Transfusion-related Acute Lung Injury (TRALI) : Pathophysiology and Prevention

Anne Eder, MD PhD
Executive Medical Officer

Sociedad Chilena de Hematologia

October 29, 2010

American Red Cross

Objectives

Transfusion-related acute lung injury (TRALI)

1. Review a clinical case of TRALI
2. Discuss the pathophysiology of TRALI
3. Describe the current strategies taken by blood donor centers to reduce the risk of TRALI

Case: Presentation

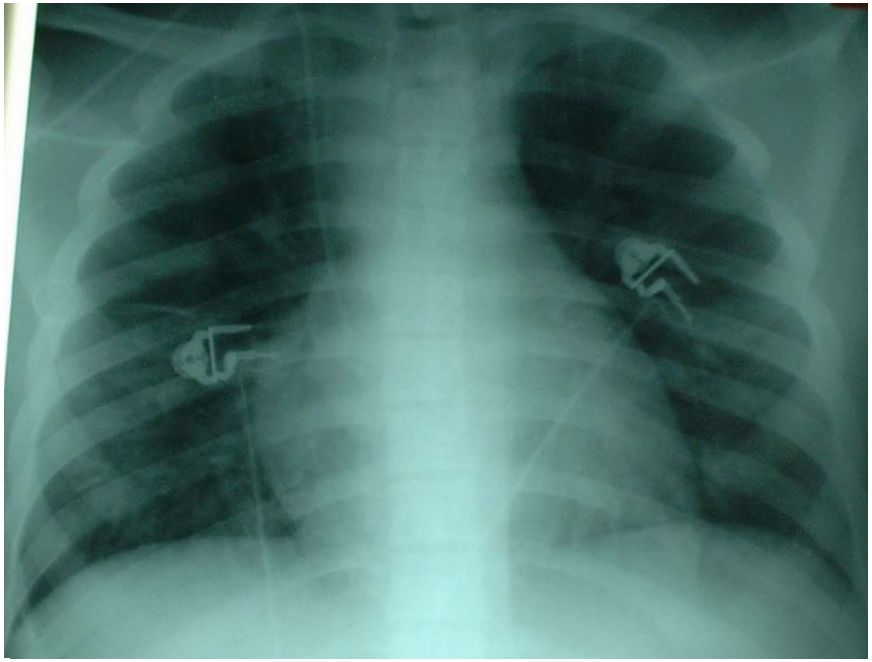
- 18-year-old male with T cell lymphoblastic lymphoma
- In the pediatric intensive care unit for 10 days recovering from bacterial (Gram-negative rod) sepsis
- Vital signs stable, no respiratory distress before transfusion
- Receives 1 apheresis platelet unit for low platelet count (12 x 10^9/L)

Case: Transfusion reaction

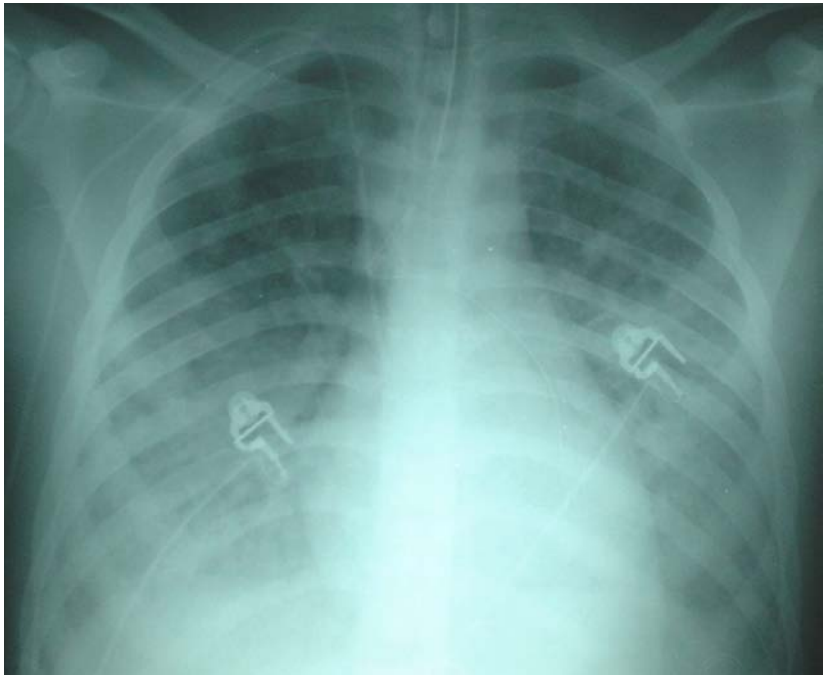
- One hour after receiving the apheresis platelet unit (450 mL; 3rd day of storage), reported chest tightness, dyspnea
- Acute respiratory distress
- Hypoxemic, O_2 sats <70s
- Intubated, noted to have copious pink frothy secretions from airway;
  Blood gas FiO_2 100%; O_2 48.7; sat 68.9

Case : Chest X-ray

Transfusion-related acute lung injury (TRALI)



Before Transfusion



20’ After

Case: Clinical Course

- Supportive treatment
  - Mechanical ventilation, low tidal volume
  - Diuretics not indicated, may be harmful
- Chest X-ray: Showed improvement of pulmonary edema within 24 hrs
- Blood center investigation revealed serologic evidence of TRALI
  - HLA Class II match between female multiparous platelet donor (anti-DR4) and patient ($DR4^{+}$)

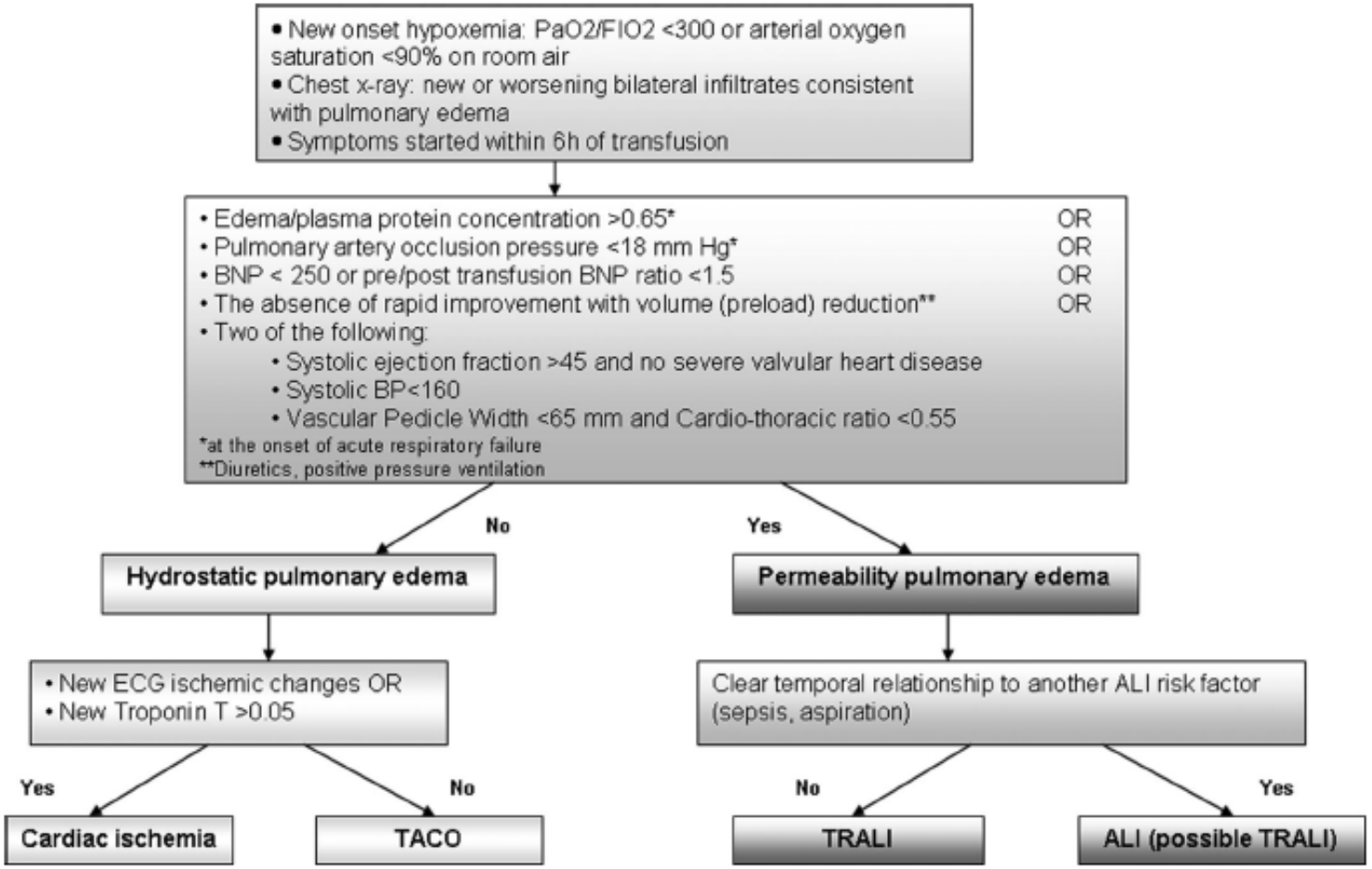
TRALI is a Clinical Diagnosis

Canadian Consensus Definition	
Acute onset (within 6 hours of transfusion)	√
Hypoxemia (SpO_2< 90% on room air)	√
Bilateral infiltrates on frontal CXR Evidence of pulmonary edema	√
No evidence of circulatory overload Pulmonary artery pressure < 18 mm Hg	√
No preexisting ALI before transfusion	√
No other risk factor for acute lung injury (e.g., sepsis, aspiration, pneumonia, cardiopulmonary bypass) (if present, Possible TRALI)	√

