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Guidelines on the prophylactic
use of Rh D immunoglobulin
(Anti-D) in obstetrics

Main Report



NHMRC

National Health and Medical Research Council

***Guidelines on the
prophylactic use of
Rh D immunoglobulin
(Anti-D) in obstetrics***

Endorsed 22 March 1999

NHMRC

National Health and Medical Research Council

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CONTENTS

EXECUTIVE SUMMARY	1
SUMMARY OF GUIDELINES	4
INTRODUCTION	7
Chapter 1 BACKGROUND	11
1.1 Purpose of anti-D in obstetrics	11
1.2 Incidence of Rh D incompatibility	11
1.3 The Rh Project in Australia	12
1.4 Reasons for the current shortage of anti-D	13
Chapter 2 CURRENT AVAILABILITY AND USE OF ANTI-D IN AUSTRALIA .	15
2.1 Current availability	15
2.2 Current demand	16
2.3 Current practice	16
Chapter 3 BEST PRACTICE FOR THE USE OF ANTI-D IN OBSTETRICS	21
3.1 Postpartum use of anti-D	21
3.2 Anti-D for antenatal sensitising events	23
3.3 Routine antenatal use of anti-D	27
Chapter 4 COSTS AND COST EFFECTIVENESS OF ANTI-D USE	31
4.1 Data	32
4.2 Results	33
4.3 Conclusions	39
Chapter 5 RATIONALE FOR GUIDELINE RECOMMENDATIONS	41
Chapter 6 STRATEGIES TO MAINTAIN AND INCREASE ANTI-D SUPPLIES	47
6.1 Promoting efficient use of anti-D	
6.2 Securing future supply of anti-D	53

CONTENTS

APPENDICES

1	Membership and terms of reference of the Working Party	61
2	The guideline development process	63
3	Communication strategy	65
4	Evaluation and monitoring strategy	67
5	Literature review — search strategy and tables of results	69
6	Cost-effectiveness analysis	93

ACRONYMS AND ABBREVIATIONS	179
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GLOSSARY	180
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BIBLIOGRAPHY	181
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EXECUTIVE SUMMARY

Background

The discovery, introduction and utilisation of Rh D immunoglobulin (anti-D) for prophylaxis against haemolytic disease of the newborn has been one of the major medical achievements of the past half century. This condition is caused by Rh blood group incompatibility between a woman and her baby, leading to the isoimmunisation (sensitisation) of a woman with Rh D negative blood against Rh D positive blood. It was previously a major cause of perinatal mortality, morbidity, long-term disability and mental handicap, and associated emotional and health costs were high.

In the 1960s, it was demonstrated that administration of Rh D immunoglobulin (anti-D) to Rh D negative mothers soon after the delivery of Rh D positive babies dramatically reduced the incidence of immunisation. A mechanism for producing Rh D immunoglobulin in Australia was then sought, and, in 1968, Australia became the first country in the world to be self-sufficient in Rh D immunoglobulin.

However, for a variety of reasons both within Australia and worldwide, antibody levels have declined, and in recent years there has been insufficient anti-D to meet Australian requirements. While the recruitment and boosting program is still underway and national production of anti-D has increased, there are continuing difficulties in rectifying the shortfall and maintaining the increased supply.

In 1997, the National Health and Medical Research Council appointed a Working Party to develop guidelines which balance best practice in the use of Rh D immunoglobulin with limited supply. These guidelines are intended to cover the two years from their publication, to address the period of constraint between now and future self-sufficiency in anti-D.

Current use of anti-D

Postpartum administration of anti-D to all Rh D negative mothers with Rh D positive babies and no preformed anti-D is standard practice in Australia and in most parts of the world, although the dose used varies between countries.

Anti-D is usually given to women during pregnancy if they experience a 'sensitising' event in which there is a risk of fetal blood crossing into the maternal circulation. These include miscarriage, termination of pregnancy, ectopic pregnancy, genetic studies such as amniocentesis and chorionic villus sampling, external cephalic version, trauma and antepartum haemorrhage.

There are conflicting views about the efficacy of routine prophylactic use of anti-D antenatally. This has resulted in inconsistencies in the way that anti-D is

used prophylactically. The situation is complicated by the current restricted supply of anti-D, as routine antenatal administration to all Rh D negative women would place immense demands on anti-D supply.

Best practice for the use of anti-D in obstetrics

The Working Party commissioned a review of the available evidence relating to the effectiveness of the prophylactic use of anti-D in obstetrics, and a review of the cost effectiveness of anti-D for a number of applications. There is very strong evidence that the use of anti-D postpartum is both effective and cost effective. There is little high level evidence supporting the use of anti-D antenatally, but the results of both reviews support the efficacy and cost effectiveness of anti-D for antenatal sensitising events and antenatal prophylaxis.

There is no evidence of adverse effects from the administration of anti-D. However, it is a blood product and this should be clear in verbal and written information given to patients

Strategies to increase and maintain anti-D supplies

Given that the evidence from the scientific literature and cost-effectiveness analysis supports the increased use of anti-D to prevent Rh D isoimmunisation, the Working Party considers it vital that there is rapid development and implementation of short and long-term strategies to promote the most efficient use of existing supply and identify a sustainable method of increasing supply to meet demand.

The main strategies which could be implemented to improve the efficiency of anti-D use include:

- use of a mini-dose of anti-D for potentially sensitising events in the first trimester, although it is unlikely that such a dose will be registered in the short term;
- increased and more accurate use of tests to assess the amount of fetomaternal haemorrhage; and
- increased compliance with guidelines on anti-D use, supported by thorough education in all areas where anti-D is used and a quality assurance program for maintenance of the guidelines.

Securing future supply of anti-D

While the source of anti-D remains blood plasma, the only mechanism to increase production will rely on expanding the collection of anti-D from human donors. In Australia, there has been no case of reported viral transmission from the administration of intramuscular immunoglobulin including Rh D immunoglobulin.

In addition, no Rh Project donor has become infected as a result of boosting with red cells from other donors. However, there are a number of ethical considerations associated with the use of blood and blood products, for both donors and recipients.

Appropriate procedures for providing information to potential donors and obtaining their voluntary consent should be in place. There should be full disclosure of information on known risks and the likely degree of unknown risks, and sufficient time allowed for potential donors to consider participation, with the opportunity to obtain further independent advice or counselling in relation to involvement.

In order to provide anti-D to all Rh D negative women who could benefit from it, efforts to increase the number of donors recruited to the Rh Project will continue. There is likely to be further exploration of alternative methods of increasing supply such as reintroduction of primary immunisation, the recruitment of women with high levels of anti-D, and increased donation by plasmapheresis.

However, constraints such as low numbers of individuals willing to be boosted or immunised and donate regularly, and indemnity issues, preclude success in the short term. As an interim measure while these issues are being resolved, consideration should be given to the registration and import of overseas products, to allow earlier introduction of antenatal prophylaxis.

SUMMARY OF GUIDELINES

1 General

For successful immunoprophylaxis, Rh D immunoglobulin should be administered as soon as possible after the sensitising event, but always within 72 hours. If Rh D immunoglobulin has not been offered within 72 hours, a dose offered within up to 9–10 days may provide protection. Blood should be taken from the mother before administration of the Rh D immunoglobulin to assess the magnitude of fetomaternal haemorrhage.

2 Postpartum administration

A dose of 125 µg (625 IU) Rh D immunoglobulin should be offered to every Rh D negative woman following delivery of a Rh D positive baby.

Rh D immunoglobulin should not be given to women with preformed anti-D antibodies, except where the preformed anti-D is due to the antenatal administration of Rh D immunoglobulin.

The magnitude of the fetomaternal haemorrhage should be assessed by a method capable of quantifying a haemorrhage of ≥ 6 ml of fetal red cells (12 ml of whole blood). Further doses should be administered sufficient to prevent maternal immunisation.

3 Antenatal administration for potentially sensitising events

First trimester

A dose of 50 µg (250 IU) Rh D immunoglobulin should be offered to every Rh D negative woman with no preformed anti-D antibodies to ensure adequate protection against immunisation for the following indications up to and including 12 weeks gestation:

- *miscarriage;*
- *termination of pregnancy;*
- *ectopic pregnancy; and*
- *chorionic villus sampling.*

A dose of 50 µg Rh D immunoglobulin is sufficient to prevent immunisation by a fetomaternal haemorrhage of 2.5 ml of fetal red cells (5 ml whole blood).

Until a 50 µg Rh D immunoglobulin vial becomes available in Australia, 125 µg Rh D immunoglobulin should be used.

The Working Party strongly recommends that women undergoing termination of pregnancy be tested to determine their Rh D type, to avoid unnecessary use of Rh D immunoglobulin.

Beyond the first trimester

A dose of 125 µg Rh D immunoglobulin should be offered to every Rh D negative woman with no preformed anti-D antibodies to ensure adequate protection against immunisation for the following indications after 12 weeks gestation:

- genetic studies (chorionic villus sampling, amniocentesis and cordocentesis);*
- abdominal trauma considered sufficient to cause fetomaternal haemorrhage;*
- each occasion of revealed or concealed antepartum haemorrhage (where the patient suffers unexplained uterine pain the possibility of concealed antepartum haemorrhage should be considered, with a view to immunoprophylaxis); and*
- external cephalic version (performed or attempted).*

As evidence for the efficacy of this dose for these indications is not available, it is recommended that the magnitude of fetomaternal haemorrhage be assessed and further doses administered as for (2), especially where transplacental access or puncture of fetal blood vessels occurs.

4 Antenatal prophylaxis

Universal prophylaxis with Rh D immunoglobulin to Rh D negative women with no preformed anti-D antibodies at 28 and 34 weeks gestation is generally regarded as best practice. However, due to supply constraints, routine antenatal prophylaxis should not be administered until further notice.

It is noted that the constraints on supply may alter in the foreseeable future. Therefore, the above recommendation should be reviewed on a regular basis by the National Health and Medical Research Council and amended according to the availability of supplies of Rh D immunoglobulin existing at the time.

INTRODUCTION

The discovery, introduction and utilisation of Rh D immunoglobulin (anti-D)¹ for prophylaxis against haemolytic disease of the newborn (HDN) has been one of the major medical achievements of the past half century. This condition is caused by Rh blood group incompatibility between a woman and her baby, leading to the isoimmunisation of a woman with Rh D negative blood against Rh D positive blood. It was previously a major cause of perinatal mortality, morbidity, long-term disability and mental handicap, and the associated emotional and health costs were high.

Rh D immunoglobulin can be used to prevent isoimmunisation and the possibility of HDN occurring in a subsequent pregnancy through administration:

- to Rh D negative women with no preformed antibodies soon after delivery of a Rh D positive infant;
- during pregnancy, for a potentially sensitising event such as miscarriage, ectopic pregnancy, amniocentesis or abdominal trauma; and
- routinely during pregnancy, usually at 28 and 34 weeks gestation, to Rh D negative women with no preformed antibodies.

The effectiveness and cost effectiveness of these strategies for preventing isoimmunisation are discussed in this report.

However, because anti-D can only be derived from human plasma, there are a number of issues associated with its supply and availability that must be considered along with gold standard usage identified through the scientific literature.

In Australia, between 1991 and 1994, supplies of anti-D declined to the extent that specific remedial action was required to avoid significant numbers of women being exposed to the risk of immunisation. Due to the shortage of locally manufactured product, an alternative product was imported from the United States between 1994 and August 1997. An intensive effort by the blood banks and CSL² is seeking to increase local supply so that Australia can regain self-sufficiency in anti-D within two years, but there are continuing difficulties in meeting demand.

Until self-sufficiency is reached, issues concerning the most effective use of limited anti-D supplies must be considered carefully.

In 1996, the National Health and Medical Research Council (NHMRC) published guidelines for the use of Rh D immunoglobulin (anti-D) in obstetrics (NHMRC 1996). While these guidelines are generally accepted as representing best practice for the use of anti-D in obstetrics, it is thought that their uniform implementation

1 In this report, the terms 'Rh D immunoglobulin' and 'anti-D' are used interchangeably.

2 Formerly known as the Commonwealth Serum Laboratories.

could have severe implications for anti-D supplies. For this reason, the NHMRC decided to issue updated guidelines which balance best practice with limited supply. These guidelines are intended to cover the two years from their publication only, to address the period of constraint between now and future self-sufficiency in anti-D.

In 1997 the NHMRC appointed a working party to review the evidence on the effectiveness and cost effectiveness of anti-D in obstetrics, to establish the availability of anti-D over the next two to five years, and to develop updated guidelines advocating the most effective use of the available supply. The Working Party was also asked to develop strategies to increase domestic production of anti-D to a self-sufficient level. The membership and terms of reference of the Working Party are at Appendix 1.

Methods

The Working Party took three main approaches to the collection of information on which to base interim guidelines.

- The Mater Perinatal Epidemiology Unit, Brisbane, was commissioned to undertake a systematic review of the scientific literature relating to the effectiveness of the prophylactic use of anti-D in obstetrics, as well as related issues such as testing, compliance, route of administration and alternative sources of anti-D. The results of the review are given in Chapter 3 and tables of results are given in Appendix 5.
- Dr J Butler of the National Centre for Epidemiology and Population Health, Australian National University, was commissioned to prepare a paper comparing the cost effectiveness of alternative strategies for the prevention of Rh D isoimmunisation. These were:
 - postpartum administration only;
 - postpartum plus administration for potentially sensitising events during pregnancy;
 - postpartum plus administration for potentially sensitising events during pregnancy plus antenatal prophylactic use for primigravidae; and
 - postpartum plus administration for potentially sensitising events during pregnancy plus routine antenatal prophylactic use.

The results of this analysis are discussed in Chapter 4, and a fuller description of the model and tables of results are given in Appendix 6.

-
- Information was collected from the blood banks and CSL about current recruitment of donors, current supply and availability of anti-D, and likely supply over the next two years.

Levels of clinical evidence

The guidelines have been developed in a way that enables readers to judge the strength of the evidence on which recommendations are based. In relation to issues of effectiveness of health care, the guidelines use the six-point rating system given below to identify the evidence base for key decision points. The rating system has been adapted from the system developed by the United States Preventive Services Task Force and is recommended by the NHMRC (1995).

Levels of evidence ratings

- Level I** Evidence obtained from systematic review of relevant randomised controlled trials (with meta-analysis where possible).
- Level II** Evidence obtained from one or more well designed randomised controlled trials.
- Level III-1** Evidence obtained from well designed controlled trials without randomisation.
- Level III-2** Evidence obtained from well designed cohort or case-control analytic studies, preferably from more than one centre or research group.
- Level III-3** Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
- Level IV** The opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees.
-

Consultations

During the guideline development process, an invitation to make submissions about the guidelines was advertised nationally. Twenty submissions were received and considered carefully along with the results of the above reviews in

formulating the guidelines.

Comments from the submissions formed a body of expert, informed academic and clinical opinion on the area of Rh D immunoprophylaxis. The main issues raised in the submissions included:

- general support for the production of a 50 µg vial of Rh D immunoglobulin for administration for potentially sensitising events in the first trimester;
- conflicting views about the efficacy of antenatal prophylaxis;
- support for the restriction of antenatal prophylaxis to primigravid women, in the current environment of restricted anti-D supply;
- the importance of recruiting new donors; and
- a questioning of the need for anti-D administration for threatened miscarriage.

After the report was developed, it was distributed to key organisations and individuals for comment, and the draft modified in the light of the 13 submissions received.

CHAPTER 1

BACKGROUND

1.1 Purpose of anti-D in obstetrics

Rh D immunoglobulin (anti-D) is given to women with Rh D negative blood who give birth to babies with Rh D positive blood, so that they do not become isoimmunised ('sensitised') to Rh D positive blood. Isoimmunisation can occur if fetal red blood cells leak into the maternal circulation during birth or from an exchange of fetal and maternal blood during the pregnancy.

A woman who has been sensitised during the pregnancy or birth of a previous child produces an antibody (anti-D) which can cross the placenta, bind to the fetal Rh D positive red blood cells and destroy them. This can result in conditions such as hydrops fetalis, icterus gravis and anaemia, which are all symptoms of HDN. Severe HDN leads to severe oedema, hepatosplenomegaly and severe anaemia, and may result in death in utero. In its milder form, HDN results in mild or moderate anaemia with jaundice shortly after birth.

The use of anti-D for prophylaxis is based on the theory that in a woman who has not already actively formed anti-D in her blood, the passive administration of anti-D can remove fetal red blood cells from her circulation so that sensitisation does not occur. However, the precise mechanism of action of prophylactic anti-D remains unclear.

Since most cases of transplacental haemorrhage occur either just before, during or shortly after delivery, anti-D is given to Rh D negative mothers soon after the delivery of a Rh D positive baby.

1.2 Incidence of Rh D incompatibility

About 83 per cent of women are positive for Rh D, meaning that about 17 per cent of pregnant women will be Rh D negative and their babies, if Rh D positive, therefore at risk of developing HDN due to Rh D incompatibility. Although HDN may develop because of incompatibilities in other red blood cell antigens, before the introduction of prophylaxis, anti-D was the most common cause of HDN. There are two reasons for this:

- about 60 per cent of Rh D negative women will have a Rh D positive baby in their first pregnancy, and all subsequent Rh D positive babies born to women who become immunised during the first pregnancy will be at risk of HDN; and
- the D antigen is the most immunogenic of the red blood cell antigens.

In a study in the late 1940s, it was found that fetal death due to HDN caused by anti-D accounted for 3.2 deaths per 1,000 births. In that series, one in 200 pregnant women developed anti-D antibodies and of these 20 per cent lost their

infants in the first affected pregnancy and 40 per cent in subsequently affected pregnancies. Until the late 1960s, HDN due to Rh D incompatibility was an important cause of fetal and neonatal morbidity and mortality.

1.3 The Rh Project in Australia³

In the 1960s, clinical trials of the administration of anti-D to Rh D negative mothers soon after the delivery of Rh D positive babies were conducted in a large number of centres, and demonstrated that the incidence of immunisation was dramatically reduced. The combined results of the trials were presented at the scientific meeting of the International Society of Blood Transfusion (ISBT) in Sydney in 1966.

After the ISBT meeting, it became immediately apparent that a mechanism for producing anti-D in Australia was required, and steps were taken to establish the Rh Project. This was a joint project between the Red Cross National Blood Transfusion Committee and the Commonwealth Serum Laboratories (now CSL) and was federally funded. The blood banks were asked to provide high titre anti-D plasma and CSL processed it into Rh D immunoglobulin. This was then issued free of charge to women at risk. Plasmapheresis was introduced to maximise the volume of plasma obtained. New South Wales and Western Australia began recruiting and boosting suitable donors, and in 1968, Australia became the first country in the world to be self-sufficient in Rh D immunoglobulin.

The first donors were Rh D negative women who had produced anti-D, and men who had become immunised to anti-D from a blood transfusion. However, it became apparent that not enough high titre anti-D was being produced by this group, even when they were boosted to maintain high levels of anti-D.

Volunteers with no anti-D present were then recruited to the project, and were deliberately immunised and boosted. Rh D negative male donors were approached and two large series began in the late 1960s. The success rate at achieving immunisation was better for the second series than for the first, but even so, not all donors became immunised despite frequent injections, and not all kept donating. In 1977, another batch of volunteers was recruited and immunised, in the last major recruitment to the Rh Project.

There are significant logistic difficulties in recruiting, immunising and retaining Rh D negative donors to the program. Fortunately, most of the Rh Project donors (volunteers who were deliberately immunised and those who were already immunised when recruited to the program) have continued donating regularly for

³ The information in this section was provided by RJ Kimber, Chairman, National Blood Transfusion Committee, Australian Red Cross.

almost 30 years. Boosting of donors was ceased in November 1991 when it appeared that more than adequate amounts of anti-D were being supplied to CSL.

Between 1967 and 1991, one million doses of Rh D immunoglobulin were produced by CSL and administered in Australia. CSL produced and issued approximately 65,000 doses of Rh D immunoglobulin annually, which over that time met the national requirements. To meet Australian needs at that time CSL required an input of approximately 12×10^6 IU/month. New South Wales was supplying about $9-10 \times 10^6$ IU/month of anti-D and Western Australia was supplying $6-7 \times 10^6$ IU/month. Some volumes of low titre anti-D were also coming from other States.

1.4 Reasons for the current shortage of anti-D

Following the decision to stop boosting Rh Project donors to maintain their high levels of anti-D, the antibody levels declined. By 1994, the supply of anti-D from New South Wales had fallen to 4.6×10^6 IU/month.

When it became apparent that CSL was receiving insufficient anti-D to meet Australian requirements, the blood banks immediately took steps to reintroduce the boosting of donors. However, there were a number of stages and a considerable lead time before levels of locally produced anti-D could increase to meet current usage patterns.

First, approval was gained from the Ethics Committee of the National Blood Transfusion Committee. A safety requirement was that red cells to be used for boosting should be kept frozen in liquid nitrogen for 12 months. This provided an additional window period in case a donor developed any disease within that period. There were further delays when it was discovered that there was a possibility of hepatitis B transfer through the liquid nitrogen in which certain blood bags were stored, and the method of freezing red blood cells for later transfusion was changed.

By mid-1994 the situation warranted immediate action. Boosting of donors recommenced in New South Wales and Western Australia, and by February 1995 these States were supplying two-thirds of the Australian requirement. Ethical approval was granted for the use of fresh red blood cells from long-term donors to allow the extension of the boosting program, and the shortfall was supplemented by an imported anti-D product, RhoGAM (Ortho Diagnostics Systems Inc, United States).

While the recruitment and boosting program is still underway and the national input of anti-D to CSL has increased, there are continuing difficulties in rectifying the shortfall and maintaining the increased supply. These include:

- the progressive retirement of Rh Project donors on the grounds of age and declining health — the average age of Rh Project plasmapheresis donors is now over 60 years;
- declining antibody levels in Rh Project donors which occur over time, and the difficulty in increasing antibody levels in these donors; and
- a large variation in the response of individual donors to boosting, and the significant effect on input if any donor withdraws from the program.

Other issues threatening the anti-D supply are discussed in the next chapter, along with the current availability and use of anti-D in Australia. Some strategies to overcome these problems, to most effectively use existing supplies of anti-D and to increase future supply are discussed in Chapter 6.

CHAPTER 2

CURRENT AVAILABILITY AND USE OF ANTI-D IN AUSTRALIA

2.1 Current availability

As well as the logistic difficulties in maintaining the Rh Project, there are wider problems with anti-D supply. A survey in 1995 confirmed a worldwide shortage of anti-D for Rh D immunoglobulin therapy, and it is unlikely that the worldwide supply of anti-D will increase greatly in the next decade.

There are various reasons why the anti-D supply is threatened:

- there has been a fall in the number of women immunised during pregnancy because of the success of the program in recent decades;
- there are also fewer men in the community with anti-D — it is now unusual to transfuse Rh D negative individuals with Rh D positive blood, whereas this was relatively common 20 years ago;
- the usage of Rh D immunoglobulin has probably increased due to inappropriate use in some cases, recommendations for the routine use of anti-D antenatally and the giving of a double dose postpartum without adequate laboratory assessment of fetomaternal haemorrhage (FMH); and
- there are ethical problems associated with the continued boosting and recruitment of Rh D negative donors.

RhoGAM issues ceased at the end of August 1997. Rh D immunoglobulin (CSL) is now the only anti-D preparation on issue in Australia.

The Australian Red Cross Blood Service (ARCBS) is continuing to maximise the collection of anti-D plasma. Donors are now being boosted in Victoria and Queensland as well as in New South Wales and Western Australia. The majority of the plasma input of anti-D to CSL comes from these boosted donors.

However, because of the problems outlined above and in the previous chapter, it is becoming increasingly difficult to increase production. Despite the maximisation of anti-D collection over the past two years by recruiting and boosting all possible acceptable donors, the combined input from New South Wales and Western Australia of anti-D has ranged from as low as 10.7×10^6 IU/month to a maximum of 20.1×10^6 IU/month. This translates into a national annual input of approximately 165×10^6 IU. Currently the yield of anti-D from plasma input to CSL is 20 per cent, so the amount of anti-D immunoglobulin available nationally per year is 35×10^6 IU.

2.2 Current demand

On the basis of current demand for anti-D, which does not include routine antenatal prophylaxis, Australia is still not self-sufficient.

Based on data from ARCBS and CSL, the current demand for anti-D is as follows:

Average anti-D usage (1992–1996)	37.84×10^6 IU per annum
Current issues to all Rh D negative mothers postpartum (based on a dose of 625 IU or 125 µg)	25×10^6 IU per annum
Current issues for abortions, antepartum haemorrhages and other antenatal uses	12.6×10^6 IU per annum

Thus current national demand of approximately 38×10^6 IU slightly exceeds current supply.

An issue to all Rh D negative women of additional doses of 125 µg at 28 and 34 weeks gestation for prophylactic reasons would require an additional 50×10^6 IU per annum, raising the annual usage to $85\text{--}90 \times 10^6$ IU. At a 20 per cent yield, this translates to about 450×10^6 IU of anti-D plasma per annum, which is almost triple the current input. An issue to all Rh D negative women expecting their first baby would require approximately 225×10^6 IU of anti-D plasma per annum.

2.3 Current practice

There is very strong evidence, from the late 1960s onwards, that the practice of administering anti-D postpartum has dramatically reduced the incidence of immunisation and HDN. Postpartum administration of anti-D to all Rh D negative women with no preformed anti-D antibodies who deliver Rh D positive babies is standard practice in Australia and in most parts of the world, although the dose used varies between countries.

