# Haemovigilance by JRCS 2024

Safety Vigilance Division, Technical Department,
Blood Service Headquarters

日本赤十字社
Japanese Red Cross Society

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# Haemovigilance by JRCS 2024

## 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 manufacture, up to recipient follow-up; analyzes and assesses the causes of such adverse events; 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 (TTIs), and transfusion-related 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 (MRs) to all JRC blood centers across Japan to collect and provide information on transfusion-related adverse reactions and TTIs. 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 centralized system to collect and analyze information on transfusion-related adverse reactions and TTIs. Then, in 1996, the JRCS began a specimen storage system that stores aliquots of all donated blood for 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 of the 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 abolished following a notification titled "Partial Amendment of the Act on Securing a 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 institution responsible for the assessment from 2021 and thereafter.

Transfusion blood products are categorized as ethical pharmaceuticals, which are regulated by the Act on Securing Quality, Efficacy, and Safety of Products Including Pharmaceuticals and Medical Devices (Pharmaceuticals and Medical Device Act: PMD Act), and require marketing approval like other pharmaceuticals. As a blood establishment, the JRCS also collects source human blood from donors based on the Act on Securing a 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 of the Blood Act in 2019, entities other than the JRCS, which have obtained a license to collect blood, are also permitted to collect blood for use in research and the development of drugs, medical devices, or regenerative medicine, and as the raw material for other products 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 Products (Good Quality Practice [GQP] Ministerial Ordinance). The JRCS performs post-marketing activities in compliance with the Ministerial Ordinance on Standards for Post-Marketing Safety Control for Pharmaceuticals, Quasi-pharmaceuticals, Cosmetics, Medical Devices, and Regenerative Medicine Products (Good Vigilance Practice [GVP] Ministerial Ordinance) through collaborative efforts among its Blood Service Headquarters (which serves as the marketing authorization holder, with its safety management section being in charge), JRC blood centers, and the Central Blood Institute facilities (the sections executing safety measures are in charge in each entity). MRs at blood centers are responsible for collecting information on transfusion-related adverse reactions and TTIs and providing information on transfusion blood products to healthcare professionals. The safety management section analyzes and assesses the information, reports serious transfusion-related 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 the collection of basic data on safety measures, product withdrawal, and the revision of precautions (electronic drug labels). The safety management section also conducts epidemiological studies related to blood safety and reports the results to the respective committees within the Committee on Blood Products of the Pharmaceutical Affairs and Food Sanitation Council, MHLW, thereby contributing to safety efforts for transfusion blood products. As transfusion blood products are categorized as “combination products classified as 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 damage caused by defects in blood bags used for patients, just as it does with transfusion-related 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/vaccine-related problems,” which is largely consistent with the post-marketing safety control 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 revised 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 concept of haemovigilance 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 distinctive feature of the Japanese haemovigilance system is its similarity 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 donation type between 2015 and 2024. A total of 5,013,064 blood donations were made in 2024, including 123,637 donations of 200 mL whole blood, 3,326,147 donations of 400 mL whole blood, and 1,563,280 donations of blood components (1,028,506 plasma donations and 534,774 platelet donations). The number of donations decreased until 2018, but plasma donations showed an increasing trend from 2019 to 2021 in response to the need for source plasma to satisfy the increasing demand in immunoglobulin products. Over the last few years, the number of blood donations has remained stable.

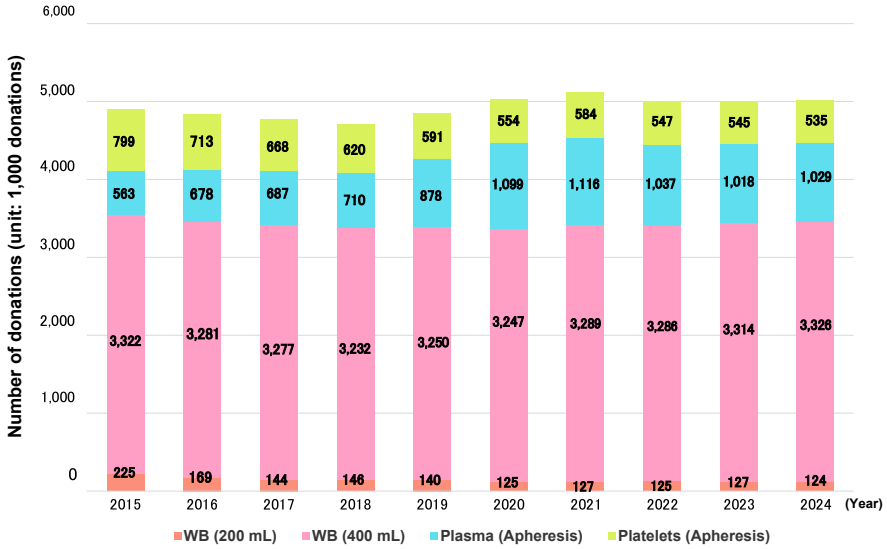



**Figure 1. Annual number of blood donations**

Figure 2 shows the supply of transfusion blood products between 2015 and 2024. In recent years, the supply of red blood cell (RBC) and plasma products showed a decreasing trend due to the promotion of their proper use. However, the supply of RBC products has been increasing since 2021. Although there was a slight increase in the supply of RBC and plasma products in 2024, the supply volume was almost unchanged from the previous year.

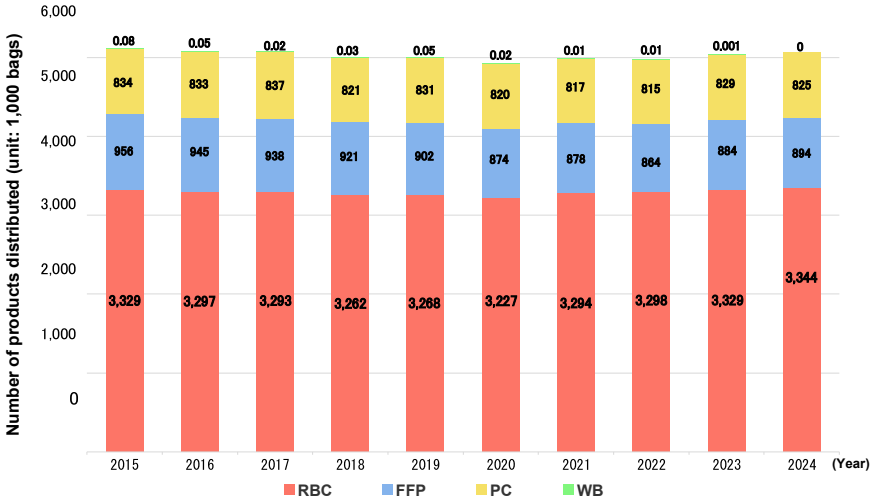



**Figure 2. Supply of transfusion blood products**

## 2. Reported transfusion-related adverse reactions and transfusion-transmitted infections

Figure 3 shows the breakdown of reported suspected cases of transfusion-related adverse reactions and TTIs (including cases reported by medical institutions and cases identified through post-donation information) from 2015 to 2024. Until 2017, all suspected cases of transfusion-related adverse reactions and TTIs were subjected to detailed investigation (i.e., The JRCS requested medical institutions to fill out case report forms). In January 2018, however, the investigation method was modified, and currently, information on transfusion-related adverse events is collected more broadly. Consequently, the number of reports of non-hemolytic transfusion reactions in particular has increased substantially. Among the collected adverse events, suspected transfusion-related adverse reactions and TTIs that are assessed as serious ((1) cases assessed as serious by physicians, (2) cases assessed as non-serious by physicians, but determined by the JRCS to require detailed investigation based on the symptoms, and (3) suspected TTIs) and transfusion-related adverse reactions not indicated in the precautions (electronic drug labels), i.e., unknown adverse reactions, are subjected to detailed investigation.

In 2024, the JRCS received 3,140 case reports on adverse reactions and infections (non-hemolytic transfusion reactions, 3,065 cases; hemolytic transfusion reactions, 26 cases; suspected transfusion-associated graft versus host disease [TA-GVHD], 0 cases; and suspected infections, 49 cases) from medical institutions across Japan. Cases assessed as serious by physicians or the JRCS (non-hemolytic transfusion reactions, 750 cases*; hemolytic transfusion reactions, 19 cases*; infections, 49 cases*) were reported as individual case safety reports (ICSRs) to the PMDA, in accordance with the PMD Act. Some adverse reaction cases that were not spontaneously reported by medical institutions to the JRCS have been published in the literature or presented at academic conferences. When the JRCS obtains such information, it investigates the causal relationship and seriousness in collaboration with the medical institution involved (See “3) Information on individual cases of transfusion-related adverse reactions and transfusion-transmitted infections obtained from the literature and academic societies”).

*Note that the cases classified into multiple categories were counted in each category separately.

