American Red Cross

Bacterial Contamination

Richard Benjamin MD PhD
Chief Medical Officer

Kuala Lumpur, December 2013

Conflicts

- Fenwal — Scientific Advisory Board
- Cerus — Scientific Advisory Board
- Immucor — Scientific Advisory Board
- TerumoBCT — Honoraria
- Verax Biomedical — Honoraria

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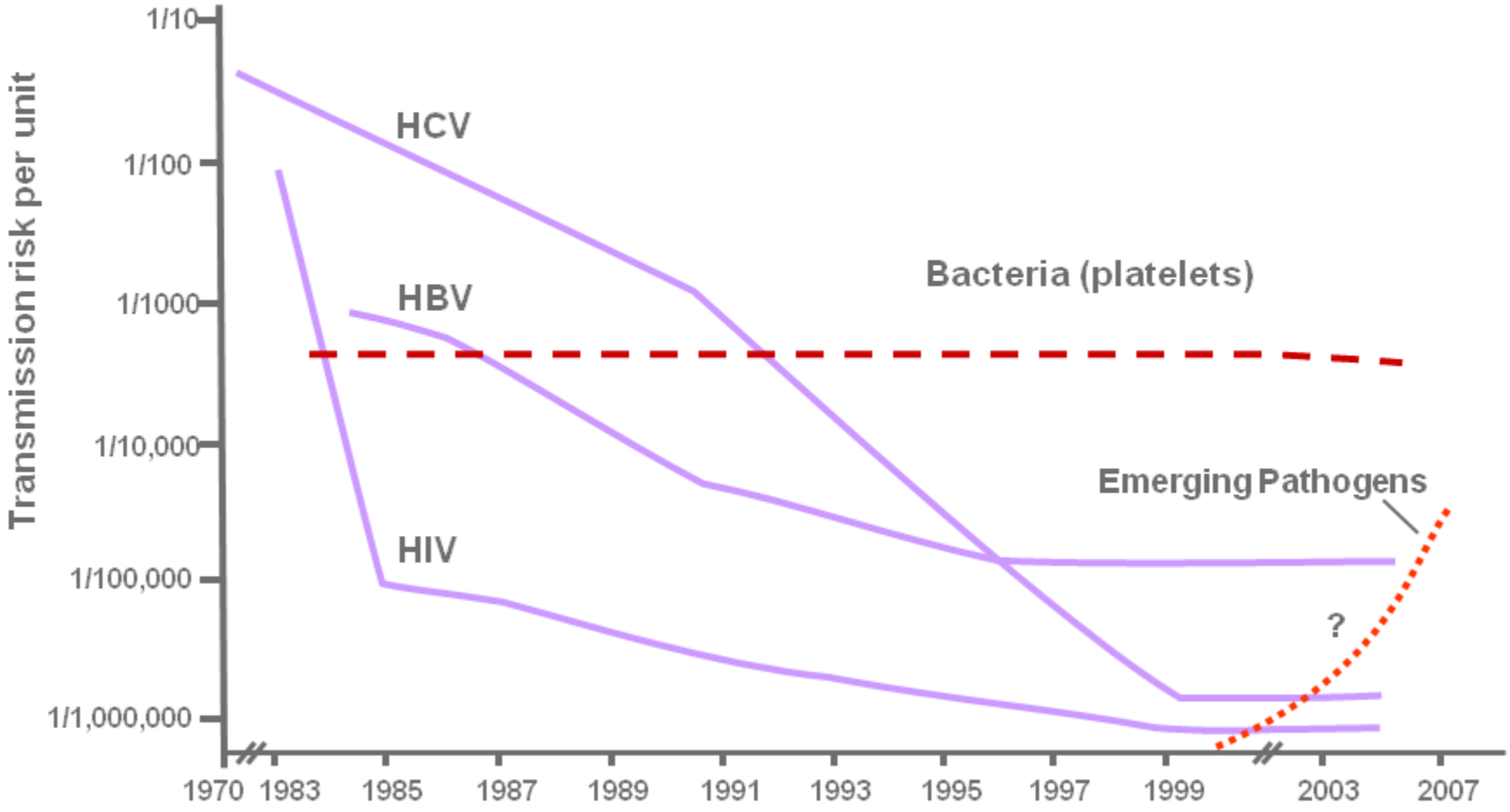
Infectious Disease Risks from Transfusion



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H. Klein, Transfusion 2007

Prevalence of Transfusion-related Sepsis

	Country	Apheresis Platelets	Whole Blood Platelets
Before Bacterial Culture			
Ness et al	US	1:13,423	1:14,925
Perez et al	France	1:31,446	1:13,927
Kuehnert et al	US	1:101,010	1:94,340

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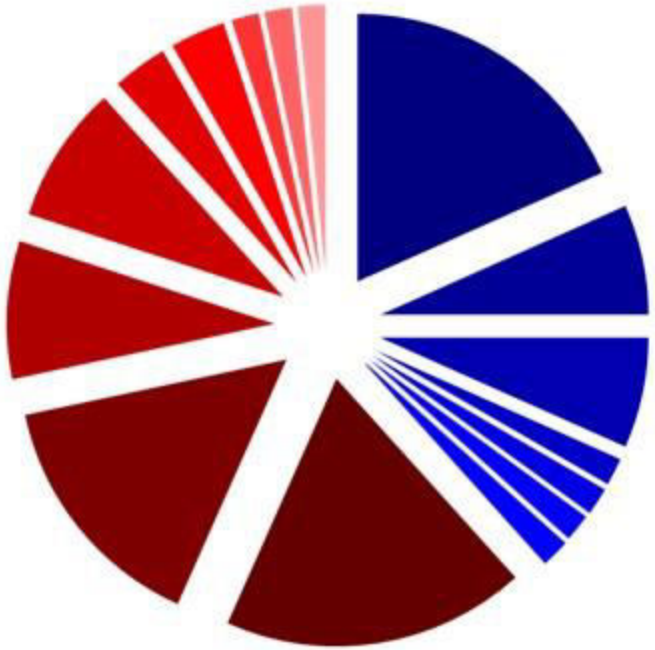
Hillyer et al. Hematology 2003, 575

US FDA Platelets Fatalities 1995-2004

(before apheresis platelet culture screening)

Fatalities ~1:250,000 transfusions



- S. epidermidis
- S. aureus
- Streptococcus spp.
- C. perfringens
- Enterococcus spp.
- Bacillus spp.
- Gram + rods
- Klebsiella spp.
- E. coli
- S. marcescens
- Enterobacter spp.
- P. aeruginosa
- Salmonella spp.
- Morganella spp.
- P. multocida
- Gram negative rods

