Transfusion-related acute lung injury (TRALI): a retrospective review of reported cases in Queensland, Australia over 20 years

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Background - Transfusion-related acute lung injury (TRALI) is a rare but potentially fatal transfusion reaction. An effective haemovigilance programme is important in implementing successful and targeted risk reduction strategies. We aim to provide a summary of TRALI cases referred for investigation in Queensland (QLD) Australia from 1999 to 2019, describing the epidemiological and laboratory features of local TRALI cases.

Materials and methods - A retrospective audit evaluated all cases reported to the QLD Australian Red Cross Lifeblood over the 20-year study period. Cases were categorised according to the 2004 Canadian consensus criteria.

Results - Of the 91 cases referred for investigation, expert review confirmed 30 of TRALI and 18 of possible TRALI. A total of 238 donors and 110 blood products were assessed in confirmed cases. TRALI affected patients of all ages. Most patients had underlying haematological malignancies (25%), surgery (15%) or liver disease (13%). TRALI incidence was measured at 1 in 130,000 per issued product in QLD. Red cells were transfused in 32 cases, platelets in 18 and plasma products in 21, with 16 cases involving multiple products. Following laboratory assessment, 23% of cases had findings supportive of antibody mediated TRALI and 21% as likely non-antibody mediated. Possible TRALI was identified in 37.5% of cases of which 25% were antibody mediated and 12.5% non-antibody mediated. Nine (18.5%) cases were uncategorised due to insufficient immunologic investigations.

Discussion - Rates of TRALI incidence measured are lower than those seen in many international studies. A reduction in confirmed cases has been noted over recent years, supporting the implementation of risk-reduction strategies. We report a relatively higher proportion of non-antibody mediated TRALI and possible TRALI cases in more recent years, suggesting the need to further understand the role of product age and biological risk modifiers.

Keywords: *transfusion-related acute lung injury (TRALI), haemovigilance, blood transfusion; adverse effects.*

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INTRODUCTION

Transfusion-related acute lung injury (TRALI) is a serious and potentially fatal transfusion complication. The 2004 TRALI Canadian consensus criteria was adopted for use by both

the International Society of Blood Transfusion (ISBT) and Australian Red Cross Lifeblood (Lifeblood)[1]. This criterion proposes separate case definitions for TRALI and possible TRALI dependent on the presence of clinical criteria and alternate risk factors for acute lung injury (ALI). Recently, there has been a consensus redefinition[2]; however, this has yet to be widely implemented and the Canadian consensus criteria remains the most used classification system.

The pathogenesis of TRALI has been described as a two-hit model[3]. This suggests that the first "hit' relates to predisposing recipient factors (e.g. sepsis) which contribute to the adhesion of primed neutrophils to the endobronchial vascular endothelium. The second "hit" is a consequence of the transfusion and results in activation of the neutrophils, causing endothelial damage[3]. TRALI is commonly differentiated into antibody mediated and non-antibody mediated depending on the second hit[4]. Non-antibody mediated TRALI may be related to biological response modifiers (BRMs) within the transfused product[5]. BRMs have been found to accumulate during blood product storage including in red blood cells leukocyte depleted (RBC) and platelets[6]. Antibody mediated TRALI is considered the result of transfusing human neutrophil antigen (HNA) or human leucocyte antigen (HLA) antibodies that match a cognate recipient antigen[7].

With a decline in infectious complications, TRALI became one of the leading causes of transfusion-related mortality[8], though it has now been surpassed by transfusion-associated cardiac overload (TACO)[9]. Estimates of TRALI incidence vary markedly between 0.08 to 15% per patient transfused and 0.0002-1.12% per transfused product[4,10-15]; however, TRALI is likely under-diagnosed and under-reported especially in critically ill patients[16]. TRALI has a mortality rate estimated between 5-25%[4,17], but can be higher among critically ill and surgical patients, with a rate of 47% reported in intensive care patients[18]. Clinical management of TRALI is supportive and consequently, efforts to reduce TRALI have focussed on preventative strategies[19]. As HLA and HNA antibodies are found most frequently in multiparous women[20], TRALI risk-reduction has focused on reducing patient exposure to plasma from female donors[19].

In Australia, the state of Queensland (QLD) has a population of approximately 5 million people[21]. Lifeblood is responsible for the collection and distribution of blood products Australia-wide[22]. About 135,000 units of RBC, 36,000 units of plasma and 31,000 units of platelets were distributed to QLD health services in 2020. To mitigate TRALI risk, male predominant plasma was introduced in Australia in July 2007, and made up 100% of clinical plasma by 2012[23]. TRALI attributed to apheresis platelets was minimised by moving to a plateletpheresis panel comprised of only male donors by July 2016[24], and reducing plasma content in apheresis platelets by resuspension in platelet additive solution (PAS) in March 2019[25]. Lifeblood produces buffy coat derived pooled platelets and apheresis platelets, both of which are resuspended in PAS. This reduces the amount of plasma in platelet concentrates from 100% to approximately 40% in apheresis platelets and 30% in pooled platelets.

