



# Haemovigilance: current practices and future developments

Layla L. de Jonge<sup>1</sup>, Johanna C. Wiersum-Osselton<sup>1,2</sup>, Arlinke G. Bokhorst<sup>1,2</sup>, Martin R. Schipperus<sup>1,3</sup>, Jaap Jan Zwaginga<sup>1,4</sup>

<sup>1</sup>Transfusion and Transplantation Reactions in Patients (TRIP) National Haemovigilance and Biovigilance Office, Leiden, The Netherlands;

<sup>2</sup>International Haemovigilance Network (IHN), Leiden, The Netherlands; <sup>3</sup>Department of Haematology, University Medical Centre Groningen (UMCG), Groningen, The Netherlands; <sup>4</sup>Department of Haematology, Leiden University Medical Centre (LUMC), Leiden, The Netherlands

*Contributions:* (I) Conception and design: All authors; (II) Administrative support: LL de Jonge; (III) Provision of study materials or patients: AG Bokhorst, LL de Jonge, JC Wiersum-Osselton; (IV) Collection and assembly of data: AG Bokhorst, LL de Jonge, JC Wiersum-Osselton; (V) Data analysis and interpretation: AG Bokhorst, LL de Jonge, JC Wiersum-Osselton; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

*Correspondence to:* Layla L. de Jonge. Schuttersveld 2, 2316 ZA, Leiden, The Netherlands. Email: l.d.jonge@tripnet.nl.

**Abstract:** Haemovigilance is the systematic surveillance of adverse events in the transfusion chain, and encompasses activities that contribute to the safety and quality in the process of blood donation and transfusion. From the start in the early 1990s, haemovigilance has put emphasis on different adverse reactions and incidents in recipients and subsequently in donors, pointing to vulnerabilities in the transfusion chain and areas for prevention. More recently, the monitoring of efficacy and efficiency of transfusion practice has been introduced in the concept of haemovigilance. The purpose of this review is to present an overview of the current status and future developments of haemovigilance. Haemovigilance is part of the quality systems of the blood collection establishments, transfusion laboratories and the transfusion institutions. The monitoring, investigation and analysis of adverse events generates relevant data for the quality cycle of these systems, driving continuous improvement in transfusion practice. Recommendations based on haemovigilance findings have led to changes in clinical guidelines and policies. Despite the progress haemovigilance has made, further developments are needed. Current challenges lie in the field of the establishment of haemovigilance systems in low resource settings, the international harmonisation of definitions and the prevention of underreporting. In addition, the causal relationship between the transfusion and the reaction is often unclear. Biomarkers may aid in the imputability assessment and their role in the diagnosis of transfusion reactions needs to be further investigated. Future developments are expected in automated reporting, the use of big data and increased shareability of international data, contributing to a better understanding of the causal mechanisms and risk factors, and to prevention of adverse events. Haemovigilance is an evolving discipline and will continue to contribute to improving the safety of blood donation and transfusion.

**Keywords:** Haemovigilance; quality system; transfusion safety; adverse events

Received: 14 January 2021; Accepted: 01 March 2022; Published: 30 June 2022.

doi: 10.21037/aob-22-2

**View this article at:** <https://dx.doi.org/10.21037/aob-22-2>

## Introduction

Blood transfusions are life-saving interventions and form an essential component of the health care of millions of patients. The first human blood transfusions were performed in the 19th century (1), and were accompanied

by numerous fatalities. Although the discovery of the ABO blood groups by Landsteiner contributed to a considerable degree to the safety of transfusions (2), the administration of blood continued to be associated with harmful consequences. The transmission of infectious diseases through contaminated blood products became a

recognized adverse complication of transfusion (3). In the early 1990s the first specialized and structured national surveillance systems for blood transfusions were developed in Europe and Asia, as a reaction to the HIV contaminated blood scandals (4). Many countries followed and nowadays, haemovigilance is an important aspect of transfusion medicine worldwide (5). The objective of this review is to present an overview of the current status and possible future developments of haemovigilance.

### **The scope of haemovigilance**

Haemovigilance is defined by the International Haemovigilance Network (IHN) as “A set of surveillance procedures covering the whole transfusion chain, from the collection of blood and its components to the follow-up of recipients, intended to collect and assess information on unexpected or undesirable effects resulting from the therapeutic use of labile blood products, and to prevent their occurrence or recurrence” (6). Although the methodology of haemovigilance finds its roots in the way surveillance of pharmaceuticals was designed in the 1960s, the scope has developed beyond that of pharmacovigilance. The World Health Organisation (WHO) has described the goal of haemovigilance as “The continuous quality improvement of the transfusion chain through corrective and preventive actions to improve donor and patient safety, improve transfusion appropriateness and reduce wastage” (7). The surveillance of haemovigilance encompasses all adverse events, including adverse reactions and incidents that occur in the donation, processing and transfusion of blood. The taxonomy of adverse events differs between international bodies and has been source of debate, with considerable variation in definitions used (8).

Adverse reactions are defined by the International Society of Blood Transfusion (ISBT) as undesirable responses or effects in patients temporally associated with the administration of blood or blood components, and range in severity from minor reactions to reactions with a fatal outcome (9). Haemovigilance systems initially focused on the risk of transfusion-transmitted infectious diseases (10). However, the transmission of HIV, HBV and HCV infections was already significantly reduced at the time the first haemovigilance systems were initiated (11), and the focus expanded to other infectious and non-infectious adverse reactions.