37 of 60 (62 %) fatalities were caused by rapid-growing Gram negative enteric organisms

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Niu et al. Trans. Med. Rev. 2006:20;149

Active versus Passive Surveillance for Bacterial Contamination

Bacterial culture at issue 1991-2006

Surveillance	Active (n=102,998)	Passive (n=135,885)	Odds Ratio (95% C.I.)
Bacterial contamination	50 1: 2,060	2 1: 67,942	32.0 (8.0-135.0)
Clinical Reactions	16 1:6,437	2 1:67,942	10.6 (2.4-45.9)
Death	1	1	1.3 (0.01-21.1)

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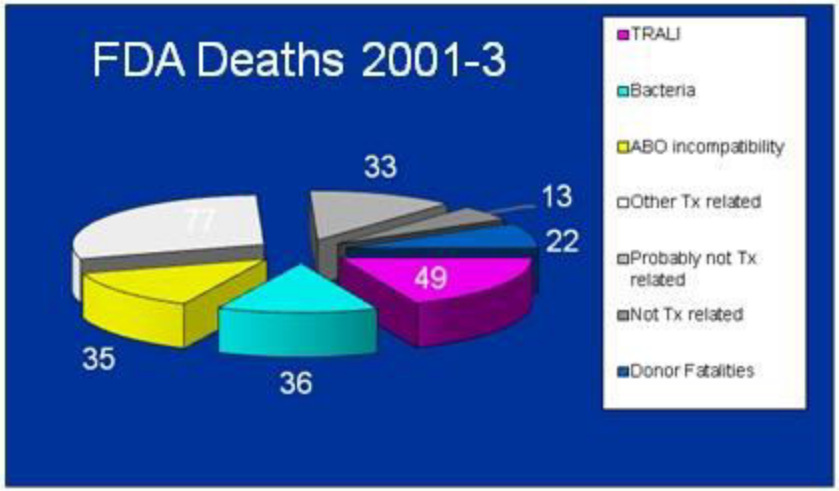
Jacobs M, Yomtovian R. CID 2008:46,1217

Bacterial Sepsis



AABB Standard 5.1.5.1 (first added in March 2004)

- The blood bank or transfusion service shall have methods to limit and detect bacterial or inactivate bacterial contamination in all platelet components.

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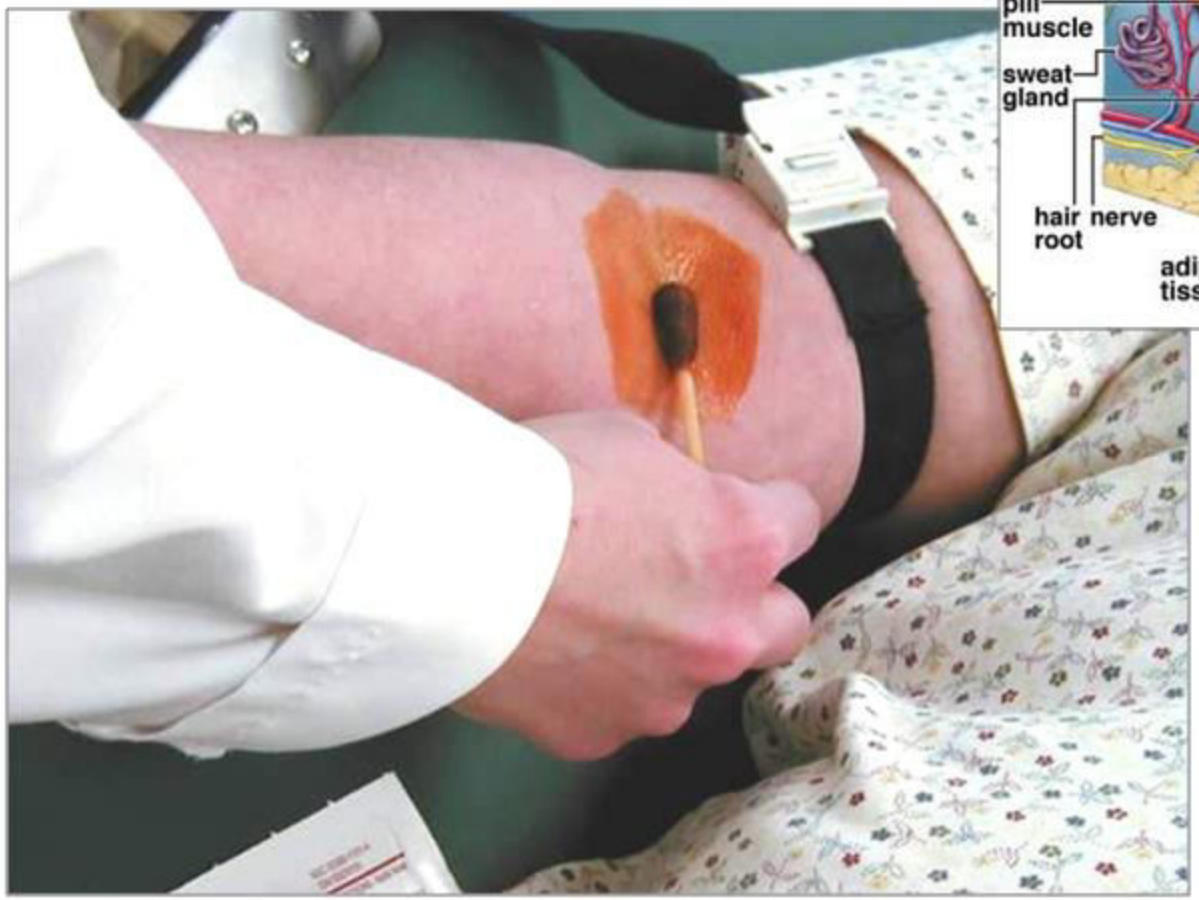
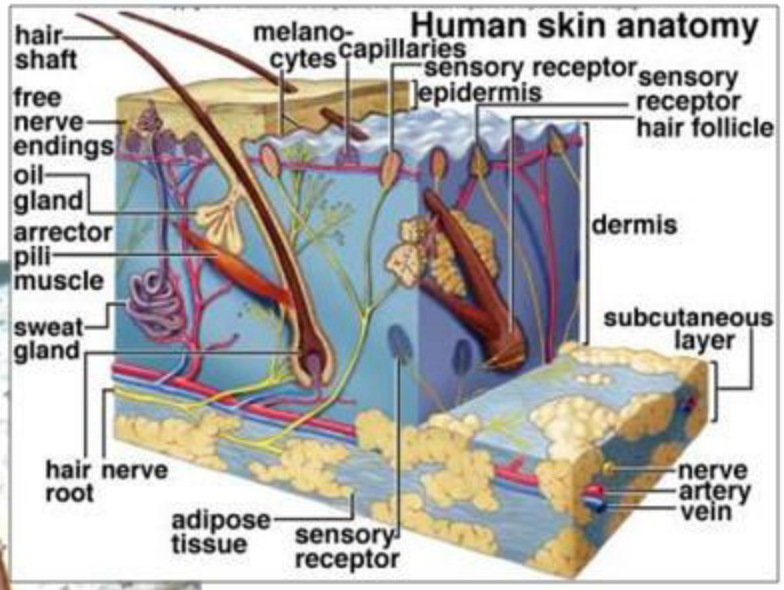
Reducing Bacterial Contamination

