日本赤十字社
Japanese Red Cross Society

Haemovigilance by JRCS

2007

Safety Vigilance Division
Blood Service Headquarters

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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.

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 (MR) across the county collect information from medical institutions. The most remarkable feature of JRCS surveillance system is storing an aliquot of all blood donations for analysis for 11 years since September 1996. Such specimen storage (repository samples) 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.

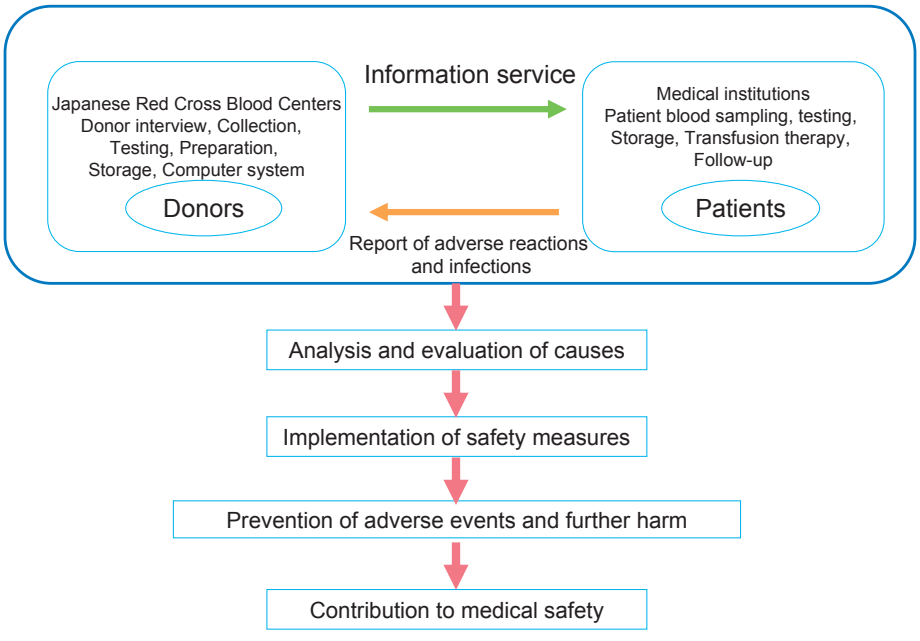


Figure 1. Outline of Haemovigilance

Furthermore, 6-month inventory hold of plasma used in manufacturing 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 to transfusion viral transmitted cases.

JRC blood centers hold the records of blood donor, collection, testing, preparation, and distribution, and these data are under consolidated management of nationwide database which enables look-back investigation when necessary.

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 approval 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 Supervision 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 approval 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 meetings, publication of articles, and other study reports
(5) Information from the Ministry of Health, Labour and Welfare and other governmental agencies, local governments, and the Pharmaceuticals and Medical Devices Agency, etc.
(6) Information from foreign governments and organizations, etc.
(7) Information from other marketing approval 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 the case that a blood donor whose blood sample is found to be positive for an infection by JRC Blood Center has a previous record of donation, the blood component for transfusion made from the previous donation may have already been distributed to medical institutions. If such a blood component has not been transfused yet, they shall be withdrawn. If it has already been transfused, the medical institution is requested to test the patient for implicated viral markers to help early detection and treatment of transfusion-related infections. This process is called lookback study.

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.

Information obtained after blood donation (safety information such as donors' health conditions and disqualifying information from the donor interview), including the foregoing is handled in accordance with the "Guidelines for Lookback Studies on Blood Products," which was established by the Blood and Blood Products Division, Pharmaceutical and Food Safety Bureau, the Ministry of Health, Labour and Welfare in April 2005.

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

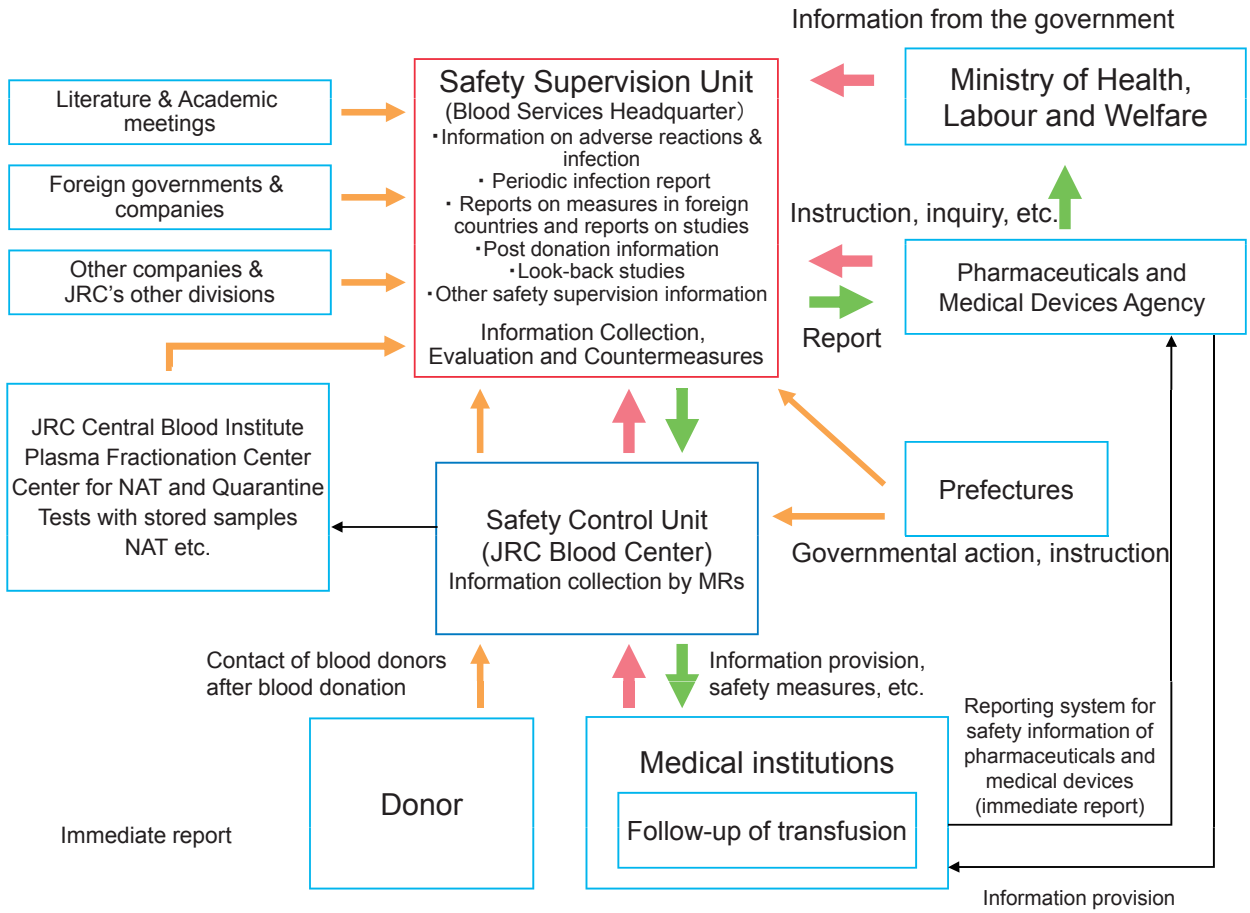


Figure 2. Flowchart of information collection and report (submission)

Summary of 2007 activity

Voluntary reports of adverse reactions and infections

A total of 1,814 possible cases of adverse reactions and infectious diseases related to transfusion were reported from medical institutions (including cases in the literature) (which is 99.2% compared to the previous year, 1,828 cases in 2006). 1,626 cases were classified into non-hemolytic adverse reactions, 153 transfusion-transmitted infections, 25 hemolytic adverse reactions, 5 suspected transfusion-associated graft-versus-host disease (TA-GVHD; no case was confirmed by microsatellite DNA analysis), and 5 adverse reactions caused by plasma derivatives (JRCS products). (Some cases were grouped into several categories.)

A detail breakdown of 153 reported cases of infection by pathogen was HBV in 74, HCV in 41, bacteria in 30, CMV in 3 (including a sub-infected case of CMV and EBV), human parvovirus B19 in 2, HTLV-1 in 2, and HAV in 1. Of these cases, the viral genome was detected in the repository samples of the implicated donor in 13 HBV and one HCV cases, suggesting that those cases were likely caused by transfusion.

Periodic infection reports for biologic products

A total of 34,377 pieces of literature was reviewed by in-house experts, and 88 of them were reported to the PMDA. Chagas' disease that was transmitted through blood transfusion from Latin American donors, avian influenza H5N1 subtype, and variant Creutzfeldt-Jakob disease (vCJD) were reported.

Reports on measures in foreign countries and reports on studies

Four reports on the measures in foreign countries related to vCJD and West Nile virus NAT, etc. and 1 report on studies were submitted to the PMDA.

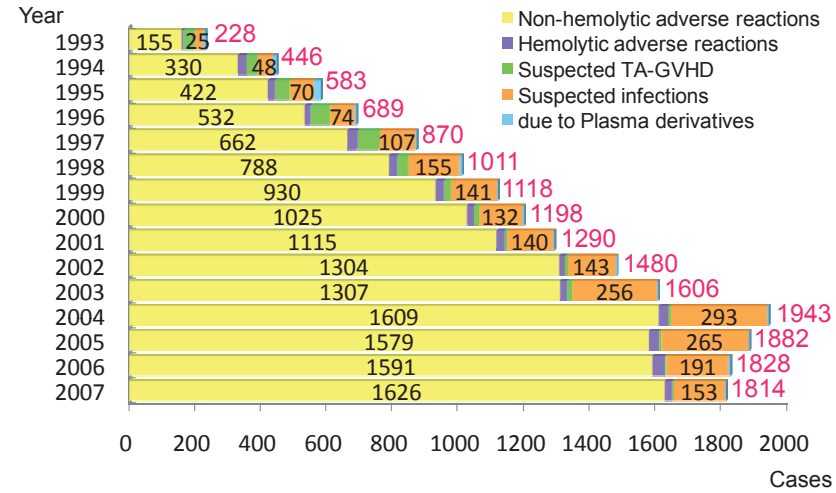
Post-donation information

A total of 4,212 post-donation pieces of information was reported and included 20 reports on self-reported AIDS information, 43 on the information on donor's health condition, 3,901 on post-donation information on ineligible donors at interview, and 248 on other safety information. Especially, 3,352 of reports on post-donation information on ineligible donors at interview, which is approximately 86% of the total, were due to travel to Europe (a stay in the UK for 1 day or more). Measures taken were as follows; 27 blood components were withdrew before being transfused, 444 FFP were discarded from the inventory hold, and, for 437 blood components, which were already transfused, information was provided to medical institutions. A total of 1,993 of source plasma for manufacturing plasma derivatives were removed from the stock or inventory hold and 3,882 were already delivered to client manufacturers.