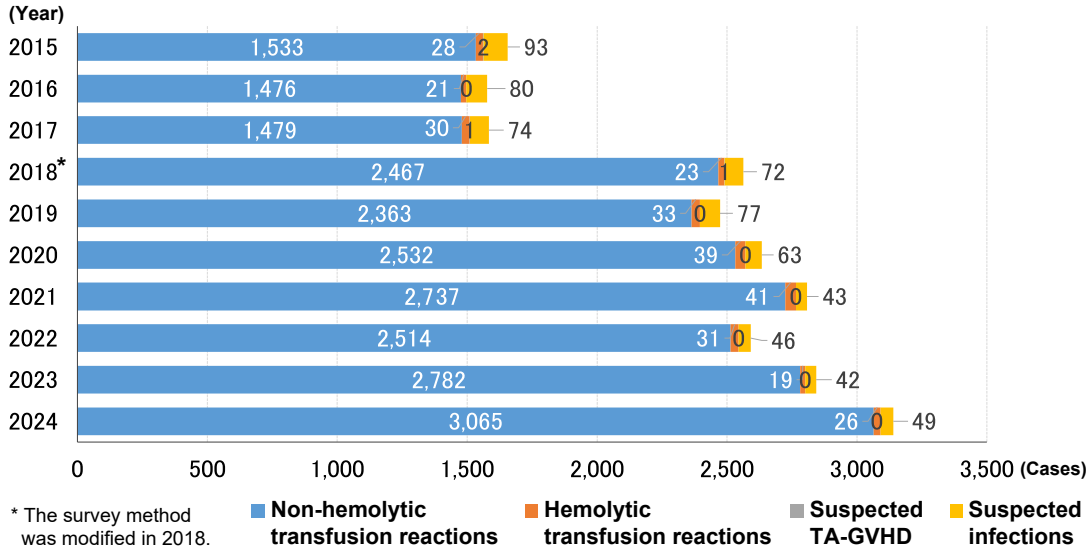



**Figure 3. Number of spontaneous case reports of transfusion-related adverse reactions and TTIs***

*Excludes cases identified through the literature or academic societies.

## 1) Transfusion-related adverse reactions

### (1) Non-hemolytic transfusion reactions

Figure 4 shows the number of cases reported as non-hemolytic transfusion reactions by medical institutions between 2020 and 2024. Figure 5 shows the breakdown by symptom in 2024, and Figure 6 shows the number of cases by seriousness (serious/non-serious) in 2024. Transfusion-related acute lung injury (TRALI) and transfusion-associated circulatory overload (TACO) cases were included under dyspnea. As in previous years, no particular category showed a marked increase (Figure 4). About 70% of the reported adverse reactions were allergic symptoms. Serious adverse reactions accounted for approximately 20% of all adverse reactions and mainly comprised severe allergy, dyspnea, and hypotension.

