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President/CEO and Medical Director

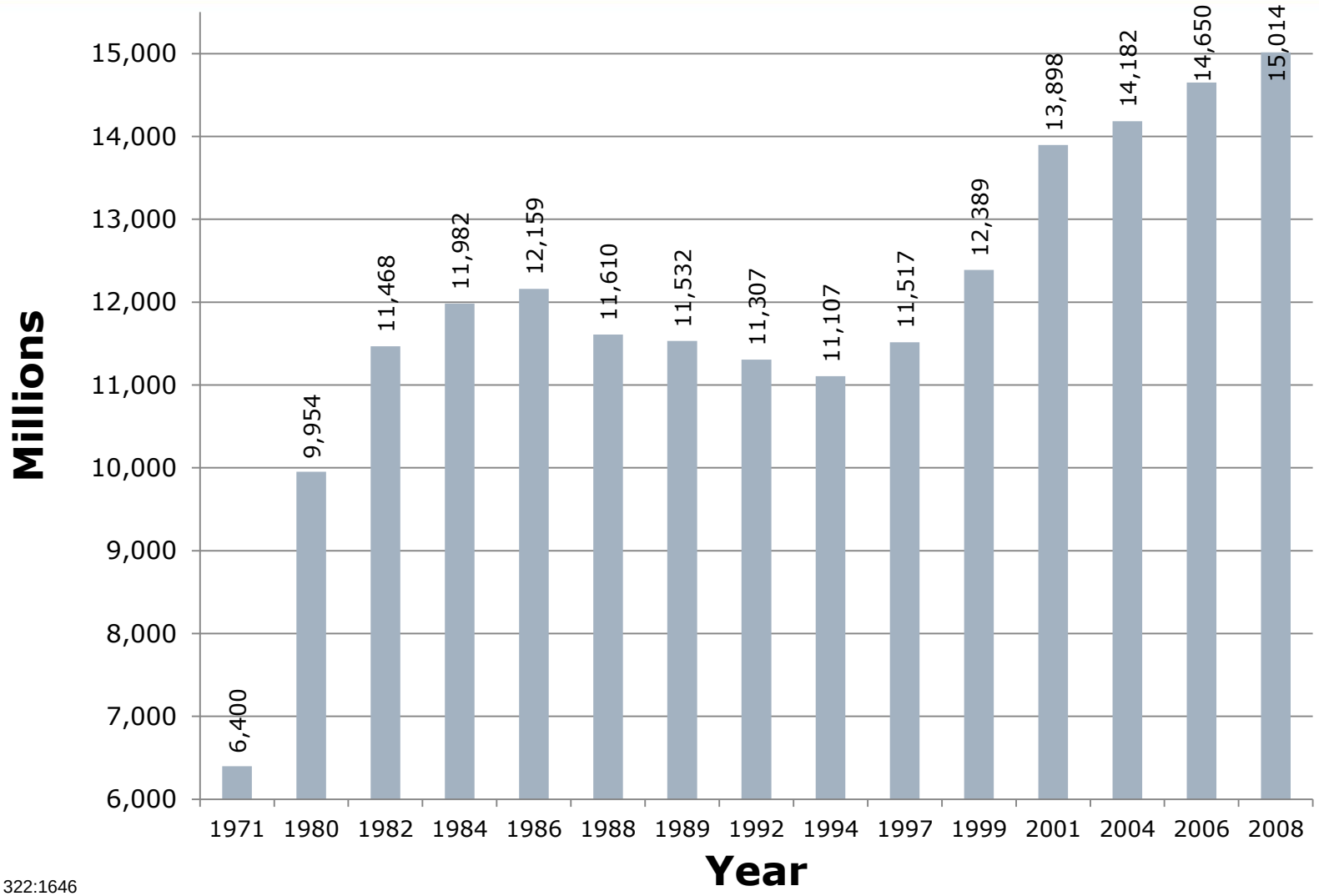
Keeping the Focus of Transfusion Medicine on Patient Care

April 30, 2013

Heart of America Association of Blood Banks

No relevant financial relationships with any commercial interests

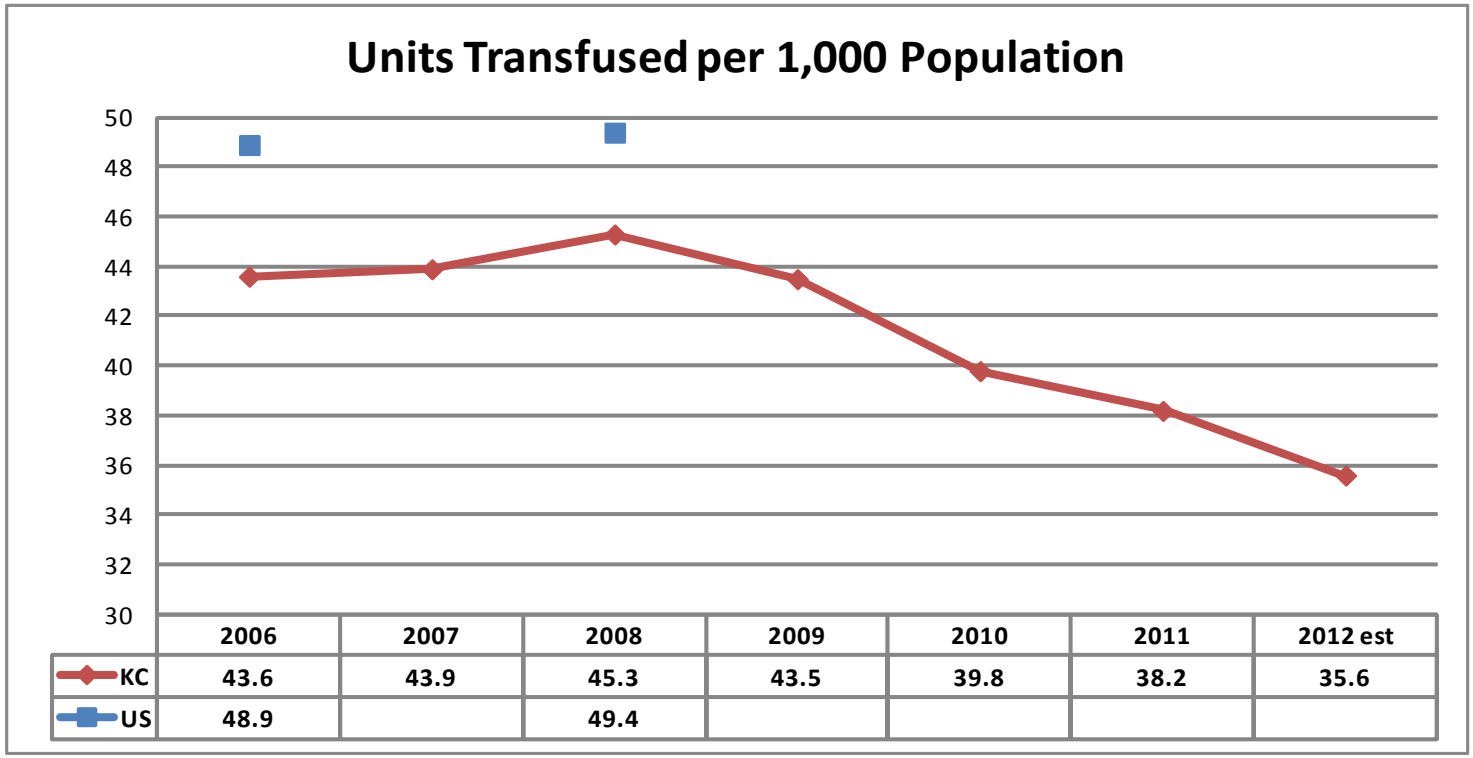
Blood Utilization – United States



- Surgenor HEJM 1990; 322:1646
- Wallace Transfusion 1995; 35: 802
- Wallace Transfusion 1998; 38: 625
- NBDRC 1997, 1999, 2002
- Nationwide Blood Collection and Utilization Survey 2005, 2007, 2009

Units Transfused per 1,000 Population

	2006	2007	2008	2009	2010	2011	2012 est
KC	43.6	43.9	45.3	43.5	39.8	38.2	35.6
US	48.9		49.4				

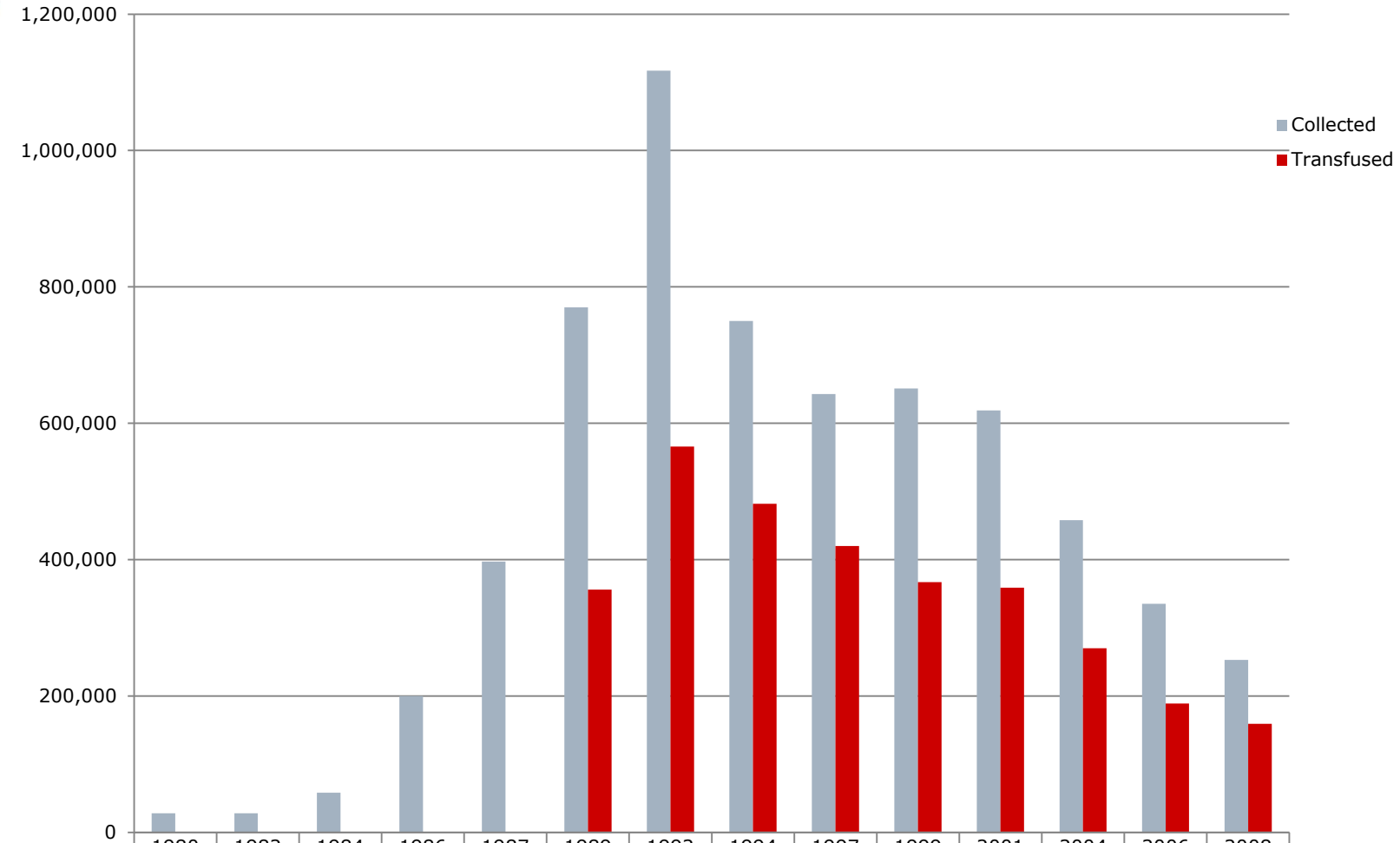


	85,403	86,862	90,630	87,802	81,160	78,383	73,132

- Hence, in my career, two significant downturns in transfusion utilization.
  - Different scenarios / causes
- Lessons to be learned?
  - Past is prologue?
- Four perspectives:
  - Patients
  - Clinicians
  - Hospitals / Health Care Institutions
  - Transfusion Medicine Specialists