Adverse reactions may result from an incident in the transfusion chain. In the broadest sense, incidents comprise

errors, deviations from standard operating procedures (SOPs) and failures, that lead to harm to the donor and recipient, including adverse reactions and the adverse effects of delay, or the risk of harm. Data from the Serious Hazards of Transfusion haemovigilance (SHOT) scheme in the United Kingdom showed that the majority of the serious reports result from errors (12), of which the most severe are ABO incompatible blood transfusions resulting in major morbidity or death. Aggregate data from the European Union member states also show that more than three quarters of all serious adverse events associated with risk of harm for donors or patients were reported in the categories human error and system failures (13). In order to enhance transfusion safety, it is essential to broaden the scope of haemovigilance beyond that of the safety of blood or blood components.

In addition to the analyses of incidents that led to harm, haemovigilance has grown to encompass the investigation of incidents where there was a risk of harm but this did not occur. Such near misses point to weak or vulnerable steps in the transfusion chain. The recording of these cases contributes to a more complete picture of the extent of the risk of adverse events (14). Analysis of near misses can identify underlying causes in working methods that should be changed to prevent future wrongful transfusion events, adding leverage to proactive improvements of transfusion safety and the prevention of transfusion reactions.

Finally, the concept of monitoring of efficacy and efficiency of the transfusion chain can be considered as part of haemovigilance in its broadest sense. By monitoring optimal blood use, not only the therapeutic outcome of transfusions is under surveillance, but also under- and overtreatment (15), and the wastage of “scarce” human resources by outdated, over-ordering or ill-timing between the ordering and the actual start of transfusion. The surveillance of efficacy and efficiency of transfusions is currently not incorporated in most of the national level haemovigilance systems. While strongly dependent on the presence of evidence-based practice and adherence to guidelines, the monitoring of efficacy and efficiency of transfusion constitutes a domain haemovigilance can progress into.

### **Methods in haemovigilance**

Haemovigilance is part of the quality systems of the blood establishments, responsible for the collection, testing, processing, storage and distribution of blood, the blood

transfusion laboratories, and the healthcare institutions involved with the actual blood transfusion. Haemovigilance data provide quantitative measures of performance for these quality systems and yield relevant information to drive quality improvement.

The cycle of haemovigilance consists of the monitoring, identification and investigation of adverse events, the assessment of individual reports and the analysis of aggregate cases, followed by feedback and preventive measures. An effective haemovigilance program requires the collaboration of all involved in the transfusion chain (16).

Haemovigilance starts at the local institutions and facilities: the blood establishments, the transfusion laboratories and the hospitals' clinical departments. These services are directly responsible for some or all of the steps in the transfusion chain, and the detection and management of adverse events. The recognition and thorough investigation of cases are of major importance for the effectiveness of a haemovigilance system. The surveillance at local institutions can be based on a proactive, systematic search for safety issues, or rely on passive reporting, based on spontaneous recognition of transfusion-associated adverse events by clinical staff. Traceability throughout the transfusion chain needs to be ensured, referring to the ability to trace unique units of blood or blood components from the donor to their final destination and vice versa (17).

Depending on the organization of haemovigilance in a country, the local institutions report to a regional or national body. The establishment of a national haemovigilance scheme enables a coordinated review of adverse event reports and data consolidation above the level of individual hospitals and blood banks. The organizational model of a regional or national surveillance system is influenced by the framework of the blood and healthcare system (7) and differs between countries. Depending on the legal status of a system, reporting can be mandatory, where there is a statutory requirement to submit reports, or voluntary, relying on the willingness of the professionals involved in the transfusion process to participate. An intermediate form, professionally mandated, can be discerned in countries where haemovigilance reporting commenced as an initiative of professional groups. Independent of the legal status, a confidential and just culture, with shared accountability for both individuals and the organization (18), encourages adequate reporting of events. The assessment of the information in the individual reports includes the categorization of the adverse reactions, and also of incidents independent of the occurrence of subsequent

harm, preferably according to internationally recognized definitions (8). Subsequent aggregate analyses of cases enable the epidemiological approach to haemovigilance (19). One of the critical components is to translate the outcomes of the individual and aggregate analyses into recommendations on preventive measures (20).

In order to effectively improve transfusion safety, the relevant findings and recommendations from the reported cases should be communicated to the healthcare professionals involved but also more broadly to educate all involved in the transfusion chain. Regular feedback and dissemination of best practices through reports, education and symposia enhances engagement and transparency. The recommendations may drive local preventive measures and quality procedures, or form a basis for the regulatory authorities to establish or improve regulations and guidelines. Ongoing monitoring to evaluate the effect of the implementation of preventive measures closes the cycle.

### **International haemovigilance**

According to the WHO global database on blood safety and availability, up to 49% of reporting countries had a haemovigilance system in place in 2018 (21). Alongside the establishment of national haemovigilance systems, there is a need for international regulation, information exchange and collaboration.

In the Europe Union a legal framework is laid down in the European Blood Directive, Directive 2002/98/EC of the European parliament and the Council, and additional implementing acts (22). In the European blood legislation standards for quality and safety of blood are set, covering the collection, testing, processing, storage and distribution of blood and blood components. A requirement is formulated for member states to ensure serious adverse reactions and events are notified to the competent authority, and to submit an annual report on the notifications to the European Commission. Annual summaries of this reporting are available on the European Commission website (13). Several EU member states set up their haemovigilance systems in response to the legislation, demonstrating a positive regulatory effect (23). In 2014 the Rapid Alert system for Blood and Blood Components (RAB) was launched, a communication and information dissemination tool for the exchange of urgent information between national competent authorities.

