日本赤十字社
Japanese Red Cross Society

Haemovigilance by JRCS 2016

Safety Vigilance Division, Technical Department,
Blood Service Headquarters

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Haemovigilance system of the 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") has addressed donor adverse reactions, transfusion-transmitted infections (hereinafter referred to as "TTIs") and transfusion-related adverse reactions since the start of the blood service, by having specified an internal procedure for reporting donor adverse reactions in 1982, and by deploying medical representatives (hereinafter referred to as "MRs") in all JRC blood centers across Japan in 1983 to deal with the problems of transfusion-related adverse reactions and infections. In parallel with this, the JRCS has also introduced the tests of donated blood for hepatitis and HIV markers as a measure against TTIs, and established a nationwide integrated system to collect and analyse information on transfusion-related adverse reactions and infections in 1993. In addition, a specimen storage system of storing aliquot of all donated blood for analysis for 11 years started in 1996. This specimen storage enabled investigation of blood components for transfusion mainly related to TTIs to confirm the causal relationship between TTIs and transfusion, in addition to being expected for the use for further studies of newly emerging adverse reactions and infections. Furthermore, the expired repository samples could be used for research and development in accordance with the policy described in the PFSB Notification No. 0801-1 "Guideline on the use of donated blood in R&D" issued by the Director of Pharmaceutical and Food Safety Bureau of the Ministry of Health, Labour and Welfare on August 1, 2012. The appropriateness of their use in R&D should be evaluated by the Steering Committee for Blood Services of the Pharmaceutical Affairs and Food Sanitation Council under the Ministry of Health, Labour and Welfare.

It should be noted that blood components for transfusion are categorized as "prescription drugs" in Japan. Based on the revision of the Pharmaceutical Affairs Law on November 25, 2014, they have since been regulated by the "Pharmaceuticals and Medical Device Act (PMD Act)." The JRCS has the marketing approval for such blood components for transfusion the same as for other prescription drugs. The JRCS is the only body that is authorized to collect and supply blood and blood components for transfusion in Japan. In addition, the JRCS provides source plasma to domestic manufacturers of plasma derivatives. For the manufacturing and distribution of blood and blood components for transfusion prepared from donated blood, the JRCS observes the PMD Act and its Enforcement Regulations, the "Ministerial Ordinance on Standards for Manufacturing Control and Quality Control for Drugs and Quasi-drugs, Good Manufacturing Practice (GMP)," and the "Ministerial Ordinance on Standards for Quality Assurance for Drugs, Quasi-drugs, Cosmetics and Regenerative Medicine Products, Good Quality Practice (GQP)." Concerning the necessary post-marketing measures, based on the "Ministerial Ordinance on Standards for Post-Marketing Safety Assurance for Drug, Quasi-drugs, Cosmetics, Medical Devices and Regenerative Medicine Products; Goop Vigilance Practice (GVP)", the Blood Service Headquarters (as a marketing authorization holder, including the General Safety Management Division), each blood center and the Central Blood Institute cooperate to take necessary measures. MRs deployed at each blood center are responsible to collect information of adverse reactions and/or TTIs and to provide information on blood components to health care professionals. The General Safety Management Division is responsible to analyse and evaluate the information. It also reports severe cases of transfusion-related adverse reactions and TTIs to the Pharmaceutical and Medical Devices Agency (hereinafter referred to as "PMDA") in accordance with the PMD Act and conducts a series of activities including management of basic data on safety measures, withdrawal of inappropriate blood components, and revision of package inserts (Precautions). 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. Note that as blood components for transfusion are categorized as "the device of the combination products corresponding to drugs" combining drugs (blood and blood components) and medical devices (blood bag), information whether the health damage caused by malfunction due to blood bags for blood components for transfusion used for patients is collected, evaluated and analyzed as well as cases of transfusion-related adverse reactions and TTIs.

The pharmacovigilance system applies to prescription drugs. The WHO defines pharmacovigilance as the

"science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems," which is in close agreement with the post-marketing safety assurance activities stipulated by the GVP Ordinance in Japan. In addition, the ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) developed the E2E Guideline, "Pharmacovigilance Planning," which has been implemented since 2005, in parallel with complete enforcement of the amended Pharmaceutical Affairs Law in April 2005. Then, observation of the GQP and GVP Ordinances became a licensing requirement for Marketing Authorization Holders.

It seems that the concept of "haemovigilance" developed in foreign countries, where blood and blood components for transfusion are mostly regulated separately from prescription drugs, and a safety monitoring system for blood and blood components for transfusion has to be prepared separately from that for prescription drugs. On the other hand, as blood and blood components for transfusion are categorized as prescription drugs in Japan, the same pharmacovigilance as for prescription drugs is applied to blood and blood components for transfusion. Therefore, the haemovigilance system in Japan is similar to the pharmacovigilance system, which is the significant feature.

1. Total number of blood donations and status of distribution of blood components for transfusion

Figure 1 shows the number of blood donations by type of donations between 2007 and 2016. The total number of blood donations in 2016 was 4,841,601, including 168,758 of 200 mL whole blood donations, 3,281,071 of 400 mL whole blood donations, and 1,391,772 of apheresis donations (678,367 of plasma apheresis donations and 713,405 of platelet apheresis donations). The number of donations had increased from 2007 to 2010 but has been on a declining trend since 2010.

Figure 2 shows the status of distribution of blood components for transfusion between 2007 and 2016. The number of distributions of red blood cell products, platelet products, and plasma products had been on an increasing trend in recent few years but has turned into a declining trend since 2013.

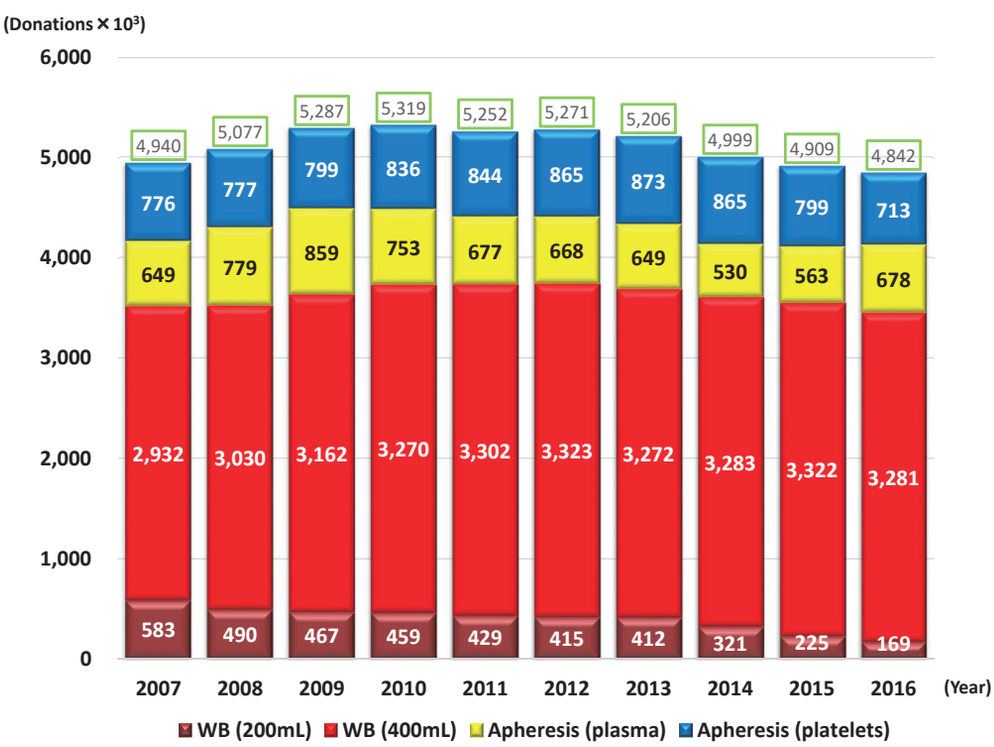


Figure 1. Changes in the number of blood donations

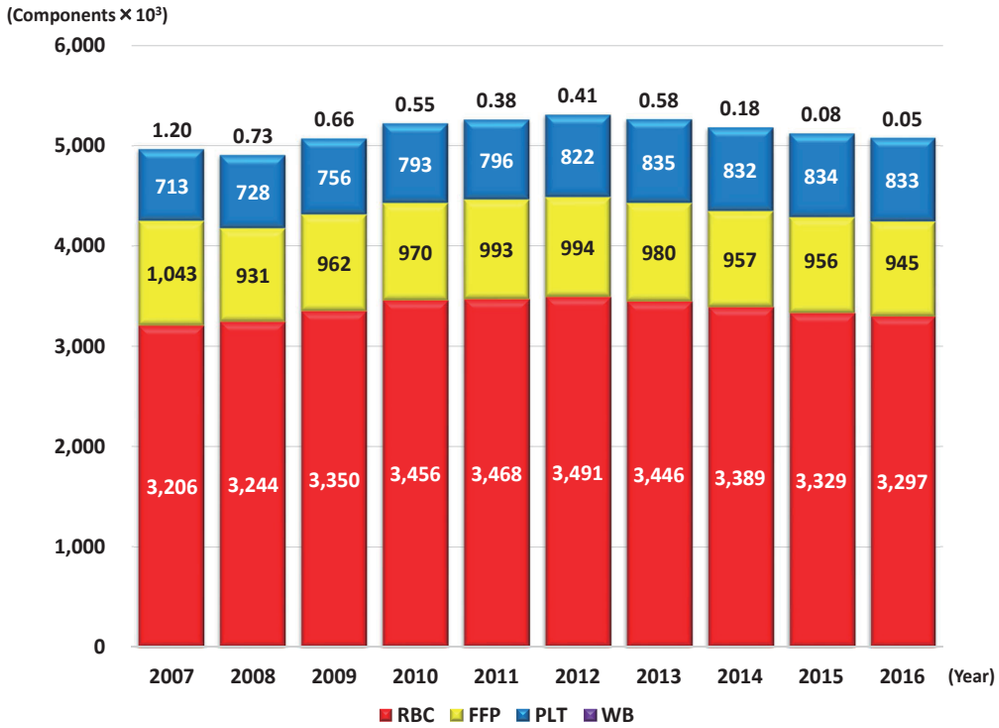


Figure 2. Changes in the status of distribution of blood components for transfusion

2. Reports on adverse reactions and TTIs

Figure 3 shows the number of case reports of transfusion-related adverse reactions and infectious diseases which were reported by medical institutions between 2007 and 2016. Note that cases assessed as unrelated to transfusion are included.

