日本赤十字社
Japanese Red Cross Society

Haemovigilance by JRCS 2014

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 from blood collections, through testing, processing, distribution, up to follow-up of recipients by analysing and evaluating the causes and to conduct 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 addition, JRCS supplies source plasma to domestic manufactures of plasma derivatives. In Japan, blood components for transfusion are categorized as prescription drugs. “Pharmaceutical Affairs Law” was revised to reinforce the safety measures for prescription drugs on November 25, 2014. 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. Additionally, the JRCS conducts epidemiological studies for 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 aforementioned Pharmaceutical Affairs Law and 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 which were reported by medical institutions between 2005 and 2014. Note that cases assessed as unrelated to transfusion are included.

In 2014, the JRCS received 1,473 case reports of adverse reactions (1,451 cases were classified as non-hemolytic adverse reactions, 21 as hemolytic adverse reactions, and 1 as suspected transfusion associated GVHD), and 81 case reports of suspected TTIs from medical institutions across Japan. Severe cases which were evaluated by reporting physicians and/or the JRCS were submitted as individual case safety reports (ICSRs) to the PMDA in accordance with the Pharmaceutical Affairs Law. The breakdown of the ICSRs is 705 non-hemolytic adverse reactions, 15 hemolytic adverse reactions and 81 infections (Note that some cases included multiple categories, eg, one case had non-hemolytic and hemolytic reactions). The JRCS also investigates and evaluates case reports of adverse reactions/ TTIs that are found by literature search and have not been reported voluntarily.

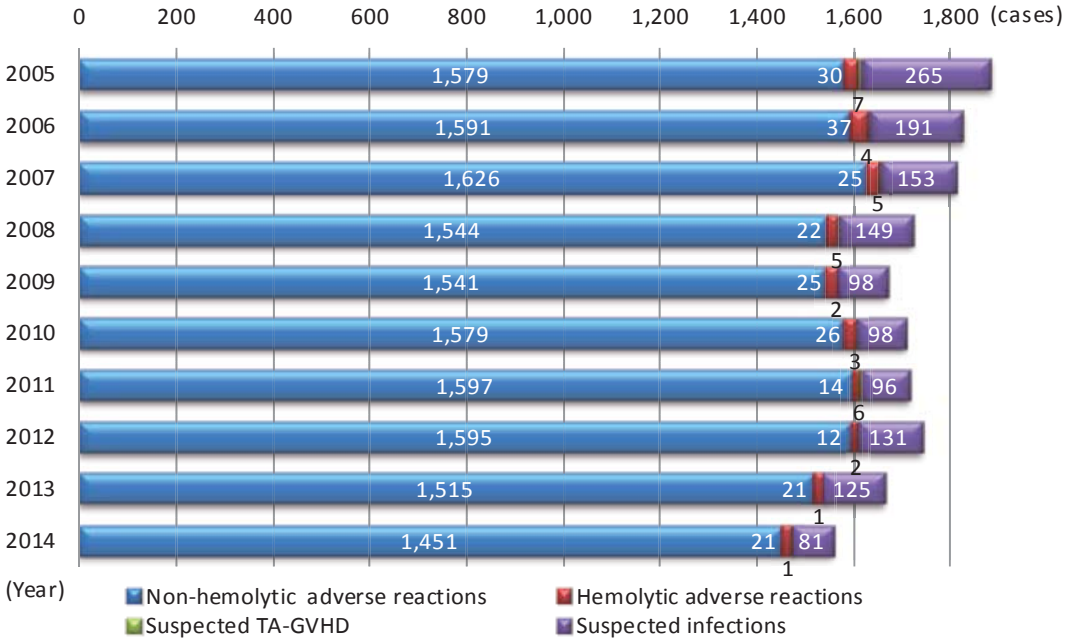

Figure 1. Changes in the number of voluntary reports of transfusion-related adverse reactions and infectious diseases

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 2005 and 2014. Figure 2 shows the breakdown in 2014. 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

	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Urticaria	566	529	578	535	523	612	606	572	608	468
Febrile reactions	241	238	197	157	176	175	140	190	174	149
Anaphylactic Shock	253	246	293	269	280	253	275	242	218	277
Anaphylaxis	175	173	155	152	128	117	129	156	110	245
Hypotension	60	62	47	57	62	70	78	90	92	74
Dyspnea	167	179	172	192	193	195	208	193	200	136
TACO★								26	29	44
TRALI★★	29	66	45	32	38	24	24	10	19	9
Others	81	98	139	150	141	129	135	116	65	49
Excluded★★★	7	0	0	0	0	4	2	0	0	0
Total	1579	1591	1626	1544	1541	1579	1597	1595	1515	1451

★ 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.

