

# Frequently Asked Questions about the Use of Rh(D) Immunoglobulin

## Introduction

In December 2014, CSL Behring updated the Rh(D) Immunoglobulin-VF Product Information (PI) to include a recommendation that the clearance of fetal cells and the presence of Rh(D) antibody be confirmed post-administration in patients with a BMI  $\geq 30$ . CSL Behring also updated the Rhophylac PI to recommend intravenous administration of this product in patients with a BMI  $\geq 30$ .

An Expert Panel was convened by the Australian Red Cross Blood Service and the National Blood Authority in order to discuss the implications of this change on clinical and laboratory practice and develop appropriate actions.

Members of the Expert Panel included:

- Assoc. Prof. Stephen Robson and Prof. Michael Permezel representing the Royal Australian & New Zealand College of Obstetricians and Gynaecologists (RANZCOG)
- Deborah Pidd, representing the Australian College of Midwives (ACM)
- Simon Benson and David Roxby, representing the Australian & New Zealand Society of Blood Transfusion (ANZSBT)
- Dr Marija Borosak, representing the Royal College of Pathologists of Australasia (RCPA)
- Dr Helen Savoia, representing the Expert Working Group and Clinical/Consumer Reference Group - Patient Blood Management Guidelines: Module 5 – Obstetrics and Maternity
- Dr Joanne Pink, Dr Janet Wong and Dr Chris Hogan, representing the Australian Red Cross Blood Service (Blood Service)
- Dr Peter Flanagan, representing the New Zealand Blood Service (NZBS)
- Michael Stone and Leia Earnshaw representing the National Blood Authority (NBA)
- Dr Darryl Maher, Annmarie Pendleton and Guilio Barrese, representing CSL Behring\*

The following questions and answers were reviewed and updated by the Expert Consensus Panel in June 2015:

- Clinical questions and answers
- Testing questions and answers
- Supply and Distribution questions and answers
- Product questions and answers
- Policy question and answers

*\*CSL Behring attended the meeting and presented data, but did not contribute to the Consensus Assessment and Recommendations.*

# Clinical Questions and Answers

## Introduction

The information provided is consistent with the recommendations of the NHMRC reports (1999 and 2003), which are based on an extensive literature review. Previous version endorsed by RANZCOG Council in November 2005. The answers below were reviewed and updated in June 2015 by the Expert Consensus Panel. Updated version currently under review by RANZCOG Council.

### Abbreviations used in this section:

FMH	Fetomaternal Haemorrhage
HDN	Haemolytic Disease of the Newborn
IU	International Units
RANZCOG	Royal Australian and New Zealand College of Obstetricians and Gynaecologists
Blood Service	Australian Red Cross Blood Service

NHMRC Report (1999): National Health and Medical Research Council (NHMRC)  
[Guidelines on the prophylactic use of Rh\(D\) immunoglobulin \(Anti-D\) in obstetrics 1999](#)

NHMRC Report (2003): National Health and Medical Research Council (NHMRC)  
[Guidelines on the prophylactic use of Rh\(D\) immunoglobulin \(Anti-D\) in obstetrics 2003](#)

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## **Clinical Questions and Answers**

### **1. Administration of Rh(D) immunoglobulin for sensitising events**

- 1.1. *During what timeframe should Rh(D) immunoglobulin be administered after a potentially sensitising event for successful immunoprophylaxis?***

For successful immunoprophylaxis, Rh(D) immunoglobulin should be administered as soon as possible after the sensitising event, but ideally within 72 hours. 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



possible, RANZCOG considers it acceptable for doses to be administered within two weeks of the recommended timing.

### ***1.3. What is the earliest time frame that an Rh(D) negative woman should receive Rh(D) immunoglobulin for a potentially sensitising event?***

The Rh(D) antigen has been identified on fetal erythrocytes as early as 38 days gestation, 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. The available evidence indicates that FMH can occur after six weeks gestation and that sensitisation has been reported as early as 6 weeks gestation.

On the basis of this evidence, the NHMRC Report (2003) recommends that Rh(D) immunoglobulin be given following therapeutic abortion (both medical or surgical), following curettage to remove products of conception (including a blighted ovum), and where bleeding occurs in an ongoing pregnancy beyond the first trimester.

There is no evidence available to determine the minimum time in pregnancy beyond which Rh(D) immunoglobulin should be given but RANZCOG recommends that 6 weeks is a reasonable minimum period of gestation.

### ***1.4. Should Rh(D) immunoglobulin be given for a first trimester spontaneous miscarriage, without a curette?***

The NHMRC Report (2003) states that there is doubt concerning the risk of sensitisation associated with bleeding in a spontaneous abortion before 12 weeks. This means that it is unclear whether or not there is a risk of sensitisation before 12 weeks.

The NHMRC report (2003) recommends that a dose of 250 IU Rh(D) immunoglobulin should be offered to every Rh(D) negative woman with no preformed anti-D to ensure adequate protection against immunisation for miscarriage (up to and including 12 weeks gestation).

The NHMRC Report (2003) strongly recommends that women undergoing termination of pregnancy be tested to determine their Rh(D) type, to avoid unnecessary use of Rh(D) immunoglobulin.

Note: the UK RCOG do not recommend routine administration of anti D for threatened miscarriage with a viable fetus <12 weeks, nor for spontaneous miscarriage without instrumentation to evacuate the products of conception.

### ***1.5. Should Rh(D) immunoglobulin be given for a missed abortion, having a curette?***

The NHMRC Report (2003) recommends that Rh(D) immunoglobulin be given following therapeutic abortion and following curettage to remove products of conception. This should include curettage for a missed abortion.

