ISBT – Working Party on Infectious Disease

POR Testing for Platelet Bacterial Contamination:

An ongoing risk under continuous improvement

8th July 2012.

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NSLIJ Health System & Hofstra NSLIJ School of Medicine

The views are those of the presenter and not of the NSLIJ Health System or Hofstra

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[1]Andrew Heaton has received research support and/or honoraria from Verax, Hemonetics, Fenwal, & Immunetics, and has consulted for Beckman-Coulter, Verax, & Novartis Diagnostics

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Objectives:

1. Describe platelet bacterial risks and recent intervention effects.
2. Discuss residual risk due to false negative bacterial cultures.
3. Relate residual bacterial contamination to clinically effects.
4. Review the Point of Release testing:
   - Outcome & Feasibility
5. Effect on Transfusion Related Death & US Regulatory process.
6. Summarize the policy related questions.

Current Situation:

- Reported US platelet bacterial contamination fatality rate is ~1.5 deaths per million PC doses transfused (~ 3 deaths/year)
- The Bacterial Testing Issue:
  - Culture as a release test has a ~ 26% sensitivity
  - 231 out of 893/million contaminated units detected
  - Only ~10% transfusion sepsis is reported

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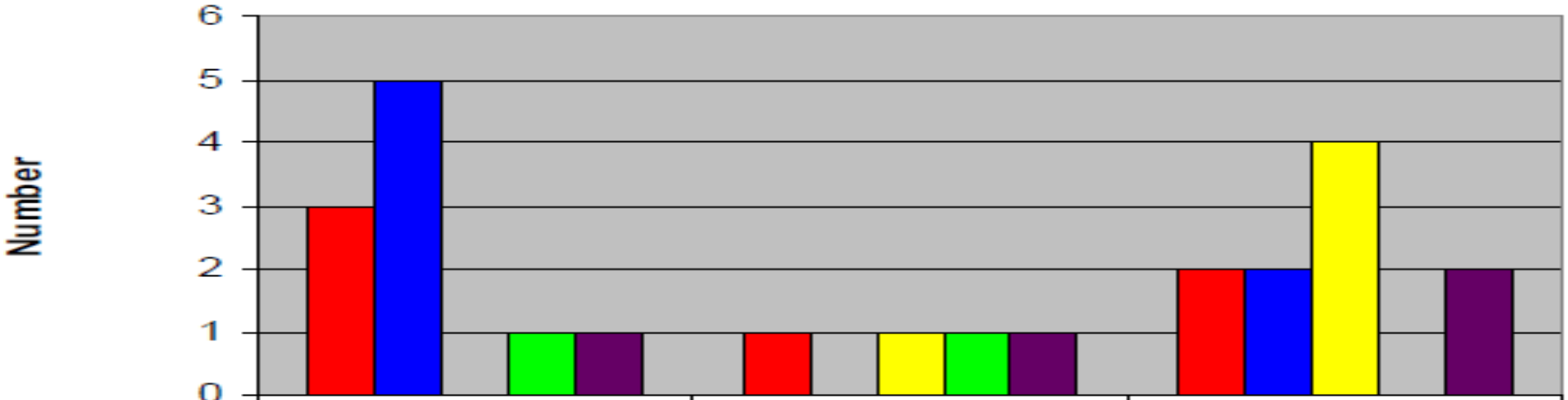
US Post Platelet Transfusion Sepsis & Morbidity



	RBC	Pooled Platelets	Platelets Pheresis
FY07	3	1	2
FY08	5	0	2
FY09	0	1	4
FY10	1	1	0
FY11	1	1	2

Oct 95 – Sep 04, 60 FDA contaminated PC reports of Post-Tx fatality

- 38 of the 60 (63.3%) cases were gram-negative organisms
- ~ 2/3 of post-transfusion sepsis organisms were gram-positive

Effect of Skin Preparation, Inlet-line Diversion & Culture Upgrade

- ARC septic reactions decreased from 1:40,000 to 1:86,000, ~ 50% reduction
- JHU decrease from 7.45/100K to 2/100K transfusions, 70% reduction

FDA reported death decreased 60% (7/yr in 2001-3) to 2.8/yr 2006-10

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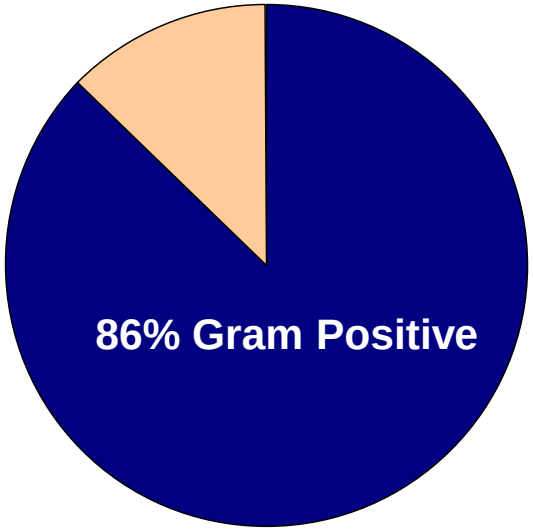
Bacterial Testing on Apheresis Platelets

Confirmed positive cases (3/1/2004 – 1/31/2007):

Gram positive (n=196):

Staphylococcus, coagulase negative	87
Staphylococcus epidermidis	22
Staphylococcus aureus	13
Staphylococcus (others)	13
Streptococcus sp.	43
Bacillus sp.	8
Enterococcus sp.	3
Listeria monocytogenes	4
Lactobacillus/Micrococcus/Unspecified	1 each



Gram negative (n=29):

Escherichia coli	12
Serratia marcescens	6
Klebsiella sp.	8
Citrobacter/Enterobacter/Unspecified	1 each

