Haemovigilance System in EU and Japan: An Overview

The objective of haemovigilance is to trace and analyse all inappropriate effects of blood transfusion with a view to correcting their cause, preventing reoccurrence and improving the safety of blood transfusion. Long-term encounters with the therapeutic use of blood products are prevalent and expertise in adverse effects occurrence is accessible, but systemic safety surveillance in clinical practice is not in place in several countries. Despite the life-saving effects of blood transfusion, it is not very concrete and is based on surrogate markers to demonstrate effectiveness. There are huge differences in therapeutic protocols and there is still limited knowledge of the best implementation of a product in a particular indication, and the optimal use of blood components. In order to enhance this knowledge, the first objective must be to collect epidemiological data as a basis. Haemovigilance has been an essential part of the principle of blood safety. National haemovigilance systems are now in place or are being developed in European Union Member States. The Japanese Red Cross (JRC) headquarters was established in Japan's haemovigilance system in 1993, with the initial purpose of collecting reports from medical facilities of adverse transfusion reactions. Although the JRC has a voluntary system of reporting, almost all severe adverse reactions caused by blood transfusion are collected in cooperation with medical facilities. Non-haemolytic transfusion reactions account for >90% of all reported events and 5–6% of transfusion-transmitted infections (TTIs). Laboratory analyses conducted at the JRC Central Blood Institute and other laboratories support the JRC haemovigilance system.

Key words:
Haemovigilance network, Red Cross, Blood transfusion

Introduction

Haemovigilance is a collection of monitoring procedures covering the entire blood transfusion chain, from donating and processing blood and its components to providing and transfusing it to patients, including their follow-up.[1]

It includes monitoring, reporting, investigating and analysing adverse events associated with blood donation, processing and transfusion, and taking action to prevent their occurrence or recurrence. Reporting systems play a key role in improving patient safety by learning from failures and then implementing changes to the system to prevent them in the future.[1]

The haemovigilance system must include all appropriate stakeholders and coordinate between the blood transfusion service, clinical hospital staff and transfusion labs, hospital transfusion committees, national regulatory agency and national health authorities.

The resulting changes in transfusion policies, standards and guidelines, as well as improvements in blood services processes and hospital transfusion practices, result in improved patient safety.[2]

A life-saving intervention is the transfusion of blood and blood products. Adverse events associated with blood donation and its components, and the transfusion of blood and blood products to patients, however, are associated with risk. Adverse events also include blood donation and transfusion-related reactions, incidents, near-misses, errors, deviations from standard operating procedures and accidents. Learning from adverse events and identifying system problems can lead to measures being introduced to improve the quality, safety, efficacy and cost-effectiveness of blood and blood products, and also the processes of donation and transfusion.

The main goal of haemovigilance is to improve the transfusion chain's continuous quality through corrective and preventive actions to improve patient safety and outcomes, improve donor safety, and reduce waste. Haemovigilance should also be completely integrated in to the quality systems of all institutions involved in blood and blood products donation and supply, including processing, inventory management, storage and distribution, and clinical transfusion.[3]

Key Elements in a Haemovigilance System

The Ministry of Health (MoH) is ultimately responsible for the quality, safety and adequacy of the supply of blood and blood products for its national blood system. A system of haemovigilance contributes to donation safety, blood products and transfusion.[4]

It improves risk management, increases confidence, and in nature should be confidential and non-punitive. The MoH should include a national haemovigilance system with effective leadership and governance, such as:[5]

Leadership and Governance[6]

1. Haemovigilance as part of the national blood policy and plan, as well as the legislative and regulatory framework
2. Haemovigilance advisory committee(s)
3. Adequate human and financial resources
4. Standards and definitions
5. Confidential and non-punitive system
6. Traceability of donor-to-patient blood and blood products
7. Quality system throughout the transfusion chain
8. Corrective and preventive action

Organisation and Coordination[7]

