

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



**NHMRC**

*National Health &  
Medical Research Council*

INVESTING IN AUSTRALIA'S HEALTH

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

**Approved by the National Health and Medical Research Council  
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## SUMMARY

In 1999, the National Health and Medical Research Council published guidelines aiming to balance best practice in the use of Rh D immunoglobulin with the limited supply. While the Working Party found that universal prophylaxis with Rh D immunoglobulin to Rh D negative women at 28 and 34 weeks gestation is generally regarded as best practice, it was unable to recommend antenatal prophylaxis due to supply constraints at that time.

Since the 1999 guidelines were issued, there have been a number of developments which have increased the supply of Rh D immunoglobulin in Australia, although self-sufficiency has not yet been reached. A 250 IU (50 µg) dose of Rh D immunoglobulin was introduced in May 2001, and its use in potentially sensitising events in the first trimester should ensure more efficient use of existing supply. In addition, an overseas product was approved for use in Australia in October 2002, to ease pressure on the domestic supply until self-sufficiency can be reached, and additional funding was provided to the Australian Red Cross Blood Service (ARCBS) to recruit more anti-D donors and to conduct primary immunisation and boosting of existing donors.

In 2001 the Working Party was reconvened to review the guidelines, particularly in regard to antenatal prophylaxis. Based on the results of an updated literature review and assessment of progress towards self-sufficiency in Rh D immunoglobulin, a range of recommendations have been made for the staged implementation of full antenatal prophylaxis. The amended guidelines will be used to implement a multi-faceted strategy for securing future supply, which includes measures to increase domestic production of Rh D immunoglobulin, as well as wide-ranging communication and education to promote its most appropriate use.

This report is intended to update rather than replace the guidelines released in 1999. It aims to inform clinicians, other health professionals and policy makers about changes to the previous guidelines and new recommendations for use of Rh D immunoglobulin in Australia. These recommendations should be reviewed within five years, according to the availability of Rh D immunoglobulin.



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## SUMMARY OF RECOMMENDATIONS

### Clinical indications and dosage – Rh D immunoglobulin

The Working Party has made a range of recommendations on the clinical indications for Rh D immunoglobulin, including postpartum administration, antenatal administration for indications, and the staged implementation of full antenatal prophylaxis. The recommendations take into account the results of an updated literature review and the current and projected future supply of Rh D immunoglobulin. The recommended doses aim to ensure that all Rh D negative women are adequately protected from immunisation against Rh D positive blood.

### Summary of dosing recommendations for Rh D negative pregnant women

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	Rh D immunoglobulin
<i>Obstetric conditions</i>	
Sensitising events in the first trimester	250 IU (50 µg)
Sensitising events beyond the first trimester	625 IU (125 µg)
<i>Pregnancy</i>	
Antenatal prophylaxis (28 and 34 weeks for first pregnancy)	625 IU (125 µg)
<i>Postpartum</i>	600 IU (120 µg)*

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\* In the short to medium term, imported product should be used for this indication to ease the pressure on the domestic supply of Rh D immunoglobulin. At the time of writing, the only imported product registered for use in Australia is presented as a 600 IU (120 µg) preparation.

### General

- For successful immunoprophylaxis, Rh D immunoglobulin should be administered as soon as possible after the sensitising event, but always within 72 hours (level I evidence). If Rh D immunoglobulin has not been offered within 72 hours, a dose offered within 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 (FMH). Where FMH quantitation shows that FMH greater than that covered by the dose already administered has occurred, administration of an additional dose/s sufficient to provide immunoprophylaxis must be administered and preferably within 72 hours.

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### **Sensitising events in the first trimester**

- A dose of 250 IU (50 µg) Rh D immunoglobulin should be offered to every Rh D negative woman with no preformed anti-D to ensure adequate protection against immunisation for the following indications up to and including 12 weeks gestation (level IV evidence):
  - miscarriage;
  - termination of pregnancy;
  - ectopic pregnancy; and
  - chorionic villus sampling.
- A dose of 250 IU (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) (level IV evidence).
- The Working Party strongly recommends that women undergoing termination of pregnancy be tested to determine whether they are Rhesus factor positive or negative, to avoid unnecessary use of Rh D immunoglobulin.
- There is insufficient evidence to support the use of Rh D immunoglobulin in bleeding prior to 12 weeks gestation in an ongoing pregnancy, although if the pregnancy then requires curettage Rh D immunoglobulin should be given. If miscarriage or termination occurs after 12 weeks gestation, 625 IU (125 µg) Rh D immunoglobulin should be offered.

### **Sensitising events beyond the first trimester**

- Although some of the recent evidence related to the use of immunoprophylaxis is based upon studies of potentially sensitising events occurring up to 20 weeks gestation, for practical purposes the Working Party recommends that a dose of 250 IU (50 µg) be used for the first trimester events (up to and including 12 weeks gestation) and 625 IU (125 µg) be used beyond first trimester. Future revisions of these guidelines may, in the face of further evidence extend the use of the 250 IU (50 µg) dose beyond 12 weeks gestation.
- A dose of 625 IU (125 µg) Rh D immunoglobulin should be offered to every Rh D negative woman with no preformed anti-D to ensure adequate protection against immunisation for the following indications after 12 weeks gestation (level IV evidence):
  - genetic studies (chorionic villus sampling, amniocentesis and cordocentesis);
  - abdominal trauma considered sufficient to cause fetomaternal haemorrhage;

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- 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);
  - external cephalic version (performed or attempted); and
  - miscarriage or termination of pregnancy.
- 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 of Rh D immunoglobulin administered if required, especially where transplacental access or puncture of fetal blood vessels occurs.

### **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 (level II evidence).
- With current availability of Rh D immunoglobulin the Working Party is able to recommend administration of 625 IU (125 µg) Rh D immunoglobulin at 28 and 34 weeks in all Rh D negative primigravidae with no preformed antibodies. It is anticipated that full antenatal prophylaxis will be able to be implemented when domestic supplies of Rh D immunoglobulin increase sufficiently to cover that increased demand.

### **Postpartum**

- Rh D immunoglobulin should be offered to every Rh D negative woman following delivery of an Rh D positive baby (level I evidence). In the short to medium term, the Working Party recommends that imported product (currently available as a 600 IU [120 µg] dose) be used for this indication, to ease pressure on domestic supply of Rh D immunoglobulin.
- 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. If it is unclear whether the anti-D detected in the mother's blood is passive or preformed, the treating clinician should be consulted. If there is continuing doubt, Rh D immunoglobulin should be administered.
- The magnitude of the fetomaternal haemorrhage should be assessed by a method capable of quantifying a haemorrhage of  $\geq 6$  ml of fetal red cells (12 ml of whole blood). Further doses should be administered sufficient to prevent maternal immunisation.