Eder AF et al, Transfusion 2007

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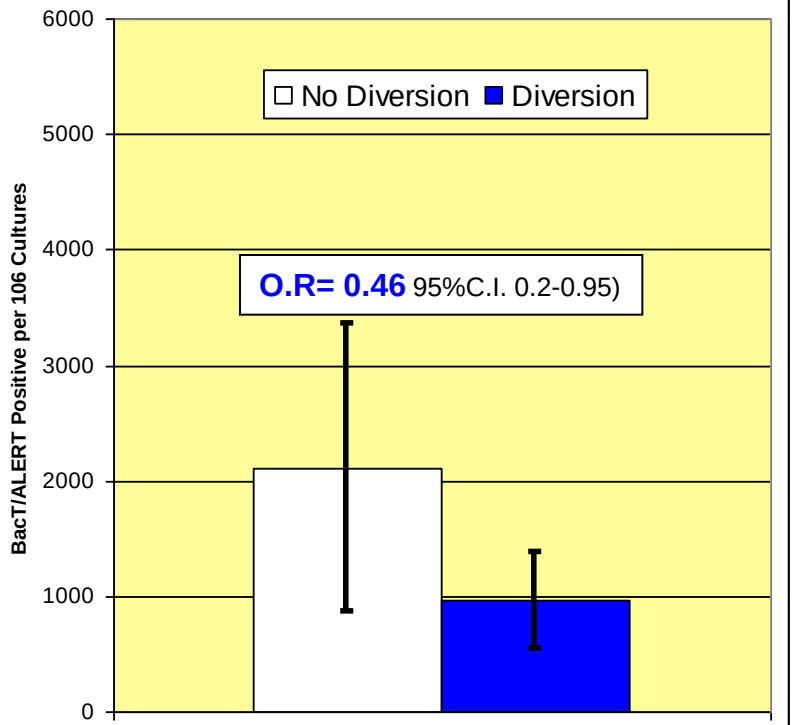
Bacterial Safety Interventions and Effects

Inline Diversion – Prestorage PC

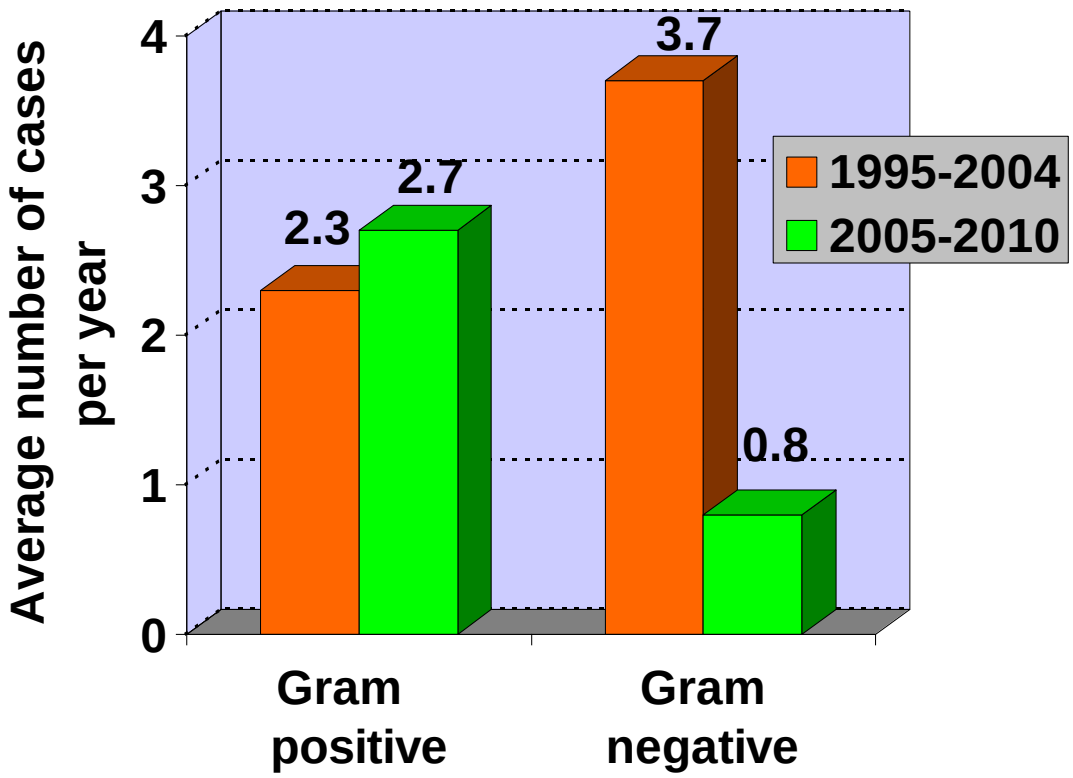


Benjamin, RJ, et al. Transfusion 2008, 48:2348-55

Arm Prep – Chloraprep Vs Povidone I_2

- **O.R= 0.47** (95%C.I. 0.21-1.03)

Platelets, USA 1995 to 2010



2005-2010:

Pooled Platelets microorganisms: *S. aureus (1), E. coli (2), S. dysgalactiae (1), S. pneumoniae (1)*
Platelets Pheresis microorganisms: *S. aureus (6), S. marcescens (1), S. lugdunensis (1), S. epidermidis (2), E. limosum (1), E. coli (1), M. morganii (1), K. oxytoca (1), S.viridans (1), S. warneri (1)*

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Niu MT, et al.Transfus Med Rev. 2006;20:149-157

Bacterial Residual Risk post BacT/Alert Screen

	# Tested	Confirmed +'ve	**Rate /10^6**	Ref.
PASSPORT	6,039	4	**662 (1:1,509)**	Dumont 2010
Irish BS Day 8	8,282	7	**1,183 (1:850)**	Murphy 2008
Irish BS Day 4	3,310	1	**3,310 (1:302)**	Murphy 2008
Welsh BS	6,438	6	**931 (1:1,074)**	Pearce 2011
Combined	24,369	18	**1,353 (1:740)**	

PASSPORT
post approval surveillance study of platelet outcomes, release tested

Sensitivity of culture for U.S. standard practice[2]

25.9%

Irish Blood Transfusion Service
Seirbhís Fuilaistriúcháin na hÉireann

Sensitivity of culture under best practice[1]

33%

UH University Hospitals Case Medical Center

Passive Surveillance results in 10.6 times less likely to detect a septic reaction