- **Patients:**
  - Transfusion associated - HIV
  - Autologous transfusions
  - "Dread fear" of transfusions

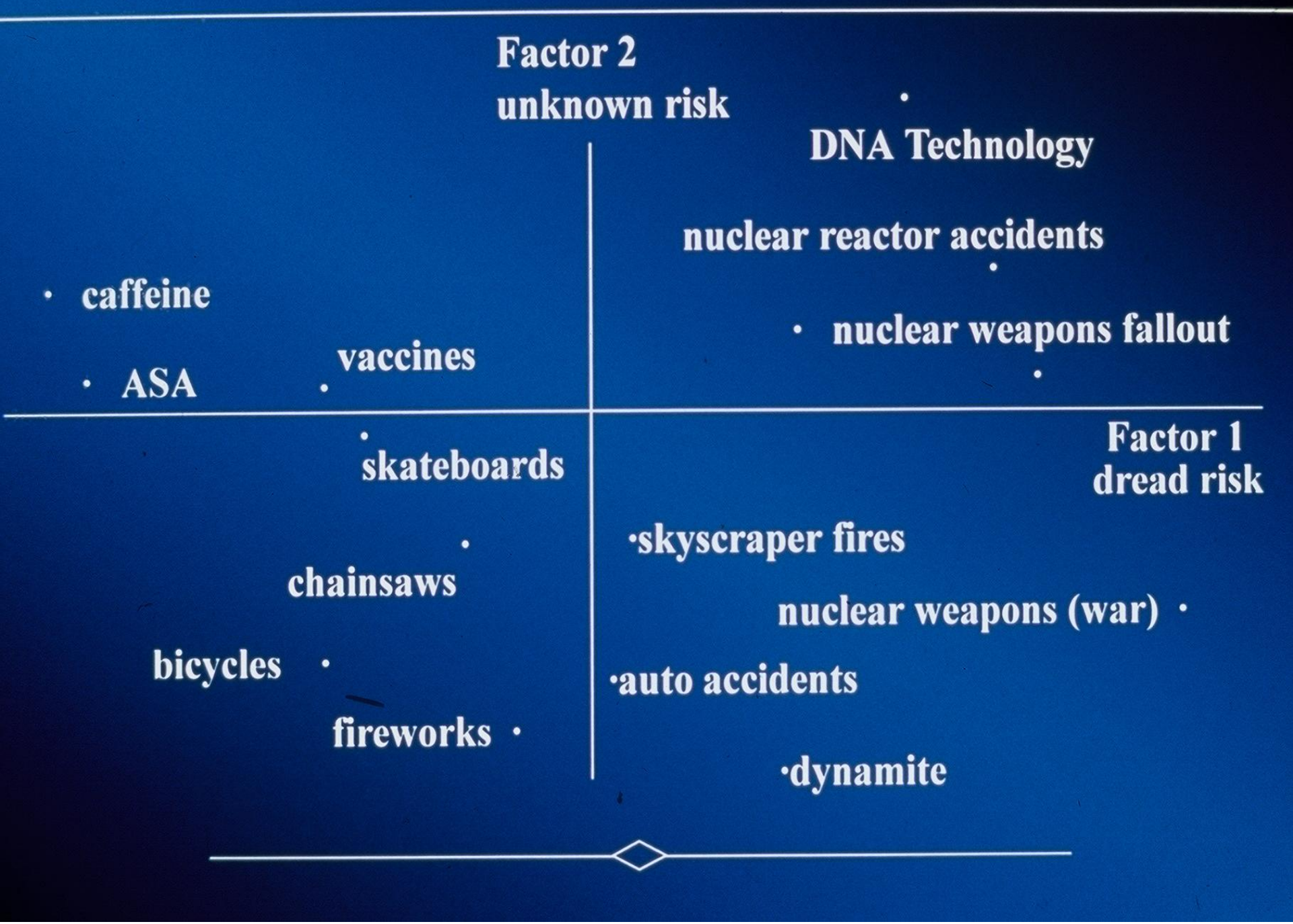
Autologous Blood Collection/Transfusion



	1980	1982	1984	1986	1987	1989	1992	1994	1997	1999	2001	2004	2006	2008
Collected	28,000	28,000	58,000	200,000	397,000	770,000	1,117,0	750,000	643,000	651,000	619,000	458,000	335,000	253,000
Transfused	0	0	0	0	0	356,000	566,000	482,000	420,000	367,000	359,000	270,000	189,000	159,000

Cognitive Map

Slovic P. Perception of Risk. Science 1987: 236: 280-5



Slovic P. Perception of Risk. Science 1987: 236: 280-5

- **Clinicians:**
  - Consensus Conferences
  - Transfusion Guidelines
  - Assure transfusions given when benefit > risk

NIH Consensus Development Conference – June 1988

Hb values ≥ 10 g/dL - rarely require peri-op transfusion

Hb values < 7 g/dL - frequently require red cell transfusion

- Decision to Transfuse
  - Depends on clinical assessment aided by lab data
    - Arterial oxygenation
    - Mixed venous oxygen tension
    - Cardiac output
    - Oxygen extraction ratio
    - Blood volume

- JAMA 1988; 260:2700-2703
- Transfusion Medicine Reviews 1988; 3:63-68

Transfusion Requirements in Critical Care (TRICC)

RCT critically ill Canadian ICU patients at 25 hospitals

	Restrictive	Liberal
N	418 patients	420
Hb Trigger	7.0 g/dL	10.0
Maintenance Hb	7-9 g/dL	10-12
Leuko Reduction	No	No
RBC txf'd	2.6 units	5.6 p=0.01
No txf p randomization	33%	0% p<0.01
Primary Outcome		
▪ Death within 30 days	18.7%	23.3% p=0.11
▪ Cardiac events (pulmonary edema, M.I.)	13.2%	21.0% p<0.001

▪ Hebert PC, et al. *N Engl J Med* 1999; 340:409

Transfusion Requirements in Critical Care (TRICC) - continued

RCT, critically ill Canadian ICU patients at 25 hospitals

Sub-group analysis – 30 day mortality

	Restrictive	Liberal	
APACHE II scores <20	8.7%	16.1%	p<0.03
Age <55 years	5.77%	13.07%	p=0.02

Conclusion: 7.0 g/dL threshold (7-9 g/dL maintenance) - effective

- **FOCUS** (Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair)
- **Liberal vs. Restrictive Transfusion Trigger Trial**
  - 10 g/dL vs. 8 g/dL or symptoms
  - High risk patients (n = 2,016 patients; greater than 50 years old; H/O cardiovascular disease; Hb < 10 g/dL post surgery)
  - Hip surgery (2004-2009)
  - 47 clinical sites
  - Randomized, controlled clinical trial
- **Primary Outcome**
  - Death at 60 days
  - Inability to walk across a room without assistance at 60 days

▪ Carson JL, et al. *NEJM 2011;* 365:2453

Strategy	Liberal	Restrictive
N	1007	1009
Age (years)	81.8	81.5
Cardiovascular Disease	63.3%	62.5%
Hypertension	82.2%	81.7%
DM	25.1%	25.5%
Hip Fracture:		
▪ Femoral Neck	43.0%	41.9%
▪ Intertrochanter	51.0%	51.8%
Hb (g/dL):		
▪ Before Transfusion	9.2	7.9
▪ Symptoms leading to transfusion: tachycardia or hypotension	4.3%	12.2%
Leukocyte reduced RBC	90.2%	88.6%
Transfusion after randomization:		
▪ 0	3.3%	59.0%
▪ 1	41.9%	24.4%
▪ 2	34.5%	12.6%

- p = significant

▪ Carson JL, et al. *NEJM 2011*; 365:2453

FOCUS
(continued)

Outcomes	Liberal	Restrictive	
Death or inability to walk 60 days	35.2%	34.7%	p = 0.90
Death 30 days	5.2%	4.3%	p = NS
Death 60 days	7.6%	6.6%	p = NS
O.R. primary outcomes:	1.01		
▪ Men	1.45		p = 0.03
▪ Women	0.91		p = NS
Function & Symptom Scale:			
▪ In hospital myocardial infarction	2.3%	3.8%	p = NS
▪ CXR Infiltrate	6.0%	4.8%	p = NS
▪ Wound infection	1.4%	0.8%	p = NS
▪ Stroke or TIA	0.8%	0.3%	p = NS
▪ Death: M.I., pneumonia	8.9%	8.9%	p = NS
▪ Randomization to discharge (days)	3.67	3.97	p = NS
No difference in mortality rates: transfusion vs. non-transfusion			

- **Conclusion:** Reasonable to withhold transfusion in absence of symptoms of anemia or decline < 8g/dL - even in elderly patients with underlying cardiovascular disease or risk factors

▪ Carson JL, et al. *NEJM 2011*; 365:2453

- **Hospitals / Health Care Institutions**
  - Risk Mitigation
  - Informed consent
  - Transfusion Committee Utilization Review

Transfusion Medicine Specialists

- Zero Risk
  - Product Safety
    - Infectious Disease Testing
    - Leukocyte reduction
  - Adherence to FDA regulations in:
    - Current Good Manufacturing Practices (cGMP)
    - Standardization

