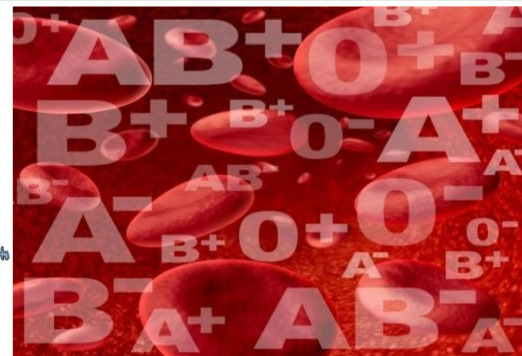
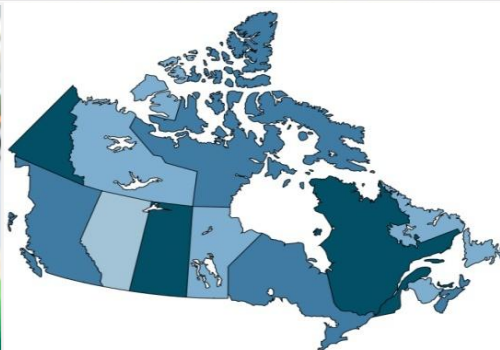


TRANSFUSION TRANSMITTED INJURIES SURVEILLANCE SYSTEM

2006-2012 REPORT



PROTECTING CANADIANS FROM ILLNESS



Public Health
Agency of Canada

Agence de la santé
publique du Canada

Canada

**TO PROMOTE AND PROTECT THE HEALTH OF CANADIANS THROUGH LEADERSHIP,
PARTNERSHIP, INNOVATION AND ACTION IN PUBLIC HEALTH.**

—Public Health Agency of Canada

Également disponible en français sous le titre :

Système de surveillance des incidents transfusionnels : Rapport pour 2006-2012

Acknowledgments: The development of the Transfusion Transmitted Injuries Surveillance System (TTISS) would not have been possible without the collaborative support and continued commitment of the provincial/territorial Blood Coordinating Offices, transfusion medicine staff at participating hospitals, the Canadian Blood Services and Héma-Québec. Their dedication to reducing adverse transfusion reactions/injuries and increasing patient safety has led to the collection and analysis of the 2006-2012 TTISS data.

N.B. This document must be cited as the source for any information extracted and used from it.

Suggested citation: Public Health Agency of Canada. *Transfusion Transmitted Injuries Surveillance System (TTISS): 2006-2012 Report*. Centre for Communicable Diseases and Infection Control, Public Health Agency of Canada, 2014.

To obtain additional copies, please contact:

Centre for Communicable Diseases and Infection Control
Public Health Agency of Canada
Tunney's Pasture, AL 0602B
Ottawa, Ontario, K1A 0K9
E-mail: ccdic-clmti@phac-aspc.gc.ca

This publication can be made available in alternative formats upon request.

© Her Majesty the Queen in Right of Canada, as represented by the Minister of Health, 2014
ISSN 2368-4186

Publication date: September 2014

This publication may be reproduced for personal or internal use only without permission provided the source is fully acknowledged. However, multiple copy reproduction of this publication in whole or in part for purposes of resale or redistribution requires the prior written permission from the Minister of Public Works and Government Services Canada, Ottawa, Ontario K1A 0S5 or copyright.droitdauteur@pwgsc.gc.ca.

Information to the reader of 2006-2012 transfusion transmitted injuries surveillance system (TTISS) report

The Centre for Communicable Diseases and Infection Control (CCDIC) of the Public Health Agency of Canada (the Agency) is pleased to present the 2006-2012 *Transfusion Transmitted Injuries Surveillance System (TTISS) Report*. This report presents transfusion transmitted injuries surveillance data submitted by Canadian hospitals participating in the Transfusion Transmitted Injuries Surveillance System (TTISS).

The TTISS is a pan-Canadian surveillance system established by the Agency to capture non-nominal data on adverse transfusion reactions in Canadian hospitals providing transfusion services. The overarching goal of the TTISS is to improve patient safety in Canadian hospitals.

CCDIC in partnership with participating hospitals is responsible for the collection, management and analysis of the TTISS data, as well as the production of reports summarizing key findings. CCDIC supports the use of these data to inform public health and policy action. In addition, CCDIC supports the Agency's ongoing commitment to improving data quality, and to defining and setting surveillance standards.

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY	1
2. INTRODUCTION.....	2
3. METHODS	3
a. Data Collection and Reporting	3
b. Data Reconciliation and Validation.....	3
c. Denominator Data and Data Reconciliation and Validation	3
4. PROGRAM COVERAGE	5
5. RESULTS	7
a. Reported Adverse Reactions	7
b. Adverse reactions related to transfusion of blood components	9
c. Adverse reactions related to transfusion of blood products	11
d. Strength of the Relationship to Transfusion	12
e. Adverse Reactions Related to Transfusion of Blood Components	13
f. Adverse Reactions Related to Transfusion of Blood Products	14
g. Rate of Reported Adverse Reactions.....	15
h. Severity of Reported Adverse Reactions.....	19
i. Severe and life-threatening reactions related to transfusion of blood components ..	20
j. Severe and life-threatening reactions related to transfusion of blood products.....	21
k. Outcomes of Reported Adverse Reactions	23
l. Deaths	25
6. SUMMARY OF SELECTED REACTIONS.....	26
a. Transfusion-Associated Circulatory Overload – TACO.....	26
b. Transfusion-Related Acute Lung Injury (TRALI).....	28
c. Possible TRALI	29
d. Acute Hemolytic Reactions	31
e. Delayed Hemolytic Reactions	Error! Bookmark not defined.
f. Severe Allergic/Anaphylactic/Anaphylactoid Reactions.....	32
g. Bacterial Infections.....	33
h. Hypotensive Reactions	34
i. Aseptic Meningitis	35
7. COMMENTARY	37
8. APPENDICES	39
a. Appendix 1: Total units of blood components transfused by hospitals of the TTISS network, by province/territory, 2006 to 2012.....	39
b. Appendix 2: Comparison of the range of annual rates (per 100,000 units of blood components transfused/issued) during 2006-2012 for major adverse reactions associated with blood transfusion, by country.	40

1. EXECUTIVE SUMMARY

This report summarizes adverse events related to transfusion of blood components and blood products reported from Canadian healthcare settings as part of the Transfusion Transmitted Injuries Surveillance System (TTISS) from 2006 to 2012. During this time period, 80.4% of blood component transfusions occurred at hospitals participating in TTISS.

From 2006 to 2012, a total of 3,957 adverse reactions were reported to the TTISS, excluding minor allergic reactions. Of these, 2,920 (73.8%) were related to transfusion of blood components (red blood cells, granulocytes, platelets, plasma, and cryoprecipitates) and 1,036 (26.2%) were from transfusion of blood products (albumin, immune globulin, coagulation factors, etc.). There was one case where the information about the blood component/blood product used was missing.

Among reactions related to transfusion of blood components, four types of reactions accounted for almost three quarters of reports: transfusion-associated circulatory overload (TACO; n = 1,242, 42.5%), severe allergic/anaphylactic/anaphylactoid reactions (n=411; 14.1%), hypotensive reactions (n=298; 10.2%) and delayed hemolytic reactions (n=211; 7.2%). Among those related to transfusion of blood products, almost one half were IVIG (intravenous immunoglobulin) headache (n = 295; 28.5%) or delayed hemolytic reaction (n = 175; 16.9%).

Overall, 1,835 reactions were severe or life-threatening (1,505 related to transfusion of blood components and 329 related to transfusion of blood products). Among 1,693 severe or life-threatening cases where patient outcome data were available, the majority (1,573; 92.9%) resulted in minor or no sequelae and 79 (4.7%) resulted in major or long term sequelae. From 2006 to 2012, a total of 41 deaths were reported to be definitely (n=1), probably (n=11) or possibly (n=29) related to transfusion, of which over one half were classified as TACO (n=13) or possible transfusion-related acute lung injury (TRALI; n=12).

Definite and probable cases of death were the most likely to have resulted from transfusion – i.e. the patient would not have died if they had not received transfusion. At a rate of one case for every 8,175,504 units of blood components transfused, death definitely attributable to transfusion of blood components was extremely rare relative to the rate for any adverse transfusion reaction reported (35.7 per 100,000 units of blood components transfused). In comparison, reactions determined to be definitely related to transfusion occurred at a rate of 5.4 per 100,000 units of blood components transfused. Additionally, it is reassuring that the majority of all reactions reported (96%), particularly those that were classified as severe and life-threatening (93%), resulted in minor or no sequelae as a long term outcome.

2. INTRODUCTION

The Transfusion Transmitted Injuries Surveillance System (TTISS) is a voluntary nationwide ongoing surveillance system established by the Public Health Agency of Canada (the Agency) in 2001 to monitor serious, moderate, and selected minor transfusion-related adverse reactions occurring in Canadian healthcare settings.

The TTISS program collects data on adverse transfusion reactions related to the transfusion of blood, blood components (red blood cells, granulocytes, platelets, plasma and cryoprecipitates) and blood products (plasma derivatives: albumin, immune globulin, coagulation factors, etc.). Reactions are reported from an extensive network of hospitals throughout the country, covering all provinces and two territories. Hospitals in most provinces and territories are also mandated to report transfusion-related adverse events to their respective provincial / territorial Blood Coordinating Offices, blood manufacturers (Canadian Blood Services and Héma-Québec) and the Marketed Health Products Directorate at Health Canada.

This report summarizes transfusion-related adverse reactions reported from hospitals participating in the TTISS network from 2006 to 2012.

3. METHODS

a. Data Collection and Reporting

Upon identification of an adverse reaction related to transfusion within hospitals participating in the TTISS, cases were investigated and categorized by reporting hospitals with respect to their relationship to transfusion; severity and outcome (see Table 1 for standard surveillance definitions). If the case reported resulted in a death, further investigation at the site was undertaken to determine to what extent death was attributed to the transfusion. Only deaths classified as definitely, probably or possibly related to transfusion are presented in this report. A surveillance protocol and user guide was developed to support hospital staff in their efforts to collect and report data on a variety of adverse reactions. Minor allergic reactions were included within the surveillance protocol to monitor consistency and completeness of reporting across participating sites.

Demographic and clinical data pertaining to adverse reactions were collected and reported to corresponding provincial / territorial (P/T) Blood Coordinating Offices and blood manufacturer (Héma-Québec for the province of Quebec and the Canadian Blood Services (CBS) for the rest of Canada). Reactions were reported to the P/T Blood Coordinating Offices who reviewed each case to validate that they met the TTISS surveillance criteria. Subsequently, data were submitted to the Agency, where they were consolidated into a single database. Only reactions determined to be definitely, probably or possibly related to transfusion are included in this report.

b. Data Reconciliation and Validation

Data reconciliation and validation was carried out in collaboration with CBS and the Marketed Health Products Directorate (MHPD) at Health Canada. CBS was involved in validating cases associated with blood components, while the MHPD validated cases associated with blood products (plasma derivatives). During this process, reactions reported to these institutions were reviewed against those reported to the Agency. Reactions not reported to the Agency were added to the consolidated database only if they met the TTISS surveillance criteria and were from a hospital within the TTISS network. Quebec data were subjected to a similar process initiated between Quebec Hemovigilance and Héma-Québec before submission to the Agency.

c. Denominator Data and Data Reconciliation and Validation

In each jurisdiction, the number of hospitals providing transfusion services and the number of hospitals participating in TTISS was monitored yearly. The annual number of units of blood components transfused in hospitals within the TTISS network was also reported by participating provinces / territories. Rates of transfusion-related adverse reactions were calculated by dividing the number of reactions reported by the total units of blood components transfused by hospitals in the TTISS network. The rates of adverse reactions due to transfusion of blood products could not be calculated due to the lack of common denominator data from all the hospitals participating in the TTISS.

Table 1. Surveillance Definitions, TTISS 2006-2012

Relationship to transfusion (Imputability)	
Definite	Clinical and/or laboratory event occurred within a time frame consistent with the administration of the blood, blood component, or blood product (plasma derivative) and was proven by investigation to have been caused by transfusion.
Probable	Clinical and/or laboratory event occurred within a time frame consistent with the administration of the blood, blood component, or blood product (plasma derivative) and did not seem to be explainable by any other cause.
Possible	Clinical and/or laboratory event occurred within a time frame consistent with the administration of the blood, blood component, or blood product (plasma derivative) but could be explained by concurrent disease(s) or by the administration of a drug or other agent.
Severity^a	
Life-threatening (Grade 3)	The recipient required major intervention following the transfusion (i.e. vasopressors, intubation, and transfer to intensive care).
Severe (Grade 2)	The recipient required in-patient hospitalization or prolongation of hospitalization directly attributable to the event; or the adverse event resulted in persistent or significant disability or incapacity; or the adverse event necessitated medical or surgical intervention to preclude permanent/significant damage or impairment of body function
Non-severe (Grade 1)	The recipient may have required medical intervention (i.e. symptomatic treatment) but lack of such would not result in permanent damage or impairment of body function
Not determined	The severity of the transfusion-related event could not be ascertained
Outcome	
Death	Death was directly or indirectly transfusion-related.
Major or long-term sequelae	Transfused patient developed an infection with a persistent infectious agent or any other long-term sequelae including difficulties with future transfusions.
Minor or no sequelae	Transfused patient developed antibodies to low –medium frequency antigens or any other minor reaction.

^a Severity was initially classified into four categories including death (as Grade 4), which was subsequently reclassified as life-threatening and the relationship between transfusion and death outcome was assessed.

4. PROGRAM COVERAGE

The number of hospitals participating in the TTISS has expanded greatly since the surveillance program was initiated. During the 2006 to 2012 time period, over 650 hospitals throughout Canada provided transfusions of blood components each year. The total number of reporting hospitals within the TTISS network increased from 382 in 2006 to 510 in 2012.

The number of hospitals within the TTISS network serves as a general indicator of program participation. However, the volume of transfusion activity varies greatly across hospitals in each jurisdiction. Appendix 1 shows the distribution of blood component units transfused by hospitals in the TTISS network in each province / territory from 2006 to 2012. During this period, a total of 8,175,504 units of blood components were transfused across all jurisdictions by TTISS participating hospitals. This represents 80.4% of the total 10,174,750 units transfused across Canada from 2006 to 2012.