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## Pathology testing

- The following recommendations are supported by the literature review and are in accordance with the Australian and New Zealand Society of Blood Transfusion (ANZSBT) *Guidelines for Laboratory Assessment of Fetomaternal Haemorrhage* (2002):
  - for potentially sensitising events that occur after the first trimester a maternal sample should be taken prior to administration of Rh D immunoglobulin to assess the volume of fetomaternal haemorrhage (FMH). However, at no time should a single dose of Rh D immunoglobulin be withheld based upon, or pending, the results to quantitate FMH.
  - flow cytometry is accepted as the most accurate quantitative test for FMH and is the method of choice for quantitation if readily available. However, until flow cytometry becomes more widely available the following recommendations must be ensured:
    - laboratories undertaking quantitative assessment of FMH by any method must show acceptable performance in internal and external quality assurance programs and have clearly defined test methods, continuing assessment protocols and documented staff training programs to ensure accuracy and reproducibility of results;
  - results should be reported in a format that allows easy correlation with product inserts of locally available Rh D immunoglobulin;
  - where FMH quantitation shows that fetomaternal haemorrhage greater than that covered by the dose already administered has occurred, administration of an additional dose/s of Rh D immunoglobulin sufficient to provide immunoprophylaxis must be administered and preferably within 72 hours.
    - for large bleeds follow up testing should be performed on a sample collected 48 hours post Rh D immunoglobulin administration, to determine if further dosing is required. Supplemental Rh D immunoglobulin should be administered if:
      1. FMH is still positive; and
      2. Rh D immunoglobulin is not detected in maternal plasma by IAT (indirect antiglobulin test).
- In the absence of evidence to the contrary, IAT testing should be used in Rh D negative women for detection of antibodies.

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## **Securing supply**

- The importation of Rh D immunoglobulin initially will allow a staged process towards full antenatal prophylaxis. Such a product should continue to be imported in adequate quantities to support the staged introduction of universal antenatal prophylaxis until self-sufficiency is reached.
- The program of immunisation of new Rh D immunoglobulin donors by the Australian Red Cross Blood Service should be maintained. Procedures for providing information to potential donors and obtaining their voluntary consent should be in place.
- CSL Bioplasma and the Australian Red Cross Blood Service should continue to pursue ways of increasing anti-D plasma supply, including:
  - increasing the number of donors recruited to the Rh Project, particularly donors who are willing to undergo primary immunisation;
  - recruiting donors with high levels of anti-D due to prior transfusion or pregnancy; and
  - increasing the yield of Rh D immunoglobulin from the anti-D plasma collected.
- Consideration could be given to investigating the appropriate dose of Rh D immunoglobulin at 28 weeks only as an alternative to a dose at both 28 and 34 weeks gestation.

## **Communication and education**

- These revised guidelines should be widely distributed to health professionals accompanied by an appropriate ongoing communication and education program that addresses:
  - use of the 250 IU (50 µg) dose in first trimester sensitising events;
  - the safety of Rh D immunoglobulin from all sources;
  - education for health professionals in areas where at-risk women may present (ie accident and emergency and general practice settings);
  - accurate, up-to-date information for Rh negative women so that they can make informed choices about the risks and benefits of Rh D immunoglobulin and be involved in their own Rh D immunisation prevention program; and
  - increasing awareness in pathology departments about the shelf life (currently one year) of Rh D immunoglobulin, to ensure product is rotated and used prior to its expiry.



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# INTRODUCTION

## Background

As indicated in the summary section at the beginning of this report, the 1999 NHMRC Working Party recommended the rapid development and implementation of short and long-term strategies to promote the most efficient use of existing supply and to identify a sustainable means of increasing supply to meet demand. These included:

- use of 250 IU (50 µg) of Rh D immunoglobulin for potentially sensitising events in the first trimester;
- increased and more accurate use of tests to assess the amount of fetomaternal haemorrhage;
- development and implementation of a strategy for self-sufficiency in Rh D immunoglobulin in Australia; and
- development and implementation of a communication and education plan to promote compliance with guidelines on Rh D immunoglobulin use.

The 1999 Working Party also recommended that the guidelines be regularly reviewed and amended according to the availability of supplies of Rh D immunoglobulin.

In 2001 the Working Party was reconvened to review and amend the guidelines for full antenatal prophylaxis, given the developments in supply. A literature search was commissioned to update the evidence base for the guidelines and the cost-effectiveness data were also reviewed. Based on the results of the literature review and the Working Party's knowledge of current supply, a range of recommendations have been made for the staged implementation of full antenatal prophylaxis.

## Scope of this report

This report is intended to update rather than replace the guidelines released in 1999. It aims to inform clinicians, other health professionals and policy makers about changes to the previous guidelines and new recommendations for usage of Rh D immunoglobulin in Australia. It is recommended that the guidelines be reviewed within five years, according to the availability of Rh D immunoglobulin.

- Chapter 1 summarises the rationale for the recommendations. This includes the evidence base for the guidelines, which comes from the results and recommendations of the updated literature review, and the results of the updated cost-effectiveness study.

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- Chapter 2 discusses the strategy developed and being implemented by ARCBS and CSL Bioplasma to increase domestic supply of Rh D immunoglobulin and promote more efficient use of existing supplies, in order to eventually regain self-sufficiency. A summary of the staged strategy for implementation of antenatal prophylaxis is also given.
  - Chapter 3 outlines the communication and education strategy being put into place to disseminate the guidelines and promote their widespread implementation.

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# 1 BASIS FOR GUIDELINE RECOMMENDATIONS

For the original guidelines (NHMRC 1999), the Working Party based its recommendations for most appropriate use of Rh D immunoglobulin on a review of the literature, a cost-effectiveness analysis, and consideration of the current supply of Rh D immunoglobulin. For this report, the Working Party asked that a further review of the literature be undertaken so that revision of the guidelines could be based on the most current evidence, and that the cost-effectiveness data be re-examined. This chapter presents the findings of both the updated literature review and cost-effectiveness analysis.

## 1.1 Evidence base for use of Rh D immunoglobulin

The findings and recommendations of the updated literature review are given below. The search strategy is outlined in Appendix C<sup>1</sup>. The methods and results of the literature review undertaken for the original guidelines are described in that report (NHMRC 1999).

### Sensitising events in the first trimester and beyond

Rh D immunoglobulin 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, invasive genetic studies for prenatal diagnosis such as amniocentesis and chorionic villus sampling, external cephalic version, trauma and antepartum haemorrhage.

No controlled trials were identified by the literature search.

#### *Miscarriage and termination of pregnancy*

The Rh D antigen has been identified on fetal erythrocytes as early as 38 days gestation (Bergstrom et al 1967), but there is doubt concerning the risk of sensitisation associated with bleeding before 12 weeks in an ongoing pregnancy or spontaneous abortion before 12 weeks (Anonymous 1999a; Lee et al 1999).

On the basis of this evidence, Rh D immunoglobulin can be recommended following therapeutic abortion, following curettage to remove products of conception and where bleeding occurs in an ongoing pregnancy (level IV evidence). The evidence suggests that the dose should be at least 250 IU (50 µg) up to and including 12 weeks. (Anonymous 1999a; Lee et al 1999).<sup>2</sup>

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<sup>1</sup> The literature review was conducted under the supervision of Dr James King of the Mater Perinatal Epidemiology Unit, Brisbane.

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### *Ectopic pregnancy*

On the basis that sensitisation has been shown to occur in Rh D negative women following ectopic pregnancy, Rh D immunoglobulin can be recommended for patients with an ectopic pregnancy (level IV evidence). The evidence suggests that the dose should be at least 250 IU (50 µg) (Anonymous 1998a; Lee et al 1999).<sup>2</sup>

### *Invasive prenatal diagnosis*

On the basis that sensitisation has been shown to occur in Rh D negative women following invasive genetic studies for prenatal diagnosis, Rh D immunoglobulin can be recommended for patients undergoing invasive prenatal diagnostic tests including chorionic villus sampling, amniocentesis and cordocentesis (level III evidence).

