日本赤十字社
Japanese Red Cross Society

Haemovigilance by JRCS 2021

Safety Vigilance Division,
Technical Department,
Blood Service Headquarters

Haemovigilance system of the Japanese Red Cross Society

Haemovigilance is a system that monitors blood products for transfusion ("transfusion blood products") for any adverse events throughout all steps from blood collection, testing, and manufacturing, up to recipient follow-up; analyzes and assesses the causes; takes appropriate safety measures; and thus prevents any transfusion blood product-related harm from occurring or expanding. The Japanese Red Cross Society (JRCS) has addressed donor adverse reactions, transfusion-transmitted infections (TTI), and transfusion adverse reactions since the start of its blood service. In 1982, the JRCS established internal procedures for reporting adverse reactions in donors, and in 1983, it assigned medical representatives (MR) to all JRC blood centers across Japan to attend to transfusion adverse reactions and infections. During this time, the JRCS also introduced hepatitis virus and HIV marker tests for donated blood as an anti-TTI measure, and in 1993, it established a system to centrally collect and analyze information on transfusion adverse reactions and TTIs. Then, in 1996, JRCS began a specimen storage system that stores aliquots of all donated blood over 11 years for analysis purposes. This system enabled investigation of transfusion blood products associated with TTIs and was useful not only in confirming causal relationships between transfusions and TTIs but also in identifying new adverse reactions and infections that may emerge in the future. Subsequently, the policies set forth in the Guideline on the Use of Donated Blood in Research and Development (Pharmaceutical and Food Safety Bureau (PFSB) Notification No.0801-1; issued by the Director of PFSB, Ministry of Health, Labour and Welfare (MHLW) on August 1, 2012) allowed expired blood specimens stored for investigational purposes to be used in research and development. Initially, the Steering Committee of Committee on Blood Products, Pharmaceutical Affairs and Food Sanitation Council, MHLW was responsible for assessing whether or not the usage of stored specimen in particular research and development programs was appropriate. This policy was later discontinued under the Partial Amendment to the Act on Securing Stable Supply of Safe Blood Products (Pharmaceutical Safety and Environmental Health Bureau (PSEHB) Notification No. 0827-2; issued by the Director of PSEHB, MHLW on August 27, 2020), which designated the JRCS as the responsible institution for the assessment from 2021.

Transfusion blood products are categorized as ethical pharmaceuticals in Japan. They are thus regulated by the Act on Securing Quality, Efficacy, and Safety of Pharmaceuticals and Medical Devices (Pharmaceuticals and Medical Device Act: PMD Act) and require marketing approval as with other pharmaceuticals. Additionally, the JRCS collects human source blood from donors as a blood establishment based on the Act on Securing Stable Supply of Safe Blood Products (Blood Act). Currently, the JRCS is Japan's only blood establishment that collects blood, markets transfusion blood products, and manufactures source plasma for plasma derivatives.

With the amendment to the Blood Act in 2019, blood establishments other than the JRCS that have obtained licenses to collect blood are also permitted to collect blood for use in research and development of drugs, medical devices, or regenerative medicine, and as source material for other items that improve the quality of medical care or health and hygiene. For the manufacturing and distribution of transfusion blood products derived from donated blood, the JRCS complies not only with the PMD Act and its enforcement regulation but also with the Ministerial Ordinance on Standards for Manufacturing Control and Quality Control for Pharmaceuticals and Quasi-pharmaceuticals (Good Manufacturing Practice (GMP) Ministerial Ordinance) and the Ministerial Ordinance on Standards for Quality Assurance for Pharmaceuticals, Quasi-pharmaceuticals, Cosmetics, and Regenerative Medicine (Good Quality Practice (GQP) Ministerial Ordinance). The JRCS performs post-marketing activities in compliance with the Ministerial Ordinance on Standards for Post-Marketing Safety Assurance for Pharmaceuticals, Quasi-pharmaceuticals, Cosmetics, Medical Devices, and Regenerative Medicine (Good Vigilance Practice (GVP) Ministerial Ordinance) through collaborative efforts among its Blood Service Headquarters (which serves as the marketing authorization holder and the section that manages safety), JRC blood centers, and Central Blood Institute facilities (both of which serve as sections that execute safety measures) MRs at blood centers are responsible for collecting information on transfusion adverse reactions and TTIs and providing information on transfusion blood products to health care professionals. The safety management section then analyzes and assesses the information, and reports serious or unknown transfusion adverse reactions and TTIs to the Pharmaceutical and

Medical Devices Agency (PMDA) pursuant to the PMD Act, and also performs a series of other activities, such as collecting basic data on safety measures, product withdrawal, and revision of electronic package inserts (on precautions). Additionally, the safety management section conducts epidemiological studies related to blood safety and reports results to respective committees in the Committee on Blood Products, Pharmaceutical Affairs and Food Sanitation Council, MHLW, thereby contributing to safety efforts for transfusion blood products. As transfusion blood products are categorized as a "combination product equivalent to pharmaceuticals" that combine pharmaceuticals (blood and blood components) and medical devices (blood bags), the safety management section also collects, assesses, and analyzes information on any health hazards caused by malfunctions in blood bags used by patients, just as it does with transfusion adverse reactions and TTIs.

Pharmaceuticals are also subject to pharmacovigilance. The World Health Organization defines pharmacovigilance as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine or vaccine-related problem," which is in close agreement with post-marketing safety assurance activities that the Japanese GVP Ministerial Ordinance stipulates. In addition, the International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) developed the E2E Guideline, "Pharmacovigilance Planning," which was implemented in 2005. Around the same time, the amended former Pharmaceutical Affairs Act was fully enforced in April 2005, mandating compliance with the GQP and GVP Ministerial Ordinances as a requirement for marketing authorization.

The haemovigilance concept is considered to have developed in Western countries, since most of such countries regulate transfusion blood products separately from pharmaceuticals and thus need to develop a different safety monitoring system for transfusion blood products. However, as transfusion blood products are categorized as pharmaceuticals in Japan, the same vigilance system as that for pharmaceuticals is applied to blood and blood components. Therefore, a characteristic feature of the Japanese haemovigilance system is that it is similar to the pharmacovigilance system.

1. Total number of blood donations and supply of blood products for transfusion

Figure 1 shows the number of blood donations by type between 2012 and 2021. The total number of blood donations in 2021 was 5,116,003, including 126,519 200 mL whole blood donations, 3,289,481 400 mL whole blood donations, and 1,700,003 blood component donations (comprising 1,116,388 plasma donations and 583,615 platelet donations). The number of donations decreased until 2018, but plasma donations have been on an increasing trend since 2019 in response to the need for source plasma to satisfy the increasing demand in immunoglobulin products, resulting in an increase in overall donations.

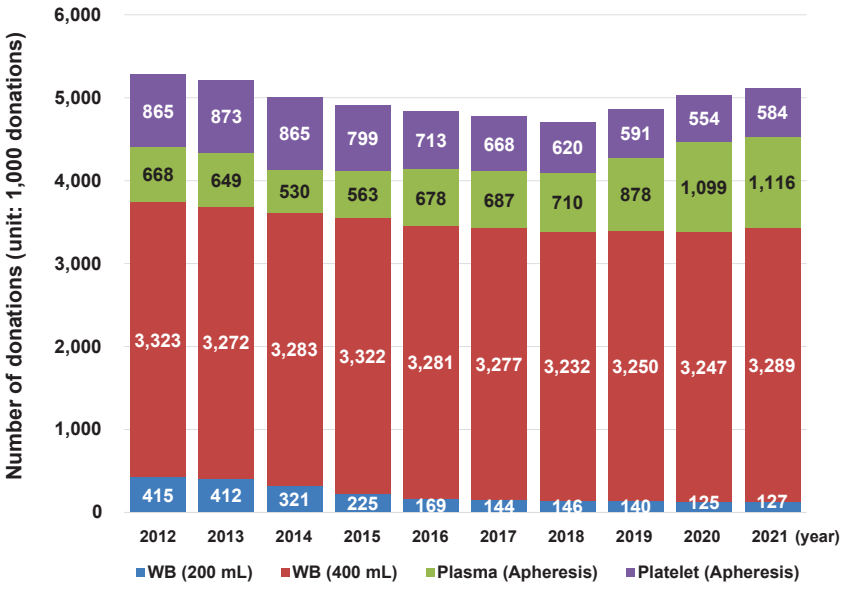


Figure 1. Number of blood donations by year

Figure 2 shows the transfusion blood product supply between 2012 and 2021. In recent years, the supply of red blood cell (RBC) products and plasma products had been on a decreasing trend due to the promotion of their proper use. However, there was a slight increase in the supply of RBC and plasma products in 2021, resulting in a slight increase in the overall supply. Although there were concerns that COVID-19 would affect the volume of supply, no large effect was noted.