In 2012, a total of 1,437,298 units of blood components were transfused by 657 hospitals across Canada, of which 1,256,160 (87.4%) units were transfused by 510 hospitals within the TTISS network. Figure 1 shows the number and proportion of total blood component units transfused in each province / territory in 2012. Overall, Ontario and Quebec accounted for the greatest proportion of transfusion activity in Canada (37.7% and 24.2%, respectively). Figure 2 shows the number of hospitals participating in TTISS, and the proportion of total blood component units transfused by TTISS hospitals in each province / territory in 2012. In most jurisdictions, almost all transfusions were monitored by TTISS; in Ontario 67.5% of total blood component transfusions were carried out at TTISS participating hospitals.

Figure 1. Distribution of total units (n=1,437,298) of blood components transfused in Canada, by province/territory, 2012

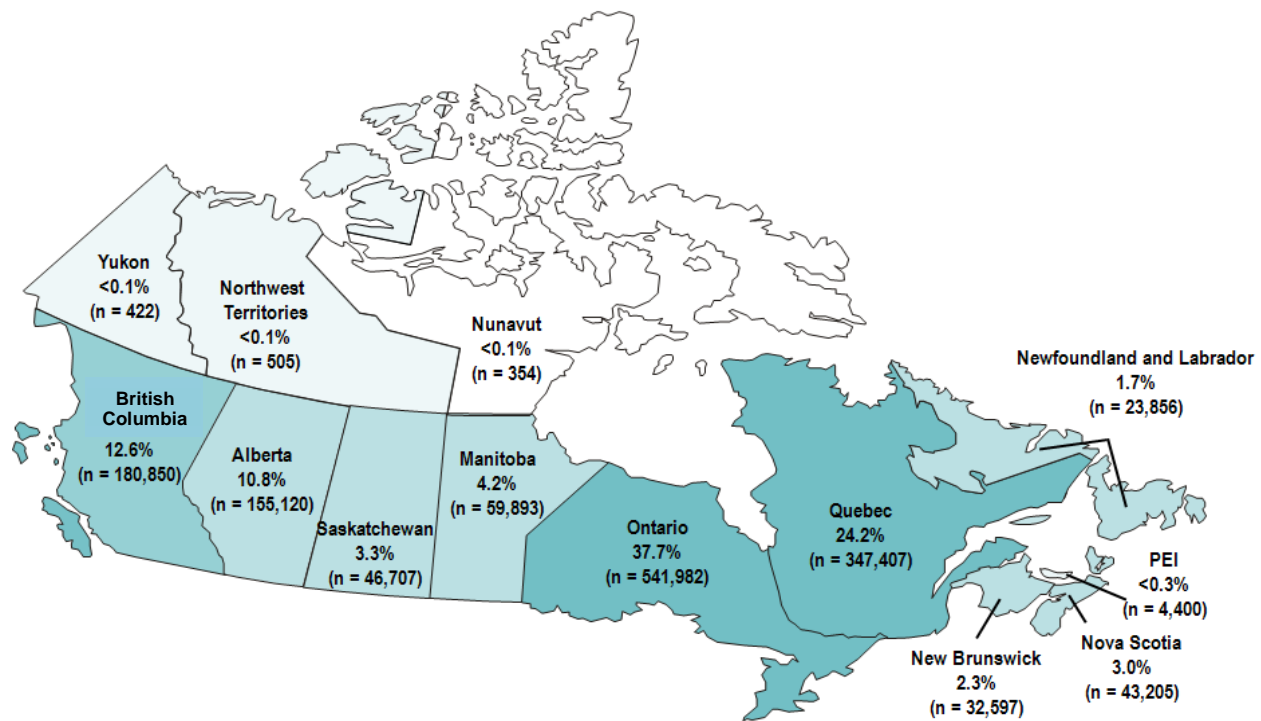
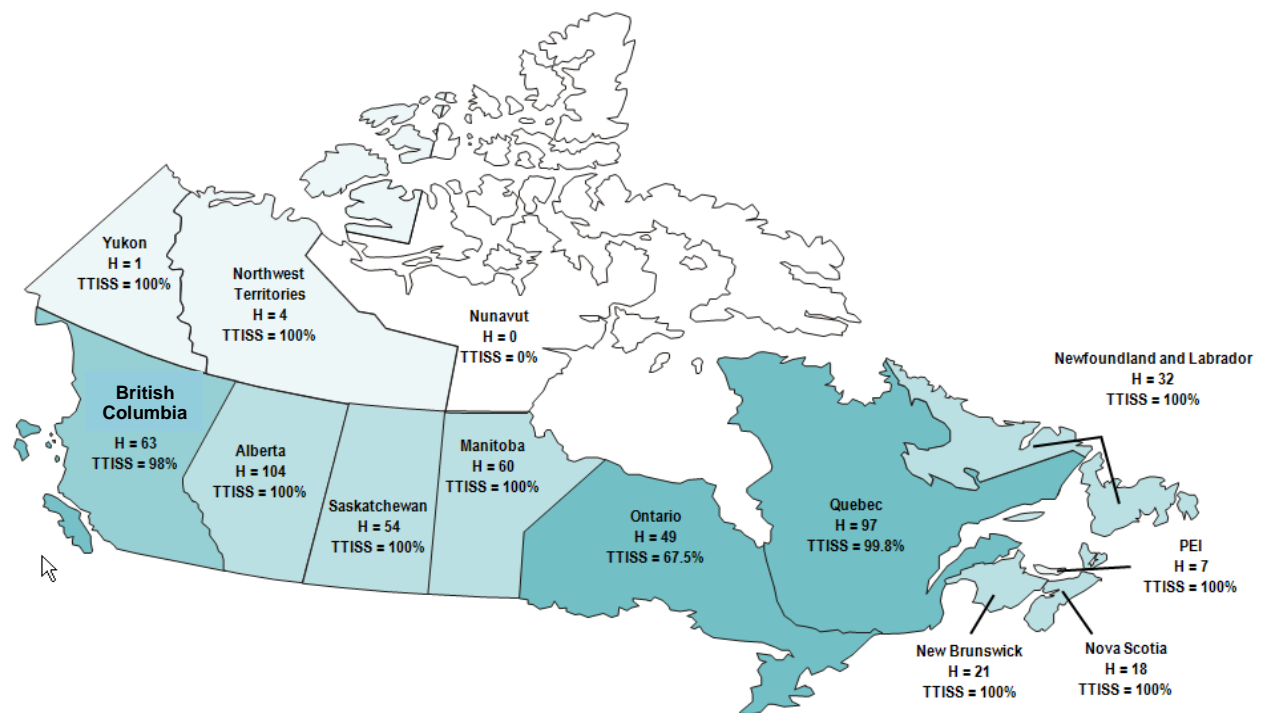


Figure 2. Number of TTISS participating hospitals (H), and proportion of total units transfused by TTISS hospitals (TTISS), by province/territory, 2012



5. RESULTS

a. Reported Adverse Reactions

From 2006 to 2012, a total of 3,957 moderate or serious adverse transfusion reactions were reported to the TTISS, of which 2,920 (73.8%) were related to transfusion of blood components and 1,036 (26.2%) to transfusion of blood products. The annual number of reactions reported varied from 462 to 769 (Table 2 and Figure 3).

Overall, the single most prevalent type of adverse reaction reported from 2006 to 2012 was transfusion-associated circulatory overload (TACO; n=1,298; 32.8%), varying from 149 to 223 cases reported annually (Table 2 and Figure 3) and comprising 28.6% to 39.4% of reactions reported each year. Other types of reactions more frequently reported were severe allergic anaphylactic reactions (n = 495; 12.5%), delayed hemolytic reactions (n = 386; 9.8%), and hypotensive reactions (n = 336; 8.5%) and headache or intolerance from IVIG (n = 295; 7.5%).

Figure 3. Number of adverse reactions reported by TTISS hospitals, 2006 – 2012

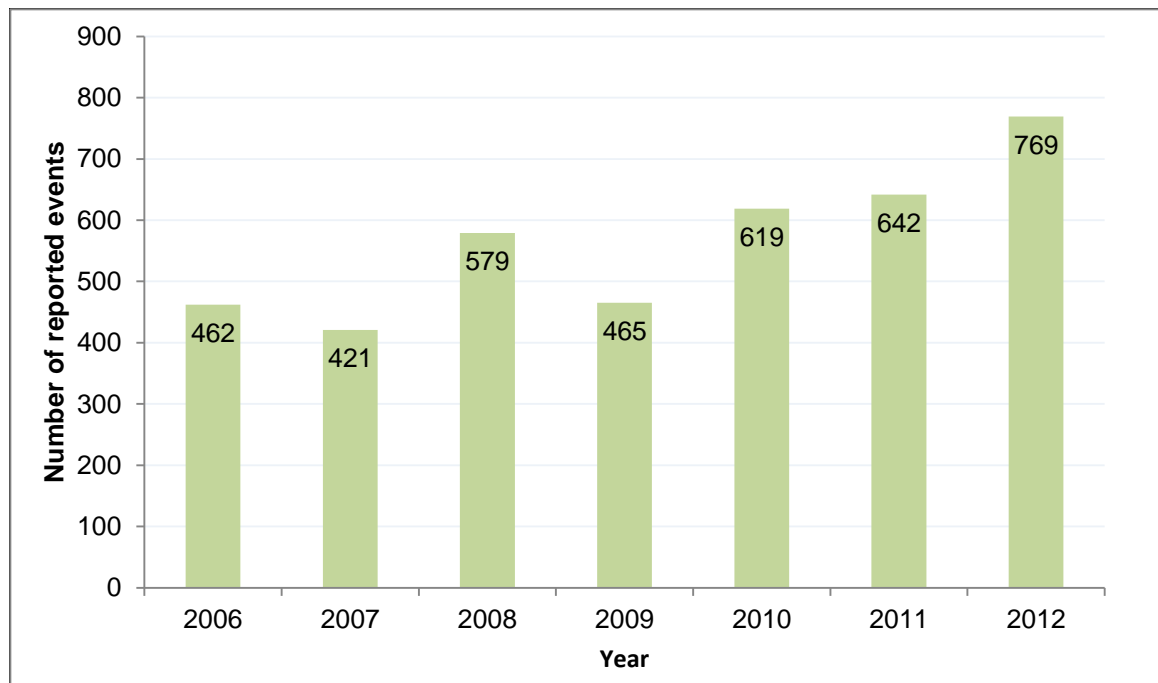


Table 2. Adverse reactions resulting from transfusion of blood components and blood products (plasma derivatives), TTISS 2006-2012

Type of transfusion-related adverse reaction	2006		2007		2008		2009		2010		2011		2012		Total	
	Freq.	%	Freq.	%	Freq.	%	Freq.	%	Freq.	%	Freq.	%	Freq.	%	Freq.	%
Transfusion-associated circulatory overload – TACO	169	36.6%	166	39.4%	181	31.3%	149	32.0%	190	30.7%	223	34.7%	220	28.6%	1,298	32.8%
Acute hemolytic reaction	36	7.8%	11	2.6%	32	5.5%	25	5.4%	32	5.2%	24	3.7%	31	4.0%	191	4.8%
Severe allergic/anaphylactic/anaphylactoid reaction	63	13.6%	60	14.3%	63	10.9%	65	14.0%	96	15.5%	61	9.5%	87	11.3%	495	12.5%
Hypotensive reaction	49	10.6%	47	11.2%	51	8.8%	41	8.8%	44	7.1%	37	5.8%	67	8.7%	336	8.5%
Delayed hemolytic reaction	24	5.2%	22	5.2%	58	10.0%	65	14.0%	62	10.0%	71	11.1%	84	10.9%	386	9.8%
Transfusion-related acute lung injury – TRALI	18	3.9%	17	4.0%	7	1.2%	10	2.2%	8	1.3%	13	2.0%	8	1.0%	81	2.0%
Possible TRALI	4	0.9%	1	0.2%	14	2.4%	9	1.9%	13	2.1%	9	1.4%	13	1.7%	63	1.6%
Transfusion-associated dyspnea – TAD	15	3.2%	8	1.9%	25	4.3%	19	4.1%	40	6.5%	19	3.0%	24	3.1%	150	3.8%
IVIG headache	3	0.6%	22	5.2%	48	8.3%	24	5.2%	39	6.3%	54	8.4%	105	13.7%	295	7.5%
Aseptic meningitis	3	0.6%	3	0.7%	6	1.0%	1	0.2%	10	1.6%	3	0.5%	13	1.7%	39	1.0%
Incompatible transfusion	3	0.6%	5	1.2%	12	2.1%	7	1.5%	7	1.1%	10	1.6%	10	1.3%	54	1.4%
Bacterial infection	3	0.6%	2	0.5%	5	0.9%	4	0.9%	7	1.1%	9	1.4%	3	0.4%	33	0.8%
Other ¹	46	10.0%	41	9.7%	58	10.0%	37	8.0%	52	8.4%	98	15.3%	76	9.9%	408	10.3%
Unusual reactions ²	26	5.6%	16	3.8%	19	3.3%	9	1.9%	19	3.1%	11	1.7%	28	3.6%	128	3.2%
Total	462	100%	421	100%	579	100%	465	100%	619	100%	642	100%	769	100%	3,957	100%