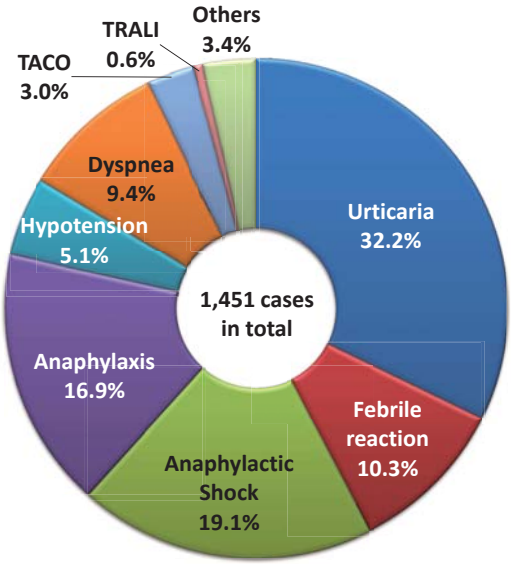

Figure 2. Breakdown of reported cases of non-hemolytic adverse reactions in 2014

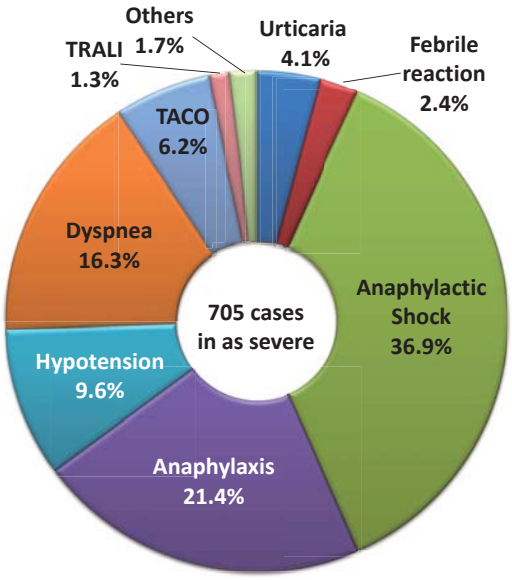

Figure 3. Breakdown of cases evaluated as severe non-hemolytic adverse reactions* in 2014

*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

Cases reported as suspected cases of TRALI or TACO by medical institutions and cases suspected to be TRALI or TACO based on symptoms of adverse reactions were evaluated using the TRALI diagnostic criteria/TACO assessment criteria. Figure 4 shows the flowchart of evaluation of cases with suspected TRALI or TACO and the number of cases in 2014.

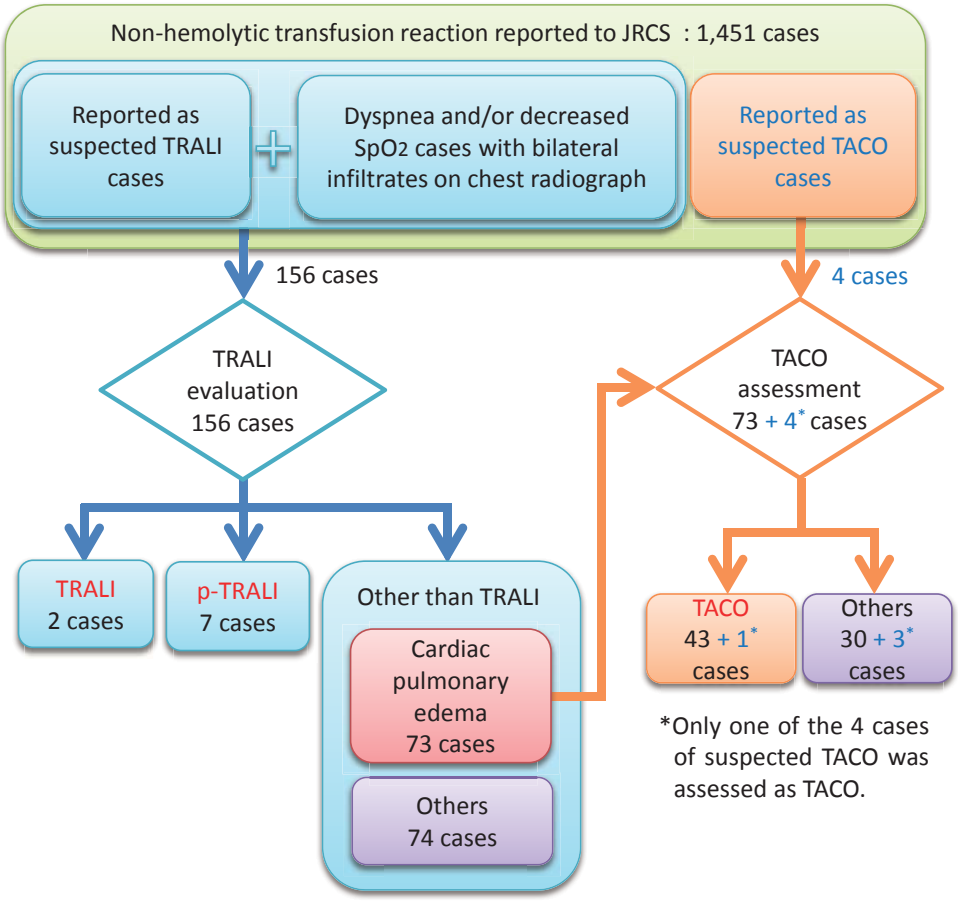

Figure 4. Flowchart of evaluation for TRALI and TACO

TRALI

- Evaluation for TRALI is based on the diagnostic criteria (Figure 5) that were proposed at the Consensus Conference held in 2004 (Transfusion. 2004; 44(12):1774-89.).
- Of the 1,451 cases of non-hemolytic adverse reactions reported in 2014 by medical institutions, 156 cases were subjected to evaluation for TRALI. TRALI evaluation was performed on cases with dyspnea and hypoxemia (decreased SpO_2), associated with bilateral infiltrates on chest x-ray, as well as cases reported as suspected TRALI.
- TRALI evaluation revealed 2 cases of TRALI, and 7 cases of possible TRALI.
- Of the 147 cases that were not diagnosed as TRALI, 73 cases had suspected cardiogenic pulmonary edema, and they were also evaluated for TACO.
- The remaining 74 cases included patients who had insufficient data (i.e. chest radiography, data of respiratory function before transfusion) required for the diagnostic criteria, or who did not meet the diagnostic criteria (i.e. cases who substantially exceeded the criteria for the time of onset and cases in whom acute respiratory failure was observed before transfusion) in addition to cases evaluated with other adverse reactions (including allergic and anaphylactic dyspnea).

