy are valued at less than 9 QALYs then the comprehensive policy would not be considered economically attractive. Conversely, a valuation of greater than 9 QALYs would imply that the comprehensive policy would be attractive.

Total costs to the NHS

In 1999 there were a total of 621,872 births in England and Wales.[34] Of these pregnancies, approximately 106,000 would have been in RhD-negative women, and approximately 45,000 of these would have been first pregnancies.

If routine AADP is given to all pregnant women who are RhD-negative, the total gross cost of drugs, using the NHS list price, would be approximately £5.7 million for the 2 × 500 IU regimen and £5.1 million for the 2 × 1250 IU regimen. The total cost of administration, based on an estimate of £10 per pregnant woman treated, would be £1.1 million. As cost savings of £400,000 are estimated from reductions in haemolytic disease of the newborn, the total net cost to the NHS in England and Wales would be £5.7–6.4 million per year.

If routine AADP is only given to RhD-negative primiparae, the total gross cost of drugs would

be approximately £2.4 million for the 2 × 500 IU regimen and £2.1 million for the 2 × 1250 IU regimen. The total cost of administration would be £450,000. Cost savings of £260,000 are estimated, giving a total net cost to the NHS in England and Wales of £2.3–2.6 million.

Conclusions on cost-effectiveness of treating RhD-negative women with AADP

Routine AADP provides a cost-effective intervention for preventing the incidence of haemolytic disease of the newborn in the pregnancies of RhD-negative women. Two preparations of anti-D are available, one of 500 IU and one of 1250 IU. There is no evidence to demonstrate any difference in the clinical effectiveness of these preparations and, though there is a small price difference, both preparations have very similar cost-effectiveness profiles. The prices used in this assessment are based upon NHS list prices for these products but, since actual prices paid by hospitals vary, the cost-effectiveness in practice may be better than that presented here. Furthermore, 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. Thus a cost-minimisation comparison between the products is not appropriate.

Routine AADP given to primigravidae has a cost per LYG that is very good in comparison to other interventions routinely funded by the NHS. The incremental cost per LYG of giving routine AADP to all pregnant women who are RhD-negative is not as good, but there is still a roughly a 90% chance of the cost-effectiveness being better than £30,000 per LYG.

In addition, routine AADP given to primigravidae has a cost per QALY gained which is economically attractive from the perspective of disability prevention alone, irrespective of attitudes to parental grief and valuation of stillbirths, neonatal and postneonatal deaths. Routine AADP given to all pregnant women who are RhD-negative is economically attractive, using a maximum acceptable cost-effectiveness ratio of £30,000 per QALY, if the lost child, associated parental grief and subsequent high intervention pregnancy are valued at more than 9 QALYs.

Chapter 4
Discussion

Maternal choice and policy with regard to prophylactic anti-D: paternal testing

Pregnant women who are RhD-negative are only at risk of becoming sensitised if they are carrying a RhD-positive child, and this can only happen if the father is RhD-positive. A RhD-negative woman who is pregnant by a man who is RhD-negative cannot be carrying a RhD-positive child, and so cannot become sensitised. Approximately one-sixth of RhD-negative women will be pregnant by men who are themselves RhD-negative. These women will therefore not benefit from antenatal anti-D, whether this is administered as part of a programme of routine AADP or in response to potential sensitising events.

It could be argued that active measures should be in place to avoid giving such women prophylactic anti-D, both in order to avoid any possible side-effects and also to avoid the trauma of an un-necessary injection and unnecessary costs. The implication of such measures would be that pregnant RhD-negative women would be asked to identify the father of the child, who would then be offered the opportunity to have his rhesus status tested. As a result, RhD-negative women who were pregnant by a RhD-negative man would not be offered AADP. This could in theory avoid up to one-sixth of RhD-negative women being offered and subsequently given anti-D.