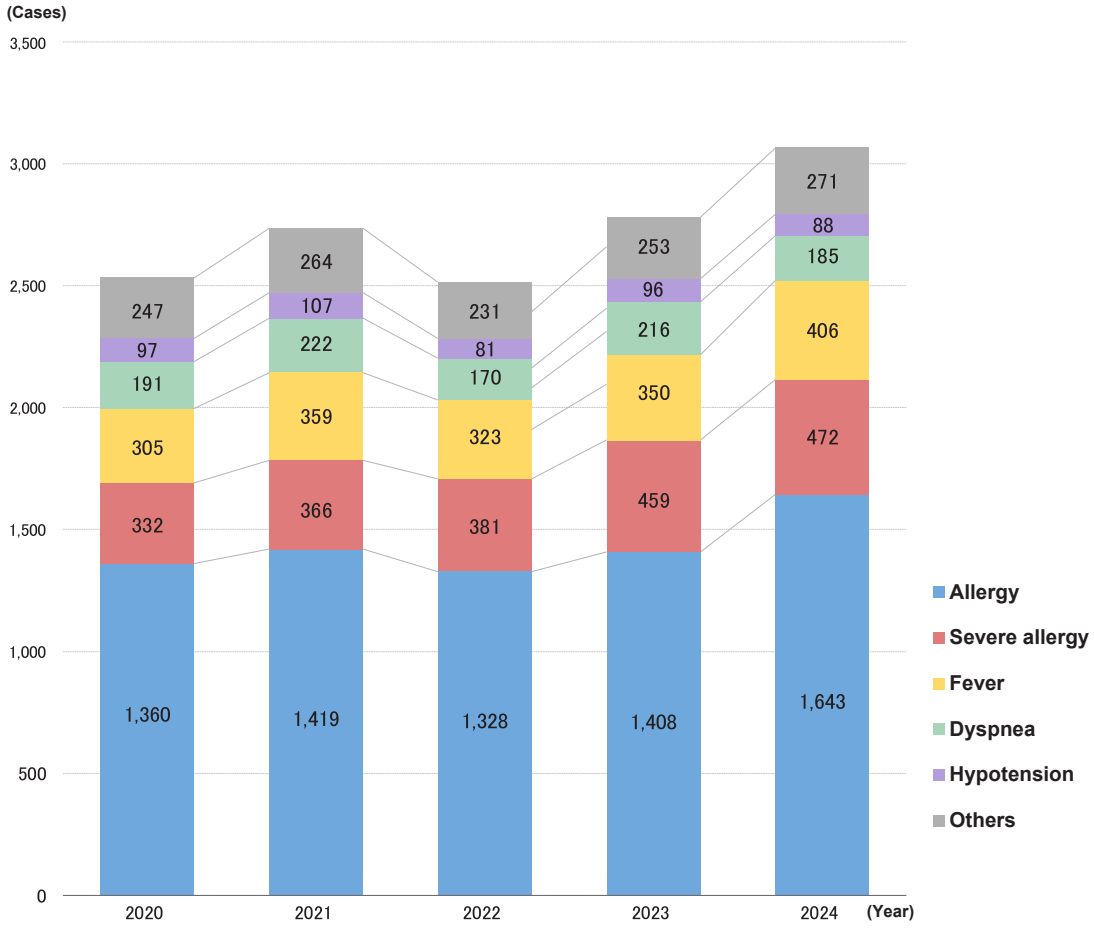



**Figure 4. Number of reported non-hemolytic transfusion reactions by symptom**

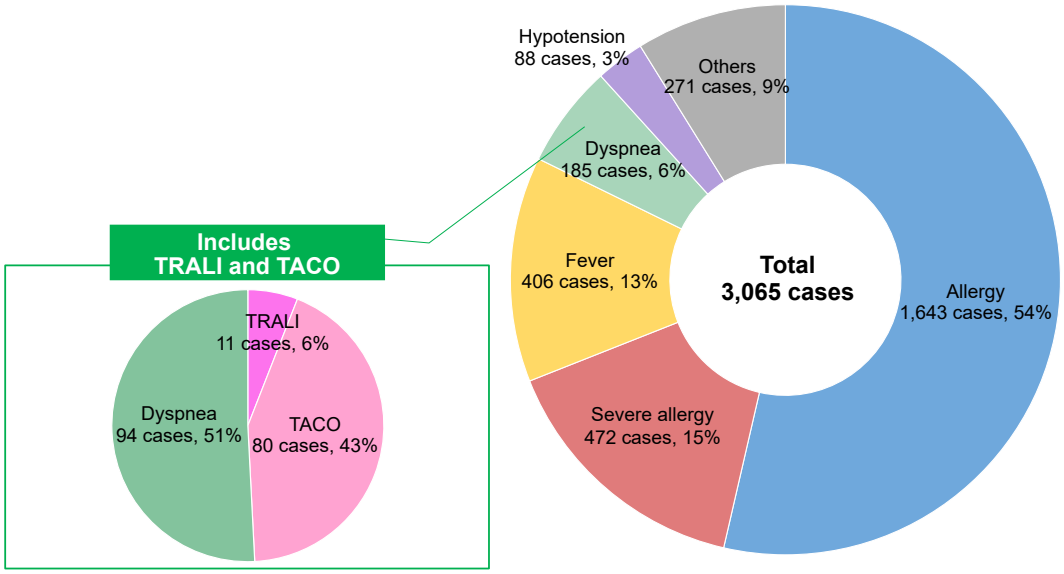



**Figure 5. Number and percentage of reported non-hemolytic transfusion reactions by symptom (2024)**

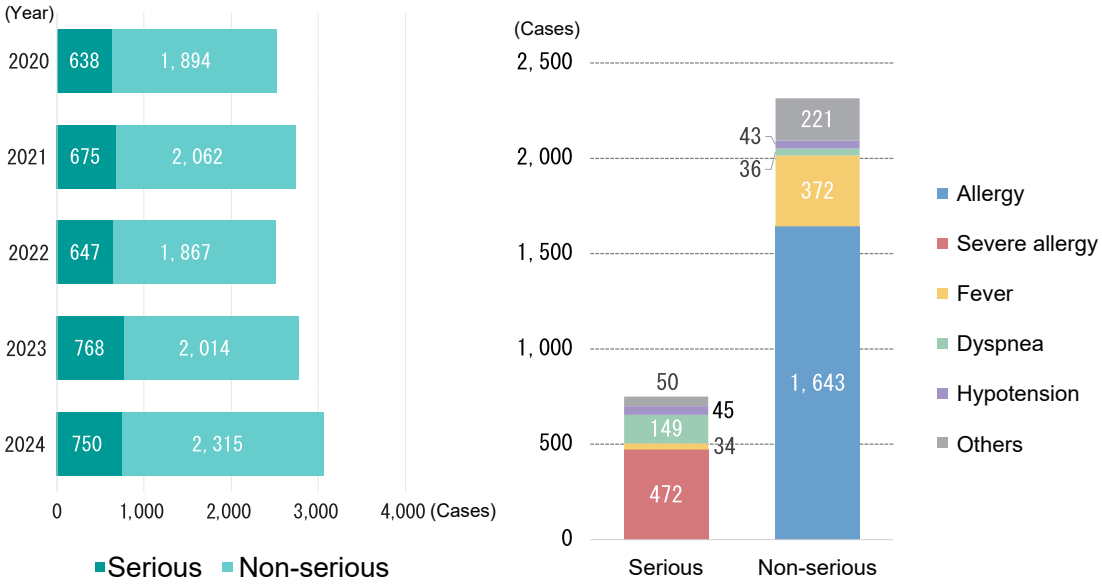



**Figure 6. Number of reported serious cases* and non-serious cases of adverse reactions (2024)**

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

## [Assessment of TRALI and TACO cases]

Among transfusion-related adverse reactions reported by medical institutions, the JRCS assesses suspected cases of TRALI and TACO in collaboration with respiratory and other specialists and shares the results with the medical institutions. In the past, TRALI was assessed 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 assessed based on JRCS's original criteria. However, in response to the revision of international criteria for assessing TRALI and TACO (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 formulated its own new criteria to assess TRALI and TACO and started the assessment of TRALI and TACO based on the new criteria from April 2021. Figure 7 shows the results from TRALI and TACO assessment in 2024.

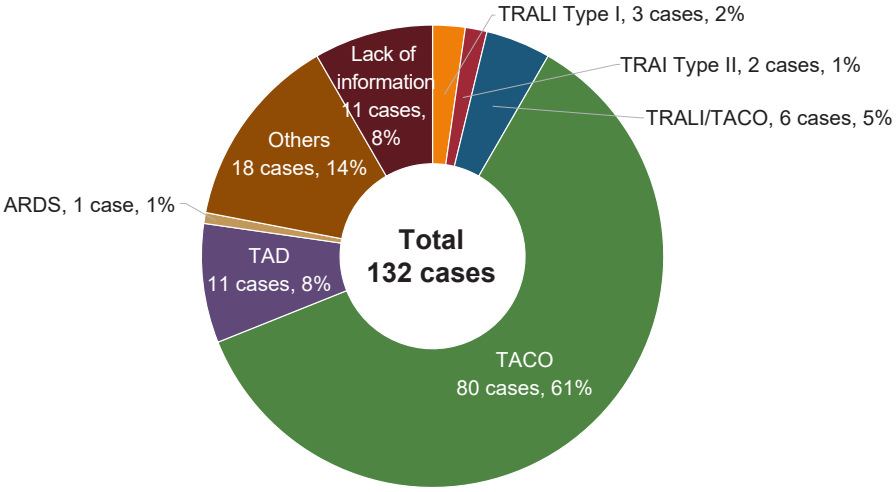
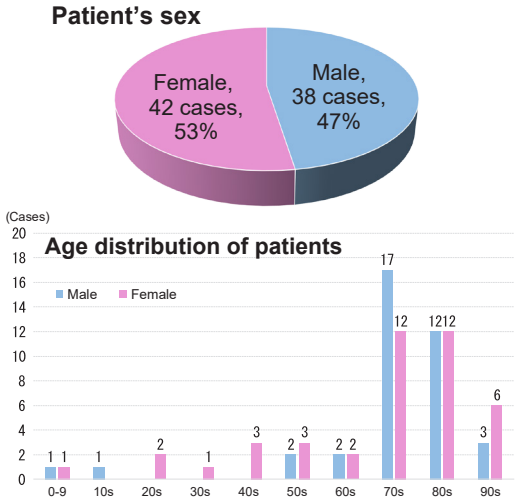



**Figure 7. TRALI and TACO assessment results in 2024**

## [TRALI and TACO]

- In April 2021, the JRCS started assessing TRALI and TACO cases based on the new criteria.
- Of the 3,065 non-hemolytic transfusion reaction cases reported by medical institutions in 2024, the JRCS assessed 132 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.
- Three cases were assessed as TRALI Type I, 2 cases as TRALI Type II, 6 cases as TRALI/TACO, 80 cases as TACO, 11 cases as transfusion-associated dyspnea (TAD), and 1 case as acute respiratory distress syndrome (ARDS).
- Among the 11 cases assessed as TRALI (TRALI Type I and Type II) or TRALI/TACO, anti-leukocyte antibodies were detected in the blood products used in 3 cases. Anti-leukocyte antibodies were detected in 4 of the suspected products, and 2 were positive in cross-matching against the patients' lymphocytes, 1 was negative. However, cross-matching could not be performed on 1 product.
- The 18 cases assessed as other adverse reactions included those assessed as adverse reactions different from TRALI or TACO (e.g., allergic and anaphylactic dyspnea).

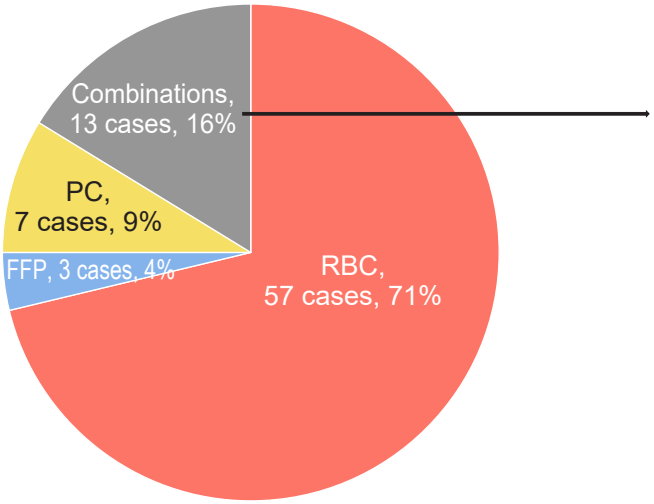
- There were 11 cases that could not be assessed due to a lack of the necessary information (e.g., chest images and detailed course of adverse reactions).
- Figure 8 shows the sex ratio, age distribution, and disease classification of the cases assessed as TACO in 2024, and Figure 9 shows the blood products used in the TACO cases in 2024. TACO tended to occur in elderly patients, and approximately 40% of patients had neoplastic diseases. Regarding the blood products used in TACO cases, RBC components, including those used in combination with other products, were involved in most cases, accounting for about 70% of the cases assessed.




**Patients' primary disease**

| Primary disease classification | Number of cases |
|---|---|
| Neoplasm (other than haematological) | 17 |
| Neoplasm (haematological) | 14 |
| Digestive system | 12 |
| Cardiovascular system | 9 |
| Blood and haematopoietic organs | 6 |
| Infection | 5 |
| Musculoskeletal system | 4 |
| Injury/poisoning | 4 |
| Pregnancy and delivery | 3 |
| Renal/genitourinary system | 2 |
| Endocrine/nutritional/metabolic disease | 2 |
| Nervous system | 1 |
| Others | 1 |

**Figure 8. Sex ratio, age distribution, and disease classification of cases assessed as TACO (2024)**




| Breakdown of blood product combinations | |
|---|---|
| RBC+FFP | 4 |
| RBC+PC | 3 |
| RBC+PC+FFP | 5 |
| PC+FFP | 1 |
| Total | 13 |

**Figure 9. Blood products used in TACO cases (2024)**

## [Discussion on and future challenges of TRALI and TACO]

- In 2024, the JRCS assessed 132 cases for TRALI and TACO. Among these, 11 cases were diagnosed as TRALI (TRALI Type I and Type II) or TRALI/TACO, while 80 cases were assessed as TACO, accounting for most of the assessed cases.
- Among the cases assessed for TRALI and TACO, 8% were diagnosed as TRALI or TRALI/TACO. There were no cases of death considered attributable to TRALI in 2024.
- As a safety measure against TRALI, the JRCS preferentially manufactures fresh frozen plasma (FFP) from 400 mL whole blood donations by male donors. While almost 100% of FFP derived from 400 mL whole blood donations is sourced from male donors, approximately 20% of FFP derived from 200 mL whole blood donations and 70% of FFP derived from apheresis donations are sourced 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 reduced renal function. This is a subject for future consideration. For patients in whom a risk of heart failure is suspected before blood transfusion, the transfusion rate and volume must be carefully considered, and the patients' condition must be closely monitored throughout the transfusion.