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

TACO

- There are no universally accepted diagnosis 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 6). JRCS's TACO criteria exclude cases with complications under which circulatory overload tends to occur, such as cardiac failure, hemodialysis or artificial heart lung machines.
- In 2014, there were 44 cases assessed to have TACO: 43 cases were classified as cardiogenic pulmonary edema when evaluated for TRALI, and were then further assessed for TACO, and 1 case was reported by the medical institution to have suspected TACO.
- Figure 7 shows the gender of the patients and blood components used in cases assessed as TACO. RBC was the most commonly involved component in up to 90% of TACO cases, including cases with multiple components. TACO appears to occur in elderly and female patients who have a lower body weight and smaller circulatory volume than males.
- Concerning the timing of TACO onset (Figure 8), TACO mainly occurs both during and after transfusion, while some patients developed TACO immediately after completion of the transfusion. The transfusion rate did not substantially exceed that described in the package insert in any cases. However, even with a lower infusion rate can volume overload develop in some patients depending on the conditions. It was observed that many cases, mostly with a low transfusion rate occurred within 120-180 minutes after the initiation of the transfusion.

ISBT haemovigilance working party
TACO Criteria

TACO is characterized by any 4 of the following:

a. **Acute respiratory distress**
b. **Tachycardia**
c. **Increased blood pressure**
d. **Acute or worsening pulmonary edema on frontal chest radiograph**
e. **Evidence of positive fluid balance**

・occurring within 6 hours of completion of transfusion.
・An elevated BNP is supportive of TACO.

JRCS TACO assessment criteria

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1. **Acute respiratory failure**
   PaO_2/FiO_2 ≦300mmHg or
   SpO_2＜90%（room air）
2. **Pulmonary congestion on chest radiograph**
3. **Evidence of transfusion and/or fluid overload**
4. **Occurring during transfusion or within 6 hours of completion of transfusion**
5. Increased blood pressure
6. Tachycardia
7. Elevated BNP or NT-pro BNP within 24 hours of completion of transfusion

From 1 to 4 are essential

Exceptional features (excluded if one of them is met)
-Patient on hemodialysis
-Patient undergoing cardiopulmonary bypass
-Patient on extracorporeal support
-Patient undergoing treatment for cardiac failure or respiratory failure

