日本赤十字社
Japanese Red Cross Society

# Haemovigilance by JRCS 2022

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# Haemovigilance by JRCS 2022


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## 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, the JRCS began a specimen storage system that stores aliquots of all donated blood over 11 years for analysis purposes. This system enabled the investigation of transfusion blood products associated with TTIs and was useful not only to confirm the causal relationship between transfusions and TTIs but also to identify 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 for research and development. Initially, the Steering Committee of the Committee on Blood Products, Pharmaceutical Affairs and Food Sanitation Council, MHLW was responsible to assess whether or not the use of the stored specimens for 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, which are 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 like other pharmaceuticals. The JRCS also collects source human 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 healthcare professionals. The safety management section then analyzes and assesses the information, reports serious 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 the revision of precautions (drug label). The safety management section also conducts epidemiological studies related to blood safety and reports the 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 malfunction 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 closely agrees with the post-marketing safety assurance activities stipulated by the Japanese GVP Ministerial Ordinance. 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 those countries regulate transfusion blood products separately from pharmaceuticals and thus have 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 2013 and 2022. The total number of blood donations in 2022 was 4,994,576, including 125,289 of 200 mL whole blood donations, 3,285,538 of 400 mL whole blood donations, and 1,583,749 blood component donations (comprising 1,037,206 plasma donations and 546,543 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, showing similar numbers in the past several years.

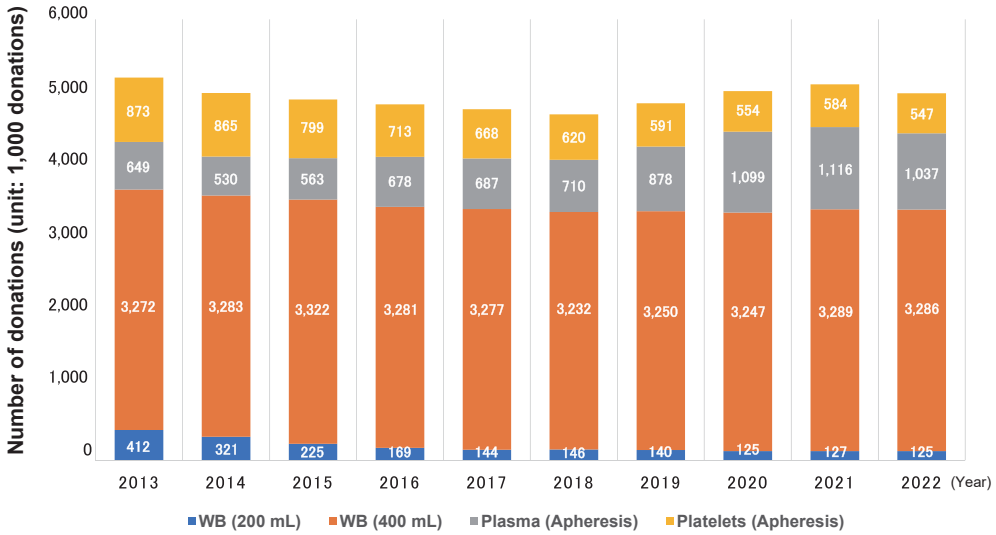



**Figure 1 Number of blood donations by year**

Figure 2 shows the transfusion blood products supply between 2013 and 2022. In recent years, the supply of red blood cell (RBC) products and plasma products has been on a decreasing trend due to the promotion of their proper use. In 2022, there was a slight increase in the supply of RBC products, and a decrease in the supply of plasma products, resulting in almost the same supply status as the previous year.

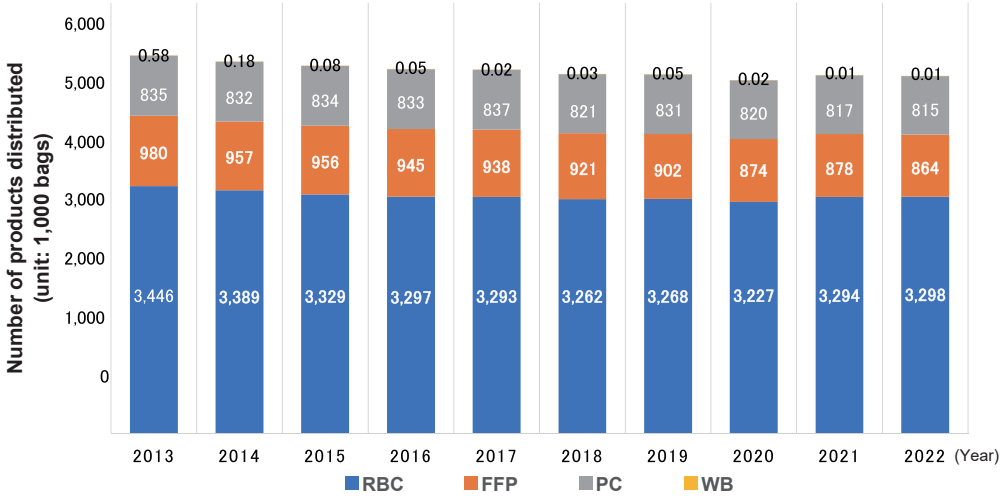



**Figure 2 Supply of transfusion blood products**

## 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 the precautions (drug label), i.e., unknown adverse reactions, are subjected to detailed investigation. Consequently, the number of non-hemolytic adverse reactions, in particular, substantially increased.

In 2022, the JRCS received 2,591 case reports on adverse reactions and infections (non-hemolytic adverse reactions, 2,514 cases; hemolytic adverse reactions, 31 cases; suspected transfusion-associated graft versus host disease (TA-GVHD), 0 cases; and suspected infections, 46 cases) from medical institutions across Japan. Cases evaluated as serious by patients' physicians or the JRCS (non-hemolytic adverse reactions, 647 cases*; hemolytic adverse reactions, 16 cases*; infections, 46 cases*) were submitted as individual case safety reports (ICSR) to PMDA, in accordance with the PMD Act. Some adverse reaction cases that were not 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 institution (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.