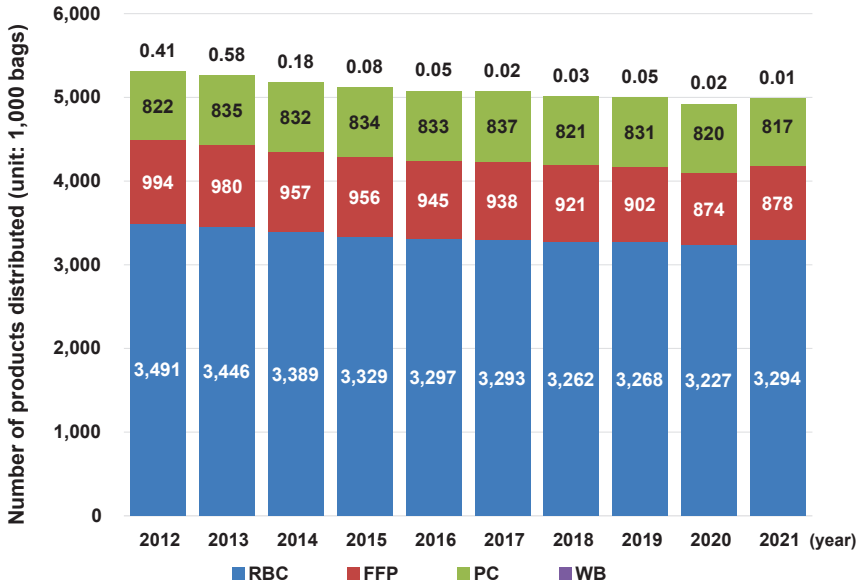


Figure 2. Supply of transfusion blood products

2. Transfusion adverse reactions and transfusion-transmitted infections

Figure 3 shows the breakdown of reported suspected transfusion adverse reactions and TTIs (including cases reported by medical institutions and cases identified through post-donation information). Until 2017, all suspected transfusion adverse reactions and TTIs were subjected to detailed investigation (i.e., requests to medical institutions to fill out case report forms). In January 2018, however, the investigation method was modified; information on transfusion-related adverse events is now collected more broadly, and among the collected adverse events, suspected transfusion adverse reactions and TTIs that are evaluated as serious (1. Cases evaluated as serious by physicians, 2. Cases evaluated as non-serious by physicians, but determined by the JRCS to require detailed investigation based on the symptoms, and 3. suspected TTIs) and transfusion adverse reactions not indicated in package inserts (i.e., unknown adverse reactions) are subjected to detailed investigation. Consequently, the numbers of non-hemolytic adverse reactions, in particular, substantially increased.

In 2021, the JRCS received 2,821 case reports on adverse reactions and infections (non-hemolytic adverse reactions, 2,737 cases; hemolytic adverse reactions, 41 cases; suspected transfusion-associated graft versus host disease (TA-GVHD), 0 cases; and suspected infections, 43 cases) from medical institutions across Japan. Cases evaluated as serious by patients' physicians or the JRCS (non-hemolytic adverse reactions, 675 cases*; hemolytic adverse reactions, 16 cases*; infections, 43 cases*) were submitted as individual case safety reports (ICSR) to PMDA, in accordance with the PMD Act. Some adverse reaction cases that have not been spontaneously reported by medical institutions to the JRCS are published in literature and by academic societies. When the JRCS obtains such information, it investigates the causal relationship and seriousness at the concerned medical institutions (see "3) Information on individual cases of transfusion adverse reactions and transfusion-transmitted infections obtained from literature and academic societies").

* Note that the figures account for some cases that fall under multiple categories.

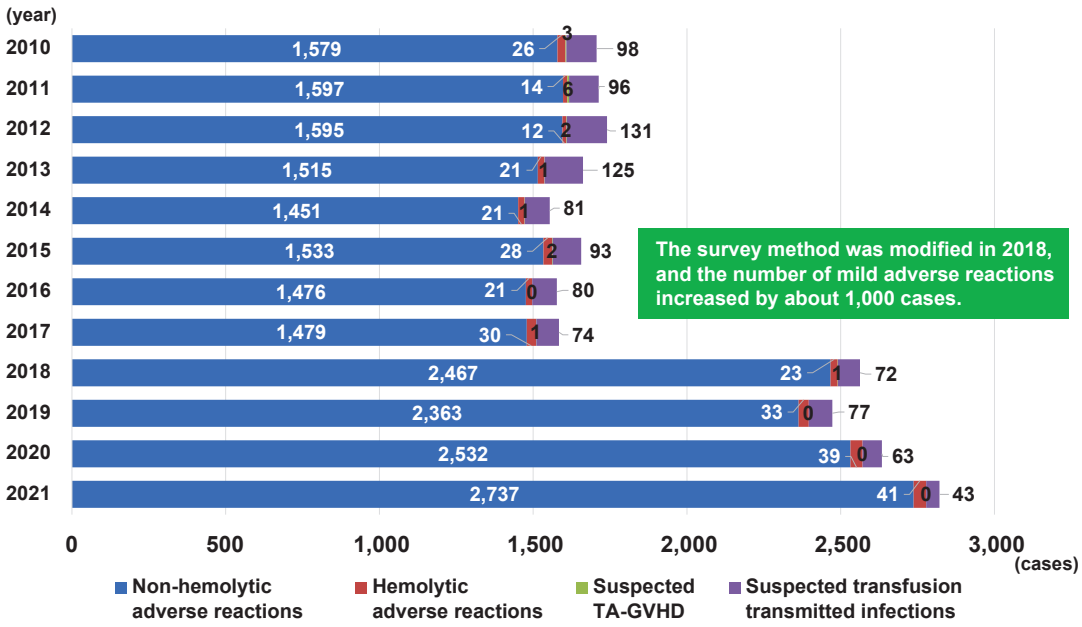


Figure 3. Number of spontaneous transfusion adverse reaction and TTI case reports*

* Excludes cases learned through literature or from academic societies.

1) Transfusion adverse reactions

(1) Non-hemolytic adverse reactions

Figure 4 shows the number of cases reported as non-hemolytic adverse reactions by medical institutions between 2018 and 2021. Figure 5 shows the breakdown and ratio (%) by symptom for 2021, and Figure 6 indicates the number of cases according to serious/non-serious for 2021. The number of transfusion-related acute lung injury (TRALI) and transfusion-associated circulatory overload (TACO) cases are included in that for dyspnea. While the total number of cases has been increasing overall (see Figure 6), no particular category indicated a marked increase. Two-thirds of the reported adverse reactions were allergic symptoms. Serious adverse reactions accounted for 24.6% of all adverse reactions and mainly comprised severe allergy, dyspnea, and hypotension.

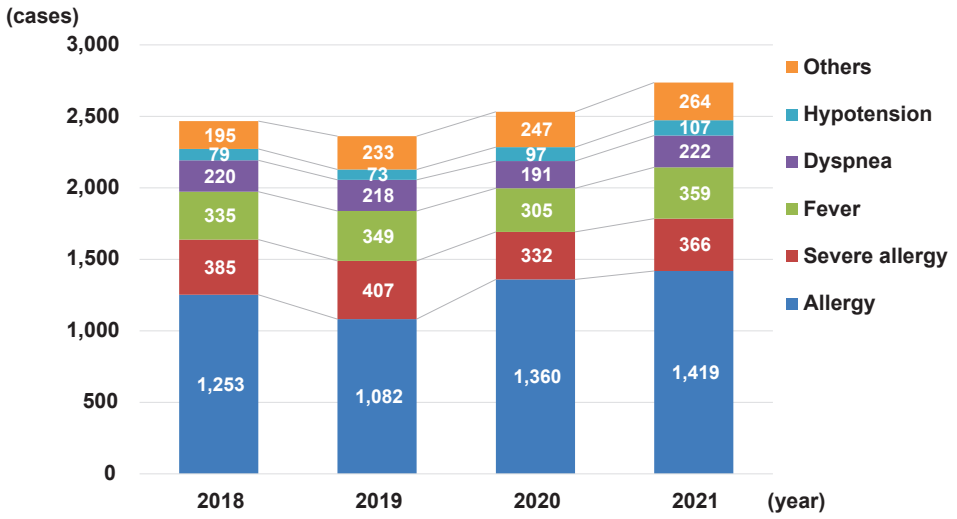


Figure 4. Number of reported non-hemolytic adverse reactions by symptom

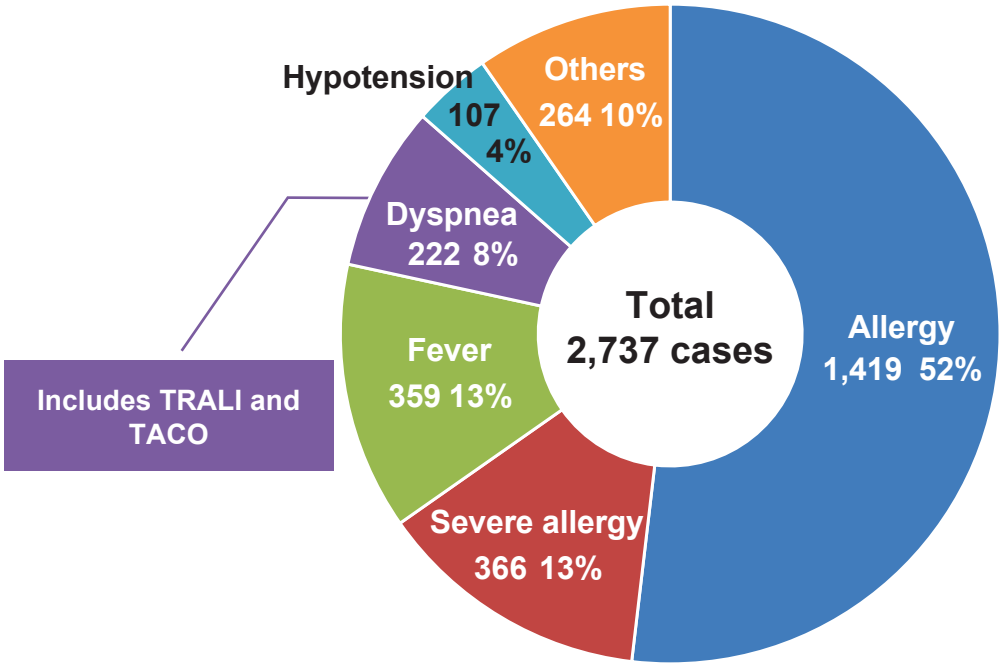


Figure 5. Number and ratio of reported non-hemolytic adverse reactions by symptom (2021)

