Haemovigilance

Annual Report

2001 and 1993-2001

Japanese Red Cross Society

Issued in July 2003

Issued by Transfusion Information Department,
Japanese Red Cross Central Blood Center

Shuwa Shiba Park Building B-14, 2-4-1 Shiba-Koen, Minato-ku,
Tokyo, 105-0011

TEL 03-5733-8226
FAX 03-5733-8235

Acknowledgment

Japanese Red Cross Society (JRCS) has been collecting information on adverse reactions and infectious diseases nationwide as part of Haemovigilance since January, 1993, in order to ensure maximum blood safety as well as to prevent adverse events caused by blood products. European and some other countries have recently been trying to establish Haemovigilance. JRCS is a pioneer in this field. Marking the tenth year of the system last year, here we issue the present annual report.

Haemovigilance is different from one country to another, depending on the national health care system and political or social perspectives on blood safety. The present report shows Haemovigilance implemented by JRCS beyond regulations, including donor tracing by collecting post-donation information based on reporting system of adverse reactions and infectious diseases defined in the Pharmaceutical Affairs Law. We focus on ensuring safety of blood product recipients by investigating and evaluating causes based on reported adverse reactions and infectious diseases provided by medical institutions and by monitoring unknown diseases in donors.

Needless to say, JRCS's Haemovigilance has been supported by the generous understanding and cooperation of donors and medical professionals. We express our gratitude to donors, medical professionals and patients throughout the country who have provided us information on adverse reactions and infectious diseases.

Japanese Red Cross Society

Table of Contents

Introduction

This annual report describes data from reported adverse reactions and infectious diseases submitted to blood centers of JRCS on a voluntary basis from medical institutions nationwide, as well as their analysis, evaluation and actions taken accordingly. We focus on detecting known and unknown adverse reactions and infectious diseases in recipients, investigating causes, evaluating causal relationships between events and transfusion based on study results, taking actions to prevent adverse reactions and infectious diseases, and monitoring potential unknown diseases in donors.

Marking the tenth year of nationwide Haemovigilance last year based on the reporting system of adverse reactions and infectious diseases, which started in January, 1993, here we report the results of Haemovigilance in 2001 along with the past data.

I. Haemovigilance by JRCS

1. Haemovigilance

Haemovigilance is defined as prospective monitoring of a series of the transfusion process from donors, blood centers, medical institutions, to recipients. The procedure starts from early detection of adverse events (adverse reactions and infectious diseases) and unknown infectious diseases in recipients, followed by analysis and evaluation of the causes. The analysis should cover not only relevant blood products and plasma derivatives, but also the practical transfusion procedure in medical institutions, testing and manufacturing process in blood centers and donors' medical condition. Especially in tracing donors related with infectious diseases, it includes epidemiological study in the population or region to which the donors belong, in addition to evaluating medical condition and donors' eligibility. When an adverse event was found to be caused by errors in a blood center or medical institution, all aspects including the operation system, procedures, and methods in the organization should be reviewed for immediate actions.

Based on such analysis and evaluation, when it is predicted that adverse events or unknown infectious diseases will reappear or damages will expand, preventive measures such as alerting or proposing countermeasures to national authority, medical institutions, blood centers or relevant organizations should be taken. This series of monitoring system from detection, analysis, evaluation to actions is called Haemovigilance.

Haemovigilance by JRCS focuses on adverse reactions and infectious diseases. At the moment, practical transfusion process is supposed to be monitored by every medical institution, not by blood centers directly. Therefore, medical institutions and blood centers should share information to promote consistent monitoring and cooperate in taking measures against adverse reactions and infectious diseases.

Fig. 1 shows the scheme of Haemovigilance.

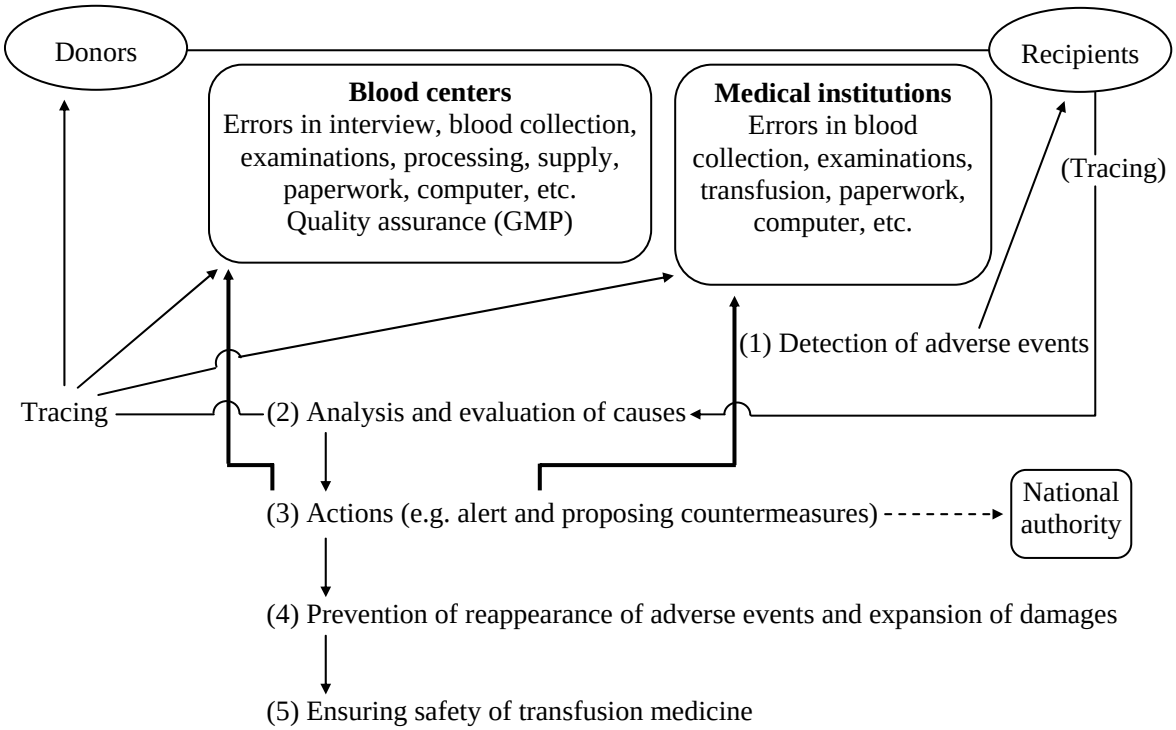


Fig. 1 Scheme of Haemovigilance

2. Procedures for dealing with voluntarily reported adverse reactions and infectious diseases

Suspected adverse reactions or infectious diseases related with blood products are reported from medical institutions to approximately 150 Medical Representatives (MRs) assigned in blood centers nationwide. The reported adverse reactions and infectious diseases include all cases from mild to severe ones. Blood centers forward information from medical institutions to Transfusion Information Department of the Central Blood Center, while they conduct tests on irregular antibodies and other items for transfused blood and recipients' blood, and review ways of handling them to search for causes. Key blood centers conduct Nucleic acid Amplification Testing (NAT) required to examine suspected post-transfusion infection. Tests for plasma proteins, potential cause for non-hemolytic adverse reactions are conducted by a laboratory in Central Blood Center. Investigation of causes related to plasma derivatives is conducted by the Plasma Derivative Center. The Division of Medical and Pharmaceutical Information, Central Blood Center controls all information related to adverse reactions and infectious diseases, and reports it to the Ministry of Health, Labour and Welfare under the Pharmaceutical Affairs Law.

The Blood Services at JRCS deals with company-wide services such as issuing instructions to blood centers nationwide. The "NAT Screening Project" established in the Blood Services is responsible for epidemiological study including analysis of viral gene in NAT-positive donors.

Reported cases are forwarded to medical institutions in order to help doctors' diagnosis. Information collected from Haemovigilance is provided to medical institutions through the media such as the journal "Transfusion Information".

Fig. 2 shows the procedures for dealing with voluntarily reported adverse reactions and infectious diseases.

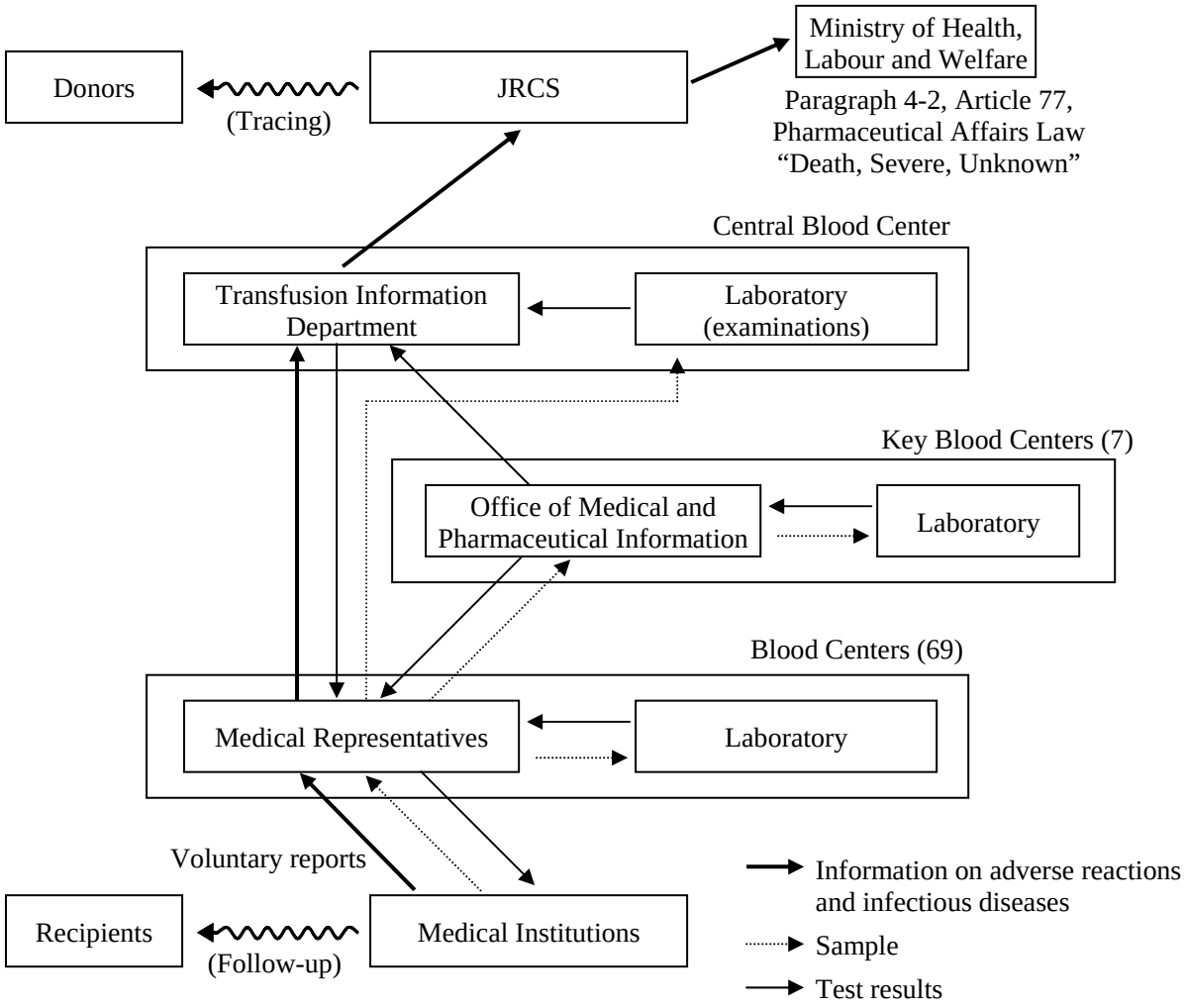


Fig. 2 Procedures for dealing with reported adverse reactions and infectious diseases

3. Establishment of the tracing system

To establish a tracing system for investigation into the causes should be prioritized in Haemovigilance. The tracing system by JRCS is characterized by storage of all donated blood samples for 10 years since September, 1996. Storing samples enables us to trace transfused blood and plasma derivatives related with adverse reactions and infectious diseases, and to confirm the causal relationship, as well as to throw light on the causes of potential unknown infectious diseases in the future. As far as we know, no other countries have stored samples for 10 years (5 years in France; not stored or data unavailable in other countries).