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

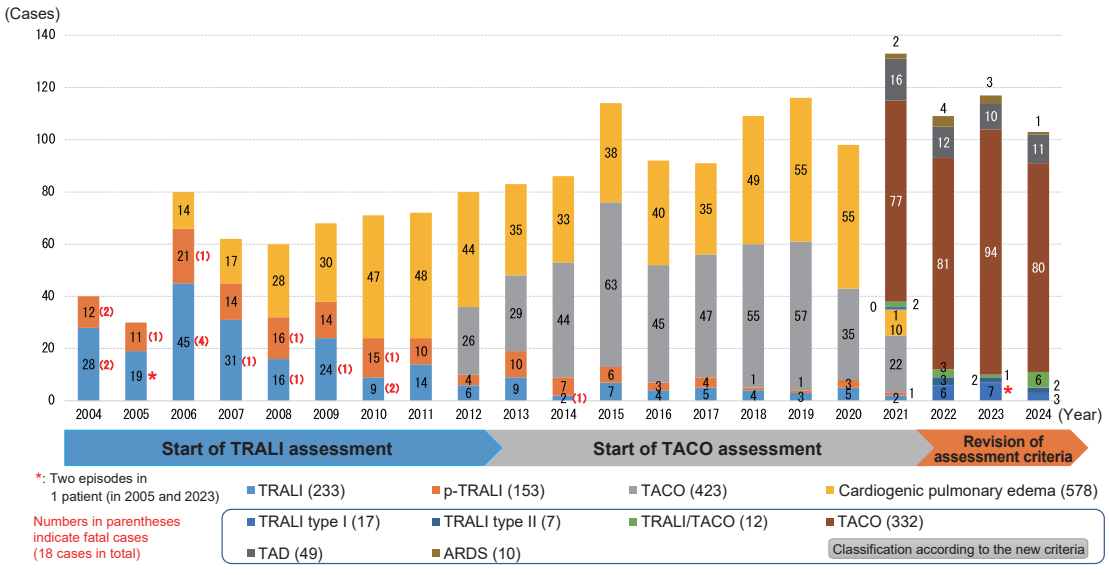
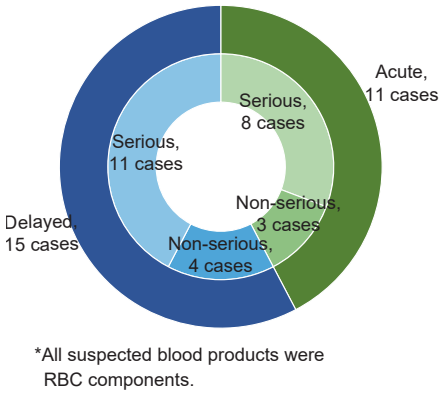



**Figure 10. Trend of TRALI and TACO cases assessed (2004 to 2024)**

### (2) Hemolytic transfusion reactions

In 2024, a total of 26 hemolytic transfusion reactions, including 19 serious cases, were reported by medical institutions (Figure 11). Of the 26 reported cases, 11 were acute reactions, and 15 were delayed reactions. According to surveys by medical institutions and the JRCS, irregular antibodies (including autoantibodies) were detected in the blood in 12 cases (3 cases of acute reactions and 9 cases of delayed reactions). The reported antibodies were mainly autoantibodies, but there was also a report of anti-Er5 antibodies against high-frequency antigens. In all cases, RBC components were used.




**Presence/absence of antibodies detection**

| | | | |
|---|---|---|---|
| Acute | Serious | Detected | 3 |
| | | Not detected | 5 |
| | Non-serious | Unknown | 3 |
| Delayed | Serious | Detected | 6 |
| | | Not detected | 5 |
| | Non-serious | Detected | 3 |
| | | Not detected | 1 |

**Antibodies detected in the 12 patients that were positive for irregular antibodies**

| | Serious | | Non-serious | |
|---|---|---|---|---|
| Acute | 3 | Autoantibody (anti-P): 1<br>Cold autoantibody (anti-I): 2 | | |
| Delayed | 6 | Anti-C: 1<br>Autoantibody: 1<br>Anti-E, anti-M, anti-Le$^{a}$, anti-Jk$^{a}$: 1<br>Anti-Er5: 1<br>Anti-E: 1<br>Anti-E, anti-Fy$^{a}$, anti-P1: 1 | 3 | Autoantibody: 1<br>Anti-Jk$^{b}$: 1<br>Anti-Jr$^{a}$: 1 |

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

**Figure 11. Number of reported hemolytic transfusion reactions and antibodies detected in patients (2024)**

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

- No cases of suspected TA-GVHD were reported by medical institutions in 2024.
- Since 2000, there have been no confirmed cases of TA-GVHD attributed to transfusion blood products manufactured and marketed by the JRCS, which introduced irradiated products.

## 2) Infection

### (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 up to 2024. In 2024, a total of 49 cases were reported, including 12 cases of suspected HBV, 4 cases of suspected HCV, 2 cases of suspected HEV, 25 cases of suspected bacterial infection, and 6 cases classified as “Others.”

Of these, confirmed TTIs in 2024 included 1 case of HBV infection and 2 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 specimens (individual donation NAT: ID-NAT; Figure 13).

A "confirmed case" refers to a case in which a pathogen, including viruses, was found in the blood product and the recipient blood. In cases of transfusion-transmitted viral infections, a confirmed case refers to a case in which genetic analysis confirmed the sequence homology between the virus identified in the blood product and the one identified in the recipient's blood, or a case in which the recipient's infection was confirmed through a lookback investigation prompted by the donor's post-donation information and the causal relationship with the donated blood was strongly suggested. In cases of transfusion-transmitted bacterial infections, a confirmed case refers to a case in which the strains in the blood product used and the recipient's sample were found to be identical or highly likely to originate from the same strain based on genotype tests such as pulsed-field gel electrophoresis (PFGE), whole genome multilocus sequence typing (wgMLST), or average nucleotide identity (ANI).

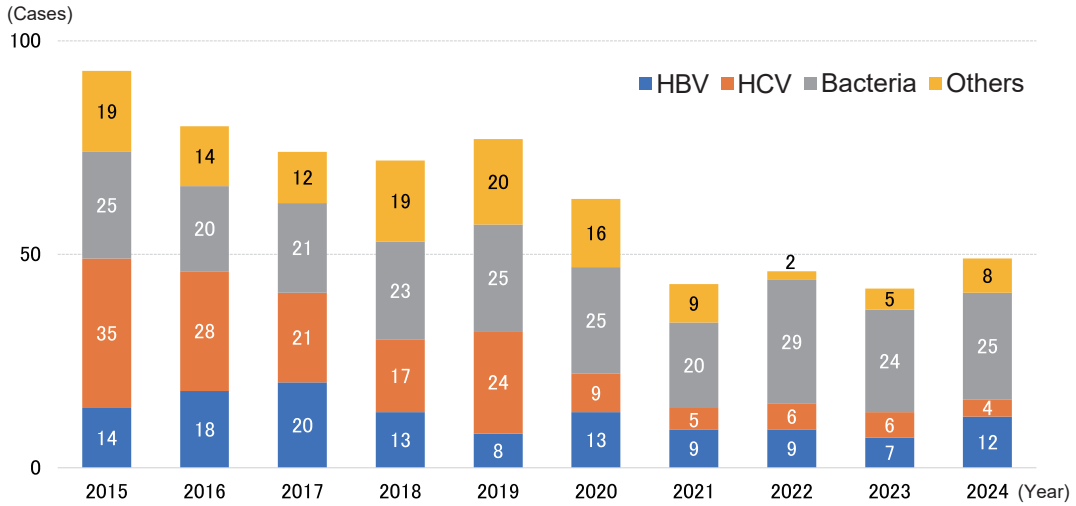



**Figure 12. Annual number of reported suspected TTI cases by pathogen**

**Table 1. Analysis results of reported suspected TTI cases by pathogen (2024)**

| Pathogen | Number of reported cases | Number of confirmed cases | Excluded cases | |
|---|---|---|---|---|
| | | | Positive in pre-transfusion test | Negative in pre- and post-transfusion tests |
| HBV | 12 | 1 | 2 | 2 |
| HCV | 4 | 0 | 0 | 2 |
| HEV | 2 | 0 | 0 | 1 |
| CMV | 6 | 0 | 0 | 0 |
| Bacteria | 25 | 2 | – | – |
| Total | 49 | 3 | 2 | 5 |