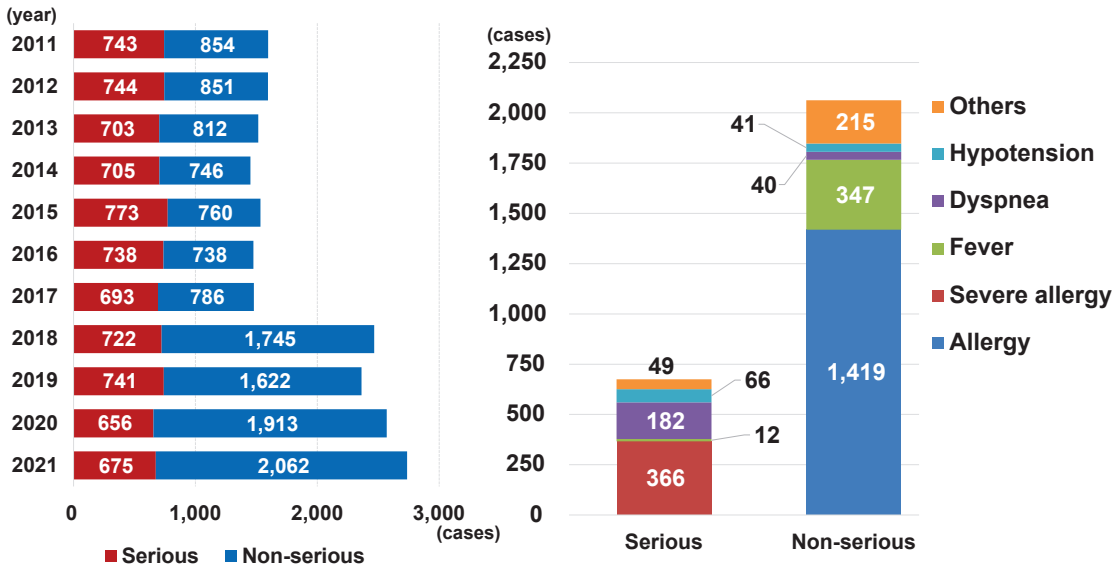


Figure 6. Number of reported serious* and non-serious adverse reaction cases (2021)

* Serious cases: cases evaluated as serious by physicians and cases evaluated as non-serious by physicians but determined to be serious by the JRCS based on the symptoms

[Evaluation of TRALI and TACO cases]

Among transfusion adverse reactions and TTIs reported by medical institutions, the JRCS evaluates suspected TRALI and TACO cases together with respiratory specialists and shares the results to the medical institutions. In the past, TRALI was evaluated based on the TRALI diagnostic criteria that were proposed at the Consensus Conference in 2004 (Transfusion. 2004; 44:1774-89), and from April 2012, TACO was evaluated based on the JRCS' original criteria. However, in response to the revision of international TRALI and TACO evaluation criteria (Transfusion. 2019; 59:2465-76, ISBT Working Party on Haemovigilance in collaboration with IHN and AABB.2018.), the JRCS formulated new criteria in April 2021, which were then used to evaluate TRALI and TACO. Figure 7 shows the classification and evaluation criteria in the new standard (used for both TRALI and TACO). Figures 8 and 9 show TRALI and TACO evaluation results in 2021 using the criteria before the change ("former criteria") and those using the criteria after the change ("new criteria"), respectively.

[Classification]

TRALI (transfusion-related acute lung injury) Type I
TRALI (transfusion-related acute lung injury) Type II
TRALI/TACO
TACO (transfusion-associated circulatory overload)
ARDS (acute respiratory distress syndrome)
TAD (transfusion-associated dyspnea)
Others

[Evaluation criteria]
(1) Acute onset
(2) Hypoxemia
(3) Clear evidence of bilateral pulmonary edema on imaging
(4) No evidence of left atrial hypertension, or if left atrial hypertension is present, it is judged to not be the main contributor to the hypoxemia
  (4)-1 Cardiovascular changes that cannot be explained by underlying conditions
  (4)-2 Fluid overload
  (4)-3 BNP (or NT-pro BNP) level that exceeds the reference range and is 150% or higher than the pre-transfusion level
(5) Onset during or within six hours of transfusion
(6) No temporal relationship to an alternative risk factor for ARDS*
(7) Stable respiratory status in the 12 hours before transfusion
(If (4) is not applicable, at least one of (4)-1 through (4)-3 should apply.)

* Risk factors for ARDS
Pneumonia
Aspiration of gastric contents
Inhalational injury
Pulmonary contusion
Pulmonary vasculitis
Drowning
Non-pulmonary sepsis
Major trauma
Pancreatitis
Severe burns
Non-cardiogenic shock
Drug overdose

Figure 7. Classification and evaluation criteria in the new standard (used for both TRALI and TACO)

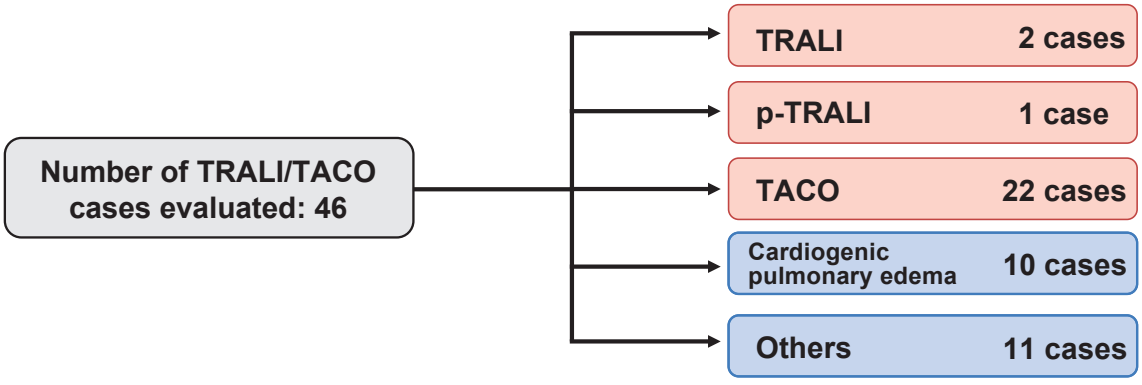


Figure 8. TRALI and TACO evaluation results based on the former criteria (January to March 2021)

