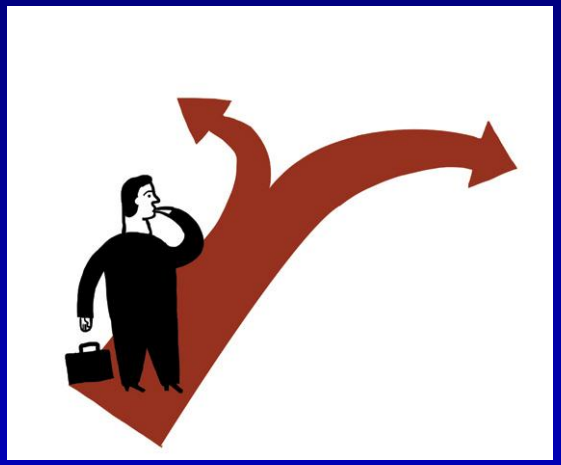
Beating the Bugs

Exploring Options to Improve Platelet Transfusions



James P. AuBuchon, MD

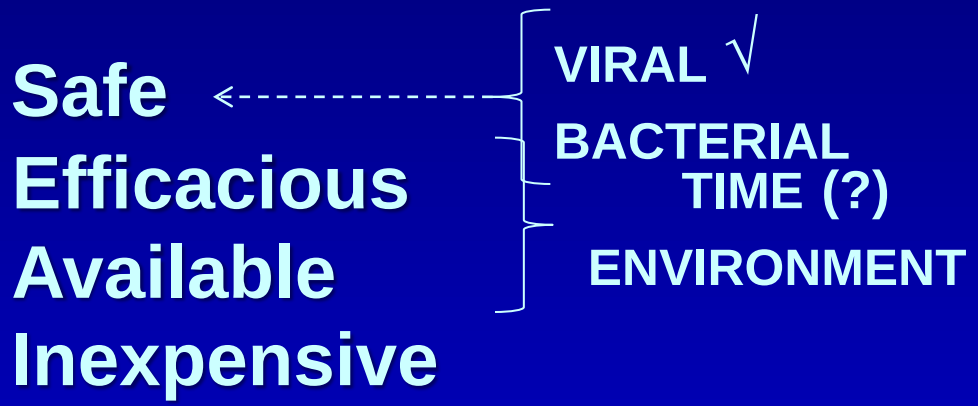
President & Chief Executive Officer
Puget Sound Blood Center

Professor of Medicine and of Laboratory Medicine
University of Washington

Seattle, Washington

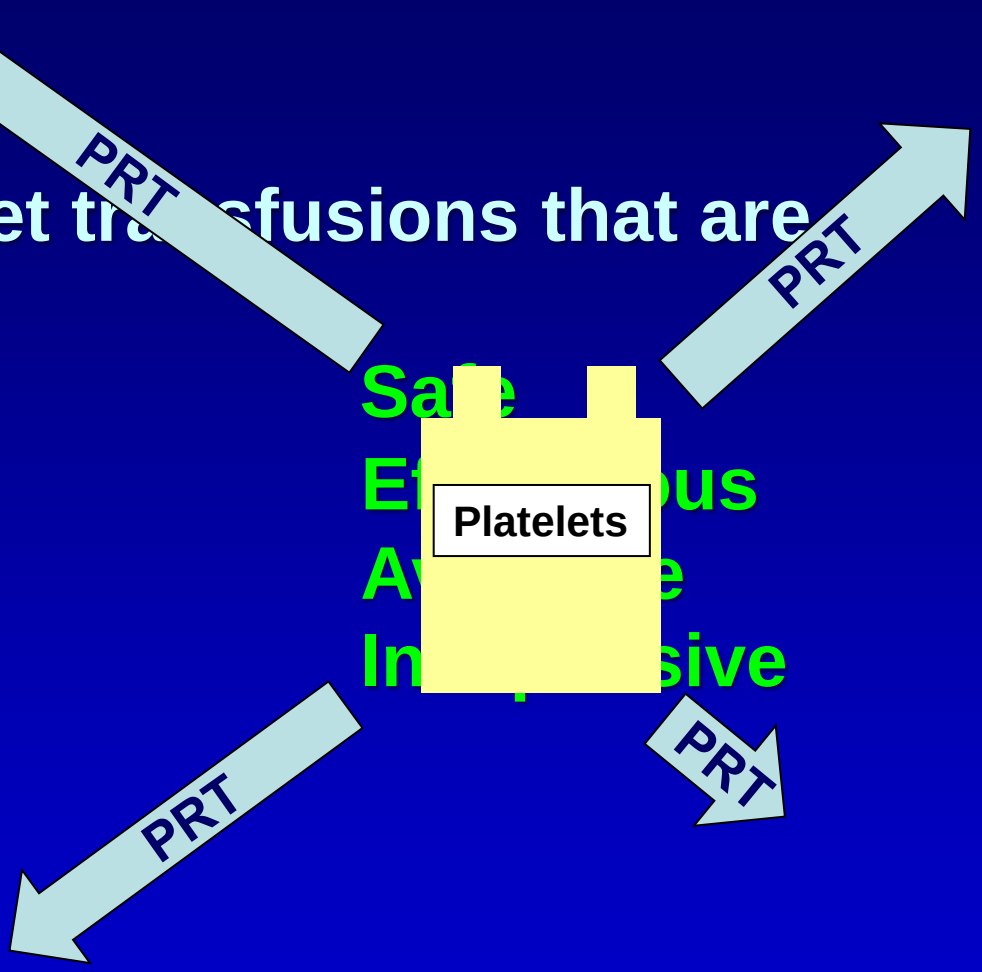
Goal:

Platelet transfusions that are



Goal:

Platelet transfusions that are



How does bacterial detection fit into this scheme?

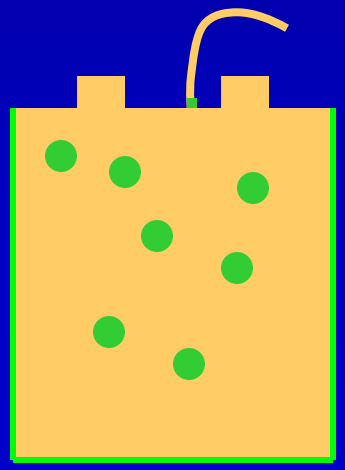
Why are we worried?

Limit

Skin disinfection
Diversion pouches

Detect

Bacterial culture (early)
Immunologic detection
PCR



Patel P *et al. Transfusion* 2012;52:1423-32.
Greco-Stewart VS *et al. Vpx Sang* 2012;102:212-20.

Why are we worried?

TRANSFUSION COMPLICATIONS

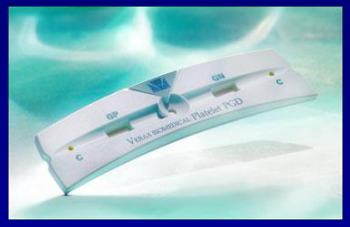
Detection of bacterial contamination in prestorage culture-negative apheresis platelets on day of issue with the Pan Genera Detection test

*Michael R. Jacobs, Daniel Smith, W. Andrew Heaton, Nicole D. Zantek, Caryn E. Good, and the PGD Study Group**

Jacobs MR *et al. Transfusion* 2011;51:2573-82.

Why are we worried?

