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Bacterial Contamination of Platelets

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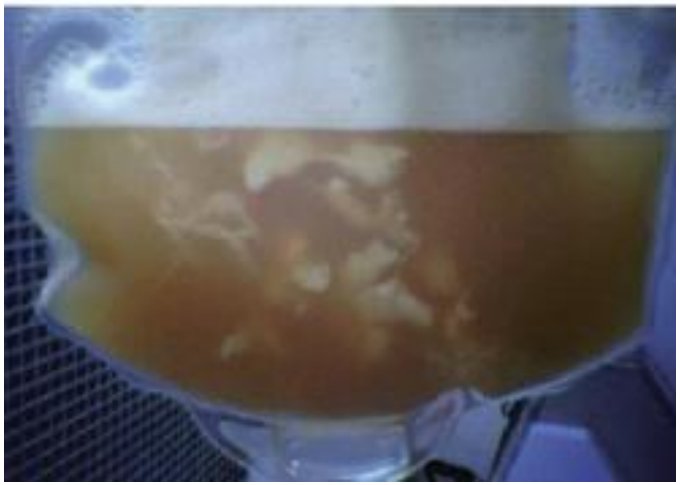
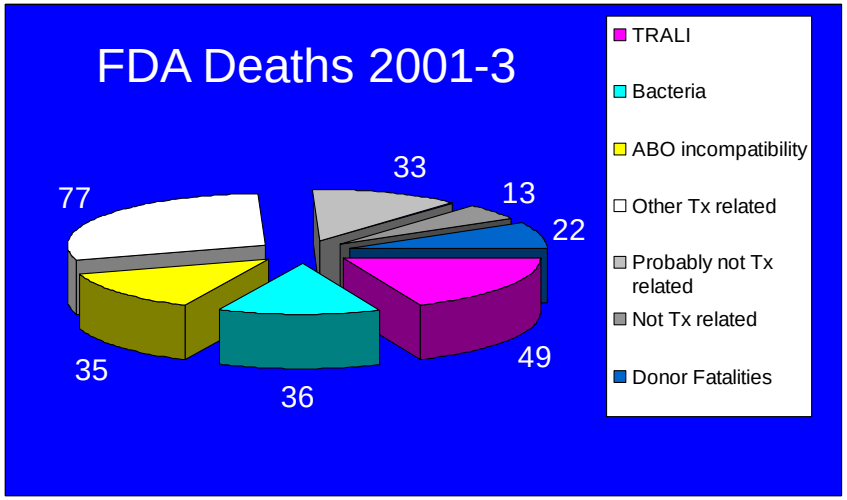
Chief Medical Officer

Objectives

- To describe the results of routine bacterial culture testing of platelets
- To estimate the residual risk of platelet bacterial contamination
- To outline approaches to minimizing risk to patients and the technologies available to further protect patients

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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BacT/ALERT^{tm} 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 > 3.4 M collections
Distributed > 6 M cultured products

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Red Cross Bacterial Testing on Apheresis Platelets

Data period: 3/1/2004 – 12/31/2011

Total collections: 3,426,573

Positive cultures:	Cases (%)	per 10^6 collections
Confirmed positive	677 (29)	198 (1: 5,061)
False pos (instrument)	924 (40)	270 (1: 3,708)
Unconfirmed pos (contamination)	495 (21)	144 (1: 6,922)
Indeterminate	236 (10)	69 (1: 14,519)
Total Positive	**2,332 (100)**	**681 (1: 1,469)**

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Bacterial Contaminant	Confirmed positives		%
Likely Skin Organisms			%
Staphylococcus, coagulase negative	271		40.2%
S. epidermidis		35	
S. lugdenensis		4	
Staphylococcus aureus	53		7.9%
Staphylocccus, other	15		2.2%
Streptococcus spp.	102		15.1%
Viridans Streptococcus sp., NOS		44	
α hemolytic Streptococcus		18	
S. mitis/oralis		13	
S. salivarius		5	
S. sanguis		3	
Bacillus spp.	15		2.2%
Other*	11		1.6%
Total	467		69.3%
Non-skin Organisms			
Streptococcus spp.	71		10.5%
β hemolytic Streptococcus		25	
S. bovis		25	
S. pneumoniae		7	
Streptococcus pyogenes gp A		2	
Escherichia coli	48		7.1%
Klebsiella spp.	29		4.3%
Serratia marcescens	23		3.4%
Listeria spp.	10		1.5%
Enterobacter spp.	9		1.3%
Enterococcus spp.	9		1.3%
Citrobacter spp.	3		0.4%
Pseudomonas spp.	2		0.3%
Salmonella spp.	2		0.3%
Other$	4		0.6%
Total	210		31.2%

* includes *Acinetobacter* spp. *(2), Corynaebacterium* spp. (4), *Lactobacillus* spp *(1).*, *Lactococcus* spp. (1), *Micrococcus* spp. *(1), & Proteobacteria* spp. *(2)*.
$ includes *Proteus* spp. (1), *Moraxella* spp. (1), *Morganella* spp. (1), *Raoutella* spp. (1).

Bacterial Species Detected By BacT/ALERT^{tm} Culture

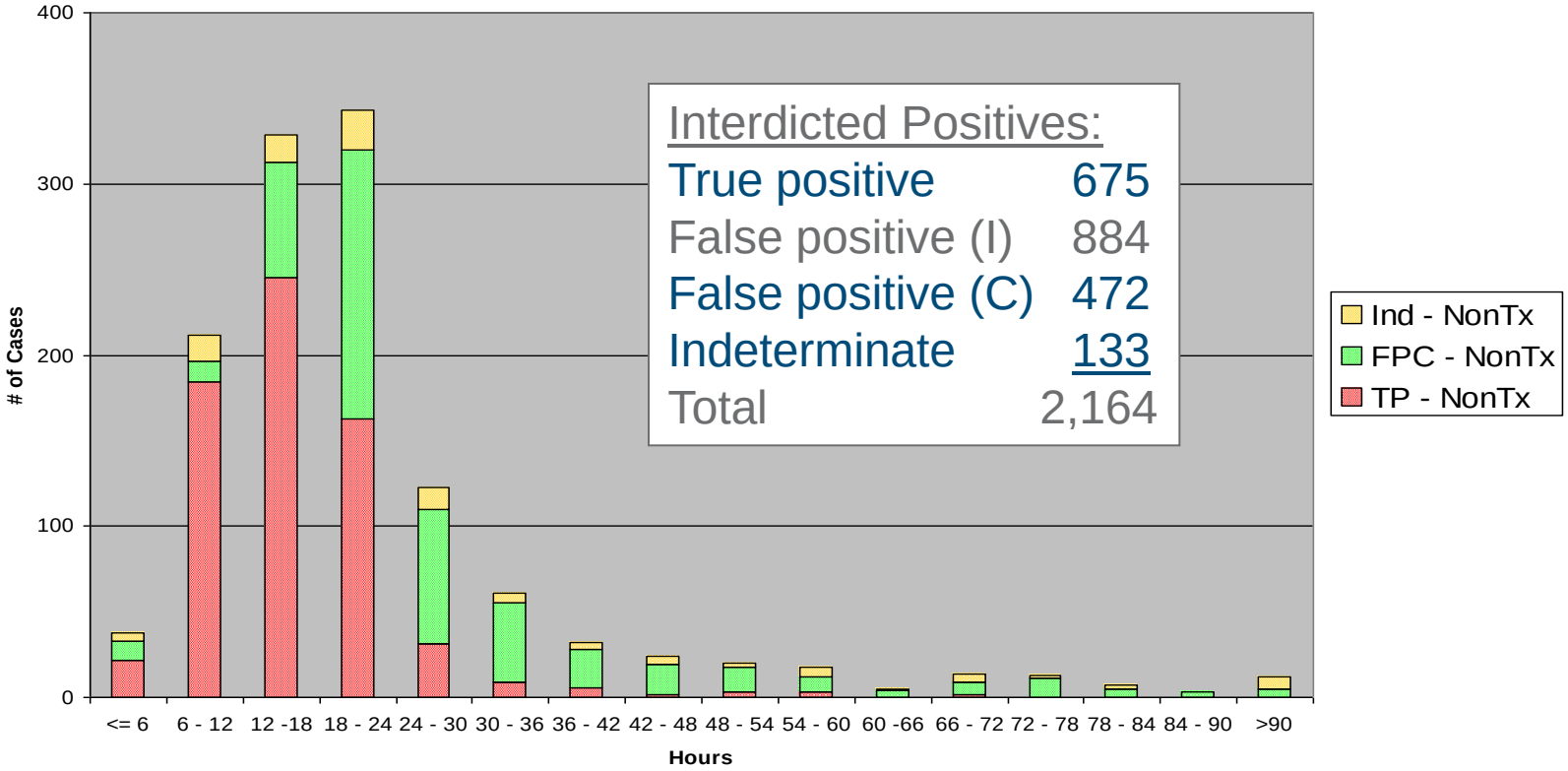
Culture Results:
3/1/2004 – 12/31/2011
677 confirmed positives