Although some of the recent evidence related to the use of immunoprophylaxis is based upon studies of potentially sensitising events occurring up to 20 weeks gestation, (Anonymous 1999a; Lee et al 1999; Sikovanyecz et al 2001) for practical purposes the Working Party recommends that a dose of 250 IU (50 µg) be used for the first trimester events (up to and including 12 weeks gestation) and 625 IU (125 µg) be used beyond first trimester. Estimations in excess of 4 ml fetomaternal haemorrhage will require an additional dose of Rh D immunoglobulin. Future revisions of these guidelines may, in the face of further evidence extend the use of the 250 IU (50 µg) dose beyond 12 weeks gestation.

### *External cephalic version*

External cephalic version near the end of pregnancy has been shown to impose a significant disturbance to the maternal-placental interface (Lau et al 2000). A significant increase in the concentration in fetal deoxyribonucleic acid in maternal serum after external cephalic version has been demonstrated (Lau et al 2000).

On the basis of this evidence, Rh D immunoglobulin can be recommended in patients following an external cephalic version, whether the procedure has been successful or not (level III evidence) (Lau et al 2000; Anonymous 1999a; Lee et al 1999). The evidence

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<sup>2</sup> The Working Party recommendation is for a dose of 250 IU (50 µg) Rh D immunoglobulin in the first trimester and the higher dose of 625 IU (125 µg) beyond the first trimester (see pages vii to viii).

suggests that the dose should be at least 500 IU (100 µg) after maternal blood has been taken for an estimation of volume of fetomaternal haemorrhage. Estimations in excess of 4 ml fetomaternal haemorrhage will require an additional dose of Rh D immunoglobulin.

#### *Abdominal trauma*

Sensitisation has been shown to occur in Rh D negative women following abdominal trauma.

On the basis of this evidence, Rh D immunoglobulin can be recommended in pregnant women following abdominal trauma (level IV evidence) (Anonymous 1999a; Lee et al 1999). The evidence suggests that the dose should be at least 250 IU (50 µg) before 20 weeks and at least 500 IU (100 µg) after 20 weeks.<sup>3</sup> Maternal blood should be tested for an estimation of volume of FMH. Estimations in excess of 4 ml will require an additional dose of Rh D immunoglobulin.

#### *Antepartum haemorrhage*

Sensitisation has been shown to occur in Rh D negative women following second or third trimester antepartum haemorrhage.

On the basis of this evidence, Rh D immunoglobulin can be recommended for patients with antepartum haemorrhage (level IV evidence) (Anonymous 1999a; Duguid 1997; Lee et al 1999).

The evidence suggests that the dose should be at least 500 IU (100 µg) after maternal blood has been tested for an estimation of volume of fetomaternal haemorrhage. Estimations in excess of 4 ml will require an additional dose of Rh D immunoglobulin.

#### *Antenatal prophylaxis*

The issue of routine antenatal Rh D immunoglobulin administration is not as clear as that of postnatal administration. There is no level I evidence to support the routine administration of Rh D immunoglobulin antenatally to all unsensitised Rh D negative women at any gestation. However, there is considerable lower level evidence supporting the efficacy of this practice.

<sup>3</sup> The Working Party recommendation is for a dose of 250 IU (50 µg) Rh D immunoglobulin in the first trimester and the higher dose of 625 IU (125 µg) beyond the first trimester (see pages vii to viii).

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The 1999 NHMRC guidelines concluded that routine antenatal prophylaxis at 28 and 34 weeks gestation was best practice, but that limited supplies of Rh D immunoglobulin at that time, did not allow its introduction in Australia. This finding has been reconsidered due to changes in the supply and use of Rh D immunoglobulin since then.

The literature search found no new randomised or other controlled trials.

The best evidence (level II) on antenatal use of Rh D immunoglobulin comes from the Cochrane Database of Systematic Reviews (Crowther 2001). A substantive amendment to the review was made in January 1999. The review looked at all published and unpublished randomised controlled trials involving the Cochrane Pregnancy and Childbirth Group trials register, the Cochrane Controlled Trials Register, and extensive bibliographies.

The Cochrane review assessed the effects of antenatal Rh D immunoglobulin and the incidence of subsequent Rh D immunisation when given to Rh D negative women without Rh D immunoglobulin antibodies, at 28 weeks or more of pregnancy.

Only two trials were considered eligible for consideration, involving over 4,500 women, in which Rh D immunoglobulin prophylaxis was compared with no treatment. The data suggested a reduced incidence of immunisation:

- during pregnancy (odds ratio [OR] 0.44, 95% CI 0.18-1.12);
- after the birth of an Rh positive infant (OR 0.44, 95% CI 0.18-1.12); and
- within 12 months after birth of an Rh positive infant (OR 0.44, 95% CI 0.19-1.01).

In women who received Rh D immunoglobulin at 28 and 34 weeks gestation, none of these differences were statistically significant.

However, in the trial which used the larger dose of Rh D immunoglobulin (Tovey et al 1983) (500 IU [100 µg], rather than 250 IU [50 µg]), there was a clear reduction in the incidence of immunisation at 2-12 months following birth in women who had received Rh D immunoglobulin at 28 and 34 weeks (OR 0.22, 95% CI 0.05-0.88). No data were available for the risk of Rh D immunisation in a subsequent pregnancy. No differences were observed in the incidence of neonatal jaundice. In the controlled trial of 500 IU (100 µg) at 28 and 34 weeks, the incidence of immunisation was reduced to 0.2 per cent, indicating that this dosage is likely to be as effective as larger doses (Tovey et al 1983).

Consistent with this finding, a non-Cochrane systematic review reported that pooled data from randomised and non-randomised studies suggested no

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reduction in the rate of immunisation among patients treated with 1,500 IU (300 µg) compared to those treated with 500 IU (100 µg) at 28 and 34 weeks or at 28 weeks gestation (Allaby et al 2001). The currently available Australian product is available as 625 IU (125 µg) Rh D immunoglobulin.

On the basis of this evidence, antenatal prophylaxis with at least 500 IU (100 µg) Rh D immunoglobulin at 28 and 34 weeks can be recommended for Rh D negative women with no preformed antibodies (level II evidence). The Australian product recommended for use in antenatal prophylaxis contains 625 IU (125 µg), which is an appropriate dose.

The Cochrane Review concluded that adoption of this policy (of antenatal prophylaxis at 28 and 34 weeks) would need to consider the costs of prophylaxis against the costs of care for women who become sensitised and their affected infants, and adequacy of the local supply of Rh D immunoglobulin.

### Postpartum administration

There is very strong evidence, from the late 1960s onwards, that the practice of administering Rh D immunoglobulin postpartum has dramatically reduced the incidence of immunisation and of HDN. Postpartum administration of Rh D immunoglobulin 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.