There are, however, some difficulties associated with this approach. First, a woman may not know, or wish to disclose, who the father of her child is. In theory this could be discussed, and a full explanation provided of the advantage of identifying the father (i.e. a one-sixth chance of avoiding the need for anti-D, with all that entails), and she could then be offered the choice as to whether or not she wished to identify and involve the father. Nevertheless, the extent to which the father's rhesus status is not identified (for whatever reason) will reduce the benefit (in terms of avoidance of unnecessary anti-D) of this approach.

Secondly, the father may not wish to be identified and, once identified, may not wish to have a blood test performed to identify his rhesus status. It could be argued that the infringement of privacy involved in identifying the father is one that men should expect once they have fathered a child. However, again, the extent to which the rhesus status of the father cannot be identified will reduce the benefit of this approach.

Thirdly, the woman may (for a variety of reasons) either knowingly or unknowingly mis-identify the father. This opens up the possibility of a woman identifying a RhD-negative man as the father when in fact it was a RhD-positive man, and therefore not being given anti-D even though the infant is RhD-positive. Because of this possibility, there would be a strong argument for continuing to test at birth the rhesus status of all babies born to women who are RhD-negative, so that those women who have had RhD-positive babies can be offered anti-D if they have not already received it (and a booster if they have). It is inevitable that this approach would lead to the identification of cases of non-paternity, where after birth the man whom the mother has identified as being the father is demonstrated not to be. How frequently this would occur cannot be stated, but one can be confident that it would happen.

The situation could be made more difficult still if one attempted to ascertain whether the mother and fetus are likely to be ABO-incompatible. Sensitisation (in the absence of prophylactic anti-D) is more common in ABO-compatible than ABO-incompatible pregnancies. Therefore, if one pursued the goal of maximising a woman's choice, one would seek to identify the likelihood of ABO compatibility as well as whether or not the infant might be RhD-positive. This would require the father's ABO type to be established as well, and thus increase the information available postnatally that could identify cases of non-paternity.

(It may be noted that the current policy of testing babies of RhD-negative mothers postnatally could reveal non-paternity if the father were aware of his rhesus status. Currently, the majority of men are not aware of their status, and are not tested. It does not therefore become an issue.)

Finally, a policy of giving women the option of identifying the father, in order that he may be

tested and that they may thus avoid AADP when the father is RhD-negative, would add to health inequalities if, as is anticipated, women from more educated middle class backgrounds were more likely to be able to synthesise the information and make an informed choice, whilst women from less privileged backgrounds may be less able to do so.

Individual versus societal benefit

Encouraging women to make an informed choice as to whether or not to have prophylactic anti-D highlights the different costs and benefits to the individual women as opposed to the costs and benefits to society at large.

As noted in chapter 2 (see page 25), the chance of an individual woman benefiting from AADP is very small (between approximately one in 5730 and one in 8690). In these circumstances, it would be entirely rational for an individual woman to decline AADP. However, from the societal perspective, a policy of routine AADP could lead to savings in terms of loss of pregnancies and adverse outcomes.

Ethical issues

The widespread administration of an intervention that will benefit only a few (unidentifiable) individuals is well established in medical practice, and does not present new ethical issues. It is imperative that women are encouraged to make an informed choice, based on adequate information.

Similarly, the administration of an intervention (with associated risks) to a mother when the benefit will accrue to her subsequent pregnancies and future children is not new, and does not present new ethical problems. It is reasonable to assume that the mother herself will benefit indirectly from the benefit that will accrue to the subsequent pregnancies and children, and that she is the person best placed to assess the costs and benefits to both herself and her potential future children.

It could, however, be argued that the exposure of the baby to (unquantifiable, but probably very small) risk through exposure to anti-D, in order to gain a possible benefit for a younger sibling (who may never exist) is a new approach, and raises significant ethical issues. While we may feel that it is reasonable for the mother to make this decision on behalf of the baby, it does constitute using the baby as a means to an end, which is generally held to be unethical. However it is worth noting in this context that the Congenital Disabilities (Civil Liability) Act 1976[75] explicitly disbars children from suing their mothers for injuries received *in utero*. A damaged child could not therefore sue his or her mother for damages, though a case might be brought against other parties.

