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for Health Services Research

WORKING GROUP ON ACUTE PURCHASING

The Use of Routine Antenatal Anti-D Prophylaxis for Rhesus Negative Women

April 1999

GUIDANCE NOTE FOR PURCHASERS 99/04
Series Editor: Nick Payne

InterDEC No: 13/1999

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Trent Development and Evaluation Committee

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The purpose of the Trent Development and Evaluation Committee is to help health authorities and other purchasers within the Trent Region by commenting on expert reports which evaluate changes in health service provision. The Committee is comprised of members appointed on the basis of their individual knowledge and expertise. It is chaired by Professor Sir David Hull.

The Committee recommends, on the basis of evidence provided, priorities for:

- the direct development of innovative services on a pilot basis;

- service developments to be secured by health authorities.

The statement that follows was produced by the Development and Evaluation Committee at its meeting on 13 April 1999 at which this Guidance Note for Purchasers (in a draft form) was considered.

THE USE OF ROUTINE ANTENATAL ANTI-D PROPHYLAXIS FOR RHESUS NEGATIVE WOMEN

AUTHORS: Allaby M, Forman K, Touch S, Chilcott J. Trent Institute for Health Services Research, Universities of Leicester, Nottingham and Sheffield 1999. Guidance Note for Purchasers: 99/04.

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(The recommendations made by the Committee may not necessarily match the personal opinions expressed by the experts)

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DECISION: The Committee recommended that Anti-D prophylaxis should be offered as a routine antenatal procedure for all Rhesus negative women regardless of the number of previous pregnancies. The Committee considered it essential that comprehensive information is made fully available to both staff and patients.

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Conflict of Interest   None of the authors of this document has any financial

interests in the drug or product being evaluated here.

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ABOUT THE TRENT INSTITUTE FOR HEALTH SERVICES RESEARCH

The Trent Institute for Health Services Research is a collaborative venture between the Universities of Leicester, Nottingham and Sheffield with support from NHS Executive Trent.

The Trent Institute:

- undertakes Health Services Research (HSR), adding value to the research through the networks created by the Institute;

- provides advice and support to NHS staff on undertaking HSR;

- provides training in HSR for career researchers and for health service professionals;

- provides educational support to NHS staff in the application of the results of research;

- disseminates the results of research to influence the provision of health care.

The Directors of the Institute are: Professor R L Akehurst (Sheffield);

                                               Professor C E D Chilvers (Nottingham); and

                                               Professor M Clarke (Leicester).

Professor Clarke currently undertakes the role of Institute Co-ordinator.

A Core Unit, which provides central administrative and co-ordinating services, is located in Regent Court within The University of Sheffield in conjunction with The School of Health and Related Research (ScHARR).

FOREWORD

The Trent Working Group on Acute Purchasing was set up to enable purchasers to share research knowledge about the effectiveness and cost-effectiveness of acute service interventions and determine collectively their purchasing policy. The Group is facilitated by The School of Health and Related Research (ScHARR), part of the Trent Institute for Health Services Research, the ScHARR Support Team being led by Professor Ron Akehurst and Dr Nick Payne, Consultant Senior Lecturer in Public Health Medicine.

The process employed operates as follows. A list of topics for consideration by the Group is recommended by the purchasing authorities in Trent and approved by the Health Authority and Trust Chief Executives (HATCH) and the Trent Development and Evaluation Committee (DEC). A public health consultant from a purchasing authority leads on each topic assisted by a support team from ScHARR, which provides help including literature searching, health economics and modelling. A seminar is led by the public health consultant on the particular intervention where purchasers and provider clinicians consider research evidence and agree provisional recommendations on purchasing policy. The guidance emanating from the seminars is reflected in this series of Guidance Notes which have been reviewed by the Trent DEC, chaired by Professor Sir David Hull.

In order to share this work on reviewing the effectiveness and cost-effectiveness of clinical interventions, The Trent Institute's Working Group on Acute Purchasing has joined a wider collaboration, InterDEC, with units in other regions. These are: The Wessex Institute for Health Research and Development and The University of Birmingham Department of Public Health and Epidemiology.

Professor R L Akehurst,
Chairman, Trent Working Group on Acute Purchasing

ABBREVIATIONS

AADP	Antenatal Anti-D Prophylaxis
AIDS	Acquired Immune Deficiency Syndrome
BPL	Bio Products Laboratory
CJD	Creutzfeldt-Jakob Disease
DoH	Department of Health
Hb	Haemoglobin
HDN	Haemolytic Disease of the New-born
IgG	Immunoglobulin
iu	International Units
IUT	Intrauterine Transfusion
LYG	Life Year Gained
MCA	Medicines Control Agency
NRCT	Non-randomised controlled trial
nv	New Variant
QALY	Quality Adjusted Life Year
RCT	Randomised controlled trial
RhD	Rhesus D

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EXECUTIVE SUMMARY

The purpose of giving routine antenatal anti-D prophylaxis (AADP) is to prevent cases of haemolytic disease of the new-born (HDN). These can occur when a woman whose blood group is RhD negative develops antibodies against the red blood cells of her RhD positive fetus. Although this is unlikely to cause harm during that pregnancy, any subsequent pregnancy with a RhD positive fetus will be at risk of HDN. The possible consequences of HDN include anaemia, jaundice, brain damage and death. Management of a pregnancy in a woman with anti-D antibodies requires intensive monitoring and may involve interventions such as fetal blood sampling, exchange transfusion and neonatal intensive care.

The production of anti-D antibodies by the mother can be prevented by injecting anti-D obtained from human donors. Over 90% of cases of HDN have been prevented by the widespread use of postnatal anti-D prophylaxis (for all RhD negative women who deliver a RhD positive infant) and of antenatal anti-D prophylaxis in defined circumstances, such as, miscarriage or abdominal trauma. Despite these measures, about 1.5% of RhD negative women will still have developed anti-D antibodies following a RhD positive pregnancy. Meta-analysis of the nine relevant published studies provides strong evidence that the sensitisation rate can be reduced to about 0.24% by giving AADP routinely to RhD negative women during the third trimester. The preferred dose regime is one dose of anti-D at 28 weeks gestation and a second at 34 weeks.

Anti-D Immunoglobulin (IgG) is a human plasma-based product and so, naturally, there is concern over its safety. Intramuscular immunoglobulins, which include anti-D, have an excellent safety record with no reported cases of viral transmission. Moreover, the available products are produced from non-UK donor plasma and the Medicines Control Agency has recommended these for antenatal prophylaxis. Patients and staff ought already to be receiving suitable information about the safety of anti-D IgG, as postnatal anti-D prophylaxis is a routine procedure.

This report identifies the costs, clinical consequences and cost-effectiveness of the three main options for purchasers:
- Option 1 - not offering routine AAPD;
- Option 2 - offering routine AADP to RhD negative primigravidae only;
- Option 3 - offering routine AADP to all RhD negative women.

For a 'typical' district of 500,000 population, Option 2 would cost approximately £12,100 per year, with cost effectiveness ratios of £3,800 per case of Rhesus disease prevented, £5,200 per Life Year Gained (LYG), or £85,300 per fetal loss avoided. Option 3 would cost approximately £33,000 per year, with cost-effectiveness ratios of £6,400 per case of Rhesus disease prevented, £9,700 per LYG, or £159,400 per fetal loss avoided.

Option 2 has a lower gross cost and is marginally more cost-effective in comparison to option 3. However, practical and ethical difficulties are foreseen in implementing option 2, and so, since option 3 is cost-effective in comparison with many other health care interventions provided by the NHS, this is the preferred option.

1.   INTRODUCTION

1.1   Incidence and Pathology

Haemolytic Disease of the New-born (HDN) 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 HDN affect Rhesus D (RhD) positive infants born to RhD negative mothers. The mothers usually make the anti-D antibody following a small foeto-maternal haemorrhage at delivery of the first RhD positive infant. This does not harm the current infant, but successive RhD positive infants are then progressively more severely affected by HDN. Maternal sensitisation can also result from the transfusion of RhD positive red cells.

Approximately 17% of women are RhD negative 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. Prior to the introduction of any immunoprophylaxis, the frequency of the disease was one per 100 births in second pregnancies and higher in subsequent pregnancies. In the mid 1950s in England and Wales, HDN was responsible for 310 deaths per year - one in 2,180 births.

Since that time prophylaxis with anti-D and advances in neonatal care alone have had a major impact. Standard anti-D prophylaxis was introduced in the UK in 1969 and by 1989 the comparable registered death rate was 1 in 65,000 births. Such registrations should be considered an underestimate because fetal loss before 28 weeks, including death due to severe hydrops for example, was not registrable.

In the UK, conventional practice is to give intravenous anti-D immunoglobulin within 72 hours of delivery to all RhD negative women who have RhD positive infants and are not already sensitised. The size of any foeto-maternal bleed is estimated and a further anti-D dose given if indicated. Any event during pregnancy with the potential to cause sensitisation should also prompt an anti-D injection within 72 hours. Such events include abdominal trauma, miscarriage, amniocentesis, chorion villous sampling, antepartum haemorrhage, external cephalic version and termination of pregnancy.

Despite this policy, however, there is a failure rate resulting in sensitisation prior to delivery of the first pregnancy. These failures have been examined and a proportion found due to

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failure to adhere to the existing policy, through lack of administration of (a) any anti-D, (b) enough anti-D or (c) timely anti-D when clearly indicated. Even after allowing for these failures, there remains a significant number of women who develop 'silent' sensitisation in the absence of any identifiable risk event and for whom post delivery prophylaxis is too late. These are the women who stand to benefit from routine antenatal anti-D prophylaxis (AADP). From the studies reviewed in this Guidance Note, it appears that approximately 1.5% of RhD negative women with RhD positive infants develop 'silent' sensitisation. It should also be noted that women who experience 'silent' sensitisation appear to be high responders who suffer a higher rate of fetal morbidity and mortality due to HDN and, consequently, require the highly specialised support services.