Despite decades of risk-reduction strategies, a comprehensive longitudinal review of cases reported to Lifeblood QLD has not been performed. We provide a summary of TRALI cases reported to Lifeblood QLD from 1999 to 2019 to describe the epidemiological and laboratory features of TRALI locally.

MATERIALS AND METHODS

Data collection and review

In Australia, suspected TRALI cases are reported to Lifeblood for further investigations and donor management. This study accessed all cases of suspected TRALI referred to Lifeblood QLD between March 1999 and December 2019. The 2004 Canadian consensus definition was applied[26] and cases were categorised as either "TRALI", "possible TRALI", "not TRALI" or "insufficient data" based on three independent reviewer assessments. Each patient and all associated donors were comprehensively reviewed, including historical records of clinical findings and interventions obtained from referring clinicians at the time of reporting the case.

TRALI clinical characteristics

Severity grades for cases were defined using criteria adopted by the French Haemovigilance Network[12]:

- Mild: spontaneous recovery or supplemental oxygen *via* face mask.
- Severe: requiring non-invasive ventilation or transfer to an intensive care unit.
- Life-threatening: requiring invasive mechanical

ventilation with or without additional therapy e.g. vasopressors.
- Death: where there was a temporal relationship between death and TRALI.

TRALI incidence

TRALI incidence was calculated from 2006-2019, as total issued blood product numbers were only available for this timeframe. Incidence rates were computed by dividing the number of TRALI and possible TRALI cases by the total number of blood products issued. Calculations did not account for blood products discarded post-issue.

The number of cases before and after 2012 were measured by TRALI subtype (antibody mediated/non-antibody mediated) to assess for changes in the proportions of TRALI cases.

Donor and recipient antibody testing

Assessing the presence of donor leucocyte antibodies and compatibility testing is a critical part of the TRALI investigative process[27]. TRALI is a clinical diagnosis and absence of antibodies does not reject or reduce the possibility of TRALI; however, the results guide the management of implicated donors and blood products. As part of Lifeblood practice, all involved donors are temporarily deferred, and available associated products quarantined while laboratory investigations conclude. If donor leucocyte antibodies are confirmed, the donor may be permanently deferred from future clinical donations, depending on antibody type and clinical significance[27].

Over the 20-year period there were several improvements in laboratory assays used; however, testing for HLA and HNA donor antibodies remained a constant. If HLA or HNA antibodies were detected, a virtual crossmatch was done. HLA and HNA genotyping were performed on the recipients' samples. HLA typing and antibody testing was earlier performed by the Victorian (V) Transplantation and Immunogenetics Service (TIS) laboratory of Lifeblood using sequence-specific oligonucleotide (SSO) for HLA typing and antibody screening by complement dependent microlymphocytotoxicity (LCT) assay. HLA antibody screening by LCT was replaced by solid phase immunoassay (Luminex LABScreen) from 2006.

The Queensland (Q) TIS laboratory implemented HLA antibody testing in 2014 and HLA genotyping in 2018 using the same methods as VTIS. Granulocyte antibody testing was performed by granulocyte immunofluorescence test (GIFT), granulocyte agglutination test (GAT) and the monoclonal antibody immobilisation of granulocyte antigen assay (MAIGA) as required[28]. HNA genotyping was performed using validated in-house methods; Real time Taqman polymerase chain reaction (PCR) and an allele specific PCR using sequence specific primers (PCR-SSP)[28].

Case definitions for antibody mediated and non-antibody mediated TRALI were based on those used by Ozier *et al.*[29]. A case was classified as "antibody mediated" if an antibody to a cognate recipient antigen was detected, a positive granulocyte crossmatch was observed, or if an antibody to a ubiquitous antigen was identified. Cases where no antibodies were found, or where an identified antibody did not meet the above criteria were labelled as "non-antibody mediated". Unlike Ozier *et al.*, cases were labelled "uncategorised" rather than "non-antibody mediated" if there were insufficient immunologic investigations including genotyping/phenotyping.

In reverse TRALI, patient antibodies react with cognate antigens on transfused cells[30]. Where possible, we also tested for recipient HNA and HLA antibodies using the methods described above, although this did not occur in all cases.

Product characteristics

The blood products associated with each referred TRALI case were assessed. Details collected included blood product type, number of units transfused and product age. Adjusted age was calculated by dividing the age of the transfused product with the product's total shelf life. This was used to assess the influence of blood product storage duration on TRALI incidence.

