Received: 8 November 2022 | Revised: 5 March 2023 | Accepted: 6 March 2023

DOI: 10.1111/trf.17336

TRANSFUSION COMPLICATIONS

TRANSFUSION

Suspected adverse reactions reported for blood, blood components, and blood products in VigiBase

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Abstract

Introduction: Since being designated as medicines by World Health Organization (WHO), blood components are subject to pharmacovigilance reporting. Using VigiBase, the WHO global database of individual case safety reports (ICSRs), we characterized reports of adverse reactions for all blood products.

Study Design and Methods: ICSRs involving blood products as the suspected medicine in VigiBase between 1968 and 2021 were extracted. MedDRA preferred terms and the International Society of Blood Transfusion haemovigilance definitions were used to stratify adverse reactions. Descriptive statistics were used to characterize ICSR demographics.

Results: A total of 111,033 ICSRs containing 577,577 suspected adverse reactions with 6152 MedDRA preferred terms were reported for 34 blood products. There were 12,153 (10.9%) reports for blood components, 98,135 (88.4%) reports for plasma-derived medicines, and 745 (0.7%) reports for recombinant products. The majority of reports (21.0% and 19.7%, respectively) were from patients aged 45–64 and over 65 years. The Americas contributed the most ICSRs (49.7%). Top reported suspected adverse reactions were for the following MedDRA preferred terms: headache (3.5%), pyrexia (2.8%), chills (2.8%), dyspnoea (1.8%), and nausea (1.8%).

Conclusion: VigiBase already has a large number of reports on blood products. When compared to other existing haemovigilance databases, our study found reports from a broader range of countries and reporters. This may provide us with new perspectives, but for VigiBase to reach its full potential in haemovigilance some alterations in what is captured in reports are required.

KEYWORDS

adverse reactions, blood products, blood safety, haemovigilance, VigiBase

1 | INTRODUCTION

The monitoring, reporting, investigation, and analysis of adverse events (AEs) related to blood donation, processing, and transfusion, as well as taking steps to prevent their occurrence or recurrence, are all part of haemovigilance.[1–5] Blood establishments, regulatory agencies, and healthcare organizations can avoid or lessen harm to donors and patients by analyzing haemovigilance data.[2]

The World Health Organization (WHO) aspires, among other things, to provide strategic direction to international efforts to promote the implementation of effective hemovigilance systems in member states through the global framework to advance universal access to safe, efficient, and quality assured blood products.[6] Other international initiatives, coordinated by the International Haemovigilance Network (IHN) and the International Society for Blood Transfusion (ISBT), have sought to standardize and provide uniformity in case definitions and criteria for causality assessment (imputability criteria) across countries. The IHN established the International Surveillance of Transfusion-Associated Responses and Events (ISTARE), a database of adverse reactions (ARs) to transfusions and blood.[7,8] This library serves as a global vigilance database for medical products of human origin. According to recently analyzed data from 25 (mainly high-income) nations that reported to the IHN database, the rate of ARs to blood transfusion was 660 per 100,000 people, with approximately 3% of these being classified as serious. Transfusion-related mortality was 0.26 per 100,000 people.[8]

The WHO added blood components to the WHO Model List of Essential Medicines (EM) in 2013,[9] recognizing the critical role that blood products, particularly whole blood, red blood cells, platelets, and fresh frozen plasma, play in health. Many countries use the WHO EM list to prioritize and select medications to include in their national essential medicine lists (NEMLs). The WHO Collaborating Centre for International Drug Monitoring's (PIDM) VigiBase database contains global data on medicine safety known as individual case safety reports (ICSR).[10] This database, which collect information on medicine safety from over 145 national pharmacovigilance centers, and can be used in conjunction with other databases to find and evaluate safety data on blood, blood components, and blood products. It is unknown whether ICSRs for these products have been submitted to VigiBase. This study was conducted as a preliminary step in screening ICSRs in the global medicine safety database for blood safety issues.

The purpose of this study was to characterize and describe ICSRs for blood products of human origin received in the VigiBase. We analyzed reporting trends for suspected ARs from 1968 to 2021. We focused on reporting suspected ARs from blood products listed on the 2021 WHO Essential Medicines (WHO EM) List.

2 | METHODS

2.1 | Setting and data source

The WHO PIDM at the Uppsala Monitoring Center in Sweden's VigiBase global ICSR database served as the study's data source.[10] Over 28 million ICSRs were contained in VigiBase as of December 2021. Age, sex, suspected medicines, ARs and AEs, severity or seriousness, cause (or imputability), reporter type, and other pertinent information were recorded in each report. According to the hierarchical structures of the WHO Drug Dictionaries (WHO-DD and -DDE), the WHO Adverse Reaction Terminology (WHO-ART), the International Classification of Diseases (ICD), and the Medical Dictionary for Drug Regulatory Authorities (MedDRA®), codes are assigned to the reported drugs and ARs.

2.2 | Identification of blood product related ICSRs

All ICSRs involving blood products of human origin and recombinant products as suspected medicines, between 1968 and December 2021, were extracted from VigiBase. Blood products of human origin were defined using the WHO Anatomical Therapeutic Chemical (ATC) classification and the WHO EM List, 2021 (Table 1). Suspected duplicate reports were excluded from this study using the duplicate records identification and deletion function in Stata Statistics / Data Analysis software version 16.1. Reports with missing information regarding the name of the suspected medicine or adverse reactions were excluded.

2.3 | Characterization of AEs

For all blood products, we identified and described possible ARs and AEs using MedDRA preferred terms. We further specifically classified ARs and AEs for blood and blood components according to the AR cluster groups from the Haemovigilance Working Party (HWP) of the International Society for Blood Transfusion (ISBT).[11–13] These groups include allergic and anaphylactic reactions, febrile non-haemolytic transfusion reaction (FNHTR), haemolytic transfusion reaction (HTR), transfusion-associated

TABLE 1 Essential blood products of human origin on the 22st edition WHO Model List of Essential Medicines (2021).