The NHMRC Report (2003) strongly recommends that women undergoing termination of pregnancy be tested to determine their Rh(D) type, to avoid unnecessary use of Rh(D) immunoglobulin.

**1.6. Should Rh(D) immunoglobulin be given for first trimester bleeds that do not result in miscarriage?**

The NHMRC Report (2003) states that 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 the bleeding is particularly heavy or associated with a visible subchorionic haemorrhage, these patients should be considered at higher risk of sensitisation and Rh(D) immunoglobulin given.

**1.7. If a sensitising event occurs up to 6 weeks after a prophylactic dose of Rh(D) immunoglobulin has been given, should a further dose of Rh(D) immunoglobulin be given?**

The magnitude of the FMH should be quantified and, if positive, the appropriate dose of Rh(D) immunoglobulin should be given. If the FMH screen is negative and anti-D is detected in the maternal serum, a further dose of Rh(D) immunoglobulin is not required.

**1.8. What should be the time frame between doses of Rh(D) immunoglobulin for recurrent bleeds in pregnancy?**

Howard et al (1997) reported that Rh(D) immunoglobulin should be given every 6 weeks if women continue to bleed, as recommended in the National Blood Transfusion Services Immunoglobulin Working Party guidelines (NBTS Immunoglobulin Working Party 1991). In such situations, it would be prudent to measure the size of any FMH.

**1.9. What dose of Rh(D) immunoglobulin is recommended for sensitising events in multiple pregnancy?**

It is recommended that 625 IU Rh(D) immunoglobulin is given for potentially sensitising events during the first trimester for multiple pregnancy. For sensitising events beyond the first trimester, it is recommended that the size of the FMH is determined and the appropriate dose of Rh(D) immunoglobulin then given.

## **2. Postpartum Prophylaxis**

**2.1. What percentage of women will develop Rh(D) antibodies if Rh(D) immunoglobulin is given only at delivery?**

The NHMRC Report (1999) states that immunisation occurs during pregnancy in about 1.5 % of Rh(D) negative women carrying an Rh(D) positive infant, where Rh(D) immunoglobulin is only given at delivery.

**2.2. If Rh(D) immunoglobulin is given for a sensitising event, is it still necessary to give Rh(D) immunoglobulin prophylactically postnatally?**

Yes, as you cannot be sure of the amount of passive antibody remaining after the sensitising event.

### **3. Antenatal Prophylaxis**

#### **3.1. What is the percentage rate of protection if Rh(D) immunoglobulin is also given antenatally?**

The NHMRC Report (1999) states that the immunisation rate can be reduced to 0.2% or less by the administration of Rh(D) immunoglobulin during pregnancy, at 28 weeks and 34 weeks, as well as after delivery.

#### **3.2. What dose of Rh(D) immunoglobulin is recommended for antenatal prophylaxis in multiple pregnancy?**

625 IU Rh(D) immunoglobulin should be given for antenatal prophylaxis in multiple pregnancy.

#### **3.3. If Rh(D) immunoglobulin is given for a sensitising event, is it still necessary to give Rh(D) immunoglobulin prophylactically at 28 and 34 weeks?**

Yes, as you cannot be sure of the amount of passive antibody remaining after the sensitising event. Antenatal prophylaxis doses should be given in addition to doses administered for sensitising events.

#### **3.4. If a patient fails to receive prophylactic Rh(D) immunoglobulin at 28 weeks, should they receive the dose at 34 weeks?**

The dose should be given as soon as possible after it is recognised that the dose was missed, rather than waiting for the 34 weeks dose. In such a case, the second dose should be delayed until 6 weeks after the first dose.

#### **3.5. What is the effect on the fetus post administration of Rh(D) immunoglobulin?**

Whilst it is reported that 10–15% of the antibody crosses the placenta into the fetal circulation, the NHMRC Report (1999) stated that there is no evidence confirming an adverse effect of passive Rh(D) immunoglobulin on the embryo or fetus. However, the studies which looked at safety for the fetus provided data that is limited to evaluation of the cord haemoglobin, bilirubin and direct Coombs' tests.

The NHMRC Report (2003) conducted a further literature review of 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. 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).

#### **3.6. Is there a need to administer a further dose of Rh(D) immunoglobulin if a delivery is delayed beyond 40 weeks' gestation?**

It is a common and widespread practice to offer induction of labour to women who have reached 10 days beyond their due date and now there are very few pregnancies which progress beyond 42 weeks.

In clinical trials, the estimated half-life of Rh(D) Immunoglobulin has been shown to be approximately 4 weeks and it is generally accepted that a dose of 625 IU (125 mcg) of Rh(D) immunoglobulin provides coverage for a period of 6 weeks.

If the half-life is approximately 4 weeks, the difference in antibody level in an uncomplicated pregnancy 6 weeks after the injection as compared to 8 weeks is unlikely to be significant.

It would be expected that any significant FMH event occurring after term would be likely to precipitate labour or lead to medical intervention to deliver the baby and this would then be followed shortly after by the administration of the postnatal dose of Rh(D) immunoglobulin.

Therefore, for an uncomplicated pregnancy that proceeds up to 42 weeks, there is no need to give a give a further dose of antenatal Rh(D) immunoglobulin.

## **4. General Questions**

### ***4.1. What is the chance that an Rh(D) negative woman will carry an Rh(D) positive fetus?***

Approximately 17% of Caucasian women and men will be Rh(D) negative.