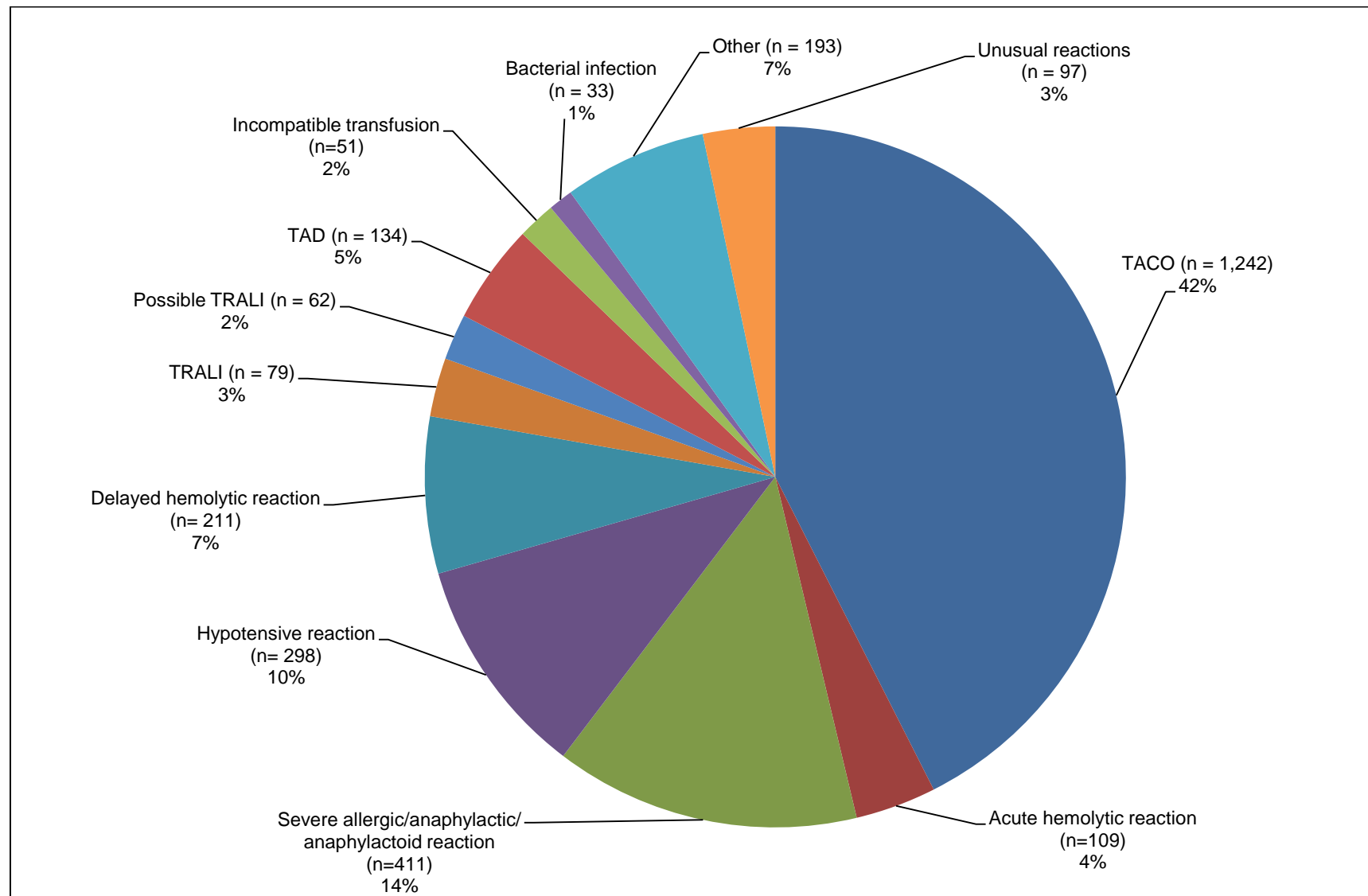
¹ **Other** = Transfusion-related adverse reactions which are well described (in the literature), but rarely occurred (e.g. atypical pain).² **Unusual reactions** = Adverse reactions that were definitely related to transfusion, but did not fit into any other categorization. These are new and unexpected reactions/effects of clinical significance

b. Adverse reactions related to transfusion of blood components

Of the 2,920 adverse reactions related to transfusion of blood components, a substantial proportion (42.5%) were TACO, followed by severe allergic anaphylactic reactions (14.1%), hypotensive (10.2%) and delayed hemolytic (7.2%) reactions (Table 3). The annual number of TACO cases was higher in more recent years (range 185 to 216 between 2010 and 2012) compared to the period 2006 – 2009 (range 142 to 173) which may be due in part to more hospital participation in the TTISS. Annual cases of acute hemolytic reactions, TRALI (together with possible TRALI), severe anaphylactic reactions and delayed hemolytic reactions have remained relatively stable in recent years.

Table 3. Adverse reactions related to transfusion of blood components, TTISS 2006 – 2012

Type of transfusion-related adverse reaction	2006		2007		2008		2009		2010		2011		2012		Total	
	Freq.	%	Freq.	%	Freq.	%	Freq.	%	Freq.	%	Freq.	%	Freq.	%	Freq.	%
Transfusion-associated circulatory overload – TACO	163	40.4%	154	44.1%	173	41.1%	142	41.9%	185	40.7%	216	48.0%	209	41.5%	1,242	42.5%
Acute hemolytic reaction	22	5.5%	7	2.0%	20	4.8%	14	4.1%	16	3.5%	15	3.3%	15	3.0%	109	3.7%
Severe allergic/anaphylactic/ anaphylactoid reaction	56	13.9%	54	15.5%	57	13.5%	50	14.7%	79	17.4%	50	11.1%	65	12.9%	411	14.1%
Hypotensive reaction	43	10.7%	43	12.3%	46	10.9%	34	10.0%	40	8.8%	30	6.7%	62	12.3%	298	10.2%
Delayed hemolytic reaction	17	4.2%	16	4.6%	34	8.1%	38	11.2%	31	6.8%	37	8.2%	38	7.5%	211	7.2%
Transfusion-related acute lung injury – TRALI	18	4.5%	17	4.9%	7	1.7%	9	2.7%	8	1.8%	12	2.7%	8	1.6%	79	2.7%
Possible TRALI	4	1.0%	1	0.3%	14	3.3%	9	2.7%	13	2.9%	8	1.8%	13	2.6%	62	2.1%
Transfusion-associated dyspnea - TAD	15	3.7%	7	2.0%	23	5.5%	16	4.7%	35	7.7%	18	4.0%	20	4.0%	134	4.6%
Incompatible transfusion	3	0.7%	5	1.4%	12	2.9%	7	2.1%	6	1.3%	8	1.8%	10	2.0%	51	1.7%
Bacterial infection	3	0.7%	2	0.6%	5	1.2%	4	1.2%	7	1.5%	9	2.0%	3	0.6%	33	1.1%
Other	39	9.7%	33	9.5%	18	4.3%	7	2.1%	21	4.6%	39	8.7%	36	7.1%	193	6.6%
Unusual reactions	20	5.0%	10	2.9%	12	2.9%	9	2.7%	13	2.9%	8	1.8%	25	5.0%	97	3.3%
Total	403	100%	349	100%	421	100%	339	100%	454	100%	450	100%	504	100%	2,920	100%

Figure 4. Distribution of adverse reactions related to transfusion of blood components (n=2,920), TTISS 2006 – 2012

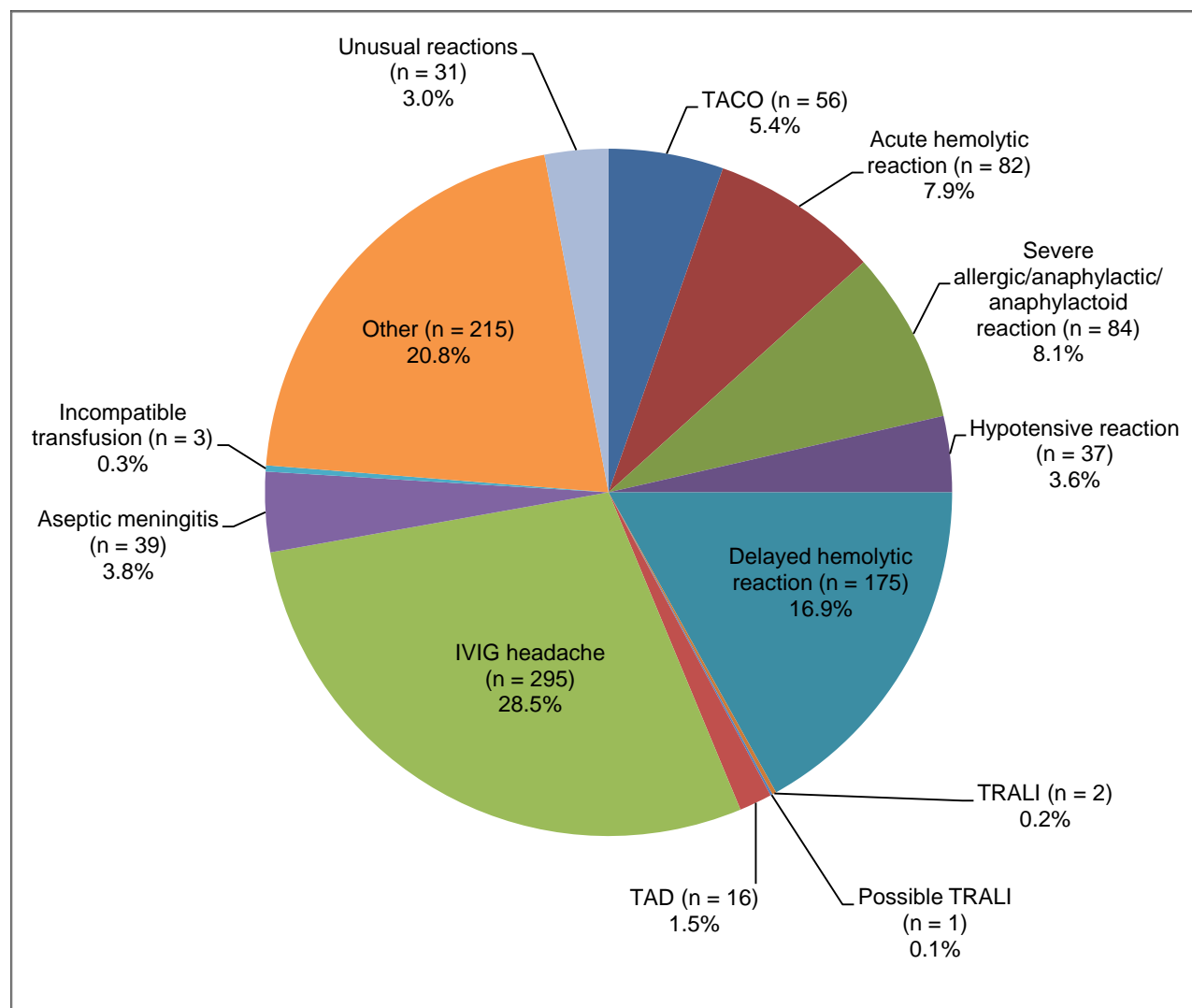
c. Adverse reactions related to transfusion of blood products

The most prevalent of the adverse reactions from transfusion of blood products were headache or intolerance from IVIG (28.5%), delayed hemolytic reactions (16.9%), severe allergic/anaphylactic/anaphylactoid (8.1%) and acute hemolytic (7.9%) reactions (Table 4). TACO accounted for 5.4% of reports from 2006 to 2012. Of 39 aseptic meningitis cases reported during this time period, one quarter (n=10) occurred in 2010. Similarly, a substantial proportion of cases of headache or intolerance due to IVIG (39.8%; n=105) were reported in one year: 2012 (Table 4).

Table 4. Adverse reactions related to transfusion of blood products (plasma derivatives), TTISS 2006 – 2012

Type of transfusion-related adverse reaction	2006		2007		2008		2009		2010		2011		2012		Total	
	Freq.	%	Freq.	%	Freq.	%	Freq.	%	Freq.	%	Freq.	%	Freq.	%	Freq.	%
Transfusion-associated circulatory overload - TACO	6	10.2%	12	16.7%	8	5.1%	7	5.6%	5	3.0%	7	3.6%	11	4.2%	56	5.4%
Acute hemolytic reaction	14	23.7%	4	5.6%	12	7.6%	11	8.7%	16	9.7%	9	4.7%	16	6.1%	82	7.9%
Severe allergic/anaphylactic/anaphylactoid reaction	7	11.9%	6	8.3%	6	3.8%	15	11.9%	17	10.3%	11	5.7%	22	8.3%	84	8.1%
Hypotensive reaction	6	10.2%	4	5.6%	5	3.2%	7	5.6%	4	2.4%	7	3.6%	4	1.5%	37	3.6%
Delayed hemolytic reaction	7	11.9%	6	8.3%	24	15.2%	27	21.4%	31	18.8%	34	17.7%	46	17.4%	175	16.9%
Transfusion-related acute lung injury - TRALI	0	0.0%	0	0.0%	0	0.0%	1	0.8%	0	0.0%	1	0.5%	0	0.0%	2	0.2%
Possible TRALI	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.5%	0	0.0%	1	0.1%
Transfusion-associated dyspnea - TAD	0	0.0%	1	1.4%	2	1.3%	3	2.4%	5	3.0%	1	0.5%	4	1.5%	16	1.5%
IVIG headache	3	5.1%	22	30.6%	48	30.4%	24	19.0%	39	23.6%	54	28.1%	105	39.8%	295	28.5%
Aseptic meningitis	3	5.1%	3	4.2%	6	3.8%	1	0.8%	10	6.1%	3	1.6%	13	4.9%	39	3.8%
Incompatible transfusion	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.6%	2	1.0%	0	0.0%	3	0.3%
Other	7	11.9%	8	11.1%	40	25.3%	30	23.8%	31	18.8%	59	30.7%	40	15.2%	215	20.8%
Unusual reactions	6	10.2%	6	8.3%	7	4.4%	0	0.0%	6	3.6%	3	1.6%	3	1.1%	31	3.0%
Total	59	100%	72	100%	158	100%	126	100%	165	100%	192	100%	264	100%	1,036	100%

Figure 5. Distribution of adverse reactions related to transfusion of blood products (n=1,036), TTISS 2006 – 2012



d. Strength of the Relationship to Transfusion

Tables 5, 6 and 7 show the distribution of adverse reactions by imputed relationship to transfusion. Of the 3,957 reported reactions related to blood components and blood products from 2006 to 2012, 699 (17.7%) were definitely related to transfusion. Of the cases definitely related to transfusion, 443 (63.4%) were among recipients of blood components.