Type		Product	ATC code
Blood and blood components		Whole blood	B05AX01, B05AX02, B05AX03, B02BD10
		Red blood cells	
		Platelets	
		Fresh-frozen plasma	
Plasma derived medicines	Human immunoglobulins	Anti-D immunoglobulin	J06BB01, J06BB02, J06BB04, J06BB05
		Anti-rabies immunoglobulin	
		Anti-tetanus immunoglobulin	
		Normal immunoglobulin	B05AA01, B05AA02
	Blood coagulation factors	Coagulation factor VIII	B02BB01, B01AB02, B02BD01, B02BD02, B02BD04, B02BD05, B02BD07, B02BD30
		Coagulation factor IX	
Recombinant alternatives[a]	Blood coagulation factors[a]	Coagulation factor VIII	B02BD02, B02BD04
		Coagulation factor IX	

[a]Not part of the 21st edition WHO Model List of Essential Medicines (2021).

circulatory overload (ta-GVHD). The category "other" was used to classify all ARs and AEs that could not be categorized using the categories mentioned above. According to the International Council for Harmonization's (ICH) E2A Clinical Safety Data Management: Definitions, the Standards for Expedited Reporting, and the ICH E2D Post Approval Safety Data Management guidelines,[14] the seriousness of all reactions and events was categorized, and the following categories are included:

- death,
- life-threatening;
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability or incapacity;
- results in a congenital anomaly (birth defect); or
- is otherwise "medically significant".

2.4 | Covariates

Data on sex, age, WHO geographic region (Africa, the Americas, Southeast Asia, Europe, Eastern Mediterranean, and Western Pacific), reporter type, WHO EM listing, and report type were retrieved from each ICSR. Age ranges were provided by VigiBase (under 2, 2–17, 18–44, 45–64, and over 65). The VigiBase list of reporter types (healthcare professionals, consumers, non-healthcare professionals, and others) and report types (spontaneous, report from study, post-marketing surveillance (PMS) / specific monitoring, and others) were used.

2.5 | Data analysis

The reported ARs at the medicine-AR pair level were quantified using descriptive statistics. One ICSR may be counted more than once if it contains several suspected ARs. ARs were divided into different groups based on sex, age, reporting region, seriousness, and adverse reaction outcomes. The number of ICSRs in the sub-group was divided by the total number of reported ARs within the stratum to determine the proportions of ICSRs by category of AR. The proportions of blood and blood components, plasma-derived medicines, and recombinant products were determined by dividing the number of ICSRs for each of the product types in a specific period by the total number of ICSRs within the product grouping. This was done to demonstrate the trends in reporting through time.

3 | RESULTS

Of the 28 million reports entered into VigiBase by December 2021, 186, 545 ICSRs from blood products of human origin were observed. Due to duplicates or the lack of information regarding ARs or AEs, we excluded 75,512 ICSRs from the analysis. Following this, 111,033 ICSRs (representing 577,577 medicine—AR pairs) were identified with 6152 unique MedDRA "preferred terms" from 34 blood products of human origin as suspected medicines. These reports included 12,153 (10.9%) reports on blood and blood components, 98,135 (88.4%) reports from plasma-derived medicines, and 745 (0.7%) reports on recombinant products.

TABLE 2 Baseline characteristics of the identified Individual Case Safety Reports (ICSRs).

Characteristic	Total ICSRs ($n = 111{,}033$)	Blood and blood components $n = 12{,}153$ (10.9%)	Plasma derived medicines $n = 98{,}135$ (88.4%)	Recombinant alternatives $n = 745$ (0.7%)
Sex *n*, (%)				
Female	59,796 (53.9)	6204 (51.0)	53,543 (54.6)	49 (6.6)
Male	44,125 (39.7)	5549 (45.7)	38,021 (38.7)	555 (74.5)
Unknown or missing	7112 (6.4)	400 (3.3)	6571 (6.7)	141 (18.9)
Age *n*, (%)				
<2	1976 (1.8)	191 (1.6)	1735 (1.8)	50 (6.7)
2–17	9673 (8.7)	839 (6.9)	8671 (8.8)	163 (21.9)
18–44	18,495 (16.7)	2446 (20.1)	15,850 (16.2)	199 (26.7)
45–64	23,341 (21.0)	2867 (23.6)	20,398 (20.8)	76 (10.2)
≥65	21,922 (19.7)	4192 (34.5)	17,685 (18.0)	45 (6.0)
Unknown or missing	35,626 (32.1)	1618 (13.3)	33,796 (34.4)	212 (28.5)
Region *n*, (%)				
Africa	395 (0.4)	264 (2.2)	130 (0.1)	1 (0.1)
The Americas	55,198 (49.7)	1150 (9.5)	53,572 (54.9)	476 (63.9)
South East Asia	3269 (2.9)	1586 (13.1)	1680 (0.8)	3 (0.4)
Europe	37,536 (33.8)	5434 (44.7)	31,849 (32.8)	253 (34.0)
Eastern Mediterranean	456 (0.4)	135 (1.1)	321 (0.3)	0 (0.0)
Western Pacific	14,179 (12.8)	3584 (29.5)	10,583 (11.1)	12 (1.6)
Reporter *n*, (%)				
Healthcare professionals	77,309 (69.6)	11,448 (94.2)	65,288 (66.5)	573 (76.9)
Consumer or non-healthcare professional	16,953 (15.3)	98 (0.8)	16,719 (17.0)	136 (18.3)
Unknown or missing	16,771 (15.1)	607 (5.0)	16,128 (16.4)	36 (4.8)
EM list *n*, (%)				
EM—listed	95,193 (85.7)	12,153 (100.0)	83,040 (84.6)	0 (0.0)
Non—EM—listed	15,840 (14.3)	0 (0.0)	15,095 (15.4)	745 (100.0)
Source *n*, (%)				
Spontaneous	90,468 (81.5)	11,373 (93.6)	78,580 (80.1)	515 (69.1)
Report from study	15,830 (14.3)	376 (3.1)	15,277 (15.6)	177 (23.8)
PMS/Special monitoring	717 (0.6)	381 (3.1)	328 (0.3)	8 (1.1)
Other	294 (0.3)	22 (0.2)	254 (0.2)	18 (2.4)
Unknown	3724 (3.4)	1 (0.0)	3696 (3.8)	27 (3.6)