Look-back studies

A total of 2,531 repeated donors had positive conversion. 2,694 repository samples were subjected to lookback study, and NAT against suspected virus was performed and 28 samples were found to be HBV-positive. Of 28 products, 26 were already transfused and the remaining 2 were discarded. The survey results in medical institutions confirmed that 4 patients treated with the relevant product had HBV-positive conversion, 9 had no change in viral marker tests, and 10 died from the primary disease, etc.

Reference. Changes in reported number of adverse reactions and infections



Reference. Number of supplied blood and blood components for transfusion and plasma derivatives in 2007

(Blood components)		(bag)
Platelet concentrates	713,174	
Fresh frozen plasma	1,043,117	
Red cell concentrates	3,205,863	
Whole blood	1,201	
Total	4,963,355	

(Plasma derivatives)		(vial)
Albumin products	516,437	
Anti-HBs human immunoglobulin	1,063	
Human blood coagulation factor VIII concentrate	106,649	
pH4-treated acidic human immunoglobulin	48,588	
Total	672,737	

1. Non-hemolytic adverse reactions

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

In 2007, 1,626 cases of non-hemolytic adverse reactions were reported and accounted for 89.6% of the total 1,814 cases of transfusion-related adverse reactions and infectious diseases. The adverse reactions cases reported in 2007 are summarized in Table 1.

Urticaria, eruption, nausea, etc., (hereinafter urticaria, etc.) were the most frequently reported adverse reactions, and consists of 578 cases, accounted for 35.5% of the total cases, followed by fever (197 cases, 12.1%). These two adverse reactions accounted for 47.6%. Anaphylactic reactions that include severe cases were found in 155 (9.5%), anaphylactic reactions with hypotension, i.e., anaphylactic shock in 293 (18.0%), and dyspnea and hypotension, in 172 (10.6%) and 47 (2.9%), respectively. Cases of transfusion-related acute lung injury (TRALI) were 45 (2.8%). Other adverse reactions, except the above 7 categories, were 139 (8.5%) and included 17 neuropsychiatric symptoms.

Table 1. Number of reported adverse reactions by symptom

Reported cases: 1,626	
Sex of patients: 889 males; 737 females	
Age of patients: 65 years (median); Range: 0 –100 years	
Number of reported cases of non-hemolytic adverse reactions by symptom and percentage:	
Urticaria, etc.: 578 (35.5%)	Fever: 197 (12.1%)
Hypotension: 47 (2.9%)	Dyspnea: 172 (10.6%)
Anaphylactic reaction: 155 (9.5%)	
Anaphylactic shock: 293 (18.0%)	
Transfusion-related acute lung injury (TRALI): 45 (2.8%)	
Other adverse reactions: 139 (8.5%)	
Neuropsychiatric symptoms: 17 (Consciousness disturbed: 7; movement disorder: 2; convulsion: 3; malaise: 2; encephalopathy: 2; cerebral infarction: 1)	

2) Changes in the number of severe cases

Changes in the number of severe cases of non-hemolytic adverse reactions and the percentage by symptom are shown in Figure 3.

The number of severe cases reported was 653 and accounted for 40.2% of the total reports, and the number of cases and the percentage increased from the previous year.

The breakdown by symptom was 256 cases (39.2%) of anaphylactic shock; 129 (19.8%) of dyspnea; 95 (14.5%) of anaphylactic reactions; 45 (6.9%) of TRALI; 36 (5.5%) of hypotension; 16 (2.5%) of fever; 13(2.0%) of urticaria, etc.; and 63 (9.6%) of others.

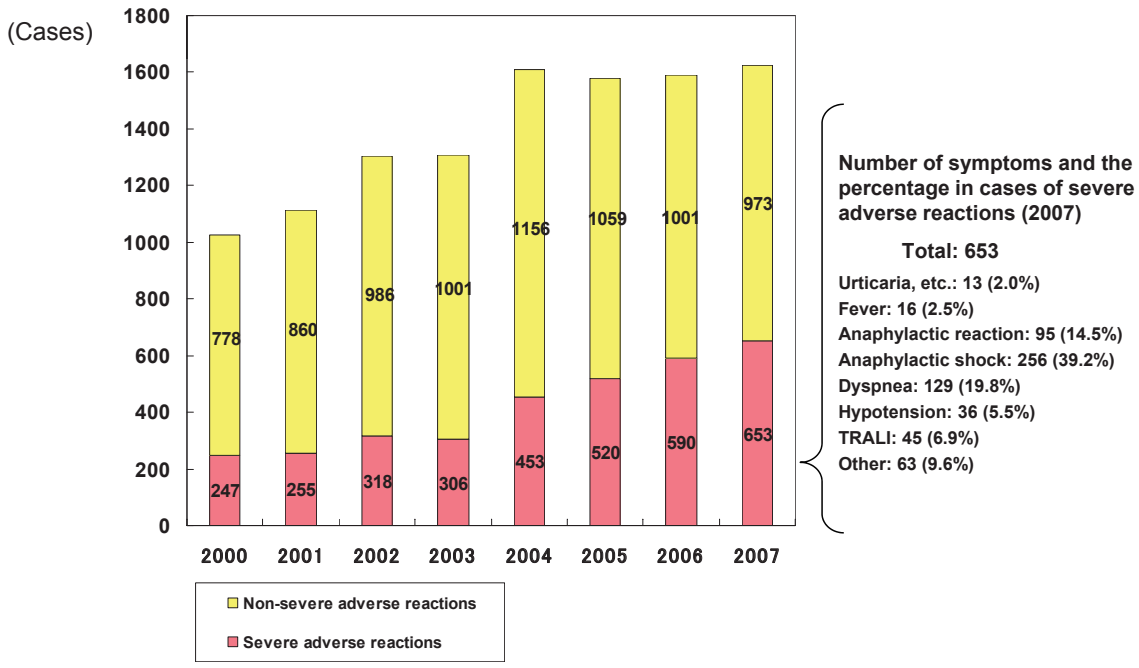


Figure 3. Changes in the number of reported cases of severe adverse reactions

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 4.

The number of reported cases of platelet concentrates (PC) used in patients developing adverse reactions was 655 (40.3%), followed by red cell concentrates (RBC) of 640 (39.4%) and FFP of 193 (11.9%). 7 (0.4%) cases of washed red cells (WRC) were reported, despite WRC is used to prevent adverse reactions caused by plasma.

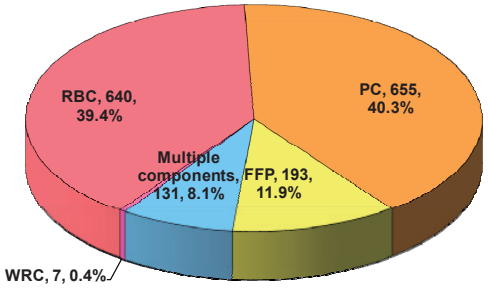


Figure 4. Percentage of blood components used in cases of reported adverse reactions by product type

4) Symptoms of adverse reactions and blood components

The percentage of symptoms of adverse reactions by blood components is shown in Figure 5.

In PC and FFP, respectively, the percentage of urticaria, etc., was the highest (40.8% and 57.5%), followed by anaphylactic shock (23.1% and 20.7%) and anaphylactic reactions (12.8% and 7.3%). On the other hand, the highest was urticaria, etc., (25.0%) in RBC, followed by fever (20.5%) and dyspnea (14.1%).

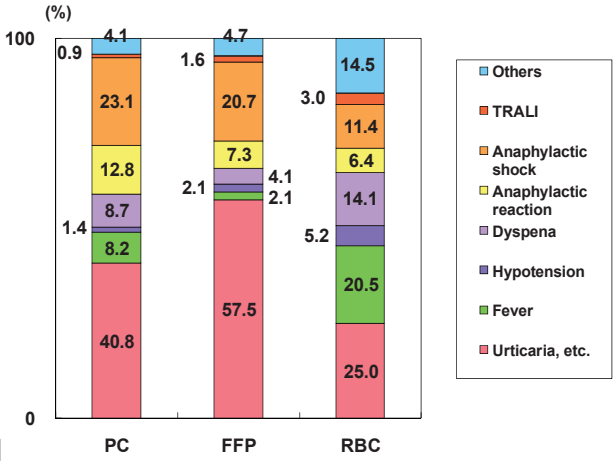


Figure 5. Percentage of symptom of adverse reactions by blood components

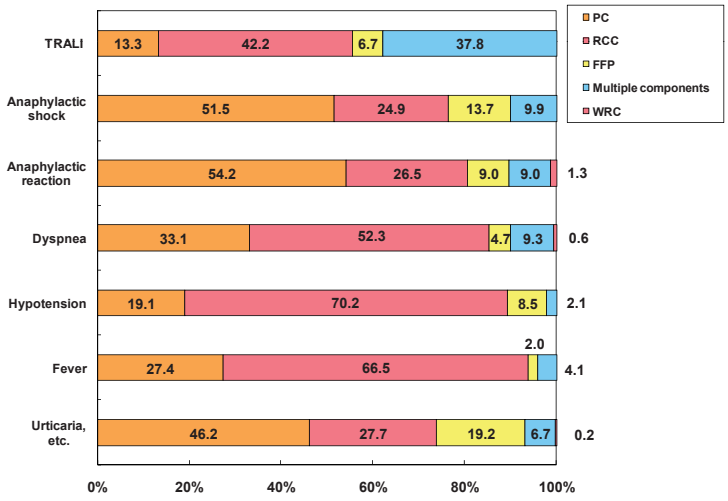


Figure 6. Percentage of blood for components by symptom of adverse reactions

Subsequently, the percentage of blood components by the symptoms of adverse reactions is shown in Figure 6.