Table 5. Relationship of adverse reaction (imputability) to transfusion of blood components and blood products (plasma derivatives), 2006-2012

Type of transfusion-related adverse reaction	Definite		Probable		Possible		Total	
	Freq.	%	Freq.	%	Freq.	%	Freq.	%
Transfusion-associated circulatory overload - TACO	91	7.0%	594	45.8%	613	47.2%	1,298	100%
Acute hemolytic reaction	106	55.5%	59	30.9%	26	13.6%	191	100%
Severe allergic/anaphylactic/ anaphylactoid reaction	76	15.4%	303	61.2%	116	23.4%	495	100%
Hypotensive reaction	10	3.0%	108	32.1%	218	64.9%	336	100%
Delayed hemolytic reaction	251	65.0%	96	24.9%	39	10.1%	386	100%
Transfusion-related acute lung injury - TRALI	16	19.8%	44	54.3%	21	25.9%	81	100%
Possible TRALI	6	9.5%	15	23.8%	42	66.7%	63	100%
Transfusion-associated dyspnea - TAD	9	6.0%	54	36.0%	87	58.0%	150	100%
IVIG headache	47	15.9%	190	64.4%	58	19.7%	295	100%
Aseptic meningitis	13	33.3%	19	48.7%	7	17.9%	39	100%
Incompatible transfusion	45	83.3%	5	9.3%	4	7.4%	54	100%
Bacterial infection	3	9.1%	6	18.2%	24	72.7%	33	100%
Other	24	5.9%	206	50.5%	178	43.6%	408	100%
Unusual reactions	2	1.6%	30	23.4%	96	75.0%	128	100%
Total	699	17.7%	1,729	43.7%	1,529	38.6%	3,957	100%

e. Adverse Reactions Related to Transfusion of Blood Components

Among reactions related to transfusion of blood components (Table 6), those with a high proportion definitely related to transfusion were acute hemolytic reaction (55.5%), delayed hemolytic reaction (70.6%) and incompatible transfusion (88.2%). Most cases of TACO (1,152/1,242; 92.8%) were probably or possibly related to transfusion, while 63.0% of severe allergic anaphylactic reactions and 54.4% of TRALI were probably related to transfusion. The certainty of the relationship between transfusion and the adverse reaction was lowest for hypotensive reactions, bacterial infection, TAD and possible TRALI.

Of the 443 reactions definitely related to transfusion of blood components, most were delayed hemolytic reactions (n=149), TACO (n=90), acute hemolytic reactions (n=60), severe anaphylactic reactions (n=51), and incompatible transfusions (n=45).

Table 6. Relationship of adverse reaction (Imputability) to transfusion of blood components only, TTISS 2006-2012

Type of transfusion-related adverse reaction	Definite		Probable		Possible		Total	
	Freq.	%	Freq.	%	Freq.	%	Freq.	%
Transfusion-associated circulatory overload – TACO	90	7.2%	573	46.1%	579	46.6%	1,242	100%
Acute hemolytic reaction	60	55.0%	33	30.3%	16	14.7%	109	100%
Severe allergic/anaphylactic/ anaphylactoid reaction	51	12.4%	259	63.0%	101	24.6%	411	100%
Hypotensive reaction	7	2.3%	99	33.2%	192	64.4%	298	100%
Delayed hemolytic reaction	149	70.6%	48	22.7%	14	6.6%	211	100%
Transfusion-related acute lung injury - TRALI	15	19.0%	43	54.4%	21	26.6%	79	100%
Possible TRALI	6	9.7%	14	22.6%	42	67.7%	62	100%
Transfusion-associated dyspnea - TAD	8	6.0%	44	32.8%	82	61.2%	134	100%
Incompatible transfusion	45	88.2%	2	3.9%	4	7.8%	51	100%
Bacterial infection	3	9.1%	6	18.2%	24	72.7%	33	100%
Other	9	4.7%	84	43.5%	100	51.8%	193	100%
Unusual reactions	0	0.0%	18	18.6%	79	81.4%	97	100%
Total	443	15.2%	1,223	41.9%	1,254	42.9%	2,920	100%

f. Adverse Reactions Related to Transfusion of Blood Products

A substantial proportion of acute hemolytic reactions (56.1%) and delayed hemolytic reactions (58.3%) were classified as definitely related to transfusion of blood products (Table 7). Among cases of IVIG headache related to transfusion of blood products, only 15.9% were definitely related to transfusion and over two thirds (64.4%) were probably related to transfusion.

There were 256 reactions definitely related to transfusion of blood products. Most were delayed hemolytic reactions (n=102), acute hemolytic reactions (n=46) or IVIG headache (n=47).

Table 7. Relationship of adverse reaction (imputability) to transfusion of blood products, TTISS 2006-2012

Type of transfusion-related adverse reaction	Definite		Probable		Possible		Total	
	Freq.	%	Freq.	%	Freq.	%	Freq.	%
Transfusion-associated circulatory overload - TACO	1	1.8%	21	37.5%	34	60.7%	56	100%
Acute hemolytic reaction	46	56.1%	26	31.7%	10	12.2%	82	100%
Severe allergic/anaphylactic/anaphylactoid reaction	25	29.8%	44	52.4%	15	17.9%	84	100%
Hypotensive reaction	3	8.1%	8	21.6%	26	70.3%	37	100%
Delayed hemolytic reaction	102	58.3%	48	27.4%	25	14.3%	175	100%
Transfusion-related acute lung injury - TRALI	1	50.0%	1	50.0%	0	0.0%	2	100%
Possible TRALI	0	0.0%	1	100%	0	0.0%	1	100%
Transfusion-associated dyspnea -TAD	1	6.3%	10	62.5%	5	31.3%	16	100%
IVIg headache	47	15.9%	190	64.4%	58	19.7%	295	100%
Aseptic meningitis	13	33.3%	19	48.7%	7	17.9%	39	100%
Incompatible transfusion	0	0.0%	3	100%	0	0.0%	3	100%
Other	15	7.0%	122	56.7%	78	36.3%	215	100%
Unusual reactions	2	6.5%	12	38.7%	17	54.8%	31	100%
Total	256	24.7%	505	48.7%	275	26.5%	1,036	100%

g. Rate of Reported Adverse Reactions

The overall rates of adverse reactions related to transfusion of blood components from 2006 to 2012 are shown in Figures 6 and 7. Relative to other reactions, cases of bacterial infection, incompatible transfusion and TRALI/possible TRALI were least frequent (≤ 1.0 case per 100,000 units transfused). TACO cases, the most prevalent reactions reported, occurred on average at a rate of 15.2 per 100,000 units transfused. This was three times higher than the rate of severe allergic anaphylactic reactions (5.0 cases per 100,000 units). Also, the annual rate for TACO since 2010 has been above this average (Figure 7). Adverse reactions of unusual characteristics occurred at rate ranged between 0.7 and 2 cases per 100,000 units transfused (Figure 7).

Figure 6. Overall rate of adverse reactions related to transfusion of blood components, TTISS 2006 - 2012

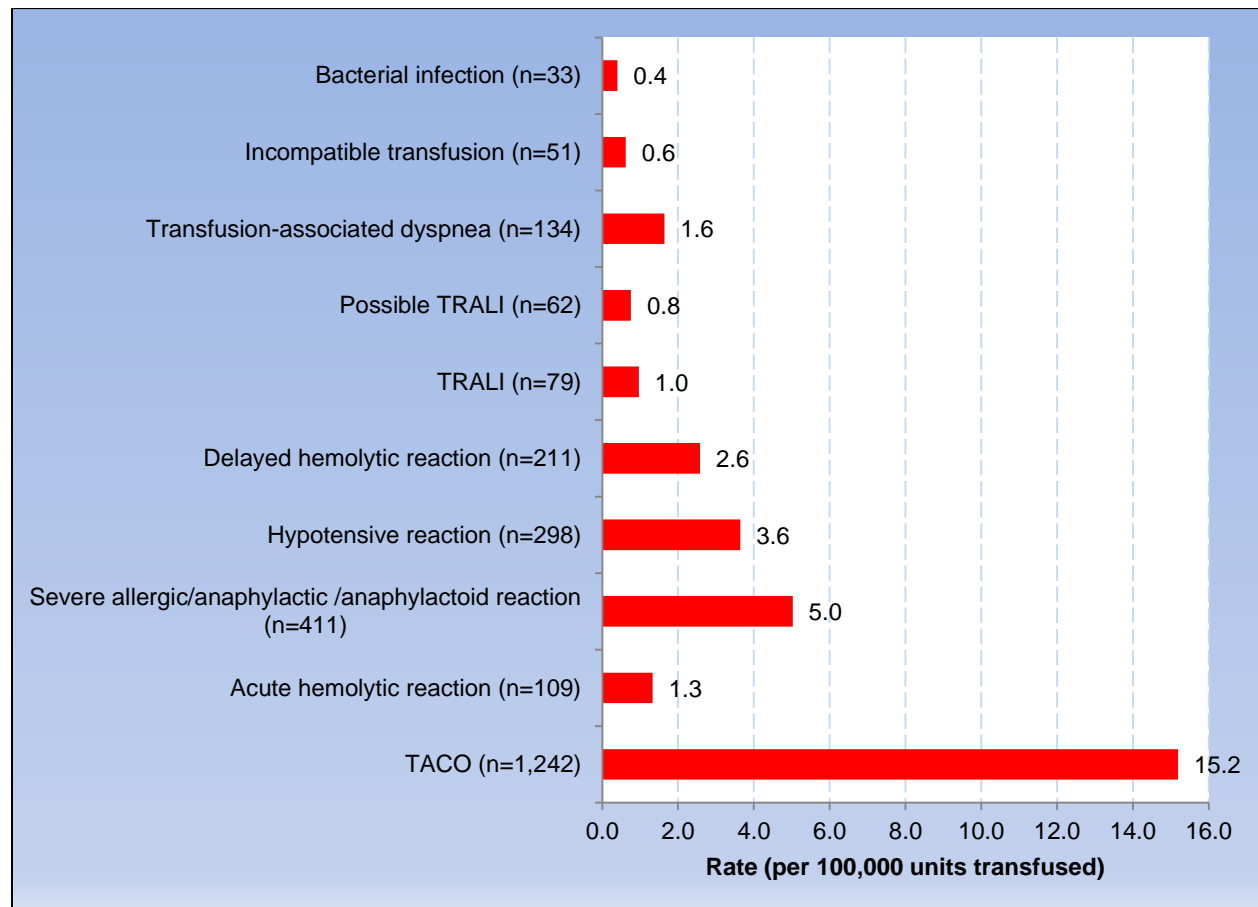
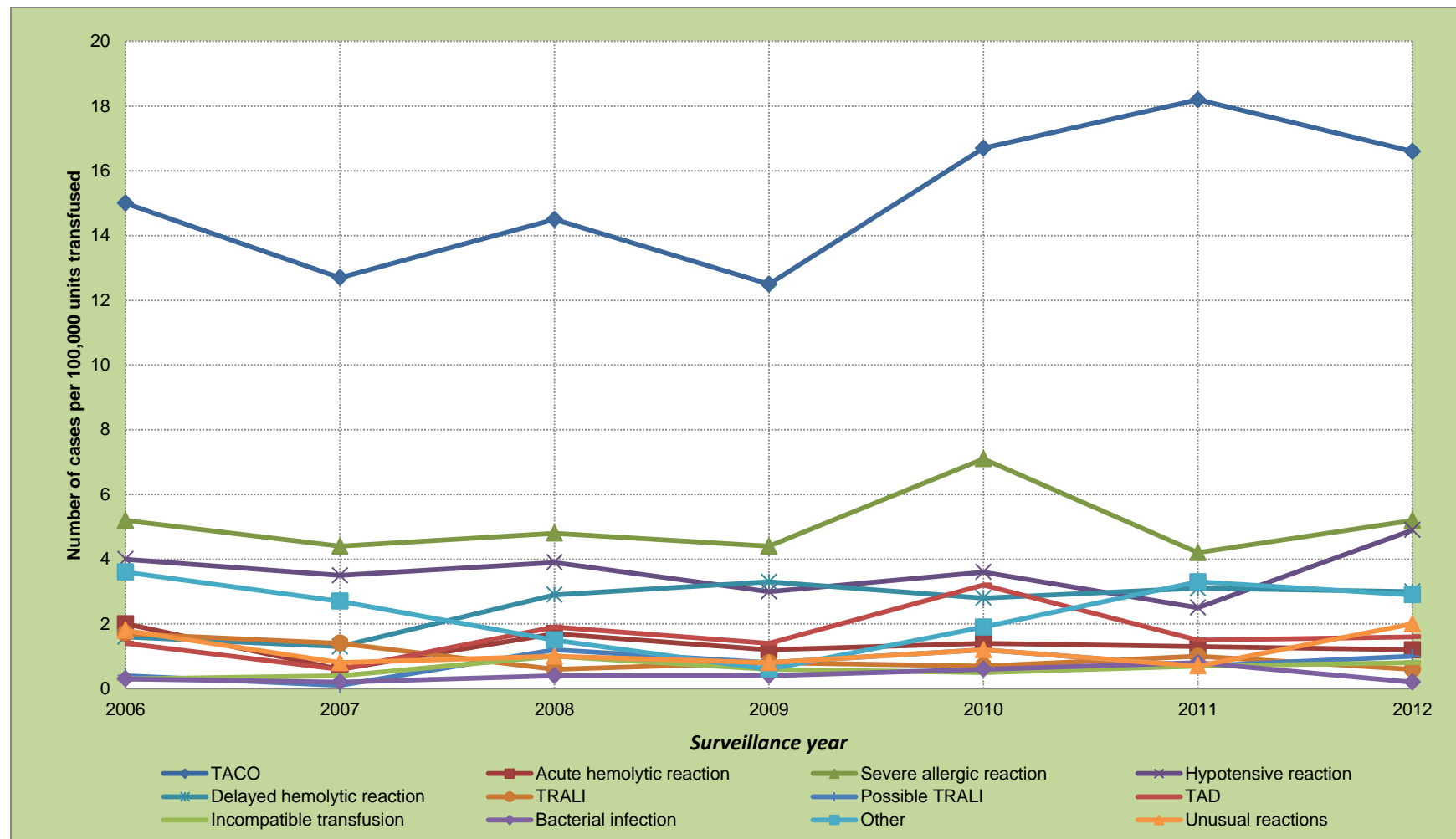


Figure 7. Annual Rate of adverse reactions related to transfusion of blood components, TTISS 2006 - 2012



With the exception of TACO that recorded rate of occurrence on annual basis exceeding 10 cases per 100,000 units of blood components transfused, all the other adverse reactions occurred at rates ranging between 0 and 7. Severe allergic/anaphylactoid reactions posted the second highest of the rates which ranged between 4.2 and 7.1 cases (Figure 7). The lowest rates were posted by bacterial infection which rarely occurred: from 2 to 8 cases per every one million units of blood component transfused (Figure 7).