Kleinman S, *et al Transfusion* 44, 1774 2004

American Red Cross

TRALI vs. TACO

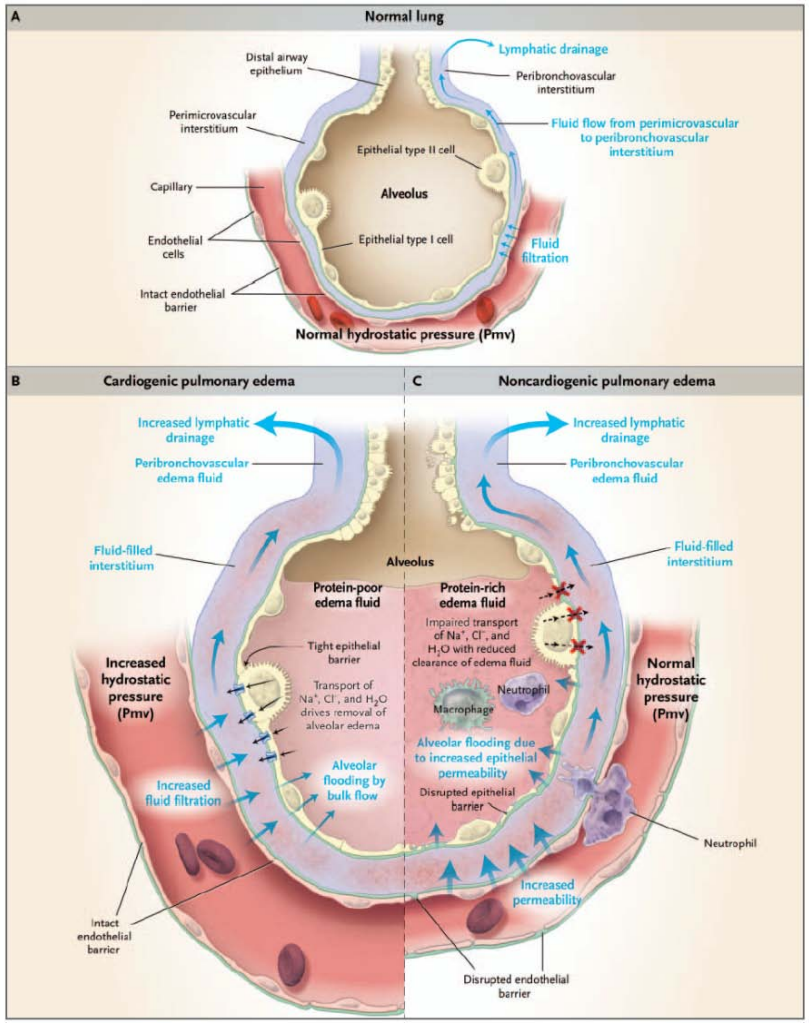


Gajic O et al..Crit Care Med. 34(5 Suppl):S109-S113; 2006

American Red Cross

TRALI: Pathogenesis

Noncardiogenic pulmonary edema



TRALI Etiology:

- Direct Granulocyte activation by HLA or HNA antibodies
- Neutrophil activation by underlying disease with triggering by transfused bioresponse modifiers

Ware and Matthay, NEJM 353:2788, 2005.

American Red Cross

TRALI : Unifying theory

Immune-mediated mechanism

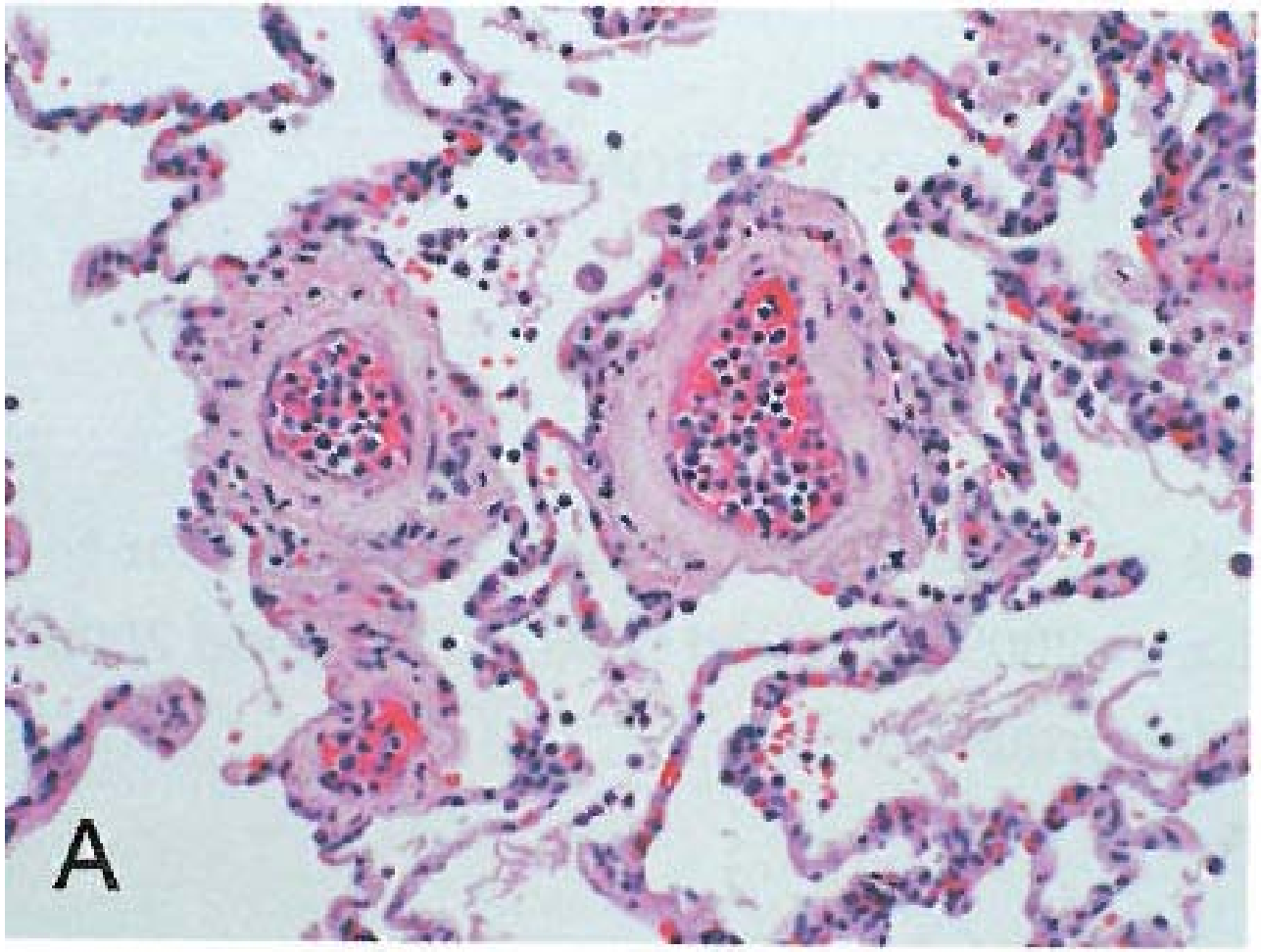
Anti-leukocyte Antibodies	"Two-hit" Hypothesis
Anti- Granulocyte antibodies HLA Class I antibodies HLA Class II antibodies	Biologically active lipids Cell membrane fragments LPS – lysophosphatidyl choline
Direct binding to neutrophils and monocytes	Underlying condition results in priming of neutrophils
Binding to endothelium - Indirect activation of neutrophils through Fc receptors	Biologic response mediators (eg. lipids) activate primed neutrophils