1.2   Prognosis

The severity of disease 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. Thus, affected pregnancies require close monitoring of both the maternal antibody level (every two weeks from 20 weeks) and the state of the fetus by 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 its mildest form the sensitised red cells are detectable in laboratory tests alone, but more commonly the infant has a mild degree of jaundice which responds to phototherapy. More severe degrees involve significant anaemia and progressive hyperbilirubinaemia. Certain neonatal brain structures, e.g. thalamus, 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 periumbilical blood sampling in the early 1980s and the ability to establish fetal RhD type and Haemoglobin (Hb) level has eased the management of potentially severely affected infants, not least by providing a return route for 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. It has to be balanced, however, against an estimated 5% fetal loss from IUT. Such intervention requires a highly specialised unit with skilled personnel, equipment (particularly radiological) and access to specialised blood products.

1.3   Scale of Problem in a 'Typical' District

The crude rate for all births is 12.5 per 1,000 population of all ages per annum, figures taken from the 1996 Birth Statistics, England and Wales – Office of National Statistics (ONS).[1] Therefore, in a 'typical' district of 500,000 population there are approximately 6,250 deliveries a year, 17% of which are in RhD negative women, i.e. 1,062 deliveries, and RhD negative women with a RhD positive baby account for 10% of deliveries, i.e. 625 per annum.

Assuming that 1.5% of RhD negative women with a RhD positive baby become sensitised antenatally, approximately nine women become sensitised per year. Eight of these women are likely to have a subsequent pregnancy, which will have to be closely monitored and in which HDN may occur. The cost of this monitoring and treatment is approximately £1,320 per case. Of these eight subsequent pregnancies, six fetuses are likely to develop Rhesus disease and one fetus is likely to be lost every five years. The net cost of treating nine sensitised women and the subsequent complications, i.e. cases of Rhesus disease, is estimated between £8,991 and £11,401.

2. USE OF ROUTINE ANTENATAL ANTI-D PROPHYLAXIS FOR RHESUS NEGATIVE WOMEN : SUMMARY OF EVIDENCE OF EFFECTIVENESS

2.1 Evidence of Effectiveness

2.1.1 Reduction in the Rate of Rhesus Sensitisation Attributable to Antenatal anti-D Prophylaxis

Trials of the effectiveness of Antenatal anti-D Prophylaxis (AADP) were identified through searching Medline, Embase, the Cochrane Database of Systematic Reviews, conference reports and reference lists. Nine relevant studies were identified, published between 1978 and 1995, of which six were non-randomised trials with historical or geographical controls,[2,3,4,5,6,7] two were randomised controlled trials,[8,9] and one was a population-based before-and-after study.[10] Because only one of the randomised controlled trials used a dosage regime which is currently considered appropriate,[8] the non-randomised studies have been retained for further consideration here.

The patient selection criteria and the dosage regimes used vary between the nine studies. In four studies AADP was given to primigravidae only,[2,7,9,10] though the results from one of these studies relate to both primigravidae who received prophylaxis and multigravidae who did not.[10] In the remaining five studies AADP was given to both primigravidae and multigravidae;[3,4,5,6,8] results for the sub-group of primigravidae were reported separately in one of these.[8] The dose of anti-D used varies six-fold between the studies, from two doses of 1,500 international units (iu) down to two doses of 250 iu. The two most widely used dosage regimes are 500 iu at 28 and 34 weeks gestation, and a single dose of 1,500 iu at 28 weeks.

In the nine trials, a total of 17,398 RhD negative women who bore RhD positive babies were given AADP and observed during the trials. Of these, 48 became sensitised. A total of 11,757 women at risk of Rhesus sensitisation were studied as control groups, of which 174 became immunised. The largest study[4] accounts for over half of the total number of intervention patients in the literature, but the design of this study is relatively weak: the intervention group received AADP between 1977 and 1986, but the results were compared with the experience of controls from the same geographical area during the period 1967 - 1974. The results are shown in Table 1. All the sensitisation rates relate to women at risk of Rhesus sensitisation i.e. RhD negative women who are pregnant with a RhD positive baby.

Table 1   Summary of Trial Results

Study	Study Design	Dosage	Patient Selection	n	r	% Sensitised in anti-D Prophylaxis Group	Upper 95% CI	Lower 95% CI	n	r	% Sensitised in Control Group	Upper 95% CI	Lower 95% CI
Bowman[2] (1978)	NRCT	2 x 1500iu (28 and 34 weeks)	Primigravidae	1,357	1	0.07	0.22	0.00	2,768	45	1.63	2.10	1.15
Bowman[3] (1978)	NRCT	1 x 1500iu (28 weeks)	Unselected	1,805	5	0.28	0.52	0.03	3,533	62	1.75	2.19	1.32
Bowman[4] (1987)	NRCT	1 x 1500iu (28 weeks)	Unselected	9,295	25	0.27	0.37	0.16	3,533	62	1.75	2.19	1.32
Trolle[5] (1989)	NRCT	1 x 1500iu (28 weeks)	Unselected	291	0	0.00	0.00	0.00	322	6	1.86	3.34	0.39
Hermann[6] (1984)	NRCT	1 x 1250iu (34 weeks)	Unselected	529	2	0.38	0.90	0.00	645	10	1.55	2.50	0.60
Tovey[7] (1983)	NRCT	2 x 500iu	Primigravidae	1,238	4	0.32	0.64	0.01	2,000	19	0.95	1.38	0.52
Huchet[8] (1987)	RCT	2 x 500iu (28 and 34 weeks)	Primigravidae Multigravidae Unselected	362 110 472	0 1 1	0.00 0.91 0.21	0.00 2.68 0.63	0.00 0.00 0.00	360 108 468	4 3 7	1.11 2.78 1.50	2.19 5.88 2.60	0.03 -0.32 0.40
Lee[9] (1995)	RCT	2 x 250iu (28 and 34 weeks)	Primigravidae	513	4	0.78	1.54	0.02	595	9	1.51	2.49	0.53
Mayne[10] (S. Derbyshire) (1997)	Before and After	2 x 500iu (28 and 34 weeks)	Unselected	1,898	6	0.32	0.57	0.06	1,426	16	1.12	1.67	0.58

Key :
NRCT = non randomised controlled trial
RCT = randomised controlled trial
n = number of Rhesus negative women with Rhesus positive babies in the trial group
r = number of sensitised Rhesus negative women in the trial group

2.1.2 Meta-Analysis

The variability in study design, randomisation and control design, patient selection criteria, primigravidae only or all women, and dosage regimes makes meta-analysis problematic. This report presents three meta-analyses:

- Group 1 includes the results of the two studies[7,8] (one randomised, one not) which used a dosage regime of 500 iu at 28 and 34 weeks and report results for primigravidae;
- Group 2 includes the results of the three studies,[3,4,5] (none of them randomised) which used a dosage regime of 1,500 iu at 28 weeks and included both primigravidae and multigravidae;
- Group 3 includes the results of all the identified studies except the trial by Lee (1995)[9] which was omitted as the dosage regime consisted of two injections of 250 iu anti-D Immunoglobulin (IgG), which is now considered to be too low.

The method of meta-analysis performed on the three groups of trials was a binary logistic regression on a fixed-effects model.[11] The study and treatment group were the variables in the model and the effect size was measured as an odds ratio. As the event rate is low, the odds ratio is a good approximation of the relative risk of sensitisation in the cohort which received antenatal prophylaxis, compared with that in the group which received no treatment. To test for heterogeneity, an interaction term between the study and treatment variables was added. This was not statistically significant and, therefore, indicated that there was no evidence to reject the hypothesis of homogeneity between the trials grouped for meta-analysis, $\chi^2 = 1.043$ on 1 df, p = 0.31, $\chi^2 = 0.77$ on 1 df, p = 0.38 and $\chi^2 = 3.62$ on 6 df, p = 0.73 for the three meta-analyses respectively. Furthermore, visual examination of the absolute results in the treatment and no treatment groups, and the odds ratio for all the studies, see figures 1-3, show a remarkable consistency in results.

The sensitisation rate for the group who received no treatment was calculated by taking the average of the sensitisation probabilities, estimated from the logistic regression model applied to each study. As the control group used in the Bowman 1987 study[4] was the control group of the Bowman 1978 study[3], the two trials were combined into one three armed study in the meta-analysis in order to prevent the control group being double counted. The results of the meta-analyses are in Table 2 .

Table 2   Results of the Meta-analyses

	Group 1 - 2x500iu Primigravidae	Group 2 - 1x1500iu Primigravidae and Multigravidae	Group 3 - All Trials except the 2 x 250iu Trial
Test for Heterogeneity (p-value)	0.31	0.38	0.73
Odds Ratio of Sensitisation with Antenatal Prophylaxis 95% CI	0.26 (0.09; 0.75)	0.15 (0.09 ; 0.23)	0.16 (0.11 ; 0.23)
Sensitisation Rate of Control Group 95% CI	0.94% (0.83%; 1.04%)	1.71% (1.58% ; 1.84%)	1.47% (1.30% ; 1.65%)
Sensitisation Rate of Antenatal Prophylaxis Group using Meta-analysis Range	0.24% (0.09%; 0.62%)	0.26% (0.17% ; 0.36%)	0.24% (0.18% ; 0.30%)