Figure 6. Diagnostic/assessment criteria of TACO

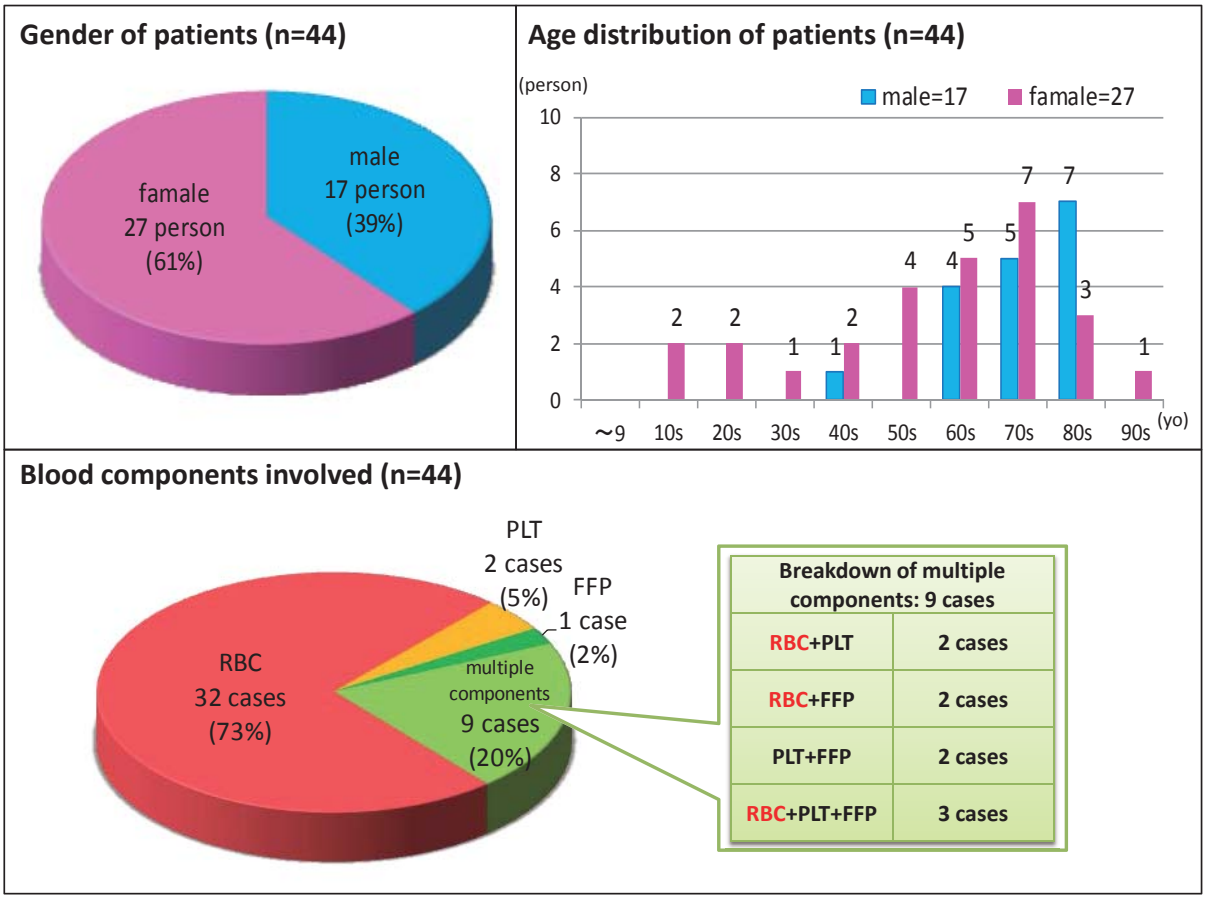

Figure 7. Gender of patients and blood components used in cases assessed as TACO

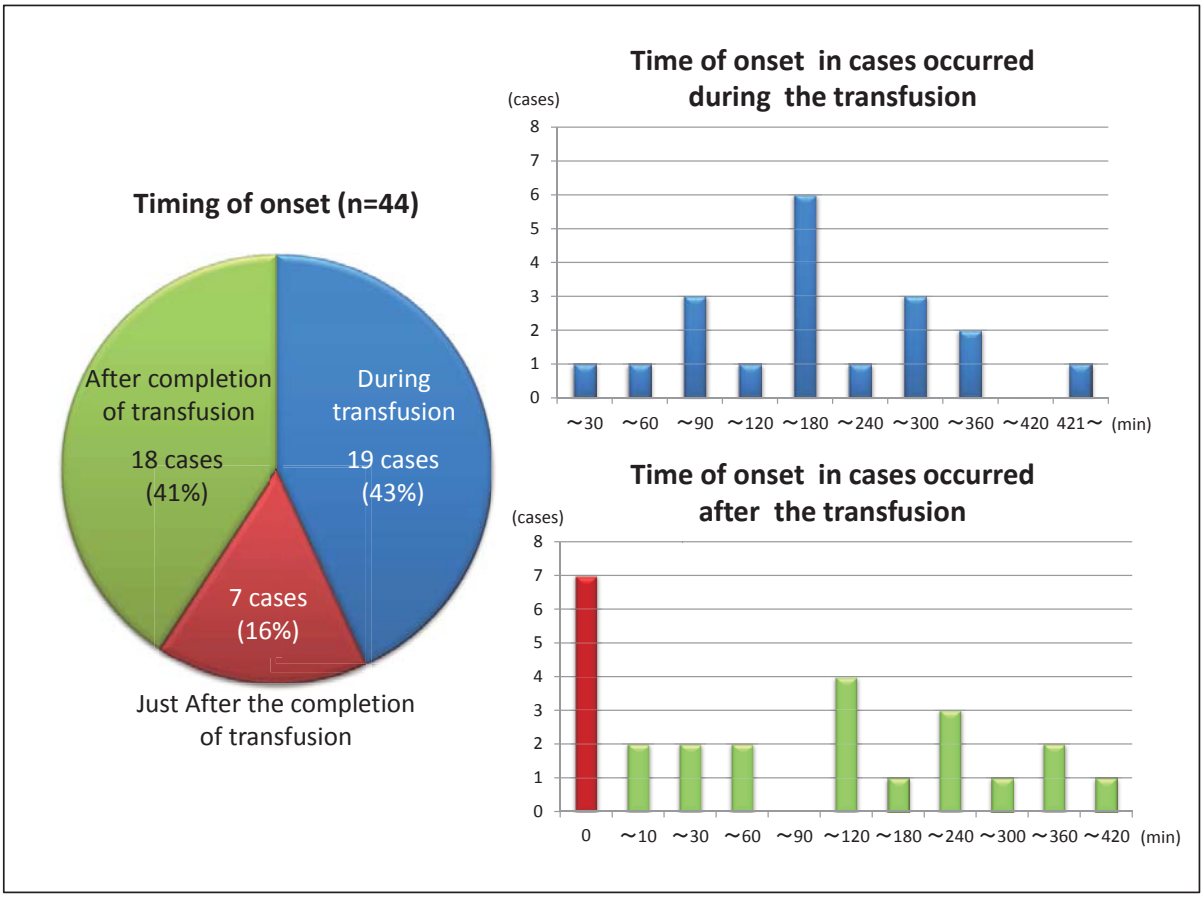

Figure 8. Breakdown of TACO onset timing

Discussion and future tasks for TRALI and TACO

- Compared to the number of case reports of suspected TRALI, the rate of cases actually diagnosed as TRALI has shown a decreasing tendency. Of the cases diagnosed as TRALI in 2014, one case had fatal TRALI.
- As a measure against TRALI, the JRCS continues the preparation of FFP derived from 400 mL of whole blood donations, mainly from male donors. It is also considered to introduce tests for anti-leukocyte antibodies against donated blood from female donors for the preparation of other blood components such as apheresis plasma components and platelet components.
- The JRCS started TACO assessment in 2012. When the "Practical guideline for transfusion medicine" was revised in March 2012, TACO was added to the section of "transfusion-related adverse reactions/complications." Therefore, TACO is becoming more widely recognized. However, most cases that were reported as "TRALI" by medical institutions were classified as cardiogenic pulmonary edema by the JRCS's TRALI evaluation, and were afterwards determined to be "TACO" based on assessment for TACO (Figure 4). Note that a similar number of cases determined to have cardiogenic pulmonary edema were reported before assessment for TACO started (Figure 9). It is not considered that TACO cases have actually increased as rapidly as it seems.
- TACO is a condition of cardiac failure due to circulatory overload. To transfuse at-risk patients who have potential cardiac and/or renal failure, it is necessary to reduce the transfusion rate and volume, and to monitor the patients closely during the transfusion.
- Future tasks to be considered for TACO cases include an association between weight and transfusion volume and transfusion rate, concomitant use of diuretics and regimen after the onset of TACO.