Skin organisms 69.3%

Staph. spp. 51.3%
Strep. spp. 25.6%
Gram neg. 18.0%

BacT/ALERT does not Prevent Transfusion of All Culture Positive Components Tested

3/1/2004 – 12/31/2011
2,332 initial culture positive collections



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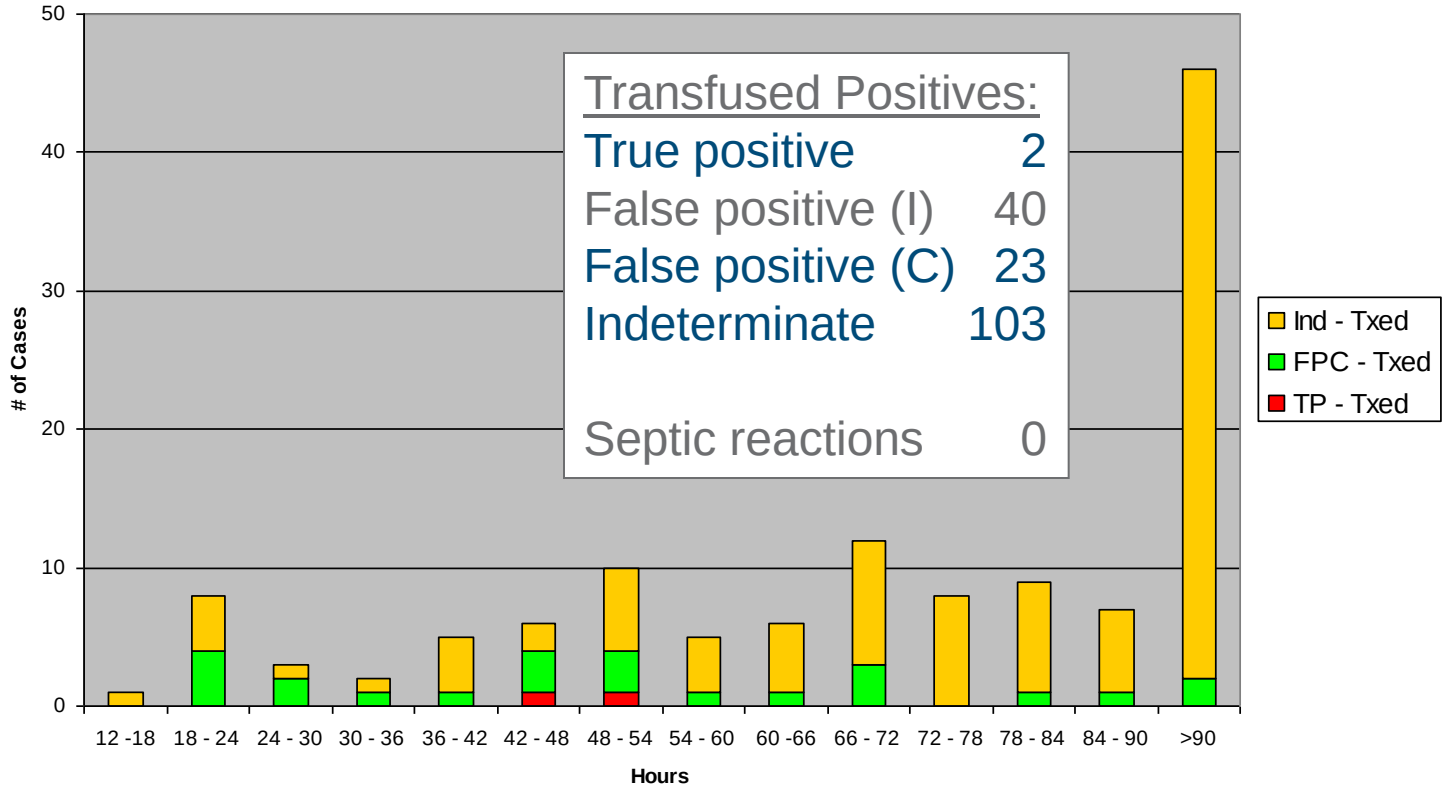
1280 potentially harmful products interdicted

BacT/ALERT does not Prevent Transfusion of All Culture Positive Components Tested