The issue of antenatal anti-D administration is less clear. There appears to be wide variation in practice and some evidence for inappropriate use of anti-D in certain situations.

Anti-D is usually given to Rh D negative women with no preformed anti-D antibodies during pregnancy if they experience a 'sensitising' event in which there is a risk of fetal blood crossing into the maternal circulation. These include miscarriage, termination of pregnancy, ectopic pregnancy, genetic studies such as amniocentesis and chorionic villus sampling, external cephalic version, trauma and antepartum haemorrhage.

There are conflicting views about the efficacy of routine prophylactic use of anti-D antenatally. This has resulted in variations in the way that anti-D is used

prophylactically. The situation is complicated by the current restricted supply of anti-D, as routine antenatal administration to all Rh D negative women would place immense demands on anti-D supply.

Specific recommendations for the most appropriate use of anti-D have been developed by the Working Party, based on a review of the literature, a cost-effectiveness analysis, and consideration of the current supply of anti-D (see Chapter 5).

Dose of anti-D

The dose of anti-D required to prevent isoimmunisation is directly related to the volume of FMH. The standard dose given in Australia is 125 µg. As shown in Pollack et al (1971) and now generally accepted, 20 µg (100 IU) of anti-D will protect against a FMH of 1 ml of fetal red blood cells (2 ml of whole blood), so this dose is sufficient to protect against a FMH of 6 ml of fetal red blood cells (12 ml of whole blood).

The majority of fetal bleeds are less than 5 ml of red blood cells.

- In about 50 per cent of cases, the bleeds are less than 0.05 ml.
- In about 5 per cent of cases, transplacental haemorrhages greater than 0.5 ml occur.
- In about 3 per cent of cases, transplacental haemorrhages greater than 1 ml occur.

Studies done in 1977 in New South Wales and Western Australia showed that 99.74 per cent of pregnancies are covered by a 250 µg dose, while 99.57 are covered by the current Australian dose of 125 µg. However, FMH among this residual 0.43 per cent may be as large as 30 ml, putting them at risk if sufficient extra anti-D is not given as required. Another study found that FMH of 30 ml or more occurs in up to 0.6 per cent of deliveries (Zipursky 1977).

There is no uniformity between different countries in the dose of anti-D given postnatally, nor in policies to ensure that sufficient anti-D has been administered. For example, 100–120 µg of anti-D is given in Canada, 100 µg in the United Kingdom, Sweden and Hungary, 300 µg in the United States and 200–250 µg in other European countries.

As most antenatal FMHs are very small in volume, particularly in the first trimester, the administration of a 50 µg dose to women undergoing sensitising events in the first trimester has been advocated. A decision to register a 50 µg vial for use during the first trimester has been deferred temporarily while some issues are addressed by CSL. The matter should be resolved within the next 9 to 12 months.

Testing to assess fetomaternal haemorrhage

There are a number of tests available to assess the volume of FMH and allow additional anti-D to be given where appropriate. The main tests used are:

- the Kleihauer acid elution test — which is widely used but relies on subjective interpretation;
- flow cytometry — which is reliable and accurate, but not widely available outside metropolitan areas; and
- the Rosette test — a qualitative test which if positive needs to be followed up by a quantitative test to determine the volume of FMH.

The accuracy and practicality of the routine use of these tests is variable and they are not used uniformly in all centres.

These tests and the evidence for their most appropriate use are discussed in greater detail in Chapter 6.

Failures of anti-D prophylaxis

Prophylaxis is not successful in every case where Rh D immunoglobulin is given postnatally, although mortality from HDN due to Rh incompatibility is now uncommon. A number of women are still becoming immunised to anti-D through failure to receive the anti-D injection after every sensitising event. Sensitisation of Rh D negative mothers who have received appropriate treatment has been shown to be due either to a major FMH for which the anti-D prophylaxis was inadequate, or to the development of anti-D antenatally.

Immunisation occurs during pregnancy in about 1.5 per cent of Rh D negative women carrying a Rh D positive infant. It has been shown that this immunisation rate can be reduced to 0.2 per cent or less by the administration of anti-D immunoglobulin during pregnancy, at 28 weeks and 34 weeks, as well as after delivery. However, as discussed, this issue remains controversial because of the quality of the evidence and the increased amount of anti-D required should antenatal administration become routine practice. As mentioned, this practice would require at least three times as much anti-D production as at present since many doses would be given to women who subsequently delivered a Rh D negative baby.

Doctor-patient communication

The Working Party felt strongly that the issue of communication with the patient and her family should be addressed as a matter of extreme importance. The current restricted supply of anti-D and the consequent limitations on its use make close monitoring of Rh D negative women and effective communication between doctor and patient especially important.

The NHMRC (1992) states that patients are entitled to make their own decisions about treatments and should be given adequate information on which to base those decisions. Information should be provided in a form which helps women to understand the problem and the options available. Ethical issues relevant to informed consent are discussed in Section 6.2.

In the past, patient information sheets have varied considerably in their content and the effects that they may be expected to have on patient acceptance of prophylaxis when offered. A concise, comprehensive, 'user-friendly' patient information sheet is required, which is applicable to Australian produced Rh D immunoglobulin, but can be modified to apply to overseas anti-D if importation resumes in the short term.

At a personal level, it is clear that there should be an emphasis on information passing between the doctor and the patient, and the responsibility for this cannot be delegated to any large degree. The importance of such communication should be stressed to the profession and included in any information that is issued when the guidelines are fully distributed.

CHAPTER 3

BEST PRACTICE FOR THE USE OF ANTI-D IN OBSTETRICS

The Mater Perinatal Epidemiology Unit, Brisbane was commissioned to undertake a review of the available evidence relating to the effectiveness of the prophylactic use of anti-D in obstetrics. The evidence for the main applications of anti-D is discussed in this chapter. Other issues such as testing to assess FMH, compliance, the ethics of boosting and administration and sources of supply of anti-D are discussed in Chapter 6. Details of the search strategy and tables of results from individual studies are given in Appendix 5.

The search strategy included articles going back to 1966. Acceptance or rejection of articles was determined by the review team according to relevance and quality of evidence. All material relevant to the topics was reviewed and only repetitive level IV evidence consisting of descriptive studies or unsubstantiated expert opinion was excluded. The abstracts of foreign language references were reviewed and the full article sought where necessary and retrieved if available.

The literature was assessed for methodological quality and given a quality of evidence rating as described in the Introduction.

3.1 Postpartum use of anti-D

The best evidence (level I) on the postpartum use of anti-D comes from the Cochrane Database of Systematic Reviews (Crowther & Middleton 1997). This review looked at all published, unpublished, and ongoing randomised trials with reported data which assess outcomes in Rh D negative women without antibodies (and their babies) who were given postpartum anti-D immunoglobulin prophylaxis compared with Rh D negative women without antibodies (and their babies) not given prophylaxis. The main outcomes considered were subsequent development of Rh D immunisation, maternal concerns and adverse effects of treatment, and neonatal morbidity in a subsequent pregnancy.

The trials of postpartum anti-D prophylaxis versus no prophylaxis show Rh D iso-immunisation is less common six months after delivery in women who received anti-D. In addition, the administration of anti-D immunoglobulin reduces the incidence of Rh D immunisation in a subsequent pregnancy.

The systematic review found that prophylaxis with postpartum anti-D immunoglobulin is effective in reducing the risk of sensitisation after pregnancy and in a subsequent pregnancy, irrespective of the blood group of mother and baby. The reviewed trials found that prophylaxis is effective when anti-D is given within 72 hours of birth.

The evidence on the optimal amount of anti-D to recommend for prophylaxis is limited. Recommendations in different countries depend on the relative availability and costs of anti-D and the costs of laboratory assessments of the volume of FMH. As discussed in Chapter 2, the standard Australian dose of 125 µg should

protect against a FMH of up to 12 ml. The data on comparative doses show that doses of up to 50 µg anti-D, compared with higher doses up to 200 µg, increase the risk of sensitisation in a subsequent pregnancy. There is no evidence to show that a lower dose of 100 µg anti-D is substantially less effective than a higher dose of 150 µg anti-D, although the number of immunisations shown are few.

There is a paucity of information about the attitudes of women towards immunisation and the health of infants in subsequent pregnancies. No adverse effects of the treatment are reported, though the risks of rare adverse effects of sensitivity reactions and transmission of infectious diseases remain.

Summary of findings — postpartum use of anti-D

- ***Prophylaxis with postpartum anti-D is effective in reducing the risk of sensitisation after pregnancy and in a subsequent pregnancy, irrespective of the ABO status of mother and baby. Prophylaxis is effective when anti-D is given within 72 hours of birth.***

Implications for research

No further placebo controlled trials are warranted to establish the effectiveness of anti-D prophylaxis postpartum.

As the evidence on the optimal dose of anti-D to recommend for postpartum prophylaxis is limited, further good quality comparative dose finding trials would be appropriate. In particular, the cost effectiveness of smaller doses of anti-D immunoglobulin combined with screening for the degree of FMH and administering additional anti-D as necessary should be compared with the use of larger doses of anti-D.

In further trials the attitudes of women towards immunisation and the health of infants in subsequent pregnancies should be evaluated. Any adverse effects of the treatment including sensitivity reactions and transmission of infectious diseases should be documented (Crowther & Middleton 1997).

3.2 Anti-D for antenatal sensitising events

Abortion, ectopic pregnancy and genetic studies

Studies were considered examining the administration of anti-D immunoglobulin in Rh D negative women up to 20 weeks gestation after:

- threatened, spontaneous, medical and surgical abortion;
- ectopic pregnancy; and
- chorionic villus sampling and amniocentesis.

The incidence of immunisation and FMH were the main outcome measures examined.

Forty-eight articles were included. No level I evidence was available. Only four level II and three level III-1 studies were retrieved. No studies were excluded. A table summarising the results of individual studies is at Appendix 5.

The available evidence establishes that transplacental haemorrhage (TPH) can occur after six weeks gestation and can be associated with medical, surgical and spontaneous abortion, ruptured ectopic pregnancy, amniocentesis and probably chorionic villus sampling.

One of the difficulties in determining which women are at risk of becoming immunised in early pregnancy is the availability of accurate tests to assess the quantity of TPH at low levels. The literature reports that 0.1-0.25 ml of Rh D positive fetal blood is required for maternal Rh D immunisation and although the Kleihauer test can detect TPH of less than 0.1 ml there are problems with specificity and false positive results.

With these problems in testing for small but potentially immunising TPH, decisions need to be made about which events in early pregnancy increase the risk of Rh D immunisation. Studies on the rate of immunisation need to be compared to the baseline rate of a control group.

The studies reviewed have the following limitations:

- They often do not differentiate between women experiencing a spontaneous abortion and those experiencing an induced abortion.
- Some studies do not specify if curettage followed spontaneous abortion.
- Other studies report on the incidence of TPH but do not provide follow-up to determine the incidence of immunisation.

Spontaneous or induced abortion

One level III-1, one level III-2 and eight level III-3 studies reported an increased rate of immunisation following spontaneous abortion with instrumentation or induced abortion. Ascari (1971, level IV) reported that Rh D immunisation ranged from 0–13 per cent in nine prospective studies of women experiencing either spontaneous or induced abortion. Bergstrom et al (1967, level IV) reported on one case in which Rh D antigen was present on fetal red blood cells as early as the 38th day post conception.

Spontaneous or threatened abortion (miscarriage)

There is very little literature reporting the incidence of immunisation in women experiencing spontaneous and threatened abortion (miscarriage). Some studies providing lower level evidence report FMH following these events but there is no clear link with the incidence of immunisation. There is only one study indicating that immunisation can occur following early and late spontaneous abortion (Goldman & Eckerling 1972, level III-1).

Kuller et al (1994, level II) included women experiencing threatened abortion up to 20 weeks gestation and found the incidence of FMH between women experiencing threatened abortion and controls was not statistically significant. Matthews and Matthews (1969, level III-3) found that although there was evidence of TPH in cases of spontaneous abortion, it was well below the minimal potential immunising dose. Goldman and Eckerling (1972, level III-1) reported a reduced rate of immunisation using 200 µg anti-D in both first and second trimester surgically induced and spontaneous abortions. However they failed to state which women experiencing spontaneous abortion also had curettage.

There is low level evidence reported by Whitfield (1997) and Portmann et al (1997) of immunisation following threatened abortion at less than 12 weeks gestation. Eklund et al (1982) report that 10–15 per cent of the antibody crosses the placenta into the fetal circulation. There is no evidence of the effect of this on the embryo or fetus. No evidence was retrieved on the timing of anti-D administration if bleeding continues. However, Howard et al (1997) reported that anti-D should be given every six weeks if women continue to bleed, as recommended in the National Blood Transfusion Services Immunoglobulin Working Party guidelines (NBTS Immunoglobulin Working Party 1991).

Surgical or medical abortion

It has been reported that immunisation can occur following surgical abortion from eight weeks gestation (Freda et al 1970). No evidence was retrieved on the incidence of immunisation following medical abortion. Available evidence (level II, III-3) supports use of a 50 µg dose of anti-D for surgically induced abortion in the first trimester to prevent immunisation in most cases.

Ectopic pregnancy

The data are scant but that which is available on ectopic pregnancy confirms that FMH can occur in association with ruptured ectopic pregnancy. There are two case study reports of immunisation following ectopic pregnancy (Krause & Goh 1996; Katz & Marcus 1972).

Genetic studies

No evidence was retrieved on the incidence of immunisation following chorionic villus sampling.

Of the eight level III-3 studies reviewed on genetic amniocentesis, Hill et al (1980) and Golbus et al (1982) reported the incidence of immunisation was increased and Tabor et al (1986) reported no difference in the incidence of immunisation. Tabsh et al (1984), Brandenburg et al (1989) and Goldstein and Pezzlo (1978), reported anti-D was successful in reducing the rate of sensitisation following genetic amniocentesis. Lenke et al (1985) compared a visual assessment of intra-amniotic bleeding with alpha-feto protein (AFP) and Kleihauer testing and found no correlation between placental location, placenta needle traversal and FMH. They reported no correlation between placental location and FMH. Henry et al (1976) reported that posterior placental localisation reduces the incidence of a bloody sample.

There is a lack of information regarding the attitudes of women towards immunisation and the health of infants in subsequent pregnancies.

Summary of findings — anti-D for antenatal sensitising events

- ***There is no level I evidence available to support the use of anti-D for potentially sensitising events during pregnancy. The available evidence indicates that transplacental haemorrhage can occur after six weeks gestation and can be associated with medical, surgical and spontaneous abortion, ruptured ectopic pregnancy, amniocentesis and probably chorionic villus sampling.***
- ***There is evidence of a risk of immunisation following surgical abortion, ruptured ectopic pregnancy and amniocentesis, supporting the use of anti-D for these potentially sensitising events (level of evidence II, III).***
- ***There is insufficient and conflicting evidence about whether Rh D negative women experiencing threatened miscarriage or spontaneous miscarriage without curettage should receive anti-D.***

Implications for research

Further information is needed on:

- the risk of immunisation following spontaneous abortion and threatened abortion at various gestations;
- the risk of immunisation following medically induced abortion at various gestations;
- the earliest gestation at which immunisation can occur following surgical abortion or ectopic pregnancy;
- the dose of anti-D required to protect women from immunisation in the second trimester when experiencing abortion, ruptured ectopic pregnancy, chorionic villus sampling or amniocentesis;
- the attitudes of women towards immunisation and the health of their infants in subsequent pregnancies. Any adverse effects of the treatment including sensitivity reactions and transmission of infectious diseases should be documented (Crowther & Middleton 1997); and
- the effects of anti-D on the embryo and fetus at early gestations since 10–15 per cent of anti-D antibody crosses the placenta (Eklund et al 1982).

External cephalic version, trauma and antepartum haemorrhage

All published, unpublished, and ongoing studies and commentaries with reported data were considered which assess the incidence of immunisation or the prevention of immunisation in Rh D negative women undergoing external cephalic version (ECV), or experiencing abdominal trauma or antepartum haemorrhage.

External cephalic version

There is no level I or level II evidence on the prevention of Rh D immunisation following ECV. Of the four studies reviewed, the only level III-1 evidence was from a trial with a small sample. There were three level III-3 studies reviewed. No studies were excluded.

There is very little evidence about the risk of immunisation or the incidence of FMH relating to ECV. Murray et al (1974) showed no statistical difference in the incidence of immunisation between women undergoing ECV and a control group. The other three studies demonstrated that significant FMH was detected following this procedure. They did not follow-up the women to report on the incidence of immunisation.

Summary of findings — external cephalic version

- *The available evidence (level III-3) supports the prophylactic use of anti-D following external cephalic version, although dosage levels have not been considered.*

Implications for research

Further research is warranted into quantification of FMH at ECV in order to determine appropriate dosage.

Trauma during pregnancy and antepartum haemorrhage

No evidence on the prophylactic use of anti-D for either of these conditions was retrieved.

3.3 Routine antenatal use of anti-D

Study types

The studies considered were all published, unpublished and ongoing studies and commentaries which reported data assessing outcomes in Rh D negative women without antibodies (and their babies) who were given anti-D immunoglobulin at 28 weeks or more of pregnancy.

Outcome measures varied but include one or more of the following:

- the number of newly sensitised women
 - at delivery of the current pregnancy
 - three days after delivery with the current pregnancy
 - six months postpartum
 - during the subsequent pregnancy (with a Rh D positive baby)
 - at delivery of a subsequent pregnancy (with a Rh D positive baby); and
- incidence of, and mortality from, HDN.

Nineteen studies were included. Two level II studies and one level III-1 study were retrieved. The remainder were level III-3 or level IV evidence.

The Cochrane review 'Anti-D Administration in Pregnancy' (Crowther & Middleton 1996), has been considered in this report as level II evidence because only one randomised controlled trial (Huchet 1987) was included.

Level IV articles which repeated expert opinion and which provided no new information were excluded.

Results

The incidence of intrapregnancy immunisation without routine antenatal prophylaxis in a first pregnancy is estimated to be between 0.3 and 5.6 per cent, with an average of 0.9 per cent (Davey & Zipursky 1979).

Intrapregnancy immunisation is most likely to occur after the 28th week of gestation (Davey & Zipursky 1979). This paper reports the incidence of fetal cells in maternal circulation as 8–14 per cent in the first trimester, 16–38 per cent in the second trimester and 48–76 per cent in the third trimester.

In an effort to further reduce the incidence of Rh D immunisation, routine antenatal anti-D has been administered to Rh D negative women using a variety of regimens. The six regimens of routine antenatal prophylaxis described in the reviewed literature are as follows:

- 240–300 µg at 28 weeks and 34 weeks (Bowman & Pollock 1978)
- 240–300 µg at 34 weeks (Bowman & Pollock 1978)
- 240–300 µg at 28 weeks (Bowman & Pollock 1983)
- 250 µg at 32–34 weeks (Hermann et al 1979)
- 100 µg at 28 and 34 weeks (Huchet et al 1987)
- 50 µg at 28 and 34 weeks (Lee & Rawlinson 1995).

There is no level I evidence to support the routine use of anti-D antenatally. The Huchet et al trial (1987) provides level II evidence supporting the routine use of two doses of antenatal anti-D at a dose of 100 µg at 28 and 34 weeks in reducing the incidence of immunisation. The Lee and Rawlinson (1995) trial provides level II evidence showing no reduction in the incidence of immunisation at a lower dose of anti-D.

Many studies providing lower level evidence (one III-1 study and six III-3 studies) support the use of routine antenatal anti-D with a dose range equal to or higher than the Huchet et al trial (1987) which used 100 µg. One level III-3 study also showed no reduction in sensitisation, again using a lower dose of 50–60 µg (Davey 1975). However, the studies were not all well designed or conducted. The studies reviewed failed to:

- follow-up women with Rh D positive babies in a subsequent pregnancy to determine the incidence of HDN with and without antenatal treatment. Both need to be assessed to determine the severity of disease in subsequent pregnancies of women sensitised in their first pregnancy;

- determine if a low level of antibody production in the first pregnancy in which antibodies appeared was predictive of the incidence of HDN in subsequent pregnancies with Rh D positive babies. Godel et al (1968) reported that women who test weakly positive for antibodies at delivery may test negative for antibodies at six months even without postpartum anti-D administration;
- follow-up women in a subsequent pregnancy with a Rh D positive baby to determine the actual failure of protection of either women receiving antenatal and postnatal anti-D or those receiving only postnatal anti-D. Testing only for immunisation postnatally, before a subsequent pregnancy, will underestimate failures of protection because a proportion of immunised women only form detectable antibodies when next exposed to Rh D positive cells (next pregnancy with a Rh D positive fetus) (Davey 1975).

Accuracy and sensitivity of the tests used differed between studies and many studies compared the results of their experimental group with historical controls which had antibody estimations performed using a different test technique. This probably affects the incidence of immunisation reported including the baseline level of intrapregnancy immunisation.

Most studies did not report on measures taken to control for accepted sensitising events of pregnancy like amniocentesis or external cephalic version.

None of the studies included long-term effects for the infant or mother. In addition, alternative methods of reducing the risk of sensitisation in pregnancy which cause HDN, other than routine antenatal anti-D administration, were not discussed in the studies reviewed.

Mackenzie (1997) reported a reduction in immunisation without routine antenatal prophylaxis between 1980–86 and 1990–95. Hensleigh (1983) stated that the incidence of Rh D disease is on a downward trend due to the decreasing pool of isoimmunised women, decreasing family size, decreasing percentage of Rh D negative women in the population due to an increased proportion of non-Caucasian women and the uptake of family planning options among women who are already immunised.

Likely impact of antenatal prophylaxis

The purpose of trying to prevent Rh D immunisation is to reduce the incidence of moderate and severe HDN. The first Rh D positive baby is unlikely to be severely affected (Tovey et al 1983) and therefore it is a subsequent pregnancy where serious morbidity or mortality may occur. Davey and Zipursky (1979) report about 40 per cent of infants from sensitised women require no treatment, 20 per cent require phototherapy only, leaving 20 per cent which require one or more

exchange transfusions and 20 per cent with severe HDN requiring intra-uterine transfusion or other special measures.

Level II and III evidence would suggest that the 1.5 per cent immunisation rate could be reduced to 0.1 to 0.2 per cent through routine antenatal prophylaxis (Huchet et al 1987; Bowman & Pollock 1978; Hermann et al 1984), relieving virtually all of this burden of mortality and moderate to severe morbidity.

Summary of findings -- routine antenatal use of anti-D

- ***There is no level I evidence to support the routine administration of anti-D antenatally to all unsensitised Rh D negative women at any gestation. However, there is considerable lower level evidence supporting the efficacy of this practice.***

Implications for research

Demonstrating effectiveness of routine antenatal anti-D administration

Based on the extent of this problem in Australia, it would seem unlikely that further randomised controlled trials are justified to evaluate the effectiveness of routine anti-D prophylaxis.

Identifying and preventing antenatal immunisation for women at risk

Scott et al (1977) state that the development of a reliable method for detecting and selectively treating those women who are destined to become Rh D immunised before parturition may be more cost effective and less risky than routine antenatal anti-D administration. It may be beneficial to investigate the factors involved in those countries which report low rates of intrapregnancy sensitisation.

Safety for the fetus/infant

The studies which looked at safety for the fetus provided data limited to evaluation of the cord haemoglobin, bilirubin and direct Coombs' tests. None of the large clinical trials reported comparable data on a series of outcomes. These include fetal death, birth weight, neonatal morbidity and mortality, neonatal immunological status, childhood illnesses and the effects on Rh D negative female fetuses exposed to Rh D immunoglobulin in utero who in adulthood bear Rh D positive fetuses.

CHAPTER 4

COSTS AND COST EFFECTIVENESS OF ANTI-D USE

A consideration of cost effectiveness is particularly important in the development of guidelines for anti-D use because of the limited supply of anti-D available relative to the number of women and babies who may benefit from its use. Therefore, some women who may potentially benefit from anti-D will be unable to obtain it. Under these circumstances, it is necessary to consider the costs and benefits of alternative policies regarding the administration of anti-D, to determine whether there are some groups of women, for example groups at relatively low risk of experiencing Rh D isoimmunisation, for whom the use of anti-D is costly in comparison with the benefits achieved.

The Working Party commissioned a cost-effectiveness analysis of five alternative strategies for the prevention of Rh D isoimmunisation in Australia. A brief description of the model, together with the results and conclusions, is given in this chapter. A full discussion of the assumptions and data used and the accompanying tables and figures are presented in Appendix 6.

The model is designed to investigate the cost effectiveness of alternative policies regarding the administration of anti-D to Rh D negative mothers. Six scenarios were considered:

- *no anti-D given* — estimates of the costs and health effects associated with isoimmunisation of Rh D negative mothers in the absence of any anti-D being administered;
- *postpartum only* — postpartum administration of a vial of anti-D to all Rh D negative mothers with no preformed anti-D following the birth of a Rh D positive baby;
- *antenatal with indications + postpartum* — antenatal administration of a vial of anti-D to Rh D negative mothers with no preformed anti-D when specific indications are present (the potentially sensitising events discussed in Section 3.2), together with postpartum administration;
- *antenatal prophylaxis (primigravidae only) + postpartum* — antenatal administration of a vial of anti-D to all Rh D negative mothers with no preformed anti-D expecting their first baby, at 28 weeks and again at 34 weeks of pregnancy, or when specific indications are present (see Section 3.2), together with postpartum administration;
- *antenatal prophylaxis (primigravidae only) + antenatal with indications + postpartum* — antenatal prophylaxis for primigravidae as defined above, together with antenatal administration of a vial of Rh D immunoglobulin to Rh D negative mothers experiencing their second or subsequent pregnancy when specific indications are present (see Section 3.2), together with postpartum administration; and

-
- *antenatal prophylaxis + postpartum* — antenatal administration of a vial of anti-D to Rh D negative mothers who do not miscarry or terminate and with no preformed anti-D, at 28 weeks and again at 34 weeks of pregnancy, administration of a vial of anti-D to Rh D negative mothers who miscarry or terminate, and postpartum administration.

