NZBLOOD
Te Ratonga Toto O Aotearoa

Haemovigilance

Annual Report
2005

Blood ready for issue

National Haemovigilance Programme

Contents

Disclaimer

Protected Quality Assurance Activity

Haemovigilance has been declared a 'protected quality assurance activity' under section 54 of the Health Practitioners Competence Assurance Act 2003 as notified by the Health Practitioners (Quality Assurance Activity: New Zealand Blood Service) Notice 2006, published in the *New Zealand Gazette* on 6 April 2006.

The effect of this declaration is that subject to certain exceptions:

- any information that becomes known solely as a result of haemovigilance is confidential; and
- any documents brought into existence solely for the purposes of haemovigilance are confidential; and
- the persons who engage in haemovigilance in good faith are immune from civil liability.

Patient Privacy

Patient identification in the form of NHI (National Health Index) number is collected as part of the initial notification of events. This identifier is used solely to enable follow up of patients in serious events or where further information is required to complete (or verify) the initial notification.

Patient information may subsequently be shared with only those DHB and NZBS health professionals directly involved in the reporting, investigation and management of individual haemovigilance events.

The electronic data relating to the cases on which this annual report are based have been placed into an archival database from which the NHI information and unique haemovigilance number have been removed. Patient identifier information has also been removed from the original notification forms. These have then been placed into secure document storage according to NZBS policy.

From the information held in the electronic and paper archives it is not possible to identify individual patients.

Abbreviations

AABB	American Association of Blood Banks
AML	Acute myeloid leukaemia
ATE	Adverse transfusion event
BNP	Brain-type natriuretic peptide
CAG	Clinical Advisory Group
CoE	Council of Europe
Cryo	Cryoprecipitate
DAT	Direct antiglobulin test
DHB	District Health Board
EHN	European Haemovigilance Network
FDA	(US) Food and Drug Administration
FFP	Fresh frozen plasma
Hb	Haemoglobin
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLA	Human leucocyte antigen
HNA	Human neutrophil antigen
HTC	Hospital Transfusion Committee
IANZ	International Accreditation New Zealand
IBCT	Incorrect blood component transfused
ISBT	International Society of Blood Transfusion
NHFTR	Non-haemolytic febrile transfusion reaction
NHI	National Health Index
NZBS	New Zealand Blood Service
PMF	Plasma master file
SHOT	Serious hazards of transfusion
SOP	Standard operating procedure
TACO	Transfusion-associated circulatory overload
TA-GvHD	Transfusion-associated graft-versus-host disease
TMS	Transfusion Medicine Specialist
TNS	Transfusion Nurse Specialist
TRALI	Transfusion-related acute lung injury
TSO	Transfusion Safety Officer
TTI	Transfusion-transmitted infection
vCJD	Variant Creutzfeldt-Jakob disease

Foreword

The publication of this, the first, annual haemovigilance report for New Zealand is a significant milestone for both NZBS and the wider health sector. The report provides information on the adverse events associated with transfusion in New Zealand. It will assist health professionals to better understand the risks associated with transfusion and to communicate these to potential recipients.

During the last few years considerable efforts have been devoted to gaining support for the haemovigilance initiative in New Zealand. The ability to produce a report of this type requires support from all those many individuals, including doctors, nurses and laboratory staff, involved in the delivery of transfusion to patients. NZBS is very appreciative of the time and effort that these individuals have given to ensuring the success of the initiative.

Easy access to blood transfusion has underpinned many of the successes of modern medicine and surgery. Each year many lives are saved and almost 200,000 blood components are transfused to patients in hospitals across New Zealand.

In recent years much emphasis has been devoted to better understanding the risks associated with transfusion. The successful development of a haemovigilance scheme in New Zealand is a further step forward in this process. It is however important to avoid overestimating the risks associated with transfusion. It remains the case that for most patients, when properly and appropriately administered, transfusion therapy is both safe and effective.

Haemovigilance schemes provide an opportunity to both understand the type and frequency of adverse events linked to transfusion. Information from similar schemes in other countries has shown that a proportion of adverse events are avoidable. These events generally result from breakdown in the complex systems used to deliver blood products to patients. Data obtained from the haemovigilance programme in New Zealand therefore provides an opportunity to review and improve these systems and in doing so increase the overall safety profile of transfusion.

Dr Peter Flanagan
NZBS National Medical Director

Trends In Blood Product Usage In New Zealand

New Zealand is self sufficient in blood and blood products. Essentially all blood products used in New Zealand are obtained from voluntary donations given by New Zealanders. NZBS is the sole supplier of blood and blood products and is responsible for provision of blood, blood products and related services to hospitals throughout the country. Given this NZBS must carefully match overall collection levels to the predicted demands for blood products. This involves monitoring of activity levels and trends in clinical demand.

Blood products can be divided into two main categories. The first type is blood components. These are produced from individual donations at NZBS sites. Blood components include red cells, platelet concentrates and fresh frozen plasma. The second type of blood product is plasma products. These are manufactured from large pools of plasma (each pool containing approximately 7.5 tonnes). NZBS sends its plasma to CSL Bioplasma in Melbourne, Australia. During processing New Zealand plasma is segregated from that of other countries. All products manufactured from New Zealand plasma are returned to NZBS for distribution to hospitals across New Zealand.

The table below shows the level of issues of blood products to hospitals by NZBS during the period 2002 to 2005. Overall demand for red cell and fresh frozen plasma (FFP) components has remained reasonably stable. Demand for platelet concentrates fluctuated markedly over the four-year period, however when analysed more closely, there appears to be an upward trend. In contrast there has been a significant, and ongoing, increase in clinical requirements for Intragam P® (intravenous immunoglobulin). The increase seen in New Zealand mirrors international trends. Clinical demand for Intragam P® is now the main driver of blood collection in New Zealand.

Table 1: Blood Products Issues

Calendar Year	Red Cells	Platelets *	FFP	Intragam P ®**
2002	135481	14423	24481	13024
2003	137031	13981	22191	13813
2004	136385	16037	24452	15110
2005	136238	15327	22303	16246

** Standard adult doses ** Intragam P® 200ml equivalents*

NZBS is using plasmapheresis to meet the increased requirement for plasma. This involves the use of automated machines to collect plasma from donors. With the use of plasmapheresis NZBS avoids excessive collection of whole blood and the consequent expiry of red cell components.

NZBS has implemented a national blood management system called Progesa. This system is used within NZBS to track donors and donations and is also used in all main District Hospital Board (DHB) Blood Banks responsible for providing blood products to patients. In international terms this is possibly unique and provides an opportunity to analyse transfusion patterns across the country.

NZBS is increasingly using data extracted from Progesa to inform and assist DHBs in improving overall practice of transfusion in New Zealand. Full national implementation of Progesa was completed in March 2005 when the Counties Manukau DHB Blood Bank went live on the system.

Table 2 provides information from Progesa on the number of people receiving blood products during the 2005 calendar year. The data on number of recipients will not include recipients transfused in Counties Manukau during the period prior to implementation of Progesa in March of that year. This will therefore be an underestimate of total patients, probably in the order of 1-2% for red cells and less for other products.

In total 25493 people were transfused with red cells during the year. These included newborn infants and people over 100 years old. A small number of transfusions will also have been given to foetuses in utero. The maximum number of red cells transfused to any recipient during the year was 123 units. The mean level of transfusion per recipient was 5 units with a median figure of 3 units.

3164 patients received platelet transfusions. Overall, recipients were younger than the pattern seen in red cells. The maximum number of adult doses given to one patient was 212, with a mean of 4 doses and a median of 2.

4531 recipients received treatment with FFP. The maximum number of units received was 106 with a mean of 5 units and a median of 2 units.

834 recipients received treatment with Intragam P®. The age range of recipients was between 0 and 92 years with a mean of 47 and a median of 45. The largest dose received by a single individual was 1755g with a mean of 220g and a median of 150g.

Table 2: Blood Product Recipients During 2005

		Red Cells	Platelets *	FFP	Intragam P®
Number recipients	Female	14483	1196	1777	385
	Male	10880	1966	2743	460
	Unknown	130	2	11	9
	Total	**25493**	**3164**	**4531**	**854**
Age of recipients	Mean	68	49	64	47
	Median	62	45	59	45
	Maximum	105	75	101	92
	Minimum	0	0	0	0
Units transfused per recipient **	Mean	5	4	5	220
	Median	3	2	3	150
	Maximum	123	212	106	1755
	Minimum	1	1	1	3

** Standard adult doses ** Intragam P® usage in grams*

In future reports data on the number of recipients and the amount of product transfused will assist in interpretation of the data on frequency of adverse events associated with transfusion provided later in this report.

Introduction To Haemovigilance

The provision of safe transfusion therapy is a basic requirement of advanced medical care. Despite major advances in viral and bacterial detection and the subsequent reduction in risk of transfusion transmitted infections there are still other significant risks associated with transfusion. For example, 81% of adverse events or reactions reported to the UK's 'Serious Hazards Of Transfusion' (SHOT) scheme were due to transfusion of a blood component (or fractionated product) that did not meet appropriate requirements or which was intended for another patient [1]. The transfusion literature also clearly shows that the risk of mistransfusion events is several orders of magnitude higher than those for viral infections such as HIV, HBV or HCV.

Haemovigilance has become an important and integral part of transfusion medicine. For example a recent international forum in the transfusion journal *Vox Sanguinis* [2] presented information and data on haemovigilance activities in 22 countries. Similarly, groups such as the 'European Haemovigilance Network' and the International Society Of Blood Transfusion (ISBT) 'Working Party on Haemovigilance' attract members from many of the countries, including New Zealand, with (or interest in introducing) haemovigilance programmes. A key activity on which these two groups are jointly working is developing a set of standard definitions for transfusion reactions and other transfusion-related events.

The Council of Europe (CoE) has a well established blood transfusion programme the aim of which is to ensure good quality of blood and blood products within its member states and which includes haemovigilance activities. An expert committee is responsible for drafting the '*Guide to the preparation, use and quality assurance of blood components*' [3], recognised internationally as a gold standard for blood services and used as the basis for many national guidelines including those under which NZBS operates. NZBS has a commitment to the principles of the CoE and has observer status on the CoE 'Committee of Experts on Quality Assurance in Blood Transfusion Services'. Furthermore, European Union Directive 2002/98, which took effect in November 2005, requires all countries of the EU to have processes by which all blood and blood components are fully traceable and where adverse events related to transfusion are monitored. These requirements subsequently become law as the directive is transposed into the national legislation of each country.

What then is haemovigilance?

There are a number of definitions of haemovigilance with the simplest being "…*traceability*…"or being able to trace each individual unit of blood, blood components or blood products from the donor to its final destination, whether this is a patient, manufacturer or disposal. NZBS has however adopted the CoE definition of haemovigilance:

"…*the organised surveillance procedures related to serious adverse or unexpected events or reactions in donors or recipients and the epidemiological follow up of donors*…" [3]

NZBS collects a wide range of data, which are considered under the umbrella of haemovigilance. In addition to transfusion-related events these include data on the number of donations collected, number of components transfused, wastage and outdating of components, bacterial monitoring of platelets, reporting of adverse reactions to fractionated products, donor-related incidents, donor infectious disease epidemiology amongst others.