Neutrophil activation

American Red Cross

TRALI: Pathology

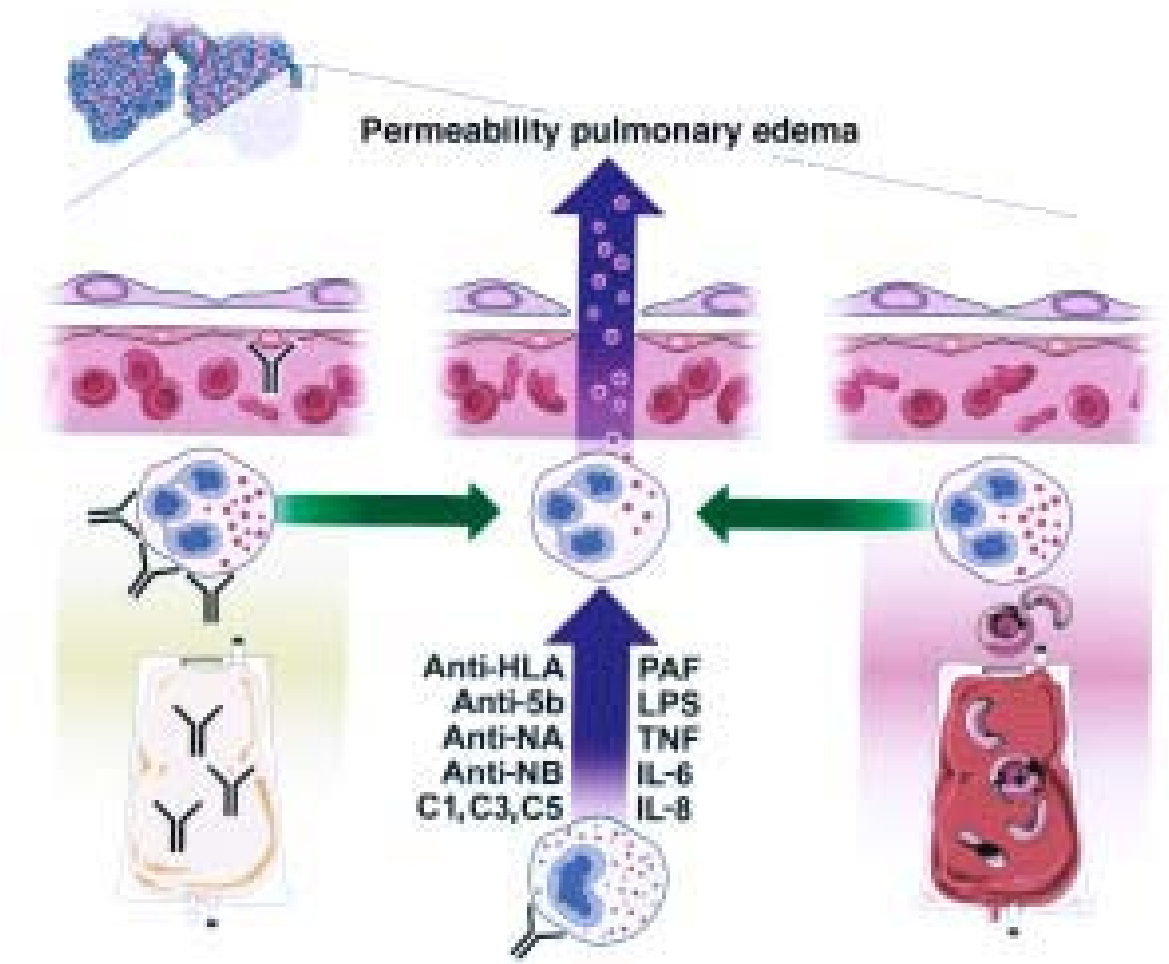
Neutrophils and pulmonary endothelium



Lima et al. Transfusion 2010; 50:1427

American Red Cross

TRALI : Pathogenesis

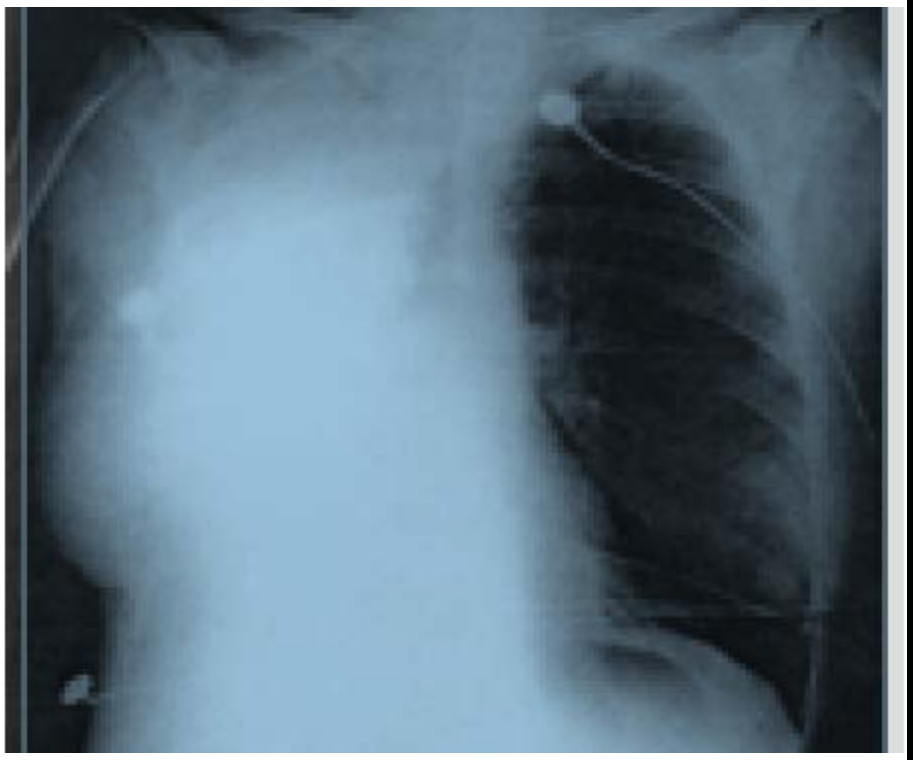


Gajic O, Moore B, Mayo Clin Proc 80:766-770, 2005.

American Red Cross

TRALI in Single Lung Transplant

Antibody binding to pulmonary endothelium



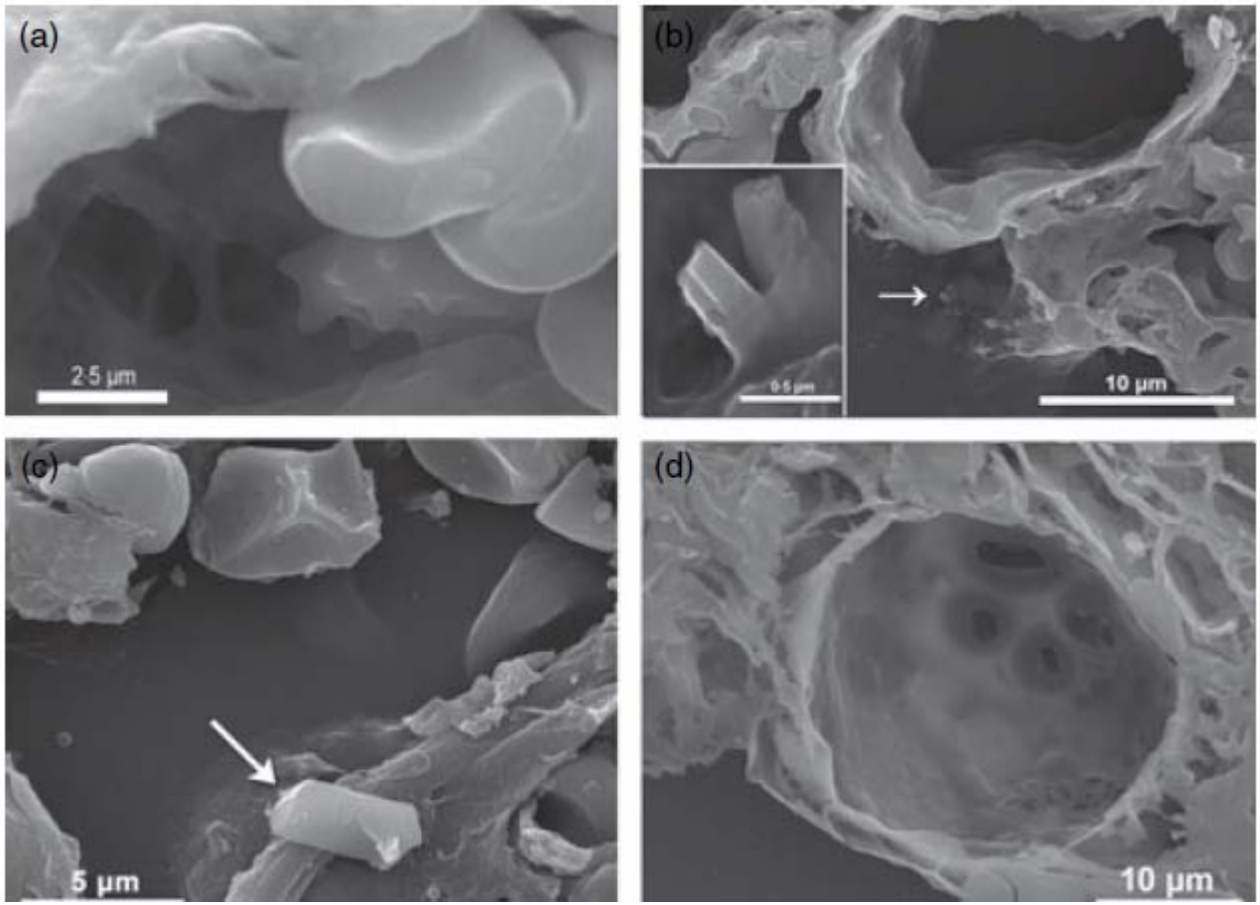
	HLA type	Anti-HLA Ab
Patient	A1,3 B35,62	None
Lung donor	A2, 3 B14, 44	Not tested
Blood donor	A2,3 B7,8	Anti-B44

Dykes et al. Br J Haem 2000:109:671-2

American Red Cross

TRALI: Pulmonary venule damage

Cholesterol crystal formation



Jensen et al. Vox Sang 2010 98:130-137

American Red Cross

Prevalence of HLA Abs in donors

- Background rate of HLA antibody in presumably non-immunized donors is similar for men and women (1-4%)
- Transfusion history in men has a minimal effect on HLA antibody prevalence (3.4% vs. 4% for untransfused vs. transfused)
- HLA antibody prevalence increases with the number of pregnancies (<1%, never pregnant; 10.4%, 1 pregnancy; 31.1% >3 pregnancies)

Triulzi et al. Transfusion 2009; 49:1779-82.