Table 2 displays the ICSRs' baseline characteristics. Of the ICSRs, 53.9% were female, 39.7% were male, and 6.4% had missing or unknown sex information. The patient age groups with the highest number of ICSRs were those aged 45–64 years (21.0% of identified ICSRs) and over 65 years (19.7%). A small number of ICSRs were observed for patients aged less than 2 years and 2–17 years (1.8% and 8.7%, respectively).

There were several regional differences in both the frequency and proportion of ICSRs. The Americas (49.7%), followed by Europe (33.8%), contributed the most ICSRs. Less than 3.0% of all identified ICSRs were contributed by the regions of Africa, South East Asia, and the Eastern Mediterranean. The annual ICSR contribution reported from the various WHO regions was typically between 0.5% and 5.0% of the total ICSRs reported from the same WHO region in that same year (Figure 1). The Western Pacific (29.5%) and European (44.7%) regions had the largest proportion of ICSRs for blood and blood components. Americas and Europe had the highest number of ICSRs from plasma-derived medicines (54.9% and 32.8%, respectively; Table 2).

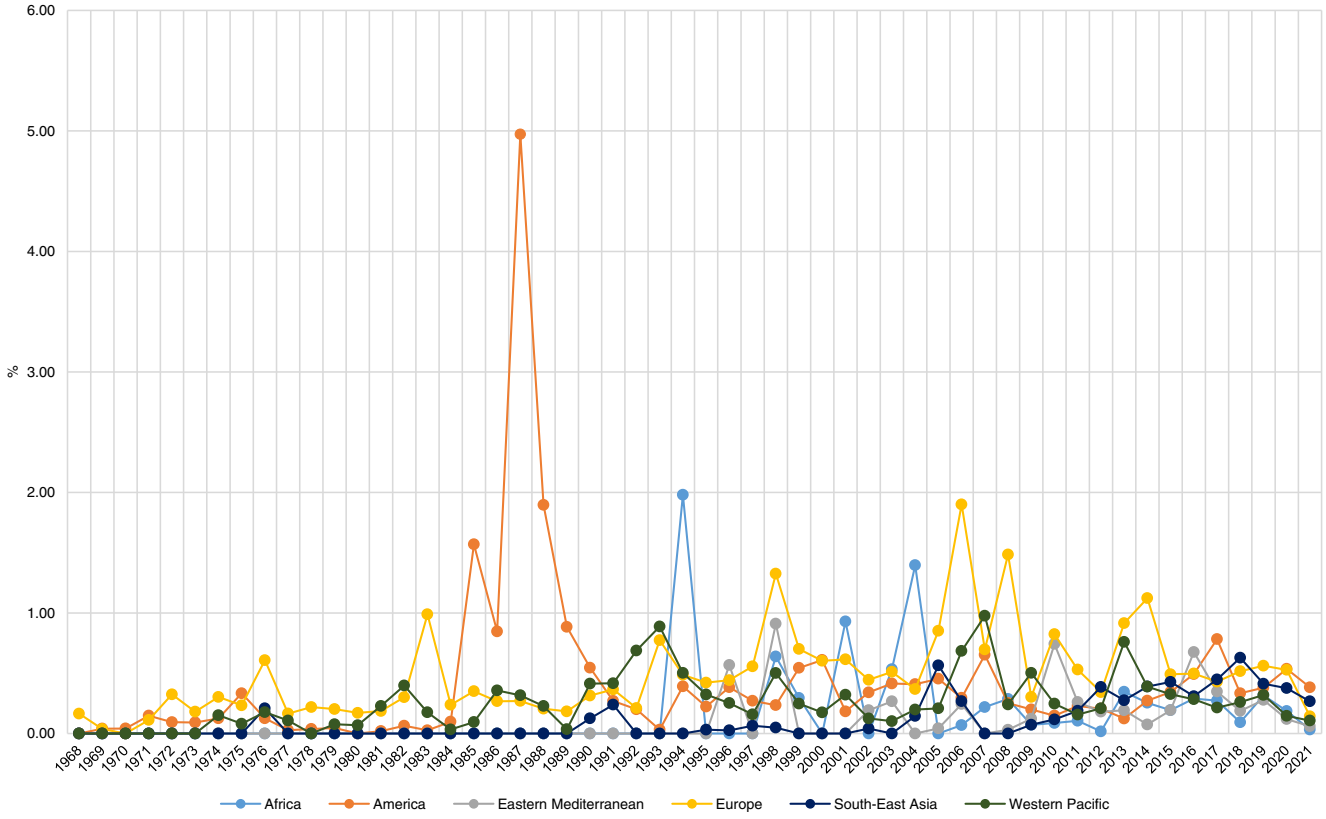

FIGURE 1 Trend of reporting of Individual Case Safety Reports (ICSRs) from different WHO regions expressed as a percent of the total number of ICSRs from that WHO region in VigiBase database, 1968–2021. [Color figure can be viewed at wileyonlinelibrary.com]

The majority of ICSRs (69.6%) were submitted by healthcare professionals, while 15.3% were from consumers or non-healthcare professionals and 15.1% were unknown. We noted that 85.7% of the reported blood products were listed as EMs on the WHO Model list, and that plasma-derived medicines, blood, and blood components had the highest percentages of EMs within their product group, at 82.9% and 12.8%, respectively.

