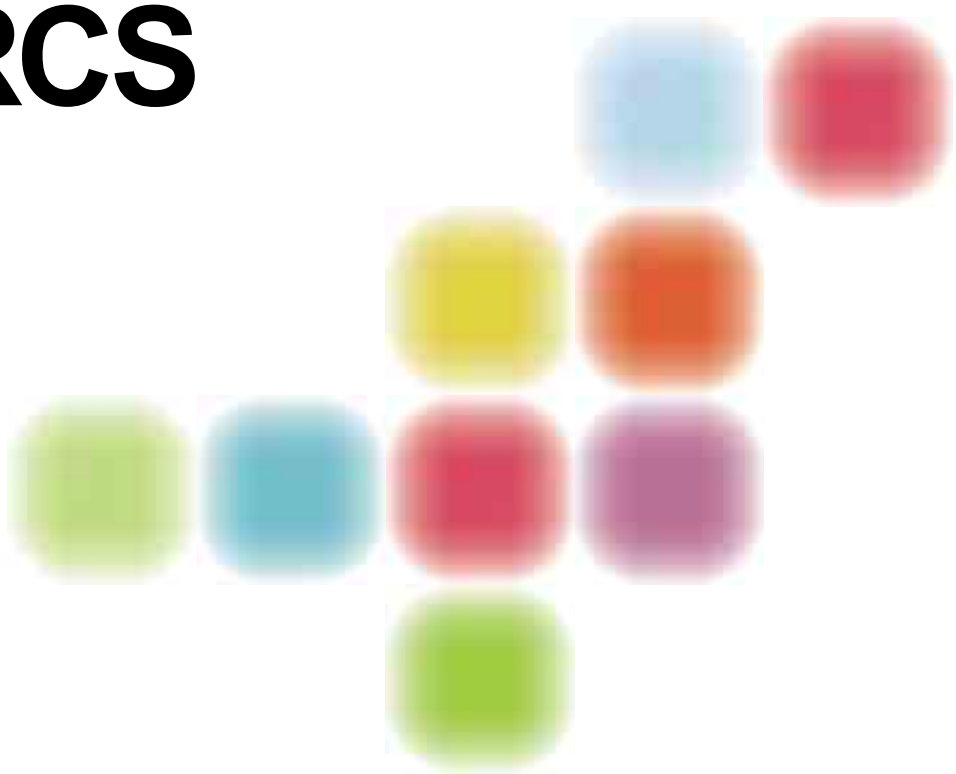
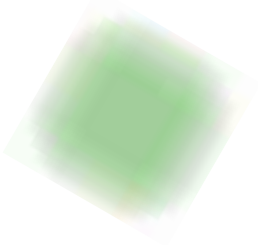
日本赤十字社
Japanese Red Cross Society

Haemovigilance by JRCS 2008





Safety Vigilance Division
Blood Service Headquarters

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I. Outline of safety vigilance

1. Haemovigilance by Japanese Red Cross Society (JRCS)

Human blood and blood components for transfusion and plasma derivatives pose a risk of adverse reactions and infectious diseases.

The safety surveillance of blood through collection, analysis, and evaluation of information of transfusion related adverse reactions and infections include consistent monitoring of donated blood in the entire process of [blood donors] – [preparation and quality control (JRC blood centers)] – [patients (medical institutions)]. It means not only to assess health conditions of donors and eligibility of blood and blood components but also to investigate donor characteristics and environments epidemiologically. Based on the analysis, JRCS evaluates blood safety and, when adverse reactions and infections are expected to increase, cooperates with the government to take appropriate and immediate measures in medical institutions and JRC blood centers to minimize the harm.

Furthermore, we contribute to medical safety with feedback of evaluated data to medical institutions and related organizations. This monitoring system of a series of processes for information collection, analysis, assessment, and taking safety measures is called Haemovigilance.

Figure 1 shows the flow from blood collection (from donors) to transfusion (to patients) and the safety measures. A description of the safety measures etc. are provided below in accordance with the illustrated flow.

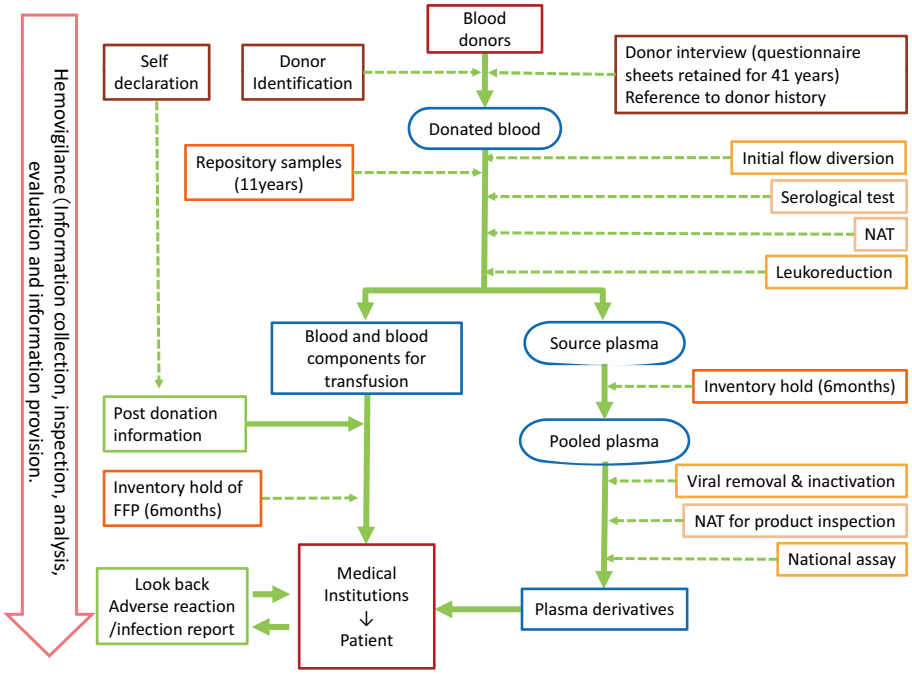


Figure 1. Flow from blood collection (from donors) to transfusion (to patients) and the safety measures

(1) Blood donation (collection)

At first, the potential donor is identified based on his/her ID card etc., then a physician interviews him/her to check that the potential donor conforms with the statutory collection criteria. The interview includes not only items concerning the protection of the health of the donor, but also items to enhance the safety of the blood and blood components, such as a history of administration of drugs that may affect the safety and efficacy of the blood and blood components, history of diseases that may be transmitted through blood, and a history of overseas travel as a countermeasure against imported infections. The physician makes a comprehensive decision about the donor's eligibility for blood collection, considering the interview and the pre-donation tests including blood specific gravity, hemoglobin content, and blood pressure.

It is extremely rare that a particularly serious adverse reaction follows blood collection. On a few occasions, vasovagal reaction (VVR) or other adverse reactions may occur due to anxiety or a mental reaction to the collection. To a donor who suffers a health problem (adverse reaction to collection), first-aid treatment is provided in accordance with the symptoms. Appropriate measures are also taken, such as follow-up concerning the subsequent health

damage status of the donor.

For donors who consulted medical institutions due to nerve damage etc. caused by the drawing of blood, the Relief System for Adverse Effects to Blood Donors has been operating since October 2006, and was enacted as set in the "Guidelines for compensation for adverse effects to blood donors." This relief system enables donors to donate with reassurance, by paying a specified amount of relief considering fairness, transparency and promptness, with appropriate involvement of the national government.

(2) Testing and manufacturing

At JRC blood centers, blood type grouping tests (e.g. ABO, Rh) and infection-related tests are conducted on all donated blood to ensure the safety of the blood. Infection-related tests include serological tests for Treponema pallidum, hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV-1 and HIV-2), human T-lymphotropic virus (HTLV-1) and human parvovirus B19, as well as a liver function test (ALT (GPT)). Nucleic-acid amplification testing ("NAT") for HBV, HCV and HIV was also started in 1999. When NAT was first introduced, it was conducted in a 500 pool, in which 500 blood samples were tested together. The pool size was reduced gradually, and the test has been conducted in a 20 pool since 2004. In 2008, serological testing was switched from the conventional coagulation method to the Chemiluminescence Enzyme Immunoassay (CLEIA) method, which is more sensitive. NAT was also changed to more sensitive apparatuses and reagents, thereby further reducing the risk of transfusion-transmitted infections. Through these safety measures, the incidence of transfusion-transmitted hepatitis, for example, has decreased substantially, as Figure 2 shows.

Nevertheless, any test has its detection limits and a window period (a period immediately after infection, during which the level of the pathogen is too low to be detected). Although the window period can be shortened by progress of the testing method, it is difficult to reduce the incidence of infections to zero.

In addition to measures to prevent viral infection due to transfusion, most of the leukocytes are removed prior to storage to avoid the immunological adverse reactions that are considered to be caused by leukocytes (e.g. febrile reaction). Various safety measures are also taken with the testing and manufacturing processes, such as diversion of the initial blood flow during blood donation, aimed at preventing bacterial infection due to contamination of the bag content by indigenous bacteria on the skin during needling. Combining these measures with lookback studies, which will be detailed later, a continuous commitment is made to reduce the risk of infection and enhance the safety.

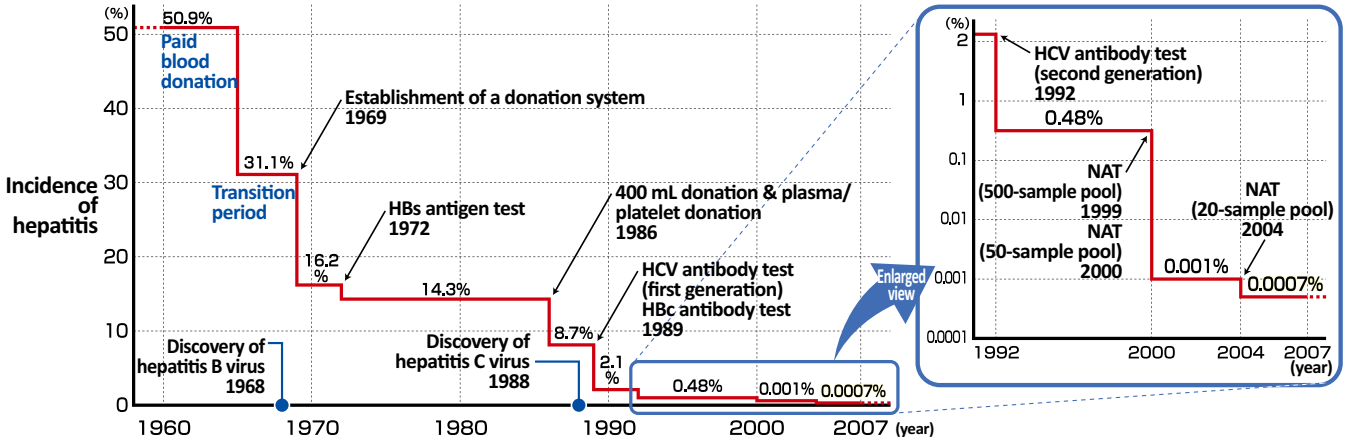


Figure 2. History of transfusion-transmitted hepatitis in Japan

Source: Transfusion Information 0811-116, Japanese Red Cross Society.

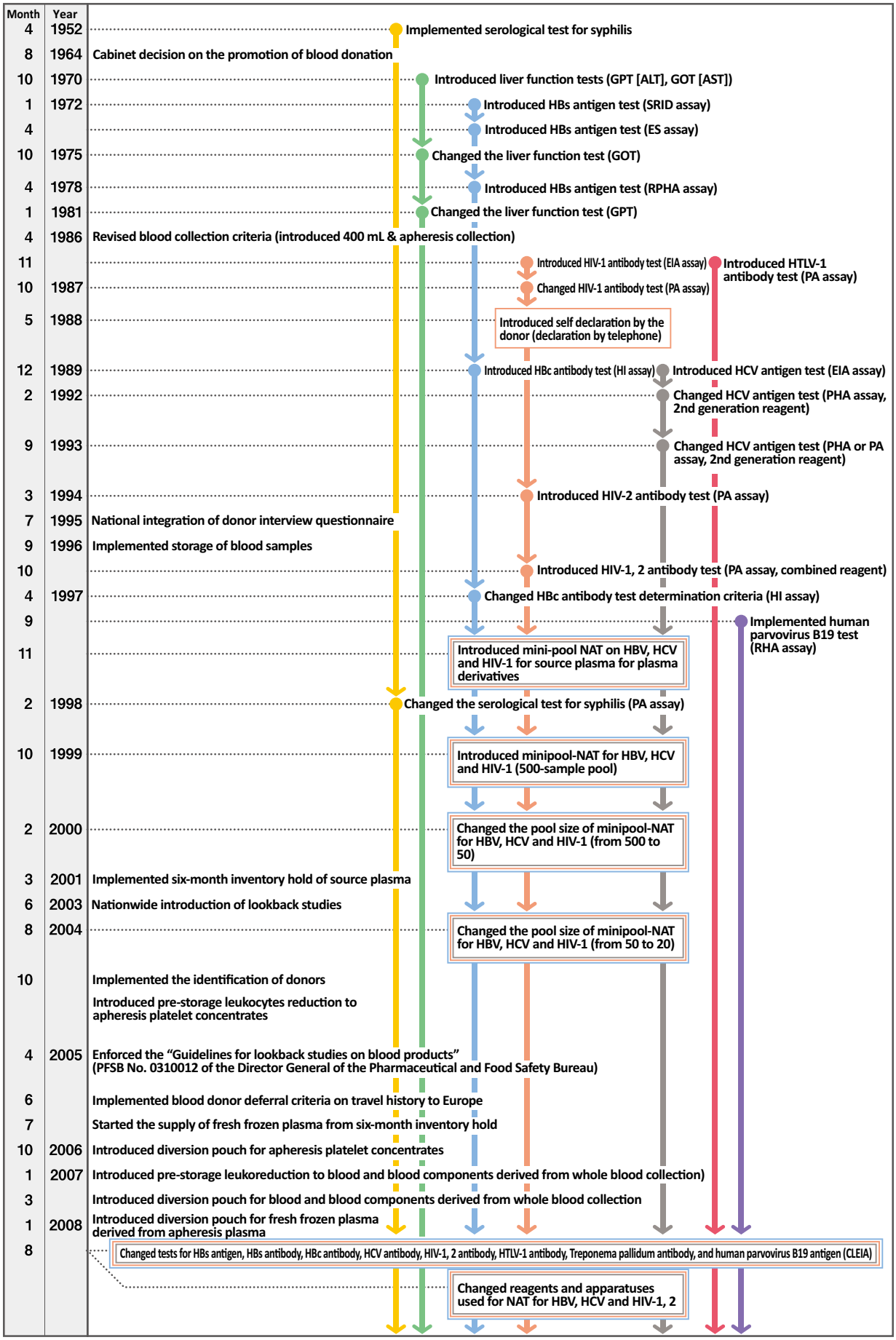


Figure 3. History of safety assurance measures for blood and blood components
Source: Transfusion Information 0811-116, Japanese Red Cross Society.