American Red Cross

Recipient tracing studies

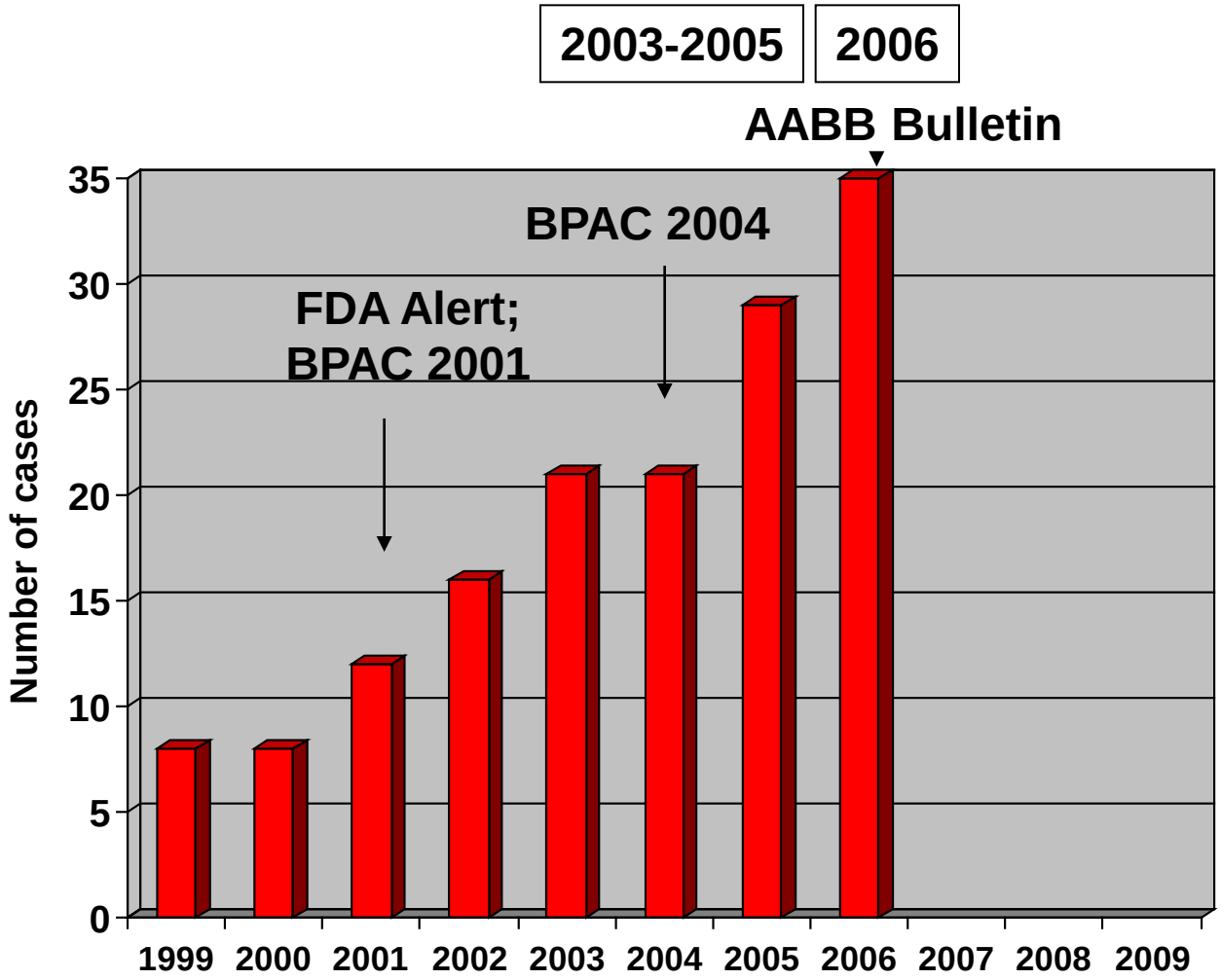
Prior recipients of blood from implicated donors

Study	Antibody	Recipients	Rxns (TRALI)
Kopko 2002	HNA-3a	36	15 (2)
Win, 2002	Multiple	30	0
Cooling, 2002	HLA-I	20	3 (2)
Fadeyi, 2007	HNA-2a	32	12 (0)
Nicolle, 2004	HLA-I,II	18	1 (1)
Toy, 2004	HLA-I,II	103	4 (0)
Zupanska, ‘07	HLA-I,II	20	0
	Total	259	35 (5)

American Red Cross

U.S. Reported TRALI Fatalities

FDA, Fiscal Years



www. FDA.GOV; Holness L et al, TMR 18:3;184-8

American Red Cross

U.K. SHOT 2003-2009

Plasma from Male Donors

2001-2002:

- FFP was involved in 60% of TRALI cases

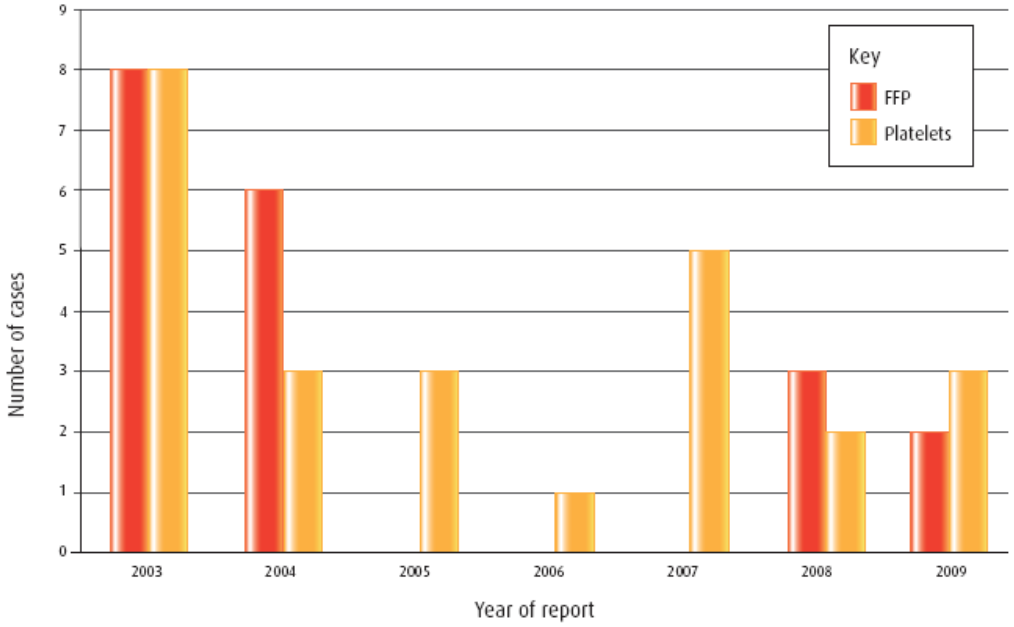
Oct 2003:

- Switch to predominantly male plasma

After 2004:

- Sustained reductions in TRALI with plasma for transfusion and platelet pooling from male donors

Figure 16
Cases of TRALI with concordant donor antibody in FFP or platelet components 2003–2009



Taylor C (Ed.), Cohen H, Mold D, Jones H, *et al*, on behalf of the Serious Hazards of Transfusion (SHOT) Steering Group. The 2009 Annual SHOT Report (2010) www.shotuk.org

American Red Cross

AABB Bulletin # 06-07

November, 2006

Recommendations to reduce the incidence of TRALI:

1. Implement interventions to minimize the preparation of high plasma-volume components from donors known to be leukocyte-alloimmunized or at increased risk
2. Work towards implementing appropriate evidence-based hemotherapy practices in order to minimize unnecessary transfusion.
3. Monitor the incidence of reported TRALI and TRALI-related mortality.

For all high plasma-volume components:

1. Complete full implementation of the measures relating to **plasma** components and whole blood by November 2007.
2. Complete full implementation of the measures relating to **platelet** components no later than November 2008.