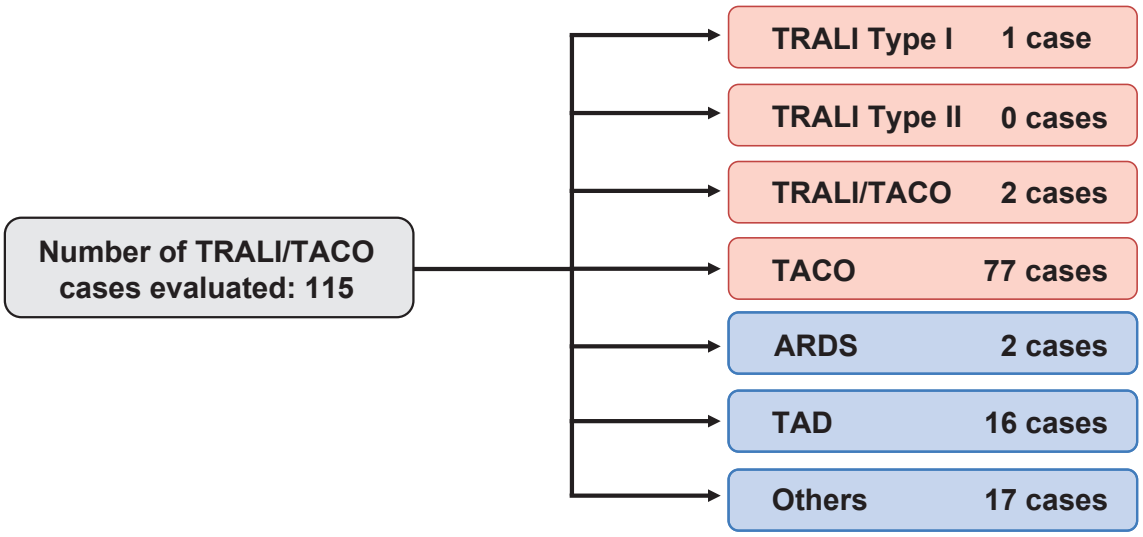
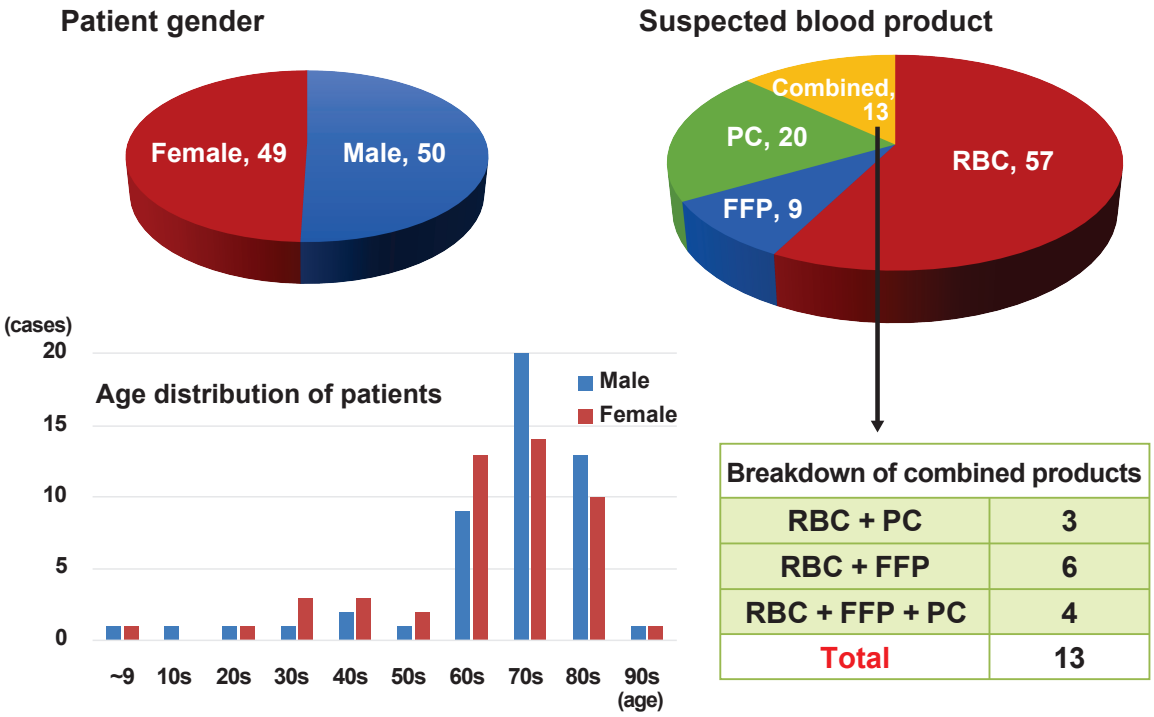


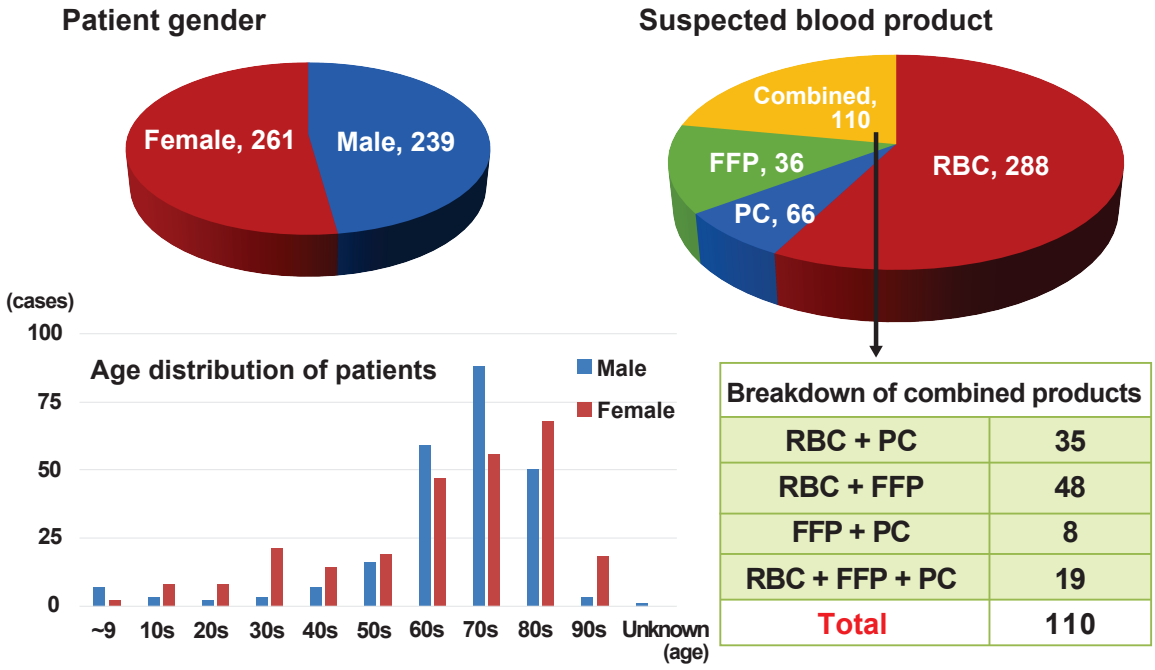
Figure 9. TRALI and TACO evaluation results based on the new criteria (April to December 2021)

- In April 2021, the JRCS started evaluating TRALI and TACO cases based on the new criteria.
- Of the 2,737 non-hemolytic adverse reaction cases reported by medical institutions in 2021, a total of 161 cases were evaluated, including suspected TRALI and TACO cases and dyspnea and hypoxemia (decreased SpO_2) cases with bilateral infiltrates on chest imaging.
- Among the 46 cases evaluated based on the former criteria until March 2021, 2 cases were evaluated as TRALI, 1 as possible TRALI, and 22 as TACO.
- Among the 115 cases evaluated based on the new criteria from April 2021, 1 case was evaluated as TRALI Type I, 2 as TRALI/TACO, and 77 as TACO.
- Among the 6 cases evaluated as TRALI, anti-leukocyte antibodies were detected in blood products in 5 cases, and a positive cross-match (including computer cross-matching) with patient lymphocytes was detected in 3 of the 4 available cases.
- The 56 cases evaluated as not TRALI or TACO included those evaluated as cardiogenic pulmonary edema and other adverse reactions (e.g., allergic or anaphylactic dyspnea and TAD/ARDS), as well as cases that lacked necessary data (e.g., chest images and data indicating pre-transfusion respiratory function) and cases that did not meet the evaluation criteria (e.g., cases that notably exceeded the time-to-onset criteria and cases with pre-existing acute respiratory failure).
- Figure 10 shows the gender ratio and the blood products involved in cases evaluated as TACO in 2021, and Figure 11 shows the cumulative figures for the same data for the period starting April 2012, when the JRCS began TACO evaluations, up to 2021. Many of the reported TACO cases involved patients aged 60s or older. RBC, including that in combined products, was involved in most cases, and in about 80% of TACO cases from April 2012 to 2021.



Breakdown of combined products	
RBC + PC	3
RBC + FFP	6
RBC + FFP + PC	4
Total	13

Figure 10. Patient gender ratio and blood products used in TACO cases (2021)



Breakdown of combined products	
RBC + PC	35
RBC + FFP	48
FFP + PC	8
RBC + FFP + PC	19
Total	110

Figure 11. Patient gender ratio and blood products used in TACO cases (April 2012 to 2021)

[Discussion on and future agendas of TRALI and TACO]

- In 2021, 161 cases were evaluated for TRALI and TACO. Among these, 6 cases were diagnosed as TRALI. On the other hand, 109 cases were evaluated as TACO or cardiogenic pulmonary edema, accounting for a large part of all evaluated cases.
- Among cases reported as suspected TRALI, less than 4% were actually diagnosed as TRALI. There were no cases of death deemed attributable to TRALI in 2021.
- As a safety measure against TRALI, the JRCS manufactures fresh frozen plasma (FFP) preferentially derived from 400 mL whole blood donations by male donors. While almost 100% of FFP made from 400 mL whole blood donations are derived from male donors, less than 20% of FFP made from 200 mL whole blood donations and 70% of FFP made from apheresis donations are derived from male donors.
- Since TACO is a form of cardiac failure due to circulatory overload, it is important to understand the patient's potential risk of cardiac failure by measuring pre-transfusion NT-proBNP* levels or confirming any kidney function insufficiency. This is an issue that needs to be addressed going forward. When transfusing to patients who have demonstrated potential heart failure risks before blood transfusion, the transfusion rate and volume need to be carefully decided and also monitored during the transfusion.
- Figure 12 shows TRALI and TACO evaluation results over the years. Some of the cases that used to be evaluated as cardiogenic pulmonary edema or as other adverse reactions based on the former criteria were evaluated as TACO based on the new criteria; consequently, TACO cases increased in 2021 compared to 2020 and earlier.
  *NT-proBNP: N-terminal pro-brain natriuretic peptide