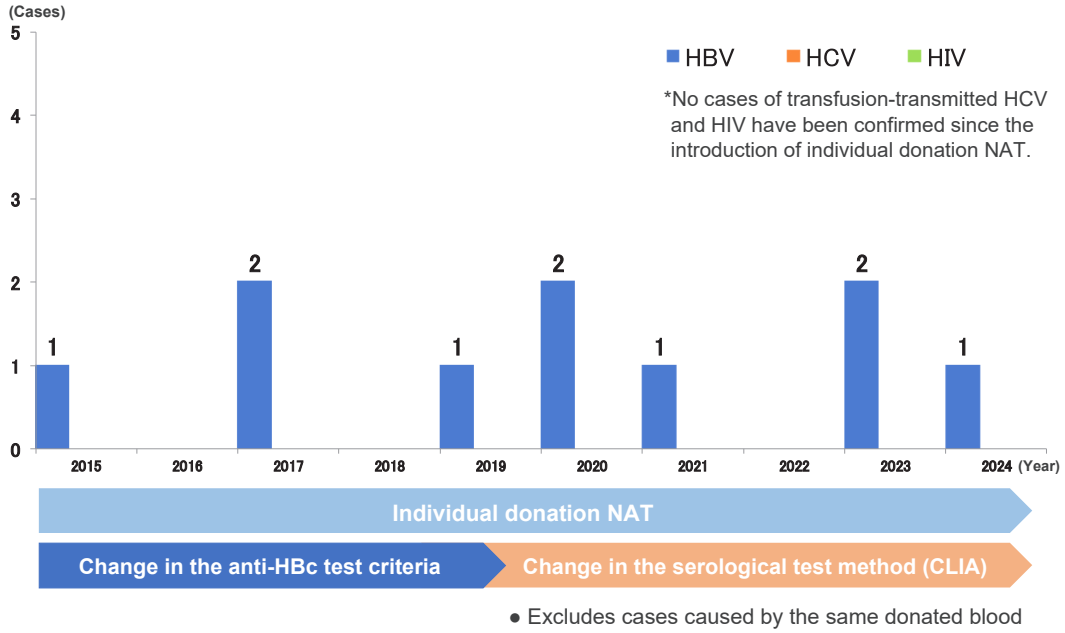



**Figure 13. TTIs by year of blood collection (HBV, HCV, and HIV)**

## (2) Summary of confirmed transfusion-transmitted infections

The following shows a summary of cases identified as transfusion-transmitted infections (TTIs).

### [HBV infection]

Of the 12 suspected cases of HBV infection reported in 2024, 1 case, which was reported by a medical institution, was confirmed to be transfusion-transmitted HBV infection (Figure 14).

This patient received multiple blood transfusions, including irradiated red blood cells, during aortic valve stenosis surgery. After discharge, the patient tested positive for HBs antigen at another hospital in June 2024 and was referred to the medical institution where the blood transfusions took place. The case was reported to the JRCS after confirming post-transfusion HBV-DNA positivity, with negative pre-transfusion HBV markers.

Investigation of blood donors of the transfused products revealed that one donor of the irradiated red blood cells had a positive NAT screening result at the time of the subsequent blood donation. The HBV viral homology between the seroconversion donor sample and the recipient's sample was confirmed, demonstrating transfusion-transmitted HBV infection.

Given that the donor tested positive for both HBs and HBc antibodies at the time of the subsequent blood donation, it was considered that the donor donated the blood during the window period of HBV infection, and that the subsequent donation occurred immediately before seroconversion. If HBV seroconversion occurs at the time of the subsequent blood donation with an HBs antibody titer of 200 mIU/mL or higher and undetectable HBV-DNA, the blood donation satisfies the release criteria. As the subsequent donation satisfied the criteria, no lookback investigations were conducted on the product derived from the previous blood donation. In response to this case, if a donor, who tested negative for both HBs and HBc antibodies at the time of the previous blood donation and tests positive for both HBs and HBc antibodies at the time of the subsequent blood donation, a lookback investigation is conducted on the products derived from the previous donation.

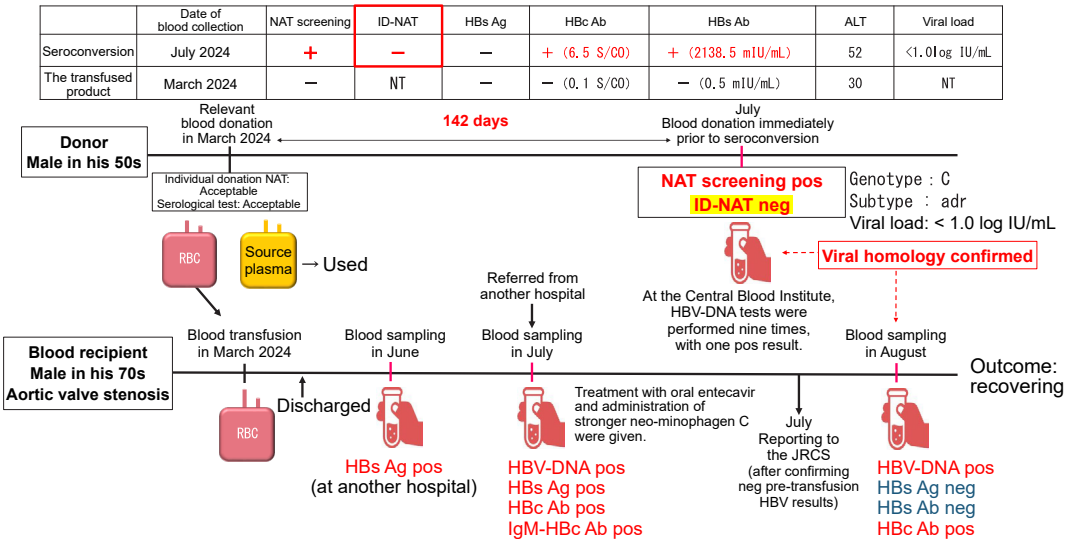



**Figure 14. A case identified as transfusion-transmitted HBV infection (2024)**

### [Bacterial infection]

Of the 25 suspected cases of bacterial infection reported in 2024, 2 cases were confirmed to be transfusion-transmitted bacterial infection, which were reported by medical institutions (Table 2).

**Table 2. Cases of transfusion-transmitted bacterial infection (2024)**

| Case No. | Blood products for transfusion (year and month of blood collection) | Primary disease | Age | Sex | Symptoms | Time of onset (after the start of administration) | Results of post-transfusion blood culture | | Patient outcome |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Blood component | Patient blood | |
| 1 | Ir-PC-LR (March 2024) | Idiopathic thrombocytopenic purpura | 30s | F | Headache, loss of consciousness, hypotension, pyrexia | 1 hour 25 minutes | *Streptococcus dysgalactiae* subsp. *equisimilis* | *Streptococcus dysgalactiae* subsp. *equisimilis* | Recovered |
| 2 | Ir-PC-LR (March 2024) | Diffuse large B-cell lymphoma | 70s | F | Chills, shivering, oxygen saturation decreased, pyrexia, blood pressure decreased | 45 minutes | *Serratia marcescens* | *Serratia marcescens* | Recovering |

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

### (1) Cases in Japan

Among domestic cases of transfusion-related adverse reactions and TTIs obtained from the literature and academic societies, there are the cases that were not reported to the JRCS by medical institutions, but were only presented in the literature or at academic conferences. For these cases, JRCS's medical representatives (MRs) interview the authors and their medical institutions about the seriousness of the adverse reactions and the blood products involved. Cases that are assessed as serious transfusion-related adverse reactions and TTIs based on the investigation results are reported as ICSRs to the PMDA. Table 3 shows domestic cases that were collected and reported in 2024.

**Table 3. Domestic cases obtained through literature searches and reported as ICSRs to the PMDA (2024)**

| Case No. | Suspected products | Age | Sex | Adverse event | Journal |
|---|---|---|---|---|---|
| 1 | RBC-LR, Ir-RBC-LR | 70 | F | Post-transfusion iron overload | Radiol Case Rep.2024;19(5):1666-1670. |
| 2 | Ir-RBC-LR, FFP-LR, Ir-PC-LR | 49 | M | Transfusion-associated circulatory overload | Journal of the Japanese Association for the Surgery of Trauma. 2024;38(2):281. |
| 3 | Ir-RBC-LR | 88 | F | Posterior reversible encephalopathy syndrome | Transfusion.2024;64(9):1791-1797. |
| 4 | Ir-RBC-LR | 50s | M | Post-transfusion iron overload | Journal of the Japanese Society for Dialysis Therapy. 2024;57(Suppl 1):552. |

## [Summary]

- No. 1 is a case in which the patient received red blood cell transfusions for 2 years for poor prognosis following peripheral blood stem cell transplantation, resulting in elevated ferritin levels on blood tests and brain abnormalities on MRI, and a diagnosis of transfusion-induced choroid plexus haemochromatosis was made.
- No. 2 is a case in which the patient received transfusion of red blood cell products, fresh frozen plasma, and platelet products for haemorrhagic shock following a traffic injury, leading to suspected transfusion-associated circulatory overload. The JRCS conducted an inquiry into the medical institution and identified this case as ARDS.
- No. 3 is a case in which the patient experienced decreased cognitive and language functions following the transfusion of red blood cell products for the treatment of myelodysplastic syndrome and subsequently received a diagnosis of posterior reversible encephalopathy syndrome based on the results of head MRI.
- No. 4 is a case in which the patient received long-term red blood cell transfusions for pure red cell aplasia, leading to post-transfusion iron overload.

## (2) Cases outside Japan

Since transfusion blood products manufactured by the JRCS are distributed (supplied) only in Japan, the JRCS monitors transfusion-related adverse reactions and TTIs outside Japan by collecting and investigating case reports on adverse reactions and TTIs caused by foreign blood products that are equivalent to those of the JRCS in terms of product type and efficacy. Among these, TTIs and unknown serious adverse reactions are reported as ICSRs to the PMDA. Table 4 shows overseas cases collected and reported in 2024.