The WHO Blood Transfusion Safety programme aims to improve blood safety worldwide through education,

advocacy and technical support. The WHO has defined strategies for the development of haemovigilance systems in the Guide to establishing a national haemovigilance system (7). This document provides policy and technical guidance to countries which are planning to implement a haemovigilance system and presents templates for the notification of adverse events, and for periodic and annual reporting. The WHO collects data on the functioning and results of national haemovigilance programs, the results of which are published in the Global Database on Blood Safety (24). The WHO, in collaboration with the Italian National Transplant Center, initiated the Notify project. The Notify Library is an open access database of adverse events associated with Medical Products of Human Origin (MPOH) and contains didactic cases, including relevant references, of adverse occurrences summarised and commented on by international experts (25). The collected cases encompass blood and blood components, as well as organs, tissues and cells. The library supports the sharing of knowledge on vigilance for educational purposes and for creating transparency on the use of MPOH (26).

Other international haemovigilance collaborations have been established to advance haemovigilance worldwide, promote standardization and to encourage national participation. The ISBT is a scientific society with individual members sharing knowledge to enhance transfusion practice. Their working party on haemovigilance focusses on the advancement and support of haemovigilance systems, aiming to improve both donor and recipient safety. The IHN evolved from the European Haemovigilance Network, which was founded in 1998 (27). The network is an organization of national-level haemovigilance systems which started with the objective to develop a common structure with regards to the safety of blood products and haemovigilance in participating European member states (28), and has grown to be a scientific forum and an international haemovigilance source worldwide. The ISBT haemovigilance working party and IHN have collaborated in developing standardized definitions for haemovigilance.

### **The role of haemovigilance in transfusion practice and safety**

Haemovigilance has a fundamental role in the quality systems of the transfusion chain and is a relevant factor in data-driven changes in transfusion practice (29). Learning from adverse events forms the basis. Haemovigilance contributes to the identification of risk factors for adverse reactions enabling

subsequent measures preventing morbidity and mortality. Several examples can be given in this respect.

Haemovigilance data revealed bacterial contamination of platelets as a reducible risk of transfusion (30). The observation that microbial contamination was commonly caused by skin flora led to the implementation of risk reducing strategies, including improved donor skin disinfection, initial sample diversion techniques, bacterial cultures of platelet concentrates, rapid test bacterial detection devices and the introduction of pathogen reduction technologies (31-33). Equally, haemovigilance can aid in the identification of patient groups at disproportionate risk of adverse reactions. A higher incidence of transfusion reactions was found in paediatric patients compared to adults, with allergic transfusion reactions and febrile nonhemolytic transfusion reactions the most common (34,35).

In addition, haemovigilance stresses the importance of preventing errors and near misses in the transfusion chain. SHOT identified ten steps from the decision to administer blood and patient consent, to the actual transfusion of the unit and monitoring for reactions (36). This demonstrates the complexity of the transfusion process and shows potential sources of complications. The performance of root-cause analysis to define the ultimate cause of adverse events is of great value. The investigation of errors shows vulnerabilities in the system and may reveal areas for prevention.

Although complications of blood transfusion are rare, because of the large number of transfusions these complications do have a significant impact not only on the health of a specific recipient but also on health care in general. The large-scale collection and analysis of haemovigilance data creates a comprehensive database, facilitating the recognition and understanding of infrequent transfusion-related events. Transfusion-related acute lung injury (TRALI) is a complication of blood transfusion associated with a high morbidity and mortality (37,38). Together with clinical and fundamental research, the structured data collection of haemovigilance contributed to the insight in the epidemiology and risk factors of TRALI (39). The implementation of plasma prepared from donations by male blood donors, limiting the exposure to leucocyte antibodies from previously pregnant female donors, significantly reduced the risk of TRALI (40-42). Dilution of HLA antibodies by plasma pooling, as is done in the production of solvent/detergent-treated plasma, is another way to minimize the risk of TRALI (43).

The transfusion-associated transmission of known blood-transmissible viral infections is significantly reduced through advances in donor screening and progress in blood testing (44-46). However, new pathogens may threaten transfusion safety. Worldwide, several systems are in place to systematically monitor the rise of infectious diseases and respond to outbreaks, such as the European Centre for Disease Prevention and Control (ECDC, [www.ecdc.europa.eu/en](http://www.ecdc.europa.eu/en)) and the US Centers for Disease Control and Prevention (CDC, [www.cdc.gov](http://www.cdc.gov)). Although haemovigilance has a minor role in the identification of emerging blood borne infectious diseases, continuous haemovigilance surveillance provides the opportunity to monitor patterns of transfusion-associated infectious disease transmission and investigate the effect of new pathogens on the transfusion chain, with SARS-CoV-2 the most recent example (47-49).

Adequate surveillance is essential to detect complications after the introduction of innovations and changes in transfusion medicine. Haemovigilance systems can be linked to post-introduction studies to investigate broad patient populations over a longer period of time (50). This is especially of value in discerning and quantifying the burden of rare adverse events, not obtainable from randomized controlled trials. In 2000 a multistate cluster of leucocyte-reduced red blood cell (RBC) transfusion reactions was identified in the United States, with back pain as the predominant feature. After evaluation of potential risk factors, a significant association was found with the processing of blood components using a specific leucocyte reduction filter (51).

Haemovigilance systems can play a role in the central collection and registration of data on new irregular allo-antibody formation. An adequate registration of irregular antibodies is of great importance to prevent alloimmune haemolysis long after primary immunisation since titres of previously detected antibodies can drop below detection levels due to antibody evanescence (52). In addition, patients regularly receive care at different health care facilities, while medical records and laboratory information systems are often not connected (53). A central antibody register provides the opportunity to perform transfusions with donor blood types that are matched for the earlier alloimmunisation but additionally preventive matching based on other immunogenic RBC antigens that are absent in the patient. Independent of the hospital providing care, this could prevent further alloimmunisation in high responder patients (54). In addition, a database of irregular antibodies enables the monitoring of the effect of

implementation of new or revised guidelines for prevention of allo-immunisation for specific patient groups (55).