- This means that approximately 1 in 6 Rh(D) negative women will have a partner who is also Rh(D) negative. If both the mother and the father of the baby are Rh(D) negative, the fetus will always be Rh(D) negative.
- Approximately 5 in 6 Rh(D) negative women will have a partner who is Rh(D) positive. Of these, approximately 45% of the fathers will be homozygous for the Rh(D) antigen and 55% will be heterozygous for the Rh(D) antigen.
- If the father of the baby is Rh(D) positive and homozygous for the Rh(D) antigen, the fetus will always be Rh(D) positive.
- If the father of the baby is Rh(D) positive and heterozygous for the Rh(D) antigen, the fetus will have a 50% chance of being Rh(D) negative and a 50% chance of being Rh(D) positive.
- These figures are correct as long as paternity can be assumed. In cases of non- paternity, the risk will depend on the rhesus genotype of the biological father. Information from prenatal diagnostic laboratories performing genetic testing has indicated that non-paternity rates may be as high as 20-30%.

### ***4.2. Where is the best site for administration of the intramuscular injection?***

The Blood Service/CSL Rh(D) immunoglobulin should be administered by deep intramuscular injection. It should not be given subcutaneously.

The deltoid muscle or the anterolateral thigh is the best site. The buttocks should be avoided.

For women with a body mass index (BMI) of 30 or more, particular consideration should be given to factors which may impact on the adequacy of the injection, including the site of administration and the length of the needle used.

### ***4.3. If a patient has an IV line, would you administer Rh(D) immunoglobulin by IV or IM?***

The Blood Service/CSL Rh(D) immunoglobulin product can only safely be given intramuscularly.



In the case of a large FMH (greater than 15mL), specialist advice should be sought regarding the most appropriate product and route of administration.

In some circumstances, access to an intravenous Rh(D) immunoglobulin preparation may be warranted. A quantity of intravenous Rh(D) immunoglobulin has been reserved for this purpose. Contact the Blood Service or your local transfusion laboratory for further information.

For women with a BMI of 30 or more who experience a FMH of greater than 6mL, consideration may be given to administering any required additional doses as intravenous Rh(D) immunoglobulin to increase bioavailability and facilitate the more rapid clearance of fetal cells.

#### **4.4. How common is HDN?**

Until the late 1960s, HDN due to Rh(D) incompatibility was an important cause of fetal and neonatal morbidity and mortality.

Mortality from HDN due to Rh(D) incompatibility is now uncommon.

There is no national dataset of women who have developed Rh(D) alloimmunisation during pregnancy; however, surrogate data suggests that the number of pregnancies complicated by severe HDN is decreasing. Australian Institute of Health and Welfare (AIHW) data show that, in the ten year period from 2003/04 to 2012/13, the number of neonatal exchange transfusions performed in Australia decreased from 124 to 29 per annum and intrauterine fetal transfusions decreased from 124 to 59. In addition, perinatal deaths due to specific perinatal conditions, including Rh(D) alloimmunisation, have decreased from 172 in 2004 to 159 in 2012.

*Reference:*

- *Australian Institute of Health and Welfare (AIHW) website ([www.aihw.gov.au](http://www.aihw.gov.au)).*

#### **4.5. What information is available for patients?**

The RANZCOG patient information leaflet, *Red Blood Cell Alloimmunisation*, provides information on HDN and is available on the RANZCOG website.

[https://www.ranzcog.edu.au/images/Patient\\_Information\\_Sheet\\_-\\_Red\\_Blood\\_Cell\\_Alloimmunisation\\_FINAL.pdf](https://www.ranzcog.edu.au/images/Patient_Information_Sheet_-_Red_Blood_Cell_Alloimmunisation_FINAL.pdf)

A further patient information leaflet is also available from the Blood Service website ([www.transfusion.com.au](http://www.transfusion.com.au)) or the CSL website ([www.csl.com.au](http://www.csl.com.au)).

#### **4.6. What other education /information materials are available for health professionals?**

The following materials are available from the Blood Service and CSL Behring:

- You and Your Baby: Important information for Rh(D) negative women: Prevention of Haemolytic Disease of the Newborn (HDN) brochure
- Important information for Rh(D) negative women: Prevention of Haemolytic Disease of the Newborn (HDN) brochure (For women who experience early fetal loss)
- Approved product information for Rh(D) Immunoglobulin-VF
- Consumer medicine information for Rh(D) Immunoglobulin-VF

To find out how to obtain these materials, visit the Blood Service website: ([www.transfusion.com.au](http://www.transfusion.com.au)) or the CSL website ([www.csl.com.au](http://www.csl.com.au)).

# Testing Questions and Answers

## Introduction

The following recommendations are supported by the literature review and are in accordance with ANZSBT Guidelines: [Laboratory Assessment of Fetomaternal Haemorrhage \(2002\)](#) and, [Guidelines for Blood Grouping & Antibody Screening in the Antenatal & Perinatal Setting, 3rd Edition \(March 2007\)](#). Previous version endorsed by the ANZSBT in 2005. The answers below were reviewed and updated in June 2015 by the Expert Consensus Panel. Updated version currently under review by the ANZSBT.

