日本赤十字社
Japanese Red Cross Society

Haemovigilance by JRCS 2013

Safety Vigilance Division

Blood Service Headquarters

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Haemovigilance system of Japanese Red Cross Society

The haemovigilance system is defined as a set of surveillance procedures intended to identify and prevent further transfusion-related adverse effects by testing, processing, distribution, up to follow-up of recipients to analyse and evaluate the causes and apply appropriate safety measures.

The Japanese Red Cross Society (hereinafter referred to as "JRCS") is the only body that is authorized to collect blood and supply blood and blood components for transfusion in Japan. In Japan, blood components for transfusion are categorized as prescription drugs that are regulated by the Pharmaceutical Affairs Law. Based on this law, the JRCS therefore collects information about transfusion-related adverse reactions and infections, and analyses and evaluates them to conduct safety measures such as reporting of severe adverse reaction cases to the Minister of Health, Labour and Welfare via the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as "PMDA"). As the marketing authorization holder, the JRCS is in charge of the series of activities including management of basic data on safety measures, withdrawal of inappropriate blood components, revision of package inserts (Precautions), and provision of information to healthcare professionals by medical representatives (MRs). The JRCS also collects and evaluates donor adverse reactions, which occur during or after blood collection. The JRCS also conducts epidemiological studies on blood safety, and reports the results to the Steering Committee for Blood Services and/or the Safety Technology Research Committee, the Pharmaceutical Affairs and Food Sanitation Council under the Ministry of Health, Labour and Welfare, contributing to the government to establish safety measures for blood components for transfusion. The haemovigilance system in JRCS covers all of the above-mentioned activities.

The JRCS established a nationwide integrated system to collect and analyse information on transfusion-related adverse reactions and infections in 1993, and have engaged in haemovigilance activities. In accordance with the revised Pharmaceutical Affairs Law, which came into effect in 2002, the Ministerial Ordinance on Standards for Post-marketing Safety Management of Drugs, Quasi-drugs, Cosmetics and Medical Devices; Good Vigilance Practice (GVP), the Blood Service Headquarters (as marketing authorization holders, including the General Safety Management Division), each blood center and the Central Blood Institute (both are part of the Safety Implementation Division) cooperate to collect, analyse, and evaluate the safety management information such as transfusion adverse reactions and transfusion-transmitted infections(TTIs), and take measures against them. MRs at each blood center are responsible to collect information of adverse reactions and/or TTIs from medical institutions and to provide information on blood components to healthcare professionals. The most remarkable feature of the JRCS surveillance system of adverse reactions/TTIs is to store an aliquot of all donated blood for analysis for 11 years. Such specimen storage (stored blood samples), started in September 1996, and enabled investigation to confirm the causal relationship between adverse reactions and/or TTIs and the implicated blood components, as well as further studies of newly emerging adverse reactions and infections. For donor adverse reactions, the JRCS has taken preventive measures, including training of nurses who have been in charge of blood collection since the 1950s, when the JRCS started blood services. In 1982, reporting of donor adverse reactions was specified in the JRCS's internal procedure. Data on the blood donor, collection, test results, preparation, and distribution are kept in a database in a nationwide unified IT system. The database is utilized to search historical records of donations and for retrospective studies, etc.

1. Reports on adverse reactions and TTIs

Figure 1 shows the number of case reports of transfusion-related adverse reactions and infectious diseases that were reported by medical institutions between 2004 and 2013, including cases assessed as unrelated to transfusion.

In 2013, the JRCS received 1,537 case reports of adverse reactions (1,515 cases were classified as non-hemolytic adverse reactions, 21 as hemolytic adverse reactions, and 1 as suspected transfusion associated GVHD), and 125 cases reports of TTIs from medical institutions across Japan. Severe cases that were evaluated by reporting physicians and/or the JRCS were submitted as individual case safety reports (ICSRs) to the PMDA (703 adverse reactions, and 125 infections) in accordance with the Pharmaceutical Affairs Law. The JRCS also investigates and evaluates case reports of adverse reactions/TTIs that are found by literature search and have not been reported voluntarily.

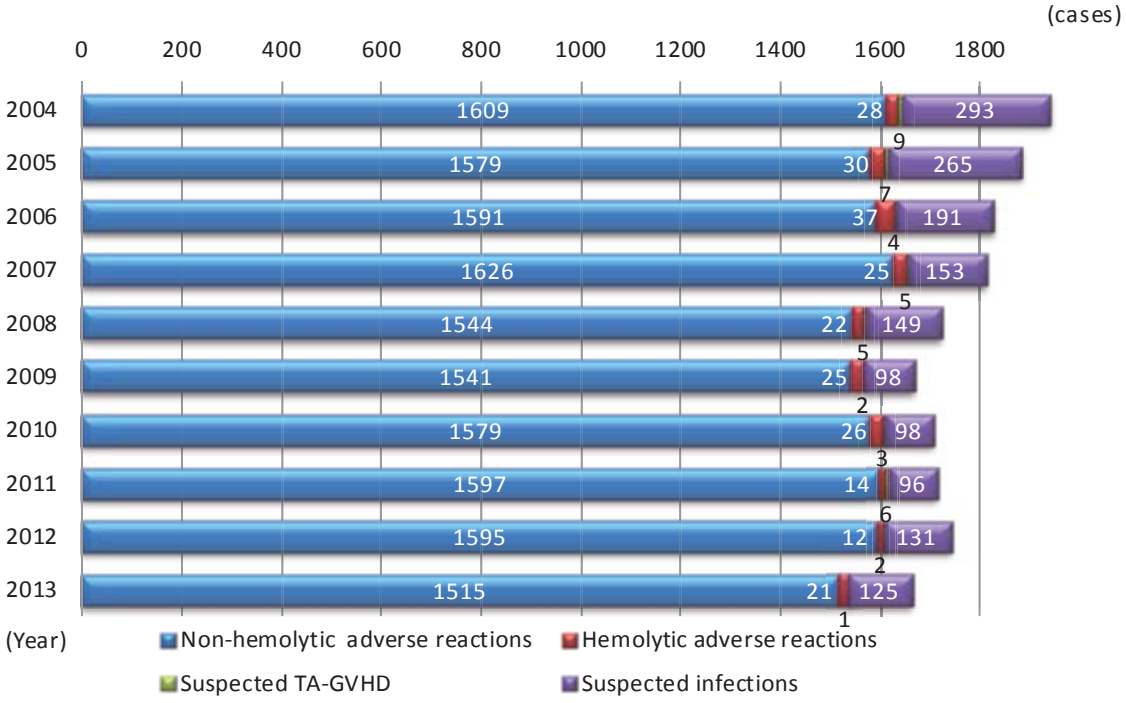

Figure 1. Changes in the number of case reports of transfusion-related adverse reactions and infectious diseases

1) Transfusion-related adverse reactions

(1) Non-hemolytic adverse reactions

Table 1 shows the number of reported cases of non-hemolytic adverse reactions by type of reaction between 2004 and 2013. Figure 2 shows the breakdown in 2013. Figure 3 shows the breakdown of cases evaluated as severe adverse reactions.