Risk Analysis -- early 1980's

- Transfusion-associated AIDS compared favorably with other more general risks
- Initially, these comparisons were helpful
- However, public eventually compared risk of transfusion-associated AIDS with less risky alternatives
- Stated comparisons involved voluntary activities
  - Blood transfusion is involuntary

Risk Analysis (cont'd)

- Number of deaths per year
  - e.g. 1 in 125,000 from leukemia
  - e.g. 1 in 588,000 from an earthquake in California
- Deaths per million hours pursuing an activity
  - e.g. 1 in 7,150 hours rock climbing
- A decision to undertake a "risk" is a personal decision based on quantifiable data

Benefits of Transfusion

- Perceived benefits ameliorate perceived risks
- "Milk - it does a body good"


milk it does a BODY GOOD
AMERICA'S DAIRY FARMERS
AMERICAN DAIRY ASSOCIATION
NATIONAL DAIRY BOARD

Trust

- Public relies on experts to provide stewardship and maintain quality
- Asymmetry between creating trust and destroying trust
  - Trust-destroying events are more noticeable than trust-building events
  - Bad news has more credibility than good news

Frame of Reference for Evaluating Improvements -- Prospect Theory

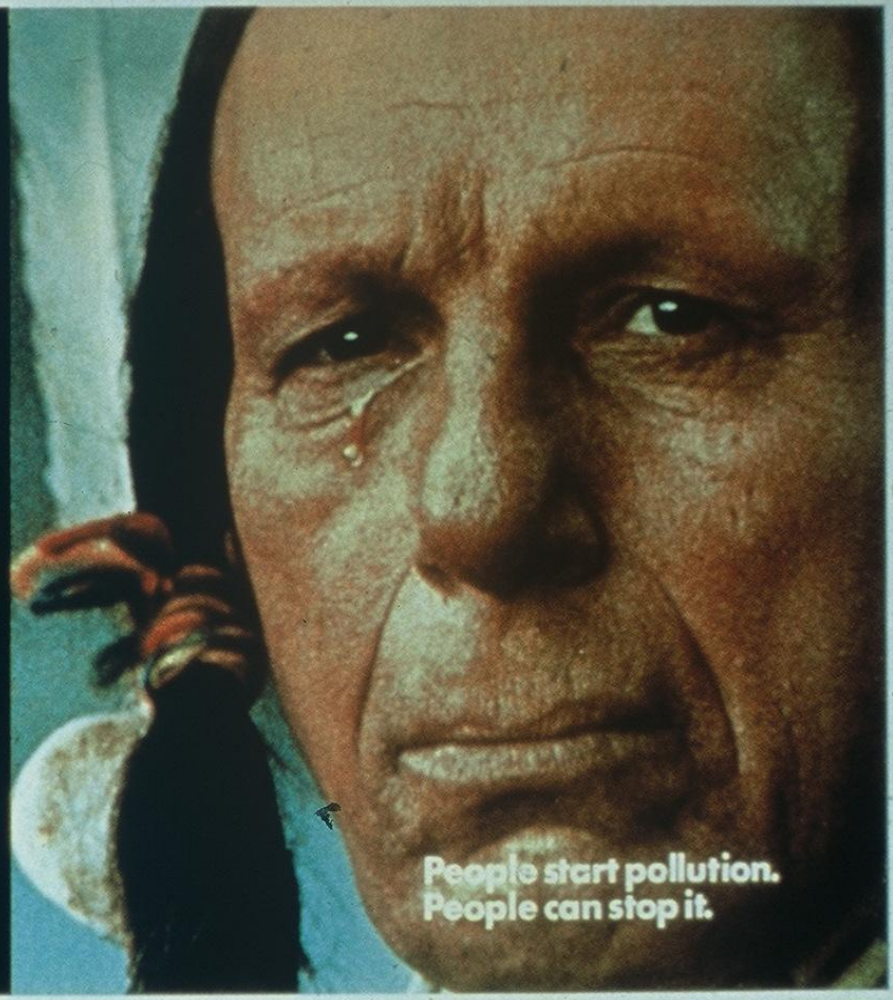
- Consider change from a reference position
- Restoration to a better, previous state versus improvement of current conditions
  - e.g. polluted river:
    - return to previous condition
    - improve the river

GET INVOLVED NOW. POLLUTION HURTS ALL OF US.

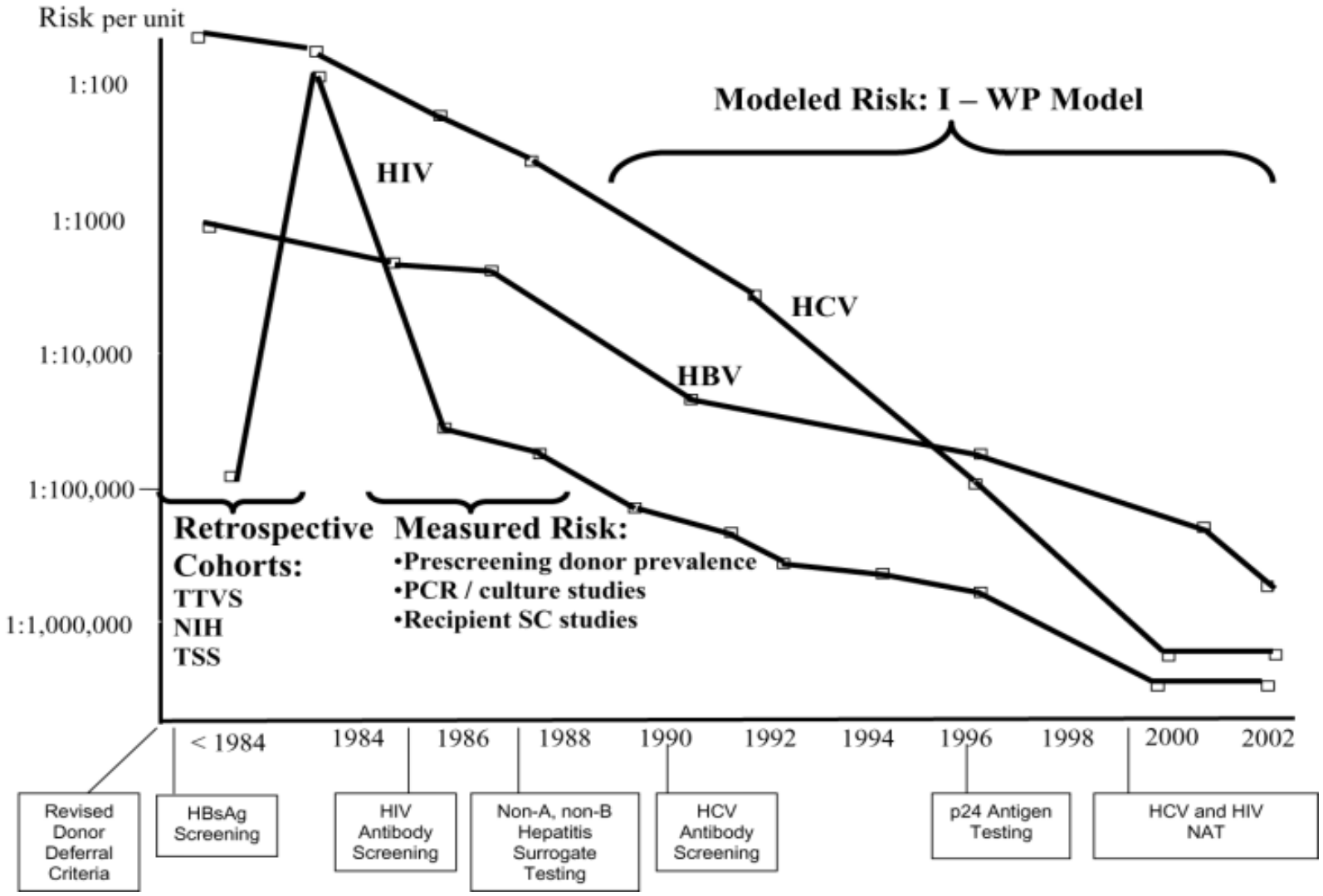
You can help by becoming a community volunteer. Write:

Keep America Beautiful, Inc.
99 Park Avenue, New York, New York 10016

A Public Service of Transit Advertising & The Advertising Council.