When viral infection is suspected, those samples are used for viral NAT for HBV, HCV, HIV, human parvovirus B19 or HTLV-1. Causal relationship between transfusion and infection

can be confirmed for these viruses by this approach.

For other viruses, we conduct maximum investigation by various approaches such as outsourcing.

Additionally, we have stored pooled source plasma for fractionation for 6 months since July, 2000. Six months is the longest storage period in the world. Storage of pooled plasma enables us to remove contaminated blood detected by tracing before it enters into the manufacturing process of plasma derivatives.

Each blood center keeps records of donors, blood collection, tests, production and supply. Central Blood Center operates a database controlling these data. The system makes tracing required for monitoring available at any time.

Table 1 Tracing system of JRCS

• Haemovigilance: Since January, 1993
• Assigned medical representatives: Approximately 150
• Storage of blood samples: Since September, 1996 6 mL, frozen, 10 years
• NAT: Individual NAT Target virus = HBV, HCV, HIV, parvovirus B19, HTLV-1, etc.
• Storing pooled source plasma: Since July, 2000 6 months
• Serological tests
• Microbiological tests

4. Descriptions of tests for adverse reactions and infectious diseases

As of March, 2003, we have conducted the following tests on blood products, plasma derivatives, and recipient blood in order to investigate into causes of adverse reactions and infectious diseases.

(1) Non-hemolytic adverse reactions

- Anti-HLA antibody
- Anti-platelet antibody
- Anti-granulocyte antibody
- Anti-plasma protein antibody: Antibody against 15 plasma proteins including anti-IgA antibody
- Plasma protein deficit

(2) Hemolytic adverse reactions

- Irregular antibody, etc.

(3) Viral infection

- Serological test, etc.: HBs antigen, HBs antibody, HBc antibody, HCV antibody, HIV-1/2 antibody, HTLV-1 antibody, human parvovirus B19 antigen, ALT
- NAT: Test for existence of viral gene, homology test for base sequence of viral gene

(4) Bacterial infection

- Blood culture test
- Bacterial identification test

(5) Post-transfusion GVHD

- Micro-satellite DNA test: Chimerism test of recipient blood

II. Results in 2001

1. Summary

In 2001, 1,290 suspected adverse reactions and infectious diseases caused by transfusion were reported by medical institutions (107.7% compared with 1,198 in 2000). It includes 1,115 non-hemolytic adverse reactions, 140 post-transfusion infection, 24 hemolytic adverse reactions, 8 post-transfusion GVHD, and 3 others. A total of 371 cases consisting of 255 non-hemolytic adverse effect, 110 post-transfusion infection (including suspected cases), and 5 hemolytic adverse reactions from voluntary reports, and 1 non-hemolytic adverse reaction from a study report was reported to the Ministry of Health, Labour and Welfare based on the Pharmaceutical Affairs Law.

The number of reported cases of suspected post-transfusion GVHD has been decreasing since 1998. Out of 8 cases reported in 2001, no case was diagnosed as post-transfusion GVHD based on clinical symptoms and micro satellite DNA test.

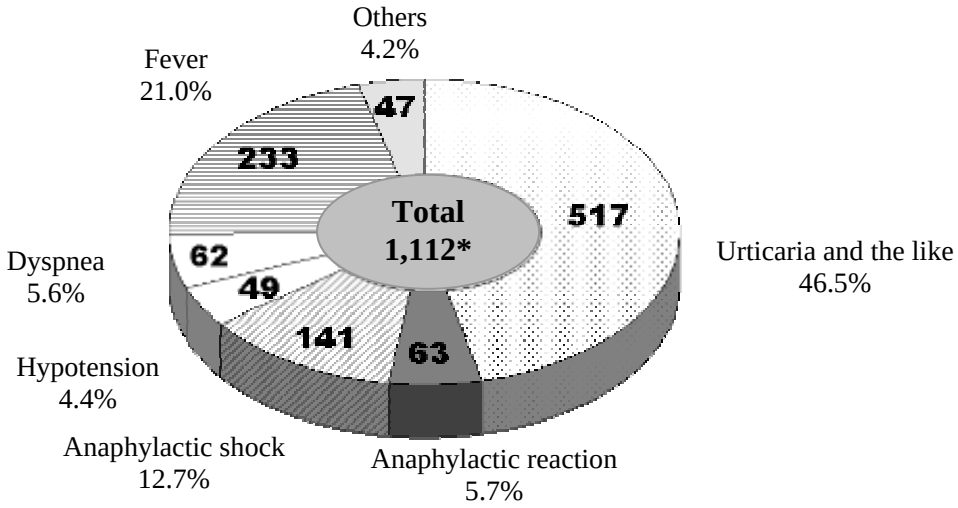
Reported post-transfusion infection contains about 50 suspected HBV and HCV cases respectively every year, but the number of suspected bacterial infection has been gradually increasing. Homology of viral gene was confirmed between recipient blood and samples of the blood product or blood products derived from the same donor only in 7 suspected HBV infection among 140 reported cases in 2001. It could not be confirmed in any HCV or HIV infection. In 10 suspected bacterial infection out of 23, recipient blood was positive and blood products were negative, while both recipient blood and blood products were negative in 13 cases. No bacterial infection was confirmed to be caused by transfusion.

While 3 suspected adverse reactions to plasma derivatives were reported, no infection was reported.

2. Non-hemolytic adverse reactions

Non-hemolytic adverse reactions occupy 86% of reported adverse reactions and infectious diseases. Fig. 3 shows the number of cases by symptom.

Urticaria and the like occupy 47% followed by 21% of fever. One of severe adverse reactions, anaphylactic reaction (anaphylactic reaction and anaphylactic shock) accounts for 18.4%. Anaphylactic shock accompanied by hypotension accounts for 12.7%, dyspnea including respiratory disorder such as lung edema 5.6%, and hypotension 4.4%.



* The total number of reported non-hemolytic adverse reactions was 1,115. Cases that a doctor in attendance observed no relationship with transfusion after reporting were excluded from analysis.

Fig. 3 The number of reported non-hemolytic adverse reactions (2001)

Fig. 4 shows the kinds of blood products in reported adverse reactions. Platelet product occupies 44% followed by 33% of red cells, and 16% of plasma products.

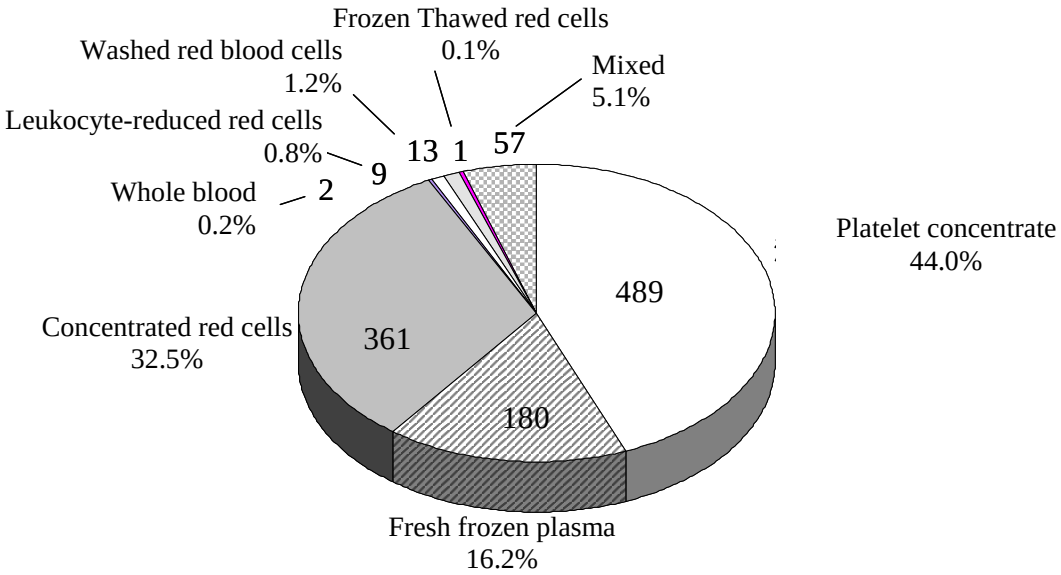


Fig. 4 Percentage of adverse reactions by kind of blood products (2001)

Fig. 5 shows symptoms of adverse reactions by kind of blood products. Many of urticaria and the like, anaphylactic reaction and anaphylactic shock were found in reports related with platelet products, and many of fever, dyspnea and hypotension were found in reports related with red cells.

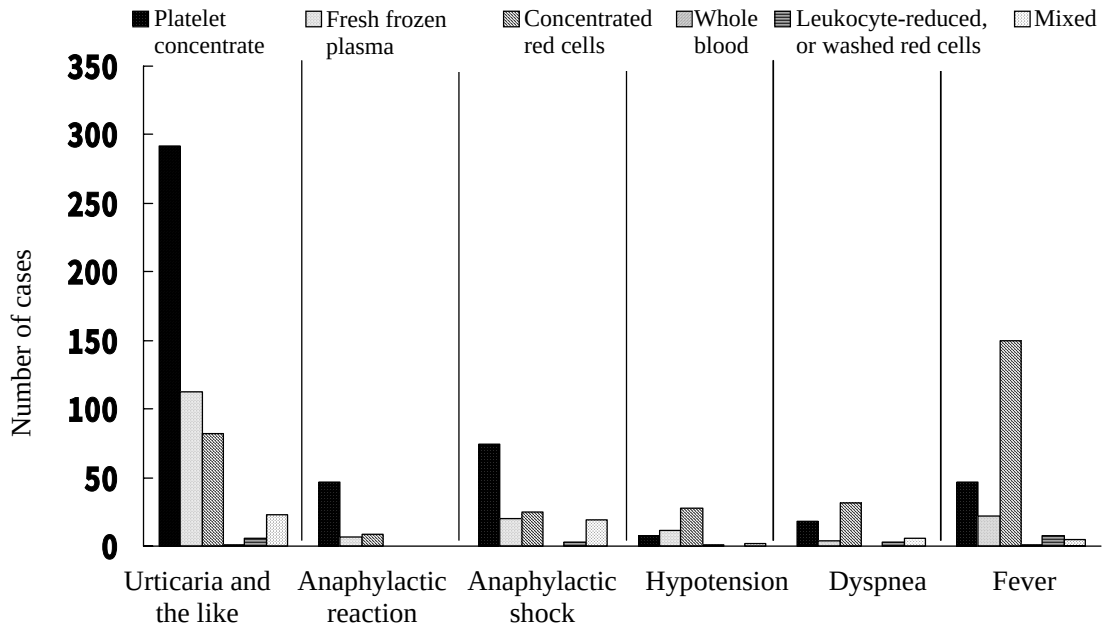


Fig. 5 Symptoms by kind of blood products (2001)

Table 2 shows the number of supply, adverse reactions and frequency by kind of blood products. Fig. 6 shows the number of adverse reactions per 10,000 dose of blood products. While only one adverse reaction was reported per 10,000 dose for plasma, red cells and whole blood each, 7 cases were reported for platelet products.