Table 1. The number of reported cases of non-hemolytic adverse reactions by type

Symptom \ Year	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Urticaria	563	566	529	578	535	523	612	606	572	608
Febrile reactions	191	241	238	197	157	176	175	140	190	174
Anaphylactic Shock	228	253	246	293	269	280	253	275	242	218
Anaphylaxis	233	175	173	155	152	128	117	129	156	110
Hypotension	81	60	62	47	57	62	70	78	90	92
Dyspnea	151	167	179	172	192	193	195	208	193	200
TACO★									26	29
TRALI★★	40	29	66	45	32	38	24	24	10	19
Others	110	81	98	139	150	141	129	135	116	65
Excluded★★★	12	7	0	0	0	0	4	2	0	0
Total	1609	1579	1591	1626	1544	1541	1579	1597	1595	1515

★ TACO evaluation based on JRCS's own criteria has started since April 2012.

★★ possible-TRALI cases are included. One case of two TRALI event in one patient was included in 2005.

★★★ Cases excluded that were evaluated as being unrelated to transfusion by reporting physitians afterwards.

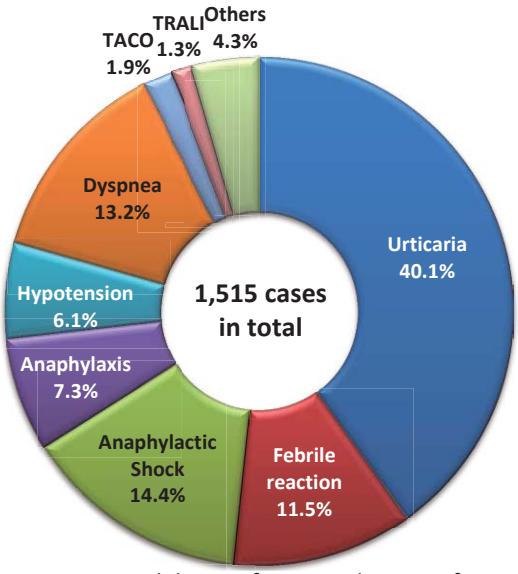

Figure 2. Breakdown of reported cases of non-hemolytic adverse reactions in 2013

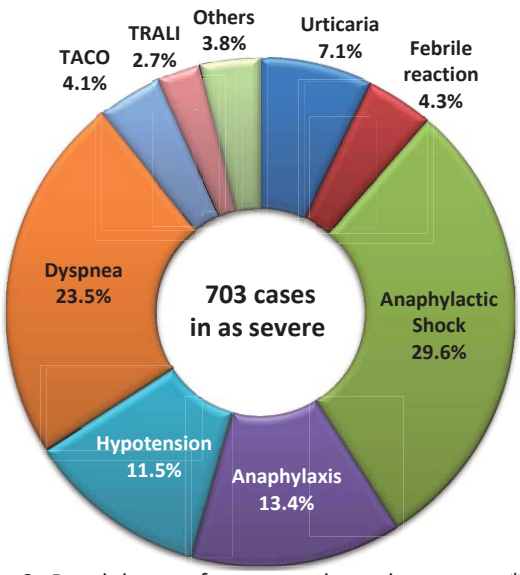

Figure 3. Breakdown of cases evaluated as severe* non-hemolytic adverse reactions in 2013

*severe cases: cases reported as severe adverse reactions by reporting physicians, and/or cases evaluated as severe according to the symptoms by JRCS although the case was reported as non-severe.

Evaluation of TRALI and TACO cases

- TRALI cases are evaluated based on the diagnostic criteria (Figure 5) proposed at the Consensus Conference held in 2004 (Transfusion. 2004;44(12):1774-89.), and TACO cases are evaluated based on the JRCS's own evaluation criteria (Figure 8).
- Of the 1,515 cases of non-hemolytic adverse reactions reported by medical institutions in 2013, 170 cases were evaluated for TRALI. TRALI evaluation was performed on cases with dyspnea and hypoxemia (decreased SpO2), associated with bilateral infiltrates on chest x-ray ,as well as cases reported as suspected TRALI.
- TRALI evaluation revealed 9 cases of TRALI, and 10 cases of possible TRALI.
- Of the 151 cases that were not diagnosed as TRALI, 60 cases had suspected cardiac pulmonary edema, and 91 cases were evaluated with other adverse reactions (including allergic and anaphylactic dyspnea).
- TACO assessment was carried out in a total of 64 cases: 4 cases were reported as suspected TACO, and 60 cases were assessed as cardiac pulmonary edema in the TRALI evaluation. As a result, 29 cases were assessed as TACO.
- Figure 4 shows the flowchart of evaluation of cases with suspected TRALI or TACO.

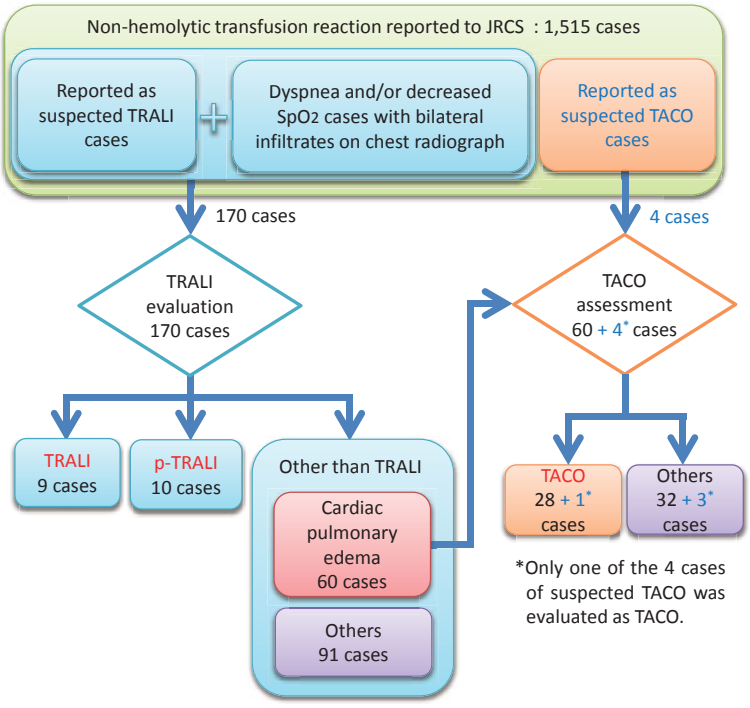

Figure 4. Flowchart of TRALI and TACO evaluation/assessment

Transfusion-related acute lung injury (TRALI)

TRALI cases are evaluated based on the diagnostic criteria (Figure 5) proposed at the Consensus Conference held in 2004 (Transfusion. 2004;44(12):1774-89.).

Figure 6 shows the number of cases diagnosed as TRALI or p-TRALI between 2004 and 2013. Among the total of 328 cases, anti-leukocyte antibodies were detected in the concerned blood components in 126 cases (38%). After the initiation of safety measures for blood donors who were related to TRALI cases and were found to be positive for anti-leukocyte antibodies, blood from 117 donors (79 cases) of 177 implicated donors were subjected to compatibility tests with patients' blood. As a result, 55 donors (48 cases) were found to be reactive in the tests, including computer cross-matching. Therefore, anti-leukocyte antibodies in these components were considered to contribute to the onset of TRALI.