Table 8. Risk of one case of an adverse reaction related to transfusion of blood components, TTISS 2006 - 2012

Type of transfusion-related adverse reaction	2006		2007		2008		2009		2010		2011		2012		Total	
	Freq.	Risk	Freq.	Risk	Freq.	Risk	Freq.	Risk	Freq.	Risk	Freq.	Risk	Freq.	Risk	Freq.	Risk
Transfusion-associated circulatory overload - TACO	163	1 : 6,650	154	1 : 7,899	173	1 : 6,886	142	1 : 8,007	185	1 : 5,978	216	1 : 5,485	209	1 : 6,010	1,242	1 : 6,583
Acute hemolytic reaction	22	1 : 49,270	7	1 : 173,786	20	1 : 59,565	14	1 : 81,217	16	1 : 69,181	15	1 : 78,979	15	1 : 83,744	109	1 : 75,014
Severe allergic Anaphylactic /anaphylactoid reaction	56	1 : 19,356	54	1 : 22,528	57	1 : 20,900	50	1 : 22,741	79	1 : 13,999	50	1 : 23,694	65	1 : 19,326	411	1 : 19,894
Hypotensive reaction	43	1 : 25,208	43	1 : 28,291	46	1 : 25,898	34	1 : 33,442	40	1 : 27,672	30	1 : 39,489	62	1 : 20,261	298	1 : 27,438
Delayed hemolytic reaction	17	1 : 63,761	16	1 : 76,031	34	1 : 35,038	38	1 : 29,922	31	1 : 35,706	37	1 : 32,018	38	1 : 33,057	211	1 : 38,751
Transfusion-related acute lung injury - TRALI	18	1 : 60,218	17	1 : 71,559	7	1 : 170,186	9	1 : 126,337	8	1 : 138,362	12	1 : 98,723	8	1 : 157,020	79	1 : 103,500
Possible TRALI	4	1 : 270,982	1	1:1,216,503	14	1 : 85,093	9	1 : 126,337	13	1 : 85,146	8	1 : 148,085	13	1 : 96,628	62	1 : 131,879
Transfusion-associated dyspnea - TAD	15	1 : 72,262	7	1 : 173,786	23	1 : 51,796	16	1 : 71,065	35	1 : 31,626	18	1 : 65,815	20	1 : 62,808	134	1 : 61,019
Incompatible transfusion	3	1 : 361,310	5	1 : 243,301	12	1 : 99,275	7	1 : 162,434	6	1 : 184,483	8	1 : 148,085	10	1 : 125,616	51	1 : 160,324
Bacterial infection	3	1 : 361,310	2	1 : 608,252	5	1 : 238,260	4	1 : 284,259	7	1 : 158,128	9	1 : 131,631	3	1 : 418,720	33	1 : 247,773
Other	39	1 : 27,793	33	1 : 36,864	18	1 : 66,183	7	1 : 162,434	21	1 : 52,709	39	1 : 30,376	36	1 : 34,893	193	1 : 42,365
Unusual reactions	20	1 : 54,196	10	1 : 121,650	12	1 : 99,275	9	1 : 126,337	13	1 : 85,146	8	1 : 148,085	25	1 : 50,246	97	1 : 84,294
Total	403	1 : 2,690	349	1 : 3,486	421	1 : 2,830	339	1 : 3,354	454	1 : 2,438	450	1 : 2,633	504	1 : 2,492	2,920	1 : 2,800

Table 8 displays the corresponding annual risk of a single case of each type of adverse reactions. Obviously, the highest risk was posed by the type of reactions that occurred more frequently like TACO and Severe allergic/anaphylactoid reactions.

h. Severity of Reported Adverse Reactions

There were 3,856 adverse reactions related to transfusion of blood components and blood products from 2006 to 2012 with adequate data to characterize severity (Table 9). Of these, 2,021 (52.4%) were classified as non-severe, 1,565 (40.6%) as severe, and 270 (7.0%) were life-threatening. Reactions with a substantial proportion of cases classified as non-severe included IVIG headache (88.2%), delayed hemolytic reaction (67.6%) and hypotensive reaction (64.3%). Overall there were 1,835 severe or life-threatening reactions, of which 1,505 (82.0%) were associated with transfusion of blood components (Table 9).

Table 9. Severity of adverse reactions that resulted from transfusion of blood components and blood products (plasma derivatives), 2006 – 2012

Type of transfusion-related adverse reaction	Grade 1 (Non-severe)		Grade 2 (Severe)		Grade 3 (Life-threatening)		Total*	
	Freq.	%	Freq.	%	Freq.	%	Freq.	%
Transfusion-associated circulatory overload - TACO	604	47.8%	565	44.7%	94	7.4%	1,263	100%
Acute hemolytic reaction	89	47.8%	83	44.6%	14	7.5%	186	100%
Severe allergic/anaphylactic/anaphylactoid reaction	110	22.9%	332	69.0%	39	8.1%	481	100%
Hypotensive reaction	209	64.3%	99	30.5%	17	5.2%	325	100%
Delayed hemolytic reaction	252	67.6%	116	31.1%	5	1.3%	373	100%
Transfusion-related acute lung injury - TRALI	6	7.6%	41	51.9%	32	40.5%	79	100%
Possible TRALI	3	4.8%	36	58.1%	23	37.1%	62	100%
Transfusion-associated dyspnea - TAD	86	57.3%	53	35.3%	11	7.3%	150	100%
IVIG headache	259	88.4%	34	11.6%	0	0.0%	293	100%
Aseptic meningitis	9	24.3%	27	73.0%	1	2.7%	37	100%
Incompatible transfusion	29	55.8%	20	38.5%	3	5.8%	52	100%
Bacterial infection	11	34.4%	16	50.0%	5	15.6%	32	100%
Other	263	65.8%	117	29.3%	20	5.0%	400	100%
Unusual reactions	91	74.0%	26	21.1%	6	4.9%	123	100%
Total	2,021	52.4%	1,565	40.6%	270	7.0%	3,856	100%

Note: Severity was unknown for 101 cases.

i. Severe and life-threatening reactions related to transfusion of blood components

Of 2,843 reactions related to transfusion of blood components, 1,256 (44.2%) were classified as severe and 249 (8.6%) were life-threatening. Two types of reactions accounted for two thirds of all severe reactions reported (Figure 8): TACO (545; 43.4%) and severe allergic anaphylactic reaction (279; 22.2%).

Among life-threatening reactions (Figure 9), the most prevalent were TACO (91; 36.5%), severe allergic anaphylactic reaction (33; 13.3%), and TRALI (31; 12.4%).

Figure 8. Distribution of severe adverse reactions related to transfusion of blood components, TTISS 2006 – 2012 (n=1,256)

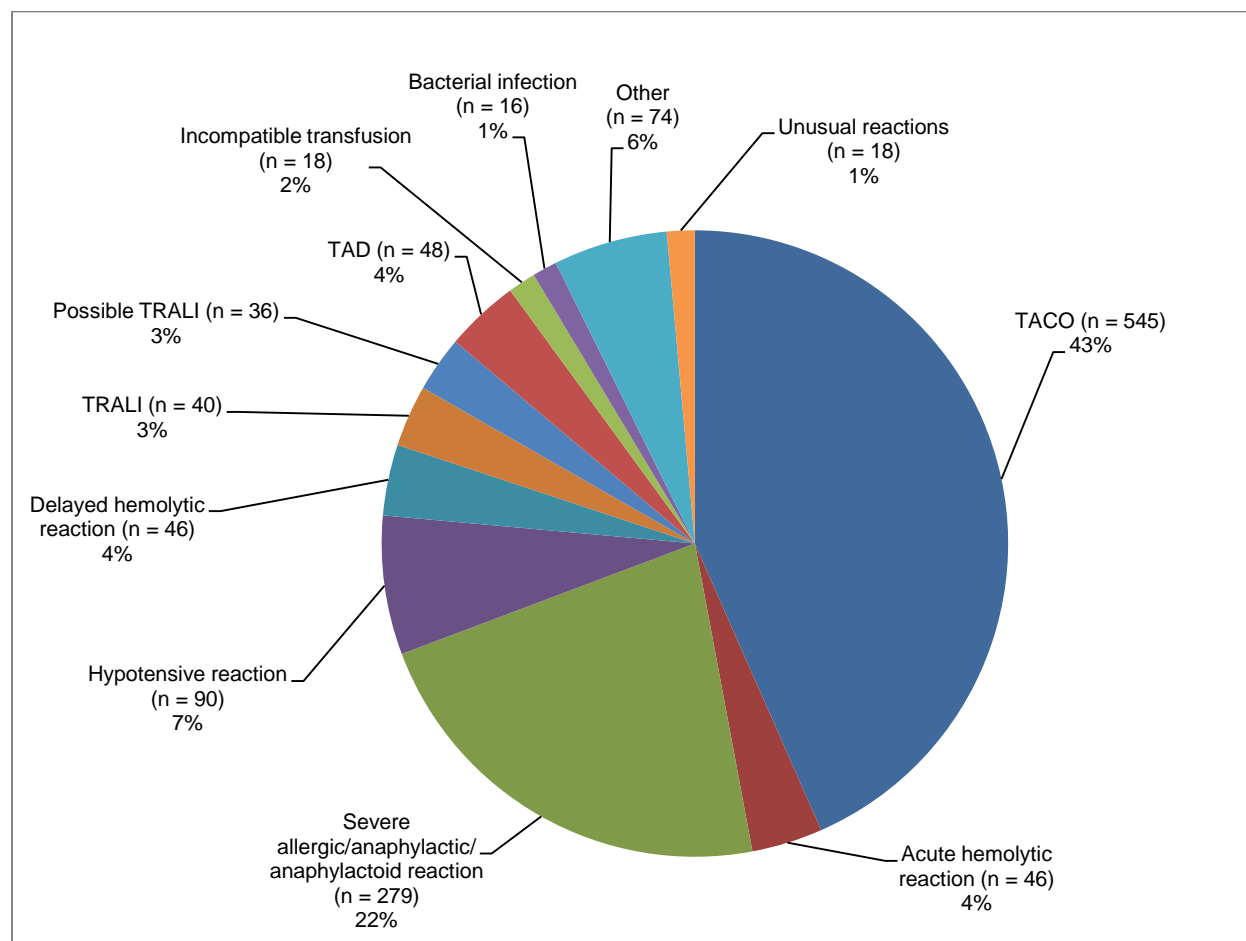
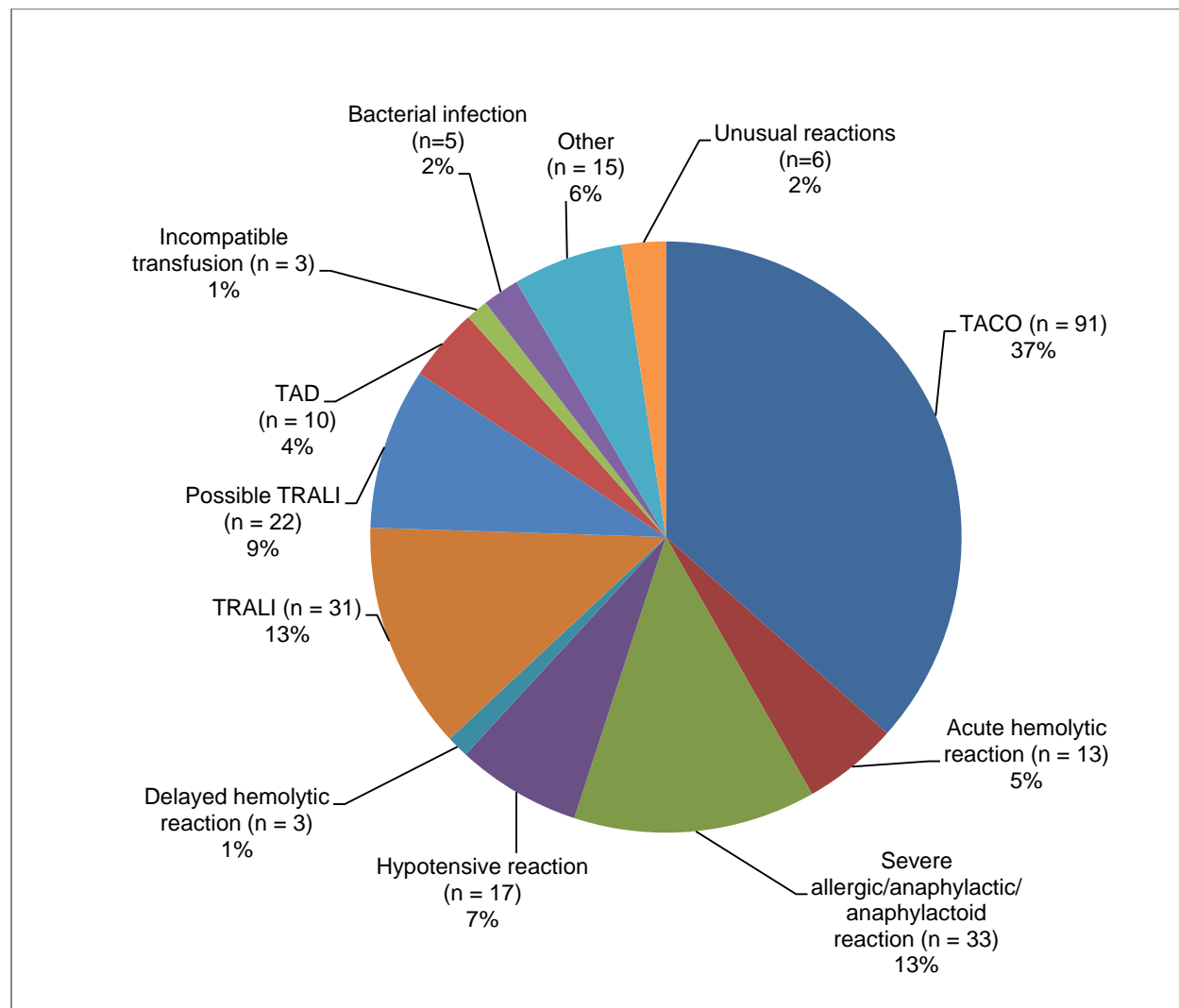


Figure 9. Distribution of life-threatening adverse reactions related to transfusion of blood components (n=249), TTISS 2006 – 2012



j. Severe and life-threatening reactions related to transfusion of blood products

Of 1,012 adverse reactions related to transfusion of blood products, 308 (30.4%) were classified as severe and 21 (2.1%) were life-threatening. The distribution of severe reactions is shown in Figure 10. Four types of reactions accounted for over 60% of severe reactions combined: delayed hemolytic reactions (n = 70; 22.7%), severe anaphylactic/anaphylactoid reactions (n = 53; 17.2%), acute hemolytic reactions (n=37; 12.0%) and IVIG headache (n = 34; 11.0%). Among life-threatening reactions (Figure 11), severe allergic/anaphylactic/anaphylactoid reactions were the most prevalent (n=6; 28.6%).