The most frequently reported suspected ARs were headache (3.5%), pyrexia (2.8%), chills (2.8%), dyspnea (1.8%), nausea (1.8%), fatigue (1.8%), pruritus (1.7%), urticaria (1.5%), rash (1.5%), sinusitis (1.2%), vomiting (1.2%), and malaise (1.0%). (Figure 2). Just over a fifth (22.7%) of all ARs recorded for all blood products in VigiBase were triggered by these preferred terms. We observed that three blood products—human immunoglobulin normal (66.6%), albumin (7.4%), and factor viii (antihaemophilic factor)—accounted for more than 75% of all suspected ARs (Figure SF1).

Most ARs among blood and blood components were for the allergic and anaphylactic reactions cluster (25.4%) (Figure 3). In addition, febrile non-haemolytic reactions (15.9%), TACO (12.5%), and haemolytic transfusion reactions (11.8%) were frequently reported AR clusters among blood and blood components. We also noted a significant number of AEs and ARs (13.6%) that we categorized as "other reactions" since they did not fit into any of the currently known cluster groupings. Malaise (19.0%), hyperhidrosis (11.3%), tremor (2.6%), and bradycardia (2.2%) were the top reported suspected reactions among these "other reactions" (Figure 4). Of all reported ARs and AEs, 25.8% were designated as serious, comprising reactions that resulted in prolonged hospitalization (18.8%), death (3.6%), incapacitating or disabling (0.6%), and life-threatening (2.9%).

The AR and AE spectrum observed among all blood products in our study was extensive; a total of 6152 distinct preferred terms were identified. In addition to hyperhidrosis ($n = 2624$), hypokalaemia ($n = 119$), hypocalcaemia ($n = 47$), post-transfusion purpura ($n = 168$), and transfusion-associated graft versus host disease ($n = 169$), we also noted the presence of a few infrequently reported TTIs, including Listeriosis ($n = 7$) and *Pneumocystis jirovecii* ($n = 67$).

When the trend of reporting for ICSRs from blood products was expressed as a percentage of the total number of ICSRs in VigiBase in a given year, the percentage of blood products rose steadily from around 0.3% before 1988 to around 0.5% after 2005. (Figure 5). The percentage of ICSRs for plasma-derived medicines among all

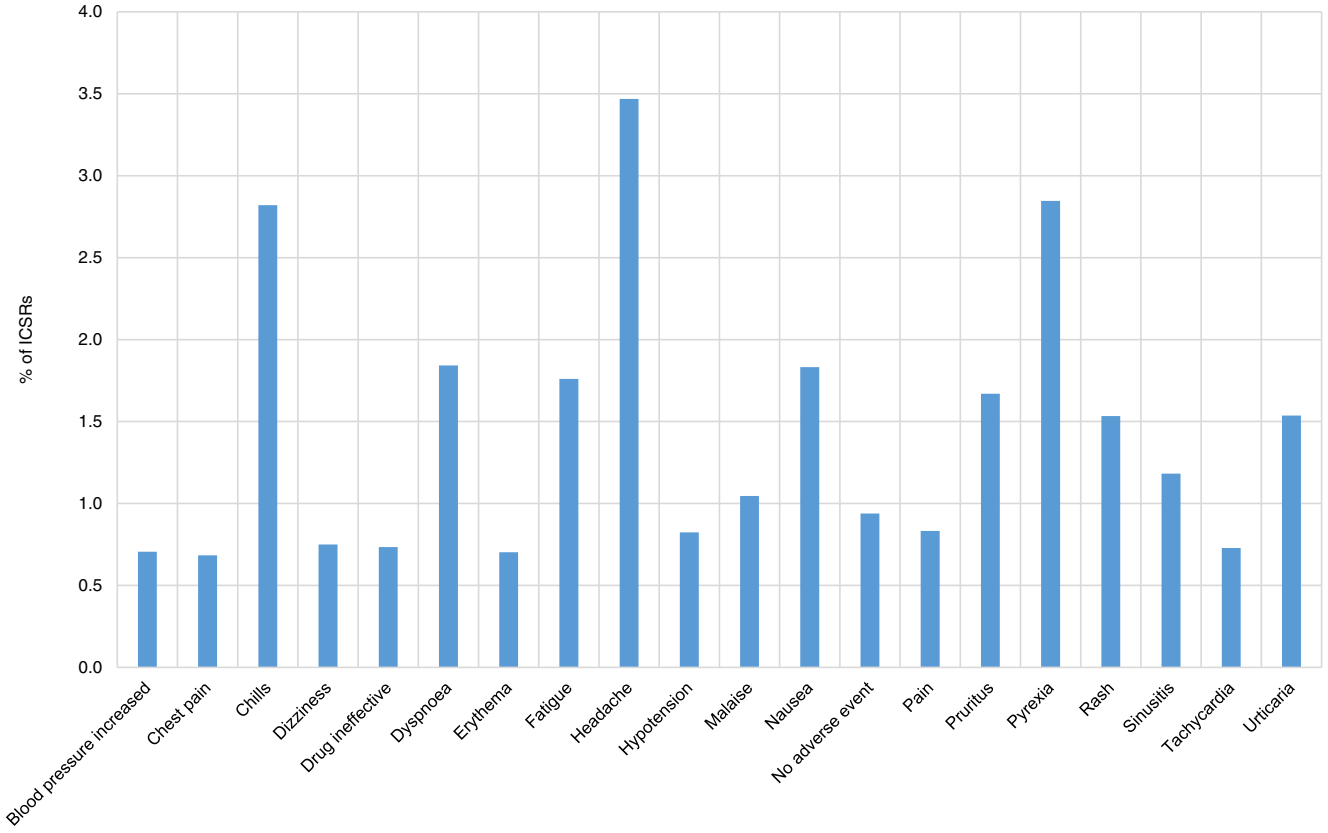

FIGURE 2 Percent distribution of the top MedDRA terms (adverse reactions) reported for blood products of human origin in VigiBase, 1968–2021. ICSRs, Individual Case Safety Reports. [Color figure can be viewed at wileyonlinelibrary.com]