Risk Reduction 1980's – 90's



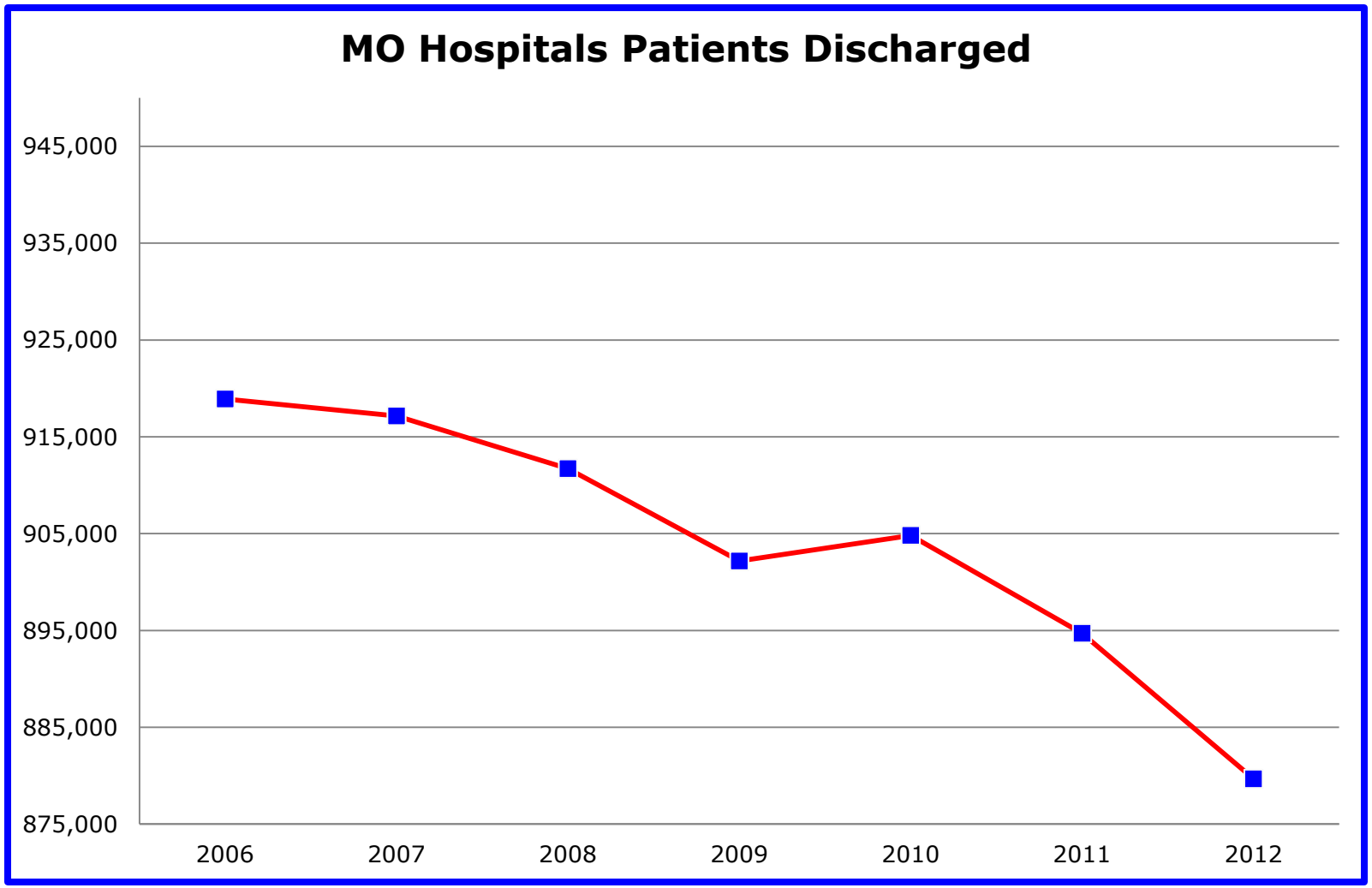
• Busch Transfusion 2006

Transfusion Medicine 1980' - 90's

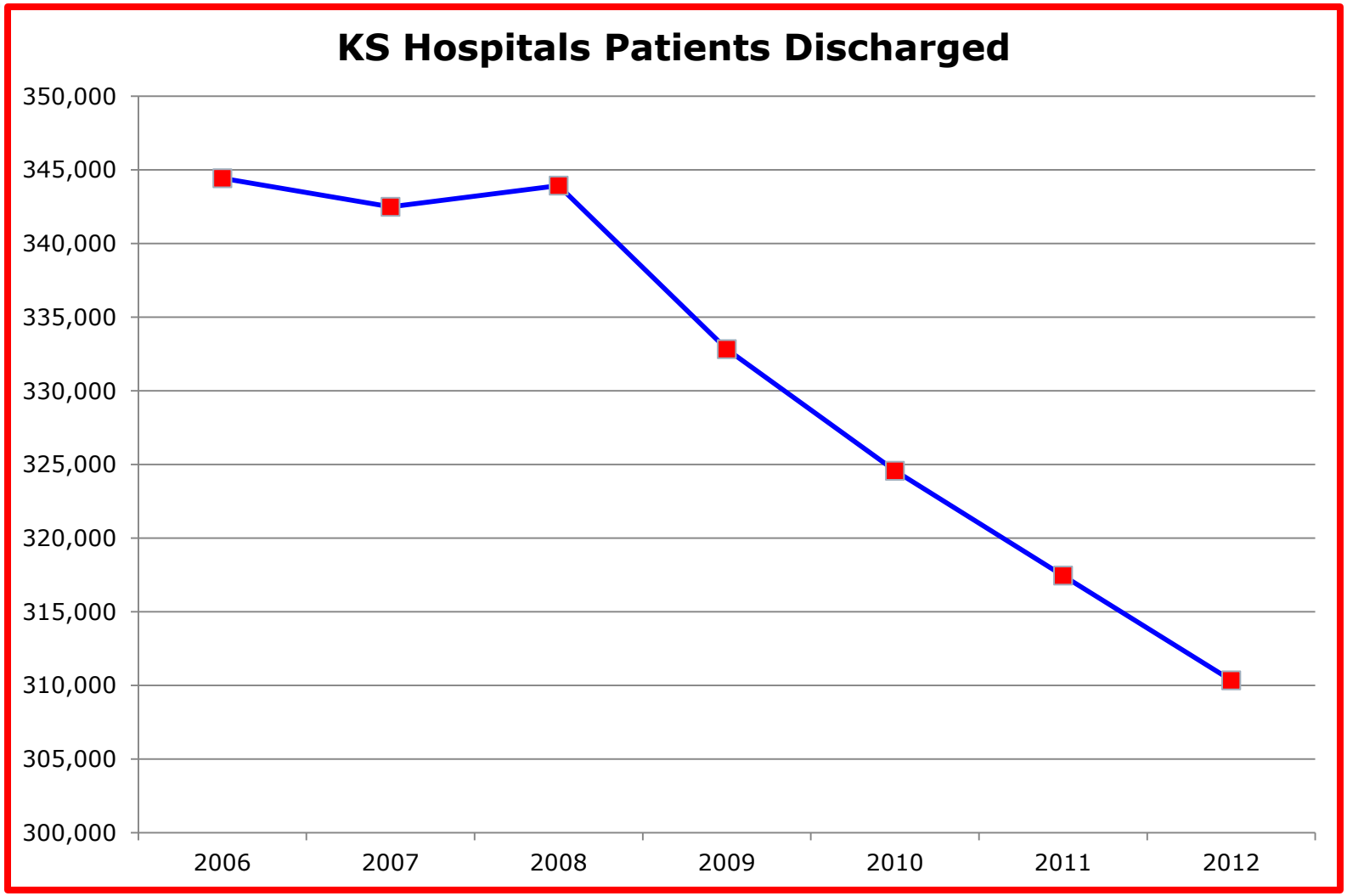
- Zero risk
  - Multiple infectious disease tests
    - NAT in addition to EIA tests to reduce "window period" donations i.e. donations made between serologic and RNA/DNA detection
      - HIV: 11 days (22 → 11 days)
      - HCV: 63 days (70 → 10-25 days)
      - HBV: 29 days (69 → 40 days)

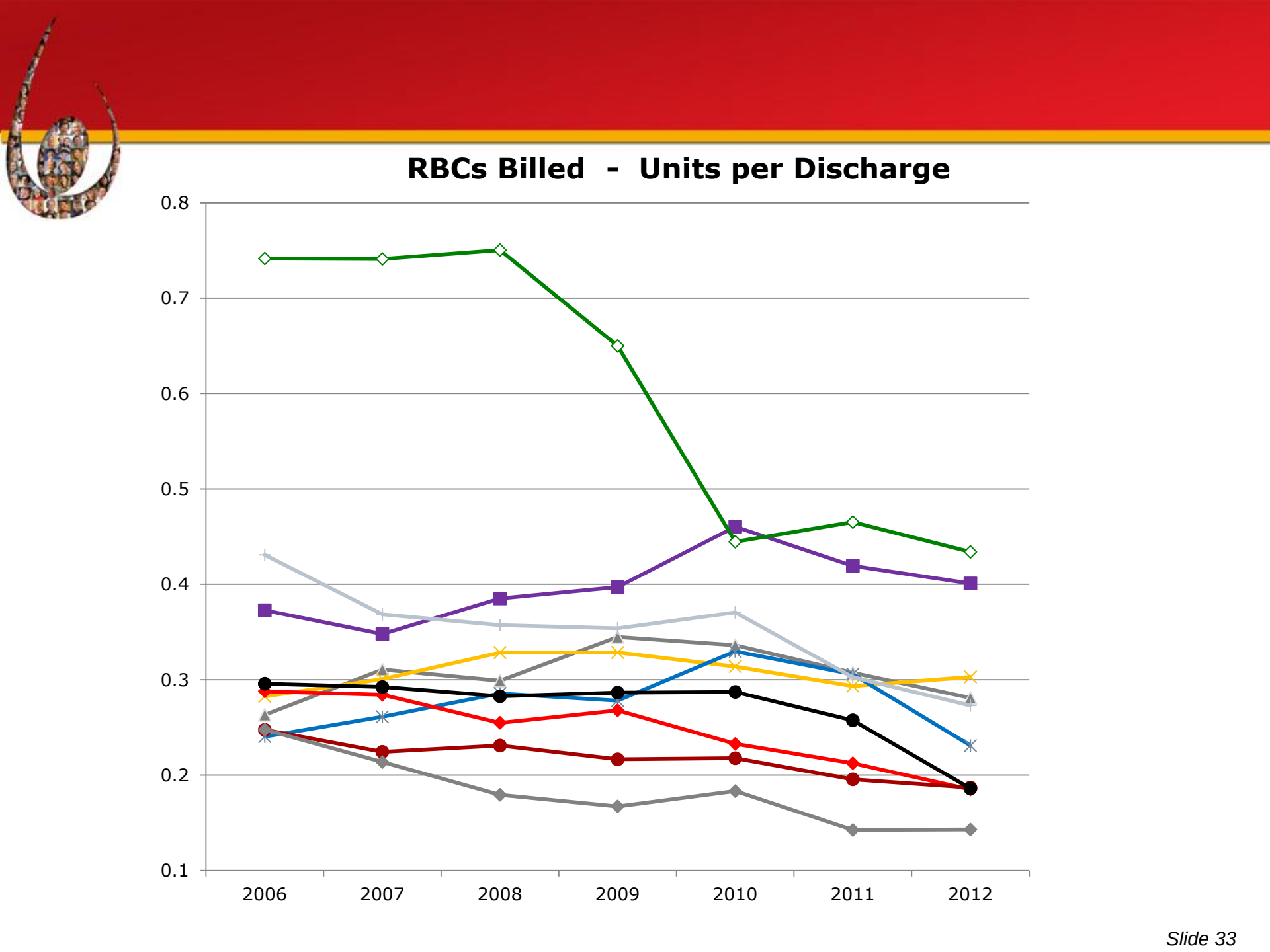
Consensus Conference and first RCT
Current Good Manufacturing Practices
Good Laboratory Practices
Blood Supply Safety = enhanced

Missouri Hospitals Patient Discharges

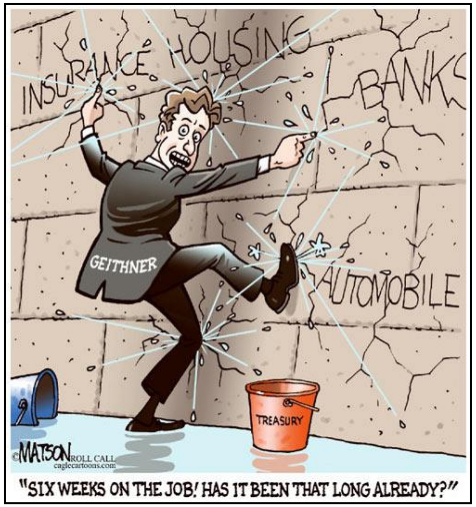


Kansas Hospitals Patient Discharges




RBCs Billed - Units per Discharge
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
2006
2007
2008
2009
2010
2011
2012

- Unemployment 8.2 % in Kansas City
  - Widespread concern about job stability
  - ?Fewer donors at mobiles
  - ? Fewer patients with insurance



- "Bad economy leads patients to put off surgery, or rush it" NY Times – March 13, 2009
  - Hip surgeries down 45%
  - Patients admitted to hospitals are sicker
  - Healthcare employment increasing