In the above descriptions, the dosage of anti-D has been specified in terms of vials rather than μg or IU because the Australian product is presently supplied only in a 125 μg vial, the recommended dosage is generally 125 μg or less, and one vial cannot be used to supply more than one dose of anti-D.

The model then investigates the cost effectiveness of the five prevention strategies.

4.1 Data

A range of probabilities was derived for decision making during first and subsequent pregnancies, for each strategy.

The cost estimates required for the model can be categorised broadly as the direct costs of HDN, the indirect costs of HDN, and the cost of prevention.

Direct costs include the costs for acute treatment of mothers and of babies born with HDN, and the continuing costs of providing ongoing support to those with long-term sequelae.

The indirect cost of an illness is the lost production that results, either from reduced productivity while at work, from time off work, or from premature death. In the case of HDN, indirect costs arise from HDN deaths and from those with HDN who survive with long-term sequelae (those who survive with long-term sequelae also give rise to direct costs — see above).

For an individual woman and her baby, the cost of prevention using anti-D comprises the cost of one or more vials of anti-D, and the costs of tests associated with administering that anti-D.

The costs of testing to determine Rh D status and anti-D status for all strategies were included, along with the cost of testing for FMH (Kleihauer test) at birth.

4.2 Results

Numbers of events

Under the no anti-D given scenario, the model predicts 78 HDN deaths across all pregnancies, or a death rate from HDN of 30.89/100,000 live births. This compares with 80 deaths recorded in Australia in 1974 as being due to HDN with Rh D incompatibility (ABS 1975). The undiscounted number of years of life lost is 6,114 (1,296 discounted). Most deaths arise from second and higher order pregnancies. The predicted number of HDN births surviving but with long-term sequelae (handicapped) is 55, which is about 70 per cent of the number of HDN deaths.

Postpartum administration of anti-D reduces the HDN mortality rate to 9.00/100,000 live births. This represents a reduction in the number of HDN deaths from 78 to 22 per year, or 56 deaths avoided (70 per cent) (see Table 4.1).⁴ Postpartum administration has no effect on HDN mortality from first pregnancies. The estimated number of life-years saved is 4,333 (or 910 discounted). The number of HDN handicapped falls from 55 to 18.

Antenatal administration of anti-D to Rh D negative women with indications in addition to postpartum administration is estimated to reduce the number of HDN deaths to 16. This is a further reduction of six deaths, and a further gain of 486 years of life lived (102 discounted years of life lived) over and above the level of HDN mortality obtained with postpartum administration of anti-D alone. The estimated number of HDN handicapped falls to 14.

4 Any discrepancies between numbers reported in this Chapter and Appendix 6 are due to rounding.

Table 4.1 Number of HDN deaths averted, number of life-years saved and cost per life-year saved under five programs for the prevention of Rh D isoimmunisation in Australia*

Postpartum Rh D Ig only compared with:

No anti-D given

Antenatal with indications + postpartum compared with:

Postpartum Rh D Ig only

Antenatal prophylaxis (primigravidae only) + postpartum compared with:

Postpartum Rh D Ig only

Antenatal with indications + postpartum

Antenatal prophylaxis (primigravidae only) + antenatal with indications + postpartum compared with:

Postpartum Rh D Ig only

Antenatal with indications + postpartum

Antenatal prophylaxis (primigravidae only) + postpartum

Antenatal prophylaxis + postpartum compared with:

Postpartum Rh D Ig only

Antenatal with indications + postpartum

Antenatal prophylaxis (primigravidae only) + postpartum

Antenatal prophylaxis (primigravidae only) + antenatal with indications + postpartum

Notes: * All results are discounted using a discount rate of 5%. Under no anti-D given, 78 HDN deaths are estimated to occur.

** Bracketed sum indicates a negative cost (ie cost savings exceed cost of prevention).

HDN deaths averted	Life years saved	Cost per life year saved**	
		Based on cost of prevention only	Based on cost of prevention minus cost savings from mothers only**
56	910	\$3,907	(\$4,864)
6	102	\$21,992	\$13,241
9	164	\$26,934	\$16,231
3	62	\$35,071	\$21,154
12	199	\$30,559	\$20,242
5	98	\$39,496	\$27,546
2	36	\$47,148	\$38,538
20	341	\$28,759	\$20,315
14	239	\$31,636	\$23,323
11	177	\$30,441	\$24,078
8	177	\$26,229	\$20,418

Antenatal prophylaxis for primigravidae only combined with postpartum administration reduces the number of HDN deaths to 13. This represents a reduction of nine deaths in comparison with postpartum administration alone, or a reduction of three deaths in comparison with the antenatal program confined to Rh D negative women with indications in conjunction with postpartum administration. The number of HDN handicapped is reduced to nine persons per year.

Antenatal prophylaxis for primigravidae only, combined with antenatal administration of anti-D to Rh D negative women with indications for second and subsequent pregnancies, and with postpartum administration, is estimated to reduce the number of HDN deaths to 11. This is two fewer deaths than occur with antenatal prophylaxis for primigravidae only, or five fewer deaths than occur with the antenatal with indications program alone. The number of HDN handicapped is reduced to seven persons per year.

Antenatal prophylaxis for all Rh D negative pregnant women with no preformed anti-D reduces the number of HDN deaths to three, and hence has the largest impact on HDN mortality of all five prevention strategies considered. Compared with the combined antenatal prophylaxis (primigravidae only)/antenatal with indications/postpartum program, it is estimated to avoid an additional eight HDN deaths. The number of HDN handicapped falls to six persons per year.

The model predicts a 96 per cent reduction in HDN mortality under antenatal prophylaxis in comparison with the no anti-D given scenario, and an 87 per cent reduction in HDN mortality compared with that predicted to occur under postpartum administration only. The remaining three deaths predicted to occur each year compares with the actual number of 10 deaths due to HDN in Australia in 1995 (10 fetal/0 neonatal) (ABS 1996) and six deaths in 1996 (4 fetal/2 neonatal) (ABS 1997).

Costs

Under no anti-D given, there is no cost of prevention. The direct costs of HDN (costs of management/treatment) under no anti-D given amount to \$15.4 million, and the indirect costs to \$18.4 million. Of the indirect costs, \$10.8 million (59 per cent) are attributable to HDN mortality. Direct costs are estimated to account for 46 per cent of the estimated total costs of HDN of \$33.8 million.

Postpartum administration of anti-D without any antenatal program has an estimated cost of prevention of \$3.6 million. This estimate includes the costs of all tests before administration of anti-D as well as the cost of the anti-D itself (based on a price of \$60 per vial). In comparison with the scenario where no anti-D is given, this strategy reduces the direct costs of HDN by \$10.7 million (a 69 per cent reduction) and the indirect costs by \$12.5 million (a 68 per cent reduction).

The estimated costs of prevention using antenatal administration of anti-D to Rh D negative women with indications together with the postpartum program are \$5.8 million. In comparison with postpartum administration of anti-D only, this program has an additional cost of prevention of \$2.2 million. The direct costs of HDN fall by \$1.2 million, and the indirect costs by \$1.4 million, in comparison with postpartum administration only.

Antenatal prophylaxis for Rh D negative primigravidae only combined with postpartum administration has an estimated cost of prevention of \$8.0 million. This is \$4.4 million greater than the cost of prevention under the postpartum program alone, and \$2.2 million greater than under the antenatal with indications plus postpartum program. The total direct and indirect cost savings of this program compared with postpartum administration only amount to \$5.3 million, giving rise to a net cost saving of \$0.9 million. Compared with the antenatal with indications plus postpartum program, the savings in direct and indirect costs amount to \$2.7 million which exceed the additional cost of prevention (\$2.2 million), again generating a net cost saving.

The combined antenatal prophylaxis (primigravidae only)/antenatal with indications/postpartum program has a total cost of prevention of \$9.6 million. This is \$3.8 million greater than the antenatal with indications plus postpartum program, and \$1.7 million greater than the antenatal prophylaxis (primigravidae) plus postpartum program. The corresponding savings in direct and indirect costs of HDN amount to \$3.6 million and \$0.9 million respectively.

Antenatal prophylaxis for all Rh D negative pregnancies with no preformed anti-D combined with postpartum administration of anti-D has a cost of prevention of \$13.4 million — more than double the cost of the antenatal with indications plus postpartum strategy, and \$5.4 million greater than with antenatal prophylaxis for primigravidae only. It is also \$3.7 million greater than the combined antenatal primigravidae/antenatal with indications/postpartum program. However, it also generates direct and indirect cost savings such that, on balance, it has a net cost after allowance for these cost savings of no more than \$1.3 million in comparison with any of the other four prevention strategies. This program also provides antenatal anti-D to 70 per cent of the Rh D negative second and subsequent pregnancies (women without the indications specified in Section 3.2) that are not covered by any of the other four programs.

It is clear that if both direct and indirect cost savings are deducted from the cost of prevention for any of the five alternative prevention programs the net cost of anti-D prevention programs is either negative or, if positive, would not exceed \$1.3 million. Even though antenatal prophylaxis has a much greater cost of prevention than the other four prevention programs, the direct and indirect

savings generated are such that, on balance, it results in a moderate net incremental cost of \$0.4 million to \$1.3 million. It also results in the greatest number of HDN deaths averted and life-years saved, features which are included in an assessment of the cost effectiveness of the five alternative strategies.

Cost-effectiveness analysis

It is of interest to consider the cost effectiveness of the five prevention programs without any deductions of estimated cost savings, and also with only the savings in direct costs deducted.

Considering the cost of prevention only, without deducting any cost savings, postpartum administration of anti-D saves life-years at a cost of \$3,907 per life-year saved (see Table 4.1). If antenatal administration of anti-D is added to postpartum administration, the additional cost per year of life saved in comparison with postpartum administration only is \$21,992. If antenatal prophylaxis for primigravidae only is added to postpartum administration, the cost per year of life saved is \$26,934 compared with the postpartum only program, and \$35,071 compared with the antenatal with indications plus postpartum program. The combined antenatal prophylaxis (primigravidae)/antenatal with indications/postpartum program has an incremental cost per life-year saved in the range \$30,559 to \$47,148, the lower end of the range being based on a comparison with the postpartum only program. Antenatal prophylaxis has an incremental cost per life-year saved in the range \$26,229 to \$31,636.

It must be emphasised that these costs per life-year saved reflect a 'worst case' scenario, as they make no allowance for any cost savings associated with any of the prevention programs. Even under this scenario, the cost per life-year saved of an antenatal prophylaxis/postpartum program suggests that it is a reasonable investment in economic terms. It also results in the greatest number of deaths averted and life-years saved in comparison with a postpartum only program. It must be emphasised also that these results are based on an average price per vial of anti-D of \$60, a price at which imported product is readily available. Hence, this analysis suggests that, even if the total demand for anti-D under an antenatal prophylaxis program were met from imported product, the program would be cost effective.

If direct cost savings arising from the reduction in treatment required for mothers during pregnancy are deducted from the cost of prevention, the net cost of the postpartum only program becomes negative, ie the program is cost saving. The cost per life-year saved for each of the antenatal programs falls by at least \$6,000 in any of the comparisons (see Table 4.1). It should be remembered that these results ignore completely any direct cost savings associated with infants, and any indirect cost savings, resulting from the prevention programs.

These results support the contention that *postnatal prophylaxis is regarded as representing self-evidently good value for money* (Vick et al 1996). It must also be emphasised that the cost-effectiveness analysis presented here has included only the mortality reduction benefits of the prevention programs. While these mortality reductions are undoubtedly important, the long-term sequelae observed in some cases of HDN are real and should not be forgotten.

Demand for anti-D

A final aspect of this analysis which is of interest is the effect of these alternative prevention programs on the demand for anti-D. With postpartum administration of anti-D only, the number of vials demanded per year is estimated to be 25,000. If antenatal administration to Rh D negative women with indications is added to postpartum administration, the demand is projected to increase to 43,000 vials per year. Antenatal prophylaxis for primigravidae only in conjunction with a postpartum program would give rise to a demand of 72,000 vials. A combined antenatal prophylaxis program for primigravidae only, combined with antenatal with indications plus postpartum administration would lead to an annual demand for 82,000 vials. Finally, if antenatal prophylaxis is introduced along with postpartum administration, the number of vials demanded in a year increases to 129,000.

It must be stressed that these estimates of demand are based on the optimal use of anti-D in each scenario. That is, they are based on ideal usage of anti-D under a range of assumptions rather than current real-life practice patterns. For this reason, these demand estimates are generally lower than one would expect based on the data on actual utilisation in Australia provided in Chapter 2 of this report (see Section 2.2).

4.3 Conclusions

Based on the results of this model, it appears that antenatal prophylaxis for all Rh D negative pregnancies with no preformed anti-D antibodies, combined with postpartum administration, is a cost-effective health care intervention.

This conclusion accords with the view of the 1997 Edinburgh consensus conference panel on anti-D prophylaxis that there was *no ethical or economic justification for limiting antenatal prophylaxis to Rh D negative primigravidae* (Robson et al 1998).

However, in the event that anti-D is unavailable in sufficient quantities to meet the demand generated with universal antenatal prophylaxis, these cost-effectiveness results indicate that postpartum administration should have first call on the available supplies of anti-D. A program of antenatal prophylaxis for women with indications would be ranked second on economic grounds, followed by antenatal prophylaxis for primigravidae only.

These cost-effectiveness analysis results highlight the need to seriously consider options for increasing the supply of anti-D in the future to enable implementation of a universal antenatal prophylaxis program for all Rh D negative pregnant women.

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CHAPTER 5

RATIONALE FOR GUIDELINE RECOMMENDATIONS

The Working Party developed the following recommendations for the most appropriate use of anti-D, based on the review of the literature, the cost-effectiveness analysis, and consideration of the current supply of anti-D. The supporting evidence for each recommendation is discussed below.

General

- *For successful immunoprophylaxis, Rh D immunoglobulin should be administered as soon as possible after the sensitising event, but always within 72 hours. If Rh D immunoglobulin has not been offered within 72 hours, a dose offered within up to 9–10 days may provide protection. Blood should be taken from the mother before administration of the Rh D immunoglobulin to assess the magnitude of fetomaternal haemorrhage.*

Postpartum administration

- *A dose of 125 µg (625 IU) Rh D immunoglobulin should be offered to every Rh D negative woman following delivery of a Rh D positive baby. Rh D immunoglobulin should not be given to women with preformed anti-D antibodies, except where the preformed anti-D is due to the antenatal administration of Rh D immunoglobulin.*
- *The magnitude of the fetomaternal haemorrhage should be assessed by a method capable of quantifying a haemorrhage of ≥ 6 ml of fetal red cells (12 ml of whole blood). Further doses should be administered sufficient to prevent maternal immunisation.*

There is evidence from a systematic review of randomised controlled trials that prophylaxis with postpartum anti-D immunoglobulin is effective in reducing the risk of sensitisation after pregnancy and in a subsequent pregnancy, irrespective of the ABO blood group status of mother and baby. The reviewed trials found that prophylaxis is effective when anti-D is given within 72 hours of birth.

The evidence on the optimal dose of anti-D to recommend for prophylaxis is limited. Standard doses vary between countries, depending on the relative availability and costs of anti-D and the costs of laboratory assessments of the volume of FMH.

It is reasonably well established that 20 µg of anti-D will protect against a FMH of 1 ml of fetal Rh D positive red cells (2 ml of whole blood). The standard Australian dose of 125 µg should protect against a FMH of up to 6 ml of fetal Rh D positive red cells (12 ml of whole blood). A FMH greater than this amount is uncommon but if it does occur, the woman will be at risk of sensitisation if she receives only the standard dose. For this reason, it is recommended that at the time the baby's blood is sent for grouping, a maternal sample is also sent for assessment of the FMH, and further doses of anti-D administered sufficient to prevent maternal immunisation.

Antenatal administration for potentially sensitising events

First trimester

- *A dose of 50 µg (250 IU) Rh D immunoglobulin should be offered to every Rh D negative woman with no preformed anti-D antibodies to ensure adequate protection against immunisation for the following indications up to and including 12 weeks gestation:*
 - *miscarriage;*
 - *termination of pregnancy;*
 - *ectopic pregnancy; and*
 - *chorionic villus sampling.*
- *A dose of 50 µg Rh D immunoglobulin is sufficient to prevent immunisation by a fetomaternal haemorrhage of 2.5 ml of fetal red cells (5 ml whole blood).*
- *Until a 50 µg Rh D immunoglobulin vial becomes available in Australia, 125 µg Rh D immunoglobulin should be used.*
- *The Working Party strongly recommends that women undergoing termination of pregnancy be tested to determine their Rh D type, to avoid unnecessary use of Rh D immunoglobulin.*

There is no level I evidence available to support the use of anti-D for potentially sensitising events during pregnancy. Despite limitations with many of the studies, the available lower level evidence indicates that TPH can occur after six weeks gestation and can be associated with medical, surgical and spontaneous abortion, ruptured ectopic pregnancy, and probably chorionic villus sampling.

There is evidence of an increased risk of immunisation following surgical abortion and ruptured ectopic pregnancy, supporting the use of anti-D for these indications.

There is insufficient and conflicting evidence about whether Rh D negative women experiencing threatened miscarriage or spontaneous miscarriage without curettage should receive anti-D.

The Working Party considers that the recommended dose of anti-D for all potentially sensitising first trimester events should be 50 µg. It is acknowledged that this recommendation will have no impact on the amount of anti-D used because of the current packaging into doses at 125 µg. However, in the long term, when the 50 µg dose is available, its use should lead to a halving of the amount of anti-D used in the first trimester.

Beyond the first trimester

- *A dose of 125 µg Rh D immunoglobulin should be offered to every Rh D negative woman with no preformed anti-D antibodies to ensure adequate protection against immunisation for the following indications after 12 weeks gestation:*
 - *genetic studies (chorionic villus sampling, amniocentesis and cordocentesis);*
 - *abdominal trauma considered sufficient to cause fetomaternal haemorrhage;*
 - *each occasion of revealed or concealed antepartum haemorrhage (where the patient suffers unexplained uterine pain the possibility of concealed antepartum haemorrhage should be considered, with a view to immunoprophylaxis); and*
 - *external cephalic version (performed or attempted).*
- *As evidence for the efficacy of this dose for these indications is not available, it is recommended that the magnitude of fetomaternal haemorrhage be assessed and further doses administered, especially where transplacental access or puncture of fetal blood vessels occurs.*

Genetic studies

The available evidence on genetic studies indicates that amniocentesis is associated with an increased rate of immunisation, and that anti-D is successful in reducing the rate of sensitisation following amniocentesis. A standard dose (125 µg) of anti-D should be offered, except where it is known that the father is Rh D negative, or where the fetal blood group is Rh D negative.

Ideally, an estimation of the FMH should be performed after all invasive tests, particularly fetal blood sampling, chorionic villus sampling, transplacental amniocentesis and insertion of fetal amniotic shunts.

Trauma, antepartum haemorrhage and external cephalic versions

The available evidence supports the prophylactic use of anti-D following external cephalic version, although dosage levels have not been considered.

No evidence on the prophylactic use of anti-D for trauma or antepartum haemorrhage was found. The incidence of such haemorrhages large enough to cause immunisation does not appear to be known.

However, it is recommended that all women with abdominal trauma considered sufficient to cause a degree of placental separation, revealed or concealed antepartum haemorrhage and performed or attempted external cephalic version should receive the standard dose (125 µg) of anti-D, with estimation of the FMH as outlined above. Where such situations arise in association with immediate delivery, the standard procedures associated with the postpartum administration of anti-D should be implemented.

Compared with the usage of anti-D post delivery and in the first trimester, the continued administration of anti-D in such cases would not significantly affect the overall volume of use. Failure to prevent an immunisation occurring in these circumstances would be undesirable from both a health care cost and human point of view.

Antenatal prophylaxis

- *Universal prophylaxis with Rh D immunoglobulin to Rh D negative women with no preformed anti-D antibodies at 28 and 34 weeks gestation is generally regarded as best practice. However, due to supply constraints, routine antenatal prophylaxis should not be administered until further notice.*

There is no level I evidence to support the routine administration of Rh D immunoglobulin antenatally to unsensitised Rh D negative women at any gestation. However, there is considerable lower level evidence supporting the efficacy of this practice.

Although the public health significance of antenatal Rh D isoimmunisation occurring in the absence of obvious precipitating factors is not large in terms of numbers of events, there is an effective and cost-effective strategy to avoid them. In a climate of limited supply of Rh D immunoglobulin, most events could still be avoided through the practice of routine antenatal prophylaxis of primigravidae only. While there is not scientific evidence available to support the efficacy of this practice, it would seem to be reasonable on clinical grounds, because it is in second and subsequent pregnancies that serious morbidity or mortality occur.

The 1997 Edinburgh Consensus Conference Panel noted that there is no ethical or economic justification for limiting antenatal prophylaxis to Rh D negative primigravidae and administration of Rh D immunoglobulin to all Rh D negative women antenatally as routine prophylaxis should be regarded as the ideal or 'gold standard' (Robson et al 1998).

However, this 'gold standard' cannot be achieved at this time as Rh D immunoglobulin is not available in sufficient quantities to meet the demand generated by

antenatal prophylaxis, universal or otherwise. The results of the cost-effectiveness study indicate that postpartum administration should have first call on the available supplies of Rh D immunoglobulin. Administration to women with potentially sensitising antenatal events ranks second on economic grounds, followed by routine antenatal prophylaxis to primigravidae only.

This recommendation should be reviewed on a regular basis and amended according to the availability of supplies of Rh D immunoglobulin existing at the time. It is noted that the supply of Rh D immunoglobulin may increase in the future, as a result of the manufacture of a 50 µg vial and an increase in donors (following resolution of indemnity issues relating to immunisation of donors without preformed anti-D antibodies). With that in mind, the Working Party reaffirms the previous recommendations of the NHMRC on monitoring of effects of guidelines on practice and use of Rh D immunoglobulin (in the *Guidelines for the use of Rh D Immunoglobulin in Obstetrics*, NHMRC 1996). The body designated for such monitoring should be empowered to amend recommendations on antenatal prophylaxis and submit such recommendations directly to the NHMRC.

CHAPTER 6

STRATEGIES TO MAINTAIN AND INCREASE ANTI-D SUPPLIES

Given that the evidence from the scientific literature and cost-effectiveness analysis supports the increased use of anti-D to prevent Rh D isoimmunisation, the Working Party considers it vital that there is rapid development and implementation of short and long-term strategies to promote the most efficient use of existing supply and identify a sustainable method of increasing supply to meet demand. An important part of this will be evaluation of the effectiveness of these guidelines and their impact on clinical care, as well as monitoring current and future use of anti-D. An evaluation and monitoring strategy, to be further developed during implementation of these guidelines, is outlined at Appendix 4.

As part of the review described in Chapter 3, the scientific literature was examined for evidence relating to a number of areas in which changes in practice could result in more efficient use of anti-D, and to some issues which must be resolved before an increased supply of anti-D can be secured.

6.1 Promoting efficient use of anti-D

The main strategies which could be implemented to improve the efficiency of anti-D use include:

- use of a mini-dose of anti-D for first trimester indications;
- increased and accurate use of tests to assess FMH; and
- increased compliance with guidelines on anti-D use.

Use of 50 µg mini-dose

There is a paucity of evidence relating to the use of a 50 µg dose for potentially sensitising events in the first trimester. The available evidence (level II, III-3) supports the use of a 50 µg dose of anti-D for surgically induced abortion in the first trimester to prevent immunisation in most cases.

The introduction of a mini-dose anti-D (50 µg or 250 IU) for use in first trimester terminations and other indications would significantly reduce the amount of anti-D required for these purposes. If such a mini-dose was used instead of the standard dose for all first trimester indications, the 12.6×10^6 IU currently used could be reduced to approximately 5×10^6 IU, amounting to a saving of about 7×10^6 IU per annum.

CSL has lodged an application for registration of the lower dose with the Therapeutic Goods Administration. However, a decision to register a 50 µg vial has been deferred temporarily because of a concern that the product lacks a specific viral inactivation step. This is being addressed by CSL and should be resolved within the next 9 to 12 months.

Once approval is given, there are a number of steps to be taken before stocks can be available for use:

- the manufacturer will have to modify production systems to accommodate two separate vials;
- the package insert will have to be rewritten to describe both the new dosages and presentation as well as the new guidelines formulated; and
- adequate information will have to be given to users on the choice of dose.

Findings — use of 50 µg mini-dose

- ***The introduction of a mini dose for potentially sensitising events during the first trimester would significantly reduce the amount of anti-D required for these purposes.***

Testing to establish need for anti-D

Methods used to detect passive or immune anti-D antibodies in maternal serum include the indirect Coombs' test, LISS (low-ionic strength additive solution), LISS addition and gel technologies. In Coomb's testing, Coombs' reagent (antiglobulin) is added to detect incomplete (non-agglutinating) antibodies coating erythrocytes. It can be done by the traditional method in a test tube as described by Coombs, using a saline, albumin, papain (enzyme) or PEG (polyethylene glycol; macromolecule) addition. The direct method of Coombs' testing is used on fetal cord blood to identify bound anti-D antibodies on red cells. A positive result is not always caused by anti-D antibodies but indicates further testing is required.