The process of drawing these activities into the formal haemovigilance programme together with other associated activities, for example sample and request form labelling errors, blood bank errors and near misses, is currently underway.

Of Transfusion-Related Adverse Events

The ***Haemovigilance*** programme for notification of transfusion-related adverse events was formally introduced by NZBS on 1 May 2005 following an initial four-month pilot programme at three North Island hospitals. The programme follows the calendar year from January through December with data gathered in the eight months from 1 May to 31 December 2005 included in this report.

Modelled on similar schemes in the UK and Ireland the programme collects data on the incidence of **all** types of transfusion-related adverse events not only so-called transfusion 'reactions'. 13 categories of event have been selected which include incorrect blood components or products transfused, immune and cardiovascular complications of transfusion, transfusion transmitted infections and events due to specific equipment or components.

Definitions for the event categories are derived from those used by SHOT and from the EHN 'Working Party on definitions of adverse transfusion events (ATEs)' released in 2004. It is hoped that an internationally agreed set of definitions produced jointly by the EHN and ISBT will be released at the 2006 ISBT Congress in Cape Town.

Events are reported using a dedicated form, copies of which are held by all blood banks in New Zealand. Accompanying the form is a 'user guide' which is intended to aid completion of the form. Depending on the type and severity of event being reported there are specific follow-up questionnaires for obtaining more detailed information about the event including the patient outcome and sequelae.

Each reported incident is categorised as serious or non-serious with serious events requiring further discussion with a NZBS Transfusion Medicine Specialist (TMS).

A serious event is defined as any adverse event that:

- requires hospitalisation or a prolonged hospital stay
- results in persistent or significant disability or incapability
- necessitates medical or surgical intervention to prevent permanent damage or impairment of a body function
- is associated with severe temporary or permanent morbidity and/or mortality

It is necessary to understand the relationship between the reported event and transfusion. At the time of transfusion there are many factors contributing to the patient's physiological status, for example their underlying condition(s), concurrent treatment or medication. One, some or all of these may cause a reaction or other observable change in the patient.

Consideration is therefore given to the likelihood that a serious adverse event or reaction can be attributed to the blood component or product being transfused.

This assessment of *imputability* is based on the following CoE classification:

Table 3: Imputability Assessment Scale

Imputability Scale		Explanation
NA	Not assessable	When there is insufficient data for imputability assessment
0	Excluded	When there is conclusive evidence beyond reasonable doubts for attributing the event to alternative causes
0	Unlikely	When the evidence is clearly in favour of attributing the event to causes other than the blood or blood components
1	Possible	When the evidence is indeterminate for attributing the event either to the blood or blood components or alternative causes
2	Likely, probable	When the evidence is clearly in favour of attributing the event to the blood or blood components
3	Certain	When there is conclusive evidence beyond reasonable doubt for attributing the event to the blood or blood components

Participation in the ***Haemovigilance*** programme is voluntary although actively encouraged. It does however appear to have gained acceptance, with all of the District Health Board's (DHB's) represented in the notifications received during the first eight months of activity.

Each hospital blood bank has a nominated 'Transfusion Safety Officer' (TSO) normally the Charge Biomedical Scientist. Whilst this role has no formal responsibility it is hoped that all events at the hospital level are notified through the TSO who then forwards a completed notification form to NZBS.

The blood banks associated with the six NZBS centres also have a Transfusion Nurse Specialist each of whom provides a valuable resource in the follow up of reported events and educating those involved in the transfusion process.

What about the upcoming year 2006 and beyond?

A major task for the ***Haemovigilance*** programme is to encourage the detection and reporting of adverse events other than 'traditional' transfusion reactions, for example transfusion of incorrect or inappropriate blood or blood components.

When a person receives a blood component or product intended for another patient or blood components or products where special requirements, e.g. irradiation, are not met, unless there is a major incompatibility the patient may not experience any obvious side effects. The event may subsequently be missed, overlooked or believed to be not worth reporting. However it is important to recognise and report these events. In common with other types of event, the transfusion of an incorrect blood component represents a breakdown in the system, which needs to be identified and subsequently corrected to prevent similar events happening in the future. Another challenge is that reporting of these events may occur through a hospital's quality or incident management system and therefore not come to the attention of the blood bank or NZBS. For haemovigilance to succeed it is important that all such incidents or events are reported to the hospital's Transfusion Safety Officer who will subsequently notify the National Haemovigilance Office. Naturally NZBS will work with hospitals to ensure that adverse events are appropriately reported in a timely manner.

Blood transfusion is a complex process involving different staff groups in the hospital including those from the laboratory, nurses, doctors and orderlies. Any breakdown in the transfusion chain has the potential to cause significant harm to, or even death of, patients. Therefore **all** personnel

involved in the transfusion process should be encouraged to be vigilant and report any untoward events that they may observe whether or not transfusion has actually occurred.

Finally, for haemovigilance to be successful there needs to be an awareness of the programme and what it hopes to achieve. Hopefully issuing this annual report will provide a stimulus for this.

Donors-Related Adverse Events

The safety of the New Zealand blood supply starts with the donors who provide the valuable resource from which all blood components and fractionated products are derived. Ensuring the welfare of its donors is vitally important for NZBS but inevitably donors will experience occasional detrimental side effects to the donation process and data regarding these from 2005 is presented in this report.

Infectious Disease Screening

Detection of transfusion-transmissible infections and in particular HBV, HCV and HIV is the cornerstone on which a safe blood supply is based. Advances in the detection of these viruses means that the risk of acquiring a transfusion-transmitted infection is now extremely low.

Collection of data regarding the number of donors found to be confirmed positive for one of the aforementioned infectious markers during routine screening is well established and figures for 2005 are presented in this report.

Reactions To Fractionated Products

Large volumes of fractionated plasma products are used in the treatment of a wide range of conditions. Although rare, patients do occasionally experience reactions to these products and these are notified both to NZBS and the manufacturer of the implicated product. Once again this is a well established process for which 2005 data is provided.

Types Of Event

The following table provides the primary definitions against which transfusion-related adverse events are classified. Further information on the complications of transfusion can be found in appendix 2.

These definitions are based on those used by the UK SHOT scheme and incorporate the NZBS categorisation of events which appears on the NZBS '*Notification And Investigation Of Adverse Transfusion Reaction*' form [4].

Table 4: Types Of Adverse Event

Type Of Adverse Event	Definition
Incorrect blood component / product transfused	Patient was transfused with a blood component or plasma product that did not meet the appropriate requirements or which was intended for another patient.
Acute haemolytic and other severe acute transfusion reactions	A reaction occurring at any time up to 24 hours following a transfusion of blood or blood components, excluding cases of acute reactions due to an incorrect component being transfused. The major concern in evaluating these is exclusion of bacterial contamination of the component or haemolysis due to incompatible red cells.
Delayed transfusion reaction	A reaction occurring more than 24 hours following a transfusion of blood or blood components. These are usually delayed haemolytic reactions due to the development of red cell alloantibodies. Simple alloantibody development without a positive DAT or evidence of haemolysis is excluded.
Non-haemolytic febrile transfusion reaction (NHFTR)	
• **Mild**	**Mild reaction** Increase of temperature <1.5°C from baseline and no other symptoms, evidence of haemolysis or infection.
• **Moderate / severe**	**Moderate / severe reaction** Increase of temperature ≥1.5°C from baseline with rigors / chills but no evidence of haemolysis or infection.
Transfusion-related acute lung injury (TRALI)	Acute dyspnoea with hypoxia and bilateral pulmonary infiltrates occurring within 6 hours of transfusion, with no other apparent cause.
Transfusion-associated graft-versus-host-disease (TA-GvHD)	The development of classical symptoms of fever, rash, liver dysfunction, diarrhoea and pancytopenia occurring 1-6 weeks following transfusion without other apparent cause. The diagnosis is supported by skin/marrow biopsy appearances and/or the presence of circulating donor lymphocytes.

Type Of Adverse Event	Definition
Post-transfusion purpura (PTP)	Thrombocytopenia arising 5-12 days following transfusion of red cells associated with the presence in the patient of antibodies directed against the HPA (Human Platelet Antigen) systems.
Allergic reaction:	
• **Minor allergic reaction**	Skin reaction characterised by transient urticarial or other skin rash. No fever or other symptoms.
• **Anaphylactoid / anaphylactic**	Anaphylactoid and anaphylactic reactions span a range of symptoms of varying severity such as stridor, wheeze, bronchospasm, laryngeal oedema and hypotension.
Transfusion associated circulatory overload (TACO)	Volume overload leading to congestive cardiac failure with symptoms of dyspnoea, cyanosis, tachycardia and hypertension with associated fluid retention and oedema occurring within 24 hours of transfusion.
Transfusion transmitted infection (TTI)	Post-transfusion infection resulting from transfusion of a component contaminated with bacteria, viruses or parasites.
Equipment-related	An adverse event resulting from use, misuse or malfunction of a piece of equipment involved in the transfusion including filters, infusion pumps, blood warmers or pressure devices.
Component-related	An adverse event related to an additional constituent of the component e.g. anticoagulant or use, misuse or defect of the component bag or container occurring at some point from collection from the donor through to the final transfusion. These may also include use of an incorrect or inappropriate IV fluid with the component.
Other type of reaction	Any adverse event that is not currently known or recognised to be associated with transfusion of blood components (or products) or one which does not fit any of the other categories provided.

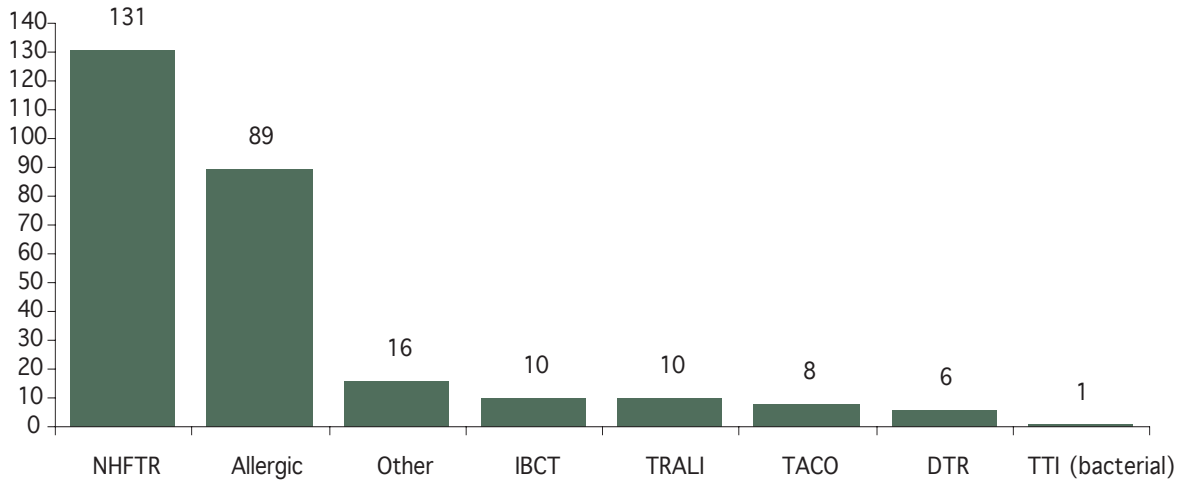
Transfusion-Related Adverse Events: Overview Of Data

Types Of Event

During the eight month period covered by this report, 271 events (involving 257 recipients) were available for analysis, having been assessed as meeting criteria for inclusion into the ***Haemovigilance*** database. A further 26 notification forms were received for which the events recorded did not meet criteria.