- **Patients:**
  - Great Recession
  - Elective surgery procedure delayed
    - 10% of blood utilization

- **Clinicians:**
  - Adoptions of TRICC findings
  - FOCUS results
  - Pediatric/Low Birth Weight Studies
  - Patient Blood Management Programs
    - Less is more

Transfusion Requirements in Pediatric Intensive Care (TRIPICU)

Hb < 7 g/dl (restrictive) versus Hb < 9.5 g/dl (liberal)

N= 320 and N= 317

Stable ICU Patients

Leukocyte-reduced RBC

Not blinded

Primary outcome: Multiple-organ-dysfunction syndrome (MODS)

	Restrictive	Liberal	
Any transfusion	46%	98%	P < 0.001
Number of txf	301	542	P < 0.001
Hb before first txf	6.7	8.1	P < 0.001
New/progressive MODS	12%	12%	

Conclusion: Restrictive Strategy

- 96% reduction in transfusion exposure
- 44% fewer RBC's transfused
- no increase in rate of new or progressive MODS in stable critically ill children (not applicable to premature infants or children with severe hypoxemia, hemodynamic instability, active blood loss, cyanotic heart disease)

- Lacroix, et al. NEJM 2007; 356:1609

RBC Transfusion Thresholds in Pediatric Patients with Sepsis

TRIPICU Sub-group Analysis

- Restrictive versus liberal strategy on MODS and adverse outcomes in critically ill stabilized children with sepsis or septic shock.
- N = 137 septic patients
- Randomization: N=69 restrictive versus N=68 liberal strategy

	Restrictive	Liberal	
Received Transfusion	56%	99%	P < 0.01
Median txf volume (mL/Kg)	7.6	15.7	p < 0.01
New/progressive MODS	18.8%	19.1%	P = NS

- **Conclusion:** Restrictive strategy may be safe for hemodynamically stabilized septic patients admitted to the PICU (most severely ill with sepsis were excluded).

• Karam, et al. Pediatric Crit Case Med. 2011; 12=512-518

Extremely Low Birth Weight Infants = Transfusion and Brain Injury

2 RCT's

Different study designs, study populations, Hb threshold

	Percent Transfused	Number Transfusions	Death/Severe Morbidity	Cognitive Delay	Adverse Brain Event	Apneic Episode
PINT/PINT-OS						
• Low Threshold	89%	4.9	74.0%	24.4%		
• High Threshold	95%	5.7	69.7%	17.6%		
• P Value	0.037	0.070	0.25	0.06		
Iowa						
• Restrictive	90%	2.7			12%	0.84
• Liberal	88%	4.8			0%	0.43
• P Value	1.0	0.006			0.012	0.004

Conclusion: Concern about brain injury; higher Hb transfusion threshold → neuro-protection

- Kirpalani, et al. J Pediatric 2000; 199:301-7
- Whyte, et al. Pediatrics 2009; 125:207-13
- Bell, et al. Pediatrics 2005; 115:1685-91

- **Hospitals:**
  - Reimbursement rates restrained
  - Lean / Six Sigma
  - Cost containment
  - Consolidation of hospitals into hospital systems

Transfusion Costs

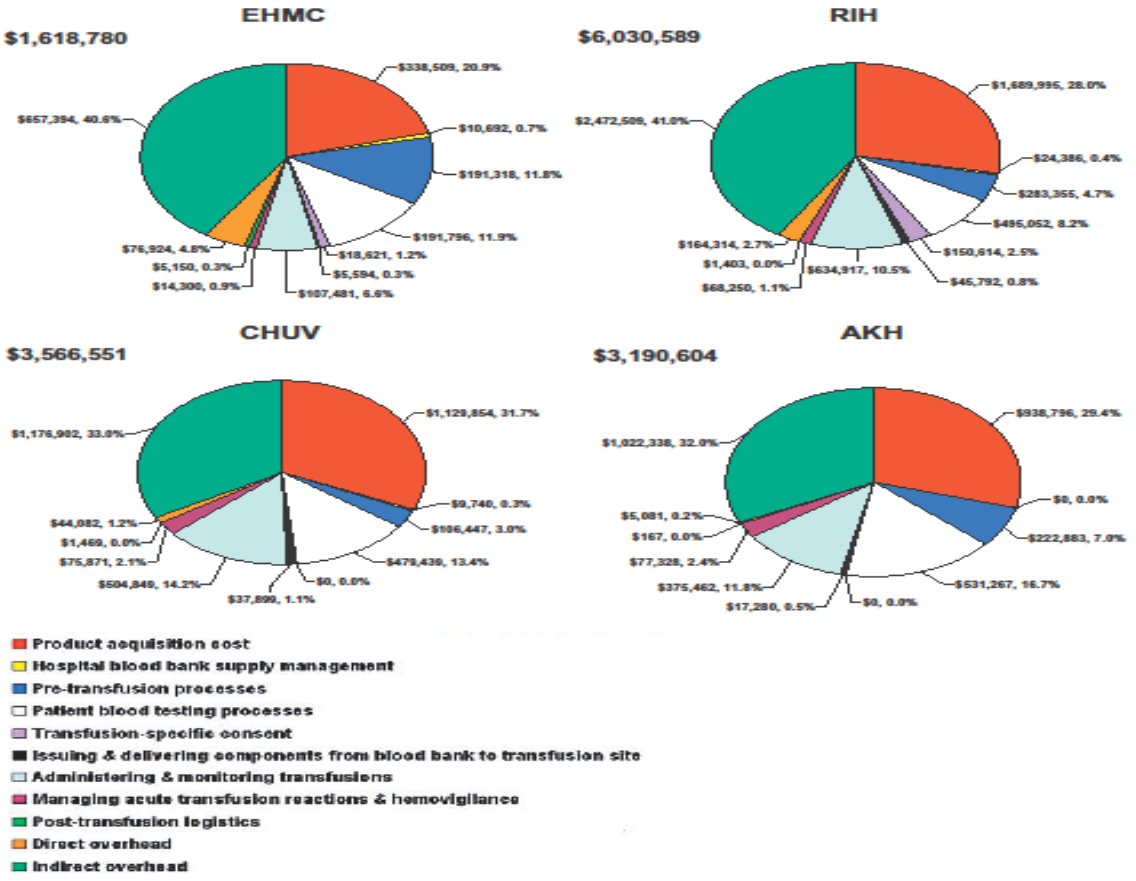


Fig. 3. Total costs of blood transfusions showing all contributing cost elements at two US and two European hospitals in 2007. Costs at CHUV (SFr) and AKH (€) converted to $USD using 1-year currency conversion average (May 2008–May 2009). Percentages of each contributing element shown next to $USD amount.

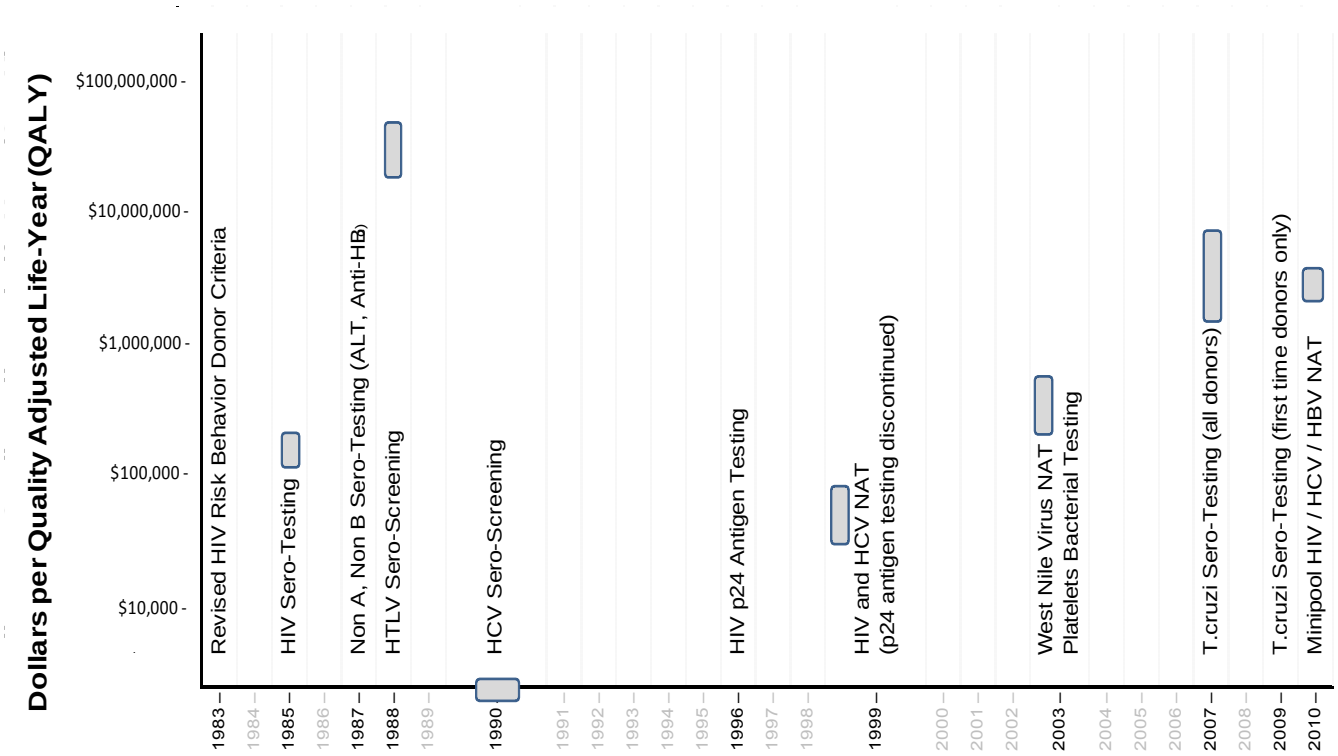
Transfusion Costs
(continued)

- Cost of transfusion in surgical setting
- Activity-based costing study
- Four Hospitals – Three Countries
- Cost of transfusion for surgical procedures higher than previously reported

	New Jersey	Rhode Island	Switzerland	Austria
Cost per Unit	$1,183	$726	$611	$522
Consent Requirements	2.5%	2.5%		
Outsource In-Hospital Management			- 4%	- 4%
Indirect Costs	40%	40%	33%	33%
Blood Management Bloodless Surgery				

- Custer. *Transfusion* 2010; 50:742
- Shander, et al. *Transfusion* 2010; 50:753