(3) Information collection and lookback studies on transfusion-related adverse reactions and infections

Japanese Red Cross Society (JRCS) has been collecting information on adverse reactions and infections due to blood and blood components since 1993 and reporting the information to the Minister of Health, Labour and Welfare (MHLW) in accordance with the Pharmaceutical Affairs Law through the Pharmaceuticals and Medical Devices Agency ("PMDA") as one of operations in Haemovigilance. The most important task in Haemovigilance is to improve the system for investigation of causal analysis. The JRCS Blood Service Headquarters, JRC Blood Centers, Central Blood Institute, Plasma Fractionation Center, and Center for NAT and Quarantine cooperate in accordance with their function to collect, analyze, and evaluate the information. Approximately 150 medical representatives (MRs) across the country collect information on adverse reactions etc. and provide information on blood and blood components.

The most remarkable feature of JRCS surveillance system is storing an aliquot of all blood donations for analysis for 11 years ("repository samples") since September 1996. Such specimen storage enables investigation to confirm the causal relationship (imputability) between adverse reactions and/or infections and implicated blood products and/or plasma derivatives as well as further studies of newly emerging adverse reactions and infections.

When a viral infection is suspected, the causal relationship between infection and transfusion can be evaluated by nucleic acid amplification testing (NAT) against hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), human parvovirus (B19), and hepatitis E virus (HEV) using patients' blood and the repository samples. The investigations against other viruses are conducted in collaboration with external testing institutions.

Furthermore, the 6-month inventory hold of source plasma used for the manufacture of plasma derivatives was started in 2001, and 6-month (180-day) inventory hold of fresh frozen plasma for transfusion in 2005. The inventory hold helps to suspend or stop distribution of blood components that were implicated in transfusion- transmitted virus cases. Records on blood donors, collection, testing, preparation and distribution are kept, and these data are under the consolidated management of a nationwide computerized system. The database is utilized for historical reference at the point of donation and for lookback studies etc. Following the notification on lookback studies of the MHLW in 2003, lookback studies have been ensured based on positive information of repeat donors. Subsequently, voluntary guidelines were formulated. Today, a lookback study scheme has been established based on the "Guidelines for lookback studies on blood products," which was enacted later by the national government.

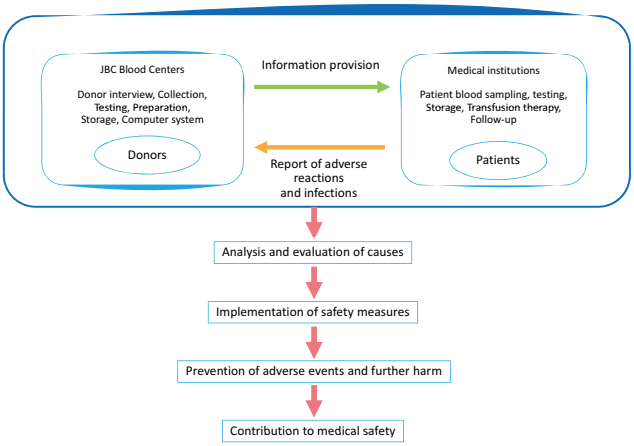


Figure 4. Information provision and safety enhancement

2. Good vigilance practice (GVP) and safety management information

The organization of the JRCS was revised and the Blood Service Headquarters (BSHQ) was established to replace the Blood Service Division in October 2004. BSHQ in the JRCS has been realigned to meet the new licensing requirements for "Marketing authorization holder" following the April 2005 enactment of amendments to the Pharmaceutical Affairs Law. Marketing Supervisor General has been established in the BSHQ, and Safety Management Supervisor has been appointed in the "Safety Supervision Unit" and quality assurance supervisor in the "Quality Assurance Unit" and subordinated under the supervision of the Marketing Supervisor General.

The "Ministerial Ordinance on Standards for Post-marketing Safety Management for Drugs, Quasi-drugs, Cosmetics and Medical Devices; Good Vigilance Practice (GVP)" has been enforced simultaneously with the amendment of the Pharmaceutical Affairs Law. The compliance of GVP is the licensing requirements for the Marketing authorization holder, and we have been performing appropriate operations in accordance with the GVP since April 2005.

The JRCS has conducted the collection and analysis of safety management information necessary for appropriate use of drugs, etc., including quality, efficacy, and safety of products, and has taken the necessary measures based on the results, i.e., safety measures, pursuant to the GVP. The safety management information to collect is as follows:

(1) Information from medical and pharmaceutical professionals
(2) Information from lookback studies
(3) Information associated with the contact from blood donors after blood donation (post-donation information)
(4) Information related to presentation at academic conferences, publication of articles, and other study reports
(5) Information from the Ministry of Health, Labour and Welfare and other governmental agencies, local governments, and

PMDA, etc.

(6) Information from foreign governments and organizations, etc.

(7) Information from other marketing authorization holders, etc.

(8) Information from Quality Assurance Manager and other divisions, etc.

The safety management tasks include the report of transfusion related adverse reactions and infections of patients who received transfusion from medical institutions. The Pharmaceutical Affairs Law requires reporting of severe cases to the Minister of Health, Labour and Welfare through the Pharmaceuticals and Medical Devices Agency. Transfusion related adverse reactions include hemolytic and non-hemolytic adverse reactions [fever, urticaria, anaphylactic shock, and transfusion-related acute lung injury (TRALI)] and the transfusion transmitted infections include suspected HBV, HCV, and bacterial infections.

In case a blood donor whose blood sample is found to be positive for an infection by JRC Blood Center has a previous record of donation, lookback studies enable the withdrawal of a blood component for transfusion that had been made from the previous donation and was already distributed to medical institutions, as necessary, if such a blood component was not transfused yet. If it was already transfused, the medical institution is requested to test the patient to help with the early detection and treatment of transfusion-related infections.

To conduct lookback studies and investigations on post-transfusion infections, furthermore, to verify the safety of blood for transfusion, it is important to keep frozen repository samples for a period of 11 years.

We collect information on actions and research papers concerning blood and blood products in other countries as the obligation of a marketing authorization holder of drugs and the latest domestic and foreign research papers on infections due to products and source materials as a marketing authorization holder of biological products.

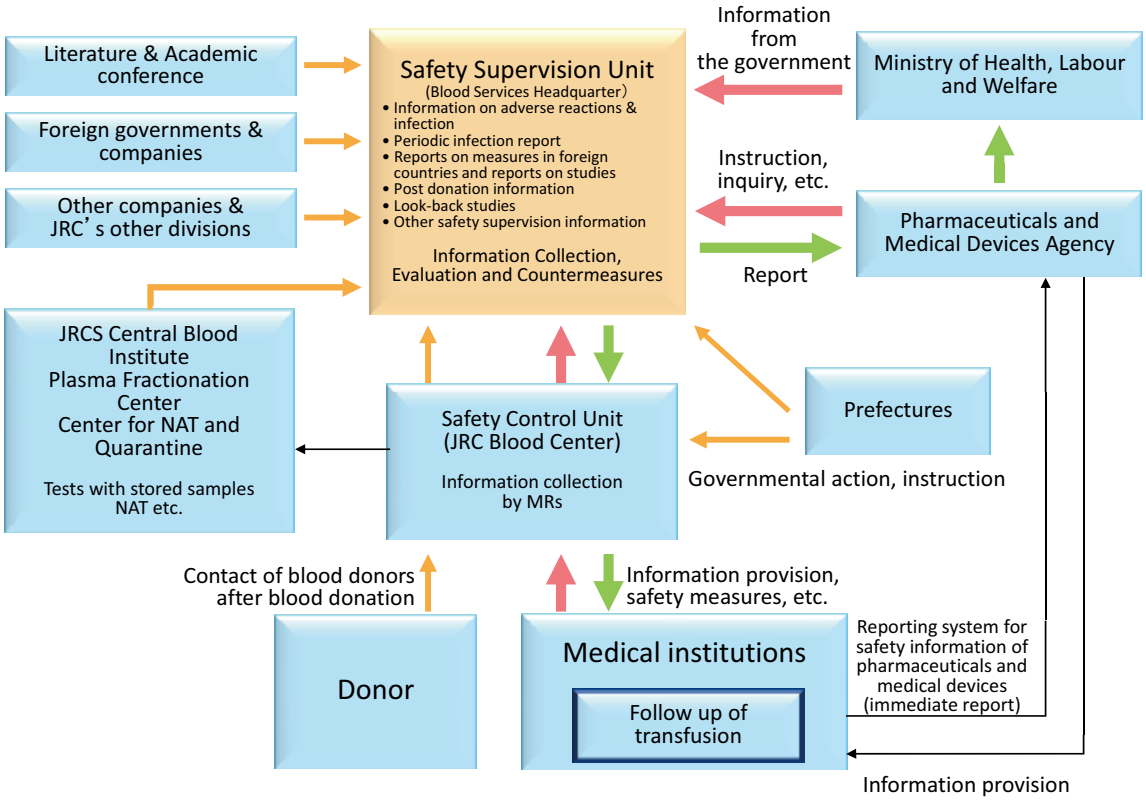


Figure 5. Flowchart of information collection and report (submission)

II. Summary of 2008 activity

Voluntary reports of adverse reactions and infections

A total of 1,727 possible cases of adverse reactions and infectious diseases related to transfusion were reported from medical institutions (which is 95.20% compared to the previous year, 1,814 cases in 2007). 1,544 cases were classified into non-hemolytic adverse reactions, 149 suspected transfusion-transmitted infections, 22 hemolytic adverse reactions, 5 suspected transfusion associated-graft versus host disease (TA-GVHD; no case was confirmed by microsatellite DNA analysis), and 7 adverse reactions caused by plasma derivatives (JRC products). Some cases were grouped into several categories.

A detail breakdown of 149 reported cases of suspected infection by pathogen was HBV in 61, HCV in 38, bacteria in 46, HEV in 2, HIV in 1, CMV in 1. Of these cases, the viral genome was detected in the repository samples of the implicated donor in four HBV cases and the bacterial culture of the relevant bags turned out to be positive in two bacteria cases, suggesting that those cases were likely caused by transfusion.

In this annual report, a new section of literature and academic conference information was added. Six reports on overseas cases were listed in this section, and comprised five transfusion-transmitted infections and one TRALI (adverse reaction of human immunoglobulin product for IV injection).

Reports on measures in foreign countries and reports on studies

Three reports on the measures in foreign countries related to the introduction of pathogen reduction technology in the US, the examination of NAT for parvovirus B19, and the impact of human immunoglobulin product for IV injection containing maltose on blood sugar measurement; and 1 report on studies were submitted to the PMDA.

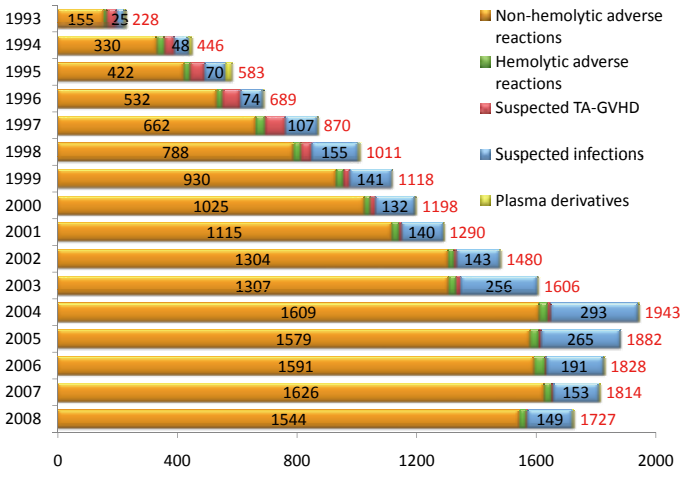


Figure 6. Changes in reported adverse reactions and infections

Periodic infection reports for biologic products

A total of 37,335 pieces of literature were reviewed by experts, and 83 of them were reported to the PMDA. In 2008, some tick-borne infections were identified, and the case report of fatal babesiosis and the spread of rickettsia etc. were submitted to the PMDA.

Post-donation information

A total of 2,709 pieces of post-donation information were reported by blood centers nationwide, and included 13 reports on self-reported AIDS information, 47 reports on donors' health condition, 2,368 reports on post-donation information on ineligible donors at the interview, and 281 reports on other safety information. Especially, 1,812 of the reports on post-donation information on ineligible donors at the interview, which is approximately 76% of the total, were due to travel to Europe (a stay of at least 1 day in the UK, etc.). Measures taken were as follows: 29 blood components were withdrawn before they were transfused, 259 fresh frozen plasma were discarded from the inventory hold, and, concerning 131 blood components that had already been transfused, information was provided to medical institutions. A total of 1,071 bags of source plasma were removed before shipment to manufacturing sites or from the inventory hold and 3,384 had already been delivered to client manufacturers etc.

Lookback studies

A total of 5,219 repeat donors had a positive conversion. NAT was performed in case of suspected virus and 103 samples were found to be HBV positive, of which 94 had already been transfused and 5 were discarded. It was identified through investigation at the medical institutions that 3 patients treated with the relevant product had an HBV-positive conversion, 30 showed no changes in viral marker tests, and 42 died from the primary disease, etc.

Table 1. Annual supplies of blood and blood components for transfusion and plasma derivatives in 2008

(Blood components)		(bag)
Platelet concentrates	**727,972**	
Fresh frozen plasma	**931,009**	
Red cell concentrates	**3,219,476**	
Red cell concentrates (washed, frozen-thawed or blood for exchange transfusion)	**24,460**	
Fresh frozen plasma*	**-1**	
Whole blood	**733**	
Total	**4,903,649**	
(Plasma derivatives)		**(Vial)**
Human serum albumin	**494,844**	
Anti-HBs human immunoglobulin	**1,044**	
Human blood coagulation factor VIII concentrate	**100,226**	
pH4-treated acidic human immunoglobulin	**65,605**	
Total	**661,719**	

* Returned in-date product due to un-leukoreduced component which was prepared prior to the introduction of leukoreduction procedure.