TRALI Criteria

- TRALI is defined as a new episode of ALI that occurs during or within 6 hours of a completed transfusion, which is not temporally related to a competing etiology for ALI.
- possible-TRALI that would have the same definition as TRALI except for the presence of a temporal relationship to an alternative risk factor for ALI .

a. Acute Lung Injury (ALI)
- **I. Acute onset**
- **II. Hypoxemia**
  - **PaO_2/FiO_2 ≦300mmHg or**
  - **SpO_2＜90%(room air)**
  - **or other clinical evidence of hypoxemia**
- **III. Bilateral infiltrates on frontal chest radiograph**
- **IV. No evidence of left atrial hypertension (i.e., circulatory overload)**

b. No preexisting ALI before transfusion
c. During or within 6 hr of transfusion
d. No temporal relationship to an alternative risk factor for ALI*

*：Risk factors for ALI…Direct lung injury (Aspiration, pneumonia, toxic inhalation, lung contusion, and near drowning), Indirect lung injury (Severe sepsis, shock, multiple trauma, burn injury, acute pancreatitis, cardiopulmonary bypass, and drug overdose)

(Transfusion. 2004;44(12):1774-89.)

Figure 5. Diagnostic criteria for TRALI

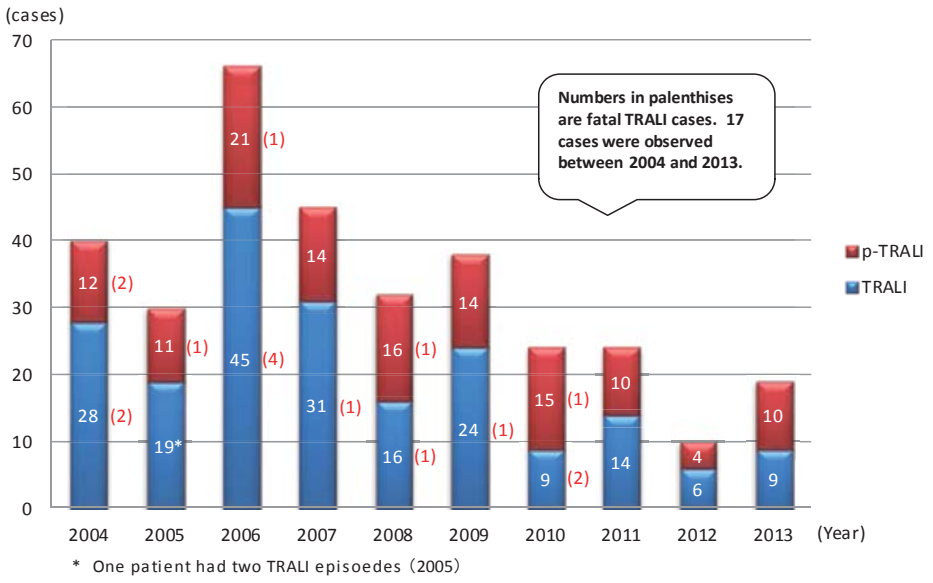

Figure 6. Changes in the number of cases diagnosed as TRALI (2004-2013)

Major causes of TRALI are considered as follows; Anti-leukocyte antibodies (HLA antibodies, HNA antibodies, etc.) in blood components for transfusion react with cognate antigens on white blood cells or vascular endothelial cells of blood recipients, resulting in increased vascular permeability of endothelial cells lining the pulmonary microvascular. Additionally, biologically active compounds such as bioactive lipids that were medicated during storage, or predisposing conditions of patient such as liver disease, sepsis or alcoholism may be associated with the onset of TRALI. Anti-leukocyte antibodies of recipients may bind to cognate allo-antigens on the leukocytes contained in the transfused blood components and cause TRALI. However, this is less possible after the implementation of universal leukoreduction in Japan.

The JRCS started dominant preparation of FFP from male donors (Male Dominant FFP; MDF) in April 2011 (distribution started in October 2011), as anti-leukocyte antibodies, considered as a cause of TRALI, are often produced after exposure to foreign white cell antigens during pregnancy. Figure 7 shows the breakdown of TRALI (including p-TRALI) cases, where the involved FFPs were positive for anti-leukocyte antibodies. After 2012, when almost all FFP derived from 400 mL of whole blood donation from male donors, the number of TRALI caused by FFP from 400 mL of whole blood decreased. In foreign countries, interviews of female donors about pregnancy and selective screening for anti-leukocyte antibodies have been performed for apheresis FFP. The JRCS considers introducing these procedures as part of the future safety measures.

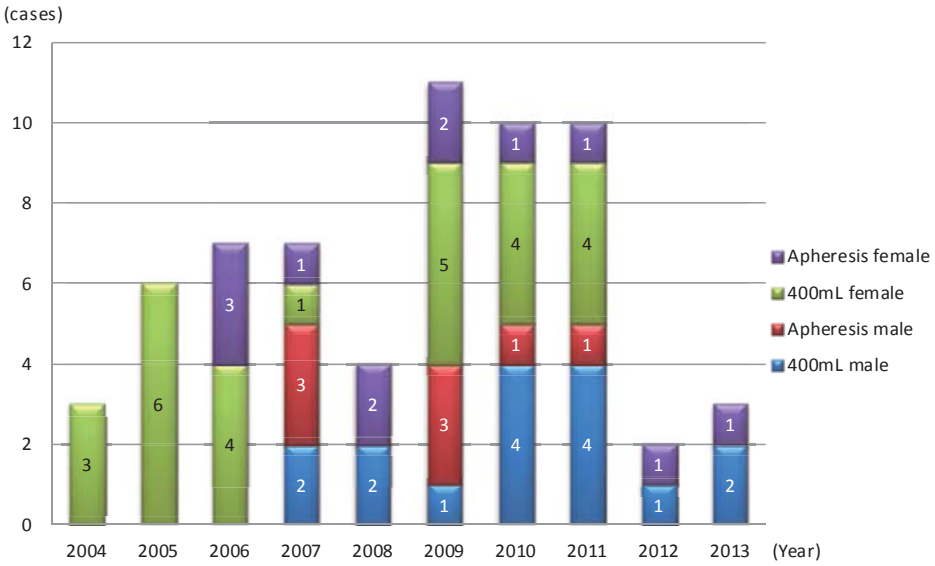

Figure 7. The number of FFP positive for anti-leukocyte antibodies, which may be the causes of TRALI (annual changes)

Transfusion associated circulatory overload (TACO)

There are no universally accepted criteria for TACO on which consensus has been reached as for TRALI, although there are some criteria such as those proposed by the International Society of Blood Transfusion (ISBT). To clarify whether only transfusion causes circulatory overload, and to investigate whether TACO may occur even if transfusion is conducted appropriately, the JRCS has started assessment in April 2012, using the original TACO assessment criteria (Figure 8). JRCS's TACO criteria exclude cases with complications under which circulatory overload tends to occur, such as heart failure, hemodialysis or artificial heart lung machine.

As a result, TACO assessment revealed 26 cases in 2012, and 29 cases in 2013.