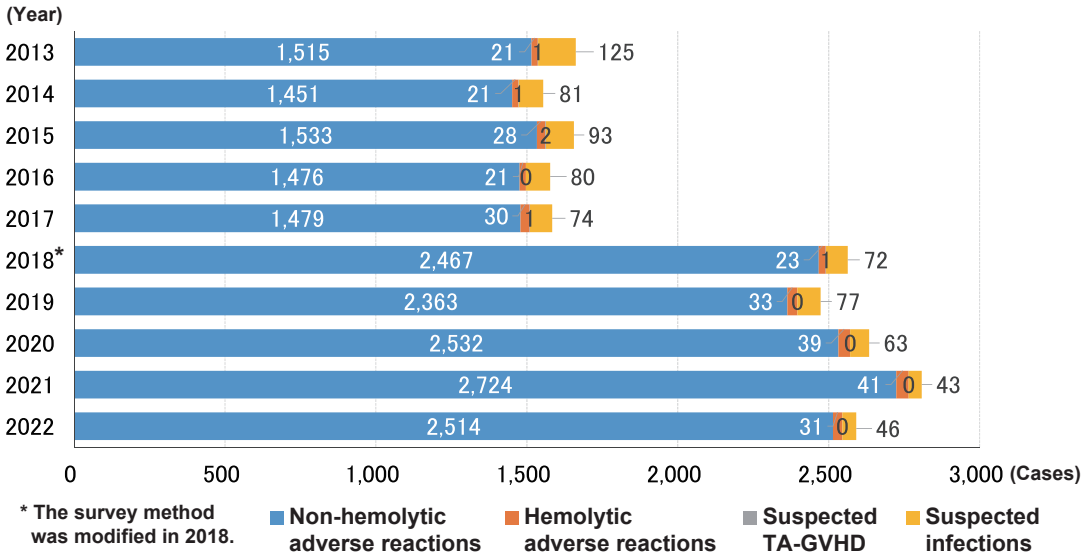



**Figure 3 Number of transfusion adverse reaction and TTI spontaneous case reports§**

§ 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 2022. Figure 5 shows the breakdown and ratio (%) by symptom for 2022, and Figure 6 indicates the number of cases according to serious/non-serious for 2022. The number of transfusion-related acute lung injury (TRALI) and transfusion-associated circulatory overload (TACO) cases is included in that for dyspnea. As in previous years, no particular category indicated a marked increase (Figure 4). About 70% of the reported adverse reactions were allergic symptoms. Serious adverse reactions accounted for approximately 30% of all adverse reactions and mainly comprised severe allergy, dyspnea, and hypotension.