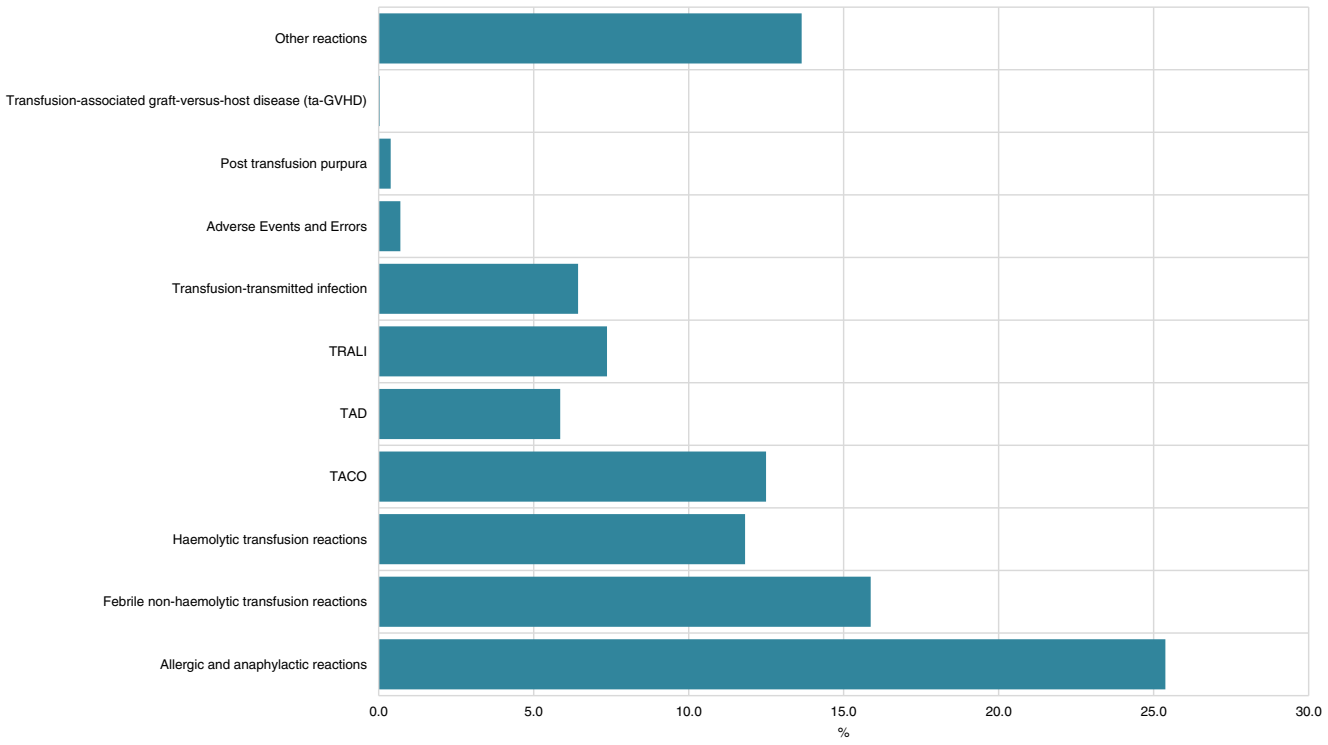

FIGURE 3 Distribution of adverse reactions and adverse events stratified according the International Society for Blood Transfusion defined adverse reaction and adverse event clusters for blood and blood components recorded in the VigiBase database, 1968–2021. [Color figure can be viewed at wileyonlinelibrary.com]