There is limited high level evidence reporting the accuracy and sensitivity of antibody detection in Rh D negative women. It has been suggested that Coombs' testing for antibodies in maternal sera is a sensitive and accurate test (Pinkerton et al 1984). The evidence on whether albumin/papain or PEG is the best addition to improve the sensitivity of the test is inconclusive.

A test currently being investigated involves determining the Rh D status of the fetus by testing the fetal DNA that circulates freely in the maternal circulation (Lo et al 1998).

Testing to assess fetomaternal haemorrhage

Tests for FMH can be qualitative, detecting fetal cells present in maternal circulation, or quantitative, measuring the volume of fetal cells present. Types of quantitative tests are Kleihauer-Betke, flow cytometry and the enzyme-linked antiglobulin test (ELAT). The main types of qualitative tests are the agglutination group, such as micro Du, PEG Du and rosette.

Types of tests

Kleihauer-Betke

The Kleihauer-Betke test is also known as the acid elution test and will be referred to here as the Kleihauer test. The test uses an acid elution method, which elutes the adult haemoglobin and leaves the stained fetal red cells visible in a field of ghost adult cells. A formula is then used to quantify by extrapolation the volume of FMH.

The Kleihauer test gives quantitative results, requiring the technician to count the number of cells per field and express this as a ratio per number of adult cells. Thus a positive test will result in a measure of the number of fetal haemoglobin cells in maternal circulation. In Australia, where the routine standard dose of anti-D is 125 µg, a FMH greater than 6 ml packed cells or 12 ml whole blood requires further anti-D to be administered. The Kleihauer is sensitive to bleeds between 0.01 and 0.06 per cent or 0.2 ml and 1 ml (Bayliss et al 1991; Lloyd-Evans et al 1996).

Kleihauer's method of 1957 is open to interpretation by the technician performing the test. Here inter-rater and intra-rater reliability become issues of concern as every step of the preparation and procedure that requires intervention introduces the possibility of inaccuracy. The reagents can be produced in a laboratory or commercial kits such as the Fetaldex can be used. The experience of the technician performing the test plays a major role in the success of the test.

Flow cytometry

Flow cytometry or fluorescent activated cell sorting is a method of quantifying FMH. Flow cytometry makes quantitative estimates of fetal D positive cells in negative maternal blood samples, using a fluorescent activated cell sorter. Flow cytometry is relatively new technology for quantifying FMH and is sensitive to 0.1 per cent or 1.8 ml fetal maternal haemorrhage (Johnson et al 1995). Flow cytometry has been used in Australia since 1993 (Nelson et al 1994). Commercial kits for the quantification of FMH are now available. In addition, methods to assess FMH by detection of HbF (fetal haemoglobin) are also being adopted.

Enzyme linked antiglobulin test

Enzyme linked antiglobulin test, referred to as ELAT, is a quantitative test for FMH. ELAT has been reported on for the last two decades.

Anti-immunoglobulin G antibody, conjugated with the enzyme alkaline phosphatase, is added to maternal blood samples previously incubated with anti-D antibodies. Phosphate is added to stain the sample to a yellow pigment and it is read in a spectrometer. The blood sample is then compared with a standard curve of Rh D positive blood cells (Ness et al 1987).

Rosette test

The rosette technique is a variation on the mixed antiglobulin reaction, first identified by Jones and Silver in 1958, to detect small numbers of foreign cells (Mollison et al 1979). Modified anti-D is added to a maternal blood sample and incubated, then washed, and detector cells are added which agglutinate in the form of rosettes around D-positive fetal cells (Mollison et al 1979). The presence of these rosettes indicates a positive result and the presence of fetal cells in the sample. A quantitative test is then required to assess the volume of fetal cells present. Commercial kits are available. The cost of the test is comparable to other qualitative tests for FMH examined in this report.

Discussion

Accurately assessing the size of FMH is thought to be crucial to administering the correct dose of anti-D, and thus avoiding either overuse or underuse of anti-D. There is variation in the use of testing within Australia.

Testing Rh D negative women for anti-D antibodies is also important, to determine whether sensitisation has occurred and prevent administration of anti-D when it is not indicated.

A correlation exists between the type of test used and the quantity of anti-D administered (Sebring & Polesky 1979). Kleihauer, particularly the Fetaldex kit, and free circulating anti-D tests correlate with the greatest use of anti-D. Health care agencies testing for FMH have a 3 to 15 times greater usage of anti-D than statistics of FMH and immunisation suggest is required (Sebring & Polesky 1979).

There is no level I evidence available comparing the accuracy of tests for FMH.

The Kleihauer test is easily available but methods have been found to vary greatly between laboratories (Johnson et al 1995). A 30 per cent false positive rate and overestimation of quantity of haemorrhage in 88 per cent of cases has also been reported (Johnson et al 1995). Poor Kleihauer test preparation, presence of HbF, and a Rh D negative fetus were all cases where the Kleihauer returned false positive results.

The lower level evidence shows a low level of reproducibility of Kleihauer results between laboratories and high levels of false positive results. This error leads to unnecessary anti-D administration. Kleihauer tests are reliant on reproducibility of pH, temperature, time and interpretation of results, making technique crucial. Unpublished evidence from the Royal College of Pathologists of Australasia found variable results from one control sample sent out to laboratories Australia wide. To attain an adequate level of precision from the Kleihauer test, a national quality assurance scheme is needed.

The most accurate quantitative test appears to be flow cytometry. In Australia, there are flow cytometers in most major centres. Due to the cost of equipment and experience of scientists required to use this equipment, rural areas do not have access to this technology at present. In some major centres, flow cytometers are used only on weekdays, risking samples from Friday afternoon missing the 72 hour efficacy period for administration of anti-D (personal communication 1997 Dr John Rowell, Director Haematology, Royal Brisbane Hospital).

Level II evidence indicates that the rosette test is the most accurate qualitative test for FMH although it is not a straightforward procedure to perform (personal communication, Laboratory staff, ASBT Scientific Subcommittee). If the standard dose of anti-D is 125 µg, which protects against a 12 ml transfusion of whole blood (6 ml packed red cells), then approximately 2–4 per cent of Rh D negative women will have a positive rosette test (Sebring & Polesky 1982). Some authors believe qualitative testing for FMH is redundant because further testing must be done to quantify the extent of the haemorrhage. Expert opinion is not congruent with the evidence from the literature about the accuracy and ease of rosette testing and for this reason this test is rarely used in Australia (personal communication 1997, Arthur Joyce, Chief scientist, Blood Bank, Mater Public Hospital).

The agglutination tests other than rosette resulted in a variable rate of false positive results from 4 per cent to 35 per cent. The PEG and micro Du are too inaccurate to test for FMH and their use in Australia is virtually obsolete. ELAT, although found to be sensitive to haemorrhages of 2–3 ml, utilises a large quantity of blood and appears to be too time consuming to be of efficient use when rosette is so accurate and around the same cost.

Findings and recommendations — tests to determine fetomaternal haemorrhage

- *Kleihauer testing is easily available but may ultimately be phased out as flow cytometry becomes more widely available.*
- *Until flow cytometry becomes more available, rigorous protocols defining the Kleihauer method, education of scientists and quality assurance need to be put in place to ensure the accuracy and reproducibility of this test.*
- *Flow cytometry is the most accurate quantitative test for FMH. It needs to be made readily available to all regions of Australia, either by providing the equipment and expertise country wide, or by developing a testing centre in each region where samples can be sent and results returned on a daily basis.*
- *Rosette testing is an acceptable screening method to test for FMH. However, any positive results need to be followed by further testing to quantify the fetomaternal haemorrhage.*

Compliance

When anti-D was first released for clinical use, it was assumed that it would eradicate the risk of immunisation completely within a short period of time. Thirty years later, there is still a 0.5–2 per cent incidence of immunisation in Rh D negative women. In the practice setting reasons for failure to administer anti-D when indicated include:

- inadequate education of health professionals;
- lack of guidelines relating to administration;
- incorrect interpretation of test results; and
- lack of clear information for women, enabling informed consent to treatment.

Education of both health professionals and Rh D negative women about anti-D and its appropriate applications is vital.

Discussion

There is no level I or II evidence documenting compliance failures. The evidence available in this area is inconclusive. From a review of the lower level evidence, it appears that failures result from many sources.

Human error has been reported as the cause in 25–75 per cent of sensitised women (US Preventive Task Force 1996; Clarke & Whitfield 1979; Tovey 1986). Incidences cited include failure to administer anti-D to 30 per cent of women identified as requiring it (Tabor et al 1982), misinterpretation of positive Kleihauer results and consequent withholding of anti-D (Howard et al 1997), and confusion in five cases where passive anti-D was present (Howard et al 1997). Human error in antenatal administration was identified as the largest area of omission of administration (Howard et al 1997).

The incidence of these types of failures highlights the need for education programs, guidelines for use and quality assurance for all relevant treatment units.

It has been reported that vials of anti-D can lose an average 10.6 per cent concentration per year (Hughes-Jones et al 1978). Therefore, supplies to areas with low usage are at risk of not being as effective as they should be (Vos et al 1973; Gunson et al 1980).

Findings and recommendations — compliance

- *The most vital implication for improved compliance in administration of anti-D is the distribution of standard guidelines, supported by adequate supply of anti-D. These guidelines should be reinforced by thorough education in all areas where anti-D is used and a quality assurance program for maintenance of the guidelines. Such guidelines should address:*
 - *standardised administration of anti-D antenatally;*
 - *education for health professionals in all areas where women at risk may present ie accident and emergency and general practice settings;*
 - *a register of anti-D use and database of information relating to recipients;*
 - *provision of information for women to make informed choices about the risks and benefits of anti-D and enable them to be involved in their Rh D immunisation prevention program; and*
 - *increasing awareness in pathology departments of the shelf life of anti-D and utilisation of the product before it loses potency.*

6.2 Securing future supply of anti-D

While the strategies discussed in Section 6.1 will increase the efficiency of anti-D use in Australia, none will result in self-sufficiency in anti-D supply. Therefore, other strategies are required to increase production of anti-D in a practical, sustainable and ethical way to achieve self-sufficiency.

Increasing recruitment of new donors

For as long as blood plasma remains the sole source of anti-D, the only way to secure future supply will be to expand the collection of anti-D from human donors, by increasing the overall number of donors and by increasing the anti-D level of existing donors through boosting. This has a number of ethical implications, for both donors and recipients, especially given increased public concern in recent years about the risk of disease transmission.

The major issues to be considered are:

- the ethical issues involved in the recruitment of volunteers to the Rh Project;
- safety;
- consent of volunteers; and
- the legal implications of recruitment.

Ethical issues

Measures to increase supply of anti-D to cover both prophylaxis and treatment have highlighted the ethical implications of recruiting and deliberately immunising donors. There is very little in the literature relating to the ethics of boosting and administration. The risk of viral transmission, immunisation to other antigens and the adverse effects of pregnancy in boosted donors are issues identified in the literature.

The issue of risk and the general ethical issue of consent were considered by the Working Party to ensure that recruitment and boosting through the Rh Project operates on a sound ethical and legal basis.

Safety — existing measures to prevent viral transmission

While every effort is made to ensure that the blood used to boost the Rh Project is safe and free from human pathogens, it is possible that an infectious agent could be present for which there is no test available at present, or for which the tests are insufficiently sensitive.

There are also rare but recognised complications associated with deliberate immunisation. Antibodies to platelet and to leucocyte antigens could be produced by the boosting and could make therapeutic transfusions or transplantation if ever needed more dangerous for these people.

In Australia, there has been no case of reported viral transmission from the administration of intramuscular immunoglobulin including Rh D immunoglobulin. In addition, no Rh Project donor has become infected as a result of boosting with red cells from other donors. Unfortunately, this is not the situation worldwide. In 1979 there was an outbreak of hepatitis in East Germany, among women who had been treated with contaminated immunoglobulin. An investigation revealed that two plasma donors developed acute hepatitis after receiving a boost of red cells from a cell donor who subsequently developed hepatitis C. More recently, the possibility that some of the Rh D immunoglobulin produced in Ireland was contaminated by hepatitis C virus led to the screening of 100,000 women who have received anti-D since 1970. This occurred before the introduction of routine hepatitis C screening of volunteer donors.

In Australia, every precaution is taken to safeguard Rh Project donors from any viral transmission. These comprehensive precautions apply to both the boosting of donors and the collection of plasma, to prevent the inadvertent infection of donors and the contamination of the anti-D pools. Red cell donors as well as Rh Project donors are tested on every donation for hepatitis B, hepatitis C, HIV1, HTLV1 and HIV2. As soon as these tests became available, all existing donors were tested and found to be negative.

The process of consent

The donors allow themselves to be boosted for the altruistic purpose of increasing the supply of anti-D. The fact that their participation is voluntary does not lessen the need to ensure they are fully informed before they are immunised. Although the complications associated with immunisation are rare, rigorous safety standards must be maintained not only for the protection of donors but for the eventual recipients of the anti-D serum.

The NHMRC, in its *Statement on Human Experimentation and Supplementary Notes* (NHMRC 1992), has established a nationally recognised set of guidelines for the orderly and ethical conduct of research and innovative practice in Australia. These guidelines also deal with the role and functioning of institutional ethics committees (IECs). These committees are set up within institutions conducting research on humans to prevent approval or commencement of any project that fails to meet the required ethical standards in the guidelines. In essence, these guidelines are directed to protect the rights of research subjects and to ensure that their interests take precedence over the expected benefits to human knowledge. IECs in this country report annually to the Australian Health Ethics Committee (AHEC of the NHMRC).

The donor is entitled, both ethically and legally, to the fullest possible disclosure of material information including the purpose, methods, demands, known or potential risks, estimated degree of unknown risk, inconveniences, discomforts and compensation of the proposed boosting procedure.

An institution or individual involved in boosting must review procedures for providing information to ensure that potential donors are given all necessary information and, in addition, can be seen to genuinely give their voluntary consent to the procedure.

Emphasis should not be on the consent form alone, but on the process by and the circumstances under which consent is obtained. After receiving all necessary information, potential subjects are entitled to decide whether they wish to participate. For the subject to give a valid, informed and voluntary consent, it is essential that the information is given in a comprehensible form, and that there is an absence of any form of coercion during the process. There should be sufficient time allowed for the subject to consider participation, and there should be an opportunity to obtain further independent advice or counselling in relation to involvement.

Legal implications of recruitment

Failure to disclose risk as part of the consent process can have significant legal as well as ethical implications. It is a principal function of an IEC to ensure that risks associated with a project are seriously investigated and disclosed to research subjects.

In Australia, liability is recognised for doctors' failures to disclose risks in relation to proposed treatment. It is arguable that research subjects are owed an even greater duty of disclosure than ordinary medical patients. The Halushka principle, which illustrates this legal liability, is based on a Canadian case, where a research subject successfully recovered damages from doctors and the relevant institution, after being paid to participate in a trial and not being fully informed of the trial or the possible consequences.

When a procedure becomes accepted in clinical practice it is no longer governed by the NHMRC guidelines for research discussed above. In clinical practice, the legal standards for the delivery of competent medical care and the general ethical standards of care for patients apply. It is the duty of all medical practitioners involved in the administration of anti-D to exercise established standards of diligence and care to ensure the safety of their patients.

Mechanisms to increase anti-D supply

Recruiting new donors to the Rh Project

The ARCBS has already conducted an extensive recruitment campaign to attract immunised donors to the Rh Project, but this has failed to significantly increase input to CSL. A proposal to consider primary immunisation of donors has also been granted ethics approval, provided risk management issues are resolved through the Commonwealth.

Another possible source of donors is the small number of women who have unusually high levels of anti-D. These women could be identified by blood banks, hospitals or pathology laboratories and approached for recruitment to the project. A targeted and systematic approach could be coordinated by the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) in the form of a letter seeking the support of obstetricians, gynaecologists and maternal fetal medicine specialists in identifying women who could be potential donors.

Boosting donors to increase supply

The ARCBS is optimising the supply of anti-D from current donors by stimulating previously boosted donors to increase their level of anti-D. Current donations will also be optimised by encouraging donation by plasmapheresis whenever possible.

Future demand

Current constraints preclude the success of these strategies in the short term. These include the low numbers of individuals willing to be immunised or boosted and donate regularly, and the risk management (indemnity) issues mentioned above. These issues will take time to resolve. As an interim measure, the registration and importation of overseas products would allow earlier introduction of antenatal prophylaxis for Australian women. This would be justifiable on both economic and ethical grounds, until local collection and production systems are able to meet the significant increase in demand.

Findings and recommendations — increasing supply of anti-D

- *In Australia, there has been no case of reported viral transmission from the administration of intramuscular immunoglobulin including Rh D immunoglobulin. In addition, no Rh Project donor has become infected as a result of boosting with red cells from other donors.*
- *Appropriate procedures for providing information to potential donors and obtaining their voluntary consent should be in place. There should be full disclosure of information on known risks and the likely degree of unknown risks, and sufficient time allowed for potential donors to consider participation, with the opportunity to obtain further independent advice or counselling in relation to involvement.*
- *A national register should be established under the aegis of the Red Cross, to provide a database of information relating to the risks, benefits and side effects of giving Rh D positive cells or of anti-D administration in Australia. Such a register would be subject to privacy principles included in Commonwealth legislation. With this information, steps could be taken to protect donors and recipients further.*
- *Efforts to increase the number of donors recruited to the Rh Project should continue, with further exploration of alternative methods of increasing supply such as the recruitment of women with high levels of anti-D, and increased donation by plasmapheresis.*
- *As an interim measure, consideration should be given to the registration and importation of overseas Rh D immunoglobulin products, to allow the earlier introduction of antenatal prophylaxis.*

Alternative sources of anti-D

Polyclonal anti-D is the current product available for prophylactic use in Rh D negative women. One of the strategies for overcoming the problem of maintaining a sufficient polyclonal anti-D supply is the development of alternate sources of anti-D which do not rely to the same degree on the collection of human plasma.

There are two possible alternatives to plasma-derived anti-D: monoclonal anti-D or genetically engineered anti-D.

As yet, no genetically engineered anti-D has been described, with the exception of some Fab fragments produced by phage display technology which were found to have completely inadequate affinity. It is likely that there will be further developments in the genetic engineering of anti-D, but this is a long-term prospect.

The development of monoclonal anti-D is a realistic possibility. The first monoclonal anti-D was described in 1983, and since then a number of researchers have expressed interest in developing monoclonal anti-D specifically for Rh D prophylaxis. One continuing difficulty is that the mechanism of action of polyclonal anti-D remains unclear. Some authors postulate that there is a relationship between rate of clearance of red cells and ability to suppress immunisation (Thomson et al 1990).

Monoclonal anti-D is produced from single cell lines, removing the need for the large donor program currently in place. However, immunised donors are still required initially to retrieve lymphocytes for cell cloning.

Discussion

There is no level I research regarding the use of monoclonal anti-D. From the level II research, it can be seen that BRAD-3 monoclonal anti-D is the most effective at clearing positive red cells. Tovey (1992) suggests that a combination of monoclonal strings or cell lines ie BRAD-3 and BRAD-5 will produce the best product.

The most successful monoclonal anti-D cell lines result from lymphocytes retrieved from boosted donors (McCann et al 1988). Therefore, there are still ethical considerations associated with donors and monoclonal anti-D production in the initial phase of production.

The authors in this field suggest monoclonal anti-D carries a higher risk of passage of infection and anaphylaxis than polyclonal anti-D (McCann et al 1988; Fletcher & Thomson 1995). Cross reactivity of monoclonal antibodies with human

tissues is a possibility and may prove a clinical risk (Thorpe & Bailey 1993). However, this risk is considered to be small.

Findings and recommendations — monoclonal anti-D

- ***At present research results are preliminary. It is not known when monoclonal anti-D will be available in sufficient quantity to relieve the burden on supply of the current preparation. It is also not known if monoclonal preparations will be safe, effective or reliable.***
- ***Due care needs to be taken in the production of monoclonal anti-D to ensure it protects women at a similar level as the conventional product and is equally safe.***
- ***There is an urgent requirement for high quality research into the safety and effectiveness of monoclonal anti-D.***

APPENDIX 1

MEMBERSHIP AND TERMS OF REFERENCE OF THE WORKING PARTY

Members

Dr David Woodhouse (Chair)	Chair, Health Care Committee, Royal Australian and New Zealand College of Obstetricians and Gynaecologists
Dr Brenton Wylie	Director, Australian Red Cross Blood Transfusion Service NSW/ACT
Professor Donald Chalmers	Chair, Australian Health Ethics Committee
Mr John Haines	State Financing Group, Department of Health and Aged Care
Dr Peter Schiff	Medical Director, Bioplasma Division, CSL Limited
Dr Jim Butler	National Centre for Epidemiology and Population Health, ANU
Dr James King	Mater Perinatal Epidemiology Unit, Brisbane

Corresponding members

Dr Sandra Deveridge	Department of Haematology, Newcastle Mater Misericordiae Hospital
Ms Elizabeth Percival	Executive Director, Royal College of Nursing
Dr Vince Roche	Elizabeth Street, Moss Vale
Dr Amanda Thomson	Department of Haematology, Concord Repatriation Hospital
Dr John Smoleniec	Department of Obstetrics and Gynaecology, Caroline Chisholm Unit, Liverpool Hospital
Professor David Henderson-Smart	NSW Centre for Perinatal Health Services Research, Queen Elizabeth II Institute for Mothers and Infants, University of Sydney
Ms Dell Horey	Convenor, Maternity Alliance

Project support:	Ms Evelyn Tulega, Office of NHMRC (to June 1998)
	Ms Krystyna Szokalski, Office of NHMRC (from June 1998)
Literature review:	Ms Jenny Gamble and Ms Alison Craswell in collabo- ration with Dr James King and Ms Vicky Flenady, Mater Perinatal Epidemiology Unit, Brisbane
Cost-effectiveness analysis:	Dr JRG Butler and Mrs Ann L Howarth National Centre for Epidemiology & Population Health, Australian National University
Writing, editing and design:	Ampersand Editorial & Design, Canberra

Terms of reference

The terms of reference of the Working Party are structured to focus on the limited supply of anti-D immunoglobulin, assessing and monitoring future supply, and potentially increasing demand as a result of the anticipated guidelines and recommendations for best practice and are as follows:

1. Establish current availability and supply of anti-D immunoglobulin for the next two years and at five years
2. Assess the impact of the endorsed NHMRC Guidelines on current and future supplies of anti-D immunoglobulin.
3. Establish current practice for the use of anti-D immunoglobulin in Australia and issue interim supplementary guidelines for a period of two years to make the most effective use of available supplies of anti-D immunoglobulin based on an economic analysis taking into account ethical, legal and medical implications.
4. Recommend effective strategies to increase and maintain domestic production of anti-D immunoglobulin to a self-sufficient level.
5. Recommend a means of monitoring current and future use of anti-D immunoglobulin.
6. Recommend a communication strategy to inform bodies affected by the current constraints on anti-D immunoglobulin usage.
7. Recommend appropriate means to evaluate the effectiveness of the supplementary guidelines and the impact on clinical care.

APPENDIX 2

THE GUIDELINE DEVELOPMENT PROCESS

Background

The document *Guidelines for the Use of Rh D Immunoglobulin (Anti-D) in Obstetrics*, prepared by a working party of the Health and Medical Services Standing Committee of the National Health Advisory Committee, was endorsed by Council at its November 1995 session and published in 1996 but was not widely distributed. Serious concerns were raised by both RACOG (now RANZCOG) and ARCBS that the widespread adoption of the endorsed guidelines would exacerbate an already worsening shortage of anti-D. It was estimated that full adoption of the NHMRC guidelines had the potential to increase demand from steady 4,000–5,000 doses per month to 8,300 doses per month. This also assumed the introduction of a mini-dose formulation (50 µg) which was recommended for use in incidences in the first trimester of pregnancy. The 50 µg mini-dose is still awaiting registration.

RACOG was of the view that although the endorsed guidelines represented the 'gold standard' for best clinical practice, they did not address the reality of the ongoing supply shortage. As it was, it was necessary to import supplies of an United States product (RhoGAM) to supplement domestic supplies of anti-D.

In January 1997, the NHMRC was asked by the then State Financing Group of the Department of Health and Family Services to review the Guidelines in the light of these concerns. It was proposed to reconvene the Working Party, which consisted of specialist pathologists and obstetricians, to review and revise the NHMRC Guidelines. The role of the reconvened Working Party was to define policy options for the optimal use of available supplies of anti-D and to develop appropriate recommendations which would be relevant and reflect best practice in a situation where there is an ongoing shortage in the supply of this product. Corresponding members were also appointed, whose expertise would provide broader advice and comments on drafts.

The terms of reference were circulated to State health departments for comment. Following comments received, revised Terms of Reference were accepted by the Working Party in March 1997 (see Appendix 1).

The key objectives of the Working Party were to undertake:

- a comprehensive cost-benefit analysis which included consideration of the ethical, legal and medical imperatives, in the light of real supply constraints;
- a comprehensive literature review;
- an investigation of ways to increase domestic production of anti-D to a point where Australia is again self-sufficient;

-
- a review of current strategies to maintain this supply; and
 - a review of the effects of the recommended NHMRC guidelines on current and future supplies.