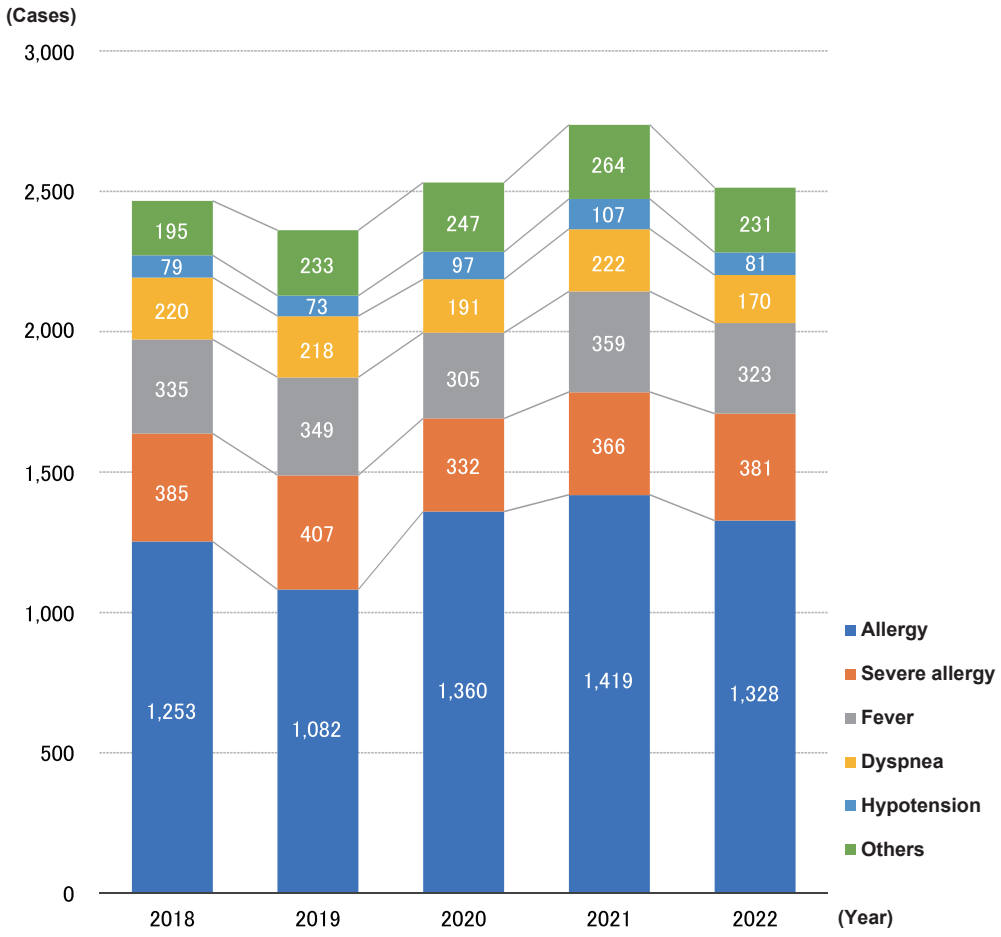



**Figure 4 Number of reported non-hemolytic adverse reactions by symptom**

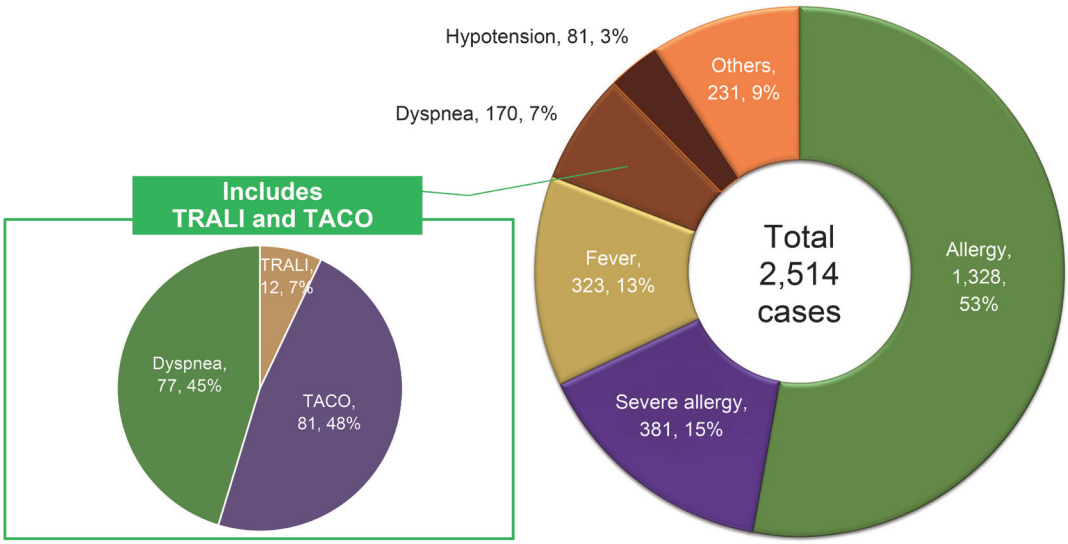



**Figure 5 Number and ratio of reported non-hemolytic adverse reactions by symptom (2022)**

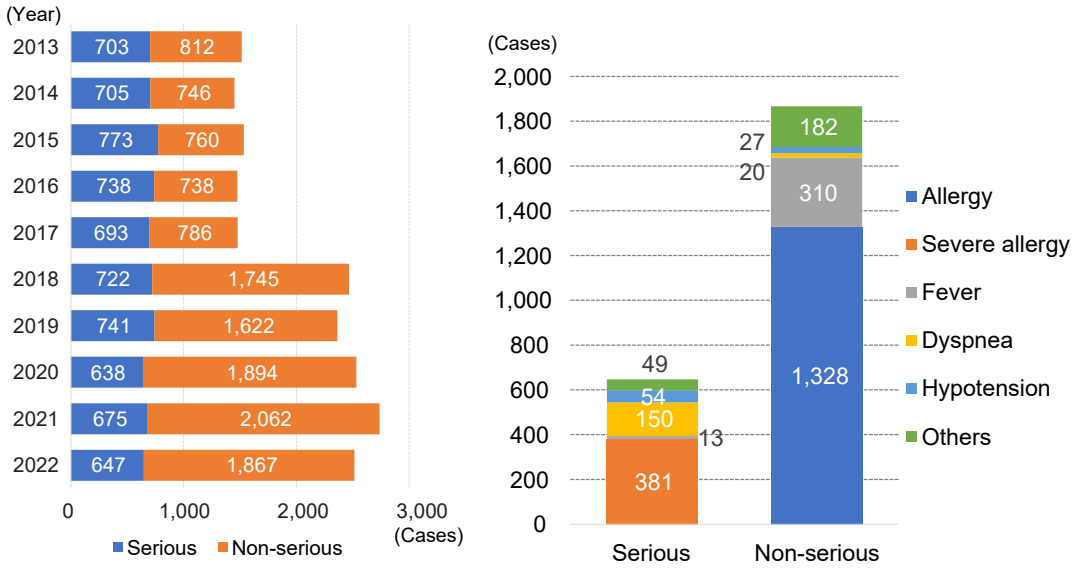



**Figure 6 Number of reported serious cases* and non-serious cases of adverse reactions (2022)**

* 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 with 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. Transfusion-associated circulatory overload (TACO) Definition (2018).), the JRCS started to evaluate TRALI and TACO based on these new criteria from April 2021. Figure 7 shows TRALI and TACO evaluation results in 2022.

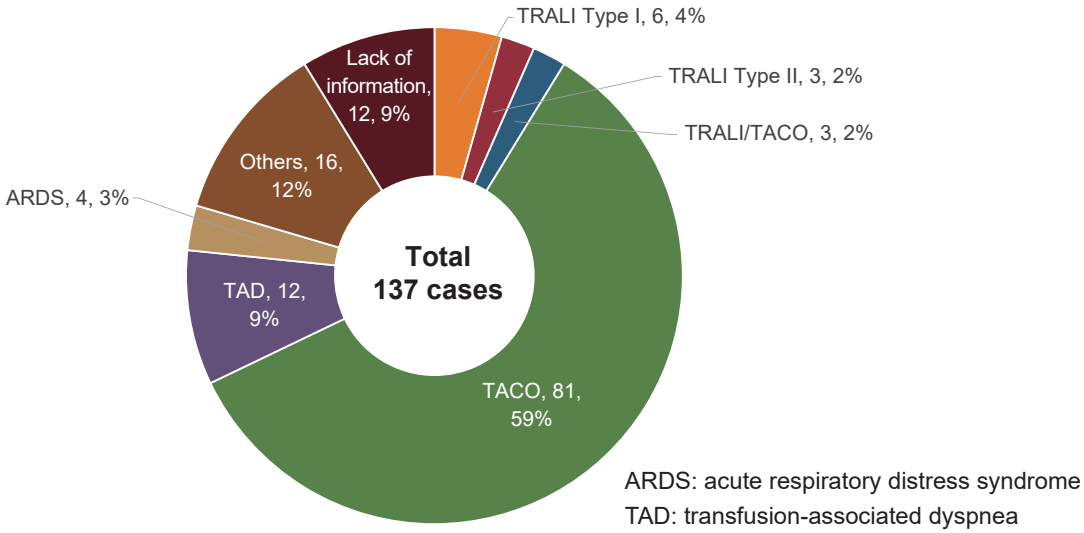
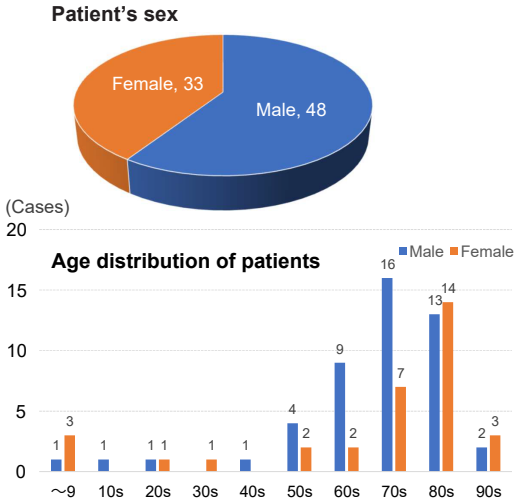



**Figure 7 TRALI and TACO evaluation results in 2022**

### [TRALI/TACO]

- In April 2021, the JRCS started evaluating TRALI and TACO cases based on the new criteria.
- Of the 2,514 non-hemolytic adverse reaction cases reported by medical institutions in 2022, we evaluated 137 cases, including suspected TRALI cases and suspected TACO cases, as well as cases of dyspnea and hypoxemia (decreased $SpO_2$) with bilateral infiltrates on chest imaging.
- Six cases were evaluated as TRALI Type I, 3 cases as TRALI Type II, 3 cases as TRALI/TACO, 81 cases as TACO, 12 cases as transfusion associated dyspnea (TAD), and 4 cases as acute respiratory distress syndrome (ARDS).
- Among the 12 cases evaluated as TRALI (TRALI Type I and Type II) or TRALI/TACO, anti-leukocyte antibodies were detected in blood products of 6 cases, and a positive cross-match (including computer cross-matching) with patient lymphocytes was detected in 3 of the 5 available cases.