Table 2 The number of supply, adverse reactions and frequency by kind of blood products (2001)

Blood products	Number of supply	Number of reported adverse reactions	Frequency of reported adverse reactions
Platelet	699,368	489	1/1,430
Plasma	1,759,913	180	1/9,777
Red cells	3,390,827	384	1/8,830
Whole blood	23,837	2	1/11,919

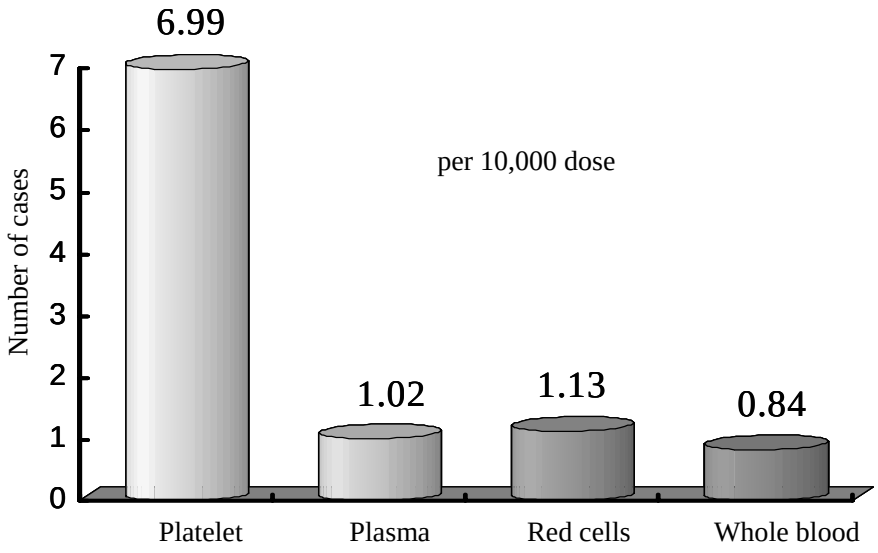


Fig. 6 The number of reported adverse reactions by kind of blood products (2001)

Fig. 7 shows the time to develop adverse reactions from starting transfusion. Hypotension develops within 10 minutes in half of cases, while most of dyspnea and fever develop after 60 minutes.

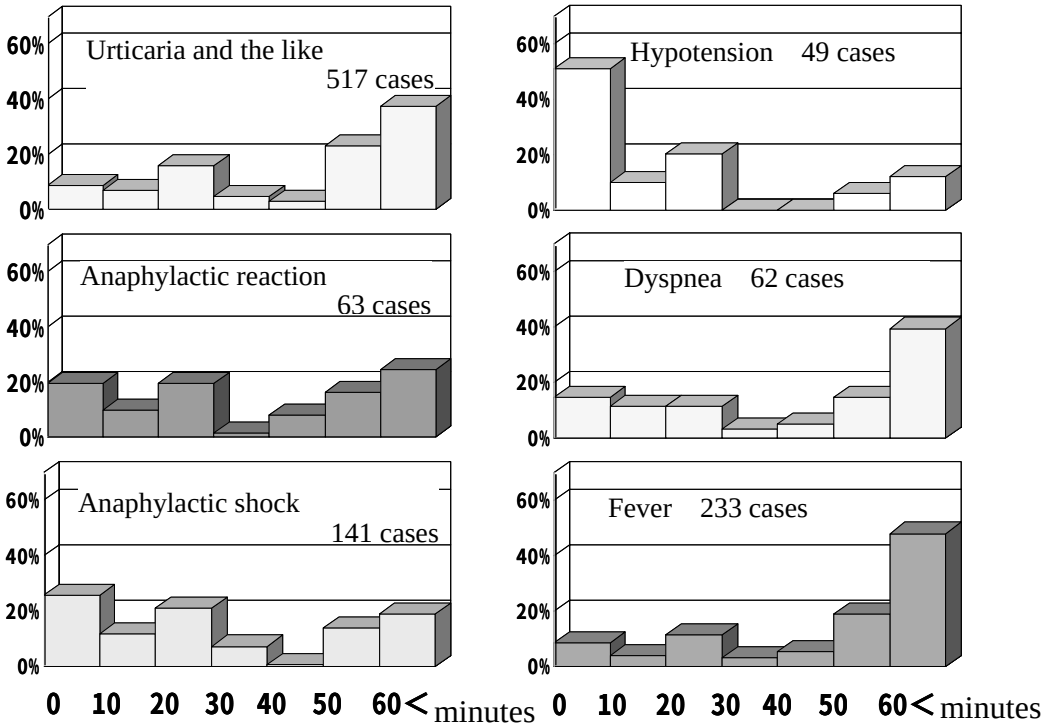


Fig. 7 Time to develop adverse reactions (2001)

Fig. 8 shows transfusion history and adverse reaction history in recipients. Seventy percent of recipients developing adverse reactions in the present report had experienced transfusion in the past. Furthermore, 30% of them had experienced post-transfusion adverse reactions. Especially, half of recipients with anaphylactic shock had experienced adverse reactions in the past.

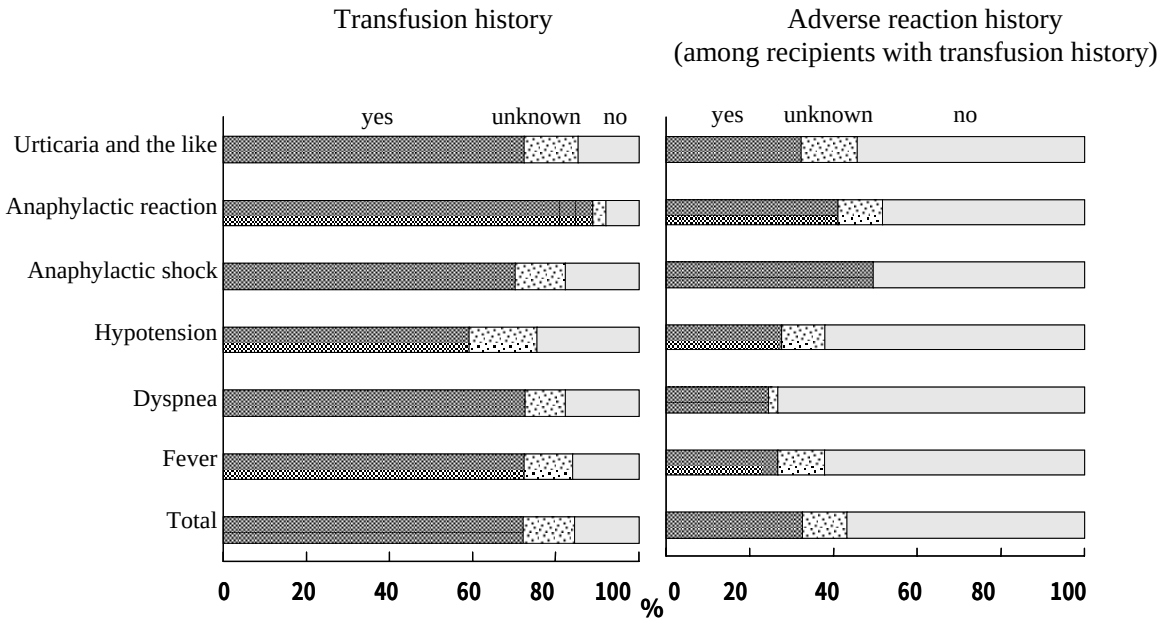


Fig. 8 Transfusion history and adverse reaction history in recipients (2001)

Fig. 9 shows the usage rate of leukocyte reduction filter in reported adverse reactions. Ninety percent of cases related with platelet transfusion used leukocyte reduction filter, while only 50% of cases related with red cells did.

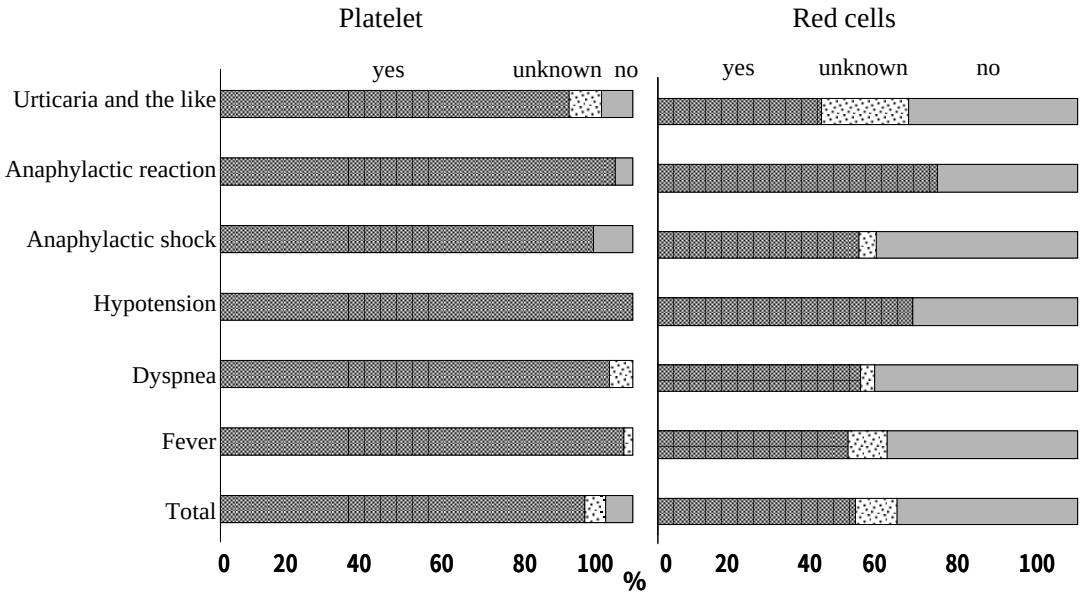


Fig. 9 Usage rate of leukocyte reduction filter (2001)

Tables 3 and 4 show the results of anti-HLA antibody and anti-platelet antibody tests in blood of recipients who developed adverse reactions and transfused blood. For anti-HLA antibody, 11.1% of recipient blood was positive. Especially, 19.3% of recipients developing fever were anti-HLA antibody positive. For anti-platelet antibody, 1.9% were positive. Half of them carried anti-HLA antibody, and 0.9% were positive only for anti-platelet antibody. Meanwhile, 2.2% of transfused blood was positive for anti-HLA antibody, and none was positive for anti-platelet antibody.