For the components implicated to anaphylactic reactions, anaphylactic shock and urticaria, etc., PC was the leading product and accounted for 54.2%, 51.5%, and 46.2%, respectively, and PC and FFP accounted for 63.2%, 65.2%, and 65.4%, respectively, of the total cases. In contrast, RBC was the leading component implicated to hypotension and fever and accounted for 70.2% and 66.5%, respectively.

5) Incidences of reported adverse reactions

The number of distributed components, reported adverse reactions and the incidence are summarized in Table 2. The incidences of reports for FFP and RBC were 1.9 and 2.0 cases per 10,000 components distributed; whereas that for PC was 9.2 cases and extremely high.

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 TRALI were also similar or higher in PC than those in RBC. However, the incidences of reported hypotension in RBC and PC were not different from each other.

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

Blood Components	Number of components (Pack)	Number of reports of adverse reactions (Case)	Incidence of report of adverse reactions (per 10,000 packs)
Platelet	713,174	655	1/1,089 (9.2 cases)
Plasma	1,043,117	193	1/5,405 (1.9 cases)
Red cell	3,205,863	640	1/5,009 (2.0 cases)

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

	Platelet	Plasma	Red cell
Urticaria, etc.	3.74	1.06	0.5
Fever	0.76	0.04	0.41
Anaphylactic reaction	1.18	0.13	0.13
Anaphylactic shock	2.12	0.38	0.23
Hypotension	0.13	0.04	0.1
Dyspnea	0.80	0.08	0.28
TRALI	0.08	0.03	0.06
Other adverse reactions	0.38	0.09	0.29
Total	9.2	1.9	2.0

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 7. 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 31.9% of the cases and within 30 minutes in 74.5%. Anaphylactic reactions and shock were observed within 30 minutes in 44.3% and 59.5% of the cases, respectively. In contrast, urticaria, etc., dyspnea, and fever developed 30 minutes or more in most cases. TRALI frequently developed between 60 and 120 minutes from the beginning of transfusion; however, it was still observed more than 360 minutes after in 7.0% of the cases.

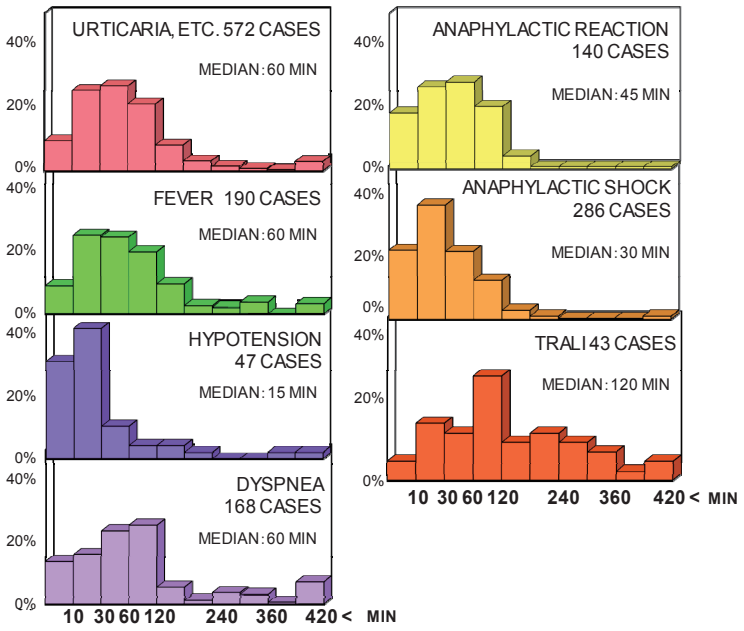


Figure 7. Time to onset of adverse reactions

7) Patient's history of transfusion and adverse reactions

The history of transfusion and adverse reactions in patients developing adverse reactions is shown in Figure 8.

The patients with transfusion history accounted for 79.5% of the patients developing adverse reactions (excluding patients with unknown transfusion history). Of them, the patients without history of adverse reactions accounted for 66.8%, while those with history were 26.5%.

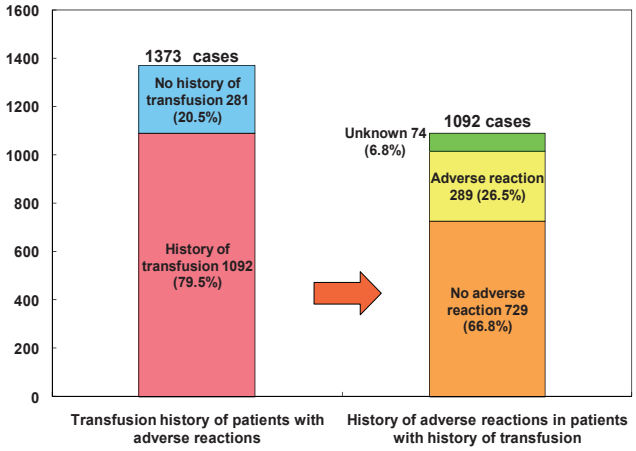


Figure 8. History of transfusion and adverse reactions of patients developing adverse reactions

8) Transfusion Related Acute Lung Injury (TRALI)

(1) Cases of TRALI

The cases of TRALI and possible TRALI (p-TRALI) diagnosed in accordance with the diagnostic criteria * are shown in Figure 9.

The number of TRALI and p-TRALI cases wes 31 and 14 in 2007, respectively.

The incidences of TRALI and p-TRALI by the type of blood components are summarized in Table 4. The RBC related TRALI and p-TRALI were 19 cases (39 including multiple components transfusion cases) and accounted for 42.2% of the total cases. The cases by PC and FFP were 5 (17) and 3 (13) and accounted for 11.1% and 6.7%, respectively.

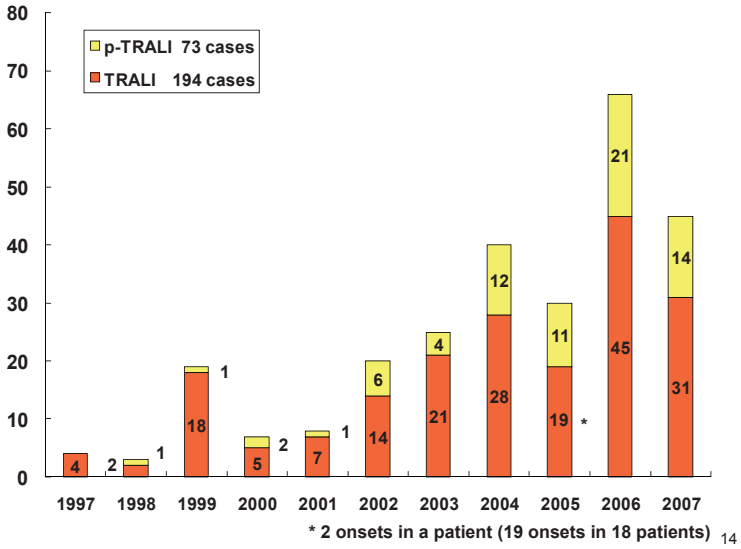


Figure 9. Changes in the number of TRALI cases

Table 4. Number of TRALI and p-TRALI cases by implicated blood components

	TRALI	p-TRALI	Total
RBC	15	4	19
FFP	2	1	3
PC	4	1	5
RBC+PC	6	2	8
RBC+FFP	2	4	6
PC+FFP	1	0	1
RBC+PC+FFP	1	2	3
Total	31	14	45

※ Diagnostic criteria for TRALI and p-TRALI

Diagnostic criteria for TRALI	Diagnostic criteria for possible TRALI
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 symptoms 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 $PaO_2/FiO_2 \leqq 300$ mmHg or $SpO_2 < 90\%$ (room air) or other clinical symptoms 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.

(2) Patient background

The patients developing TRALI were 19 men and 12 women; 31 in total. The patients developing p-TRALI were 8 men and 6 women; 14 in total. The age of patients with TRALI and p-TRALI widely ranged from 0 to 83 and 0 to 93 years, respectively.

Table 5. Patient background (29 cases)

	TRALI	p-TRALI
Male-Female ratio	M 19:F 12	M 8:F 6
Age	0～83 yrs	0～93 yrs
Median	71 yrs	54.5 yrs
	70 yrs	

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

Table 6 shows the positive rate of anti-leukocyte antibody of patients and blood components involved in TRALI/p-TRALI cases.

The anti-leukocyte antibody was positive in 12 patients with TRALI/p-TRALI and the positive rate was 28.6%. The positive rate of anti-leukocyte antibodies in patients developing other transfusion-related adverse reactions (control) was 29.4%, which was higher than that of patients with the TRALI/p-TRALI. The anti-leukocyte antibody was positive in 16 blood components related to TRALI/p-TRALI cases and the positive rate was 35.6%. The positive rate of anti-leukocyte antibodies in blood components related to other transfusion-related adverse reactions was 14.2% and the rate in the TRALI/p-TRALI cases was higher.

Table 7 shows the breakdown of anti-leukocyte antibody-positive donors involved in TRALI/p-TRALI cases.

A total of 27 donors (16 cases) were antibody-positive and included 18 women and 9 men and women accounted for 66.7%. In September 2004, a interim safety measure against TRALI started, which is to stop delivery of the blood component in stock made of the same donation of the TRALI-implicated WBC antibody positive components, and the subsequent donated blood from the donor will not be used for blood components for transfusion.

Table 6. Number of anti-leukocyte antibody-positive cases

	Patient's blood (n = 42)	Blood components (n = 45)
TRALI case	6	12
p-TRALI case	6	4
Positive ratio	28.6% (12/42)	35.6% (16/45)
Other transfusion related adverse reaction	29.4% (123/419)	14.2% (41/288)

Table 7. Breakdown of anti-leukocyte antibody-positive donors

	Female	Male
Positive cases	18	9
Percentage	66.7%	33.3%
Total	27	

2. Hemolytic adverse reactions

In 2007, 25 cases of hemolytic adverse reactions were reported and decreased from the previous year (37 cases). Of these cases, 17 were immediate reactions developing within 24 hours after the beginning of transfusion while 8 were delayed reactions developing more than 24 hours after.

The details of immediate hemolytic adverse reactions are as follows:

- The patient blood (pre transfusion) was anti-P1 + anti-Jk^b-positive and transfused 2 units of RBC were Jk (b+).
- The patient blood (pre transfusion) was anti-Jr^a-positive and transfused 2 units of RBC were Jr (a+).

The above 2 cases were considered to have a probable imputability between transfusion and adverse reaction.