Chart 1 shows the number of events reported categorised by type of event:

Chart 1: Types Of Event Reported (n=271)



Profile Of Recipients

The proportion of females compared to males is slightly higher (53.3% versus 46.7%) although the median age is similar for both sexes.

The age distribution is clearly weighted towards the older end of the spectrum with over half of recipients (53.3%) aged 60 years or more. In contrast, paediatric recipients (defined as those aged 18 years or less) account for only 12.5% of events. This reflects the age profile of patients receiving blood products in New Zealand

Table 5 shows the age and sex distribution of the 257 recipients included in the database:

Table 5: Age And Gender Profile Of Recipients (n=257)

Gender	No.	Median Age	Mean Age	Max Age	Min Age
Female	137	63	54.4	95	2
Male	120	62	55.4	88	0*

* 6 weeks

Origin Of Notification Forms

Notification forms were received from 34 hospitals (30 public and 4 private). Reports were received from all 21 DHBs. In one instance however (Lakes DHB) the only report related to a transfusion occurring in a private hospital.

A monthly summary of the number of notification forms received is shown in the following table:

Table 6: Origin Of Reports

DHB	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Total
Auckland	7	6	6	9	8	9	3	6	**54**
Bay Of Plenty	3	3	3	1	1	1		1	**13**
Canterbury	4	3	4	2	3	1	1	3	**21**
Capital and Coast	5	1	5	4	3	9	2	4	**33**
Counties Manukau	7	1	3	4	2	2	3		**22**
Hawkes Bay	2	2	1	1	1	1	2	1	**11**
Hutt Valley	1					2		1	**4**
MidCentral	1	2	1	3	5	2	3	1	**18**
Nelson Marlborough			1						**1**
Northland		1		2	1				**4**
Otago	2	1		3		3	4	3	**16**
South Canterbury			1			1		1	**3**
Southland	2			2	2			1	**7**
Tairawhiti				1	1		2		**4**
Taranaki					1			1	**2**
Waikato		3	5	5	8	7	5	7	**40**
Waitemata	1	1				1	3	1	**7**
Wairarapa	1		1					1	**3**
West Coast		2							**2**
Whanganui				1				1	**2**
Private Hospitals		1	1			1	1		**4**
Totals	**36**	**27**	**32**	**38**	**36**	**40**	**29**	**33**	**271**

Clearly not all hospitals (or other facilities) performing transfusions are represented in the notifications received. For those hospitals not present it cannot be assumed that no transfusion-related adverse events or reactions occurred but simply that none were notified to the haemovigilance office.

Total Numbers Of Blood Components Issued And Transfused

During the period for which data relating to transfusion-related adverse events was available (1 May to 31 December 2005) the following components were transfused:

Table 7: Total Numbers Of Blood Components Transfused

Component	Transfused
Red cells	81545
Platelets (apheresis) *	4401
Platelets (pooled) *	3289
Fresh frozen plasma	14063
Cryoprecipitate	1217
Cryodepleted plasma	419
Total	**104934**

** Equivalent to one standard adult dose*

Blood Components/Products Implicated In Events

The notification form provides information on the component(s) implicated in the event being notified. In some cases only the unit being transfused at the time of the event is recorded whilst in others all units transfused up until the event are included.

Of the 271 events analysed, 246 reportedly involved a single component (or product). Based on information provided at notification the following table shows whether single or multiple components (or products) were recorded:

Table 8: Single Or Multiple Components/Products Implicated In Events

	Single Component Type Reported						
	Red Cells	Platelets (Apheresis)	Platelets (Pooled)	FFP	Cryo-depleted Plasma	Other *	Multiple Components
NHFTR	121	5		2			3
Allergic	37	13	8	16	3		12
Other	12	1		2			1
IBCT	3		1	2		3	1
TRALI	4	1		1	1		3
TACO	2			2			4
DTR	5						1
TTI			1				
Total	**184**	**20**	**10**	**25**	**4**	**3**	**25**

** 2 cases of blood products and 1 case of serum eye drops*

Incidence Of Transfusion-related Adverse Events

Using data from tables 7 and 8 above the incidence of transfusion-related adverse events is as follows:

*Table 9: Incidence Of Transfusion-Related Adverse Events By Component Type **

Component	% Of Components Transfused	Rate
Red cells	0.25	1:402
Platelets (apheresis)	0.68	1:147
Platelets (pooled)	0.52	1:193
Fresh frozen plasma	0.31	1:327
Cryoprecipitate	0.16	1:609
Cryodepleted plasma	0.95	1:105
All	**0.26**	**1:392**

** Figures for individual components include those from events where multiple components implicated.*

Non-Haemolytic Febrile Transfusion Reactions (NHFTR)

Definition

Non-haemolytic febrile transfusion reactions are defined as mild, moderate, or severe dependent on the symptoms experienced by the patient:

- **Mild febrile transfusion reaction**
  Fever ≤ 38.5°C or an increase of <1.5°C from pretransfusion value without any other symptoms e.g. due to a haemolytic transfusion reaction [HTR] or bacterial infection.
- **Moderate / severe febrile transfusion reaction**
  Fever ≥ 38.5°C or an increase of ≥1.5°C from pretransfusion value plus one or more of the following: chills, cold, rigor, headache or nausea / vomiting.

NHFTR account for 131/271 (48.3%) of events analysed and involve 129 recipients. Although NHFTR are the most common type of transfusion-related event they are generally under-reported.

The table below categorises the events according to severity, either 'mild' or 'moderate / severe' as defined above:

Table 10: NHFTR Events Categorised According To Severity (n=131)

Type Of Event	No.
NHFTR – mild	45
NHFTR – moderate / severe	86

Profile Of Recipients

NHFTR were more prevalent in female patients (55% versus 45%) although the median ages for both sexes were similar. The older age groups were predominant among this category with those 50 years or older responsible for 72.9% of cases and those 60 years or older 62%.

Conversely the paediatric age group only accounted for 9/129 (7%) cases. The age and sex profile of recipients is shown below:

Table 11: Age And Gender Profile Of NHFTR Cases (n=129)

Gender	No.	Median Age	Mean Age	Max	Min
Female	71	65	57.1	93	3
Male	58	67	61.9	88	5

It was not always possible to clearly assign one specific event to a case report with a number of what were thought to be NHFTR's seemingly accompanied by other types of event (as defined by the symptoms provided). These are summarised below and in all cases the primary event was assumed to be the NHFTR:

Table 12: Other Events Reported Alongside NHFTR

Secondary Event	No.
Allergic reaction	3
Possible IBCT – Inappropriate transfusion	1
Possibly inappropriate transfusion for menorrhagia	1
Possible myocardial infarction associated with transfusion	1

Factors Affecting The Prevalence Of NHFTR

NHFTR occur more frequently in patients who have been pregnant or multitransfused. NHFTR represent an inflammatory response and are described as being due to the release of endogenous pyrogens (i.e. cytokines and chemokines) from the patient's macrophages or donor white cells. However the nature and occurrence of NHFTR is not entirely predictable and certainly depends on other factors such as the patient's characteristics or underlying condition.

Classically NHFTR have been attributed to transfusion of contaminated white cells in blood components. The use of leucocyte-depleted blood components has undoubtedly reduced the occurrence of NHFTR (by up to 50%). The relatively large number of reactions still routinely seen clearly suggests the involvement of other mechanisms and risk factors.

A recent article in the journal *Transfusion Medicine* [5] proposes that polymorphic variation in the inflammatory genes responsible for cytokine production and a consequent increase in production of cytokine proteins have a significant role in the occurrence of NHFTR particularly in multitransfused patients. However in a cautionary note it is observed that other gene polymorphisms, environmental factors and associated diseases may also affect cytokine production and so more studies are needed to determine if the proposed relationship is real.

Allergic Reactions

Definition

Allergic reactions are categorised according to the nature and severity of the symptoms observed in the recipient:

- ***Allergic reaction***
  One or more of the following: rash, allergic dyspnoea (stridor, cyanosis, wheezing), angioedema, generalised pruritis or urticaria, without hypotension during or within 24 hours of transfusion.
- ***Anaphylactoid reaction***
  An allergic reaction with hypotension (drop in systolic blood pressure by ≥ 30 mm Hg) during or within 24 hours of transfusion.
- ***Anaphylactic shock***
  Shock associated with blood transfusion without any signs of shock of other origin.

Allergic reactions are the second most numerous category of events after NHFTR, accounting for 89/271 (32.8%) of events reported. The table below further categorises the events according to severity, either 'allergic reaction or 'anaphylactic/anaphylactoid' reaction as defined above:

Table 13: Allergic Reactions (Categorised According To Severity)

Type Of Event	No.
Allergic reactions	83
Anaphylactic / anaphylactoid reaction	6

Of the 6 anaphylactic/anaphylactoid events 3 involved platelets, 1 involved FFP and 1 both FFP and platelets. The remaining event was attributed to red cells.

Profile Of Recipients

The patients in this category of event are evenly split between male and female whilst the median age for males is slightly higher than that for females, although in comparison to the NHFTR category the median ages are lower overall. The youngest recipient in this group was 4 months old with the paediatric age group accounting for 26.5% allergic events overall.

Table 14: Age And Gender Profile Of Allergic Reaction Cases (n=83)

Gender	No.	Median Age	Mean Age	Max Age	Min Age
Female	42	42	45.3	95	2
Male	41	49	42.0	87	0*

* 4 months

In a few cases an allergic reactions could not solely be assigned to the case report as additional symptoms suggested another coincidental event had also occurred:

Table 15: Other Events Reported Alongside Allergic Reactions

Secondary Event	No.
NHFTR	3
Transfusion-associated hypertension	1

Incorrect Blood Component Transfused (IBCT)

Definition

Where a patient was transfused with a blood component or fractionated blood product that did not meet the appropriate requirements or which was intended for another patient.

10 IBCT events were reported which represent 3.7% of all events. There are a number of categories associated with IBCT not all of which were seen during the period covered by this report.