In the review of the literature, no new randomised controlled trials were identified. The best evidence (level I) on the postpartum use of Rh D immunoglobulin comes from the Cochrane Database of Systematic Reviews (Crowther & Middleton 2001). The last substantive amendment to the Cochrane review of postpartum use of Rh D immunoglobulin was made in February 1997. The review looked at all published and unpublished randomised controlled trials involving the Cochrane Pregnancy and Childbirth Group Trials Register, the Cochrane Controlled Trials Register, and extensive bibliographies.

Six randomised controlled trials in which postpartum Rh D immunoglobulin prophylaxis was compared with no treatment or placebo were considered eligible for analysis. The trials involved over 10,000 women, but trial quality varied.

Rh D immunoglobulin lowered the incidence of Rh D immunisation six months after birth (relative risk 0.04, 95% confidence interval [CI] 0.02–0.06),

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and in a subsequent pregnancy (relative risk 0.12, 95% CI 0.07–0.23). These benefits were seen regardless of the ABO status (blood group) of the mother and baby, when Rh D immunoglobulin was given within 72 hours of birth. Higher doses (up to 1,000 IU [200 µg]) were more effective than lower doses (up to 250 IU [50 µg]) in preventing Rh D immunisation in a subsequent pregnancy.

On the basis of this evidence, Rh D immunoglobulin can be recommended for routine postpartum prophylaxis in Rh D negative women with no preformed antibodies following birth of an Rh D positive infant (level I evidence).

In Australia a dose of 625 IU (125 µg) is currently recommended for prophylaxis within 72 hours of delivery. There is insufficient evidence in the literature to recommend changing this dosage for routine prophylaxis, although in a circumstance of liberal supply, a higher dosage (ie 1,250 IU [250 µg]) could be justified.

Administration of 100 IU (20 µg) Rh D immunoglobulin has been demonstrated to protect against 1 ml of fetal red cells or 2 ml of whole blood. Therefore 500 IU (100 µg) should protect against fetomaternal haemorrhage of up to 5 ml of fetal red cells and 1,500 IU (300 µg) Rh D immunoglobulin against fetomaternal haemorrhage of approximately 15 ml of fetal red cells. A fetomaternal haemorrhage of 30 ml or more can occur in approximately 0.6 per cent of births (Zipursky 1977).

On the basis of this evidence, it is recommended that a maternal sample be taken prior to the administration of Rh D immunoglobulin for assessment of FMH. Additional doses of Rh D immunoglobulin should be administered as indicated by assessment of the volume of FMH.

The Cochrane Reviewers highlighted the following implications for research in this area:

As the evidence on the optimal amount of Rh D immunoglobulin to recommend for postpartum prophylaxis is limited, further good quality comparative trials would be appropriate. In particular, the cost-effectiveness of smaller doses of Rh D immunoglobulin, combined with screening for the degree of fetomaternal haemorrhage and administering additional Rh D immunoglobulin as necessary, should be compared with the use of larger doses of Rh D immunoglobulin. In further trials, the attitudes of women towards Rh D immunoglobulin prophylaxis and the health of infants born in subsequent pregnancies should be evaluated. Any adverse effects of the treatment, including sensitivity reactions and transmission of infectious diseases, should be documented.

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## Update on risks and/or disadvantages of Rh D immunoglobulin

A search of the literature for new evidence on the risks of Rh D immunoglobulin showed the following.

### *The effect of circulating prophylactically administered Rh D immunoglobulin in the fetal circulation*

One study was found that evaluated signs of haemolysis in babies of Rh D negative mothers who underwent prophylaxis with one or two doses of Rh D immunoglobulin during pregnancy (Maayan-Metzger et al 2001). No statistically significant differences were found for any of the haematological variables between the babies of mothers who received one or two doses of Rh D immunoglobulin, or between the Rh D negative babies and the controls. Therefore the literature search failed to find any new evidence for concern about fetal effects of prophylactic Rh D immunoglobulin (either one or two doses).

### *The risk of transmission of infectious organisms by administering Rh D immunoglobulin*

Rh D immunoglobulin is derived from pooled donor plasma and therefore carries the potential of transmission of viral or other infectious organisms. The literature was searched for evidence of transmission of infection via the use of Rh D immunoglobulin.

In February 1994, batches of Rh D immunoglobulin used in Ireland during 1977 and 1978 to prevent Rh isoimmunisation were found to be contaminated with hepatitis C virus (HCV) from a single infected donor (Kenny-Walsh 1999). In March 1994, a national screening program was initiated for all women who had received Rh D immunoglobulin between 1970 and 1994. Of the 62,667 women who had been screened when this study began, 704 (1.1 per cent) had evidence of past or current HCV infection, and 390 of those 704 (55 per cent) had positive tests for serum HCV RNA on reverse-transcription-polymerase-chain-reaction analysis (Kenny-Walsh 1999).

With the subsequent introduction of a range of safety features including careful donor selection, plasma testing, solvent-detergent viral inactivation and nanofiltration, no further instances of transmission of infectious disease have been reported.

No evidence was found of this problem from any other country, and specifically none were found from the United Kingdom, Canada, the United States or Australia.

Evidence was sought to evaluate the safety of the imported Rh D immunoglobulin product. This product is manufactured with multiple

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processes to minimise the risk of transmitting blood-borne diseases such as viruses. There have not been any cases of viral transmission in association with the use of this imported product (Hong et al 1998).

*Update on the most appropriate means of quantifying the volume of fetal red cells in the maternal circulation*

There are a number of tests available to assess the volume of fetomaternal haemorrhage and allow additional Rh D immunoglobulin 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 fetomaternal haemorrhage.

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

A number of studies were identified comparing Kleihauer testing with flow cytometry with the following findings.

- Flow cytometry seems to have a number of advantages in that results are more accurate and more reproducible than those of the Kleihauer test (Anonymous 1999b; Fung et al 1998; Nelson et al 1998a). Flow cytometry detects Rh D positive cells that have been relabelled using an anti-D reagent (Anonymous 1999b).
- Kleihauer testing appears to be precise only in small volumes of transplacental haemorrhage (Lee et al 1999). It gives quantitative results but is open to interpretation by the technician performing the test, which has resulted in a number of cases of inaccurate results. The experience of the technician performing the test plays a major role in the success of the test. In addition, Kleihauer testing involves identification of haemoglobin F (HbF), which may lead to false positive results in the presence of inherited conditions resulting in elevated levels of HbF in adult circulation.

One study evaluated an indirect immunofluorescence flow cytometry technique in a series of patients with large fetomaternal haemorrhage and compared the results with those produced by the Kleihauer acid elution test (Johnson et al 1995). Patient samples identified by Kleihauer testing in local laboratories as having fetomaternal haemorrhage greater than 4 ml were sent

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for flow cytometric analysis. Forty-three cases of fetomaternal haemorrhage were studied. The correlation between Kleihauer and flow cytometry results was poor. Centralised review of the original Kleihauer films using a calibrated microscope resulted in improved, but still suboptimal correlation with flow cytometry results. In 15 cases in which Rh D immunoglobulin was given according to the flow cytometer estimation of fetomaternal haemorrhage size, there was a 58 per cent reduction in the amount of Rh D immunoglobulin given. None of the patients were immunised when tested six months later.

Recent studies confirm the earlier finding that flow cytometry is the most accurate quantitative test for assessing fetomaternal haemorrhage. However, it remains more expensive and not as widely available as the Kleihauer test. This is particularly problematic in smaller regional-based health facilities where hospital budgets are already limited.