- Donor Health History
- Phlebotomy Site Inspection
- Skin Preparation
- Sample Diversion

Arm Preparation





Standardized protocol
1 or 2 step:

- *Tincture of iodine/IPA*
- *Povidone Iodine*
- *2% Chlorhexidine/IPA*

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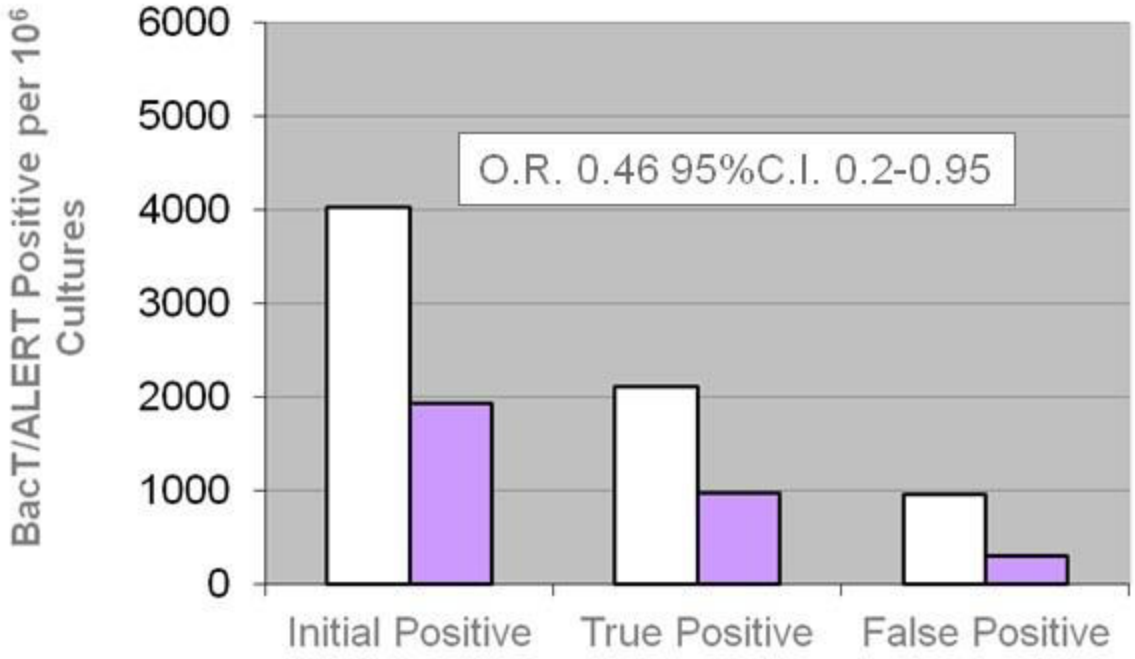
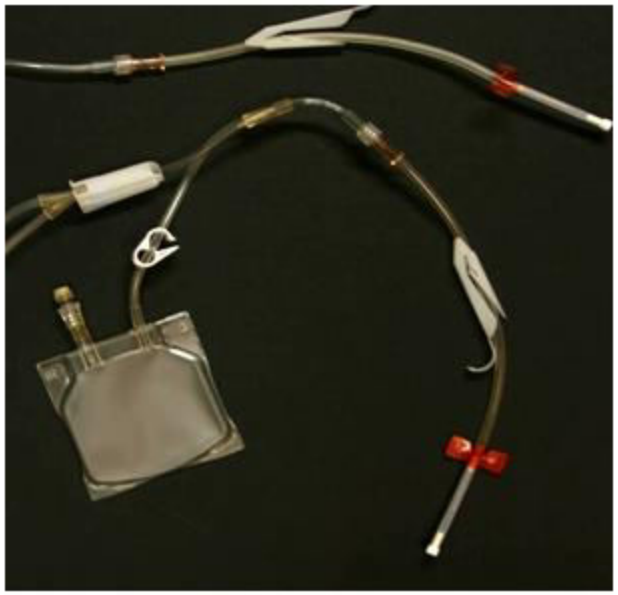
Inlet-line Diversion





Culture Outcome in Prestorage-pooled Platelets

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Benjamin, Kline et al. Transfusion 48:2348, 2008

Detecting Contamination

- Prerelease culture testing
  - Pall eBDS™
  - bioMerieux BacT/ALERT™
- Day of transfusion testing
  - Verax PGD™
  - Immunetics BacTx™
  - PCR assays
  - Bactiflow ALS

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BacT/ALERT™ Bacterial QC Culture

Transfusion "Neg to date"

24 – 36 hrs

48hr

72 hr

96 hr

120 hr

Collection

Outdate

BacT bottle monitoring

Inoculate

Release (12 hrs)

Apheresis platelets since March 2004
Aerobic culture only
Tested > 3.8 M collections
Distributed > 6 M cultured products

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Bacterial Detection in Apheresis Platelets

March 1, 2004 – December 31, 2012
Total APLT Donations: 3,859,114

Interpretation	n	%	Rate	Rate per 10^6
Confirmed positive	757	51%	1 : 5,098	196
False positive (unconfirmed)	521	36%	1 : 7,407	135
Unable to Determine	178	12%	1 : 21,680	46
Total	1,465	100%	1 : 2,634	380

Isolate identified in initial BacT aerobic bottle (2,540 APLT components)