The platelet product type was assessed. This included platelet-rich plasma (PRP) platelets, buffy coat derived pooled platelets and apheresis platelets. Pooled platelet processing was introduced in July 2002, though PRP platelets continued to be produced until June 2007. Therefore, there was a mixed inventory of the two types from July 2002 to June 2007. Leucodepletion (RBC and platelets) was introduced in October 2008.

Statistical analysis

Fisher's exact tests or chi-squared tests were used to compare incidence data. Unpaired t-tests were used to analyse continuous variables. Results were considered significant if the two-tailed p-value was ≤0.05.

RESULTS

Overall description (1999-2019)

A total of 91 cases were referred to Lifeblood QLD over the 20-year study period (*Online Supplementary* **Figure S1**). Thirty cases were categorised as TRALI and 18 as possible TRALI. Of the remaining 43 cases, 33 were categorised as not TRALI, nine had insufficient information for categorisation, and one was withdrawn from investigation.

Patient and clinical characteristics

The patient's clinical condition can contribute to the development of TRALI[4]. Therefore, the clinical characteristics of TRALI and possible TRALI patients were reviewed (**Table I**) and found to be similar. TRALI was seen in all ages and affected genders similarly. Incidence was highest in persons aged 41-50 years and referrals were equal among metropolitan and regional hospitals. Most patients had underlying haematological and non-haematological malignancies, surgery and liver disease. For cases of possible TRALI, the most common ALI risk factors included shock (28%), pneumonia (28%) and sepsis (22%).

Symptoms were seen within an hour of transfusion onset in 86.7% of TRALI cases and 55.6% of possible TRALI cases.

Table I - *Demographics and clinical characteristics of TRALI and possible TRALI cases between 1999 and 2019*

Characteristics		TRALI	Possible TRALI	All categories
Number		**30**	**18**	**48**
Sex	• Males	15 (50.0%)	11 (61.1%)	26 (54.2%)
	• Females	15 (50.0%)	7 (38.9%)	22 (45.8%)
	• Sex ratio M/F	1.0	1.6	1.2
Age (years)	• Mean	47.1	48.5	47.6
	• Median	46.5	47.5	47.5
	• Range	4-84	2-87	2-87
Hospital Location	• Metropolitan	16 (53.3%)	8 (44.4%)	24 (50.0%)
	• Rural/Regional	14 (46.7%)	10 (55.5%)	24 (50.0%)
Fatalities		**0 (0%)**	**2 (11.1%)**	**2 (4.2%)** [a]
Primary clinical condition	• Haematological malignancy	8 (26.7%)	4 (22.2%)	12 (25.0%)
	• Surgery	2 (6.7%)	5 (27.8%)	7 (14.6%)
	• Liver disease	4 (13.3%)	2 (11.1%)	6 (12.5%)
	• Non-haematological malignancy	4 (13.3%)	1 (5.6%)	5 (10.4%)
	• Aplasia/MDS	3 (10.0%)	1 (5.6%)	4 (8.3%)
	• Trauma	3 (10.0%)	1 (5.6%)	4 (8.3%
	• Immunological disorder	2 (6.7%)	0 (0.0%)	2 (4.2%)
	• Other	4 (13.3%)	4 (22.2%)	8 (16.7%)
ALI risk factors	• Shock		5 (27.8%)	
	• Pneumonia		5 (27.8%)	
	• Sepsis		4 (22.2%)	
	• Cardiopulmonary bypass		3 (16.7%)	
	• Multi-trauma		1 (5.6%)	
Timing of onset (hr)	• <1 hr post	26 (86.7%)	10 (55.6%)	36 (75.0%)
	• 1-3 hrs post	2 (6.7%)	4 (22.2%)	6 (12.5%)
	• 3-6 hrs post	2 (6.7%)	4 (22.2%)	6 (12.5%)
Clinical features	• Evidence of hypoxia and/or respiratory distress [b]	30 (100%)	18 (100%)	48 (100%)
	• Chest radiological findings	30 (100%)	18 (100%)	48 (100%)
Admitted to ICU[c]		**6 (20.0%)**	**6 (33.3%)**	**12 (25.0%)**
Treatment	• Oxygen	26 (86.7%)	17 (94.4%)	43 (89.6%)
	• Furosemide	13 (43.3%)	6 (33.3%)	19 (39.6%)
	• Respiratory support	9 (30.0%)	7 (38.9%)	16 (33.3%)
	• Steroids	7 (23.3%)	2 (11.1%)	9 (18.8%)
	• Other	6 (20.0%)	6 (33.3%)	12 (25.0%)
	• Treatment not stated	1 (3.3%)	1 (5.6%)	2 (4.2%)
Severity	• Mild	15 (50.0%)	4 (22.2%)	19 (39.6%)
	• Severe	5 (16.7%)	4 (22.2%)	9 (18.8%)
	• Life threatening/Death	10 (33.3%)	10 (55.6%)	20 (41.7%)

[a]excludes fatality events unrelated to TRALI; [b]Hypoxia presenting with either low oxygen saturations or need for oxygen/ntilator support; [c]Admitted to ICU at time of reporting.