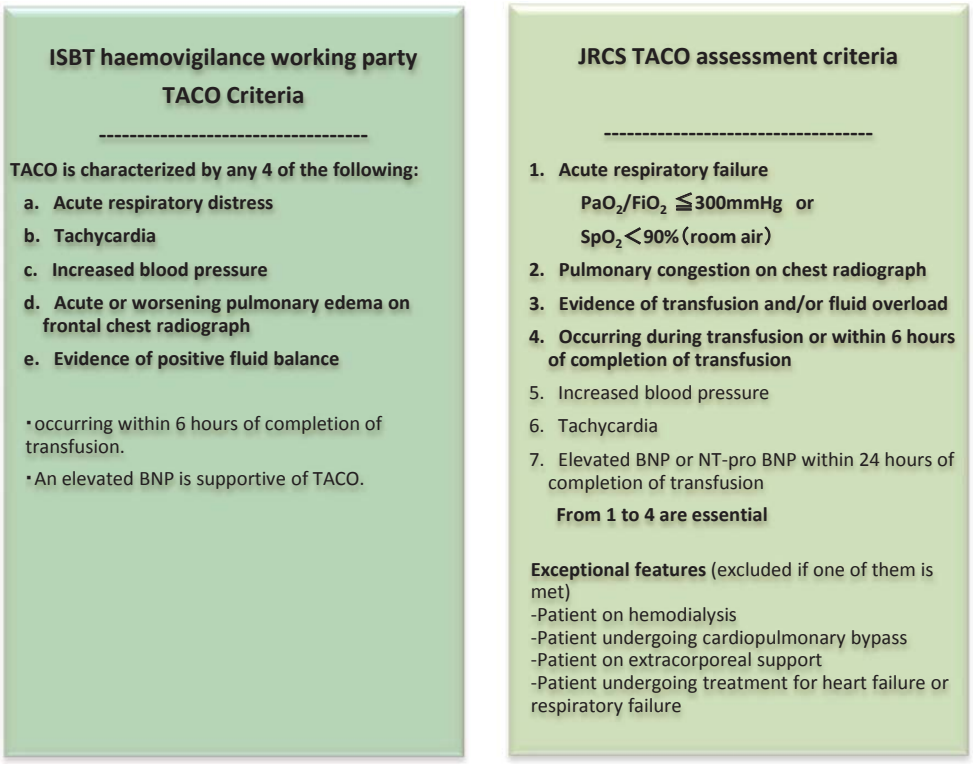

Figure 8. Diagnostic/assessment criteria of TACO

Discussion and future tasks of TRALI and TACO

- Compared to the number of case reports of suspected TRALI, the rate of cases diagnosed as TRALI has been tending to decrease. Of the 328 cases diagnosed as TRALI after 2004, 17 were fatal cases, possibly due to TRALI.
- As a measure against TRALI, MDF is conducted on FFP derived from 400 mL of whole blood donation. Considering the shortage of blood components for transfusion due to Japan's declining birth rate and aging population, it is considered to introduce tests for anti-leukocyte antibodies for other blood components (apheresis plasma components and platelet components from female donors).
- The JRCS has started evaluation of TACO in 2012 and it was revealed that approximately 30 cases of TACO occur annually. To alert healthcare professionals, the JRCS added TACO to the "over-transfusion" section under [Precautions] in the package inserts of blood components for transfusion (April 2014).
- JRCS's TACO criteria are reviewed according to the evaluation results of TACO, thus contributing to the development of diagnostic criteria with international consensus through cooperation to develop revised ISBT diagnostic criteria.
- We are preparing a leaflet about TACO, and will distribute it to healthcare professionals to disseminate information and alert against TACO from the viewpoint of medical safety.

(2) Hemolytic adverse reactions

Table 2 shows the breakdown of case reports of hemolytic adverse reactions in 2013.

Table 2. Number of case reports of hemolytic adverse reactions in 2013

	Severe	non-Severe	Total
AHTR	6	1	7
DHTR	8	6	14
Total	14	7	21

Acute Hemolytic Transfusion Reaction (AHTR) : Onset within 24 hours of a transfusion
Delayed Hemolytic Transfusion Reactions (DHTR) : Onset after 24 hours of a transfusion

- Case investigation by the JRCS revealed 9 cases with irregular antibodies in the patients' specimens which consisted of 4 immediate reactions and 5 delayed reactions. Of the immediate reactions, the patients had transfusion histories in three cases. The details of the cases are shown in Table 3.
- As the patients in immediate reaction cases No.3 and No.4 had irregular antibodies, red cell s without cognate antigens were transfused. However, hemolytic reactions were observed.
- Nine cases of hemolytic adverse reactions also had non-hemolytic adverse reactions at the same time: 4 cases of immediate hemolytic adverse reactions (all severe) and 5 cases of delayed hemolytic adverse reactions (2 of which were severe).

Table 3. Irregular antibodies in the patient's blood positive cases

		Component	Patients	Symptoms	Test results conducted by JRCS after onset			
					Pre-transfusion		Post-transfusion	
					Patient's serum	Crossmatch	Patient's serum	Crossmatch
Acute	1	RBC	F 80s	Hemolysis	Anti-E, DAT-	Incompatible	Anti-E, DAT-	Incompatible
	2	RBC	F 40s	Hemolysis, Hematourea	Anti-E, DAT-	Incompatible	Anti-E, DAT+	Incompatible
	3	RBC	F 60s	Hemolysis, Hematourea	Anti-Jr^a, DAT-	Compatible	Anti-Jr^a, DAT-	Compatible
	4	RBC	M 50s	Hemolysis	Anti-E,Anti- c, Anti-Jk^b, Anti-Di^a,DAT-	Incompatible	Anti-E,Anti- c, Anti-Jk^b, Anti-Di^a,DAT+	Incompatible
Delayed	1	RBC	M 50s	Hemolysis	Anti-Di^a	Incompatible	Anti-Di^a DAT+	Incompatible
	2	RBC	M 70s	Hemolysis, LDH/T-Bil increasing	Neg	n/t	Anti-C, Anti-e	n/t
	3	RBC	M 70s	Hemolysis, Red urea	Neg, DAT-	n/t	Anti-C, Anti-e, Anti-P1, DAT-	n/t
	4	RBC	M 60s	T-bil increasing	Anti-Di^a	n/t	Anti-Di^a, Anti-Jk^b, DAT+	n/t
	5	RBC	F 80s	AST, ALT, LDH increasing	Anti-KANNO, DAT+	n/t	Anti-KANNO, DAT+	n/t

(3) Transfusion-associated graft-versus-host disease (TA-GVHD)

- One case of suspected TA-GVHD was reported in 2013. However, microsatellite DNA analysis of the patient's blood revealed no chimerism, thus TA-GVHD was ruled out.
- There have been no confirmed cases of TA-GVHD that were caused by blood components for transfusion distributed by the JRCS since 2000.

2) Transfusion transmitted infections

(1) Cases of suspected transfusion-transmitted infections reported in 2013

Table 4 shows the breakdown of cases of suspected transfusion-transmitted infections (including reported cases from medical institutions and cases of post-donation information) reported in 2013.

Table 4. The breakdown of suspected TTI cases by pathogen reported in 2013

Pathogens	Reported cases	Confirmed cases
HBV	52	7
HCV	32	1
Bacteria	25	1
HIV	2	1
HEV	2	1
CMV	11	0
Human Parvovirus B19	1	0
Total	125	11

Confirmed cases include cases in which pathogens such as viruses were found both in the transfused blood components and in the post-transfusion patients' blood with homology. Homology was confirmed by viral genome sequence analysis or by genotype-specific tests (pulsed-field gel electrophoresis: PFGE), drug susceptibility tests and toxin-type tests of bacterial strains.