Dr Jim Butler and Mrs Ann Howarth, from the National Centre for Epidemiology and Population Health, Australian National University, were contracted in February 1997 to undertake a cost-effectiveness analysis to consider health effects of the regimen and calculate benefits of life years lost, followed by a comparison across different subgroups looking at different options. This was completed in November 1997.

A joint Royal College of Physicians of Edinburgh and Royal College of Obstetricians and Gynaecologists Consensus conference on Anti-D Prophylaxis took place in Edinburgh (United Kingdom) in April 1997. The Conference provided a valuable forum for exchanging information regarding scarcity of supply dosages and prophylaxis. Dr Schiff (a member of the Working Party) in his capacity as an employee of CSL Limited attended this conference. Dr Joanne Pink, then Assistant Director of the NSW Blood Bank, was co-opted to the Working Party to attend the Conference and both she and Dr Schiff provided reports to the Working Party upon their return.

A systematic review and critical evaluation of the scientific literature from 1970 to the present was undertaken in July 1997 by Ms Jenny Gamble and Ms Alison Craswell, in collaboration with Dr James King and Ms Vicky Flenady, of the Mater Hospital in Queensland. This was completed in September 1997. Ms Elizabeth Hall was engaged as the Technical Writer immediately following the review to prepare the draft report.

First stage consultation submissions were invited through an advertisement in the press, with a closing date of late August 1997. Twenty submissions were received, from a range of stakeholders including academics, practitioners and organisations. Each submission was considered carefully during the development of the report.

The draft report was released for second stage consultation in June 1998. Thirteen submissions were received, which were supportive of the direction of the draft report, with only minor editorial changes being suggested.

A final draft was presented to the Health Advisory Committee in early March 1999, and to NHMRC at its meeting on 22 March 1999.

APPENDIX 3

COMMUNICATION STRATEGY

The Working Party recognises the importance of the timely and accurate communication of the recommendations contained in this document, in order to maximise the appropriate use of Rh D immunoglobulin and minimise use which could adversely affect continuation of adequate supplies.

A summary document which gives the background to the issue and the rationale for the guideline recommendations has also been published.

As stated throughout this report, the recommendations within apply only until supplies of Rh D immunoglobulin increase. The situation will require careful and regular review and, very importantly, effective communication of review findings and any subsequent change in recommendations.

This can be achieved through specialist colleges, position papers published in medical journals, updating the summary document and recommendations on the Internet, and general media releases.

In the meantime, the Working Party endorses the communication strategy developed for the *Guidelines for the use of Rh D Immunoglobulin (Anti-D) in obstetrics* (NHMRC 1996), as follows.

A detailed multi-level communication strategy is required to ensure effective clinical care at all levels. This strategy should be targeted at general practitioners, specialist obstetricians, midwives, termination clinics, obstetric units and consumers. Four levels of communication are required for the strategy. These are:

1. detailed discussion and guidelines suitable for publication as an editorial in the *Medical Journal of Australia* and/or other medical publications;
2. media releases aimed at health care professionals;
3. information for non-medical consumers; and
4. media release for the general public.

Electronic publishing of the summary document on the Internet will augment the following dissemination of printed information to the target groups.

Target group	Means of communication	Level of communication
General practitioners	Australian Doctor	2
	Medical Observer	2
	AMA State newsletters	2
	Divisions of general practice	
	- associated rural divisions	2
	- associated urban divisions	2
	Shared care doctors via area health services	1,2
	Rural Doctors Association Australia via State newsletters	2
	Diplomates newsletter via RANZCOG	1,2
	Medical Journal of Australia	1
	Australian Family Physician via RACGP	1
Specialist obstetricians	RANZCOG	1,3
Midwives	ACMI	1,2
	State nurses associations	1,2
Termination clinics	Family Planning Association	1,2,3
	Abortion Providers Federation of Australia	1,2,3
Obstetric Units	Public and Private via State Health Departments	1,2,3
	Consumers	Maternity Alliance
Consumers	Consumers' Health Forum	1,2,3
	General media distribution (print and electronic)	4
	Blood transfusion services	Australian Red Cross Blood Service
Australasian Society of Blood Transfusion		1,2,3
Pathologists	Royal College of Pathologists of Australasia	1,2,3
Scientists	Australian Institute of Medical Scientists	1,2,3
State/Territory Health Authorities		1,2,3

The Working Party recognises that difficulties may exist in communication of these changes to Indigenous and ethnic groups and organisations involved in the obstetric care of these groups. The Working Party recommends that these areas be specifically looked at in the development of the final communication strategy.

APPENDIX 4

EVALUATION AND MONITORING STRATEGY

The Working Party endorses the evaluation and monitoring strategy published in the previous guidelines.

That is, the establishment of a system that has the ability to:

- produce interpretable and useable data on ongoing usage;
- detect changes in usage profiles;
- identify potential problem areas in a timely fashion;
- institute procedures to ensure the reporting of any new cases of Rh D immunisation that arise; and
- predict future requirements for anti-D by monitoring trends in use and supply.

It is recommended that monitoring of the use of Rh D immunoglobulin be conducted on the basis of regular surveys and that the methodology be reviewed at regular intervals in view of the rapidly changing nature of information and communication technology.

APPENDIX 5

LITERATURE REVIEW — SEARCH STRATEGY AND TABLES OF RESULTS

Search strategy

All material from 1970 onwards in relation to the prophylactic use of anti-D was sought. Computer systems were accessed which enable several CD ROM databases to be searched simultaneously.

An initial search was conducted using key words and phrases within the following topics. Further key words were added after revision throughout the searching process.

- Maternal issues
- Neonatal
- Testing/screening
- Administration regime
- Economics and anti-D administration/ prophylaxis/ HDN
- Supply of anti-D.

Search method

CD ROM data bases

The following databases were searched back to 1970 using the same key words and phrases.

- Cochrane
- Medline
- Cinahl
- Healthrom
- (Socfile)

Consultation with experts in the field

- Arthur Joyce, Chief Scientist Blood Bank Dept MPH
- Dr John Rowell, Director of Haematology, Chairman RCPA
- Transfusion Serology QAP
- Dr Robyn Rodwell, Chief Scientist MPH
- Dr Amanda Thomson, Australasian Society of Blood Transfusion Scientific Subcommittee
- Tania Bold, Queensland Red Cross
- Dr Peter Schiff, CSL

Unpublished data sources

There were discussions with some authors of existing literature about:

- any additional data;
- research currently being conducted;
- referrals to other researchers with unpublished data; and
- any other data sources.

Internet search

The initial search was done using Hot Bot/Alta Vista search engines. This was followed by an investigation of page links. Lastly, all listed search engines were reviewed as a group.

Revised search

After a teleconference on 17 July 1997, a decision was made to search back to 1966. Some even earlier literature has also been accessed. All retrieved articles were reference checked to find other relevant articles of interest and to assess the quality of the search performed.

A MESH search was also done using MESH terms with the Medline database. Retrieved references were cross-referenced with those already retrieved.

Analysis of evidence

Acceptance or rejection of articles was determined by the review team according to relevance and quality of evidence. All material relevant to the topics was reviewed and only repetitive level IV evidence consisting of descriptive studies or expert opinion excluded. The abstracts of foreign language references were reviewed and the full article sought where necessary and retrieved if available.

The literature was assessed for methodological quality and awarded a Quality of Evidence Rating as recommended by NHMRC (1995) (see page 9).

Tables of results

Findings on postpartum anti-D administration

These can be found in the Cochrane Collaboration Review of postpartum anti-D administration by Crowther and Middleton.

Findings on the use of anti-D prophylaxis following abortion, ectopic pregnancy, chorionic villus sampling and amniocentesis

Abortion	Level of evidence	References
Includes women up to 20 weeks gestation. Incidence of FMH in the control (women without a history of bleeding) and experimental group (with threatened abortions) was not statistically different as measured by Kleihauer.	II	Kuller et al 1994
50 µg dose of anti-D was effective in preventing immunisation six months following induced abortion.	II	Stewart, Burnhill & Bozorgi 1978
Showed 50 µg was as effective as 300 µg following first trimester abortion in preventing Rh D antibodies at 6 months post abortion. Rationale based on a total fetal circulation at 12 weeks gestation of 4.2 ml.	II	Keith & Borzorgi 1977
The formula of 20 µg of anti-D to protect against 1 ml of fetal RBCs was used to determine correct dose of anti-D for excessively large FMH. Microhaemorrhages cannot be quantitated with precision therefore it is not intended for this ratio to be used to reduce the dose of anti-D.	II	Pollack et al 1971
Alpha feto protein (AFP) to investigate the occurrence of FMH in women undergoing medical abortion. AFP rises in women having gemprost or mifepristone significantly more than in controls. (Study can't comment on FMH because there is no data to say that AFP is linked to FMH at this stage of pregnancy.) Medical abortion under 12 weeks gestation.	III-1	Thong, Norman & Baird 1993
Confirms the risk of immunisation following early and late spontaneous and induced abortion. Reduced the rate of immunisation from 4.1% to 0. anti-D dose of 200 µg Followed up for 6 months.	III-1	Goldman & Eckerling 1972

Abortion	Level of evidence	References
<p>Showed an increase in fetal haemoglobin in maternal circulation following induced abortion.</p>	III-1	Gellen et al 1965
<p>Determines the incidence of post abortion immunisation averages 3-4%. The risk of immunisation increases with gestational age -virtually negligible at one month, 2% at 2 months and approx 9% at 3 months. Rh D negative women followed up to subsequent pregnancy. Recommends anti-D be administered post abortion and ectopic.</p>	III-2	Freda et al 1970
<p>Of thirty six patients undergoing spontaneous abortion, thirteen had fetal erythrocytes in their circulation compared with only two in the control group. D&C for incomplete abortion increased the volume and number of transplacental haemorrhages. Anti-D should be given following abortion.</p>	III-2	Litwak, Taswell & Banner 1969
<p>Authors postulate that 2 of 7 women who were not given anti-D with first trimester threatened miscarriage became immunised.</p>	III-3	Portmann et al 1997
<p>Half life of anti-D 24 days for non-pregnant women and 21 days for pregnant women.</p>	III-3	Eklund et al 1982
<p>A dose of 50 µg anti-D was administered following induced abortion up to 12 weeks. FMH was detected in 12% of women. After 6 months 82% of women were followed up - none were immunised - no controls.</p>	III-3	Gjode et al 1982
<p>Between 1.81% and 2.64% of women were immunised following induced abortion depending on serological test used. Papain vs. antiglobulin test (Coombs'). Follow up to second pregnancy.</p>	III-3	Simonovits, Timor & Bajtai 1980
<p>40% of the 35 sensitised women in the Leeds region from 1977-78 seemed to have become sensitised following abortion where no anti-D was administered.</p>	III-3	Tovey 1979

Abortion (cont)	Level of evidence	References
Confirms risk of post-abortion sensitisation and recommends a lower dose of anti-D following abortion. A dose of 73µg and 155µg of anti-D were compared with the standard USA dose of 300 µg. No sensitisations in any of the three groups. Women were followed up for 6 months.	III-3	Hensleigh et al 1977
Recommends 50µg anti-D following induced abortion under 12 weeks gestation. Reduced incidence of immunisation from approximately 3-4% to 0.25%. Used data from other studies on the rate of immunisation following abortion. No controls. Followed up for 6 months.	III-3	Simonovits 1974
Spontaneous abortion with operative procedure Equivocal about the use of anti-D following spontaneous abortion followed by curettage.	III-3	Queenan et al 1971
7.2% of patients undergoing suction curettage and 20.2% of patients undergoing intraovular saline injection had a FMH. The frequency of FMH rose with increasing gestation. Combined with other studies gives an incidence of 5.5% of women who become immunised post abortion.	III-3	Queenan et al 1971

Abortion (cont)	Level of evidence	References
<p>No difference reported in the incidence or quantity of TPH following induced abortion versus spontaneous abortion with curettage in women with no evidence of TPH prior to operation. 11.6 % of women with spontaneous or induced abortion had evidence of TPH prior to operation. A preoperative TPH of more than 0.1 ml occurred in over 9% of women admitted with spontaneous abortion. Kleihauer used in this study.</p> <p>In 14 (2.9%) cases out of 473 the TPH was estimated to be 0.1 ml.</p> <p>No evidence that the length of gestation, maternal age, parity or the method of termination significantly affected the incidence of TPH.</p> <p>Blood taken after evacuation of the uterus and again 6–48 hours after operation prior to discharge. The later test uncovered 21 cases of TPH that would have been missed by the test following evacuation of the uterus alone.</p>	III-3	Murray, Barron & McNay 1970
<p>Spontaneous and induced abortion</p> <p>The incidence of TPH for spontaneous abortion (K=>15 weeks) was around 6% but no significant haemorrhage was noted (over 5 cells per 100 low power fields). It is therefore calculated that the TPH in these cases did not exceed 0.02 ml of blood which is well below the minimal potential immunising dose suggested by Mollison (1968) (Mollison regarded 0.25 ml of mature fetal blood as the minimal potential immunising dose. 25% of women experiencing termination had evidence of TPH. Potentially immunising haemorrhages in the order of 0.25 ml of fetal blood were noted in 3% of cases.</p>		

Abortion (cont)	Level of evidence	References
4% of women experiencing induced abortion had TPH of 0.1 ml or more and in half of these the amount was 0.25 ml or more. 47 women who had spontaneous abortions (probably some of these were illegal abortions) 13% of these had evidence of TPH but none had a TPH of more than 0.1 ml. 1 out of 8 Rh D negative primigravidae became immunised. 2 out of 22 Rh D negative multigravidae became immunised even though there was no evidence of TPH after the abortion by Kleihauer.	III-3	Jorgensen 1969
There was no significant increase in FMH was found between patients having either an incomplete or threatened abortion. There was a statistically significant increase in fetal cells in the maternal circulation after curettage. Suggests Rh D negative women should be administered anti-D following curettage associated with abortion. Cites Zipursky - the dose of fetal blood required to induce a primary immunisation response is 1.3 ml.	III-3	Katz 1969
Recommends giving anti-D following induced abortion at 12 weeks or more gestation. Kleihauer technique was used to estimate TPH. 4 different abortion methods were included in the study. 26.4% of women undergoing induced abortion had a TPH with 6.6% having TPH of 0.25 ml or more. No major TPH (0.25 ml or more) occurred before 12 weeks gestation.	III 3	Voigt & Britt 1969
It is possible to become sensitised from spontaneous abortion or threatened abortion less than 12 weeks. An analysis of initiating circumstances of sensitisation in 458 pregnancies in Glasgow over 20 years. 3 of 458 cases of Rh D sensitisation occurred secondary to bleeding before 12 weeks gestation.	IV	Whitfield 1997

Abortion (cont)	Level of evidence	References
The standard Australian dose of 625 IU (125 µg) protects against immunisation of up to 6 ml of fetal red cells or approximately 12 ml of whole blood. The approximate total fetoplacental circulating volume at 12 weeks gestation is 3 ml - therefore the standard dose of anti-D is enough to destroy the entire circulating fetoplacental blood volume until around 14 weeks. Recommends lower dose anti-D without Kleihauer testing - 30 µg for all situations of possible FMH up to 12 weeks gestation. Second trimester 30 µg plus Kleihauer testing.	IV	de Crespigny & Davison 1995
Critical of the logistic possibility of new Department of Health guidelines recommending anti-D for threatened abortion under 12 weeks gestation.	IV	Everett 1991
Critical of the Department of Health guidelines recommending anti-D for spontaneous or threatened abortion.	IV	Everett 1990
Recommended anti-D be given for all therapeutic abortions; spontaneous abortions if there is surgical intervention; spontaneous abortion after 12-13 weeks gestation; and threatened abortion after 12-13 weeks.	IV	Tovey 1990
Recommends dose before 20 weeks gestation - 50 µg (250 IU). Dose after 20 weeks 100 µg (500 IU)	IV	Tovey 1990
Critical of the lack of evidence for anti-D for spontaneous abortion managed at home and threatened abortion.	IV	Everett 1988
Concerned over failure to administer anti-D to women following complete abortion in women under 10 weeks gestation.	IV	Contreras, de Silva & Hewitt 1986
Umbilical cord blood typing is possible in about 30% of cases at 14 weeks gestation and in 75% of cases by 16 weeks making it possible to determine which Rh D negative women have Rh D positive fetuses and therefore require anti-D.	IV	Munsick 1986

Abortion (cont)	Level of evidence	References
Quoted experimental data by Zipursky 1965—able to immunise Rh D positive volunteers with repeated injections of 0.1 ml of fetal Rh D positive blood.	IV	Woodrow & Donohue 1968
There is one case study report of Rh D antigen present on the fetal red blood cells as early as day 38 of gestation.	IV	Bergstrom et al 1967
Ectopic pregnancy		
A case report. A woman with an ectopic pregnancy at 5 weeks - Kleihauer estimated 1 ml of fetal red blood cells in maternal circulation—laparoscopy plus 300µg anti-D. Uneventful recovery.	IV	Krause & Goh 1996
Significant amount of fetal erythrocytes were found in maternal blood in 24% of women following ruptured ectopic pregnancy. Recommends anti-D following this event. Case study reports of immunisation following ruptured ectopic pregnancy	IV	Katz & Marcus 1972
Chorionic villus sampling		
A significant increase in AFP levels suggests FMH.	III-3	Brambati et al 1986
Accurate Rh D phenotyping may be done on red blood cells obtained from chorionic villi weighing 2–8 mg. CVS as early as 9-11 weeks gestation enables Rh D phenotyping.	IV	Kickler et al 1992

Amniocentesis	Level of evidence	References
No reported cases of sensitisation in 944 Rh D negative women receiving 100 μg anti-D following amniocentesis. Follow-up only 28 and 32 weeks of current pregnancy. Compared with control data from the literature.	III-3	Brandenburg et al 1989
Visualised intra-amniotic bleeding showed no correlation to FMH as assessed primarily by AFP but also by Kleihauer. No correlation was found between placental location and FMH.	III-3	Lenke et al 1985
5 out of 361 women became immunised between amniocentesis and 6 months postpartum which the authors argue is no higher than the spontaneous immunisation rate in pregnancy. Do not recommend anti-D at genetic amniocentesis.	III-3	Tabor, Jerne & Bock 1986
0.3% incidence of sensitisation following amniocentesis in women who received anti-D after the procedure.	III-3	Tabsh, Lebherz & Crandall 1983
2.1% of 615 Rh D negative women sensitised subsequent to amniocentesis. Experience of practitioner and concurrent ultrasound may reduce the incidence of sensitisation.	III-3	Golbus et al 1982
5.4% of 78 Rh D negative women undergoing amniocentesis became sensitised during the pregnancy in which the amniocentesis was performed. Recommended 150 μg of anti-D be administered.	III-3	Hill, Platt & Kellog 1980
Advocated anti-D administration following amniocentesis even though the incidence of FMH was only slightly increased in volume and frequency from pre-amniocentesis estimation of FMH.	III-3	Goldstein & Pezzlo 1978
Recommends anti-D following amniocentesis. Placental localisation reduces the incidence of obtaining a bloody sample. The half life of Rh D immune globulin is 25-27 days which is significantly reduced by the 'Suck' phenomenon of a Rh D positive fetus. Doesn't mention the dose of anti-D administered - presumably 300 μg .	III-3	Henry, Wexler & Robinson 1976

Findings on the use of anti-D prophylaxis following external cephalic version

ECV	Level of evidence	References
No statistical difference in the rate of immunisation between women who experienced attempted ECV and those who didn't. Small sample. Only 13 were followed up in a subsequent pregnancy—all negative antibodies.	III-1	Murray, Dewhurst & Archer 1974
The incidence of FMH over 4 ml was 1.8% in 167 patients after ECV. Recommends anti-D administration to Rh D negative patients and FMH assessment to detect the 2% of women not adequately covered by the routine dose of 100 µg.	III-3	Lau, Stock & Rogers 1995
FMH of 0.1 to 1.5 ml were detected in 28% of women undergoing attempted ECV. Recommends anti-D be administered routinely.	III-3	Gjode, Rasmusen & Jorgensen 1980
FMH detected in 6 out of 100 women who had attempted ECV. FMH was greater in patients with "failed" ECV. Recommends fetal cell counts and anti-D if necessary.	III-3	Marcus et al 1975

Findings on routine antenatal anti-D prophylaxis

Antenatal prophylaxis	Level of evidence	References
Reduced incidence of immunisation at 2–12 months following delivery of primiparae and primigravidae who had received 100 µg (500 IU) anti-D at 28 and 34 weeks gestation. No data were available for the risk of immunisation in a subsequent pregnancy.	II	Huchet et al 1987
No difference noted between experimental group and control group. Experimental group received 250 IU (50µg) anti-D at 28 and 34 weeks gestation. They experienced a large drop out to follow-up. Did not attempt to follow-up to a subsequent pregnancy. The expected difference between control and experimental group was not emerging and it was decided to terminate the trial.	II	Lee & Rawlinson 1995

Antenatal prophylaxis (cont)	Level of evidence	References
Reduction in immunisation during pregnancy or within 3 days of delivery from 1.8%-0.07%. The experimental group received 300 µg (1500 IU) of anti-D initially at 34 weeks but this was changed to 300 µg at 28 and 34 weeks 6 months into the study. The assumption that sensitisation occurring within 3 days of birth is equivalent to intrapregnancy sensitisation was not explained. This trial followed up on 343 women, of 1357 women who were treated antenatally in the first pregnancy, who delivered a Rh D positive baby again in a subsequent pregnancy and reported on the incidence of sensitisation without comparison to the control group.	III-1	Bowman et al 1978
Used the data from the Tovey et al (1983) trial. Reduced incidence of immunisation in women given 100 µg (500 IU) of anti-D at 28 and 34 weeks gestation. Some suggestion that the protective value persists into at least the second pregnancy. No evidence of alterations in hypertension, proteinuria in the mother. No evidence of alterations in birth weight, gestational age at delivery and perinatal death in the control versus experimental group.	III-3	Thornton et al 1989
Reduced incidence of immunisation from 1.8%- 0% (p< 0.05) in primigravidae and multigravidae who received 300 µg (1500 IU) anti-D at 28 weeks.	III-3	Trolle 1989
Reduced incidence of immunisation at 8 months from 1.6%-0.4% in 830 primigravidae and multi-gravidae who received 250 µg anti-D about 32-34 weeks of pregnancy. The Hb and bilirubin levels in the babies did not differ.	III-3	Hermann et al 1984
Reduced incidence of sensitisation and number of affected babies in women given 240-300 µg (1200 -1500 IU) of anti-D at 28 weeks gestation. There is no mention of controlling for sensitising events.	III-3	Bowman & Pollock 198

Antenatal prophylaxis (cont)	Level of evidence	References
<p>Reduction in immunisation from 0.9–0.16% in women who had received 100 µg (500 IU) at 28 weeks and 34 weeks gestation. Of the 18 women in the control group who developed antibodies during pregnancy only 2 were moderately affected and required an exchange transfusion. One of the Rh D negative women in the control group who developed antibodies during pregnancy delivered a Rh D negative infant. In the experimental group 2 women developed unexplained sensitisation, one woman had an amniocentesis and no anti-D injection until 28 weeks the other had no known sensitising event. 325 women from the experimental group were followed up in a subsequent pregnancy with a Rh D positive infant. Of these, 2 developed antibodies for the first time. Of the 582 women in the control group with a Rh D positive infant in a subsequent pregnancy antibodies were detected in 11 women who had demonstrable antibodies in the first pregnancy. Five infants were mildly affected, 2 infants were moderately affected and 1 was severely affected. In a further 11 women in whom antibodies had not developed during the first pregnancy 2 infants were Rh D negative the remaining 9 were Rh D positive and only mildly affected. Although there is discussion on the 2 women who became sensitised in the experimental group there is no discussion of possible sensitising events of women in the control group.</p>	III-3	Tovey et al 198
<p>250 µg anti-D given at 28 weeks gestation the concentration at delivery was at least 1 ng/ml. There are great individual variations in uptake and recovery rates following anti-D administration. Half life of anti-D of 24 days for non-pregnant women and 21 days for pregnant women. The lower mean value in the pregnant women reflects the well documented (no reference) transfer of 10–15% of the antibody across the placenta into the fetal circulation.</p>	III-3	Eklund et al 198

Antenatal prophylaxis (cont)	Level of evidence	References
No damage to the fetus was reported in the babies of 130 Rh D negative primigravidae and multigravidae who received 250 µg (1250 IU) at 32–34 weeks gestation.	III-3	Hermann, Kjellman & Ljunggren 1979
Reduced incidence of immunisation in primigravidae and multigravidae who received one injection of 300 µg (1500 IU) of anti-D at 28 weeks gestation. Antenatal anti-D is 88% effective in preventing Rh D immunisation during pregnancy in Rh D negative primigravidae and 75% effective in preventing Rh D immunisation in multi-gravidae untreated antenatally in previous pregnancies. No mention of controlling for sensitising events.	III-3	Bowman & Pollock 1978
No reduction in sensitisation in women given 250–300 IU (50–60 µg) of anti-D at 28 and 34 weeks gestation. Follow up in a subsequent pregnancy did not demonstrate a reduction in sensitisation. No mention of controlling for sensitising events.	III-3	Davey 1975
Demonstrated areas for improvement in the Rh D prevention program particularly in the treatment of antenatal sensitising events and postpartum. Suggested women should be more involved in their Rh D prevention program care. GPs and hospital obstetric staff should be better educated about the significance of potentially immunising events in pregnancy and incorporate the Rh D prevention program in their own audits schedules.	IV	Ghosh & Murphy 1994
Critical of routine antenatal anti-D. Concerned about the quality of the studies. Concerned about the long term effects on the fetus and about false positive antibody tests from women passively immunised confusing their treatment.	IV	Hussey 1989
Compares rate of immunisation with antenatal prophylaxis with rate of immunisation of 1.8% without antenatal anti-D.	IV	Bowman & Pollock 1987
Concerns raised about the possible risks of antenatal anti-D and the paucity of evidence supporting its use.	IV	Hensleigh 1983