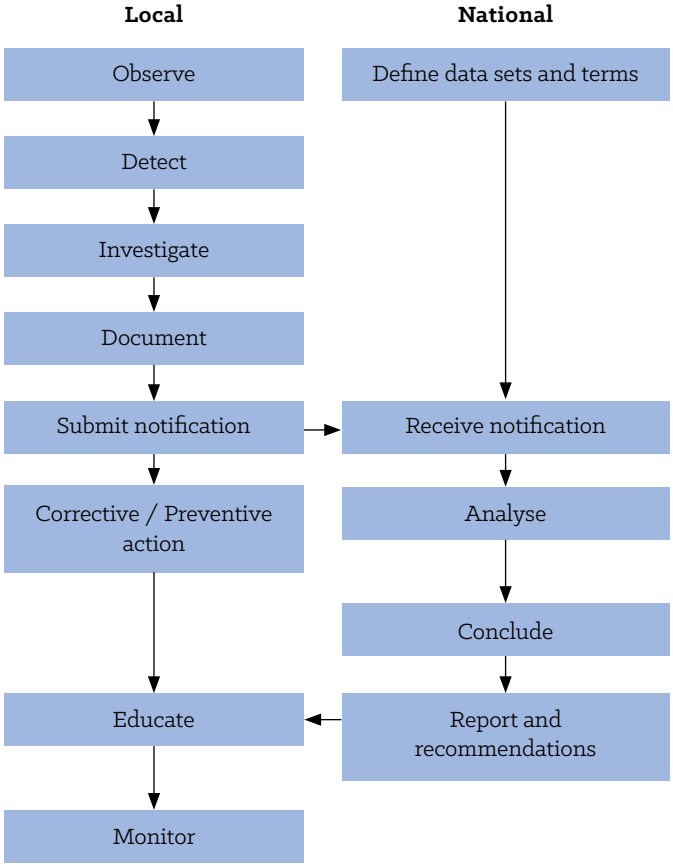
1. Identification of stakeholders and institutions responsible
2. Organisational arrangements for the haemovigilance system
3. Coordinated links with organisations and institutions involved in the system
4. Defined roles and responsibilities of all stakeholders
5. Haemovigilance education and training for all healthcare staff
6. Monitoring, reporting, investigating and analysing adverse events, with safety and quality improvements recommendations.

Haemovigilance in the Donation and Provision of Blood and Blood Products[8]

1. Donor haemovigilance: recognition of adverse events associated with donation, clinical management, monitoring, reporting, investigation and analysis
2. Policies, guidelines, protocols and standard operating procedures for all processes
3. Reporting of errors and deviations associated with these processes
4. Post-donation information and look-back
5. Liaison among blood transfusion services and hospital blood banks, clinical services and transfusion committees.

Haemovigilance in Clinical Transfusion[9]

1. Patient haemovigilance: recognition, clinical management, monitoring, reporting, investigation and analysis of adverse events associated with transfusion
2. Clinical guidelines, hospital protocols, standard operating procedures, patient identification and sample labelling
3. Hospital transfusion committees
4. Response to recall and look-back notification
5. Coordination between hospital departments and services, and liaison with blood transfusion services.



Flow of Haemovigilance Data

Discussion

European Union

The European Medicines Agency (EMA) is accountable for scientific analysis, supervision and safety monitoring of medicines developed by pharmaceutical companies for use in the EU. Before 2004, it had been known as EMEA. It tries to harmonise (but not replace) the work of existing national medication control bodies roughly parallel to USFDA.[10]

The extra requirements to those set down in Directive 2001/83/EC and Regulation (EC) 726/2004 Article fourteen[4] of Regulation (EC) No 1394/2007 presented by the Legal Basis Regulation (EC) No 1394/2007 of the European Parliament and of the Council requires monitoring of effectiveness and adverse reactions, and also hazard management after authorisation. Procedures for electronic data exchange with other vigilance systems like haemovigilance is also required under pharmacovigilance system, whenever it is applicable.

But No Guidelines are Formulated for Haemovigilance by EMA.

Haemovigilance – European Union Countries

The four European Blood Directives are the prime legal framework on blood

- 2002/98/EC (pertaining to principles involved and organisation)
- 2004/33/EC (specifies control over donations, donors and products)
- 2005/61/EC (requirements on traceability and notifications – haemovigilance)
- 2005/62/EC (specifications on quality management)

Article 14: Traceability

1. MS will take every essential measure in order to ensure that blood or components collected, manufactured, tested or released should be traced either from donor to the recipient or vice versa and should be as per the provisions in Article 29(a).
2. MS will take all the measures to ensure that the framework for the labelling is ensured in all the steps of blood collected, stocked or released and thereby identification has paramount importance.
3. Records should be maintained for at least thirty years.

Article 15: Notification of serious events to the authority is mandatory and an SOP should be there for each establishment for the timely withdrawal of the product for which any untoward effects have been observed, and should follow official formats for reporting, as specified in Article 29(i).