### **Donor haemovigilance**

Historically, haemovigilance systems focused on recipient safety, but more recently emphasis was put on donor safety and the reporting of donor complications (56). Incorporation of donor safety in haemovigilance surveillance is essential to the full quality cycle of the transfusion chain. Although blood donation generally is a safe procedure, several risk factors for complications have been described. A study based on 24 haemovigilance systems covering 155 million donations, showed an overall complication rate of 6.3 per 1,000 donations (57). Vasovagal reactions and complications related to the venepuncture are common reactions (58-62).

The systematic monitoring of adverse events in the donation process enables data aggregation and triggers research, ultimately improving donor safety. Blood establishments have long recorded complications of blood donation internally. However, a uniform and transparent vigilance system, preferably operating independently of blood establishments, is needed for purposes of data comparison and independent oversight.

Inclusion of donor haemovigilance in regional or national haemovigilance systems has increased over the years. Harmonized definitions for donor complications have been formulated and validated (63,64) and a severity grading tool with objective criteria for blood donor adverse events has been developed (65), strengthening donor vigilance. With time, standards for blood and plasma collectors may increasingly incorporate recommendations about donor management to minimize complications, and monitor and act on rates of donation complications.

### **Current challenges**

Despite the importance of haemovigilance in the quality and safety of the blood transfusion process, many countries do not have an effective national haemovigilance program. Specific challenges are encountered, depending on the organization of the blood transfusion system in a country. A national policy on blood transfusion may be absent, as may be the coordination of blood transfusion processes at the national level, complicating the implementation of a haemovigilance program (66). Furthermore, traceability of blood and blood components may be insufficient (67). In addition, setting up and managing a haemovigilance



system requires resources and expertise that may not be available. This results in lack of information about adverse transfusion events and preventable factors in countries without a haemovigilance system (68), while studies show that transfusion reactions are not uncommon in resource-limited settings (69,70). Established haemovigilance systems provide quality data that may aid in the development, implementation, maintenance, evaluation, and refinement of a transfusion system in resource-limited environments, in addition to sharing tools and resource materials to support countries in the development of an effective haemovigilance system.

Haemovigilance programs, including well-established systems, are challenged by underreporting of adverse reactions and incidents. Symptoms of transfusion reactions are often non-specific and delayed symptoms of adverse events in intrinsically sick patients may be difficult to recognize. Underreporting decreases the accuracy of the data and leads to underestimation of the true incidence of transfusion reactions (71). It is well recognized that active reporting, characterized by the evaluation of the response to a transfusion regardless of the outcome, leads to increased reporting rates (72,73). In a large retrospective study in tertiary care hospitals discrepancies were found in the number of cardiopulmonary reactions identified through the active surveillance in the study versus the number of reactions reported to the transfusion medicine service (74). Most haemovigilance systems however, rely on passive reporting. Incorporating elements of active surveillance in passive systems, for example through the application of wearable devices (75), may improve reporting. Algorithms to actively screen electronic medical records for signs of transfusion reactions may be of value to extract relevant data (76), although automated electronic surveillance has not been widely implemented.

Although the IHN and the ISBT working party on haemovigilance worked on the development and validation of definitions of adverse events (8), not all areas in haemovigilance are adequately harmonised. Assessment and classification of errors constitute a major challenge when it comes to comparability of data between systems. In addition, there is no agreement between haemovigilance definition systems, the pharmacovigilance definition system and international organizations such as the EU and the WHO on shared terms, for example in the meaning attached to the term adverse events (8). To accomplish comparability and aggregability of data between haemovigilance systems, harmonised standardized

definitions and a common approach to case analysis are essential. This will enable more extensive studies as well as benchmarking and the evaluation of working practices and possible safety measures.

A further challenge of haemovigilance is the often ambiguous relationship of symptoms to the blood transfusion. The strength of the causal relationship of the transfusion of blood to the reaction, graded by the imputability (8), may not be certain. Imaging and biomarkers have the potential to aid in the diagnosis of transfusion reactions and contribute to the imputability assessment. Findings of pulmonary oedema on chest X-ray support the diagnosis of both TACO and TRALI (77). B-type natriuretic peptide (BNP) and the N-terminal prohormone of BNP (NT-proBNP) are examples of biomarkers contributing to the identification of pulmonary transfusion reactions and their cause (78,79). However, the potential role of several biomarkers has not been sufficiently investigated for use in clinical practice (80). In addition, biomarkers and diagnostic imaging modalities are not widely available in low resource countries.

### Future developments

At the time of writing it is some 25 years since the first haemovigilance systems were launched. There have been important advances in transfusion safety. Various types of transfusion reactions and sources of errors have been reduced through changes impacting the blood product, transfusion laboratory and component selection, and clinical transfusion practice. However, the original objectives of detecting rare or new complications as well as providing transparency remain. The current SARS-Cov-2 pandemic and possible effects on donor blood and the patients receiving this blood for example can only be solved by haemovigilance. Do patients with active or clinically resolved COVID-19 infection show a different vulnerability to TACO or to TRALI from patients without COVID-19 infection in their medical history? Might blood from donors recently recovered from COVID-19 or recently vaccinated against it contain higher cytokine levels and be more prone to raise minor or even serious transfusion reactions? Haemovigilance-related studies in specific patient groups can yield additional learning on risks, mitigation and help to optimise transfusion practice in these groups.

For the success of international collaboration, efforts to further harmonise the definitions and “mappability” of data between systems should continue, improving comparability

of data and creating opportunities for benchmarking and joint studies. Could a haemovigilance equivalent of the “Common Terminology Criteria for Adverse Events” for medical treatment or procedures of the US National Cancer Institute be developed to support harmonisation of severity assessment of transfusion reactions (81), as has been done for complications of blood donation (65)? Continuous quality improvement and harmonization of classification of transfusion reactions could be set up under the auspices of the International Haemovigilance Network or the WHO. Future collaborative work between haemovigilance systems is needed to develop new metrics, for instance for the monitoring of iron overload or for studies on possible long-term immune consequences of blood transfusions.