Figure 1   Meta-analysis of Group 1

2 x 500 iu in Rhesus Negative Primigravidae
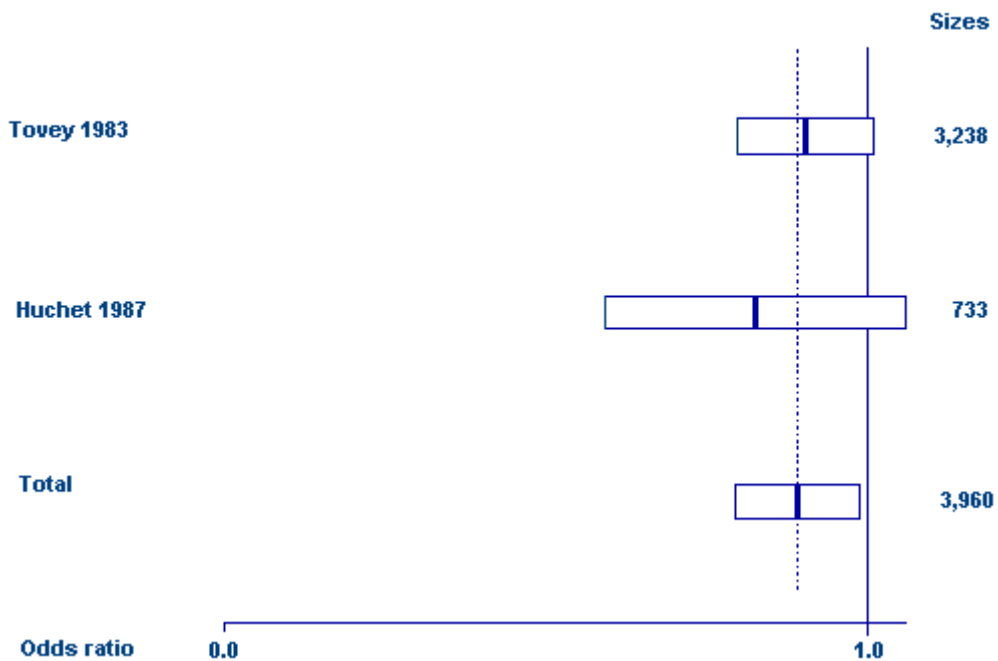
Odds Ratio = 0.26
95% confidence Intervals = (0.09 ; 0.75)

Figure 2   Meta-analysis of Group 2

1 x 1,500 iu in Unselected Rhesus Negative Women

Odds Ratio = 0.15
95% Confidence Interval = (0.09 ; 0.23)
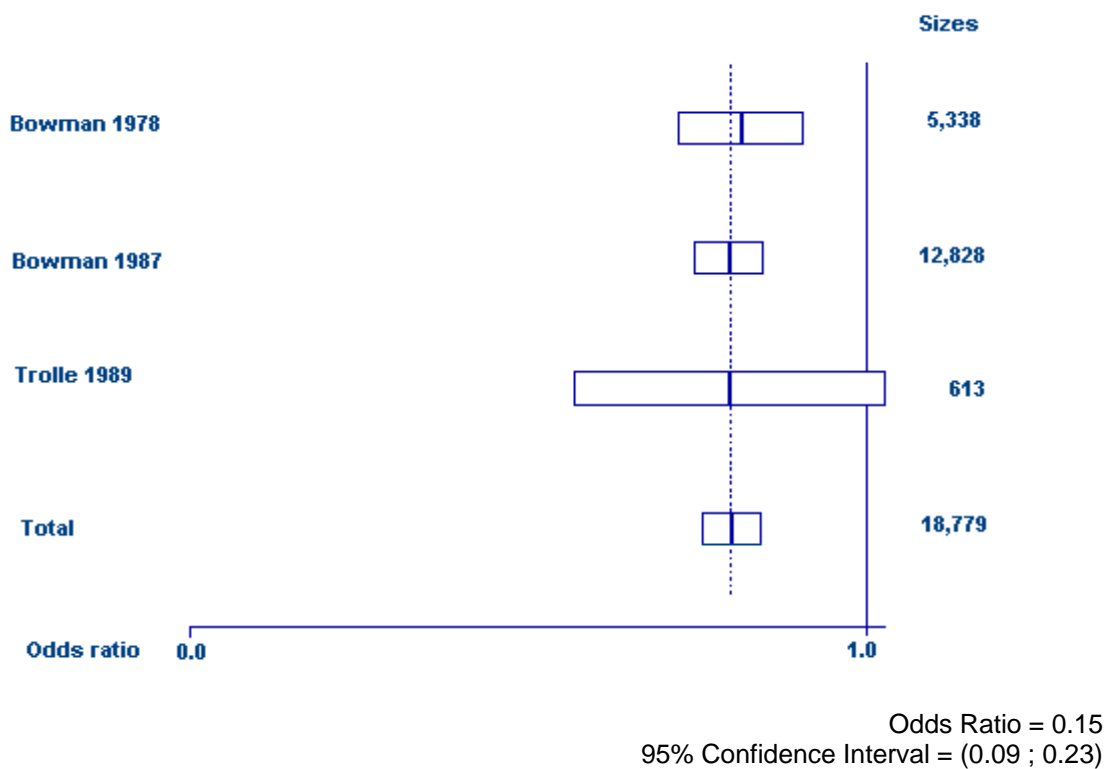
Figure 3   Meta-analysis of Group 3

All Trials of Dose Regimes Currently Considered to be Effective

Odds Ratio = 0.16 95%
Confidence Interval = (0.11 ; 0.23)
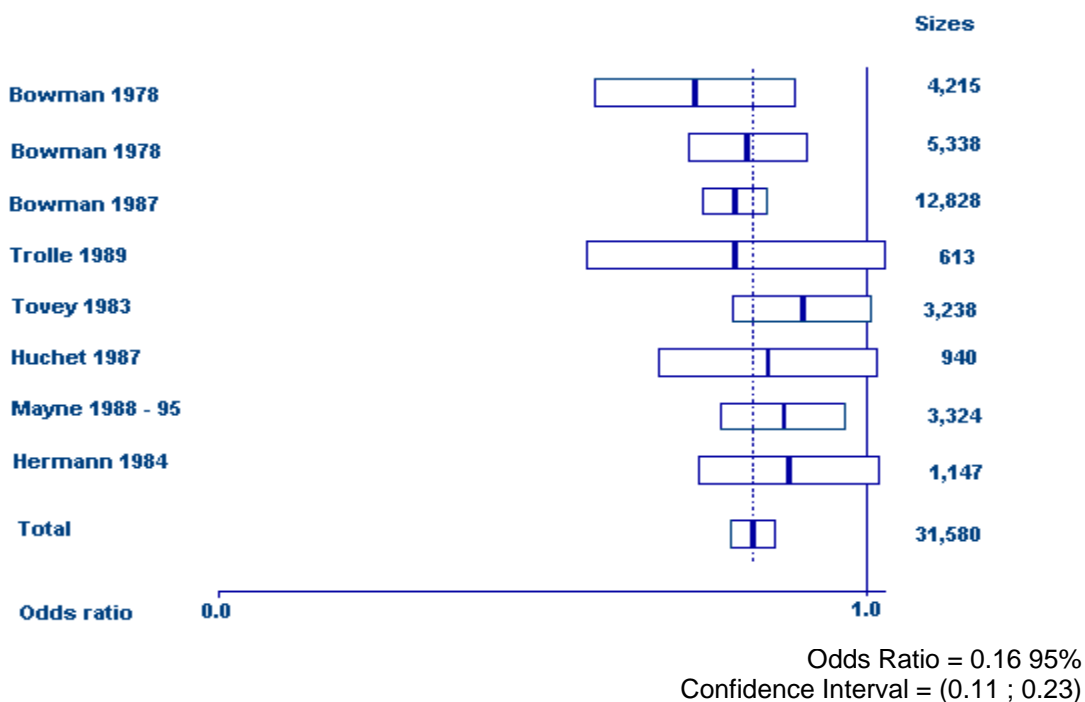
In all three meta-analyses AADP produced a significant reduction in the rate of Rhesus sensitisation. The summary odds ratio for the 2 x 500 iu dose regime (0.26) is higher than that for the 1 x 1,500 iu regime (0.15). However, the confidence intervals of these odds ratios overlap widely. Figure 3 shows that the results of the non-randomised studies are very similar to those of the one randomised study which used a currently recommended dose of anti-D.[8] This suggests that the non-randomised studies are unlikely to be seriously biased.

In order to assess the possibility of publication bias, a funnel plot is presented in Figure 4. In the absence of publication bias, because of sampling variability, the graph should have the shape of an upside down funnel, with the large opening down and the tip pointing up and centred on the true effect size. This can be seen to be the case in Figure 4. Publication bias would result in the funnel being skewed either to the left, positive bias, or to the right, negative bias.

Figure 4   Assessing the Possibility of Publication Bias
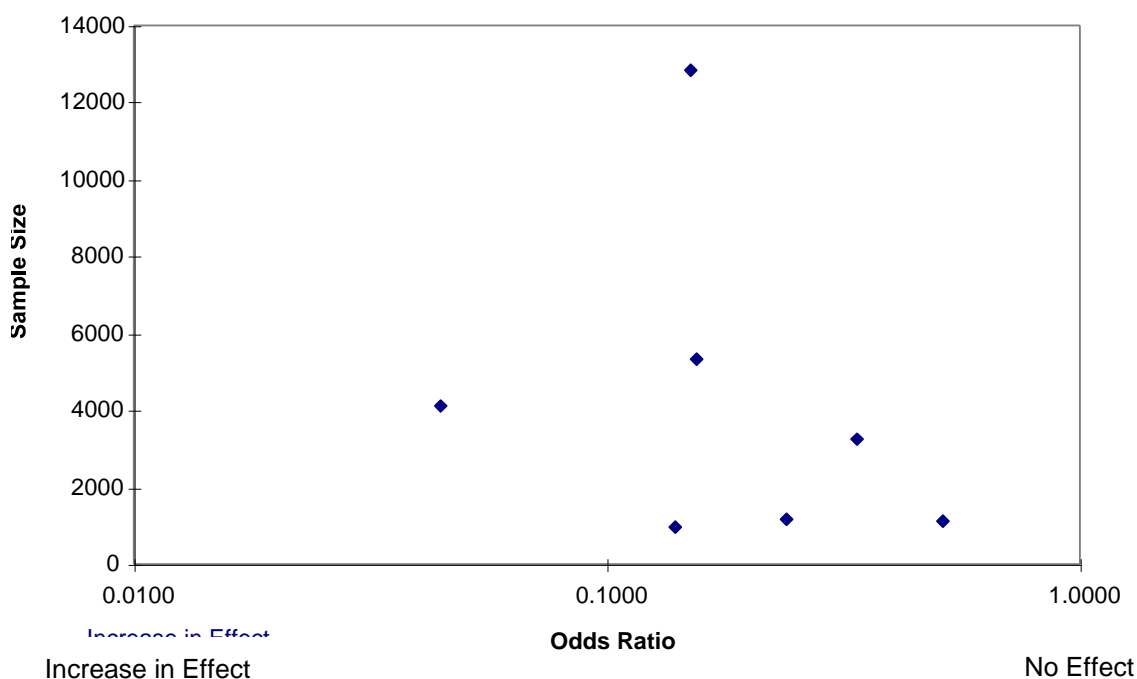
The odds ratio for the randomised trial of 2 x 250 iu [9] was 0.51 (95% CI 0.16 -1.67). This is considerably higher than the summary relative risks from each of the meta-analysis groups.