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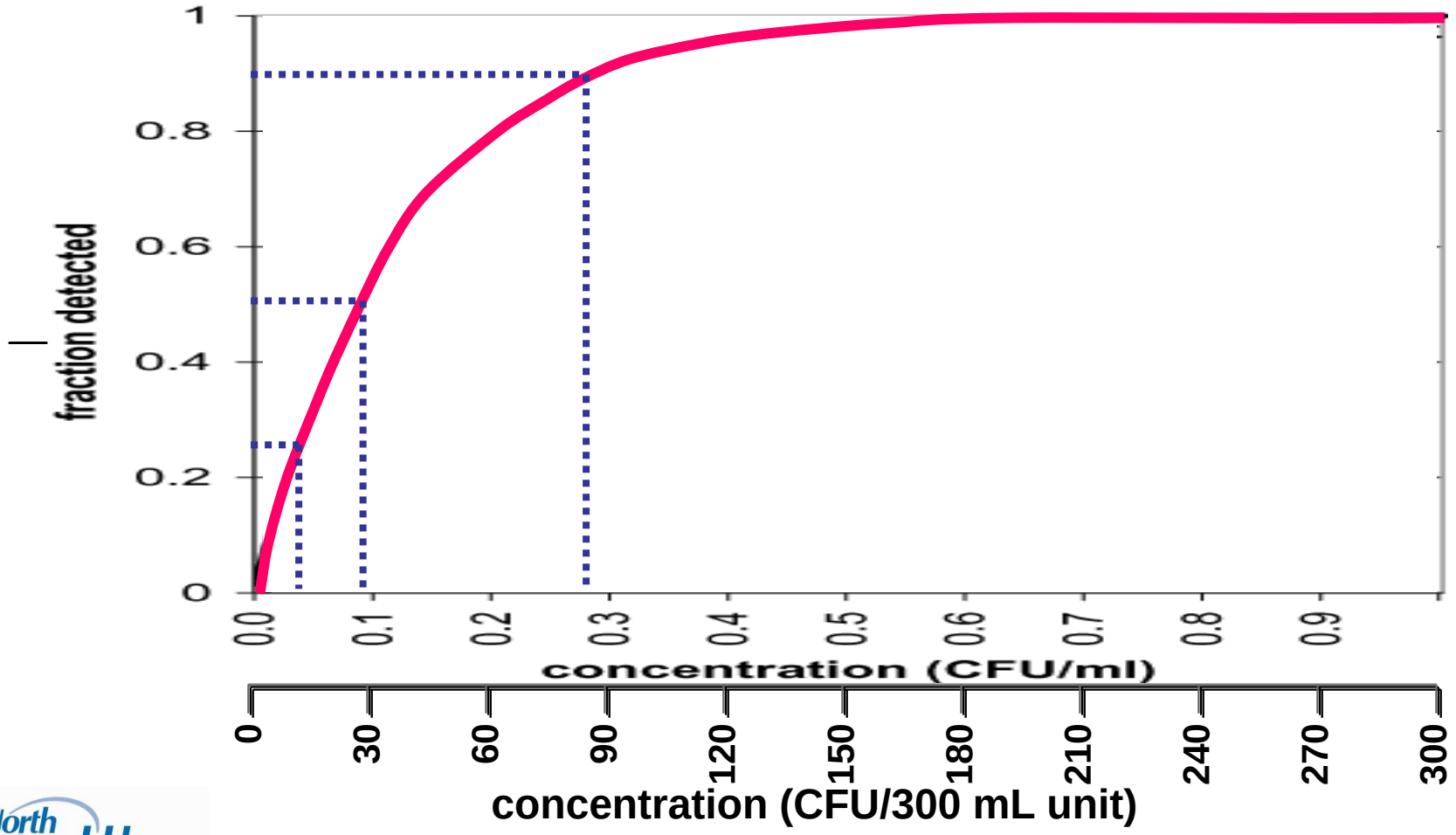
Murphy et al. Vox Sanguinis 2008
Dumont et al. Transfusion: 50; 589; 2010.

Limitations of Early Culture Testing

Modeling the effect of concentration on bacterial detection when a 300 mL unit is contaminated with 0-300 CFUs (0-1 CFU/mL). The figure shows the probability curves for an 8-mL sample divided into two culture bottles.



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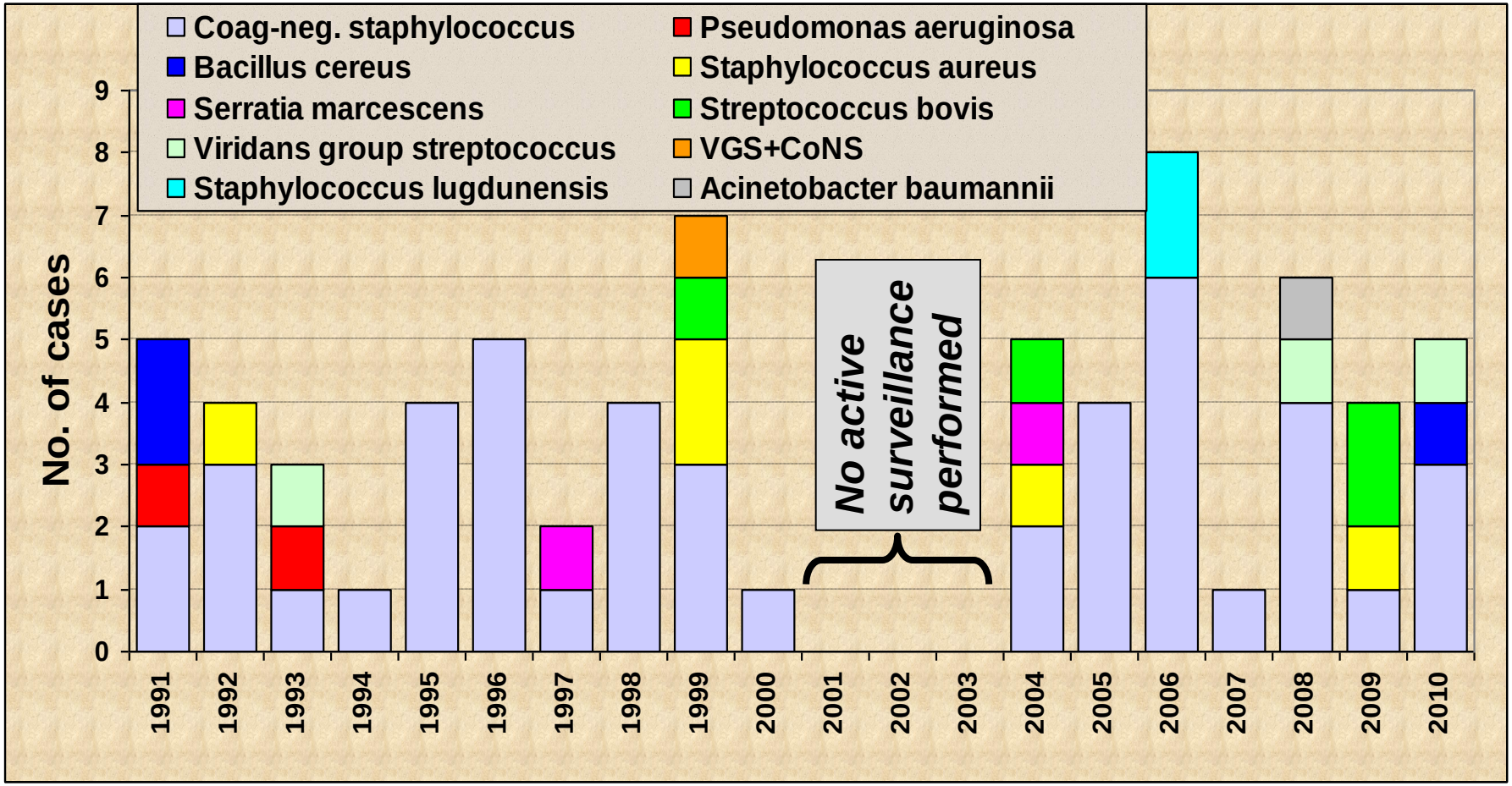
Benjamin, R. J., and S. J. Wagner.. Transfusion 2007: 47:1381-9.