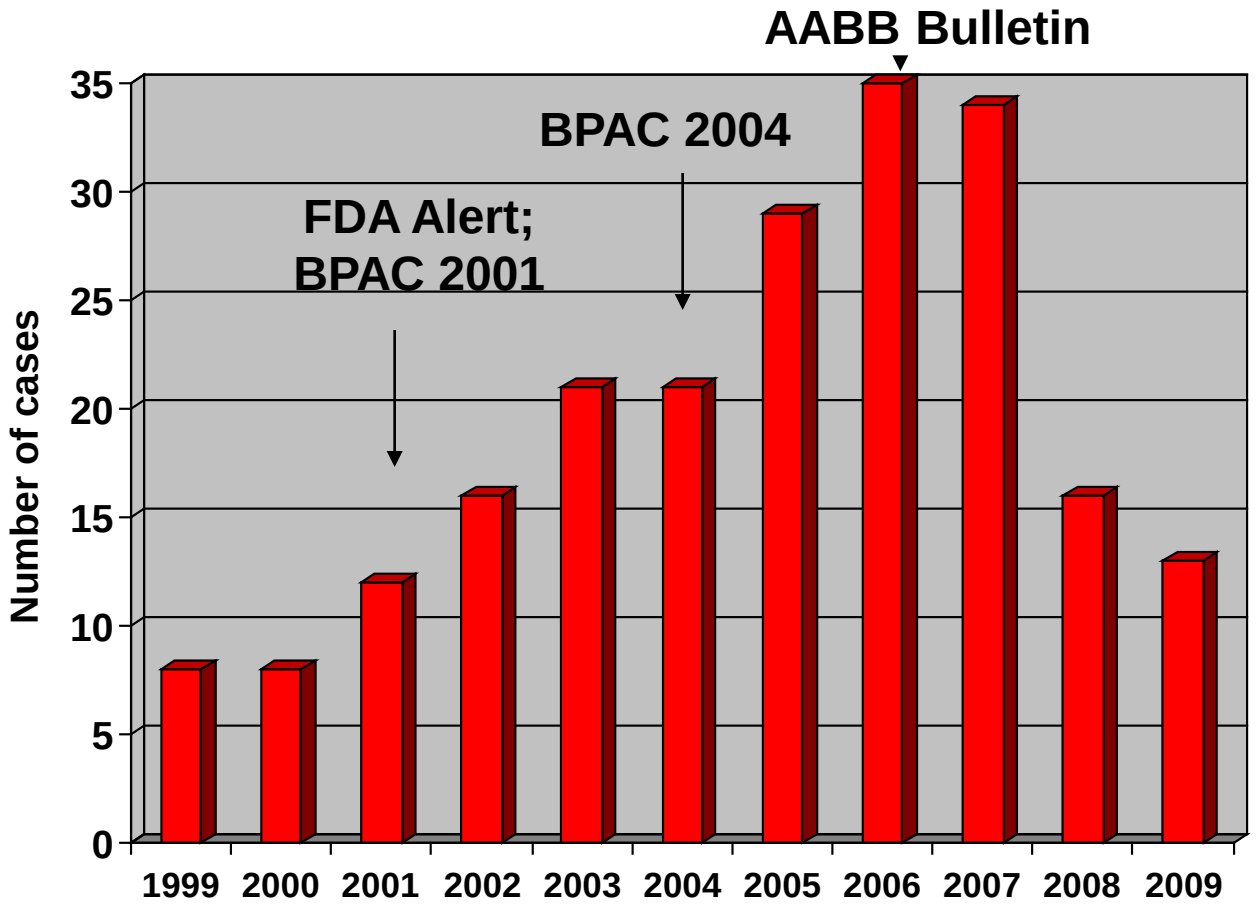
AABB Bulletins 06-07 and 07-03
www.aabb.org/resources/publications/bulletins

American Red Cross

U.S. Reported TRALI Fatalities

FDA, Fiscal Years

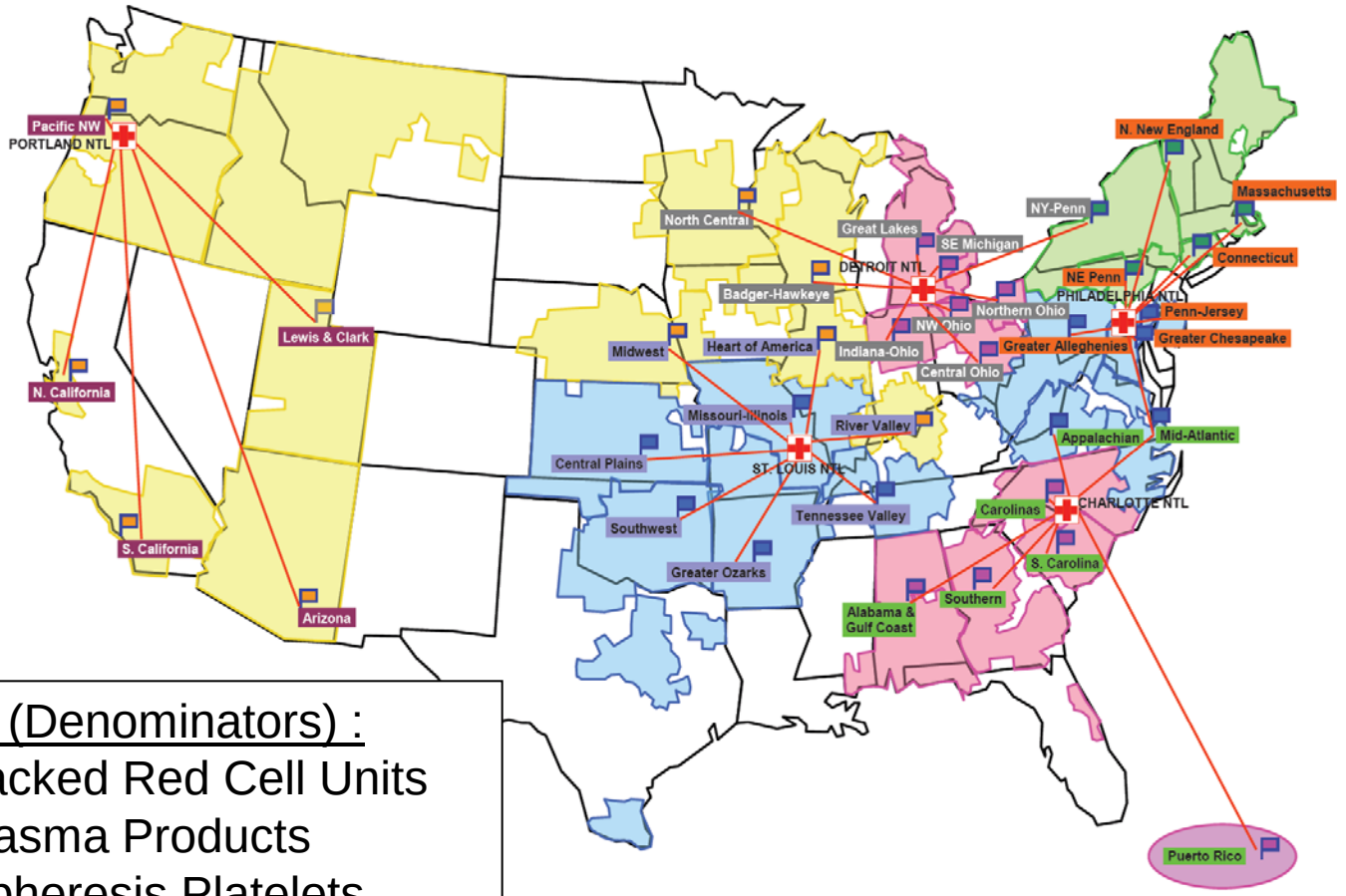
2003-2005	2006-2008	2009



www. FDA.GOV; Holness L et al, TMR 18:3;184-8

American Red Cross

American Red Cross, 2010



Distributions (Denominators) :

6 M	Packed Red Cell Units
1.7 M	Plasma Products
850,000	Apheresis Platelets
250,000	Random Donor Platelets
40,000	Pooled Platelets