The table below details the types of IBCT event notified to NZBS:

Table 16: IBCT Events Categorised By Type

Type Of Event	No.	Patient Outcome
ABO and/or Rh(D) incompatible transfusion	1	Recovered with no ill effects
Special requirements not met	1	Patient at risk of acquired CMV infection, but none reported
Inappropriate transfusion	8	Four patients recovered with no ill effects Two patients died unrelated to transfusion Two patients outcome not recorded

Profile Of Recipients

Male recipients predominate in this category although their median age is lower than that of the females. 7/10 (70%) recipients were aged 60 years or older whereas 2 of the remaining 3 recipients were 18 years old or younger (paediatric) with the youngest patient being only 6 weeks old.

Table 17: Age And Gender Profile Of IBCT Cases (n=10)

Gender	No.	Median Age	Mean Age	Max	Min
Female	4	77	63.5	83	17
Male	6	63	52.7	81	0*

* 6 weeks

Site Of Primary Error

One of the parameters collected during the follow up of IBCT events is the location where the observed cause of the event took place and the data obtained is shown in the table overleaf:

Table: 18: Site Of Primary Error

Site Of Error	No.
Prescription, sampling and request	4
Blood Bank / laboratory	4
Collection and administration	2

ABO And/or Rh(D) Incompatible Transfusion

The transfusion of ABO-incompatible red cells is an extremely serious event with the potential for causing serious harm or even death to the recipient.

In the single example notified to NZBS, two patients in the same ward, one group O and the other group B, were both having transfusions at the same time during early evening. The two nurses performing the pretransfusion checking of the blood did so in the ward's medication room and not at the patients bedsides, in violation of the hospital's transfusion protocol. The identity of neither patient was confirmed against their respective identification wristbands.

Consequently the group O patient received around 100ml of incompatible group B red cells (infused over a period of 2.5 hours) but fortunately made a full recovery with no ill effects. Incidentally whilst signs and symptoms of a haemolytic reaction were reported within 15 minutes of starting the transfusion these were initially thought to be due to the patient's underlying condition and so it was decided (after discussion with a NZBS TMS) to continue with the transfusion but more slowly.

In contrast the group B patient received group O blood which although compatible was not intended for them. This patient suffered no ill effects from receiving the 'wrong' blood.

What this case shows, and it cannot be over emphasised, is that the bedside check is vital for ensuring both that the correct patient is receiving transfusion and that the right blood component (or product) has been received. This is the final opportunity to detect earlier error, however international evidence shows that the bedside is the commonest site of failure in the transfusion process!

Special Requirements Not Met

In the one case reported, a CMV-negative liver transplant patient received a unit of platelets of unknown CMV-antibody status. 13 days post-transfusion no evidence of CMV infection was found in the patient.

The blood bank was informed of the recipient (and donor's) CMV-negative status prior to transplant but the 'special requirement' for CMV-negative blood components was not entered into the blood bank laboratory information system (Progesa). The blood bank staff member issuing the platelets was unaware that the patient was a liver transplant recipient and so accordingly did not select CMV-negative platelets for issue.

Information technology provides a tool for ensuring safer transfusion. In the context of special requirements, for the system to be effective blood bank must be made aware of these requirements, where known they must be entered into the laboratory information system and finally at the point of issue they must be observed.

A number of factors undeniably contributed to this event. Certainly poor communication was evident and this is well recognised as an important cause of adverse events. Subsequent review of

the event by the blood bank concerned also found that their SOP for dealing with liver transplant patients had deficiencies and was therefore a contributory factor.

The requirement for continuing CMV-antibody screening in blood services that undertake universal pre-storage leucodepletion of blood components is controversial. Whilst some blood services have ceased antibody screening, others believe that the combination might be more effective than either strategy alone for those patients at highest risk of CMV disease. NZBS introduced universal pre-storage leucodepletion in 2000. CMV antibody negative blood components continue to be provided for susceptible recipients. NZBS is working with clinician groups to agree which recipients should continue to receive CMV-antibody negative components.

Inappropriate Transfusion

In each of the events in this category a patient either received a transfusion that they did not need or received the wrong component or product (whether wrongly prescribed or incorrectly issued). The causes of inappropriate transfusion were as follows:

Table 19: Causes Of Inappropriate Transfusion

Cause Of Inappropriate Transfusion	No.
Red cells transfused on basis of erroneous Hb result	1
Patient transfused despite Hb of 120 g/L	1
FFP prescribed and transfused instead of platelets	2
FFP transfusion not in accordance with Australasian guidelines	1
Autologous serum eye drops issued by blood bank to (and used by) another patient	1
Albumex® 20 incorrectly issued by blood bank (instead of Albumex® 4)	1
Albumex® 4 labelled for one patient taken from ward refrigerator and transfused to another	1

Appropriate and timely transfusion of the right patient requires that a number of steps are followed with due care and attention to detail. It requires accurate laboratory results on which to base the decision to transfuse, prescription of the correct component or product based on relevant guidelines, issue of the correct component or product by the blood bank and selection by the ward of the component or product for the correct patient.

In each of the above cases inherent safeguards which may have prevented the event from happening obviously failed, were overlooked or simply ignored exposing the patient to unnecessary risk.

Transfusion-Associated Circulatory Overload (TACO)

Definition

TACO is characterised by respiratory distress, tachycardia and increased blood pressure within 12 hours of completion of the transfusion. Diagnosis is supported by typical signs of cardiogenic pulmonary oedema in the chest x-ray and a positive fluid balance and/or a known compromised cardiac status.

TACO is especially a risk in transfusion of patients with low body weight, the elderly, infants/children and those with histories of cardiac, respiratory or renal insufficiency or chronic anaemia. 8 cases of TACO were reported, accounting for 2.9% of events.

Profile Of Recipients

5/8 patients were aged 60 years or more with the remainder having ages of 23, 41 and 48 respectively):

Table 20: Age And Gender Profile Of TACO Cases (n=8)

Gender	No.	Median Age	Mean Age	Max	Min
Female	5	48	52.0	81	23
Male	3	71	71.7	77	67

Imputability Assessment And Patient Outcome

The following assessment of imputability and associated patient outcome were assigned to the reported TACO events:

Table 21: Imputability Assessment Of TACO Cases

Imputability	No.	Patient Outcome	Comment
1	4	Two patients recovered no ill effects Two patients died, relationship to transfusion not recorded	One case where TACO or TRALI not clearly distinguished
2	1	Patient died, possibly related to transfusion	
2 / 3	1	Patient recovered no ill effects	
3	2	One patient recovered no ill effects One patient died, probably related to transfusion	

Transfusion-Related Acute Lung Injury (TRALI)

Definition

Transfusion-Related Acute Lung Injury (TRALI) is characterised by acute respiratory distress and non-cardiogenic lung oedema developing during or within 6 hours of transfusion and which is not temporally related to another cause of acute lung injury (ALI).

The diagnosis of TRALI is a clinical and radiographic diagnosis and is not dependent on the results of laboratory tests or any proposed pathophysiologic mechanisms. TRALI should be considered a clinical syndrome rather than a disease with single cause.

A consensus definition of TRALI was developed at a conference in Canada in April 2004 and subsequently reported in the transfusion literature [6]. The definition used by NZBS is consistent with this.

10 cases of TRALI were reported representing 3.7% of events. TRALI is a significant transfusion-related event and undoubtedly poorly recognised and under-reported. The UK SHOT programme has consistently identified TRALI as one of the most common causes of fatal transfusion reactions.

Profile Of Recipients

The age and gender profile of the reported TRALI cases is as follows:

Table 22: Age And Gender Profile Of TRALI Cases (n=10)

Gender	No.	Median Age	Mean Age	Max	Min
Female	4	31.5	40.3	73	25
Male	6	56.5	54.5	75	25

Imputability Assessment And Patient Outcome

The following assessment of imputability and associated patient outcome were assigned to the reported TRALI events:

Table 23: Imputability Assessment Of TRALI Cases

Imputability	No.	Patient Outcome
1	4	One patient outcome not available Two patients recovered no ill effect One patient died, possibly related to transfusion
1 / 2	1	Patient recovered no ill effects
2	3	One patient outcome not available One patient recovered no ill effects One patient not recovered at time of notification of event to NZBS
3	2	Both patients recovered no ill effects

Testing Of Donors Implicated In TRALI Events

One proposed mechanism for TRALI is the interaction between donor white cell (HLA) or neutrophil (HNA) antibodies and the recipient's white cells. Therefore the investigation of suspected TRALI should include testing of the donor(s) and recipient for HLA class I and II antibodies (identifying specificity if detected) and for HNA-specific antibodies. A crossmatch between donor serum and recipient white cells is also useful, with a positive result strongly implicating the particular donor(s).

NZBS has developed a standard procedure for investigating TRALI events which includes HLA and HNA antibody testing. Information regarding the presence/absence of HLA or HNA antibodies in the cases notified during 2005 was not available.

Male-Only Fresh Frozen Plasma

A number of countries have introduced a strategy for reducing the frequency of TRALI involving the use of FFP manufactured from plasma collected only from male donors. Female donors and in particular multiparous women often have HLA antibodies. The use of male-only donors for FFP may therefore reduce the incidence of TRALI.

NZBS has undertaken a feasibility study for implementing a male-only FFP programme. A system for implementation of this is currently being developed.

An Analysis Of Events With Respiratory Features

Several transfusion-related adverse events have respiratory symptoms or signs though the underlying pathogenesis may be varied. Such events are significant in terms of both frequency and severity and differentiation between them may be difficult. An attempt was made to systematically review them with respect to clinical features, the type of blood components they were associated with and severity.

All reports were analysed for the presence of specific respiratory features including dyspnoea, wheeze, stridor, abnormal chest x-ray, pulmonary oedema and falling O_2 saturation. Of the 271 reports available, 51 (18.8%) described one or more of these features.

Table 24: Number Of Events With Respiratory Features (n=51)

	Recipient Age			
Type Of Event	**< 18**	**19 - 60**	**> 61**	**Total**
Allergic reaction	3	8	6	**1**
Other *		2	12	**14**
TACO		2	5	**7**
TACO / TRALI		1	1	**2**
TRALI		6	2	**8**
TRALI / allergic reaction		2	1	**3**
Total	**3**	**21**	**27**	**51**

** Transfusion-related events not conforming to those traditionally associated with respiratory features*

Table 25: Implicated Components

	Red Cells	Platelets Aph [(a)]	Platelets Pooled	FFP	Cryo [(b)]	Multiple [(c)]	Total
Allergic reaction	8	5	1	2		1	**17**
Other	12			2			**14**
TACO	2			2		3	**7**
TACO / TRALI	1					1	**2**
TRALI	3	1		1	1	2	**8**
TRALI / allergic reaction	2					1	**3**
Total	**28**	**6**	**1**	**7**	**1**	**8**	**51**

Notes

a) Apheresis platelets

(b) Cryoprecipitate

(c) More than one component type implicated in event

Table 26: Patient Outcome

	Recovered	Died	Unrelated Death	Unknown	Total
Allergic reaction	10			7	**17**
Other	3		2	9	**14**
TACO	4	3			**7**
TACO / TRALI	1			1	**2**
TRALI	4			4	**8**
TRALI / allergic reaction	2			1	**3**
Total	**24**	**3**	**2**	**22**	**51**

These results show that adverse events with respiratory features are not uncommon in association with transfusion.