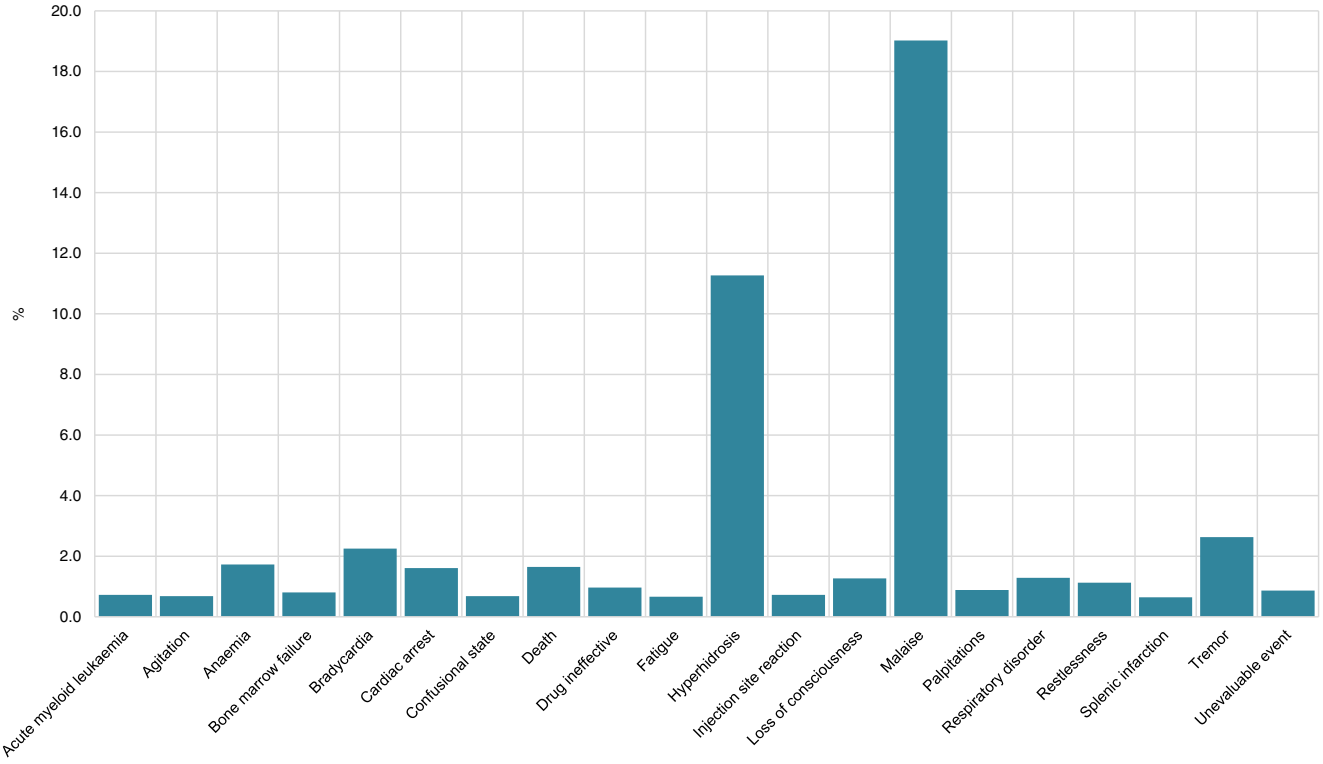

FIGURE 4 Percent distribution of the top MedDRA terms (adverse reactions) reported under the 'Other Reactions' cluster for blood and blood components in VigiBase, 1968–2021. [Color figure can be viewed at wileyonlinelibrary.com]

ICSRs for blood products increased over time, beginning with a slow annual increase from around 0.1 to 2.0% between 1968 and 2010, and then increasing sharply after 2011 from around 2.0% to over 8% in 2017. (Figure 6). Analysis of all blood product reports entered in VigiBase revealed that more than half of all blood product reports were entered during the most recent decade, particularly after 2010, with a total of 88,272 reports entered from 2010 to 2021.

4 | DISCUSSION

We describe and characterizecharacterised the ICSRs of ARs for blood products of human origin in VigiBase. The most relevant finding of this study is that VigiBase already has a large number of reports for blood products of human origin that have been collected and recorded from 1968 to 2021. Our findings revealed a broader spectrum of ARs and AEs from use of blood products reported by more countries and reporters compared to other databases collecting haemovigilance data. We also found that while the trend of reporting of blood products increased since 1968 from approximately 0.1% to 0.4% of all ICSRs in VigiBase, blood products of human origin contributed a very small proportion of all the ICSRs in VigiBase.

4.1 | Legislation and reporting practices

We found that only 0.5% of the 28 million reports in VigiBase concerned blood products. Regardless, the total absolute number of reports and ARs/AEs observed was at least double that of other studies.[8,15,16] When compared to the ISTARE and the National Healthcare Safety Network (NHSN) Haemovigilance Module databases, the reports in our study were contributed by over 145 countries over a longer period and with more member country contributions. Furthermore, in our study, ICSRs listed more products. Nonetheless, our findings suggest that there is significant underreporting of ARs and AEs from blood products in VigiBase, and the reports in our study may only represent a small proportion of ARs and AEs associated with blood product use. ARs and AEs from blood products are underreported in various national haemovigilance schemes.[4,8,17] Many countries use passive reporting systems to collect ARs and AEs, which leads to underreporting.[17–19] The extent of AR and AE underreporting varies across countries, possibly due to widely disparate practices.[8,17]

The variability in the reporting of ARs and AEs from blood products observed in different WHO regions could be attributed to the use of different surveillance systems with different legal and mandatory reporting requirements[8] or using different case definitions or criteria to