Antenatal prophylaxis (cont)	Level of evidence	References
Reviewed data used in a previous study and concludes it is cost effective to administer anti-D to primigravidae.	IV	Tovey & Taverner 1981
Uses the decline in the number of Rh D immunised pregnant women and the reduction in perinatal mortality from Rh D erythroblastosis fetalis as the basis for recommending routine antenatal prophylaxis. Only mentions other contributing factors in a reduction of Rh D disease and HDN such as reduced parity.	IV	Bowman et al 1977

Findings on testing

Kleihauer	Level of evidence	References
Wide variability of test practices found between laboratories. Kleihauer tests showed a 72% rate of overestimating haemorrhages, increasing quantities of anti-D administered. 30% false positive rate using prepared samples.	II	Johnson et al 1995
Two quantitative methods of screening FMH, Kleihauer and flow cytometry were compared. Both methods were found equally accurate at measuring prepared samples. However, one technician performed the tests in one laboratory removing inter-rater error. Both techniques underestimated the number of cells in the samples over 0.6% FMH or 15 ml fetal cells. Therefore in this study, women with bleeds equal or more than 15 ml would have received less than adequate or no further anti-D.	II	Bayliss et al 1991
Kleihauer results were 50-100% greater than the true value on prepared samples of levels greater than 1%. Excess unnecessary anti-D would be administered in these cases.	III-1	Greenwalt et al 1992
The Kleihauer test when compared with a commercial kit, Fetaldex, showed results correlated at a coefficient of 0.998. The Kleihauer test requires accuracy in preparation of fixative, buffer and reagents; all are pre-prepared in the Fetaldex kit.	III-1	Virgilio & Simon 1977

Kleihauer (cont)	Level of evidence	References
A questionnaire was used to analyse methods of testing with Kleihauer in 12 hospitals and found no uniformity between technique and cell counting methods. 10 hospitals did not perform routine interpretation of result and recommend further anti-D unless specifically asked.	III-3	Duguid & Bromilow 1994
Reagents produced by lab are open to variation. May come with kit with a shelf life of only 7 days.	III-3	Dupre et al 1993:
The Fetaldex commercial kit resulted in the highest rate of false positives in this study. 86% of laboratories found fetal cells in the 100% adult cell sample. Laboratories using this kit also gave the most additional vials of anti-D.	III-3	Polesky & Sebring 1981
Questioned 1,630 of 2,332 hospitals and blood banks and found the highest volumes of anti-D administered were related to the tests used to measure FMH. The highest volumes administered correlated with use of Kleihauer and free circulating anti-D tests. Found laboratories performing routine testing had 3-15 times greater usage of anti-D than those without.	III-3	Sebring & Polesky 1979
As part of the quality assurance program for pathologists, a questionnaire and blood sample was sent out Australia wide. Unpublished findings showed large variation between results of prepared sample tested by different laboratories. There was also variation in whether tests for FMH were routinely performed or performed by request.	IV	Thomson, unpublished
Unpublished, unreferenced work found methods of performing and interpreting Kleihauer tests varied markedly between laboratories arising because there are variations in published interpretations of Kleihauer method.	IV	MacLennan & Flanagan 1994
Reviewed and reported the quality assurance of the Kleihauer test to be poor and the method had not been updated since 1978. Suggested Kleihauer is the cheapest method of quantifying FMH.	IV	Letsky & de Silva 1994

Kleihauer (cont)	Level of evidence	References
The routine use of the Kleihauer-Betke is prevented by the difficulty in preparing reagents and stabilising their pH. They acknowledge that regardless of type of test kit, observer bias is still an area of potential error.	IV	Scott & Warensky 1982
In 2 case studies of hereditary persistent fetal haemoglobin, Kleihauer failed to determine fetal cells, measuring fetal haemoglobin, which is found in 1-2% of normal adults.	IV	Fadel & Krauss 1986
Report of a case where the fetal cells failed to stain using the Kleihauer test until after they had been rinsed in saline. The cell membrane could not be permeated in this case.	IV	Stockley et al 1986
Kleihauer failed to detect fetal cells in a blood stained sample.	IV	Ahmed & Brown 1986
Flow cytometry		
Tested flow cytometry and Kleihauer on a range of prepared samples from 0.2-7 ml and found flow cytometry more accurate than Kleihauer when testing FMH between 1-7 ml. Found Kleihauer more accurate on 3 test samples less than 1 ml.	II	Lloyd-Evans et al 1996
Flow cytometry is sensitive to 0.1% or 1.8 ml FMH. As mentioned earlier, the decreased quantity of FMH determined by flow cytometry compared to Kleihauer results, leads to a decreased use of anti-D with equal effectiveness.	II	Johnson et al 1995
Flow cytometry is effective in analysing large numbers of cells with accurate and reproducible results.	II	Bayliss et al 1991
Found flow cytometry when compared to Du testing, rosette testing and Kleihauer to be a simple accurate and reproducible method of detecting and quantifying FMH. Flow was found sensitive at 0.125% D positive cells in D negative samples with a variation of 11%. At 0.06%, the variation increased to 44% suggesting the accuracy of flow cytometry was decreasing at this level of sensitivity	II	Nance et al 1989

Flow cytometry (cont)	Level of evidence	References
These authors used flow cytometry to measure 16 cases of FMH and suggest the test is time consuming and expensive although very sensitive. They see it as a research tool only in determining which antenatal events are the most sensitive and indicate anti-D administration.	III-3	Medearis et al 1984
Rosette		
The rosette test, in comparison to the microscopic Du and PEG Du, was found to be the most sensitive and accurate at detecting fetal cells on 10 prepared samples of 0.06%, 0.12%, 0.25%, 0.50%, 0.75%, 1% and 2%. The rosette test was 100% accurate to 0.12% fetal cells.	II	Bayliss et al 1991
Compared rosette with microscopic Du using controlled samples and found at 0.6% fetal positive rosette was accurate in 100% cases. Rosette was found sensitive to 2.5 ml at 75% accuracy. If the sample was not washed properly, rosette gave false positive results. Scientists performing rosette tests required 5 minutes more hands-on time than there were only 20 scientists in the group and further artificial samples were not tested and compared by both techniques.	II	Sebring & Polesky 1982
Rosette compared to Du resulted in significantly increased sensitivity for rosette. Rosette was equal in cost to Du. A 100% accuracy rate was found for rosette tests with 70 simulated FMH samples sensitive from 2.5 ml to 70 ml. Rosette was found to be sensitive, easy to interpret and reasonable cost.	III-1	Stedman et al 1986
Results of 112 tests by rosette were compared with micro Du. Rosette was sensitive to FMH > 5 ml.	III-1	Taswell & Reisner 1983

ELAT	Level of evidence	References
Found ELAT, when compared to Du testing, was reproducible and objective. Sensitive to 3 ml FMH. Eliminates the subjectivity of the Du test. As a test for FMH antenatally, ELAT is not sensitive enough.	II	Riley et al 1982
A modified ELAT is tested for quantifying fetal cells utilising glutaraldehyde fixation of red blood cells. In comparison to Kleihauer, ELAT was more accurate on prepared samples. ELAT was sensitive and accurate to 0.25% FMH.	III-1	Greenwalt et al 1992
No correlation found between antibody level at 48 hours and size of FMH as calculated by ELAT in 30 patients. Followed up at six months.	III-3	Ness & Salamon 1986
Found ELAT had greater sensitivity than the Du test and fewer false positive results than Kleihauer on samples from 186 women.	III-3	Ness 1982
Coombs'		
Reviewed Coombs' method of detection of anti-D in 240 laboratories using several prepared control samples of different percentages of anti-D and found >98% laboratories reported detecting anti-D at all levels of control preparation. Addition of enzyme and albumin did not increase sensitivity.	II	Pinkerton et al 1984
Comparison of PEG antiglobulin test with albumin antiglobulin test. Agglutination was stronger in the PEG test in 70.2% cases. Authors concluded PEG to be superior to albumin from these results.	III-1 or 3	de Man & Overbeeke 1990
Comparison of PEG antiglobulin test with papain/albumin indirect antiglobulin test. Reported 3.5% false positive rate with papain/albumin and only 0.8% with PEG. They also noted a decrease in the number of clinically insignificant antibodies detected.	III-3	Reisner et al 1996
Tested indirect agglutination test at detecting candidates for anti-D over and above the standard dose. Found Coombs' an alternative for detecting FMH.	III-3	Turner et al 1986

Compliance	Level of evidence	References
Found anti-D preparations stored at 4oC had a 10.6% (range 6.8–14.7%) fall in concentration believed to be a change in tertiary structure of the molecule. No change in the physical properties of the drug was noted.	III-1	Hughes-Jones 1978
Immunisation resulted from failure to administer anti-D in 66% of cases. Authors suggest education in both developed and developing countries to improve level of successful administration. Improved adherence to guidelines is more cost effective than routine prophylaxis.	III-3	Belfrage et al 1992
Suggested presence of allotype antibodies could inhibit Rh D prophylaxis. Their trial found a significant increase in the presence of allotype antibodies in isoimmunised women in whom prophylaxis failed. A weakness in this study was the method of testing of these failures, as they were tested years after immunoprophylaxis was administered.	III-3	Jerne 1976
This UK study found post-natal compliance of anti-D administration in 95% women. Confusion was found among women who had received antenatal prophylaxis. Noted 5 cases of missed postpartum administration due to presence of passive anti-D. Poor compliance antenatally with only 20% rate of appropriate administration in cases of abdominal trauma. Kleihauer results poorly understood by the health professional administering the drug.	IV	Howard et al 1997
Anti-D prone to loss of potency during storage. The manufacturer should be responsible for ensuring product maintains its dose during shelf life.	IV	Tankersley 1997
Author cites Tabor et al (1982)Denmark study where in 30% of cases of immunisation, women had not received immunoglobulin.	IV	Trolle 1989
This case report suggests passive anti-D augmented the formation of other antibodies.	IV	Tovey et al 1982

Compliance (cont)	Level of evidence	References
In this case example, a fetal Du variant red blood cell was resistant to anti-D and led to a failure of anti-D prophylaxis.	IV	Revill et al 1979
Highlighted the importance of record keeping to ensure all appropriate women receive anti-D.	IV	Lister 1980
Reviewed census details in the US and estimated that 80% of women who required anti-D were given the drug. Presented evidence from the Connecticut registry where accurate information was collected and feedback given to staff of 33 hospitals, improving rates of administration from 93% to 99% in 1 year.	IV	Wysowski et al 1979
Reports pregnant Rh D negative women who fail to report to a health care provider for antenatal care or a health care provider who does not order appropriate blood tests may result in failure to administer anti-D appropriately.	IV	Bowman 1988
Reports the risk of an inexperienced technician testing maternal blood samples using the micro Du test after large macro transfusion. The result can be misread, reporting the mother weakly D positive rather than identifying large agglutinates of fetal cells in the sample. Author reports failures have occurred when anti-D is withheld from mothers in this circumstance.	IV	Gorman 1983

Findings on the ethics of boosting and administration

Ethics of boosting and administration	Level of evidence	References
Immunised 113 volunteers for donor program. Red cells were matched for antigens. Donors formed anti-M, anti-N and anti-P.	III-3	Teesdale et al 1991
Tested 29 women injected with HIV contaminated anti-D for sero-conversion. All were negative at 14 -38 weeks after administration. Authors suggested concentrations of inactivated HIV were not great enough to immunise.	III-3	Babu et al 1990
Evidence showed no significant difference between groups for index and subsequent pregnancies. Assessed babies for birth weight, gestation of delivery and neonatal survival at one month. No significant differences were seen in the blood pressure and proteinuria in the mothers. This trial used historical controls and Rh D positive women for comparison.	III-3	Thornton et al 1989
Discussed a difficulty in antenatal prophylaxis - presence of passive antibody in antenatal period or at delivery may mask active immunisation or may lead to antibody enhancement.	III-3	Tovey et al 1983
No adverse reaction to primary dose of red cells administered for boosting of 28 or 29 volunteers respectively. However, 5 developed antibodies other than anti-D. The authors suggested this was more a problem when boosting with fresh red blood cells.	III-3	Urbiank & Robertson 1981 Gunson et al 1976
Suggested from his presentation on viral markers for HIV, Hepatitis C and HTLV that there was not an implication for anti-D in viral transmission. Donor red blood cells are frozen for 12 months and then re-tested before use in recipients.	IV	Tankersley 199
National self-sufficiency should be the aim of each country. Reports on the method of informed consent for donors utilising a witness.	IV	Taylor 1997

Ethics of boosting and administration (cont)	Level of evidence	References
One of two tested of a group of six women who received anti-D from a batch of infected serum from 1977 have tested seropositive to Hepatitis C. Batches were prepared in Eire, Ireland.	IV	Communicable Disease report UK 1994
Case report of severe serum sickness after anti-D administration postpartum. Author fails to rule out possible effect of rubella vaccine also administered.	IV	Jones et al 1984
Two case reports of boosted female donors becoming pregnant after failed sterilisation and suffering termination and miscarriage. Ethics of informing potential female donors of risks of pregnancy after boosting.	IV	Fisher 1982
Risks of anti-D administration are increased in populations where routine antenatal prophylaxis is used. Identifies the significant lack of evidence regarding potential risks to fetus from antenatal administration.	IV	Hensleigh 1985
Report preliminary observations on tests from 54 of 240 women who received anti-D known to be infected with HIV. None tested positive. Re-testing in 12 months for late seroconverters.	IV	Dumasia et al 1989

Findings on sources of supply of anti-D

Sources of supply of Anti-D	Level of evidence	References
IgG3-‘BRAD-3’ monoclonal anti-D had a better rate of clearance of positive red cells than IgG1-‘FOG-1’. Compared with historical results from polyclonal clearance, BRAD-3 were still superior. Found monocyte activity varied between subjects.	II	Thomson et al 1990
Authors compared characteristics and plasma half-lives of BRAD-3 and BRAD-5 with polyclonal anti-D. BRAD-3 half-life of 10.2 days, BRAD-5, 22.2 days and polyclonal 15.6 days. This study had a very small sample size of 6.	II	Goodrick et al 1994
These authors found both BRAD-3 and BRAD-5 had faster red cell clearance than polyclonal anti-D. Subjects responded differently. All groups were protected by the initial injection of anti-D. The authors failed to record whether the subjects were randomly selected into one of the 3 groups.	III-1	Kumpel et al 1995
Study of the antigen binding properties of monoclonal anti-D immunoglobulins showed some cross reactivity with human tissues. The authors thought that although this was a risk, it was unlikely to cause clinical problems.	III-3	Thorpe & Bailey 1993
Monoclonal anti-D developed using Epstein-Barr virus-transformed or hybridoma cell lines puts recipient at risk of viral transmission of infection, risk of transfer of human or murine oncogenes and risk of foreign protein transfer which could lead to anaphylaxis. Donors, who undergo boosting, are still required for retrieval of lymphocytes for monoclonal anti-D production.	IV	McCann et al 1988
Authors report that the quality control required for production for a safe monoclonal product needs to be stricter than with polyclonal production. Sources for microbiological contamination are increased in cell line production of monoclonal product. Suggest that large scale monoclonal production will be in practice in the next decade.	IV	Fletcher & Thomson 1996

APPENDIX 6

COST-EFFECTIVENESS ANALYSIS

This appendix presents results of a cost-effectiveness analysis of five alternative strategies for the prevention of Rh D isoimmunisation in Australia (summarised in Chapter 4).

Cost-effectiveness analysis is a technique of economic evaluation that allows both the costs and effectiveness of alternative health interventions to be compared (where allowing a disease to follow its natural history can be regarded as one possible 'intervention'). It allows for the fact that health interventions usually have both costs and benefits, and that a systematic approach to comparing these costs and benefits can assist in reaching decisions about the allocation of scarce resources among competing uses in the health sector.

In the present context, the problem of scarcity arises because of the limited supply of anti-D which is available relative to the number of women and babies who may benefit from its use. Therefore, some women who may potentially benefit from anti-D will be unable to obtain it. Under these circumstances, it is necessary to consider the costs and benefits of alternative policies about the administration of anti-D. This may identify any groups of women, for example groups at relatively low risk of experiencing Rh D isoimmunisation, for whom the use of anti-D is costly in comparison with the benefits achieved. Cost-effectiveness analysis can assist in providing answers to questions such as these.

Methods

In a comparison of two alternatives to the management of Rh D isoimmunisation, (referred to as Strategy A and Strategy B), Strategy A is Usual Care which involves treating women and their babies if Rh D isoimmunisation occurs, while Strategy B is a prevention strategy involving the use of anti-D. Both policies have costs and health effects associated with them. Under Strategy A, the costs will arise from the management of HDN that results from Rh D isoimmunisation in some women. The health effects will be the infant morbidity and mortality associated with HDN. Under Strategy B, costs will arise from the production of anti-D and its administration, and from the management of any HDN that the Strategy fails to prevent. Again, the health effects will be any HDN-related infant morbidity and mortality arising in those for whom the disease was not prevented.

What are the costs and effects of Strategy B compared with Strategy A? Strategy B involves an additional cost (the cost of the prevention program) in comparison with Strategy A, but because some disease is prevented the costs of management of HDN will be lower, ie Strategy B will give rise to treatment cost savings (there may be other cost savings also, but these will be ignored for the moment). The net cost of Strategy B can therefore be defined as follows:

$$\text{Net cost of Strategy B} = \text{Cost of prevention program} - \text{treatment cost savings}$$

It is evident from this definition that the net cost of Strategy B may be negative. If the treatment cost savings are sufficiently large, they may more than offset the cost of the prevention program itself. In this situation, as long as Strategy B provides any additional health benefits at all in comparison with Strategy A, it would be preferable on economic grounds.

Of course, it is also possible that the net cost of Strategy B will be positive, in which case the issue arises as to whether the additional health benefits conferred by Strategy B are 'worth' this additional cost. Under these circumstances, the results of the analysis are usually presented in the form of the net cost per unit of additional health effect, or the ratio of the incremental cost of Strategy B to its incremental health effect. Concentrating on the effect of Strategy B on mortality, and measuring health in terms of years of life lived, the cost-effectiveness ratio for Strategy B would be calculated as follows:

$$\text{Cost per life-year saved} = \frac{\text{net cost of Strategy B}}{\text{additional life-years lived due to Strategy B}}$$

Before presenting the model developed in the present study, the concept of discounting of costs and health effects must be mentioned. The costs and health effects of a health intervention often occur at different points in time. A prevention program, for example, may entail vaccine costs being incurred now but treatment cost savings accruing from disease prevention being reaped over the next 20 years. Similarly, when deaths are averted, the resulting additional years of life lived may not be experienced for some time and will extend into the future (eg mortality reductions from an anti-smoking campaign for adolescents). A cost incurred now is not generally regarded as being of the same significance as a cost to be incurred in one year's time, nor is a year of life saved in one-year's time thought of as having the same significance as a year of life saved now. Discounting is designed to allow for the different values which society places on costs and benefits that accrue at different points in time.

Discounting requires the specification of a discount rate. If the discount rate were 5%, then the present value of one dollar to be received in one year's time, or the present value of a cost of \$1.00 to be incurred in one year's time, is \$0.95. The present value of one dollar to be received in two year's time is \$0.91. If the discount rate were 10%, then the present value of \$1.00 in one year's time would be \$0.90, and in two year's time \$0.83. This example illustrates that higher discount rates result in future costs and benefits being 'marked down' more heavily. In other words, higher discount rates result in future costs and benefits receiving lower weights in cost-effectiveness calculations.

The model

This model is designed to investigate the cost effectiveness of alternative policies about the administration of anti-D to Rh D negative mothers. Six scenarios are considered, as follows.

A No anti-D given

This scenario provides estimates of the costs and health effects associated with isoimmunisation of Rh D negative mothers in the absence of administration of anti-D. No anti-D given includes prediction of severity of disease based on assessment of fetal condition, selective early induction of labour, intra-uterine fetal transfusion and exchange transfusions.

B Postpartum only

This scenario is defined as postpartum administration of one vial of anti-D to all Rh D negative mothers with no preformed anti-D antibodies following the birth of a Rh D positive baby.

C Antenatal with indications + postpartum

This scenario is defined as antenatal administration of one vial of anti-D to Rh D negative mothers with no preformed anti-D antibodies when specific indications are present, together with administration of an additional vial of anti-D postpartum as defined in B.

D Antenatal prophylaxis (primigravidae only) + postpartum

This scenario is defined as antenatal administration of immunoglobulin to all Rh D negative pregnant women experiencing their first pregnancy and with no preformed anti-D antibodies, together with postpartum administration as defined in B. Antenatal administration consists of one vial of anti-D given at 28 weeks and again at 34 weeks of pregnancy, except for those who miscarry or terminate who are assumed to receive one vial of anti-D.

E Antenatal prophylaxis (primigravidae only) + antenatal with indications + postpartum

This scenario is defined as antenatal administration of immunoglobulin as defined in D, together with antenatal administration of one vial of anti-D to Rh D negative mothers experiencing their second+ pregnancy when specific indications are present, as well as postpartum administration as defined in B.

F Antenatal prophylaxis + postpartum

This scenario is defined as for D but with antenatal prophylaxis now being given to all Rh D negative pregnant women.

In the above descriptions, the dosage of anti-D has been specified in terms of vials rather than μg or IU because the Australian product is presently supplied only in a 125 μg vial, the recommended dosage is generally 125 μg or less, and one vial cannot be used to supply more than one dose of anti-D.

A model has been developed to investigate the cost effectiveness of the five prevention strategies. Results are presented for the following comparisons:

- Strategy B compared with Strategy A
- Strategy C compared with Strategy B
- Strategy D compared with Strategies B and C
- Strategy E compared with Strategies B, C and D
- Strategy F compared with Strategies B, C, D and E.

The model is based on the decision trees contained in Figures 1 to 4 (presented at the end of the appendix). The general process begins with a first pregnancy, with Rh D negative women then being classified as experiencing either indications or proceeding to full term. Those who miscarry or have their pregnancies terminated may or may not become isoimmunised, and may or may not proceed to a second pregnancy. Women with other indications and those without indications then proceed to full term. If a baby is Rh D positive, the mother proceeds through a submodule which allows for antenatal and postnatal isoimmunisation (Figure 2). Within that Baby Rh D+ submodule, an infant experiencing HDN proceeds through a further submodule which tracks health outcomes (and costs) for that infant (Figure 3). At either the end of the Baby Rh D+ submodule or following the birth of a Rh D negative baby, the mother may or may not proceed to a second pregnancy.

The process for second and subsequent pregnancies is illustrated in Figure 4. A mother isoimmunised during or after her first pregnancy will have preformed anti-D antibodies at the beginning of her second pregnancy. The process for these women is different from those without preformed anti-D antibodies, the latter going through a process which is the same as for first pregnancies. A woman with preformed anti-D antibodies and a Rh D positive baby does not pass through the Baby Rh D+ submodule again (Figure 2) as she is already isoimmunised. The issue is not then whether the woman is isoimmunised but whether her baby develops HDN. Babies developing HDN are passed directly to the HDN submodule (Figure 3) to determine their health outcomes and costs.

The model is longitudinal in that it tracks relevant events and costs for a cohort of women from first through to fourth and subsequent pregnancies, allowing for spacing between births. The average time between births is relevant to the

analysis as it affects the discounted results. Although longitudinal, the model can be used to draw cross-sectional inferences about events and costs in Australia in any one year as long as the values of the variables in the model do not differ across different pregnancies/births (in a one year cross section, each order of pregnancy/birth arises in a different cohort of women).

The model's structure allows investigation of the costs and effects of the preventive strategies defined above. These can be viewed as having their impact at three different points in the processes of pregnancy shown in Figures 1 to 4. Specifically, Strategy B affects the probabilities at the points marked [1] on Figure 1 (although within the Baby Rh D+ submodule it affects only postnatal and not antenatal isoimmunisation rates). Strategy C has an impact on the probabilities at points [1] and [2], while Strategies D, E and F have their impact on the probabilities at points [1] and [3].

To implement this model, values must be attached to the relevant variables in Figures 1 to 4. In addition, estimates of unit costs for each relevant event must be obtained, and life expectancies must be employed to provide estimates of the effects of the strategies on the number of years of life lived under each scenario. The sources of data employed in the model are discussed below.

Data

Probabilities for decision trees: no anti-D given scenario

The probabilities used in the decision trees in Figures 1 to 4 are provided in Table A6.1. They will be discussed in the general order in which they are presented in that table. It should be noted that the complete set of values for no anti-D given is presented first, followed by those for variables that are assumed to change in response to the various prevention strategies (the latter are discussed below).