In addition, the administration of an intervention with unknown side-effects is not new. This is, after all, the case for all new drugs (even though the rigorous prelicensing testing allows one to be confident that the risk of serious adverse side-effects is very low indeed, of necessity any side-effect that is rare, or only manifest after prolonged use, cannot be ruled out).

It could be argued that what **does** present a new ethical issue in the case of AADP is the risk, which is unquantifiable (though probably very small indeed), that the administration of anti-D may transmit an infectious viral or prion disease. The results of this are potentially catastrophic – a worst case scenario would be that, if nvCJD were to be transmitted in this way, all RhD-negative women who become pregnant (i.e. up to 16% of the childbearing population) could contract the disease, which is fatal. Furthermore, their children might also be affected.

A number of points must be noted in this context. First, all RhD-negative women who deliver RhD-positive babies (60% of them) are currently offered anti-D postnatally, and the majority accept the intervention. If, therefore, there is a real risk of transmission of nvCJD (or other prion disease), then these women are already at risk. Thus the worst case scenario within current practice is that all RhD-negative women who have or have had RhD-positive infants (about 13% of all childbearing women) will contract nvCJD. If we are seriously concerned about nvCJD transmission in the context of AADP, we ought to be equally concerned about its transmission in the context of current practice.

Secondly, and more reassuringly, as noted above there is good evidence that the transmission of viral infections by the administration of immunoglobulins as currently prepared is extremely unlikely. Although the risk of transmission of prion disease is not known, it is minimised by the use of anti-D derived from countries in which BSE (bovine spongiform encephalopathy) has not been identified (see chapter 2, Concerns relating to the possible transfer of viral or prion infection, page 28).

Need for further research

Further research is required to:

- attempt to identify any characteristics which might identify the 10% of RhD-negative women who are at risk of sensitisation, in order to allow antenatal prophylaxis to be targeted specifically at these women
- confirm or disprove the preliminary findings that the protection against sensitisation provided by AADP in primigravidae extends beyond the first pregnancy.

Chapter 5
Conclusions

The evidence reviewed in this report suggests that routine AADP is effective in reducing the number of RhD-negative pregnant women who are sensitised during pregnancy. Eleven studies were found which compared women given routine AADP with a control group. In these studies, AADP was given to, or available for, a total of 29,288 RhD-negative women who then bore 30,917 RhD-positive babies. Of these women, 147 (0.5%) became sensitised. The control groups in ten of the eleven studies comprised a total of 12,153 women, who were at risk of RhD sensitisation; these women gave birth to 12,871 babies, and 167 women (1.4%) became sensitised. In the eleventh study,[55] 0.8% of a control group of unspecified size became sensitised.

Of the 147 women in the intervention groups who were reported to have been sensitised or sensibilised, it appears that:

- 51 represented possible or probable failures of treatment (i.e. cases in which sensitisation occurred despite appropriate administration of anti-D)
- more than 51 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)
- 27 were sensitised as a result of a previous delivery in a place where routine antenatal prophylaxis was either certainly or probably not provided.

Although some instances of sensitisation or sensibilisation are inevitable, occurring either despite or before appropriate administration of anti-D, others are attributable to failure to provide prophylaxis when appropriate despite the existence of a policy of routine AADP. The aggregated data indicate that as few as 51/29,288 eligible women were sensitised or sensibilised despite receiving antenatal prophylaxis (0.17%; 95% CI, 0.1 to 0.2%). This figure would rise to over 102/29,288 (0.35%; 95% CI, 0.3 to 0.4%) 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. It has been shown that some cases of sensitisation in the UK are due to failure to adhere to the existing guidelines for the administration of anti-D either post-partum or in response to potential sensitising events (see page 1). The avoidance of cases attributable to failure to administer appropriate routine antenatal prophylaxis would therefore require careful adherence to guidelines, and any programme of antenatal prophylaxis would need to be introduced in the context of watertight mechanisms to ensure that prophylaxis is offered at the appropriate time to all women at risk of sensitisation. The success of the programme would then depend upon the extent to which the intervention is acceptable to those women at risk of sensitisation.