Figure 10. Distribution of severe adverse reactions related to transfusion of blood products (n = 308), TTISS 2006 – 2012

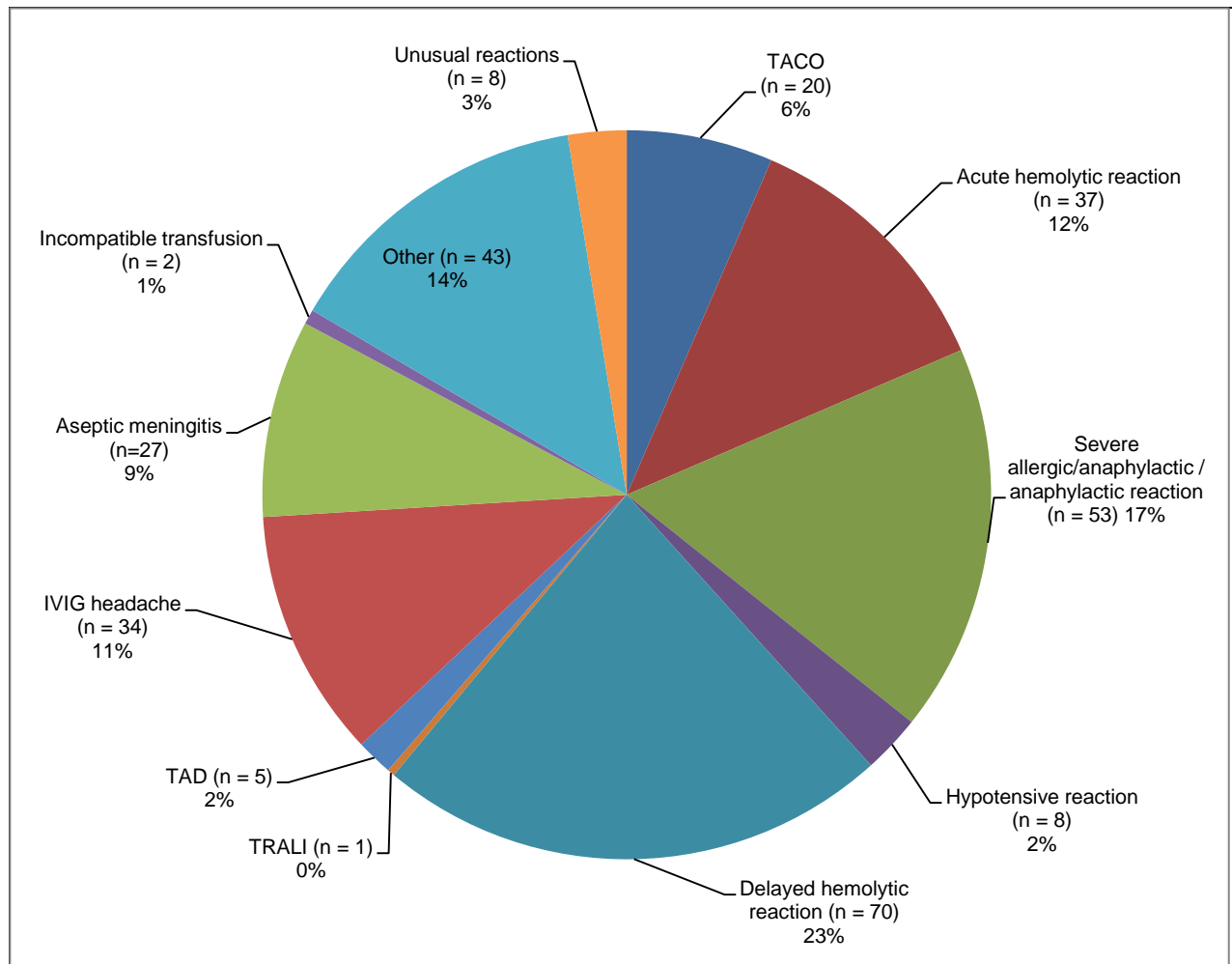
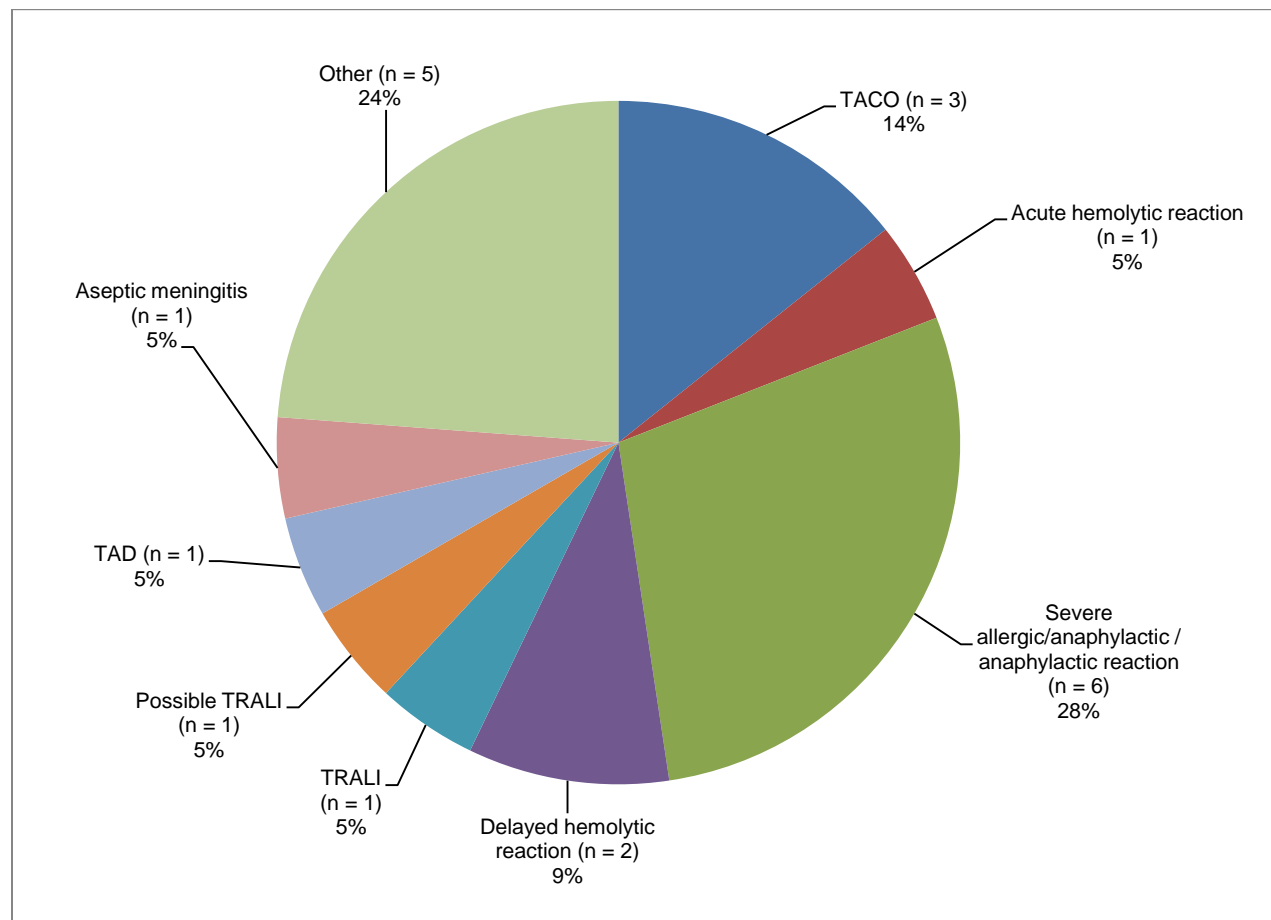


Figure 11. Distribution of life-threatening adverse reactions related to transfusion of blood products (n= 21), TTISS 2006 – 2012



k. Outcomes of Reported Adverse Reactions

Data on patient outcomes were available for 3,763 of the 3,957 adverse reactions reported to the TTISS from 2006 to 2012. Outcome could not be determined for 176 cases and was missing for 18 cases. Of cases where outcome was determined, 3,598 (95.6%) resulted in minor or no sequelae and 107 (2.8%) resulted in major sequelae. There were 58 deaths reported, of which 17 were ruled out as being related to the transfusion. The remaining 41 were deemed to be definitely, probably or possibly related to the transfusion.

Among reactions classified as severe or life-threatening, outcome was missing or could not be determined for 123 of 1,505 (8.2%) reactions related to blood components and 28 of 329 (8.5%) reactions related to blood products. Table 10 shows outcomes for severe and life-threatening events where outcome data were available. Overall, among 1,693 such events, the majority (92.9%) resulted in minor or no sequelae and 4.7% (n=79) resulted in major or long term sequelae. For the 41 deaths related to transfusion 30 were life-threatening reactions involving blood components. Table 11 shows the distribution of these deaths by year and type of adverse reaction.

Table 10. Outcomes of severe and life-threatening adverse reactions, TTISS 2006 – 2012

Outcome	Adverse transfusion reactions related to blood components		Adverse transfusion reactions related to blood products	
	Severe (n= 1,170)	Life-threatening (n = 212)	Severe (n=294)	Life-threatening (n=17)
Minor / No sequelae	1,121 (95.8%)	155 (73.1%)	284 (96.6%)	13 (76.4%)
Major sequelae	40 (3.3%)	27 (12.7%)	9 (3.1%)	3 (17.6%)
Death	9 (0.83%)	30 (14.2%)	1 (0.3%)	1 (5.9%)

Note: Cases with unknown outcome (n=141), or where death was doubtfully related or ruled out are not shown.

Table 11. Transfusion-related deaths in the TTISS network from 2006 to 2012

	TACO	TRALI	Possible TRALI	Acute hemolytic reaction	Bacterial infection	Hypotensive reaction	Other	Total
Total	13	5	12	4	2	1	4	41
Year								
2006	2	2	2	1	0	1	0	8
2007	1	0	0	1	0	0	1	3
2008	4	0	1	2	1	0	1	9
2009	1	0	2	0	0	0	1	4
2010	1	1	3	0	0	0	0	5
2011	1	1	2	0	1	0	0	5
2012	2	1	2	0	0	0	1	6
Relationship of death to transfusion								
Definite ¹	0	1	0	0	0	0	0	1
Probable ²	4	1	4	0	1	1	1	12
Possible ³	9	3	8	4	1	0	3	28

¹ **Definite** = The patient's death occurred within a time frame consistent with the administration of the blood, blood component, or blood product (plasma derivative) and was proven by investigation to have been caused by transfusion.

² **Probable** = The patient's death occurred within a time frame consistent with the administration of the blood, blood component, or blood product (plasma derivative) and did not seem to be explainable by any other cause.

³ **Possible** = The patient's death occurred within a time frame consistent with the administration of the blood, blood component, or blood product (plasma derivative) but could be explained by concurrent disease(s) or by the administration of a drug or other agent.

I. Deaths

Of the 41 deaths reported that were determined to be definitely, probably or possibly related to transfusion, all but two were related to transfusion of blood components. Over one half of deaths reported were cases of TACO (n=13, 32%) or *possible* TRALI (n = 12, 29%).

Deaths definitely attributable to transfusion (n=1)

Over the entire time period, only one death was definitely related to transfusion. This resulted from TRALI in a 74 year old male patient who received red blood cells in 2010 following intervention for trauma and burns, and developed acute respiratory syndrome and acute renal insufficiency.

Deaths probably attributable to transfusion (n=12)

There were 11 cases where death was probably related to transfusion of blood components and 1 case of TACO from transfusion of blood products. Deaths related to the transfusion of blood components included reports of TACO (n=3), TRALI (n=1) and possible TRALI (n=4), bacterial infection (n=1), and a hypotensive reaction (n=1). The other case of death probably related to transfusion was from an unspecified adverse transfusion reaction. These cases are described further within the respective summary of reactions that follow this section.

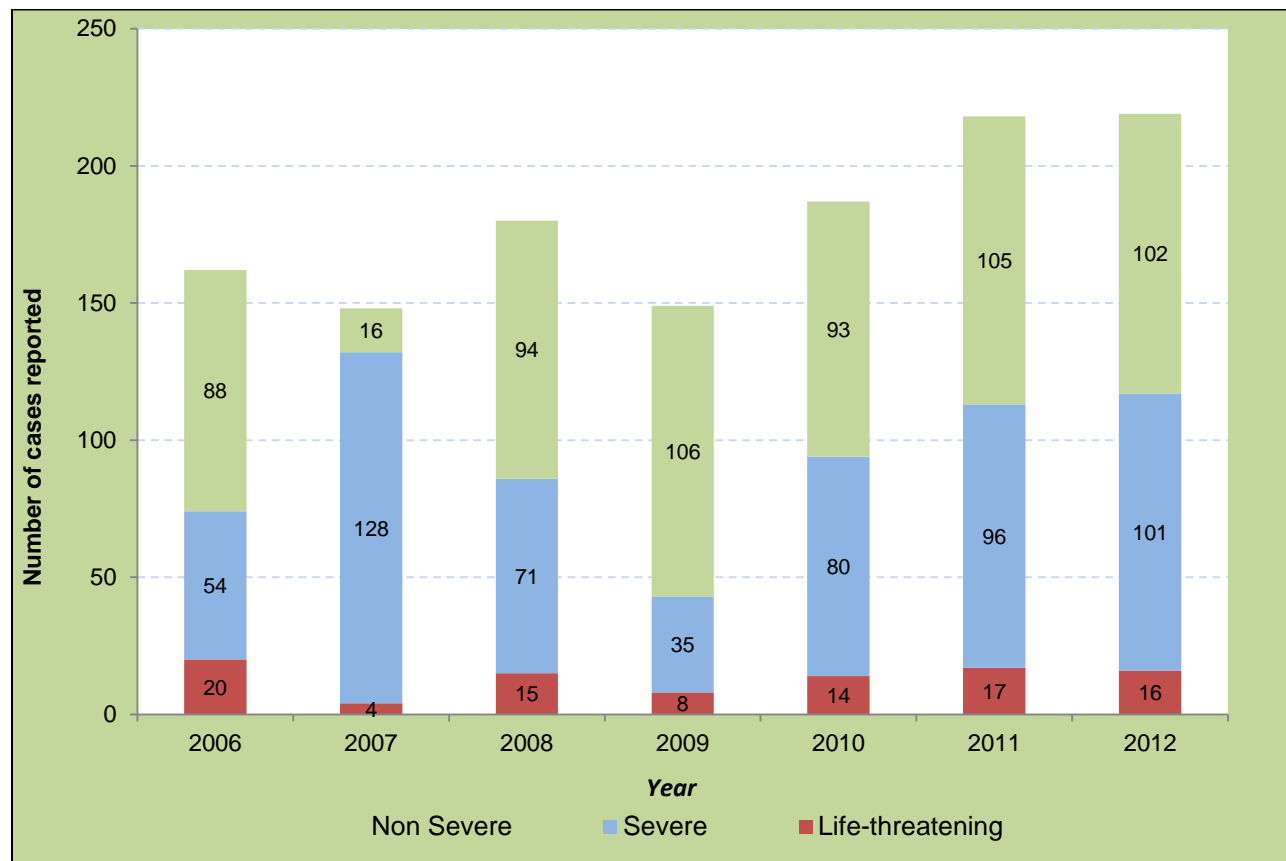
The 1 case where death was probably related to transfusion of blood products was reported in a 47 year old female patient who received Factor FVIIa in 2012 after prolonged bleeding following extensive cardiac surgery which required cardiopulmonary resuscitation, defibrillation, and massive inotropic support.