Laboratories undertaking quantitative assessment of fetomaternal haemorrhage by any method must show acceptable performance in internal and external quality assurance programs and have clearly defined test methods, continuing assessment protocols and documented staff training programs to ensure accuracy and reproducibility of results.

## **1.2 Cost-effectiveness analysis**

The analysis for the 1999 guidelines investigated the cost-effectiveness of six alternative policies for administration of Rh D immunoglobulin (NHMRC 1999). As the intention of the guidelines is progression towards full antenatal prophylaxis, the updated analysis focused on the effect of the price of Rh D immunoglobulin on the cost-effectiveness of its use both postpartum and antenatally. This was to examine whether full antenatal prophylaxis remains cost-effective at varying costs of Rh D immunoglobulin (imported and domestic supply) as well as being indicated by current evidence.

The model used in the analysis was that developed for the NHMRC guidelines.<sup>4</sup> Results are provided for the cost per life-year saved with and without any treatment cost savings deducted. When treatment cost savings are deducted, they are confined to the treatment costs that would have been incurred because of the additional maternal and neonatal resources required when Rh D negative women develop anti-D antibodies during pregnancy or birth. No results are presented on years lived with disability due to long-term sequelae of HDN.

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<sup>4</sup> Full details of this model have been published elsewhere (see Butler & Howarth 1999)

## Costs of prevention and care

- *Maternal and neonatal care* - the estimate used in the previous report (taken from the study by Vick et al [1996]) was adjusted for inflation by updating the previous estimate of \$4,530 to 2000 prices using the Consumer Price Index (Australian Bureau of Statistics 2001). The resulting treatment cost estimates are shown in Table 1.1.
- *Tests* - the unit costs of tests relating to antenatal and postpartum administration of Rh D immunoglobulin were updated for the present report using the Medicare Benefits Schedule released in November 2000. These updated costs are also shown in Table 1.1.

**Table 1.1 Unit costs of prevention and treatment for Rh D isoimmunisation (Australian dollars, 2000 prices)**

	Pregnancy			
	1 <sup>st</sup>	2 <sup>nd</sup>	3 <sup>rd</sup>	4 <sup>th</sup>
Cost of treating Rh D isoimmunisation in pregnant women				
<i>Cost per Rh D isoimmunisation in pregnant women</i>				
Undiscounted	4,960	4,960	4,960	4,960
Discounted (r = 5%)	4,960	4,285	3,886	3,525
Cost of testing related to prevention				
<i>Cost of testing for postpartum administration</i> *				
Undiscounted	62	62	62	62
Discounted (r = 5%)	62	53	48	44
<i>Cost of testing for antenatal administration</i> #				
Test for Rh status				
Undiscounted	11	11	11	11
Discounted (r = 5%)	11	9	9	8
Test for circulating antibodies				
Undiscounted	40	40	40	40
Discounted (r = 5%)	40	35	32	29

\* Test mother for circulating antibodies (MBS item no. 65096, schedule fee (s.f.) \$40.40); Kleihauer test (item no. 65066, s.f. \$10.25); determine Rh status of baby (item no. 65090, s.f. \$10.90).

# Determine Rh status of mother (item no. 65090, s.f. \$10.90); test mother for circulating antibodies (item no. 65096, s.f. \$40.40).

Sources: Updated from Butler & Howarth (1999; Table A6.2) using Medicare Benefits Schedule issued in November 2000 and ABS Consumer Price Index at 30 June 1995 and 30 June 2000 (All Groups, weighted average of eight capital cities).

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- *Rh D immunoglobulin* - the price of Rh D immunoglobulin is an important component of the cost of prevention and is the focus of the analysis. In the earlier study, results were presented for prices of Rh D immunoglobulin of \$45, \$60 and \$72. The various preventive strategies considered were all found to be cost-effective across this range of prices.

These prices were based upon the use of a 625 IU (125 µg) vial in all programs. While a 250 IU (50 µg) vial is now available, the current analysis assumes that the price of the 250 IU (50 µg) vial is the same as the price of the 625 IU (125 µg) vial. The prices used in the earlier analyses reflected the price of domestically produced Rh D immunoglobulin. As the price of imported product may be higher than \$72, a re-evaluation of the cost-effectiveness is needed if imported product is used to augment domestic product in the prevention program.

The model does not allow for the direct calculation of cost-effectiveness using two different prices for Rh D immunoglobulin in the one strategy (one price for domestic and one price for imported product). However, this limitation can be overcome by interpreting the price used in the model as a weighted mean price of Rh D immunoglobulin, where the weights are the proportions of total Rh D immunoglobulin requirements sourced from domestic or foreign sources. For example, if imported product is used in the postpartum program and domestic product in the antenatal prophylaxis program, then the proportions of total Rh D immunoglobulin requirements that need to be imported can be ascertained from the model and used to calculate the mean price. The previous analysis indicated that the postpartum component of the prevention program gave rise to around 20 per cent of the total demand for Rh D immunoglobulin in the program embracing antenatal prophylaxis and postpartum administration (Butler & Howarth 1999; Table A6.8).

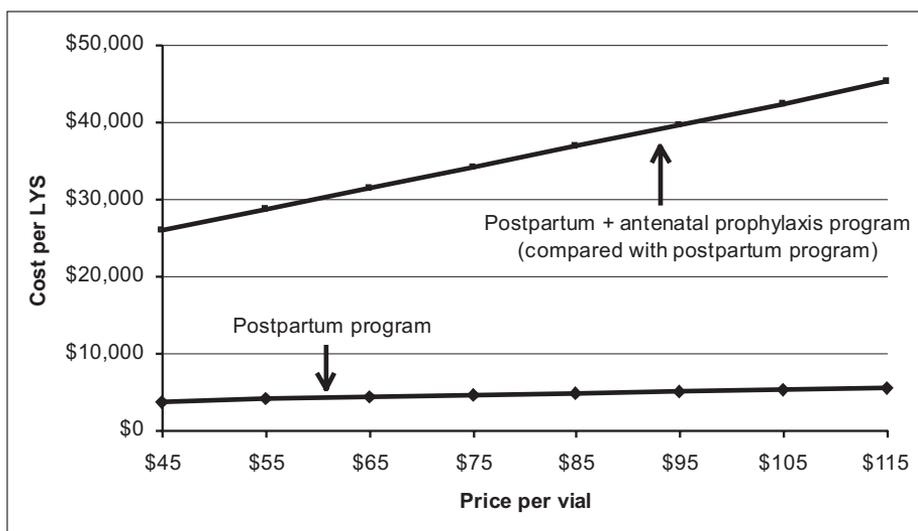
## **Results**

### **Without treatment cost savings deducted**

The costs per life-year saved for various prices of Rh D immunoglobulin for the two programs considered are shown in Figure 1.1. These results have no treatment cost savings deducted from the costs of the prevention programs.

In these analyses, the postpartum program is compared with 'no Rh D immunoglobulin given'. Even at a price of \$115 per vial, the cost per life-year saved in this program remains well below \$10,000. The incremental cost per life-year saved of adding the antenatal prophylaxis program to the postpartum program ranges from \$26,000 (at a price per vial of \$45) up to \$45,000 (at a price per vial of \$115). When it is considered that drugs with a cost per life-year saved of up to \$50,000 are commonly listed on the Pharmaceutical

**Figure 1.1 Cost per life-year saved for postpartum program, and postpartum plus antenatal prophylaxis program – no treatment cost savings deducted\***



\* The cost effectiveness results of the postpartum plus antenatal prophylaxis program are incremental costs per life-year saved compared with the postpartum program.