Table 3 Results of anti-HLA antibody and anti-platelet antibody tests (recipients) (2001)

Symptoms	Reported cases	Anti-HLA antibody*1			Anti-platelet antibody*2		
		Total	Positive	Percent	Total	Positive	Percent
Urticaria and the like	517	471	37	7.9%	378	8 (6)	2.1% (1.6%)
Anaphylactic reactions	63	59	5	8.5%	51	1 (0)	2.0% (0%)
Anaphylactic shock	141	127	11	8.7%	107	1 (0)	0.9% (0%)
Hypotension	49	45	3	6.7%	29	0	0 % (0%)
Dyspnea	62	60	7	11.7%	40	1 (0)	2.5% (0%)
Fever	233	218	42	19.3%	167	3 (1)	1.8% (0.6%)
Others	47	38	8	21.1%	24	1 (0)	4.2% (0%)
Total	1,112	1,018	113	11.1%	796	15 (7)	1.9% (0.9%)

*1: Excludes PC-HLA transfusion.
*2: Figure in the parentheses indicate anti-HLA antibody negative; positive only for anti-platelet antibody.

Table 4 Results of anti-HLA antibody and anti-platelet antibody tests (blood products) (2001)

Symptoms	Reported cases	Anti-HLA antibody			Anti-platelet antibody		
		Total	Positive	Percent	Total	Positive	Percent
Urticaria and the like	517	247	6	2.4%	161	0	0%
Anaphylactic reactions	63	40	0	0%	25	0	0%
Anaphylactic shock	141	76	2	2.6%	53	0	0%
Hypotension	49	31	1	3.2%	17	0	0%
Dyspnea	62	38	0	0%	18	0	0%
Fever	233	97	2	2.1%	67	0	0%
Others	47	19	1	5.3%	13	0	0%
Total	1,112	548	12	2.2%	354	0	0%

Table 5 shows the results of anti-plasma protein antibody tests for blood of recipients who developed adverse reactions. Anti-plasma protein antibody was detected in 98 cases out of 1,080 (9.1%). Table 6 shows the description.

Table 5 Results of anti-plasma protein antibody tests (recipients) (2001)

Symptoms	Reported cases	Anti-plasma protein antibody[*1]	
Urticaria and the like	517	39/502	(7.8%)
Anaphylactic reactions	63	2/62	(3.2%)
Anaphylactic shock	141	16/141	(11.3%)
Hypotension	49	4/49	(8.2%)[*2]
Dyspnea	62	5/60	(8.3%)
Fever	233	23/222	(10.4%)
Others	47	9/44	(20.5%)
Total	1,112	98/1080	(9.1%)

*1: ELISA (+), WB(+)
*2: One haptoglobin deficit

Table 6 Description of anti-plasma protein antibody positive cases (2001)

Symptoms	α2M	C9	IgA	Cp	ProS	Hp	C4	Total
Urticaria and the like	12	9	11	7	1		1	41
Anaphylactic reactions			1	1				2
Anaphylactic shock	6	5	3	2				16
Hypotension	1		1			2*		4
Dyspnea	2	1	1		1			5
Fever	10	4	5	2	1	1	1	24
Others	3	6			1			10
Total	34	25	22	12	4	3	2	102

α2M: α2Macroglobulin, ProS: Protein S, Cp: Ceruloplasmin, Hp: Haptoglobin
Multiple antibody positive (4 cases) * One Hp deficit
Urticaria and the like: α2M+C9, α2M+Cp; Fever: α2M+IgA; Others: α2M+C9

Table 7 shows the results of anti-leukocyte antibody tests for recipient blood and transfused blood in suspected pulmonary edema cases. In 3 out of 15 recipient blood, anti-HLA antibody or anti-granulocyte antibody was detected, while neither was detected in blood products.

Table 7 Detection of anti-leukocyte antibody in suspected pulmonary edema cases (2001)

In 15 cases

	Anti-HLA antibody	Anti-granulocyte antibody	Anti-HLA or anti-granulocyte antibody
Recipient	2*/15 (13.3%)	1*/15 (6.7%)	3/15 (20.0%)
Blood product	0/12 (0%)	0/12 (0%)	0/12 (0%)

* Cross reaction test with donor leukocyte was not implemented.

Fig. 10 shows the results of IgE test in 95 cases with anaphylactic shock. In more than 40%, total IgE was above the standard value.

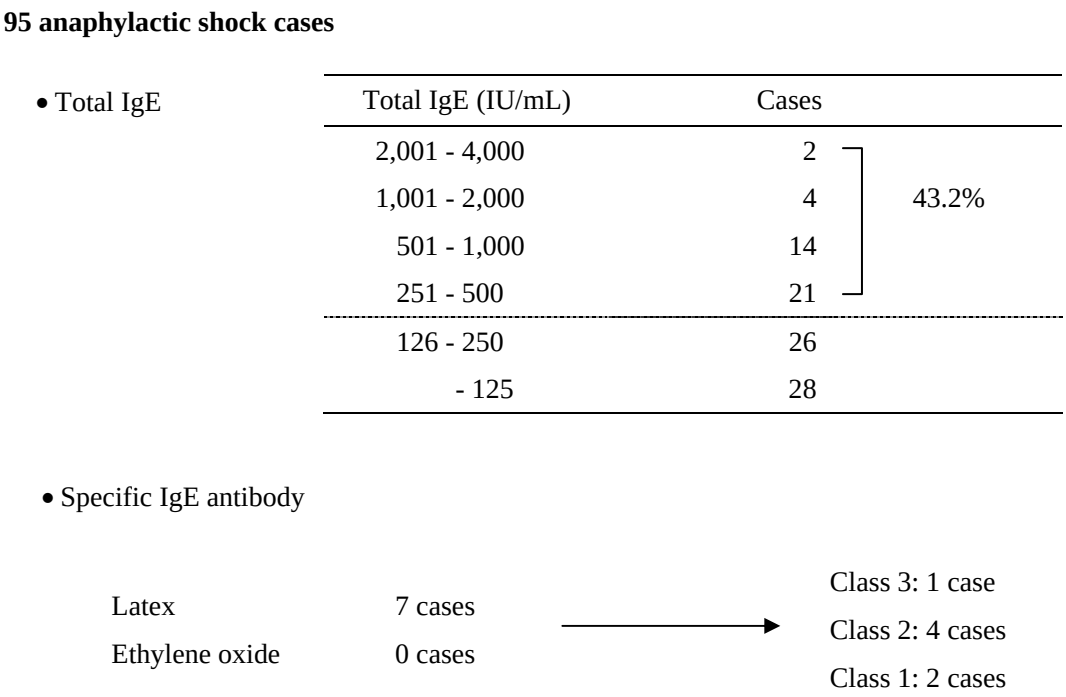


Fig. 10 Results of IgE antibody tests (recipients) (2001)

It is suggested that recipients who develop anaphylactic shock have underlying allergy diathesis. Latex specific IgE antibody positive cases were observed, although the relationship with post-transfusion adverse reactions is unclear.

3. Hemolytic adverse reactions

Of the 24 reported hemolytic adverse reactions, 16 were immediate types, and 8 were delayed types. Immediate cases are defined as one developed within 24 hours after transfusion, and delayed cases are defined as one developed after 24 hours.

Immediate hemolytic adverse reactions include 1 heterotransfusion in which group B red blood cells (MAP) was transfused into a group O patient, 1 irregular antibody positive case in which anti-E antibody and anti-c antibody were detected in recipient blood, 1 hemolysis potentially caused by heated blood before transfusion, and 1 hemolysis caused by a heater used in transfusion. For hemolysis caused by heating, medical institutions insisted on performing proper heating, but these cases were likely to be caused by heating judged from the appearance of the products.

Delayed hemolytic adverse reactions include 1 anti-E antibody positive in recipient blood (positive in cross reaction test conducted for confirmation after development of adverse reactions), 1 anti-Jk^a antibody positive, and 1 suspected anti-JMH antibody positive. In other 5 cases, nothing specific was observed.

4. Post-transfusion GVHD

As mentioned earlier, no post-transfusion GVHD was observed in 2001 as in the previous year. It is believed that this is due to deepened understanding of this disease among medical professionals and expanded usage of irradiated blood.

5. Post-transfusion infection

1) Assessment of causal relationship

In assessing the causal relationship between viral infection and transfusion, infection is thought to be caused by transfusion when markers for virus such as HBs antigen, HBs antibody, HBc antibody, HBe antibody, HCV antibody, HIV antibody, and viral gene were converted from negative to positive after transfusion, viral gene was detected in samples, and base sequence of viral gene detected from recipient blood and sample were identified in the studied area.

Table 8 shows the results of 140 cases analyzed in 2001.

Table 8 Assessment of voluntarily reported post-transfusion infection (2001)

140 cases

Causal relationship with transfusion	HBV	HCV	HIV	HTLV-1	Parvovirus B19	Bacterial infection	Hepatic damage
I*	7	0	0	0	0	0	0
II*	42	51	1	0	1	23	0
Unknown	0	0	0	0	0	0	0
Excluded	5	10	0	0	0	0	1
Total	54	61	1	0	1	23	1

I*: Likely to be caused by transfusion
II*: Unlikely to be caused by transfusion

Only 7 cases of infection were likely to be caused by transfusion based on the detection of virus by individual NAT in blood sample or blood donated at the same time, and confirmation of homology of viral gene between the sample and recipient blood. There were 42 HBV, 51 HCV, 1 HIV (simultaneous infection with HBV), and 1 parvovirus B19 infection cases that were unlikely to be caused by transfusion based on negative results in individual NAT of blood sample or blood donated at the same time and no detection of virus. In no cases, causal relationship was clear due to factors such as no sample. Moreover, 10 HCV and 5 HBV cases were excluded because recipient blood was positive before transfusion or negative after transfusion in re-examination.

On the other hand, in 23 suspected bacterial infection, no bacteria was detected either in blood bag after transfusion or blood product manufactured from one donor at the same time.

One hepatic damage was withdrawn by a medical institution.

2) Investigation of HBV-DNA

Table 9 and 10 show the results of viral DNA analysis for 7 donated blood with potential HBV infectivity.

Table 9 Analysis of 7 cases with potential HBV infectivity-1 (2001)

No.	Results by 50 pool NAT	Results by individual NAT	DNA amount (copies/mL)
1	Negative	Positive (2/7)*	under 100
2	Negative	Positive	120
3	Negative	Negative	under 100
4	Negative	Positive	under 100
5	Negative	Positive	250
6	Negative	Positive	2,800
7	Negative	Positive	400-600

* 2 positive in 7 tests

NAT, as the fundamental test for donated blood (screening), has been implemented for 50 donated blood pool (50 pool NAT) since February, 2000. Table 9 shows the results and HBV-DNA amount in individual test of samples. All 7 cases were found negative in 50 pool NAT, but 1 negative, 5 positive, 1 weak positive (2 positive in 7 tests) in individual NAT. One individual NAT negative case was judged to be infected based on the test result of the donor at the time of next transfusion as shown in after-mentioned case report 3. For HBV-DNA amount, most cases contain a small amount like 100 copies/mL, and 2,800 copies/mL at most. Cases 1 and 3 show that the infection risk cannot be 0 even in individual NAT.