In 2016, the JRCS received 1,497 case reports of adverse reactions (1,476 cases were classified as non-hemolytic adverse reactions, and 21 as hemolytic adverse reactions: There were no case reports of suspected transfusion associated GVHD), and 80 case reports of suspected TTIs by 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 Pharmaceuticals and Medical Device Act. (The breakdown of the ICSRs is 738* non-hemolytic adverse reactions, 10* hemolytic adverse reactions, and 80* infections.) Some cases of adverse reactions that have not been reported voluntarily to the JRCS by medical institutions may be presented in the literature and/or at academic conferences, and when the JRCS obtains such information, the JRCS additionally investigates the concerned medical institutions regarding the severity. (See "3 Information about individual cases of transfusion adverse reactions and TTIs obtained from the literature or academic conference").

*Note that some cases included multiple categories were overlapped, e.g., one case had non-hemolytic and hemolytic reactions.

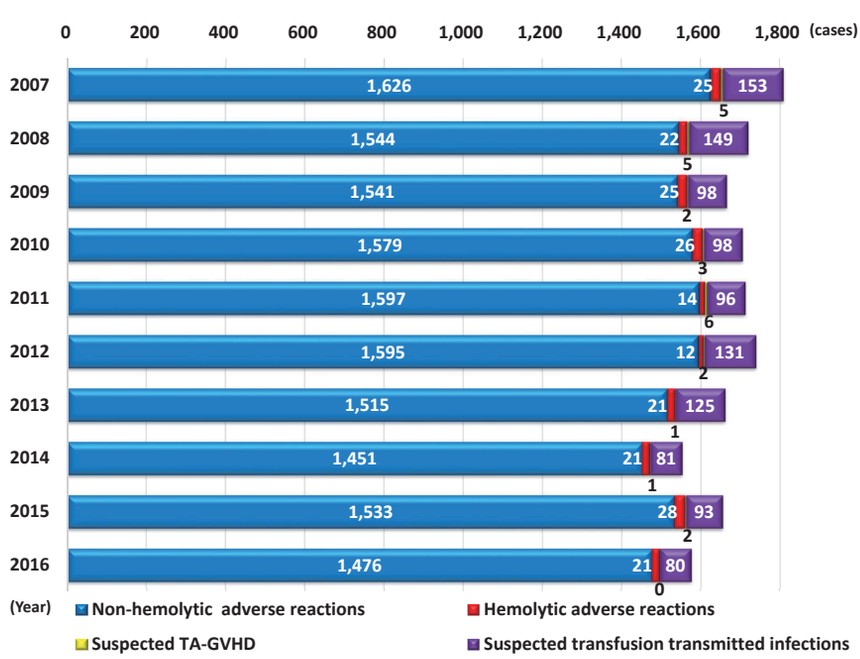


Figure 3. Changes in the number of voluntary reports of transfusion-related adverse reactions and infectious diseases*

*Excluded cases that were obtained from the literature or academic conference.

1) Transfusion-related adverse reactions

(1) Non-hemolytic adverse reactions

Table 1 shows the number of cases reported as non-hemolytic adverse reactions by medical institutions between 2007 and 2016. Figure 4 shows the breakdown of adverse reactions by symptom reported in 2016. Figure 5 shows the breakdown of cases evaluated as severe adverse reactions and the annual changes in number of severe and non-severe adverse reactions. The cases of TRALI (transfusion-related acute lung injury) and TACO (transfusion-associated circulatory overload) were included under dyspnea. The severe adverse reactions mainly include the symptoms of anaphylactic shock, anaphylaxis, hypotension, and dyspnea, which account for 51.4% of non-hemolytic adverse reactions reported from medical institutions in 2016.

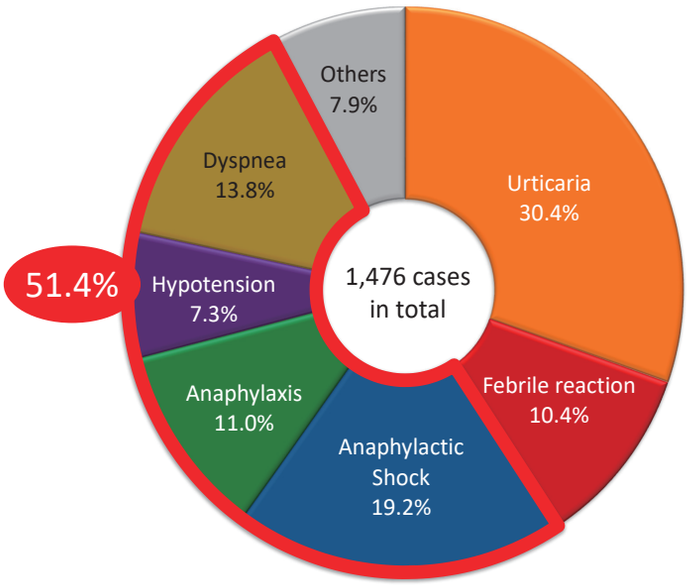


Figure 4. Breakdown of reported cases of non-hemolytic adverse reactions in 2016

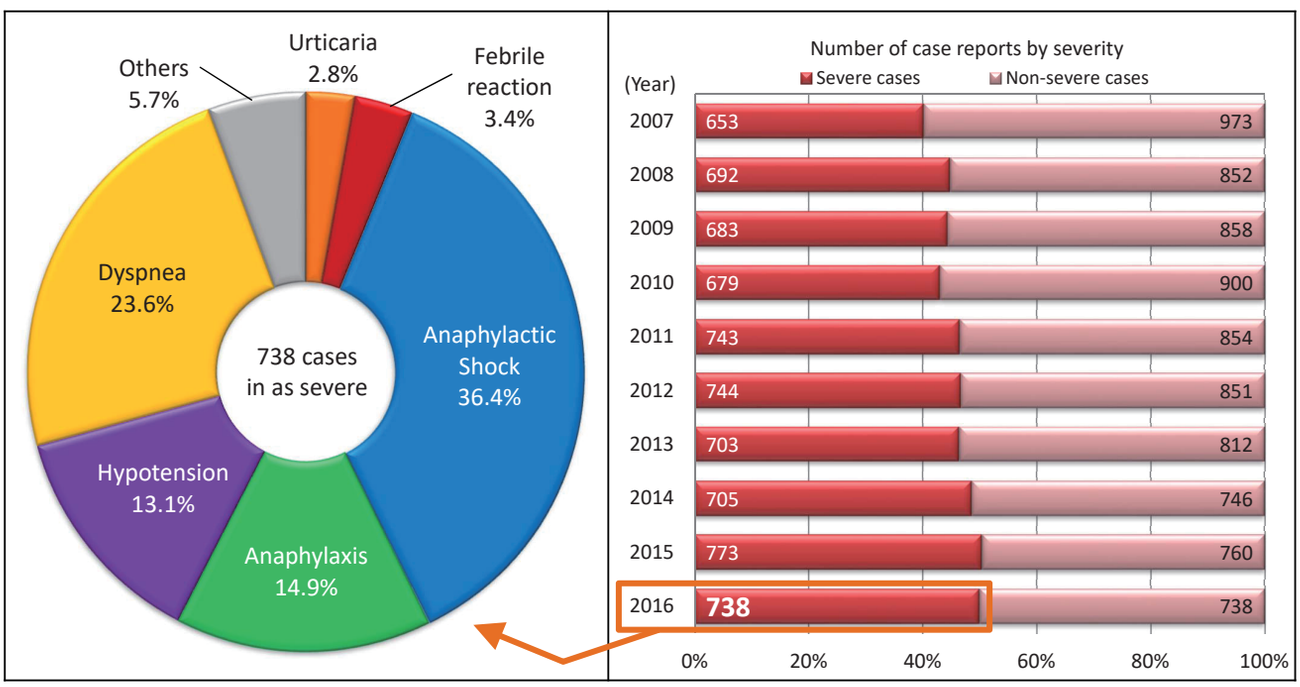


Figure 5. Breakdown of cases evaluated as severe non-hemolytic adverse reactions* in 2016 and annual changes in number of severe and non-severe cases

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

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

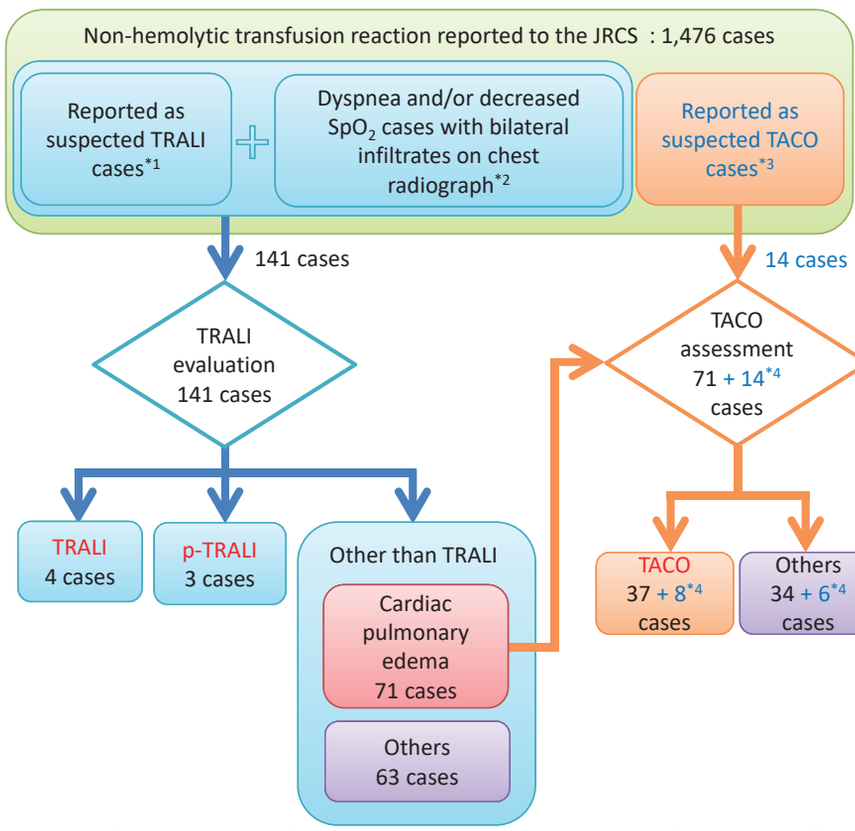
Symptom \ Year	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Urticaria	578	535	523	612	606	572	608	468	458	448
Febrile reactions	197	157	176	175	140	190	174	149	175	153
Anaphylactic Shock	293	269	280	253	275	242	218	277	305	284
Anaphylaxis	155	152	128	117	129	156	110	245	245	163
Hypotension	47	57	62	70	78	90	92	74	67	108
Dyspnea*1	217	224	231	219	232	229	248	189	214	204
Others	139	150	141	129	135	116	65	49	69	116
Excluded*2	0	0	0	4	2	0	0	0	0	0
Total	1626	1544	1541	1579	1597	1595	1515	1451	1533	1476

*1 TRALI, possible-TRALI and TACO cases are included in dyspnea.