An even greater challenge for harmonisation efforts is that of collecting and comparing data on errors. The WHO presented a conceptual framework for the international classification for patient safety (82), with an initiative to improve metrics. These were recently incorporated in the WHO guidance document on patient safety incident reporting and learning systems (83), but have not been adopted within haemovigilance. We call for collaboration between national haemovigilance systems and international bodies to develop and disseminate harmonised tools to support analysis and reporting of errors and their underlying causes. This will allow benchmarking, targeted improvement measures as well as incorporation of lessons on human factors in ongoing quality improvement.

In the future, the use of electronic data sources will likely increase, including bedside transfusion-associated vital parameters of patients undergoing transfusion, more accessible nowadays through the use of bedside scanning as a means of preventing wrong transfusions. New ICT solutions facilitate the logistics for clinicians to improve monitoring and reporting transfusion reactions with more comprehensive data. These parameters can be linked to haemovigilance reports and medication and imaging data. In secured settings allowing anonymised data-based studies, data mining and artificial intelligence can yield information about signals of an impending transfusion reaction. Continuously recorded peri-transfusion vital parameters using wearables can be employed as study tools and validated, contributing to the development of patient-reported outcome measures to study the benefits of transfusion on patients’ quality of life.

An area for exploration is the use of “big data” linked to haemovigilance results. This may partly compensate for the limitations of passive surveillance. The term “big

data” refers to electronic data which are routinely collected. Algorithms can be designed to actively ascertain possible transfusion reactions from hospital electronic patient dossiers or health insurance claims (84). The Scandinavian Donations and Transfusions (SCANDAT) database, containing electronically available data on blood donors, donations and transfusions in Denmark and Sweden, has already yielded useful analyses of follow-up data on both blood donors and transfused patients through automated linking of the transfused patients’ demographic and follow-up data to haemovigilance results, electronic blood component data (age of components, extensive blood grouping data) and data made available with the consent of blood donors (85,86).

Beyond the recognised blood components which are administered intravenously, blood is processed into novel products or applied in new ways. Where pharmaceutical products undergo a process of market authorisation before they can be used to treat patients outside a trial setting, for novel blood products adoption for patient treatment comes under the responsibility of the blood organisations in collaboration with the advisory committees of clinical professional groups (87). Regulation of blood novelties is guided by Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP). Existing haemovigilance reporting systems can contribute to this process by collecting surveillance data following introduction of new products (e.g., serum eye drops). Some blood products however, due to the nature of the production process and the relevant manipulation, are already considered pharmaceutical products. The best known are the plasma derived medicinal products (PDMP) and pooled pathogen inactivated (PI) plasma. Here haemovigilance and pharmacovigilance converge, since the adverse reactions related to these products should be reported to pharmaceutical bodies whereas donor safety is part of haemovigilance (88). In most settings the routes for reporting adverse reactions are different because of the different surveillance systems whereas fresh blood products and PI plasma are often used together as part of the same transfusion scheme. Close collaboration between haemovigilance and pharmacovigilance reporting bodies on sharing and analysing these reports is therefore essential to fully cover the clinical setting and maximise learning. These mixed involvements will increase as blood-derived treatments advance—not only with pharmacovigilance systems, but also with medical devices (materiovigilance) in relation to specific collection devices, e.g., reinfusion drains, single

unit pathogen reduction technologies or plasticizers in containers (89). Of specific interest within the field of blood, tissue and cell vigilance is blood-derived source material used in the production of cellular therapies as advanced therapy medicinal products (ATMPs). These ATMPs are regulated within a pharmaceutical framework (90). The donor-derived raw material (e.g., donor mononuclear cells as source material, or serum employed as culture medium) however is overseen by the Blood directive and therefore haemovigilance principles apply (22).

## Conclusions

Haemovigilance provides essential data for the quality systems in the transfusion chain, necessary for continuous quality improvement. The surveillance of the transfusion chain through haemovigilance contributes to the safety of both donors and recipients. The shape and scope of the haemovigilance systems need to be adapted to meet the requirements of establishments and countries. Ensuring collaboration with all relevant bodies and professional groups is essential in order for the lessons learned to be translated into prevention of harm and improvement of quality, safety and outcomes.

## Acknowledgments

*Funding:* None.

## Footnote

*Provenance and Peer Review:* This article was commissioned by the Guest Editor (Paul D. Mintz) for the series “Transfusion Therapy: Principles and Practices” published in *Annals of Blood*. The article has undergone external peer review.

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://aob.amegroups.com/article/view/10.21037/aob-22-2/coif>). The series “Transfusion Therapy: Principles and Practices” was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are

appropriately investigated and resolved.