Haemovigilance in France[11]

In 1993 by law, in France, haemovigilance turned into a national arrangement of surveillance and alert, from blood collection to the follow-up of the beneficiaries with the intention to prevent untoward effects, and reporting is mandatory, disregarding their seriousness and their transfusion, in contrast to other Member States. The law expresses that "anybody, professionals, specialists, medical attendant or attendant, [who] detects any unexpected effects probably due to a blood component, should report it without delay to the haemovigilance officer and [the] haemovigilance officer should report it further to French Security Agency" (ANSM).

The organisation of haemovigilance is in three dimensions:

1. National
2. Regional
3. Local.

A haemovigilance officer (HVO) is there in every establishment (HE) dedicated for transfusion steps (1482 HVO) and at each blood centre site (153 no).

Local healthcare establishments are attached to regional blood centres which supply labile blood products. A regional

haemovigilance officer is appointed in each region. A regional coordinator (RHC) is delegated in each administrative region.

Haemovigilance in Germany[12]
Directive 89/381/EEC has special provisions for products obtained from human blood or plasma. The Paul-Ehrlich-Institute is the responsible authority for the annual surveillance of blood supply in conjunction with sec 21 of the German Transfusion Act. Haemovigilance was started in 2001. Confidential and obligatory coverage is observed.

In Germany, the labile blood products are listed under medications and are controlled by German drug law. In keeping with the national legal provisions covering medicines, untoward effects are reportable to the pharmacovigilance programme. It ought to be mentioned that the recent German Transfusion Law conjointly establishes haemovigilance as a separate entity and assessment of the reports of severe adverse transfusion reactions are consistent to Section 63i AMG (German Medicines Act).

Haemovigilance Italy[13]
In Italy, haemovigilance was activated in 2004 by the National Institute of Health. The Italian system of haemovigilance is considerably in line with the EU Directive, though it lacks the monitoring of adverse or sudden events in donors and registration at a national level of severe incidents associated with collection and handling of blood that may have effects on the standard and safety of the blood component.

Haemovigilance Austria[14]
The business segment of AGES Medicines and Medical Devices is responsible for a wide range of tasks in pharmaceutical licensing, clinical testing of medicines and medical devices, pharmacovigilance and vigilance in medical devices as well as inspection. The main customer and owner is the Austrian Republic, represented by the Federal Ministry of Health and Women's Affairs (BMGF).

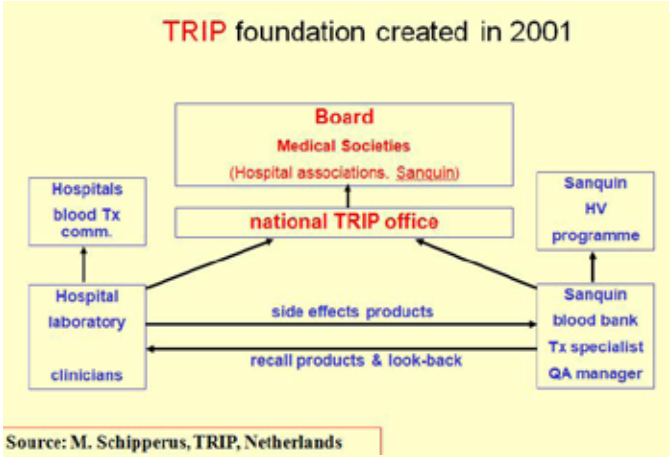
Around 280 employees employ medicines and medicinal devices. This business segment is ISO 9001 certified and the Official Medicines Control Laboratory (OMCL) testing activities are recognised by Accreditation Austria.

The Austrian Federal Office for Healthcare Safety (BASG), an agency subordinated to the BMGF, has been entrusted with the performance of statutory tasks in line with the work of the Medicines & Medicinal Devices segment.

Haemovigilance – UK[15]
In the UK, the Blood Safety and Quality Regulations (2005) controls the blood services (called blood establishments and hospital transfusion laboratories). The competent authority is the Medicines and Healthcare Products Regulatory Agency (MHRA). The data are confidential and individual patient details are not included. The adverse events are reported to SHOT, which is the independent haemovigilance scheme of the UK.

Haemovigilance – The Netherlands[14]
Reporting Procedure
The Netherlands provides a digital reporting system referred to as TRIP. Reporting of transfusion-related events by clinicians and patients to TRIP is anonymous. Though voluntary, it is widely practised. After analysis, it provides an annual overview of serious adverse reactions (grade 2 or higher) to the European Commission. In addition, the reporter can directly make a report available to the IGZ (Health Inspectorate) and / or the blood supply organisation, Sanquin, via the TRIP digital reporting system.