Bacterial Contamination of Platelets

University Hospitals Case Medical Center, Cleveland, OH
1991-2010 N=68



Yomtovian & Jacobs Surveillance methods….1991 through 2004. Transfusion 46:719-30;2006. – 2010 update

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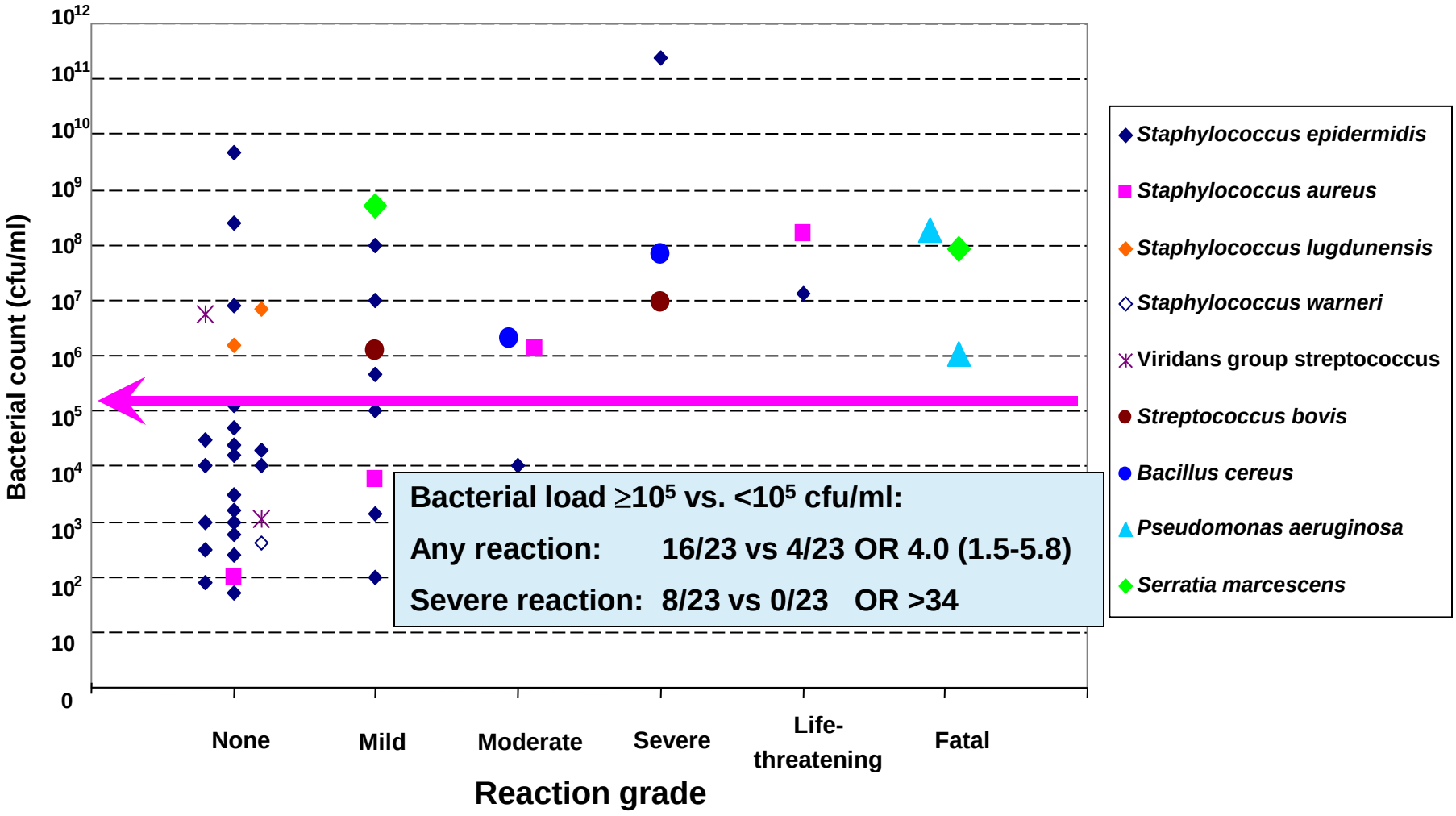
Bacterial load, species virulence, & Tx reaction



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Jacobs MR, Good CE, Lazarus HM and Yomtovian RA. Clin Infect Dis 2008;46:1214-20

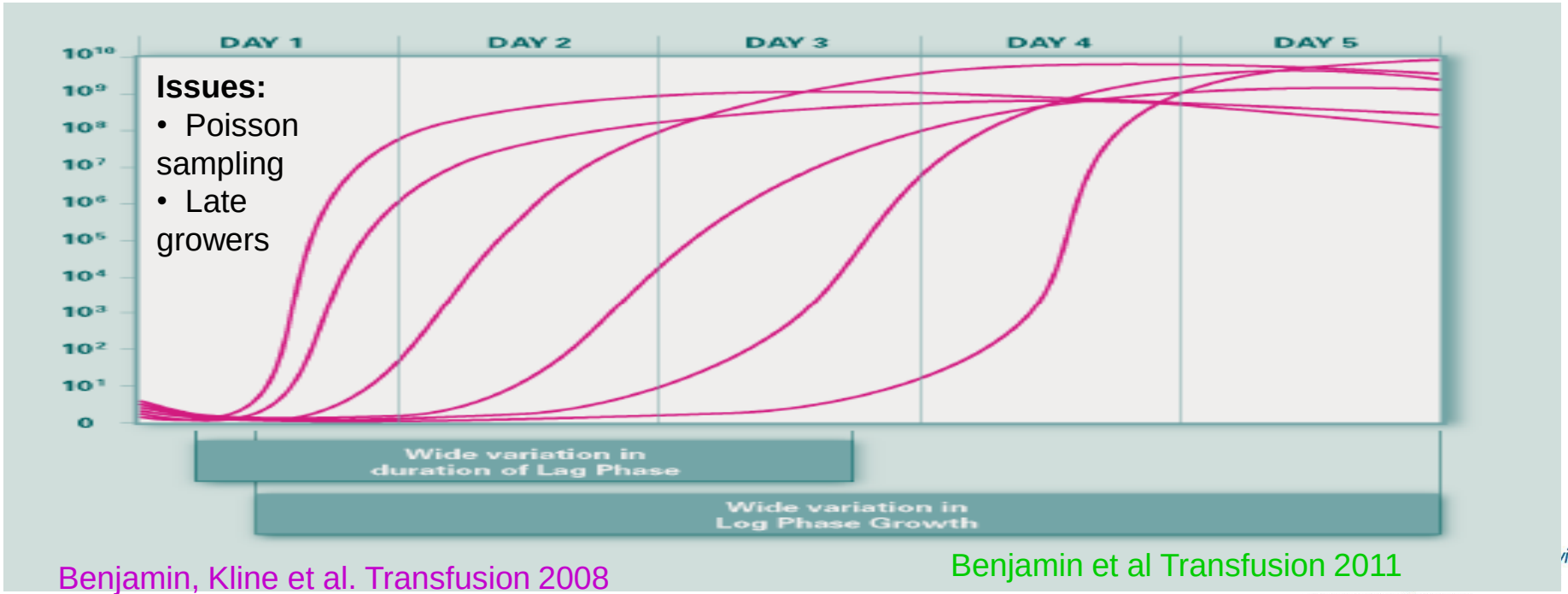
Bacterial Contamination Sampling Time Issues