### Abbreviations used in this section:

ANZSBT	Australian and New Zealand Society of Blood Transfusion
FMH	Fetomaternal Haemorrhage
Blood Service	Australian Red Cross Blood Service

National Blood Authority (2003) [Approved by the NHMRC]: [Guidelines on the prophylactic use of Rh\(D\) immunoglobulin \(Anti-D\) in obstetrics](#)

## List of Testing Questions

### 1. FMH screening

- 1.1. *When should I perform a FMH screen?*
- 1.2. *What tests are available to quantify a FMH?*
- 1.3. *What is the best test to quantify a FMH?*
- 1.4. *What should I do if the FMH quantitation shows that the FMH is greater than that covered by the dose of Rh(D) immunoglobulin already administered?*
- 1.5. *What is the average size of a FMH?*

### 2. Red cell antibody screening

- 2.1. *What test should be performed to detect red cell antibodies?*
- 2.2. *When should red cell antibody screening be performed?*
- 2.3. *Do you still need to perform a red cell antibody screen if Rh(D) immunoglobulin is given prophylactically?*
- 2.4. *When should the blood sample for the red cell antibody screen be collected in relation to the administration of Rh(D) immunoglobulin at 28 and 34 weeks?*
- 2.5. *How should the results of a red cell antibody screen be interpreted if antenatal prophylaxis has been previously given?*
- 2.6. *Is it possible to distinguish between passively-acquired and actively-acquired anti-D?*
- 2.7. *From a laboratory perspective, sometimes information is missing regarding whether a patient has received Rh(D) immunoglobulin prophylactically. What would you recommend?*

**2.8. At 28 weeks presentation, is antibody screening advised as well as assessment of FMH?**

### **3. Other**

**3.1. Is it necessary to quantitate the amount of Rh(D) antibody that has been given to check if there is enough antibody?**

**3.2. For women with a body mass index (BMI) of 30 or more, is it necessary to confirm the clearance of fetal cells and the presence of anti-D in the maternal serum post-administration of Rh(D) immunoglobulin?**

## **Testing Questions and Answers**

### **1. FMH Screening**

**1.1. When should I perform a FMH screen?**

For potentially sensitising events that occur after the first trimester.

In this circumstance, a maternal sample should be taken prior to administration of Rh(D) immunoglobulin, to assess the volume of FMH. However, at no time should a single dose of Rh(D) immunoglobulin be withheld based upon, or pending, the results to quantitate FMH.

**1.2. What tests are available to quantify a FMH?**

There are a number of tests available to assess the volume of FMH 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. Kleihauer testing appears to be precise only in small volumes of transplacental haemorrhage. It gives quantitative results but is open to interpretation by the laboratory staff performing the test, which has resulted in a number of cases of inaccurate results. Consequently, the experience of the laboratory staff 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 the adult circulation. If the Kleihauer shows an FMH of greater than 6mL, it may be beneficial to repeat the quantification using a more accurate test, such as flow cytometry.
- **Flow Cytometry** — which is reliable and accurate, but not widely available outside metropolitan areas.

**1.3. What is the best test to quantify a 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 NHMRC Report (2003) has stated that the following recommendations must be ensured:

- laboratories undertaking quantitative assessment of FMH by any method (such as Kleihauer-Betke test) 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.

#### **1.4. What should I do if the FMH quantitation shows that the FMH is greater than that covered by the dose of Rh(D) immunoglobulin already administered?**

Where FMH quantitation shows that FMH greater than that covered by the dose already administered has occurred, an additional dose(s) of Rh(D) immunoglobulin sufficient to provide immunoprophylaxis must be administered and preferably within 72 hours.

For large bleeds (i.e. FMH greater than 15mL), 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:

- Rh(D) immunoglobulin is not detected in maternal plasma by IAT (indirect antiglobulin test); and
- FMH quantitation is still positive.

It should be noted that, if the fetus is Rh(D) negative, the Kleihauer will remain positive despite the presence of detectable anti-D in the maternal plasma. In the antepartum setting, consideration should be given to repeating the FMH quantitation by flow cytometry.

Management of large FMH is complex and needs to be individualised, taking into consideration the size of the FMH, the presence of anti-D in the maternal serum and the rate of clearance of fetal cells.

#### **1.5. What is the average size of a FMH?**

About:

- 99% of fetal bleeds are less than 5 mL of red blood cells.
- 50 % of bleeds are less than 0.05 mL
- 0.6% of bleeds may be higher than 30 mL.

## **2. Red cell antibody screening**

### **2.1. What test should be performed to detect red cell antibodies?**

In the absence of evidence to the contrary, antibody screening using an indirect antiglobulin test (IAT) should be performed.

### **2.2. When should red cell antibody screening be performed?**

**When no clinically significant antibodies are detected at the first trimester**, the value of repeat testing in all pregnancies at 28 weeks or later has been questioned (Judd 2001). However, repeat testing of RhD negative women prior to administering RhD immunoprophylaxis at 28 weeks is the accepted protocol in most Australian centres, as is the elimination of the antibody screen at 34-36 weeks. Red cell antibody screening at 34-36 weeks is not routinely recommended in the absence of any other clinical indication.

Reference:

- Judd WJ and for the Scientific Section Coordinating Committee of the AABB. *Practice Guidelines for Prenatal and Perinatal Immunohematology, Revisited. Transfusion 2001; 41: 1445-1452.*

**2.3. Do you still need to perform a red cell antibody screen if Rh(D) immunoglobulin is given prophylactically?**

Yes, as other clinically significant red cell antibodies may be detected.

**2.4. When should the blood sample for the red cell antibody screen be collected in relation to the administration of Rh(D) immunoglobulin at 28 weeks?**

It is paramount that the blood sample is taken **before** the administration of the antenatal Rh(D) immunoglobulin, and it is acceptable for the Rh(D) immunoglobulin to be given immediately after the blood has been taken, before the results are available. This is because the vast majority of Rh(D) negative women will not be sensitised and this is the most practical approach for optimising patient care.

**2.5. How should the results of a red cell antibody screen be interpreted if antenatal prophylaxis has been previously given?**

If anti-D is detected and there is documented evidence in the clinical notes of Rh(D) immunoglobulin administration within the past 6 weeks, then this anti-D is likely to be passively-acquired.