All patients presented with recorded evidence of hypoxia, respiratory distress and supportive chest radiograph findings. The severity of symptoms differed between patients; ranging from needing supplemental oxygen to mechanical ventilation. All cases where treatment was recorded had supplemental oxygen, in conjunction with additional respiratory support, diuretics (e.g. furosemide) and corticosteroids in many cases.

Two fatalities were observed, therefore the mortality rate of TRALI/possible TRALI patients in QLD was 4.2%. These fatalities were possible TRALI cases and categorised as non-antibody mediated. Plasma was implicated in one case, while multiple products were involved in the other. In terms of clinical characteristics, the two patients were similarly aged (46 *vs* 47 years) but had differing clinical conditions (liver disease *vs* haematological malignancy).

TRALI incidence

TRALI is associated with all blood products; however, typically incidence is higher in high plasma-containing products (e.g. plasma and platelets)[13,15,29,31]. Therefore, the risk of TRALI and possible TRALI per blood product issued was calculated (**Table II**). Considering 4,174,356 units were issued from 2006-2019, the risk of TRALI was calculated at 1 in 130,000 per any issued product. The risk of TRALI was highest in plasma products, calculated at 1 in 13,000 units compared to 1 in 42,000 and 1 in 21,000 units for RBC and platelet products respectively. The different platelet types were all implicated, though cases involving pooled platelets were most common (10 cases), followed by PRP (6 cases) and apheresis platelets (4 cases). Buffy coat derived pooled platelets in Australia includes donations from female donors. Mixed sex pools accounted for 80% of cases involving pooled platelets, compared to 20% from all male pools.

Various risk-reduction strategies were implemented during the study period (**Figure 1**), including the use of plasma exclusively from male donors in 2012 and male plateletpheresis donors in 2016. There was a notable decline in TRALI and possible TRALI cases following the implementation of these strategies, with only five TRALI and four possible TRALI cases observed since 2012. There were no confirmed cases of TRALI between 2016 and 2018.

Table II - *Risk of TRALI per product issued, in QLD from 2006 to 2019*

Blood Product	All	Red cells	Platelets	Plasma[a]
No. of units issued	4,174,356	2,068,022	344,288	616,656
Number of units associated with TRALI cases[b]				
TRALI (19 cases)[c]	66	27	11	28
Possible TRALI (13 cases)	47	22	6	19
Total (32 cases)	113	49	17	47
Risk of blood product being associated with a case				
TRALI (19 cases)	1 in 220,000	1 in 76,000	1 in 33,000	1 in 22,000
Possible TRALI (13 cases)	1 in 320,000	1 in 94,000	1 in 57,000	1 in 32,000
Total (32 cases)	1 in 130,000	1 in 42,000	1 in 21,000	1 in 13,000

[a]Includes FFP and cryoprecipitate. [b]Some cases had multiple products associated. [c]Includes only cases from 2006-2019, as issued blood product numbers were only available for this timeframe.

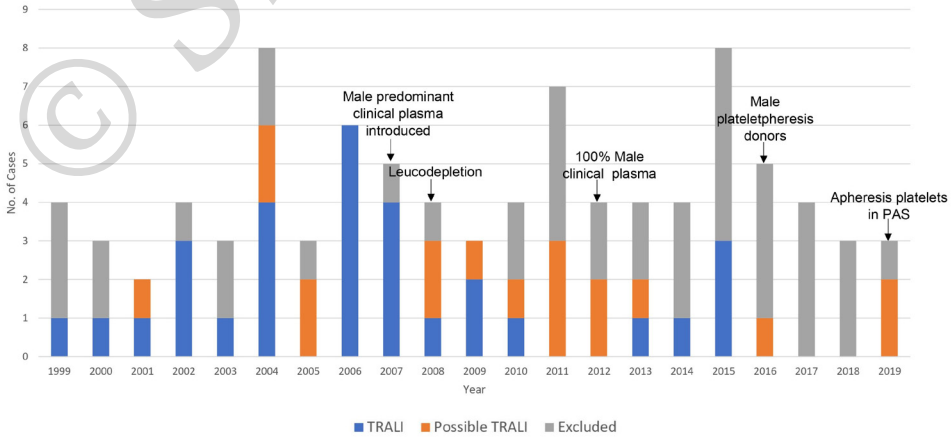

Figure 1 - Number of cases referred for TRALI investigations to Lifeblood QLD from 1999-2019 and display of case categorisation by year. Shows key risk reduction strategies implemented in QLD during study period by year

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Donor antibody testing

Antibody investigations are important for donor management and reducing the risk of TRALI[27]. The 48 TRALI/possible TRALI patients received blood products from 238 donors, with a mean of 4.9 donors per case (median 4, range 1-17). The male to female ratio of donors was 131: 107 (55%: 45%) (**Table III**). In 10 cases, only male donors were implicated. In 11 cases, only female donors were associated and this was only noted prior to 2011.