The trial itself concluded that two doses of 250 iu were not as effective as either of the higher dosage regimes and could not be recommended for routine prophylaxis.

In the absence of any firm evidence to the contrary, this report assumes that there is no difference in effectiveness between any of the dose regimes assessed except for the 2 x 250 iu regime, which appears to be less effective. (It is acknowledged that when the 1 x 1,500 iu at 28 weeks regime has been used, about 30% of women have required a further dose at 36 weeks).[2] In order to use the greatest possible amount of trial data consistent with this assumption, the subsequent analyses in this report use the results of the third meta-analysis, that is, it incorporates in a single estimate the results of all the trials of dose regimes that are currently considered to be effective.

2.1.3   Reduction in the rate of fetal loss attributable to antenatal prophylaxis

Fetal loss due to Rhesus disease has become a relatively rare event since the widespread introduction of postnatal anti-D prophylaxis. It was, therefore, not used as an outcome measure in any of the trials of effectiveness of AADP. The rate of sensitisation has been used as an intermediate endpoint and is assumed to be directly related to fetal loss rates. In order to estimate the potential reduction in the rate of fetal loss attributable to a policy of routine antenatal prophylaxis the following steps have been taken:

- the rate of fetal loss over a defined time period is obtained;
- it is assumed that the no treatment polices represented in the control arms of the studies typify practice in the UK over the above period, and that, therefore, the sensitisation rate of 1.5% can be related to the underlying fetal loss rate;
- it is further assumed that a reduction in the sensitisation rate will lead to proportionate reduction in the prevalence of sensitisation, HDN and fetal loss.

From 1977 to 1989 all deaths registered as due to haemolytic disease of the new-born (HDN) in England and Wales have been analysed by individual case note review.[12,13] In order to be registered as a death during that period a baby had to be either stillborn, that is at least 28 weeks' gestation, by definition, or born alive at any gestation, including a proportion below 28 weeks' gestation. The published analysis used six categories to classify the likely cause of the haemolytic disease:

1. Mother believed to have been immunised by a pregnancy following which she was not given anti-D.
2. Mother immunised during first pregnancy.
3. Mother immunised despite having been given anti-D after one or more previous pregnancies.
4. Mother immunised to D by blood transfusion.
5. Haemolytic disease due to an antibody other than anti-D.
6. Death not due to haemolytic disease.

The deaths which are potentially preventable by AADP are those in categories 2 and 3. Over the period 1977 to 1989 there were 195 deaths in these two categories, an average of 15 per year. This equates to a rate of loss of 0.02% among RhD negative women with a RhD positive baby, assuming that they constituted 10% of all births during this period. This rate does not include fetal losses that occurred prior to 28 weeks' gestation, unless the fetus was born alive. A review of fetal losses due to haemolytic disease at one tertiary referral centre in Glasgow over a 15 year period found that 21 out of 46 losses (46%) occurred before 28 weeks' gestation.[14] Therefore, taking the rate of fetal loss before 28 weeks' gestation to be half of the total loss, the rate of loss among RhD negative women with a RhD positive baby would be 0.04%.

More recently, the Trent Confidential Enquiry into Stillbirths and Deaths in Infancy (CESDI) report[15] includes data regarding cause of death for late fetal losses (defined as 20-23 weeks' gestation), stillbirths and infant deaths in England, Wales and Northern Ireland. In 1995, 14 such deaths were attributed to Rhesus disease, out of a total of 676,737 late fetal losses, still and live births. If one assumes that 10% of these were accounted for by RhD negative women with RhD positive babies, this represents a rate of loss of 0.02%. Since a detailed analysis of the proportion of these deaths which might have been prevented by antenatal AADP is not available, this figure includes an uncertain proportion of losses which will have been due to failures of postnatal prophylaxis or sensitisation following blood transfusion. No information is available regarding the distribution of these losses before and after 28 weeks' gestation.

2.2   Effective Antenatal Dose Regimes

There are two anti-D products licensed for AADP in the UK. One, produced by Bio Products Laboratory (BPL), is a 500 iu dose and the other, produced by Baxter Healthcare, is a 1,250

iu dose, 'Partobulin'. Both product licenses are for a two injection regime at 28 and 34 weeks.

There is evidence of the efficacy of a single dose of 1,500 iu at 28 weeks, but this product is not available in the UK. In addition, there appear to be a significant number of women who require a further injection in order to maintain an adequate protective anti-D level until delivery.

There is no available evidence for the efficacy of a single injection of 1,250 iu at 28 weeks, nor of its ability to maintain a protective level until delivery. Theoretical calculations based on the half-life of IgG suggest that this may be inadequate. Moreover, such use of Partobulin is outside the terms of its Product Licence.

For these reasons the remainder of this report considers the 28 and 34 week regime only. Such AADP is given to all RhD negative women. Those (~60%) who subsequently have a RhD positive infant must be given further standard post-delivery prophylaxis. This need is not replaced by routine AADP.

2.3 Safety of Anti-D Immunoglobulin

For the Infant

There is no evidence that anti-D given to the mother during pregnancy is harmful to the infant, 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 sub-clinical and does not result in anaemia, jaundice or the need for phototherapy.

For the Mother

The only source of therapeutic IgG is human plasma. Monoclonal anti-D is under development, but remains several years away from routine use. Intramuscular immunoglobulins, which include anti-D, have an excellent safety record which extends prior to the introduction of specific virology testing of donors and viral inactivation of the end product. There have been no reported cases of viral transmission from either product licensed in the UK. Safety starts with correct donor selection and anti-D donors are the most committed, highly selected and frequently tested of all blood donors. Each donation is screened for Hepatitis B, Hepatitis C, HIV 1 and 2 and Syphilis. There was a report of Hepatitis C transmission by IgG in Ireland in the early 1990s, but this involved an

intravenous product and significant concerns were raised about the manufacturing system. Moreover, intramuscular immunoglobulins have always had a better safety profile than when used intravenously.

As with other human-derived blood products, the risk of new variant CJD (nvCJD) transmission is unknown. BPL, the UK manufacturer of the 500 iu product, is in the process of switching its production from UK to North American plasma. Until this has been completed, due to a recommendation by the Department of Health (DoH) and in consultation with the Medicines Control Agency (MCA), BPL has removed the use of anti-D for antenatal prophylaxis as one of the licensed indications for this product. This change does not imply that there has been any new information which makes the risk of transmission of nvCJD from blood products anything more than 'theoretical' and this measure is purely precautionary. BPL believes that anti-D manufactured from US plasma will be available by mid-1999.

The use of UK derived IgG for routine conventional practice is still licensed as there is a known higher risk of HDN if IgG is not administered at the appropriate time.

The recommendation by the MCA for this change in use of anti-D from UK plasma has occured as it was considered that since antenatal prophylaxis involved exposure of two people to the unknown risks of nvCJD (the pregnant woman and her unborn baby), it would be preferable to delay introduction of the guidelines until a certain supply of product manufactured from outside the UK was available. The MCA feels that this is a temporary issue and, as soon as an adequate supply of non-UK anti-D is available, universal routine antenatal prophylaxis can be recommended.[16] There is, at present, a licensed product, Partobulin, which is manufactured from non-UK plasma and for which the indications of routine antenatal prophylaxis are retained.

Baxter Healthcare, the manufacturer of Partobulin, the only currently UK-licensed product (1,250 iu), declined to be specific about the source of its anti-D plasma, but stated that donor plasma for its range of products was collected in the USA, Austria, Germany and Sweden.

As anti-D IgG is a human plasma-based product there is, naturally, public concern over its safety. However, as anti-D IgG is given to all Rhesus negative mothers who give birth to a

Rhesus positive infant as a routine procedure, all patients and staff should already be receiving suitable information about the product.

Anti-D Immunoglobulin supply position

At the time of writing, BPL has given assurance of its ability to meet the increased demand for the product consequent on the introduction of routine AADP. However, Baxter Healthcare said it was not in a position to supply the product in addition to existing contracts for conventional prophylaxis.

2.4 Conclusion on Direction of Evidence and its Quality

The various studies, covering different patient groups and different treatment regimes, all have remarkably consistent results in terms of risk reduction. The 95% CI for the sensitisation rates for all trials overlap, indicating that there are no significant differences between the results of any of the trials. Furthermore, tests for heterogeneity between the studies are negative and visual inspection of the results shows similar conclusions. Although most of the studies are non-randomised, their results are very similar to those of the one randomised controlled trial of a current dosage regime. The studies provide strong evidence that routine AADP reduces the risk of antenatal sensitisation by approximately 80%.

The rate of fetal loss due to antenatal sensitisation and, consequently, the mortality benefit from a reduced sensitisation rate is more difficult to determine. Published studies indicate that, over a period prior to the widespread introduction of routine AADP, the fetal loss rate was approximately 0.04% of all RhD negative women with RhD positive fetuses.

3.   COST AND BENEFIT IMPLICATIONS OF ADOPTING INTERVENTION

The aim of this section is to evaluate the health service cost and cost-effectiveness of providing routine AADP for RhD negative pregnancies. There are several possible options for implementing a programme of prophylaxis. This evaluation considers the following:

Treatment groups:

- providing AADP for all RhD negative pregnancies;

- providing AADP only to RhD negative primigravidae;

Dosage regime:

- providing treatment consisting of two 500 iu injections of anti-D IgG, one at 28 weeks and the second at 34 weeks.

The costs and benefits associated with each treatment group are evaluated in comparison to conventional management of RhD negative pregnancies, which is defined as:

- anti-D prophylaxis given within 72 hours of identified potentially sensitising events, such as, abdominal trauma etc;

- postnatal anti-D IgG given within 72 hours of delivery to all RhD negative women who have RhD positive infants and are not already sensitised.