American Red Cross

TRALI Investigation

Probability Codes

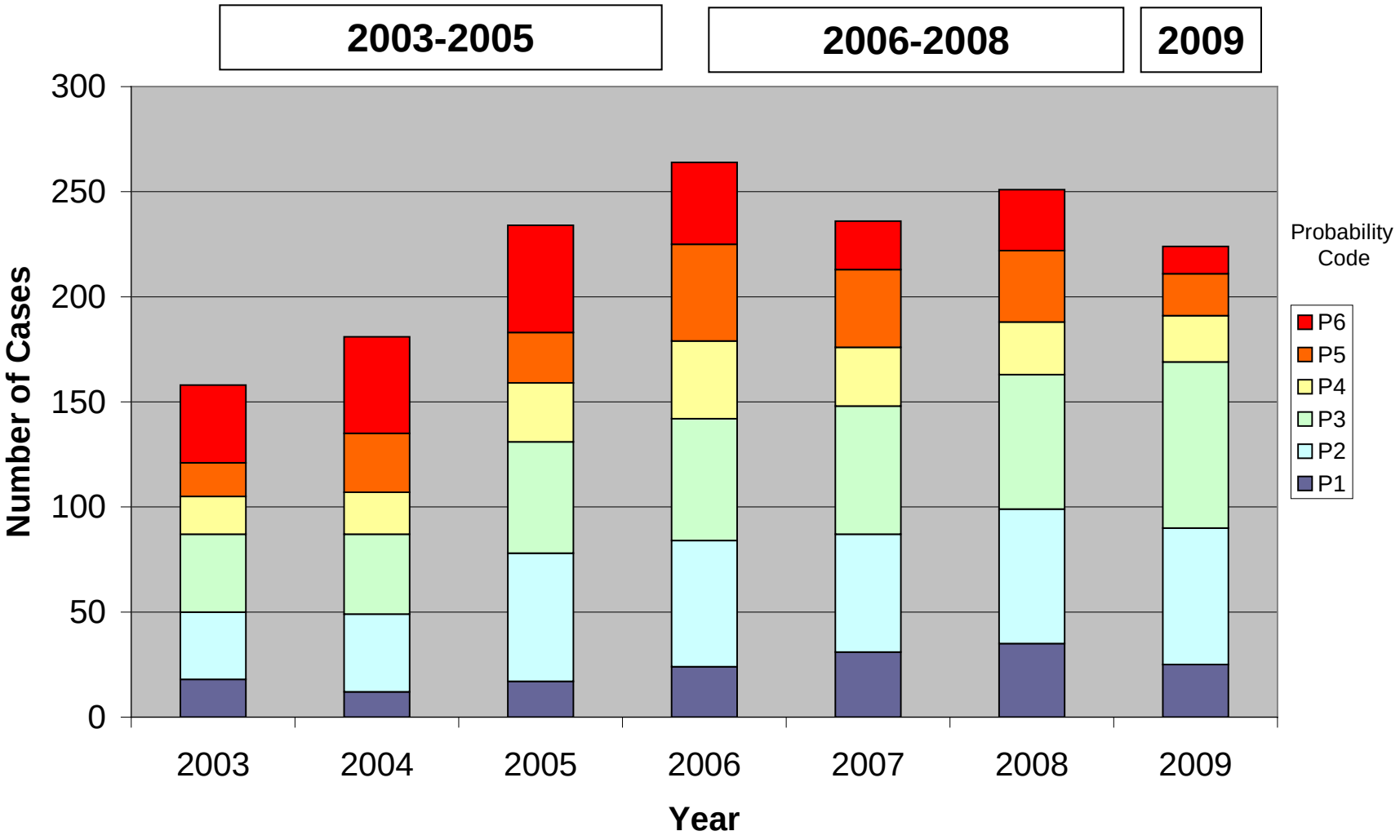
HIGH	P6	Consistent with TRALI/Possible TRALI, donor source identified/donor implicated
HIGH	P5	Consistent with TRALI/Possible TRALI, donor source not confirmed
	P4	TRALI/Possible TRALI cannot be excluded
LOW	P3	TRALI/Possible TRALI unlikely, other cause more likely
LOW	P2	TRALI/Possible TRALI not supported
LOW	P1	Case rescinded

Eder et al. ARC Hemovigilance Program

American Red Cross

TRALI Investigation

All cases ARC regions, 2003-9

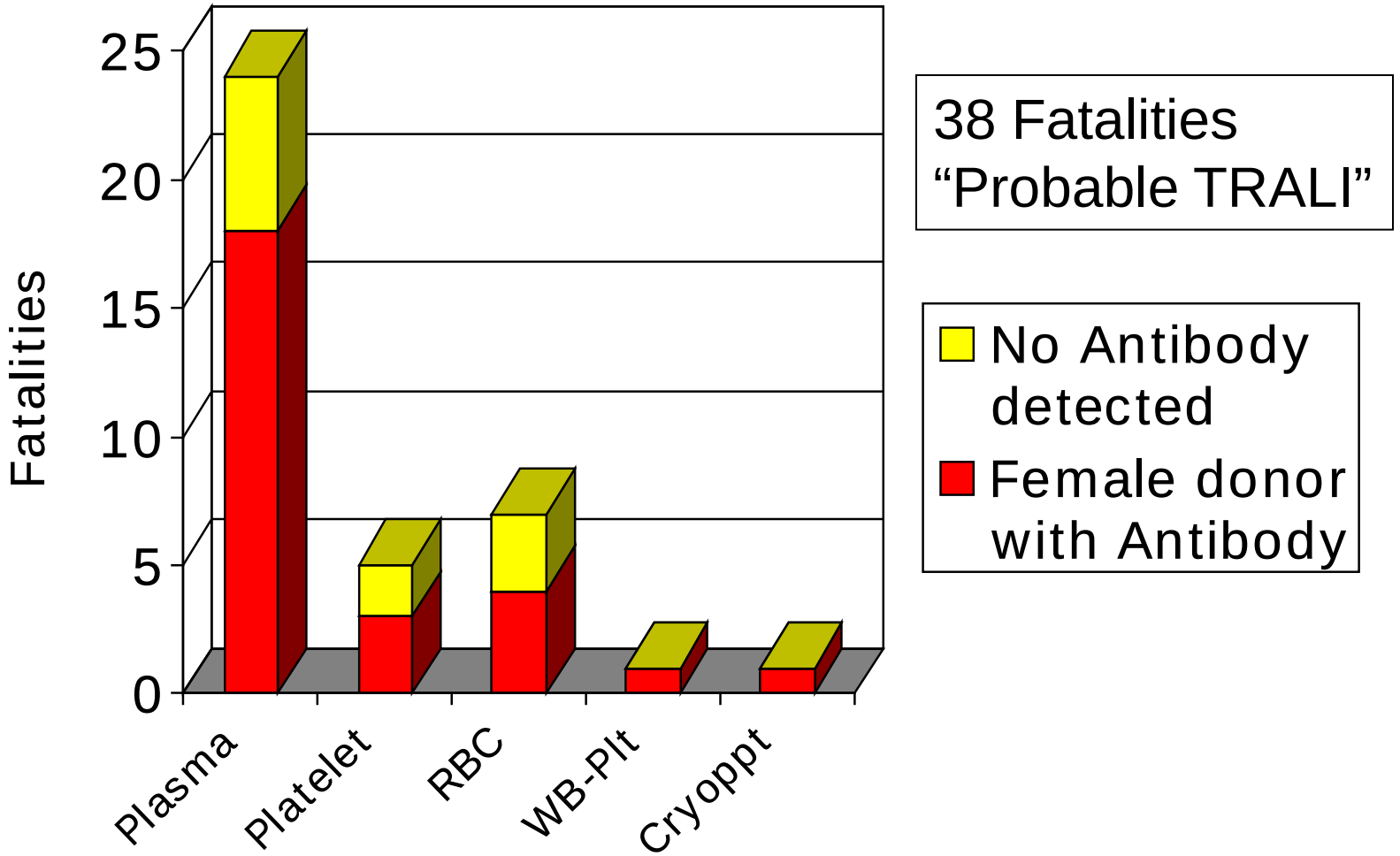


2006-8: Eder et al. Transfusion, 2010; 50:1732-1742
2009: ARC Hemovigilance Program

American Red Cross

Probable TRALI by Component

Fatalities reported to ARC, 2003 to 2005



Eder et al. Transfusion. 2007; 47:599-607

American Red Cross

Summary : ARC Experience

Reported fatalities, 2003-5

Transfusion-related Acute Lung Injury

- **Plasma components** were responsible for most TRALI cases reported to the American Red Cross Hemovigilance Program between 2003-2005
- Most TRALI cases and associated fatalities were linked to **female, HLA or HNA antibody-positive donors**
- "Prudent measures to limit transfusion of HLA/HNA antibody-containing plasma components **may prevent as many as 6 fatalities per year** …"