Table 10 shows the results of analyzed HBV-DNA type, genotype and pre-core region. All corresponds to patients' HBV-DNA. Genotype of case 3 was group A. Genotype of most Japanese chronic hepatitis patients is group C (85%) and group B (12%), and hardly group A (less than 2%).

Table 10 Analysis of 7 cases with potential HBV infectivity-2 (2001)

	Viral analysis				Homology with patient HBV-DNA
No.	DNA amount	Viral type			
	(copies/mL)	Subtype	Genotype	Pre-core	
1	under 100	adr	C	mutant	corresponding
2	120	N.T.	C	wild	corresponding
3	under 100	adw	A	wild	corresponding
4	under 100	N.T.	C	N.T.	corresponding
5	250	adr	C	wild	corresponding
6	2,800	adr	C	wild	corresponding
7	400-600	adw	B	wild	corresponding

3) Case report

These cases are described below.

(1) Case-1

This patient had an operation for esophagus cancer, and 2 Ir-RC-MAP and 3 FFP were transfused perioperatively and on the following day. Within 21.6 weeks from transfusion, he/she visited a hospital due to malaise and anorexia, and was diagnosed as hepatitis based on 1,163 IU/L of ALT and 1,010 IU/L of AST. Within 22.3 weeks after transfusion, post-transfusion hepatitis was suspected based on the results of HBs antigen positive, HBe antigen positive, HBe antibody positive, and HBc antibody positive. The highest ALT value was 1,163 IU/L within 21.6 weeks after transfusion. FFP was thought to be the causal factor,

and blood sample collected at the time of donation was negative in 50 pool NAT. Individual NAT showed a weak positive result for relevant blood sample, and the HBV-DNA amount was below the detection limit (under 100 copies/mL). Blood donated 5 months later was 50 pool NAT negative, HBs antigen negative, HBc antibody negative, (2^3 by HI method; within the JRCS standard), and HBe weak positive. Viral genotype both in plasma and patient blood was C, and viral gene sequence corresponded within the tested region.

(2) Case-2

This patient had gastrectomy, and received 3 Ir-RC-MAP, 4 FFP transfusion perioperatively, and 1 Ir-RC-MAP on the following day. He/she was HBs antigen negative before transfusion, but within 11.9 weeks after transfusion, post-transfusion hepatitis was suspected based on HBs antigen seroconversion. At the time, patient sample was HBV-DNA positive, HBs antigen positive, HBs antibody negative, and HBc antibody negative. FFP was thought to be the causal factor. The highest ALT value was 1,065 IU/L within 18.9 weeks after transfusion. Donation sample was 50 pool NAT negative and individual NAT positive, but HBV-DNA amount was as small as 120 copies/mL. Viral genotype both in sample and patient blood was C, and viral gene sequence corresponded within the tested region.

(3) Case-3

This patient received Ir-PC transfusion due to a platelet reduction resulting from AML, and post-transfusion hepatitis was suspected within 8 months. Pre-transfusion test results showed HBs antigen negative, and HBV-DNA negative. The highest ALT value was 90 IU/L within 29.0 weeks after transfusion. Within 34.3 weeks, he/she became HBV-DNA positive, HBs antigen positive, and HBs antibody negative.

No HBV-DNA was detected in blood sample of the relevant donor (under 100 copies/mL). Blood collected from the donor 2 weeks later was HBV-DNA negative in 50 pool NAT, and positive in individual NAT (140 copies/mL; detection limit). Since blood collected at the time was source plasma for plasma derivatives, it had been pooled for 6 months, and could be quarantined without being used. In blood donated 2 weeks later, 50,000 copies/mL of HBV-DNA was detected, and deemed improper in 50 pool NAT.

(4) Case-4

This patient received 13 Ir-RC-MAP in 3 months due to anemia. He/she was HBs antigen negative before transfusion, but HBs antigen seroconverted within 14.9 weeks after transfusion. Ir-RC-MAP was thought to be the causal factor. HBV-DNA was confirmed positive in patient blood sample, but there was low fluctuation in ALT, and the highest was 25 IU/L within 4.1 weeks after transfusion falling in the normal range. Blood sample at the time of donation was negative in 50 pool NAT and positive in individual NAT, but the HBV-DNA amount was below the detection limit (under 100 copies/mL). Viral genotype both in sample and patient blood was C, and viral gene sequence corresponded

within the tested region.

(5) Case-5

This patient was found to be positive in 50 pool NAT at the present donation, and tracing of the previous blood revealed positive in individual NAT. He/she received 10 Ir-PC for bone marrow suppression in chemotherapy, and was HBV-DNA positive within 3.9 weeks after transfusion. The highest ALT value was 121 IU/L within a week after transfusion. Blood sample was positive in individual NAT, but HBV-DNA was as small as 250 copies/mL. Viral genotype both in sample and patient blood was C, and viral gene sequence corresponded within the tested region.

(6) Case-6

As in case-5, this patient was found positive in 50 pool NAT at the present donation, and tracing of the previous blood revealed positive in individual NAT. He/she received 10 Ir-PC due to thrombocytopenia after chemotherapy, and was HBV-DNA positive within 3.6 weeks after transfusion. The highest ALT value was 1,370 IU/L within 36.4 weeks after transfusion. Blood sample was positive in individual NAT, but HBV-DNA was as small as 2,800 copies/mL. Viral genotype both in sample and patient blood was C, and viral gene sequence corresponded within the tested region.

(7) Case-7

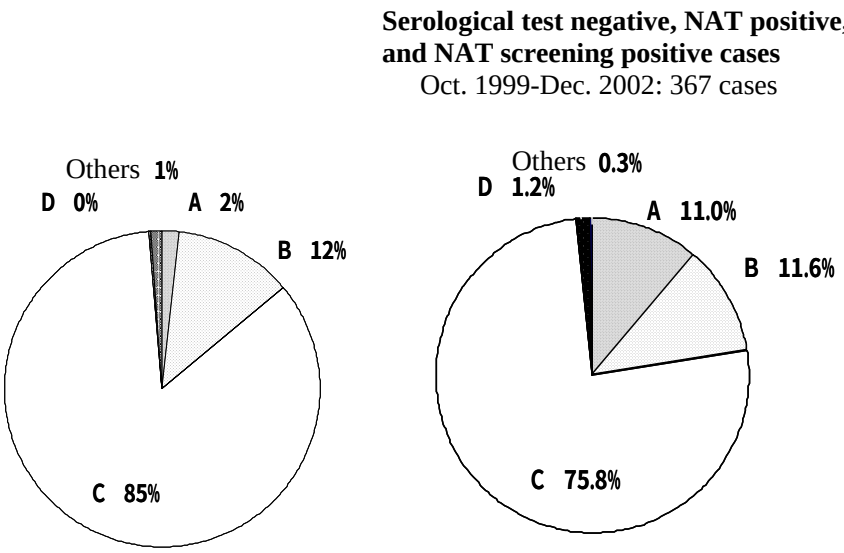
This patient received transfusion perioperatively for colon cancer. FFP donated 5 months before was thought to be the causal factor. He/she was HBs antigen negative before transfusion, but HBs antigen seroconverted within 14.7 weeks after transfusion, and post-transfusion hepatitis was suspected. Patient blood sample was found to be HBV-DNA positive, HBs antigen positive, HBs antibody negative, and HBc antibody positive. The highest ALT value was 1,217 IU/L within 13.9 weeks after transfusion. Blood sample at the time of donation was negative in 50 pool NAT, and positive in individual NAT, but HBV-DNA was as small as 400-600 copies/mL. Viral genotype both in sample blood and patient blood was B, and viral gene sequence corresponded within the tested region.

These 7 cases were caused by donation in the window period just after a donor was infected, or donation by a carrier who has virus below the NAT detection limit.

4) Donors whose NAT (HBV, HCV, or HIV) was seroconverted

We analyzed the donation pattern in donors who are negative in serological tests, but positive in NAT.

Fig. 11 shows the genotype of 119 donors who are negative in serological tests, while positive in HBV-NAT, compared with reported genotype. Carriers who are detected in NAT, but not in serological test, tend to belong to group A.



Left chart: Cited from Orito et al.: Hepatology 34:590-594, 2001

Fig. 11 Percentage of HBV Genotype

The 119 donations include 73 first donation, 18 second donation, 14 third donation, and 14 more than 4.

The increased number of donations can be translated into the increased number of examination for detection. This includes multiple donations in a few months, and there seems to be donations aimed at examination.

III. Results in 1993-2001

1. Transition of reported adverse reactions and infectious diseases

Fig. 12 shows the transition of the reported cases from 1993 to 2001.

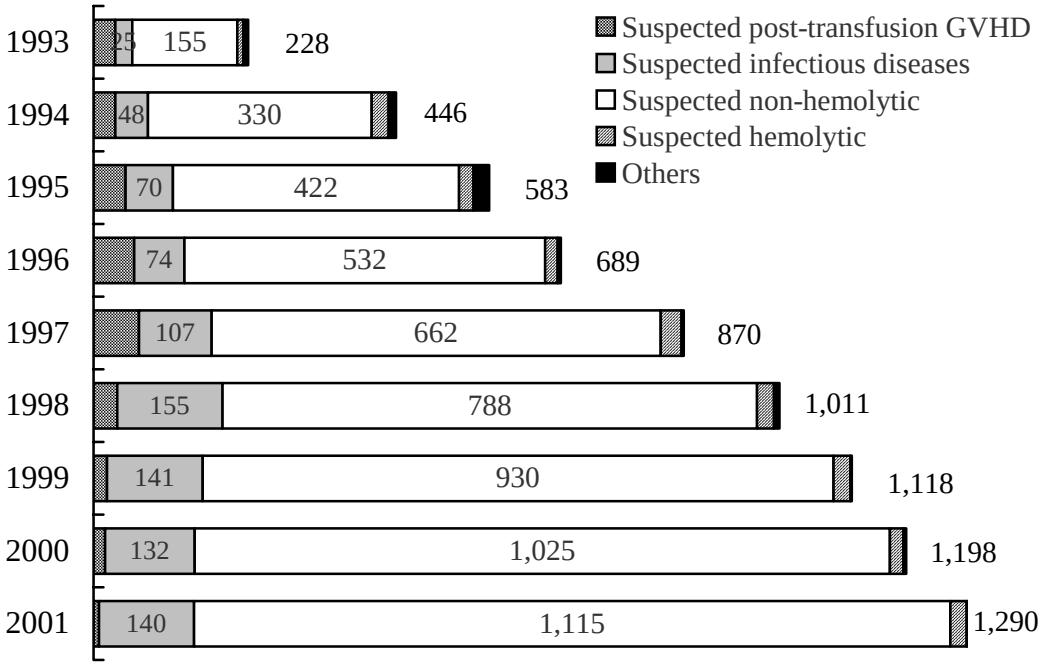


Fig. 12 Transition of reported adverse reactions and infectious diseases (1993-2001)

Adverse reactions are categorized into non-hemolytic adverse reactions, hemolytic adverse reactions, suspected post-transfusion GVHD, suspected post-transfusion infection, and others including plasma derivatives. The number has increased year by year from 228 in 1993 to 1,290 in 2001. This means that the understanding of Haemovigilance has deepened among medical professionals.