(2) Summary of case reports in 2013

TTI cases in which viral nucleic acid or bacteria were detected in the repository samples and/or relevant blood components described as follows:

HBV

Voluntary reports: Cases reported by medical institutions

Case no.	Primary disease	Blood component (year and month of blood collection)	Age	Sex	Pre-transfusion test			Post-transfusion test			ALT	
					Test items	Result	Period to transfusion	Test items	Result	Period from transfusion	Maximum (IU/L)	Period from transfusion
1	Chronic renal failure Glomerulonephritis	Ir-RCC-LR (2012.6)	50s	F	HBV-DNA, HBsAg, HBcAb	Neg.	0 day	HBsAg	Pos.	34 wks	738	34 wks
2	Metastatic liver cancer Diabetes mellitus/renal failure	Ir-RCC-LR (2012.8)	60s	M	HBV-DNA, HBcAb	Neg.	0 day	HBsAb, HBcAb	Pos.	27 wks	252	24 wks
3	Myelodysplastic syndrome	Ir-RCC-LR (2011.7)	90s	M	HBV-DNA	Neg.	143 days	HBV-DNA	Pos.	74 wks*	◆	◆
4	Pure red cell aplasia Granular lymphocytosis	Ir-RCC-LR (2013.5)	70s	M	HBsAg, HBsAb, HBcAb	Neg.	220 days	HBsAg	Pos.	13 wks	◆	◆

* A positive conversion of HBV-DNA was confirmed in the samples obtained from 8-weeks after transfusion by JRCS's investigation.

Post donation information: Cases reported by medical institutions based on lookback studies of positive conversion of a repeat donor

Case no.	Primary disease	Blood component (year and month of blood collection)	Age	Sex	Pre-transfusion test			Post-transfusion test			ALT	
					Test items	Result	Period to transfusion	Test items	Result	Period from transfusion	Maximum (IU/L)	Period from transfusion
5	Multiple injuries	FFP-LR (2010.8)	70s	F	HBsAg	Neg.	0 day	HBV-DNA, HBsAg, HBcAb	Pos.	93 wks	◆	◆
6	Trochanteric fracture of left femur	Ir-RCC-LR (2012.3)	90s	F	HBsAg	Neg.	1 day	HBsAg	Pos.	47 wks	◆	◆
7	Mitral incompetence	RCC-LR (2013.5)	80s	F	HBsAg	Neg.	20 days	HBV-DNA, HBsAg	Pos.	16 wks	◆	◆

HCV

Post donation information: A case reported by a medical institution based on lookback studies of positive conversion of a repeat donor

Case no.	Primary disease	Blood component (year and month of blood collection)	Age	Sex	Pre-transfusion test			Post-transfusion test			ALT	
					Test items	Result	Period to transfusion	Test items	Result	Period from transfusion	Maximum (IU/L)	Period from transfusion
1	Basal fracture of the left femoral neck	Ir-RCC-LR (2009.6)	90s	F	HCV-Ab	Neg.	2 days	HCV-Ab	Pos.	212 wks	◆	◆

HIV

Post donation information: A case reported by a medical institution based on lookback studies of positive conversion of a repeat donor

Case no.	Primary disease	Blood component (year and month of blood collection)	Age	Sex	Pre-transfusion test			Post-transfusion test			ALT	
					Test items	Result	Period to transfusion	Test items	Result	Period from transfusion	Maximum (IU/L)	Period from transfusion
1	Chronic pancreatitis	FFP-LR (2013.2)	60s	M	HIV-Ab	Neg.	8 days	HIV-Ab	Pos.	5 wks	◆	◆

◆ No increase in ALT or no comparative available.

HEV

Post donation information: A case reported by a medical institution based on lookback studies of positive results at quality control of the source plasma for the manufacturing of plasma derivative

Case no.	Primary disease	Blood component (year and month of blood collection)	Age	Sex	Pre-transfusion test			Post-transfusion test			ALT	
					Test items	Result	Period to transfusion	Test items	Result	Period from transfusion	Maximum (IU/L)	Period from transfusion
1	Unstable angina, Type 2 diabetes mellitus	Ir-RCC-LR (2012.12)	70s	M	HEV-RNA, IgM-HEV-Ab, IgG-HEV-Ab	Neg.	0 day	HEV-RNA	Pos.	6 wks	379	13 wks

Bacteria

Voluntary report: A case reported by a medical institution as suspected transfusion transmitted bacterial infectious case

Case no.	Primary disease	Blood component (year and month of blood collection)	Age	Sex	Results of post-transfusion blood culture		Symptom	Expression time (after administration)	Recipient's outcome
					Blood component	Recipient's blood			
1	Myelodysplastic syndrome	Ir-PC-LR (2013.12)	70s	M	*Streptococcus equisimilis (group G hemolytic streptococcus)*	*Streptococcus equisimilis (group G hemolytic streptococcus)*	Precordial pressure Chills, Fever	Approx. 150 min.	Recovery

3) Information about individual cases of transfusion adverse reactions and TTIs obtained from the literature or academic conference information

Table 5 shows domestic case reports obtained from literature or academic conference information in 2013. Although the domestic cases in Table 5 were only reported in the literature or at academic conferences, the JRCS investigated the severity of adverse reactions and blood components used in those cases at the medical institutions. If the cases were classified as severe adverse reactions, we submitted them as ICSR to PMDA.

Although the blood components for transfusion prepared by the JRCS are not distributed in other countries, we have to submit ICSR of overseas cases of TTIs and unknown severe adverse reactions caused by foreign blood components that are therapeutically equivalent, according to the PAL. In 2013, there were no overseas case reports of unknown severe adverse reactions in the literature (Table 6).

Table 5. Domestic cases of transfusion-related adverse reactions obtained in the literature search in 2013 (including cases not reported individually)

No.	Suspected Component	Age	Sex	Symptoms	Journal etc.
1	FFP-LR-Ap	62	M	Transfusion-related acute lung injury	J. Jpn. Soc. Dial. Ther. 2013;46(4):435-441
2	FFP-LR-Ap	52	F	Eczema	Japanese journal of apheresis. 2013;32(3):218-221
3	FFP-LR-Ap	35	F	Redness, Nausea, Hypotension	Japanese journal of apheresis. 2013;32(3):218-221
4	FFP-LR-Ap	26	F	Redness, Pruritus, Hypotension, Heart rate decreased	Japanese journal of apheresis. 2013;32(3):218-221
5	RCC-LR PC-LR	2	M	Transfusion-related circulatory overload	The 55th Annual Meeting of the Japanese Society of Pediatric Hematology and Oncology Abstracts. 2013;84
6	Ir-RCC-LR	77	F	Delayed haemolytic transfusion reaction	Japanese journal of transfusion and cell therapy. 2013;59(2):324
7	RCC-LR PC-LR	74	F	Delayed haemolytic transfusion reaction	Japanese journal of transfusion and cell therapy. 2013;59(2):327
8	Ir-RCC-LR	9	F	Cerebral infarction	Yomiuri Shimbun. 2013. 7. 25
9	Ir-RCC-LR	70	M	Delayed haemolytic transfusion reaction	Iyakunomon. 2013;52(6):484
10	Ir-RCC-LR	70	F	Delayed haemolytic transfusion reaction	Japanese journal of transfusion and cell therapy. 2013;59(3):521

FFP-LR-Ap : Fresh Frozen Plasma, Leukocytes Reduced, Apheresis
RCC-LR : Red Cells Concentrates-Leukocytes Reduced
PC-LR : Platelet Concentrate, Leukocytes Reduced
Ir-RCC-LR : Irradiated Red Cells Concentrates-Leukocytes Reduced

(Summary)

- A case of TRALI (No.1) indicating worsening respiratory condition after receiving 2 bags of 5 units of FFP during ABO-incompatible renal transplantation.
- Rash, redness, queasy, blood pressure decreased etc., were reported in 3 cases (No. 2, 3, 4) treated with plasma exchange (PE) using FFP of patients with myasthenia gravis (MG).
- TACO was reported in one case (No.5) who had acute lymphocytic leukemia with severe anemia and who received transfusion of red blood cell products. The patient had preexisting heart failure.
- Cases of delayed hemolytic transfusion reactions (No 6, 7, 9, 10) were due to anti-C, anti-E, anti-Jkb antibodies, etc.
- One case (No. 8) developed cerebral infarction at 3 days after transfusion of type-AB red blood cells in a patient with blood type A.