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

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 dyspnea were evaluated using the TRALI diagnostic criteria and/or TACO assessment criteria. Figure 6 shows the flowchart of evaluation of cases with suspected TRALI or TACO and the number of cases in 2016.



*1 Of the reported cases of non-hemolytic transfusion reactions, cases reported to the JRCS as "suspected TRALI" by medical institutions.

*2 Of the reported cases of non-hemolytic transfusion reactions, cases reported to the JRCS as "dyspnea," "acute lung injury," "respiratory failure," "hypoxemia (decreased SpO_2)", and "anaphylaxis," etc. cases associated with bilateral infiltrates on chest x-ray. The cases in which the infiltrates are not confirmed due to unavailability of chest radiograph image are excluded from the evaluation of TRALI.

*3 OF the reported cases of non-hemolytic transfusion reactions, cases reported to the JRCS as "suspected TACO" by medical institutions.

*4 Of the reported cases of suspected TACO to the JRCS, 8 cases were assessed as TACO, and rest of the 6 cases were assessed as other adverse reactions .

Figure 6. Flowchart of evaluation for TRALI and TACO

TRALI

Evaluation for TRALI is based on the diagnostic criteria (Figure 7) that were proposed at the Consensus Conference held in 2004 (Transfusion. 2004; 44(12):1774-89).

- Of the 1,476 cases of non-hemolytic adverse reactions reported in 2016 by medical institutions, 141 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 4 cases of TRALI, and 3 cases of possible TRALI.
- Of the 134 cases that were not diagnosed as TRALI, 71 cases had suspected cardiogenic pulmonary edema, and they were also evaluated for TACO.
- The remaining 63 cases included cases in which data of the required diagnostic criteria were insufficient (including images of chest radiography and data of respiratory function before transfusion), and cases which did not meet the diagnostic criteria (including substantially exceeded the criteria for the time of onset and acute respiratory failure observed before transfusion), in addition to cases which were evaluated as 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 7. Diagnostic criteria for TRALI

TACO

Dyspnea due to transfusion overload has been known as a transfusion-related complication since the 1950s. Among the activities of the International Society of Blood Transfusion (ISBT) to establish definitions of transfusion-related adverse reactions and standardize their evaluation criteria from the mid-2000s, some criteria have been defined for the diagnosis of TACO. However, there are no universally accepted diagnostic criteria for TACO, whereas consensus has been reached as for TRALI. 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). The 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 2016, there were 85 cases assessed to have TACO, of which 71 cases were classified as cardiogenic pulmonary edema when evaluated for TRALI and were then further assessed for TACO, and 14 cases were reported by medical institutions to have suspected TACO. Cases diagnosed as TACO after the evaluation were 37 and 8 cases, respectively.
- Figure 9 shows the gender of the patients and the blood components used in cases which assessed for TACO in 2016, and Figure 10 shows the data on TACO evaluation by the JRCS from April 2012 to 2016. TACO appears to occur in elderly and female patients. For females, because of a lower body weight and smaller circulatory volume than males, circulatory overload is likely to occur. RBC was the most commonly involved component in about 80% of TACO cases, including cases with multiple components.

ISBT haemovigilance working party TACO Criteria	JRCS TACO assessment 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.	**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 8. Diagnostic/assessment criteria of TACO

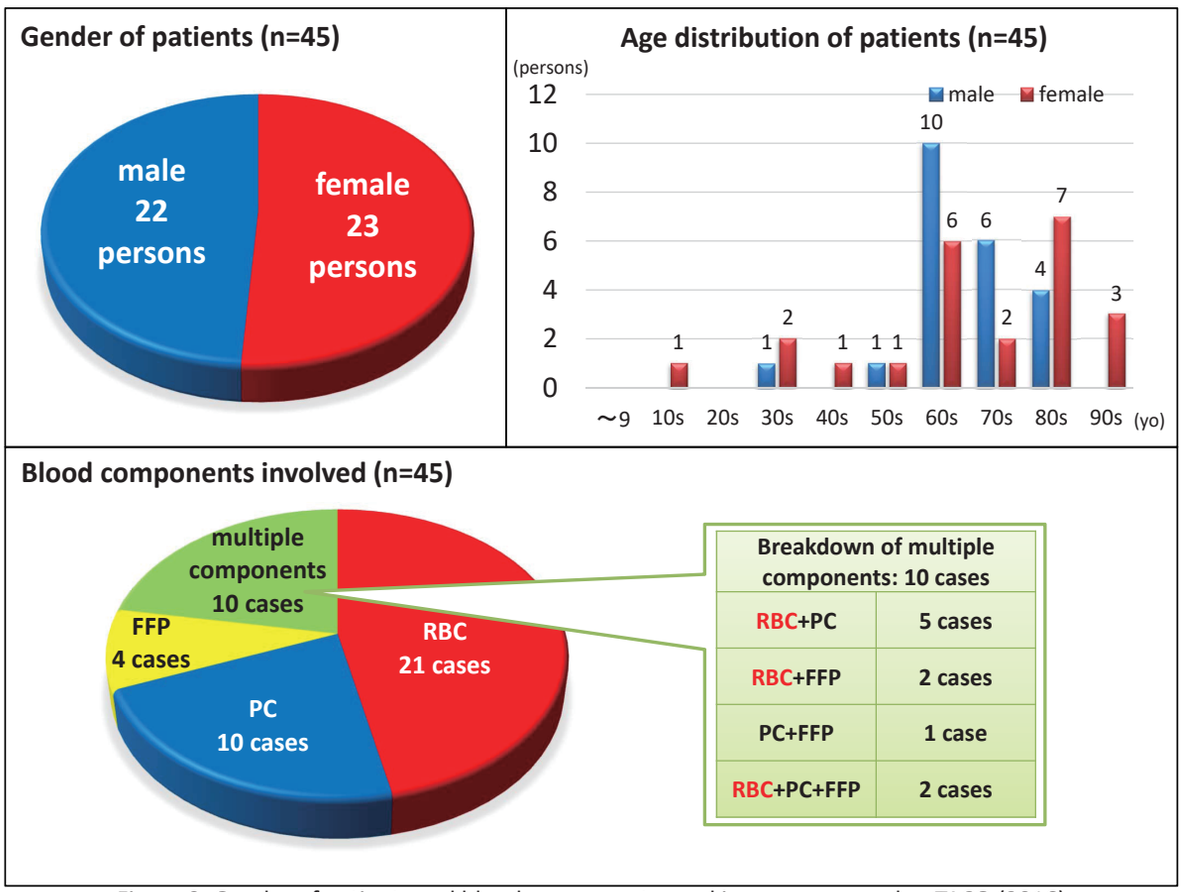


Figure 9. Gender of patients and blood components used in cases assessed as TACO (2016)

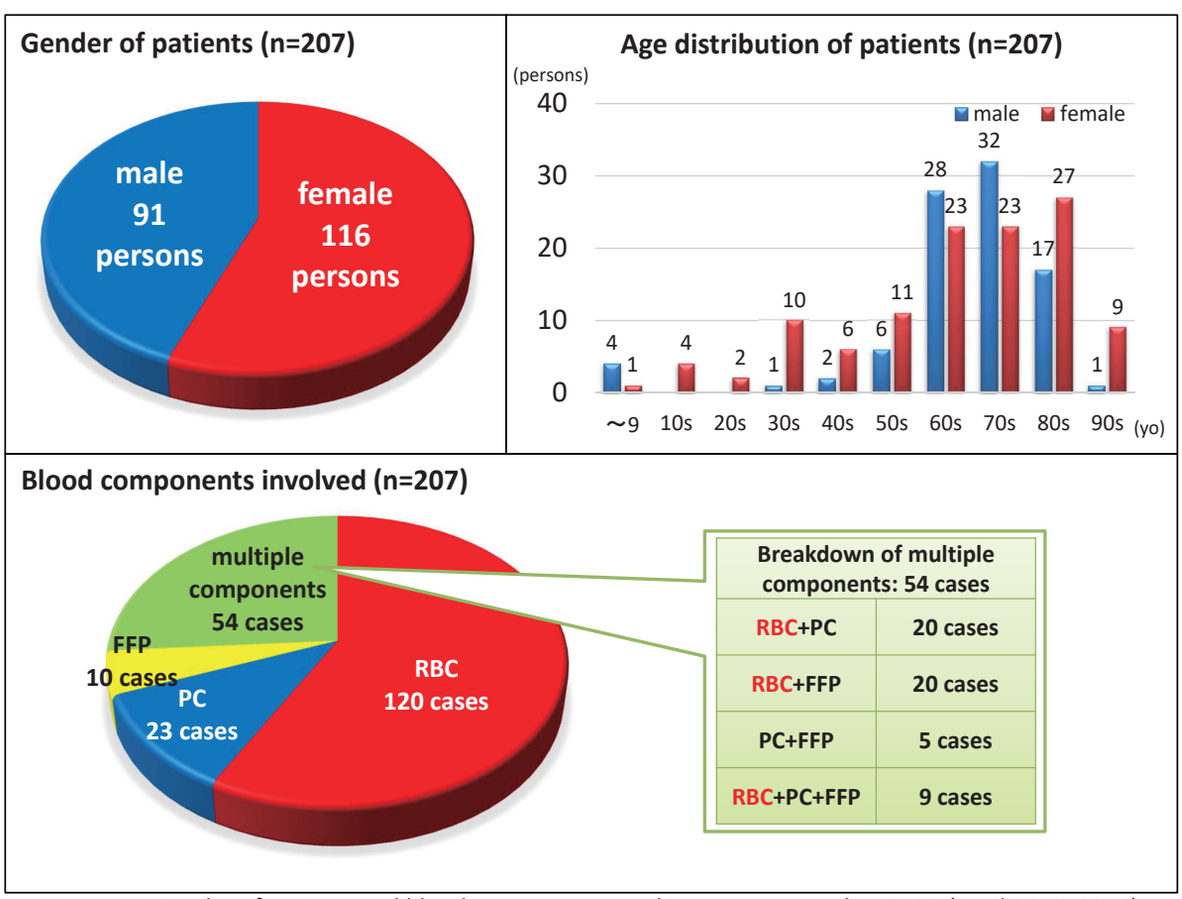


Figure 10. Gender of patients and blood components used in cases assessed as TACO (April 2012–2016)