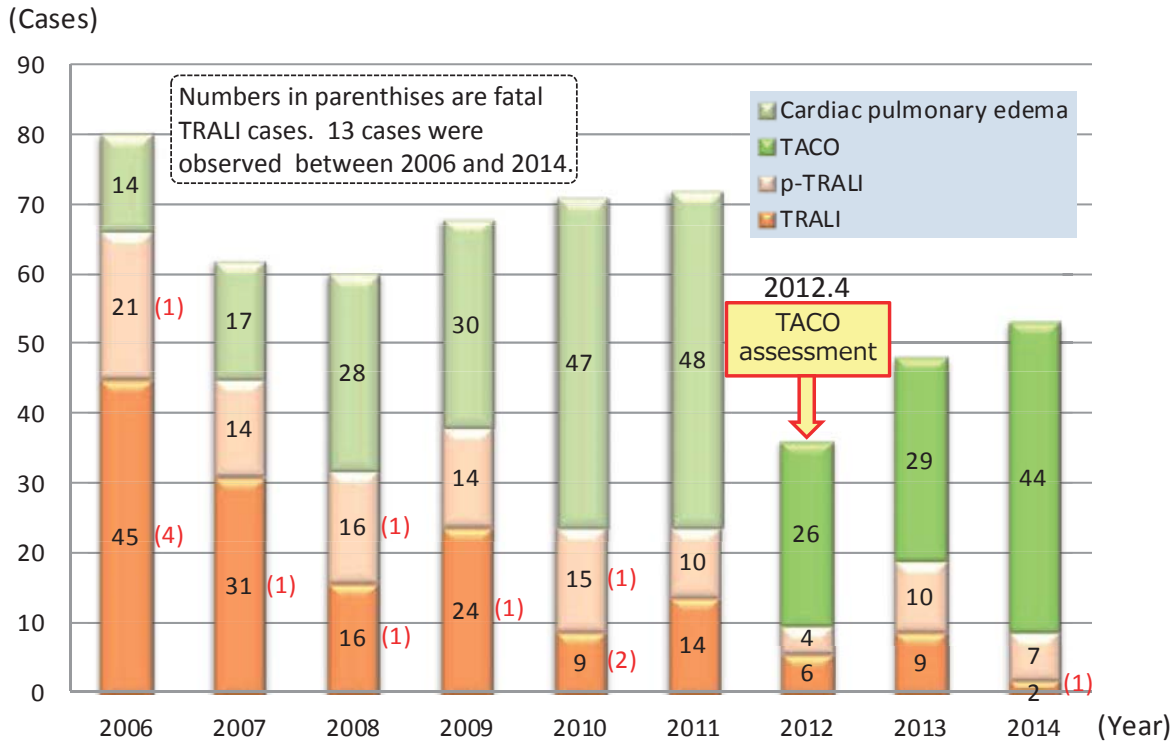

Figure 9. Evaluation of TRALI and TACO cases (2006-2014)

(2) Hemolytic adverse reactions

Table 2 shows the breakdown of case reports of hemolytic adverse reactions in 2014.

- Case investigation by the JRCS revealed 8 cases with irregular antibodies in the patients' specimens which consisted of 2 immediate reactions and 6 delayed reactions. One of the patients with an immediate reaction and 3 of the patients with delayed reactions had a history of transfusion. The details of the cases are shown in Table 3.
- As the patient in immediate reaction cases No.2 had irregular antibodies, red cells without cognate antigens were transfused. However, hemolytic reactions were observed.

Table 2. Number of case reports of hemolytic adverse reactions in 2014

	Severe	Non-severe	Total
AHTR	8	2	10*
DHTR	7	4	11
Total	15	6	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

*Six cases with immediate hemolytic adverse reactions also had non-hemolytic adverse reactions (5 of which were severe) and one case was also suspected to have a bacterial infection at the same time.

Table 3. Positive cases of irregular blood antibodies

		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 70s	Hemolysis, dyspnoea	Neg.	Compatible	Anti-Jk^a	Compatible
	2	RBC PLT	F 60s	Hematourea, Tachycardia	Anti-E, Anti-M, Anti-Jk^b	Incompatible	Anti-E, Anti-M, Anti-Jk^b	Incompatible
Delayed	1	RBC	M 80s	DHTR	Anti-E, Anti-Di^a	n/t	Anti-E, Anti-Di^a, Anti-Jk^a	n/t
	2	RBC	M 80s	Hemolysis	Anti-Jk^a	n/t	Anti-Jk^a	n/t
	3	RBC	F 90s	DHTR	Anti-Jr^a	Incompatible	Anti-Jr^a	Incompatible
	4	RBC	M 60s	Hemolysis	n/t	n/t	*3 days after transfusion* Anti-c *10 days after transfusion* Anti-c, Anti-E, Anti-Jk^b	n/t
	5	RBC PLT FFP	F 60s	Hemolytic anaemia	Neg.	n/t	Anti-E	n/t
	6	RBC	M 80s	DHTR	Neg.*		Anti-Jk^a*	

* Test result obtained from medical institutions. Patient's specimen was unavailable for the testing at JRCS.
DHTR: Delayed Hemolytic Transfusion Reaction

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

- One case of suspected TA-GVHD was reported in 2014. 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 which 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 2014

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 2014.

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.

Table 4. The breakdown of suspected transfusion-transmitted infection cases by pathogen reported in 2014

Pathogens	Reported cases	Confirmed cases
HBV	27	2
HCV	26	0
Bacteria	17	0
HEV	4	4
HAV	1	0
CMV	6	0
Total	81	6

(2) Summary of case reports in 2014

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	Period from transfusion	Maximum (IU/L)	Period from transfusion
1	Unstable angina	FFP-LR (2013.6)	60s	M	HBV-DNA, HBsAg, HBsAb, HBcAb	Neg.	1-2 days	HBV-DNA	19 wks	1107	36 wks

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	Period from transfusion	Maximum (IU/L)	Period from transfusion
2	Gastric cancer Alzheimer's dementia	Ir-RCC-LR (2013.9)	90s	M	HBsAg	Neg.	220 days	HBV-DNA	13 wks	◆	◆

◆No increase in ALT or no comparative available.

HEV

Voluntary reports: Cases reported by medical institutions suspected virus infection by transfusion

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	Period from transfusion	Maximum (IU/L)	Period from transfusion
1	Burkitt's lymphoma	Ir-PC-LR (2011.11)	30s	F				HEV-RNA	126 wks	347	9 wks
2	Primary biliary hepatic cirrhosis (Liver transplant)	FFP-LR (2012.3)	60s	F	HEV-RNA	Neg.	3 days	HEV-RNA, IgG-HEV-Ab	37 wks	315	3 wks
3	Hepatic cirrhosis, hepatic cancer (Liver transplant)	Ir-PC-LR (2014.7)	40s	M	HEV-RNA, IgM-HEV-Ab, IgG-HEV-Ab, IgA-HEV-Ab	Neg.	1 day	HEV-RNA, IgM-HEV-Ab	12 wks	93	26 wks

Post donation information: Case reported by the medical institution receiving the co-components of the case No.2.