Arm Prep	Inlet Diversion
↓ Risk ~ 0.47	↓ Risk ~ 0.46

Positive units (Gram- 've+) <u>are</u> Interdicted

- Day 2+ Negative Units released:
- Any late positives recalled

Days 3-5 Late Positives:
Usually Gram +'ce cocci



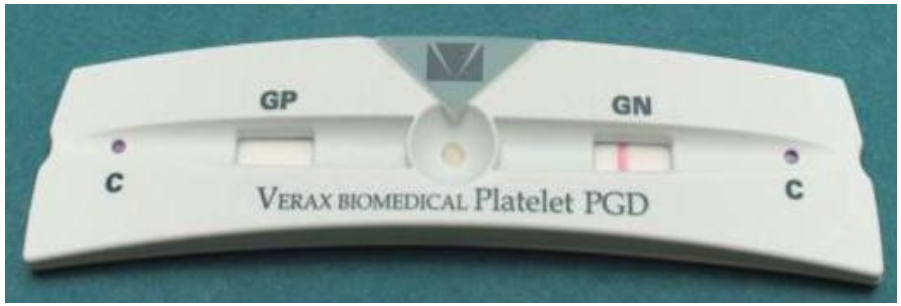
Benjamin, Kline et al. Transfusion 2008

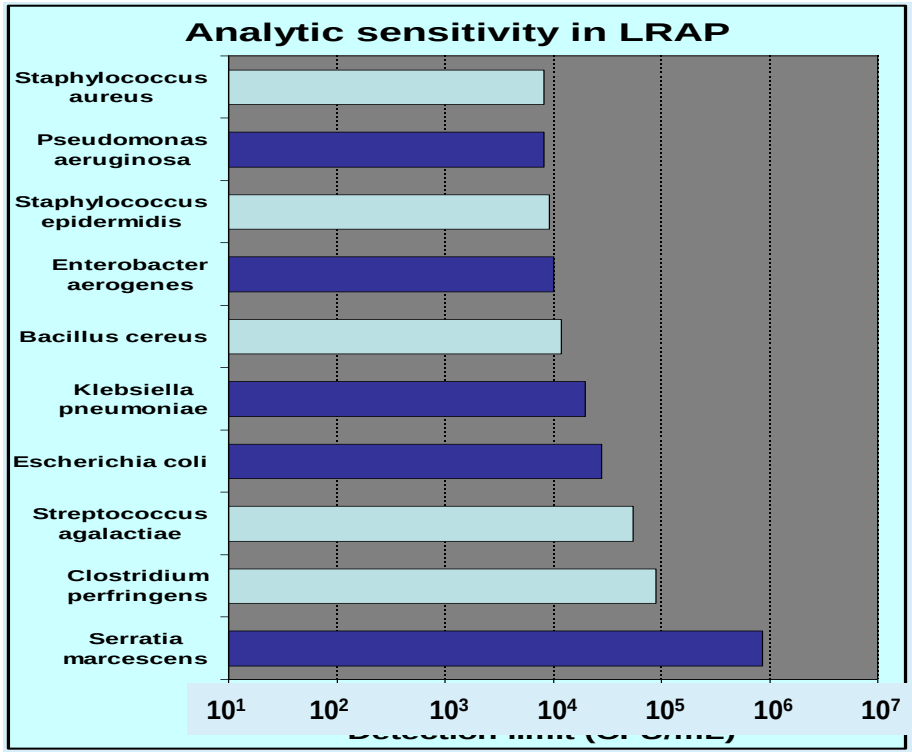
Benjamin et al Transfusion 2011

Multi-site Study of 27,682 PC with PGD® Assay

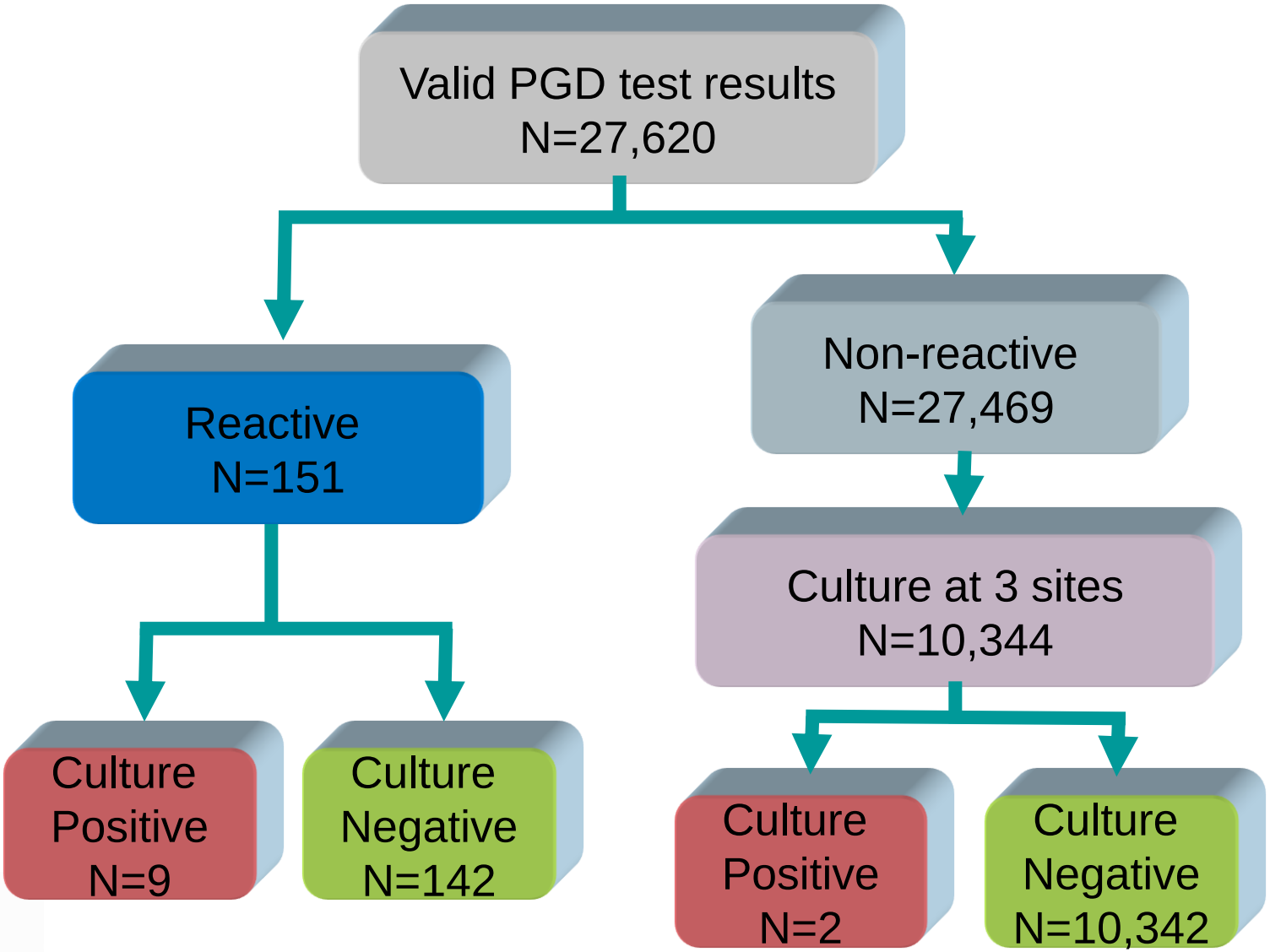
- Study performed at 18 study sites by over 160 technologists on apheresis units previously tested by culture negative (BacT/ALERT or eBDS) PC
- Doses tested by Platelet PGD test on day of issue (16 sites) or shortly after issue (2 sites) according to the manufacturer's directions
- Positive PGD results repeated in duplicate and plate cultures performed
- Concurrent aerobic plate cultures were also performed on 10,430 units at three of the study sites, with quantitation of positives at one study site

- Single-use, qualitative test
- Detects the presence of conserved bacterial surface cell wall antigens, lipoteichoic acid and lipopolysaccharide, using specific antibodies





Multi-site Study of 27,682 PC with PGD® Assay



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Jacobs: Transfusion 51: 2573: 2011

Platelet Bacterial Contamination – TP results

Bacterial species isolated by culture at issue	Age of unit (days)	Confirmation method*	Bacterial load (CFU/ml)**	Transfusion status
Bacillus sp; P. acnes	3	BC	NT	Not Tx
CoNS (split collection)	3	PC, GS	NT	Not Tx
CoNS (split collection)	3	PC, GS	NT	Not Tx
Enterococcus faecalis	3	PC, GS	NT	Not Tx
CoNS; Peptostrep	4	PC, BC, GS	NT	Not Tx
CoNS	4	PC	NT	Not Tx
CoNS	5	PC, GS	1.3 x 10e6	Tx – no rxn
Bacillus sp.	5	PC, GS	1 x 10e7	Not Tx
CoNS	5	PC, GS	1.2 x 10e7	Tx – septic shock***

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*BC = broth culture; PC = plate culture; GS = Gram stain; **NT = Not Tested for quantity
***documented bacteremia with same organism