Other cases in which irregular antibodies were detected in the patient blood were evaluated to have a unlikely imputability are listed below:

- The patient blood (post transfusion) was anti-Le^b-positive and transfused 2 units of RBC were Le(a-b-).
- The patient blood (pre and post transfusion) was anti-E + anti-c + antiDi^a + autoantibody positive while transfused RBC was E(-), c(-), and Di(a-).
- The patient blood (pre and post transfusion) was direct anti-globulin test positive; however, no specificity was found in an elution test.

In addition, no specific test results were found and the imputability between transfusion and adverse reactions was unknown in 12 cases including 3 cases in which blood warmer was used. The symptoms reported from medical institutions included 7 cases each of fever and hemolysis; 5 of hematuria; 3 each of chill, renal impairment/failure, and dyspnea; 2 each of tachycardia, serum bilirubin increased, and hypotension; and 1 each of cyanosis, urticaria, pain, shivering, bradycardia, wheal, eruption, and decreased oxygen saturation.

The details of delayed hemolytic adverse reactions are as follows:

- The patient blood (post transfusion) was anti-E + unidentified antibody positive and 3 of the 4 units of transfused RBC were E(+).
- The patient blood (post transfusion) was anti-E + anti-Jk^b-positive (despite both were negative in pre transfusion) and 1 of the 2 units of transfused RBC was Jk(b+), E(-), and another was Jk(b-), E(+).
- The patient blood (post transfusion) was anti-Jk^a + anti-Fy^b + anti-Xg^a-positive and the transfused RBC was Jk (a+) and Fy (b+).

The above 3 cases were considered to have a possible imputability between transfusion and adverse reactions. The symptoms reported from medical institutions included 4 cases hemolysis, 2 of hematuria, and 1 each of fever, hemolytic anemia, and renal impairment/failure.

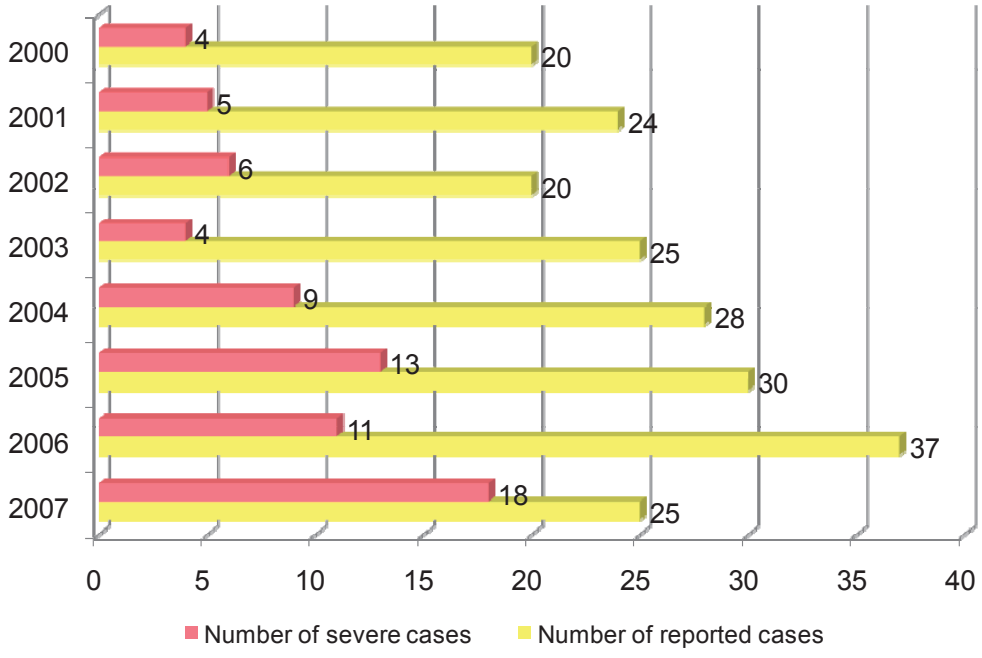


Figure 10. Changes in reported cases of hemolytic adverse reactions

3. Transfusion transmitted infections

In 2007, a total of 153 suspected cases of transfusion transmitted infections (TTI) were reported to JRCS from medical institutions.

A detail breakdown of the reported cases of TTI by pathogen was HBV in 74, HCV in 41, bacteria in 30, CMV in 3 (including a subinfected case of CMV and EBV), human parvovirus B19 in 2, HTLV-1 in 2, and HAV in 1.

1) Evaluation criteria for imputability

(1) Further testing for suspected cases of TTI

[1] Viral infection

a) Donor's specimen

The test for the relevant viral genome (individual NAT) was conducted with repository samples or samples of subsequent donation of the implicated donors.

b) Recipient's (Patient's) specimen

If the recipient's specimen was provided from medical institutions, the test for the relevant viral genome (individual NAT) was conducted with a recipient's specimen pre and post transfusion.

c) Evaluation of imputability (comparison of viral genome sequences)

If the viral genomes were detected in both a) and b), the viral genome sequences were compared to evaluate the homology.

(a) Analyzed region of HBV-DNA

1,550 bp (1,556 bp) in the early P region including Pre S/S [nt 2,333–3,215 (3,221)/1–667]

(b) Analyzed region of 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)

[2] Bacterial infections

a) Donor's specimen

The bacterial culture test with residual blood in the relevant blood bag or sterilization test with the component simultaneously manufactured plasma was conducted.

b) Evaluation of bacterial homology

If bacteria were detected in a), the genotype-specific test was conducted between the donor's bacterial strain and that of patient strain provided from medical institutes to evaluate the homology.

(2) Evaluation of imputability

[1] Viral infection

Table 8. 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"	Recipient's specimen: - Infected before transfusion - Uninfected after transfusion

[2] Bacterial infection

Table 9. Evaluation of imputability (bacterial infection)

Probable	Unknown	Unlikely
Donor's specimen: Blood Culture "Positive"	Donor's specimen (plasma simultaneously manufactured): Blood Culture "Negative"	Donor's specimen (relevant bag): Blood Culture "Negative"

※ If not consistent in the viral homology test, the case was evaluated to be "unlikely"

2) Evaluation results by pathogen

(1) HBV

[1] Number of reported cases and implicated components in 2007

A total of 74 cases were reported from medical institutions and the implicated blood components were 559 RBC, 161 FFP, and 405 PC; 1,125 in total.

[2] Results of examinations by JRCS

14 of the 1,125 repository samples of implicated components (14/74 cases) were found to be "positive" by individual HBV-NAT. All of the remaining 1,111 relevant repository samples (60 cases) were "negative."

[3] Evaluation of imputability

a) Repository sample "Positive" cases (14 cases)

- In 13 of the 14 cases, the homology was confirmed between the donor and patient HB viruses; therefore, the imputability of these cases was evaluated "probable".

- In 1 case, the HB viral genotype differed between the donor and the recipient; consequently, the infection by the relevant positive blood was ruled out. Furthermore, all of other concomitant blood components were "negative" in individual NAT; therefore, imputability of this case was evaluated "unlikely."

b) Repository sample "Negative" cases (60 cases)

- "Unlikely" cases (46 cases)

In 3 cases, all of the implicated donors had subsequent blood donations with negative infectious test; therefore, considering the viral window period, the imputability between infection and blood components of these cases were evaluated "far unlikely." In the remaining 43 cases, not all the donors had subsequent blood donation; therefore, these cases were evaluated "unlikely".

- "Denied" cases (14 cases)

9 cases were expected to be a HBV carrier on the basis of positive results in the viral genome assay of the recipient's specimen before transfusion.

4 cases were confirmed to be uninfected with HB virus, which was supposed to be a non-specific reaction in the post-transfusion test by a medical institution.

One case was confirmed to be nosocomial infection in the test later by a medical institution.

[4] Cases of HBV infection (cases evaluated to have a "probable" imputability)

The summary of the cases of transfusion transmitted HBV are shown in Table 10.

Table 10. Transfusion transmitted HBV cases evaluated to have a "probable" imputability

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	Hemorrhagic gastric ulcer	Ir-RBC (2006.9)	50's	F	HBsAg/HBsAb HBcAb	Negative	0 days	HBV DNA	Positive	18 weeks	1505	18 weeks	Yes
2	Hip osteoarthritis	RBC (2006.9)	70's	F	HBsAg	Negative	7 days	HBsAg	Positive	23 weeks	1544	24 weeks	No
3	Ischemic heart disease, chronic renal failure, etc.	FFP (2006.2)	60's	M	HBsAg	Negative	14 days	HBsAg	Positive	17 weeks	1341	19 weeks	Yes
4	Bladder cancer	Ir-RBC-LR (2007.1)	70's	M	HBsAg/HBsAb HBcAb	Negative	1 day	HBsAg	Positive	16 weeks	◆	◆	Yes
5	Myelodysplastic syndrome	PC (2007.2)	10's	M	HBsAg/HBsAb	Negative	43 days	HBsAg	Positive	24 weeks	96	28 weeks	Yes
6	Atonic bleeding after vaginal birth	Ir-RBC-LR (2007.6)	30's	F	HBV DNA/HBcAb	Negative	0 days	HBV DNA	Positive	16 weeks	2884	26 weeks	Yes
7	Prostate cancer	Ir-RBC-LR (2007.8)	60's	M	HBsAg/HBsAb HBcAb	Negative	0 days	HBsAg	Positive	9 weeks	◆	◆	Yes
8	Aplastic anemia	Ir-PC (2006.11)	60's	M	HBsAg	Negative	252 days	HBsAg	Positive	9 weeks	◆	◆	Yes
9	Myelodysplastic syndrome	Ir-PC (2006.9)	70's	M	HBsAg/HBsAb HBcAb	Negative	79 days	HBV DNA	Positive	15 weeks	◆	◆	Yes
10	Chronic renal failure	Ir-RBC (2006.9)	80's	M	HBsAg	Negative	19 days	HBV DNA	Positive	29 weeks	105	33 weeks	No
11	Heart failure, aortic stenosis, ascending aortic aneurysm	Ir-RBC (2006.6)	70's	F	HBsAg/HBsAb	Negative	15 days	HBsAg IgM-HBcAb	Positive	35 weeks	◆	◆	Yes
12	Acute renal failure, disseminated intravascular coagulation	Ir-PC (2007.1)	70's	M	HBsAg	Negative	1 day	HBsAg	Positive	11 weeks	73	17 weeks	No
13	Gastric premalignant lesion	RBC-LR (2007.6)	80's	M	HBsAg	Negative	11 days	HBsAg	Positive	16 weeks	◆	◆	No

* No.1–7: voluntary-report, No.8–13: post-donation information.
◇: Blood components in which viral nucleic acid was detected.
◇-◇: Test results by medical institution (Positive result-confirmed point)
◆: Case with no increased ALT, or lacking comparison data

[5] Others

Considering HBV reactivation after immunosuppressive therapy and/or chemotherapy in patients with a history of HBV infection, the repository sample negative cases (unlikely and far unlikely cases: 46 in total) were classified into 3 groups by the results of serological test before transfusion (HBcAb and HBsAb): 20 cases of HBV-uninfected, 7 cases of retrospective HBV infection, and 19 cases of unknown HBV infectious status. The patients with hematologic disease and/or solid tumor who underwent immunological therapy/chemotherapy in the above groups were 7 (35%), 6 (86%), and 12 (63%), respectively.