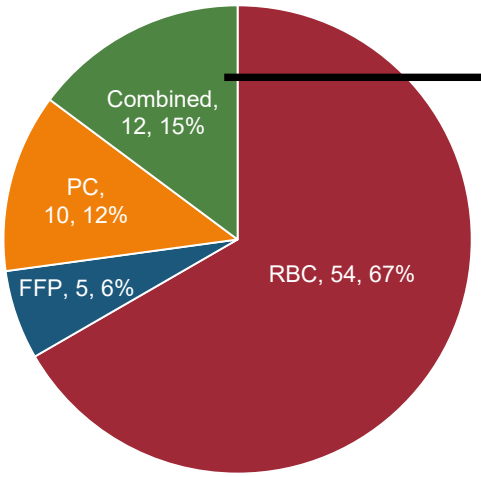
- The 16 cases evaluated as other adverse reactions included those evaluated as adverse reactions which were different from TRALI or TACO (e.g., allergic or anaphylactic dyspnea, etc.).
- There were 12 cases that could not be evaluated due to a lack of necessary information (e.g., chest images (X-ray, CT, etc.) and data indicating pre-transfusion respiratory function).
- Figure 8 shows the sex ratio, age distribution, and disease classification involved in cases evaluated as TACO in 2022, and Figure 9 shows the blood products used in the TACO cases in 2022. TACO tended to occur in elderly patients, and approximately 70% of patients had neoplastic diseases or hematological disorders. Regarding the blood products used in TACO cases, RBC, including that in combined products, was involved in most cases, and in about 80% of TACO cases from April 2012 to 2022.




**Patients' primary disease**

| Primary disease classification | Number of cases |
|---|---|
| Neoplasm (hematological) | 25 |
| Blood and hematopoietic organs | 15 |
| Neoplasm (other than hematological) | 13 |
| Cardiovascular system | 5 |
| Musculoskeletal system | 5 |
| Respiratory system | 4 |
| Renal/genitourinary system | 4 |
| Injury/poisoning | 3 |
| Digestive system | 2 |
| Infection | 1 |
| Psychiatric system | 1 |
| Pregnancy and delivery | 1 |
| Others | 2 |

**Figure 8 Patient sex ratio, age distribution, and disease classification involved in cases evaluated as TACO (2022)**




| Breakdown of combined products | |
|---|---|
| RBC+PC | 6 |
| RBC+FFP | 2 |
| PC+FFP | 2 |
| RBC+FFP+PC | 2 |
| Total | 12 |

**Figure 9 Blood products used in TACO cases (2022)**

**[Discussion on and future agenda of TRALI and TACO]**

- In 2022, we evaluated 137 cases for TRALI and TACO. Among these, 12 cases were diagnosed as TRALI (TRALI Type I and Type II) or TRALI/TACO. On the other hand, 81 cases were evaluated as TACO, accounting for a large part of all evaluated cases.
- Among the cases evaluated for TRALI and TACO, 8% were actually diagnosed as TRALI or TRALI/TACO. There were no cases of death considered attributable to TRALI in 2022.
- 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 testing for 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 the patients' condition should be monitored during the transfusion.

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

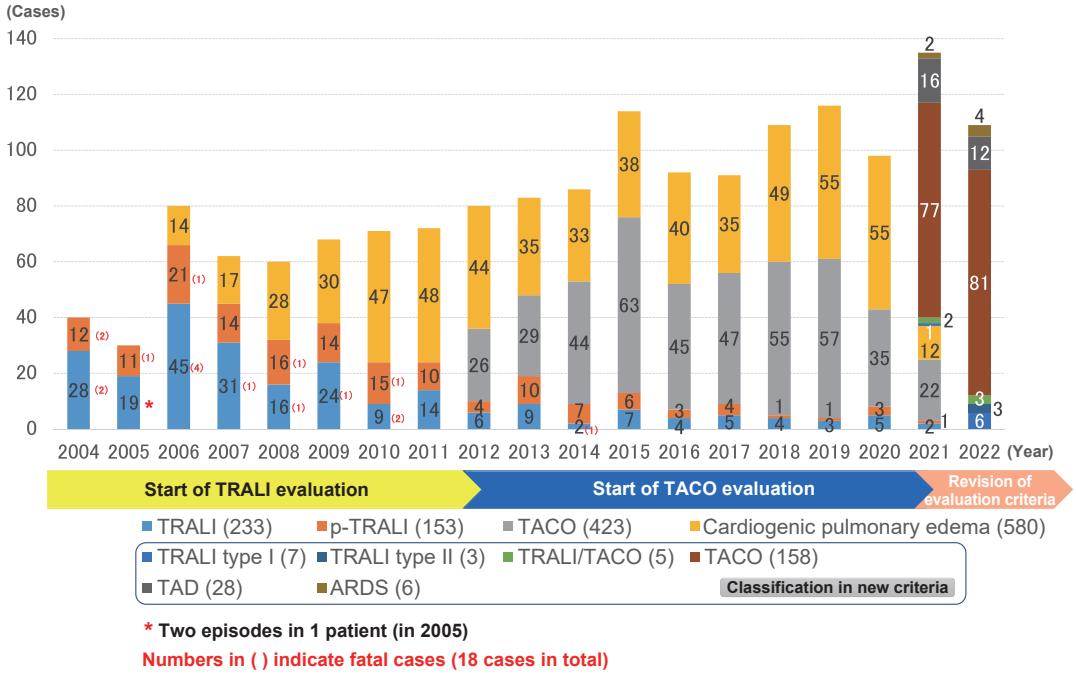
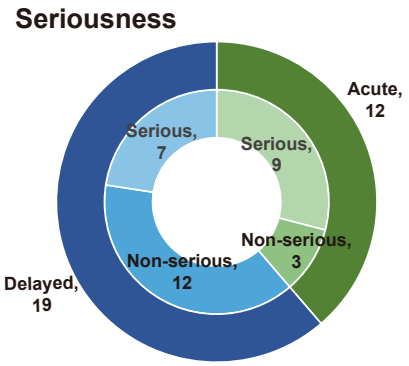



**Figure 10 Evaluation of TRALI and TACO cases (2004 to 2022)**

### (2) Hemolytic adverse reactions

In 2022, 31 hemolytic adverse reactions were reported by medical institutions, including 16 serious cases (Figure 11). Of the 31 reported cases, 12 cases were acute reactions, and 19 cases were delayed reactions. According to surveys by medical institutions and the JRCS, irregular antibodies were detected in patient blood in 18 cases, including 6 cases of acute reactions and 12 cases of delayed reactions. The reported antibodies mainly included those against the Rh and Kidd system antigens, $Jr^a$, as well as high-frequency antigens. In all cases, RBC components were used.