III. Reports on adverse reactions and infections

1. Blood and blood components for transfusion—voluntary reporting by medical institutions

(1) Non-hemolytic adverse reactions

1) The number of reports of non-hemolytic adverse reactions by symptom

In 2008, 1,544 cases of non-hemolytic adverse reactions were reported and accounted for 89.4% of the total 1,727 cases of transfusion-related adverse reactions and infectious diseases. The patients were 824 males and 719 females (1 unknown). The age range was wide, namely, from 0 to 95, with a mean of 66.

Figure 7 shows breakdown by symptoms. Urticaria, eruption, nausea, etc., (hereinafter, "urticaria, etc.") were the most frequently reported adverse reactions, namely, 535 cases, accounting for 34.7% of all cases, followed by fever (157 cases, 10.2%). These two adverse reactions accounted for 44.9% of all cases. Anaphylactic reactions including severe cases were found in 152 (9.8%), anaphylactic reactions with hypotension, i.e., anaphylactic shock in 269 (17.4%), and dyspnea and hypotension in 192 (12.4%) and 57 (3.7%), respectively. Cases of transfusion-related acute lung injury (TRALI) were 32 (2.1%). In addition to the above 7 categories, there were 150 cases (9.7%) of other adverse reactions, and included 23 neuropsychiatric symptoms that comprised consciousness disturbed: 4; movement disorder: 3; sensory function disorder: 1; convulsions: 5; malaise: 6; behavior disorder: 1; restlessness: 1; encephalopathy: 1; and cerebral hemorrhage: 1.

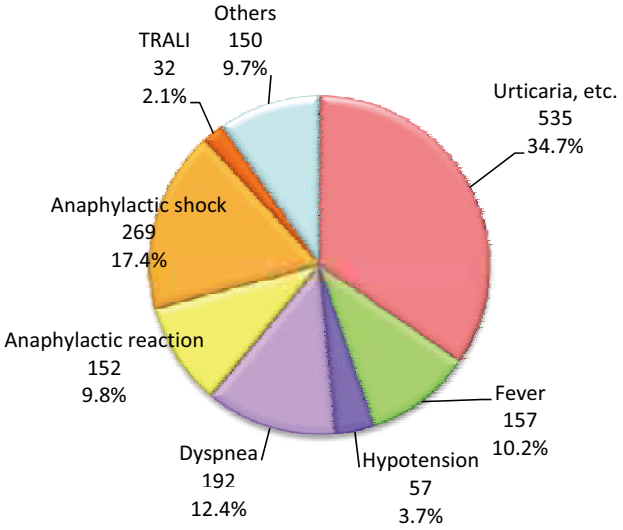


Figure 7. Breakdown of 1,544 cases of non-hemolytic adverse reactions by symptom

2) Changes in the number of severe cases

Among the cases reported to JRCS, 692 were evaluated to be severe adverse reactions, and were reported individually to the PMDA based on the Pharmaceutical Affairs Law. These accounted for 44.8% of all cases, and both the number and percentage of severe cases had increased from the previous year.

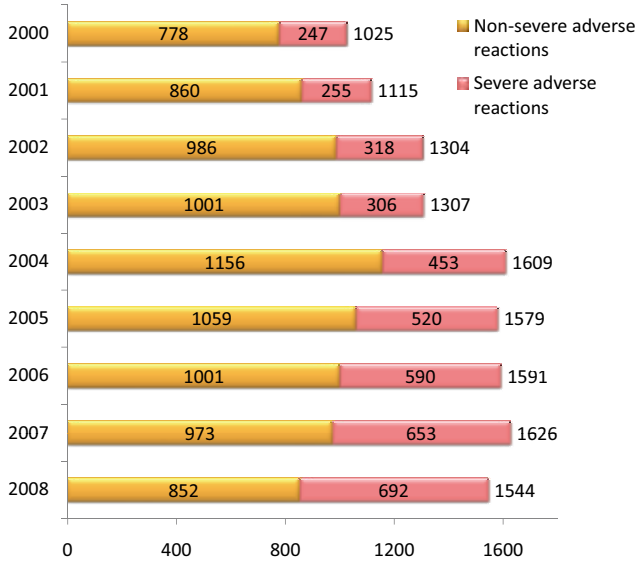


Figure 8. Changes in the number of severe cases

The breakdown by symptom was 254 cases (36.7%) of anaphylactic shock; 146 (21.1%) of dyspnea; 90 (13.0%) of anaphylactic reactions; 48 (6.9%) of hypotension; 32 (4.6%) of TRALI; 19 (2.7%) of fever; 14 (2.0%) of urticaria, etc.; and 89 (12.9%) of others.

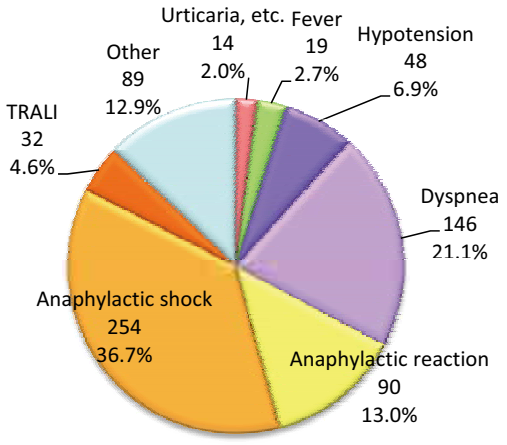


Figure 9. Breakdown of 692 severe cases by symptom

3) Blood components implicated in patients developing adverse reactions

The percentage of blood components used in patients developing adverse reactions by products are shown in Figure 10.

The number of reported cases of platelet concentrates (PC) used in patients developing adverse reactions was 621 (40.2%), followed by red cell concentrates (RBC) of 546 (35.4%) and fresh frozen plasma (FFP) of 233 (15.1%). Three (0.2%) cases of washed red cells (WRC) were reported, despite WRC is used to prevent adverse reactions caused by plasma.

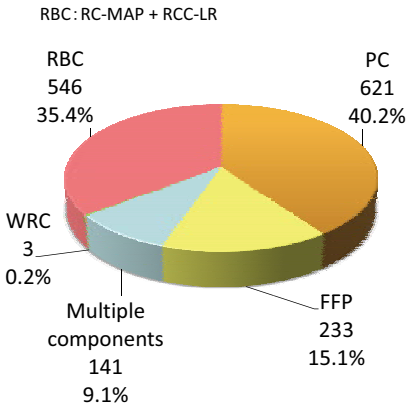


Figure 10. Percentage of blood components used in cases of reported adverse reactions by product type

4) Symptoms of adverse reactions and blood components

The percentage of symptoms of adverse reactions by blood components is shown in Figure 11.

In PC and FFP, respectively, the percentage of urticaria, etc., was the highest (39.6% and 50.2%), followed by anaphylactic shock (18.2% and 22.7%) and anaphylactic reactions (16.1% and 9.4%). On the other hand, the highest was urticaria, etc., (22.9%) in RBC, followed by fever (18.1%) and dyspnea (17.9%).

Subsequently, the percentage of blood components by the symptoms of adverse reactions is shown in Figure 12.

For the components implicated to anaphylactic reactions, urticaria, etc. and anaphylactic shock, PC was the leading product

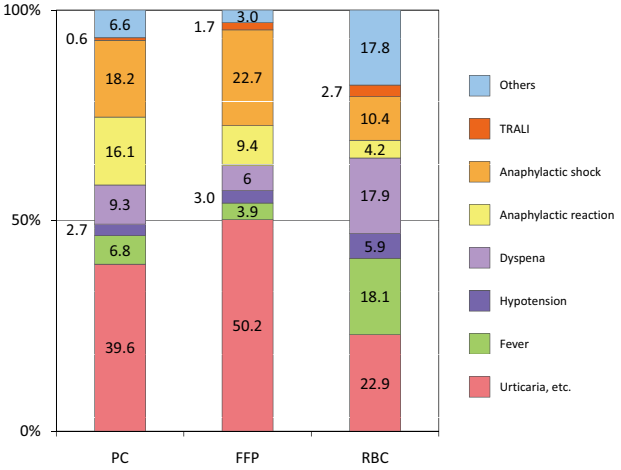


Figure 11. Percentage of symptom of adverse reactions by blood components

Figure 12. Percentage of blood components by symptom of adverse reactions

and accounted for 65.8%, 46.0%, and 42.0%, respectively, and PC and FFP accounted for 80.3%, 67.9%, and 61.7%, respectively, of the total cases. In contrast, RBC was the leading component implicated to fever and hypotension and accounted for 63.1% and 56.1%, respectively.

5) Incidences of reported adverse reactions

The number of distributed components, reported adverse reactions and the incidence are summarized in Table 2. The incidence of adverse reaction reports for FFP and RBC was one in 3,996 and 5,826 distributed bags, respectively, whereas that for PC was one in 1,172, which was extremely high.

Table 2. Number of supplied blood components and reports on adverse reactions

Blood Components	Number of components (Bag)	Number of reports of adverse reactions (Case)	Incidence of report of adverse reactions
Platelet	727,972	621	1/1,172
Plasma	931,009	233	1/3,996
Red cell	3,219,476	546	1/5,896

Platelet: PC, PC-HLA / Plasma: FFP / Red cell: RCC-LR

Subsequently, the incidences of reports of adverse reactions per 10,000 products distributed by symptom by product are shown in Table 3. The incidences of reported urticaria, etc., anaphylactic reactions and anaphylactic shock were remarkably high in PC. The incidences of reported dyspnea, fever, and hypotension were also similar or higher in PC than those in RBC. However, the incidences of reported TRALI in RBC and PC were not different from each other.

Table 3. Incidence of symptoms of adverse reactions per 10,000 blood components distributed

	Platelets	Plasma	Red cells
Urticaria, etc.	3.38	1.26	0.39
Fever	0.58	0.10	0.31
Anaphylactic reaction	1.37	0.24	0.07
Anaphylactic shock	1.55	0.57	0.18
Hypotension	0.23	0.08	0.10
Dyspnea	0.80	0.15	0.30
TRALI	0.05	0.04	0.05
Other adverse reactions	0.56	0.08	0.30
Total	8.5	2.5	1.7

6) Time to onset of symptoms of adverse reactions

The time to onset of symptoms of adverse reactions from the beginning of transfusion is shown in Figure 13. The reported adverse reactions with unknown time to onset are excluded herein.

Hypotension had the earliest time to onset and was observed within 10 minutes after the beginning of transfusion in 40.4% of the cases and within 30 minutes in 75.5%. Anaphylactic reactions and shock were observed within 30 minutes in 43.1% and 54.7% of the cases, respectively. In contrast, urticaria, etc., dyspnea, and fever developed within 30 minutes or more in most cases. TRALI frequently developed between 60 and 180 minutes from the beginning of transfusion; however, it was still observed more than 300 minutes after in 23.4% of the cases.

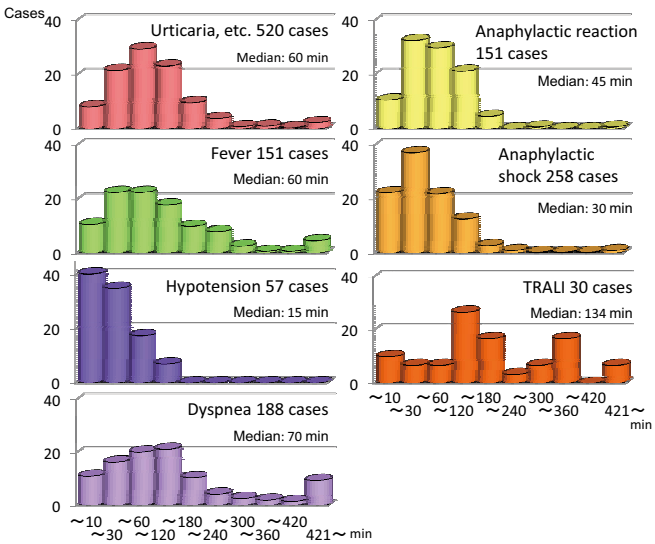


Figure 13. Time to onset of adverse reactions

7) Patient's history of transfusions and adverse reactions

The history of transfusion and adverse reactions in patients developing adverse reactions is shown in Figure 14.

The patients with transfusion history accounted for 79.4% of the patients developing adverse reactions (excluding patients with unknown transfusion history). Of them, the patients without history of adverse reactions accounted for 70.6%, while those with history were 29.4%.

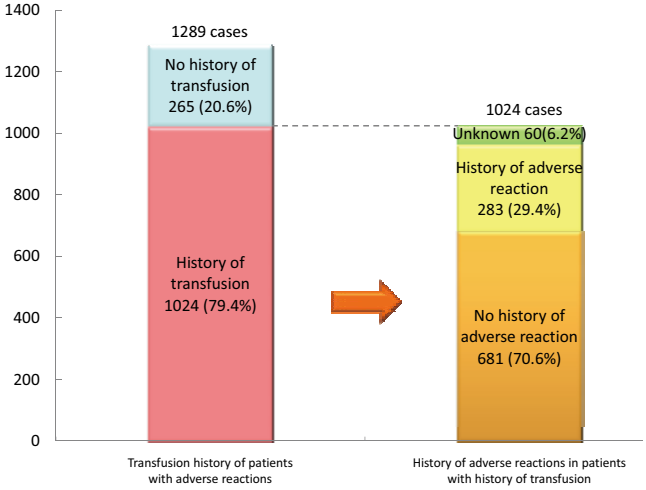


Figure 14. History of transfusions and adverse reactions of patients developing adverse reactions

8) Transfusion Related Acute Lung Injury (TRALI)

i Cases of TRALI

Cases of dyspnea with pulmonary edema were evaluated based on the diagnostic criteria in Table 4. Figure 15 shows changes in the number of cases determined as TRALI or possible TRALI (p-TRALI) through this evaluation. In 2008, a total of 139 cases were evaluated, and 16 were determined to be TRALI (including 1 fatal case) and 16 to be p-TRALI (including 1 fatal case).

The number of TRALI and p-TRALI cases by the type of blood components is summarized in Table 5. The RBC-implicated TRALI and p-TRALI were 15 cases (24 including multiple components transfusion cases) and accounted for 46.9% of the total cases. The cases by PC and FFP were 4 (11) and 4 (9) and accounted for 12.5% and 12.5%, respectively.

Table 4. Diagnostic criteria for TRALI and p-TRALI

TRALI criteria	Possible TRALI criteria
a. ALI (acute lung injury) i. Acute onset ii. Hypoxemia $PaO_2/FiO_2 \leq 300$ mmHg 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	a. ALI (acute lung injury) i. Acute onset ii. Hypoxemia $PaO_2/FiO_2 \leq 300$ mmHg 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. A clear temporal relationship to an alternative risk factor for ALI

Reference: Kleinman S, et al. Transfusion.2004, 44, 1774-1789.