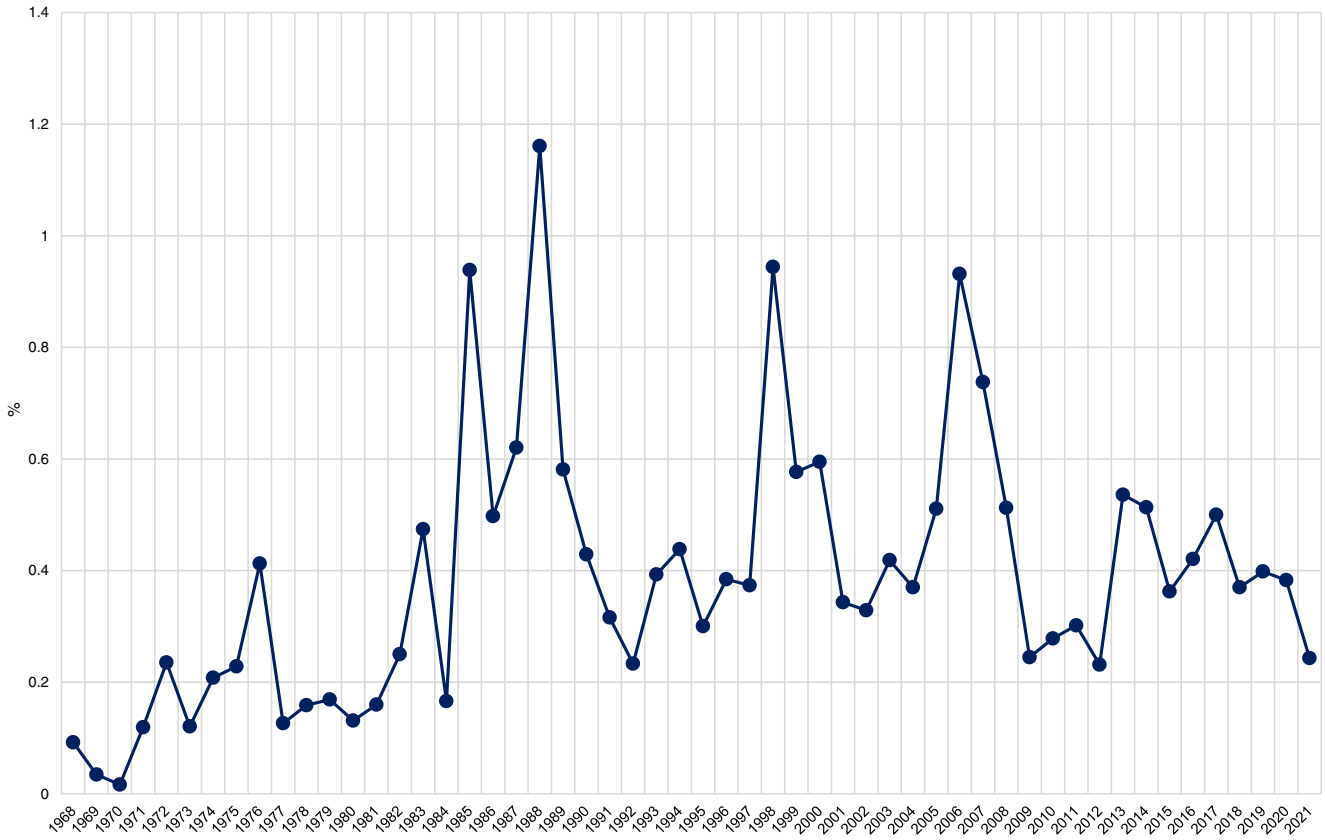

FIGURE 5 Trend of reporting of Individual Case Safety Reports (ICSRs) from blood products expressed as a percent of the total number of ICSRs in VigiBase database, 1968–2021. [Color figure can be viewed at wileyonlinelibrary.com]

determine ARs, differences in patient populations,[20] non-standard definitions for at-risk populations, and the use of different product formulations. Some countries report all reactions, while others only report serious reactions; for example, New Zealand reports both serious and non-serious reactions,[20] while Germany only reports serious ARs.[21] This applies to all medicine groups and may have an impact on the reporting of blood product events to VigiBase.

We observed a high number of ICSRs related to blood and blood components from the Western Pacific region, with only the European region having a higher proportion of such ICSRs. This is because of legislative requirements for reporting ARs and AEs from the use of blood and blood components in Europe and Western Pacific countries such as Japan and Australia.[8,22] European countries have common legislation on quality and safety standards for blood products, including traceability requirements and notifications of serious ARs and events.[8] The low proportion of ICSRs involving all blood products observed in Africa and the Eastern Mediterranean regions could be attributed to a number of these regions joining the WHO PIDM much later than other regions, as well as relatively slow progress in establishing national haemovigilance systems.[4,5] Haemovigilance has also lacked the same focused advocacy and technical support provided by the WHO PIDM, which appears to have contributed to the slow pace of development of Global Supply national haemovigilance centres, particularly in low- and middle-income countries.[23]

4.2 | Inequitable supply of plasma-derived medicines

Our findings revealed considerable variation in the types of blood products for which ARs/AEs were reported across WHO regions. Human normal immunoglobulin, albumin, coagulation factor viii, red blood cells, and anti-d immunoglobulin accounted for nearly three-quarters of all suspected ARs, and AEs reported. Human normal immunoglobulin and albumin, for example, have been reported to be in high demand in the Americas and Europe in particular.[24,25] The supply, distribution, and availability of these products have also been widely reported to be limited to high-income countries in the same regions.[24,25] The Americas region produced most reports containing human normal immunoglobulin,