Of the 238 donors, 76 (32%) had a positive HLA/HNA antibody screen, with a male to female ratio of 30: 46 (**Table III**). HLA antibodies were most commonly detected. Many donors had more than one antibody type, and this was more common in female donors. Parity information was available for 73 out of 107 female donors and 57 (78%) had a previous history of pregnancy. Female donors of increased parity had a greater incidence of HLA antibodies. Testing was not completed for one female donor. Following investigations, 117 (49.2%) donors were permanently deferred from blood donation (**Table III**).

Antibody mediated and non-antibody mediated TRALI/possible TRALI

Detection of donor antibodies does not necessarily implicate them as the causative agent in a TRALI case as the recipient may not express the cognate antigen and not all cases are associated with antibodies[32]. Therefore, we used similar methods to Ozier *et al.*[29] to distinguish between antibody mediated and non-antibody mediated cases. HLA/HNA antibodies were detected in 75% of cases (**Table IV**), of which 48% had laboratory findings supportive of antibody mediated TRALI and possible TRALI. Excluding the nine uncategorised cases resulted in antibody mediated TRALI/possible TRALI accounting for 59% of categorised cases compared to 41% of non-antibody mediated TRALI/possible TRALI categorised cases.

Of the antibody types, HLA class I antibodies were most commonly detected (45.8%), followed by HLA class II antibodies (33.3%) either in isolation or in combination with other antibody types. In cases of antibody mediated TRALI, multiple antibody specificities were common, of which HLA class II antibodies were most observed (81.8%) in combination with other types. There was a notable decrease in proportions of antibody mediated TRALI/possible TRALI over the study period (*Online Supplementary* **Figure S2**), with non-antibody mediated presentations being more frequent after 2012 (8 *vs* 3 cases, p=0.03).

The majority of cases involved only RBC transfusions (37.5%), though many were associated with multiple products (33.3%) (**Table V**). We observed a higher proportion of non-antibody mediated TRALI cases were associated with only RBC units (**Table V**). Pooled platelets were the most common platelet product type involved in cases. Of the cases involving pooled platelets, 70% were involved in antibody mediated TRALI/possible TRALI, 20% in non-antibody mediated TRALI/possible TRALI and 10% in uncategorised cases (*data not shown*).

Blood product storage is associated with BRM accumulation that is thought to precipitate non-antibody mediated TRALI[33]. Accordingly, various laboratory and animal models have demonstrated non-antibody mediated TRALI following transfusion with fractions of date-of-expiry blood products[6]. Therefore, we examined the storage duration of blood products associated with cases (**Table V**). The mean age of transfused RBC, platelets and plasma was 19.3, 3.7 and 43.6 days respectively. There was no significant difference in the mean storage duration of transfused RBC or platelets between non-antibody mediated and antibody mediated TRALI cases or between non-antibody mediated and antibody mediated possible TRALI cases (**Table V**).

Table III - *HLA/HNA antibody investigations in donors associated with TRALI cases between 1999-2019*

Investigations	All donors	Male	Female
Antibody screen	**(n=238 donors)**	**(n=131 donors)**	**(n=107 donors)**
HLA/HNA antibodies detected	76 (31.9%)	30 (12.6%)	46 (19.3%)[a]
HLA/HNA antibodies not detected	158 (66.4%)	98 (41.2%)	61 (25.6%)
Not tested	4 (1.7%)	3 (1.3%)	1 (0.4%)
Antibody specificity	**(n=76 donors)**	**(n=30 donors)**	**(n=46 donors)**
HNA only	18 (23.7%)	8 (10.5%)	10 (13.2%)
HLA class I only	22 (28.5%)	13 (17.1%)	9 (11.8%)
HLA class II only	16 (21.1%)	7 (9.2%)	9 (11.8%)
Multiple types (HLA class I, II and/or HNA)	20 (26.3%)	2 (2.6%)	18 (23.7%) [a]
Donor outcomes	**(n=238 donors)**	**(n=131 donors)**	**(n=107 donors)**
Donor deferred	117 (49.2%)	52 (21.8%)	65 (27.3%) [a]
Donor cleared	121 (50.8%)	79 (33.2%)	42 (17.6%)[a]

[a]p-value <0.05 *vs* male donors.