Table 6. Overseas cases obtained in the literature search in 2013 that have been submitted ICSR to PMDA

No.	Country	Suspected blood product	Age	Sex	Symptoms	Journal etc.
1	Colombia	Red cell concentrates	-	F	Plasmodium vivax infection	Biomedica. 2012;32 Suppl 1:8-12
2	U.S.	Whole blood Platelet concentrates	31	M	Human T-cell lymphotropic virus infection	Transfusion. 2013;53(10);2176-2182
3	China	Fresh frozen plasma	13	M	HIV infection	Iran J Peditr. 2012;22(3):417-420
4	China	Red cell concentrates	4	F	HIV infection	Iran J Peditr. 2012;22(3):417-420
5	U.S.	Platelet concentrates	9	M	Human granulocytic ehrlichiosis	Clin Infect Dis. 2013;19(7):e105-e107
6	France	Red cell concentrates	58	M	Bacterial infection	Emerg Infect Dis. 2013;19(7):1118-1120
7	France	Red cell concentrates	55	M	Hepatitis E	Transplantation. 2013;96(2):e4-e6
8	U.S.	Platelet concentrates	-	M	West Nile viral infection	MMWR Morb Mortal Wkly Rep. 2013;62(31):622-624
9	Malaysia	Red cell concentrates	12	M	Plasmodium vivax infection	Malaria J. 2013;12(1):308
10	Sweden	Red cell concentrates	9	M	Hepatitis C	Scand J Infect Dis. 2013;45(10):796-799
11	U.S.	Red cell concentrates	76	M	Plasmodium malariae infection	MMWR Surveill Summ. 2013;62(5):1-17
12	France	Platelet concentrates	5	F	Septic shock	BMJ Case Rep. 2013
13	Netherlands	Red cell concentrates	59	F	Plasmodium malariae infection	Malaria J. 2013;12:439

(Summary)

- In all cases of *plasmodium vivax* (No. 1) and *plasmodium malariae* (No. 11, 13), the donors of the involved red blood cells had a history of visiting or residing in endemic areas.
- In cases of HIV (No. 3, 4), the donors of the concerned blood components were men who have sex with men (MSM), but they did not provide the information during the interview.
- In one case of Human T-cell leukemia virus type 1 (HTLV-1), the HTLV-1 was detected in one of the 13 concerned donors of fresh blood that was transfused to a soldier who was injured on a battlefield.
- Cases of bacterial infections were caused by red blood cells contaminated with *P.arenosus* (No.6) and platelet components contaminated with *E.coli* (No.12).
- In one case of hepatitis E (No.7), the implicated donors of the red blood cells had contact with livestock and a habit of eating raw pork.
- For one case of hepatitis C (No. 10), HCV RNA was detected on quality inspection of source plasma for plasma derivatives, and the red blood cells, which were simultaneously prepared, were transfused to the patient who was positive.
- In one case of human granulocytic ehrlichiosis (No.5), the donor of the concerned platelet components had a history of tick bite.

2. Reports on measures in foreign countries and reports of studies

Reports on measures in foreign countries are submitted when the JRCS obtains information concerning the enforcement of measures to prevent health hazards from occurring or spreading, including discontinuation of manufacturing, importing or distributing, or recall or disposal of foreign pharmaceutical products. Reports of studies are submitted when the JRCS obtains information concerning study reports showing that cancer or another serious disease, disorder, or death was possibly caused by a relevant pharmaceutical product or a foreign pharmaceutical product, or infection due to its use, or that the incidence of adverse reactions to the relevant pharmaceutical product or foreign pharmaceutical product or infection by its use has significantly changed, or that the relevant pharmaceutical product did not show its approved efficacy or effect.

Reports on measures in foreign countries and reports of studies are submitted based on Article 68-10 of the Pharmaceutical Affairs Law and Article 228-20 of the Enforcement Regulations of the Pharmaceutical Affairs Law, even if the blood components manufactured by JRCS are not marketed (supplied) in other countries. Such products involve products used in other countries that have the same active ingredients as the blood components manufactured or distributed by the JRCS, including such products with a different administration route and dosage, or efficacy and effect.

In 2013, there had been no reports of studies applicable to the above. Table-7 shows measures in foreign countries that have been reported.

Table 7. Reports on measures in foreign countries obtained in 2013

	Source	Description
1	U.S. (FDA)	Guidance for Industry Recommendations for Screening, Testing, and Management of Blood Donors and Blood and Blood Components Based on Screening Tests for Syphilis (DRAFT GUIDANCE). March 2013.
2	Canada (Health Canada)	Health Canada Approves Proposals To Change Deferral Period For Certain Blood Donors- Regulatory decision will not compromise the safety of Canada's blood system.
3	U.S. (AABB)	Association Bulletin #13-03-Updated Criteria for Donor Deferral and Blood Component Retrieval in Known or Suspected Common Source Outbreaks of Hepatitis A Virus Infection.
4	U.S. (AABB)	1)TRALI Risk Reduction Requirements in the 29th Edition of BBTS Standards. 2)Association Bulletin #14-02 TRALI Risk Mitigation for Plasma and Whole Blood for Allogeneic Transfusion.

(Summary)

1. Guidance for industry recommendations for screening, testing, and management of blood donors and blood and blood components based on screening tests for syphilis was issued. This is a revised version of the draft guidance issued in June 2003, describing differences in syphilis testing methods (treponemal assays and non-treponemal assays to detect anti-cardiolipin antibodies), management of donors, and disposal of products based on the results of the screening. When this guidance is finalized, it will replace the memorandum, "FDA recommendations for suspension of blood donation and disposal of products based on the results of syphilis tests" issued in December 1991.
2. Regarding the indefinite blood donation deferral period for MSM, Health Canada approved the proposal that MSM may donate blood if they have not had sexual contact with men for the previous 5 years.
3. An updated version of criteria for donor deferral and blood component retrieval in known or suspected common source outbreaks of hepatitis A virus (HAV) infection was published. The updated criteria state that volunteer blood donors who may have been exposed to HAV must have an additional deferral period of 120 days regardless of the HAV vaccination history.
4. The next edition of Blood Banks/Transfusion Service (BBTS) Standards, which is effective on April 1, 2014, announced the inclusion of new TRALI risk-reducing requirements, for example, that donors associated with TRALI cases have to undergo donor eligibility assessments, and that high plasma volume components have to be manufactured from blood collected from men, women without a history of pregnancy, and women who have negative HLA antibody tests taken after the most recent pregnancy. The AABB publication for blood manufacturer approved by the AABB suggested to include a summary of the latest scientific findings of TRALI risks and a risk mitigation plan for plasma transfusion, the recommendation of methods that are consistent with the new criteria, procedures for application of the new criteria, and points to be taken into consideration for operational plans.