Discussion and future tasks for TRALI and TACO

- Compared to the number of cases reported as suspected TRALI, the rate of cases actually diagnosed as TRALI has been decreasing. There were no cases that were diagnosed as fatal TRALI in 2016.
- As a measure against TRALI, the JRCS continues the preparation of FFP derived from 400 mL of whole blood donations, preferentially from male donors.
- The JRCS has 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" in the guideline. Therefore, TACO has been becoming more widely recognized. However, most cases that were firstly reported as "TRALI" by medical institutions were classified as cardiogenic pulmonary edema by the JRCS's TRALI evaluation and were followed by TACO assessment, resulting in "TACO" (Figure 6). Although the number of cases evaluated as TACO has been on the increase (Figure 11), the number of cases as much as the current ones were evaluated as cardiogenic pulmonary edema before assessment for TACO started. It is not considered that TACO cases have actually increased as rapidly as it seems.
- The number of cases reported to the JRCS from medical institutions as "TACO" was assumed to increase because the JRCS prepared and distributed the "Transfusion Information" that included TACO's pathophysiology, clinical presentation, risk factors, and treatment to call attention to healthcare professionals in February 2016 (see "Haemovigilance by JRCS 2015") (4 cases in 2013, 4 cases in 2014, 9 cases in 2015, and 14 cases in 2016).
- As TACO is a condition of cardiac failure due to circulatory overload, it is important to understand the potential risk of cardiac failure by observing pre-transfusion level NT-proBNP* or the decline in renal function, which is a subject of future investigation. For the patients who have the risk of cardiac failure before blood transfusion, it is necessary to pay attention to the transfusion rate and volume and to monitor the patients closely during the transfusion.
- Since April 2016, the diagnostic criteria and the evaluation results of TRALI and TACO should be described in the investigation reports to medical institutions to call further attention.

*NT-proBNP: N-terminal pro-brain natriuretic peptide

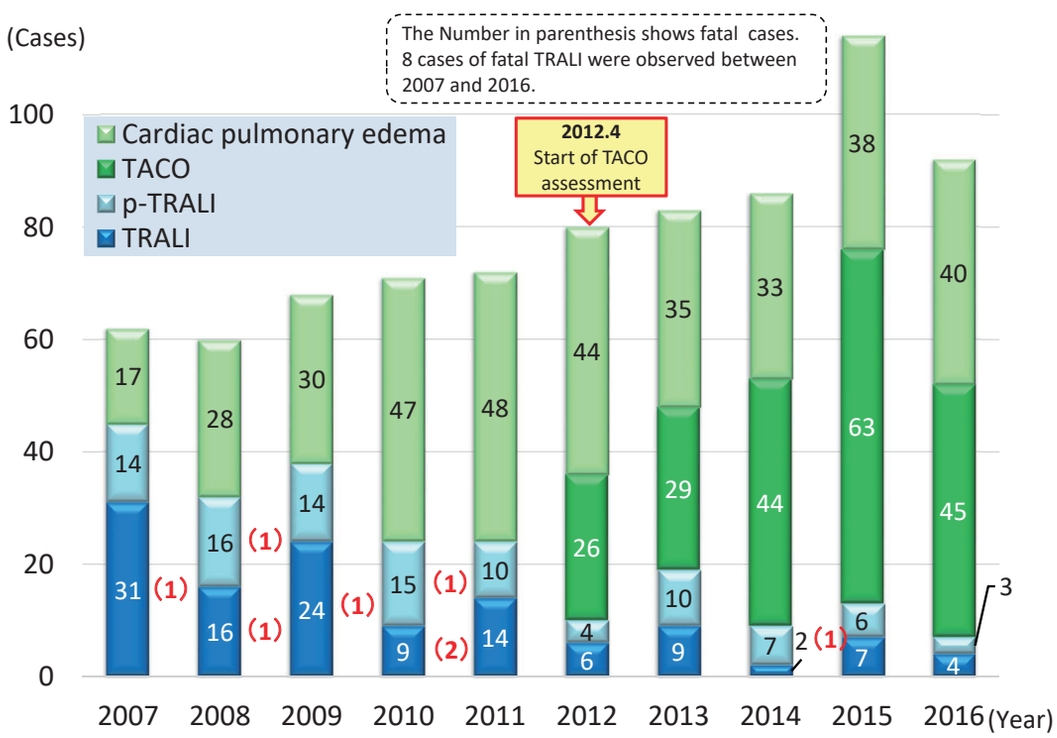


Figure 11. Evaluation of TRALI and TACO cases (2008-2016)

(2) Hemolytic adverse reactions

Table 2 shows the breakdown of cases reported as hemolytic adverse reactions by medical institutions in 2016. Case investigation by the JRCS revealed 8 cases with irregular antibodies in the patients' specimens, which consisted of 2 cases with acute reaction, 5 cases with delayed reaction and 1 case of onset time unknown (Table 3). In addition, 1 patient with acute reaction, 2 patients with delayed reaction, and 1 patient with onset time unknown had history of transfusions.

Case No. 1 was evaluated as "incompatible" in the pre-transfusion crossmatch test conducted at the medical institution but underwent transfusion with the selected components with weak reactivity due to an emergency case. Case No. 3 was evaluated as "compatible" in the pre-transfusion crossmatch test conducted at the medical institution but was evaluated as "incompatible" in the test results conducted at the JRCS. For Case No. 8, the detailed information on adverse reactions was not available.

Table 2. Number of case reports of hemolytic adverse reactions in 2016

	Severe	Non-severe	Total
AHTR	4	8	12
DHTR	5	3	8
Unknown	0	1	1
Total	9	12	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

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

No cases with suspected TA-GVHD were reported in 2016. There have been no confirmed cases of TA-GVHD which were caused by blood components for transfusion distributed by the JRCS since 2000.

Table 3. Positive cases of irregular blood antibodies

		Component	Patients	Symptoms	Test results conducted by JRCS after onset					
					Pre-transfusion			Post-transfusion		
					Crossmatch	Patient's serum	DAT	Crossmatch	Patient's serum	DAT
Acute	1	RBC	F 70s	Fever, Hemolysis	Incompatible	Anti-Jr^a	Neg.	Incompatible	Anti-Jr^a	Neg.
	2	RBC	F 80s	Hemolysis	Compatible	Neg.	n/t	Incompatible	Anti-E Anti-P1 Anti-Jk3	Pos.
Delayed	3	RBC	F 80s	DHTR	Incompatible	Anti-E	n/t	Incompatible	Anti-E Anti-c	Neg.
	4	RBC	F 50s	DHTR	n/t	Neg.	n/t	n/t	Anti-C	Neg.
	5	RBC	M Child	Hemolysis	n/t	n/t	n/t	n/t	Anti-E Anti-Jk^a	n/t
	6	RBC	F 40s	DHTR	Compatible	Neg.	Neg.	Incompatible	Anti-E	Neg.
	7	RBC	F 60s	Jaundice	n/t	Anti-E Anti-c	Neg.	Incompatible	Anti-E Anti-c Anti-Jk^b	Pos.
Unknown	8	RBC	F 70s	Hemolysis	n/t	n/t	n/t	n/t	Anti-C Anti-e	Neg.

DHTR: Delayed Hemolytic Transfusion Reaction

2) Transfusion transmitted infections

(1) Cases reported as suspected post-transfusion-transmitted infections

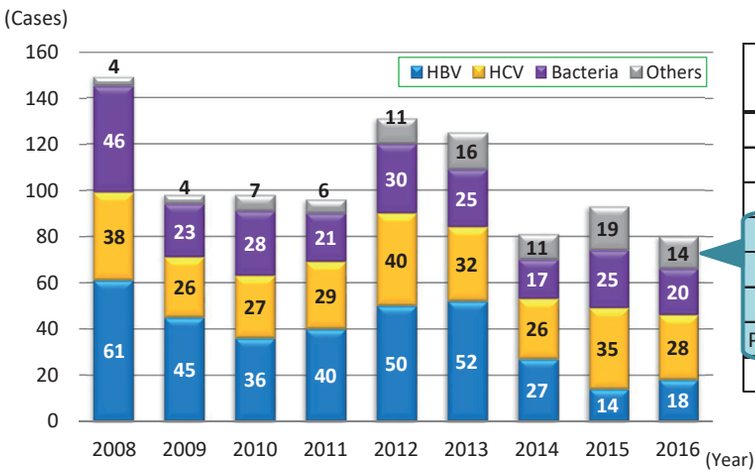
Figure 12 shows the breakdown of cases of suspected post-transfusion transmitted infections (including reported cases by medical institutions and cases of post-donation information) reported in 2016 and annual changes of the number of cases.

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. Viral homology was confirmed by viral genome sequence analysis, while the consistency of bacterial strain was confirmed by genotype (PFGE: Pulsed Field Gel Electrophoresis), drug susceptibility, and toxinotype.

In 2016, there was 1 case identified as HBV infection, which was the first identified case after the individual NAT in August 2014 (see "Haemovigilance by JRCS 2014"). This case was revealed from the result of the retrospective investigation on a donor whose HBV-DNA had turned to be positive in January 2016. The concerned donor had donated

blood in November and December in 2015 and the results of the individual NAT conducted at those times were negative. At both times, platelet products were manufactured from the donated blood and were transfused to the same patient. In the investigation, the patient was found to be negative before the transfusion and positive after the transfusion (see the following "(2) Summary of cases reports identified as TTIs"). For HCV and HIV, no cases were identified as TTIs after the introduction of individual NAT.

The homology of genome sequence could not be confirmed in 2 of 3 identified cases of HEV infection, but these cases were determined as TTIs judging from the clinical course.



Pathogen	Number of reported cases	Number of confirmed cases
HBV	18	1
HCV	28	0
Bacteria	20	1
CMV	7	0
HEV	4	3
HAV	1	0
Parvovirus B19	2	0
Total	80	5

Figure 12. Breakdown of cases of suspected transfusion-transmitted infections by pathogen in 2016 and annual changes in the number of cases

(2) Summary of cases reports identified as TTIs

A summary of cases identified as TTIs is described as follows:

HBV

Post-donation information: A case revealed by Lookback studies based on positive conversion identified at screening of donated blood

Case no.	Primary disease	Blood component (year and month of blood collection)	Age	Sex	Pre-transfusion test			Post-transfusion test		ALT		Recipient's outcome
					Test items	Test results	Period to transfusion**	Positive conversion items	Interval after transfusion**	Maximum (IU/L)	Interval after transfusion**	
1	Acute myeloid leukemia	Ir-PC-LR (2015. 11)* Ir-PC-LR (2015. 12)*	70s	F	HBV-DNA HBs-Ag HBs-Ab HBc-Ab	Neg.	400 days 9 days 9 days 9 days	HBV-DNA HBs-Ag	12 wks 13 wks	38	10 wks	Remission

* The concerned donated blood was negative for HBV-NAT, but positive for HBV-NAT at the time of donation in January 2016.
** It was reckoned from the date of transfusion with blood components collected in November 2015.