The commonest cause of such events appears to be allergic-type phenomena but TACO and TRALI are substantial minorities. Interestingly, the 'other' category including all those events not conforming to those traditionally associated with respiratory features accounted for 14/51 (27.5%) cases.

Not unexpectedly, given their pre-existing cardio-respiratory problems, mainly elderly recipients were reported to have these features. However TACO appeared to have occurred in 2 relatively young recipients, one of whom was 41 years old. Adverse events suggestive of allergic or TRALI type were quite common in younger recipients.

In the 51 cases studied there were 3 (5.8%) transfusion-attributable deaths and 24 (47.0%) survived the event. The outcome in the remaining 22 cases is not known.

Whilst this preliminary analysis has proved useful, there are inevitably caveats:

- Numbers are still small. Though reporting of events is encouraged, it is voluntary. Significant under-reporting of recognised events, not to mention under-recognition and the selective reporting of the more serious events does undoubtedly occur and could skew data.
- In many cases it is not always clear if transfusion was the cause of the event, or merely coincidental with the respiratory features described. Many of these adverse events occurred in patients with serious and complex problems. Even where transfusion seems the most likely cause of the event, the components mentioned in the reports may not necessarily have been the ones responsible.
- Information provided in the reports is incomplete. It is not always clear if a certain symptom or sign did, or did not, occur. Results of diagnostic work-ups and post-event outcomes were mostly unavailable. For instance, only 7/51 (13.7%) of the reports analysed mentioned the results of a chest x-ray. Even if only the more severe of these events (TACO, TRALI, TACO/TRALI or TRALI/allergic reaction) are considered, only 6/20 (30%) of reports provide chest x-ray findings.

It is hoped that similar analyses will continue in the future and will be able to provide more meaningful data.

Use Of Brain-type Natriuretic Peptide (BNP) In The Differential Diagnosis OF TACO And TRALI

Acute respiratory distress during or shortly following transfusion may be due to TRALI, TACO, allergic reactions or the patient's underlying condition.

Unfortunately many of the signs and symptoms of TRALI or TACO can occur in other types of event such as NHFTR and allergic reactions, however most allergic reactions and NHFTR can be readily identified as such.

It is important to distinguish between TRALI and TACO because of the relatively high mortality for TRALI. Invasive measurements such as central venous and pulmonary wedge pressures may be useful (should be normal in TRALI but elevated in TACO) but are not consistently diagnostic or readily available.

It has been suggested that measurement of brain-type natriuretic peptide (BNP) might be useful in the differential diagnosis of TACO [7]. BNP is secreted from the cardiac ventricles as a result of ventricular pressure overload and volume expansion such as occurs with TACO. Low levels of BNP can exclude TACO, however whilst high levels may favour TACO they do not necessarily exclude TRALI or allergic reactions as these can coexist.

Transfusion-Transmitted Infection (Bacterial)

Definition

Transfusion-transmitted infections (TTI) are classified as clinically suspected, possible or confirmed:

Infection <u>clinically</u> suspected
If within 4 hours of transfusion the patient experiences:

- *fever ≥ 38.5°C or a change of ≥ 1.5°C from pretransfusion value and*
- *rigors and*
- *tachycardia ≥ 120 beats / min or a change of ≥ 40 beats / min from pretransfusion value or a rise or drop of 30 mm Hg in systolic blood pressure*

Possible infection
A clinically suspected infection supported by:

- *the detection of bacteria in the transfused blood product but no positive blood culture; or*
- *a positive blood culture but no detectable bacteria in the transfused blood product if the blood culture is in a timely manner with the transfusion and no other reasons are ascertainable for the positive blood culture*

Confirmed infection
Detection of the same bacterial strain in both the recipient's blood and transfused blood component / product (using approved techniques).

A single TTI was reported in a 49 year old male, recipient of a unit of apheresis platelets.

Unlike transfusion-transmitted viral infections such as HBV, HCV or HIV that may not manifest themselves for a significant length of time following transfusion of an infected blood component or product, bacterial infections are normally associated with acute symptoms and are clinically evident soon after transfusion.

However in this case a potentially infectious unit of platelets was identified during routine post-production bacterial monitoring. The unit was found to have been transfused by the time this finding was made, prompting follow up of the patient. Blood cultures taken from three lumens of the patient's central line, a venous blood sample from the patient and the implicated component all grew coagulase negative Staphylococci.

A transfusion reaction was not reported. However during follow-up by NZBS of the positive culture, it was identified that the recipient had suffered rigors and shivering four days post transfusion. It is not clear whether or not these symptoms were due to the transfusion. A course of antibiotics was commenced and the patient subsequently recovered with no ill effects.

Other Types Of Reaction

The final category of transfusion-related adverse events are those 'other types of reaction' which do not clearly fit into those categories already described.

In this category 16 events were reported as follows:

Table 27: Types Of Event Classified As 'Other Types Of Reaction'

Type Of Event	No.
Hypotension	4
Transfusion-associated hyperventilation	1
Transfusion-associated dyspnoea / possible TACO	1
Transfusion-associated dyspnoea	1
Rigors + falling O_2 saturation	1
Rigors	1
Rigors with hypotension, possibly drug related	1
Possible line infection	1
Possible anaphylaxis due to platelets or protamine; Cardiac surgery	1
Non-specific reaction to FFP / acute transfusion-associated pain	1
Isolated severe drop in BP	1
Hypertension	1
Haemolysed red cells ex-liquid Nitrogen	1

Profile Of Recipients

The age and gender profile of the recipients experiencing 'other types of reaction' patients is shown below.

Table 28: Age And Gender Profile For 'Other Types Of Reaction' Cases (n=16)

Gender	No.	Median Age	Mean Age	Max	Min
Female	8	67.5	67.3	81	49
Male	8	64.0	63.5	71	53

Adverse Reactions In Donors

NZBS takes the wellbeing of its donors very seriously. A key aspect of this is monitoring the occurrence of adverse reactions during the donation process.

Adverse reactions are either observed during donation by collection staff or reported to the collection centre by the donor after they have left the collection venue.

Initial care and advice to the donor as well as follow-up of the reaction is provided by a Registered Nurse. A Medical Officer reviews the adverse reaction report and provides clinical advice and support if required.

Reports are entered into the NZBS electronic quality reporting system (Q-Pulse) and statistics are collated by individual NZBS sites and on a national basis. The following categories of adverse reactions are currently used by NZBS:

- Faints
- Soft tissue/tendon damage (including bruises and haematomas)
- Arterial puncture
- Nerve damage
- Thrombophlebitis
- Injury (occurring as the result of an accident at the session, or in the vicinity of the session, or otherwise related to donation and may include, for example, a fall resulting in head injury or a car accident)
- Medical/fits (including symptoms and/or signs not otherwise differentiated such as a fit, stroke or a suspected myocardial infarct)
- Other events (including skin infections and allergic reactions)

Events are not currently graded according to severity nor are they differentiated as to whether they occur during automated procedures or during manual whole blood collection. This aspect of data collection is presently under review and awaits internationally standardised definitions for both the types of event and assessment of severity.

Types Of Donor Adverse Reactions Reported

During 2005 there were 659 donor adverse reactions reported from the total of 168261 donations collected. This represents an overall risk of 0.39% or 1:255 donations bled.

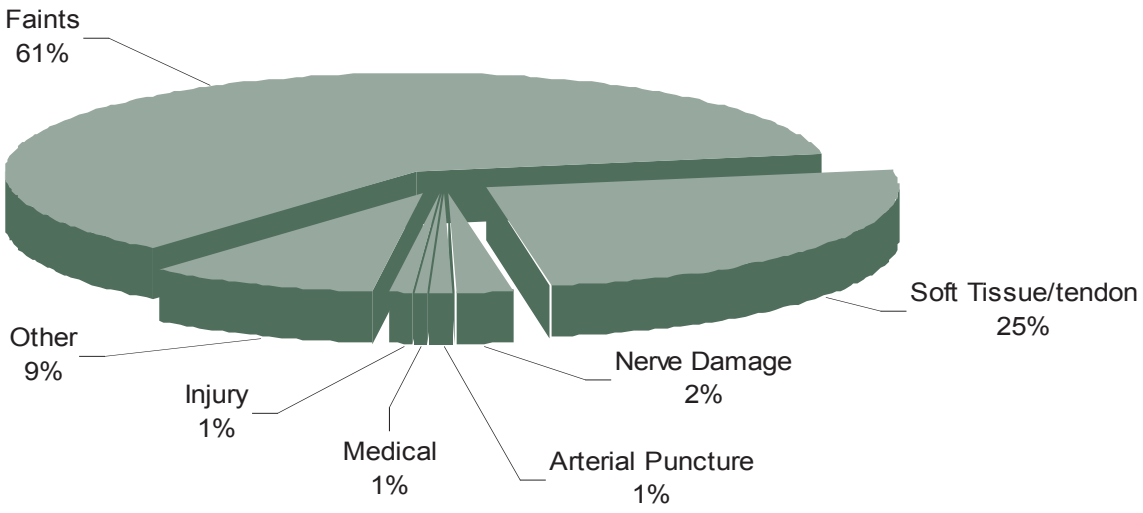
Table 29 shows the total numbers of each type of donor adverse reactions:

Table 29: Total Number Of Donor Adverse Reactions Reported

Donor reaction	Number	% of donations collected	Rate
Faints	403	0.240	1:418
Soft Tissue/tendon	166	0.099	1:1014
Nerve Damage	15	0.009	1:11217
Arterial Puncture	5	0.003	1:33652
Medical	5	0.003	1:33652
Injury	4	0.002	1:42065
Other	61	0.036	1:2758
Total	**659**	**0.392**	**1:255**

Faints and soft tissue reactions are the two most frequently reported events, between them accounting for 86% of the total.

Chart 2: Percentage Distribution Of Adverse Reactions In Donors (n=659)



Donor Infectious Disease Screening

Donor epidemiological data relating to the number of donations that are confirmed positive for Hepatitis B, C and HIV is collected nationally by NZBS.

This data is also reported annually to CSL Bioplasma (the plasma fractionator) as part of the regulatory process associated with manufacturing human-derived plasma products, and in particular to meet the scientific data requirements for the plasma master file (PMF) [8]. The data for 2005 is shown in the table below:

Table 30: Blood Donor Epidemiological Data (2005)

	HBsAg	HIV 1/2 Antibody	HCV Antibody
Total Number of Donations Screened	170583	170583	170583
Regular Donors [(a)]			
Number of Donations from Regular Donors	146089	146089	146089
Positive Donations from Regular Donors [(b)]	2 [(c)]	2 [(d)]	4 [(e)]
% Positive Donations from Regular Donors	0.001	0.001	0.002
New Donors			
Number of Donations from New Donors	24494	24494	24494
Number of Positive Donations from New Donors	48	0	15
% Positive Donations from New Donors [(f)]	0.196	0	0.061

Notes

(a) A regular donor is defined as one who has previously undergone serological testing (following donation) with a negative result.