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	Period from transfusion	Maximum (IU/L)	Period from transfusion
4	Myelodysplastic syndrome	Ir-RCC-LR (2012.3)	80s	F	HEV-RNA, IgM-HEV-Ab, IgG-HEV-Ab	Neg.	0 day	HEV-RNA, IgM-HEV-Ab, IgG-HEV-Ab	10 wks	811	10 wks

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 found by the periodical searching of the literature and academic conference information in 2014 in accordance with the GVP ordinance. The domestic cases in Table 5 were only reported in the literature or at academic conferences. For these cases, the JRCS investigated the severity of adverse reactions and blood components used of 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 2014, there were no oversea 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 2014 (including cases not reported individually)

No.	Suspected Component	Age	Sex	Symptoms	Journal etc.
1	Ir-RCC-LR RCC-LR Ir-PC-LR PC-LR FFP-LR-Ap	59	F	Anaphylactic shock	The Journal of Japan Society for Clinical Anesthesia. 2013;33(6):S355
2	Ir-PC-LR	72	M	Anaphylactic shock	The Journal of Japan Society for Clinical Anesthesia. 2013;33(6):S355
3	PC-LR	11 months	F	Transfusion-related acute lung injury	Journal of Japanese Society of Emergency Pediatrics. 2014;13(2):264
4	Ir-RCC-LR	64	F	Delayed haemolytic transfusion reaction	Japanese Journal of Transfusion and Cell Therapy. 2014;60(1):90
5	Ir-RCC-LR	74	M	Delayed haemolytic transfusion reaction	Japanese Journal of Transfusion and Cell Therapy. 2014;60(2):332
6	Ir-RCC-LR	60	F	Delayed haemolytic transfusion reaction	Japanese Journal of Transfusion and Cell Therapy. 2014;60(2):331
7	WRC-LR	65	F	Delayed haemolytic transfusion reaction	Japanese Journal of Transfusion and Cell Therapy. 2014;60(2):331
8	RCC-LR	Unknown	Unknown	Delayed haemolytic transfusion reaction	Journal of Japanese Society for Dialysis Therapy. 2014;47(Suppl.1):774
9	Ir-RCC-LR	40	M	Delayed haemolytic transfusion reaction	Journal of Japanese Society for Dialysis Therapy. 2014;47(Suppl.1):626

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

(Summary)

- Anaphylaxis was reported in 2 cases (No. 1, 2): one case received massive transfusion before and after a living donor liver transplantation (No.1) and another case received platelets during vascular prosthesis implantation (No. 2). Elevated central venous pressure (CVP) and wheals were observed in both cases.
- One case (No.3) was suspected to have TRALI after transfusion for the treatment of hemorrhagic shock and encephalopathy syndrome. The respiratory status improved with the treatment, but the patient died of multiple organ failure. Evaluation for TRALI was not performed because no clinical data were available.
- Cases of delayed hemolytic transfusion reactions (No 4-9) were due to anti-E, anti-M, anti-Jk^a, and anti-Wr^a antibodies, etc.

Table 6. Overseas cases obtained in the literature search in 2014 that have been submitted ICSR to PMDA

No.	Country	Suspected blood product	Age	Sex	Symptoms	Journal etc.
1	U.S.	Fresh frozen plasma	15	F	Hepatitis A	Transfusion. 2014;54(9):2202-2206
2	U.S.	Platelet concentrates	41	M	Human anaplasmosis	Transfusion. 2014;54(11):2828-2832
3	Germany	Platelet concentrates	47	M	Hepatitis E	Euro Surveill. 2014;19(21). pii:20812
4	Germany	Platelet concentrates	6	M	Hepatitis E	Euro Surveill. 2014;19(21). pii:20812
5	France	Red cell concentrates	75	F	Plasmodium falciparum infection	J Hosp Infect. 2014;87(3):179-181
6	Italy	Platelet concentrates	36	F	Listeriosis	Blood Transfus. 2014;12(4):611-614
7	U.S.	Platelet concentrates	29	F	Staphylococcus aureus septicaemia	Transfusion. 2014;54(7):1704
8	U.S.	Red cell concentrates	34	F	Human anaplasmosis	Transfusion. 2015;55(4):719-725

(Summary)

The post-transfusion HAV case (No.1) was revealed by post-donation information of hepatitis A of a donor who had traveled to South Africa. Post-transfusion HEV cases (Nos.3&4) were traced to a single donor. A post transfusion HEV case was investigated to find a blood component with HEV-RNA positive (No.3). The investigation of a recipient of other components revealed another case (No.4). Other post transfusion infection cases of human anaplasmosis (No.2, 8), malaria (No.5), listeria (No.6) and Staphylococcus aureus sepsis (No.7) were revealed by investigation of the suspected TTI cases.

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.

Table-7 and Table-8 show measures in foreign countries and reports of studies that have been reported in 2014.

Table 7. Reports on measures in foreign countries obtained in 2014

	Source	Description
1	U.S. (AABB)	Association Bulletin #14-04 Clinical Recognition and Investigation of Suspected Bacterial Contamination of Platelets July 18, 2014
2	U.S. (AABB)	Association Bulletin #14-05 Babesiosis July 18, 2014
3	U.S. (AABB)	Association Bulletin #14-08 Deferral for Blood Donation of Persons Under Public Health Surveillance for Possible Exposure to Ebola Virus October 14, 2014 .

(Summary)

- (No. 1) The American Association of Blood Banks (AABB) published recommendations for the residual risk of bacterial contamination of platelet components in 2012 (Association Bulletin#12-04). This time, to complement the recommendation, AABB published recommendations in Association Bulletin#14-04 for clinical recognition, investigation of suspected contaminated products including blood culture and management of co-components.
- (No. 2) AABB published Association Bulletin #14-05 on transfusion-transmitted Babesiosis (TTB), including recommendations on case investigations and measures to mitigate the risk of TTB, in addition to providing information to medical institutions and blood services.
- (No. 3) AABB published Association Bulletin #14-08 on blood donation deferral by persons under public health surveillance for possible exposure to the Ebola virus.