Most of the reported cases are non-hemolytic adverse reactions, followed by post-transfusion infection. Recently, suspected post-transfusion GVHDs have been apparently decreasing. Suspected infection had gradually increased by 1998, and has leveled off since then.

No adverse events caused by human errors have been reported. However, 6 hemolytic adverse reactions have been found to be caused by heterotransfusion of ABO blood group.

2. Non-hemolytic adverse reactions

1) Transition of reported non-hemolytic adverse reactions

Fig. 13 shows the transition of reported non-hemolytic adverse reactions from 1993 to 2001. The number has increased year by year from 155 in 1993 to 1,115 in 2001, 7 times in 8 years. The percentage of each symptom has been almost consistent.

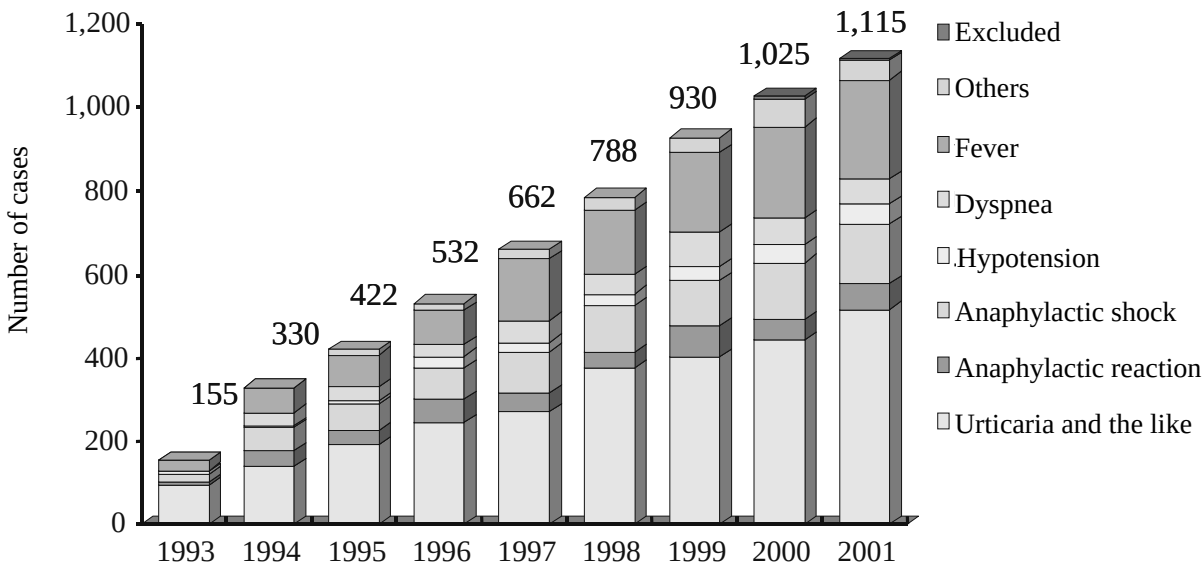
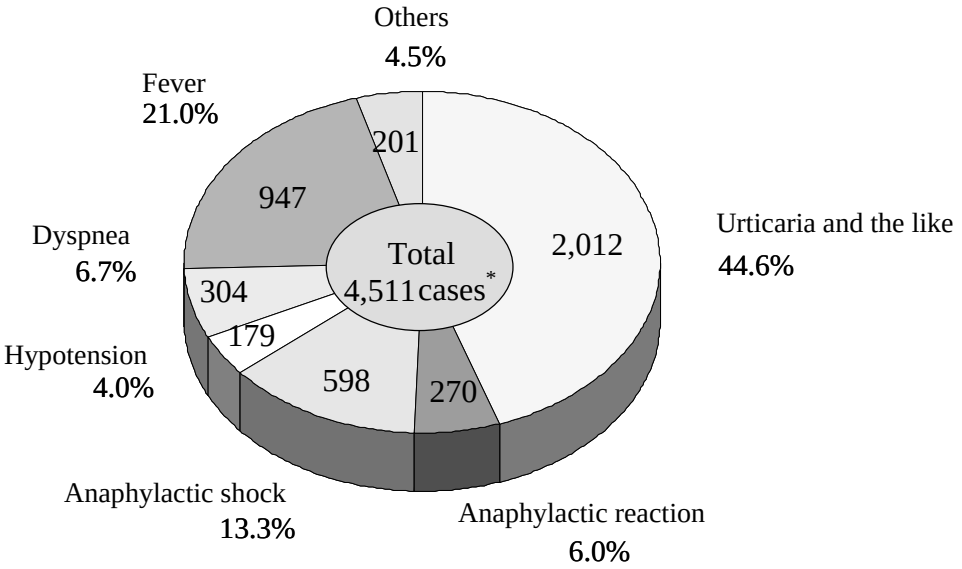


Fig. 13 Transition of reported non-hemolytic adverse reactions

2) Reported cases by symptom

Fig. 14 shows the reported cases by symptom from 1997.

In the 5-year period from 1997 to 2001, 4,511 non-hemolytic adverse reactions have been reported. Urticaria and the like occupy 45%, followed by fever (21%) and anaphylactic shock (13%).



* Cases that doctors in attendance observed no relationship with transfusion were excluded.

Fig. 14 Reported cases by symptom (1997-2001)

3) Reported cases by kind of blood products

Fig. 15 shows reported cases by kind of blood products in 5 years from 1997. Adverse reactions caused by concentrated platelet were reported the most with 2,109 cases, followed by concentrated red blood cells with 1,294, fresh frozen plasma with 696, and whole blood with 47. The number of reported cases involving leukocyte-reduced red blood cells and washed red blood cells was almost the same for that of whole blood.

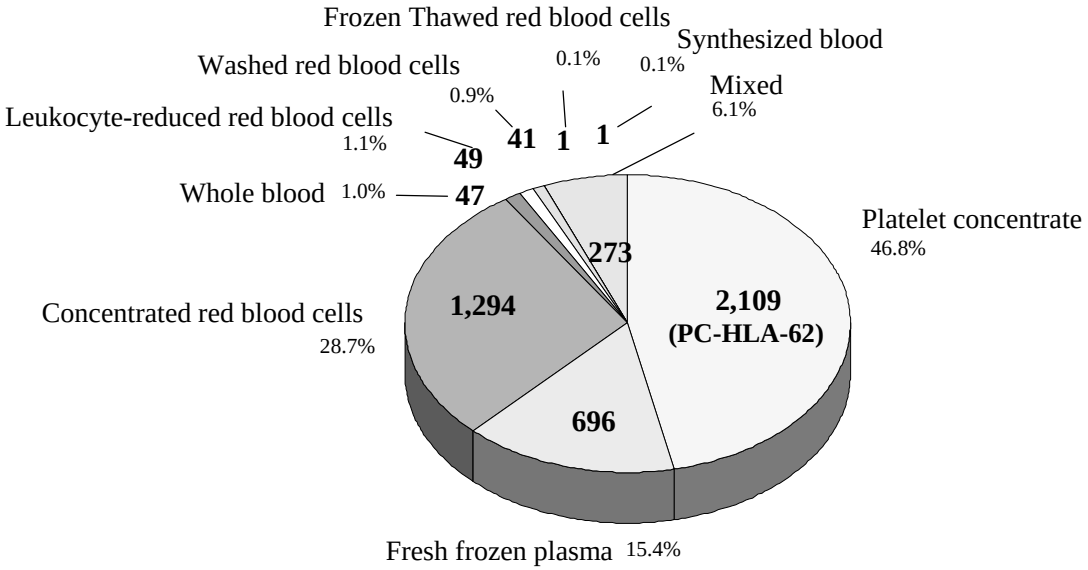


Fig. 15 Reported cases by kind of blood products (1997-2001)

4) Blood products and adverse reactions

Tables 11 and 12 show symptoms by blood products. Urticaria and the like and anaphylactic shock are more likely to be caused by platelet products, and fever more likely by red cells.

Table 11 Blood products and kinds of adverse reactions-1 (1997-2001)

Symptoms	Reported cases	Blood products			
		Platelet concentrate	Fresh frozen plasma	Concentrated red blood cells	Whole blood
Urticaria and the like	2,012	1,113 (30)	424	313	21
Anaphylactic reaction	270	193 (5)	36	32	1
Anaphylactic shock	598	366 (9)	82	85	5
Hypotension	179	38 (0)	28	103	2
Dyspnea	304	120 (7)	29	114	2
Fever	947	249 (8)	80	512	14
Others	201	30 (3)	17	135	2
Total	4,511	2,109 (62)	696	1,294	47

Figures in parentheses indicate platelet concentrate HLA.

Table 12 Blood products and kinds of adverse reactions-2 (1997-2001)

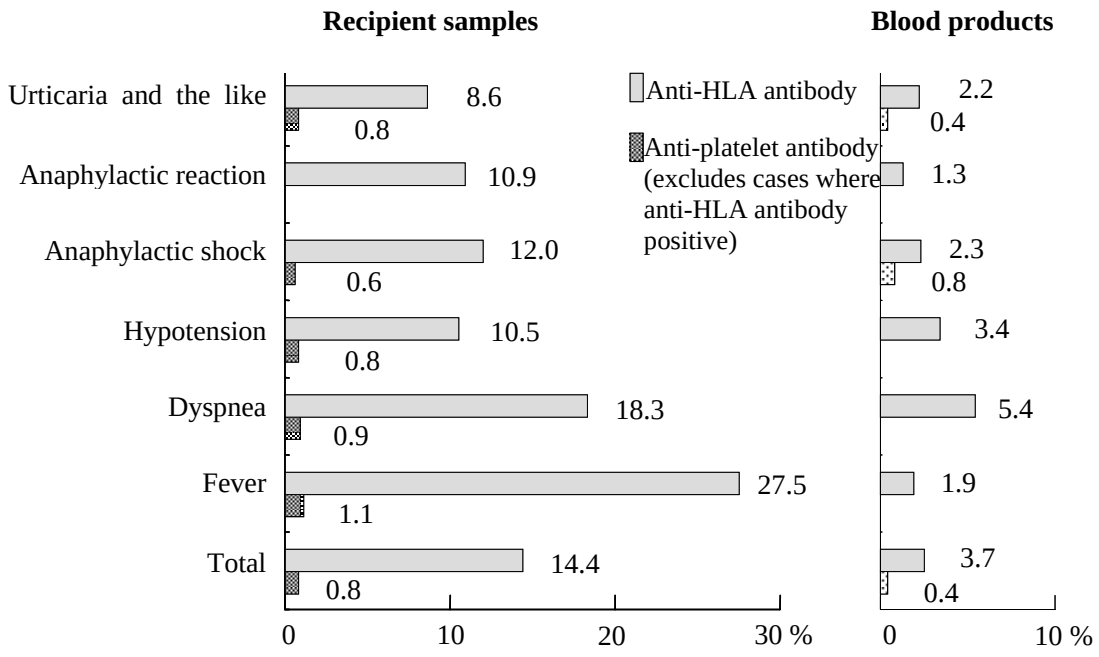
Symptoms	Reported cases	Blood products				
		Leukocyte-reduced red blood cells	Washed red blood cells	Frozen Thawed red blood cells	Synthesized blood	Mixed
Urticaria and the like	2,012	11	9			121
Anaphylactic reaction	270		1			7
Anaphylactic shock	598	2	5		1	52
Hypotension	179		3			5
Dyspnea	304	8	3			28
Fever	947	24	16			52
Others	201	4	4	1		8
Total	4,511	49	41	1	1	273

5) Detection rate of anti-HLA antibody and anti-platelet antibody

Fig. 16 shows the detection rate of anti-HLA antibody and anti-platelet antibody by symptom.