*Open Access Statement:* This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

## References

1. Learoyd P. The history of blood transfusion prior to the 20th century--part 2. *Transfus Med* 2012;22:372-6.
2. Schwarz HP, Dorner F. Karl Landsteiner and his major contributions to haematology. *Br J Haematol* 2003;121:556-65.
3. Perkins HA, Busch MP. Transfusion-associated infections: 50 years of relentless challenges and remarkable progress. *Transfusion* 2010;50:2080-99.
4. Renaudier P. The French Hemovigilance Network: From the Blood Scandal to Epidemiologic Surveillance of the Transfusion Chain. In: de Vries RRP, Faber JC, editors. *Hemovigilance: An Effective Tool for Improving Transfusion Safety*. John Wiley and Sons, Ltd., 2012:147-58.
5. Wood EM, Ang AL, Bisht A, et al. International haemovigilance: what have we learned and what do we need to do next? *Transfus Med* 2019;29:221-30.
6. de Vries RR, Faber JC, Strengers PF, et al. Haemovigilance: an effective tool for improving transfusion practice. *Vox Sang* 2011;100:60-7.
7. World Health Organization. *A Guide to Establishing a National Haemovigilance System*. 2016. Available online: <https://apps.who.int/iris/handle/10665/250233> (Accessed 03 September 2021)
8. Wiersum-Osselton JC, Wood E, Bolton-Maggs PHB, et al. Definitions in haemovigilance: guiding principles and current state of development of international reference definitions. *ISBT Science Series*. 2014;9:91-7.
9. ISBT working party on haemovigilance. Proposed standard definitions for surveillance of non-infectious adverse transfusion reactions. July 2011. Available online: <https://www.isbtweb.org/resource/proposeddefinitionssurveillancenoninfectiousadversereactionshaemovigilance.html> (Accessed 10 September 2021)



10. Noel L, Debeir J, Cosson A. The French haemovigilance system. *Vox Sang* 1998;74 Suppl 2:441-5.
11. Schreiber GB, Busch MP, Kleinman SH, et al. The risk of transfusion-transmitted viral infections. The Retrovirus Epidemiology Donor Study. *N Engl J Med* 1996;334:1685-90.
12. Bolton-Maggs PHB, Watt A. Transfusion errors - can they be eliminated? *Br J Haematol* 2020;189:9-20.
13. European Commission Directorate-General for Health and Food Safety. Summary of the 2020 annual reporting of serious adverse reactions and events for blood and blood components. 2021. Available online: [https://ec.europa.eu/health/latest-updates/summary-2020-annual-reporting-serious-adverse-reactions-and-events-blood-and-blood-components-2021-11-08\\_en](https://ec.europa.eu/health/latest-updates/summary-2020-annual-reporting-serious-adverse-reactions-and-events-blood-and-blood-components-2021-11-08_en) (Accessed 25 November 2021)
14. Callum JL, Kaplan HS, Merkley LL, et al. Reporting of near-miss events for transfusion medicine: improving transfusion safety. *Transfusion* 2001;41:1204-11.
15. Pirie L, McClelland DB, Franklin IM, et al. The EU optimal blood use project. *Transfus Clin Biol* 2007;14:499-503.
16. World Health Organization. Aide-Mémoire for ministries of health: National Haemovigilance System. 2015. Available online: <https://apps.who.int/iris/handle/10665/340564> (Accessed 12 November 2021)
17. Commission directive 2005/61/EC implementing Directive 2002/98/EC of the European Parliament and of the Council as regards traceability requirements and notification of serious adverse reactions and events. 2005. Available online: <http://data.europa.eu/eli/dir/2005/61/oj> (Accessed 10 September 2021)
18. Boysen PG 2nd. Just culture: a foundation for balanced accountability and patient safety. *Ochsner J* 2013;13:400-6.
19. Offergeld R, Hamouda O, Burger R. Epidemiological Data - an Important Part of the Hemovigilance System. *Transfus Med Hemother* 2010;37:125-30.
20. Whitaker BI, Belov A, Anderson SA. Progress in US hemovigilance: can we still learn from others? *Transfusion* 2019;59:433-6.
21. World Health Organization. Blood safety and availability. 2020. Available online: <https://www.who.int/news-room/fact-sheets/detail/blood-safety-and-availability> (Accessed 12 October 2021)
22. Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC. 2003. Available online: <http://data.europa.eu/eli/dir/2002/98/oj> (Accessed 4 October 2021)
23. Wiersum-Osselton JC. Hemovigilance: is it making a difference to safety in the transfusion chain? 2013.
24. Kanagasabai U, Selenic D, Chevalier MS, et al. Evaluation of the WHO global database on blood safety. *Vox Sang* 2021;116:197-206.
25. Petrisli E, Carella C, Navarro A, et al. Vigilance for Medical Products of Human Origin-Progress on the Notify Library's Global Effort to Share Information and Learning. *Transplantation* 2021;105:1921-9.
26. Whitaker BI, Strong DM, Gandhi MJ, et al. Hemovigilance and the Notify Library. *Immunoematology* 2017;33:159-64.
27. Faber JC. Haemovigilance in Europe: the European Haemovigilance Network. *Transfus Clin Biol* 2001;8:285-90.
28. Faber JC. Work of the European Haemovigilance Network (EHN). *Transfus Clin Biol* 2004;11:2-10.
29. Faber JC, Nascimento F. Achievements Through Hemovigilance. In: de Vries RRP, Faber JC. editors. *Hemovigilance: An Effective Tool for Improving Transfusion Safety*. John Wiley and Sons, Ltd., 2012:281-301.
30. Stainsby D, Jones H, Asher D, et al. Serious hazards of transfusion: a decade of hemovigilance in the UK. *Transfus Med Rev* 2006;20:273-82.
31. Jenkins C, Ramírez-Arcos S, Goldman M, et al. Bacterial contamination in platelets: incremental improvements drive down but do not eliminate risk. *Transfusion* 2011;51:2555-65.
32. de Korte D, Curvers J, de Kort WL, et al. Effects of skin disinfection method, deviation bag, and bacterial screening on clinical safety of platelet transfusions in the Netherlands. *Transfusion* 2006;46:476-85.
33. Garraud O, Lozano M. Pathogen inactivation/reduction technologies for platelet transfusion: Where do we stand? *Transfus Clin Biol* 2018;25:165-71.
34. Sostin N, Hendrickson JE. Pediatric Hemovigilance and Adverse Transfusion Reactions. *Clin Lab Med* 2021;41:51-67.
35. Vossoughi S, Perez G, Whitaker BI, et al. Analysis of pediatric adverse reactions to transfusions. *Transfusion* 2018;58:60-9.
36. Narayan S (Ed), Poles D, on behalf of the Serious Hazards of Transfusion (SHOT) Steering Group. *The 2020 Annual SHOT Report*. 2021.