Benefits Scheme in Australia (George et al 1998), antenatal prophylaxis appears to be a cost-effective addition to a postpartum program even at a relatively high price of Rh D immunoglobulin of \$115 per vial.

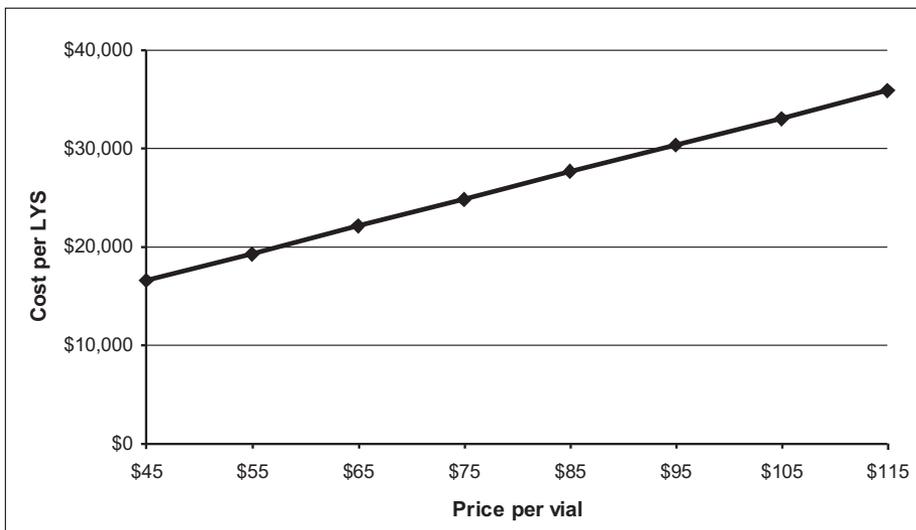
Depending upon the extent of reliance on imported product in the prevention program, the price per vial shown in Figure 1.1 may reflect a considerably higher price for imported product. For example, if domestic product is priced at \$75 per vial and is used to supply 80 per cent of total Rh D immunoglobulin requirements, then the price of imported product consistent with an average price of, say, \$95 is \$175 ( $= 0.8 \times \$95 + 0.2 \times \$175$ ). Alternatively, even if all Rh D immunoglobulin requirements for the programs were satisfied with imported product at \$95 per vial, the incremental cost per life-year saved for antenatal prophylaxis is \$40,000.

Finally, the price per vial at which the incremental cost per life-year saved for antenatal prophylaxis reaches \$50,000 is \$133. Again, depending upon the extent of reliance on imported product in the program, this could be consistent with a much higher price per vial for the imported product.

### With treatment cost savings deducted

Deducting treatment cost savings from the cost of prevention in calculating the cost-effectiveness results reduces the cost per life-year saved and enhances the cost-effectiveness of the two programs. The relevant results are shown in Figure 1.2.

**Figure 1.2 Cost per life-year saved for postpartum plus antenatal prophylaxis program – treatment cost savings deducted\***



\* These results are incremental costs per life-year saved compared with the postpartum program.

Several points should be noted. First, the cost-effectiveness results for the postpartum program are not shown in Figure 1.2 because, when treatment cost savings are deducted, the net cost of the program is negative over the range of prices shown in the figure – that is, the postpartum program is actually cost-saving. Second, when treatment cost savings are deducted, the incremental cost per life-year saved for the antenatal prophylaxis program remains well below \$40,000 even with a price per vial of \$115. Third, to the extent that imported product is used to supply less than the total Rh D immunoglobulin requirements, then the price per vial shown in Figure 1.2 is consistent with a higher price per vial for the imported product. Finally, the incremental cost per life-year saved would reach \$50,000 only if the average price per vial rose to \$166.

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## **Conclusion**

The results of the updated cost-effectiveness analysis indicate that both a postpartum program, and a postpartum plus antenatal prophylaxis program, appear to remain well within the usual bounds of cost-effectiveness at prices per vial of Rh D immunoglobulin up to \$115 and beyond.

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## 2 SECURING SUPPLY – MOVING TOWARDS SELF-SUFFICIENCY IN RH D IMMUNOGLOBULIN

Securing future supply of Rh D immunoglobulin is integral to full implementation of the NHMRC guidelines. While imported products can be used to ease the pressure on the supply in the short to medium term, self-sufficiency in Rh D immunoglobulin will be required to sustain the full Rh immunisation prevention program in the longer term.

Key issues for self-sufficiency are:

- promoting efficient use of Rh D immunoglobulin;
- securing the future supply of Rh D immunoglobulin; and
- addressing issues associated with the staged implementation of routine antenatal prophylaxis.

### **2.1 Promoting the efficient use of Rh D immunoglobulin**

Introduction of the 250 IU (50 µg) dose of Rh D immunoglobulin in Australia will greatly assist progress towards self-sufficiency by ensuring more efficient use of anti-D plasma. The 250 IU (50 µg) dose was introduced in May 2001 and has been widely promoted through a joint communication plan by the ARCBS, CSL Bioplasma and the Commonwealth Department of Health and Ageing (see Chapter 3). The 250 IU (50 µg) dose is indicated for sensitising events up to and including 12 weeks gestation. To ensure that it is used for the appropriate indication requires communication to general practitioners, obstetricians and gynaecologists, accident and emergency physicians, termination clinics and hospital blood banks.

Action to promote the more efficient use of existing supply will also include continuing promotion of increased and accurate use of tests to assess fetomaternal haemorrhage and increased compliance with guidelines on Rh D immunoglobulin use.

The use of the 250 IU (50 µg) dose of Rh D immunoglobulin in first trimester sensitising events should continue to be broadly promoted to increase uptake. A program of continuing education for health professionals on efficient use of Rh D immunoglobulin is also required.

### **2.2 Securing future supply of Rh D immunoglobulin**

Strategies are required to increase the production of Rh D immunoglobulin in a practical, sustainable and ethical way.

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Mechanisms to increase donors to the Rh program include:

- ARCBS recommencing recruitment of new donors to undergo primary immunisation to anti-D; and
- blood banks, hospitals or pathology laboratories identifying people with high levels of anti-D antibodies due to previous transfusion or pregnancy – these people can be approached for recruitment.

The importation of Rh D immunoglobulin initially will allow a staged process towards full antenatal prophylaxis. Such a product should continue to be imported in adequate quantities to support the staged introduction of universal antenatal prophylaxis until self-sufficiency is reached.

To increase domestic supply, CSL Bioplasma and the Australian Red Cross Blood Service will continue to pursue ways of increasing anti-D plasma supply, including:

- increasing the number of donors recruited to the Rh Project, particularly donors who are willing to undergo primary immunisation;
- recruiting donors with high levels of anti-D due to prior transfusion or pregnancy; and
- increasing the yield of Rh D immunoglobulin from the anti-D plasma collected.

### **2.3 Staged implementation of antenatal prophylaxis**

A strategy has been developed that will allow the staged introduction of antenatal prophylaxis in the short term while working toward self-sufficiency in the longer term.