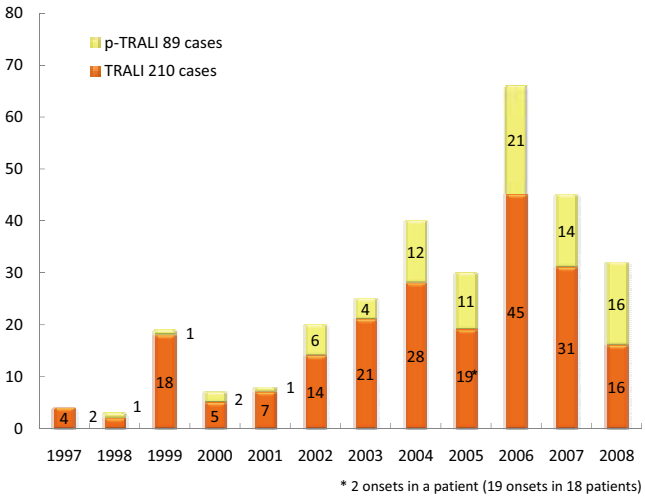


Figure 15. Changes in the number of TRALI cases

Table 5. Number of TRALI and p-TRALI cases by implicated blood components

	TRALI	p-TRALI	Total
RBC	8	7	15
FFP	2	2	4
PC	2	2	4
RBC+PC	2	2	4
RBC+FFP	0	2	2
PC+FFP	0	0	0
RBC+PC+FFP	2	1	3
Total	16	16	32

ii Patient background

The patients developing TRALI were 12 males and 4 females; 16 in total. The patients developing p-TRALI were 7 males and 9 females; 16 in total. The age of patients with TRALI and p-TRALI widely ranged from 18 to 91 and 30 to 85 years, respectively.

Table 6. Patient background (32 cases)

	TRALI	p-TRALI
Male-Female ratio	M 12:F 4	M 7:F 9
Age	18 to 91 yrs	30 to 85 yrs
Median age	68 yrs	72 yrs
	68.5 yrs	

iii Anti-leukocyte antibody (HLA antibody, anti-granulocyte antibody)

Table 7. shows the positive rate of anti-leukocyte antibody of patients and blood components involved in TRALI/p-TRALI cases.

Anti-leukocyte antibody was positive in 8 of the 28 patients

with TRALI/p-TRALI, who were included in the investigation, and the positive rate was 28.6%. The positive rate of anti-leukocyte antibodies in patients who developed other transfusion-related adverse reactions was 38.8%, which was higher than that of patients with TRALI/p-TRALI. Anti-leukocyte antibody was positive in 15 blood components, and the positive rate was 46.9%. The positive rate of anti-leukocyte antibodies in other transfusion-related adverse reactions was 17.1% so the rate in TRALI/p-TRALI cases was relatively higher.

Table 8 shows the breakdown of anti-leukocyte antibody-positive donors involved in TRALI/p-TRALI cases.

A total of 17 donors (15 cases) were antibody-positive, and included 12 females and 5 males. Females accounted for 70.6%. In September 2004, an interim safety measure against TRALI/p-TRALI started, which was to stop the delivery of blood components in stock and source plasma that were made of the same donated TRALI-implicated leukocyte antibody-positive components, and to temporarily suspend the use of subsequent donated blood from the relevant donor for blood components for transfusion or for source plasma.

Table 7. Positive cases of anti-leukocyte antibody in TRALI/p-TRALI cases

	Patient's blood (n = 28)	Blood components (n = 32)
TRALI case	5	9
p-TRALI case	3	6
Positive ratio in TRALI/p-TRALI	28.6% (8/28)	46.9% (15/32)
Positive ratio in other transfusion related adverse reaction	38.8% (80/206)	17.1% (12/70)

Table 8. Breakdown of anti-leukocyte antibody-positive donors

	Female	Male
Positive cases	12	5
Percentage	70.6%	29.4%
Total	17	

(2) Hemolytic adverse reactions

Throughout 2008, a total of 22 cases of hemolytic adverse reactions were reported, and consisted of 12 immediate reactions that developed within 24 hours after the beginning of transfusion, and 10 were delayed reactions that developed more than 24 hours later. Of the cases reported to JRCS, 13 were evaluated to be severe adverse reactions, and were reported to the PMDA based on the Pharmaceutical Affairs Law. This accounted for 59% of all cases.

In almost all of these cases, red blood cells (RBC) were considered as the causal blood component for transfusion, except in one case that was considered to be caused by ABO-incompatible platelet concentrate (PC) transfusion during emergency surgery. As for the profiles of patients with adverse reactions, there were equal for male and female (both 11), of whom 2 were in their 40s, 6 in their 50s, 9 in their 70s, 4 in their 80s and 1 in the 90s. Patients with a previous transfusion history stood at 14 (64%).

Of the 2 incompatible cases of ABO in Table 9, Case 1 occurred when red blood cells of blood type AB, which was intended for another patient, was administered to a patient in the same room (blood type O) by error. In Case 2, ABO-incompatible platelet transfusion was conducted during emergency surgery. Although hemolysis due to anti-A or anti-B antibodies contained in platelet concentrate cannot be denied, the reporting physician concludes that the hemolysis was probably caused by the extracorporeal circulation.

Of hemolytic adverse reaction cases reported to JRCS, the implication of adverse reactions could not be denied for 2 fatalities. However, the patients had dyspnea in addition to hemolysis, and serological hemolysis was not considered a direct cause for death. Since adverse reaction reporting by medical institutions is voluntary, it does not represent the actual number of hemolytic adverse reactions that occur.

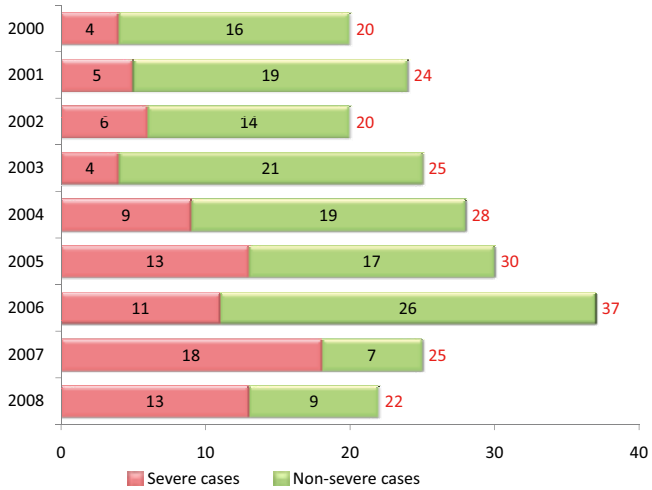


Figure 16. Changes in reported cases of hemolytic adverse reactions

Table 9. Cases in which antibody was detected in the patient's blood, suggesting a probable causal relationship with transfusion

		Suspected component	Type	Symptoms	Antibody in patient's serum or blood type	Antigen in blood component for transfusion or blood type	Irregular antibody test before transfusion	History of transfusion
ABO incompatibility	1	RBC	Immediate	Hemolysis	O	AB		Yes
	2	PC	Immediate	Hemolysis	A	2 type-B bags and 2 type-O bags		Unknown (not shown)
Other irregular antibodies	3	RBC	Delayed	Fever and hemolysis	Anti-E, anti-c and anti-Jk^a	5 RBC bags included E(+), c(+) and Jk(a+)	Negative	Unknown
	4	RBC	Delayed	Hematuria	Anti-E	E+	Unknown (not shown)	Yes
	5	RBC	Delayed	Hemolysis	Anti-C and anti-e	C+, e+	Negative	Yes
	6	RBC	Immediate	Fever and increase in blood LDH	Anti-M	M+	Positive (anti-M)	Yes

(3) Transfusion Associated-Graft Versus Host Disease (TA-GVHD)

1) Causes and prevention of TA-GVHD

TA-GVHD is a severe adverse reaction caused by the donor's lymphocytes contained in blood components for transfusion, attacking and damaging the tissues of the patient's body. Once TA-GVHD occurs, almost all cases result in death. In typical TA-GVHD, fever and erythema appear one or two weeks after transfusion, followed by liver failure, diarrhea, melena and other symptoms. Eventually, the patient suffers bone marrow hypoplasia and pancytopenia, as well as multiple organ failure, and almost all the cases progress to death within one month after the transfusion.

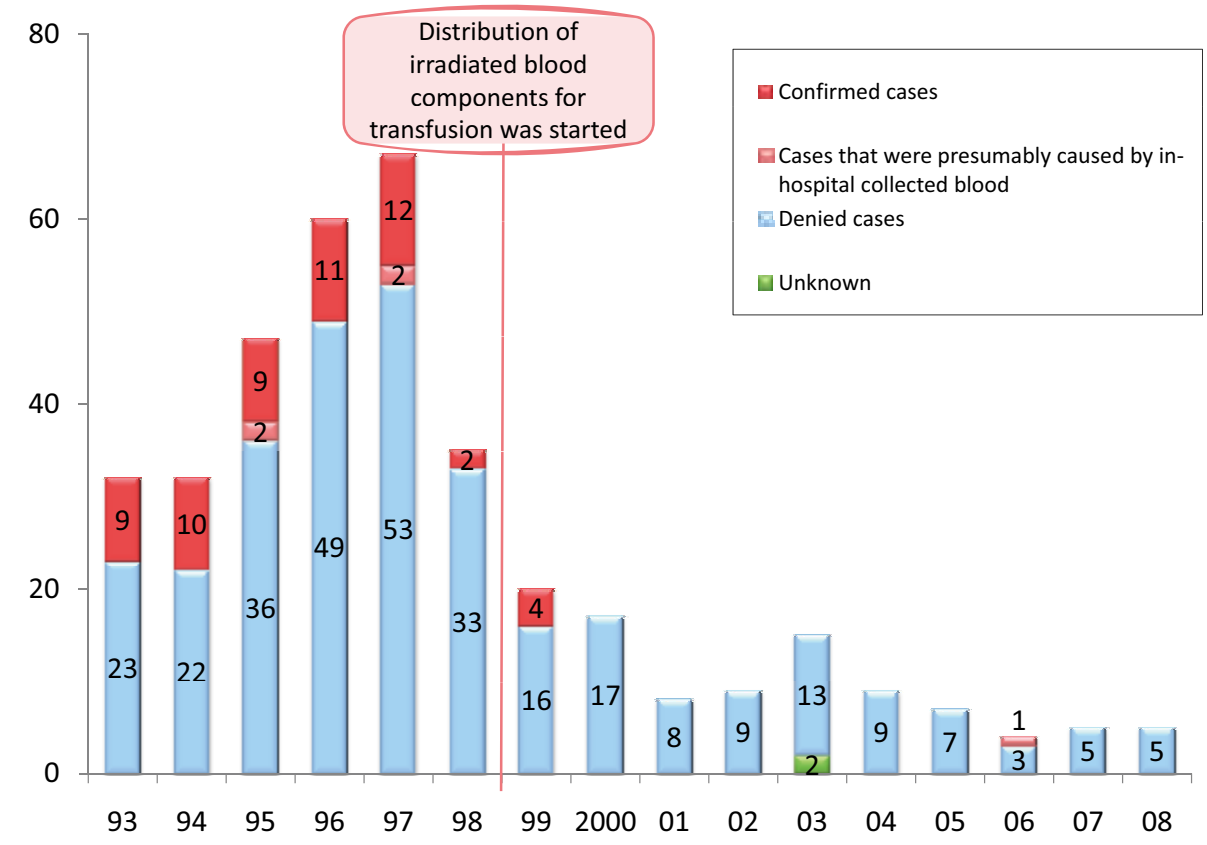
Since no effective treatment has been established, prevention is the only possible solution. The most effective prevention is to irradiate all blood components for transfusion, except plasma components*. JRCS irradiated blood components for transfusion as technological cooperation. In 1998, irradiated blood and blood components for transfusion were approved, and JRCS started their distribution.

* FFP contains few lymphocytes, and there have been no reports of TA-GVHD to date.

2) Voluntary reporting and causal investigation

Figure 17 shows changes in suspected TA-GVHD cases reported by medical institutions, and the results of analysis. For cases suspected of TA-GVHD based on clinical symptoms and general laboratory findings, that have been reported to JRCS, micro-satellite DNA analysis has been conducted using lymphocytes from the patient's pre-transfusion peripheral blood (or the patient's nails or hair), lymphocytes from the patient's peripheral blood of post-transfusion, and leukocytes from the repository samples of implicated donors, thereby confirming the chimerism of the patient's peripheral blood and investigating the causal blood. Although there have been more than 10 confirmed cases annually until 1997, the number of reports decreased substantially since 1998, when the distribution of irradiated blood was started. No TA-GVHD cases caused by blood components for transfusion supplied by JRCS have been confirmed since 2000.

In 2008, a total of 5 suspected cases of TA-GVHD were reported, but none were confirmed as TA-GVHD after the confirmation test (detection of chimerism by micro satellite DNA analysis).



* As for the 2 "unknown" cases, clinical symptoms of GVHD were observed, though a relationship with the blood from JRCS was denied, and the use of BMT or in-hospital collected blood was verified.

Figure 17. Suspected TA-GVHD cases reported by medical institutions, and the results of analysis

(4) Transfusion transmitted infections

In 2008, a total of 149 suspected cases of transfusion transmitted infections (TTI) were reported to JRCS by medical institutions nationwide. A detailed breakdown of the reported cases of TTI by pathogen was 61 cases of HBV, 38 cases of HCV, 46 cases of bacteria, 2 cases of HEV, 1 case of HIV, and 1 case of CMV.

1) Testing items and evaluation criteria for imputability

i Further testing for suspected cases of TTI

In case of suspected viral infection, the test for the relevant viral genome (individual NAT) is conducted. As the donor's specimen, repository samples of the blood components for transfusion are mainly used. If the recipient's (patient's) specimen is provided by the medical institution, the test for the relevant viral genome (individual NAT) is conducted on the recipient's pre- and post-transfusion specimens. Furthermore, if the viral genomes are detected both in the donor's and the patient's specimens, the viral genome sequences are compared to evaluate homology. (See Table 10.)

In case of suspected bacterial infection, the bacterial culture test using the residual blood in the relevant bag of blood components transfused, or the sterility test of components that were simultaneously manufactured, is conducted. If bacteria are detected in these tests, the patient's bacterial strain is obtained from the medical institution and genotype-specific tests are conducted to evaluate homology.