3/1/2004 – 12/31/2011
2,332 initial culture positive collections



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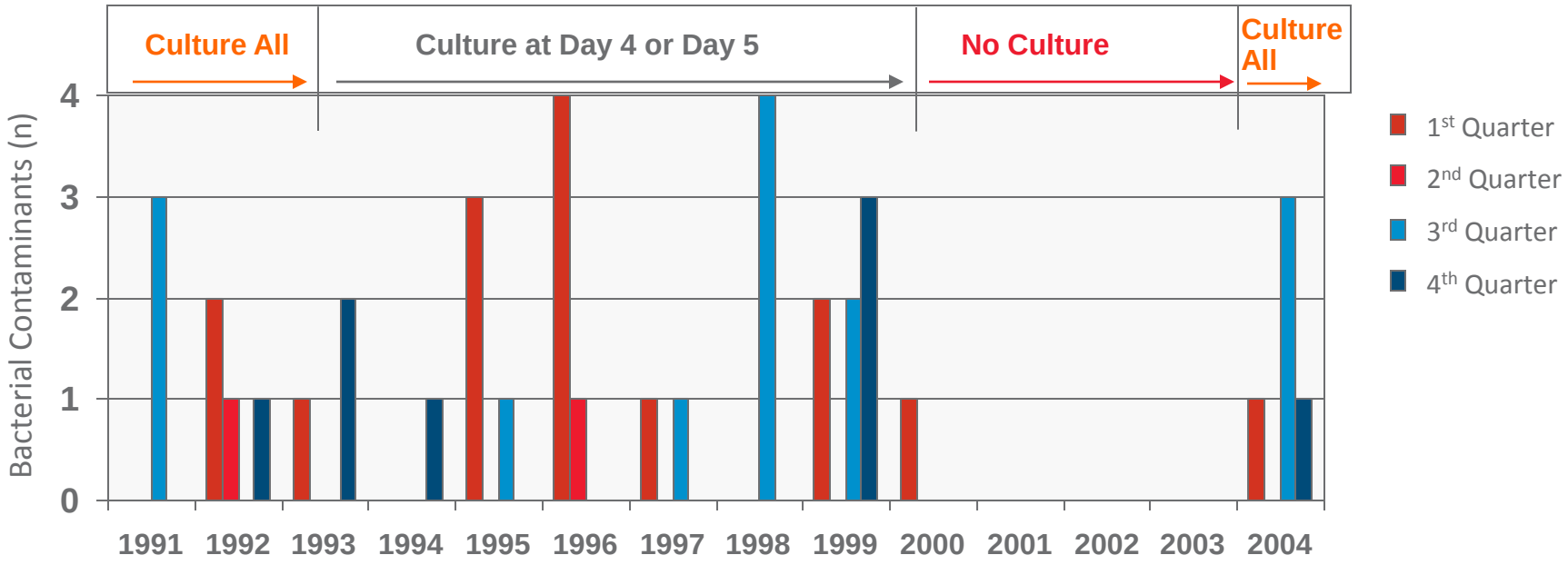
128 of 1408 (9.1%) of potentially harmful units not interdicted

Active and Passive Surveillance for Bacterial Contamination

216,283 Units (48,067 SDP and 168,216 RDP)



Yomtovian RA et al, Transfusion 2006

- Active surveillance detected 38 contaminated units
- During active surveillance 16 septic reactions were detected, while only 2 reactions were detected during passive surveillance

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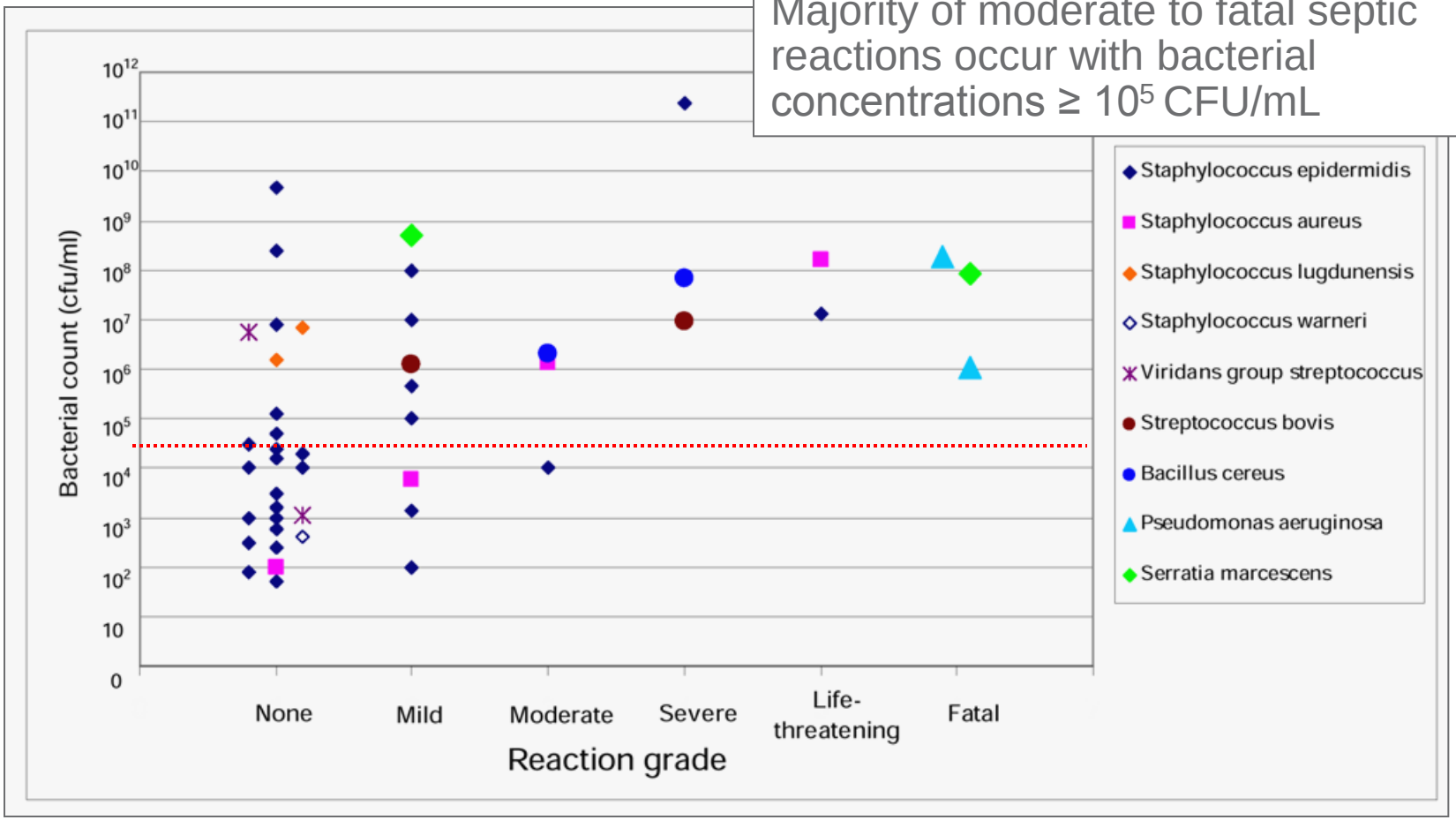
Jacobs M, Yomtovian R. CID 2008:46,1217

Reaction Severity vs. Bacterial Concentration

Majority of moderate to fatal septic reactions occur with bacterial concentrations ≥ 10^5 CFU/mL



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Jacobs MR et al. CIin Inf Dis 2008