(2) HCV

[1] Number of reported cases and implicated components in 2007

A total of 41 cases were reported from medical institutions and the implicated blood components were 210 RBC, 60 FFP, and 108 PC; 378 in total.

[2] Results of examinations by JRCS

In individual HCV-NAT, 1 of 378 repository samples (1/41 cases) was found to be "positive." All of the remaining 377 relevant repository samples (40 cases) were "negative."

[3] Evaluation of imputability

a) Repository sample "Positive" case (1 case)

The homology was confirmed between the donor and patient HC viruses; therefore, this case was evaluated to have a "probable" imputability.

b) Repository sample "Negative" cases (40 cases)

• "Unlikely" cases (32 cases)

In 27 cases, some of the donors did not have subsequent blood donation; therefore, these cases were evaluated to have a "unlikely" imputability between infection and blood components considering the HC viral window period. In the remaining 5 cases, all of the donors has subsequent blood donation with negative infection test; therefore, these cases were evaluated to have an "far unlikely" imputability.

• "Denied" cases (8 cases)

4 cases were expected to be HCV carriers on the basis of positive results in the viral genome assay of the recipient's specimen before transfusion.

4 cases were confirmed to be uninfected with HCV which supposed to be non-specific reaction in the post-transfusion test by medical institution.

[4] Case of HCV infection (evaluated to have a "probable" imputability)

The case of HCV infection is shown in Table 11.

[5] Others

Of the 32 cases with a "unlikely" imputability, 21 (66%) were HCV "negative" before transfusion and "positive" after transfusion, and invasive treatment that can be a cause of iatrogenic infection was conducted in 15 of them.

Table 11. HCV-positive cases (cases evaluated to have a "probable" imputability)

Case 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	Aplastic anemia	Ir-RBC-LR (Aug. 2007)	50s	F	HCV RNA HCV-core antigen HCV antibody	Negative	64 days	HCV-core antigen	Positive	6 weeks	◆	◆	Yes

* This case is reported by information of look back study. (see the following page)

◇ Type of donated blood in which viral nucleic acids were detected

◇◇ Test results in medical institutions (date of positive definition)

◆◆ Case with no increase in ALT or no comparative data

(3) Bacterial infection

[1] Number of reported cases and implicated blood components in 2007

A total of 30 cases were reported from medical institutions and the implicated blood components were 29 RBC, 6 FFP, and 12 PC; 47 in total.

[2] Results of examinations by JRCS

All 47 implicated components (30 cases) were "negative" in the bacterial culture test with blood used for transfusion (the relevant bag) or sterilization test with the component simultaneously manufactured plasma.

[3] Evaluation of imputability

a) Bacterial culture of blood component "Positive" cases (0 case)

b) Bacterial culture of blood component "Negative" cases (30 cases)

• "Unknown" cases (13 cases)

The result of the sterilization test with the component simultaneously manufactured plasma was negative.

• "Unlikely" cases (17 cases)

The results of the bacterial culture test with blood used for transfusion (the relevant bag) were negative.

[4] Analysis results of suspected cases of bacterial infection

Table 12. Summary of examination by patient's blood culture result

	Results of recipient's blood culture			Total
	Positive	Negative	Unknown	
Case examined with the implicated blood components (relevant bag)	12	4	1	17 (57%)
Case examined with plasma simultaneously manufactured	5	6	2	13 (43%)
Total	17 (57%)	10 (33%)	3 (10%)	30

* Test results of all implicated blood components were negative.

[5] Others

A) Bacteria detected in recipient's blood culture of 12 "negative" cases in the bacterial culture test with the relevant bag

(a) RBC recipients (8 cases)

- CN-*Staphylococcus,*
- *Staphylococcus epidermidis,*
- *MRSE,*
- *Citrobacter freundii,*
- *Staphylococcus aureus (Staphylococcus aureus, Pseudomonas aeruginosa,* and MRSA were detected in pre transfusion blood culture)
- *Klebsiella pneumoniae/Pseudomonas fluorescens/ Pseudomonas putida,*
- *Enterobacter aerogenes/Staphylococcus hominis (CNS),*
- *Enterococcus faecalis*

(b) PC recipients (4 cases)

- *MRSA,*
- *Streptococcus mitis,*
- *Eubacterium sp.*
- *Staphylococcus haemolyticus (Pantoea agglomerans* was detected in pre transfusion blood culture)

(4) CMV

[1] In 2007, 2 cases were reported from medical institutions. Both cases involved extremely low birth weight infants (birth weights were 562 and 798 g at the 24th and 27th week of gestation, respectively) and the implicated blood components were 6 RBC, 1 FFP, and 1 PC ; 8 in total. CMV negative blood components were not requested by medical institute in both cases.

* Case 1 (birth weight 562 g at 24th week of gestation), implicated components (RBC, 5; FFP, 1; PC, 1) and Case 2 (798 g at 27th week of gestation), implicated component (RBC, 1)

[2] Results of examinations by JRCS

CMV IgG and IgM antibodies were tested with repository samples of the implicated donor.

- No. 1: CMV IgG-positive /IgM-negative in 6 specimens and CMV IgG-negative/ CMV IgM-negative in 1 specimen.
- No. 2: CMV IgG-positive/IgM-negative

[3] Evaluation of imputability

Both the cases were evaluated to have an "unknown" imputability between infection and blood components.

(5) CMV and EBVsubinfection

[1] In 2007, 1 case was reported from a medical institution. The case was an extremely low birth weight infant (birth weight was 674 g at the 24th week of gestation) and the implicated blood components were 2 RBC suspected subinfection of CMV and EBV and 3 RBC and 1 FFP suspected infection of EBV; 6 components in total.

[2] Results of examinations by JRCS

CMV IgG and IgM antibodies and/or EBV anti-Viral capsid antigen (VCA) IgG, and IgM antibodies were tested with repository samples.

- CMV and EBV subinfection (2 specimen):
  One specimen was CMV IgG-positive/IgM-negative, anti-VCA IgG-positive, the other was CMV IgG –false positive/IgM-negative, anti-VCA IgG-positive.
- EBV(4 specimen):
  Anti-VCA IgG-positive/IgM-positive in 4 specimens

[3] Evaluation of imputability

This case was evaluated to have an "unknown" imputability between infection and blood components.

(6) Human parvovirus B19

[1] In 2007, 2 cases were reported from medical institutions. The implicated blood components used in 2 cases were 32 RBC, 45 FFP, and 30 PC; 107 components in total.

* One of the two cases had a liver transplantation and the implicated components were 27 RBC, 45 FFP, and 30 PC.

[2] Results of examinations by JRCS

- Case of liver transplantation

Of 102 repository samples of the implicated components, 9 were parvovirus B19 DNA-positive, IgM antibody-negative, and IgG antibody-positive, and the remaining 93 were DNA-negative.

- the Other case

All 5 repository samples of the implicated components were B19 DNA-negative.

[3] Evaluation of imputability

- Repository sample "Positive" case

The recipient had a IgG antibody-positive alone before and after transfusion and was a liver-transplant patient,; therefore, the case was evaluated to have an "unknown" imputability between infection and blood components because the patient had increased susceptibility to infection and the infection from viral marker positive components was not confirmed.

- Repository sample "Negative" case

The case was evaluated to have a "unlikely" imputability between infection and blood components. The physician in charge who was informed of the survey result showed his revaluation, "The cause of pure red-cell aplasia (PRA) was unknown; however, it is difficult

to conclude that the cause of PRA was infection with human parvovirus B19. Reticulocytes increased 5 days after and provided relief of PRA. Therefore, this case is evaluated to have no causal relationship."

(7) Human T-cell leukemia virus type 1 (HTLV-1)

[1] In 2007, 2 cases were reported from medical institutions. The implicated blood components used in 2 cases were 10 RBC.

[2] Results of additional examinations by JRCS

All 10 repository samples of implicated components were negative in the HTLV-1 antibody test (PA, EIA, and IF methods).

[3] Evaluation of imputability

• Repository sample "Negative" cases (2 cases)

In 1 case, the possibility of infection by implicated componets was "Denied" because the recipient already had a positive serological test before transfusion. Another case was evaluated to have a "Unlikely" imputability between infection and blood for transfusion because none of the donors had subsequent blood donation.

(8) HAV

[1] In 2007, 1 case was reported from a medical institution. The implicated blood products were 4 RBC, 6 FFP, 10 in total.

[2] Results of additional examinations by JRCS

All 10 repository samples of implicated components were negative in the HAV-RNA test, and 1 of them was IgG antibody-positive in the HAV antibody test.

[3] Evaluation of imputability

• Repository sample "Negative" case

The initial report from a medical institution presented that no hepatitis finding was observed although HAV antibody was positive after transfusion. However, it was considered that the HAV antibody transferred from the transfused FFP, and the case was evaluated to have a "unlikely" imputability between infection and blood components. The physician in charge who was informed of the survey result showed his revaluation, "This is a positive case due to the antibody transfer and is evaluated to have no causal relationship."

4. Periodic infection reports for biologic products

1) Procedures of periodic infection reports

A new system for periodic infection reports was established in accordance with the enforcement of the revised "Pharmaceutical Affairs Law" in July 2003 and JRCS started to submit the periodic infection reports according to the specified form to the Minister of Health, Labour and Welfare through the Pharmaceuticals and Medical Devices Agency as a marketing approval holder of biological products. The Law requires submitting the report for each product approved for manufacturing and marketing every 6 months and the details of the report are specified to 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 government, JRCS collects information from academic journals, various literature, and websites specified by the government and reviews and assesses them. Furthermore, JRCS collects, assesses, and reports novel studies and information on prion diseases such as Creutzfeldt-Jakob disease (CJD).