No statistically significant difference in effectiveness between any of the dose regimes assessed has been identified, except for the 2 x 250 iu regime. Therefore, as discussed in Section 2.2, the results from the meta-analysis of all acceptable studies, have been used to evaluate the cost-effectiveness of all dose regimes of AADP.

Furthermore, since there is no evidence of a differential effectiveness between a 2 x 500 iu regime and a 2 x 1,250 iu regime, it can be inferred that the relative cost-effectiveness will purely depend on the difference in anti-D IgG costs.

3.1 The Costs of Routine Antenatal Prophylaxis

This evaluation takes a health service perspective of costs; indirect and societal costs have not been considered. The effect of discounting future costs and future benefits is explored over a range of rates varying between 0% and 10%, with a central estimate of 6%.

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 from the programme are the direct savings due to the avoidance of additional treatment costs, which would have been incurred as a result of a subsequent pregnancy in a sensitised woman.

The cost of a 500 iu vial of anti-D IgG is £16.43 (BPL). Therefore, the cost of providing the lower dose regime is £32.86 per woman at risk. The cost of a 1,250 iu vial of anti-D IgG is £15.90 (Baxter Healthcare). Consequently, the cost of the higher dose regime is £31.80 per woman at risk. As there is very little information on the 1,250 iu dose, it is assumed that the protection of the 2 x 1,250 iu dose is the same as the 2 x 500 iu and 2 x 1,500 iu regime.

It is envisaged that the anti-D injections can be administered by a midwife during a normal routine antenatal visit. Therefore, the logistic cost of implementing the policy has been estimated at £5 per RhD negative woman treated.

The gross annual cost of undertaking routine AADP in a 'typical' district of 500,000 population would be approximately £34,900 for the 2 x 500 iu regime and £33,800 for the 2 x 1,250 iu dose when treating all RhD negative women.

The direct savings due to the prevention of sensitisation are estimated at £1,320 per affected pregnancy avoided, i.e. sensitised in the previous pregnancy and pregnant with another child. This cost includes a longer and more intensive hospital stay for the baby, costs for amniocenteses, fetal blood sampling, neonatal follow-up visits, possible Intrauterine Transfusion (IUT), phototherapy and exchange transfers. These costs are taken from the Oxford RHA in 1996 and are shown in Table 3 as they were published in the report 'Building on Success: Antenatal Prophylaxis'.[17] The costs are likely to represent an underestimate of the true savings as they do not include a longer hospital stay for the mother, the cost of a greater number of caesarean sections and induction of labour, and the possibility of problems in future pregnancies.

The median length of time between the birth of the first and second child is 35 months (all women in Great Britain).[15] The intervals from second to third birth and between third and fourth are also of a similar magnitude. As the savings from the programme are due to the avoidance of additional treatment costs which would have been incurred as a result of a subsequent pregnancy in a sensitised woman, the value of the savings have been discounted at 6% for three years. This results in the current value of the savings being estimated at £1,108.

The cost of caring for infants with a long-term disability resulting from Rhesus disease has not been included in this analysis. Severe disability due to Rhesus disease is now rare, but several papers have reported instances of extreme handicap resulting from IUT, with rates of up to 10%.[18,19,20] The lifetime cost of caring for a disabled child is enormous. A paper by Stevenson et al.[21] on the cost of care of disabled low birthweight infants to the age eight - nine years quotes a figure of £6,926 per disabled low birthweight child compared with £4,027 for a non-disabled low birthweight 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 birthweight child will impose no extra cost on the exchequer after age nine, and will receive mainstream education to age 18, to estimate a lifetime cost of disability to be £69,597 per disabled child. Therefore, the prevention of sensitisation could not only prevent the birth of a disabled infant but also all the associated costs of care.

This estimate of the savings achieved through preventing anti-D sensitisations is substantially lower than that produced by a team in Aberdeen.[22] They estimated that £2,164 would be saved during the current pregnancy (i.e. the pregnancy during which sensitisation would occur in the absence of AADP), and a further £2,262 in future pregnancies. Since sensitisation is very unlikely to cause clinical harm during the current pregnancy, it has been assumed that AADP would not produce any savings until future pregnancies. Comparison of methods used may enable a reconciliation of the difference between these estimates of savings in future pregnancies (£1,320 v. £2,262). The authors aim to clarify these issues with the Aberdeen team, but have yet to receive a response to their enquiries.

Table 3   Cost of Treating 100 Pregnancies in Sensitised Women (After Selinger)[17]

Number of new cases with immunisation per year	**100**
No. of cases requiring intensive antibody monitoring (A)	90
No. of cases severe enough to require fetal assessment/treatment	10
No. of cases undergoing serial fetal blood sampling (B)	5
No. of cases undergoing serial intrauterine transfusion (C)	5
No. of cases requiring neonatal care only (D)	10

Cost of A		
5 antenatal serology investigations + management in 90 cases		£22,500
	Sub total A	**£22,500**

Cost of B		
5 cases requiring 3 fetal blood sampling + 5 days high-dependency neonatal unit = 5 x [(3 x £500) + (5 x £800)]		£27,500
5 cases requiring 2 neonatal follow-up visits = 5 x £100		£500
	Sub total 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 x [(3 x £1200) + (3 x £1200) + (5 x £800)]		£56,000
5 cases requiring 2 neonatal follow-up visits = 5 x £100		£500
	Sub total C	**£56,500**

Cost of D		
10 cases requiring phototherapy / exchange transfer only = 10 x (3 x £800)		£24,000
10 cases requiring 2 neonatal follow-up visits = 10 x £100		£1,000
	Sub total D	**£25,000**

Cost per 100 Rhesus negative pregnant women, sensitised in a previous pregnancy.	**Total A+B+C+D**	**£132,000**

3.2   Cost-effectiveness

A range of cost-effectiveness outcomes is calculated; cost per sensitisation prevented, cost per case of Rhesus disease prevented, cost per fetal loss avoided and cost per life year gained (LYG). The intermediate outcome, cost per sensitisation avoided, is included as this

can be estimated directly from the study evidence with a high degree of certainty and allows comparison with other health economic studies. The measures of cost per fetal loss avoided and cost per LYG have been included in order to provide a comparison of cost-effectiveness with other health care interventions. However, it should be noted that these are based upon an assumed relationship between reduced sensitisation and fetal loss rates.

Furthermore, there is an issue of quality of life for babies born with Rhesus disease, as several papers have reported instances of severe handicap resulting from IUT, with rates of up to 10%.[18,19,20] Also the quality of life of the mother and baby, in the short term, is undoubtedly enhanced by the birth of a healthy baby as compared to a Rhesus diseased infant. Unfortunately, quality of life measures of morbidity associated with Rhesus disease do not currently exist, thus, the cost per Rhesus disease avoided cannot be translated into a cost per quality adjusted life years (QALYs) measure.

Table 4 lists the baseline parameters used to evaluate the cost-effectiveness of providing AADP as a routine antenatal procedure for the different treatment options. The calculations are based on a fetal loss rate per woman at risk of 0.04%. An average life expectancy of 74 years has been assumed which gives a discounted life expectancy of 16.4 years, when future years are discounted at 6% per annum.

Table 4   Baseline Parameters for Evaluation of Cost-effectiveness

Sensitisation rate with no AADP	1.5%	
Sensitisation rate with antenatal AADP	0.24%	
Relative risk reduction	84%	
Fetal loss rate per woman at risk under conventional management	0.04%	
Average Life Expectancy	74 years	
Discounted Life Expectancy (6% discount rate)	16.4	
Dosage Regime	2x500 iu	2x1500 iu
Cost of anti-D IgG	£32.86	£31.80
Cost of Administration	£5	
Economic Savings (discounted at 6% for 3 years)	£1,108	
Median Interval between Pregnancies	35 months	

The effects of offering AADP to all RhD negative women, or to RhD negative primigravidae only, can be modelled by constructing a cohort of women to whom national fertility rates are applied. Assuming that fertility patterns are stable, the experience of this cohort over time would match the experience of a mixed population of primigravidae and multigravidae during any one year.

The most up-to-date data on fertility patterns of women who have completed their childbearing are from those born in 1956.[1] A cohort of 450 such women would eventually produce 1,062 deliveries, i.e. the annual number of deliveries in a 'typical' district of 500,000 population accounted for by RhD negative women. Full workings of this method are shown in Appendix A. The effectiveness results are shown in Table 5.

Table 5   Effectiveness of Treating Rhesus Negative Primigravidae and all Rhesus Negative Women

1.   Conventional Management - No Routine Prophylaxis:

Pregnancy No.	No. of RhD Negative Pregnancies	No. Sensitised for First Time in Current Pregnancy	No. of Cases of Rhesus Disease	Death Rate 0.04% No. of Fetuses Lost
First	450	3.90	0.00	0.00
Second	387	3.33	2.69	0.11
Third	170	1.44	2.35	0.09
Subsequent	54	0.45	1.12	0.05
TOTAL	**1,062**	**9.12**	**6.16**	**0.25**

2.   Prophylaxis to Primigravidae Only, Effective in Current Pregnancy Only:

Pregnancy No.	No. of RhD Negative Pregnancies	No. Sensitised for First Time in Current Pregnancy	No. of Cases of Rhesus Disease	Death Rate 0.04% No. of Fetuses Lost
First	450	0.64	0.00	0.00
Second	387	3.35	0.44	0.02
Third	170	1.46	1.37	0.06
Subsequent	54	0.46	0.81	0.03
TOTAL	**1,062**	**5.91**	**2.62**	**0.11**

3.   Prophylaxis to all Women, Effective in Each Pregnancy:

Pregnancy No.	No. of RhD Negative Pregnancies	No. Sensitised for First Time in Current Pregnancy	No. of Cases of Rhesus Disease	Death Rate 0.04% No. of Fetuses Lost
First	450	0.64	0.00	0.00
Second	387	0.55	0.44	0.02
Third	170	0.24	0.39	0.02
Subsequent	54	0.08	0.18	0.01
TOTAL	**1,062**	**1.50**	**1.01**	**0.04**

Note: Full workings are detailed in Appendix A

3.3   Cost-effectiveness of Routine Antenatal anti-D Prophylaxis in Primigravidae and all Rhesus Negative Women

The cost-effectiveness outcomes associated with providing routine AADP for RhD negative primigravidae and for all RhD negative women are shown in Table 6 for the 2 x 500 iu dosage regime with a fetal loss rate of 0.04%. The results relate to treating a cohort of 450 primagravidae RhD negative women who would, in the course of their life, experience 1,062 deliveries. Whilst the 2 x 1,250 iu dosage represents a lower cost regime, due to the price of the anti-D IgG, the analysis has been based on the higher cost 2 x 500 iu dosage as this reflects a conservative view of clinical practice.