3. Safety measures for blood components for transfusion

Safety measures are taken based on cases of transfusion-related adverse reactions and TTIs reported by medical institutions and the results of assessment and evaluation of post-donation information obtained from donors. The following are the safety measures taken in 2013:

1) Information provision regarding suspected cases of transfusion-transmitted cytomegalovirus infection in very-low-birth-weight infants

- Medical institutions reported 19 cases of suspected cytomegalovirus (CMV) infection caused by blood components between 2004 and March 2013. There were no confirmed cases of transfusion-transmitted infection, but all cases were infants <1 year old.
- However, most of these cases were extremely-low-birth-weight infants, very-low-birth-weight infants, and low-birth-weight infants. Even though they were high-risk patients, CMV antibody-negative blood was not used in all cases.
- Therefore, the JRCS distributed a leaflet about the use of CMV antibody-negative blood as necessary for perinatal health care professionals.
- In addition, the JRCS revised the package inserts of all blood components for transfusion, except plasma components, to add the risk of CMV infection (April, 2014).
- Table 8 shows the case reports after 2010.

Table 8. Cases of CMV infection after transfusion reported between 2010 and 2013

Year	Patient	Primary diseases	Blood components	CMV markers	
				Pre-TF	Post-TF*
2010	5months Male	Ventricular and Atrial septal defect Repair of defect	RCC-LR FFP-LR	IgM (—) IgG (—)	N.T.
	1 month Female	Preterm infant (<1000g), Patent ductus arteriosus ligation, Anemia of prematurity	Ir-RCC-LR FFP-LR	N.T.	DNA(+)
2011	2months Female	Preterm infant (<1000g), Patent ductus arteriosus ligation	RCC-LR Ir-PC-LR FFP-LR	N.T.	IgM (+)
2012	3months Male	Preterm infant (<1000g), Anemia of prematurity	Ir-RCC-LR	N.T.	N.T.
	2months Male	Preterm infant (<1000g), Anemia of prematurity, Intra-cerebral haemorrhage, DIC	Ir-RCC-LR FFP-LR	N.T.	DNA (+) IgM (+) IgG (+)
	1month Male	Preterm infant (<1000g), Patent ductus arteriosus ligation, Anemia of prematurity	RCC-LR	N.T.	N.T.
2013	Infant Female	Twins, Severe pulmonary artery stenosis, Pulmonary valve repair	Ir-RCC-LR RCC-LR Ir-PC-LR	N.T.	DNA(+) IgM (+) IgG (+)
	2months Male	Preterm infant (<1500g), Anemia of prematurity	RCC-LR	N.T.	DNA(+) IgM (-) IgG (+)
	1month Female	Preterm infant (<1500g), Anemia of prematurity	Ir-RCC-LR	N.T.	DNA(+) IgM (+) IgG (+)

*: The results of confirmation tests conducted by the JRCS in patients who had positive results of post-transfusion testing at medical institutions
N.T.: Not tested (no specimens)

- CMV-DNA was not detected in any repository specimens of the concerned donated blood in the above 9 cases, and anti-CMV IgM antibody was negative in all cases (anti-CMV IgG antibody was also negative in one case). There were no cases that were evaluated to have a probable causal relationship with transfusion so far.

2) Further safety measures for blood from donors with a hepatitis B virus (HBV) infection history (changes in the criteria for hepatitis B virus core antibody: HBcAb)

In October 1999, nucleic-acid amplification testing ("NAT") of HBV, HCV and HIV was introduced using a 500-sample pool. The pool size was reduced from 500 to 50 in February 2000, and from 50 to 20 in August 2004. The NAT system was replaced by a new platform with more sensitive reagents and apparatuses in August 2008. Therefore, confirmed TTI cases due to blood donated during the window period, which was NAT positive, were decreasing as shown in Figure 9. However, there were still some confirmed cases due to blood from donors with a history of HBV infection.

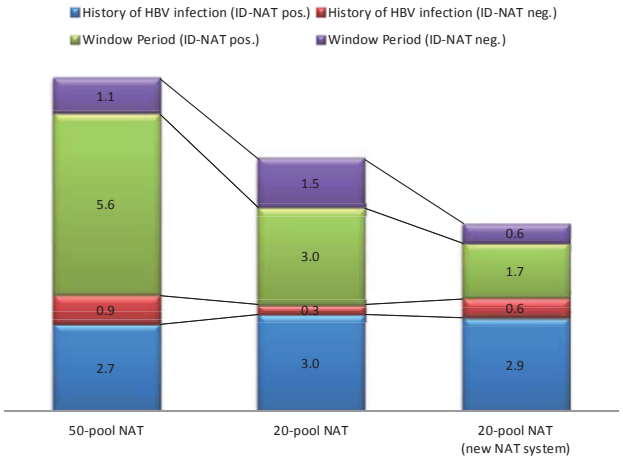

Figure 9. Changes in transfusion-transmitted HBV infection sources
(confirmed cases of transfusion-transmitted HBV per year)

Therefore, to enhance safety, measures were taken to achieve a stricter cut-off index value threshold against HBc antibody in the chemiluminescence enzyme immunoassay: CLEIA method. Thus donors with a history of HBV infection, who had been eligible, could be eliminated.

Revised eligibility criteria for HBsAb and HBcAb

		【Old】 HBcAb (C.O.I.)			【Revised】 HBcAb (C.O.I.)	
		<12.0	12.0≦		<1.0	1.0≦
HBs titer	200mIU/mL≦*	qualified	qualified		qualified	qualified
	<200mIU/mL	qualified	inqalified		qualified	inqalified

* There have been no report of transfusion transmitted HBV by blood components with HBsAb titer more than 200IU/mL.

The new HBcAb test criteria have been implemented since August 6, 2012. As the number of donors with a history of HBV infection is tapering, transfusion-transmitted infection cases in recipient are expected to decrease.

Table 9 shows a summary of look-back studies of blood donors from fiscal year 2010 to FY 2013. Although the number of look-back studies that were subjected to individual NAT increased both in FY2012 and FY2013, after implementation of the stricter criteria for HBcAb testing , the number was expected to decrease because the concerned donors were requested to stop donating from the next time.

Table 9. Lookback Studies of post donation information

	FY2010 April 2010 - March 2011			FY2011 April 2011- March 2012			FY2012 April 2012 - March2013			FY2013 April 2013 - April 2014		
	HBV	HCV	HIV	HBV	HCV	HIV	HBV	HCV	HIV	HBV	HCV	HIV
(1) Breakdown of Lookback studies												
① Donations intended for lookback studies												
1) Total	1,852			2,491			10,997			9,016		
2) Numbers by pathogens	1,730	74	48	2,407	59	25	10,892	60	45	8,932	58	26
② Blood components intended for lookback among the ① above												
1) Total	2,072			2,749			11,428			9,854		
2) Numbers by pathogens	1,934	82	56	2,659	67	23	11,313	61	54	9,752	69	33
③ Information provision to medical institutions among the ② above												
1) Total	2,072			2,749			11,428			9,854		
2) Numbers by pathogens	1,934	82	56	2,659	67	23	11,313	61	54	9,752	69	33
(2) Individual NAT results												
① Donations with ID-NAT positive in Lookback studies (1)①												
1) Total	100			116			149			96		
2) Numbers by pathogens	100	0	0	116	0	0	149	0	0	94	1	1
② Details of involved blood components privided to medical institutions												
1) Transfused	98	0	0	119	0	0	146	0	0	93	1	2
2) under investigation	0	0	0	0	0	0	0	0	0	0	0	0
3) Discarded	5	0	0	3	0	0	6	0	0	4	0	0
4) Unknown	3	0	0	0	0	0	0	0	0	0	0	0
Total	106	0	0	122	0	0	152	0	0	97	1	2
③ Status of recipients revealed among the ② above												
1) Positive conversion	5	0	0	6*	0	0	5	0	0	2	1	1
2) Non conversion	28	0	0	46	0	0	59	0	0	34	0	1
3) Death (due to primary disesases)	44	0	0	56	0	0	56	0	0	45	0	0
4) Details unknown	15	0	0	7	0	0	23	0	0	11	0	0
5) PreTF Unknown	6	0	0	4	0	0	3	0	0	1	0	0
Total	98	0	0	119	0	0	146	0	0	93	1	2
④ Individual case reports submitted to JRCS among the ③ above												
Case reports	5	0	0	4	0	0	5	0	0	2	1	1

*Two cases of the 6 cases were positive onversion of HBsAb which were considered as antibody transmission from blood components.