Table 8. Reports of studies obtained in 2014

	Source	Description
1	U.S. (FDA)	1) Mikhail Menis. Posttransfusion purpura occurrence and potential risk factors among the inpatient US elderly, as recorded in large Medicare databases during 2011 through 2012. TRANSFUSION 2014. 2) FDA study identifies occurrence and potential risk factors for posttransfusion purpura (PTP) in elderly patients
2	U.S. (FDA)	FDA study identifies occurrence and risk factors for TRALI, a post-transfusion respiratory complication, among the U.S. elderly during 2007 through 2011.

(Summary)

Two Medicare database-derived studies were reported. One identified the occurrence and risk factors for post-transfusion purpura(PTP) and the other for TRALI in US elderly patients.

3. Safety measures against 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 2014:

1) Introduction of individual donation nucleic-acid amplification test (NAT)

The JRCS performs microbiology tests on all blood donations using serological tests and NAT. In October 1999, NAT for HBV, HCV and HIV was launched using a 500-sample pool. The pool size was reduced to 50 in February 2000, and to 20 in August 2004. In August 2008, a microbiology test system with improved sensitivity was introduced. From August 2014, the NAT system was changed, and NAT of individual samples (individual NAT) was initiated.

Individual NAT is expected to shorten the window period compared to the conventional NAT using the 20-sample pool. Figure 10 shows cases of transfusion-transmitted infections (confirmed cases) classified by year of concerned blood donation. No confirmed cases of HBV, HCV and HIV infections have been identified by blood donated after the introduction of individual NAT. However, individual NAT does not eliminate the window period. Pre- and post-transfusion testing for infectious disease are still required.

In association with the introduction of individual NAT, “Notification on lookback studies on blood products” was partly revised in July 2014. This revision includes changes in the handling of individual NAT using repository samples when transfusion-transmitted infections are suspected. *

*If the concerned blood components for transfusion suspected as the source of infection had been screened in ID-NAT and the concerned donors had donation records afterwards, eligibility can be evaluated based on the results of the ID-NAT of the later donation, instead of performing individual NAT on repository samples.

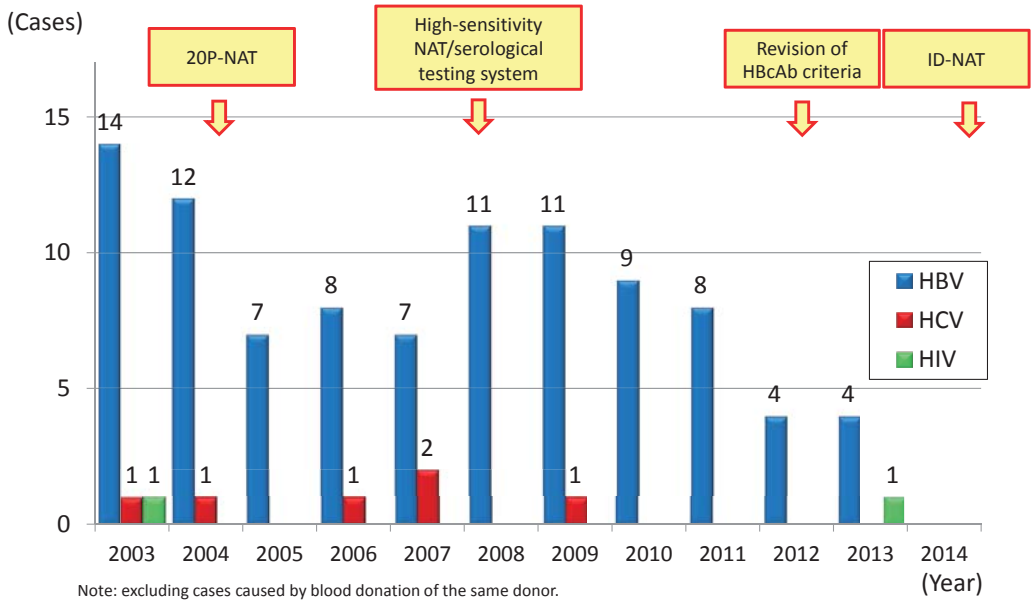

Figure 10. Changes in the number of confirmed cases of transfusion-transmitted infections by year of donation (2003-2014)

2) Measures against domestic cases of dengue fever

In the summer of 2014, domestic cases of dengue fever were confirmed. According to a national notification (HSB/TIDCD Notification No.0827-1 dated August 27, 2014 “domestic cases of dengue fever / first report”), the JRCS started geographical donor deferral by visiting the affected areas in Tokyo and Saitama on August 27, 2014, and then nationwide in September 5.

- Location: all blood donation facilities in Japan
- Measures for donors: people who had visited the affected areas (i.e. Yoyogi Park) were deferred to donate for 4 weeks.
- Donor history questionnaire on blood donation: donors were asked whether they had visited the affected areas. Body temperature was measured with a non-contact thermometer if necessary.
- Post-donation reporting: distributing leaflets (Figure 11) to donors to report it if they developed acute fever (accompanied by headache or rash) within 14 days after donation. These were handled as post-donation information.

Yoyogi park was reopened on October 31, 2014. Therefore, the above donor deferral was lifted 14 days later, on November 14.

In the above-mentioned donor deferral period, Dengue virus was not detected in repository specimens of 23 donors who reported to have developed fever after donation.