HEV

Voluntary report: Cases reported by medical institutions as a suspected transfusion transmitted viral infection

Case no.	Primary disease	Blood component (year and month of blood collection)	Age	Sex	Pre-transfusion test			Post-transfusion test		ALT		Recipient's outcome
					Test items	Test results	Period to transfusion	Positive conversion items	Interval after transfusion	Maximum (IU/L)	Interval after transfusion	
1	Acute myeloid leukemia	Ir-RBC-LR (2015. 9)	70s	F	HEV-RNA	Neg.	140 days	IgA-HEV-Ab	11 wks	1252	11 wks	Recovery
2	Myelodyspl-astic syndrome	Ir-PC-LR (2016. 6)	50s	M	IgA-HEV-Ab	Neg.	49 days	IgA-HEV-Ab	9 wks	1200	9wks	Remission

Post-donation information: A case revealed by Lookback studies based on close investigation of source plasma for plasma derivatives

Case no.	Primary disease	Blood component (year and month of blood collection)	Age	Sex	Pre-transfusion test			Post-transfusion test		ALT		Recipient's outcome
					Test items	Test results	Period to transfusion	Positive conversion items	Interval after transfusion	Maximum (IU/L)	Interval after transfusion	
1	Mitral valve Incompete-nce	Ir-RBC-LR (2015. 6)	80s	F	HEV-RNA IgM-HEV-Ab IgG-HEV-Ab	Neg.	3 days	IgG-HEV-Ab	56 wks	267	7 wks	Recovery

Bacteria

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

Case no.	Primary disease	Blood component (year and month of blood collection)	Age	Sex	Blood culture results of post-transfusion		Symptoms	Onset time (after administration)	Recipient's outcome
					Blood components	Recipient's blood			
1	Aplastic anemia	Ir-PC-LR (2016.5)	60s	M	*Citrobacter koseri*	*Citrobacter koseri*	Abdominal pain, vomiting, diarrhea, shivering, fever, inflammatory response	47 min.	Recovery, with sequelae

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

(1) Domestic cases

Table 4 shows domestic case reports found by the periodical searching of the literature and academic conference in 2016. The domestic cases in Table 4 were only reported in the literature or at academic conferences, and not to the JRCS. For these cases, the JRCS made contact with the authors of the literature of relevant cases and their belonging medical institutions and investigated the severity of adverse reactions and the blood components transfused at the medical institutions via the JRCS's MRs. The cases classified as severe adverse reactions were submitted as ICSR to PMDA.

Table 4. Domestic cases of transfusion-related adverse reactions obtained in the literature search in 2016 (including cases not submitted as ICSR to PMDA)

No.	Suspected Components	Age	Sex	Symptoms	Journal etc.
1	RBC-LR	60	F	Transfusion-associated dyspnoea	Japanese Journal of Transfusion and Cell Therapy. 2016; 62(2): 344.
2	RCC-LR Ir-RCC-LR FFP-LR120 FFP-LR240 Ir-PC-LR	78	F	Respiratory failure	The Journal of Japan Society for Clinical Anesthesia. 2016; 36(3): 297-304.
3	RBC-LR PC-LR	45	F	Allergy	Kanagawa journal of obstetrics and gynecology. 2016; 53(1): 6-9.
4	Ir-RBC-LR	75	F	DHTR	Japanese Journal of Transfusion and Cell Therapy. 2016; 61(1): 54.
5	Ir-RCC-LR	82	F	DHTR	Journal of the Japanese Society of Intensive Care Medicine. 2014; 21(Suppl): [DP-157-4].
6	Ir-RBC-LR	89	M	Chills, Shivering	Japanese Journal of Transfusion and Cell Therapy. 2016; 62(2): 309.
7	Ir-RCC-LR RBC-LR	79	M	Human parvovirus B19 infection	Practical Dermatology. 2016; 38(3): 275-278.
8	Ir-RBC-LR	0	F	Cytomegalovirus infection	Journal of Japan Society for Neonatal Health and Development. 2016; 28(3): 600.
9	Ir-RBC-LR	0	F	Cytomegalovirus infection	Journal of Japan Society for Neonatal Health and Development. 2016; 28(3): 600.

RCC-LR : Red Cells Concentrates, Leukocytes Reduced
Ir-RCC-LR : Irradiated Red Cells Concentrates, Leukocytes Reduced
RBC-LR : Red Blood Cells, Leukocytes Reduced
Ir-RBC-LR : Irradiated Red Blood Cells, Leukocytes Reduced
FFP-LR120 : Fresh Frozen Plasma, Leukocytes Reduced, 120 mL
FFP-LR240 : Fresh Frozen Plasma, Leukocytes Reduced, 240 mL
PC-LR : Platelet Concentrate, Leukocytes Reduced
Ir-PC-LR : Irradiated Platelet Concentrate, Leukocytes Reduced
DHTR : Delayed Haemolytic Transfusion Reaction

(Summary)

- Case No. 1, for which TACO had been suspected, was revealed that it was not a transfusion-related adverse reaction but a symptom of septicemia by the inquiry to the medical institution.
- Case No. 2 had the possibility to develop cardiogenic pulmonary edema and respiratory failure due to the heart overload after blood and fluid transfusion for severe bleeding.
- Case No. 3 presents that a patient with uterine fibroid, hypermenorrhea, and aplastic anemia, developed an allergic reaction at the time of blood transfusion.
- Cases from No. 4 to No. 6 were suspected to involve the irregular antibodies. Case No. 4 was negative for irregular antibodies in the pre-transfusion test but turned to be positive after the transfusion. It was revealed that the relevant patient had an experience of transfusion by the

inquiry of her medical history, and the adverse reaction seemed to be due to a secondary immune response. Case No. 5 was the case where E-antigen negative blood was used for the transfusion to the patient with an anti-E, and the adverse reaction seemed to be due to newly produced irregular antibodies (anti-Jkb and anti-Dib). The adverse reaction of Case No. 6 seemed to be caused by an anti-M that had no reactivity at 37°C.

- One case with parvovirus B19 infection (No. 7) was the case where the patient had systemic papules and purpura during chemotherapy and transfusion for myelodysplastic syndrome (MDS) and was diagnosed as an infection of parvovirus B19 based on the titer of antibody and positive serum B-19 DNA. As a route of infection, a droplet infection and transfusion were suspected. As an investigation conducted afterward revealed that the patient was negative to B19V-DNA and positive to IgG-B19V-Ab both before and after transfusion and that the individual NATs of the stored specimen of the product used for transfusion were all negative to B19V-DNA, the infection seemed not to be associated with transfusion.
- Two cases with cytomegalovirus (CMV) infection (No. 8 and 9) were ones that an investigation was conducted on the causal relationship between transfusion and the acquired cytomegalovirus infectious disease observed in extremely low-birth-weight infants. In both cases, it was unknown whether the blood components used for transfusion were CMV positive or not. After a further investigation, the transfusion components were revealed to be all negative to CMV-DNA, and the imputability between CMV infection and the transfusion is low.

(2) Overseas cases

Since the blood components for transfusion prepared by the JRCS are distributed only in Japan, we collect and investigate the case reports on adverse reactions and TTIs caused by foreign blood components that are therapeutically equivalent in accordance with PMD Act. Overseas cases of TTIs and unknown severe adverse reactions are submitted as ICSR to PMDA. Table 5 shows the overseas cases collected in 2016.

Table 5. Overseas cases obtained in the literature search in 2016 that have been submitted ICSR to PMDA

No.	Country	Suspected blood products	Age	Sex	Symptoms	Journal etc.
1	Brazil	Platelet	27	M	Hepatitis A	Transfus Med Hemother. 2016; 43(2): 137-141.
2	Brazil	Packed Red cells	39	M	Hepatitis A	Transfus Med Hemother. 2016; 43(2): 137-141.
3	Spain	Packed Red cells	61	M	Hepatitis E	Transfusion. 2017; 57(2):244-247.
4	Germany	Plasma	71	M	Hepatitis E	Clin Infect Dis. 2016; 63(4): 569-70.
5	Germany	Platelet	61	F	Hepatitis E	Clin Infect Dis. 2016; 63(4): 569-70.
6	Germany	Packed Red cells	33	M	Hepatitis E	Clin Infect Dis. 2016; 63(4): 569-70.
7	France	Platelet	Unknown	M	Hepatitis E	Emerg Infect Dis. 2017; 23(1): 146-147.
8	U.K.	Plasma	46	M	Hepatitis E	Journal of Clinical Virology, 2015; 70(Suppl 1): S124.
9	Switzerland	Platelet	70	Unknown	Trypanosoma cruzi infection	Transfus Med Hemother. 2016; 43(3): 169-176.
10	Brazil	Platelet	14	F	Zika virus infection	N Engl J Med. 2016; 375(11): 1101-1103.
11	Brazil	Platelet	54	F	Zika virus infection	N Engl J Med. 2016; 375(11): 1101-1103.
12	Brazil	Platelet	55	M	Zika virus infection	Transfusion. 2016; 56(7): 1684-1688.
13	Pakistan	Plasma	73	M	Dengue fever	Transfus Apher Sci. 2017; 56(2):151-153.
14	Pakistan	Platelet	59	M	Dengue fever	Transfus Apher Sci. 2017; 56(2):151-153.
15	Switzerland	Platelet	74	F	Human parvovirus B19 infection	Transfus Med Hemother. 2016; 43(3): 198-202.
16	Canada	Packed Red cells	81	M	Bacterial infection	Transfusion. 2016; 56(Suppl S4): 200A.
17	France	Platelet	8	F	Bacterial infection	Transfusion. 2016; 56(6): 1311-1313.
18	France	Platelet	Unknown	F	Bacterial infection	Transfus Med. 2016; 26(4): 308-310.
19	U.S.	Platelet	59	M	Bacterial infection	Transfusion. 2016; 56(Suppl S4): 199A.
20	U.S.	Platelet	74	M	Bacterial infection	Transfusion. 2016; 56(Suppl S4): 199A.
21	U.S.	Packed Red cells	76	M	Plasmodium malariae infection	Transfusion. 2016; 56(9): 2221-2224.
22	U.S.	Packed Red cells	18	M	Plasmodium falciparum infection	Crit Care Med. 2016; 44(12 Suppl 1): 505.
23	Malaysia	Whole blood	23	F	Plasmodium knowlesi infection	Malar J. 2016; 15(1): 357.
24	U.S.	Packed Red cells	3	M	Babesiosis	J Clin Microbiol. 2016; 54(11): 2632-2634.
25	Germany	Packed Red cells Plasma Platelet Noradrenaline	74	F	Abdominal compartment syndrome	J Med Case Rep. 2016; 10(1): 294.