JRCS performs the following procedures for the selection and assessment of information for periodic infection reports:

(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 JRC 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.

An example of the flowchart of information selection and its schedule are shown in Figures 11 and 12, respectively.

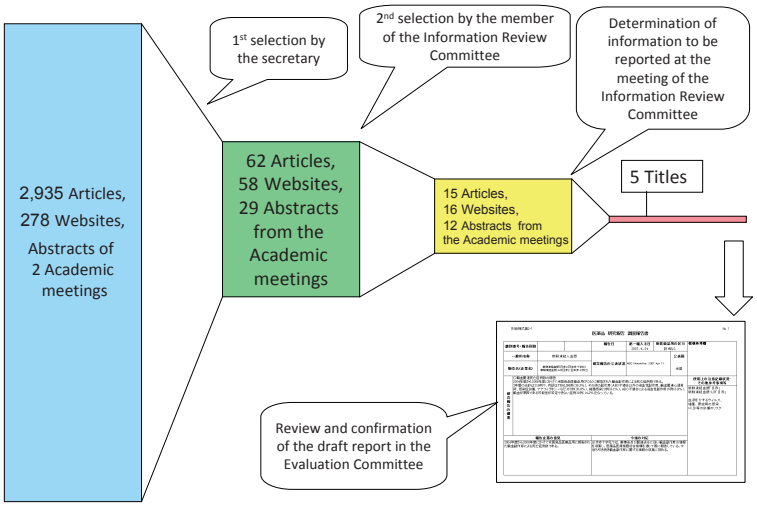


Figure 11. Flowchart of information selection (example)

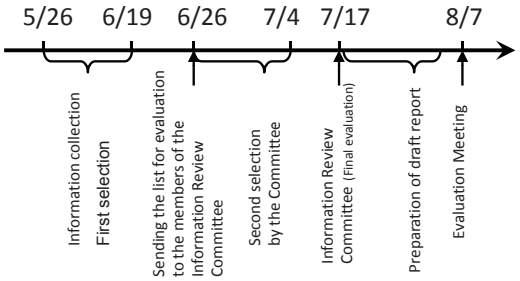


Figure 12. Schedule for monthly evaluation (example)

2) Information collected in 2007

88 cases of information were selected and reported to the Minister of Health, Labour and Welfare, out of 33,271 studies, 811 websites, and 295 academic meetings.

Chagas disease was one of the major issues in 2007, affecting the safety of blood products of Latin American immigrants in Europe and the United States. Since Japanese-Latin American workers have been increasing also in Japan, safety measures will be required in future. Therefore, JRCS reported the information of the approval of a test reagent for Chagas disease by FDA and the implementation of blood donor screening in the U.S., the increasing infections due to transfusion and transplantation in regions other than Latin America, and the possibility of transfusion related transmission in Japan.

Regarding avian influenza (H5N1), JRCS reported the information that the H5N1 virus was first detected from poultry in Japan and that the virus is inactivated by normal inactivation procedures for plasma derivatives.

As the information concerning prion, JRCS reported the prion detection in human breast milk, animal milk and commercial milk and the fourth vCJD patient with possible infection by transfusion in the UK.

For the spreading chikungunya virus infection, which became problem in 2005, JRCS reported the information that a Japanese living in Sri Lanka was infected and a large domestic outbreak occurred in Italy.

Among other emerging and reemerging infectious diseases, arbovirus infections were mainly reported: Kunjin virus and Ross River virus outbreak in Australia, Rift Valley fever virus in Kenya, and Zika virus in Micronesia.

Table 13. Number of reports for the past 3 years

	2005	2006	2007
Articles	34,268	35,261	33,271
Websites	703	645	811
Presentations of academic meetings	282	274	295
Total information reviewed	35,253	36,180	34,377
Information reported	81	63	88

* The number of articles and websites is the total information to be reviewed, and the presentations of academic meetings 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 meetings to be reviewed in the year.
* Information reported is the amount of information reported after review.

5. Reports on measures in foreign countries and reports on studies

The reports on measures in foreign countries and reports on studies are provided by the Article 77-4(2) of the Pharmaceutical Affairs Law and Article 253 of the Ordinance for Enforcement of the Pharmaceutical Affairs Law. Reports on measures in foreign countries are submitted when JRCS obtains information concerning "the enforcement of measures for preventing health hazards from occurring or spreading including discontinuation of manufacturing, importing or distributing, or recall or disposal of foreign pharmaceutical products," which is related to JRC products approved for manufacturing and marketing. Reports on studies are submitted when JRCS obtains information concerning "the study reports showing that cancer or other serious disease, disorder, or death is possibly caused by the relevant pharmaceutical product or a foreign pharmaceutical product or infection by its use, or incidences of adverse reactions due to the relevant pharmaceutical product or a foreign pharmaceutical product or that of infection by its use significantly changed, or the relevant pharmaceutical product has no efficacy or effect approved", which is related to JRC products approved for manufacturing and marketing.

Reports on measures in foreign countries and reports on studies may be submitted even if the pharmaceutical product is not manufactured or distributed by JRCS. Such products refer to products used in other countries whose active ingredients are same as that of blood products manufactured or distributed by JRCS, including such products with different administration route, administration and dosage, or efficacy and effect.

1) Reports on measures in foreign countries

The reports on countermeasures to the Minister of Health, Labour and Welfare in 2007 are listed in Table 14.

Table 14. Reports on countermeasures taken in foreign countries in 2007

Information source	Title	Product item
FDA (US)	FDA Proposes Barring Certain Cattle Material From Medical Products As BSE Safeguard	Cross Eight M (FVIII)
AABB (US)	Blood Donor History Questionnaire Version updated (incorporating criteria from the draft FDA vCJD guidance, Aug 2006, regarding screening donors for a history of receiving a transfusion in France since 1980)	Blood and blood components for transfusion
AABB (US)	West Nile Virus – Recommendations for Triggering Individual Donation Nucleic Acid Testing and Developing a Communication Plan	Blood and blood components for transfusion
FDA (US)	"Look back" for Hepatitis C Virus (HCV): Product Quarantine, Consignee Notification, Further Testing, Product Disposition, and Notification of Transfusion Recipients Based on Donor Test Results Indicating Infection with HCV	Blood and blood components for transfusion

FDA: The U.S. Food and Drug Administration
AABB: The American Association of Blood Banks

2) Reports on studies

The studies reported to the Minister of Health, Labour and Welfare in 2007 are listed in Table 15.

Regarding the post hoc study on resuscitation of critically ill patients with brain injury, a study report submitted described that the mortality rate in fluid resuscitation with albumin was higher than that in fluid resuscitation with saline.

Table 15. Reports on studies in 2007

Information source	Title	Product item
N Engl J Med 2007; 357:874-884	Comparison of fluid resuscitation with between saline and albumin in patients with traumatic brain injury	Red Cross Albumin

6. Post-donation information

Of post-donation information (PDI), self-reported AIDS information (PDI-1), information on donor's health condition (PDI-2), post-donation information on ineligible donors at interview (PDI-6), and other safety information (PDI-other) are described below.

1) Number of cases surveyed on the basis of PDI

The number of cases surveyed on the basis of PDI is summarized in Table 16.

A total of 4,212 reports on post-donation information were submitted and included 20 reports on self-reported AIDS information (PDI-1), 43 on information on donor's health condition (PDI-2), 3,901 on post-donation information on ineligible donors at interview (PDI-6), and 248 on other safety information (PDI-other).

Table 16. Number of surveyed cases on the basis of post-donation information by month

	Jan.	Feb.	Mar.	Apr.	May	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.	Total
PDI-1 (Self-reported AIDS information)	3	1	2	3	1	0	4	0	0	3	2	1	20
PDI-2 (Information on donor's health condition)	2	2	5	2	5	6	4	7	1	4	1	4	43
PDI-6 (Post-donation information on ineligible donors at interview)	468	430	335	330	359	302	314	330	285	295	237	216	3,901
PDI-other (Other safety information)	13	14	15	22	27	19	31	18	17	25	21	26	248
Total	486	447	357	357	392	327	353	355	303	327	261	247	4,212

(1) The breakdowns of the post-donation information is shown in Figure 13.

[1] The information on donor's health condition included HCV infection (12 cases), measles (5), HBV infection (4), herpes zoster (3), Parvovirus B19 infection (3), influenza (3), varicella(chicken pox) (3), HIV infection (2), possible cancer (2), leukemia (2), HAV infection (1), mumps (1), idiopathic viral infection (1), and fever and diarrhea (1).

[2] The post-donation information on ineligible donors at interview included 3,352 cases related to travel to Europe (3,289 cases of 1 day or more stay in the UK among them), 30 of blood donation within 4 weeks after return from abroad, 422 of transfusion history, 54 of hepatitis virus carrier, 10 related to nonexclusive heterosexual contact etc., 10 of malaria history, 8 of relatives diagnosed with CJD or a related disease, 4 of idiopathic liver disease, 3 of hematological malignancy history, 2 of psoriasis (Tigason treatment unknown), 2 of growth hormone treatment, 2 of syphilis history, 1 of cancer history, and 1 of corneal transplant.

It was confirmed that the Japanese patient developed variant Creutzfeldt-Jakob disease (vCJD) who stayed for 24 days in the UK and 3 days in France; consequently, the blood donor deferral criteria was revised from a person with a history of UK stay for 30 days or more, which was set on February 21, 2005, to a person with a history of UK stay for 1 day or more between 1980 and 1996, which was set on June 1, 2005. As a result, reports immediately increased. The reports related to travel to Europe decreased by 3,627 from those in 2006 (6,979 reports) but accounted for approximately 86% of total of post-donation information.

[3] Other safety information included history of travel to malaria-epidemic regions (172 cases), piercing and tattoo-related (28), medication (12), animal bite (8), puncture accident (7), history of travel to Leishmania-epidemic regions (5), misrepresentation of age (5), blood donation using an alias (2), blood donation for HIV test (1), and others (8).