6. Summary of Selected Reactions

a. Transfusion-Associated Circulatory Overload – TACO

Total Number of TACO Cases: 1,298			
Age	Years	Type of transfusion	Frequency (%)
Median	74	Blood component	1,242 (95.7%)
Range	[0, 100]	Blood product	56 (4.3 %)
		Unknown	0 (0.0%)
Sex	Frequency (%)	Severity	Frequency (%)
Male	551 (42.4%)	Life-threatening	94 (7.2%)
Female	745 (57.4%)	Severe	565 (43.5%)
Unknown	2 (0.15%)	Non severe	604 (46.5%)
		Unknown/Not determined	35 (2.7%)
Relationship to transfusion	Frequency (%)	Outcome	Frequency (%)
Definitely related to transfusion	91 (7.0%)	Deaths definitely due to transfusion	0 (0.0%)
Probably related to transfusion	594 (45.8%)	Deaths probably due to transfusion	4 (0.31%)
Possibly related to transfusion	613 (47.2%)	Deaths possibly due to transfusion	9 (0.69%)
Unknown/Not determined	0 (0.0%)	Death not related to transfusion:	
		• Relationship doubtful	0 (0.0%)
		• Relationship ruled out	0 (0.0%)
		Major sequelae	21 (1.6%)
		Minor sequelae	1,191 (91.8%)
		Unknown/Not determined	73 (5.6%)

The number of TACO cases reported per year varied from 149 to 223. Nearly all of the 1,298 TACO cases (95.7%) were associated with transfusion of blood components. Almost one half (46.5%) were classified as non-severe, 43.5% were severe and 94 (7.2%) were life-threatening. The annual distribution of TACO reports by severity is shown in Figure 11. Outcomes for 91.8% of cases were minor or no sequelae, including 504 (89.2%) of the 565 cases reported as severe and 64 (68.1%) of the 94 cases reported as life-threatening.

Figure 12. Reports of TACO by severity, TTISS 2006 – 2012*Cases with major or long term sequelae (n=21)*

Almost all of these cases had a severity reported as severe (n=14) or life-threatening (n=6). There were five cases with outcomes resulting in major or long term sequelae that were definitely attributable to transfusion.

Deaths (n=13)

None of the deaths reported over this time period were coded as definitely related to transfusion; however, 4 cases were coded as probable and 9 cases were coded as possible. The 13 deaths coded as probably or possibly related to transfusion were as follows:

- 90 year old male post chemotherapy and who received red blood cells and developed shortness of breath, diaphoresis and cough
- 91 year old female with a low haemoglobin who received red blood cells and developed shortness of breath, pulmonary edema and nausea.
- 82 year old male post chemotherapy who received transfusion of apheresis platelets and developed shortness of breath, chest pain and tachycardia
- 71 year old male developed disseminated intravascular coagulation following transfusion of red blood cells
- 85 year old male on a medical ward received red blood cells and developed shortness of breath

- 79 year old female in emergency room received red blood cells and developed elevated blood pressure, shortness of breath and chest pain
- 83 year old male on a medical ward received red blood cells and developed shortness of breath, and an elevated temperature
- 84 year old female in the emergency room received red blood cells and developed hypertension, shortness of breath and pain (location not specified)
- 90 year old male post chemotherapy received red blood cells and developed shortness of breath, O2 desaturation and diaphoresis
- 84 year old female post chemotherapy who received platelets and developed increased temperature, shortness of breath, hypertension and diaphoresis
- 80 year old female with severe diverticulitis who received red blood cells and developed shortness of breath and hypertension
- 79 year old female who received red blood cells
- 80 year old female with myasthenia gravis who received several grams of IVIG

b. Transfusion-Related Acute Lung Injury (TRALI)

Total Number of <i>TRALI</i> Cases: 81			
Age	Years	Type of transfusion	Frequency (%)
Median	56	Blood component	79 (97.5 %)
Range (min, max)	[0, 88]	Blood product	2 (2.5 %)
		Unknown	0 (0.0%)
Sex	Frequency (%)	Severity	Frequency (%)
Male	41 (50.6%)	Life-threatening	32 (39.5%)
Female	39 (48.2%)	Severe	41 (50.6%)
Unknown	1 (1.2%)	Non severe	6 (7.4%)
		Unknown/Not determined	2 (2.5%)
Relationship to transfusion	Frequency (%)	Outcome	Frequency (%)
Definitely related to transfusion	16 (19.8%)	Deaths definitely due to transfusion	1 (1.2%)
Probably related to transfusion	44 (54.3%)	Deaths probably due to transfusion	1 (1.2%)
Possibly related to transfusion	21 (25.9%)	Deaths possibly due to transfusion	3 (3.7%)
Unknown/Not determined	0 (0.0%)	Death not related to transfusion:	
		• <i>Relationship doubtful</i>	0 (0.0%)
		• <i>Relationship ruled out</i>	0 (0.0%)
		Major sequelae	3 (3.7%)
		Minor sequelae	68 (84.0%)
		Unknown/Not determined	5 (6.2%)

The number of TRALI cases reported per year varied from 8 to 18. One half of cases (41/81) were reported as severe, but most (68; 84.0%) had an outcome of minor or no sequelae. Of the 16 cases definitely related to transfusion, 12 had an outcome of minor or no sequelae, one had major or long term sequelae, one died, one had an outcome of death unrelated to transfusion, and one had an undetermined outcome of unknown. A total of 32 cases were classified as life-threatening; of these 20 had minor or no sequelae, 3 had major sequelae, and 5 patients died and are briefly described below. The remaining 4 deaths coded as probably or possibly related to transfusion were as follows:

- 74 year old male patient that received red cells and developed shortness of breath following intervention for trauma and burns, and as a result developed acute respiratory syndrome and acute renal insufficiency.
- 78 year old female and received red cells and developed shortness of breath
- 42 year old female with renal failure who received plasma and apheresis fresh frozen plasma and became hypoxic and short of breath.
- 66 year old male who had undergone surgery and received multiple plasma and fresh frozen plasma and became hypotensive
- 81 year old male with an upper GI bleed who received red blood cells

c. Possible TRALI

Of the 64 possible TRALI cases reported, a substantial proportion (n=36; 56.3%) were classified as severe and 37.5% were classified as life-threatening. However, over one half of cases (33; 51.6%) had outcomes of minor or no sequelae. There were 12 deaths coded as probably (n=4) or possibly (n=8) related to transfusion. Those probably related to transfusion included the following individuals:

- 52 year old female in OR and on cardiopulmonary bypass received red blood cells and developed hypotension and acute massive non-cardiogenic pulmonary edema.
- 52 year old female with clinical history of AIDS and hepatitis C received apheresis fresh frozen plasma and developed shortness of breath and hypertension
- 33 year old female in the ICU who received apheresis platelets and developed progressive respiratory failure, shock and acidosis.
- 63 year old male with cirrhosis of the liver who received red blood cells and developed hypertension, shortness of breath and went into shock.

Total Number of Possible TRALI Cases: 64			
Age	Years	Type of transfusion	Frequency (%)
Median	51	Blood component	63 (98.4 %)
Range (min, max)	[0, 83]	Blood product	1 (1.6 %)
		Unknown	0 (0.0%)
Sex	Frequency (%)	Severity	Frequency (%)
Male	35 (54.7%)	Life-threatening	24 (37.5%)
Female	29 (45.3%)	Severe	36 (56.3%)
Unknown	0 (0.0%)	Non severe	3 (4.7%)
		Unknown/Not determined	1 (1.6%)
Relationship to transfusion	Frequency (%)	Outcome	Frequency (%)
Definitely related to transfusion	7 (10.9%)	Deaths definitely due to transfusion	0 (0.0%)
Probably related to transfusion	15 (23.4%)	Deaths probably due to transfusion	4 (6.3%)
Possibly related to transfusion	42 (65.6%)	Deaths possibly due to transfusion	8 (12.5%)
Unknown/Not determined	0 (0.0%)	Death not related to transfusion:	
		• Relationship doubtful	2 (3.1%)
		• Relationship ruled out	0 (0.0%)
		Major sequelae	7 (10.9%)
		Minor sequelae	33 (51.6%)
		Unknown/Not determined	10 (15.6%)

Cases classified as possibly related to transfusion involved the individual whose brief description is provided below:

- 65 year old male with prostate cancer who received red blood cells and developed an increased temperature and hypertension
- 75 year old male in the OR who received fresh frozen plasma and developed an increased temperature and hypotension
- 81 year old female who received red blood cells and developed nausea
- 21 year old female in the ICU with ARDS and who received fresh frozen plasma and developed shortness of breath, hypotension and hypoxia.
- 63 year old male who received apheresis fresh frozen plasma and developed shortness of breath
- 66 year old male in the OR who received three units of red blood cells and developed hypotension and hypoxemia.
- 69 year old female with COPD, CHF and anemia received red blood cells and developed shortness of breath
- 48 year old female received pooled buffy coat platelets and developed shortness of breath, hypertension.

d. Acute Hemolytic Reactions

Over half of acute hemolytic reactions (55.5%) were definitely related to transfusion. A small proportion (7.3%) was classified as life-threatening; others were severe (43.5%) or non-severe (46.6%). Overall, 156 (81.7%) had minor or no sequelae as an outcome, including 67 (80.7%) of the 83 cases classified as severe. Four patients died; one in 2006, one in 2007 and two in 2008. All four deaths were possibly related to transfusion and coding details were:

- 28 year old female who received red blood cells and developed shortness of breath, hypoxia, hemorrhage and shock (incorrect patient sample tested)
- 81 year old female who received red blood cells and developed hemoglobinuria (possible unidentified antibody)
- 82 year old male who received red blood cells and developed was identified with multiple antibodies and increased temperature
- 82 year old female who received red blood cells and developed an increased temperature, dyspnea, hypertension (possible unidentified antibody)

Total Number of Acute Hemolytic Reaction Cases: 191			
Age	Years	Type of transfusion	Frequency (%)
Median	60	Blood component	109 (99.1%)
Range (min, max)	[0, 88]	Blood product	1 (0.9 %)
		Unknown	0 (0.0%)
Sex	Frequency (%)	Severity	Frequency (%)
Male	85 (44.5%)	Life-threatening	14 (7.3%)
Female	106 (55.5%)	Severe	83 (43.5%)
Unknown	0 (0.0%)	Non severe	89 (46.6%)
		Unknown/Not determined	5 (2.6%)
Relationship to transfusion	Frequency (%)	Outcome	Frequency (%)
Definitely related to transfusion	106 (55.5%)	Deaths definitely due to transfusion	0 (0.0%)
Probably related to transfusion	59 (30.9%)	Deaths probably due to transfusion	0 (0.0%)
Possibly related to transfusion	26 (13.6%)	Deaths possibly due to transfusion	4 (2.1%)
Unknown/Not determined	0 (0.0%)	Death not related to transfusion:	
		• Relationship doubtful	0 (0.0%)
		• Relationship ruled out	1 (0.5%)
		Major sequelae	14 (7.3%)
		Minor sequelae	156 (81.7%)
		Unknown/Not determined	16 (8.9%)

e. Delayed Hemolytic Reactions

Delayed hemolytic reactions were distributed relatively equally among transfusions related to blood components and blood products. Nearly two thirds (65.3%) were classified as non-severe and the majority (86.3%) resulted in minor or no sequelae. There were no deaths reported that were attributable to transfusion. Of the 30 cases with major or long term sequelae, 11 were classified as severe and 2 as life-threatening.

Total Number of <i>Delayed Hemolytic Reaction</i> Cases: 386			
Age	Years	Type of transfusion	Frequency (%)
Median	60	Blood component	211 (54.7 %)
Range (min, max)	[1, 97]	Blood product	175 (45.3 %)
		Unknown	0 (0.0%)
Sex	Frequency (%)	Severity	Frequency (%)
Male	152 (39.4%)	Life-threatening	5 (1.3%)
Female	234 (60.6%)	Severe	116 (30.1%)
Unknown	0 (0.0%)	Non severe	252 (65.3%)
		Unknown/Not determined	13 (3.4%)
Relationship to transfusion	Frequency (%)	Outcome	Frequency (%)
Definitely related to transfusion	251 (65.0%)	Deaths definitely due to transfusion	0 (0.0%)
Probably related to transfusion	96 (24.9%)	Deaths probably due to transfusion	0 (0.0%)
Possibly related to transfusion	39 (10.1%)	Deaths possibly due to transfusion	0 (0.0%)
Unknown/Not determined	0 (0.0%)	Death not related to transfusion:	
		• <i>Relationship doubtful</i>	1 (0.26%)
		• <i>Relationship ruled out</i>	1 (0.26%)
		Major sequelae	30 (7.8%)
		Minor sequelae	333 (86.3%)
		Unknown/Not determined	21 (5.4%)

f. Severe Allergic/Anaphylactic/Anaphylactoid Reactions

Of the 495 severe allergic/anaphylactic/anaphylactoid reactions reported, most (n=411; 83.0%) were related to transfusion of blood components. Relatively few (n=76; 15.4%) were definitely related to transfusion. Most (n=93.5%) resulted in minor or no sequelae, including 32 of the 39 cases classified as life-threatening (82%). There were no deaths reported.