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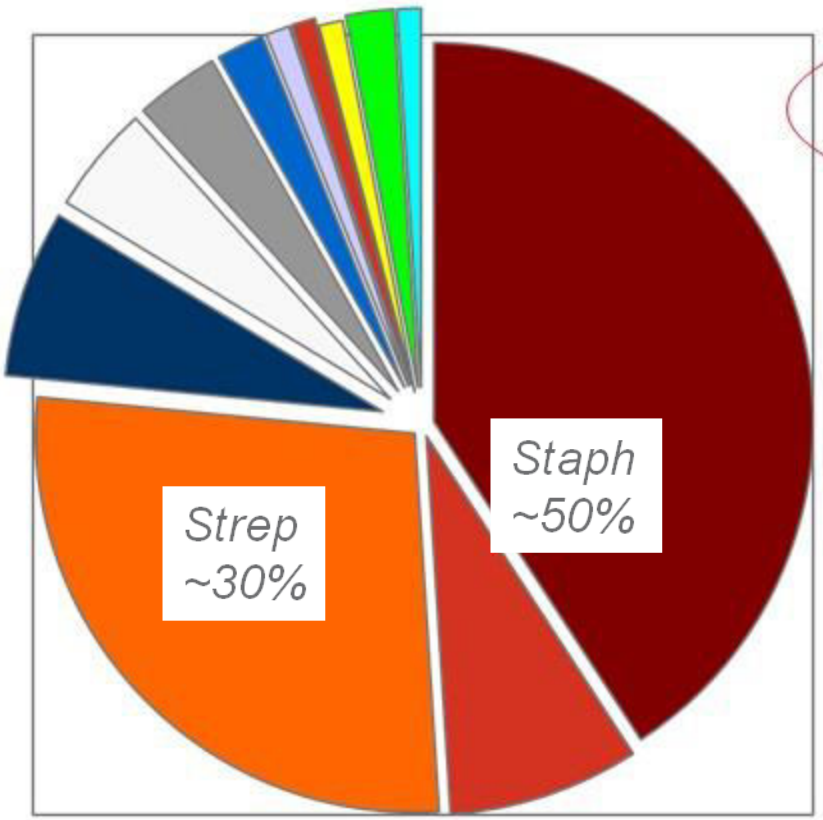
Eder et al. Transfusion 2013; ePub Ahead of Print

Bacteria Confirmed by Re-culture

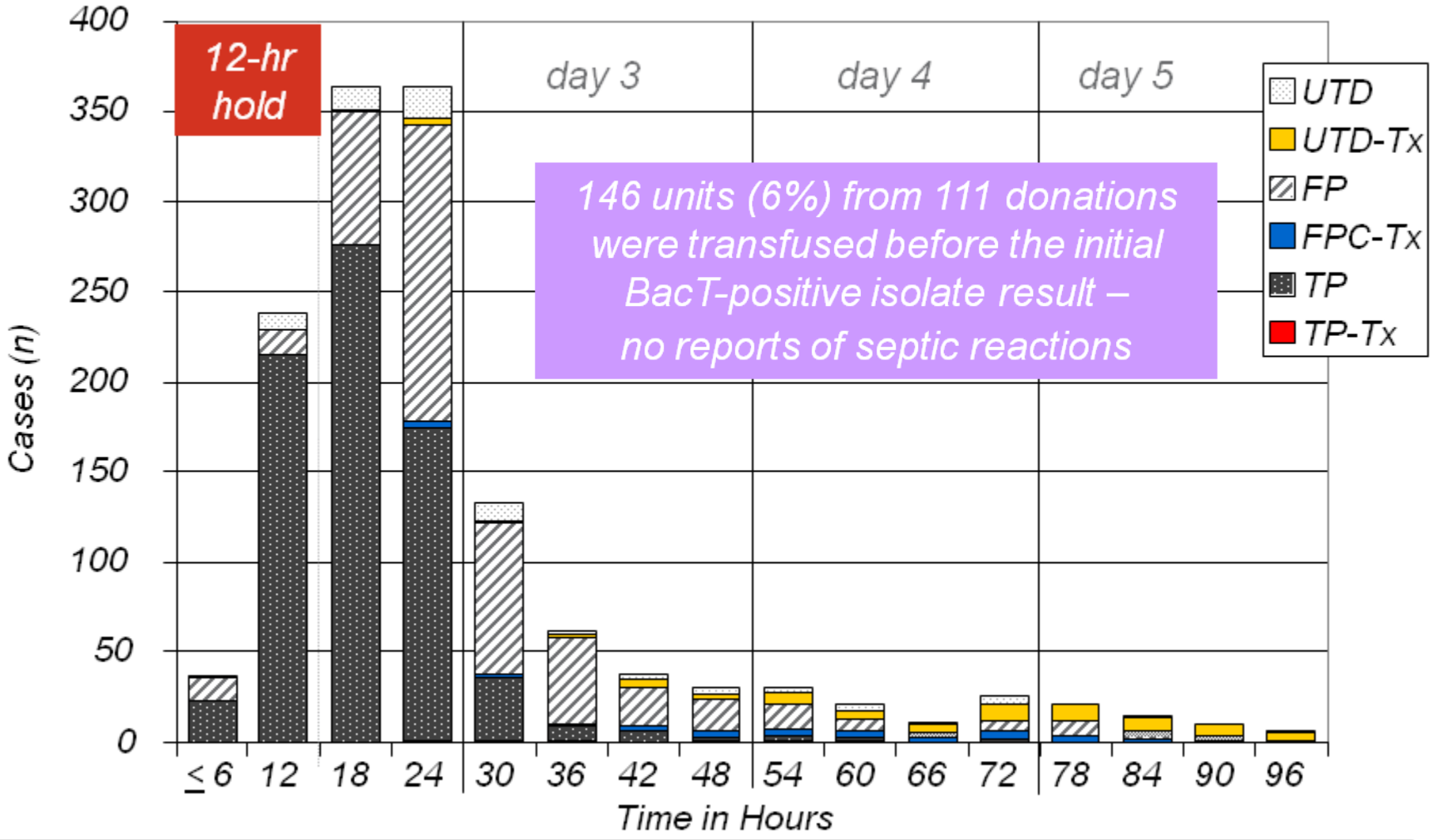
March 1, 2004 – December 31, 2012
Total APLT Donations: 3,859,114



80%

- Coag-neg Staph
- S. aureus
- Streptococcus spp.
- E. coli
- Klebsiella spp.
- Serratia spp.
- Bacillus spp.
- Listeria mono.
- Enterobacter spp.
- Enterococcus spp
- Other Gram-negative
- Other Gram-positive