Similarly, the hospitals are also endowed with haemovigilance officers (staff members officially responsible for reporting to TRIP) supported by haemovigilance assistants who prepare the report to TRIP (visit ward, collect and collate information), as well as providing education and training on blood transfusion.



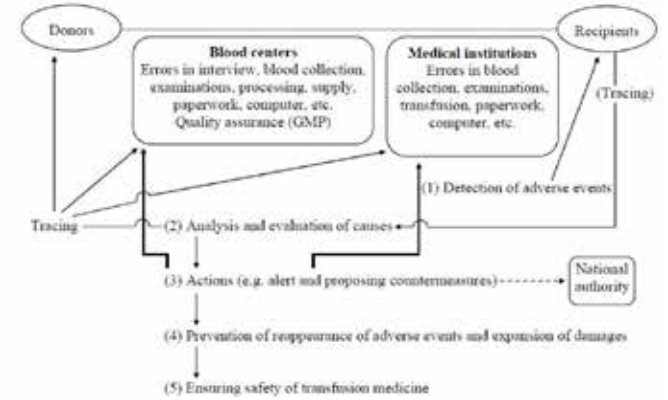
Japan
Haemovigilance is defined as prospective surveillance from donors, blood centres and medical institutions, to recipients of a series of transfusion processes. The method begins with early diagnosis of adverse events (adverse reactions and infectious diseases) and unknown infectious diseases in recipients, followed by causal analysis and assessment.

The analysis should also cover relevant blood products and plasma derivatives, as well as the practical transfusion process in medical institutions, testing and manufacturing processes in the medical condition of blood centres and donors. It includes epidemiological study in the population or region to which the donors belong, in addition to evaluating the medical condition and the eligibility of donors, particularly in tracing donors related to infectious diseases. When an adverse event in a blood centre or medical institution was found to be caused by errors, all aspects including the organisation's operating system, procedures, and methods should be reviewed for immediate action.[15]

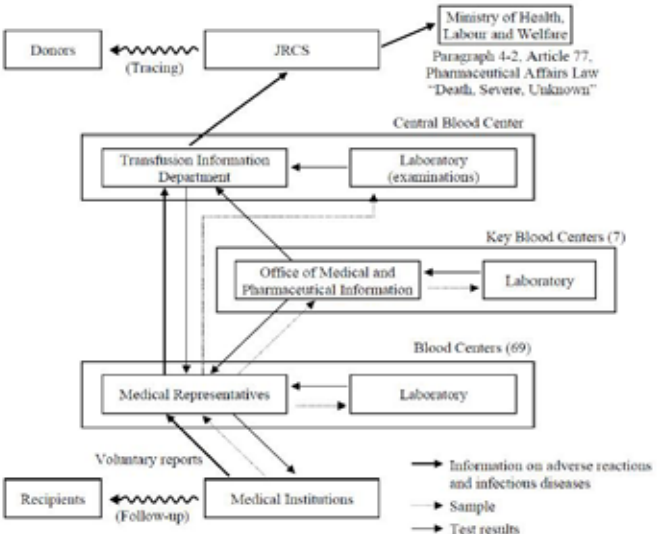
Establishment of the Japanese Red Cross (JRC) Haemovigilance System
The JRC is Japan's only organisation that deals with the blood business, from collecting, processing, and manufacturing blood to delivering blood components to healthcare providers. In 1993, the JRC set up its own nationwide haemovigilance system to collect reports of blood transfusion-related adverse events. This is a voluntary reporting system, not a compulsory system, where doctors report to JRC blood centres cases of moderate and severe adverse events. Some doctors may not report such events to the JRC; however, reporting to the Ministry of Health, Labor and Welfare (MHLW) of serious cases is compulsory and the MHLW routinely refers such reports to the JRC.

History of Transfusion Medicine in Japan
In 1918, Japan's first transfusion experience was reported. Most of the blood components from sold blood have since been transfused. In 1964, a law came into force and new JRC statutes were established. At the same time, the Cabinet decided that all blood components should be derived from donations rather than

blood sales, and all blood components have been supplied through donated blood since 1969. In 1972, hepatitis B surface antigen (HBsAg) screening was started. In 1986, the test for HTLV-I Ab was added.[16]



Scheme of Haemovigilance in Japan



Procedures for dealing with reported adverse reactions and infectious diseases

Establishment of the Tracing System

In haemovigilance, priority should be given to setting up a tracing system for investigating the causes. Since September 1996, the JRCS tracing system has been characterised by storing all donated blood samples for 10 years. Sampling enables us to trace transfused blood and plasma derivatives related to adverse reactions and infectious diseases, confirm the causal relationship, and shed light on the causes of future potential unknown infectious diseases.