Total Number of Severe Allergic/Anaphylactic/Anaphylactoid Reaction Cases: 495			
Age	Years	Type of transfusion	Frequency (%)
Median	54	Blood component	411 (83.0 %)
Range (min, max)	[0, 95]	Blood product	84 (17.0 %)
		Unknown	0 (0.0%)
Sex	Frequency (%)	Severity	Frequency (%)
Male	246 (49.7%)	Life-threatening	39 (7.9%)
Female	249 (50.3%)	Severe	332 (67.1%)
Unknown	0 (0.0%)	Non severe	110 (22.2%)
		Unknown/Not determined	14 (2.8%)
Relationship to transfusion	Frequency (%)	Outcome	Frequency (%)
Definitely related to transfusion	76 (15.4%)	Deaths definitely due to transfusion	0 (0.0%)
Probably related to transfusion	303 (61.2%)	Deaths probably due to transfusion	0 (0.0%)
Possibly related to transfusion	116 (23.4%)	Deaths possibly due to transfusion	0 (0.0%)
Unknown/Not determined	0 (0.0%)	Death not related to transfusion:	
		• Relationship doubtful	0 (0.0%)
		• Relationship ruled out	1 (0.2%)
		Major sequelae	11 (2.2%)
		Minor sequelae	463 (93.5%)
		Unknown/Not determined	20 (4.0%)

g. Bacterial Infections

All 33 bacterial infections were associated with transfusion of blood components, but only 3 were definitely related to transfusion. Three quarters (25; 75.8%) resulted in minor or no sequelae. There were 21 cases classified as severe or life-threatening, of which 2 died. The two deaths were coded as one probable and one possible and coding detail included:

- 81 year old male with a clinical history of severe heart failure who received a transfusion of red blood cells. He developed a fever, with chills, shortness of breath, hypotension, and shock. The bacteria identified was *Serratia liquefaciens*
- 30 year old male hematology patient who received a transfusion of red blood cells. He developed nausea, abdominal pain, jaundice and hemogloburemia. The bacterium identified was *clostridium perfringes*.

Total Number of <i>Bacterial Infection</i> Cases: 33			
Age	Years	Type of transfusion	Frequency (%)
Median	57	Blood component	33 (100 %)
Range (min, max)	[0, 89]	Blood product	0 (0.0 %)
		Unknown	
Sex	Frequency (%)	Severity	Frequency (%)
Male	19 (57.6%)	Life-threatening	5 (15.2%)
Female	14 (42.4%)	Severe	16 (48.5%)
Unknown	0 (0.0%)	Non severe	11 (33.3%)
		Unknown/Not determined	1 (3.0%)
Relationship to transfusion	Frequency (%)	Outcome	Frequency (%)
Definitely related to transfusion	3 (9.1%)	Deaths definitely due to transfusion	0 (0.0%)
Probably related to transfusion	6 (18.2%)	Deaths probably due to transfusion	1 (3.0%)
Possibly related to transfusion	24 (72.7%)	Deaths possibly due to transfusion	1 (3.0%)
Unknown/Not determined	0 (0.0%)	Death not related to transfusion:	
		• <i>Relationship doubtful</i>	0 (0.0%)
		• <i>Relationship ruled out</i>	0 (0.0%)
		Major sequelae	0 (0.0%)
		Minor sequelae	25 (75.8%)
		Unknown/Not determined	6 (18.2%)

h. Hypotensive Reactions

Most (298; 88.7%) hypotensive reactions were associated with transfusion of blood components, and only 10 were definitely related to transfusion. Nearly all (319; 94.9%) cases resulted in minor or no sequelae, including 94 of the 99 cases classified as severe. Of the 17 cases reported as life-threatening, 13 resulted in minor or no sequelae, 2 had major sequelae or long term and one died. The death was determined to be probably due to transfusion and involved a 70 year old female patient who underwent surgery for a brain tumour and received a transfusion of red blood cells.

Total Number of Hypotensive Reaction Cases: 336			
Age	Years	Type of transfusion	Frequency (%)
Median	78	Blood component	298 (88.7%)
Range (min, max)	[0, 100]	Blood product	37 (11.0%)
		Unknown	1 (0.3%)
Sex	Frequency (%)	Severity	Frequency (%)
Male	191 (56.8%)	Life-threatening	17 (5.1%)
Female	145 (43.2%)	Severe	99 (29.5%)
Unknown	0 (0.0%)	Non severe	209 (62.2%)
		Unknown/Not determined	11 (3.3%)
Relationship to transfusion	Frequency (%)	Outcome	Frequency (%)
Definitely related to transfusion	10 (3.0%)	Deaths definitely due to transfusion	0 (0.0%)
Probably related to transfusion	108 (32.1%)	Deaths probably due to transfusion	1 (0.3%)
Possibly related to transfusion	218 (64.9%)	Deaths possibly due to transfusion	
Unknown/Not determined	0 (0.0%)	Death not related to transfusion:	
		• <i>Relationship doubtful</i>	0 (0.0%)
		• <i>Relationship ruled out</i>	0 (0.0%)
		Major sequelae	4 (1.2%)
		Minor sequelae	319 (94.9%)
		Unknown/Not determined	12 (3.6%)

i. Aseptic Meningitis

Of 39 aseptic meningitis cases reported, most (n=28) were classified as severe or life-threatening; however, only two of these cases had an outcome of major or long term sequelae. There were no deaths reported.

Total number of Aseptic Meningitis cases: 39			
Age	Years	Type of transfusion	Frequency (%)
Median	37	Blood component	0 (0.0%)
Range (min, max)	[0, 81]	Blood product	39 (100%)
Sex	Frequency (%)	Severity	Frequency (%)
Male	13 (33.3%)	Life-threatening	1 (2.6%)
Female	26 (66.7%)	Severe	27 (69.2%)
Unknown	0 (0.0%)	Non severe	9 (23.1%)
		Unknown/Not determined	2 (5.1%)
Relationship to transfusion	Frequency (%)	Outcome	Frequency (%)
Definitely related to transfusion	13 (33.3%)	Deaths definitely due to transfusion	0 (0.0%)
Probably related to transfusion	19 (48.7%)	Deaths probably due to transfusion	0 (0.0%)
Possibly related to transfusion	7 (18.0%)	Deaths possibly due to transfusion	0 (0.0%)
Unknown/Not determined	0 (0.0%)	Death not related to transfusion:	
		• Relationship doubtful	0 (0.0%)
		• Relationship ruled out	0 (0.0%)
		Major sequelae	2 (5.1%)
		Minor sequelae	36 (92.3%)
		Unknown/Not determined	1 (2.6%)

7. Commentary

The cases summarized here represent adverse reactions related to transfusion of blood components and blood products reported from hospitals participating in TTISS from 2006 to 2012, supplemented by data reported to the Canadian Blood Services and Health Canada's Marketed Health Products Directorate over this time period. While the TTISS network covered almost 80% of transfusion activity in Canada, it is important to note that events included in this report are likely an underestimate of all adverse reactions related to transfusion in Canada. Awareness of reactions to be reported, completeness and timeliness of reporting, and potential bias towards reporting of more serious reactions may have affected the number and type of reactions included in this report.

Although there were no obvious trends over time with respect to reporting of specific reactions, implementation of strategies to reduce the risk of certain types of reactions such as Bacterial Contamination, TRALI and *possible* TRALI have occurred since 2006. These included the implementation of the Buffy Coat and male donor plasma. The Buffy Coat process has added in reducing the number of platelets being pooled at the hospitals and the patient's bedside as this is now done primarily during the blood collection phase at CBS and HQ. The male donor plasma strategy has been implemented to help reduce the number of TRALI and *possible* TRALI cases as predominately male plasma is being used in platelet pools. The idea behind this is that the antibodies associated with TRALI and *possible* TRALI are found most frequently in women who have had multiple pregnancies, or people (men or women) who have had blood transfusions themselves as described by the CBS^d. The American Association of Blood Banks has been advocating this best practice solution since November 2006 when it issued on November 06, 2006 *Association Bulletin # 06-07: Transfusion-Related Acute Lung Injury* (AABB Membership required to access). Success with this strategy has been reported not only in the USA^e, but also in countries such as the United Kingdom^f although not across the board^g.

Transfusion-associated circulatory overload (TACO) was the most commonly reported reaction related to transfusion of blood components. These cases comprised 42.5% of reported cases, at a rate of 15.2 cases per 100,000 units of components transfused. However, almost one half were classified as non-severe and over 90% resulted in minor or no sequelae. Of the 13 deaths associated with TACO, none were determined to be definitely related to transfusion.

There was one death definitely attributable to transfusion among all reactions reported from 2006 to 2012. This death was related to TRALI and was very rare relative to the rate of other reported cases (0.012 per 100,000 units of blood components transfused). A comparison of reactions reported over the same time period is shown below in Table 12.

Table 12. Rates of occurrence of different categories of adverse reactions related to transfusion of blood components, TTISS 2006-2012

^d [http://www.blood.ca/centreapps/internet/uw_v502_mainengine.nsf/page/Transfusion Related Acute Lung Injury-TRALI](http://www.blood.ca/centreapps/internet/uw_v502_mainengine.nsf/page/Transfusion%20Related%20Acute%20Lung%20Injury-TRALI)

^e Eder AF, Herron RM Jr, Strupp A, et al. Effective reduction of transfusion-related acute lung injury risk with male-predominant plasma strategy in the American Red Cross (2006-2008). *Transfusion* 2010; 50:1732.

^f Chapman CE, Stainsby D, Jones H, et al. Ten years of hemovigilance reports of transfusion-related acute lung injury in the United Kingdom and the impact of preferential use of male donor plasma. *Transfusion* 2009; 49:440.

^g http://corporate.dukemedicine.org/news_and_publications/news_office/news/restrictions_on_female_plasma_may_not_be_warranted

Type of adverse reaction	Frequency	Rate (per 100,000 units transfused)
Any adverse reaction (excluding minor allergic reactions)	2,920	35.7
Severe or life-threatening reaction	1,505	18.4
Reaction definitely related to transfusion	443	5.4
Reaction resulting in death	39	0.5

The occurrence rates of major transfusion-related adverse reactions such as TRALI or bacterial infections in Canadian hospitals were among the lowest reported by industrialized countries (Appendix 2). TACO was the only major transfusion reaction for which Canadian hospitals reported higher rates. While the causes of this difference are not investigated, it should be noted that the surveillance systems monitoring transfusion adverse reactions in these countries (the **SHOT** in the UK, the **Hémovigilance** in France and the **TRIP** in the Netherlands) have each recognized significant underreporting of TACO and poor syndrome recognition^{h, i & j}. Moreover, unlike the **TTISS** which uses the number of units of blood components transfused as denominator in the calculation of the rates, these other systems use the number of units issued which would lead to a lower calculated rate. It is noteworthy that the rates of death definitely, probably or possibly related to blood transfusion were similar in all four countries (Appendix 2).

Overall, it is reassuring that the majority (96%) of all reported reactions for which outcomes were determined resulted in outcomes of minor or no sequelae. This was also found for reactions classified as severe or life-threatening (93% of these cases had an outcome of minor or no sequelae). The TTISS is now well established in Canada and captures the bulk of adverse reactions occurring in Canadian hospitals. Current initiatives underway by the national TTISS working group include developing an algorithm to help front line healthcare professionals distinguish between TACO and TRALI and determining a way to calculate a denominator for blood products. The continued partnership by the Agency with P/Ts and their hospital communities is vital to ensuring collection of quality data that will lead to better policies and procedures within Transfusion and ultimately enhance patient safety for all Canadians.

^h Taylor C (Ed.), Cohen H, Mold D, Jones H, *et al*, on behalf of the Serious Hazards of Transfusion (SHOT) Steering Group. The 2008 Annual SHOT Report (2009).

ⁱ Rapport hémovigilance 2008. Agence Française de sécurité sanitaire des produits de santé (afssaps).

^j TRIP annual report 2010. Hemovigilance Extended version

8. APPENDICES

a. Appendix 1: Total units of blood components transfused by hospitals of the TTISS network, by province/territory, 2006 to 2012

Province/Territory	2006		2007		2008		2009		2010		2011		2012	
	Freq.	%	Freq.	%	Freq.	%	Freq.	%	Freq.	%	Freq.	%	Freq.	%
Alberta	0	0%	10,091	1%	62,895	5%	68,561	6%	71,978	7%	114,734	10%	155,120	12%
British Columbia	181,391	17%	176,588	15%	172,415	14%	173,993	15%	172,696	16%	177,387	15%	177,299	14%
Manitoba	58,676	5%	57,578	5%	60,955	5%	52,525	5%	55,317	5%	54,819	5%	59,893	5%
New Brunswick	33,877	3%	35,144	3%	34,677	3%	29,973	3%	31,242	3%	29,276	2%	32,597	3%
Newfoundland & Lab.	22,485	2%	24,135	2%	23,610	2%	20,556	2%	23,549	2%	23,464	2%	23,856	2%
Nova Scotia	48,331	4%	49,019	4%	34,830	3%	39,965	4%	40,646	4%	42,893	4%	43,205	3%
Northwest Territories	394	0.0%	519	0.0%	560	0.0%	440	0.0%	393	0.0%	348	0.0%	505	0.0%
Ontario	337,340	31%	459,889	38%	390,350	33%	351,611	31%	349,176	32%	378,422	32%	365,591	29%
Prince Edward Island	4,871	0.4%	5,152	0.4%	4,775	0.4%	4,736	0.4%	4,430	0.4%	4,607	0.4%	4,400	0%
Québec	348,364	32%	345,910	28%	352,424	30%	338,005	30%	304,220	28%	310,047	26%	346,565	28%
Saskatchewan	47,647	4%	52,030	4%	53,154	4%	56,082	5%	51,700	5%	48,182	4%	46,707	4%
Yukon Territory	553	0.1%	448	0.0%	654	0.1%	590	0.1%	551	0.0%	499	0.0%	422	0.0%
Total	1,083,929	100%	1,216,503	100%	1,191,299	100%	1,137,037	100%	1,105,898	100%	1,184,678	100%	1,256,160	100%

b. Appendix 2: Comparison of the range of annual rates (per 100,000 units of blood components transfused/issued) during 2006-2012 for major adverse reactions associated with blood transfusion, by country.

	Bacterial Infection	Transfusion-Associated Circulatory Overload (TACO)	Transfusion-Related Acute Lung Injury (TRALI)	Deaths
The United Kingdom	0.0-0.1	0.1-2.7	0.2-0.4	0.2-0.5
France	0.3-0.6	5.9-9.9	1.4-2.3	0.2-0.7
The Netherlands	1.0-9.1	4.4-9.0	1.4- 4.4	0.3-1.0
Canada	0.2-0.8	12.5-18.2	1.5-2.0	0.3-0.8