Table 6   Results and Cost-effectiveness of Providing Routine Antenatal Treatment for Rhesus Negative Primigravidae and for all Rhesus Negative Women

	Treatment Given to Primigravidae Only	Treatment Given to all RhD Negative Women
Fetal loss rate in pregnancies at risk under conventional management	0.04%	0.04%
Number of sensitisations avoided	3.21	7.62
Number of cases of Rhesus Disease Prevented	3.53	5.15
Number of Fetal Losses Prevented	0.14	0.21
Number of LYG	2.34	3.41
2 x 500 iu Dosage Regime		
Net Cost	£12,140	£33,064
Cost per Sensitisation Avoided	£3,782	£4,341
Cost per case of Rhesus Disease Prevented	£3,434	£6,420
Cost per Fetal Loss Prevented	£85,262	£159,383
Cost per LYG	£5,185	£9,693

From Table 6 it is evident that it is much cheaper to treat just primigravidae (net cost £12,140) than all RhD negative women (net cost £33,064). Much of this difference is due to the number of women being treated under each scenario and, therefore, the total cost of the drugs administered. However, when treating all Rhesus negative women more cases of Rhesus disease are being prevented, 5.15 compared to 3.54, and, therefore, a greater saving due to the avoidance of the treatment costs, which would have been incurred by the birth of a baby with Rhesus disease, is being made.

Antenatal anti-D prophylaxis (AADP) would, of course, be non-mandatory were it to become a routine procedure. A low uptake rate of the medication would have little effect on the cost-effectiveness of the procedure. This is because there would be the possibilty of a greater number of births affected by HDN and so an increase in costs, but also a reduction in the total cost of drugs administered. Moreover, in areas where AADP is a routine procedure, the uptake rate is very high.

Both treatment scenarios presented are at a cost-effective level when compared to other health care interventions. Cost per LYG is £5,185 and £9,693 and cost per case of Rhesus disease prevented is £3,434 and £6,420 when treating primigravidae only and all Rhesus negative women respectively.

3.4   Sensitivity Analysis of Cost-effectiveness of Antenatal Anti-D Prophylaxis

3.4.1   The Range of Effectiveness of AADP

In order to estimate the range of effectiveness of routine AADP, the sensitisation rate for the cohort which received antenatal prophylaxis and for the group receiving no treatment was varied. The range and the 95% confidence interval for the sensitisation rate, as calculated by the meta-analysis in section 2.1.2, was used for the treatment group and the control group respectively. The resultant range in cost-effectiveness is given in Table 7.

The cost-effectiveness of routine AADP is not sensitive to the errors in the estimates of effectiveness of prophylaxis within the range of estimates obtained from the meta-analysis. Of specific note is the stability of the number of fetal losses avoided under the different assumptions.

Table 7   The Range of Effectiveness of Antenatal Anti-D Prophylaxis

	Sensitisation Rate (%)
95% CI for the Control Group	(1.30; 1.65)
Range for the Antenatal Prophylaxis Group	(0.18; 0.30)

	Treatment Given to Primigravidae Only	Treatment Given to all RhD Negative Women
No. of Sensitisations Avoided	(2.61; 3.83)	(6.20; 9.09)
No. of Cases of Rhesus Disease Prevented	(2.88; 4.22)	(4.19; 6.15)
No. of Fetal Losses Prevented	(0.14; 0.14)	(0.21; 0.21)
No. of LYG	(2.34; 2.35)	(3.41; 3.42)
2 x 500 iu Dosage Regime		
Net Cost	(£11,188; £13,053)	(£31,674; £34,396)
Cost per Sensitisation Avoided	(£2,923; £4,992)	(£3,483; £5,551)
Cost per case of Rhesus Disease Prevented	(£2,650; £4,540)	(£5,148; £8,212)
Cost per Fetal Loss Prevented	(£78,743; £91,493)	(£152,909; £165,576)
Cost per LYG	(£4,789; £5,564)	(£9,299; £10,070)

3.4.2   Long-term Savings from AADP

The figure used for the net present value of future savings through the reduction of subsequent pregnancies in sensitised women is £1,108 per affected pregnancy. Some of the aspects which make up this cost may in fact not be recoverable, e.g. a longer, more intensive hospital stay. Therefore, as a worse case scenario, there may be no savings achieved. If this were the case, then the absolute gross cost of providing AADP for all Rhesus negative women in a 'typical' district of 500,000 population is estimated at £40,199 and £17,037 when providing AADP only for Rhesus negative primigravidae.

However, as discussed in section 3.1, the net present value of savings used as the central estimate is likely to be an underestimate of the potential treatment costs. In the absence of

any further quantitative information on the likely range of costs, the threshold for the present net value of savings, at which routine AADP becomes cost neutral, is tabulated below for both treatment groups using the 2 x 500 iu dosage regime. Note that all other parameters are set at their baseline values. The amount varies from just over three times to six times the baseline estimate.

Table 8   Variation in Savings from AADP

2 x 500 iu Dosage Regime	Treatment Given to Primigravidae Only	Treatment Given to all RhD Negative Women
Gross Cost of Providing AADP (No savings)	£17,037	£40,199
Original Estimate of Treatment Costs Avoided	£1,108	£1,108
Threshold for Present Net Value of Savings at which AADP becomes Cost Neutral	£3,856	£6,244

3.4.3   Variation in Fetal Death Rate

In this evaluation, the baseline fetal death rate after 20 weeks' gestation due to Rhesus disease under conventional management is estimated at 0.04%. However, a death rate of 0.02% has been quoted in Clarke,[12] Hussey[13] and the CESDI report[15] for fetal loss after 28 weeks' gestation. The value of the death rate does not effect the net cost of providing AADP, only the cost per fetal life prevented and cost per LYG. The cost per fetal life prevented and cost per LYG for a death rate of 0.02%, 50% lower than the base line, and 0.06%, 50% higher than the base line, is tabulated below for both treatment groups using the 2 x 500 iu dosage regime. As can be seen from Table 9, the cost per fetal loss and cost per LYG are highly sensitive to variation, especially a reduction, in the fetal loss rate under conventional management.

3.4.4   Variation in Discounting Rate

In this evaluation, the potential life years expected for a viable fetus are given equal weighting to new born individuals. Fetal loss prior to 20 weeks, though potentially significant, has not been included in the analysis. Whilst it is recognised that there is considerable controversy over the valuation of different life expectancies,[23] the uncertainty is addressed in

this evaluation by considering a range of different discounting rates applied to the average life expectancy of 74 years. This variation in discounting rates has also been applied to the value of the direct savings due to the prevention of sensitisations.

Table 9   The Range of Costs of AADP due to Variation in Fetal Death Rate

2 x 500 iu Dosage Regime	Treatment Given to Primigravidae Only	Treatment Given to all RhD Negative Women
Death rate 0.02%		
Cost per Fetal Loss Prevented	£170,523	£318,766
Cost per LYG	£10,370	£19,386
Death Rate 0.06%		
Cost per Fetal Loss Prevented	£56,841	£106,255
Cost per LYG	£3,457	£6,462

The baseline analysis uses a discounting rate of 6%, giving a life expectancy of 16.4 years and estimated savings of £1,108. Table 10 presents the cost-effectiveness under no discounting, giving a life expectancy of 74 years and savings of £1,320, and 10%, giving a life expectancy of 10 years and estimated savings of £745. Clearly the cost per LYG is highly sensitive to the relative valuation of life expectancy for the unborn fetus.

3.4.5   Variation in the Cost of Implementation of AADP Treatment

It has been envisaged that the anti-D injections can be administered by a midwife at an estimated cost of £5 per Rhesus negative woman. However, this was thought to be an underestimate by many midwives due to the amount of time it would take them to explain clearly all the issues and procedures involved with AADP. Therefore, the cost-effectiveness of AADP has been re-calculated for both treatment groups using the 2 x 500 iu dosage regime with the cost of implementation of AADP at £10 per Rhesus negative women. Note that all other parameters are set at their baseline values. The results are shown in Table 11.

The potential cost-effectiveness of a treatment programme is sensitive to large increases in the logistic costs of administration. Appendix 2 discribes a simple, yet effective, strategy of

implementing an antenatal anti-D treatment programme which has been carried out successfully in Southern Derbyshire Health Authority.

Table 10   The Range of Costs of AADP under Different Discounting Rates

2 x 500 iu Dosage Regime	Treatment Given to Primigravidae Only	Treatment Given to all RhD Negative Women
10% Discount Rate		
Net Cost	£13,745	£35,402
Cost per Sensitisation Avoided	£4,282	£4,648
Cost per case of Rhesus Disease Prevented	£3,888	£6,874
Cost per Fetal Loss Prevented	£96,533	£170,654
Cost per LYG	£9,662	£17,080
0% Discount Rate		
Net Cost	£11,204	£31,701
Cost per Sensitisation Avoided	£3,491	£4,162
Cost per case of Rhesus Disease Prevented	£3,170	£6,155
Cost per Fetal Loss Prevented	£78,692	£152,813
Cost per LYG	£1,063	£2,065

Table 11   The Range of Costs of AADP due to Variation in Implementation Costs

2 x 500 iu Dosage Regime	Treatment Given to Primigravidae Only	Treatment Given to all RhD Negative women
Net Cost	£14,390	£38,372
Cost per Sensitisation Avoided	£4,483	£5,038
Cost per case of Rhesus Disease Prevented	£4,071	£7,451
Cost per Fetal Loss Prevented	£101,064	£184,974
Cost per LYG	£6,146	£11,249

3.4.6   Variation in the Costs of anti-D Immunoglobulin

As anti-D Immunoglobulin is a human-derived blood product, there are important issues of safety and the likelihood of contracting infections to consider with the introduction of routine AADP. At present, human plasma is the only source of therapeutic IgG and is priced by BPL at £16.43 per 500 iu vial. At the time of writing BPL has given assurance of the stability of the cost of its IgG.