(Summary)

- Two cases with hepatitis A (No. 1 and 2) were ones caused by the blood components manufactured from the same donated blood. A patient who received the red cell product (No. 2) and a patient who received the pooled platelet product (No. 1) turned to be positive to HAV-RNA after transfusion, and the homology of genome sequence detected from the donor and the patient was confirmed with the HAV.

- Of the patients with hepatitis E (No. 3-8), No. 4 to 6 were the cases where each of the red cell products, pooled platelet products, and plasma products manufactured from the same donated blood was transfused to the different patients. No. 4 showed the patient who underwent transplantation of the heart, No. 5 showed a patient with acute myelogenous leukemia (AML), and No. 6 presented the patient who received a transplantation of stem cells. Case No. 8 in the U.K. showed the patient with transplanted liver, and there were many hepatitis E cases where an involvement of immunosuppressive conditions was suspected.
- The case with *Trypanosoma cruzi* (*T. cruzi*) infection (No. 9) was suggested to be infected through transfusion from the donor who was identified to be positive to anti-*T. cruzi* antibody screening test. A retrospective study of the blood donations by this donor in the past revealed that the patient (already dead at the time of the retrospective study) who received the relevant platelet product in 2008 was determined to have a heart muscle inflammation with infiltration of *T. cruzi* in the autopsy.
- Cases with Zika virus (ZIKV) infection (No. 10-12) were revealed in the notification from a blood center that the donor developed a rash, fever, and other symptoms of ZIKV infection after blood donation. All 3 cases were ZIKV infections associated with the transfusion of platelet products, and the base sequences of ZIKV detected from the bloods of post-transfusion patients and donated bloods were found to be identical. Note that patients had no symptoms in all 3 cases (the patient No. 10 had no symptoms despite an immunosuppressive therapy).
- Cases with Dengue virus (DENV) infection (No. 13 and 14) were caused by the blood components manufactured from the same donated blood. Fever and a decrease in platelets were seen in the patient who received fresh frozen plasma (No. 13) and the patient who received the platelet product (No. 14), and DENV-RNAs were detected from them. It was revealed that the donor of the suspected blood had developed fever and systemic pain on the next day of the donation, and had positive IgM-DENV antibody on the examination.
- The case with parvovirus B19 (B19V) infection (No. 15) was revealed in a retrospective study of donors who were identified as positive in the NAT screening of B19V (screening in a pool of 480 patients with an implementation of individual NAT for positive cases). B19V was detected from the bloods of the patients who received the product manufactured from pool platelet treated with pathogen reduction, which was subject to the retrospective study, and its genome sequence matched with that of B19V detected from the donor of the relevant product. With the high viral load of the relevant product, it was assumed that the virus was not fully eliminated in the pathogen reduction process.
- Of the cases with bacterial infection (No. 16-20), No. 16, No. 17, and No. 18 were cases that died due to the infection with *Aeromonas veroii*, *Citrobacter koseri*, and *Escherichia coli*, respectively. No. 19 and No. 20 were cases with a bacterial infection caused by the platelet product separately manufactured from the same donated blood that was contaminated with *Staphylococcus aureus*. A total of 3 bags of platelet products was manufactured from the same blood, 2 of which were transfused to the cases No. 19 and No. 20 5 days after donation. The remaining one was transfused to another patient 3 days after donation, but no adverse reaction was observed. It was suggested that the risk of bacterial infection may increase according to the stored period of the platelet products.
- Of the cases with malaria (No. 21-23), No. 21 had a history of multiple transfusions in the past. An investigation of the donors involved in these transfusions revealed that 1 donor was positive to the *P. malariae* antibody (also positive to *P. malariae*-DNA in a test conducted afterward). Case No. 22 showed a patient with sickle cell disease who regularly received transfusions. The patient developed a failure of multiple organs and it was determined to be a falciparum malaria parasite infection after an examination. As this patient had never been to abroad, the possibility of transfusion-related infection could not be denied. Case No. 23 showed a patient with thalassemia major who underwent splenectomy and regularly received transfusions. In an examination conducted with a complaint of fever, *P. knowlesi* (*Plasmodium knowlesi*) was found. It was revealed that the donor of the transfused blood consulted with a medical institution due to poor health 12 days after the donation and *P. knowlesi* was detected.
- In the case of babesiosis (No. 24), fever was observed after transfusion, and *B. microti* infection was determined with a detailed examination. The product used for the transfusion was examined, but the causal relationship with transfusion was unknown because the donor of the suspected blood could not be specified. The donor of the heart that was transplanted to the patient was also examined, but the transplantation-related infection was denied.
- The case with abdominal compartment syndrome (ACS) (No. 25) seemed to have developed ACS due to a bolus catecholamine administration in addition to a total of 10.5 L blood and fluid transfusion to a patient with polytrauma. It is generally said that a mass fluid infusion becomes

a trigger of ACS, but it is also suggested that ACS may develop with the mass transfusion. The restriction on the volume of transfusion seemed to be useful to reduce the incident of ACS.

3. 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 for manufacture, import or discontinuation of sale, recall, disposal of foreign medicine to prevent health damage. Reports of studies are submitted when the JRCS obtains information concerning study reports showing that cancer or another serious disease, disorder, or death would be possibly caused by relevant pharmaceutical products or a foreign pharmaceutical products, or infection due to their use, or that the incidence of adverse reactions and infection has significantly changed caused by relevant pharmaceutical products or foreign pharmaceutical products, or that relevant pharmaceutical products would 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 PMD Act and Article 228-20 of the Enforcement Regulations of the PMD Act even if the blood components manufactured by the JRCS are not marketed (supplied) in other countries. The products used in other countries that have the same active ingredients as the blood components manufactured or distributed by the JRCS, even if such products have a different administration route and dosage, or efficacy and effect.

Table 6 shows the measures in foreign countries reported in 2016. There were no reports of studies to be reported in 2016.

Table 6. Reports on measures in foreign countries obtained in 2016

No.	Source	Title
1	Canada (HC)	(1)Statement from the Minister of Health on one year blood donor deferral period for MSM June, 20, 2016 (2)Regulatory decision summary: MSM Blood Donor Deferral June, 16, 2016
2	U.S. (AABB)	Association Bulletin #15-02 Transfusion-Associated Circulatory Overload (TACO) December 28, 2015
3	U.S. (FDA)	Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease and Variant Creutzfeldt-Jakob Disease by Blood and Blood Products; Guidance for Industry Updated January 2016
4	WHO	Maintaining a safe and adequate blood supply during Zika virus outbreaks, interim guidance February 2016
5	EU (ECDC)	RAPID RISK ASSESSMENT Zika virus disease epidemic: potential association with microcephaly and Guillain-Barre syndrome Second update, 8 February 2016
6	U.S. (AABB)	(1)Association Bulletin #16-03 Zika, Dengue, and Chikungunya Viruses February 1, 2016 (2)Association Bulletin #16-04 Zika, Dengue, and Chikungunya Viruses March 1, 2016 (3)Association Bulletin #16-07 Updated Recommendations for Zika, Dengue, and Chikungunya Viruses September 28, 2016
7	U.S. (FDA)	(1)Recommendations for Donor Screening, Deferral, and Product Management to Reduce the Risk of Transfusion- Transmission of Zika Virus February 2016 (2)Revised Recommendations for Reducing the Risk of Zika Virus Transmission by Blood and Blood Components; Guidance for Industry August 2016
8	U.K. (NHSBT, JPAC)	(1)Introduction of Hepatitis E Virus (HEV) screened negative components. 28 January 2016. (2)NHSBT Hepatitis E Virus (HEV) Factsheet for Hospital Transfusion Teams – January 2016. (3)Change Notification UK National Blood Services No. 12 - 2016. 27 January 2016. (4)News Release: Change to NHSBT pricing of products in 2017/18 and introduction of universal screening for Hepatitis E. 21st December 2016.
9	U.S. (FDA)	Implementation of Acceptable Full-Length and Abbreviated Donor History Questionnaires and Accompanying Materials for Use in Screening Donors of Blood and Blood Components; Guidance for Industry May 2016
10	U.S. (FDA)	Implementation of Acceptable Full-Length and Abbreviated Donor History Questionnaires and Accompanying Materials for Use in Screening Donors of Source Plasma; Guidance for Industry July 2016

(Summary)

- (No. 1: Shortening of the indefinite deferral for MSM to 1 year) Canada had a policy of deferral for men who have sex with men (MSM), which means they were unable to donate blood if they have had sexual relationships with men during the past 5 years. However, the request to reduce the deferral period to 1 year was submitted by blood organizations (Canadian Blood Services and Hema-Quebec) to Health Canada, which approved this request.

- (No. 2: Provision of information on TACO) A recommendation on the risk factors of transfusion associated circulatory overload (TACO) (elderly, left ventricular insufficiency, congestive cardiac failure, pre-transfusion circulatory overload excessive transfusion, rate of transfusion), preventive measures (reduce transfusion rate, etc.), treatments (administrations of oxygen and diuretics), and the necessity of education for relevant responsible doctors was issued by the American Association of Blood Banks (AABB) as an official bulletin.
- (No. 3: Update of guidance on CJD and vCJD) A revised version of the guidance to reduce the possible risk of transmission of CJD and vCJD by transfusion was released. The major changes included the update of the situation of the global epidemic of vCJD and BSE, clarification of the re-entry criteria for donors who have a family history of CJD, clarification of the requirements for deviation reports, etc.
- (No. 4-7: Responses to the outbreak of Zika virus) In response to that an Emergency Committee of WHO held on February 1, 2016, on the microcephaly and other neurologic disorders in the endemic areas of Zika virus (ZIKV), the "Public Health Emergency of International Concern (PHEIC)" about the cluster of microcephaly and other neurologic disorders was announced, and the regulatory authority in each country released a recommendation on the reduction of ZIKV infection risk. The major measures include a certain period of deferral of donation for those who have a travel history to the endemic areas of ZIKV and who have any contact with ZIKV-infected persons and those who have sexual contact with ZIKV-infected persons. In addition, it was recommended that collection for blood components for transfusion should not be implemented in the ZIKA endemic areas and the distribution of products from non-epiedemic area or implementation of ZIKV tests and pathogen reduction process should be considered. In the U.S., ZIKV individual NAT is implemented for all donated bloods as of November 2016.
- (No. 8: Introduction of HEV screening tests for donated blood) The National Health Service Blood and Transplant (NHSBT) in the UK has implemented selective HEV screening tests for the blood components for transfusion to patients having solid organ transplantation or neonates from March 2016 and started the supply of HEV negative components for transfusion (see "Haemovigilance by JRCS 2015"). Then, the Advisory Committee on the Safety of Blood Tissues and Organs (SaBTO) recommended NHSBT to implement HEV screening tests for all donors, and NHSBT decided to implement it based on this recommendation.
- (No. 9 and 10: Update of the criteria of a questionnaire at a blood donation) Donor history questionnaire and the accompanying materials for screening blood donors were updated and the FDA approved it. Donor history questionnaires and the accompanying materials for screening blood donors of source plasma* for plasma derivatives were also updated and approved.