Note: All suspected blood products were RBC components.

**Presence/absence of antibody detection**

| | | | |
|---|---|---|---|
| Acute | Serious | Detected | 5 |
| | | Not detected | 4 |
| | Non-serious | Detected | 1 |
| | | Not detected | 2 |
| Delayed | Serious | Detected | 6 |
| | | Not detected | 1 |
| | Non-serious | Detected | 6 |
| | | Not detected | 6 |

**Antibodies detected in the 18 patients that were positive for irregular antibodies**

| | Serious | | Non-serious | |
|---|---|---|---|---|
| Acute | 5 | Anti-C, anti-e: 1<br>Anti-E, anti-c, autoantibodies: 1<br>Anti-M (IgG type): 1<br>Anti-AnWj: 1<br>Anti-$Jr^a$: 1 | 1 | Anti-$Jk^b$: 1 |
| Delayed | 6 | Anti-C, anti-e: 1<br>Anti-C, anti-e, anti-$Jk^a$: 1<br>Anti-E, anti-$Jk^b$: 1<br>Anti-E, anti-c, anti-$Le^a$, anti-$Le^{bH}$: 1<br>Anti-C, anti-e, anti-$Jk^b$: 1<br>Autoantibodies: 1 | 6 | Anti-E: 2<br>Anti-E, anti-$Jk^a$: 1<br>Anti-E, autoantibodies: 1<br>Anti-$Jk^b$: 1<br>Anti-e, anti-$Fy^b$, anti-S: 1 |

Note: The results of antibody identification tests performed at medical institutions are shown in blue.

**Figure 11 Number of reported hemolytic adverse reactions and antibodies detected in patients (2022)**

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

- No cases of suspected TA-GVHD were reported by medical institutions in 2022.
- There have been no confirmed cases of TA-GVHD attributable to the JRCS's transfusion blood products since 2000, when the JRCS introduced irradiated products.

## 2) Infections

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

Figure 12 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 2022. In 2022, a total of 46 cases were reported, including 9 cases of suspected HBV, 6 cases of suspected HCV, 29 cases of suspected bacterial infection, and 2 cases of suspected HEV.

Of these, confirmed TTIs in 2022 included 1 case of HBV infection and 4 cases of bacterial infection (Table 1). No cases of transfusion-transmitted HCV and HIV have been confirmed since the introduction of the nucleic acid amplification test (NAT) on individual samples (individual donation NAT: ID-NAT; Figure 13).

A “confirmed case” refers to a case in which pathogens including viruses are found in the blood product and recipient blood. In case of viruses, 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 and suggests a probable causal relationship between the donated blood and the recipient’s infection. In case of bacterial TTI, a confirmed case refers to a case in which the same strain is found in the blood product and the recipient blood based on genotype tests (pulsed field gel electrophoresis: PFGE) and toxinotype tests.

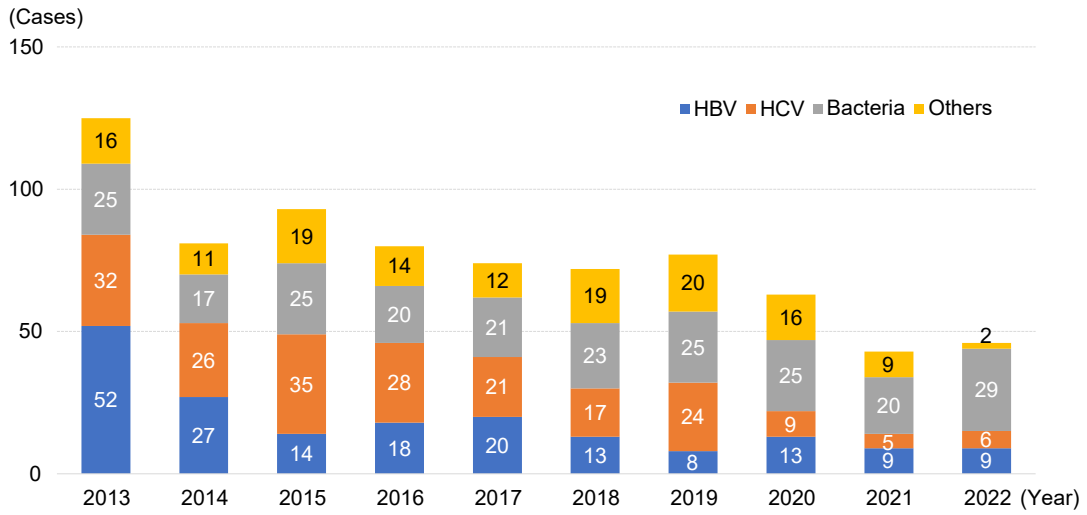



**Figure 12 Number of reported suspected TTI cases by pathogen**

**Table 1 Analysis results of reported suspected TTI cases by pathogen (2022)**

| 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 | 1 | 1 | 0 |
| HCV | 6 | 0 | 3 | 0 |
| Bacteria | 29 | 4 | 0 | 0 |
| HEV | 2 | 0 | 0 | 0 |
| Total | 46 | 5 | 4 | 0 |

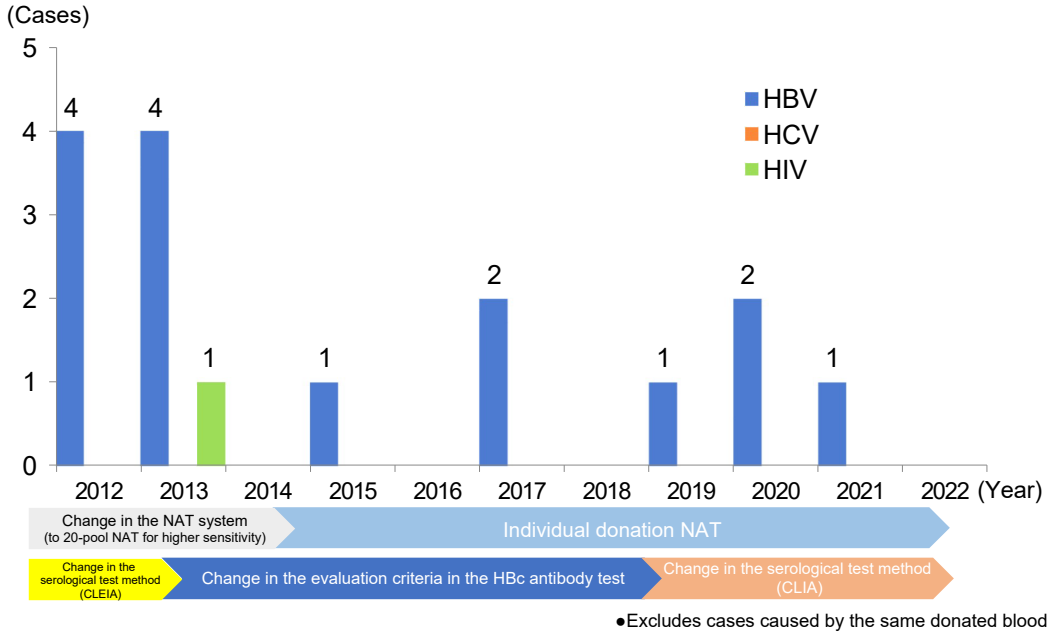



**Figure 13 TTIs by year of blood collection (HBV, HCV, and HIV)**

### (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 2022, 1 case was confirmed to be a transfusion-transmitted HBV infection, which was identified through a lookback study following positive conversion of the donor on NAT testing (Table 2).