If there is no history of Rh(D) immunoglobulin administration or no clinical notes have been provided, this anti-D must be considered actively-acquired unless proven otherwise and careful monitoring is required.

**2.6. Is it possible to distinguish between passively-acquired and actively-acquired anti- D?**

No, that is why the patient's history and clinical notes on request forms are so important.

**2.7. From a laboratory perspective, sometimes information is missing regarding whether a patient has received Rh(D) immunoglobulin prophylactically. What would you recommend?**

In the case that the information is missing, it is beneficial to contact the patient's clinical team (i.e. GP, obstetrician or midwife) to confirm whether or not the patient has received prophylactic Rh(D) immunoglobulin.

As part of practice improvement, it is important to relay to the clinician or midwife the value of providing the patient's antenatal Rh(D) immunoprophylaxis history on the request form; thereby better informing the interpretation of any positive red cell antibody screens.

**2.8. At 28 weeks presentation, is antibody screening advised as well as assessment of FMH?**

Antibody screening should be done at 28 weeks. There is no requirement for FMH screening at 28 weeks unless there is a concern over a potential sensitising event.

### 3. Other

**3.1. *Is it necessary to quantitate the amount of Rh(D) antibody that has been given to check if there is enough antibody?***

Quantitation of the presence of Rh(D) immunoglobulin is not a reliable approach to determining if sufficient Rh(D) immunoglobulin has been given. This is why it is important to quantitate the magnitude of the FMH.

Additional doses of Rh(D) immunoglobulin may be required if the bleed is greater than that covered by the dose of Rh(D) immunoglobulin already given.

**3.2. *For women with a body mass index (BMI) of 30 or more, is it necessary to confirm the clearance of fetal cells and the presence of anti-D in the maternal serum post-administration of Rh(D) immunoglobulin?***

No specific additional testing is required because a woman has a BMI of 30 or more. Routine post-administration testing is not required unless there has been a large FMH; in which case, testing should be performed in accordance with the established guidelines.

# Supply and Distribution Questions and Answers

## Introduction

The answers below were reviewed and updated in June 2015 by the Expert Consensus Panel. The following answers have been endorsed by the Australian Red Cross Blood Service.

### Abbreviations used in this section:

Blood Service	Australian Red Cross Blood Service
IU	International Units

NHMRC Report (1999): National Health and Medical Research Council (NHMRC)  
[Guidelines on the prophylactic use of Rh\(D\) immunoglobulin \(Anti-D\) in obstetrics 1999](#)

NHMRC Report (2003): National Health and Medical Research Council (NHMRC)  
[Guidelines on the prophylactic use of Rh\(D\) immunoglobulin \(Anti-D\) in obstetrics 2003](#)

## List of Supply and Distribution Questions

- 1. How will Australia maintain national self-sufficiency for Rh(D) immunoglobulin?*
- 2. Is there a difference in yield between male and female anti-D donors?*
- 3. If the UK dose of Rh(D) immunoglobulin is 500 IU, why not alter the 625 IU to this dose and save this precious resource?*
- 4. How can I order Rh(D) Immunoglobulin products?*
- 5. What intravenous Rh(D) immunoglobulin product is currently available in Australia and how can I access it?*

## Supply and Distribution Questions and Answers

- 1. How will Australia maintain national self-sufficiency for Rh(D) immunoglobulin?*

One of the most successful medical advances has been the prevention of Haemolytic Disease of the Newborn (HDN) by the discovery, introduction and clinical usage of Rh(D) immunoglobulin. In 1968, Australia became the first country in the world to be self-sufficient in production of Rh(D) immunoglobulin. As a result, we have seen a dramatic decline in mortality rates among unborn and newborn Rh(D) positive children of Rh(D) negative mothers.

There are several challenges in maintaining the supply of Rh(D) immunoglobulin including:

- the progressive retirement of Rh(D) plasmapheresis donors, primarily on the grounds of age
- declining levels of Rh(D) antibody in Rh(D) plasmapheresis donors, which occurs over time
- a reduction in the number of potential donors with Rh(D) antibodies due to a fall in the number of women immunised during pregnancy (because of the success of the HDN prevention program in recent decades) and less people receiving Rh(D) incompatible transfusions due to an improvement in the supply of Rh(D) negative blood
- ethical considerations associated with increasing the Rh(D) antibody levels in blood donors by primary immunization and boosting, as this requires a small transfusion of incompatible blood
- the significant effect on input if any donor withdraws from the program, as we rely on a small number of Rh(D) plasmapheresis donors across Australia.

With the introduction of antenatal prophylaxis programs, the Australian demand for Rh(D) immunoglobulin has considerably increased. To ensure that the Australian demand for Rh(D) immunoglobulin can be met from domestic supply, the Blood Service runs a special blood donor program. The purpose of this program is to maintain and increase the Australian supply of Rh(D) immunoglobulin as required. This involves actively recruiting new donors for Rh(D) primary immunisation and boosting to increase the pool of donors contributing to the supply of plasma for the production of Rh(D) Immunoglobulin. The Blood Service also regularly boosts the levels of anti-D in existing donors. There are currently over 150 active Rh(D) plasmapheresis donors.

Blood banks, hospitals or pathology laboratories can assist by identifying people with high levels of anti-D antibodies due to previous transfusion or pregnancy and asking whether they are interested in joining the Blood Service Rh(D) Plasmapheresis Donor Program.

## **2. Is there a difference in yield between male and female anti-D donors?**

There is no known sex difference in the yield from immunised donors. Historically, prior to the advent of primary immunisation programs, the majority of donors with high levels were women who had multiple pregnancies.