Key issues that will need to be addressed with the introduction of imported product are:

- potential confusion as to which product and dose to use for different indications; and
- possible concern of clinicians and patients about the safety of an imported product.

Under the strategy:

- Rh D immunoglobulin 625 IU (125 µg) (Australian product) should be recommended for routine antenatal prophylaxis;
- Rh D immunoglobulin 250 IU (50 µg) should be recommended and supplied for first trimester indications;

- imported Rh D immunoglobulin (currently available as a 600 IU [120 µg] dose) should be recommended and supplied for postpartum indications; and
- there should be a wide-ranging communication program about the safety of Rh D immunoglobulin from all available sources.

In the strategy, 'worst case scenarios' have been used, to allow for a buffer stock to be maintained. The doses required could be less than estimated if all clinicians adopted the guidelines and there was increased and accurate use of tests to assess fetomaternal haemorrhage for all indications.

The following table summarises the proposed strategy for implementing full antenatal prophylaxis.

Situation to October 2002	Routine antenatal prophylaxis unable to be recommended
Short-term strategy (began November 2002)	Routine antenatal prophylaxis at 28 and 34 weeks for Rh negative women during their first pregnancy Supply augmented with imported product
Mid-term strategy	Routine antenatal prophylaxis at 28 and 34 weeks for all Rh D negative women Supply augmented with imported product
Long-term strategy	Routine antenatal prophylaxis at 28 and 34 weeks for all Rh D negative women Australia self-sufficient in Rh D immunoglobulin



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### 3 COMMUNICATION AND EDUCATION

Communication and education will be vital to the implementation of the guidelines, particularly as a staged implementation is recommended and supply issues will continue to change.

Since May 2001, a joint communication program of CSL Bioplasma, ARCBS and the Commonwealth Department of Health and Ageing has widely promoted the 250 IU (50 µg) dose of Rh D immunoglobulin, to encourage more efficient use of existing supplies. With the importation of Rh D immunoglobulin and progress towards the short-term stage of antenatal prophylaxis during first pregnancy, the communication program will broaden to include information on:

- the safety of Rh D immunoglobulin from all sources (to allay concerns about the safety of imported product); and
- which Rh D immunoglobulin product to use and when (promoting three different products/doses for different stages).

The Communication Strategy will occur in two stages as outlined below.

#### **Introduction of the 250 IU (50 µg) dose**

The introduction of domestic Rh D immunoglobulin 250 IU (50 µg) is occurring in consultation with the ARCBS, CSL Bioplasma, Commonwealth, State and Territory health authorities, the NHMRC, general practitioners, specialist obstetricians, pathologists and others. In addition, the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) will distribute the information via its website and mailing lists, prepared fliers will be distributed to health care facilities nationally.

#### **Introduction of imported product and antenatal prophylaxis**

The ARCBS and CSL Bioplasma will play a vital role in the introduction of imported Rh D immunoglobulin and antenatal prophylaxis. Target groups will be identified, staff in both organisations trained and customer service guidelines developed. Information brochures, posters and education packages which describe the three products and the appropriate use and dosages will be publicised and circulated. Articles will be published in such professional periodicals as the *Australian Society of Blood Transfusions Newsletter*, the *Australian and New Zealand Journal of Obstetrics and Gynaecology* and the general practitioner's weekly newsletter. The Royal College of Pathologists of Australia and the Australian College of Midwives will be included in the dissemination of information to members.

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State and Territory health officers will be involved throughout the process and will provide information via their respective health systems. Finally, a letter from the Commonwealth's Chief Medical Officer will be forwarded to all State and Territory health officers advising on the products and appropriate dosages. This letter will also be made available for ongoing inclusion in all three products before distribution to the end user.

Ongoing support and information on the use of products will continue through the customer service centres of the ARCBS and CSL Bioplasma.

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## APPENDIX A

### TERMS OF REFERENCE AND MEMBERSHIP OF THE WORKING PARTY

#### **Terms of reference**

In accordance with recommendations of the Guidelines on the prophylactic use of Rh D immunoglobulin in obstetrics (NHMRC 1999) the then Department of Health and Aged Care established a working party to review and amend the guideline for full antenatal prophylaxis according to the availability of supplies of Rh D immunoglobulin existing at the time.

In undertaking that task the Working Party has assessed and reported on:

- the current and future supply requirements including full antenatal prophylaxis;
- the impact on supply of the newly registered products as well as a communication strategy to ensure their efficient use;
- the projected anti-D plasma input data provided by the ARCBS;
- the contribution and cost of using imported products to supplement domestic supply; and
- the role of the Kleihauer test in Rh D immunoglobulin treatment.

The Working Party will make recommendations to the Department on a timetable and strategy for providing full antenatal prophylaxis to the extent that this is appropriate within likely future supply limitations.

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## **Membership of Working Party**

### **Members**

Dr David Woodhouse (Chair)	Royal Australian and New Zealand College of Obstetricians and Gynaecologists
Dr Elizabeth Campbell	Marketing Manager, CSL Bioplasma
Ms Eileen Conway	Product Manager, Immunotherapy, CSL Bioplasma
Dr Mark Dean	Assistant Director, ARCBS (until March 2002)
Mr John Haines	Blood and Organ Donation Taskforce, Department of Health and Ageing
Professor David Henderson-Smart	NHMRC Health Advisory Committee representative; Centre for Perinatal Health Services Research, University of Sydney
Dr James King	Mater Perinatal Epidemiology Unit, Brisbane
Dr Amanda Thomson	Medical Specialist, ARCBS
Ms Marlene Williams/ Ms Susan Croft	Secretariat, Blood and Organ Donation Taskforce, Department of Health and Ageing

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## APPENDIX B

### GUIDELINE DEVELOPMENT PROCESS

In 1996, the National Health and Medical Research Council (NHMRC) released *Guidelines for the Use of Rh D Immunoglobulin in Obstetrics*. The 1996 Guidelines were considered by the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) and the Australian Red Cross to be the “gold standard” in terms of clinical practice. However, they did not address the ongoing shortage of Rh D immunoglobulin in Australia.

In January 1997, the NHMRC was asked by the State Financing Group of the then Department of Health and Family Services to review the 1996 guidelines in the light of the supply concerns. Subsequently, the NHMRC endorsed *Guidelines for the Use of Rh D Immunoglobulin in Obstetrics* on 22 March 1999. These new guidelines aimed to balance best practice in the use of Rh D immunoglobulin with the limited available supplies of product. The 1999 guidelines recommended, among other things, that the recommendation relating to antenatal prophylaxis be reviewed on a regular basis by the NHMRC and assessed according to the availability of supplies of Rh D immunoglobulin.

Since the publication of the 1999 Guidelines, there have been a number of developments in the availability of Rh D immunoglobulin, such as the introduction of a new smaller domestic dose of Rh D immunoglobulin, the importation of a product from Canada and the re-establishment of boosting programs for existing donors and the recruitment of new donors. A letter was sent to all stakeholders from the Commonwealth Chief Medical Officer Professor Richard Smallwood advising of the developments in November 2002.