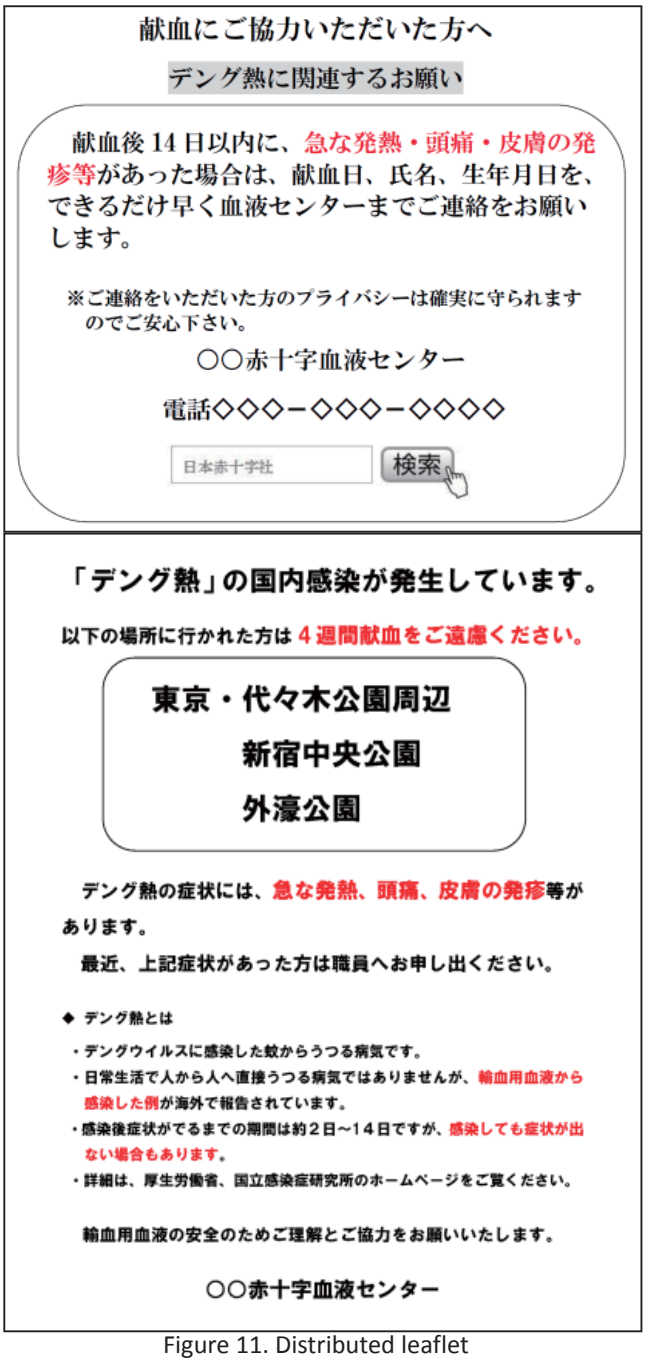

Figure 11. Distributed leaflet

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 9 shows the cases of donor adverse reactions in 2014, and Figure 12 shows the breakdown by symptoms.

Table 9. Number of donor adverse reaction cases in 2014

Category	Number of cases	Frequency(%)
VVR mild*	33,921	0.680%
VVR severe*	4,323	0.087%
Hematoma	8,710	0.175%
Nurve injury	233	0.005%
Citric reactions	324	0.006%
Nurve disorder	297	0.006%
Localized pain	1,949	0.039%
Others	1,586	0.032%
Total	51,343	1.029%

Total donation	4,990,460

*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 severe.

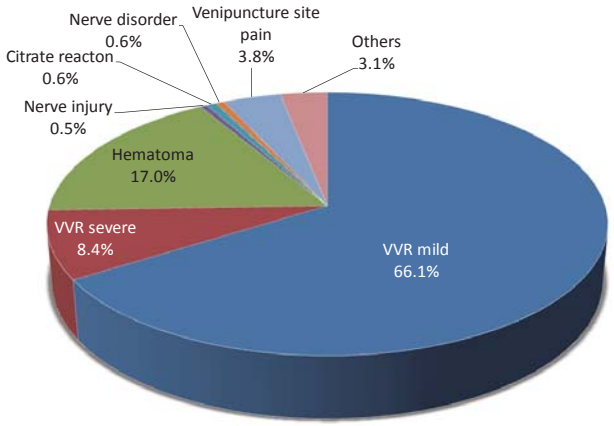

Figure 12. Breakdown of donor adverse reactions that occurred in 2014

2) Actions against donor adverse reactions

Leg muscle tension exercise

The working group of donor adverse reactions was established in 2012. They introduced a study entitled, “leg muscle tension exercise as a VVR preventive action” at 27 blood centers across Japan from July, 2013.

The following is a summary of this study:

- Objective: to evaluate the efficacy of “leg muscle tension exercise” to reduce the incidence of VVR
- Methods: In 6 blocks (total 27 regional blood centers) in Japan, the incidence of VVR was compared and evaluated between a group performing the exercises and a group not performing the exercise (control). The two groups were classified by the days when they performed the exercise and by the days when they did not perform the exercise at a blood center. The number of donors on exercise days included donors who didn’t exercise, and vice versa. The incidents were calculated for all donors on exercise days regardless of whether the donor performed the exercises or not.
- How to perform exercises
  - Whole blood donation: exercise was initiated during donation, and performed continuously until leaving the blood donation chair/bed.
  - Apheresis donation: exercise was initiated at the final return flow, and performed continuously until leaving the blood donation chair/bed.
- Results: The incidence of VVR during whole blood donation was significantly decreased in the group with exercise (P <0.001, males: days without exercise, 0.52%; days with exercise, 0.32%; and females: days without exercise, 0.82%; days with exercise 0.47%). On the other hand, the incidence of VVR during apheresis donation showed a tendency to decrease both in males and females, but the decrease was not significant (males: days without exercise, 0.27%; days with exercise, 0.24%; and females: days without exercise, 1.51%; days with exercise, 1.41%).
- Conclusion: For whole blood donation, leg muscle tension exercise was effective to decrease the incidence of VVR both in males and females. Leg muscle tension exercise will be implemented nationwide to whole blood donation by the end of 2015.

Figure 13. Leaflet for “leg muscle tension exercise”

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 summarises 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 2014"

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