**Table 4. Cases outside Japan that were obtained through literature searches and reported as ICSRs to the PMDA (2024)**

| Case No. | Country | Suspected products (equivalent products in Japan) | Age | Sex | Adverse event | Journal |
|---|---|---|---|---|---|---|
| 1 | U.S. | RBC-LR | 64 | F | Bacterial infection | Transfusion.2024;64(4):751-754. |
| 2 | The Netherlands | RBC-LR | 47 | M | Cerebral amyloid angiopathy | Eur J Neurol.2024;31(6):e16277. |
| 3 | | RBC-LR | 57 | F | | |
| 4 | U.S. | RBC-LR | 14 | F | Reversible cerebral vasoconstriction syndrome | Transfusion.2024;64(11):2038-2042. |
| 5 | Saudi Arabia | RBC-LR | 29 | M | Posterior reversible encephalopathy syndrome | Turk J Emerg Med.2024;24(3):180-184. |
| 6 | India | FFP-LR | 31 | M | Bacterial infection | J Infect Chemother.2025;31(2):102545. |
| 7 | U.S. | RBC-LR | 20 | M | Babesiosis | Oxf Med Case Reports.2024;2024(11):omae133. |
| 8 | Brazil | RBC-LR, PC-LR | 17 | F | Dengue fever | Lancet Infect Dis.2025;25(1):e10. |
| 9 | | RBC-LR, PC-LR | 2 | M | | |
| 10 | | RBC-LR, FFP-LR, PC-LR | 2 | F | | |
| 11 | | RBC-LR, FFP-LR, PC-LR | 0 | F | | |
| 12 | | RBC-LR, PC-LR | 0 | M | | |
| 13 | | RBC-LR | 0 | F | | |

## [Summary]

- No. 1 is a case of bacterial infection in the United States. *Anaplasma phagocytophilum* was identified by PCR testing in the patient's blood sample after transfusion of red blood cell products. In a lookback investigation, *A. phagocytophilum* was identified by PCR testing in the blood donor sample, and a diagnosis of human anaplasmosis (HGA) was made. This case is a confirmed case of transfusion-transmitted HGA.
- Nos. 2 and 3, reported in the Netherlands, are cases described as a possible transmission of cerebral amyloid angiopathy (CAA) through blood transfusion. The patients (Nos. 2 and 3) were diagnosed with CAA at the ages of 47 and 57, respectively. Both patients experienced severe CAA at a relatively young age, and they had a history of red blood cell transfusion during infancy, suggesting a relationship between blood transfusion and the onset of CAA.
- No. 4 was reported in the United States. This patient experienced severe headache after transfusion of red blood cell products, and reversible cerebral vasoconstriction syndrome (RCVS) was suspected. Given that no other factors were found on brain imaging and that thunderclap headache occurred after repeated blood transfusions, the patient's clinical presentation was reported to be most consistent with RCVS.

- No. 5 is a case of suspected posterior reversible encephalopathy syndrome (PRES) due to blood transfusion in Saudi Arabia. The patient received massive blood transfusions within 24 hours due to a gunshot injury and experienced quadriplegia after cessation of sedation. It was reported that post-transfusion PRES may have developed due to the sudden increase in haemoglobin caused by the rapid transfusion.
- No. 6 is a case of bacterial infection in India. Pyrexia with chills and tachypnoea developed 10 minutes after starting transfusion of a plasma product, and the transfusion was thus discontinued. A few days later, the patient experienced septic shock and subsequently died from haemodynamic instability due to the underlying condition. Although a bacterial culture test on the patient's blood after administration of an antibacterial drug showed a negative result, *Burkholderia cepacia* was detected by a bacterial culture test on the suspected product and the central line blood. It was reported that contamination was caused by the thawing device and cracks in the plasma bag.
- No 7 is a case of Babesia infection in the United States. The patient presented with lower back pain, frontal headache, general malaise, and persistent fever about 1 month after red blood cell transfusion. A test revealed the presence of erythrocyte inclusion bodies, and *Babesia microti* was detected by PCR. The patient did not have a history of travelling to a babesiosis endemic area or tick exposure, but had received blood transfusion before onset of the symptoms, and transfusion-transmitted Babesia infection was suspected.
- Nos. 8 to 13 are six reported cases of dengue virus infection that occurred in a CICU in Brazil. These six pediatric patients received blood transfusion after cardiac surgery for congenital heart disorders during the peak of the dengue epidemic in Brazil. After transfusion, fever and thrombocytopenia developed, and dengue virus infection was confirmed by the DENG-NS1 antigen test. Some patients (No. 8, and Nos. 11 to 13) died. The risk of infection from mosquito exposure was considered to be low under CICU management. Although no confirmatory testing for dengue virus was performed on the blood donors, transfusion-transmitted dengue viral infection was suspected.

## 3. Measures in foreign countries and studies

The JRCS reports to the PMDA when it obtains information on measures that countries outside 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 of the foreign pharmaceuticals; and other measures to prevent health hazards from occurring or expanding" in Article 228-20 of the Enforcement Regulations of the PMD Act. Regarding foreign products equivalent to the JRCS's transfusion products, the JRCS also files reports to the PMDA when it obtains information from "studies reporting risks of cancers, other serious diseases, disabilities, or death caused by side effects of the pharmaceuticals or foreign pharmaceuticals; significant changes in trends of cases affected by side effects of the pharmaceuticals or foreign pharmaceuticals or infectious diseases resulting from their use; or the lack of approved efficacies or effects of the pharmaceuticals" 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 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 these products share the same active ingredients, regardless of any differences in administration route, dosage, and efficacy.

Among the information on measures in foreign countries and study reports obtained in 2024, those reported to the PMDA are shown in Table 5 and Table 6.

**Table 5. Reports of measures in foreign countries that the JRCS collected and reported to the PMDA in 2024.**

| No. | Country (agency) | Original title |
|---|---|---|
| 1 | New Zealand (NZBS) | New Zealand Blood Service lifts 'mad cow' (vCJD) restriction |

### [Summary]

- The above information regarding the lifting of variant Creutzfeldt-Jakob disease (vCJD) donor restrictions was provided by New Zealand Blood Service. The blood donation restriction on people who had lived in the UK, France, or Ireland for 6 months or longer between 1980 and 1990, which had been introduced in 2000, was abolished, making it possible to make reservations to donate blood from February 29, 2024.

**Table 6. Study reports collected and reported to the PMDA by the JRCS in 2024.**

| No. | Country (agency) | Original title |
|---|---|---|
| 1 | Thailand (NBC) | Inadvertent Platelet Transfusion from Monkeypox Virus-Infected Donor to Recipient, Thailand,2023. |

**[Summary]**

- Thai Red Cross Society reported that a pooled platelet product derived from the blood of an Mpox virus (MPXV)-infected donor was used for transfusion. The donor was confirmed to be infected with MPXV 2 days after donating the blood. Although the incubation period of MPXV is 3 to 17 days, MPXV-DNA was not detected in the recipient sample by 2 weeks after the transfusion. There were also no symptoms 4 weeks after the transfusion. It was therefore concluded that MPXV infection did not occur due to the transfusion.

## 4. Safety measures for blood products for transfusion

### [Safety measures for transfusion-transmitted infections]

[Safety measures for transfusion-transmitted bacterial infections – 10 years since the introduction of individual donation NAT]

The JRCS has implemented various pathogen tests (serological tests and NAT) on all donated blood as part of its efforts to ensure the safety of blood products for transfusion.

Regarding serological tests, in order to improve their accuracy, the measurement method was changed from the conventional agglutination method to chemiluminescent enzyme immunoassay (CLEIA) in 2008, and then to chemiluminescent immunoassay (CLIA) in 2019. In September 2012, the criteria for the HBc antibody test were also strengthened to increase the ability to detect previous infections.

Regarding NAT, 500-sample pool NAT screening for 3 viruses including HBV, HCV, and HIV was introduced in October 1999 for the first time in the world. In February 2000, the sample pool size was reduced to 50 samples to increase the sensitivity of virus detection. However, in 2003, the first case of transfusion-transmitted HIV-1 infection occurred after the introduction of NAT. The cause of this event was found to be that the donor's HIV-RNA load was too low to be detected by 50-sample pool NAT, resulting in a negative result. In the lookback investigation, the individual donation NAT showed a positive result. In response to this finding, measures were taken to switch to 20-sample pool NAT to improve the detection sensitivity in August 2004. In August 2008, a screening system with improved testing accuracy was also introduced (changes in testing equipment and reagents), leading to the improved detection sensitivity for each virus as well as the detection of HIV-2 by NAT. From August 2014, NAT screening using individual samples (individual donation NAT) was started to further increase the sensitivity. In August 2020, HEV was added to the list of target viruses, and individual donation NAT screening is currently conducted for four types of viruses.