**Table 2 A case of transfusion-transmitted HBV infection (2022)**

| Case No. | Blood component (year and month of blood collection) | Primary disease | Age | Sex | Pre-transfusion test | | Post-transfusion test | | ALT | | Patient outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Test item | Test result | Positive conversion items | Duration after transfusion | Maximum (IU/L) | Duration after transfusion | |
| 1 | Ir-PC-LR (2021.07)* | Aplastic anemia | 80s | F | HBs-Ag | Negative | HBV-DNA<br>HBs-Ag | 21 weeks | ♦ | ♦ | Unknown |

*The implicated donor tested negative for HBV-NAT at the time but turned positive at a subsequent donation 4 weeks later.
♦No comparative data.
Ir: Irradiated, LR : Leukocytes Reduced.

### [Bacterial infections]

Of the 29 suspected cases of bacterial infection reported in 2022, 4 cases were confirmed to be transfusion-transmitted bacterial infections, which were reported from medical institutions (Table 3).

**Table 3 Cases of transfusion-transmitted bacterial infections (2022)**

| Case No. | Blood component (year and month of blood collection) | Primary disease | Age | Sex | Symptoms | Time of onset (from start of administration) | Results of post-transfusion blood culture | | Patient outcome |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Blood component | Patient blood | |
| 1 | Ir-PC-LR (2022.11)* | Malignant tumor | 70s | M | Headache, nausea, cough, fever | 50 minutes | *Morganella morganii* | *Morganella morganii* | Recovered (with sequelae) |
| 2 | Ir-PC-LR (2022.11)* | Emergency surgery for angina pectoris | 70s | M | Hypotension, multiple organ failure | Following day | *Morganella morganii* | *Morganella morganii* | Death |
| 3 | Ir-PC-LR (2022.11) | Myelodysplastic syndrome | 70s | F | Chills, shivering, fever, vomiting, dyspnea | 1 hour | *Staphylococcus aureus* | *Staphylococcus aureus* | Recovered |
| 4 | Ir-PC-LR (2022.03) | Myelodysplastic syndrome | 50s | F | Chills, shivering, dyspnea, fever, hypotension | 40 minutes | *Escherichia coli* | *Escherichia coli* | Recovered |

*Separated platelet components prepared from a single blood collection

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

### (1) Cases in Japan

Table 4 indicates domestic case reports obtained from literature and academic societies in 2022. Although the domestic cases in Table 4 were not reported by medical institutions to the JRCS but 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 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 4 Domestic transfusion adverse reaction cases identified through literature search (2022)**

| Case No. | Blood component | Age | Sex | Adverse event | Journal |
|---|---|---|---|---|---|
| 1 | Ir-RBC-LR | 67 | F | Delayed hemolytic transfusion adverse reaction | The Japanese Journal of Thoracic Surgery. 2022; 75(2):111-113. |
| 2 | Ir-RBC-LR | Unknown | M | Delayed hemolytic transfusion adverse reaction | Japanese Journal of Transfusion and Cell Therapy. 2022; 68(1):78. |
| 3 | Ir-RBC-LR | 67 | F | Delayed hemolytic transfusion adverse reaction | The 71st congress of the Japanese Association of Medical Technologists (proceedings). 2022; 396. |

**[Summary]**

All 3 cases were suspected of being delayed hemolytic transfusion reactions (DHTR).

- In Case No. 1, preoperative tests revealed anti-$Di^a$ in the patient with a history of blood transfusion. Although compatible blood was transfused, the patient developed DHTR. As a result of detailed examination, anti-$Jk^b$ was newly detected. The patient recovered without hemolytic symptoms after a transfusion of $Jk^b$-antigen negative blood.

- In Case No. 2, hemolysis was observed after RBC transfusion. As a result of investigation at the medical institution, no irregular antibodies were detected after the transfusion. Given that the hemolysis symptoms disappeared after discontinuation of the antibiotics, the event was considered a potential effect of the antibiotics. Therefore, a causal relationship with the transfusion was ruled out.
- In Case No. 3, the patient developed DHTR after the transfusion of 4 units of RBC in total within 2 days. Although the results of tests for irregular antibodies were negative at the time of the first transfusion, post-transfusion tests identified anti-$Jk^a$, anti-C, and anti-e. Of the 4 units of blood products used, 3 units were positive for $Jk^a$, C, and e antigens, and 1 unit was positive for C and e antigens. Given the above, these antibodies may have caused the adverse reaction.

### (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 ICSRs to the PMDA. Table 5 indicates overseas cases identified in 2022.

**Table 5 Cases outside of Japan obtained through literature search and submitted as ICSR to the PMDA (2022)**

| Case No. | Country | Blood component (equivalent product in Japan) | Age | Sex | Adverse event | Journal |
|---|---|---|---|---|---|---|
| 1 | China | RBC-LR | 0 | M | Necrotizing enterocolitis | Zhong Nan Da Xue Xue Bao Yi Xue Ban. 2021; 46(11):1306-1309. |
| 2 | Italy | Ir-PC-LR | 9 | M | Bacterial infection | Emerg Microbes Infect.2022; 11(1): 1325-1334. |
| 3 | Italy | Ir-PC-LR | 4 | M | Bacterial infection | Emerg Microbes Infect.2022; 11(1): 1325-1334. |
| 4 | Italy | Ir-PC-LR | 9 | M | Bacterial infection | Emerg Microbes Infect.2022; 11(1): 1325-1334. |
| 5 | U.S. | RBC-LR | 60 | F | Cache Valley virus | Clin Infect Dis.2023; 76(3):e1320-e1327. |
| 6 | U.K. | PC-LR | 50s | M | Hepatitis E | Emerg Infect Dis.2022; 28(9):1805-1813. |
| 7 | U.K. | PC-LR | 40s | M | Hepatitis E | Emerg Infect Dis.2022; 28(9):1805-1813. |
| 8 | Austria | RBC-LR | 84 | F | *Plasmodium falciparum* infection | Transfus Med Hemother.2022; 49(4): 230-2 |

### [Summary]

- No. 1 is a case of necrotizing enterocolitis in China. The transfusion was given to an extremely low birth weight infant with a gestational duration of 28 weeks. The infant presented with symptoms such as abdominal distension and currant jelly stool 8 hours after the transfusion, and thus a diagnosis of necrotizing enterocolitis was made. Based on comprehensive evaluation of the infant patient's gestational duration, clinical findings, test results, and other such factors, transfusion-associated necrotizing enterocolitis was suspected.