International Experience with BacT/ALERT Culturing

Reference	Year published	apheresis	Buffy coat WB platelets	PRP WB platelets	Country	Diversion	Skin Prep	Delay before sampling	aerobic cultures	anaerobic cultures	volume (ml) per bottle	Number tested	Confirmed positive rate (10^6)
Jenkins et al	2011	X			Canada	100%	IPA/TI/Chl	24-48	X		4-10	210,554	128
Souza et al	2012	X			USA	100%	Chloro (1)	24-36	X		8	180,263	139
Su (5d)	2008	X			USA	91%	Chloro (1)	24-36	X		4-5	191,521	157
Eder et al	2009	X			USA	100%	PI (2)	24-36	X		8-10	781,936	166
McDonald et al	2012	X			England	100%	Chloro (1)	36-48	X	X	8 (x 1-3)	144,964	179
Eder	2007	X			USA	39%	PI (2)	24-36	X		4-5	1,004,206	185
Dumont et al	2009	X			USA	99%	?	24-36	X	X	4-5	388,903	231
Pearce et al	2010	X			Wales	100%	Chloro (1)	>16	X	X	8-10	17,235	348
Schrezenmeier et al	2007	X			Germany	100%	IPA (2)	18	X	X	7.5-10	15,198	855
Murphy et al	2008	X			Ireland	100%	?	> 12	X	X	7.5-10 (1-3x)	12,823	312
Larsen	2005	X	X		Norway	?	?	3-24	X		5-10	36,896	325
Murphy et al	2008		X		Ireland	100%	?	>36	X	X	7.5-10	30,407	329
Jenkins et al	2011		X		Canada	100%	IPA/TI/Chl	24-48	X		8-10	228,142	127
Pearce et al	2010		X		Wales	100%	Chloro (1)	24	X	X	8-10	37,594	771
Schrezenmeier et al	2007		X		Germany	100%	IPA (2)	18	X	X	7.5-10	37,045	648
McDonald et al	2012		X		England	100%	Chloro (1)	36-48	X	X	8	26,007	731
Munksgaard	2004	X (1,296)	X		Denmark	0%	Chloro (2)	3-30	X		10	22,057	771
Jenkins et al	2011			X	Canada	100%	IPA/TI/Chl	>24	X		7.5-10	51,151	176
Benjamin et al	2008			X	USA	100%	PI (2)	24-36	X		8-10	20,725	965

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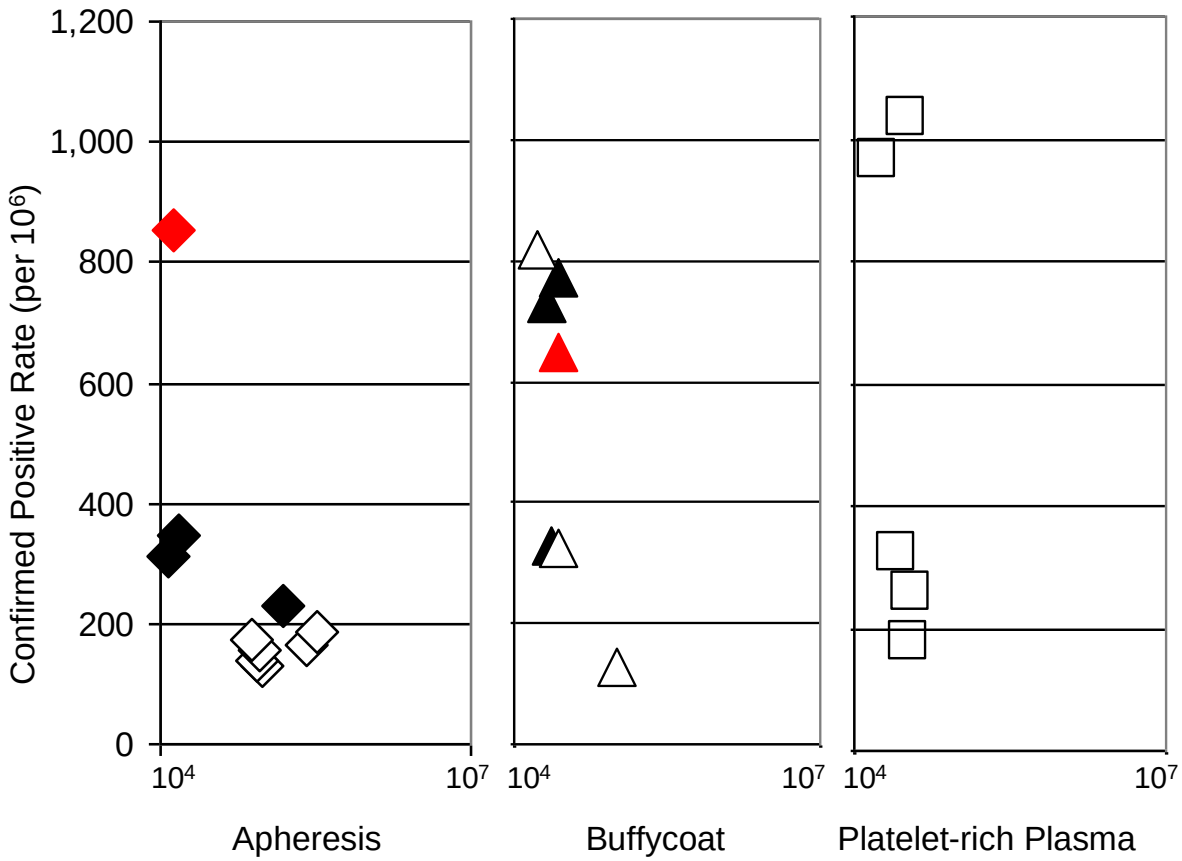
International Experience with BacT/ALERT Culture (Confirmed Positive)



Open symbol: Aerobic bottle only
Solid symbol: An/Aerobic bottles

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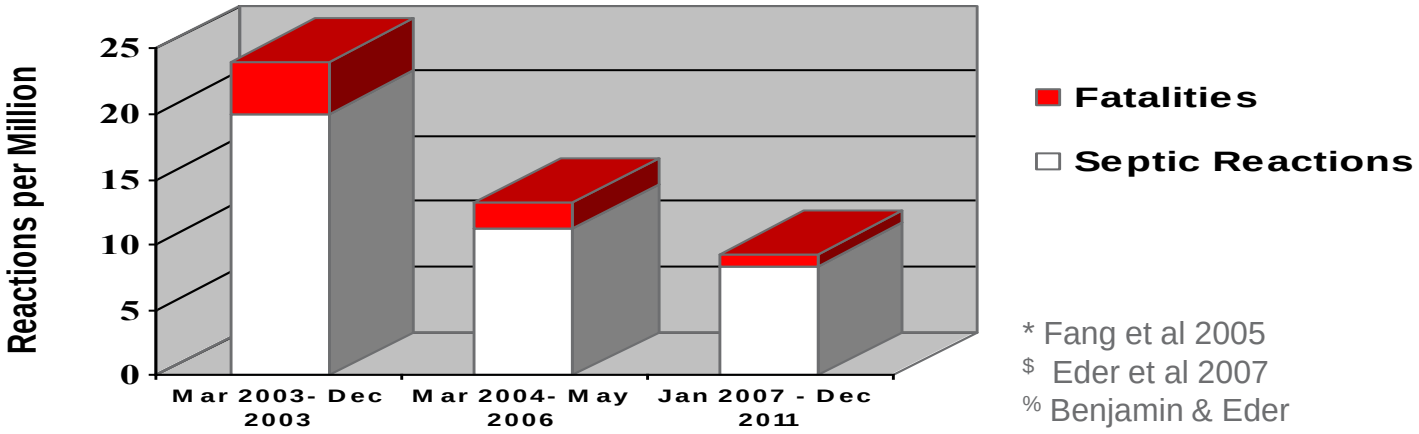
Declining Risk of Sepsis in the Red Cross

	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



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

Considerations Regarding the Estimation of Sepsis Rates by Hemovigilance

- Rates are determined by distributed, not transfused components
- Rates do not include reactions that don't meet the definition of definite or probable sepsis
  - 38 of 381 suspected sepsis cases in our hemovigilance program met the definition of definite or probable sepsis
  - 8 of 46 (17.4%) bacterially contaminated transfusions described by Jacobs et al met our definition of sepsis
- Rates are determined by passive hemovigilance and likely underestimate risk due to underreporting
  - Jacobs et al suggest a 10.6 fold underreporting of clinical reactions by passive hemovigilance.