(b) Where a donor who has previously donated is found to have a confirmed positive result an extensive look-back process is initiated to investigate previous donations

(c) 2 repeat donors were found to have seroconverted for HBsAg as a result of Hepatitis B vaccination immediately prior to donation. In July 2005, Medsafe approved the introduction of a 7 day deferral for donors who have had a hepatitis B vaccination (for non-exposure to the virus). This deferral was implemented operationally on 24th April 2006 and will overcome the difficulties associated with interpreting these results.

(d) 2 repeat donors who seroconverted for HIV antibody. Both donors had not donated for at least 5 years prior to the index donation and did not volunteer the likely risk factors during counselling.

(e) 4 repeat donors were found to have seroconverted for HCV antibody. This is higher than in previous years.

(f) The number of new donors in 2005 was approximately the same as in 2004, (24494 compared with 24578) however the number of new donors who were positive for HBsAg (48) and HCV antibody (15) was significantly lower than in 2004. There is no easily identifiable reason for this but one contributing factor could be the closure of three of the collection sites during 2004.

Adverse Reactions To Fractionated Blood Products

The New Zealand Blood Service national process for reporting adverse reactions to fractionated blood products has been in operation for six years. Adverse reactions are reported to CSL Bioplasma, which acts as the fractionator for NZBS. An annual report of all adverse reactions that have occurred is prepared for the New Zealand regulator Medsafe.

CSL Bioplasma manufactures 10 fractionated blood products for NZBS using plasma from New Zealand donors. These products are - Albumex®, Intragam P®, AHF (now Biostate®), MonoFIX-VF™, Thrombotrol, Prothrombinex™, Hepatitis B Immunoglobulin, Rh(D) Immunoglobulin, Normal Immunoglobulin and Zoster Immunoglobulin. During 2005, CSL Bioplasma supplied the Cangene product WinRho-SDF to meet the demand for Rh(D) Immunoglobulin for New Zealand patients.

Other products that are supplied by NZBS include the commercial products, Hyper HepB, Berinert P and Fibrogammin.

During 2005 there were sixteen suspected adverse reactions to fractionated blood products reported to NZBS.

- One reaction implicated WinRho™
- One reaction implicated AHF
- One reaction implicated Albumex® 20
- One reaction implicated two products (Albumex® 20 and Intragam®P)
- Ten reactions implicated Intragam®P
- Two reactions implicated Biostate®

The sixteen adverse reactions reported in 2005 was an increase over the five reactions reported in 2004. This apparent increase may be due in part to the introduction of the NZBS ***Haemovigilance*** programme raising awareness of the importance of reporting adverse reactions not only to blood components but also fractionated blood.

Events associated with fractionated products are notified to NZBS using the NZBS '*Notification of adverse reaction to a fractionated product form*' [9]. Each event is assessed for outcome and causality according to the following table:

Table 31: Outcome And Causality Criteria

Outcome	Causality
Recovered	Certain
Not yet recovered	Probable
Unknown	Possible
Fatal	Unknown
Congenital abnormality/birth defect	Not related

Finally it is recorded whether each event is serious or not, with a serious event defined as one that:

- is life threatening; or
- causes hospitalisation (or prolonging of existing hospitalisation); or
- causes significant disability/incapacity.

The NZBS criteria for outcome, causality and severity are based on the international terminology used by CSL and others for pharmacovigilance reporting. Information on the reported reactions is included in Table 32.

Table 32: Summary Of Reactions Reported To Fractionated Blood Products

Product(s)	Gender	Age (yrs)	Description Of Event	Outcome	Causality	Serious
AHF	M	8	Patient found to be positive for anti-HAV IgG (Hepatitis A) [(a)]	Not known	Possible	No
Albumex® 20	M	11	Pyrexia after infusion of the product (had developed a rash, felt unwell and shivery prior to infusion) The same batch had been transfused the preceding day without effect.	Recovered	Possible	No
Biostate®	F	39	Chest tightness, blood pressure reading increased post infusion	Recovered .	Possible	No
	M	53	Blotchy itchy rash behind the knees and under arms	Recovered	Probable	No
Intragam® P Albumex® 20	M	13	Fall in haemoglobin over 7 days, weakly positive direct antiglobulin test and drop in platelet count [(b)]	Patient became anaemic and was transfused	Possible	Yes
Intragam®P	F	15	Positive dipstick test for glucose in urine. [(c)] A random blood glucose showed 4.2mmol/L.	Event settled promptly following completion of infusion	Probable	No
	M	25	Urticarial reaction after infusion on two occasions, 3 weeks apart.	Recovered	Probable	No
	F	61	Generalised urticarial rash	Recovered	Probable	No
	M	81	Generalised maculopapular rash which tended to become confluent.	Not yet recovered	Probable	No

Product(s)	Gender	Age (yrs)	Description Of Event	Outcome	Causality	Serious
Intragam®P continued	F	17	Aseptic meningitis following high dose intravenous immunoglobulin. [(d)]	Recovered	Possible	No
			Second event for patient, with same symptoms i.e. severe headache, consistent with a diagnosis of aseptic meningitis.	Recovered	Probable	No
	F	68	Generalised papulomacular rash with severe itch.	Recovered	Possible	No
	F	35	Pyrexial reaction and rigor (the platelet count also) fell	Recovered	Possible	No
	M	56	Loose bowel motions after each treatment (symptoms apparent since treatment commenced in July 2004)	Not yet recovered	Possible	No
	F	15	Nausea, fever, frontal headache, vomiting	Recovered	Possible	No
WinRho	F	28	Shock, five minutes after receiving Rh(D) Immunoglobulin. Event later attributed to cervical shock (clot or products of conception in the cervix and causing a vasovagal reaction).	Recovered	Not Related	No

Notes

(a) Possible causes of the seroconversion are either community exposure to the hepatitis A virus, or from receipt of the AHF. CSL undertook a review of medical literature related to HAV transmission by Factor VIII/IX products. All cases reported related to products that use solvent/detergent treatment as the virus inactivation step. No pasteurised or severe dry heat-treated inactivated products have transmitted HAV. AHF was heated at 80°C for 72 hours and falls in the latter category.

(b) Multiple causes exist for the fall in haemoglobin in this patient, including possible blood loss related to thrombocytopenia and blood sampling, haemolysis of engrafted red cells by patient's own anti-A, GvHD and its treatment, and anti-A known to be present in Intragam P®.

(c) Literature reports discuss urinary excretion rates of maltose and glucose after intravenous infusion of a 10% maltose solution infusion. They report that intravenously administered maltose is hydrolysed to glucose in the proximal tubules in the kidney. Glucose is then re-adsorbed, however if the amount of glucose in the kidneys exceeds the renal threshold for re-adsorption, excess glucose will be excreted and detected in the urine.

(d) Aseptic meningitis is a rare, but recognised reaction to intravenous immunoglobulin treatment, especially high dose regimens.

Other Haemovigilance-Associated Activities

DHB Clinical Oversight Programme

The NZBS 'DHB Clinical Oversight Programme' was introduced on 1 January 2005. It was developed in response to the increasing number of requests from DHBs for specialist transfusion medicine support (both clinical and technical) needed to meet the requirements of NZS/ISO 15189:2003 '*Medical Laboratories - Particular requirements for quality and competence*' [10]. Outside of the six NZBS-operated blood banks the requisite support for hospital blood banks and laboratories particularly in the smaller provincial centres had become increasingly scarce, and where available, inconsistent.

The programme's key activities provide DHBs with the aforementioned clinical and technical support as well as assistance in implementing strategies to enhance transfusion medicine knowledge and best practice and efficient utilisation of blood. The four components of the programme are as follows:

- **Clinical Audit Of DHB Transfusion Policies And Procedures**
  One clinical audit every two years of hospitals where transfusions are carried out, encompassing blood storage and refrigeration, informed consent, dispensing systems and clinical records documenting transfusion and traceability.
- **Site Visits**
  One formal site visit per year (to non-NZBS) blood banks or laboratories where pretransfusion testing is performed) intended as a collaborative review of systems and processes to promote best practice. Wherever possible a TMS will also attend DHB HTC meetings or education sessions e.g. grand rounds and 24 hour, 7 day access to a clinical advice is available via the NZBS TMS on-call roster.
- **Regional Meetings/Seminars**
  Three 'customer focussed' meetings per year are held by each of the four main NZBS centres (Auckland, Waikato, Wellington and Christchurch). These regional meetings and/or seminars are intended to supplement the site visit programme.
- **Education**
  Developing and maintaining appropriate educational and training resources.

The programme is now well established with only one DHB choosing not to participate (in favour of local arrangements). During 2005 more than 20 hospitals received site visits and/or clinical audits. Regional meetings were hosted by the four main NZBS centres.

Sample And Request Form Labelling Errors

The international transfusion literature shows that labelling errors are a major contributing cause to transfusion-related adverse events or near misses. Requests with labelling errors create a significantly higher risk of a patient receiving the wrong or inappropriate blood.

A national NZBS procedure has been developed for reporting sample and request form labelling errors associated with requests for pretransfusion testing or for blood components/ products. The data collected will be entered into a database for subsequent analysis.

A pilot version of this procedure was introduced to Wellington Hospital Blood Bank on 1 December 2005, with full national implementation at all NZBS blood banks scheduled for 1 May 2006.

Near Misses

In the context of transfusion, 'near misses' are defined as situations where an error occurred somewhere in the transfusion process but was detected before transfusion actually took place. Reporting near misses can provide a useful tool for identifying deficiencies in the transfusion process.

NZBS is currently working on a process for collecting data on near misses as well as other blood bank errors.

Bacterial Monitoring Of Platelet Concentrates

Bacterial contamination of blood components was first recognised as a complication of transfusion over 60 years ago. Sources of contamination include donor skin, donor bacteraemia, faulty blood collection or contamination during blood processing. The organisms detected are usually aerobic and those most frequently implicated in clinical cases of transfusion-associated sepsis include *Staphylococcus, Streptococcus, Bacillus cereus, E. coli, Salmonella* and *Serratia*.

The rate of bacterial contamination of platelet concentrates varies widely across studies but averages approximately 1 in 2000. In comparison the reported fatality rate is within the range of 1 in 50,000 to 1 in 500,000 platelet concentrates transfused. For platelet transfusions in particular it is the most commonly reported cause of mortality and morbidity arising from transfusion-transmitted infections (TTI). For example data reported by the UK's SHOT haemovigilance scheme for the years 1995 to 2001, showed 21/38 reported TTIs were due to bacterial contamination, 17 of which were bacterial contamination of platelets and for which there were six fatalities.

A variety of potential strategies to reduce bacterial contamination are used by the NZBS. These include detailed donor screening with deferral of those identified to be at risk of bacteraemia, augmented disinfection of the venepuncture site to reduce the entry of skin flora into the unit and diversion of the first 10-40ml of blood collected prior to collection of the unit. This latter approach has been shown to significantly reduce the rate of bacteria contamination in several studies and this was introduced by NZBS during 2002.