Current Risks in Transfusion[17]

1. Transfusion-transmitted Infectious Diseases (TTI)

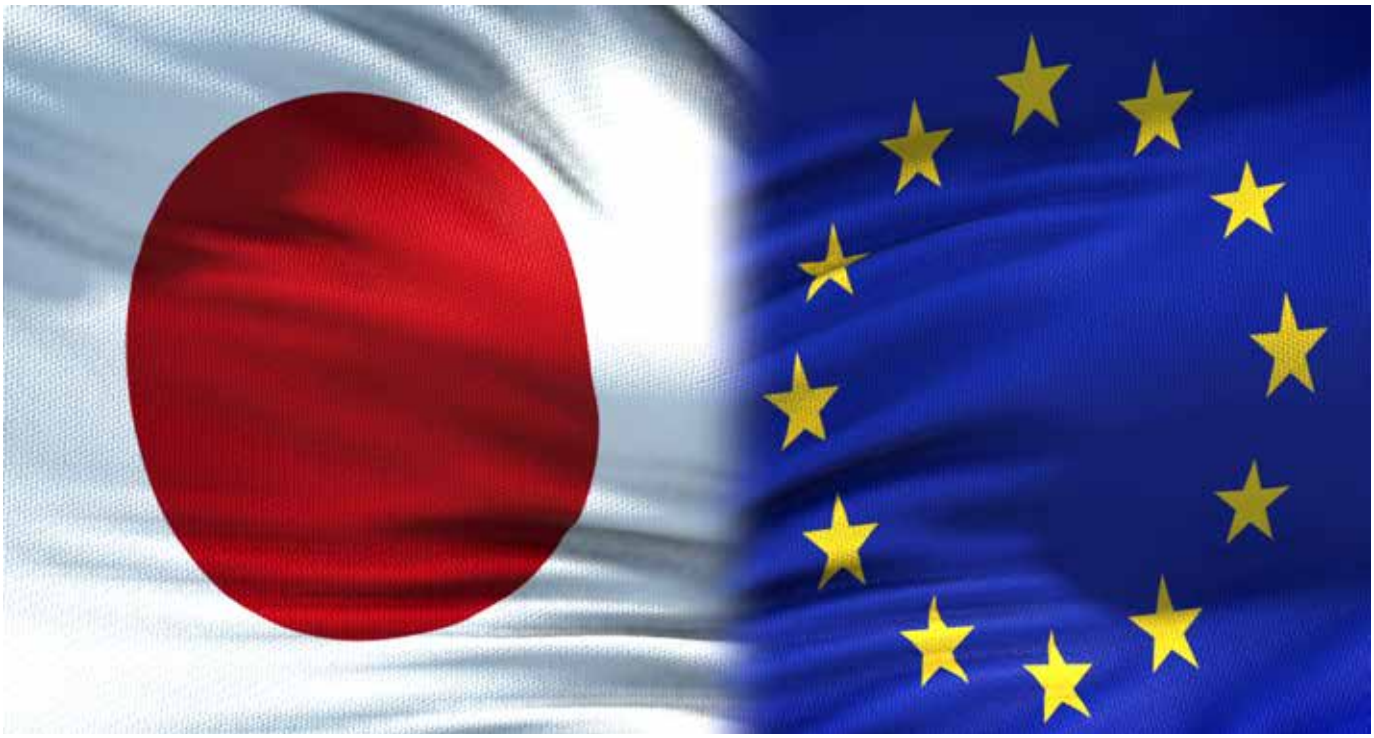
In recent years, between 80 and 100 suspected TTI cases have been reported annually. For example, the JRC reported 18 hepatitis B (HBV), 28 hepatitis C (HCV), 20 bacterial, seven human cytomegalovirus (CMV), four hepatitis E (HEV), one hepatitis A (HAV) and two human parvovirus B19 suspected TTIs in 2016. Only one HBV, one bacterium and three HEV infections were confirmed as transfused by evaluating the gene sequence identity between donor and patient-derived microorganisms, e.g. HBV, HCV, HIV.