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Jacobs M, Yomtovian R CID 2008:46,1217

Bacterial Species Involved in Sepsis (2007-2011)

	Septic reactions	(%)	Confirmed positive	(%)
Coagulase-negative Staphylococcus	22	58%	139	33.7%
Streptococcus spp.	4	11%	126	30.5%
Staphylococcus aureus	8	21%	39	9.4%
Bacillus spp.		0%	6	1.5%
Corynebacterium spp.		0%	3	0.7%
Micrococcus spp.		0%		0.0%
Enterococcus spp.		0%	4	1.0%
Clostridium perfringens	1	3%	0	0.0%
E. coli		0%	32	7.7%
Klebsiella spp	1	3%	20	4.8%
Listeria spp		0%	5	1.2%
Proteus mirabilis		0%	1	0.2%
Serratia spp.		0%	15	3.6%
Pseudomonas spp.		0%	2	0.5%
Citrobacter spp.		0%	2	0.5%
Haemophilus spp.		0%		0.0%
Salmonella spp.		0%	2	0.5%
Enterobacter spp.	1	3%	8	1.9%
Other	1	3%	9	2.2%
Total	38		413	

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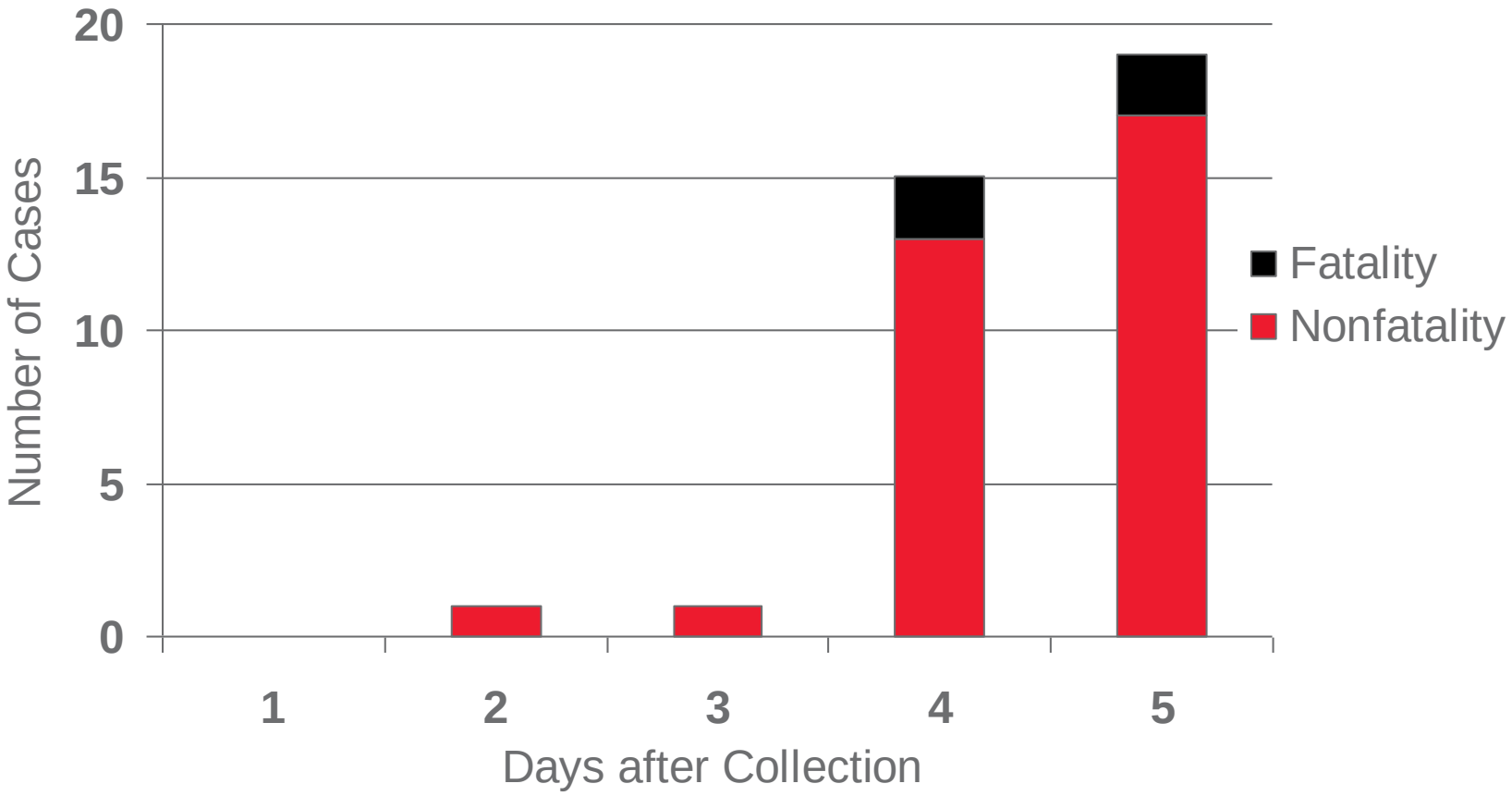
4 fatalities involving *S. aureus* (3) and Coag. Neg. Staph. (1)

Septic Reactions – Day of Storage

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



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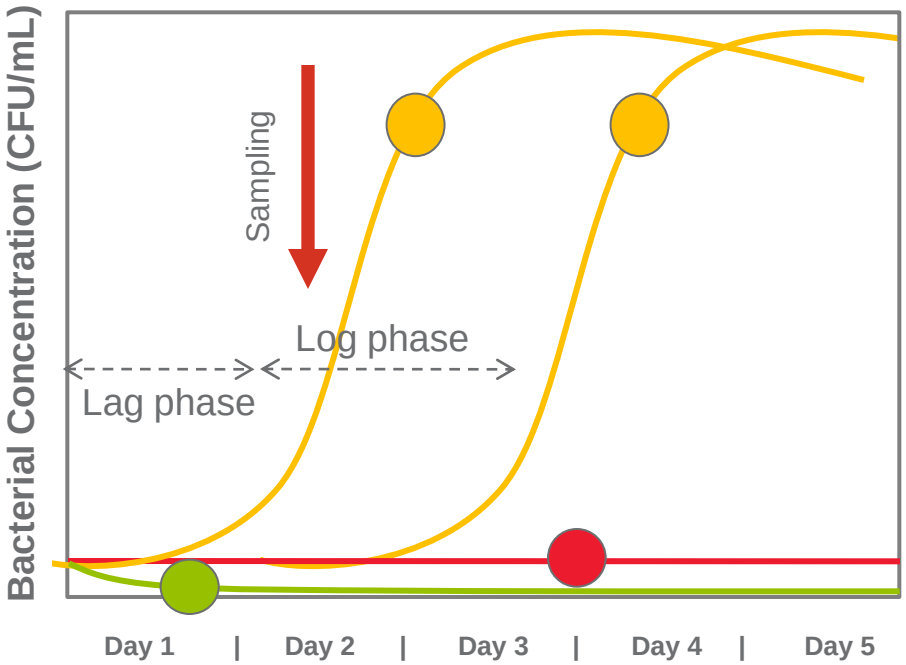
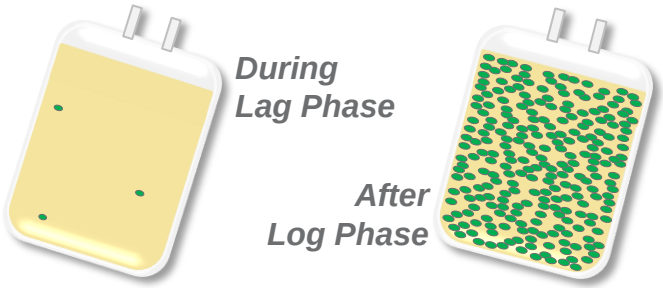
Why Do Early Cultures Fail?