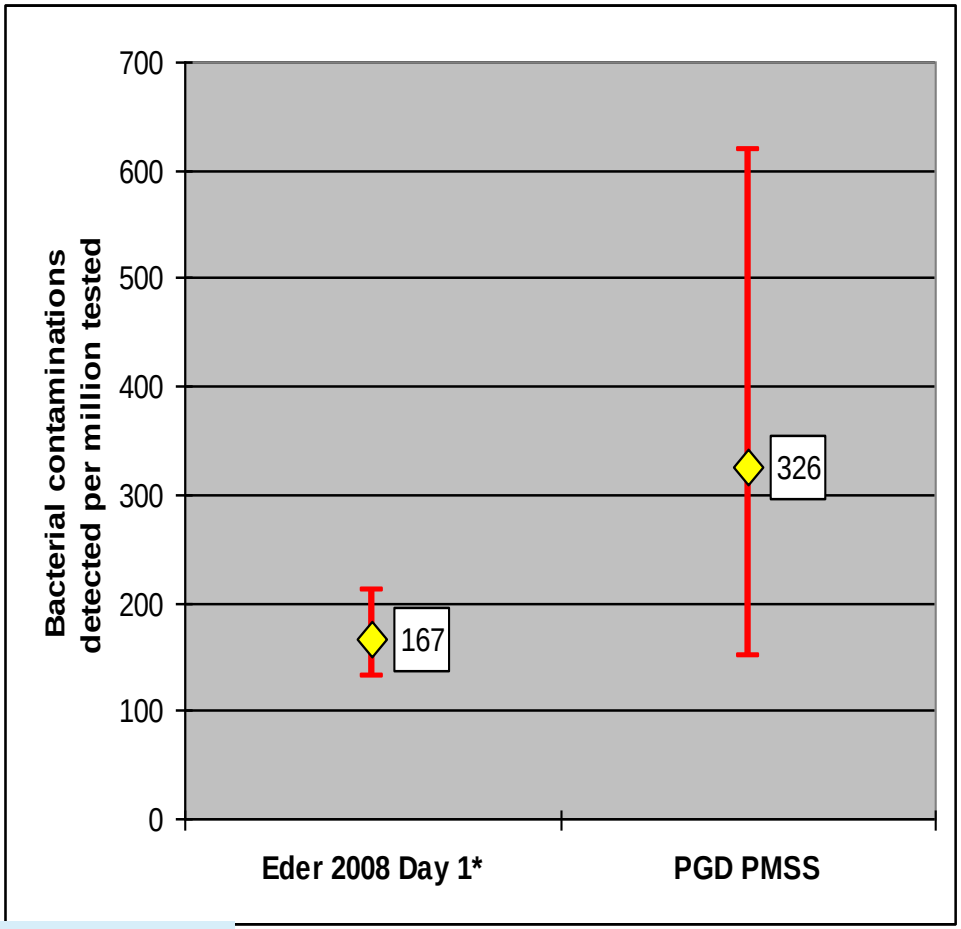
Jacobs: Transfusion 51: 2573: 2011

PGD Detection Rates On Day of Release

Day 2 culture negative Apheresis Inventory – sampled on day 1

9/27,620 apheresis units PGD positive

- Rate of detection was 1/3,069 units (95% CI 1/6,711 - 1/1,617)
- Estimated 326 contaminated units per million units (95% CI 149-618)
- Based on 1.7 million LRAP units per year in the U.S., the estimated number of breakthroughs would be expected to be 554 per year (95% CI 253-1051)



Start with 893/MM contaminated:
- Culture detects 150-200/MM
- POR detects 326/MM
- Undetected ~ 192/MM

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- Eder: Transfusion 49: 1554:2009
- Jacobs: Transfusion 51: 2573: 2011

PGD® PC Trial Outcomes

Description	Platelet Age (Days)				Total
	≤2	3	4	≥5*	
Number Units Tested (% of Total Tested)	4,036 (15%)	8,375 (30%)	6,660 (24%)	8,549 (31%)	27,620
True positive PGD Test	0	4	2	3	9

- Bacterial contamination @ **1:3,069** doses (326/million; 95% CI 149-618/million)
- 7 of 9 PGD+ units showed Gram Stain + contamination (~10^7 cfu)
- 2 false negatives detected in 10,424 doses (192/million) on DOR culture
- There were 142 PGD false positives (0.51%)
- Based on reaction rate in recipients transfused with >10^5 CFU/mL:
  - This could prevent ~300 major Tx reactions & several fatalities/year

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Jacobs: Transfusion 51: 2573: 2011

Operational Trial of PGD® SDP Testing

NSUH participated in an 18 center evaluation study of a rapid bacterial point-of-care screening assay (PGD®, Verax Biomedical)

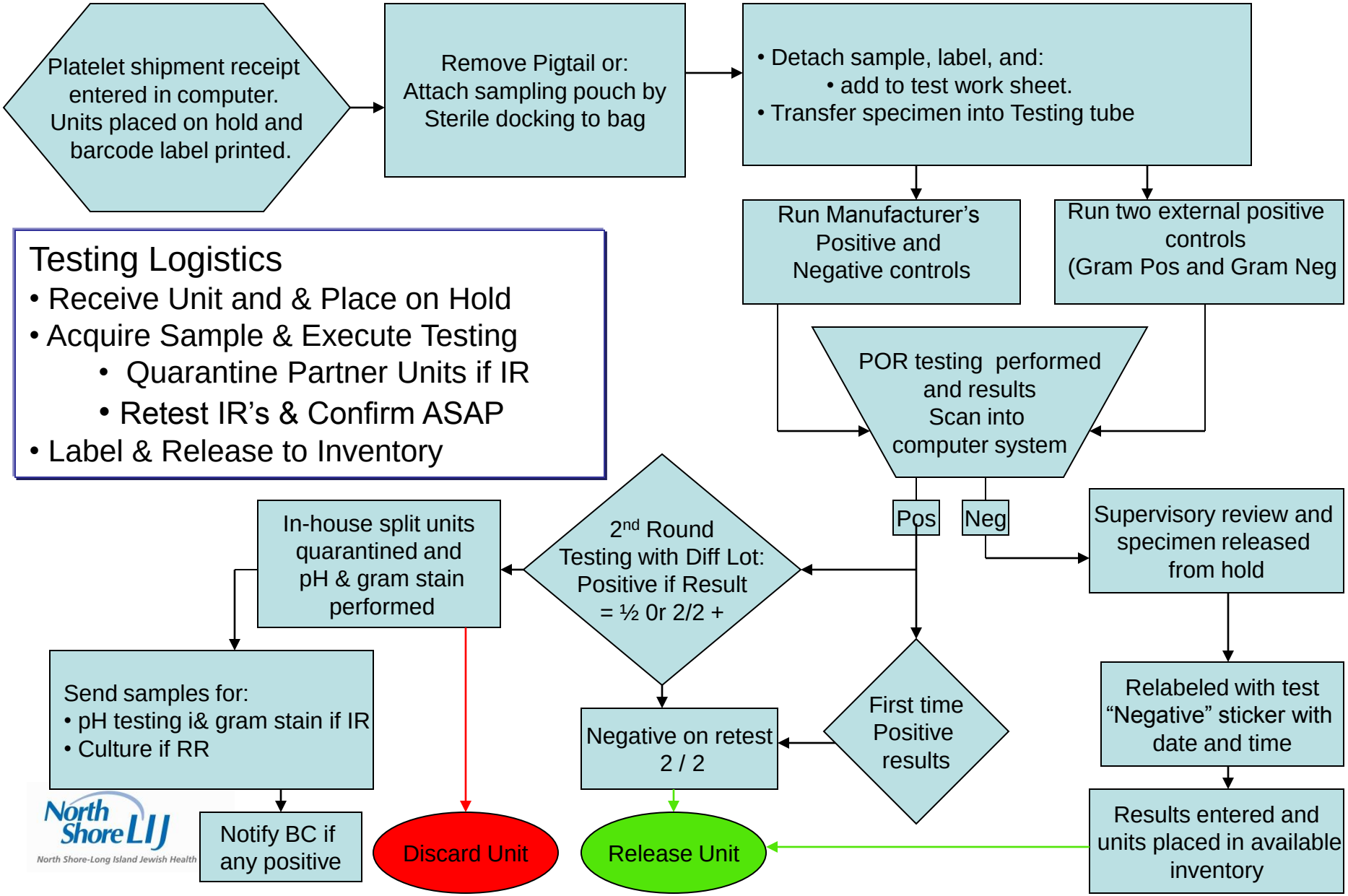
- One of 3 sites that performed concurrent culture at issue.
- The PGD Test performed on day of receipt & daily thereafter.