37. Vlaar AP, Juffermans NP. Transfusion-related acute lung injury: a clinical review. *Lancet* 2013;382:984-94.
38. Toy P, Gajic O, Bacchetti P, et al. Transfusion-related acute lung injury: incidence and risk factors. *Blood* 2012;119:1757-67.
39. Chapman CE, Williamson LM. National Blood Service TRALI Reduction Policies: Implementation and Effect. *Transfus Med Hemother* 2008;35:93-6.
40. Bolton-Maggs PHB. Serious hazards of transfusion - conference report: celebration of 20 years of UK haemovigilance. *Transfus Med* 2017;27:393-400.
41. Andreu G, Boudjedir K, Muller JY, et al. Analysis of Transfusion-Related Acute Lung Injury and Possible Transfusion-Related Acute Lung Injury Reported to the French Hemovigilance Network From 2007 to 2013. *Transfus Med Rev* 2018;32:16-27.
42. Müller MC, van Stein D, Binnekade JM, et al. Low-risk transfusion-related acute lung injury donor strategies and the impact on the onset of transfusion-related acute lung injury: a meta-analysis. *Transfusion* 2015;55:164-75.
43. Sachs UJ, Kauschat D, Bein G. White blood cell-reactive antibodies are undetectable in solvent/detergent plasma. *Transfusion* 2005;45:1628-31.
44. Busch MP, Bloch EM, Kleinman S. Prevention of transfusion-transmitted infections. *Blood* 2019;133:1854-64.
45. Godbey EA, Thibodeaux SR. Ensuring safety of the blood supply in the United States: Donor screening, testing, emerging pathogens, and pathogen inactivation. *Semin Hematol* 2019;56:229-35.
46. Zou S, Dorsey KA, Notari EP, et al. Prevalence, incidence, and residual risk of human immunodeficiency virus and hepatitis C virus infections among United States blood donors since the introduction of nucleic acid testing. *Transfusion* 2010;50:1495-504.
47. Cho JH, Rajbhandary S, van Buren NL, et al. The safety of COVID-19 convalescent plasma donation: A multi-institutional donor hemovigilance study. *Transfusion* 2021;61:2668-76.
48. Politis C, Papadaki M, Politi L, et al. Post-donation information and haemovigilance reporting for COVID-19 in Greece: Information supporting the absence of SARS-CoV-2 possible transmission through blood components. *Transfus Clin Biol* 2021;28:55-9.
49. Cappy P, Candotti D, Sauvage V, et al. No evidence of SARS-CoV-2 transfusion transmission despite RNA detection in blood donors showing symptoms after donation. *Blood* 2020;136:1888-91.
50. Corash L, Benjamin RJ. The role of hemovigilance and postmarketing studies when introducing innovation into transfusion medicine practice: the amotosalen-ultraviolet A pathogen reduction treatment model. *Transfusion* 2016;56 Suppl 1:S29-38.
51. Alvarado-Ramy F, Kuehnert MJ, Alonso-Echanove J, et al. A multistate cluster of red blood cell transfusion reactions associated with use of a leucocyte reduction filter. *Transfus Med* 2006;16:41-8.
52. Tormey CA, Stack G. The persistence and evanescence of blood group alloantibodies in men. *Transfusion* 2009;49:505-12.
53. Hauser RG, Hendrickson JE, Tormey CA. TRIX with treats: the considerable safety benefits of a transfusion medicine registry. *Transfusion* 2019;59:2489-92.
54. van Gammeren AJ, van den Bos AG, Som N, et al. A national Transfusion Register of Irregular Antibodies and Cross (X)-match Problems: TRIX, a 10-year analysis. *Transfusion* 2019;59:2559-66.
55. Transfusion and Transplantation Reactions In Patients Foundation. TRIP annual report 2014, extended version: Hemovigilance. 2015. Available online: <https://www.tripnet.nl/pages/nl/documents/TRIP2014Hemo-enBiovigilantie.pdf> (Accessed 07 September 2021)
56. Storch EK. Donor hemovigilance: a call to arms. *Transfusion* 2020;60:1115-7.
57. Wiersum-Osselton JC, Politis C, Richardson C, et al. Complications of blood donation reported to haemovigilance systems: analysis of eleven years of international surveillance. *Vox Sang* 2021;116:628-36.
58. Eder AF, Dy BA, Kennedy JM, et al. The American Red Cross donor hemovigilance program: complications of blood donation reported in 2006. *Transfusion* 2008;48:1809-19.
59. Newman BH. Vasovagal reaction rates and body weight: findings in high- and low-risk populations. *Transfusion* 2003;43:1084-8.
60. Eder AF, Hillyer CD, Dy BA, et al. Adverse reactions to allogeneic whole blood donation by 16- and 17-year-olds. *JAMA* 2008;299:2279-86.
61. Wiersum-Osselton JC, Marijt-van der Kreek T, Brand A, et al. Risk factors for complications in donors at first and repeat whole blood donation: a cohort study with assessment of the impact on donor return. *Blood Transfus* 2014;12 Suppl 1:s28-36.
62. Bravo M, Kamel H, Custer B, et al. Factors associated with fainting: before, during and after whole blood donation. *Vox Sang* 2011;101:303-12.