(2) The cases related to HBV, HCV, and HIV, history of transfusion, nonexclusive heterosexual contact etc., and piercing and puncture accident were examined on HBV, HCV, and HIV using repository samples by individual NAT following 2006; however, no virus was detected in any specimens. The cases of history of travel to malaria-epidemic regions and post-donation information on ineligible donors at interview concerning history of malaria were examined by the following test items; however, no plasmodium was detected in all the 230 specimens (183 cases including 1 doubled with other information).

<Malaria-related tests>

- Giemsa staining and acridine orange staining … direct observation of plasmodium by microscope
- Serological determination … detection of enzymes produced by plasmodium
- DNA genetic diagnosis … malaria DNA is extracted and DNA is amplified for detection

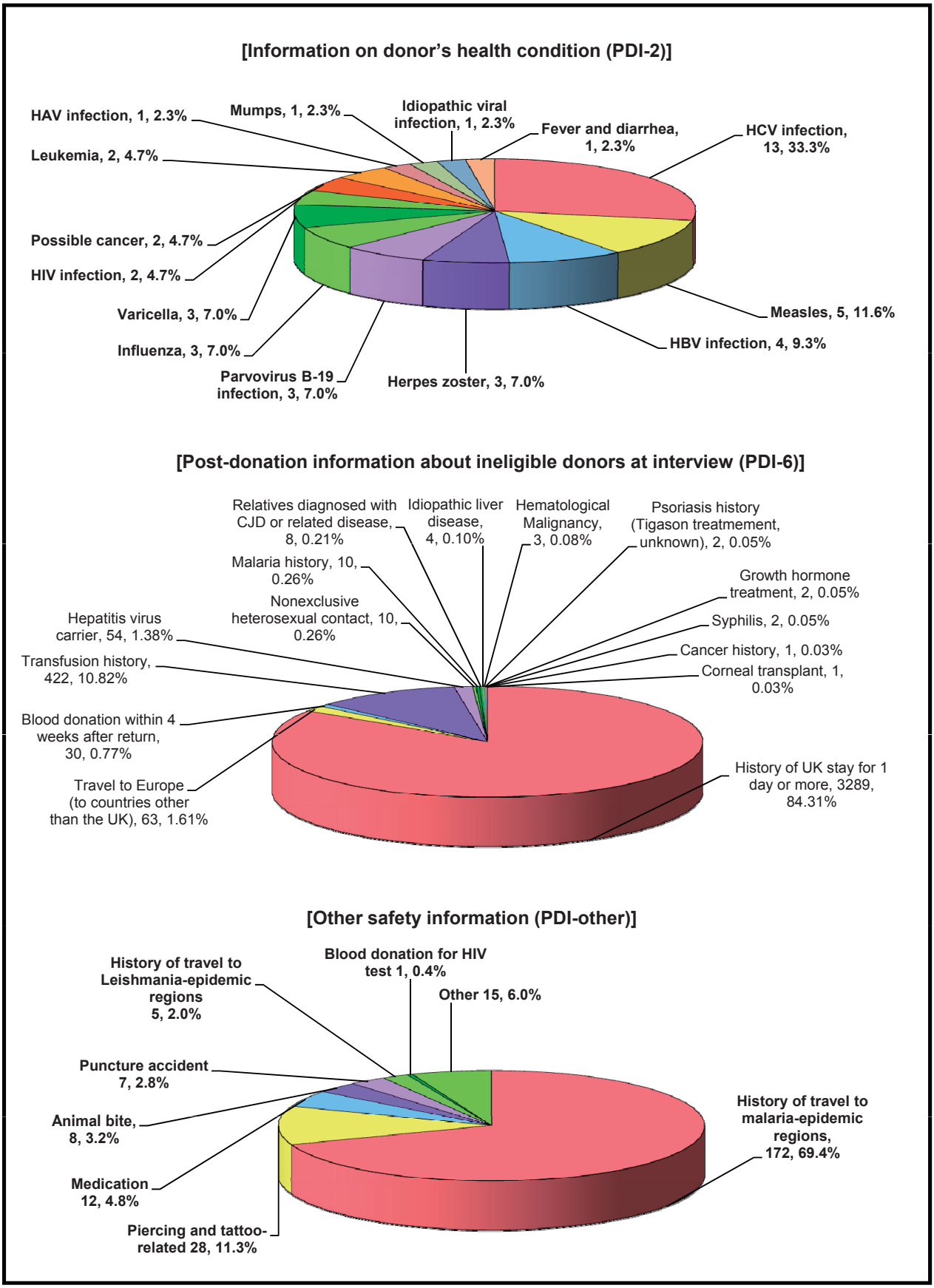


Figure 13. Breakdowns of post-donation information (2007)

2) Detailed countermeasures

(1) The countermeasures for blood components and source plasma for manufacturing plasma derivatives are shown in Figure 14.

[1] Blood components

a) Cases of witndrawing from medical institution

In a total of 27 cases, blood components which were distributed to medical institutions but not used yet were withdrawn. The cases we reported to the Minister of Health, Labour and Welfare pursuant to Article 77-4(3) of the Pharmaceutical Affairs Law included 2 cases on self-reported AIDS information (PDI-1), 1 on information on donor's health condition (PDI-2), 22 on post-donation information on ineligible donors at interview (PDI-6; including 17 cases of UK stay for 1 day or more), and 2 on other safety information (PDI-other).

b) FFP in inventory hold

A total of 444 cases were FFP in inventory hold in JRC blood centers, and they were discarded.

c) Provision of information to medical institutions

In 437 cases, information was provided to medical institutions that the transfused or expired components were implicated to some PDI cases.

[2] Source plasma for manufacturing plasma derivatives

a) Awaiting shipment

In 16 cases, the implicated blood components were not distributed from JRC blood center to storage facilities of source plasma for plasma derivatives.

b) Inventory hold in storage facilities

A total of 1,977 cases were in the condition that the implicated source plasma was stored in storage facilities of source plasma (Plasma Fractionation Center and Center for NAT and Quarantine).

c) Delivered to client manufacturer

A total of 3,882 cases were in the condition that the implicated source plasma was already put into the manufacturing process in JRC Plasma Fractionation Center or already delivered to client manufacturer of plasma derivatives.

The reasons of many cases used or delivered are that the operating procedures for post-donation information were partially revised in April 2005 and all manufacturers were informed of cases within 1 year after the date of obtaining information; furthermore, in June 2005 or after, information were provided within 4 years after for the case of history of UK stay for 1 day or more.

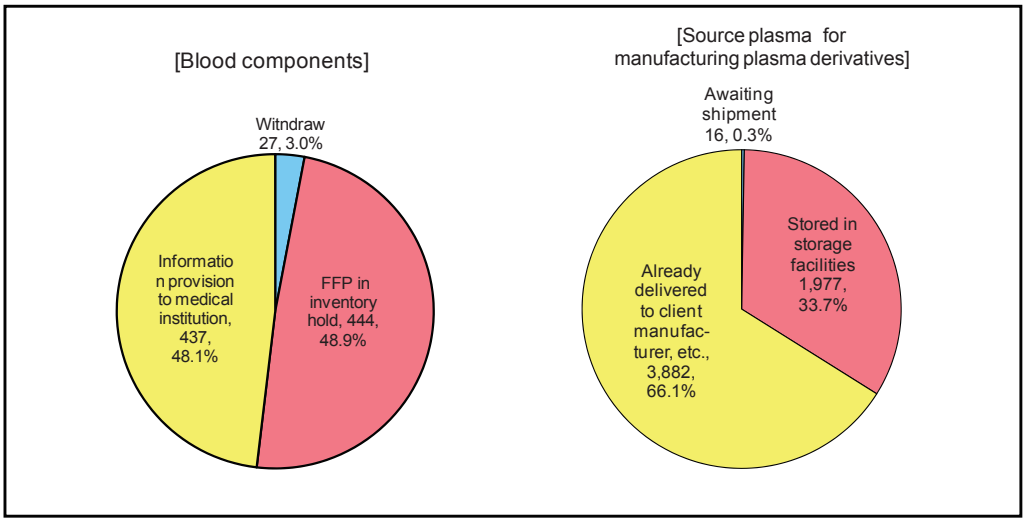


Figure 14. Countermeasures for blood components and source plasma for manufacturing plasma derivatives (2007)

(2) The breakdowns of countermeasures for post-donation information are shown in Figures 15 and 16.

[1] Blood components

The cases that the implicated blood components were withdrawn or FFP in inventory hold was discarded accounted for approximately 32% on self-reported AIDS information, approximately 24% on information on donor's health condition, approximately 51% on post-donation information on ineligible donors at interview, and approximately 81% on other safety information.

[2] Source plasma for manufacturing plasma derivatives

The cases that the implicated blood components was not delivered from JRC blood center or stored in inventory hold, it was not put into the manufacturing process of plasma derivatives accounted for approximately 88% on self-reported AIDS information, approximately 83% on information on donor's health condition, approximately 34% on post-donation information

on ineligible donors at interview, and approximately 28% on other safety information. The remaining cases were in the condition that the implicated blood component was already put into the manufacturing process in JRC Plasma Fractionation Center or already delivered to client manufacturer of plasma derivatives.