In 2001 the then Department of Health and Aged Care reconvened the Working Party to review supplies of product and update the 1999 Guidelines for full antenatal prophylaxis according to the supplies of Rh D immunoglobulin. The Working Party was asked to assess and report on:

- current and future supply requirements to meet full antenatal prophylaxis;
- impact on supply of the newly registered mini-dose as well as communication;
- projected Rh D immunoglobulin plasma input data supplied by the ARCBS;
- contribution and cost of using imported products to supplement domestic supply; and the role of the Kleihauer test in Rh D immunoglobulin treatment.

The literature review was updated by the Mater Perinatal Epidemiology Unit in Queensland and considered all relevant studies and commentaries published in English or French from 1995 onwards. The cost effectiveness analysis was also reviewed by Dr James Butler and A L Howarth of the National Centre of Epidemiology and Population Health, Canberra.

Ampersand Editorial and Design was re-engaged as the technical writers to prepare the draft Report as they had been involved with the 1999 guidelines. Submissions were invited from the public through advertisements in the press with a closing date of 21 March 2003. Four submissions were received from medical practitioners and medical administrators. The submissions ranged from issues relating to self-sufficiency, safety and cost-effectiveness of the products to testing for pre-formed antibodies in women. Each submission, which was discussed by the Working Party, is addressed in the Guidelines and each received an individual response.

The 2003 draft Guidelines was presented to the Health Advisory Committee (HAC) on 4 April 2003 and to the NHMRC on 1 May 2003.

### **Table of Submissions**

Name	Submissions	Action
Dr Jules Black	Self-sufficiency, safety of product and cost-effectiveness	Addressed in the Guidelines Individual response
Associate Professor Lachlan de Crespigny	Use of Anti-D for amniocentesis and chorionic villus sampling	Addressed in the Guidelines Individual response
Professor Michael Bennett	Passive or pre-formed antibodies	Addressed in the Guidelines Individual response
Department of Human Services, Victoria	Testing for passive Anti-D	Addressed in the Guidelines Individual response

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## APPENDIX C

### LITERATURE REVIEW ON THE USE OF RH D IMMUNOGLOBULIN IN OBSTETRICS – SEARCH STRATEGY AND RESULTS

The literature review was undertaken for the Blood and Organ Donation Taskforce of the Commonwealth Department of Health and Ageing by:

- James F King, MPH, FRANZCOG (Consultant in Perinatal Epidemiology);
- Lynne Rigg, RN, RM, BAppSci (Research Midwife); and
- Shane Higgins, MRCOG (Fellow in Maternal/Fetal Medicine).

The full report of the literature review can be obtained from the Blood and Organ Donation Taskforce.

#### **1. Search scope**

- 1.1 Update (articles published from 1995 onwards) on evidence for the effectiveness of Rh D immunoglobulin in obstetrics:
  - a) for antenatal prophylaxis,
  - b) following antenatal sensitising events (abortion, ectopic, invasive genetic studies, external cephalic version, trauma, antepartum haemorrhage etc), and
  - c) for postpartum prophylaxis.
- 1.2 Update on evidence addressing the risks and/or disadvantages of Rh D immunoglobulin.
- 1.3 Update on evidence addressing the most appropriate dose of Rh D immunoglobulin to prevent immunisation for both antenatal and postnatal prophylaxis and following sensitising events.
- 1.4 Update on evidence addressing the most appropriate means of evaluating the effectiveness of Rh D immunoglobulin in clearing fetal Rh positive cells from maternal circulation.

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## **2. Methods**

### **2.1 Search strategy**

The OVID interface was used to search the following electronic databases:

- PREMEDLINE and MEDLINE: January 1995 - April 2 2001
- CINAHL: January 1995 - March 2001
- BEST EVIDENCE: January 1995 - February 2001
- HEALTHSTAR: January 1995 - December 2000
- Cochrane Database: 2001 Issue 2
- Review of article citations and Cochrane Reviews for relevant additional citations

### **2.2 Search terms**

Terms used to identify relevant citations included:

- Antenatal or pregnant: or obstetric or prenatal or maternity or postnatal and Rh D immunoglobulin (Rho (D) Immunoglobulin or Rh isoimmunisation)
  - Rh immunoglobulin
  - Rhesus
  - Fetomaternal haemorrhage/haemorrhage or transfusion
  - Rhesus alloimmunisation
  - Haemolytic or Haemolytic disease
  - Flow cytometry
  - Rosette
- Kleihauer and fetomaternal transfusion/haemorrhage/haemorrhage
- ELAT (Enzyme linked antiglobulin testing)
- Coombs'
- Rh D immunoglobulin [Rho (D)] Immune Globulin, Rh Isoimmunization and
  - Abortion (therapeutic, criminal, threatened, habitual, incomplete, induced, legal, missed, septic, spontaneous, eugenic)
  - Hepatitis C

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### **3. Search findings**

Citations were screened and selected using the process outlined in Appendix IV of the full report. The search retrieved 366 citations.

These citations were triaged into:

- those possibly containing new evidence or authoritative opinion (98 publications).
- those unlikely to contain new evidence or authoritative opinion (268 publications).

The publications from the 98 citations were retrieved and subjected to critical appraisal by the review team with respect to quality of methodology, and relevance to Australian practice. As a result of this exercise, 28 articles were classified as key citations.

The evidence within these 28 key citations fell into the following levels (as defined by NHMRC):

- level I evidence: 2 Cochrane systematic reviews (one of which was recently updated),
- level II evidence: 1 publication,
- level III evidence: 11 publications, and
- level IV evidence: 14 publications.

The publications and the level of evidence ratings are listed in the bibliography.

#### **Commentary on and interpretation of publications reviewed**

This updated literature review considered all relevant studies and commentaries published in English or French, from 1995 onwards.



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## ACRONYMS AND ABBREVIATIONS

ANZSBT	Australian and New Zealand Society of Blood Transfusion
ARCBS	Australian Red Cross Blood Service
CI	confidence interval
FMH	fetomaternal haemorrhage
HbF	haemoglobin F
HCV	hepatitis C virus
HDN	haemolytic disease of the newborn
NHMRC	National Health and Medical Research Council
OR	odds ratio
RANZCOG	Royal Australian and New Zealand College of Obstetricians and Gynaecologists
RNA	ribonucleic acid
TGA	Therapeutic Goods Administration



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NHMRC (1999) *Guidelines on the Prophylactic use of Rh D Immunoglobulin (Anti-D) in Obstetrics*. Main Report. National Health and Medical Research Council, Canberra.

### Literature review – key citations (full articles retrieved and reviewed)

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#### Levels of evidence ratings

- I Evidence obtained from a systematic review of all relevant randomised controlled trials.
- II Evidence obtained from at least one properly-designed randomised controlled trial.
- III-1 Evidence obtained from well-designed pseudo-randomised controlled trials (alternate location or some other method).
- III-2 Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group.
- III-3 Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group.
- IV Evidence obtained from case series, either post-test or pre-test/post-test.

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Source: NHMRC (1999) *A Guide to the Development, Implementation and Evaluation of Clinical Practice Guidelines*. National Health and Medical Research Council, Canberra.

Allaby M, Forman K, Touch S et al (2001) The use of routine antenatal anti-D prophylaxis for rhesus negative women (Database of Abstracts of Reviews of Effectiveness). *In the Cochrane Library*, Issue 2, 2001. Oxford Update Software. (Level III)

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