For the sake of safety, monoclonal anti-D is under development and is considered to be a safer option than human plasma, were it to become available for routine use. The cost of monoclonal anti-D is not known, but it could be considerably more expensive than IgG taken from human donors.

Figure 5 shows the net cost of AADP for both treatment groups using the 2 x 500 iu regime for a 'typical' district of 500,000 population, when increasing the cost of IgG up to ten times the present cost. All the other parameters which affect the cost of AADP are set at their baseline values.

The baseline cost-effectiveness of routine AADP is just over £30,000 per LYG when the cost of the anti-D Immunoglobulin is three times the present cost.

Figure 5   The Effect of Varying the Cost of Anti-D Immunoglobulin on the Net Cost of AADP
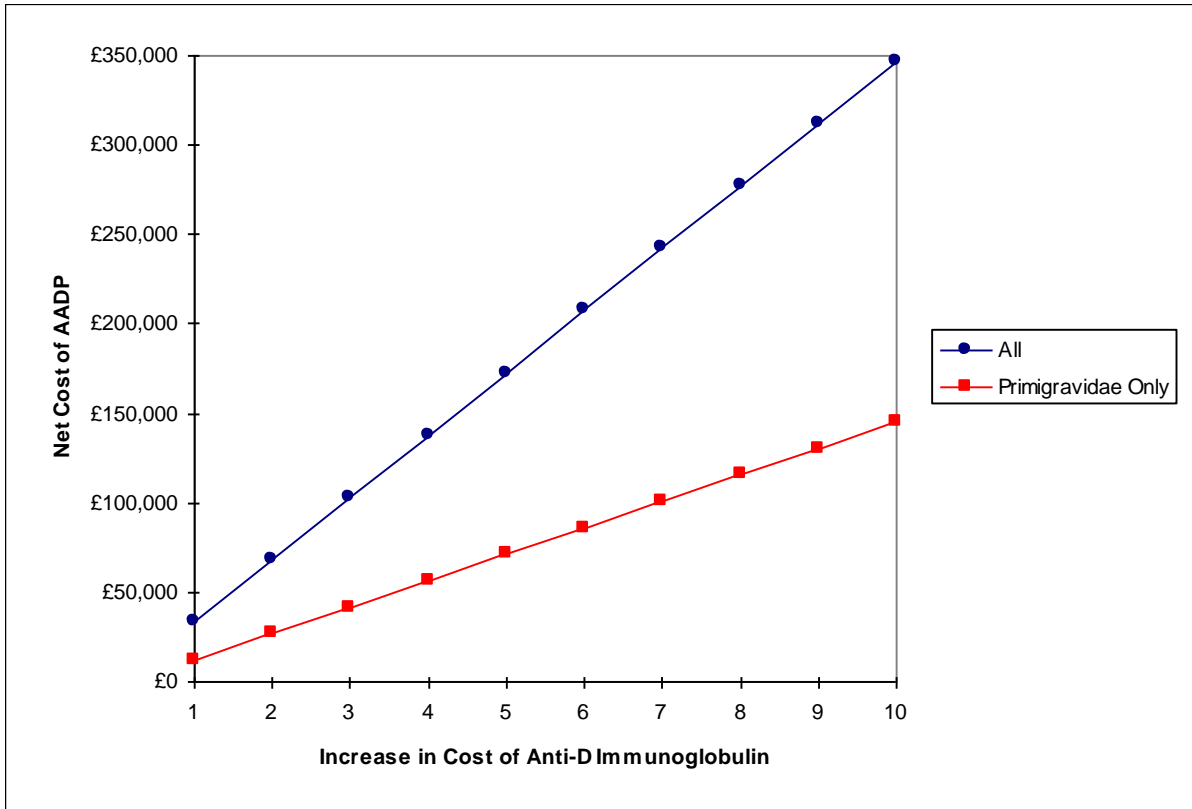
3.4.7   Worst Case Scenario: Variation of all Baseline Parameters

In order to create a worst case scenario for the cost-effectiveness outcomes associated with providing routine AADP, all baseline parameters have been varied at once. This has meant varying the rate of sensitisation for the treatment and no treatment groups in order to calculate a range of costs, setting the discounting rate at 10%, the fetal death rate at 0.02%, the cost of implementation of AADP at £10 and assuming no savings are achieved by the reduction of subsequent pregnancies in sensitised women. The cost of the IgG was not varied as this is a known fixed value. Table 12 presents the cost-effectiveness under these variations for both treatment groups using the 2 x 500 iu dosage regime.

The net cost for treating all Rhesus negative women in the worst case scenario is £45,507, compared to the original net cost of £33,064, an increase of £12,443. This is equivalent to £8,836 (£7,396; £10,865) per case of Rhesus disease prevented, compared to £6,420 (£5,148; £8,212) as calculated before. Even in the worst case scenario, the range of the costs per case of Rhesus disease prevented overlaps with the range originally calculated as shown in Table 7.

Table 12   The Range of Costs of AADP due to Variation of all Baseline Parameters

2 x 500 iu Dosage Regime	Treatment Given to Primigravidae Only	Treatment Given to all RhD Negative Women
Net Cost	£19,287	£45,507
- Range	(£19,287; £19,287)	(£45,507; £45,507)
Cost per Sensitisation Avoided	£6,009	£5,975
- Range	(£5,038; £7,376)	(£5,004; £7,344)
Cost per case of Rhesus Disease Prevented	£5,456	£8,836
- Range	(£4,568; £6707)	(£7,396; £10,865)
Cost per Fetal Loss Prevented	£19,287	£438,737
- Range	(£19,287; £19,287)	(£438,128; £439,383)
Cost per LYG	£27,115	£43,912
- Range	(£27,173; £27,060)	(£43,851; £43,976)

3.5   Conclusion on Cost-effectiveness

The total annual gross cost to a 'typical' health authority when treating all Rhesus negative women is estimated to be in the region of £35,000. However, it should be recognised that the potential benefits to be derived are also small.

Such a health authority may expect to prevent one fetal loss approximately every seven years under a primagavidae only policy and every five years under a policy to treat all Rhesus negative mothers; probably more important is the role of routine prophylaxis in preventing treatable Rhesus disease.

As discussed in Section 2, the treatment has been shown to be effective in reducing sensitisation. The cost-effectiveness is sensitive to:

- the cost of treating pregnant women who are found to have been sensitised in an earlier pregnancy;
- assumptions regarding the relationship between sensitisation and fetal loss;
- the valuation of fetal loss in terms of LYGs;
- errors in estimating the actual fetal loss rate under conventional management.

Overall, the cost-effectiveness under the baseline assumptions compares favourably with other treatments which are currently funded. For example, the use of 'statins' in the secondary prevention of coronary heart disease has a cost per LYG of £5,100 and haemodialysis for end-stage renal failure, which is widely recognised as a high cost intervention, has a cost per LYG of more than £20,000. Furthermore, the sensitivity analysis undertaken indicates that the estimated cost-effectiveness is robust in relation to these comparator treatments.

4. OPTIONS FOR PURCHASERS AND PROVIDERS

Two questions have been considered in this report:

a) Who to provide antenatal prophylaxis for?
b) What regime of anti-D to administer?

As there was no firm evidence to the contrary, this report has assumed that there is no difference in effectiveness between dosage regimes which are currently considered to be appropriate. Thus, at the time of writing, as the 1,250 iu treatment option was cheaper, this is the dosage regime recommended. However, the cost differential between the two regimes is small and if the cost or availability were to change, then so too would the advice.

The options considered in respect of the first question are as follows:

Option 1   Do not provide anti-D prophylaxis as a routine antenatal procedure.

Option 2   Provide anti-D prophylaxis as a routine antenatal procedure for Rhesus negative primigravidae only.

Option 3   Provide anti-D prophylaxis as a routine antenatal procedure for all Rhesus negative women regardless of the number of previous pregnancies.

Both options 2 and 3 provide low-cost and cost-effective strateges for preventing HDN. Option 2, which is restricting the provision of routine AADP to primigravidae, has a lower gross cost and is marginally more cost-effective in comparison to option 3. However, practical and ethical difficulties are foreseen in the implementation of option 2, and thus, since option 3 is cost-effective in comparison to conventional management, this is the preferred option.

5. DISCUSSION AND CONCLUSIONS

5.1 Implementing a Policy of Routine Antenatal Anti-D Prophylaxis

Considering the practicalities of routine administration of anti-D in Sheffield, the following points were made by local community midwives:

- That women are, in general, unaware of what anti-D is and that it is a blood product. If prescribed, there would be a definite need to supply women with more information about routine administration of anti-D, why it was recommended and if administration would pose any risk to the women's own health. The supplier of anti-D should ideally provide written information about its product and an assurance against the likelihood of contracting infections from the specimen, in particular, Creutzfeldt-Jakob Disease (CJD), Acquired Immune Deficiency Syndrome (AIDS) and hepatitis.

- Women should be encouraged to exercise their choice of having antenatal anti-D routinely or only as a result of the currently recognised sensitisation events, i.e. abdominal trauma, abortion, amniocentesis, chorion villous sampling, antepartum haemorrhage, external aphalalic version and termination of pregnancy. Information should be available to women to support such a decision.

- The demand for anti-D for routine administration to antenatal women could technically exceed the current supply.

- At present, it is not clear who is incurring the cost of supplying anti-D for routine administration to Rhesus negative women. Either the local maternity hospital pharmacy department or the women's general practitioners could incur the expense.

5.2 Information to Patients

Anti-D Immunoglobulin is a human plasma-based product and so, naturally, there is concern over its safety. Intramuscular immunoglobulins, which include anti-D, have an excellent safety record with no reported cases of viral transmission. Moreover, the available products are produced from non-UK donor plasma and the Medicines Control Agency has recommended these for antenatal prophylaxis. Patients and staff ought already to be

receiving suitable information about the safety of anti-D IgG, as postnatal anti-D prophylaxis is a routine procedure.