Table 10. Region of genomic sequence comparison for pathogens

HBV-DNA	1,550 bp (1,556 bp*) (nt 2,333-3,215 (3,221*) / 1-667) in the first part of P region, including pre-S/S region * In case of Genotype A
HCV-RNA	196 bp (nt 508-703) in the core region; 1,279 bp in the core-E1-E2 region, including the hypervariable region (HVR)

ii Evaluation of imputability

- Viral infection

Table 11. Evaluation of imputability (viral infection)

Probable	Unknown	Unlikely	Denied
Donor's specimen: ID-NAT Positive*	Donor's specimen: Unable to test	Donor's specimen: ID-NAT Negative	Patient's specimen: - Infected before transfusion - Uninfected after transfusion

* Cases of incompatibility between the viral homology tests are evaluated as unlikely related.

- Bacteria infection

Table 12. Evaluation of imputability (bacterial infection)

Probable	Unknown	Unlikely
Donor's specimen: Blood Culture Positive*	Donor's specimen (simultaneously manufactured FFP): sterility test Negative	Donor's specimen (relevant bag): Blood Culture Negative

* Cases with bacterial species that differ between the donor's specimen and the patient's specimen are evaluated as "unlikely related."

2) Evaluation results by pathogen

i HBV

There were 61 suspected cases of transfusion-transmitted HBV infection reported by medical institutions. There were 788 bags of suspected blood components in total, comprising 374 bags of red blood cells (RBC), 250 bags of fresh frozen plasma(FFP), and 164 bags of platelet concentrate (PC). On average, 12.9 bags of suspected products were used per case (6.1bags of RBC, 4.1 bags of FFP and 2.7 bags of PC). The individual HBV-NAT was conducted using repository samples of the relevant products, and 4 samples (4 cases) of the 788 suspected products turned out to be HBV-DNA positive, and the other 784 bags (57 cases) were negative.

Concerning the 4 positive cases, homology was confirmed between the HB virus from the donor and that from the patient, and the causal relationship was evaluated to be "probable." An overview of these 4 cases is shown in Table 13.

Table 13. HBV cases evaluated to have a "probable" imputability with transfusion

No.	Primary disease	Blood components◇ (Collection date)	Age/Sex		Pre transfusion			Post transfusion◇◇			ALT		Patient's specimen
					Test item	Result	Period to transfusion	Test item	Result	Period after transfusion	Max (IU/L)	Period after transfusion	Pre transfusion
1*	Internal carotid artery stenosis	RCC-LR (2008.1)	60s	F	HBsAg/HBsAb HBcAb	Negative	0 day	HBV DNA	Positive	13 weeks	7700	13 weeks	Yes
2	Sigmoid colon cancer	RCC-LR (2008.6)	60s	F	HBsAg/HBsAb HBcAb	Negative	0 day	HBsAg	Positive	13 weeks	5362	13 weeks	No
3	Acute leukemia	Ir-RCC-LR (2008.3)	40s	M	HBV-DNA/ HBsAg/HBsAb HBcAb	Negative	11 days	HBsAg	Positive	25 weeks	186	25 weeks	Yes
4**	Acute myelogenous leukemia	Ir-PC (2008.5)	<10	F	HBsAg	Negative	16 days	HBsAg	Positive	10 weeks	131	18 weeks	No

* Case 1 died of fulminant hepatitis.
** Case 4 was derived from post-donation information.
◇Types of blood components transfused in which viral nucleic acid was detected in the repository samples, etc.
◇◇ Test results at medical institutions (date of positive results confirmed)

Concerning the 57 negative cases, a causal relationship was denied for 12 cases. In 7 of these cases, the patients were assumed to have been HBV carriers because genetic testing of pre-transfusion specimens gave positive results. In the other 5 cases, the positive results of post-transfusion testing at medical institutions were presumed to be non-specific, and infection by HB virus was improbable. Considering the window period, in 15 cases all the implicated donors had subsequent donation with a negative infection test, therefore the imputability of these cases was evaluated as extremely unlikely. In another 30 cases, their imputability was evaluated as unlikely because some of the relevant donors didn't have subsequent donation.

ii HCV

There were 38 suspected cases of transfusion-transmitted HCV infection reported by medical institutions. There were 417 bags of suspected blood components in total, comprising 223 bags of RBC, 95 bags of FFP, and 99 bags of PC. On average, 11.0 bags of suspected products were used per case (5.9 bags of RBC, 2.5 bags of FFP and 2.6 bags of PC). The individual HCV-NAT was conducted using repository samples of the relevant products, and all 417 of the suspected products were negative.

Concerning these 38 cases, imputability with blood components was denied in 9 cases, including 6 patients who were assumed to have been HCV carriers because genetic tests of pre-transfusion specimens were positive, as well as 3 cases in whom the positive results of post-transfusion tests at medical institutions were considered to be non-specific. Considering the window period, in 2 cases all the implicated donors had subsequent donation with a negative infection test, therefore the imputability of these cases was evaluated as extremely unlikely. In another 27 cases, their imputability was evaluated as unlikely because some of the relevant donors didn't have subsequent donations.

iii Bacterial infection

There were 46 suspected cases of transfusion-related bacterial infection reported by medical institutions. There were 65 bags of suspected blood components in total, comprising 40 bags of RBC, 4 bags of FFP, and 21 bags of PC. According to the bacterial culture test using the relevant bag of the blood components, or the sterility test on the FFP that was simultaneously manufactured, 2 of the 65 bags turned out to be positive (2 cases), and the other 63 bags (44 cases) were negative.

The 2 positive bags (cases) were both platelet concentrate on the fourth day after collection. *Staphylococcus aureus* and *Streptococcus dysgalactiae* ssp. *equisimilis*, respectively, were detected in these two bags, and homology with the patient's bacterial strain was confirmed for both by the genotype test. An overview of these two cases is shown in Table 14.

Concerning the 44 cases that turned out to be negative, the bacterial culture test using the residual blood of the relevant bag was conducted in 33 cases, and the imputability was evaluated to be unlikely. In the other 11 cases, in which the sterility test on FFP or source plasma that was simultaneously manufactured was conducted, the imputability was evaluated to be unknown.

Table 14. Bacterial infection cases that were evaluated to have a "probable" causal relationship with transfusion

Case No.	Primary disease	Blood components for transfusion ◇ (date of collection)	Days after collection	Age & sex		Test results of blood/bacterial culture		Symptoms	
						Blood components	Patient's blood	Major complaints	Time of onset
1	Recurrent breast cancer	Ir-PC (2008.6)	4	60s	F	*Staphylococcus aureus*	*Staphylococcus aureus*	Fever, chills, shivering and hypotension	Approx. 60 min.
2	Burkitt's lymphoma	Ir-PC (2008.8)	4	50s	M	*Streptococcus dysgalactiae* ssp. *Equisimilis*	*Streptococcus dysgalactiae* ssp. *Equisimilis*	Angiopathy, hypotension and chest tightness	Approx. 40 min.

◇ Types of blood components for transfusion in which bacteria were detected

[Reference] Blood culture of the recipient (patient) in suspected cases of bacterial infection

Table 15 describes the results of blood culture of the patient blood by medical institutions, and the status of investigation of suspected blood components for transfusion. Table 16 shows the types of bacteria identified by blood culture of the recipient (patient) blood at the medical institutions, with regards to cases in which the result of blood culture of the patient was positive, though the bacterial culture of the relevant bag was negative.

Table 15. Results of blood culture of the recipient

	Results of recipient's blood culture			Total
	Positive	Negative	Unknown	
Case examined with the implicated blood components (relevant bag)	19(4)	13(2)	3	35(76%)
Cases in which plasma that was simultaneously manufactured was examined	9	2(1)	0	11(24%)
Total	28(61%)	15(33%)	3(6%)	46

* Figures in brackets show cases in which tube segments on the blood bags were used.
* Test results of all implicated blood components were negative.

Table 16. Types of bacteria identified by blood culture of the patient at the medical institutions

Patients in whom red blood cells (RBC) were transfused (13)	Patients in whom platelet concentrate (PC) was transfused (3)
Pseudomonas aeruginosa (2)	***Escherichia coli***
Klebsiella pneumoniae (2)	***Acinetobacter calcoaceticus***
Enterobacter cloacae	***Staphylococcus epidermidis***
Escherichia coli(ESBL)	
Acinetobacter lwoffi	RBC, PC and FFP (1)
Burkholderia pickettii	***Aeromonas hydrophila***
Anaerobic gram negative bacteria (species were not identified)	
Staphylococcus epidermidis	
Bacillus cereus	
Enterococcus faecium	
MRSA	

iv. HEV

There were 2 suspected cases of transfusion-transmitted HEV infection reported by medical institutions. The case investigations started based on the information that the source plasma turned out to be HEV-RNA positive at the quality inspection of the partner manufacturer, prior to the processing plasma derivatives. The RBCs that were simultaneously processed were transfused to the two patients.

Individual HEV-NAT was conducted using the repository samples of the two suspected products, and both turned out to be positive.

In one of the cases, homology was confirmed for the HE virus from the donor and the patient, and the imputability was evaluated to be probable. In the other case, liver function disorder developed after transfusion, and seroconversion was confirmed with the patient's post-transfusion specimen. Therefore, viral homology was unavailable in this case, though the imputability was considered to be probable.

v. HIV-1

There was 1 suspected case of transfusion-transmitted HIV-1 infection reported by a medical institution. The suspected blood components were 3 bags of RBC. Individual HIV-NAT was conducted using the repository samples of the relevant products, and all three suspected samples tested negative. The imputability between the infection and the blood components was evaluated to be unlikely, because the donors did not have subsequent blood donation.

vi. CMV

There was 1 suspected case of transfusion-transmitted CMV infection reported by a medical institution. The suspected blood components were 5 bags of RBCs, 2 bags of FFP, and 3 bags of PC. The patient was a very-low-birth-weight infant (two months, 1.3 kg), and a request for CMV(-) blood had not been received from the medical institution.

An antibody test was conducted using the repository samples of the relevant blood components, and all turned out to be CMV IgG positive and CMV IgM negative. Therefore, the imputability between the infection and the blood components was evaluated to be unknown.

Table 17. HEV cases that were evaluated to have a "probable" imputability with transfusion

No.	Primary disease	Blood components◇ (Collection date)	Age/Sex		Pre transfusion			Post transfusion			ALT		Patient's specimen
					Test item	Result	Period to transfusion	Test item	Result	Period after transfusion	Max (IU/L)	Period after transfusion	Pre transfusion
1	Prostate cancer	Ir-RCC-LR (2008.4)	80s	M	NT			IgM-HEV-Ab IgG-HEV-Ab	Positive	32 weeks	486	4 weeks	Unavailable
2	Stomach cancer	Ir-RCC-LR (2008.4)	60s	M	HEV-RNA IgM-HEV-Ab IgG-HEV-Ab	Negative	10 day	HEV-RNA	Positive	3 weeks	39	7 weeks	Available

◇Types of blood components for transfusion in which viral nucleic acid was detected in the repository samples, etc.

2. Plasma derivatives

(1) Plasma derivatives manufactured by JRCS

In 1983 JRCS established the Plasma Fractionation Center, which has manufactured plasma derivatives by fractionating, purifying and concentrating protein components contained in blood donated in Japan. The Law on Securing a Stable Supply of Safe Blood Products ("New Blood Law") took effect in July 2003, advocating domestic self-supply of blood products based on the donation system. On the basis of this new law, the blood service was changed under the shared responsibility of the national government, local governments, marketing authorization holder (MAH) and health care professionals. JRCS endeavors to achieve domestic self-supply of plasma derivatives in collaboration with JRC blood centers nationwide, and with other domestic MAHs of plasma derivatives, to which source plasma is delivered.

As of 2008, JRCS has been manufacturing and distributing human albumin products (20% and 25%), human immunoglobulin product for IV injection (IVIG), anti-HBs human immune globulin product, and human coagulation factor VIII product.

Table 18. Changes in delivered plasma derivatives (2006 – 2008)

	SEKIJUJI Albumin (Human Albumin) (in 25%/50 mL)	Anti-HBs Human Immune Globulin (anti-HBs IMIG) (in 200 units)	Cross Eight M (coagulation factor VIII) (in 1,000 units)	NISSEKI Polyglobin-N 5%* (IVIG) (in 2.5 g)
2006	452,087	2,382	92,225	7,831
2007	463,378	2,255	88,156	59,772
2008	443,357	2,196	84,691	81,542

* NISSEKI Polyglobin-N was released in 2006.

(2) Safety of plasma derivatives

As with blood components for transfusion, the source plasma for manufacturing plasma derivatives has passed serological tests for infectious pathogens and NAT for HBV, HCV and HIV. During the manufacturing process, virus removal and inactivation steps are taken as shown in Table 19, including Cohn Process (cold ethanol fractionation) and several different types of filtration. The final products are tested for HBV, HCV, HIV and human parvovirus B19 by NAT, and the products are confirmed to be negative for these viral genes before they are delivered.

To improve the safety of plasma derivatives, mini-pool NAT for HBV, HCV and HIV on source plasma was introduced in 1997, before it was introduced for blood components for transfusion (subsequently, NAT on source plasma was discontinued when mini-pool NAT was started for those viruses on all donated blood in 1999). Since 2000, a six-month inventory hold of source plasma has been implemented. This inventory hold of source plasma not only enables pre-manufacturing exclusion of plasma that is suspected of being contaminated by viral infection, during the hold in terms of safety assurance, but also serves as an effective measure to support a stable domestic supply of plasma derivatives in case of a sudden shortage and/or emergency production during times of disaster, etc.

Table 19. Virus removal and inactivation methods used

SEKIJUJI Albumin 20% and SEKIJUJI Albumin 25%
○ Cohn Process
○ Liquid heating at 60°C for 10 hours
NISSEKI Polyglobin-N 5% (IVIG)
○ Cohn Process
○ Depth filtration
○ S/D (solvent/detergent) treatment
○ Low-pH liquid incubation
Anti-HBs Human Immune Globulin (anti-HBs IMIG)
○ Cohn Process
○ Virus removal membrane treatment (nanofiltration)
Cross Eight M (coagulation factor VIII)
○ S/D (solvent/detergent) treatment
○ Immunoaffinity chromatography
○ Virus removal membrane treatment (nanofiltration)
○ Ion exchange chromatography

(3) Changes in adverse reactions

Figure 18 shows spontaneously reported adverse reactions for which a causal relationship with plasma derivatives was suspected from medical institutions over the past ten years.

Six cases of adverse reactions concerning NISSEKI Polyglobin-N 5% were reported in 2008, a rate of 0.74 cases per 10,000 vials delivered (in 2.5 g vial conversion). JRCS only started marketing NISSEKI Polyglobin-N 5% in August 2006, and there are too few cases to reasonably estimate the frequency of adverse reactions due to this product. A post-marketing surveillance study of NISSEKI Polyglobin-N 5% will be started in 2009.