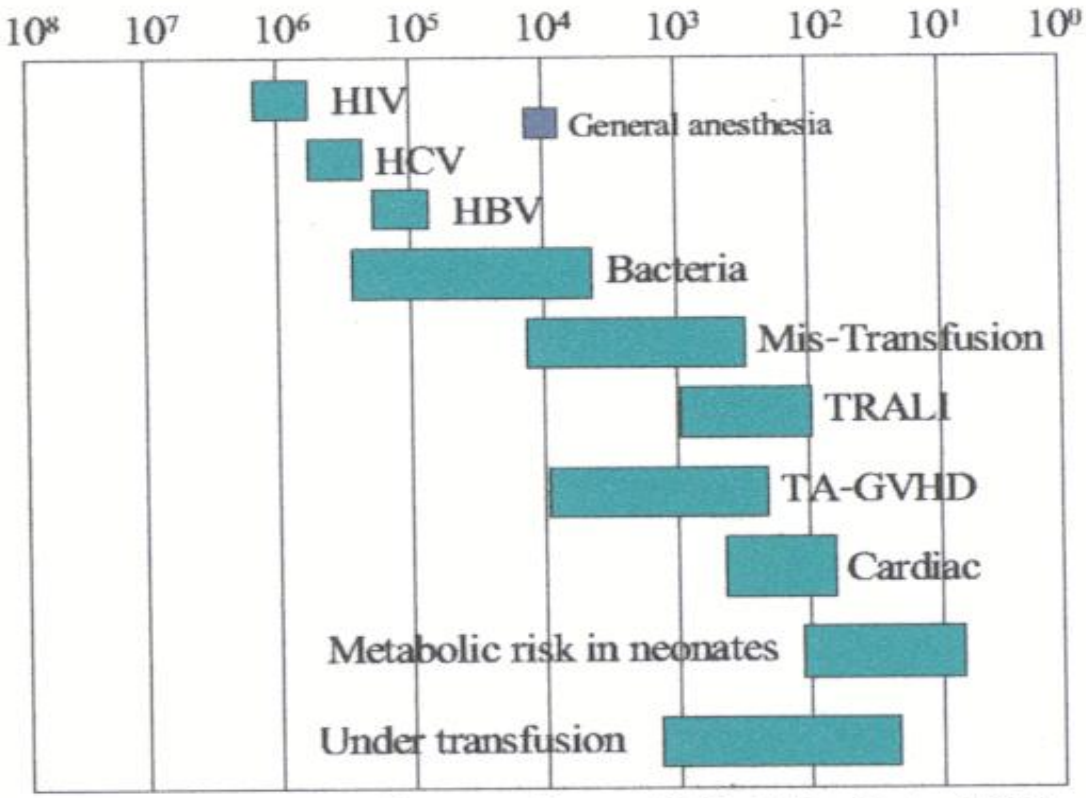
Donor Testing and QALY



- **Transfusion Medicine Specialists**
  - Transfusion related fatalities
  - Patient based innovations
    - Match RBC & FFP
    - Antibody Registry
    - Gift of Smiles Program
    - Patient Blood Management – Outcomes

Non-infectious Serious Hazards of Transfusion (NISHOT)

Figure 1. Paling Risk Scale for Major Transfusion Hazards

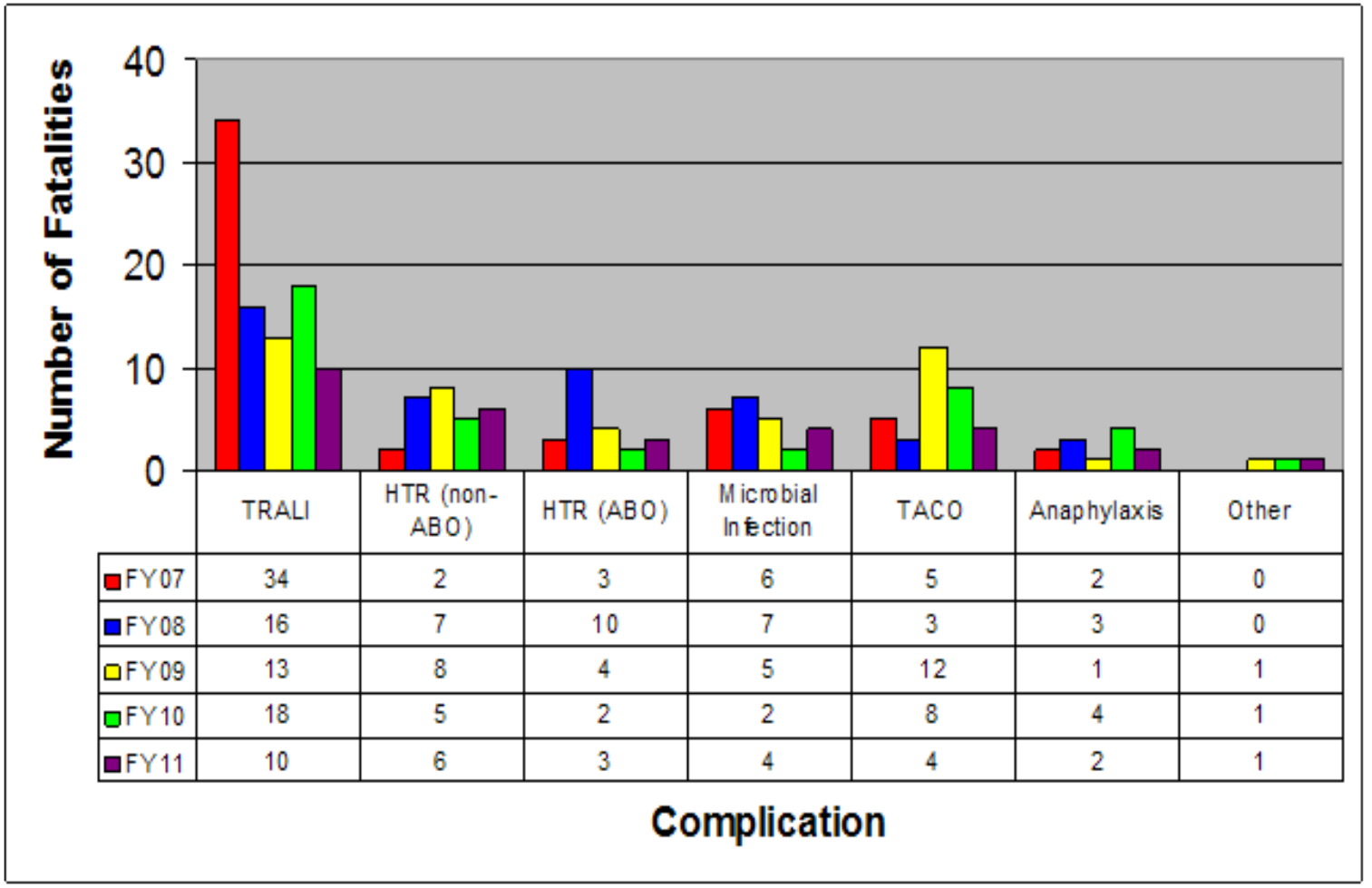


Source: Sunny Dzik, MD. Data: 2001

- *ABC Blood Bulletin* May 2002, Vol 5.

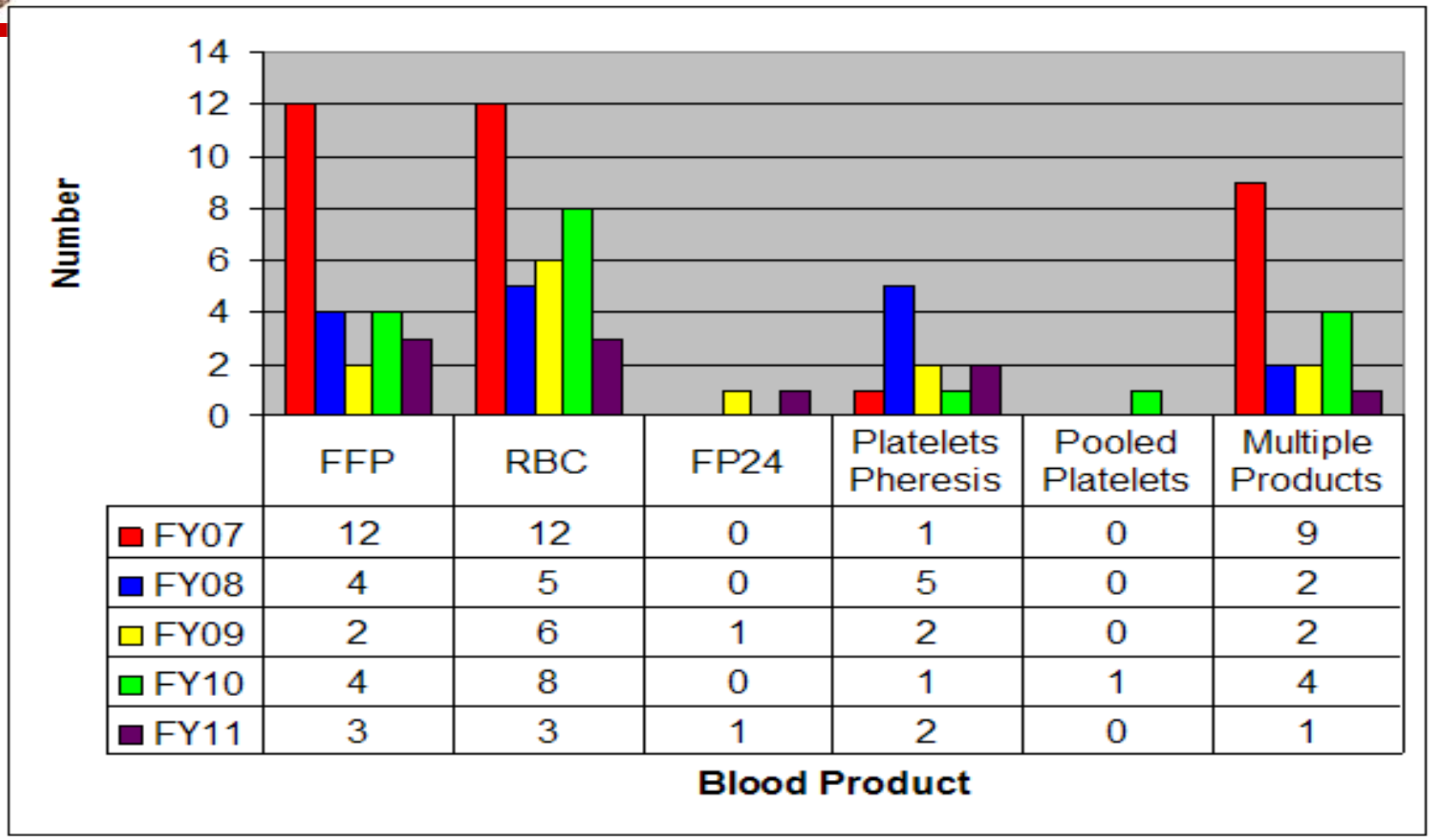
Transfusion Related Fatalities Reported to FDA