The best indication of the likely efficacy of a programme of AADP use in England and Wales comes from the two non-randomised community-based studies.[43,46] 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%. Although the NNT to avoid one case of sensitisation is 166 (1/0.006), antenatally a RhD-negative woman will not know if she is carrying a RhD-positive child. Thus all RhD-negative pregnant women would require treatment, and not just the 60% who are carrying a RhD-positive child, making the overall NNT 278 (10/6 × 166).

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 RhD haemolytic disease of the newborn in that infant which constitutes the clinical benefit of AADP.

We estimate that, currently, 625 sensitisations of RhD-negative women per year lead to at least 30 fetal or neonatal losses per year. Avoidance of

sensitisation could thus be expected to avoid fetal/neonatal loss in 4.8% of cases. The NNT to avoid a fetal or neonatal loss in a subsequent pregnancy can therefore be estimated as approximately 5790.

Routine AADP provides a cost-effective intervention for preventing the incidence of haemolytic disease of the newborn in the pregnancies of RhD-negative women. Two preparations of anti-D are available, one of 500 IU and one of 1250 IU. There is no evidence for any difference in the clinical effectiveness of these preparations and, though there is a small price difference, both preparations have very similar cost-effectiveness profiles. The prices used in this assessment are based upon NHS list prices for these products. However, since the actual prices paid by hospitals vary, the cost-effectiveness in practice may be better than that presented here. Furthermore, 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. Thus a cost-minimisation comparison between the products is not appropriate.

Routine AADP given to RhD-negative primigravidae has a cost per LYG that is very good in comparison to other interventions routinely funded by the NHS. The incremental cost per LYG of giving routine AADP to all RhD-negative pregnant women is not as good, but there is still roughly a 90% chance of the cost-effectiveness being better than £30,000 per LYG.

In addition, routine AADP given to primigravidae has a cost per QALY gained which is economically attractive from the perspective of disability prevention alone, irrespective of attitudes to parental grief and valuation of stillbirths, neonatal and postneonatal deaths. Routine AADP given to all pregnant women who are RhD-negative is economically attractive, using a maximum acceptable cost-effectiveness ratio of £30,000 per QALY, if the lost child, associated parental grief and subsequent high intervention pregnancy are valued at more than 9 QALYs.

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Catherine Beverley (Systematic Reviews Information Officer, ScHARR) undertook the electronic literature searches.

Dr Myfanwy Lloyd Jones (Research Fellow, ScHARR) and Dr Jeremy Wight (Honorary Senior Lecturer in Public Health, ScHARR) carried out the reviews of clinical effectiveness.

Jim Chilcott (Senior Operational Research Analyst, ScHARR) carried out the economic analysis with the assistance of Paul Tappenden (Operational Research Analyst, ScHARR).

Katie Forman (Consultant Haematologist, Queen's Medical Centre) and Julie Wray, RCM (Lecturer/Research Fellow, School of Nursing, University of Salford) provided clinical advice.

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Appendix 1

MEDLINE search strategies

MEDLINE (Ovid) search strategy 1966–present

Anti-D prophylaxis

1 rh-hr blood-group system/
2 "rh0(d) immune globulin"/
3 rh isoimmunization/
4 anti-d prophylaxis.tw
5 or/1-4

Pregnancy

1 exp pregnancy/
2 exp pregnancy complications/
3 exp pregnancy trimesters/
4 pregnan$.tw
5 prenatal care/
6 postnatal care/
7 or/6-11

Guidelines filter

1 guideline.pt
2 practice guideline.pt
3 exp guidelines/
4 health planning guidelines/
5 or/14-17