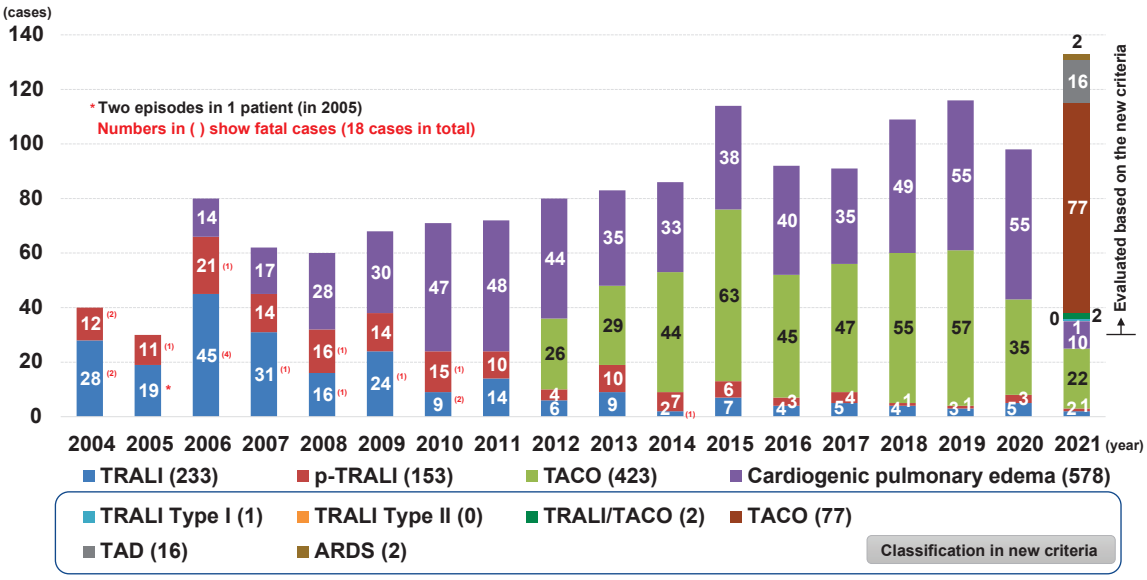
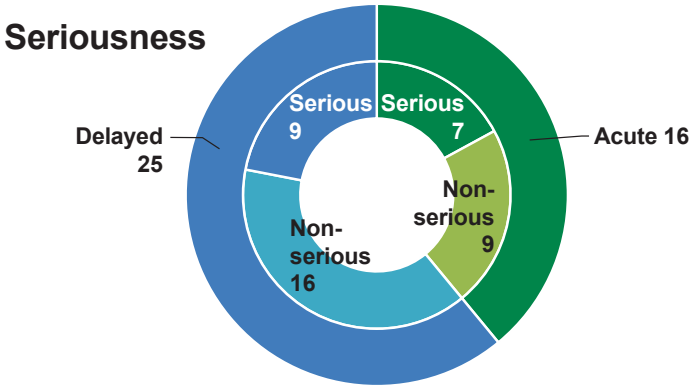


Figure 12. Evaluation of TRALI and TACO cases (2004 to 2021)

(2) Hemolytic adverse reactions

In 2021, 41 hemolytic adverse reactions were reported by medical institutions, including 16 serious cases (Figure 13). Of the 41 reported cases, 16 cases were acute reactions, and 25 cases were delayed reactions. According to surveys by medical institutions and the JRCS, irregular antibodies were detected in patient blood in 17 cases, including 5 cases of acute reactions and 12 cases of delayed reactions. The antibodies included those against Rh, Kidd, JR and other blood types, as well as autoantibodies. In all cases, RBC components were used.



	Serious		Non-serious	
Acute	**4**	**Jr^a: 2** **Jk^a, E, c, M (cold): 1** **P1 (cold): 1**	**1**	**E: 1**
Delayed	**7**	**Jk^a: 1** **C, e, Jk^b: 1** **E, c, Jk^b: 1** **E, c: 1** **C, e: 1** **Autoantibodies: 2**	**5**	**E, c: 1** **C, e + α (unidentifiable): 1** **e + α (unidentifiable): 1** **Autoantibodies, P1, E: 1** **Autoantibodies (anti-c): 1**

Figure 13. Number of reported hemolytic adverse reactions and antibodies detected in patients (2021)

(3) Transfusion-associated graft versus host disease

- No cases of suspected TA-GVHD were reported by medical institutions in 2021.
- There have been no confirmed cases of TA-GVHD attributable to JRCS's transfusion blood products since 2000, when the JRCS introduced irradiated products.

2) Infections

(1) Cases reported as suspected transfusion-transmitted infections

Figure 14 shows the annual number and breakdown of suspected TTIs (including TTIs reported by medical institutions and detected through post-donation information) reported during the past 10 years until 2021. In 2021, a total of 43 cases were reported, including 9 cases of suspected HBV, 5 cases of suspected HCV, 20 cases of suspected bacterial infection, and 9 cases of other infections.

Of these, confirmed TTIs in 2021 included 2 HBV infections (Table 1). No transfusion-transmitted HCV and HIV cases have been confirmed since the introduction of the nucleic acid amplification test (NAT) on individual samples (individual donation NAT: ID-NAT; Figure 15).

In viral TTI, a "confirmed case" refers to a case in which a virus is found in the blood products and recipient blood, and either sequential homology of the virus in both is confirmed via genetic analysis, or the recipient's infection is confirmed through a lookback investigation that is prompted by the donor's post-donation information (on, for example, positive viral marker conversion) and suggests a probable causal relationship between the donated blood and recipient's infection. Meanwhile, in bacterial TTI, a confirmed case refers to a case in which bacteria are found in the blood product and recipient blood, and the consistency in bacterial strain is confirmed via genotype tests (pulsed field gel electrophoresis: PFGE) and toxinotype tests.

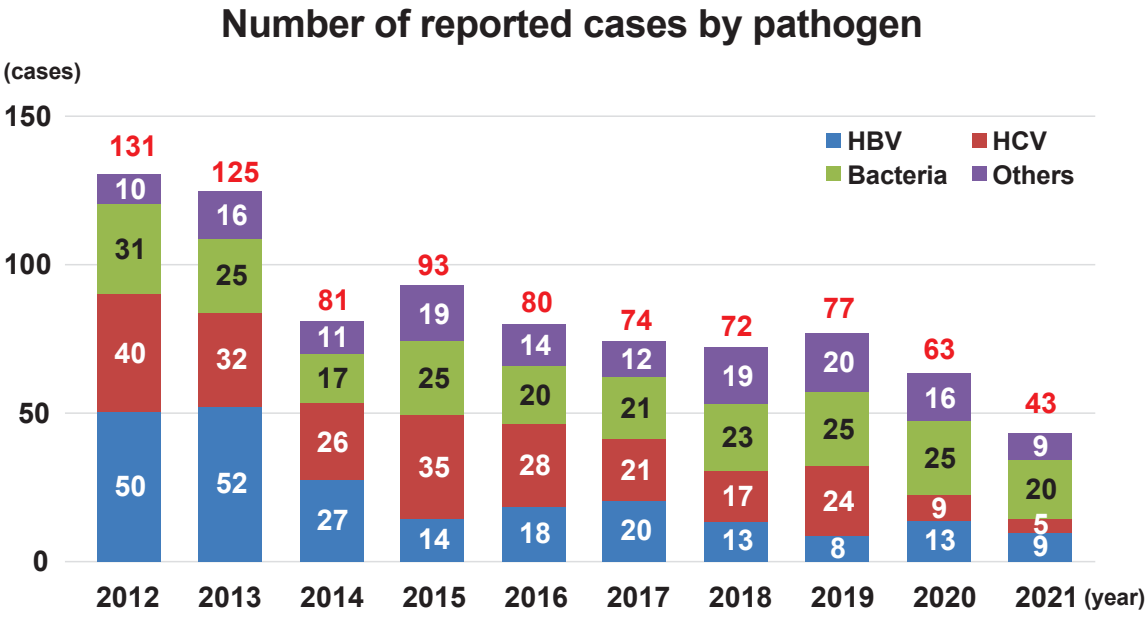


Figure 14. Number of reported suspected TTI cases by pathogen

Table 1. Analysis results of reported suspected TTI cases by pathogen (2021)

Pathogen	Number of reported cases	Number of confirmed cases	Excluded cases	
			Positive in pre-transfusion test	Negative in pre- and post-transfusion tests
HBV	9	2	1	1*1
HCV	5	0	0	0
Bacteria	20	0	0	0
CMV	5	0	2*2	0
HEV	4	0	0	1*3
Total	43	2	3	2

*1: Considered unrelated to transfusion based on HBV-DNA negativity in a post-transfusion test at the medical institution

*2: Considered unrelated to transfusion but related to transmission through breast milk

*3: Considered unrelated to transfusion based on HEV-RNA negativity and HEV-IgA antibody positivity in pre- and post-transfusion tests

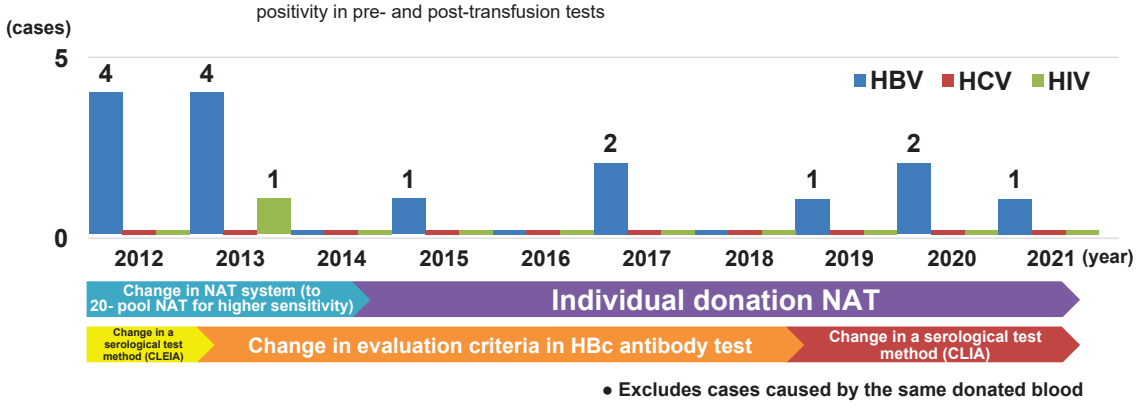


Figure 15. TTI by year of blood collection (HBV, HCV, and HIV)

(2) Summary of confirmed transfusion-transmitted infections

The following shows a summary of cases confirmed to be TTIs.