In 2024, it has been 10 years since the introduction of individual donation NAT. Between 1999 and 2011, an average of 9 cases of transfusion-transmitted HBV infection occurred annually, but the number of infection cases caused by transfusion from donors with a history of infection decreased as the criteria for HBc antibody testing were strengthened. After the introduction of individual donation NAT, the number of infection cases caused by individual donation NAT-negative blood has remained around 0 to 2 cases per year. These infection cases included some caused by an HBV genotype with a slower growth rate and longer window period (Genotype A). As a result, the Guidelines for Lookback Studies were partially revised in 2021, and the lookback period was changed. In response to the infection cases reported in 2024 (see Figure 14), appropriate measures were also taken in December of the same year to address new findings, for example, if a repeat blood donor contracts hepatitis B after donating blood and is completely cured by the time of a subsequent donation (HBV-NAT negative, HBs antigen negative, HBs antibody positive, HBc antibody positive), a lookback investigation of the products from the previous blood donation has to be initiated.

Regarding HCV and HIV, no cases of transfusion-transmitted infection have been reported since the introduction of individual donation NAT. In addition, no cases of transfusion-transmitted HEV infection have been identified since the introduction of HEV-NAT (Figure 15). Currently, the risk of transfusion-transmitted infection (residual risk) of each virus is estimated to be less than one in a million (approximately 1/1,600,000) for HBV, while the residual risk for HCV, HEV, and HIV has not been determined as there have been no cases of infection.

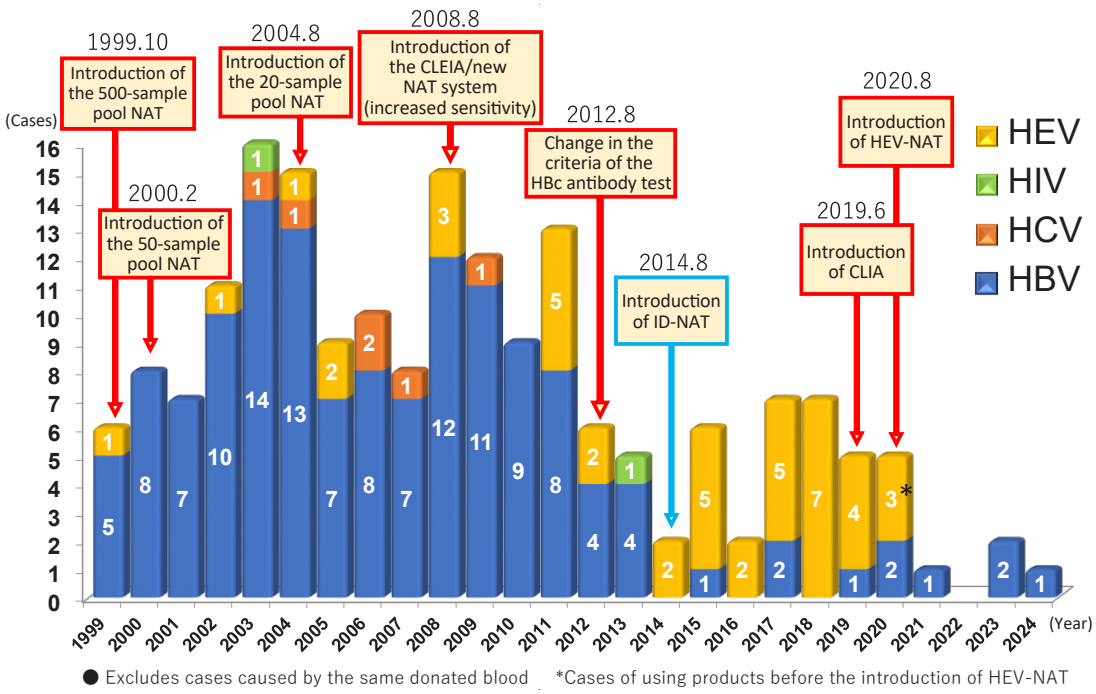
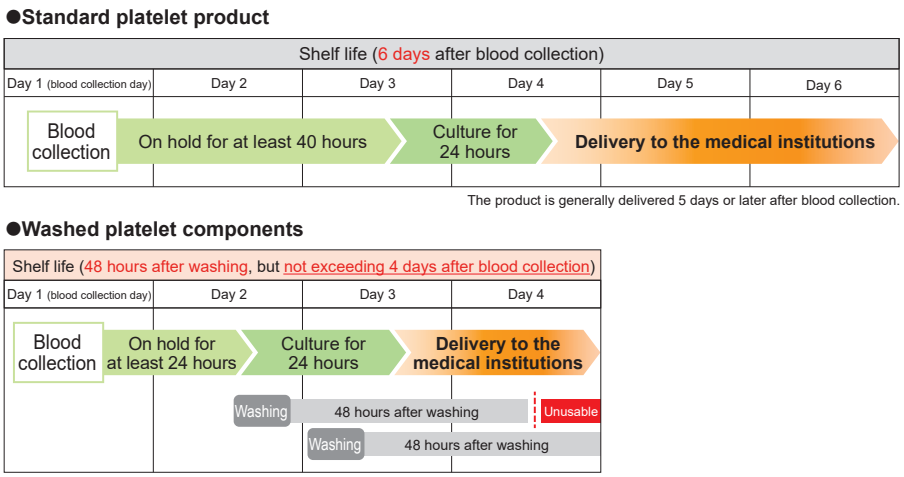



**Figure 15. TTIs (HBV, HCV, HIV, HEV) by year of blood collection and history of testing system**

[Introduction of new safety measures - bacterial screening of platelet products -]

As a further safety measure, an application for manufacturing and marketing approval was filed in February 2024 to introduce bacterial screening of platelet products, with the aim of starting this screening in the summer of 2025. After its introduction, bacterial screening will be performed on all platelet products to be supplied, and it is also planned to extend the shelf life of platelet products (including PC-HLA) from 4 to 6 days after blood collection. Washed platelet components will also undergo bacterial screening, but the post-wash shelf life will remain the same as before, namely, within 48 hours (but not exceeding 4 days after blood collection) (see Figure 16).

Information has been provided to medical professionals through lectures at various academic conferences regarding the history of its introduction and the safety of bacterial screening, as well as the operational aspects associated with the changes.




Note: In Japan, the blood collection date is counted as day 1 of the shelf life.

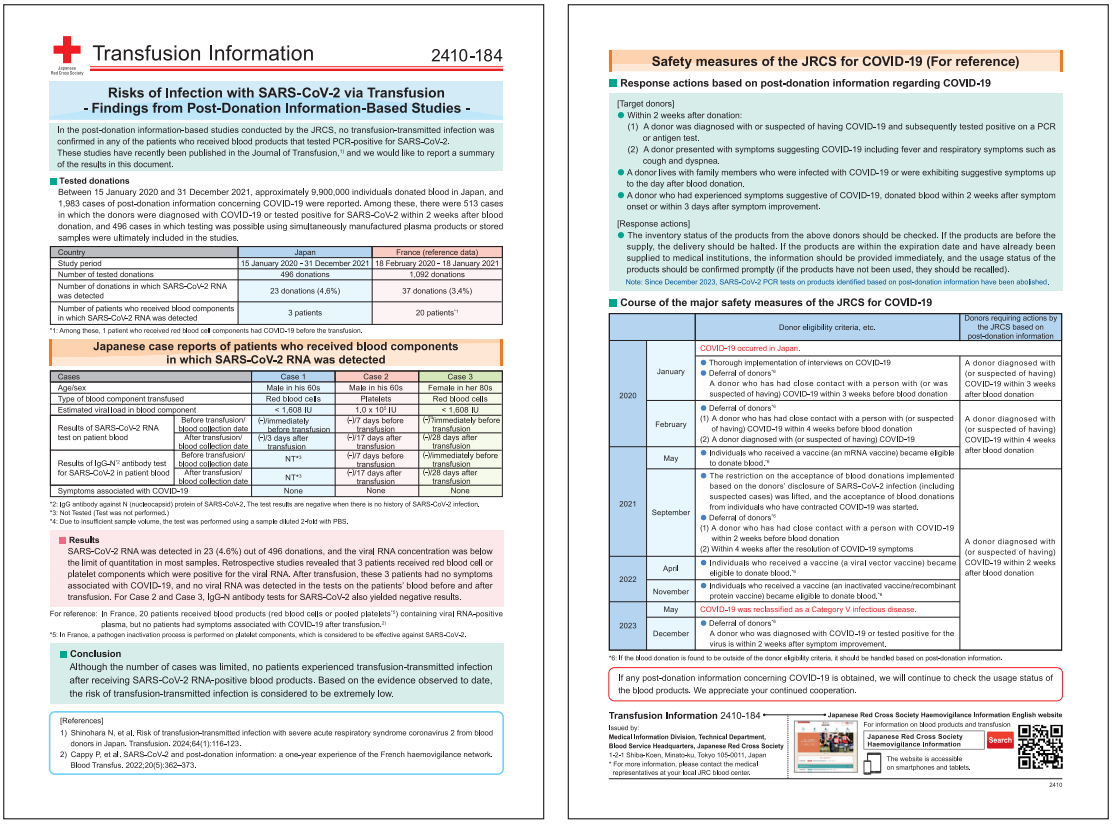
**Figure 16. Management of platelet products after introduction of bacterial screening**

## [Safety measures for novel coronavirus]

The JRCS has been taking various safety measures against the novel coronavirus, and has conducted a lookback investigation as part of the measures. For approximately 9.9 million blood donations between January 2020 and December 2021, the JRCS investigated cases in which blood products from donors who tested positive for novel coronavirus RNA were used for transfusion. As a result, no cases of transfusion-transmitted infection were observed among 3 patients who received transfusion of novel coronavirus-positive products, and the findings were published in the journal Transfusion[1]. Based on the findings of this investigation and the evidence confirmed to date, it is believed that the risk of infection with novel coronavirus through blood transfusion is extremely low.