Although many vials of SEKIJUJI Albumin have been distributed, there are very few reports of adverse reactions related to Albumin, that is, an average of 3.3 cases annually over the past decade. Concerning Cross Eight M, no adverse reactions have been reported after the one in 2000. No adverse reactions have been reported for Anti-HBs Human Immune Globulin either.

Not a single confirmed case of viral infection has reported with any of the plasma derivatives manufactured by JRCS.

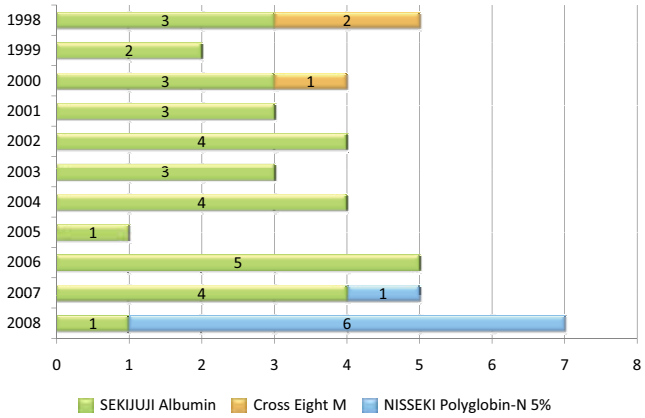


Figure 18. Changes in reported cases of adverse reactions by plasma derivative

(4) Overview of recent cases

An overview of the cases over the past three years (2006 - 2008) is shown in Table 20. Wheals (rash and eruption) were reported most frequently, namely, in five cases, followed by chills, fever, hypotension and dyspnea (pulmonary edema and respiratory depression), respectively, in three cases each.

Since the indications for NISSEKI Polyglobin-N 5% include many serious diseases, the reported adverse reactions also include severe symptoms. Adverse events included two cases of a transient increase in urinary glucose. Neither of the two cases were severe, and they were "not considered adverse reactions" by the reporting physicians. These adverse events were considered to be caused by maltose that is added to NISSEKI Polyglobin-N 5% as a stabilizer, and is hydrolyzed into glucose in the body and discharged into the urine.

Table 20. Adverse reactions reported from 2006 to 2008

Reported year	Primary disease	Age/sex		Suspected product	Adverse reactions	Date of onset	Severity	Remarks
2006	Colorectal cancer Diabetes mellitus	60s	M	SEKIJUJI Albumin 25% (12.5g/50mL)	Pulmonary edema	Jan. '06	Severe	
	Pneumonia Hypoalbuminemia	90s	F	SEKIJUJI Albumin 25% (12.5g/50mL)	Wheals	Feb. '06	Non-severe	
	Purpura nephritis	Infant child	M	SEKIJUJI Albumin 20% (4g/20mL)(10g/50mL)	Shivering, chills and fever	Apr. '06	Non-severe	Adverse reactions occurred following more than one doses
	HBV infection Cirrhosis Hepatocellular carcinoma	50s	M	SEKIJUJI Albumin 25% (12.5g/50mL)	Fever, vomiting, hypotension and chills	Jun. '06	Severe	
	Myelodysplastic syndrome	80s	F	SEKIJUJI Albumin 20% (10g/50mL)	Rash, dyspnea and bradycardia	Aug. '06	Severe	Adverse reactions occurred following more than one doses
2007	Hypoalbuminemia	80s	M	SEKIJUJI Albumin 25% (12.5g/50mL)	Face flushing	Feb '07	Non-severe	
	HUS	Infant child	F	Red Cell Concentrates SEKIJUJI Albumin 20% (4g/20mL)	Hypotension, pallor and respiratory depression	Mar. '07	Non-severe	
	HCV infection Cirrhosis	70s	F	SEKIJUJI Albumin 20%	Fever and eruption	May '07	Non-severe	
	Kawasaki disease	Infant baby	M	NISSEKI Polyglobin-N 5% (2.5g/50mL)	Liver dysfunction	May '07	Severe	
	Chronic heart failure Hypoalbuminemia	80s	M	SEKIJUJI Albumin 25% (12.5g/50mL)	Hypotension	May '07	Severe	
2008	Acute promyelocytic leukemia	60s	F	NISSEKI Polyglobin-N 5% (5g/100mL) Irradiated Platelet Concentrate	Chills, rush	Apr. '08	Severe	
	Idiopathic thrombocytopenic purpura	Infant child	M	Nisseki Polyglobin-N 5% (5g/100mL)	Aseptic meningitis	Jul. '08	Serious	
	Kawasaki disease	Infant child	M	Nisseki Polyglobin-N 5% (5g/100mL)	Urinary glucose increased	Jul. '08	Non-severe	Was not recognized as an adverse reaction by the reporting physician
	Lymphoma Hypogammaglobulinemia	60s	M	NISSEKI Polyglobin-N 5% (2.5g/50mL)	Anaphylactic shock	Aug. '08	Severe	
	Cirrhosis	60s	M	SEKIJUJI Albumin 20% (10g/50mL)	Systemic flushing and itching	Oct. '08	Non-severe	
	Multiple myositis Diabetes mellitus	50s	M	NISSEKI Polyglobin-N 5% (2.5g/50mL)	Mental disorder	Oct. '08	Severe	
	Kasawasaki disease	Infant child	M	NISSEKI Polyglobin-N 5% (5g/100mL)	Urinary glucose increased	Nov. '08	Non-severe	Was not recognized as an adverse reaction by the reporting physician

3. Information from the literature and academic conferences (including overseas cases)

(1) Significance of collecting information from the literature and academic conferences

The information sources of the adverse reaction reporting, based on the Pharmaceutical Affairs Law and its Enforcement Regulations are not limited to voluntary reporting by medical institutions. It is also important to collect, examine and evaluate cases that are reported at academic conferences, published in the literature, or otherwise posted on the Internet etc., in terms of enhancing safety. Therefore, JRCS has collected the relevant information since many years ago. Following the enforcement of the GVP Ordinance in April 2005, JRCS renewed its organization and has actively collected, examined and evaluated the literature and academic conference information for safety management.

(2) Flow of information collection

The process of collecting information from the literature and academic conferences is undertaken once every two weeks, based on Notification 0328007 of the Director of the Safety Division, Pharmaceutical and Food Safety Bureau, MHLW, "Post-approval Safety Data Management: Definitions and Standards for Expedited Reporting," dated March 28, 2005. Domestic information is mainly collected from Japan Medical Abstracts Society (*Ichushi*), and information in foreign journals is collected using PubMed (a database of citations and abstracts of biomedical literature from MEDLINE and other life science journals.) and other sources.

PubMed is searched using specified keywords. From 40 to 100 papers are picked up in a single search on adverse events following blood transfusion or administration of plasma derivatives. Subsequently, their abstracts are browsed to collect mainly case reports and other safety management information. The collected information is examined and evaluated in order to determine, in case of domestic cases, whether they have already been reported to JRCS; whether the reported adverse reactions are known (i.e. stated on the package insert of the relevant product); and in case of overseas cases, whether they have to be reported based on the Pharmaceutical Affairs Law.

(3) Changes in collected information

Figure 19 shows the changes in the pieces of information collected from the literature and academic conferences. While the volume of information changes depending on the transfusion-related conferences and other factors, the average pieces of information collected per month (hits in the search using the specified keywords) remained within the same range, namely, 114.5 in 2006, 115.7 in 2007 and 129.9 in 2008.

The collected information is examined and evaluated by more than one members of the Safety Supervision Unit, to ensure that there are no omissions in the collection of cases to be reported. JRCS endeavors to catch up with the occurrence of new transfusion-transmitted infections and unknown adverse reactions, as well as changes in blood services. The keywords are updated as necessary, so that the latest information can always be obtained.

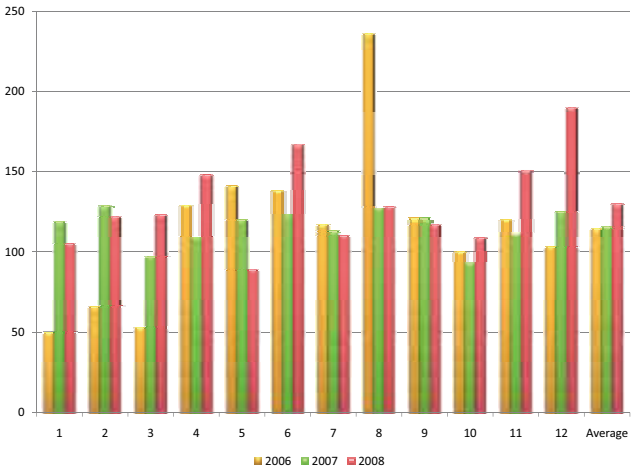


Figure 19. Changes in pieces of information collected per month over the past three years

(4) Recently reported cases (including overseas cases)

Among the cases collected over the past three years, those that were determined to be reported to the Minister of Health, Labour and Welfare, in accordance with the Pharmaceutical Affairs Law, are shown in Table 21. Since the blood components and plasma derivatives manufactured by JRCS are not marketed in other countries, overseas reports of cases involve infections and unknown severe adverse reactions caused by blood products used in other countries that are therapeutically equivalent or comparable.

Although some domestic cases of adverse reactions due to transfusion were not voluntarily reported by medical institutions to the JRCS, we picked them up to report as severe adverse reaction cases caused by blood components in Japan. The overseas cases include many transfusion-transmitted infections that have not yet been observed in Japan, such as Dengue fever. JRCS collects information in case such diseases appear in Japan.

JRCS also accumulates information on the literature and overseas cases, and discusses the revision of package inserts and domestic safety measures against emerging transfusion-transmitted infections as necessary.

Table 21. Cases identified in the information from the literature and academic conferences that were reported to MHLW over the past three years

Domestic cases

Year of reporting	Primary disease	Age/sex		Suspected blood product	Adverse reactions	Journal etc.
2006	Duodenum hemorrhage	85	M	Irradiated Red Cell Concentrates	Hemolysis	The Japanese Journal of Transfusion and Cell Therapy 2006,52(2),307
2007	Sacral chordoma	68	F	Irradiated Red Cell Concentrates	Cardiac arrest	The Journal of Japan Society of Clinical Anesthesia 2007,27(3),273-277
2007	Chronic renal failure	40	F	Irradiated Red Cell Concentrates	Reversible leukoencephalopathy	Journal of Japanese Society for Dialysis Therapy 2007,40(8),655-661

Overseas cases

Year of reporting	Primary disease	Age/sex		Country	Suspected blood product	Adverse reactions	Journal etc.
2008	Emergency operation	64	M	Germany	Red cell concentrates	HIV infection	Vox Sanguinis ,2008,95(s1),56
2008	Diabetes mellitus	64	M	Singapore	Fresh frozen plasma	Dengue fever	N Engl J Med ,2008,359(14),1526-5127
2008	Diabetes mellitus	72	M	Singapore	Red cell concentrates	Dengue fever	N Engl J Med ,2008,359(14),1526-5127
2008	Hepatocellular carcinoma	74	M	Singapore	Platelet concentrates	Dengue viral infection	N Engl J Med 359(14) ,2008,1526-5127
2008	Streptococcal chest cellulitis	38	M	Canada	pH4-treated acid human immunoglobulin	Transfusion-related acute lung injury	Canadian Adverse Reaction Newsletter ,2008,18(4),pp3
2008	Chronic renal failure	38	M	U.S.	Red cell concentrates	Human granulocytic ehrlichiosis	Morbidity and Mortality Weekly Report ,2008,57(42),1145-1148

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

1. Regulations and methods of reports on measures in foreign countries and reports of studies

Reports on measures in foreign countries and reports of studies are provided according to Article 77-4 (2) of the Pharmaceutical Affairs Law and Article 253 of the Enforcement Regulation of the Pharmaceutical Affairs Law. Reports on measures in foreign countries are submitted when the JRCS obtains information concerning "the enforcement of measures to preventing health hazards from occurring or spreading, including the discontinuation of manufacture, import or distribution, or recall or disposal of a foreign pharmaceutical product" that is related to a JRC product that has been approved for manufacture and marketing. Reports on studies are submitted when JRCS obtains information concerning "study reports showing that cancer or another serious disease, disorder, or death was possibly caused by the relevant pharmaceutical product or a foreign pharmaceutical product, or infection due to its use, or that the incidences of adverse reactions due to the relevant pharmaceutical product or a foreign pharmaceutical product or that of infection due to its use significantly changed, or the relevant pharmaceutical product did not show its approved efficacy or effect," related to the JRC product approved for manufacture and marketing. Reports on measures in foreign countries and reports of studies may be submitted even if the pharmaceutical product is not manufactured or distributed by JRCS. Such products involve products used in other countries that have the same active ingredients as the blood products manufactured or distributed by JRCS, including such products with a different administration route and dosage, or efficacy and effect.

Information is collected from JAPIC Daily Mail (a news mail service summarizing information on overseas regulatory measures concerning the safety of drugs and medical devices), provided by the Japan Pharmaceutical Information Center, as well as the Regulations View, an information leaflet on overseas regulations. Information is also collected from news mail services and websites provided by regulatory authorities of other countries.

2. Reports on measures in foreign countries

The reports on measures in foreign countries submitted to the Minister of Health, Labour and Welfare in 2008 are listed in Table 22.

Many of them were countermeasures against transfusion-transmitted infections, such as the introduction by the U.S. government of pathogen reduction technology for blood components for transfusion, and the introduction of NAT for human parvovirus B19 by the same government.

Regarding the effect of human immunoglobulin product for IV injection containing maltose on the measurement of the blood sugar level, Safety Information was issued by the Japanese Ministry of Health, Labour and Welfare in 2004 and 2005, pertaining to a

Table 22. Measures in foreign countries that were reported to MHLW

Source	Description	Relevant product
US HHS	The Advisory Committee on Blood Safety and Availability (ACBSA) of HHS recommended the application of pathogen reduction technology to all blood for transfusion to the Secretary of HHS.	Blood and blood components for transfusion
US FDA	Fatal Iatrogenic Hypoglycemia: Falsely Elevated Blood Glucose Readings with a Point-of-Care Meter Due to a Maltose-Containing Intravenous Immune Globulin Product	NISSEKI Polyglobin-N 5% (IVIG)
US FDA	Guidance for Industry Nucleic Acid Testing(NAT) to Reduce the Possible Risk of Parvovirus B19 Transmission by Plasma-Derived Products DRAFT GUIDANCE	Source plasma for manufacturing plasma derivatives

FDA: Food and Drug Administration
HHS: Department of Health and Human Services

higher GDH-PQQ-based blood sugar measurement than the actual level, due to drugs containing maltose. JRCS has stated this issue on the package insert since the release of NISSEKI Polyglobin-N 5%, and has called attention to it.