Transfusion-Related Fatalities by Complication, FY2007 through FY2011



	TRALI	HTR (non-ABO)	HTR (ABO)	Microbial Infection	TACO	Anaphylaxis	Other
FY07	34	2	3	6	5	2	0
FY08	16	7	10	7	3	3	0
FY09	13	8	4	5	12	1	1
FY10	18	5	2	2	8	4	1
FY11	10	6	3	4	4	2	1

Reports of TRALI by Implicated Blood Product FY2007 through FY2011



	FFP	RBC	FP24	Platelets Pheresis	Pooled Platelets	Multiple Products
FY07	12	12	0	1	0	9
FY08	4	5	0	5	0	2
FY09	2	6	1	2	0	2
FY10	4	8	0	1	1	4
FY11	3	3	1	2	0	1

Pump Priming – Heart Surgery in Infants

- Fresh whole blood versus reconstituted whole blood → no advantage*
- Decrease donor exposure
  - Children's Mercy Hospital, Kansas City**
  - Match RBC's and FFP from same donor
    - Saved 132 exposures for 166 patients (3-month period)
    - 81 of 83 open-heart operations – primed with RBC and FFP from same donor (Jan-Jun, 2004)

* Mou. et al. NEJM 2004; 351:1635

** Hamilton, Menitove. NEJM 2005; 352:731

Antibody Registry

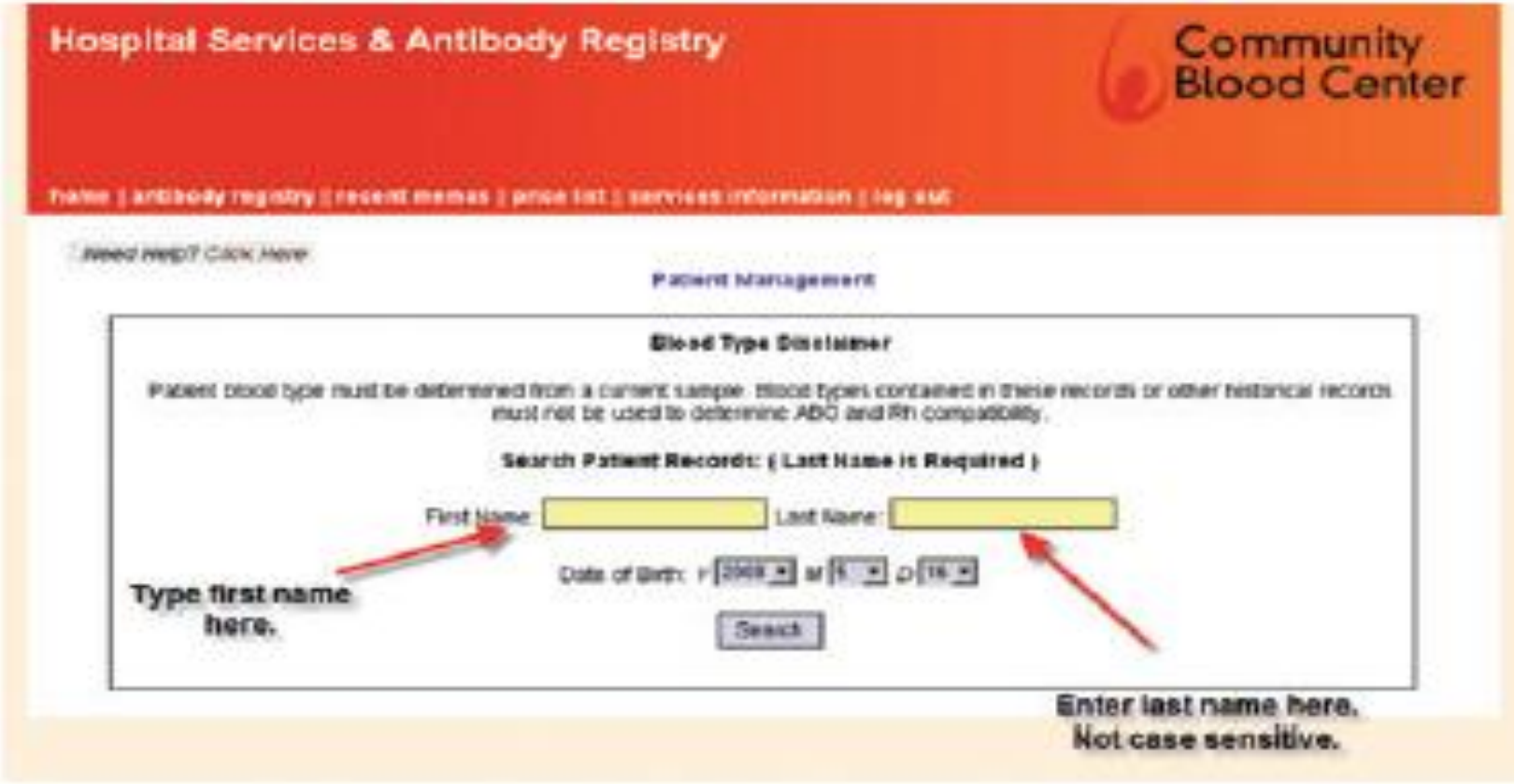


Fig. 1. Searching for a patient record.

Schwickerwath, et al Transfusion; 50: 1465

Antibody Registry

TABLE 3. Registry experience reported by hospitals and IRL

Antibody(-ies) recorded in registry	Registry checked before transfusion	Antibody(-ies) detected at the hospital
Anti-K_1, -C_1, and -V	Yes	None
Anti-K_1, -E_1, and -c	Yes	Anti-K only
Anti-E and -Fy^b	Yes	Anti-E only
Anti-K	Yes	None
Anti-Lu^b and -S	No	None
Anti-Tc^a	No	Antibody detected, not identified as anti-Tc^a
Anti-C_1, -E_1, and -Le^a*	No	None
Anti-D_1, -E_1, -C^w_1, -Fy^a_1, and -S*	No	Anti-D and -E only

* Reported in first 6 months of the second year.

Schwickerwath, et al Transfusion; 50: 1465

Transfusion by the Numbers: August 2009 – July 2011

1442 RBC Tx

33 Patients Total

100 % Antigen Matched

9 Days Average RBC Age

20 Patients
Sept 2011

941 Donors
Gift of Smiles Program

Tx: Donor Ratio

1.2 Sept 11

1.18 July 11

1.14 Feb 11

ZERO

New Antibodies

Critical Hb Concentration

- **Jehovah's Witness' patients**
  - N = 2,083
  - Surgical procedures (13 hospitals, 1981-1994)
  - Average age = 57 years

Hb Concentration	Morbidity	Mortality Rate
7.1 – 8.0 g/dL	09.4%	0%
6.1 – 7.0	22.0%	08.9%
5.1 – 6.0	28.6%	09.3%
4.1 – 5.0	57.7%	34.4%
3.1 – 4.0	52.6%	25.0%
2.1 – 3.0	91.7%	54.2%
1.1 – 2.0	100%	100%

Arrhythmia, CHF, M.I., bacteremia, pneumonia, wound infection, death

- Carson, et al. *Transfusion* 2002; 42:812

Hemoglobin Concentration & Time to Death

Re-analysis of *Transfusion* 2002; 42:812

Hb Concentration	Median Days Prior to Death
4.1 – 5.0 g/dL	11
3.1 – 4.0 g/dL	2
2.1 – 3.0 g/dL	2.5
< 2.0 g/dL	1.0

- Temporal latitude exists for treating profound anemia
- Only 10% developed cardiac arrhythmias
- Absence of cardiac sx's understates poor clinical outcome

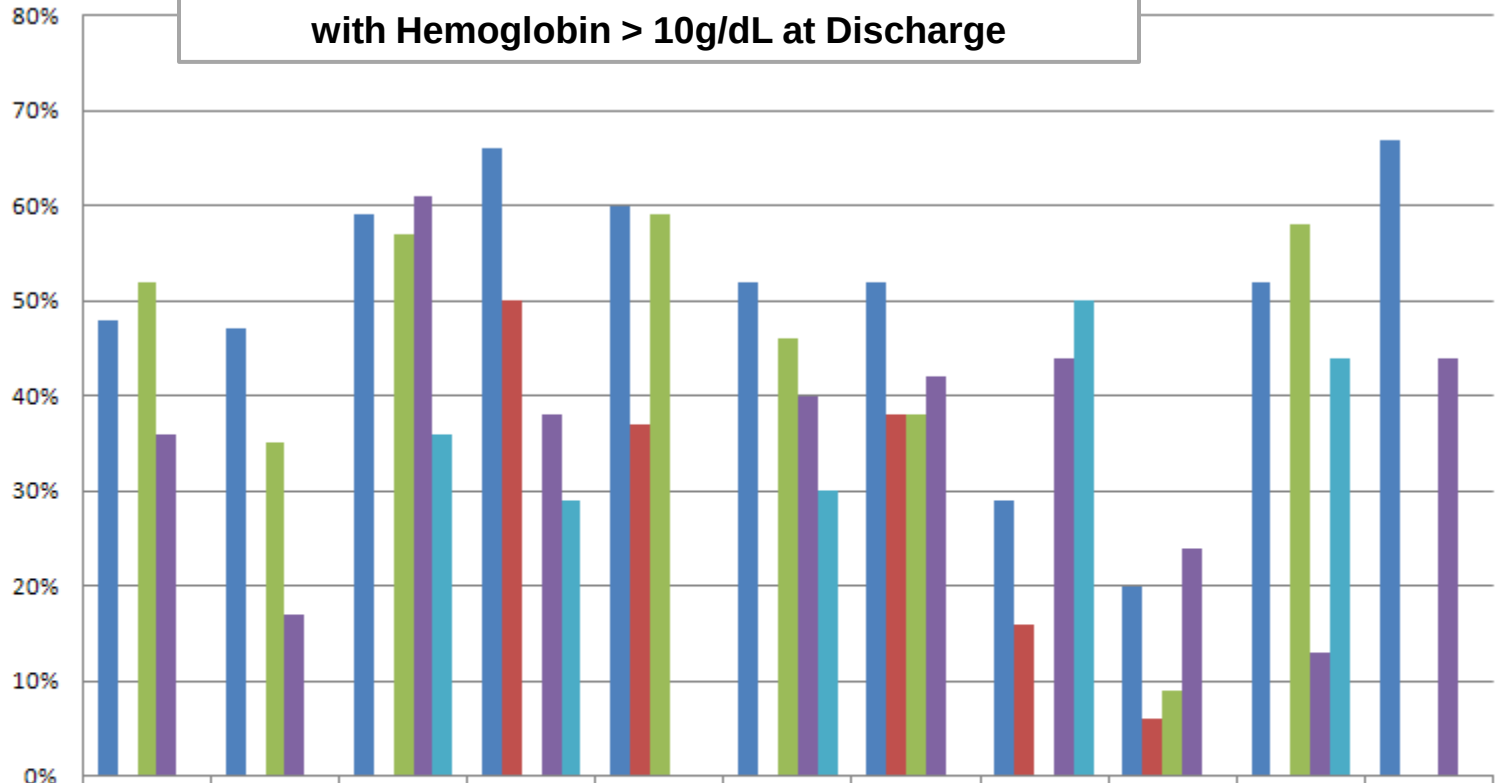
▪ Tobian N, et al. *Transfusion* 2009; 49:1395