* In some foreign countries and areas including the US, there are Source Plasma establishments that collect only source plasma for manufacturing plasma derivatives.

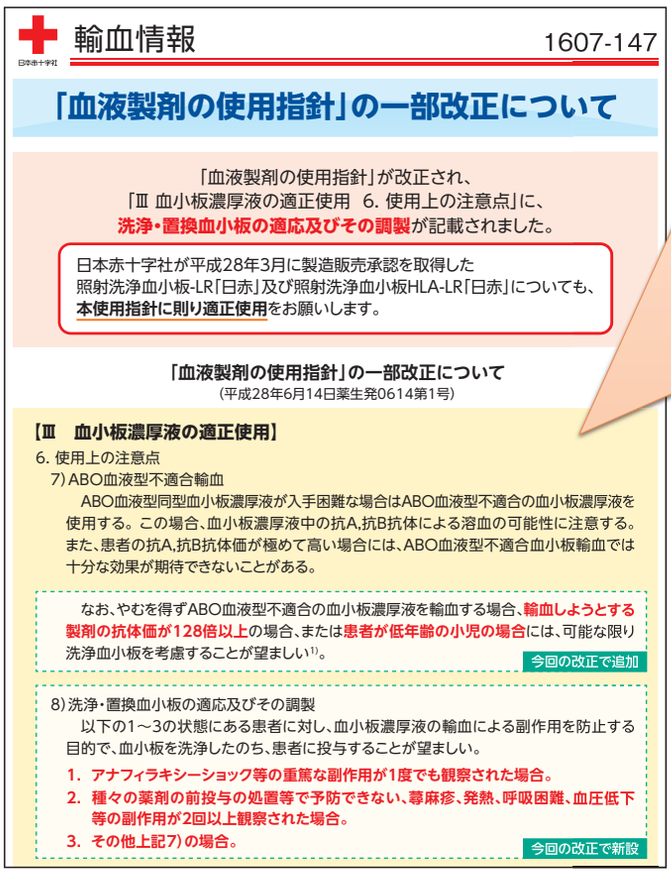
4. Safety measures against blood components for transfusion

Safety measures has been taken based on the result of assessment and evaluation for cases of transfusion-related adverse reactions and TTIs reported by medical institutions post-donation information obtained from donors. The following are the safety measures taken in 2016:

1) Marketing authorization and launch of washed platelet

In March 2016, the JRCS obtained the approval for manufacturing and marketing of the washed platelet products, "Irradiated Washed Platelet Concentrate, Leukocytes Reduced, Nisseki (Ir-WPC-LR)" and "Irradiated Washed Platelet Concentrate HLA, Leukocytes Reduced, Nisseki (Ir-WPC-HLA-LR)". They are platelet concentrates washed with platelet additive solutions* to reduce a greater part of the blood plasma, and then suspended in the same solutions. In addition, the "Guideline on the Use of Blood Products" was partially amended based on the Notification PB No. 0614-1 issued by the Pharmaceutical Safety and Environmental Health Bureau on June 14, 2016, and it indicates the patient group of whom washed platelet concentrates should be administered to. In order to ask for the proper use of Ir-WPC-LR and Ir-WPC-HLA-LR in accordance with this Guideline on the Use of Blood Products, the JRCS prepared and distributed "Transfusion Information" (Figure 13) to provide information to relevant medical professionals. The JRCS started to distribute WPC products in September 2016.

* Mixture in the proportion of approximately 1:20 of ACD-A (acid-citrate-dextrose formula A) solution with bicarbonate Ringer's solution



輸血情報 1607-147

「血液製剤の使用指針」の一部改正について

「血液製剤の使用指針」が改正され、
「Ⅲ 血小板濃厚液の適正使用 6. 使用上の注意点」に、
洗浄・置換血小板の適応及びその調製が記載されました。

日本赤十字社が平成28年3月に製造販売承認を取得した
照射洗浄血小板-LR「日赤」及び照射洗浄血小板HLA-LR「日赤」についても、
本使用指針に則り適正使用をお願いします。

「血液製剤の使用指針」の一部改正について
(平成28年6月14日薬生発0614第1号)

【Ⅲ 血小板濃厚液の適正使用】
6. 使用上の注意点
7) ABO血液型不適合輸血
ABO血液型同型血小板濃厚液が入手困難な場合はABO血液型不適合の血小板濃厚液を使用する。この場合、血小板濃厚液中の抗A,抗B抗体による溶血の可能性に注意する。また、患者の抗A,抗B抗体価が極めて高い場合には、ABO血液型不適合血小板輸血では十分な効果が期待できないことがある。

なお、やむを得ずABO血液型不適合の血小板濃厚液を輸血する場合、**輸血しようとする製剤の抗体価が128倍以上**の場合、または**患者が低年齢の小児の場合**には、可能な限り洗浄血小板を考慮することが望ましい[1]。 今回の改正で追加

8) 洗浄・置換血小板の適応及びその調製
以下の1～3の状態にある患者に対し、血小板濃厚液の輸血による副作用を防止する目的で、血小板を洗浄したのち、患者に投与することが望ましい。
1. **アナフィラキシーショック等の重篤な副作用が1度でも観察された場合。**
2. **種々の薬剤の前投与の処置等で予防できない、蕁麻疹、発熱、呼吸困難、血圧低下等の副作用が2回以上観察された場合。**
3. **その他上記7)の場合。**

今回の改正で新設

Patients who should be transfused WPC as following cases.

1. Cases in which only ABO-mismached platelet is available.

   When ABO antibody titer is >128x, or the patient is a small child, it is desirable to transfuse washed and replaced platelets as much as possible.

2. Cases in which serious adverse reactions such as anaphylactic shock are observed at least once.

3. Cases in which adverse reactions that cannot be prevented with pre-medication of various drugs are observed twice or more.

Figure 13. "Partial Amendment of 'Guideline on the Use of Blood Products'" on June 14, 2016
(Extract from Transfusion Information 1607-147)

2) Change of safety measures for Chagas disease

Since October 2012, the JRCS has started a manufacturing restriction to only use for the blood donated by donors who were born or grew up, or had stayed in Latin America (hereinafter referred to as "relevant donors") as source plasma to manufacture plasma derivatives, in order to reduce the risk of Chagas disease through transfusion (*Trypanosoma cruzi* infection). In addition, *Trypanosoma cruzi* (*T. cruzi*) antibody tests (as an epidemiological survey) were implemented nationwide from April 2013 for relevant donors who provided separate consent[*1] (see "Haemovigilance by JRCS 2013"). An amendment to the permanent safety measures against Chagas disease was proposed based on the results of the epidemiological survey in the "2nd Safety Technology Research Committee of the Committee of Blood Products in 2014" held on October 21, 2014, and the safety measures based on the algorithm shown in Figure 14 was agreed in the Safety Technology Research Committee held on February 24, 2016 and the Committee of Blood Products held on March 2, 2016. Then, this safety measure was started in August 2016 with the preparation of the system including screening test device, reagent, change in procedure, etc., of anti-*T. cruzi* screening tests for relevant donors, and the manufacturing of blood components for transfusion (except for platelet products[*2]) from these donors became possible if their results of anti-*T. cruzi* screening were negative. The epidemiological survey ended with the implementation of this safety measure. The summary of the results of the epidemiological survey shows that the total number of relevant donors from January 2013[*1] to August 2016 were 38,690 donors, of which 3 of the 13,706 donors who gave consent for the anti-*T. cruzi* screening were positive to the anti-*T. cruzi* antibody. It was the first donation for 2 of the 3 donors with anti-*T. cruzi* antibody positive. However, the one donor had a history of multiple blood donations. A retrospective investigation was conducted on using repository samples of this donor, but fortunately no TTI had been confirmed. (For the details of the results of retrospective studies, see "Haemovigilance by JRCS 2013").

*1: The tests were performed as a pilot study in a few blood centers from January 2013 and expanded to blood centers nationwide from April 2013.

*2: At the moment, apheresis platelet donations from these donors are inacceptable because of the short shelf life of PLT components with 4 days including the day of collection, and the difficulty of the confirmation of anti-*T cruzi* in the 4 days of expiry.