Systematic reviews filter

1 meta-analysis/
2 exp review literature/
3 (meta-analy$ or meta analy$ or metaanaly$).tw
4 meta analysis.pt
5 review academic.pt
6 review literature.pt
7 letter.pt
8 review of reported cases.pt
9 historical article.pt
10 review multicase.pt
11 or/20-25
12 or/26-29
13 30 not 31

RCT filter

1 randomized controlled trial.pt
2 controlled clinical trial.pt
3 randomized controlled trials/
4 random allocation/
5 double blind method/
6 single blind method/
7 or/34-39
8 clinical trial.pt
9 exp clinical trials/
10 (clin$ adj25 trial$).ti,ab
11 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab
12 placebos/
13 placebos.ti,ab
14 random.ti,ab
15 research design/
16 or/41-48
17 comparative study/
18 exp evaluation studies/
19 follow up studies/
20 (control$ or prospectiv$ or volunteer$).ti,ab
22 prospective studies/
22 or/50-54
23 40 or 49 or 55

Economic evaluations filter

1 economics/
2 exp "costs and cost analysis"/
3 economic value of life/
4 exp economics, hospital/
5 exp economics, medical/
6 economics, nursing/
7 economics, pharmaceutical/
8 exp models, economic/
9 exp "fees and charges"/
10 exp budgets/
11 ec.fs
12 (cost or costs or costed or costly or costing$).tw
13 (economic$ or pharmacoeconomic$ or price$ or pricing).tw
14 or/61-73

Appendix 2

Characteristics of included studies

Bowman *et al.*, 1978[49]

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. It was stated that, by January 1972, enough untreated women had been accumulated to act as controls, and antenatal prophylaxis was therefore 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 isoimmunisation who had been given immunoglobulin after all previous RhD-positive abortions and deliveries, in Manitoba between 1 March 1967 and 15 December 1974: these appear to have been all such women who gave birth to RhD-positive babies in Manitoba during the period (clarification from Bowman, JM, MD OC, 231 Handsart Boulevard, Winnipeg, MB, Canada: personal communication, 2001).

Participants

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

Interventions

Approximately 1500 IU intramuscular anti-D at 34 weeks' gestation; 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 post-partum.

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 were 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 isoimmunisation 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 all women in the reported control group were screened at 6–9 months, or only those 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 isoimmunised before 34 weeks. No information is given regarding these women, who presumably belonged to the intervention group.

It is possible that there may have been differences in treatment during pregnancy between those women who gave birth in Winnipeg and those who gave birth elsewhere in Manitoba.

Quality

Poor.

Bowman and Pollock, 1978[50]

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 isoimmunisation who had been given immunoglobulin after all previous RhD-positive abortions and deliveries, in Manitoba between 1 March 1967 and 15 December 1974, whose data were reported in Bowman *et al.*, 1978[49]).

Participants

All pregnant RhD-negative women in Manitoba, Canada, with RhD-positive husbands and without evidence of RhD isoimmunisation in their current pregnancy who were treated in the antenatal Rh-D prophylaxis service programme between March

1976 and June 1977. These women 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 isoimmunised 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 intramuscular 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
The use of historic controls limits the value of this study as it is not clear to what extent sensitisation rates may have been influenced by changes in obstetric practice over time as well as by the use of antenatal prophylaxis.

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

Quality
Poor.

Bowman and Pollock, 1987[51]

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 isoimmunisation who had been given immunoglobulin after all previous RhD-positive abortions and deliveries in Manitoba between 1 March 1967 and 15 December 1974, whose data were reported in Bowman *et al.*, 1978[49]). Although, according to Urbaniak,[2] this study included 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.

Participants
RhD-negative women delivered of RhD-positive babies in Manitoba, Canada, 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 3 days of delivery.

Notes
The use of historic controls limits the value of this study as it is not clear to what extent sensitisation rates may have been influenced by changes in obstetric practice over time as well as by the use of antenatal prophylaxis.