## **3. If the UK dose of Rh(D) immunoglobulin is 500 IU, why not alter the 625 IU to this dose and save this precious resource?**

Recommended doses vary internationally from 500 IU to 1500 IU. There are no comparative studies of one manufacturer's product versus another. To reduce the dose would require additional efficacy studies. This would be a lengthy and expensive exercise.

## **4. How can I order Rh(D) Immunoglobulin products?**

Approved health providers can place orders for Rh(D) immunoglobulin (Blood Service/CSL 250 IU and 625 IU) from the Blood Service.

## **5. What intravenous Rh(D) immunoglobulin product is currently available in Australia and how can I access it?**

A quantity of Rhophylac is available in reserve where access to an intravenous preparation is warranted. This product may be accessed via the Blood Service. Contact the Blood Service Transfusion Medicine Specialist in your capital city.

### *References:*

- *Approved Product Information for Rhophylac*



# Product Questions and Answers

## Introduction

The following answers to frequently asked questions are intended for use by healthcare professionals and have been endorsed by CSL Behring. If you have received or expect to receive Rh(D) Immunoglobulin-VF, please direct any queries to your healthcare provider. The answers below were reviewed and updated in June 2015 by the Expert Consensus Panel.

### Abbreviations used in this section:

Blood Service	Australian Red Cross Blood Service
MMR	Measles, Mumps and Rubella
IU	International Unit
FMH	Fetomaternal Haemorrhage
NHMRC	National Health and Medical Research Council
FDA	Food and Drug Administration (USA)
TGA	Therapeutic Goods Administration

NHMRC Report (2003): National Health and Medical Research Council (NHMRC)  
[Guidelines on the prophylactic use of Rh\(D\) immunoglobulin \(Anti-D\) in obstetrics 2003](#)

## List of Rh(D) Immunoglobulin-VF Questions

- 1. What is the half-life of Rh(D) Immunoglobulin-VF and how long is it detectable in the patient's circulation?***
- 2. What dose of Rh(D) Immunoglobulin-VF will protect against 1 mL of fetal Rh D positive red cells?***
- 3. What are the recommendations regarding the administration of Rh(D) Immunoglobulin-VF and the MMR vaccination?***
- 4. For Rh(D) negative women who are not rubella immune, what is the recommended administration regimen for Rh(D) Immunoglobulin-VF and the rubella vaccine?***
- 5. What is the risk of viral transmission with Rh(D) Immunoglobulin-VF?***
- 6. Does Rh(D) Immunoglobulin-VF contain thiomersal?***
- 7. Does Rh(D) Immunoglobulin-VF contain red blood cells?***
- 8. What are the storage requirements for Rh(D) Immunoglobulin-VF?***
- 9. What intravenous Rh(D) immunoglobulin product is currently available in Australia and how can I access it?***

## Rh(D) Immunoglobulin-VF Questions and Answers

### 1. **What is the half-life of Rh(D) Immunoglobulin-VF and how long is it detectable in the patient's circulation?**

The half-life of the Blood Service/CSL Rh(D) Immunoglobulin-VF is approximately 3-4 weeks. It can be detected in a patient's serum up to 6 weeks after administration. If there are ongoing silent bleeds during pregnancy, Rh(D) Immunoglobulin-VF will be removed from circulation, considerably shortening its half-life and duration of effect.

If there is a sensitising event\* at any time, even within a few weeks of administration, it is important to quantify the magnitude of the FMH. Depending on the magnitude of the FMH, more than one dose of Rh(D) Immunoglobulin-VF may be required.

\* Sensitising events include normal delivery, ectopic pregnancy, miscarriage, termination of pregnancy and ultrasound needle guided procedures such as chorionic villus sampling, amniocentesis, cordocentesis and fetoscopy. Also abdominal trauma considered sufficient to cause fetomaternal haemorrhage, external cephalic version or antepartum haemorrhage.

Reference:

- Pollack W, Ascari WQ, Kochesky RJ et al. *Studies on Rh prophylaxis. Relationship between doses of anti-Rh and size of antigenic stimulus. Transfusion 1971; 11: 333-9.*

### 2. **What dose of Rh(D) Immunoglobulin-VF will protect against 1 mL of fetal Rh(D) positive red cells?**

It is reasonably well established that 100 IU of Rh(D) Immunoglobulin-VF 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 625 IU should protect against a FMH of up to 6 mL of fetal Rh(D) positive red cells (12 mL of whole blood).

References:

- Pollack W, Ascari WQ, Kochesky RJ et al. *Studies on Rh prophylaxis. Relationship between doses of anti-Rh and size of antigenic stimulus. Transfusion 1971; 11: 333-9.*
- *Guidelines on the prophylactic use of Rh(D) Immunoglobulin (Anti-D) in obstetrics. NHMRC Report. 2003.*

### 3. **What are the recommendations regarding the administration of Rh(D) Immunoglobulin-VF and the MMR vaccination?**

MMR (Measles, Mumps, Rubella) is a live attenuated vaccine. The Blood Service/CSL Rh(D) Immunoglobulin-VF approved Product Information cautions that passively acquired antibody from the administration of Rh(D) immunoglobulin can interfere with the response to live attenuated vaccines. Thus, it is recommended that administration of live attenuated vaccines like poliomyelitis and MMR be deferred until approximately 3 months after passive immunisation. By the same token, it is recommended that immunoglobulins should not be administered for at least 2 weeks after a live attenuated vaccine has been given.

The Australian Immunisation Handbook, however, states that Rh(D) immunoglobulin does not interfere with the antibody response to the MMR vaccine. The Handbook suggests the two injections may be given at the same time in different sites with separate syringes, or at any time in relation to each other. With this in mind, administration of live attenuated vaccines and Rh(D) Immunoglobulin should be at the healthcare professional's discretion.