Table IV - *HLA/HNA antibody investigations in TRALI cases between 1999-2019*

Investigations		All	Antibody mediated TRALI	Non-antibody mediated TRALI	Antibody mediated possible TRALI	Non-antibody mediated possible TRALI	Uncategorised TRALI[a]
Number of cases [cases (% of all cases)]		48	11 (22.9%)	10 (20.8%)	12 (25.0%)	6 (12.5%)	9 (18.8%)
HLA/HNA antibody screen [cases (% of cases for column)]	Antibodies detected	36 (75.0%)	11 (100%)	1 (10.0%)	12 (100%)	3 (50.0%)	9 (100%)
	• Concordant	23 (63.9%)	11 (100%)	0 (0%)	12 (100%)	0 (0%)	N/A
	• Non-concordant	4 (11.1%)	0 (0%)	1 (10.0%)	0 (0%)	3 (50.0%)	N/A
	No antibodies detected	12 (25.0%)	0 (0%)	9 (90.0%)	0 (0%)	3 (50.0%)	0 (0%)
Concordant antibody specificity [cases (% of cases for column)]	HLA Class I only	4 (8.3%)	1 (9.1%)	0 (0%)	3 (27.3%)	0 (0%)	N/A
	HLA Class II only	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	N/A
	HNA only	1 (2.1%)	1 (9.1%)	0 (0%)	0 (0%)	0 (0%)	N/A
	Multiple specificities[b]	18 (37.5%)	9 (81.2%)	0 (0%)	9 (75.0%)	0 (0%)	N/A
	HLA class I +II	4 (8.3%)	2 (18.2%)	0 (0%)	2 (16.7%)	0 (0%)	N/A
	HLA class I + HNA	3 (6.3%)	0 (0%)	0 (0%)	3 (25.0%)	0 (0%)	N/A
	HLA class II + HNA	4 (8.3%)	3 (27.2%)	0 (0%)	1 (8.3%	0 (0%)	N/A
	HLA class I/II + HNA	7 (14.6%)	4 (36.4%)	0 (0%)	3 (25.0%)	0 (0%)	N/A
Non-concordant antibody specificity [cases (% of cases for column)]	HLA Class I only	3 (6.3%)	0 (0%)	1 (10.0%)	0 (0%)	2 (33.3%)	N/A
	HLA Class II only	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	N/A
	HNA only	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	N/A
	Multiple specificities	1 (2.1%)	0 (0%)	0 (0%)	0 (0%)	1 (16.7%)	N/A
	HLA class I + II	1 (2.1%)	0 (0%)	0 (0%)	0 (0%)	1 (16.7%)	N/A

[a]Uncategorised TRALI cases lacked donor testing to define concordance, and in these cases antibody detection was as follows: only HLA class I in 1 (11.1%) case, only HLA class II antibodies in 3 (33.3%) cases, only HNA antibodies in 2 (22.2%) cases and multiple specificities in 3 (33.3%) cases. [b]Some cases had more than one antibody type.

Table V - *Products associated with referred TRALI cases in Queensland, 1999-2019*

Products	All cases (n=48)	Antibody mediated TRALI (n=11)	Non-antibody mediated TRALI (n=10)	Antibody mediated possible TRALI (n=12)	Non-antibody mediated possible TRALI (n=6)	Uncategorised TRALI (n=9)
Red cells only	18 (37.5%)	1 (9.1%)	7 (70.0%)[a]	3 (33.3%)	3 (50.0%)	4 (44.4%)
Plasma products only	10 (20.8%)	4 (36.4%)	1 (10.0%)	1 (8.3%)	2 (33.3%)	2 (22.2%)
Platelets only	4 (8.3%)	2 (18.2%)	0 (0%)	2 (16.7%)	0 (0%)	0 (0%)
Multiple products	16 (33.3%)	4 (36.4%)	2 (20.0%)	6 (50.0%)	1 (16.7%)	3 (33.3%)
Red cell cases	32	4	9	8	4	7
Units	80	11	18	28	8	15
Mean age (days)	19.3	16.2	16.7	17.7	18.0	28.0
Mean adjusted age	0.46	0.36	0.40	0.43	0.43	0.67
Platelets cases	18	5	2	8	1	2
Units	26	4	2	9	2	2
Mean age (days)	3.5	3.7	4.5	3.5	3.0	3.0
Mean adjusted age	0.70	0.74	0.9	0.67	0.60	0.6
Plasma cases	21	8	2	5	2	4
Units	75	25	3	22	5	20
Mean age (days)	43.6	24.5	130	63.6	29.2	37.1
Mean adjusted age	0.12	0.09	0.36	0.17	0.08	0.1

[a]p-value <0.05 *vs* antibody mediated TRALI.