[HBV infections]

Of the 9 suspected HBV infections reported in 2021, two were confirmed to be transfusion-transmitted HBV infections, including a spontaneous report on an HBV infection that was identified following hepatitis in the recipient (Case 1) and a case identified through a lookback study that was prompted by the positive conversion of the donor on NAT testing (Case 2; Table 2).

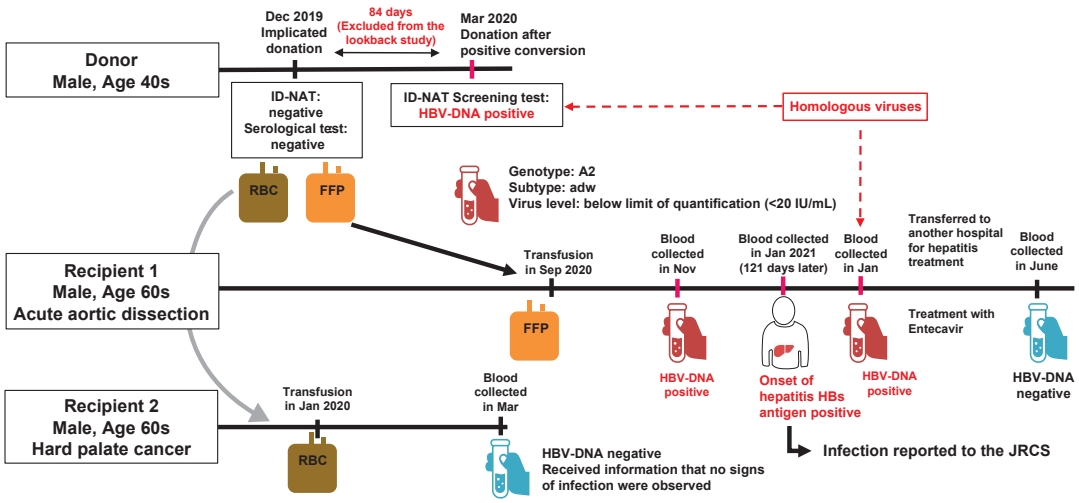
In Case 1, the patient received multiple transfusion blood products including FFP during surgery for acute aortic dissection. The patient tested positive for HBV-DNA at a medical institution in November 2020, but was not reported to the JRCS at the time. The case was then reported as suspected transfusion-transmitted HBV infection following the onset of hepatitis in January 2021. The donors of the transfused products were investigated, and it was found that the blood of the donor of one of the FFPs had turned HBV positive during a NAT screening test for the following donation. This screening test was performed 84 days after the implicated donation, after the 72-day lookback study period at the time. The HBV found in the post-conversion donor blood was homologous with that in the recipient, thereby confirming the TTI. One RBC product was also manufactured from the donor's whole blood donation, but it was confirmed that the recipient of the RBC tested negative on a post-transfusion HBV-DNA test and showed no signs of infection. This case demonstrated HBV transmission by a donor of multiple donations who turned positive after the lookback study period and prompted the *Guidelines for Look-back Studies on Blood Products* to be revised in September 2021 (see p. 17).

In Case 2, an HBV infection caused by a trace amount of the virus was identified through a lookback study. Two bags of platelets had been produced from the donated blood examined in the lookback study and transfused to two patients with hematological disorders. One recipient turned HBV-DNA positive 155 days after the transfusion. The virus detected in the recipient was found to be homologous with the virus detected from the donor after positive conversion, confirming the TTI. Follow-up on the other recipient also confirmed similar positive conversion and viral homology, though this was excluded from the 2021 data since it was reported in 2022. Both TTI cases could not be easily detected during the conventional post-transfusion infection test period (three months).

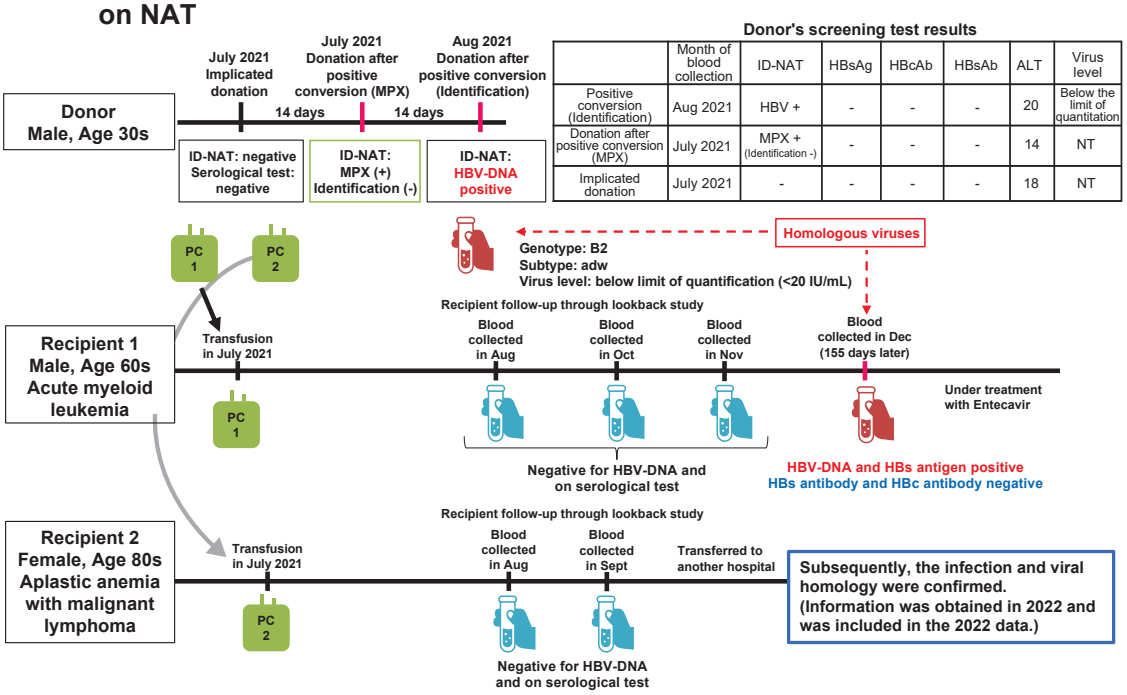
Table 2. Confirmed transfusion-transmitted HBV infections (2021)

Case 1: Spontaneous report of infection identified following hepatitis in a recipient

	Month of blood collection	ID-NAT	HBsAg	HBcAb	HBsAb	ALT	Virus level
Positive conversion	Mar 2020	+	-	-	-	34	Below the limit of quantification
Implicated donation	Dec 2019	-	-	-	-	20	NT



Case 2: Identified through a lookback study following the donor's positive conversion on NAT



3) Information on individual cases of transfusion adverse reactions and transfusion-transmitted infections obtained from literature and academic societies

(1) Cases in Japan

Table 3 shows domestic case reports obtained from literature and academic societies in 2021. Although the domestic cases in Table 3 were not reported by medical institutions to the JRCS and were only found in literature or information from academic societies, the JRCS's MRs interviewed the authors and medical institutions they are associated with on the seriousness of the adverse reactions and on the blood products involved. Cases that were evaluated as serious transfusion adverse reactions and infections based on investigation results were submitted as ICSR to the PMDA.

Table 3. Domestic transfusion adverse reaction cases identified through literature search (2021)

No	Implicated blood product	Age	Sex	Adverse event	Journal
1	Ir-RBC-LR, Ir-PC-LR, and FFP-LR	29	F	Pulmonary edema, wheals, and TACO	The Journal of Japan Society for Clinical Anesthesia. 2020; 40(6):323.
2	Ir-RBC-LR	40s	F	Delayed hemolytic transfusion adverse reaction	Japanese Journal of Transfusion and Cell Therapy. 2021; 67(2):313.
3	RBC-LR, PC-LR, and FFP-LR	43	M	Delayed hemolytic transfusion adverse reaction	Int J Hematol.2022;115:440-445.
4	Ir-RBC-LR	80	F	Delayed hemolytic transfusion adverse reaction	Journal of the Japanese Society of Intensive Care Medicine. 2021; 28:461-462.