The findings of the investigation and the safety measures that have been taken to date were summarized and published in Transfusion Information, “Risks of infection with the novel coronavirus via transfusion: Findings from post-donation information-based studies” (Figure 17), and it was disseminated to medical professionals and others.

The JRCS will continue to closely monitor trends in each country and implement safety measures based on the latest scientific knowledge. Preparedness for emerging infectious diseases is an essential task of the blood service. By applying our experience gained in responding to the current novel coronavirus outbreak, the JRCS continues striving to ensure a safe and stable blood supply system.



Transfusion Information 2410-184

**Risks of Infection with SARS-CoV-2 via Transfusion - Findings from Post-Donation Information-Based Studies -**

In the post-donation information-based studies conducted by the JRCS, no transfusion-transmitted infection was confirmed in any of the patients who received blood products that tested PCR-positive for SARS-CoV-2. These studies have recently been published in the Journal of Transfusion,[1] and we would like to report a summary of the results in this document.

**Tested donations**

Between 15 January 2020 and 31 December 2021, approximately 9,900,000 individuals donated blood in Japan, and 1,983 cases of post-donation information concerning COVID-19 were reported. Among these, there were 513 cases in which the donors were diagnosed with COVID-19 or tested positive for SARS-CoV-2 within 2 weeks after blood donation, and 496 cases in which testing was possible using simultaneously manufactured plasma products or stored samples were ultimately included in the studies.

| Country | Japan | France (reference data) |
|---|---|---|
| Study period | 15 January 2020 - 31 December 2021 | 18 February 2020 - 18 January 2021 |
| Number of tested donations | 496 donations | 1,092 donations |
| Number of donations in which SARS-CoV-2 RNA was detected | 23 donations (4.6%) | 37 donations (3.4%) |
| Number of patients who received blood components in which SARS-CoV-2 RNA was detected | 3 patients | 20 patients*1 |

*1: Among these, 1 patient who received red blood cell components had COVID-19 before the transfusion.

**Japanese case reports of patients who received blood components in which SARS-CoV-2 RNA was detected**

| Cases | | Case 1 | Case 2 | Case 3 |
|---|---|---|---|---|
| Age/sex | | Male in his 60s | Male in his 60s | Female in her 80s |
| Type of blood component transfused | | Red blood cells | Platelets | Red blood cells |
| Estimated viral load in blood component | | < 1,608 IU | $1.0 \times 10^5$ IU | < 1,608 IU |
| Results of SARS-CoV-2 RNA test on patient blood | Before transfusion/ blood collection date | (-)/immediately before transfusion | (-)/7 days before transfusion | (-)/immediately before transfusion |
| | After transfusion/ blood collection date | (-)/3 days after transfusion | (-)/17 days after transfusion | (-)/28 days after transfusion |
| Results of IgG-N*2 antibody test for SARS-CoV-2 in patient blood | Before transfusion/ blood collection date | NT*3 | (-)/7 days before transfusion | (-)/immediately before transfusion |
| | After transfusion/ blood collection date | NT*3 | (-)/17 days after transfusion | (-)/28 days after transfusion |
| Symptoms associated with COVID-19 | | None | None | None |

*2: IgG antibody against N (nucleocapsid) protein of SARS-CoV-2. The test results are negative when there is no history of SARS-CoV-2 infection.
*3: Not Tested (Test was not performed.)
*4: Due to insufficient sample volume, the test was performed using a sample diluted 2-fold with PBS.

**Results**

SARS-CoV-2 RNA was detected in 23 (4.6%) out of 496 donations, and the viral RNA concentration was below the limit of quantitation in most samples. Retrospective studies revealed that 3 patients received red blood cell or platelet components which were positive for the viral RNA. After transfusion, these 3 patients had no symptoms associated with COVID-19, and no viral RNA was detected in the tests on the patients' blood before and after transfusion. For Case 2 and Case 3, IgG-N antibody tests for SARS-CoV-2 also yielded negative results.

For reference: In France, 20 patients received blood products (red blood cells or pooled platelets*5) containing viral RNA-positive plasma, but no patients had symptoms associated with COVID-19 after transfusion.[1]

*5: In France, a pathogen inactivation process is performed on platelet components, which is considered to be effective against SARS-CoV-2.

**Conclusion**

Although the number of cases was limited, no patients experienced transfusion-transmitted infection after receiving SARS-CoV-2 RNA-positive blood products. Based on the evidence observed to date, the risk of transfusion-transmitted infection is considered to be extremely low.

[References]
1) Shinohara N, et al. Risk of transfusion-transmitted infection with severe acute respiratory syndrome coronavirus 2 from blood donors in Japan. Transfusion. 2024;64(1):116–123.
2) Cappy P, et al. SARS-CoV-2 and post-donation information: a one-year experience of the French haemovigilance network. Blood Transfus. 2022;20(5):362–373.

**Safety measures of the JRCS for COVID-19 (For reference)**

**Response actions based on post-donation information regarding COVID-19**

[Target donors]
- Within 2 weeks after donation:
  (1) A donor was diagnosed with or suspected of having COVID-19 and subsequently tested positive on a PCR or antigen test.
  (2) A donor presented with symptoms suggesting COVID-19 including fever and respiratory symptoms such as cough and dyspnea.
- A donor lives with family members who were infected with COVID-19 or were exhibiting suggestive symptoms up to the day after blood donation.
- A donor who had experienced symptoms suggestive of COVID-19, donated blood within 2 weeks after symptom onset or within 3 days after symptom improvement.

[Response actions]
- The inventory status of the products from the above donors should be checked. If the products are before the supply, the delivery should be halted. If the products are within the expiration date and have already been supplied to medical institutions, the information should be provided immediately, and the usage status of the products should be confirmed promptly (if the products have not been used, they should be recalled).

Note: Since December 2023, SARS-CoV-2 PCR tests on products identified based on post-donation information have been abolished.

**Course of the major safety measures of the JRCS for COVID-19**

| | | Donor eligibility criteria, etc. | Donors requiring actions by the JRCS based on post-donation information |
|---|---|---|---|
| 2020 | January | COVID-19 occurred in Japan. | |
| | | • Thorough implementation of interviews on COVID-19<br>• Deferral of donors*6<br>A donor who has had close contact with a person with (or was suspected of having) COVID-19 within 3 weeks before blood donation | A donor diagnosed with (or suspected of having) COVID-19 within 3 weeks after blood donation |
| | February | • Deferral of donors*6<br>(1) A donor who has had close contact with a person with (or suspected of having) COVID-19 within 4 weeks before blood donation<br>(2) A donor diagnosed with (or suspected of having) COVID-19 | A donor diagnosed with (or suspected of having) COVID-19 within 4 weeks after blood donation |
| 2021 | May | • Individuals who received a vaccine (an mRNA vaccine) became eligible to donate blood.*6 | |
| | September | • The restriction on the acceptance of blood donations implemented based on the donors' disclosure of SARS-CoV-2 infection (including suspected cases) was lifted, and the acceptance of blood donations from individuals who have contracted COVID-19 was started.<br>• Deferral of donors*6<br>(1) A donor who has had close contact with a person with COVID-19 within 2 weeks before blood donation<br>(2) Within 4 weeks after the resolution of COVID-19 symptoms | A donor diagnosed with (or suspected of having) COVID-19 within 2 weeks after blood donation |
| 2022 | April | • Individuals who received a vaccine (a viral vector vaccine) became eligible to donate blood.*6 | |
| | November | • Individuals who received a vaccine (an inactivated vaccine/recombinant protein vaccine) became eligible to donate blood.*6 | |
| 2023 | May | COVID-19 was reclassified as a Category V infectious disease. | |
| | December | • Deferral of donors*6<br>A donor who was diagnosed with COVID-19 or tested positive for the virus is within 2 weeks after symptom improvement. | |

*6: If the blood donation is found to be outside of the donor eligibility criteria, it should be handled based on post-donation information.

If any post-donation information concerning COVID-19 is obtained, we will continue to check the usage status of the blood products. We appreciate your continued cooperation.

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**Figure 17. Transfusion Information, “Risks of infection with the novel coronavirus via transfusion: Findings from post-donation information-based studies”**

## [References]

1) Shinohara N, et al. Risk of transfusion-transmitted infection with severe acute respiratory syndrome coronavirus 2 from blood donors in Japan. Transfusion. 2024;64(1):116-123.

## Afterword

This annual report describes the JRCS's safety measures, which were 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 reactions and infection cases reported by medical institutions and post-donation information.

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

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

"Haemovigilance by JRCS 2024"

Edited by

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