- Platelet unit self sterilizes making bacteria non-viable
- Bacteria persist at low concentrations throughout the platelet shelf life
- Bacteria moves from period of *lag phase* to *log phase* of growth

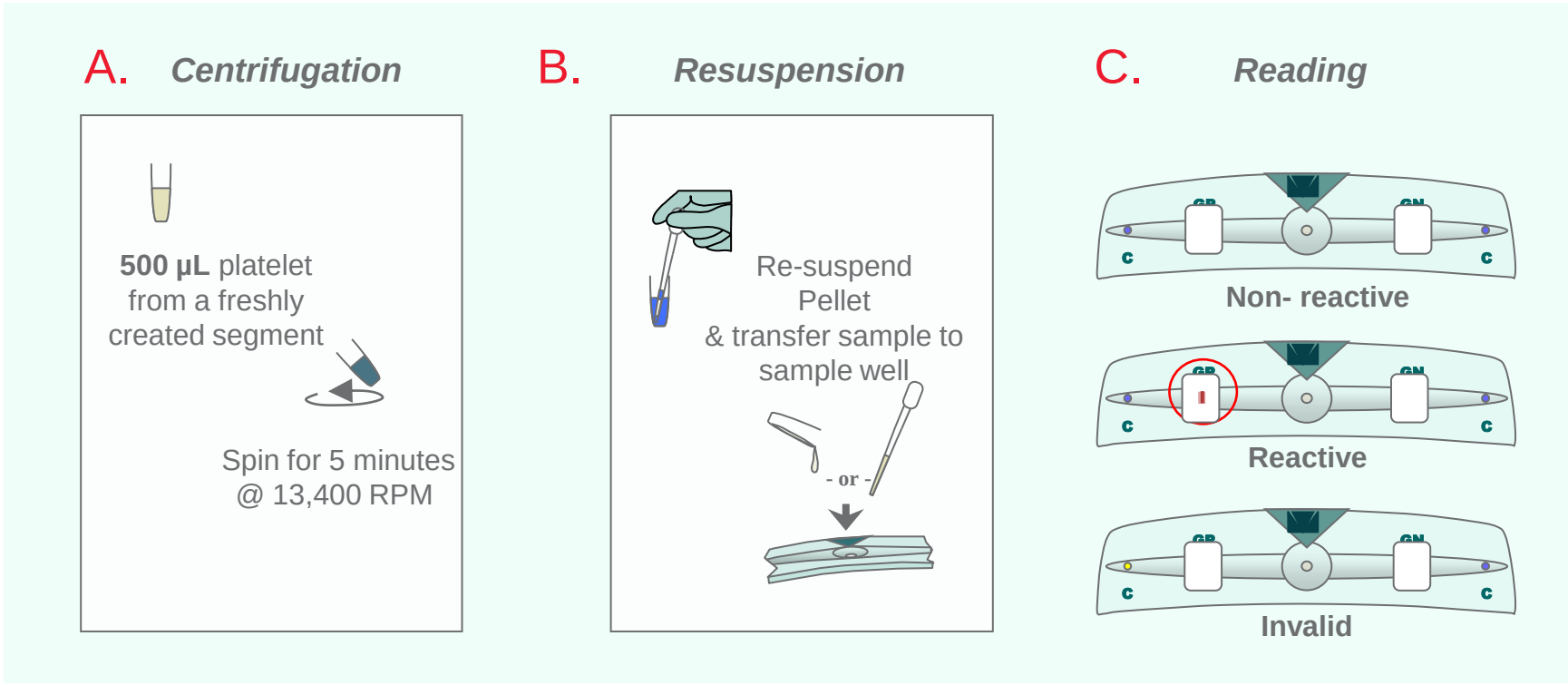
- BacT/ALERT is validated to detect bacteria at 1-10 CFU/ml
- Initial inoculum ~0.01 CFU/mL
- 24-36 hr delay in sampling to allow bacterial proliferation



What Risk Data Should We Use for Bacteria?

- Passive hemovigilance data of sepsis
- Active surveillance data on contamination
  - Jacobs MR et al, Transfusion 2011 Dec;51(12):2573-82
  - PASSPORT, Irish and Welsh Blood Service studies
- Best calculated assessment of patient risk exposure

The Verax Platelet PGD Test Procedure



Performed on the day of transfusion by Transfusion Service/Hospital Blood Bank

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Sensitivity >$10^{4\text{-}5}$ CFU/ml

Verax PGD: Surveillance at Point of Issue

- Jacobs MR et al Transfusion 51:2573-82, 2011
- Apheresis platelets tested at blood center with either eBDS or BacT/Alert cultures
  - 18 hospital sites
  - 9 confirmed positives in 27,620 components tested
  - Detected on days 3 (4); 4 (2) and 5 (2)
  - 6 CNStaph, 2 Bacillus sp.; 1 Enterococcus; 1 P. acnes
  - Risk of contamination: **326 per million (1:3,069)**

Despite culture testing, a substantial number of platelets contain high levels of pathogenic bacteria as early as day 3 after collection