Eder et al. *Transfusion*. 2007; Apr;47(4):599-607

American Red Cross

Plasma from Male Donors

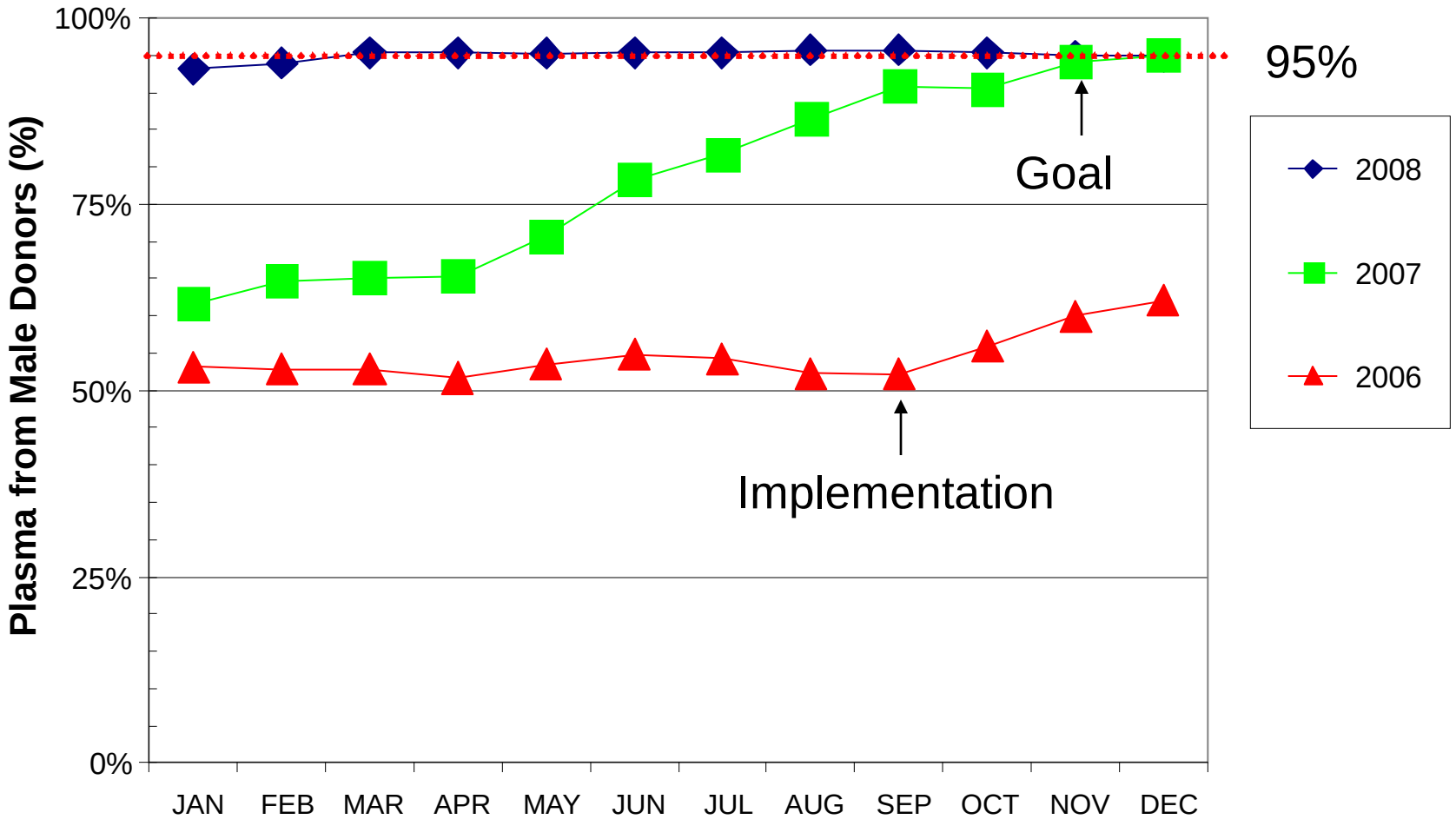
Calendar Years 2006-8

- In 2006, the American Red Cross began preferentially distributing **plasma collected from male donors** for transfusion in an effort to reduce the risk of TRALI
- Evaluate the effect of the male-predominant plasma strategy on the rate of reported TRALI cases and associated fatalities

American Red Cross

Plasma from Male Donors

Calendar Years 2006-8



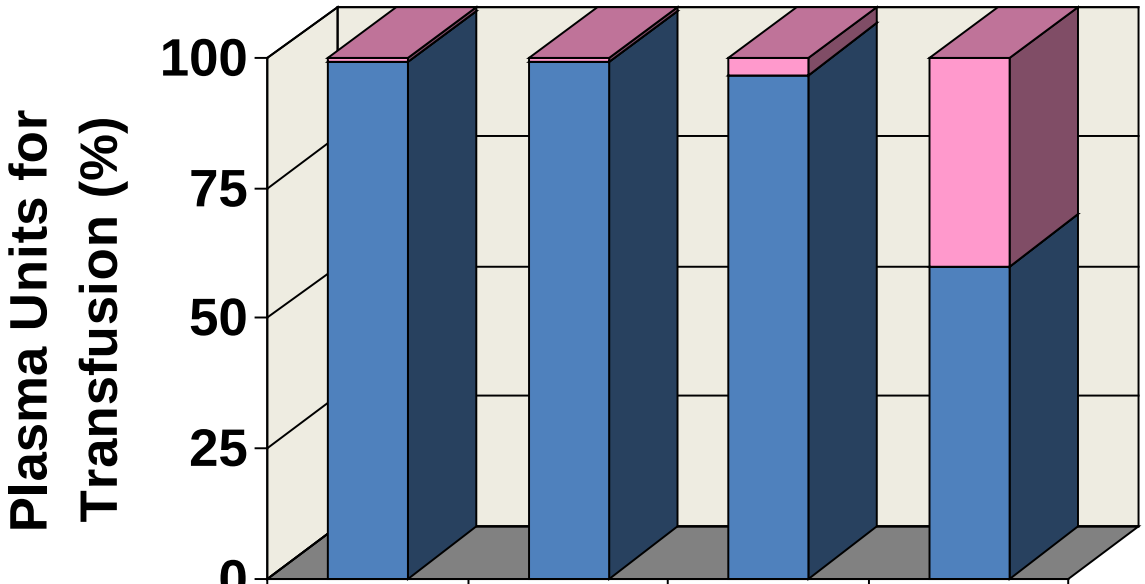
Eder et al. Transfusion, 2010; 50:1732-1742