3) Epidemiological studies of Chagas disease

Based on the recommendation by the Subcommittee on Safety of Blood Products, the Committee of Blood products, the Pharmaceutical Affairs and Food Sanitation Council meeting held on July 6, 2012, JRCS has set a safety measure against donors who answer 'yes' to any of the following questions (1) to (3) at the interview, since October 15, 2012. Blood from these donors are only used as source plasma to manufacture plasma derivatives.

(1)You were born or grew up in Latin America.
(2)Your mother was born or grew up in Latin America.
(3)You do not fall into the above (1), but have stayed in Latin America for more than a total of 4 weeks.

Trypanosoma cruzi (*T. cruzi*) antibody tests (ELISA methods) were performed as a pilot study in case of donors who fell into any of the above (1) to (3) and provided separate consent in 4 prefectures of the Tokai area (Aichi, Shizuoka, Mie and Gifu), where many people from Latin America live. It was implemented nationwide from April 23, 2013.

As of December 10, 2013, among 4,356 donors who underwent epidemiologic studies, 2 donors were positive for *T. cruzi* antibody. One was a first-time donor. However, the other one had nine records of previous donations which were all *T. cruzi* antibody positive in look-back study using repository samples of each donation. A total of 9 bags of red blood cells, 2 bags of plasma, and 7 units of source plasma had been prepared. The source plasma was supplied to a manufacturer of plasma derivatives, all red blood cell components and plasma components were supplied to medical institutions and transfused to patients. Table 10 shows the results of retrospective studies.

Table 10. The results of retrospective studies of Chagas disease

Past Donation	Donation	Components	Recipient		Test results of recipients
1	Whole Blood	Red Cells-LR	M	60s	Not tested
		FFP-LR	M	60s	Anti-T.cruzi neg (ELISA)
2	Whole Blood	Red Cells-LR	M	60s	Anti-T.cruzi neg (ELISA)
3	Whole Blood	Red Cells-LR	M	60s	Anti-T.cruzi neg (ELISA)
		FFP-LR	M	50s	Anti-T.cruzi neg (ELISA)
4	Whole Blood	Red Cells-LR	F	80s	Not tested
5	Whole Blood	Red Cells-LR	F	70s	Not tested
6	Whole Blood	Red Cells-LR	F	80s	Not tested
7	Whole Blood	Red Cells	M	80s	Not tested
8	Whole Blood	Red Cells	F	30s	Anti-T.cruzi neg (ELISA)
9	Whole Blood	Red Cells	M	60s	Not tested

LR: Leukoreduction

4. Donor adverse reactions

1) Cases of donor adverse reactions

More than 70% of donor adverse reactions are vasovagal reactions (VVR), which have the highest incidence among all cases of donor adverse reactions. Symptoms of mild VVR include feeling bad, pallor facial, cold sweat, and symptoms of severe VVR include loss of consciousness (including associated falling), or convulsions in addition to the symptoms found in mild cases.

Table 11 shows the cases of donor adverse reactions in 2013, and Figure 10 shows the breakdown by symptoms.

Table 11. shows the cases of donor adverse reactions in 2013

Category	Number of cases	Frequency(%)
VVR mild*	34,329	0.67%
VVR severe*	4,572	0.09%
Hematoma	9,569	0.19%
Nurve injury	261	0.01%
Citric reactions	322	0.01%
Nurve disorder	344	0.01%
Localized pain	2,251	0.04%
Others	1,747	0.03%
Total	53,395	1.04%

Total donation	5,156,325

*Evaluation and categorization of VVR

Severity	Category	sBP（mmHg） pre-donation → post donation	Heart rate(/min) pre-donation → post donation	Respiratory rate(/min)
mild	Feel bad, palor, yawn, nausea, vomiting, cold sweat	120< → 80< <119 → <70	60< → 40< <59 → <30	10<
severe	In addition to mild ones, Loss of conciousness, convulsion, Incontenence, Defecating	120< → <79 <119 → <69	60< → <39 <59 → <29	<9

Notice）Accident accompanied with faint should be categolized to ssevere.

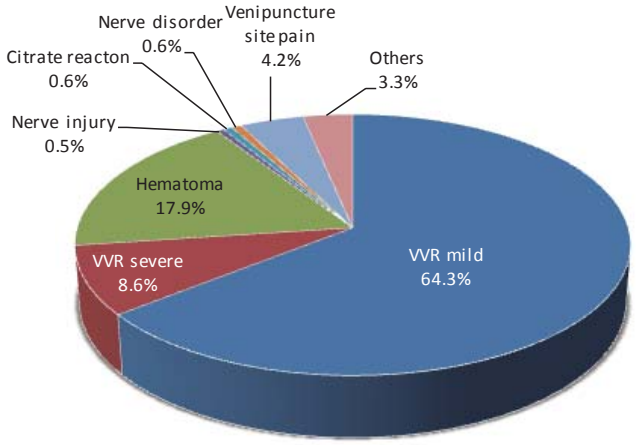

Figure 10. Breakdown of donor adverse reactions in 2013

2) Actions against donor adverse reactions

Educational activities to prevent falling caused by VVR

The JRCS started enlightenment by leaflets explaining that donors should squat or lie down immediately when they feel strange or different from usual after blood donation to prevent injuries caused by falling from September 30, 2013 (Figure 11).

Figure 11. Educational leaflet for measures to prevent fainting and falling after blood donation

Establishment of a Review Committee of Donor Adverse Reactions

Donor adverse reactions occur in approximately 50,000 cases per year. Procedures to respond to the onset of these reactions are described in the Standard Operation Procedures (SOPs) of blood collection, and are complied by all staff members. In addition to taking a rest and replenishing fluids to prevent VVR, various preventive actions were taken at each local blood center. However, examination of the efficacy of measures was insufficient and a conclusion was not reached. Therefore, the Review Committee of Donor Adverse Reactions of JRCS was established on November 20, 2012 to provide effective measures for early detection and prevention of donor adverse reactions which can be implemented nationwide, through risk analysis and assessment of previous measures, studies and trials.

Afterword

This annual report describes information including those on transfusion-related adverse reactions and infectious diseases reported by medical institutions nationwide to JRC Blood Centers, and infectious cases based on post-donation information as well as other safety information. This report also summarizes the safety measures conducted through evaluation and analysis of the safety information in accordance with the Pharmaceutical Affairs Law and GVP ordinance.

We extend our sincere appreciation for the cooperation of health care professionals and members of JRC Blood Centers to conduct these safety vigilance activities.

The JRCS will contribute to haemovigilance in Japan and the international community in compliance with the applicable laws and regulations, and endeavor to improve the safety of transfusions.

"Haemovigilance by JRCS 2013"

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