RBC Transfusion: AABB Practice Guideline

- Recommendation 1:
  - Restrictive strategy (7-8 g/dL Hb)
    - Hospitalized, stable patients
- Recommendation 2:
  - Restrictive strategy
    - Hospitalized patients with pre-existing cardiovascular disease
    - Consolidation of txf for patients with sx's or Hb $\leq$ 8 g/dL
- Recommendation 3:
  - No recommendation for hospitalized, hemodynamically stable patients with acute coronary syndrome
- Recommendation 4:
  - Txf decisions influenced by sx's as well as Hb

- Carson, et al.
  AIM doi:10.1059/0003-4819-156-12-201206190-00429
  March 26, 2012

Percent of Patients Receiving Transfusions with Hemoglobin > 10g/dL at Discharge



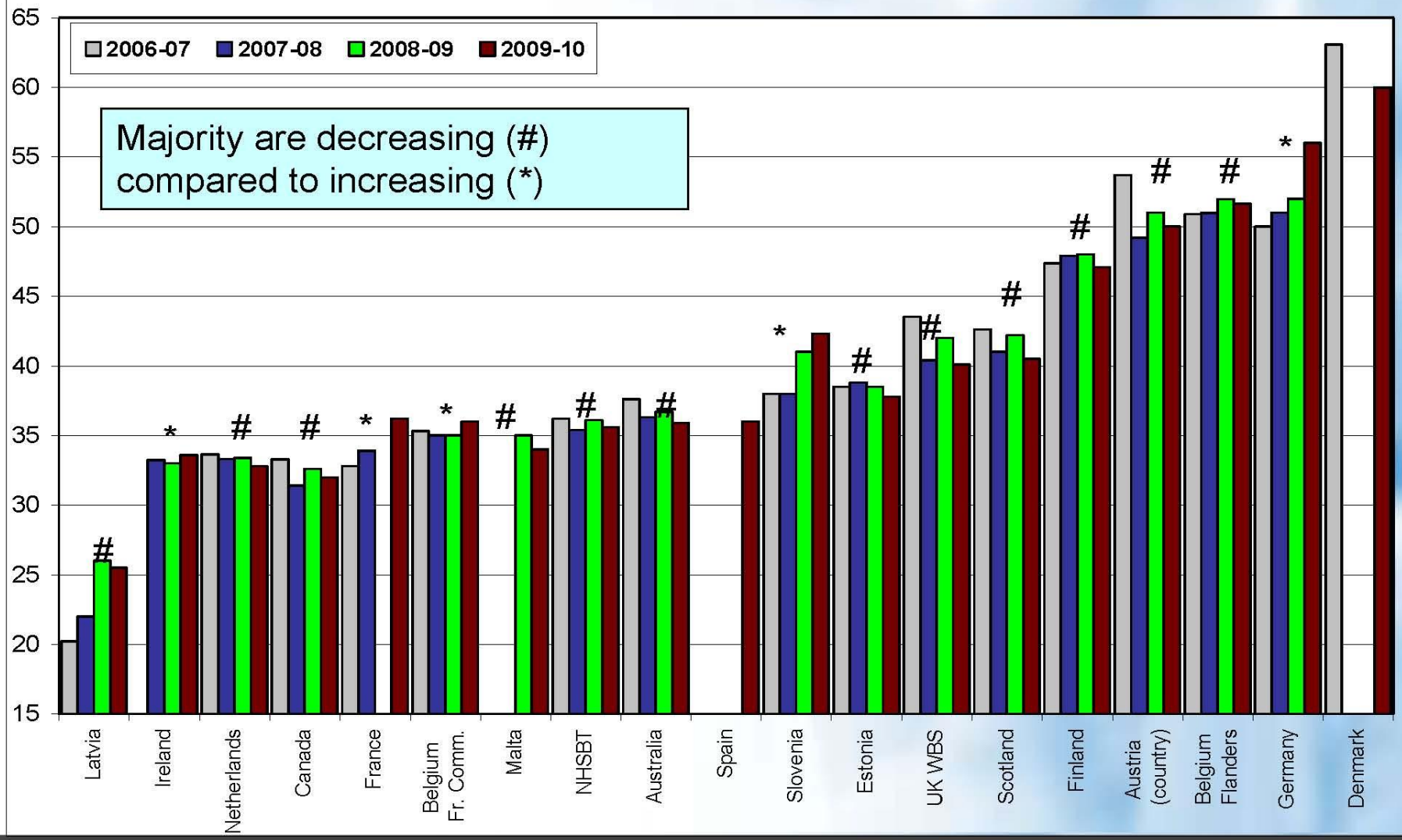
	CV	ER	FP	GI	Gen Surg	Med	Neph	Onc	OB/GYN	Ortho	Pulm
HOSPITAL A - 2Q09	48%	47%	59%	66%	60%	52%	52%	29%	20%	52%	67%
HOSPITAL B - 2009	0%	0%	0%	50%	37%	0%	38%	16%	6%	0%	0%
HOSPITAL C - 2Q09	52%	35%	57%	0%	59%	46%	38%	0%	9%	58%	0%
HOSPITAL F - 3Q10	36%	17%	61%	38%	0%	40%	42%	44%	24%	13%	44%
HOSPITAL G - 3Q10	0%	0%	36%	29%	0%	30%	0%	50%	0%	44%	0%

Local Hospital Blood Utilization

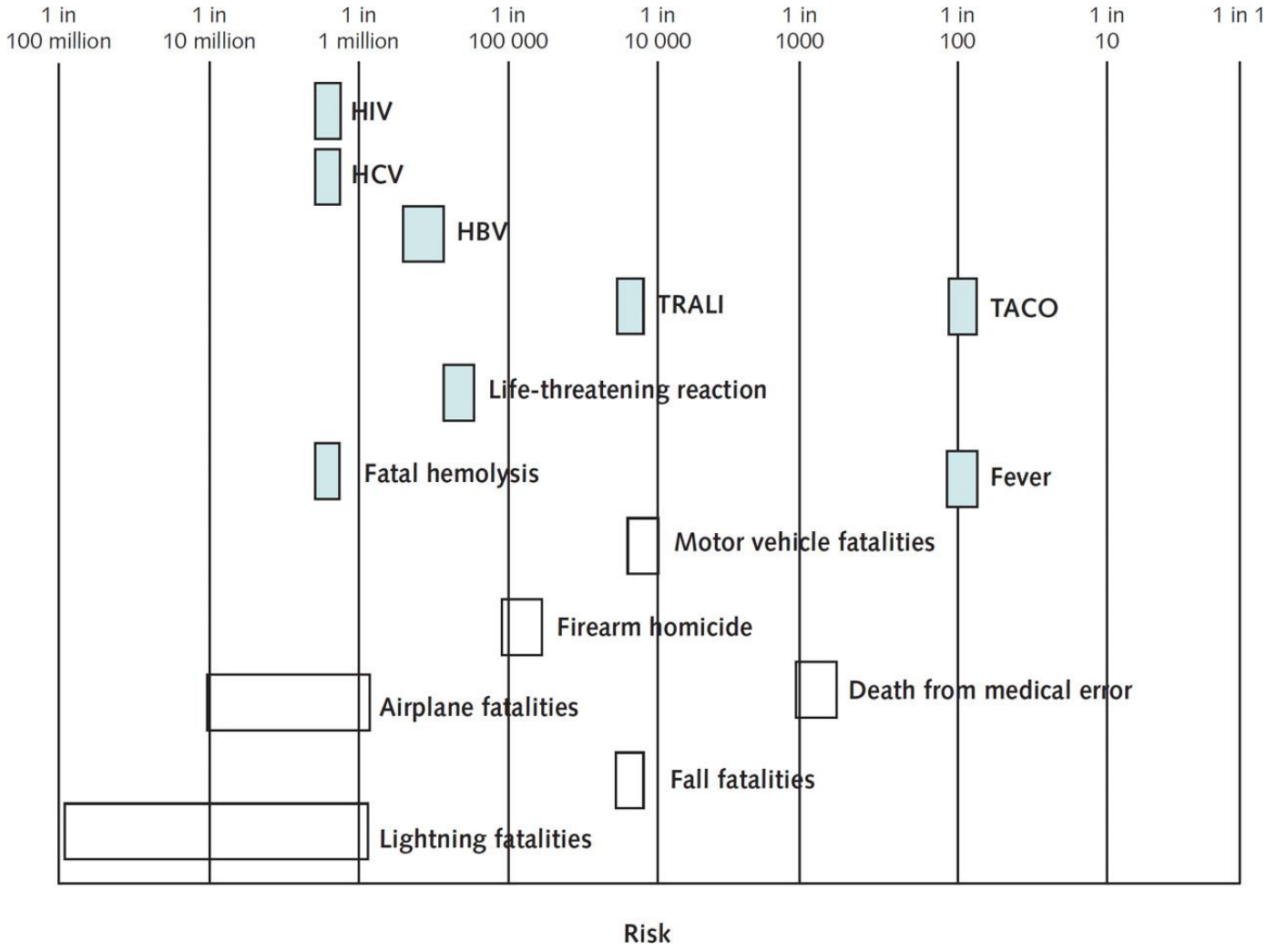
Local Hospital Blood Utilization		
Hospital	**2009-10**	**2012**
A	48%	17%
B	27%	25%
F	40%	27%
G	38%	50%

NHS Blood and Transplant

ABO Red Cell Issues per 1,000 of Population



Adverse effects of RBC transfusion contrasted with other risks.Risk is depicted on a logarithmic scale.



Carson J L et al. Ann Intern Med doi:10.1059/0003-4819-156-12-201206190-00429

Annals of Internal Medicine

Transfusion Medicine

- Utilization peaks and valleys
  - Reflect safety and efficacy, the economy, and outcomes
- Product safety standards – highest achieved to date
- Next generation
  - Less is more – patient outcomes and cost
  - Continued focus on patient support
    - Cellular therapy including cancer vaccination protocols
    - Regenerative medicine
- Paradigm change
  - Zero risk → Risk based decision making
  - Pathogen reduction (chemical, photo/chemical treatments of red cells, platelets and plasma

Questions and Answers

Community Blood Center

Save a Life. Right Here, Right Now.

For more information visit:

www.savealifenow.org

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