A number of pathogen inactivation methods involving photochemical treatment of blood components are also under development. These have an ability to destroy both bacteria and viruses.

Another strategy is to perform bacterial testing on platelet concentrates. A 2003 pilot study by Northern Ireland Blood Transfusion Centre used the BacT/ALERT automated microbial detection system (bioMérieux Inc) to test 4885 platelet concentrates on day 2 (day 0 being day of collection), over a 1 year period. There were 13 reproducible positive cultures (1 apheresis and 12 pooled platelets). It was concluded that routine bacterial testing with day 2 sampling and a negative culture result after 24 hours as a mandatory release criterion would improve transfusion safety.

In March 2004 the AABB introduced the mandatory requirement for bacterial testing of all platelet components. The FDA has approved BacT/ALERT and Pall BDS (Bacterial Detection System) for testing.

Using a similar approach to the Irish study, NZBS commenced a pilot in 2004 to determine the bacterial contamination rate of platelet concentrates in NZ. Platelet units were initially sampled on day 2 post-collection (day of collection = day 0) using non-destructive sampling methods so as to have no impact on the availability of platelets for clinical use. Similarly any units originally sampled on day 2 that had not been issued for use by day 5 (expiry) were held for a further two days until day 7 post-collection and retested.

All samples were tested using the BacT/ALERT 3D. Any initially positive results were further investigated and all components associated with the positive sample traced and any not already transfused placed into quarantine. Samples of the implicated components were sent to an accredited microbiology laboratory for gram stain, culture and identification of any bacteria present.

During 2005 all four NZBS manufacturing sites: Auckland, Waikato, Wellington and Christchurch participated in the study with Auckland and Christchurch participating for the full year, Wellington for nine months and Waikato for ten months.

A total of 3675 platelet concentrates were sampled at day 2 with the results shown in table 33 below:

Table 33: Bacterial Monitoring Of Platelet Concentrates

Site	Number sampled	Nonreproducible Positive *	Reproducible Positive **
Wellington	357	1	1
Christchurch	563	1	0
Waikato	273	0	0
Auckland	2485	5	0
Totals	**3675**	**7**	**1**

* ***Nonreproducible positive****: confirmatory culture performed on sample taken from the implicated unit, or if already transfused taken from the initial sample pouch, was negative.*

** ***Reproducible positive****: confirmatory culture performed on sample taken from the implicated unit, or if already transfused taken from the initial sample pouch, was positive.*

The one confirmed positive result was subsequently shown to be due to the presence of a coagulase negative Staphylococcus. The unit associated with this sample had already been transfused by the time the result was obtained and so could not be recovered. However the clinician treating the recipient was notified and microbiological follow-up initiated.

Clinical Audits

Because transfusion is not without risks, and because blood is a precious gift, it is important to ensure that transfusions are given appropriately.

In addition to being the sole national supplier of blood components and products, NZBS also operates the blood banks at six of the country's largest hospitals. The scope and volume of transfusion activity at these hospitals and the six DHBs in which they are located creates a unique opportunity for NZBS to oversee and audit clinical transfusion practice.

NZBS employs six Transfusion Nurse Specialists (TNS) with one situated in each of the six NZBS blood banks. Each year audits encompassing the six DHBs and, in some cases, other DHBs, are undertaken by the TNS team, co-ordinated by a NZBS TMS, on different aspects of transfusion medicine. In addition local audits may be performed, some of which act as pilots for larger collective audits.

In the last two years, five collective audits have been undertaken, looking at: overnight transfusion practice, cryoprecipitate use and non-use, Intragam P use, irradiation of cellular blood components and platelet use respectively. These audits have concentrated on issues around clinical practice as well as appropriateness of use.

Reports of each audit are provided to the hospital transfusion committees in draft form for comment, to allow the DHBs an opportunity to provide input into the audit conclusions. Final reports are circulated to the hospital transfusion committees and CEOs of all 21 DHBs.

This partnership between NZBS and DHBs has enabled audit work to provide useful insight into blood component and product use in New Zealand. This has, to a large extent, reassured clinicians and managers of the appropriateness of use and helped concentrate improvement in areas shown to have problems.

New Zealand Blood Service Standards

New Zealand Blood Service was established in 1998 with responsibility for the provision of safe and effective blood and blood products to the people of New Zealand. NZBS standards outline the technical requirements used in the collection, manufacture, distribution and storage of blood and blood components. These standards in conjunction with the 'Code of Good Manufacturing Practice' (GMP) [11] provide the basis for the NZBS Quality System.

The standards are in two volumes; Firstly, the *Collection Standards* [12], detail the requirements relating to donors and include detailed information on the selection and care of donors including an A-Z Guide; Secondly, the *Manufacturing Standards* [13], detail the requirements for premises, equipment and personnel. Also included are the requirements for processes used in the manufacture of blood and blood components. A separate document, the NZBS Quality Manual, outlines NZBS quality system policies and procedures.

The standards are owned by NZBS with the Clinical Advisory Group (CAG) being responsible for their development and maintenance. The CoE '*Guide to the preparation, use and quality assurance of blood products*', which is updated annually, is used as an external reference standard and NZBS has observer status on the CoE committee responsible for its maintenance. In developing standards, CAG takes account of other international standards relating to blood with the intention of ensuring that the standards are consistent with International best practice.

The standards are managed as controlled documents within the NZBS document control system. Changes to the standards are undertaken through a controlled process involving consultation with Medsafe (New Zealand Medicines and Medical Devices Safety Authority).

The standards apply uniquely to human blood, blood components intended for transfusion and source plasma destined for fractionation. They do not apply to the fractionation process of blood plasma, finished fractionated blood products or human blood products destined for diagnostic or other laboratory purposes except where specified.

In New Zealand, blood and blood products intended for therapeutic purposes are defined as medicines and, therefore subject to the *Medicines Act 1981*, *Medicines Regulations 198*4 and subsequent amendments. Medsafe is responsible for administering this legislation which includes the issuing of licenses to manufacturer medicines. Medsafe carries out annual audits of all NZBS Manufacturing sites to ensure that good manufacturing practice standards are being met.

Regulatory Approval Of Hepatitis B Vaccination Deferral

Medsafe approved one change to the NZBS *Collection Standards* during 2005 namely the introduction of a new 7 day deferral for donors who have recently been vaccinated for hepatitis B.

The change was introduced in response to the difficulties faced by NZBS in interpreting HBsAg testing results from donors who had recently been vaccinated for hepatitis B. Antigenaemia following vaccination is well documented but in otherwise healthy donors creates what is essentially a 'false-positive' test result. However the donor is still treated as if having a true infection until the true nature of the test results is resolved. If the donor is a regular donor, a 'lookback' process is automatically triggered and all donations given by the donor within the previous two years are re-examined.

The introduction of the new deferral for these donors should reduce the level of additional testing associated with 'false positive' results, reduce the number of notifications to such donors that they have abnormal test results and reduce the level of concern felt by donors associated with such notifications.

Regulatory Approval Of Changes To Decision Rules In Relation To Travel And Malarial Exposure Risk

Medsafe approved in principle the introduction of a validated malarial antibody test (Newmarket Laboratories Ltd). This approval enables formal validation of the assay and test system to take place based on the malarial risk decision rules contained in the final version of the 12th edition of the CoE '*Guide to the preparation, use and quality assurance of blood products*'.

Once validation has been completed NZBS will make the necessary changes to the *Collection* and *Manufacturing Standards* and submit these to Medsafe before formal implementation of malarial antibody testing

Acknowledgements

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Haemovigilance Steering Group

NZBS Haemovigilance Steering Group

The haemovigilance programme is overseen by the NZBS 'Haemovigilance Steering Group' under the auspices of the NZBS 'Clinical Advisory Group' (CAG) and direction of the NZBS National Medical Director.

The members of the steering group are as follows:

- Dr Krishna Badami, Transfusion Medicine Specialist, NZBS-Christchurch
- Simon Benson, Clinical Support Officer, NZBS National Office
- Dr Susanta Ghosh, Transfusion Medicine Specialist, NZBS-Waikato

In addition to the above the following also contributed to the writing of the annual report:

- Dr Peter Flanagan, NZBS National Medical Director
- Dr Richard Charlewood, Transfusion Medicine Specialist, NZBS-Auckland
- Irene Wai-Poi, Clinical Support Officer, NZBS National Office

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References

1. Serious Hazards of Transfusion Steering Group: Serious Hazards of Transfusion (SHOT) annual report 2004 (downloaded from www.shotuk.org)

2. Englefriet CP, Reesink HW: International forum – haemovigilance. *Vox Sanguinis* (2006); **90**, 207-241

3. Council Of Europe Publishing: Guide to the preparation, use and quality assurance of blood components. (Chapter 30); 12th Edition 2006

4. NZBS '*Notification and investigation of adverse transfusion reaction*' (Form 111F009)

5. Addas-Carvalho TS, Salles TSI, Saa STO: The association of cytokine gene polymorphisms with febrile non-hemolytic transfusion reaction in multitransfused patients. *Transfusion Medicine* (2006); **16**, 184-191

6. Kleinman S, Caulfield T, Chan P et al: Toward an understanding of transfusion-related acute lung injury: statement of a consensus panel. *Transfusion* (2004); **44**: 1774-1789

7. Zhou L, Giacherio D, Cooling L, Davenport RD: Use of B-natriuretic peptide as a diagnostic marker in the differential diagnosis of transfusion-associated circulatory overload. *Transfusion* (2005); **45**: 1056-1063

8. The European Agency for the Evaluation of Medicinal Products: Guideline on the scientific data requirements for a plasma master file (PMF) (EMEA/CPMP/BWP/3794/03; accessed through the EMEA website www.emea.eu.int/pdfs/human/bwp/379403en.pdf)

9. NZBS '*Notification of adverse reaction to a fractionated blood product*' (Form 111F003)

10. Standards New Zealand: NZS/ISO 15189 '*Medical Laboratories - Particular requirements for quality and competence*' (2003)