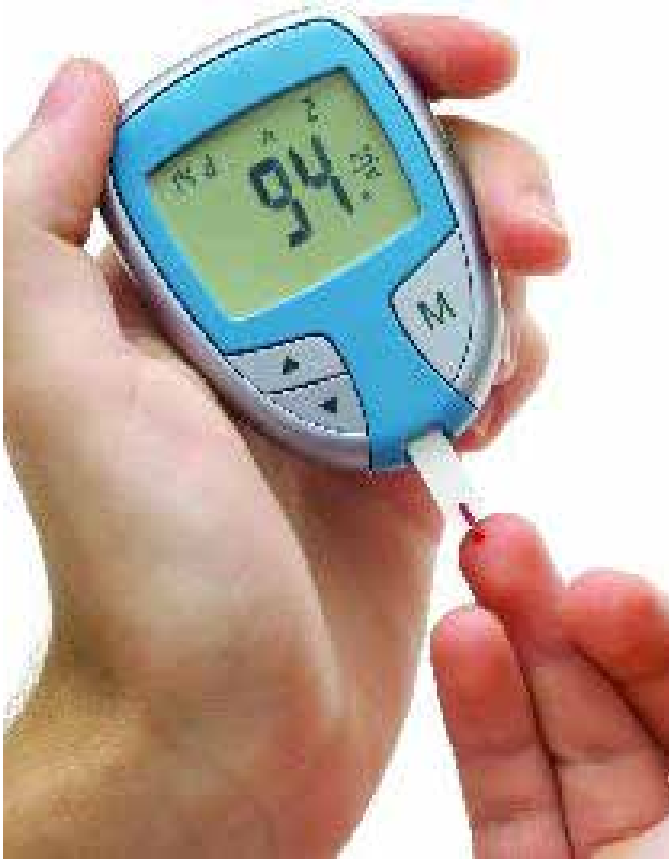
2. Transfusion-associated Circulatory Overload (TACO)

Despite the fact that circulatory overload has been a recognised transfusion complication for decades, there is still relatively little attention in the scientific literature paid to what constitutes TACO. Patients develop respiratory distress during or several hours after transfusion and may develop orthopnea, cyanosis, tachycardia, and hypertension. On auscultation, rales can be identified, and some patients may have jugular venous distention, cardiac auscultation S3, or lower extremity edema.

3. Transfusion-related Acute Lung Injury (TRALI)

TRALI is an acute injury to the lungs (ALI) that occurs during or after transfusion. It has emerged as the leading cause of transfusion-related fatality reported to the Food and Drug Administration of the United States. Recently transfused patients show respiratory distress, hypoxemia, auscultation rates, and diffuse bilateral chest radiograph infiltration. Breathing distress may be sufficiently severe to require mechanical ventilation.





4. Allergic Reactions

Non-haemolytic transfusion reaction symptoms vary and may include one or more of the following: hives, fever, anaphylaxis, anaphylactic shock, hypotension, and / or dyspnoea. Eighty per cent of reported platelet or FFP transfusion non-haemolytic reactions are allergic in nature. Symptom distribution is similar in both platelet and FFP transfusion reactions, which suggests that reactions to both components are caused by similar mechanisms.

Summary

Haemovigilance plays a vital role in reporting blood-related problems to the authorities. When cases have been increasing day by day, these should be standard guidelines for reporting such issues to the authorities. The European Union has established the European Haemovigilance Network (EHN) where all Member States are requested to post blood-related reports to maintain uniformity for all Member States.

In Japan, haemovigilance is carried out by the Japanese Red Cross Society (JRC), established in 1993. There is a well-developed haemovigilance network in Japan and the reporting is divided into TRALI, TACO and TTI for the better evaluation of the blood-related reporting and the measures to be taken to overcome the issues under the Red Cross Society.

Conclusion

Haemovigilance is an indispensable component of quality management in a blood system and is needed for the persistent augmentation of quality and safety of blood products and the transfusion process by monitoring and safeguarding the undesirable events associated with the use of blood products.

In comparison to the EU Haemovigilance Network, Japan has well-developed guidance and a better evaluation procedure for blood-related issues. The EHN is in a development process and there is a need for stricter regulations and guidance for blood-related issues.

In order to comprehend this progress, the observation of suitable or best possible blood use in a more exhaustive way, e.g. through the assortment of a set of indicators that may be provided simply by most hospital information systems, has to be started. At the same time, assessment methods should be more adapted to measure and analyse critical parameters for optimal blood use.

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