- No. 2 to No. 4 are cases of bacterial infection in Italy. Platelet components which were obtained from one donor by apheresis collection and separated were given to 3 pediatric patients with acute lymphocytic leukemia or neuroblastoma. Symptoms including fever started in all 3 patients the day after the transfusion, and *Lactococcus garvieae* was detected in each patient's blood. In addition, metagenomic analysis of the suspected products also identified *L. garvieae*, suggesting suspected transfusion-transmitted bacterial infection.
- No. 5 is a case of Cache Valley virus (CVV) infection in the U.S. The patient developed encephalopathy 43 days after the leukocyte-reduced RBC transfusion. CVV infection was confirmed on a cerebrospinal fluid examination of the patient 114 days after the transfusion. Anti-CVV antibodies were detected by additional examinations (performed at 8 and 11 months after the donation) on the donor of the suspected product, suggesting suspected transfusion-transmitted CVV infection.
- No. 6 and No. 7 are cases of HEV infection identified through lookback studies in the U.K. Since the platelet donors were found to be HEV-RNA positive on pooled NAT, ID-NAT tests were retrospectively performed on the donor's past blood donation samples, indicating HEV-RNA positivity. In the first case, the patient developed viremia 8 weeks after the transfusion. HEV disappeared after administration of ribavirin. In the second case, HEV infection was found about 2 months after the transfusion. The patient died of hepatitis accompanied by renal failure. Transfusion-transmitted infections were confirmed in both cases by the HEV gene sequencing testing of the patient and donor samples.
- No. 8 is a case of malaria infection in Austria. A fever started 13 days after RBC transfusion, and *P. falciparum* was subsequently detected in the patient's blood. One of the 3 donors of the suspected products donated 2 weeks after travelling to a malaria-endemic area and was diagnosed with malaria infection 11 days after donation. Transfusion-transmitted *P. falciparum* infection was suspected because the patient had no history of travel abroad.

## 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 the 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 differences in administration route, dosage, and efficacy.

Table 6 shows measures taken in foreign countries in 2022 that the JRCS reported. The JRCS reported no studies in 2022.

**Table 6 Measures in foreign countries that the JRCS noted and reported (2022)**

| No. | Country/agency | Original title |
|---|---|---|
| 1 | U.S. (FDA) | Updated Information for Blood Establishments Regarding the COVID-19 Pandemic and Blood Donation.(2022/01/11) |
| 2 | | Recommendations to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease and Variant Creutzfeldt-Jakob Disease by Blood and Blood Components.(2022/05) |
| 3 | | Recommendations to Reduce the Risk of Transfusion-Transmitted Malaria.(2022/12) |
| 4 | | Important Information for Blood Establishments and Transfusion Services Regarding Bacterial Contamination of Platelets for Transfusion.(2022/12/22) |
| 5 | U.S. (AABB) | Monkeypox Resources to Consider.(2022/08/01) |
| 6 | France (French Ministry of Health and Solidarity) | Evolution des conditions d'accès au don du sang.(2022/01/11) |
| 7 | U.K. (NHS) | Change Notification UK National Blood Services No.01-2022/ Coronavirus Infection and Convalescent Plasma.(2022/01/20) |
| 8 | | Change Notification UK National Blood Services No.40-2022/Monkeypox.(2022/05/31) |
| 9 | Canada (Health Canada) | Health Canada authorizes Canadian Blood Services' submission to eliminate donor deferral period for men who have sex with men.(2022/04/28) |
| 10 | | Health Canada authorizes Héma-Québec submission to move to sexual behaviour-based screening criteria for all blood donors.(2022/09/06) |
| 11 | Europe (ECDC) | Rapid Risk Assessment/Monkeypox multi-country outbreak.(2022/05/23) |
| 12 | Australia (TGA) | TGA approval to change blood donation rules relating to vCJD deferral.(2022/07/25) |

## [Summary]

- No. 1 to No. 4 were issued by the U.S. Food and Drug Administration (FDA) for blood establishments. No. 1 provides updated information on the COVID-19 outbreak, including the deferral period for blood donors infected with COVID-19 being reduced from 14 to 10 days. No. 2 is an update of the guidance on reducing the risk of transfusion-transmitted infections due to variant Creutzfeldt-Jakob disease (vCJD), which recommended the removal of indefinite deferral of individuals who are at a geographic risk or received transfusion in the U.K., France, and Ireland, and the reassessment of donors who were deferred in the past due to geographic risk. No. 3 is the latest guidance on reducing the risk of transfusion-transmitted malaria infection. During the COVID-19 public health emergency, the deferral period for blood donors who traveled to malaria-endemic areas had been shortened from 12 months to 3 months as a time-limited measure; however, this became applicable to ordinary times. No. 4 provides the latest information concerning bacterial contamination of platelets for transfusion. Septic transfusion reactions from platelets contaminated with *Acinetobacter species* and certain other bacterial species have been continuously reported since 2018. Genetic testing in these 7 septic reaction cases revealed that the causative bacteria were closely related species, and the materials from a single manufacturer were used for all suspected products. FDA cautioned that it is important to continuously take account of the risk of bacterial contamination of platelets, including in bacterially tested and pathogen-reduced platelet components.