63. Land KJ, Townsend M, Goldman M, et al. International validation of harmonized definitions for complications of blood donations. *Transfusion* 2018;58:2589-95.
64. Goldman M, Land K, Robillard P, et al. Development of standard definitions for surveillance of complications related to blood donation. *Vox Sang* 2016;110:185-8.
65. Townsend M, Kamel H, Van Buren N, et al. Development and validation of donor adverse reaction severity grading tool: enhancing objective grade assignment to donor adverse events. *Transfusion* 2020;60:1231-42.
66. Ayob Y. Hemovigilance in developing countries. *Biologicals* 2010;38:91-6.
67. Sawadogo S, Nebie K, Millogo T, et al. Traceability of Blood Transfusions and Reporting of Adverse Reactions in Developing Countries: A Six-Year Postpilot Phase Experience in Burkina Faso. *Adv Hematol* 2018;2018:7938130.
68. Tagny CT, Mbanya D, Tapko JB, et al. Blood safety in Sub-Saharan Africa: a multi-factorial problem. *Transfusion* 2008;48:1256-61.
69. Musumari PM, Mbikayi SM, Srithanaviboonthai K, et al. Symptoms of acute transfusion reactions at a general referral hospital in Kinshasa, Democratic Republic of Congo: a cross-sectional study. *BMJ Open* 2021;11:e045081.
70. Owusu-Ofori AK, Owusu-Ofori SP, Bates I. Detection of adverse events of transfusion in a teaching hospital in Ghana. *Transfus Med* 2017;27:175-80.
71. Raval JS, Mazepa MA, Russell SL, et al. Passive reporting greatly underestimates the rate of transfusion-associated circulatory overload after platelet transfusion. *Vox Sang* 2015;108:387-92.
72. Hong H, Xiao W, Lazarus HM, et al. Detection of septic transfusion reactions to platelet transfusions by active and passive surveillance. *Blood* 2016;127:496-502.
73. Rogers MA, Rohde JM, Blumberg N. Haemovigilance of reactions associated with red blood cell transfusion: comparison across 17 Countries. *Vox Sang* 2016;110:266-77.
74. Hendrickson JE, Roubinian NH, Chowdhury D, et al. Incidence of transfusion reactions: a multicenter study utilizing systematic active surveillance and expert adjudication. *Transfusion* 2016;56:2587-96.
75. Tonino RPB, Larimer K, Eissen O, et al. Remote Patient Monitoring in Adults Receiving Transfusion or Infusion for Hematological Disorders Using the VitalPatch and accelerateIQ Monitoring System: Quantitative Feasibility Study. *JMIR Hum Factors* 2019;6:e15103.
76. Roubinian NH, Hendrickson JE, Triulzi DJ, et al. Incidence and clinical characteristics of transfusion-associated circulatory overload using an active surveillance algorithm. *Vox Sang* 2017;112:56-63.
77. Semple JW, Rebetz J, Kapur R. Transfusion-associated circulatory overload and transfusion-related acute lung injury. *Blood* 2019;133:1840-53.
78. Roubinian NH, Looney MR, Keating S, et al. Differentiating pulmonary transfusion reactions using recipient and transfusion factors. *Transfusion* 2017;57:1684-90.
79. Roubinian NH, Chowdhury D, Hendrickson JE, et al. NT-proBNP levels in the identification and classification of pulmonary transfusion reactions. *Transfusion* 2020;60:2548-56.
80. Klanderma RB, Bosboom JJ, Migdady Y, et al. Transfusion-associated circulatory overload-a systematic review of diagnostic biomarkers. *Transfusion* 2019;59:795-805.
81. National Cancer Institute Division of Cancer Treatment & Diagnosis. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. 2017. Available online: [https://ctep.cancer.gov/protocoldevelopment/electronic\\_applications/docs/ctcae\\_v5\\_quick\\_reference\\_5x7.pdf](https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf) (Accessed 07 September 2021)
82. World Health Organization. Conceptual Framework for the International Classification for Patient Safety Version 1.1: final technical report. 2009. Available online: <https://apps.who.int/iris/handle/10665/70882> (Accessed 10 September 2021)
83. World Health Organization. Patient safety incident reporting and learning systems: technical report and guidance. 2020. Available online: <https://apps.who.int/iris/handle/10665/334323> (Accessed 14 September 2021)
84. Menis M, Anderson SA, Forshee RA, et al. Transfusion-related acute lung injury and potential risk factors among the inpatient US elderly as recorded in Medicare claims data, during 2007 through 2011. *Transfusion* 2014;54:2182-93.
85. Edgren G, Hjalgrim H. Epidemiology of donors and recipients: lessons from the SCANDAT database. *Transfus Med* 2019;29 Suppl 1:6-12.
86. Edgren G, Hjalgrim H, Rostgaard K, et al. Transmission of Neurodegenerative Disorders Through Blood Transfusion: A Cohort Study. *Ann Intern Med* 2016;165:316-24.
87. Joint United Kingdom (UK) Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee. Guidelines for the Blood Transfusion Services

- in the United Kingdom, 8th edition 2013. Chapter 8: Evaluation of novel blood components, production processes and blood packs: generic protocols. 2013. Available online: <https://www.transfusionguidelines.org/red-book> (Accessed 14 September 2021)
88. Saadah NH, van Hout FMA, Schipperus MR, et al. Comparing transfusion reaction rates for various plasma types: a systematic review and meta-analysis/regression. *Transfusion* 2017;57:2104-14.
89. Sampson J, de Korte D. DEHP-plasticised PVC: relevance to blood services. *Transfus Med* 2011;21:73-83.
90. Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004, (2007). Available online: <http://data.europa.eu/eli/reg/2007/1394/oj> (Accessed 10 September 2021)

doi: 10.21037/aob-22-2

**Cite this article as:** de Jonge LL, Wiersum-Osselton JC, Bokhorst AG, Schipperus MR, Zwaginga JJ. Haemovigilance: current practices and future developments. *Ann Blood* 2022;7:23.