[Summary]

- No.1 is a case of pulmonary edema caused by massive transfusion of FFP, RBC, and PC. The case was evaluated as TACO based on an in-depth investigation at the medical institution.
- In Case No.2, hemolysis was observed 10 days after RBC transfusion. The transfusion of crossmatch- compatible RBCs was continued, resulting in exacerbated hemolytic condition suspected of being a delayed hemolytic transfusion reaction (DHTR). When RBCs that were Rh-compatible and patient antigen-negative (Fy^b and Di^a) were transfused, no hemolysis was observed, and the patient was able to benefit from the transfusions.
- No. 3 is a case of DHTR caused by anti-Fy^a associated with HLA-DRB1*04:03. The case was evaluated as non-serious based on an in-depth investigation at the medical institution, and reports to PMDA were considered unnecessary.
- In Case No.4, the patient developed DHTR following transfusion for burn treatment. Tests for irregular antibodies revealed anti-Rh (Hr0), anti-E, and anti-e. The test also identified the patient's blood type to be D--.

(2) Cases outside of Japan

Since transfusion blood products manufactured by the JRCS are distributed (supplied) only in Japan, the JRCS monitors transfusion adverse reactions and TTIs outside of Japan by collecting and investigating case reports on adverse reactions and TTIs caused by foreign blood products that are equivalent to the JRCS's in terms of product type and efficacy. Among them, TTIs and unknown serious adverse reactions are submitted as ICSR to the PMDA. Table 4 indicates overseas cases identified in 2021.

Table 4. Cases outside of Japan learned through literature search and submitted as ICSR to the PMDA (2021)

No	Country	Implicated blood product (equivalent product in Japan)	Age	Sex	Adverse event	Journal
1	U.S.	RBC-LR	40	F	*Cytomegalovirus* infection	BMJ Case Rep 2021; 14:e236892.
2	Sri Lanka	RBC-LR	17	M	*Plasmodium falciparum* infection	Malar J. 2021; 20(352).
3	U.S.	RBC-LR	1	M	*Plasmodium ovale* infection	J Pediatric Infect Dis Society. 2021; 10(12):1092-1095.
4	U.S.	RBC-LR	13	M	*Plasmodium falciparum* infection	J Pediatric Infect Dis Society. 2021; 10(12):1092-1095.
5	Italy	RBC-LR	70	M	*Plasmodium malariae* infection	Healthcare.2021; 9:1558.
6	France	PC-LR	Unknown	M	Hepatitis A	Emerging Infectious Diseases. 2022; 28(1):219.

[Summary]

- No. 1 is a case of CMV infection in the U.S. Fever, tachypnea, and rales on chest auscultation were observed about one month after the RBC transfusion. Transfusion-transmitted CMV infection was suspected because high titers of CMV-DNA, CMV-IgM, and CMV-IgG were detected and no immunosuppressive therapy was performed during surgery.
- No. 2 is a case of malaria infection in Sri Lanka. A fever and headache started 13 days after transfusion. Transfusion-transmitted malaria infection was suspected because *P. falciparum* was detected in both the patient and the donor, Sri Lanka was not a malaria-endemic area, and the patient had no history of travel abroad.
- No. 3 is a case of malaria infection in the U.S. The patient developed a fever for 9 days after the RBC transfusion, and pancytopenia and elevated inflammation markers were observed. Malaria parasites were detected on smear microscopy. A serological test confirmed a history of *P. ovale* and *P. falciparum* infection. Transfusion-transmitted malaria infection was suspected because the patient had no history of travel abroad.

- No. 4 is a case of malaria infection in the U.S. The patient received repeated transfusions for sickle cell disease and developed fever and other symptoms that prolonged for more than one week, followed by acute hypoxic respiratory failure. *P. falciparum* was detected on smear microscopy of the patient blood. One of the donors from Nigeria was found to have a history of malaria infection and tested negative on a PCR test but positive on a serological test. Transfusion-transmitted malaria infection was suspected because the patient had no history of travel to a malaria-endemic area.
- No. 5 is a case of malaria infection in Italy. The patient had recurrent spiking fever for four days after transfusion and was diagnosed with *P. malariae* infection. Transfusion-transmitted malaria infection was suspected because *P. malariae* was also detected in the donor's blood and the patient had no history of travel to a malaria-endemic area.
- No. 6 is a case of HAV infection that came to light through post-donation information in France. In response to reported information that the donor developed fever five days after donation, plasma derived from the donor was tested, and HAV-RNA was detected. Pathogen-reduced pooled platelets were manufactured from the index donation and transfused to an immunosuppressed patient, who developed abnormalities in hepatic function and tested positive for HAV-RNA, HAV-IgG, and IgM two months later. The confirmed homology between the HAV detected in the donor and in the patient suggested that the HAV had been transmitted through the transfused PC.

3. Measures in foreign countries and studies

The JRCS reports to the PMDA when it obtains information on measures that countries outside of Japan have taken for pharmaceuticals equivalent to the JRCS's transfusion blood products. Foreign measures that require such reporting are defined as "the discontinuation of production, import, or distribution; recall; disposal; and other measures taken for relevant foreign pharmaceuticals to prevent health hazards from occurring or expanding" in Article 228-20 of the Enforcement Regulations of the PMD Act. The JRCS also files reports to the PMDA when it obtains information on studies demonstrating that: "adverse reactions or infectious diseases associated with JRCS's pharmaceuticals or equivalent foreign pharmaceuticals may cause cancer, other serious diseases, disorders, or death;" "trends in adverse reactions or infectious diseases associated with the JRCS's pharmaceuticals or equivalent foreign pharmaceuticals have significantly changed;" or that "the JRCS's pharmaceuticals do not demonstrate efficacy for which they were approved" as specified in Article 228-20 of the Enforcement Regulations of the PMD Act.

Although the JRCS does not distribute (supply) its transfusion blood products outside of Japan, based on Article 68-10 of the PMD Act and Article 228-20 of the Enforcement Regulations of the PMD Act, it files reports to the PMDA on non-JRCS transfusion blood products used abroad as long as they use the same active ingredients, regardless of any difference in administration route, dosage, and efficacy.

Table 5 shows measures taken in foreign countries in 2021 that JRCS reported. There were no studies that JRCS reported in 2021.

Table 5. Measures in foreign countries that JRCS noted and reported (2021)

No.	Country	Title
1	New Zealand (NZBS)	New Zealand Blood Service makes changes to donor behaviour criteria (14 December 2020)
2	U.S. (FDA)	Updated Information for Blood Establishments Regarding the COVID-19 Pandemic and Blood Donation (19 January 2021)
3		Information for Blood Establishments Regarding FDA's Determination that Zika Virus is no Longer a Relevant Transfusion-Transmitted Infection: Withdrawal of Guidance titled "Revised Recommendations for Reducing the Risk of Zika Virus Transmission by Blood and Blood Components" (May 2021)
4		Notifying FDA of Fatalities Related to Blood Collection or Transfusion (August 2021)
5	U.K. (NHS)	Change Notification UK National Blood Services No.16-2021: Changes required for implementation of the FAIR study (26 May 2021)
6		Change Notification UK National Blood Services No.45-2021: Steering group concludes that donors no longer need to be asked about a partner's sexual contact in parts of the world where HIV is very common (11 October 2021)
7	Germany (PEI)	Updated - Uniform Blood and Plasma Donor Questionnaire (1 November 2021) Uniform Blood and Plasma Questionnaire (25 October 2021) Hemotherapy Guideline Updated - Period for Donor Reservation Shortened (24 September 2021)

[Summary]

- No. 1 was information concerning changes to the donor eligibility criteria in New Zealand. The New Zealand Blood Service (NZBS) reduced the deferral period from 12 to 3 months for persons with a history of living in an HIV-endemic area, persons who accepted payment in exchange for sex, and men who have had oral or anal sex with other men. The NZBS also set forth a new deferral period of 3 months for persons who have taken medication to prevent HIV infection (i.e., pre or postexposure prophylaxis).
- No. 2 to No. 4 were information issued by the U.S. Food and Drug Administration (FDA) to blood establishments. No. 2 provided the latest information concerning the COVID-19 outbreak, recommending the deferral of donors who received COVID-19 vaccination. No. 3 notified that a re-evaluation of transfusion-transmitted Zika virus (ZIKV) risks indicated that ZIKV no longer falls under the FDA's definition of "relevant transfusion-transmitted infection" and that the guidance titled, "Revised Recommendations for Reducing the Risk of Zika Virus Transmission by Blood and Blood Components" was therefore withdrawn. No. 4 notified updates on procedures for reporting to the FDA deaths associated with blood donation or transfusion.
- No. 5 and No. 6 were on revisions of the donor eligibility criteria and questionnaire in the U.K. The deferral period for men who have sex with men used to be 3 months, but the revised criteria determine a donor's eligibility based on the individual's behavioral risks, regardless of sexual orientation. Additionally, the deferral for donors whose sexual partners have had sexual intercourse in an HIV-endemic area was discontinued.
- No. 7 was on revisions of donor eligibility criteria and questionnaire in Germany. The deferral period was reduced from 12 to 4 months for donors who engage in sexual acts that are associated with a particularly high TTI risk, and the donor questionnaire was revised accordingly.