- No. 5 was issued by the Association for the Advancement of Blood & Biotherapies (AABB) and pertains to the monkeypox (Mpox) virus. Although the 2022 global Mpox virus outbreak was considered to be predominant among men who have sex with men (MSM), a 3-month deferral period for MSM donors was believed to be well beyond the duration of a putative Mpox virus infectious viremia. Since the Mpox virus is not known to be transfusion-transmissible, there are no particular questions in the questionnaire for blood donation, though the publication indicated the option to take measures such as deferral of donors for at least 21 days after symptom onset at the discretion of physicians responsible for blood collection. In addition, No. 5 describes procedures to accept blood donation from donors who received Jynneos vaccine or ACAM2000 vaccina vaccine, which are vaccines that are applicable to the virus.
- No. 6 was issued by the French Ministry of Health and Solidarity and describes changes in the deferral period and questionnaire for MSM donors. The question concerning MSM was removed on March 16, 2022, allowing all individuals to donate blood based on the same eligibility criteria regardless of sexual orientation. Also, questions regarding the use of HIV pre-/post-exposure prophylaxis were added.
- No. 7 and No. 8 were issued by the National Health Service (NHS) in the U.K. No. 7 addresses donor eligibility criteria related to COVID-19 infection. The deferral period for donors who contracted COVID-19, close contacts of infected persons, and vaccine recipients was reduced, and the period of blood product recalls made based on post-donation information was also reduced. It also notified that recipients of COVID-19 convalescent plasma are not allowed to donate blood. No. 8 concerns information on blood donation during the Mpox outbreak. The deferral periods were determined to be 28 days for donors who received a diagnosis of Mpox infection and 21 days for close contacts of infected persons. In addition, the smallpox vaccine, Imvanex, was deemed to be as a non-live vaccine, and recipients of Imvanex were allowed to donate blood if other blood donation requirements were met.
- No. 9 and No. 10 were issued by the Canadian Ministry of Health, concerning the discontinuation of MSM donor deferral. No. 9 and No. 10 were on approvals of requests made by the Canadian Blood Services and Hema-Quebec, respectively, to interview donors based on the individual's behavioral risks regardless of gender or sexuality.
- No. 11 was issued by the European Centre for Disease Prevention and Control (ECDC) and describes risk assessment in blood donation during the Mpox outbreak. Generally, Mpox virus does not spread easily between people. However, the ECDC issued the rapid risk assessment because many cases of Mpox infection among MSM have been reported during the current outbreak. The measures indicated in No. 11 include: careful interview with donors should be conducted about their history of Mpox infection, contact with infected animals, or travel to endemic areas, and asymptomatic donors who had close contact with infected persons should be deferred for 21 days after the last contact.
- No. 12 was issued by the Australian Therapeutic Goods Administration (TGA) and concerns vCJD-related deferral. The TGA conducted a scientific, epidemiological and clinical assessment of the risk model submitted by the Australian Red Cross Lifeblood (Lifeblood), and concluded that the modelled risk is reliable and that the risk of transfusion-transmitted vCJD would remain very low even if the vCJD deferral was removed. Thus, the TGA approved the submission to remove the deferral of the donors with a history of residence in the U.K.

## 4. Safety measures for blood products for transfusion

The JRCS takes safety measures that are based on the assessment and evaluation of adverse transfusion reactions and TTIs reported by medical institutions and identified through post-donation information from donors. The following are the JRCS's safety measures in 2022.

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

Figure 14 shows confirmed HEV TTI cases over the past 20 years. As a safety measure for transfusion-transmitted HEV infection, a trial HEV-NAT (20-sample pools) was implemented only in Hokkaido in 2006. In 2011, an HEV-IgA diagnostic agent 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 2022, no cases were reported.

In the past, when HEV-NAT identified a positive conversion in a donor, if HEV ID-NAT test results were negative in blood collected before the conversion, the use of such blood products and the recipients' HEV infection were not investigated. However, given that the HEV window period is unknown even for blood products that have been confirmed negative by individual HEV-NAT, the 3rd Steering Committee of the Committee on Blood Products discussed in 2021 how to secure safety against transfusion-transmitted HEV infection. It was decided that if, after the nationwide HEV ID-NAT implementation, a donor turns positive on HEV ID-NAT, recipients who received the donor's blood within 6 months prior to the positive conversion would be tested for potential HEV infection. From August 2020 to January 2023, we investigated 6,902 transfusion blood products, and 3,949 donors tested positive or converted to positive for HEV. As a result of the investigation on HEV infection in recipients, there were no cases of suspected transfusion-transmitted HEV infections.

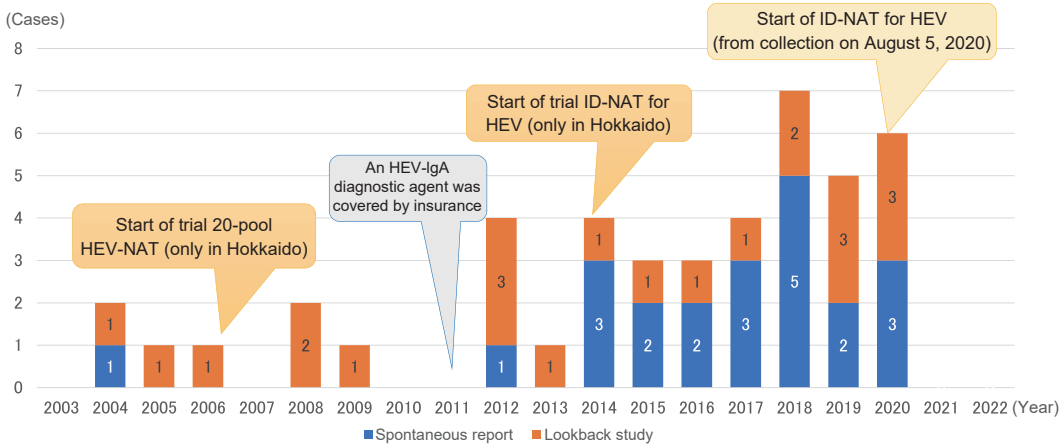



**Figure 14 Confirmed cases of transfusion-transmitted HEV infections**

### 2) 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 measure against COVID-19 for transfusion blood products, the JRCS defers blood donation from the following persons as of October 2023.

1) Persons who have been diagnosed with COVID-19 infection, or who have tested positive for a COVID-19 test (PCR or antigen test): deferred for 4 weeks from the resolution of symptoms (in case of asymptomatic persons, from the day when the positive sample was collected)
2) Persons who present with symptoms that are suggestive of COVID-19 infection, such as fever, cough, dyspnea, or other acute respiratory symptoms: deferred for 2 weeks from the onset of such symptoms and for 3 days from the resolution of such symptoms
3) Persons who live with COVID-19 patients: deferred for 1 week from the patient's onset date

By December 2022, 9,147 cases of post-donation information about COVID-19 infection were identified. If blood products that had been derived from the blood of the concerned donors had already been supplied to medical institutions when the information was obtained, a COVID-19 test was conducted on co-component products. By December 2022, the COVID-19 test was conducted on 3,005 cases, and 22 cases were found to be positive. There were no suspected transfusion-transmitted COVID-19 among recipients who used the COVID-19-positive blood products.

No cases of transfusion-transmitted COVID-19 infection have 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 the applicable laws and regulations and strive to improve the safety of transfusion medicine.

Haemovigilance by JRCS 2022

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