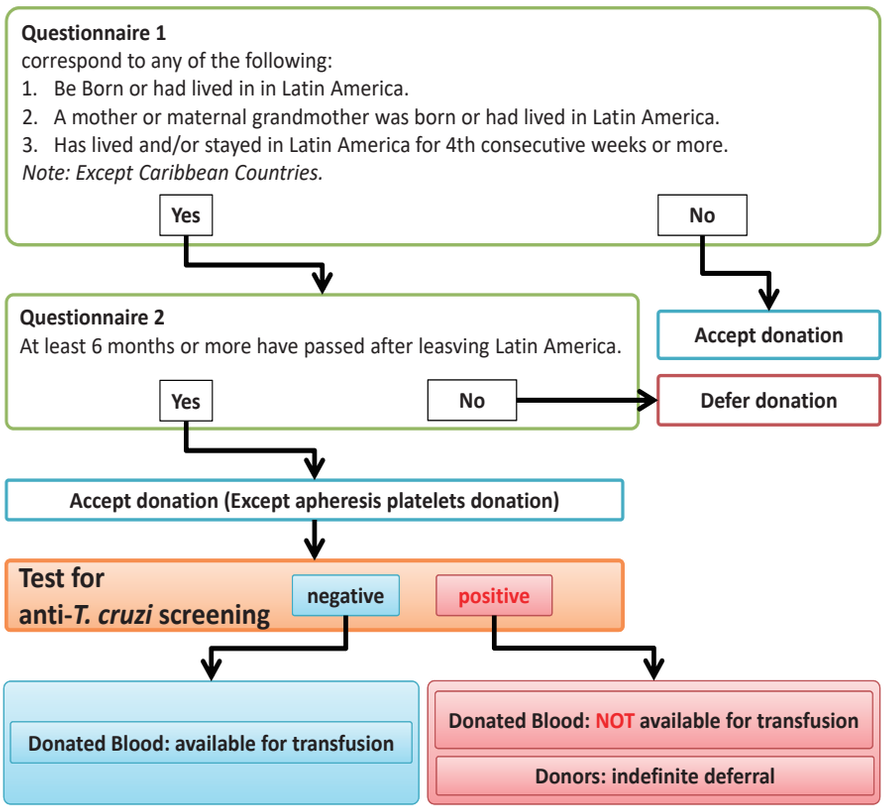


Figure 14. Algorithm of safety measures for Chagas disease

3) Safety measures for “Zika virus infection” (Zika fever)

At the beginning of 2015, Zika virus outbreak was observed in Latin American countries. Then, an Emergency Committee of WHO was held on February 1, 2016, on microcephaly and other neurologic disorders in the endemic areas of Zika virus (ZIKV), and the “Public Health Emergency of International Concern (PHEIC)” about the cluster of microcephaly and other neurologic disorders was announced.

In response to this matter, Notification of the Blood and Blood Products Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labor, and Welfare issued on February 3, 2016 the “WHO statement of Public Health Emergency of International Concern on the increase of microcephaly suspected to be caused by Zika virus (caution)”. The JRCS asked blood donors about oversea travel in the donor history questioner on every donation. If the donor has come back to Japan in 4 weeks, he/she is ineligible to donate. In accordance with the notification, the JRCS implemented the confirmation of the days after returning to Japan. Then, the donors who have been diagnosed as ZIKA infection are ineligible for blood donation until one month has passed after full recovery as a further safety measure (Figure 15). Note that no TTI cases have been reported in Japan as of December 2016, but have been reported from overseas (see “3) about individual cases of transfusion adverse reactions and TTIs obtained from the literature or academic conference”).

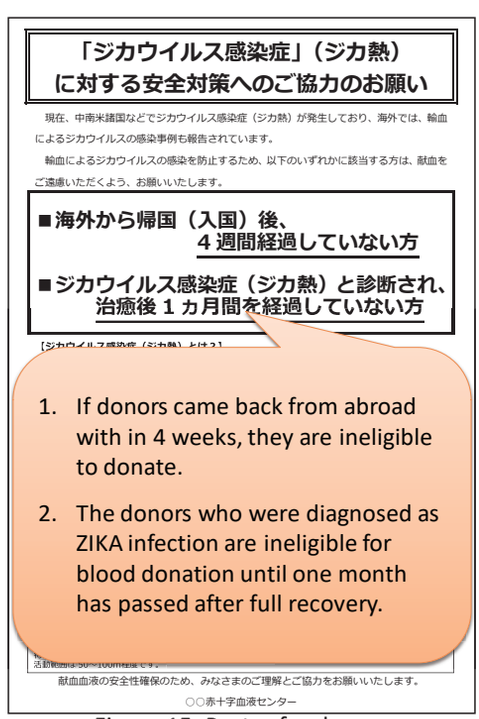


Figure 15. Poster for donors

5. Donor adverse reactions

1) Cases of donor adverse reactions

Approximately 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 7 shows the cases of donor adverse reactions in FY2016, and Figure 16 shows the breakdown by symptoms.

Table 7. Number of donor adverse reaction cases in FY2016

Category	Number of cases	Incidence
VVR mild*	25,273	0.523%
VVR severe*	3,262	0.068%
Hematoma	8,105	0.168%
Nerve injury	283	0.006%
Citric reaction	510	0.011%
Nerve disorder	177	0.004%
Localized pain	1,492	0.031%
Others	1,245	0.026%
Total	40,347	0.835%

Total donations	4,829,172

Severity	Symptoms	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.

2) Actions against donor adverse reactions

Nationwide introduction of leg muscle tension exercise

The internal working group of donor adverse reactions was established in 2012. A study entitled “Leg muscle tension exercises as a VVR preventive action” was introduced at 27 blood centers across Japan from July 2013, and verified the effect of leg muscle tension exercises to decrease the incidence of VVR. The results confirmed that it was effective to decrease the incidence of VVR in whole blood donation (see “Haemovigilance by JRCS 2014”).

Therefore, the introduction of leg muscle tension exercises to all donors has been launched all over Japan since October 2015. After its introduction, a decreasing trend in the overall VVR incidence was observed, especially due to a decrease in the VVR incidence with 400 mL whole blood donation (Figure 17). Regarding the effect of leg muscle tension exercise to decrease the VVR incidence with apheresis blood donation, a slight decreasing trend in the VVR incidence was seen in the verification result described above, which indicated less effective. However, since apheresis process repeats blood drawing and returning and it takes a longer time to complete, it cannot be said that the blood circulation dynamics of apheresis process is the same as whole blood donation. As the blood collection process and time are significantly different in whole blood donation and apheresis donation, the JRCS will continue to examine the effect of leg muscle tension exercises including the method to decrease the incidence of VVR with apheresis donation.

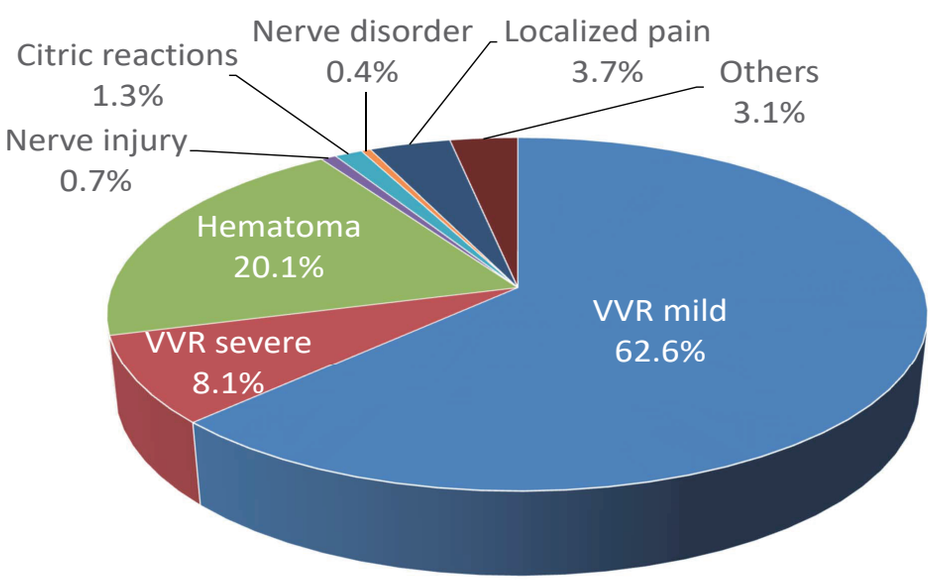
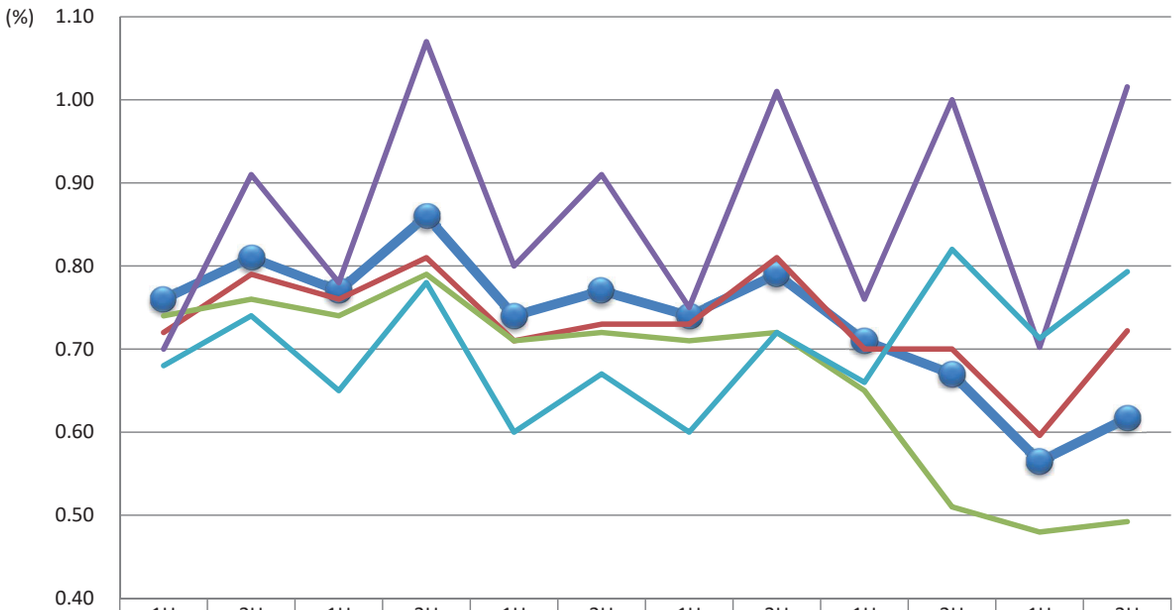


Figure 16. Breakdown of donor adverse reactions that occurred in FY2016



	1H FY 2011	2H FY 2011	1H FY 2012	2H FY 2012	1H FY 2013	2H FY 2013	1H FY 2014	2H FY 2014	1H FY 2015	2H FY 2015	1H FY 2016	2H FY 2016
Total	0.76	0.81	0.77	0.86	0.74	0.77	0.74	0.79	0.71	0.67	0.56	0.62
WB (200mL)	0.72	0.79	0.76	0.81	0.71	0.73	0.73	0.81	0.70	0.70	0.60	0.72
WB (400mL)	0.74	0.76	0.74	0.79	0.71	0.72	0.71	0.72	0.65	0.51	0.48	0.49
Apheresis (plasma)	0.70	0.91	0.78	1.07	0.80	0.91	0.75	1.01	0.76	1.00	0.70	1.02
Apheresis (platelets)	0.68	0.74	0.65	0.78	0.60	0.67	0.60	0.72	0.66	0.82	0.71	0.79

1H FY: April to September
2H FY: October to March

Figure 17. Changes in the incidence of VVR

Afterword

This annual report describes information including those on transfusion-related adverse reactions and infectious diseases reported by medical institutions nationwide to the 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 the 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 2016"

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