3. Reports of studies

The study reported to the Minister of Health, Labour and Welfare in 2008 is listed in Table 23.

In Germany, transfusion-transmitted HIV-1 infection occurred due to blood, even though it tested negative on 96-sample mini-pool NAT screening. According to the study, this detection failure might have been caused by mismatches in the probe and the downstream primer of the CAP/CTM HIV-1 Test. This study was also reported to the Minister of Health, Labour and Welfare as a case report on overseas infection, as per "3. Literature and academic conference information," because the paper included case identifiable information, such as the age and sex of the recipient and the type of product used.

JRCS conducts 20-pool screening NAT in addition to HIV antibody testing, thereby excluding positive blood.

Regarding serological testing, testing apparatuses based on the Chemiluminescence Enzyme Immunoassay (CLEIA) method which are more sensitive than the conventional coagulation method were introduced in January 2008. In August 2008, a new NAT system for viral screening with higher sensitivity was introduced.

Table 23. Study reported

Source	Description	Relevant product
Vox Sanguinis. 2008 Jul; 95 (S1): 56.	First transmission of HIV-1 by a cellular blood product after mandatory NAT blood screening in Germany. Vox Sanguinis, 2008, 95(s1), 56	Blood and blood components for transfusion

V. Periodic infection reports for biologic products

1. About periodic infection reports of biologic products

A new system of periodic infection reports was established in accordance with the enforcement of the revised Pharmaceutical Affairs Law in July 2003 and JRCS started to submit periodic infection reports to the Minister of Health, Labour and Welfare through the PMDA as a marketing authorization holder of biological products. The Law requires submitting a report for each product approved for manufacturing and marketing every 6 months. The details of the report are specified by the Law and its notifications.

The core of the report comprises study reports on infections. In accordance with the review criteria and policy specified by the Notification of Direct of the Safety Division, Pharmaceutical and Food Safety Bureau, MHLW, JRCS collects information from academic journals, other literature, and websites also specified by the notification, and reviews and assesses them. Furthermore, JRCS collects, assesses, and reports novel studies and information on prion diseases such as Creutzfeldt-Jakob disease (CJD).

(1) Selection and assessment of information on periodic infection reports of biologic products

Figure 20 shows the status of information selection in 2008.

1) The information is collected every month and the first selection is made by the secretary.
2) The information after the first selection is sent to the members of the information review committee consisting mainly of in-house physicians, such as the directors of JRC blood centers. Further selection is made.
3) Meetings of the information review committee are held at the JRCS Blood Services Headquarters, to select the information to report.
4) A submission form for each piece of information is prepared and the summary of study reports and manufacturer's opinions and measures are reviewed and evaluated in the evaluation meeting.

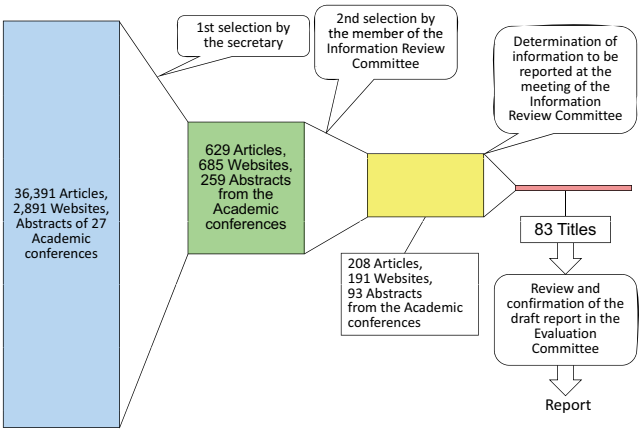


Figure 20. Annual status of information selection

(2) Reports submitted to the PMDA by product

Reports were submitted to the PMDA as shown in Table 24, at approximately six-month intervals for each product, as per the specified reporting criteria.

Table 24. Reports submitted by product

Blood products	1st submission	2nd submission
Red Cell Concentrates-LR	36	41
Irradiated Red Cell Concentrates-LR		
Fresh Frozen Plasma	41	39
Fresh Frozen Plasma-LR		
Platelet Concentrates	41	39
Irradiated Platelet Concentrates		
Platelet Concentrates HLA		
Irradiated Platelet Concentrates HLA		
SEKIJUJI Albumin 20%	33	27
SEKIJUJI Albumin 25%		
Cross Eight M (coagulation factor VIII) (250・500・1000)	36	26
Albumin as an additive to Cross Eight M (250・500・1000)	36	26
Human Immune Globulin	35	26
NISSEKI Polyglobin N 5%	35	26
Anti-HBs Human Immune globulin	32	30

Blood products	1st submission	2nd submission
Whole Blood-LR	36	41
Irradiated Whole Blood-LR		
Washed Red Cells	41	14
Irradiated Washed Red Cells		
Washed Red Cells-LR		
Irradiated Washed Red Cells-LR		
Frozen-Thawed Red Cell Concentrates	37	39
Irradiated Frozen-Thawed Red Cell Concentrates		
Frozen-Thawed Red Cell Concentrates-LR		
Irradiated Frozen-Thawed Red Cell Concentrates-LR		
Blood for Exchange Transfusion	42	26
Irradiated Blood for Exchange Transfusion		
Blood for Exchange Transfusion-LR		41
Irradiated Blood for Exchange Transfusion-LR		

* Reports have to be submitted for each approval. This table shows an overview of the submitted reports.

2. Information collected in 2008

Eighty-three pieces of information were selected and reported to the Minister of Health, Labour and Welfare, out of 36,391 studies, 685 websites, and 259 presentations at academic conferences.

In February, the U.S. FDA announced that it would promote strong considerations of the inactivation of pathogens in blood components. Therefore, issues related to evaluation of pathogen inactivation by chemicals, ultraviolet rays etc. were highlighted in the reports.

Regarding hepatitis B and C, information on intranasal viral infections among drug abusers via inhaling equipment, and on nosocomial infection was reported. Although transfusion-transmitted HBV and HCV infection has become extremely rare in Japan, a case of infection with an HBV escape mutant and the first case of HCV infection after the introduction of 20-pool NAT were reported.

Regarding prion diseases, more than one group published the evaluation of prion transmission risk by transfusion, which was considered to be lower than had been assumed. JRCS also reported its study results on a prion detection method and removal of prions from blood components through filtration.

Studies during this year included a certain amount of tick-borne infections. Reported information included a fatal case of transfusion-transmitted babesiosis in the U.S., a case of human granulocyte anaplasmosis in China, and a report on the spread of rickettsia and leishmania.

Table 25. Number of reports for the past 3 years

	2006	2007	2008
Articles	35,261	33,271	36,391
Websites	645	811	685
Presentations of academic conferences	274	295	259
Total information reviewed	36,180	34,377	37,335
Information reported	63	88	83

* The number of articles and websites is the total information to be reviewed, and the presentations of academic conferences are the number of presentations selected from the relevant academic societies.
* Total information reviewed is the total number of articles, websites, and presentations of academic conferences to be reviewed in the year.
* Information reported is the amount of information reported after review.

3. Reports at the Pharmaceutical Affairs and Food Sanitation Council

Reports that were submitted to the national government in 2008 were also reported at the Drug Safety Measures Meeting and at the Steering Committee for the Blood Service Meeting, the Pharmaceutical Affairs and Food Sanitation Council.

New reports presented by JRCS at each meeting are shown in Table 26.

Table 26. New reports presented by JRCS at the Council

	Drug Safety Measures Meeting	Steering Committee for the Blood Service Meeting
1st session/FY2008	40	8
2nd session	Periodic infection reports for biologic products were not included in the agenda.	26
3rd session	36	8
4th session	No session	20
1st session/FY2009	23	14

* The number of reports at the Council varies because the scope of the period depends on the date of the meeting.

VI. Post-donation information

1. Number of cases surveyed on the basis of PDI

Based on post-donation information (PDI), the number of cases surveyed regarding self-reported AIDS information (PDI-1), information on the donor's health condition (PDI-2), post-donation information on ineligible donors at the interview (PDI-6), and other safety information (PDI-other) are summarized in Table 27.

In 2008, a total of 2,709 reports on post-donation information were collected and included 13 reports on self-reported AIDS information (PDI-1), 47 reports on information on the donor's health condition (PDI-2), 2,368 reports on post-donation information on ineligible donors at the interview (PDI-6), and 281 on other safety information (PDI-other).

Table 27. Monthly changes in the numbers of surveyed cases on the basis of PDI

	Jan.	Feb.	Mar.	Apr.	May	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.	Total
PDI-1 (Self-reported AIDS information)	2	1	3	2	0	1	1	1	0	0	1	1	13
PDI-2 (Information on the donor's health condition)	2	11	1	1	4	7	3	4	3	6	1	4	47
PDI-6 (Post-donation information on ineligible donors at the interview)	244	209	237	174	217	191	212	177	187	174	173	173	2,368
PDI-other (Other safety information)	17	18	26	22	23	34	23	19	33	25	21	20	281
Total	265	239	267	199	244	233	239	201	223	205	196	198	2,709

(1) Breakdown of the post-donation information

Breakdown of PDI-2, 6 and other is shown in Figure 21.

1) Information on the donor's health condition (PDI-2)

Information on the donor's health condition included HBV infection (6 cases), HCV infection (9), HIV infection (3), chickenpox and herpes zoster (8), cancer (7), fever, diarrhea, gastroenteritis etc. (3), pneumonia (2), and one case each of seasonal influenza, herpes, human parvovirus B19 infection, measles, Basedow disease, impaired liver function, elevated CRP value (internal inflammation) and hand-foot-and-mouth disease.

2) Post-donation information on ineligible donors at interview (PDI-6)

The post-donation information on ineligible donors at interview included 1,812 cases involving travel to Europe (of which 1,761 cases had stayed in the UK for 1 day or longer), 373 with a history of transfusion, 58 that were hepatitis virus carriers, 41 with a history of cancer (other than blood cancer), 3 with a history of cancer (blood cancer), 21 involving nonexclusive heterosexual contact, 19 with CJD-related information, 17 who donated blood within 4 weeks after returning from abroad, 11 with liver disease, 8 with a history of malaria, 2 with psoriasis (history of Tigason treatment unavailable), 2 with organ or skin transplants, and 1 with a history of a neurological disorder.

While reported cases involving travel to Europe decreased by 1,540 from 3,352 in 2007, they still made up 76% of the total.

3) Other safety information (PDI-other)

Other safety information included a history of travel to malaria-endemic regions (124 cases), a history of travel to Leishmania-endemic regions (3), piercing and tattoos (34), needle puncture accidents (14), needle sharing among intravenous drug abusers (2), HEV research-related lookback (10), bacterial infection (3), contact with patients with sexually transmitted diseases (3), medication (30), vaccination and immunotoxin administration (6), injuries and therapeutic activities (3), autoimmune diseases (3), diseases for which a donor is deferred from blood donation (cerebral or heart diseases etc.) (25), and other information (21).

(2) Additional testing using repository samples

The cases related to HBV, HCV and HIV, a history of transfusion, nonexclusive heterosexual contact, and piercing and puncture accident were examined for HBV, HCV, and HIV using repository samples by individual NAT, and no virus was detected in any of the tested samples. Cases with a history of travel to malaria-endemic regions and post-donation information on ineligible donors at interview concerning a history of malaria were examined by testing 171 samples from 132 cases concerning the following items, and no plasmodium was detected in any of the tested samples.

<Malaria-related tests>

Microscopy, antigen testing and PCR testing for Malaria DNA

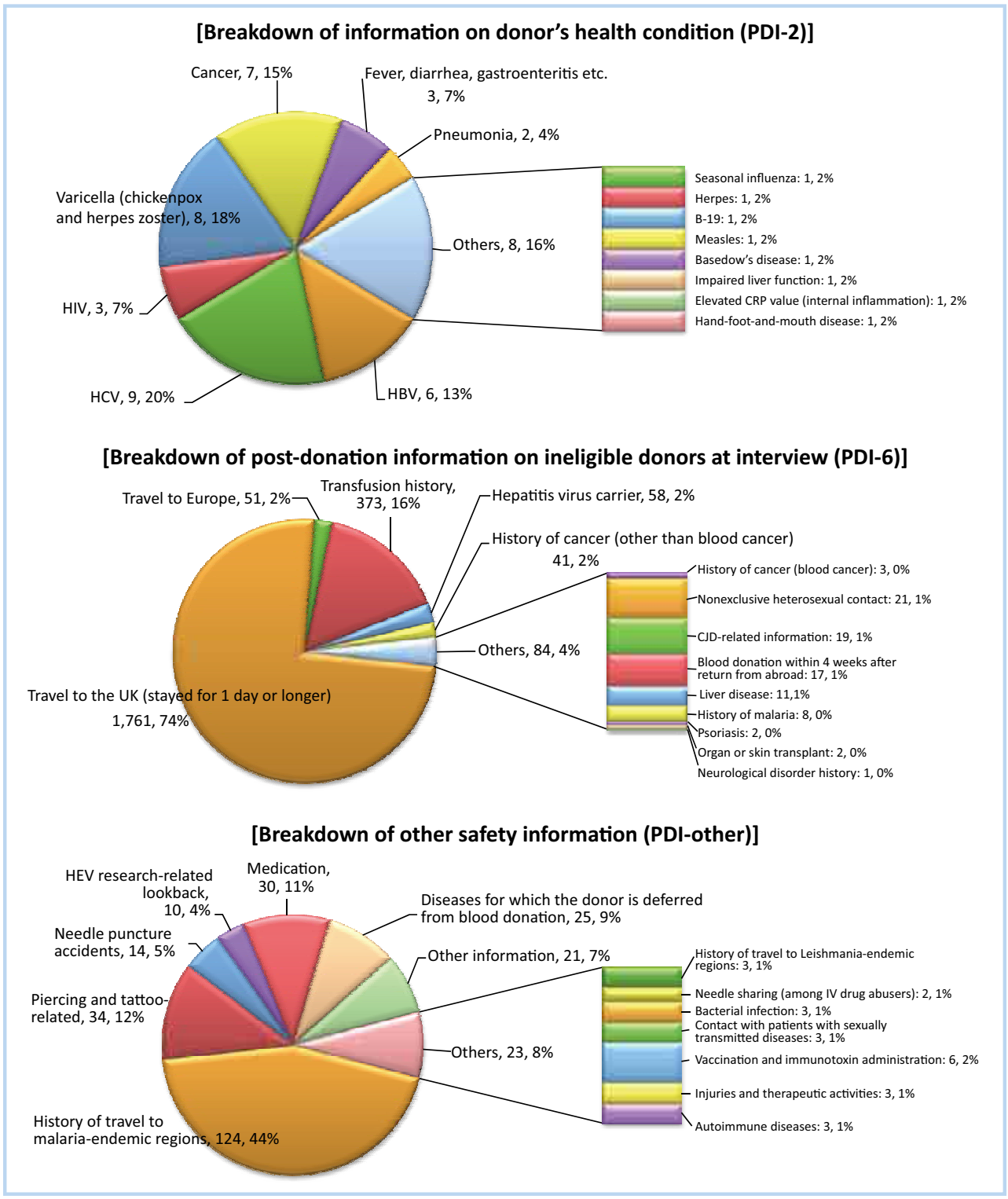


Figure 21. Breakdowns of post-donation information

2. Detailed countermeasures

(1) Countermeasures for blood components for transfusion and source plasma for manufacturing plasma derivatives

1) Blood components

i Cases of withdrawing from medical institution

In a total of 29 cases, blood components that were distributed to medical institutions, but had not been used yet, were withdrawn. The cases that JRCS reported to the Minister of Health, Labour and Welfare pursuant to Article 77-4 (3) of the Pharmaceutical Affairs Law included 1 case with information on the donor's health condition (PDI-2), 23 on post-donation information of ineligible donors at interview (PDI-6; including 15 cases that had stayed in the UK for 1 day or longer), and 5 with other safety information (PDI-other).

ii. FFP in inventory hold

A total of 259 cases were FFP in inventory hold at JRC blood centers.

iii. Provision of information to medical institutions

In 131 cases, products had been distributed to medical institutions, and had expired or had already been used for transfusion by the time the PDI was provided. Products could not be withdrawn in these cases.