4. Safety measures for blood products for transfusion

The JRCS takes safety measures that are based on the assessment and evaluation of transfusion adverse reactions and TTIs reported by medical institutions and identified through post-donation information from donors. The following are the JRCS's safety measures in 2021.

1) Lookback study based on post-donation information

Figure 16 shows post-donation information that was primarily obtained from donors from 2017 to 2021, and was categorized into: (1) information on HIV infection or HIV-related risks, (2) donor's health information, (3) information on positive conversion in donors of multiple donations, (4) post-donation notifications concerning criteria in questionnaires, and (5) other safety information. In 2021, the total number of lookback studies increased because those performed based on "(2) donor's health information" above included safety measures taken against COVID-19 and because those initiated based on "(5) other safety information" above included the withdrawal of unexpired transfusion blood products that were previously collected from donors who later turned positive on predefined TTI markers, regardless of whether such products fell within the designated lookback study period (see 2) of this section). In lookback studies based on (3) positive conversion in donors of multiple donations, a case of HBV infection transmitted by PC transfusion was confirmed (see p. 14). Cases of positive conversion in donors of multiple donations increased following the update in the infection test system in 2019, but are now gradually decreasing.

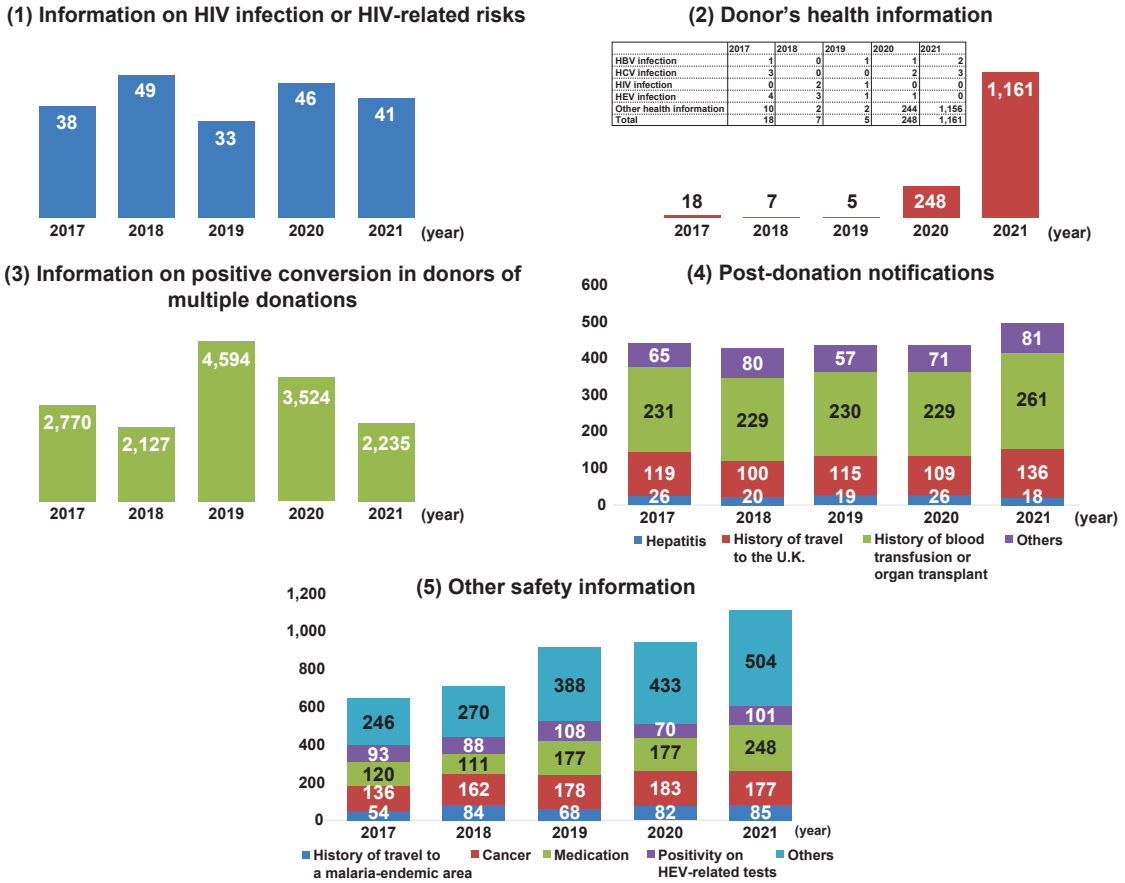


Figure 16. Lookback studies based on post-donation information

2) Revision of the *Guiselines for Look-back Studies on Blood Products*

In response to the HBV infection that occurred outside the lookback study period as described on p. 14, the *Guiselines for Look-back Studies on Blood Products* was revised under the Partial Amendment to the Guiselines for Look-back Studies on Blood Products Pertaining to Blood Products (Pharmaceutical Safety and Environmental Health Bureau (PSEHB) Notification No. 0915-3; issued by the Director of PSEHB, MHLW on September 15, 2021). The main points of revision were: (1) extension of the lookback period for HBV to a window period based on the slow replication speed of HBV Genotype A, and (2) additional requirement to notify medical institutions of any unexpired transfusion blood products derived from the past donations of donors who have turned positive on ID-NAT and other tests for HBV, HCV, and HIV, and to withdraw such products if they have not been used.

3) Safety measures for blood products for transfusion through implementation of HEV-nucleic acid amplification test

Figure 17 shows confirmed HEV TTI cases over the past 20 years. As a safety measure for HEV, a trial HEV-NAT (20-sample pools) was implemented only in Hokkaido in 2005. In 2011, HEV-IgA testing was covered by insurance, and the number of tests performed at medical institutions increased, and thus, the number of confirmed cases started to increase from 2012.

In August 2020, ID-NAT for HEV was introduced nationwide. Since then, no confirmed HEV infections transmitted by blood products have been observed, and in 2021, no cases were reported.

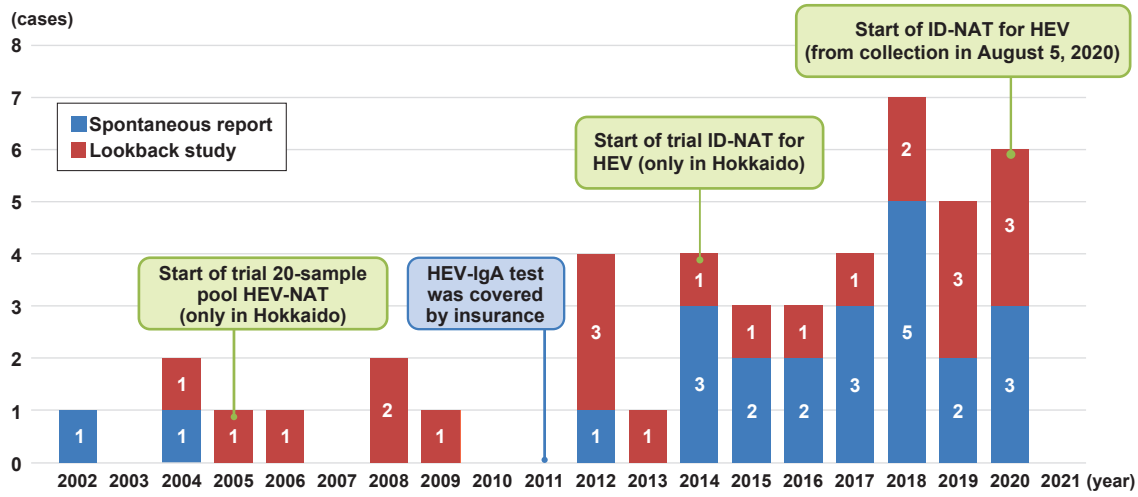


Figure 17. Confirmed cases of transfusion-transmitted HEV infections

4) Safety measures against COVID-19

Since its emergence in China in 2019, COVID-19 has spread on a global scale and is showing no signs of subsiding. As a safety measures against COVID-19 for transfusion blood products, the JRCS defers blood donation from the following persons.

1) Persons who have been diagnosed with COVID-19, or who have tested positive on a COVID-19 test (PCR or antigen test): deferred for four weeks from the resolution of symptoms (in case of asymptomatic persons, from the day the positive sample was collected)
2) Persons who present with symptoms that are suggestive of COVID-19, such as fever, cough, dyspnea, or other acute respiratory symptoms, or abnormalities in taste and smell: deferred for two weeks from the onset of such symptoms and for three days from the resolution of such symptoms
3) Persons who have had close contact with patients with COVID-19: deferred for two weeks from the last close contact

Although the JRCS is restricting blood donation for safety, no transfusion-transmitted COVID-19 infection has been confirmed in any country. The JRCS will continue to review its anti-COVID-19 safety measures as further findings of the disease emerge.

Afterword

This annual report describes the JRCS's safety measures which are designed and implemented based on analysis and assessment of safety information collected pursuant to the PMD Act, GVP Ministerial Ordinance, and other applicable laws and regulations, primarily including adverse reaction and infection cases reported by medical institutions and post-donation information.

We extend our sincere appreciation to health care professionals and members of the JRC blood centers for their cooperation in our post-marketing safety vigilance operations.

The JRCS will continue contributing to haemovigilance in Japan and in the international community in compliance with applicable laws and regulations and strive to improve safety in transfusion medicine.

Haemovigilance by JRCS 2021

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