First pregnancy and second+ pregnancies without preformed anti-D antibodies

These variables are included in the decision trees illustrated in Figures 1 and 4. With regard to first pregnancies, the process begins with classification of all first pregnancies according to the Rh D status of the mother. Rh D negative mothers (17 per cent of all pregnancies — see Section 1.2) are then classified according to whether they have 'indications' or whether they proceed directly to full term.

The relevant indications defined in these guidelines are miscarriage, termination of pregnancy, ectopic pregnancy and chorionic villus sampling. The proportion of Rh D negative pregnancies with indications in the model is set at 30 per cent. This figure has been arrived at by taking the estimated number of births in Australia in 1996 (253,834) (ABS 1998) and adding to it the estimated number of first and second trimester terminations in Australia in that year (102,317) (Commonwealth

Department of Human Services and Health), thus arriving at a total of 356,151 pregnancies in Australia in 1996 with first and second trimester terminations constituting 28.7 per cent of these pregnancies.⁵ To allow for other indications, it has been assumed that 30 per cent of Rh D negative women have indications and that 95.8 per cent of these are miscarriages or terminations (note that $0.30 \times 0.958 = 0.287$, ie 28.7 per cent of Rh D negative women miscarry or have their pregnancies terminated). Other indications then account for just over 4 per cent of all indications.

In this model, miscarriage/termination ends the pregnancy and in 59 per cent of these cases, the fetus is Rh D positive (Mollison 1979). Of those mothers who miscarry/terminate, some proportion may become isoimmunised. The no anti-D given scenario uses an isoimmunisation rate of 4 per cent for these women. These guidelines state that immunisation occurs during pregnancy in approximately 1.5 per cent of Rh D negative women carrying a first Rh D positive infant, but early terminations can result in this rate increasing to as much as 5 per cent. Isoimmunisation rates of 4 per cent following miscarriage/termination with a Rh D positive fetus, and 1.5 per cent and 1.0 per cent for the first two and third-plus pregnancies respectively as the antenatal immunisation rates for full-term pregnancies (as in the Baby Rh D+ submodule) have been used.

The probabilities discussed above are all assumed to remain constant across first and subsequent pregnancies. For example, it is assumed that the proportion of Rh D negative women with indications is 30 per cent regardless of the order of the pregnancy, although it may be that termination rates are higher with first and fourth or later pregnancies than with second and third pregnancies. However, there are no data to confirm any hypotheses on this matter.

It should also be noted that the proportion of Rh D negative mothers having Rh D positive fetuses/babies is assumed to be 59 per cent whether or not the mother has indications and whether or not women with indications miscarry or terminate their pregnancy.

The proportions of women proceeding to second and higher order pregnancies are based on data provided in Jain and McDonald (1997). Three points should be noted about the calculation of these proportions. First, the authors do not provide these proportions directly, but rather give a breakdown of births by order. Thus they state that 45 per cent of total fertility is contributed by first order births, 32 per cent by second order births, 15 per cent by third order births, and 8 per cent by fourth and higher order births. These proportions have been used to infer the (longitudinal) probabilities of a woman proceeding to another pregnancy,

⁵ The actual number of pregnancies will be less than 356,151 to the extent that any pregnancies give rise to multiple births.

depending on her already having experienced a given number of previous pregnancies. Second, the data provided by Jain and McDonald (1997) are not national but relate only to Western Australia, South Australia, Tasmania and the Australian Capital Territory. An important advantage of their data is that they include both nuptial and ex-nuptial births. Third, the data pertain to births. It has therefore been assumed that the probabilities of a woman proceeding to second and higher pregnancies are the same as for her proceeding to second and higher order births.

The proportions proceeding to higher order pregnancies are assumed to be the same at all the relevant branches in the model.

Second+ pregnancies with preformed anti-D

Women passing through this part of the model are all Rh D negative, and have preformed anti-D. The proportion of these women having Rh D positive fetuses/babies is 59 per cent, the same as for women without preformed anti-D. The proportion of these women experiencing miscarriage/termination is also assumed to be the same as in the no preformed anti-D group (28.7 per cent). The proportion of Rh D positive babies that develop HDN is set at 72.5 per cent. Where the current process differs from the previous process is that, given that the mothers are already isoimmunised, all Rh D positive babies are at risk of HDN. With first pregnancies and second+ pregnancies with no preformed anti-D, only those Rh D positive babies born to mothers who experience antenatal isoimmunisation are at risk of HDN.

Submodule: baby Rh D positive with no preformed anti-D

Mothers going through this submodule have no preformed anti-D and have full-term pregnancies. The antenatal isoimmunisation rate is set at 1.5 per cent for the first two pregnancies, and 1.0 per cent for subsequent pregnancies. The lower rate for third and subsequent pregnancies reflects the argument put by Tovey (1990) that the chances of a mother becoming sensitised are much greater in the first and second Rh D positive pregnancies.

The postnatal isoimmunisation rate is derived from the fact that, of all Rh D negative women with Rh D positive fetuses/babies, 17 per cent are isoimmunised by the time of their next pregnancy. Since 1.5 per cent are isoimmunised antenatally, 15.5 per cent has been used as the postnatal isoimmunisation rate. Where antenatal isoimmunisation has occurred, the Rh D positive baby has a 0.725 probability of developing HDN, as in the process for second+ pregnancies with preformed anti-D.

HDN submodule

This submodule requires evidence on the proportion of Rh D negative mother/Rh D positive fetus pregnancies where the baby is stillborn and, of those babies born alive, the proportions dying shortly thereafter, surviving but with long-term sequelae, and surviving with no long-term sequelae.

For HDN deaths, it is necessary to consider first the natural history of HDN. Tovey (1990), using data from Queen Charlotte's Hospital, London, between 1946 and 1949, indicates that of 11,035 babies delivered in that period, 34 died because of Rh D antibodies -- a mortality rate of 320 per 100,000 live births. He also indicates that, of mothers who developed Rh D antibodies, 20 per cent lost their infants in their first affected pregnancy and 40 per cent in subsequently affected pregnancies. In the context of the present model, several points must be made about these data. First, the proportions refer to all Rh D negative mothers with Rh D positive babies. Since it is assumed that 72.5 per cent of these Rh D positive babies will develop HDN, then expressed as a proportion of HDN babies, the rate becomes 28 per cent ($0.20/0.725$) for the first affected pregnancy and 55 per cent for second and subsequent affected pregnancies. Second, the proportions refer to the first and subsequent affected pregnancy. It is possible that the first affected pregnancy may be the woman's first, second or higher order pregnancy. Third, the rates refer to all HDN deaths, both stillborn and born alive but dying subsequently from HDN.

A second paper of interest in relation to mortality from HDN under natural history is that by Peddle (1984) who states 'Rh D hemolytic disease occurs in those cases in which a mother who is isoimmunised to Rh D antigen is pregnant with a Rh D positive fetus. Without any form of treatment, approximately 45-50 per cent of these infants will survive. A further 25-30 per cent will be born alive but without treatment will succumb to their disease in the first few days of life. The remaining 20-25 per cent, if not adequately managed, will be stillborn or hydropic prior to term.' Again, these proportions relate to Rh D positive babies. Expressing the mortality rate as a proportion of HDN babies suggests that 70-76 per cent of such babies would die in the absence of any treatment.

In short, Tovey (1990) implies that 28 per cent of HDN babies from first affected pregnancies, and 55 per cent from subsequent affected pregnancies, will not survive. Peddle (1984) suggests that 70-76 per cent of HDN babies will not survive, without distinguishing between order of birth. However, as these mortality rates refer to the natural history of HDN, they cannot be used in the baseline scenario in our model (Strategy A) as that scenario is defined as no anti-D given. It is necessary to determine the effect of no anti-D given on HDN mortality.

Peddle (1984) identifies a number of major breakthroughs in the treatment of HDN which had a marked effect on HDN mortality. He estimates that exchange transfusions, the use of which became widespread in the 1950s, reduced mortality from 50 per cent of Rh D positive babies to 25 per cent. In the 1950s and 1960s, further improvements in management involving 'prediction of severity of disease in utero and selective early induction of labor' using amniotic fluid spectrophotometry meant that it was 'theoretically possible' to reduce this mortality rate to 8 per cent. Intra-uterine fetal transfusion, first performed in 1963, offered hope of even further reductions in mortality. It was in the 1960s that the possible prevention of Rh D isoimmunisation by administration of anti-D was discovered, although routine postpartum prophylaxis did not become widespread, in England at least, until the early 1970s (Urbanik 1997). But it is clear that developments in no anti-D given prior to the introduction of postpartum prophylaxis had achieved considerable reductions in HDN mortality.

Further data on deaths from HDN are available in a series compiled by Clarke and Hussey (1994) for the period 1977 to 1992 in the United Kingdom. In 1977, there were 18.4 deaths per 100,000 live births from HDN due to anti-D, a considerable reduction from the 320 deaths per 100,000 live births found by Tovey (1990) using the 1946–49 series. Clarke and Mollison found that the death rate fell progressively to 3.9 deaths per 100,000 live births in 1984 and remained approximately constant for the next three years (5.0 in 1985, 4.5 in 1986 and 3.9 in 1987). It then began falling again, reaching 1.3 deaths per 100,000 live births in 1992 (Clarke & Hussey 1994). Since routine postpartum prophylaxis was introduced in the United Kingdom in the early 1970s, these mortality rates undoubtedly reflect the effects of this prevention strategy.

In Australia, ABS statistics indicate that there were 80 deaths, or 35 deaths per 100,000 live births, due to Rh D incompatibility in 1974 (ABS 1975). In 1995 and 1996, the numbers of deaths due to HDN (but not necessarily due to Rh D incompatibility) were 10 and 6 respectively (ABS 1996; ABS 1997). These translate into rates per 100,000 live births of 3.90 and 2.36 respectively. As with the Clarke and Hussey series, this considerable decline in the HDN death rate would reflect the effect of passive immunisation with anti-D.

A general difficulty with mortality data is that they are known to underestimate the number of deaths due to HDN. This can arise from ascribing an HDN death to a cause other than HDN where HDN is the real underlying cause. Another source of underestimation, identified by Clarke and Mollison (1989), is that stillbirths occurring before the 28th week of pregnancy are not registered. They had previously estimated that their mortality data may capture only two-thirds of the total number of deaths from HDN, although they argue that the data used in their present paper may be underestimating the real numbers of deaths to a lesser

degree because of increasing success in treating severe cases in utero (Clarke & Mollison 1989). A more recent study on Scottish Rh D HDN mortality has found the actual number of deaths due to this cause to be five times greater than the mortality data obtained from the Registrar General's Office (Raafat et al 1997).

There are no comparable studies on possible underestimation of HDN deaths in Australia. However, data on the number of hospitalisations for HDN, hydrops fetalis and kernicterus due to Rh D isoimmunisation (ICD codes 773.0, 773.3 and 773.4) were supplied by the Commonwealth Department of Health and Family Services. These data indicate that, in the 1994–95 financial year alone, there were 161 discharges with HDN and three discharges with hydrops fetalis recorded as principal diagnosis, and 101 discharges with HDN recorded as a secondary diagnosis and three discharges with hydrops fetalis recorded as a secondary diagnosis. Given that there was an average of eight deaths per year due to HDN in 1995 and 1996, this suggests a low mortality rate relative to the number hospitalised for Rh D HDN.

On the basis of this discussion, an overall mortality rate has been used among HDN babies in the no anti-D given scenario without Rh D Immunoglobulin (Strategy A) of 2 per cent among first births, with 1 per cent being stillborn and another 1 per cent dying within one month of birth. For second and subsequent births, the overall mortality rate is taken as 6 per cent, with 3 per cent being stillborn and another 3 per cent dying within one month of birth. These rates should be interpreted as indicative of the success rates of current treatment regimes for those babies developing HDN. Across all HDN births, they suggest a mortality rate of about 5.5 per cent. This can be compared with the mortality rate among Rh D positive babies of 8 per cent suggested by Peddle (1984) as being attained before the development of intra-uterine transfusion and before prevention with anti-D. If Peddle's estimate is recalibrated in terms of the number of HDN babies rather than the number of Rh D positive babies, it suggests a mortality rate among HDN babies of 11 per cent ($= 0.08/0.725$). The rate of 5.5 per cent, which is one-half of this, makes some allowance for the effects of the introduction of intra-uterine transfusion and for any other improvements in diagnostic and treatment capabilities.

It is assumed that 4 per cent of HDN babies survive with long-term sequelae. This is based on a reported proportion of 4 per cent of infants undergoing intra-uterine transfusion who survive having major disabilities (Davey & Zipursky 1979).

Probabilities for decision trees: prevention scenarios

The foregoing discussion of the values attaching to the variables in the decision trees all relate to the no anti-D given scenario. This section discusses the values adopted for the probabilities in each of the prevention scenarios.

Postpartum anti-D only

The set of variables labelled 'Postpartum only' in Table A6.1 shows the set of variables within which one or more values will change in response to Strategy B (postpartum administration of anti-D without any antenatal administration).

Postpartum administration of anti-D reduces the rate of postnatal isoimmunisation following delivery of a Rh D positive baby (this rate is within the Baby Rh D+ submodule illustrated in Figure 2). Under no anti-D given, a value of 15.5 per cent was employed for this proportion. With postpartum administration of anti-D this proportion is assumed to drop to 0.2 per cent in the first and second pregnancies, and 0.1 per cent in third and subsequent pregnancies. It should be noted that the probability of a woman becoming isoimmunised antenatally has not changed with this strategy, and hence remains at 1.5 per cent.

Antenatal with indications + postpartum

In comparison with postpartum administration only, this strategy affects two additional probabilities in the decision trees. First, the rate of isoimmunisation following miscarriage/termination falls from 4 per cent in each pregnancy to 0.16 per cent. This assumes that the risk of isoimmunisation in women with indications falls to the same level as that for women without indications (ie 0.16 per cent) following antenatal prophylaxis (NHMRC 1996). Second, the rate of antenatal isoimmunisation for women with other indications proceeding to full term and having Rh D positive babies is assumed to fall from 1.5 per cent to 0.16 per cent for the first two pregnancies, and from 1 per cent to 0.1 per cent for the third and subsequent pregnancies.

Antenatal prophylaxis (primigravidae only) + postpartum

In comparison with the previous strategy, this involves provision of anti-D to all Rh D negative women experiencing their first pregnancy. While this encompasses both women with other indications and all other Rh D negative women proceeding to full term, it excludes women having their second and subsequent pregnancies from antenatal prophylaxis. Consequently, the probability of antenatal isoimmunisation is reduced only during the first pregnancy. For women who miscarry or terminate, this probability falls from 4 to 0.16 per cent. For women proceeding to full term, with or without other indications, the probability falls from 1.5 to 0.16 per cent.

For second and subsequent pregnancies, the probabilities of antenatal isoimmunisation are assumed to remain as they were in the absence of any antenatal prophylaxis (4 per cent for miscarriage or termination, and 1.5 per cent and 1.0 per cent for second and third+ pregnancies respectively for women proceeding to full term).

Antenatal prophylaxis (primigravidae only) + antenatal with indications + postpartum

This strategy complements the antenatal prophylaxis program for primigravidae only with antenatal administration of anti-D to a subset of Rh D negative mothers experiencing their second+ pregnancy. That subset comprises those women with specific indications as detailed earlier (miscarriage/termination etc). In comparison with antenatal prophylaxis for primigravidae only, this strategy reduces:

- the probability of isoimmunisation in second+ pregnancies ending in miscarriage or termination from 4 per cent to 0.16 per cent;
- the probability of antenatal isoimmunisation in second pregnancies for women with other indications proceeding to full term from 1.5 per cent to 0.16 per cent; and
- the probability of antenatal isoimmunisation in third and subsequent pregnancies for women with other indications proceeding to full term from 1 per cent to 0.1 per cent.

Antenatal prophylaxis + postpartum

In comparison with the previous strategy, this program provides antenatal prophylaxis to all Rh D negative mothers in their second and subsequent pregnancies and not just the subset of these with indications. Consequently, it reduces the probability of antenatal isoimmunisation for Rh D negative mothers in second and subsequent pregnancies without indications also. For such women, the probability of antenatal isoimmunisation falls as a result of this program from 1.5 to 0.16 per cent for the second pregnancy, and from 1 to 0.1 per cent for the third and subsequent pregnancies.

Costs

The cost estimates required for the model can be categorised broadly as the direct costs of Rh D isoimmunisation and HDN, the indirect costs of HDN, and the cost of prevention. These will be discussed in turn.

Direct cost of Rh D isoimmunisation and HDN

Direct costs are costs incurred in the management/treatment of an illness. They include the costs of medical services, drugs, nursing services etc. The detection of circulating antibodies in a Rh D negative pregnancy marks the beginning of a course of tests and treatment that can vary markedly between women depending upon the severity of the case. Serology, ultrasound examinations, amniocenteses and intra-uterine transfusions may all be involved during the pregnancy. The neonate may then require phototherapy if only mildly affected and exchange transfusion if severely anaemic, with additional hospital care also a possibility.

In a recent paper, Vick et al (1996) provided estimates of the cost of the additional maternal and neonatal resources required for Rh D negative women developing anti-D antibodies during pregnancy. These estimates are based on a sample of 338 pregnancies in Scotland over the period 1987–91 and include antenatal serology, antenatal maternity care, pre-delivery care, delivery care and neonatal care. They estimate that the average additional cost of a pregnancy characterised by Rh D isoimmunisation is £2,164 (1995 prices). Converting this to Australian dollars using GDP purchasing power parities (OECD 1996) gives an estimate of \$4,530 as the average additional cost involved in managing a pregnancy where Rh D isoimmunisation has occurred.

This can be compared with the estimate employed by Torrance and Zipursky (1984) of \$1,640 per case of Rh D Disease (1983 Canadian dollars). Converting this to Australian dollars in 1995 prices gives \$2,445. At least part of the difference between this estimate and that of Vick et al (1996) may be due to technological improvements in tests and treatments associated with Rh D isoimmunisation. Hence, although a conservative approach might dictate the use of the lower estimate, the higher estimate is being used in the present analysis as it may be more reflective of the costs associated with contemporary management of Rh D Disease.⁶

The unit cost of \$4,530 is multiplied by the number of Rh D negative pregnant women proceeding to full term, to provide an estimate of the total cost of managing Rh D isoimmunisation under each strategy. The unit cost estimate by birth order along with its discounted equivalent is reported in Table A6.2. For second and subsequent pregnancies, the discounted value of this cost is less than the undiscounted value because of the time between births. Demographic data for Australia indicate that, for birth cohorts during the period 1981–85, the average birth interval from first to second birth was 27.9 months, from second to third birth 29.4 months, and from third to fourth birth 25.8 months (Adam 1991). All estimates of discounted costs in Table A6.2 are based on an allowance of two years as the average interval between births.

This estimate of direct cost includes all antenatal and neonatal management costs, but excludes any costs associated with the ongoing care and support required by HDN babies that suffer long-term sequelae. For these cases, mental handicap is a common problem. Neither Torrance and Zipursky (1984) nor Vick et al (1996)

⁶ Although this estimate is based on an empirical study, it may nevertheless underestimate costs in the Australian setting. The 1996 NHMRC guidelines state the following: 'The health costs of failing to prevent Rh D isoimmunisation are high. They include preterm birth and the need for neonatal intensive care at \$2,000 per day, and continuing care for infants with disabilities which could reach \$2–3 million for the lifetime care of a person with severe cerebral palsy and mental retardation' (NHMRC 1996).

include any estimates of these costs in their analyses. Such costs may, however, be considerable and their exclusion could substantially affect the results.

To obtain estimates of the lifetime costs of management of HDN cases with long-term sequelae, it has been assumed that their life expectancy at birth is the same as in the population at large (78 years; AIHW 1996).⁷ Average per capita health expenditures in Australia in 1995–96 were approximately \$2,294 (AIHW 1997, preliminary estimate). Therefore, in undiscounted terms, average lifetime health expenditures in Australia can be expected to be \$179,000. The costs of management for an HDN case with long-term sequelae can be expected to lead to lifetime treatment costs in excess of this average, but by how much more is not known. The results in Table A6.2 are based upon an assumption that they are twice the average, ie that they amount to \$358,000 over the lifetime of the individual.⁸ When discounted at 5 per cent per annum, the estimated lifetime cost ranges from around \$67,000 to nearly \$90,000 depending upon the birth order of the affected baby.

Indirect cost of HDN

The indirect cost of an illness is the lost production that results, either from reduced productivity while at work, from time off work, or from premature death. In the case of HDN, indirect costs arise from HDN deaths and from those with HDN who survive with long-term sequelae. The model assumes that the mental handicap afflicting survivors with long-term sequelae is such as to render them unsuitable for paid employment. For both HDN deaths and HDN handicapped cases, the indirect costs can therefore be approximated as the lifetime earnings foregone as a result of HDN. Using age-earnings data for 1993 from the ABS, the average of the lifetime earnings for a person in Australia is \$1,077,884 (undiscounted — see Table A6.2). Using a discount rate of 5 per cent, the average lifetime earnings lost due to one HDN death or handicap ranged from \$121,000 to \$170,000 depending upon the birth order.

Cost of prevention

For an individual woman and her baby, the cost of prevention using anti-D comprises the cost of one or more vials of anti-D and the costs of tests associated with administering that anti-D. An indicative cost of \$60 per vial has been used. For all tests associated with the administration of anti-D, 100 per cent accuracy is assumed and any issues concerning sensitivity and specificity of these tests have been ignored.

7 The AIHW reports life expectancy at birth in 1994 for males (75.0 years) and females (80.9 years) separately. The overall life expectancy has been obtained by taking the population-weighted mean of these two figures using the male (8,884,737) and female (8,953,664) population estimates as at 30 June 1994 (ABS 1997).

8 See footnote 6.

For postpartum administration (Strategy B), it is assumed:

- that the Rh D status of the mother is known;
- that three tests are conducted simultaneously: the mother is tested for circulating antibodies and for fetomaternal haemorrhage (Kleihauer), and the baby is tested to determine Rh D status; and
- only those with Rh D positive babies and with no preformed anti-D will actually receive anti-D.

The unit cost of these tests combined is \$57 (undiscounted — see Table A6.2). Under these assumptions, the number of women tested will considerably exceed the number finally receiving anti-D for two reasons: first, because a number of women tested will have Rh D negative babies but that is known only when the result of the blood test to determine the Rh D status of the baby is revealed; and second, because some of these women will be found to have preformed anti-D. In the model, the estimated number of women tested is 43,152 while the number finally receiving anti-D is 24,812.

For antenatal administration of anti-D to those Rh D negative women with indications, combined with postpartum administration (Strategy C), it is assumed:

- the Rh D status of each woman with indications is not known, necessitating a test of all pregnant women with indications to ascertain Rh D status prior to antenatal administration of anti-D (106,841 women are tested in the model);
- those women with indications who are Rh D negative, and for whom this is not their first pregnancy, are tested for preformed anti-D (9,985 women) (note that it is assumed that there is no need to test for preformed anti-D in first pregnancies before antenatal administration of anti-D);
- those Rh D negative women without preformed anti-D, together with those for whom this is their first pregnancy, receive one vial of anti-D (18,053 women);
- all Rh D negative women going to full term then undergo the same testing procedure as in the postpartum strategy above (43,152 women); and
- only those with Rh D positive babies and no preformed anti-D will actually receive postpartum anti-D (24,960 women). (Note that the number of women receiving postpartum administration is slightly higher here than with postpartum administration only, because the antenatal administration prevents antenatal isoimmunisation in some women. These women will now qualify for anti-D at birth while they would not have so qualified under the postpartum only strategy).

For antenatal prophylaxis given to primigravidae together with postpartum administration (Strategy D) it is assumed:

- the Rh D status of each woman is not known, necessitating a test of all primigravidae to ascertain Rh D status before antenatal administration of anti-D (160,268 women are tested in the model);
- those Rh D negative women who miscarry or terminate receive one vial of anti-D (7,827 women) (note that women with 'other indications' are included in the remaining group to receive two vials of anti-D);
- those Rh D negative women with 'other indications' together with all other Rh D negative women proceeding to full term receive two vials of anti-D, one at 28 weeks and the other at 34 weeks (19,418 women);
- all Rh D negative women going to full term (including first and subsequent pregnancies) then undergo the same testing procedure as in the postpartum strategy above (43,152 women);
- only those with Rh D positive babies and no preformed anti-D will actually receive postpartum anti-D (25,133 women) (note that the number of women receiving postpartum administration is higher here than with Strategies B and C because the antenatal administration prevents antenatal isoimmunisation in some women).

For antenatal prophylaxis given to primigravidae and to women experiencing their second or higher order pregnancy with indications, together with postpartum administration (Strategy E), it is assumed:

- the Rh D status of each woman is not known, necessitating a test of all primigravidae to ascertain Rh D status prior to antenatal administration of anti-D (160,268 women are tested in the model);
- those Rh D negative primigravidae who miscarry or terminate receive one vial of anti-D (7,827 women) (Note that women with 'other indications' are included in the remaining group to receive two vials of anti-D);
- those Rh D negative primigravidae with 'other indications' together with all other Rh D negative primigravidae proceeding to full term receive two vials of anti-D, one at 28 weeks and the other at 34 weeks (19,418 women);
- the Rh D status of all women with second or subsequent pregnancies and who miscarry or terminate is not known, necessitating a test of all these women to determine Rh D status prior to the administration of anti-D (58,763 women are tested in the model);

- those women with second or subsequent pregnancies who miscarry or terminate and who are Rh D negative are then tested for preformed anti-D before the administration of anti-D (9,988 women are tested in the model);
- those without preformed anti-D are then given one vial of anti-D at the time of miscarriage or termination (9,935 women);
- all Rh D negative women going to full term (first and subsequent pregnancies) then undergo the same testing procedure as in the postpartum strategy (43,152 women);
- only those with Rh D positive babies and no preformed anti-D receive postpartum anti-D (25,187 women).