Day Tested	# Tested	# IR / # RR		% Specificity	% FP	pH < 6.8
DAY 1	2040	26 / 10		99.5	1.3	6 / 15
DAY 2	291	0	0	NA	NA	NA

- Of the 59% tested, 14% retested @ 48 hours, & 1% @ 72 hours.
- Feasibility was confirmed with next steps identified as:
  - Definition of 'acceptable' hold periods following testing
  - Implementation of IT to track inventory testing status.
  - Identification of the 'real' as opposed to 'reported' risk

Vox Sang 101S; 170: 2011

Testing Logistics in Hospital Blood Bank



Testing Logistics

- Receive Unit and & Place on Hold
- Acquire Sample & Execute Testing
  - Quarantine Partner Units if IR
  - Retest IR's & Confirm ASAP
- Label & Release to Inventory

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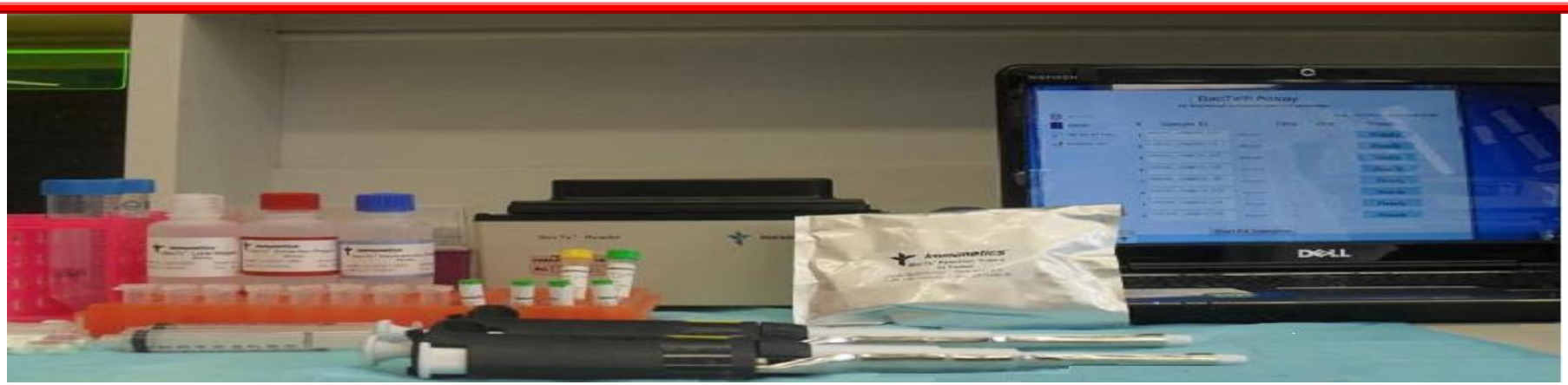
BacTx® Test Train & Sensitivity (510k Approved)



Species	# 1 Sensitivity	# 2 Sensitivity	Overall
Escherichia coli	5.1×10^3	8.7×10^3	8.7×10^3
Pseudomonas aeruginosa	9.6×10^3	5.0×10^4	5.0×10^4
Klebsiella oxytoca	6.8×10^3	9.9×10^3	9.9×10^3
Serratia marcescens	5.8×10^4	6.7×10^3	5.8×10^4
Propionibacterium acnes	7.2×10^3	1.1×10^3	7.2×10^3
Staphylococcus aureus	2.1×10^3	4.0×10^3	4.0×10^3
Staphylococcus epidermidis	2.0×10^3	2.4×10^3	2.4×10^3
Streptococcus agalactiae	3.6×10^3	2.7×10^4	2.7×10^4
Clostridium perfringens	2.8×10^3	4.5×10^3	4.5×10^3
Bacillus cereus	1.3×10^3	1.7×10^3	1.7×10^3

Galloway-Haskins & Heaton:Transfusion 2011/2; Supp: Abstract

Bacterial Contamination Testing Standards

AABB standard 5.1.5.1 (effective March 2004)[1]
The blood bank or transfusion service shall have methods to limit and detect bacterial contamination in all platelet components

Apheresis - Collection facilities adopted culture
- FDA cleared culture-based QC (BacT Alert & eBDS)
- Culture at 24hrs, release 12-24hrs later

WBD
- Culture not practical for WBD units
- Hospitals validated non FDA cleared tests

AABB standard 5.1.5.1.1 (effective Jan 2011)[2] for WBDP
Detection methods shall either be approved by the FDA or validated to provide sensitivity equivalent to FDA-approved methods.

First High Profile Litigation affecting Hospital/Blood Center
- Testing and Recall Standards of Practice
- Policies & Procedures pertinent to Transfusion Reaction

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1. AABB Standards for Blood Banks, March 2003
2. AABB Interim Proposed Standard, Posted Feb 2010
3. http://www.tampabay.com/incoming/hillsborough-girl-had-cancer-but-suit-pins-death-on-tainted-blood/1179600

Policy Review

Issue	For action	Opposed to action
Clinical Issue ?	Well described sepsis/death risk: • Reports credible & conservative Actual sepsis ?? 10 X under-reported: • Clinical significance hard to evaluate • Increasingly G+ cocci - skin contaminant	None reported locally: • Small reported fraction = ↓ perceived risk • No standard-of-care & minimal litigation Sepsis symptoms unlinked to cause: • Sick patients with many other issues • MD's are used to high risk patients
Economic Question	Reimbursement focused on outcomes • Quality = purchaser selection criterion • DRG rates affected by readmissions Culture already factored into unit cost: • Maybe avoid BacT/Alert cost • No studies available	BC's reluctant to reduce product cost:: • Low direct cost… not avoidable expense • Hospital cost of sepsis is not reported Testing not the standard of practice: • FDA & aaBB do not require it • Low assessment of liability
Feasibility	NSUH participated in trial (no yield): • Only tested routine units • Showed feasibility in a study	Manufacturing not Distribution: • BC should ↑ culture sensitivity • Hospitals 'cannot' test completely
Options North Shore LIJ North Shore-Long Island Jewish Health System	• Test all PC pre-release: • Test 'at-risk' patient's PC • TPGD test reactions (define problem)	Take no action: • Await regulatory leadership • Request BC's to improve capture rate

Policy Related Questions

- **Clinical Questions:**
  - There is clinical evidence that Point-of-Release Testing is needed
- **Feasibility Questions:**
  - These tests are do-able in a Blood Bank Environment
- **Inventory Questions raised:**
  - Tested inventory can be maintained & could dating be extended ?
- **Evaluations/studies that are needed**
  - Larger culture samples & later sampling offer some improvement
    - Current data suggests that it would be less than equivalent
  - Affirmative studies are needed to define the test frequency interval
- **Where we are today:**
  - Simple and effective Point-of-Release Testing is becoming available
    - aaBB/FDA workshop on 17th July to review evidence Vs. standards

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