2) Source plasma

i. Awaiting shipment

In 5 cases, the implicated blood components had not yet been distributed from JRC blood centers to storage facilities of source plasma or to manufacturing facilities of plasma derivatives.

ii. Inventory hold at storage facilities

A total of 1,071 cases were in a condition where the implicated source plasma was stored at JRCS' storage facilities of source plasma (Plasma Fractionation Center and the Center for NAT and Quarantine).

iii. Delivered to the client manufacturer, etc

A total of 3,384 cases were in a condition where the implicated source plasma had already entered the manufacturing process at JRC Plasma Fractionation Center or had already been delivered to the client manufacturers of plasma derivatives.

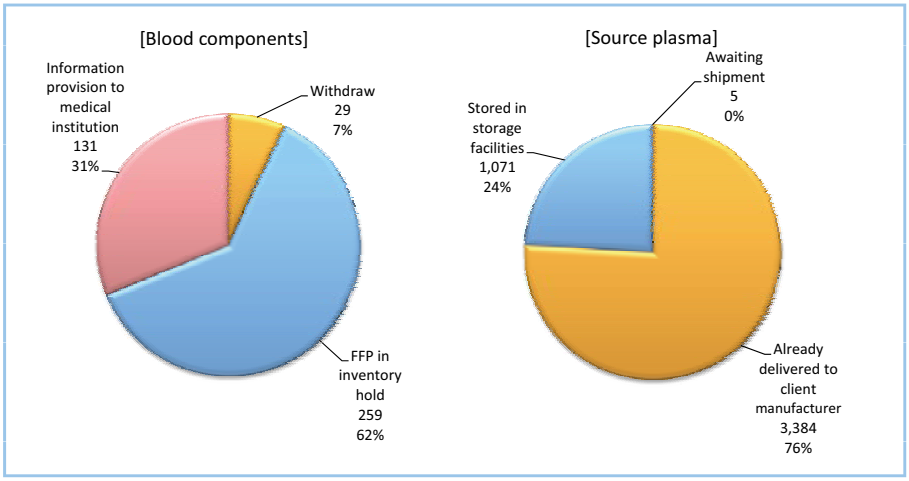


Figure 22. Lookback on blood components for transfusion and source plasma for the manufacture of plasma derivatives

(2) Breakdown of countermeasures for post-donation information

1) Blood components

Cases where the implicated blood components were excluded from transfusion by being withdrawn or FFP inventory hold accounted for approximately 69% of those with information on the donor's health condition, approximately 67% of those with post-donation information on ineligible donors at interview, and approximately 85% of those with other safety information.

2) Source plasma

Cases where the implicated source plasma had not yet been delivered from JRC blood centers, or was stored in inventory hold, and had thus not entered the manufacturing process of plasma derivatives, accounted for approximately 40% of those with self-reported AIDS information, approximately 31% of those with information on the donor's health condition, approximately 24%

of those with post-donation information on ineligible donors at interview, and approximately 22% of those with other safety information. The remaining cases were in a condition where the implicated blood components had already entered the manufacturing process at JRC Plasma Fractionation Center or had already been delivered to the client manufacturers of plasma derivatives.

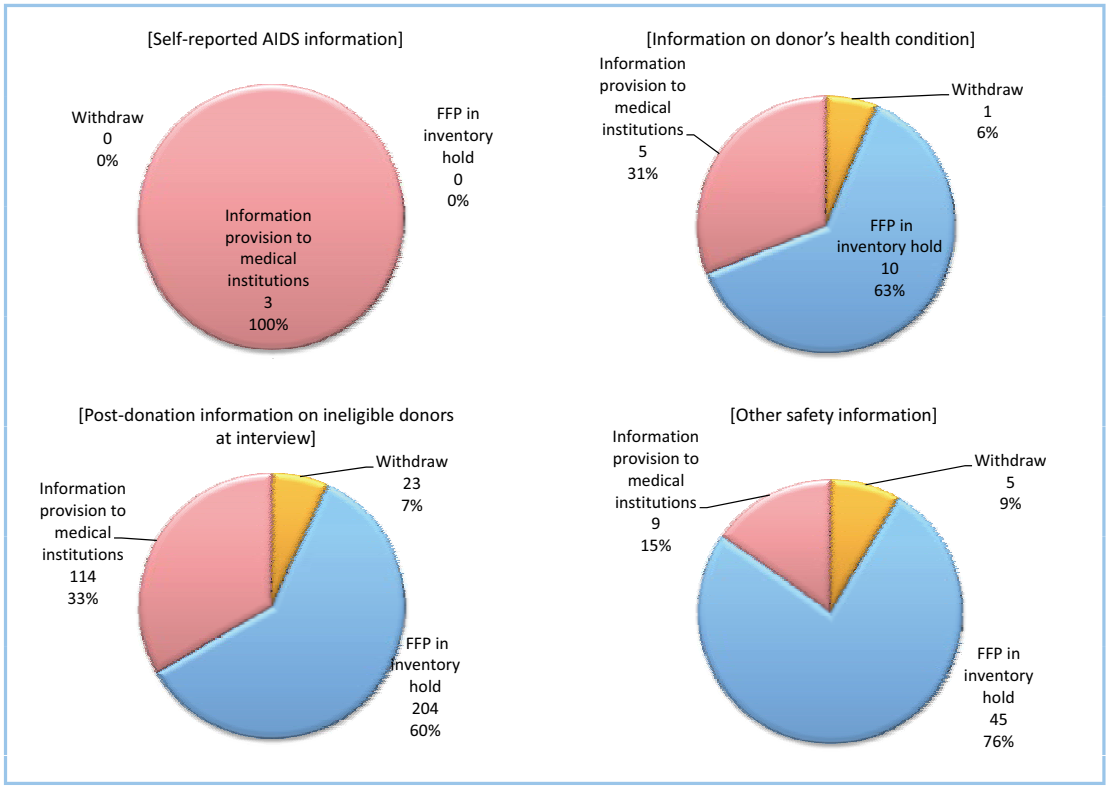


Figure 23. Breakdowns of countermeasures by type of post-donation information [blood component]

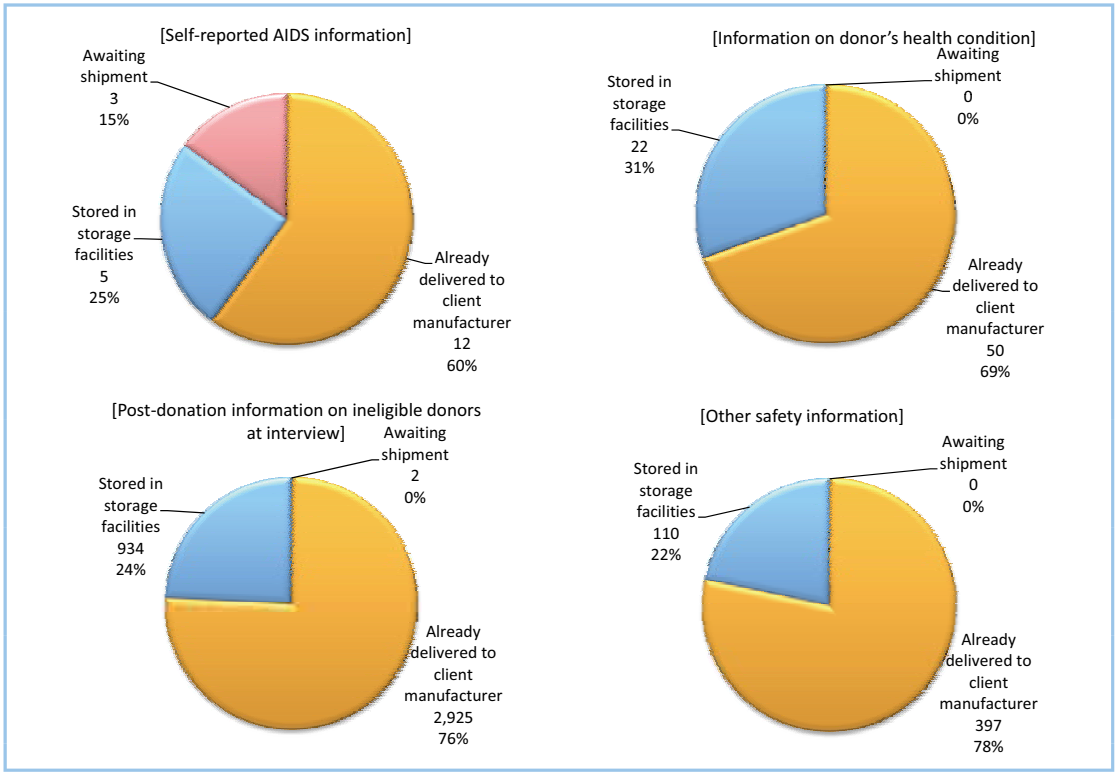


Figure 24. Breakdowns of countermeasures by type of post-donation information [source plasma for plasma derivatives]

VII. Lookback studies

Lookback studies have been conducted pursuant to the 'Guidelines for lookback studies on blood products' (partially revised in December 2008) which was notified in accordance with PFB No. 0310009 "Notification on lookback studies on blood products," dated March 10, 2005.

The scope of lookback studies is determined in consideration of the results of serological testing, verification testing and individual NAT.

1. Cases intended for lookback studies

Figure 25 shows a total of 5,219 cases that required studies concerning repeat donors. By test item, HBs antigen was involved in 2,266 cases, HBc antibody in 1,737 cases, HCV antibody in 1,009 cases, HIV antibody in 57 cases, HBV-NAT in 123 cases, HCV-NAT in 0 cases, HIV-NAT in 1 case, and a combination of 2 or more test items (complex) in 26 cases. HBV-related lookback studies accounted for approximately 80% of the total.

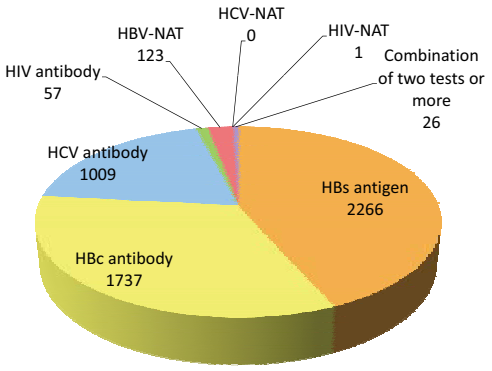


Figure 25. Cases intended for lookback studies concerning repeat donors

2. Individual NAT results

Individual NAT against HBV, HCV and HIV was conducted for each item of positive conversion in 5,219 samples in the scope of lookback studies. Positive results of individual NAT were only provided for HBV, which accounted for 103 cases. The breakdown is shown in Figure 26.

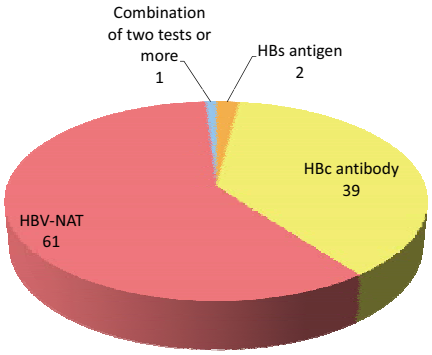


Figure 26. Positive cases in individual NAT by item of positive conversion

3. Details of blood recipients

Information was provided to medical institutions in which the implicated 3,469 blood components (HBV: 3,150; HCV: 254; and HIV: 65) were distributed.

The information on the status of HBV individual NAT positive blood was obtained for 99 components. Of them, 94 components had already been used for transfusion at medical institutions. Three recipients showed HBV-positive conversion, 30 did not show positive conversion, and 42 had died. The remaining 5 components had been disposed of by the medical institutions.

Table 28. Identified ID-NAT positive blood components; condition of the implicated components and the involved recipients

Condition of implicated blood components	
	HBV
Used in medical institutions	94
Disposed by medical institutions	5
Total	99

Condition of the involved recipients	
	HBV
Positive conversion of HBV marker	3
Non-conversion of HBV marker	30
Death (due to primary disease)	42
Details unknown	19

Afterword

This annual report describes information including those on transfusion related adverse reactions and infectious diseases collected from nationwide medical institutions by JRC Blood Centers, and infection information based on post-donation information as well as analysis, evaluation and countermeasures of it. This report also summarizes the collection, assessment and management of other safety information, pursuant to the Pharmaceutical Affairs Law and GVP Ordinance. The authors are members of the Adverse Reactions Section 1 (Infections, Hemolytic Adverse Reactions), Adverse Reactions Section 2 (Non-Hemolytic Adverse Reactions), Lookback Study Section (Post-Donation Information, Lookback Studies), Infection Disease Section (Periodic Report on Infections), and the respective teams on adverse reactions of plasma derivatives, reports on measures in foreign countries and reports on studies.

The authors extend their sincere appreciation for the cooperation of health care professionals and members of JRC Blood Centers and other related organizations, during the conduct of these safety control activities.

JRCS will continue to 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 2008

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