Time to Initial Positive



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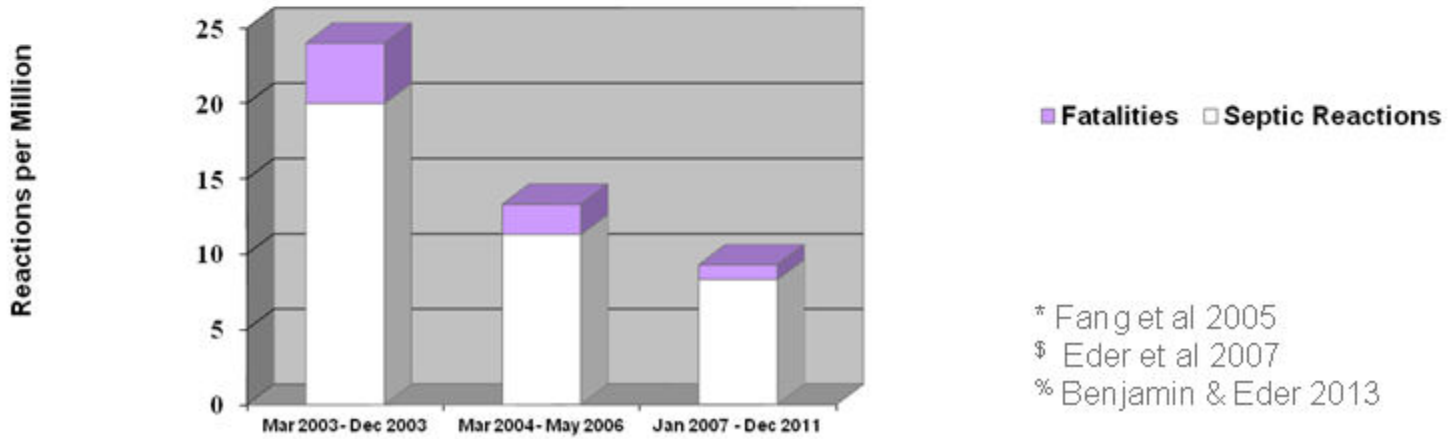
Sample for culture taken from donation after at least 24 hours
BacT initial results with isolate, 3/1/2004 to 12/31/2012

Declining Risk of Sepsis in the Red Cross

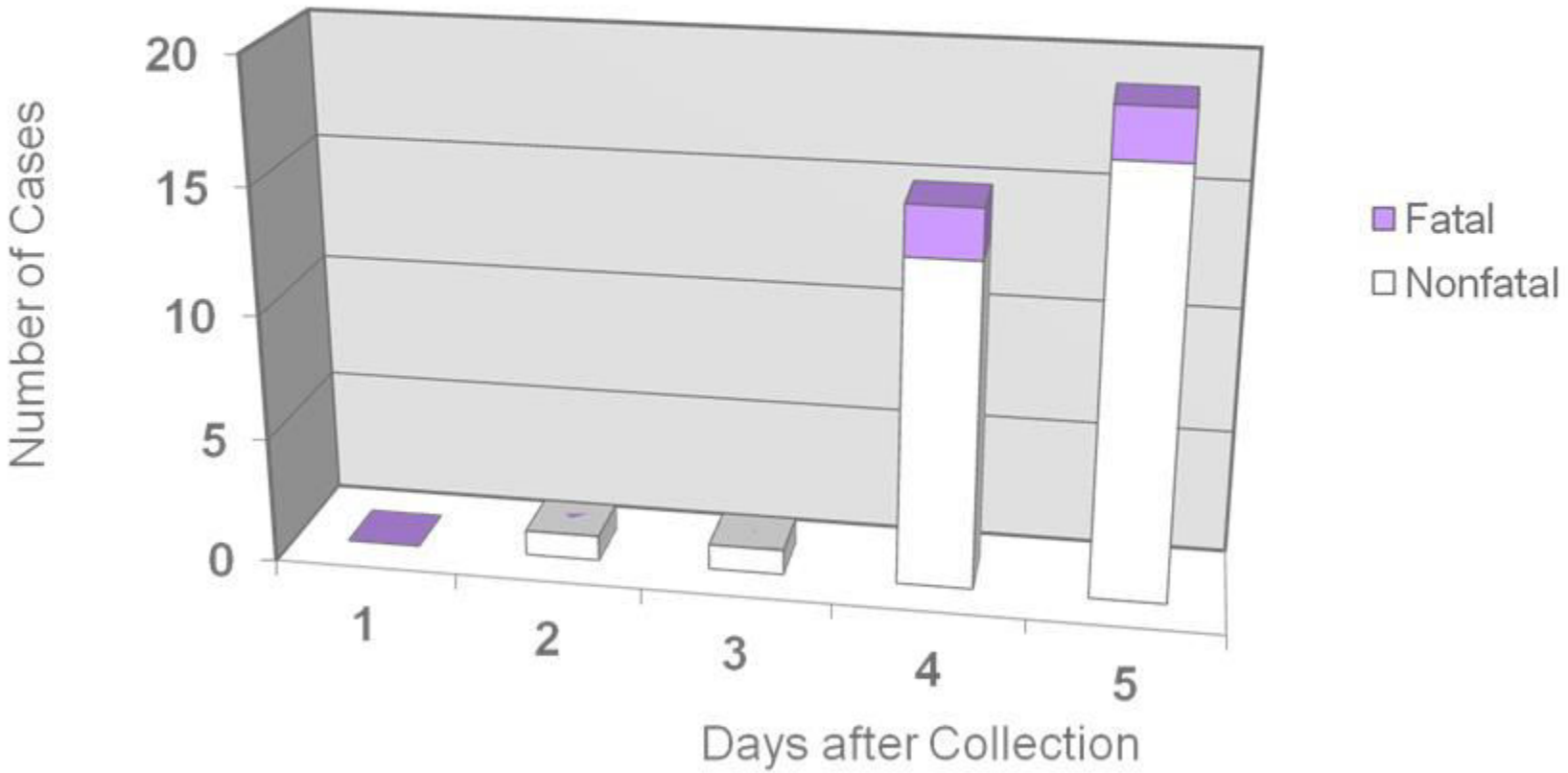
	Before Culture*	39% Diversion & 4ml Culture$	100% Diversion & 8ml volume%
	March 2003-Dec 2003	March 2004-May 2006	Jan 2007–Dec 2011
Components	~500,000	1,496,134	4,063,371
Septic Reactions	12 reactions ~1:40,000	20 reactions ~1:75,000	38 reactions ~1:107,000
Deaths	2 fatalities ~1:250,000	3 fatalities ~1:500,000	4 fatalities ~1:1,016,000