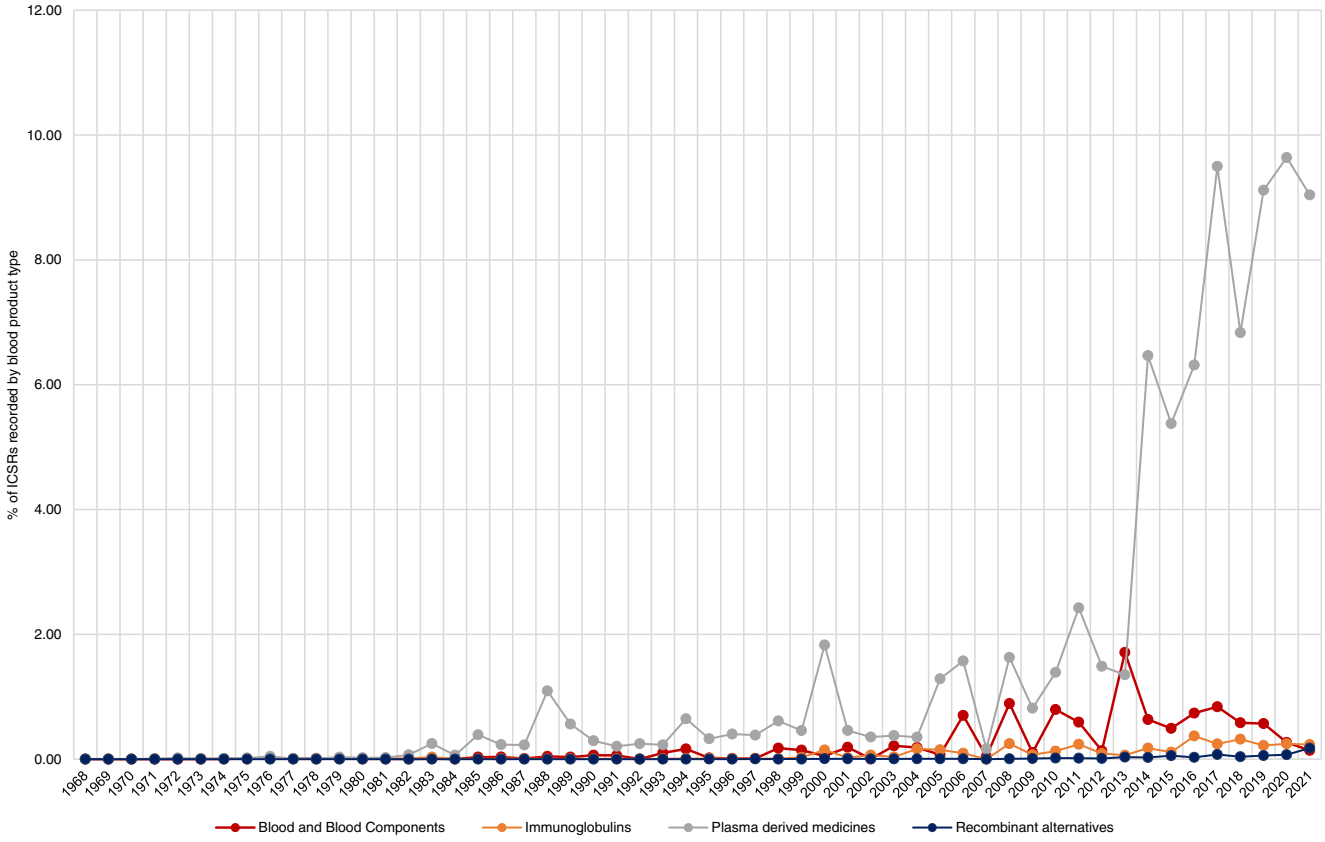

FIGURE 6 Trend of reporting of Individual Case Safety Reports from blood products expressed as a percent of the blood product group from 1968 to 2021. [Color figure can be viewed at wileyonlinelibrary.com]

albumin, and coagulation factor viii as suspected medicines. The current study's findings could be result of a disparity in supply and inequitable distribution of plasma-derived medicines.

4.3 | Patient and consumer reporting

VigiBase is the world's largest repository of safety information and ICSRs from over 145 countries. It now includes patient and consumer reporting as well as information on medicine safety. This makes VigiBase a potentially useful database for many countries that may not be using it as part of their blood product safety surveillance program. In our study, consumer reporters contributed 15% of the reports, which is not typical in haemovigilance reporting. The inclusion of consumer reporting in pharmacovigilance has been found to increase the overall number of reports in pharmacovigilance databases.[26] These additional data from patient and consumer reporting provides complementary information to healthcare professional data, such as the effects on quality of life.[26] VigiBase provides an opportunity for greater participation by patients and consumers in haemovigilance reporting, and the inclusion of their voices can help improve haemovigilance processes. It is important to note that when using data from patients or consumers, it must be verified or analyzed further by healthcare professionals.[26]

4.4 | Rare ARs and AEs

For reactions involving blood and blood components, we found that approximately 13.9% of the reactions fell into the category 'other.' ARs and AEs that could not be sorted into the AR clusters suggested by the IBST were placed in this category. Additionally, we observed some infrequently seen suspected AEs, such as hyperkalemia, hypocalcemia, PTP, and TA-GVHD, as well as infections like listeriosis and *Pneumocystis P. jirovecii*. These reports enhance VigiBase's value as a comprehensive source of information on ARs and AEs of blood products and allow for a more thorough quantitative analysis[8,27] along with the other helpful data it contains.

4.5 | Limitations of the study

Utilizing a comprehensive database like VigiBase makes it possible to record all ARs and AEs attributable to blood

transfusion, including "near-miss" incidents and transfusion errors that endanger the health and quality of life of the recipient. Despite its value, VigiBase primarily focuses on safety issues impacting transfusion recipients and does not take a comprehensive strategy to gathering safety data affecting the blood supply chain. It does not document blood donor ARs and AEs, denominators such as numbers of certain types of blood components issued and transfused, or numbers of recipients. We also noted cases of misreporting where conditions or consequences such as knee arthroplasty that are not actual ARs or AEs were recorded as ARs and AEs. Information on causality assessments is not available in all reports because of the diverse practices of reporting centers, which also use a range of different methods for assigning causality. We did not examine the causality of the reports or establish the incidence rates for all cases included in this study. Furthermore, UMC does not validate or verify the reports received in VigiBase.

An additional limitation is the use of different definitions by other international stakeholders in hemovigilance. The ISBT Working Party on Haemovigilance and other international stakeholders in the hemovigilance community have also agreed upon standard definitions, but VigiBase does not use them. One example is the ISBT Working Party's use of the terms "seriousness" and "severity" in VigiBase, as well as the application of the "seriousness/severity" categories.

The strength of our study is that we obtained information from the global ICSR database, which contains reports from many countries participating in the international pharmacovigilance program. Unfortunately, the likelihood that the reported event was caused by medicine varied between reports. Some countries, such as the United States, collect only suspected ARs and AEs with the possibility of a causal relationship between medicine and the reported event. As a result, the findings of this study should be regarded as hypothesis-generating, and further research is required to characterize and confirm the potential risk of using blood products in patients and blood donors.

5 | CONCLUSION

This study demonstrated the broad range and high number of ARs and AEs associated with the use of blood products in VigiBase from 1968 to 2021. We found a rather high contribution of ICSRs from many countries and reporters, which is higher than any other existing hemovigilance data-collection database. We recognized VigiBase's potential as an important source of safety data for blood product use, such as providing alternative insights on ARs and AEs, including the occurrence of rare ARs. This data and information can be used to augment safety data, analyze reports, and identify and prioritize potential blood product safety issues. However, considerable effort is required at the local, national, and international levels to raise awareness among users of blood products and healthcare professionals of the importance of considering, identifying, and reporting cases of suspected ARs and AEs associated with the use of blood products of human origin, particularly in countries from regions where very few reports were observed (Africa, South-East Asia, and Eastern Mediterranean). More research is needed to characterize the rates and incidences of ARs and AEs for the various product groups in this study.

FUNDING INFORMATION

No funding was received for this study.

CONFLICT OF INTEREST STATEMENT

The authors have disclosed no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Samukange WT, Lu T-A, Souverein PC, Gardarsdottir H, Mantel-Teeuwisse AK. Suspected adverse reactions reported for blood, blood components, and blood products in VigiBase. Transfusion. 2023;63(5):982–92. https://doi.org/10.1111/trf.17336