Of the recipient samples, 14.4% was anti-HLA antibody positive. Especially, 27.5% of fever and 18.3% of dyspnea was positive. Anti-HLA antibody was detected in 3.7% of blood products.

Anti-platelet antibody tends to be detected with anti-HLA antibody. Anti-platelet antibody alone was detected only in 0.8% of the recipient samples, and 0.4% of blood products.



Number of cases
(Recipient samples) Anti-HLA antibody: 4,108; anti-platelet antibody: 3,440
(Blood products) Anti-HLA antibody: 2,104; anti-platelet antibody: 1,609

Fig. 16 Detection rate of anti-HLA antibody and anti-platelet antibody (1997-2001)

6) Plasma protein deficit cases

Table 13 shows the plasma protein deficit cases.

A total of 13 plasma protein deficit cases was observed by 2001, including 3 IgA deficit, 7 haptoglobin deficit, and 3 C9 deficit. Most of them were reported with severe transfusion adverse reactions such as hypotension and anaphylactic shock. Since then, in these cases, severe adverse reactions have been prevented by usage of washed blood or pre-transfusion administration of steroid.

Table 13 Plasma protein deficit cases (1997-2001)

Year	Protein deficit	Blood products and adverse reactions		Following transfusion and adverse reactions	
97	IgA	MAP	Sweating, rigors, vomiting, hypotension	MAP WRC	(1/1) Fever (0/1)
00	IgA	MAP	Hypotension	MAP LPRC (washed) FFP	(1/1) Fever, hypertension (0/1) (0/2)
00	IgA	PC	Anaphylactic shock	-	
98	Haptoglobin	MAP*2	Anaphylactic shock	-	
98	Haptoglobin	PC	Shock	WRC	(0/4)
99	Haptoglobin	PC	Anaphylactic shock	MAP PC*3	(0/3) (1/1) Itching
99	Haptoglobin	PC*3	Eruption, vomiting, dyspnea	MAP PC*3 WRC*3 Washed PC*3	(0/4) (1/6) Diarrhea, vomiting (1/30) Edema (0/17)
00	Haptoglobin	FFP, PPF	Anaphylactic shock	-	
00	Haptoglobin*1	MAP	Hypotension	Washed PC	(0/2)
01	Haptoglobin	PC	Hypotension	Washed PC*3 Washed PC WRC	(0/1) (0/2) (0/2)
99	C9	PC*3	Anaphylactic shock	-	
00	C9	MAP	Rash	MAP	Unknown
00	C9	PC	Redness, hypotension (mild)	PC*3 MAP*3	(3/9) Itching, suffusion (0/3)

*1: Antibody negative at the development of adverse reactions, seroconverted later
*2: Anaphylactic shock by ALB and PPF the day before
*3: Pre-transfusion administration of steroid

7) Detection of anti-leukocyte antibody in suspected pulmonary edema

Table 14 shows the results of anti-leukocyte antibody detection in recipient blood and blood products of suspected lung edema cases. Detection rate of anti-HLA antibody or anti-granulocyte antibody was 30% in recipient blood, and 25% in blood products. These antibodies were detected in either recipient blood or blood products in 48% of the cases.

Table 14 Detection of anti-leukocyte antibody in suspected pulmonary edema

1997-2001

	Anti-HLA antibody	Anti-granulocyte antibody	Anti-HLA or anti-gramulocyte antibody
Recipient blood	13/69 (18.8%) (13/67 cases)	10/69 (14.5%) (10/67 cases)	21/69 (30.4%) (21/67 cases)
Blood products	6/65 (9.2%)	11/64 (17.1%)	16/65 (24.5%)
Recipient blood or blood products	19/69 (27.5%)	21/69 (30.4%)	33/69 (47.8%)

3. Hemolytic adverse reactions

The following 6 cases among hemolytic adverse reactions were caused by ABO blood group heterotransfusion (Table 15). Table 16 shows hemolytic adverse reactions in which irregular antibody was identified in recipient serum. Many Rh or Kidd types were observed.

Table 15 Hemolytic adverse reactions caused by ABO blood group heterotransfusion

Year	Blood products	Blood group		Recipient blood group
1996	Ir-RC-MAP	B	→	A
1997	Ir-RC-MAP	AB	→	O
1998	Ir-RC-MAP	B	→	O
2001	Ir-RC-MAP	B	→	O
1997	FFP	B	→	A
1997	Ir-PC	O	→	AB

Table 16 Hemolytic adverse reactions and irregular antibody

(No.: cases)

1996	1997	1998	1999	2000	2001
E 2	E 1	E 1	C+e 2	E 1	E 1
Jk^a 1	E+c 1	Jk^a+E+c 1	Jk^b 1	C+M+Jk^a 1	E+c 1
Jk^a+E+P_1 1	Jk^a+E 1	Jk^a+E 1	I+P_1 1	Fy^b+Jk^b 1	Jk^a 1
	Jk^a+E+c 1	Jk^b 1	Bg^a 1	M 1	JMH 1
	C 1			St^a 1	
	C+e 1			pdl 1	
	Jk^a+Hr_o 1				
	Jk^a 2				
	Jr^a 2				

4. Post-transfusion GVHD

Fig. 17 shows the transition of reported post-transfusion GVHD.

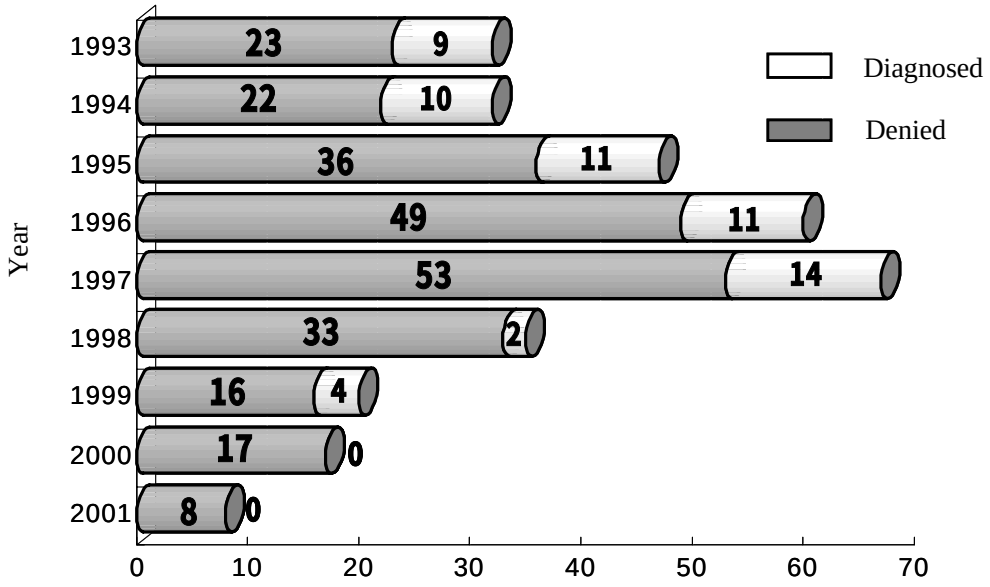


Fig. 17 Annual transition of suspected post-transfusion GVHD

The number of suspected post-transfusion GVHD has been decreasing since 1998 with the peak in 1997. Since 2000, no post-transfusion GVHD has been reported.

Post-transfusion GVHD is an extremely severe adverse reaction. The first case in Japan was diagnosed as post-operative erythroderma in 1955 and was later acknowledged as post-transfusion GVHD in 1987. JRCS had collected data in cooperation with the Japan Society of Blood Transfusion, and conducted a national questionnaire survey in 1991. Based on the results, we have provided information annually to medical institutions through the media such as the journal “Transfusion Information” and posters. In 1996, we issued “Dear Dr. Letter” to medical institutions twice. At the same time, we have engaged in developing diagnostic methods for post-transfusion GVHD since a differential diagnosis was extremely difficult. We successfully developed an HLA cross match test and micro satellite DNA method for the disease.

On the other hand, reacting to the demand for rapid response, since 1993 we have promoted the use of irradiation in blood centers nationwide by establishing irradiation facilities as a preventive measure against the disease. We have been supplying irradiated blood since the manufacturing approval was obtained in 1998. Usage rate of irradiated blood has been increasing year by year, and presumably today it has reached over 90% for platelet and red cell products taking internal irradiation into consideration.

5. Post-transfusion infection

1) HBV

Fig. 18 shows the number of suspected HBV infection by transfusion from 1994.

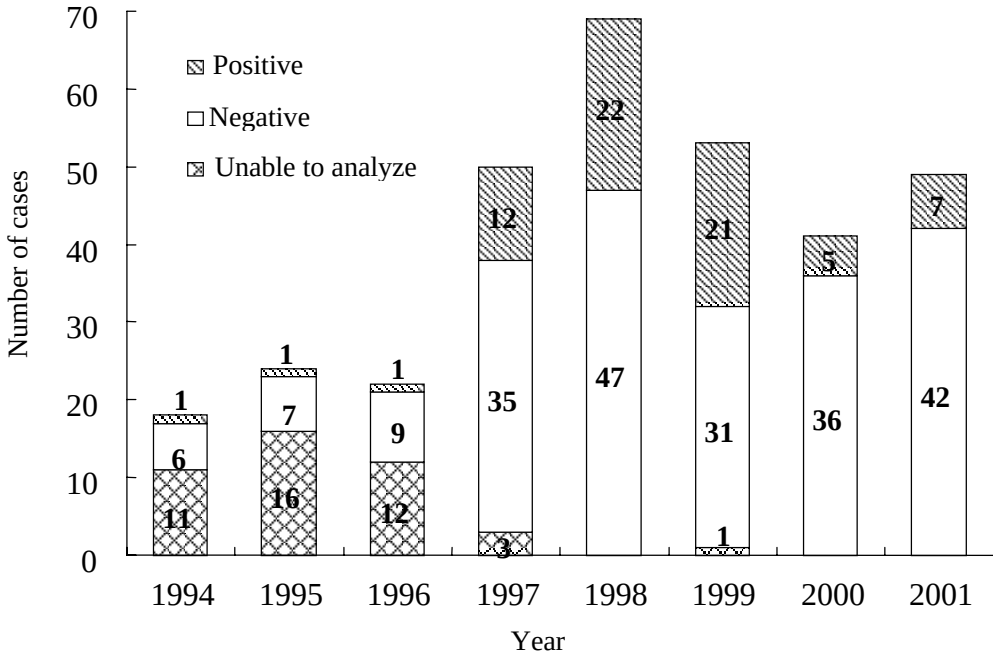


Fig. 18 Post-transfusion infection reported by medical institutions (HBV)

Approximately 20 cases had been reported annually in 1994-1996. Every year 1 case was likely to be caused by transfusion, but more than half could not be analyzed because no blood sample was available. Almost 50 cases have been reported annually since 1997. We started the storage of samples in September 1996, and analysis has been conducted in almost all cases since 1997. In November 1997, mini-pool NAT was introduced for source plasma for plasma derivatives. We have traced recipients who received blood products manufactured when NAT positive plasma was produced. The number of diagnosed cases has increased due to this post-transfusion information, and 10-20 infection was likely to be caused by transfusion annually in 1998 and 1999 including voluntarily reported cases. Since 2000, the number has decreased to less than 10, presumably proving the effectiveness of the NAT screening of all blood products introduced in October 1999. Although we shifted the NAT pool size from 500 to 50 in February 2000, we have not accomplished the complete prevention of HBV infection through transfusion due to the NAT window period.