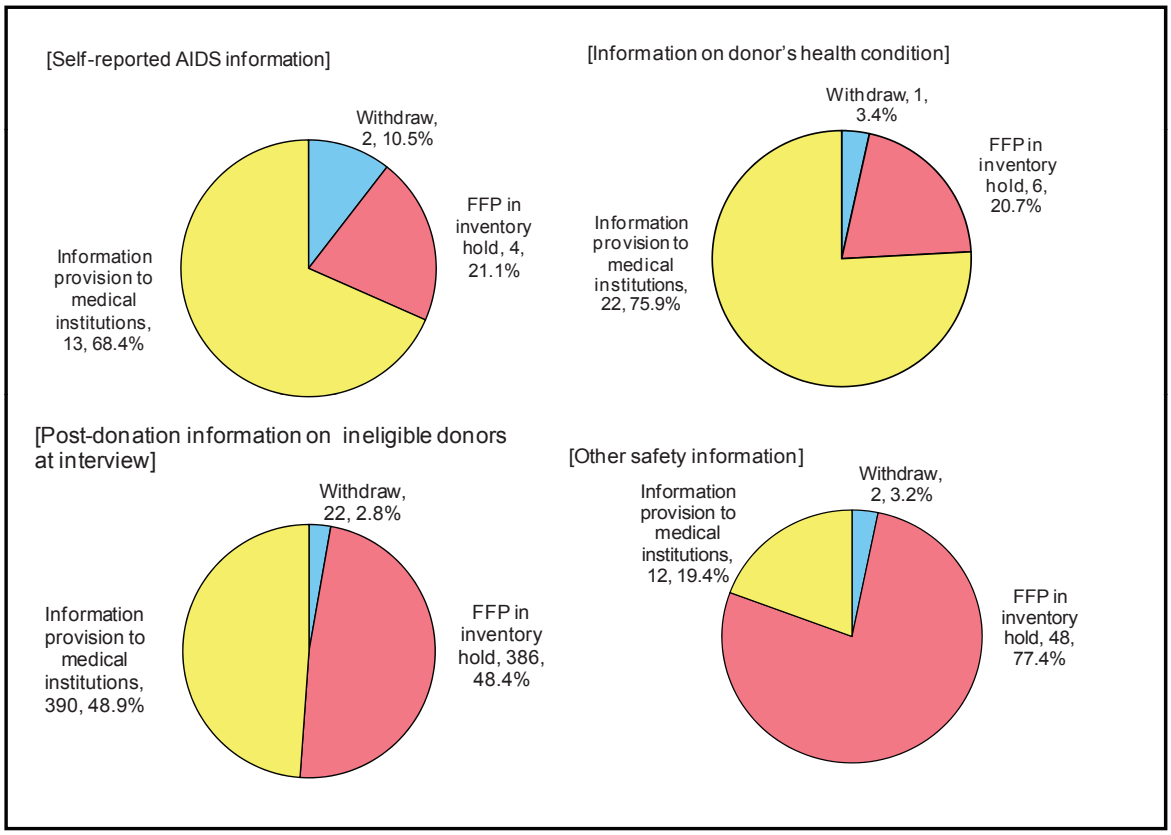


Figure 15. Breakdowns of countermeasures by type of post-donation information [blood component] (2007)

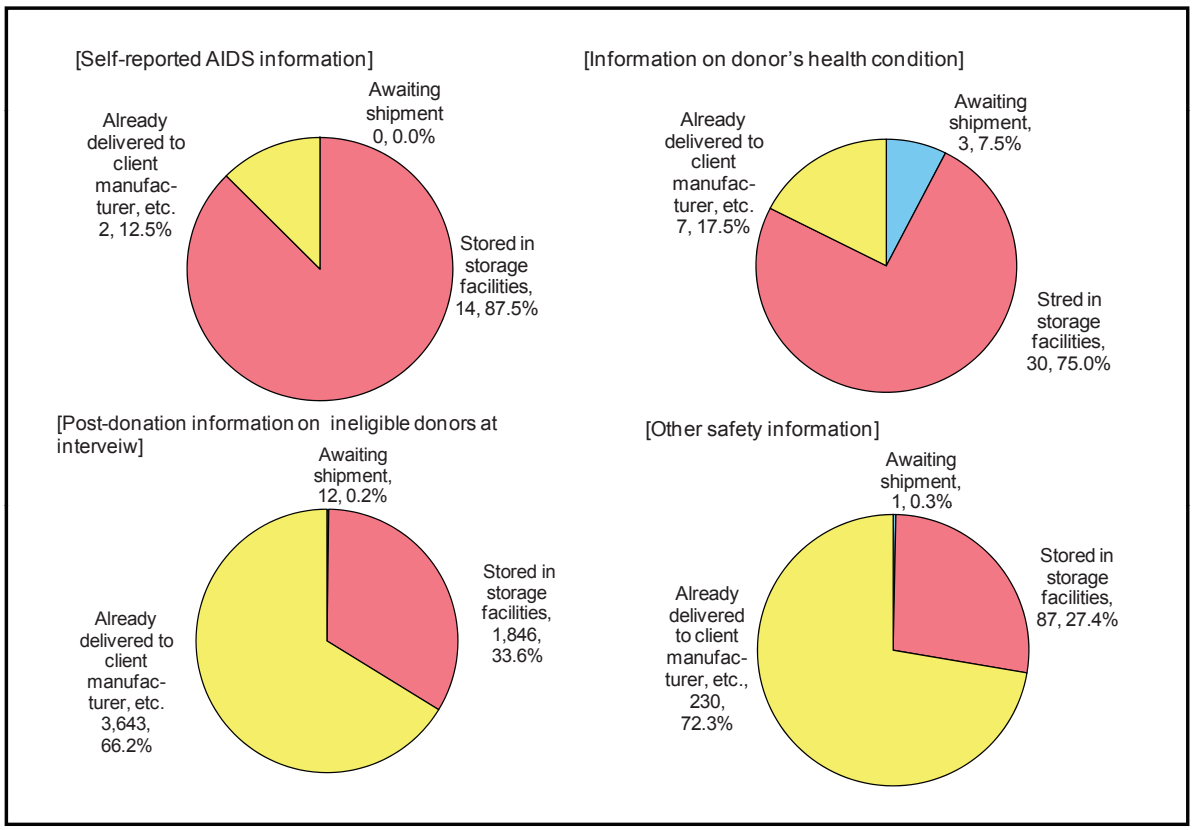


Figure 16. Breakdowns of countermeasures by type of post-donation information [source plasma for plasma derivatives] (2007)

7. Lookback studies

Lookback studies have been conducted pursuant to the "Guidelines for lookback studies on blood products," which was notified in accordance with the No. 0310009 of PFB "Notification on lookback studies on blood products," dated of March 10, 2005.

In FY 2007, the CLEIA method for serological test has been gradually introduced into JRC Blood Centers since January 2, 2008 and the test sensitivity was improved and positive conversion cases were increased.

* Lookback studies are conducted and counted by fiscal year (April 2007 to March 2008).

1) Cases of positive conversion

A total of 2,531 (121.6% to the previous year) cases were positive conversion of test results in repeat donors. By test item, HBs antigen was 296 cases (580.4% to the previous year), HBc antibody was 1,801 (109.3% to the previous year), HCV antibody was 307 (121.3% to the previous year), HIV antibody was 60 (130.4% to the previous year), HBV-NAT was 31 (64.6% to the previous year), HCV-NAT was 2 (200.0% to the previous year), HIV-NAT was 3 (100.0% to the previous year), and a combination of 2 test items or more (other multiple) was 31 (96.9% to the previous year). Substantial increases in serological test positive are considered to be the result of the introduction of CLEIA method.

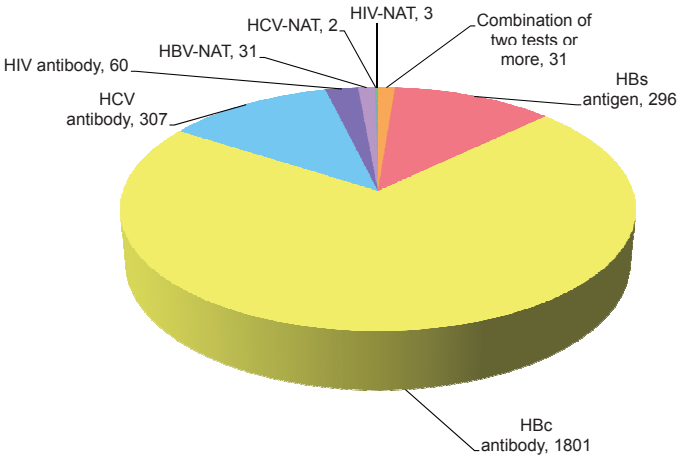


Figure 17. Number of positive conversion in repeat donors

2) Individual NAT results

Individual NAT against HBV, HCV, and HIV was conducted on items of positive conversion in 2,694 repository samples. The number of tests for HBs antigen was 386 cases (643.3% to the previous year), HBc antibody was 1,813 (108.0% to the previous year), HCV antibody was 338 (126.1% to the previous year), HIV antibody was 67 (131.4% to the previous year), HBV-NAT was 50 (51.5% to the previous year), HCV-NAT was 2 (200.0% to the previous year), HIV-NAT was 3 (100.0% to the previous year), and combination of 2 test items or more (other multiple) was 35 (100.0% to the previous year). The positive result in individual NAT was observed in only HBV in 28 cases.

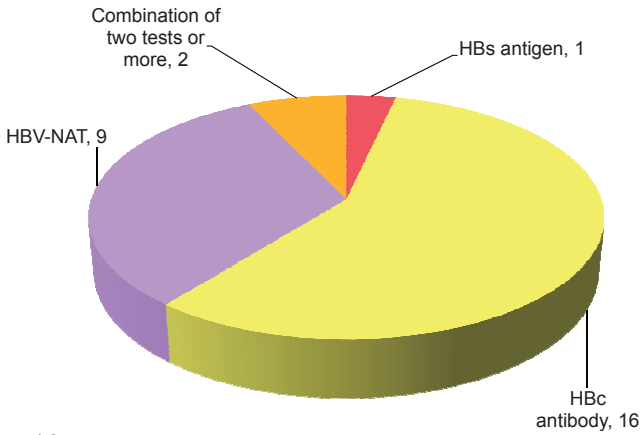


Figure 18. Positive cases in individual NAT (percent of positive conversion types)

3) Details of blood recipients

Information was provided to medical institutions in which the implicated 2,708 blood components (HBV, 2,314; HCV, 317; HIV, 72; and multiple, 5) were used.

The information from medical institutions indicated that 26 of 28 products were used and 4 patients had HBV-positive conversion, 9 did not have positive conversion, and 10 died from the primary disease. The remaining 2 products were disposed in medical institutions.

Table 16. Information on blood recipients

Positive blood in individual NAT	
	HBV
Used in hospital	26
Disposed in hospital	2
Total	28

Table 17. Details of blood recipients

Conditions of recipients	
	HBV
Positive conversion of HBV marker	4
Non-conversion of HBV marker	9
Death (due to primary disease)	10
Details unknown	3

Afterword

This annual report describes information including adverse reactions and infectious diseases from nationwide medical institutions to JRC Blood Centers and infection information based on post-donation information etc. and their analysis and evaluation and countermeasures. The authors are the Adverse Reactions Section 1 (Infections, Hemolytic adverse reactions), Adverse Reactions Section 2 (Nonhemolytic adverse reactions), Lookback Study Section (Post-donation information, Lookback studies), Infection Disease Section (Periodic Report on Infections), and respective teams on Reports on measures in foreign countries and reports on studies.

JRCS will contribute to Haemovigilance in Japan and improvement of transfusion safety.

Haemovigilance by JRCS 2007

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