American Red Cross

Plasma from Male Donors

By Labeled ABO Type, CY2009

Total distributed: 1,673,099

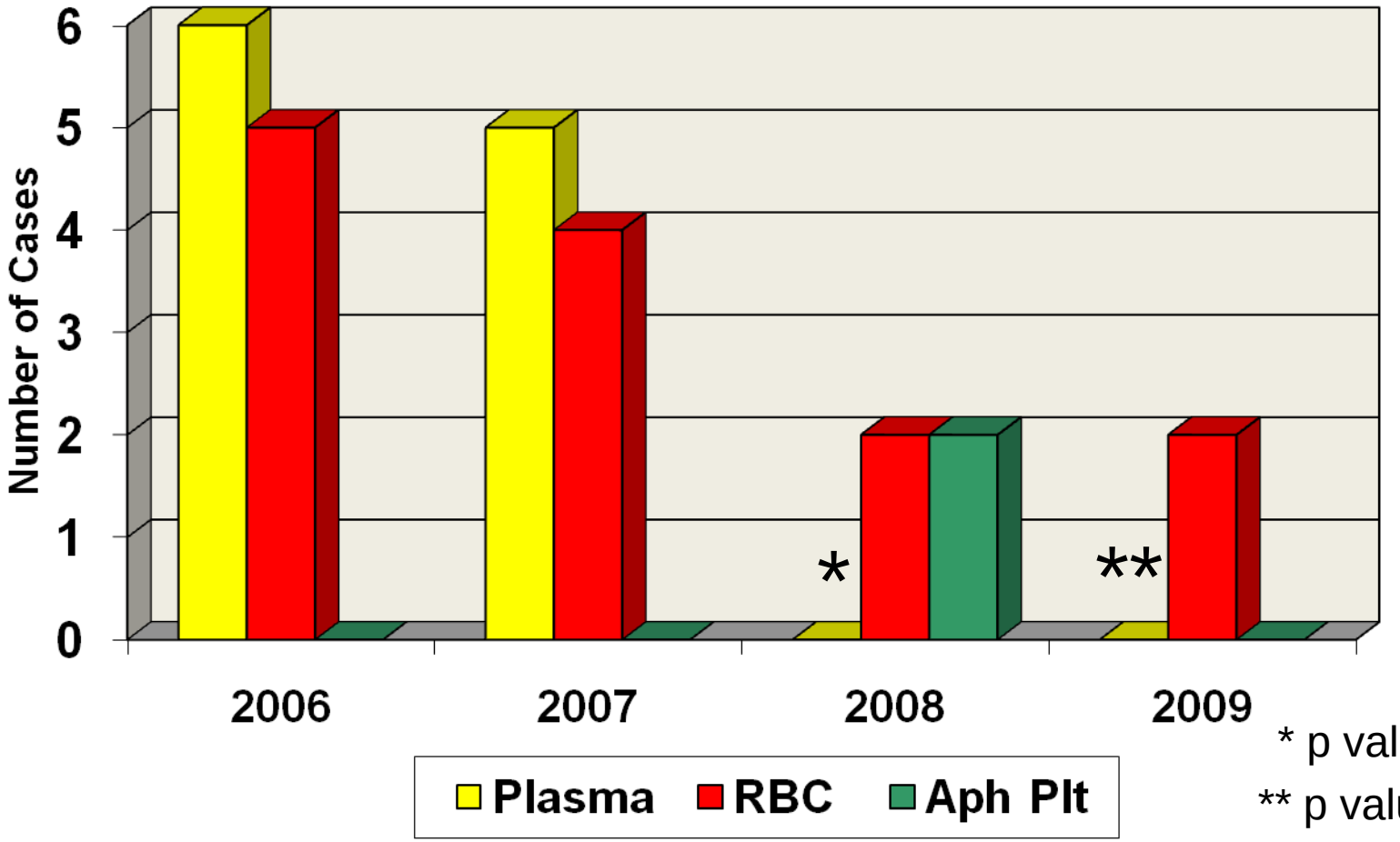


	O	A	B	AB
Female Donors	0.8	0.9	3.2	40.1
Male Donors	99.2	99.1	96.8	59.9

Blood Type

Probable TRALI

Reported fatalities, 2006-9



Single Component Type Investigated

* p value 0.01

** p value, 0.02 vs. 2006

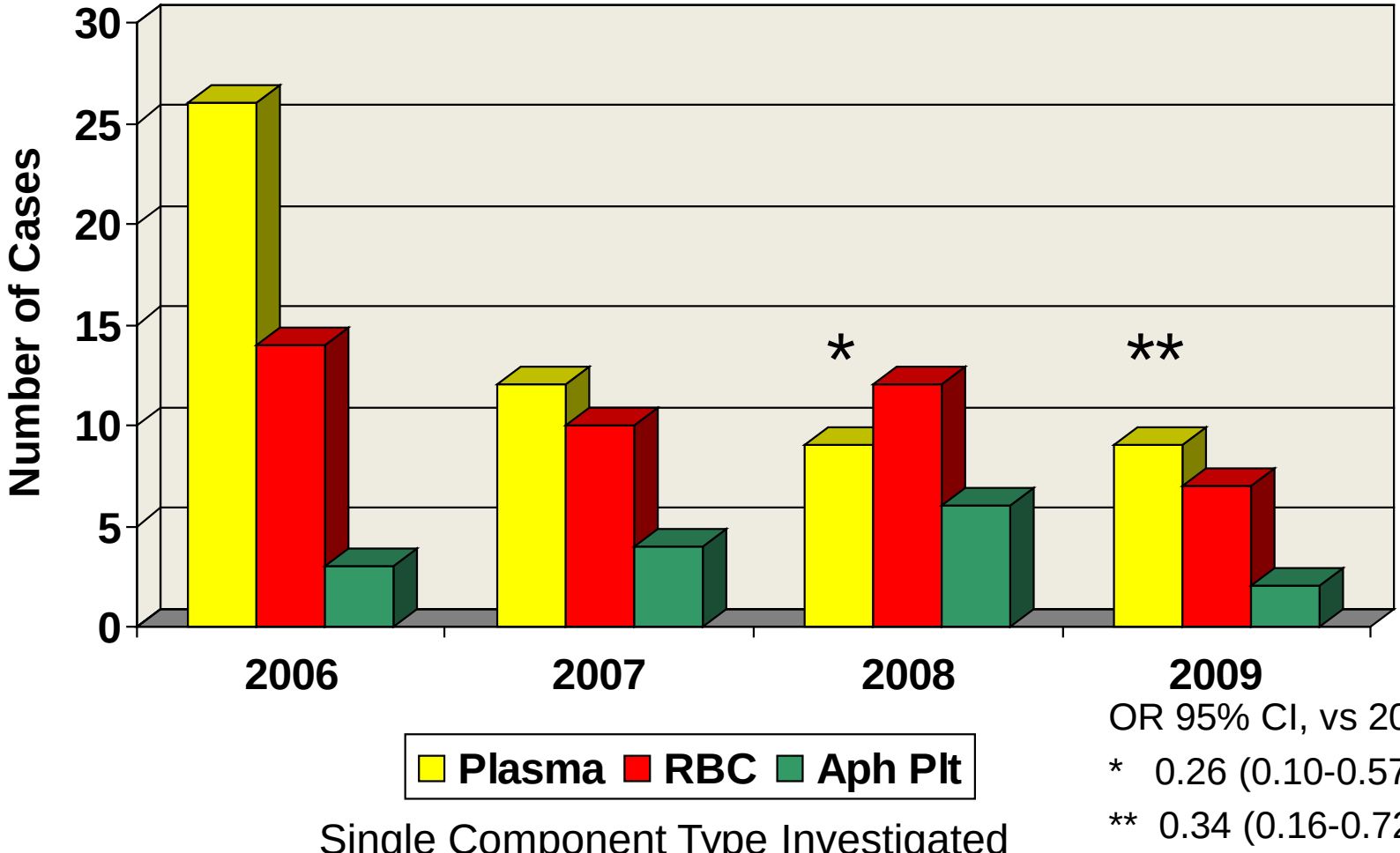
2006-8: Eder et al. Transfusion, 2010; 50:1732-1742

2009: ARC Hemovigilance Program

American Red Cross

Probable TRALI

Nonfatal cases, 2006-9



OR 95% CI, vs 2006

* 0.26 (0.10-0.57)

** 0.34 (0.16-0.72)

Single Component Type Investigated

2006-8: Eder et al. Transfusion, 2010; 50:1732-1742
2009: ARC Hemovigilance Program

American Red Cross

Reported TRALI, CY2009

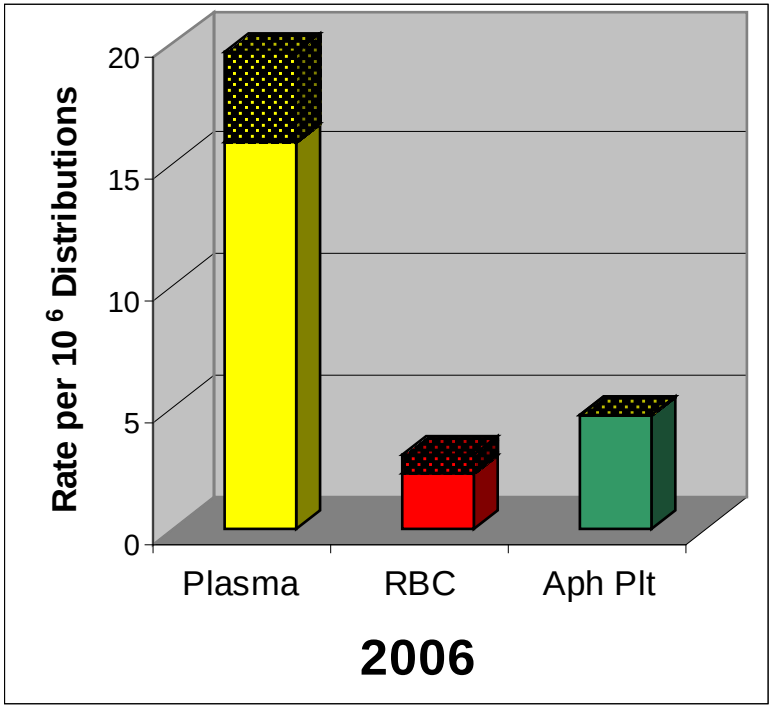
Plasma transfusion

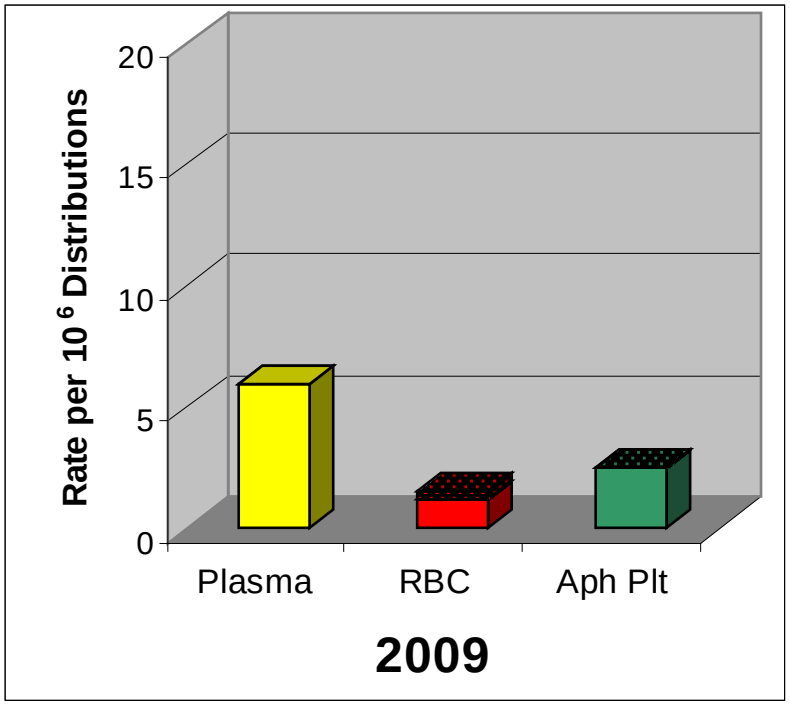
Plasma	RBC	Gender	ABO	Plasma Antibody
1 (1)	(1)	F (M,F)	**AB+**	A9,25,32; Bw4,Cw2,5,6,15,18; and HNA-3a(5b)
1		F	B+	Multiple Class I and Class II (DQ6; DR15)
1(1)		F, (M)	**AB+**	Multiple Class I (A3) and Class II specific
1		F	**AB+**	A2,9,28;B8,17;DR7,9;DQ2,4,9
2		F	**AB-**	Class II positive
2		F	**AB+**	Multiple Class I and II (both donors)
2		F,M	**AB+**	Not tested
2		F,M	**AB+**	Not tested
1		M		HNA-1a; HNA-1b
1 (1)		F (M)	**AB+**	Negative

No fatalities reported from plasma transfusion

Effect of Male-Predominant Plasma

Fatal and Nonfatal Cases, 2009 vs. 2006





Conclusion: TRALI from plasma transfusion was significantly reduced in 2009 vs. 2006 (10 vs 32 cases; OR 95% CI 0.31 (0.15-0.62)

Conclusions

- Male-predominant plasma strategy effectively reduced the risk of TRALI in the American Red Cross
- Residual risk associated with plasma in 2008-9 (1 in ~200,000 distributed plasma units) is from female antibody-positive donors
  - aim is to reach 100% plasma from male donors
  - challenge is to meet demand for group AB plasma
- Strategies for apheresis platelets are being implemented

- Questions?

Anne Eder, MD PhD

edera@usa.redcross.org

Acknowledgements

- Dr. Richard Benjamin, MD PhD
  Chief Medical Officer, American Red Cross
- Beth Dy
  Manager, American Red Cross Hemovigilance Program
- Ed Notari, MPH
  Holland Laboratory, American Red Cross
- Dr. Ross Herron MD
  Divisional Chief Medical Officer, ARC, Western Division
- Michele Rambaud
  National Plasma Planner, ARC, Biomedical Headquarters
- Jan Forey

  Process Design, ARC, Biomedical Headquarters