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DISCUSSION

This was the first longitudinal review of TRALI cases reported in QLD, Australia. It covered a 20-year period with changes in clinical practice, investigation policies, and HLA/HNA testing platforms as well as the introduction of risk-reduction strategies. We observed a low incidence of TRALI and possible TRALI in QLD, with a decrease in cases following the implementation of risk-reduction strategies. Proportions of antibody mediated and non-antibody mediated TRALI/possible TRALI were similar, though non-antibody mediated cases were comparatively higher after 2012.

The cohort of patients included in this review were referred to Lifeblood prior to publication of the 2019 re-definition[2]. Therefore, our study used the 2004 Canadian consensus definition for TRALI as this was the definition applied in Australia at the time of these cases. Furthermore, this remains the definition currently in use in Australia and is still widely used worldwide[34-37]. Its use in this study also allowed for comparison with previous reports of TRALI cases[4,29]. Nonetheless, the 2019 re-definition is likely to be increasingly adopted around the world in the coming years as validation studies are completed[37, 38] and in this context its implementation in Australia is under consideration[34]. Due to the recognition of under-reporting[17], Lifeblood has a low threshold for initiating TRALI investigations upon referral of an adverse reaction. The reporting of suspected TRALI cases to Lifeblood does not influence clinical management and referrals are predominately considered from a donor management perspective. In the cases categorised as "not TRALI", either the required clinical criteria were not met, or it became apparent following discussion with clinicians that an alternative transfusion reaction or non-transfusion complication caused the presentation.

TRALI mortality in QLD was estimated as 4.2%. This was comparable to the 5-25% reported elsewhere[4,15,17,29,39-41], considering that lower rates in this range are more common[4,29,39-41]. Possible TRALI might be associated with higher mortality and severity than TRALI due to underlying ALI risk factors[42]. The two fatalities that we observed were both possible TRALI cases, with no fatalities observed in the TRALI group.

TRALI incidence in QLD was estimated as 1 in 130,000 (0.0008%) per issued product. Reported TRALI incidence rates vary widely. Our finding was comparable with reports ranging from 0.0002 to 0.03%[10,11,13,15], and aligned with rates from passive reporting systems[11-13,15]. TRALI is thought to be grossly under-diagnosed and under-reported especially among the critically ill[16], which may also be the case in our study. It is considered that since ALI is so common among the critically unwell, TRALI is rarely recognised[16]. Several cases included in this study were managed with interventions that are not indicated in TRALI management, including the use of diuretics and corticosteroids. While this clinical management may have been tailored to the clinical features seen at the time of the reaction (e.g. to exclude fluid overload), this might reflect a lack of understanding of TRALI. We noted a reduction in the number of confirmed TRALI cases over the study period; however, TRALI referrals were consistent and this may reflect increased clinical consideration.

Reporting of haemovigilance data in Australia is voluntary and based on state-based haemovigilance programs. Until 2013, the QLD haemovigilance system was centralised but now haemovigilance data validation occurs at the hospital and health services level. Passive reporting systems such as this underestimate incidence rates when compared with active systems[43-46]. Likewise prospective studies that review transfused patients[14,46], and prospective observational studies[16] report higher incidence rates. TRALI incidence also varies between patient groups, with higher rates amongst those who are critically unwell or have specific clinical risk factors[4,43,47], including haematological malignancies and surgical patients[13-15,29]. The patient groups in our cohort reflected those reported in most studies[12,13,15,29,41]; however, certain at-risk groups (e.g. cardiopulmonary bypass patients), were under-reported. TRALI incidence was highest in patients aged 41-50 years, which was younger than the average age of patients receiving RBC products in Australia (65-84 years)[23]. Similar numbers of TRALI referrals were from metropolitan and regional QLD hospitals, despite metropolitan hospitals being issued more units of blood. Considering this, TRALI rates were comparatively low in QLD tertiary centres. This may relate to differences in reporting practices among different sites. Variations in reporting practices can be observed between hospitals in addition to variations from year-to-year[48].

Risk-reduction strategies, such as male predominant/

exclusive plasma, male-only plateletpheresis panels and reducing the volume of plasma in blood products, all address antibody mediated TRALI[6]. Accordingly, QLD TRALI incidence decreased with the introduction of risk-reduction measures. For example, following the introduction of a male-only plateletpheresis panel in 2015, we observed only three cases of possible TRALI. Similar findings have been reported elsewhere[10,15,19,43]. Differences in when risk-reduction strategies were implemented in different jurisdictions could account for variations in reported rates of TRALI[49]. Considering the risk-reduction strategies implemented by Lifeblood, our findings may align better with recent studies[12].