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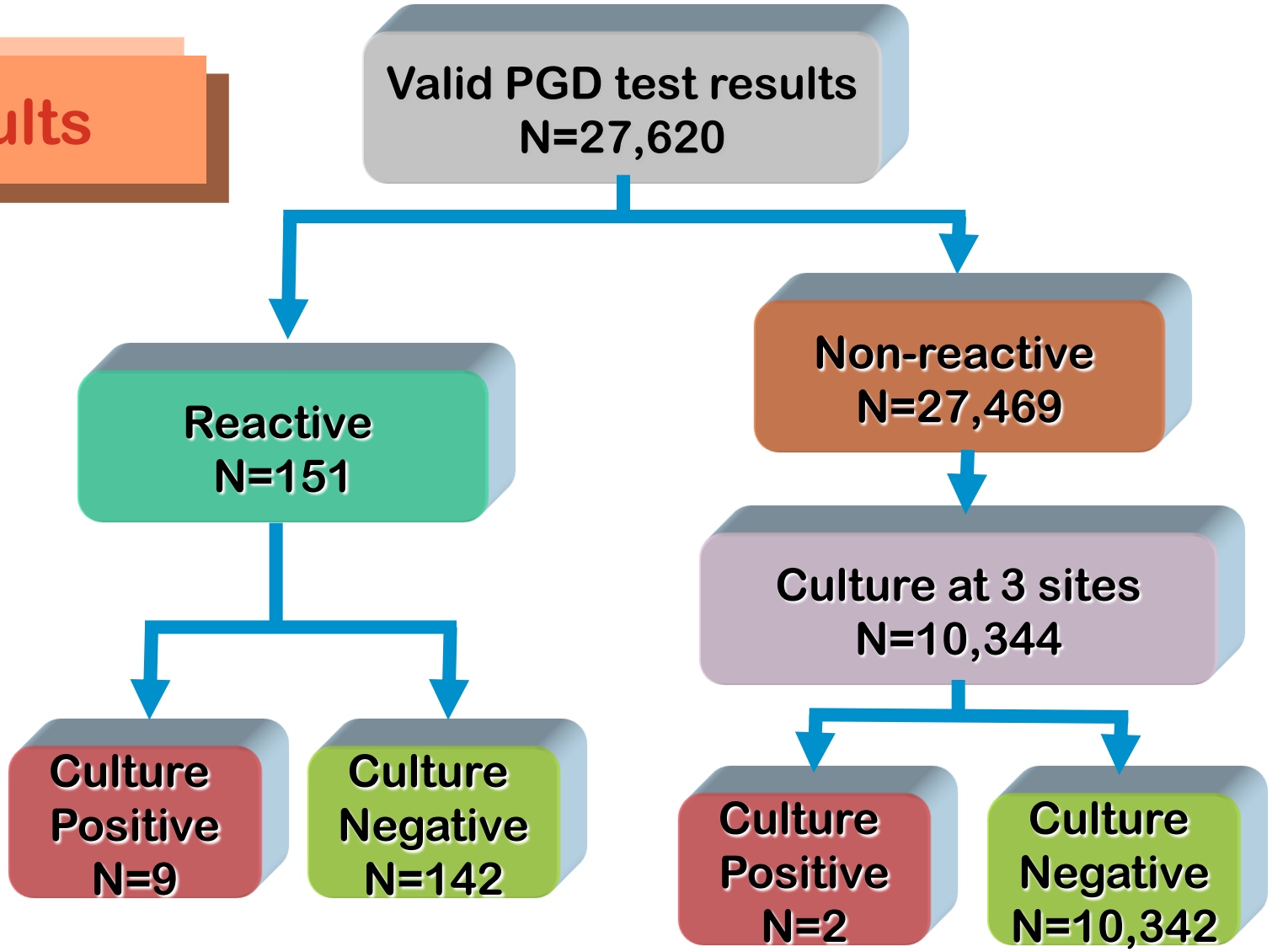
Analytical sensitivity ~10^3-10^5 cfu/ml, tested on days 3, 4 & 5

Results



True Positive	False Positive	False Negative
0.032%	0.51%	0.019%

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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
Combined	24,069	32	1,329 (1:752)		

60 - 74% of contaminated collections are missed by day 0/1 culture

BacT/ALERT has an analytical sensitivity ~10^{-1} cfu/ml for aerobes and anaerobes

Residual Patient Risk of a Contaminated Product, accounting for Multiple Transfusions

	Patients in P.I. Study Arm	Mean # of P.I. Platelets Transfused	Patient Risk*	Upper 95% C.I.	Lower 95% C.I.	References
		1.0	1,329 (1:752)	869 (1:1,151)	1,790 (1:559)	
Miracle Study	56	5.4	7,177 (1:139)	4,693 (1:213)	9,666 (1:103)	Goodrich et al 2010
Hovon Study	85	4.6	6,113 (1:164)	3,997 (1:250)	8,234 (1:121)	Kerkhoffs et al 2010
Sprint Study	391	8.4	11,164 (1:90)	7,300 (1:137)	15,036 (1:67)	McCullough et al 2004
Combined	532	6.3	8,373 (1:119)	5,475 (1:183)	11,277 (1:89)	

•Patient risk of receiving a contaminated unit per million patients

Best Current Estimate of per Patient Risk

Combined	532	6.3	8,373 (1:119)	5,475 (1:183)	11,277 (1:89)	

There is an approximate 0.8% (0.5-1.1%) risk
that a Hematology/Oncology patient
will be exposed to a
bacterially-contaminated platelet product
despite BacT/ALERT culture screening
during a course of treatment that
might involve pathogen-reduced platelets

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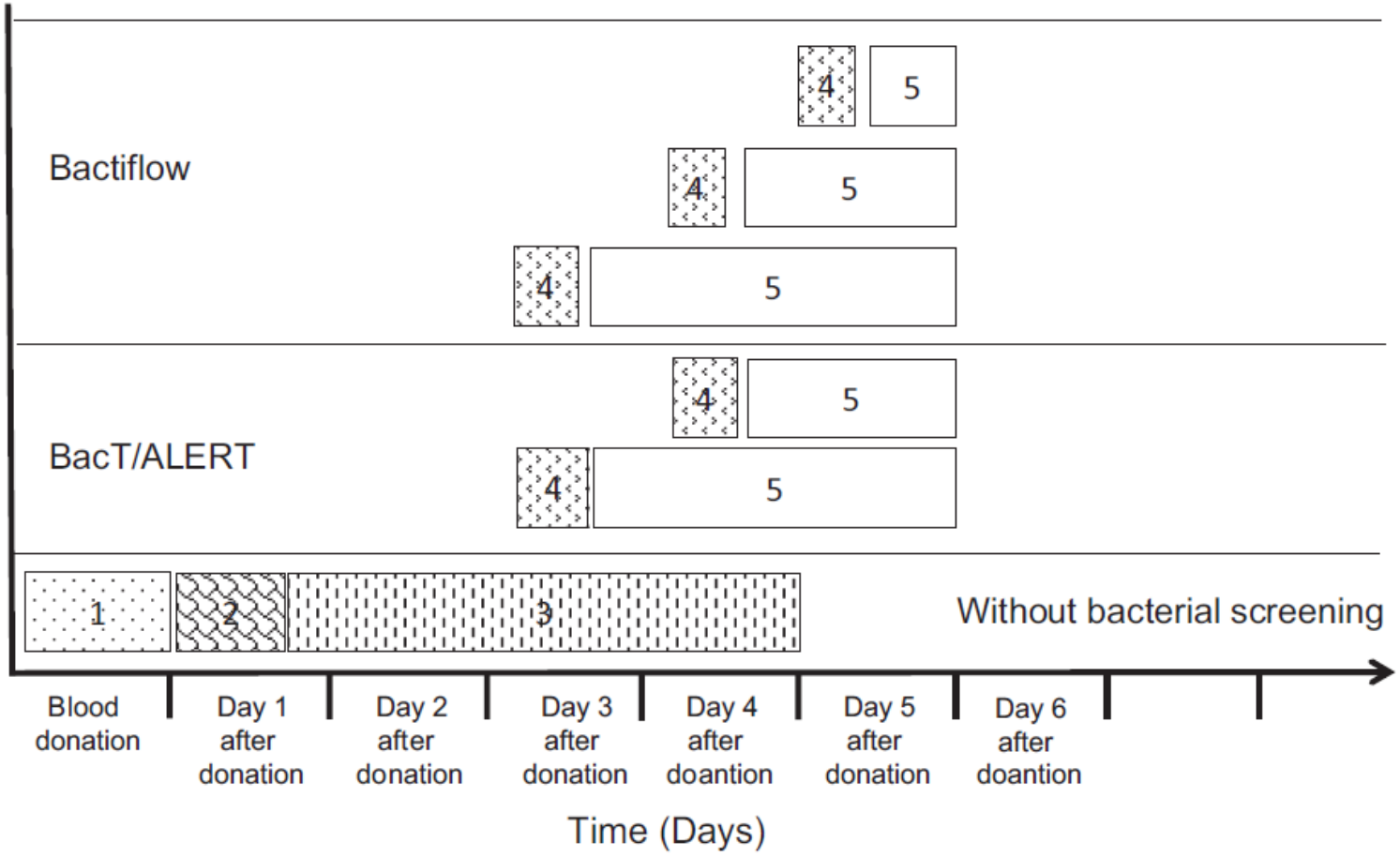
R.J. Benjamin, AABB 2010