*References:*

- *Approved Product Information for Rh(D) Immunoglobulin-VF*
- *The Australian Immunisation Handbook 10th Edition (NHMRC)*

**4. For Rh(D) negative women who are not rubella immune, what is the recommended administration regimen for Rh(D) Immunoglobulin-VF and the rubella vaccine?**

The approved Product Information for the Blood Service/CSL Rh(D) Immunoglobulin-VF states that a live attenuated vaccine, such as rubella, should not be administered within 3 months of an injection of Rh(D) Immunoglobulin-VF. Passively acquired antibody can interfere with the response to live attenuated virus vaccines. If a patient has been vaccinated with the rubella vaccine and subsequently requires Rh(D) immunoglobulin, the Rh(D) immunoglobulin should be administered at least 2 weeks after the rubella vaccine to avoid interference with the immune response to the rubella vaccine. If the need to administer Rh(D) immunoglobulin is urgent, for example after a FMH, the patient should be checked for seroconversion two months after vaccination and revaccinated if seroconversion has not occurred.

In clinical practice, it is standard for women who are rubella seronegative on antenatal screening to be vaccinated after delivery, before discharge from the maternity unit of the hospital. For optimum efficacy, Rh(D) Immunoglobulin-VF must be administered within 72 hours post partum.

The Australian Immunisation Handbook states that Rh(D) immunoglobulin and the rubella vaccine may be given at the same time, or at any time in relation to each other, in different sites with separate syringes. In such cases, it is recommended that the patient's General Practitioner is alerted to test for seroconversion two months after vaccination and revaccinate the patient if necessary.

*References:*

- *Approved Product Information for Rh(D) Immunoglobulin-VF*
- *The Australian Immunisation Handbook 10th Edition (NHMRC)*

**5. What is the risk of viral transmission with Rh(D) Immunoglobulin-VF?**

There has never been a confirmed case of viral transmission by the Blood Service/CSL Rh(D) Immunoglobulin-VF.

*Reference:*

- *Data held on file by CSL Behring*

**6. Does Rh(D) Immunoglobulin-VF contain thiomersal?**

(Thiomersal is a mercury based antibacterial preservative used in some products).

No, the Blood Service/CSL Rh(D) Immunoglobulin-VF does not contain thiomersal.

*Reference:*

- *Data held on file by CSL Behring*

**7. Does Rh(D) Immunoglobulin-VF contain red blood cells?**

Rh(D) Immunoglobulin does not contain red blood cells.

## **8. What are the storage requirements for Rh(D) Immunoglobulin-VF?**

The Blood Service/CSL Rh(D) Immunoglobulin-VF should be stored under appropriate cold-chain conditions (refrigerate at 2° to 8°C, do not freeze, protect from light). Do not use after the expiry date shown on the label. Any unused product should be discarded in a medically acceptable manner.

Reference:

- *Approved Product Information for Rh(D) Immunoglobulin-VF*

## **9. What intravenous Rh(D) immunoglobulin product is currently available in Australia and how can I access it?**

A quantity of Rhophylac is available in reserve where access to an intravenous preparation is warranted. This product may be accessed via the Blood Service. Contact the Blood Service Transfusion Medicine Specialist in your capital city.

Reference:

- *Approved Product Information for Rhophylac*

## **List of Rhophylac Questions**

- 1. Is Rhophylac as safe as the Rh(D) Immunoglobulin-VF product fractionated by CSL Behring?**
- 2. What are the major differences between the Blood Service/CSL Rh(D) Immunoglobulin-VF and Rhophylac Rh(D) immunoglobulin?**
- 3. Does Rhophylac contain thiomersal?**
- 4. Does Rhophylac contain red blood cells?**
- 5. What are the storage requirements for Rhophylac?**

## **Rhophylac Questions and Answers**

- 1. Is Rhophylac as safe as the Rh(D) Immunoglobulin-VF product fractionated by CSL Behring?**

The plasma used to manufacture Rhophylac comes from US donors who are carefully screened and briefed about their responsibility and is collected at TGA and FDA approved blood centres. The quality assurance measures performed in the manufacture of Rhophylac are comparable to those used by the Blood Service and CSL Behring during the collection of plasma for, and manufacture of, Rh(D) Immunoglobulin-VF.

The pathogen safety measures in place for Rhophylac include the careful selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Solvent-detergent treatment and virus filtration clearance steps included in the manufacturing process ensure the viral safety of the product. The measures taken are considered effective for enveloped viruses such as HIV, HBV, and HCV and for the non-enveloped viruses HAV and parvovirus B19.

References:

- *Approved Product Information for Rhophylac*
- *Approved Product Information for Rh(D) Immunoglobulin-VF*

**2. What are the major differences between the Blood Service/CSL Rh(D) Immunoglobulin-VF and Rhophylac?**

Feature	Blood Service/CSL Rh(D) Immunoglobulin- VF	Rhophylac
<b>Viral Inactivation Steps</b>	Pasteurisation & nanofiltration	Solvent detergent & nanofiltration
<b>Administration</b>	Intramuscular only	Intramuscular or Intravenous
<b>Formulation</b>	Liquid, ready to use	Ready to use, pre-filled syringe
<b>Presentation</b>	250 IU, 625 IU	1500 IU

**3. Does Rhophylac contain thiomersal?**

(Thiomersal is a mercury based antibacterial preservative used in some products).

No, Rhophylac does not contain thiomersal.

Reference:

- *Approved Product Information for Rhophylac*

**4. Does Rhophylac contain red blood cells?**

No, Rhophylac does not contain red blood cells.