The authors' comparison is with the primigravidae only in the 'control' group reported in Bowman *et al.*, 1978.[49] It is not clear why their comparison was not with the unselected group. Six-week and 6-month postdelivery 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.

Trolle, 1989[52]

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

Participants
All pregnant RhD-negative women in Kolding, Denmark in 1980–85 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 1972–77).

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 feto-maternal transfusion was estimated to be less than 15 nl blood.

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

Notes
The use of historic controls limits the value of this study as it is not clear to what extent sensitisation rates may have been influenced by changes in obstetric practice over time as well as by the use of antenatal prophylaxis.

The authors claim that the control group was comparable to the study group in all respects with regard to the number of first pregnancies and factors known to provoke feto-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 fetal blood, compared with only 7.9% in the intervention group ($p < 0.001$). Moreover, only the intervention group underwent antenatal antibody screening in the 28th week, as a result of which, although the control group may have included women who were isoimmunised before the 28th week, the intervention group did not. A total of 84% of the intervention group and 91% of the control group were screened at 10 months after delivery. For all of these reasons, isoimmunisation was more likely to be found in the control group.

Quality
Poor.

Parsons *et al.*, 1998[55]

Method
Retrospective review.

Participants
All RhD-negative women delivered of RhD-positive infants over 500 g birth weight or 20 weeks' gestation in Nova Scotia, Canada, from 1988–95. Data is compared with similar data from Scotland, UK.

Interventions
28-week antenatal prophylaxis (presumably 1500 IU, in line with Canadian policy).

Outcomes
Sensitisation at unspecified time point.

Notes
This report is only published in abstract form. The numbers of women at risk and sensitised in Nova Scotia, with sensitisation rate, are compared with only the sensitisation rate for Scotland. The use of geographic controls limits the value of this study as it is not clear to what extent sensitisation rates in the two study areas are influenced by differences in obstetric practice as well as by the use of antenatal prophylaxis.

The effect of excluding women delivered of very premature or low birth weight infants is not clear, but may favour the intervention.

Quality
Poor.

Hermann *et al.*, 1984[53]

Method
Prospective study with historic controls.

Participants
RhD-negative primigravidae, and multigravidae who had previously been treated with anti-D post-partum or after abortion, and had been followed up serologically after 8 months; the control group was drawn from an earlier, unpublished, study in Sweden by the same authors.

Interventions
1250 IU intramuscular anti-D given at about the 32nd to 34th week of gestation; all women in both the intervention group and the historic control group who were delivered of RhD-positive babies also received 1250 IU anti-D within 72 hours of delivery.

Outcomes
Incidence of immunisation at delivery and at 8 months; safety; cord and capillary bilirubin; cord and capillary haemoglobin.

Notes
The use of historic controls limits the value of this study as it is not clear to what extent sensitisation rates may have been influenced by changes in obstetric practice over time as well as by the use of antenatal prophylaxis.

Women were excluded from the intervention group if they showed signs of immunisation at the first antibody screen test in the first trimester or prior to the first dose of anti-D in the 32nd–

34th week (three women were excluded on this basis). It is not clear whether the control group was also tested at the 32nd–34th week and women with antibodies excluded from the study. No information is given regarding the proportion of women in either group who were screened at 8 months. Some women were in the study for more than one pregnancy. Of the 529 RhD-negative women who delivered RhD-positive babies, 39 were said to have given birth to a RhD-positive infant subsequently; they received anti-D antenatally and again just after the delivery, and none were sensitised at 8 months. These figures do not seem to have been included in the analysis of results.

Quality
Poor.

Tovey *et al.*, 1983;[45] Thornton *et al.*, 1989[54]

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

Participants
Non-sensitised RhD-negative primigravidae in the Yorkshire region (UK) 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 post-partum 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; fetal survival at 1 month.

Notes
The use of historic controls limits the value of this study as it is not clear to what extent sensitisation rates may have been influenced by changes in obstetric practice over time as well as by the use of antenatal prophylaxis. However, the historic controls were close in time to the intervention group.