2) HCV

Fig. 19 shows the number of suspected HCV infection by transfusion from 1994.

Approximately 30 cases had been reported annually by 1997. About 50-60 cases have been reported annually since 1998 as in the case of HBV. Although 7 cases in 1998 and 5 in 1999 were reported to likely be caused by transfusion based on post-transfusion information, no suspected infection has been reported since 2000 as in the case of HBV.

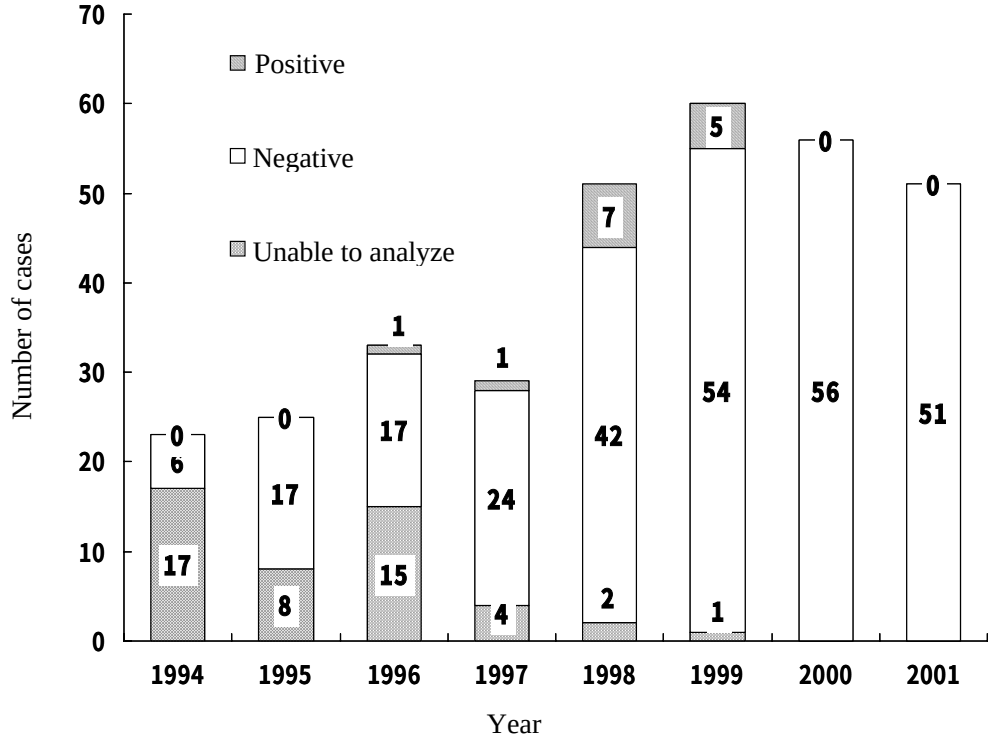


Fig. 19 Post-transfusion infection reported by medical institutions (HCV)

3) HIV

Although 3 cases of HIV infection, 1 in 1997 and 2 in 1999 (2 recipients from 1 donor), had been reported, no HIV cases has been reported since the introduction of NAT.

4) Bacteria and parasite

Fig. 20 shows the number of suspected bacterial infection by transfusion from 1995.

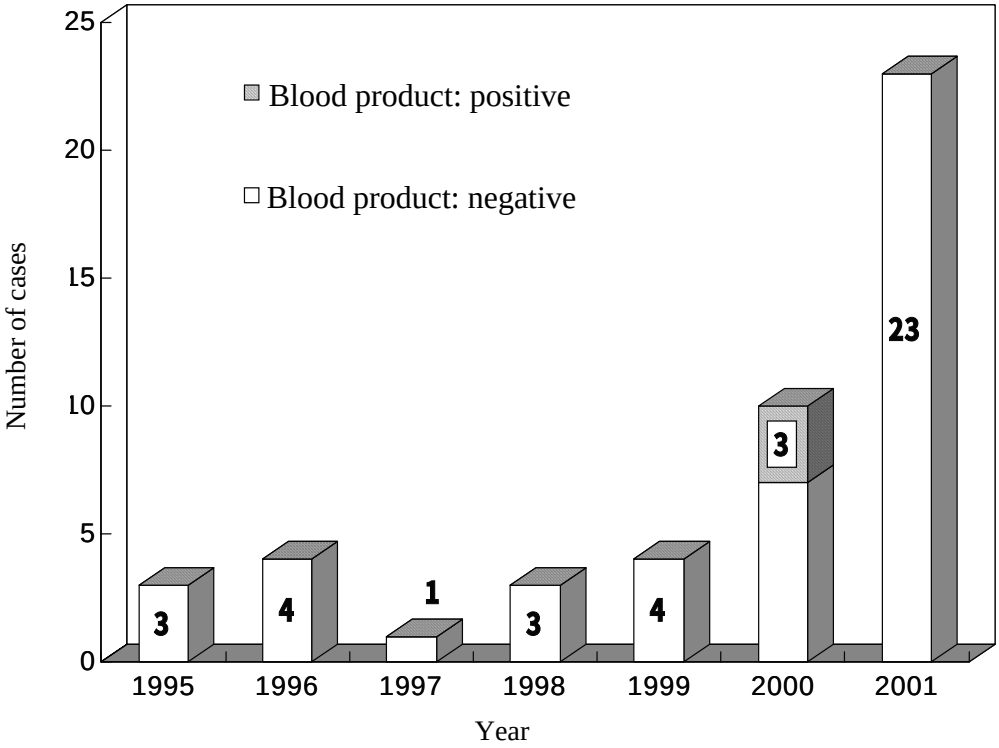


Fig. 20 Transition of suspected bacterial infection by transfusion

The number of cases has been increasing year by year. In only 3 cases in 2000, bacteria was detected both in blood products and recipient blood. Among them, bacteria detected in blood products and recipient blood corresponded in 2 cases. Since bacteria detected in blood products were different from one in recipient blood in the remaining case, infection is unlikely to be caused by transfusion. Bacteria detected in blood products were *Streptococcus pneumoniae*, *Bacillus cereus*, and *Propionibacterium acnes*. Bacteria detected in recipient blood were *Streptococcus pneumoniae* and *Bacillus cereus.*

Haemovigilance has to pay attention to bacterial infection for which further study is required.

Regarding protozoiasis, one babesia infection was reported in 1999. Hemolytic anemia was diagnosed after Ir-RC-MAP transfusion, and *Babesia microti* was detected both in Ir-RC-MAP and recipient blood.

In addition, 1 malarial parasite infection was reported in 1995. Since the patient had no record of travelling overseas, and no malarial parasite was detected in recipient blood before transfusion, it is likely to be caused by platelet concentrate (PC) with red cells contaminated with the parasite.

5) Others

One HGV by FFP in 1997 and 1 human parvovirus B19 by Ir-RC-MAP in 2000 were likely to be caused by transfusion based on the detection of virus in blood products.

6. Adverse reactions and infectious diseases by plasma derivatives

Table 16 shows reported adverse reactions and infectious diseases related with plasma derivatives since 1997. Twelve adverse reactions from albumin, and 3 from cross eight M (coagulant factor VIII) were reported, while no infection was reported.

Table 16 Reported adverse reactions by plasma derivatives

Product	Cases	Adverse reactions	Severity
Albumin	97-1	Rigors, shivers, fever	Severe
	98-1	Erythema	Moderate
	98-2	Urticaria	Moderate
	98-3	Anaphylactic shock	Severe
	99-1	Facial redness	Mild
	99-2	Fever, rash	Mild
	00-1	Vomiting, hypotension	Moderate
	00-2	Fever, itching	Mild
	00-3	Dull headache, malaise, sleepiness, edema	Mild
	01-1	Facial hot flushes	Mild
	01-2	Urticaria	Moderate
	01-3	Rigors, shivers, fever (causal relationship denied)	
Cross eight M250	97-1	Dyspnea	Moderate
Cross eight M1000	98-1	Urticaria	Mild
Cross eight M500	00-1	Dyspnea, rigors, shivers, fever	Severe

IV. Summary

1. Achievement

Results achieved from Haemovigilance are summarized below.

1) We were the world's first to set up Haemovigilance, implementing in January, 1993.

2) Understanding and support among medical professionals have been progressively built year by year, reflecting the 10-year activities.

3) The number of reported adverse reactions and infectious diseases reached 1,290 in 2001. This is the highest among nations adopting a voluntary reporting system.

4) We have investigated into the causes of reported cases, and reported the results to medical institutions in order to support doctors in diagnosis and treatment.

5) We have established unprecedented Haemovigilance characterized by the assignment of MRs, storage of donated blood samples, NAT and storage of pooled source plasma.

6) Viral NAT is an effective tool to evaluate the possibility of infection by transfusion for suspected cases, as well as to provide effective information on viral infection epidemiology in public health.

7) We have successfully brought post-transfusion GVHD under control.

8) We have engaged in the analysis of adverse reactions by transfused plasma protein that has yet been considered in most other countries. These data might contribute to the safety of transfusion in the future.

2. Challenges

1) Adverse reactions

Most adverse reactions are non-hemolytic, and frequently transfused recipients repeat the same adverse reactions. For recipients with frequent transfusion history and transfusion needs in the future, usage of blood products in which potential causal ingredients have been reduced by washing or filtration should be considered in cooperation with medical institutions.

2) Infectious diseases

We have not achieved complete prevention of HBV infection as yet. The infection is likely to be attributed to technical matters such as the NAT window period as well as blood donated during a few weeks just after viral infection or blood donated by a carrier with an extremely small amount of virus. We need to consider the introduction of preventive measures such as viral inactivation technology.

3) Donations aimed at examination

Some donors donate blood with an intention of taking blood tests. We need to promote correct donation attitude.

4) Haemovigilance

The present Haemovigilance covers only adverse reactions and infectious diseases related with blood products. It can hardly be called a comprehensive monitoring system that covers donors, blood centers, medical institutions and recipients. We have to develop measures to establish a comprehensive monitoring system in cooperation with medical institutions. In addition, we need to establish nationwide monitoring system by sharing information with the Steering Committee of the Pharmaceutical and Food Sanitation Council.