For antenatal prophylaxis together with postpartum administration (Strategy F), it is assumed:

- the Rh D status of each woman is not known, necessitating a test of all these women to ascertain Rh D status prior to antenatal administration of anti-D (356,151 women are tested in the model);
- all Rh D negative women having a second or subsequent pregnancy are tested for preformed anti-D (33,300 women);
- those Rh D negative women who miscarry or terminate receive one vial of anti-D (17,368 women) (Note that women with 'other indications' are included in the remaining group to receive two vials of anti-D);
- those Rh D negative women with 'other indications' together with all other Rh D negative women proceeding to full term receive two vials of anti-D, one at 28 weeks and the other at 34 weeks (43,088 women);
- all Rh D negative women going to full term then undergo the same testing procedure as in the postpartum strategy above (43,152 women) (note that the extra 64 women tested here in comparison with those going to full term who received antenatal prophylaxis are women with preformed antibodies who we assume will be tested again at full term);
- only those with Rh D positive babies and no preformed anti-D will actually receive postpartum anti-D (25,385 women) (note that the number of women receiving postpartum administration is higher here than with Strategies B, C, D and E because the antenatal administration prevents more antenatal isoimmunisation).

Life expectancies and life-years saved

As discussed above, the life expectancy at birth in Australia, averaged across males and females, is 78 years. This is assumed to be the life expectancy of HDN survivors with long-term sequelae, and of those infants whose death from HDN is averted.

Discounting of both costs and health effects occurs in the model. It was also pointed out earlier that, since the model is a longitudinal one, birth spacing is relevant. As well as affecting the cost estimates, birth spacing affects the discounted numbers of life-years saved in the model. For example, from time of first pregnancy, the model assumes that it will be six years before a fourth pregnancy occurs (if it does occur). Therefore, preventing an HDN death from the fourth pregnancy means that the stream of life-years saved does not commence until six years hence. As a result, the discounted value of these life-years saved will be lower than for an HDN death averted from, say, the second pregnancy.

The effect of discounting on the number of life-years saved in the model is shown in Table A6.3. Without discounting, the number of life-years saved from one infant death averted is 78 years regardless of birth order. If the discount rate is set at 5 per cent per annum, then the discounted value of life-years saved is 19.6 years if the death averted is from the first birth, falling to 14.6 years if the death averted is from the fourth birth. A discount rate of 10 per cent per annum further reduces the present value of life-years saved for each birth order.

Results

Numbers of events

The numbers of the more important events predicted by the model under the no anti-D given and four alternative prevention scenarios are presented in Table A6.4. The discount rate used in obtaining these results, where relevant, is 5 per cent.⁹ Under each scenario, the number of live births plus the number of HDN deaths in the model is equal to the actual number of live births in Australia in 1996 (253,834). Hence, although the model is longitudinal, the numbers of births and HDN deaths in this cohort can be used to provide a cross-section estimate of events in Australia during one year. Note also that if the HDN mortality rate in the model fell to zero, the number of live births predicted by the model would equal the number of live births in Australia in 1996.

⁹ This is the rate recommended by the Commonwealth Department of Health and Family Services for use in economic evaluations of drugs submitted for listing on the Pharmaceutical Benefits Scheme (Commonwealth Department of Human Services and Health 1995).

Under the no anti-D given scenario, a scenario that involves no use of anti-D, the model predicts 78 HDN deaths across all pregnancies, or a death rate from HDN of 30.89 per 100,000 live births. This compares with 80 deaths recorded in Australia in 1974 as being due to HDN with Rh D incompatibility (ABS 1975). Although prophylactic use of anti-D commenced in Australia in the late 1960s, a number of women would already have been sensitised and so still at risk of giving birth to an HDN baby. The model's prediction of the number of HDN deaths under no anti-D given does not, therefore, appear to be unreasonable. The undiscounted number of years of life lost as a result of these deaths is 6,114 (1,296 discounted). All but two deaths arise from second and higher order pregnancies. The predicted number of HDN births surviving but with long-term sequelae (handicapped) is 55, which is about 70 per cent of the number of HDN deaths. Thus, the morbidity associated with long-term sequelae consequent to HDN is not trivial relative to the burden of mortality.

Postpartum administration of anti-D (Strategy B) reduces the HDN mortality rate to 9.0 per 100,000 live births. This represents a reduction in the number of HDN deaths from 78 to 23, or 55 deaths avoided (70 per cent). (The sections in Table A6.4 headed 'marginals over ...' provide the differences in the number of events between the scenarios specified as being compared.) Postpartum administration has no effect on HDN mortality from first pregnancies. The estimated number of life-years saved is 4,333 (or 910 discounted). The number of HDN handicapped falls from 56 to 18.

Antenatal administration of anti-D to Rh D negative women with indications in addition to postpartum administration (Strategy C) is estimated to reduce the number of HDN deaths to 16.6, or 6.55 per 100,000 live births. This is a further reduction of six deaths, and a further gain of 486 years of life lived (102 discounted years of life lived) over and above the level of HDN mortality obtained with postpartum administration of anti-D alone. Strategy C is estimated to have only a marginal impact on HDN mortality arising from first pregnancies (a reduction of 0.04 deaths). The estimated number of HDN handicapped falls to 14.

Antenatal prophylaxis for primigravidae combined with postpartum administration (Strategy D) reduces the number of HDN deaths to 13.5 (or 5.31 per 100,000 live births), ie three fewer deaths than obtained with antenatal prophylaxis for Rh D negative women with indications across all pregnancies. This yields an additional 244 years of life lived (62 years discounted). It is interesting to note that, even though this Strategy is confined to primigravidae compared with the antenatal program for Rh D negative women with indications which is provided to all pregnancies, the antenatal program for primigravidae provides greater overall effectiveness (although not better effectiveness for third and fourth pregnancies).

Antenatal prophylaxis for primigravidae combined with antenatal prophylaxis for second and subsequent pregnancies with indications and postpartum administration (Strategy E), reduces the number of HDN deaths to 11.17 (or 4.40 deaths per 100,000 live births). Compared with either 'antenatal with indications' or 'antenatal prophylaxis (primigravidae only)', it reduces HDN mortality (by 5.44 deaths and 2.32 deaths respectively). This result reflects the assumption that antenatal prophylaxis for primigravidae does not reduce the isoimmunisation rate in second and subsequent pregnancies.

Antenatal prophylaxis for all Rh D negative pregnancies combined with postpartum administration (Strategy F) reduced the number of HDN deaths to 2.69 (or 1.06 per 100,000 live births). This represents a reduction of 20.16 deaths in comparison with postpartum administration alone, a reduction of 13.93 deaths in comparison with the antenatal program for Rh D negative women with indications, a reduction of 10.8 deaths in comparison with antenatal prophylaxis confined to primigravidae, and a reduction of 8.49 deaths in comparison with the combined antenatal prophylaxis for primigravidae/antenatal with indications program. The number of HDN handicapped is reduced to 2.12 persons per year. Of the five alternative prevention programs, Strategy E has the largest impact on HDN mortality.

Table A6.6 summarises the life-years saved with each prevention Strategy.

Costs

The estimated total direct and indirect costs of HDN, and the total costs of each of the three prevention programs, are presented in Table A6.5. Under no anti-D given, of course, there is no cost of prevention. The direct costs of Rh D isoimmunisation and HDN (costs of management/treatment) under no anti-D given amount to \$15.4 million, and the indirect costs to \$18.4 million (of which \$10.8 million is attributable to HDN deaths). Direct costs are estimated to account for 46 per cent of the estimated total costs of HDN of \$33.8 million.

Postpartum administration of anti-D without any antenatal program (Strategy B) has an estimated cost of prevention of \$3.6 million. This estimate includes the costs of all tests prior to administration of anti-D as well as the cost of the anti-D itself. The direct and indirect costs of HDN not prevented with this Strategy are \$4.7 million and \$5.9 million respectively. In comparison with the no anti-D given scenario, this Strategy reduces the direct costs of HDN by \$10.7 million and the indirect costs by \$12.5 million.

The estimated costs of prevention using antenatal administration of anti-D to Rh D negative women with indications together with the postpartum program are \$5.8 million. The direct costs of HDN fall to \$3.5 million and the indirect costs to

\$4.5 million. In comparison with postpartum administration of anti-D only, this program has an additional cost of prevention of \$2.2 million. The direct cost savings amount to \$1.2 million and the indirect cost savings to \$1.4 million.

Antenatal prophylaxis for Rh D negative primigravidae combined with postpartum administration has a total cost of prevention of \$8.0 million. In comparison with postpartum administration only, the additional cost of prevention is \$4.4 million but it yields direct cost savings of \$2.5 million and indirect cost savings of \$2.8 million. Compared with the antenatal with indications + postpartum strategy, it has an additional cost of prevention of \$2.2 million but yields direct and indirect cost savings of \$1.3 million and \$1.4 million respectively.

Antenatal prophylaxis for primigravidae combined with antenatal administration to women with indications in their second or subsequent pregnancy and with postpartum administration, has a cost of prevention of \$9.6 million. However, while this is \$6.1 million more than the cost of prevention with postpartum administration alone, the direct and indirect costs of HDN fall by \$6.2 million, so that the program yields a net cost saving. When both direct and indirect cost savings are included, this Strategy is also cost saving in comparison with both 'antenatal with indications + postpartum' and 'antenatal prophylaxis (primigravidae only) + postpartum' strategies.

Antenatal prophylaxis combined with postpartum administration of anti-D has the highest cost of prevention of all five strategies of \$13.4 million — more than double the cost of the antenatal with indications + postpartum strategy, nearly 70 per cent greater than the antenatal (primigravidae only) + postpartum strategy, and nearly 40 per cent greater than the combined antenatal prophylaxis for primigravidae/ antenatal with indications strategy. However, it also generates direct and indirect cost savings over these three strategies, the total cost savings being \$6.8 million, \$4.1 million and \$3.2 million respectively.

The results on the costs of HDN and the costs of prevention are summarised in Table A6.6. It is clear from this table and the above discussion that, if both direct and indirect cost savings are deducted from the cost of prevention, the postpartum only strategy, the antenatal with indications' strategy and the 'antenatal prophylaxis (primigravidae only) strategy have a negative incremental cost in all comparisons, i.e. the additional cost of prevention is more than offset by the savings in direct and indirect costs. The remaining two strategies have a positive incremental cost in most of the comparisons, but this incremental cost never exceeds \$1.3 million.

Cost-effectiveness analysis

Estimates of cost savings which are offset against the cost of a health care intervention are sometimes greeted with a degree of scepticism. It is therefore of interest to consider the cost effectiveness of the five prevention programs without any deductions of estimated cost savings, and also with deductions only for the estimated savings in direct costs. The resulting cost-effectiveness results are presented in Table A6.7. The discount rate used in this analysis is 5 per cent.

Postpartum anti-D only

In comparison with no anti-D given, postpartum administration of anti-D saves life-years at a gross cost of prevention of \$3,907 per life-year saved. If direct cost savings from the reduction in the number of women treated during pregnancy for Rh D isoimmunisation are deducted from the gross cost of prevention, postpartum administration has a negative net cost, ie it results in a cost saving of \$4,864 per life-year saved. This cost saving is even larger if the direct cost savings associated with treatment of both mother and infant are deducted from the gross cost of prevention.

Antenatal with indications + postpartum

If antenatal administration of anti-D for women with indications is added to postpartum administration, the additional gross cost of prevention per year of life saved in comparison with postpartum administration only is \$21,992. If estimated direct cost savings are offset against the cost of prevention, the cost per life-year saved falls to \$13,241 or \$10,183 depending on the direct cost savings which are deducted.

Antenatal prophylaxis (primigravidae only) + postpartum

If antenatal prophylaxis for primigravidae is added to postpartum administration, the additional cost per year of life saved is \$26,934 without any deductions for savings in direct costs. If compared with the antenatal with indications program, the additional cost per life-year saved is \$35,071. Deducting direct cost savings associated with treatment of mothers only reduces the costs per life-year saved to \$16,231 and \$21,154 respectively. The costs per life-year saved are, of course, even lower if all savings in direct costs are deducted (see the third column of results in Table A6.7).

Antenatal prophylaxis (primigravidae only) + antenatal with indications + postpartum

The gross cost of prevention per life-year saved in comparison with postpartum administration is \$30,559, but this is reduced considerably to a range of \$15,000 to \$20,000 if direct cost savings are deducted from the gross cost of prevention.

The other results for this program are, however, potentially more interesting as they compare this strategy with either the antenatal prophylaxis (primigravidae only) or the antenatal with indications programs. In other words, they cast some light on the cost effectiveness of combining these two strategies in comparison with each strategy individually. The gross cost of prevention per life-year saved for this program combined with an antenatal with indications program is \$39,496, and is \$47,148 if added to a antenatal prophylaxis (primigravidae only) program. Deducting treatment cost savings reduces the cost per life life-year saved, but it always remains above \$20,000 even if all direct cost savings are deducted.

These costs per life-year saved are higher than for either program considered individually. The reason for this lies in the fact that the two programs overlap to some degree – the antenatal with indications program includes primigravidae with indications, while the antenatal prophylaxis (primigravidae only) encompasses this group also. When the two programs are combined, therefore, the cost of the combined program is less than the sum of the costs of each program individually, but the life-years saved from the combined program are also less than the sum of the life-years saved from the two programs individually (see Table A6.6).

Antenatal prophylaxis + postpartum

Antenatal prophylaxis for all Rh D negative pregnancies is associated with a gross cost of prevention per life-year saved of \$28,759 when compared with postpartum administration only. This cost per life-year saved falls to \$20,315 or \$16,526 if direct cost savings for mothers only, or for mothers and the affected infants, respectively are deducted.

Of more interest are the cost-effectiveness results for antenatal prophylaxis compared with the three foregoing selective antenatal programs, as these comparisons provide some insight into the costs and effects of extending any of the selective programs to a universal program (ie universal to all Rh D negative mothers). If universal antenatal prophylaxis is compared with the antenatal with indications program, the gross cost of prevention per life-year saved is \$31,636. Deduction of treatment cost savings reduces this figure to \$23,323 or \$19,223 depending upon the extent of the treatment cost savings deducted.

Comparison of universal antenatal prophylaxis with the other two selective programs produces more favourable results than this. Extending the antenatal prophylaxis for primigravidae only to all Rh D negative mothers saves years of life at a gross cost of prevention of \$30,441 per life-year saved. In comparison with the combined selective program, the corresponding cost per life-year saved is \$26,229. Again, these costs per life-year saved will be reduced by if treatment cost savings are offset against the cost of prevention as shown in the last two columns of Table A6.7.

Demand for anti-D

It is important to consider the implications of each of the five alternative prevention strategies for the demand for anti-D. The estimated number of vials demanded under each prevention strategy is presented in Table A6.8. With postpartum administration of anti-D only, the number of vials demanded per year is estimated to be nearly 25,000. If antenatal administration to Rh D negative women with indications is added to postpartum administration, the demand is projected to increase to around 43,000 vials per year. Antenatal prophylaxis for primigravidae added to postpartum administration increases this to nearly 72,000 vials per year. For the combined antenatal prophylaxis (primigravidae only)/antenatal with indications/postpartum program, demand increases to nearly 82,000 vials per year. Finally, if antenatal prophylaxis for all Rh D negative pregnancies is introduced along with postpartum administration, the number of vials demanded increases to nearly 129,000 per year.

It must be stressed that these estimates of demand are based on the optimal use of anti-D in each scenario. That is, they are based on ideal usage of anti-D under a range of assumptions rather than current real-life practice patterns. For this reason, these demand estimates are generally lower than one would expect based on the data on actual utilisation in Australia provided in Chapter 2 of this Report (see Section 2.2).

Ranking of programs

At the outset, it must be emphasised that, if the cost effectiveness of these programs is considered solely in terms of the gross cost of prevention, ie without any deductions for treatment cost savings, the resulting costs per life-year saved reflect 'worst case' scenarios. Even when viewed from this perspective, the cost per life-year saved of a universal antenatal prophylaxis/postpartum program suggests that it is a reasonable investment in economic terms. It also results in the greatest number of life-years saved in comparison with a 'postpartum only' program (see Table A6.6). This result is based on an average price per vial of anti-D of \$60, a price at which imported product is readily available. Hence, this analysis suggests that, even if the total demand for anti-D under an antenatal prophylaxis program was met from imported product, the program would be cost effective.

If, for whatever reason, the demand for Rh D immunoglobulin under antenatal prophylaxis cannot be satisfied with existing product sourced from either domestic or overseas suppliers this cost-effectiveness analysis could be used to provide a ranking of the alternative prevention programs.

From Table A6.7 it is evident that, on cost-effectiveness grounds, postpartum administration should receive first call on available supplies of anti-D. Given that postpartum administration is then ranked first, what program should be ranked second? In comparison with postpartum administration only, the antenatal with indications + postpartum program delivers additional years of life at the lowest cost per life-year saved with or without deductions for treatment cost savings. These two programs together are estimated to generate a demand of 43,000 vials per year.

Given that the antenatal with indications + postpartum program is ranked second, what program should be ranked third? The following conclusions can be derived from the results in Table A6.7:

- based only on the gross cost of prevention per life-year saved, the antenatal prophylaxis + postpartum program would be ranked third, followed by the primigravidae program (fourth); but
- if treatment cost savings are deducted from the gross cost of prevention, then regardless of whether the treatment cost savings pertain to mothers only or mothers and affected infants, the primigravidae program would be ranked third and universal antenatal prophylaxis would be ranked fourth.

Since it is highly likely that direct cost savings will be reaped, it can be argued that the antenatal prophylaxis for primigravidae only should be ranked third for implementation after postpartum administration and the antenatal with indications program. If this does not exhaust available supplies of anti-D, then antenatal prophylaxis can be extended to women not covered by the first three programs to the extent that the limited supply will allow.

Sensitivity analysis

In this section, the sensitivity of these results to changes in two variables used in the model is investigated. These two variables are: (a) the discount rate, which is changed from 5 per cent to 10 per cent; and (b) the price of a vial of anti-D, which is changed from \$60 to \$72 (this is the current price of the most expensive imported product available) and to \$45 (the price of the least expensive imported product).

The effect on the cost effectiveness of increasing the discount rate to 10 per cent is shown in Table A6.9. This results in a considerable increase in the cost per life-year saved for all four antenatal prevention programs (the postpartum program continues to be cost saving if treatment cost savings are deducted from the gross

cost of prevention). The incremental cost per life-year saved of a number of options now exceeds \$60,000.¹⁰ Under these circumstances, the estimates of indirect cost savings would become important in ascertaining the cost effectiveness of the various strategies.

The effect of changing the price of a vial of anti-D on the cost per life-year saved for the antenatal prophylaxis programs is shown in Table A6.10. The cost per life-year saved results are based on the gross cost of prevention less the direct cost savings associated with reduced Rh D isoimmunisation in mothers, ie they correspond to the results in the second column of Table A6.7. Clearly, the price variation has an impact on the cost per life-year saved, with higher prices of anti-D increasing the cost per life-year saved of all programs.

An interesting result is that, as the price of anti-D increases, the cost per life-year saved of the primigravidae program increases more rapidly than that of the universal program. At a price per vial of \$72, the cost per life-year saved of the former program is \$27,090 compared with \$27,204 for the latter. At a price not much greater than \$72, the universal program would actually have a cost per life-year saved which is less than for the primigravidae program, ie the rankings of these two programs would be reversed compared to the baseline results.

This may seem to be a counter-intuitive result, as the universal program results in a much larger number of women being given anti-D than the selective primigravidae program. It is true that any given increase in the price of anti-D will have a greater impact on the absolute cost of prevention under universal antenatal prophylaxis. But it has a greater proportionate impact on the cost of the primigravidae program, so that while cost effectiveness of both programs deteriorates as the price of anti-D increases, the cost effectiveness of the primigravidae program deteriorates more quickly.

¹⁰ The reason that the cost per life-year saved increases is that cost per life-year saved is obtained as a ratio of incremental costs to incremental life-years lived. Given that the incremental costs are incurred over a relatively short period of time (up to 6-8 years) while the life-years saved extend over 78 life-years (the life expectancy at birth), the higher discount rate has a much greater impact on the present value of life-years saved (which extend for a long period into the future) than on the incremental costs.

Conclusions

This appendix presents some results of a cost-effectiveness analysis of alternative prevention strategies for Rh D isoimmunisation in Australia. A number of the values of variables in the model are subject to some uncertainty. Nevertheless, the results suggest that any of the prevention programs could be defended on economic grounds. This is particularly so when it is considered that the estimates of direct costs of HDN used in this analysis may be conservative, as these direct cost estimates form the basis of the cost savings from the prevention of Rh D isoimmunisation.

The difficulty is that anti-D is in limited supply, and there may be insufficient quantities available for the program that generates the greatest demand for it, ie antenatal prophylaxis combined with a postpartum program. Without suggesting that any of the programs are necessarily uneconomical, the results of this analysis can be used to rank the various programs in view of the supply constraints.

In terms of cost per life-year saved, a postpartum program is clearly to be ranked first, followed by a targeted program of antenatal prophylaxis aimed at Rh D negative women with specified indications.

In considering which program might be ranked third, it should be borne in mind that the baseline results which underlie the suggested rankings are predicated on the price of a vial of anti-D of \$60. At this price, and taking into account the savings in direct costs associated with the treatment of mothers, the antenatal program for primigravidae only is ranked third on cost-effectiveness grounds, followed by the universal antenatal prophylaxis program for Rh D negative women. However, if the price of a vial of anti-D were to increase beyond \$72, the universal antenatal prophylaxis program would be ranked third.

In closing, it must be emphasised that the fourth place ranking (at a price per vial of \$60) should not be taken to imply that antenatal prophylaxis for all Rh D negative pregnancies with no preformed anti-D is economically inefficient in an absolute sense. As already mentioned, this program appears to be quite defensible on economic grounds. This conclusion accords with the view of the 1997 Edinburgh consensus conference panel on anti-D prophylaxis that there was no ethical or economic justification for limiting antenatal prophylaxis to Rh D negative primigravidae (Robson et al 1998).

If antenatal prophylaxis is not to be recommended because of supply constraints, this highlights the need to consider seriously options for increasing the supply of anti-D in the future to enable implementation of a universal antenatal prophylaxis program for all Rh D negative pregnant women.

Table A6.1 to Table A6.10 - and FIGURES 2, 3, and 4, are not available electronically. Please contact the NHMRC Publications Officer on:

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ACRONYMS AND ABBREVIATIONS

ACM	Australian College of Midwives
AFP	alpha-feto protein
AHEC	Australian Health Ethics Committee
ARCBS	Australian Red Cross Blood Service
CSL	formerly known as the Commonwealth Serum Laboratories
ECV	external cephalic version
ELAT	enzyme-linked antiglobulin test
FMH	fetomaternal haemorrhage
HbF	fetal haemoglobin
HDN	haemolytic disease of the newborn
HIV	human immunodeficiency virus
HTLV	human T-cell leukaemia virus
IEC	institutional ethics committee
ISBT	International Society of Blood Transfusion
LISS	low-ionic-strength additive solution
LYS	life-years saved
NHMRC	National Health and Medical Research Council
PEG	polyethylene glycol
RACOG	Royal Australian College of Obstetricians and Gynaecologists (now RANZCOG)
RANZCOG	Royal Australian and New Zealand College of Obstetricians and Gynaecologists
RBC	red blood cell
TPH	transplacental haemorrhage

GLOSSARY

Amniocentesis

Transabdominal perforation of the amniotic sac for the purpose of obtaining a sample of amniotic fluid that contains cells shed from the skin of the fetus as well as biochemical substances. Amniocentesis allows analysis of changes in chemical and cellular composition of the fluid to determine maturation and viability of the fetus. It also provides for prenatal diagnosis of certain genetically transmitted errors of metabolism, congenital abnormalities and chromosomal disorders.

Anti-D

Rh D immunoglobulin. Antibody against D antigen, the most immunogenic of the Rh antigens.

Chorionic villus sampling

A procedure used for prenatal diagnosis of trisomies, haemoglobinopathies and biochemical disorders of the fetus at 9–12 weeks gestation. Fetal tissue is aspirated by catheter through the cervix from the villous area of the chorion under ultrasound guidance.

Ectopic pregnancy

Pregnancy in which the fertilised ovum becomes implanted outside of the uterus instead of in the endometrium.

External cephalic version

Turning of the fetus by outside manipulation so that the head presents.

Haemolytic disease of the newborn (HDN)

A condition marked by excessive blood destruction in newborn infants, caused by transplacental transfer of antibodies produced by the mother in response to passage of incompatible blood from the fetal to the maternal circulation. Severe HDN leads to severe oedema, hepatosplenomegaly and severe anaemia, and may result in death in utero. In its milder form, HDN results in mild or moderate anaemia with jaundice shortly after birth. Also known as erythroblastosis fetalis.

Hydrops fetalis

Gross oedema of the entire body of the newborn infant.

Icterus gravis

Massive hepatic necrosis.

Isoimmunisation

Development of antibodies in response to isoantigens.

Plasmapheresis

The removal of plasma from withdrawn blood, with retransfusion of the formed elements into the donor.

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