A total of 85% of the intervention group were screened 6 months after their first delivery. No information is given regarding the proportion receiving such screening after subsequent deliveries, or the proportion of women in the control group who were screened.

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.

Huchet *et al.*, 1987[42]

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, France.

Interventions
500 IU intramuscular anti-D at 28 and 34 weeks (in practice this was administered between weeks 26–29 and 32–36). All women in the intervention and control groups delivered of RhD-positive babies received 500 IU intravenous post-partum 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 fetal red blood cells during pregnancy; cost-effectiveness of treatment.

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

Quality
Good.

Mayne *et al.*, 1997[46]

Method
Retrospective before-and-after study, comparing data from 1993–95, when the antenatal anti-D programme was fully operational, with data from

1988–90, before its introduction; intention-to-treat analysis.

Participants
All pregnant RhD-negative primiparae in Southern Derbyshire, UK.

Interventions
500 IU of anti-D given intramuscularly at 28 and 34 weeks' gestation, plus post-partum 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 use of historic controls limits the value of this study as it is not clear to what extent sensitisation rates may have been influenced by changes in obstetric practice over time as well as by the use of antenatal prophylaxis.

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.

MacKenzie *et al.*, 1999[43]

Method
Community intervention trial with historical and contemporary controls:

- a retrospective analysis of the rate of isoimmunisation in RhD-negative women delivered of their first child between 1 January 1980 and 31 December 1986 in Oxfordshire or Northants, UK, who underwent a second continuing pregnancy; data were derived from a prospectively maintained serology laboratory register and verified from individual case records.
- a prospective study of the rates of isoimmunisation in RhD-negative women undergoing a second continuing pregnancy with an expected date of delivery between 1 January 1987 and 31 December 1996 in two similar populations; in one of these populations (Oxfordshire), routine antenatal prophylaxis had been offered since April 1986 to all RhD-negative women with no living children booked for confinement in the county, and in the other (Northants) it had not.

Intention-to-treat analysis.

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 post-partum, but in Northamptonshire it was only offered 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 appropriately-designed study demonstrates 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 isoimmunisation prior to the introduction of the antenatal anti-D programme, and that subsequent differences in those rates could therefore reasonably be attributed to that programme.

Quality
Good.

Lee and Rawlinson, 1995[44]

Method
RCT (treatment allocation by sealed envelopes at each Regional Transfusion Centre).

Participants
RhD-negative primigravidae without anti-D (other than passive) at 28 weeks' gestation, recruited from obstetric units throughout the UK handling an estimated 75,000 births a year.

Interventions
250 IU anti-D given at 28 and 34 weeks' gestation. All women in intervention and control groups delivered of RhD-positive babies received 500 IU intravenous post-partum anti-D.

Outcomes
Incidence of immunisation 6 months post-partum (or, where this sample gave an equivocal result, at a later date).

Notes
No data (not even RhD status of infant) were available relating to 205 women in the control group and 264 in the intervention group. Over 30% of women in each group who had a RhD-positive infant were not screened at 6 months, and it is not clear whether they differed in any significant way from those women who were screened.

Women were excluded from the analysis if they were not tested for anti-D at delivery (19 in the treatment group and 53 in the control group) or if, in the treatment group, they had not received both doses of anti-D (52 women). One woman from the control group was excluded from the analysis because she had immune anti-D at randomisation with a history of threatened abortion at 13 weeks; one woman from the treatment group was excluded from the analysis because she was sensitised and appeared to have had a concealed antepartum haemorrhage at 31 weeks for which additional anti-D was not given.

It had been calculated that 2600 women would be required in each arm to have an 80% chance of finding significant protection if the true reduction in sensitisation in response to prophylaxis were five-fold. However, the trial was concluded prematurely when approximately 2000 women had been randomised because the expected difference between treatment and control groups was not emerging and it was calculated that around 7500 women would be required in each arm to detect a significant difference.

Quality
Good.

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We look forward to hearing from you.

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