Reference:

- *Approved Product Information for Rhophylac*

**5. What are the storage requirements for Rhophylac?**

Rhophylac has a shelf life of 3 years (36 months) when stored at 2-8°C and protected from light. It must not be frozen. Do not use after the expiry date.

Reference:

- *Approved Product Information for Rhophylac*

For further medical and/or technical inquiries, please contact the Medical Affairs Department at CSL Behring:

Free Phone: 1800 642 865

Phone: +61 3 9389 1932

Email: [MedicalInformation.Aust@csl.com.au](mailto:MedicalInformation.Aust@csl.com.au)

# Policy Questions and Answers

## Introduction

The following answers to frequently asked questions are intended for use by healthcare professionals and have been endorsed by the National Blood Authority. The answers below were reviewed and updated in June 2015 by the Expert Consensus Panel.

### Abbreviations used in this section:

IU	International Units
FMH	Fetomaternal Haemorrhage
NBA	National Blood Authority
NHMRC	National Health and Medical Research Council
Blood Service	Australian Red Cross Blood Service

NHMRC Report (1999): National Health and Medical Research Council (NHMRC)  
[Guidelines on the prophylactic use of Rh\(D\) immunoglobulin \(Anti-D\) in obstetrics 1999](#)

NHMRC Report (2003): National Health and Medical Research Council (NHMRC)  
[Guidelines on the prophylactic use of Rh\(D\) immunoglobulin \(Anti-D\) in obstetrics 2003](#)

## List of Policy Questions

- 1. What is the Australian policy regarding Rh(D) antenatal immunoprophylaxis?**
- 2. Where do I obtain further information on Rh(D) immunoglobulin?**
- 3. Am I able to access an intravenous Rh(D) immunoglobulin preparation?**

## Policy Questions and Answers

- 1. What is the Australian policy regarding Rh(D) antenatal immunoprophylaxis?**

In 1999, the National Health and Medical Research Council (NHMRC) published guidelines aiming to balance best practice in the use of Rh(D) immunoglobulin with 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 the 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, including

- the introduction of a 250 IU dose of Rh(D) immunoglobulin in May 2001 and its use in potentially sensitising events in the first trimester,
- approval was obtained for the use of an overseas Rh(D) immunoglobulin product in October 2002 to ease the pressure on the domestic supply until self-sufficiency could be reached,
- notwithstanding the above, Governments developed a supply risk mitigation strategy to ensure continuity of supply for any product in the event of an inability to supply; and
- additional funding was provided by Governments to the Blood Service 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, the Working Party recommended a staged implementation of full antenatal prophylaxis as follows:-

- Stage 1 provided for routine antenatal prophylaxis at 28 and 34 weeks gestation for Rh(D) negative women without preformed anti-D having their first baby reaching at least 28 weeks gestation. During this stage, an overseas Rh(D) immunoglobulin product, WinRho SDF™, was used for postnatal prophylaxis. This stage commenced in November 2002.
- In Stage 2, routine antenatal prophylaxis at 28 and 34 weeks gestation was extended to all Rh(D) negative women without preformed anti-D and still required the use of WinRho SDF™ for postnatal prophylaxis. Stage 2 of the program commenced in January 2005.
- In Stage 3, the final stage of the program, both antenatal and postnatal Rh(D) immunoprophylaxis are now fully supported by Australian sourced Rh(D) immunoglobulin. Stage 3 commenced in March 2006.

Arrangements have also been put in place to ensure there is sufficient Rh(D) immunoglobulin available in Australia in the case of unexpected events.

For Stage 3, the available Rh(D) immunoglobulin products should be used as indicated below:

- First trimester sensitising events<sup>1</sup> (<12 weeks): Rh(D) Immunoglobulin 250 IU
- First trimester sensitising events<sup>1</sup> (multiple pregnancies <12 weeks): Rh(D) Immunoglobulin 625 IU
- Second and third trimester sensitising events<sup>1</sup> (>12 weeks): Rh(D) Immunoglobulin 625 IU
- All Rh(D) negative women without preformed anti-D: Rh(D) Immunoglobulin 625 IU at 28 and 34 weeks gestation
- Postnatal prophylaxis: Rh(D) Immunoglobulin 625 IU

**Note 1:** Sensitising events include ectopic pregnancy, miscarriage, termination of pregnancy and ultrasound guided procedures such as chorionic villus sampling, amniocentesis, cordocentesis and fetoscopy, as well as abdominal trauma considered sufficient to cause fetomaternal haemorrhage, external cephalic version, antepartum haemorrhage and normal delivery.

## **2. Where do I obtain further information on Rh(D) immunoglobulin?**

Further information is available from the Blood Service website [www.transfusion.com.au](http://www.transfusion.com.au) and the CSL website [www.csl.com.au](http://www.csl.com.au).

## **3. Am I able to access an intravenous Rh(D) immunoglobulin preparation?**

In some circumstances, access to an intravenous Rh(D) immunoglobulin preparation may be warranted. A quantity of intravenous Rh(D) immunoglobulin will be made available for this purpose. This product may be accessed via the Blood Service.

It should be noted that the NBA has only approved the use of intravenous Rh(D) immunoglobulin for the following indications within Australia:

- For the management of large FMH where administration of intramuscular Rh(D) immunoglobulin is either contraindicated or not practical.
- To prevent alloimmunisation in Rh(D) negative females of child-bearing potential who have been transfused with Rh(D) positive red cells or blood components.

Specifically, intravenous Rh(D) immunoglobulin is not authorised for use in immune thrombocytopenic purpura (ITP) within Australia.