* Fang et al 2005
$ Eder et al 2007
% Benjamin & Eder 2013

Septic Reactions – Day of Storage

38 Definite/Probable Septic reactions, Apheresis Platelets, 2007-2011



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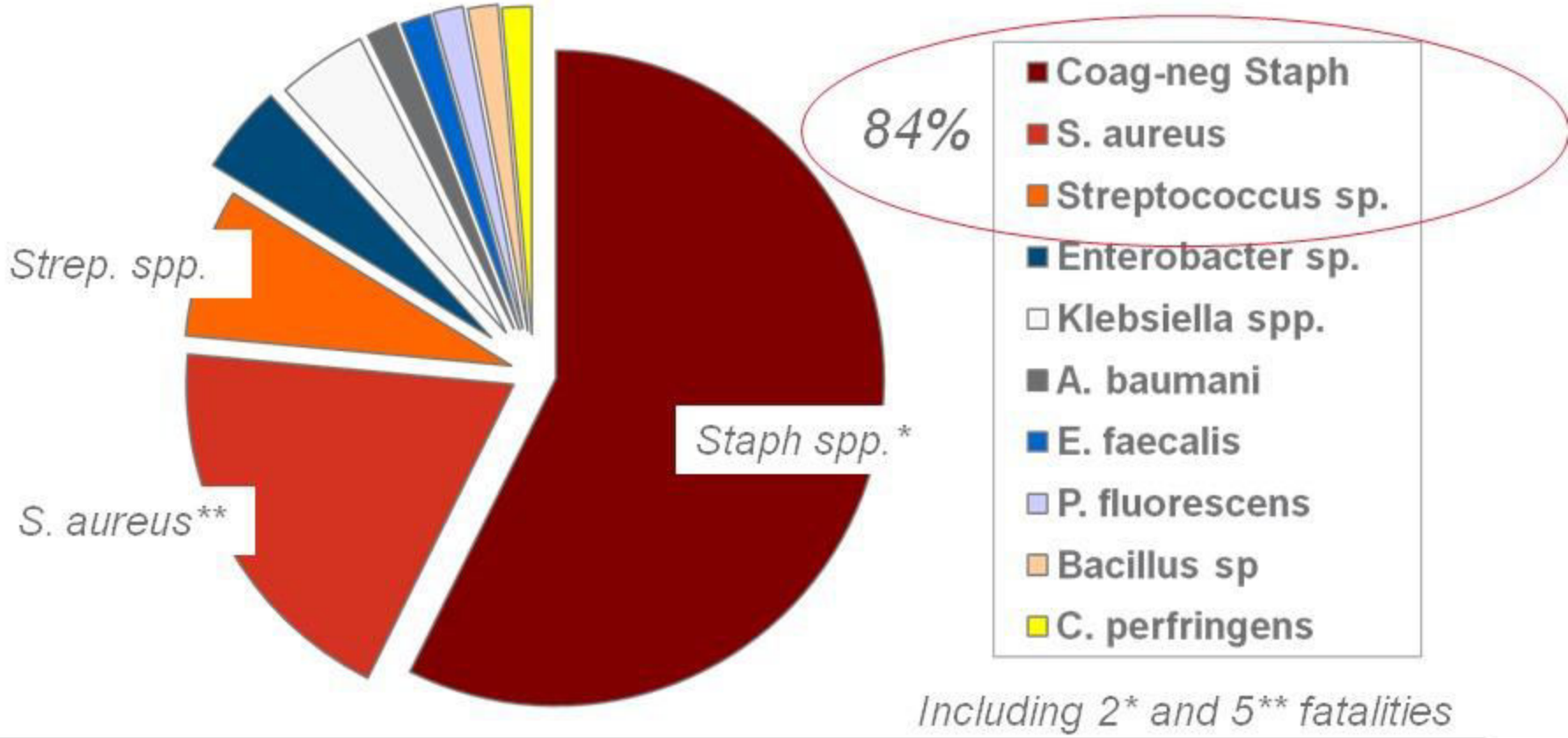
American Red Cross Hemovigilance Program

Implicated Bacteria, Septic Reactions

March 1, 2004 to December 31, 2012
68 septic reactions; 6,401,463 distributed apheresis platelets



Including 2 and 5** fatalities*

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Eder et al. Transfusion 2013; ePub Ahead of Print

Bacterial Residual Risk at Outdate, after BacT/ALERT Screening

	# Tested	Confirmed Positives	Rate per million	Sensitivity of Day 1 Test	Reference
PASSPORT	6,039	4	662 (1:1,509)	25.9%	Dumont et al 2010
Irish BS Day 8	8,282	18	2,200 (1:460)	29.2%	Murphy et al 2008
Irish BS Day 4	3,310	4	1,200 (1:828)		Murphy et al 2008
Welsh BS	6,438	6	931 (1:1,073)	40.0%	Pearce et al 2011

60 - 74% of contaminated collections are missed by day 0/1 culture
Mostly slow growing Staphylococcus spp. P. acnes, but occasional pathogens