Paul Erlich Institute Approach to Sepsis



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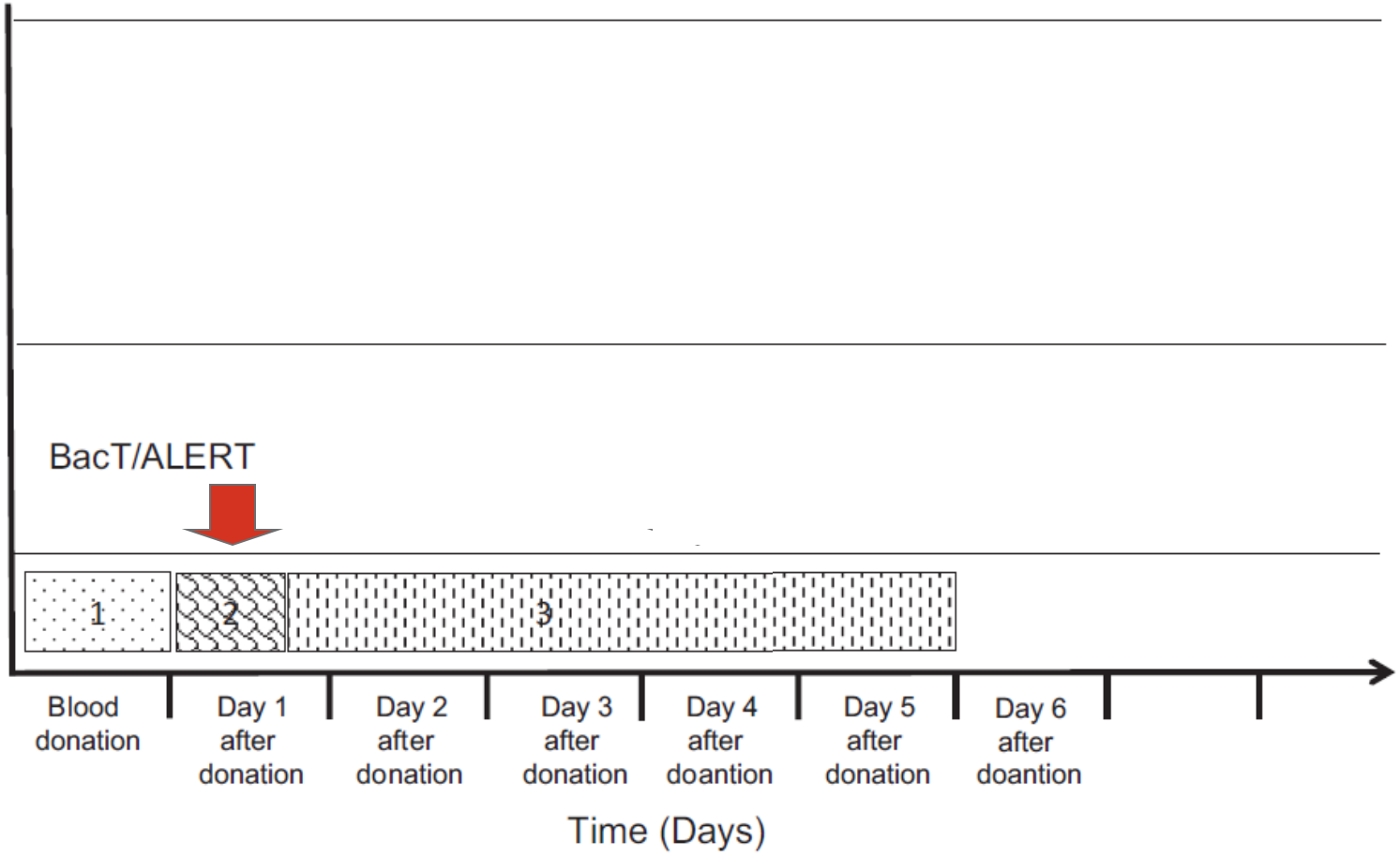
Sireis et al. Vox Sanguinis 101:191-99,2011

FDA Proposal at BPAC



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104th FDA BPAC Meeting: Bacterial Safety

- **Q1:** Are additional measures necessary to decrease the current risk of transfusion of bacterially-contaminated platelet products?
  - Vote: **YES** 17 ✓, 0 X
- **Q2:** Would reduction in platelet product shelf-life from 5 to 4 days and early culture decrease the risk of transfusion-associated septic reactions sufficiently to obviate the need for additional testing.
  - Vote: **NO** 0 ✓, 17 X
- **Q3:** For platelets limited to 5 days of storage do the available data support a strategy to culture platelets after the first 24 hours of storage and then retest day 4 and day 5 platelets just once with a rapid test on day of transfusion?
  - Vote: **YES** 16 ✓, 1 X, 1 abstain
- **Q4:** Should the same strategy apply to retesting of day 3 platelets?
  - Vote: **MAYBE** 5 ✓, 5 X, 7 abstain

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104th BPAC Meeting, September 20, 2012, Rockville, MD , Issue Summary, "Considerations for Options to Further Reduce the Risk of Bacterial Contamination in Platelets "

AABB Recommendations for Bacterial Safety of Platelets (Bulletin #12-04)

- Develop policies to further reduce the residual risk of bacterial contamination of apheresis platelets

  → **The current screening methodology is not effective**

- Improve the recognition and monitoring of septic transfusion reactions (STRs) of all platelet components

  → **STRs currently go unrecognized**

- Optimize appropriate transfusion practice for all platelet components

  → **Conduct a risk-benefit analysis and eliminate risk**

- *"…additional steps to detect bacteria in apheresis platelets* ***should not be needed in facilities located in countries that treat platelets with a regulatory-approved pathogen inactivation (PI) system[1]*** ***The PI bacterial sepsis mitigation option is the most definitive approach*** *– but remains unavailable in the United States at this time. Ongoing experience from those countries adopting pathogen inactivation may eventually influence decisions by US policy makers regarding PI."*

Options to Improve Platelet Safety

- Minimize contamination
  - Collection with diversion pouch ☑
  - Optimal skin preparation ☑
- Maximize culture sensitivity
  - Consider BacT/ALERT vs. eBDS culture
  - Delay sampling as long as possible
  - Increase volume cultured
  - Perform both aerobic & anaerobic culture
- Transfuse earlier rather than later
- Point of issue testing
- Pathogen inactivation

Summary

- The introduction of bacterial culture testing has identified areas for process improvement and dramatically improved platelet safety.
- Substantial residual risk for sepsis remains and is likely understated by current passive hemovigilance efforts.
- Risk is predominantly from Gram positive organisms following false negative cultures, although other modes of failure have been demonstrated.
- Available technologies, if fully implemented, would further improve platelet safety.