APPENDIX A   The Full Workings to Calculate the Results of Treating All Rhesus Negative Women and Rhesus Negative Primigravidae

Complications due to sensitisation of the mother only occur in subsequent Rhesus positive pregnancies. In order to achieve the treatment of 1,062 pregnancies, a cohort of 450 Rhesus negative primigravidae need to be considered. This is calculated as shown in Table 1 which shows the results for all Rhesus negative women. Table 2 shows the results for Rhesus primigravidae. The method of calculation when no antenatal prophylaxis is given is as follows:

The number of Rhesus negative pregnancies treated in each pregnancy [Table 1 - Col. B] is the number in the previous pregnancy multiplied by the percentage going on to a further pregnancy: i.e. B3 = B2 x H2. Therefore, the total number of Rhesus negative pregnancies treated is just the sum of these and totals the 1,062 pregnancies in a 'typical' district.

450 non-sensitised Rhesus negative women have a first pregnancy, [C1]. Of these, 59%, [D1], will have a Rhesus positive baby and, therefore, their pregnancy will be at risk. This results in 266 pregnancies at risk, [E1]. In the case described, the mothers are not given antenatal prophylaxis and, therefore, 1.5%, [F1], will become sensitised. This results in 3.90 sensitisations, [G1]. Of these women, 86% will go on to have a second pregnancy, [H1], of which 80% of these second pregnancies, [J2], will be Rhesus positive and with an affected fetus. This results in 2.69 cases of Rhesus disease, [K2].

This cycle is then repeated. The number of non-sensitised Rhesus negative women entering a second pregnancy, [C2], is the original number of non-sensitised women, [C1], minus the prevalent number of women sensitised during earlier pregnancies, [N1], multiplied by 86%, [H1], the percentage of women having a second pregnancy. This results in 384 non-sensitised Rhesus negative women entering a second pregnancy, [C2]. Of these, 59%, [D2], will have a Rhesus positive baby and, therefore, their pregnancy will be at risk. This results in 226 pregnancies at risk, [E2]. As no prophylaxis is given, 1.5%, [F2], of these will become sensitised for the first time, i.e. 3.33 sensitisations, [G2]. The number of sensitised women going on to a further pregnancy is recorded in column I. The number entering a third pregnancy equals the number sensitised for the first time in the second pregnancy, [G2], plus the number sensitised in the first pregnancy who continued on to a second pregnancy,

[I2], multiplied by 0.44, [H2], the percentage of women having a third pregnancy. Of these fetuses, 80% will be Rhesus positive and, therefore, will be affected This results in 2.35 cases of Rhesus disease, [K3].

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%, [H3].

This method of calculation has been used for all scenarios, so in the case where antenatal prophylaxis is administered, the sensitisation rate reduces to 0.24%, [F6], instead of 1.5%, [F1]. In the scenario of just treating primigravidae, only the first 450 pregnancies are given antenatal prophylaxis and, therefore, the risk of sensitisation in second and subsequent pregnancies returns to 1.5%.

Appendix A   Table 1   Results of Treating all Rhesus Negative Women

1. Treatment - No Prophylaxis

| | Pregnancy No. | No. of Rh Negative Pregnancies | No. of Non-Sensitised RhD Negative | Proportion of Women who will have a RhD Positive Baby (i.e. at risk) | No. at Risk | Sensitisation Rate | No Sensitised for First Time in Current Pregnancy | Proportion Proceeding to Next Pregnancy | No. Sensitised from Previous Pregnancies | Risk of Rh Positive Fetus in Current Pregnancy Having Been Sensitised in Previous Pregnancy | No. of Cases of Rhesus Disease | Death Rate 0.04% No. of Fetuses Lost | Prevalent No. of Sensitised Women During Each Pregnancy |
	A	B	C	D	E	F	G	H	I	J	K	L	M
1.	First	450	450	0.59	266	1.5%	3.90	0.86	0.00	0.00	0.00	0.00	3.90
2.	Second	387	384	0.59	226	1.5%	3.33	0.44	3.36	0.80	2.69	0.108	6.68
3.	Third	170	166	0.59	98	1.5%	1.44	0.32	2.94	0.80	2.35	0.095	4.38
4.	Subsequent	54	52	0.59	30	1.5%	0.45		1.40	0.80	1.12	0.045	1.85
5.	**TOTAL**	**1,062**	**1,051**		**620**		**9.12**		**7.70**		**6.16**	**0.25**	**16.82**

2. Treatment - Prophylaxis to All Women, 84% Effective in Each Pregnancy

	Pregnancy No.	No. of Rh Negative Pregnancies	No. of Non-Sensitised RhD Negative	Proportion of Women who will have a RhD Positive Baby (i.e. at risk)	No. at Risk	Sensitisation Rate	No Sensitised for First Time in Current Pregnancy	Proportion Proceeding to Next Pregnancy	No. Sensitised from Previous Pregnancies	Risk of Rh Positive Fetus in Current Pregnancy Having Been Sensitised in Previous Pregnancy	No. of Cases of Rhesus Disease	Death Rate 0.04% No. of Fetuses Lost	Prevalent No. of Sensitised Women During Each Pregnancy
6.	First	450	450	0.59	266	0.24%	0.64	0.86	0.00	0.00	0.00	0.00	0.64
7.	Second	387	386	0.59	228	0.24%	0.55	0.44	0.55	0.80	0.44	0.02	1.10
8.	Third	170	170	0.59	100	0.24%	0.24	0.32	0.48	0.80	0.39	0.02	0.72
9.	Subsequent	54	54	0.59	32	0.24%	0.08		0.23	0.80	0.18	0.01	0.31
10.	**TOTAL**	**1,062**	**1,060**		**625**		**1.50**		**1.26**		**1.01**	**0.04**	**2.76**

Appendix A Table 2   Results of Treating Rhesus Negative Primigravidae

1. No Prophylaxis

	A	B	C	D	E	F	G	H	I	J	K	L	M
	Pregnancy No.	No. of Rh Negative Pregnancies	No. of Non-Sensitised RhD Negative	Proportion of Women who will have a RhD Positive Baby (i.e. at risk)	No. at Risk	Sensitisation Rate	No Sensitised for First Time in Current Pregnancy	Proportion Proceeding to Next Pregnancy	No. Sensitised from Previous Pregnancies	Risk of Rh Positive Fetus in Current Pregnancy Having Been Sensitised in Previous Pregnancy	No. of Cases of Rhesus Disease	Death Rate 0.04% No. of Fetuses Lost	Prevalent No. of Sensitised Women During Each Pregnancy
1.	First	450	450	0.59	266	1.5%	3.98	0.86	0.00	0.00	0.00	0.00	3.98
2.	Second	387	384	0.59	228	1.5%	3.39	0.44	2.42	0.80	2.74	0.11	6.82
3.	Third	170	166	0.59	100	1.5%	1.47	0.32	3.00	0.80	2.40	0.09	4.47
4.	Subsequent	54	52	0.59	30	1.5%	0.46		1.43	0.80	1.14	0.05	1.89
5.	**TOTAL**	**1,062**	**1,051**		**620**		**9.30**		**7.86**		**6.28**	**0.25**	**17.16**

2. Prophylaxis to Primigravidae Only, 84% Effective in Current Pregnancy Only

	Pregnancy No.	No. of Rh Negative Pregnancies	No. of Non-Sensitised RhD Negative	Proportion of Women who will have a RhD Positive Baby (i.e. at risk)	No. at Risk	Sensitisation Rate	No Sensitised for First Time in Current Pregnancy	Proportion Proceeding to Next Pregnancy	No. Sensitised from Previous Pregnancies	Risk of Rh Positive Fetus in Current Pregnancy Having Been Sensitised in Previous Pregnancy	No. of Cases of Rhesus Disease	Death Rate 0.04% No. of Fetuses Lost	Prevalent No. of Sensitised Women During Each Pregnancy
6.	First	450	450	0.59	266	0.24%	0.64	0.86	0.00	0.00	0.00	0.00	0.64
7.	Second	387	386	0.59	228	1.5%	3.35	0.44	0.55	0.80	0.44	0.02	3.90
8.	Third	170	168	0.59	99	1.5%	1.46	0.32	1.72	0.80	1.37	0.06	3.18
9.	Subsequent	54	53	0.59	31	1.5%	0.46		1.02	0.80	0.81	0.03	1.47
10.	**TOTAL**	**1,062**	**1,058**		**624**		**5.91**		**3.28**		**2.66**	**0.11**	**9.19**

APPENDIX B   Antenatal Anti-D Prophylaxis Treatment - It Does Work in Practice

In Southern Derbyshire health district a routine antenatal anti-D prophylaxis treatment programme has been implemented successfully. Before the programme began, the rate of sensitisation in Rhesus negative women was 1.12%, (1988 - 90), whereas during 1993 - 95, the earliest date at which any effects of the programme might be detected, the rate had reduced to 0.28%[a].

Women who need prophylaxis are identified by hospital staff, general practitioners and community midwives, and a record of them is kept in a specific diary. The anti-D Immunoglobulin is stored at Derby City General Hospital Blood Bank. Where each week, a clerk looks in the diary and dispatches the anti-D to the appropriate general practice surgery or community clinic for the women needing treatment that week. The shelf life of the anti-D Immunoglobulin is stated to be two years. The clerical work takes about an hour each week. The anti-D is delivered to the appropriate centre by the routine van run and the delivery of the anti-D Immunoglobulin is, therefore, at no extra cost to the health authority. The packages are addressed to the midwives and treatment is given at 28 and 34 weeks' gestation during a normal routine visit. Confirmation of dosage is then returned to the clerk.

In Southern Derbyshire, the cost of the prophylaxis has been estimated at around £30 per pregnancy and the overall cost is about £15,000 per annum**.** The major expense of the programme is the anti-D Immunoglobulin. The time taken by the clerk and the midwife also contributes to the cost, but this is not considered to be a major factor. This treatment programme was originally implemented for primigravidae only, but with extra funding it was extended to cover all Rhesus negative women.

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[a] Mayne S, Parker JH, Harden TA, et al. Rate of RhD sensitisation before and after implementation of a community based antenatal prophylaxis programme. *British Medical* 1997; 315:1588.

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