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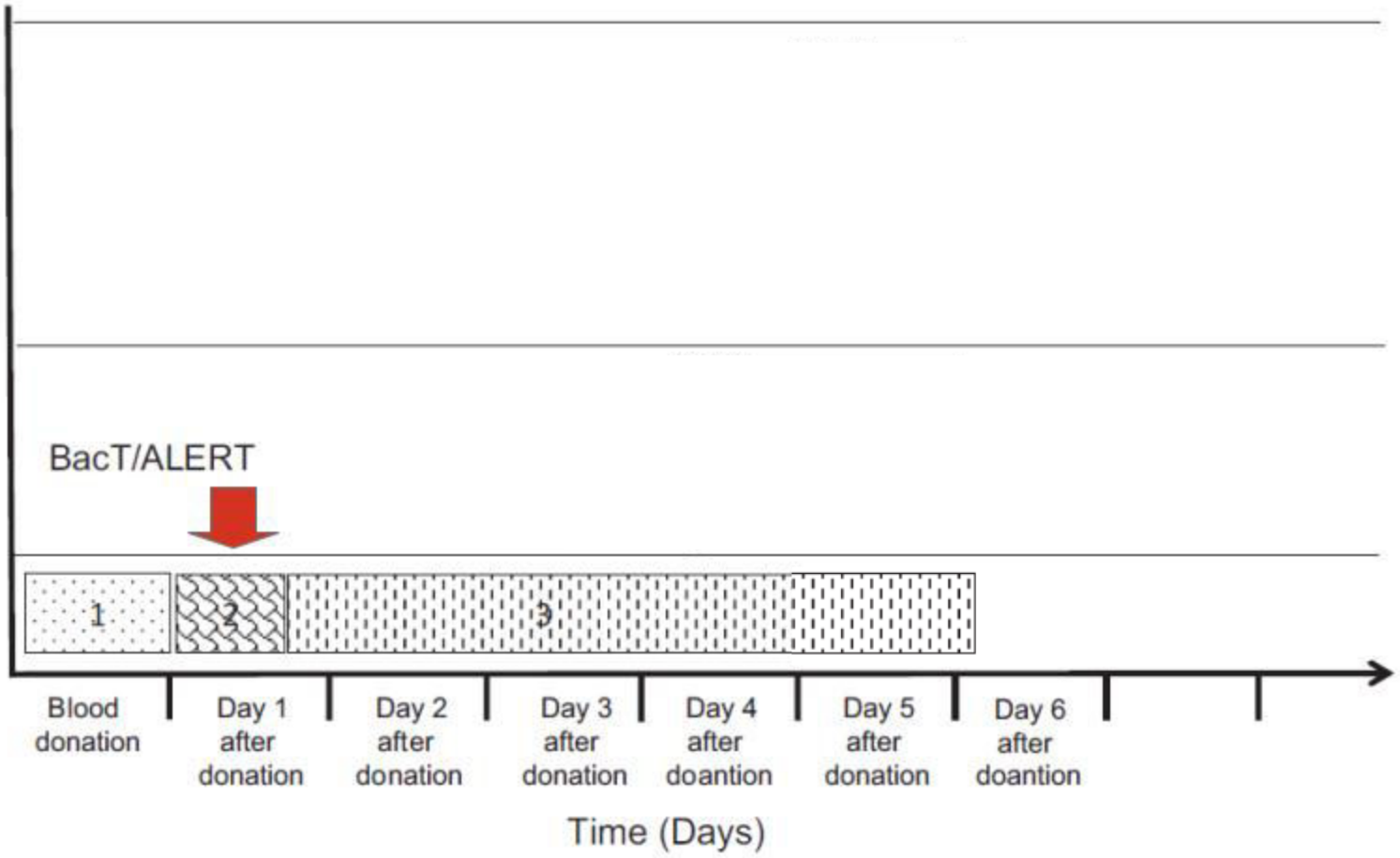
FDA Proposal at BPAC



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Day of Transfusion Testing

Verax PGD Test

Immunetics BacTx Test

BactiFlow Test

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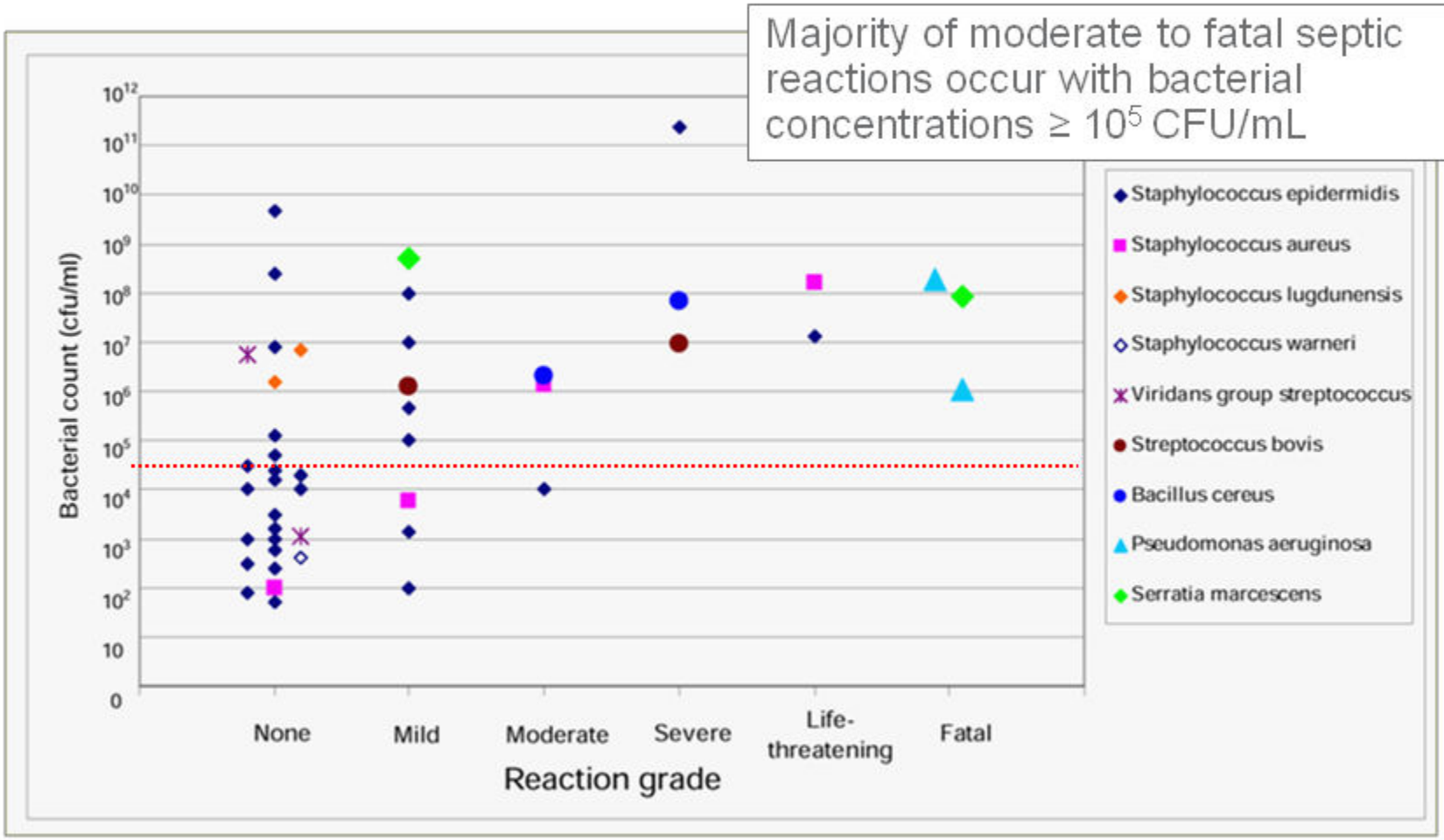
Reaction Severity vs. Bacterial Concentration