TRALI occurs with most blood products[50], but high plasma volume products, including FFP and some platelet products (e.g. PRP and apheresis platelets), are most frequently implicated[13,15,29,31]. We observed cases related to RBC, platelets, FFP, and cryoprecipitate. RBC were most involved, particularly in non-antibody mediated TRALI. However, comparatively more RBC units were issued, and once adjusted for this they had the lowest relative risk of TRALI. Similar findings were noted in France[41]. We observed that pooled platelets were more frequently implicated compared to other platelet products. This differs from other studies where platelet products with higher plasma volumes were more commonly associated[29]. However, residual plasma volume as small as 10-20 mL can contain leukocyte antibodies and cause TRALI[49].

Laboratory investigations are important for blood donor management[27], and as seen elsewhere[15], have evolved over time. In QLD, testing for HLA and HNA donor antibodies was performed throughout the entire study period, while antigen-antibody concordance by HLA/HNA genotyping of recipients was introduced after 2004. The reported frequency of antibodies in TRALI varies widely, with HNA antibodies in 0.0 to 33.3% of cases, and HLA antibodies in 11.4 to 67% of cases[13, 51-53]. HLA class II antibodies (either in isolation or in combination with other antibodies) were detected in at least one donor for 82% of antibody mediated TRALI cases in QLD. This corresponded with other reports that HLA class II antibodies are the most frequently detected antibody type in antibody mediated TRALI[13,15,29,51,52].

Historically, antibodies are associated with up to 80% of TRALI cases[7,54]. In QLD, we observed only 23% of antibody mediated TRALI cases. This increased to 48% when including antibody mediated possible TRALI. Notably, nine cases (19%) did not have HLA/HNA genotyping performed. This meant that antibody-antigen concordance could not be assessed, and we reported these cases as "uncategorised TRALI". This might have contributed to our lower antibody mediated TRALI rate, as some studies consider cases as antibody mediated if positive leucocyte antibodies are present irrespective of antigen/antibody compatibility[7,54]. However, a mechanism for how non-concordant antibodies might cause TRALI is unexplained, and studies that took a similar approach to ours reported similar rates of antibody mediated TRALI from 20 to 58%[12,13,29]. Excluding the nine uncategorised TRALI cases from our analyses resulted in antibody mediated TRALI/possible TRALI accounting for 59.0% of cases.

Cases in which antibodies are not detected can be referred to as non-antibody mediated TRALI[52]. In QLD, non-antibody mediated TRALI comprised 20.8% of cases, which increased to 33.3% when including non-antibody mediated possible TRALI. When uncategorised TRALI cases were excluded, these rates increased to 25.6% and 41.0% respectively. These rates were similar to those reported in other retrospective studies[12,29,54]. For instance, reports from the French and German haemovigilance networks reported non-antibody mediated TRALI in 26% and 25% of cases respectively[12,54]. Experimental models have demonstrated non-antibody mediated TRALI development following exposure to date-of-expiry RBC or platelet units, and to specific BRMs[6]. Therefore it seems likely that non-antibody mediated TRALI is dependent upon BRMs that accumulate in RBC and platelet units during routine storage[6]. However, the average age of RBCs transfused for TRALI cases in our study was 19.3 days with no difference in RBC storage time between antibody mediated and non-antibody mediated TRALI. Similarly, we observed no difference in platelet storage duration between antibody mediated and non-antibody mediated TRALI cases. We note that clinical evidence for an association between storage duration and TRALI is limited and many clinical studies have similarly failed to show an association between blood product age and TRALI risk[18,43]. It is also recognised that differences in storage variables can be partially donor dependent[55] and information about "good" and "poor" storers was

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unknown in this study. Furthermore, reverse TRALI may account for some of the cases in this cohort which were identified as non-antibody mediated. Leukoreduction had been considered to reduce the risk of reverse TRALI; however, recent case reports suggest it is still a concern[30]. Laboratory experiments and a case report provided evidence that soluble antigens released during blood component processing could induce reverse TRALI when transfused to pre-immunised recipients[56]. The continued possibility of reverse TRALI highlights the importance of testing for recipient neutrophil and HLA antibodies. While we completed this in many of the investigations, it was not always possible, and this highlights an area for improvement in the future.

CONCLUSIONS

TRALI incidence in QLD was comparatively lower than other studies. Risk-reduction strategies have decreased the incidence of antibody mediated TRALI/possible TRALI, resulting in a higher proportion of non-antibody mediated TRALI/possible TRALI cases in recent years. Further investigations into blood product age and the role of BRMs is needed to inform the development of additional TRALI risk-reduction strategies.

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AUTHORSHIP CONTRIBUTIONS

FS, SB, JPT, NG and AS were involved in extracting and interpreting the data. SB, JPT and FS were involved in reviewing the referred cases. AS and FS were involved in preparing the initial manuscript. All Authors were involved in preparing the final manuscript and approved the submitted version.

The Authors declare no conflicts of interest.

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