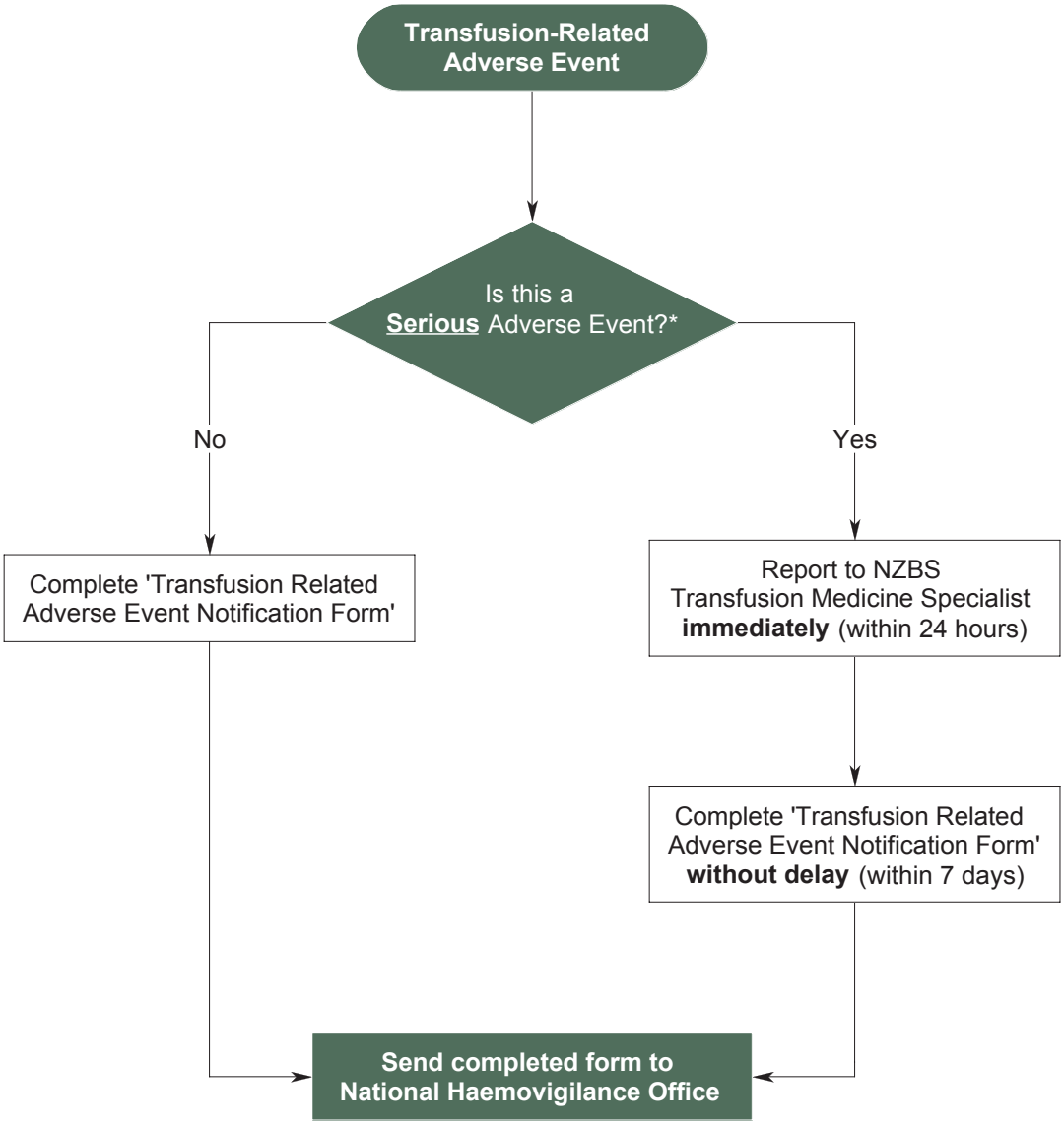
11. Ministry of Health: *New Zealand Code of Good Manufacturing Practice for Manufacture and Distribution of Therapeutic Goods*

12. NZBS: *Collection Standards* (2003)

13. NZBS: *Manufacturing Standards* (2003)

Appendix 1:
Reporting Transfusion-Related Adverse Events

Flowchart For Reporting 'Transfusion Related Adverse Events'



Serious Events

A serious event is defined as any adverse event that:

- requires hospitalisation or a prolonged hospital stay
- results in persistent or significant disability or incapability
- necessitates medical or surgical intervention to prevent permanent damage or impairment of a body function
- is associated with severe temporary or permanent morbidity and/or mortality

All such should be reported to a NZBS Transfusion Medicine Specialist **immediately** (i.e. within 24 hours).

Appendix 2: Complications Arising From Transfusion

Complications Arising From Transfusion

The following definitions of complications arising from transfusion are based on a consultation document produced by the European Haemovigilance Network (EHN) 'Working Party on definitions of adverse transfusion events (ATEs)' in 2004:

Table 34: Complications Arising From Transfusion

1. Transfusion-transmitted infections (TTI)

Infectious agent	Definition
Viral infection	The recipient has evidence of viral infection post-transfusion where there was no evidence of infection prior to transfusion; and **Either** at least one component received by the infected recipient was donated by a donor who had evidence of the same infection **Or** at least one component received by the infected recipient was shown to be contaminated with the infective agent.
Bacterial infection	***Infection clinically suspected*** If within 4 hours of transfusion the patient experiences: • fever ≥ 38.5°C or a change of ≥ 1.5°C from pretransfusion value and • rigors and • tachycardia ≥ 120 beats / min or a change of ≥ 40 beats / min from pretransfusion value or a rise or drop of 30 mm Hg in systolic blood pressure ***Possible infection*** A clinically suspected infection supported by: • the detection of bacteria in the transfused blood product but no positive blood culture or • a positive blood culture but no detectable bacteria in the transfused blood product if the blood culture is in a timely manner with the transfusion and no other reasons are ascertainable for the positive blood culture ***Confirmed infection*** Detection of the same bacterial strain in both the recipient's blood and transfused blood component / product (using approved techniques).
Parasite infection	Detection of a parasite infection in the recipient's blood with no means of acquiring the infection other than transfusion.

2. Immune Complications of Transfusion

Complication	Definition
Haemolytic transfusion reaction (HTR) Reactions may be further defined as ***Acute*** or ***Delayed***	HTR is clinically suspected if one or more of the following is present in a temporal association with transfusion: • fever and a variety of other symptoms (including dyspnoea, hypotension, tachycardia, flank or back pain, etc) • inadequate rise of the hemoglobin level after red cell transfusion • drop in haemoglobin level (≥ 2g/dl within 24 hours) • rise in LDH (≥ 50% within 24 hours) • rise in bilirubin, free haemoglobin (in plasma or urine), decrease in haptoglobin HTR is confirmed by a: • a positive direct antiglobulin test and • a positive red cell cross-match Two types of HTR are distinguished clinically: • *Acute HTR*: reaction occurs within 24 hours of transfusion • *Delayed HTR:* reaction occurs within 1 - 28 days after transfusion
Non-haemolytic febrile transfusion reaction (NHFTR) Reactions may be further defined as **mild**, **moderate**, or **severe**	***Mild febrile transfusion reaction*** Fever ≤ 38.5°C or an increase of <1.5°C from pretransfusion value without any other symptoms (including HTR and bacterial infection). ***Moderate / severe febrile transfusion reaction*** Fever ≥ 38.5°C or an increase of ≥1.5°C from pretransfusion value plus one or more of the following: • chills • cold • rigor • headache • nausea / vomiting
Transfusion-related acute lung injury (TRALI)	***Clinical diagnosis of TRALI and possible TRALI*** • acute respiratory distress • hypoxaemia ($PaCO_2/FiO_2$ < 300 or oxygen saturation < 90% or other clinical evidence) • bilateral lung infiltrations in the chest radiograph • occurrence during or within 6 hours of the transfusion • no evidence of TACO • no other risk factors for acute lung injury (ALI) present: sepsis, aspiration, multiple trauma, pneumonia, cardiopulmonary bypass, burn injury, inhalation injury, lung contusion, acute pancreatitis, drug overdose

Complication	Definition
	Possible TRALI TRALI with one or more risk factors for ALI: sepsis, aspiration, multiple trauma, pneumonia, cardiopulmonary bypass, burn injury, inhalation injury, lung contusion, acute pancreatitis, drug overdose ***TRALI subtypes*** • *Immunogenic (antibody-mediated) TRALI* I Confirmed by the detection of leucocyte antibodies in the donor's or recipient's blood and a corresponding leucocyte antigen typing or a positive granulocyte crossmatch • *Non-immune (not antibody-mediated) TRALI*
Transfusion-associated graft versus host disease (TA-GvHD)	Fever, rash, liver dysfunction, diarrhoea and cytopenia 1 - 6 weeks following transfusion with no other apparent cause. TA-GvHD is confirmed by GvHD-typical biopsy and by genetic analysis confirmed identity of recipient's lymphocyte chimerism and donor lymphocytes.
Post transfusion purpura (PTP)	Purpura and thrombocytopenia within 12 days of transfusion. Confirmed by the detection of platelet-specific antibodies (usually anti-HPA-1a) in the recipient's blood and corresponding platelet antigen typing of the donor or by a positive platelet cross-match.
Allergic reaction	One or more of the following: • Rash • allergic dyspnoea (stridor, cyanosis, wheezing) • angioedema • generalized pruritis • urticaria without hypotension during or within 24 hours of transfusion.
Anaphylactoid reaction	Allergic reaction with hypotension (drop in systolic blood pressure by ≥ 30 mm Hg) during or within 24 hours of transfusion.
Anaphylactic shock	Shock associated with blood transfusion without any signs of shock of other origin.
Alloimmunisation	Formation of alloantibodies to RBC, HLA, HPA and HNA antigens which were not detectable pretransfusion.
Transfusion-associated autoimmune haemolytic anaemia	Haemolysis-related symptoms (paleness, tachycardia, hyperventilation etc) in a temporal association with transfusion. Confirmed by a drop in hemoglobin level, a positive direct antiglobulin test and an eluate revealing a red cell autoantibody that was not present in the recipient's blood pretransfusion.

3. Cardiovascular and Metabolic Complications of Transfusion

Complication	Definition
Transfusion-associated circulatory overload (TACO)	Respiratory distress, tachycardia and increased blood pressure within 12 hours of the completion of the transfusion. TACO is supported by typical signs of cardiogenic lung oedema in the chest x-ray and a positive fluid balance and/or a known compromised cardiac status.
Transfusion-associated dyspnoea	Respiratory distress in temporal association with blood transfusion and no evidence of TRALI, allergic dyspnoea or TACO.
Hypothermia	Decrease of body temperature after transfusion resulting in dyspnoea, hypotension and/or cardiac dysfunction.
Hyperkalaemia	Abnormal increase of the potassium level after transfusion, which can result in cardiac arrhythmias and/or dysfunction.
Hypocalcaemia	Abnormal decrease of the calcium level after transfusion, which can result in carpopedal spasm and/or cardiac arrhythmias and/or dysfunction.
Haemosiderosis	Iron overload as indicated by laboratory findings or biopsy due to chronic transfusion which can result in injury of heart, liver, lung and/or endocrine glands.
Hypotension	Drop in systolic blood pressure by ≥ 30 mm Hg during or within 4 hours of the completion of the transfusion and no evidence of other complications described above.
Hypertension	Rise in systolic blood pressure by ≥ 30 mm Hg during or within 4 hours of the completion of the transfusion and no evidence of other complications described above.

4. Previously Unknown Complication of Transfusion

Occurrence of an adverse effect or reaction associated with transfusion and which cannot be attributed to other side effects or complications (defined in 1 - 3 above) and no other risk factor(s) than transfusion present in recipient.