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Jacobs MR et al. Clin Inf Dis 2008

Active Surveillance at Point of Issue

- Apheresis platelets tested at blood center with either eBDS or BacT/Alert cultures
- Verax PGD test: Analytical sensitivity ~10^3-10^5 cfu/ml, tested on days 3, 4 & 5 at 18 hospitals
  - 9 confirmed positives in 27,620 components tested
  - Detected of days 3 (4); 4 (2) and 5 (2)
  - All Gram positive organisms
  - Risk of contamination: **326 per million (1:3,069)**
  - 1 in 200 false positives and 2 in10,000 false negatives

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Jacobs MR et al. Transfusion 51:2573, 2011

Pathogen Reduction by Inactivation

Platelets

- Amotosalen/UV-A light (Intercept^{tm})
- Riboflavin/UV light (Mirasol^{tm})
- UV-C light (Theraflex^{tm} UV-platelets)

Bacterial Inactivation at High Concentrations

(log_{10} reduction)	Amotosalen/UVA	Riboflavin/UV	UVC
Staphylococcus, coag neg	>6.6	≥ 4.6	4.8
S. aureus	6.6	4.8	>4.8
Streptococcus spp.	>6.8	2.6-3.7	
P. acnes	>6.7		4.5
Bacillus spp.	3.6	2.6	4.3
E. coli	>6.4	≥ 4.4	>4.0
Klebsiella spp.	>5.6	2.8	4.8
Pseudomonas spp.	4.5	>4.5	>4.9
S. marcescens	>6.7	4.0	>5.0
E. cloacae			>4.3
A. baumannii		1.8	
Y. enterocolitica		3.3	
L. monocytogenes	>6.3		

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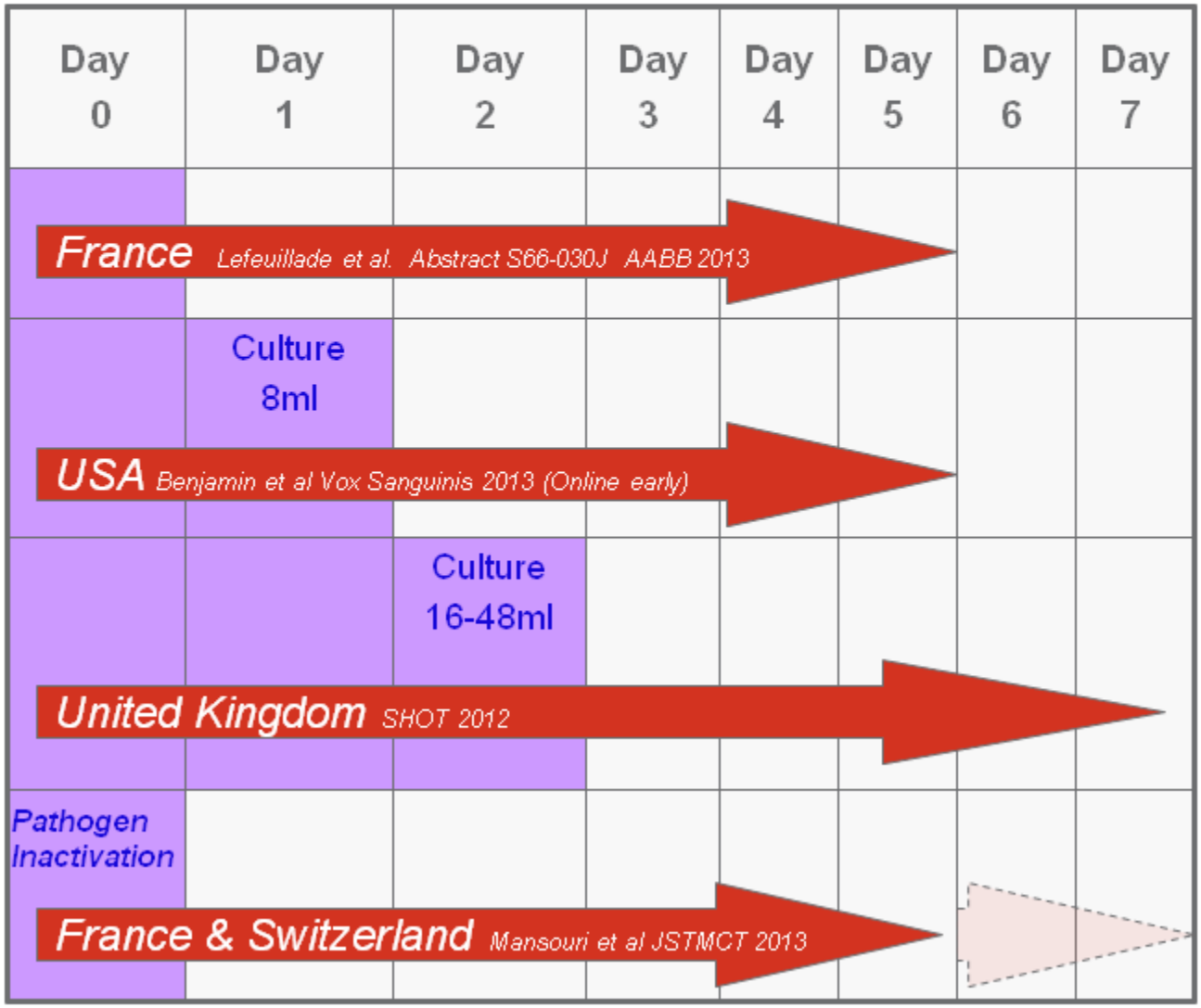
Ruane et al. Transfusion 2004:44; 877; Goodrich et al. Trans Apher Sci 2006:35;5
Lin et al. Transfusion 2004:44;1496; Mohr et al. Transfusion 2009:49;1958

Bacterial Sepsis: Hemovigilance State of the Art



Units	Sepsis Rate
3.3×10^6	**1:50,000**
4.1×10^6	**1:107,000**
~500,000	**<1:500,000**
190,636	**<1:190,636**

Conclusions

- Bacterial sepsis is a major risk of platelet transfusion that can be reduced by improved collection techniques and the introduction of culture testing
- Substantial residual risk for sepsis remains and is likely understated by passive hemovigilance
- Point of Issue testing and pathogen inactivation technologies are likely to be useful but imperfect solutions that will require extensive hemovigilance monitoring to demonstrate efficacy

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