Apheresis Platelets



9 contaminated units

FN: 1/3,100
CULTURE

n = 27,620
CULTURE
NEGATIVE

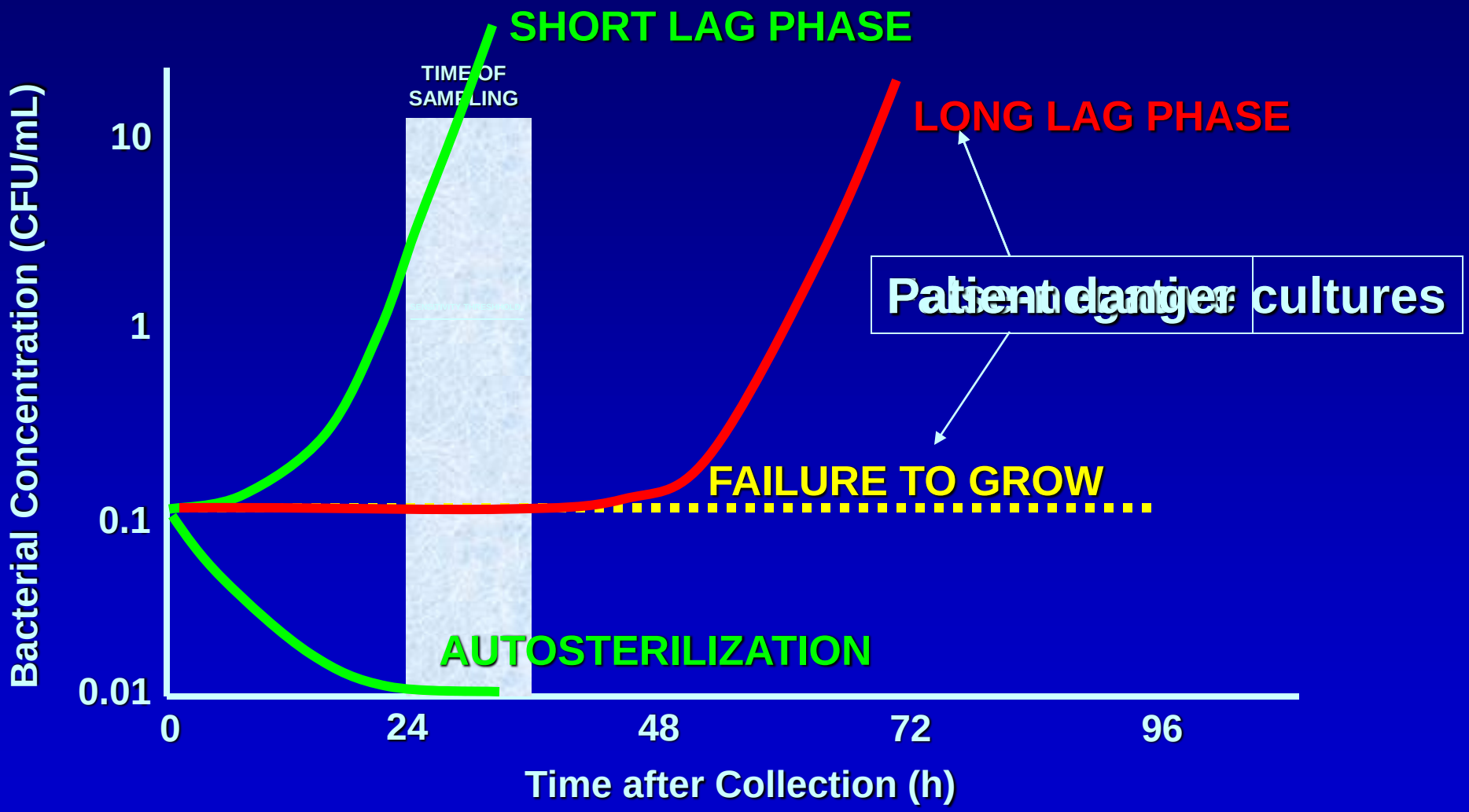
2 FN PGD
FP: 1/200

Coag neg *Staph* (6)
***Bacillus* (2)**
***Enterococcus* (1)**

Day 3: 4
Day 4: 2
Day 5: 3

Jacobs MR *et al. Transfusion* 2011;51:2573-82.

Predicting Culture Sensitivity

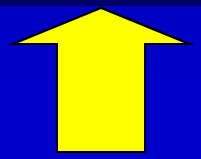


Benjamin RJ, Wagner SJ. *Transfusion* 2007;47:1381-9.
Model validation: Brecher ME, Hay SN. *Transfusion* 2008;48:569-70.

Deducing Initial Concentration

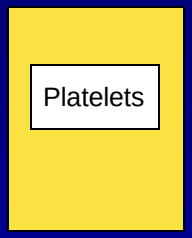
From clinical reports of 1- vs. 2-bottle positivity

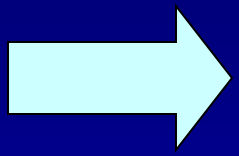
Bacterium	Concentration at Sampling (CFU/mL)	False Negative
K. pneumoniae	0.74	<1%
S. marcescens	0.07	57%
S. viridans	0.46	3%
Coag-neg *Staph.*	0.02-0.09	26-74%
Staph. aureus	<0.02	>74%
Bacillus spp.	0.03-0.20	5-64%
Strep spp.	0.15-0.21	4-11%



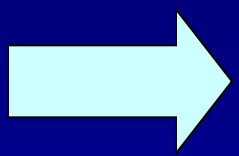
Benjamin RJ, Wagner SJ. *Transfusion* 2007;47:1381-9.
Model validation: Brecher ME, Hay SN. *Transfusion* 2008;48:569-70.

Practical Experience: Ireland





Reculture: Day 4



Reculture: Day 7

43,230 doses screened

3,310 doses cultured

8,282 doses cultured

≥ 36h after collection

First 15,000:
8 mL➔ aerobic bottle

Last 28,000:
15 mL➔ aerobic+anaerobic bo

14 confirmed positive

1 confirmed positive

18 confirmed positives

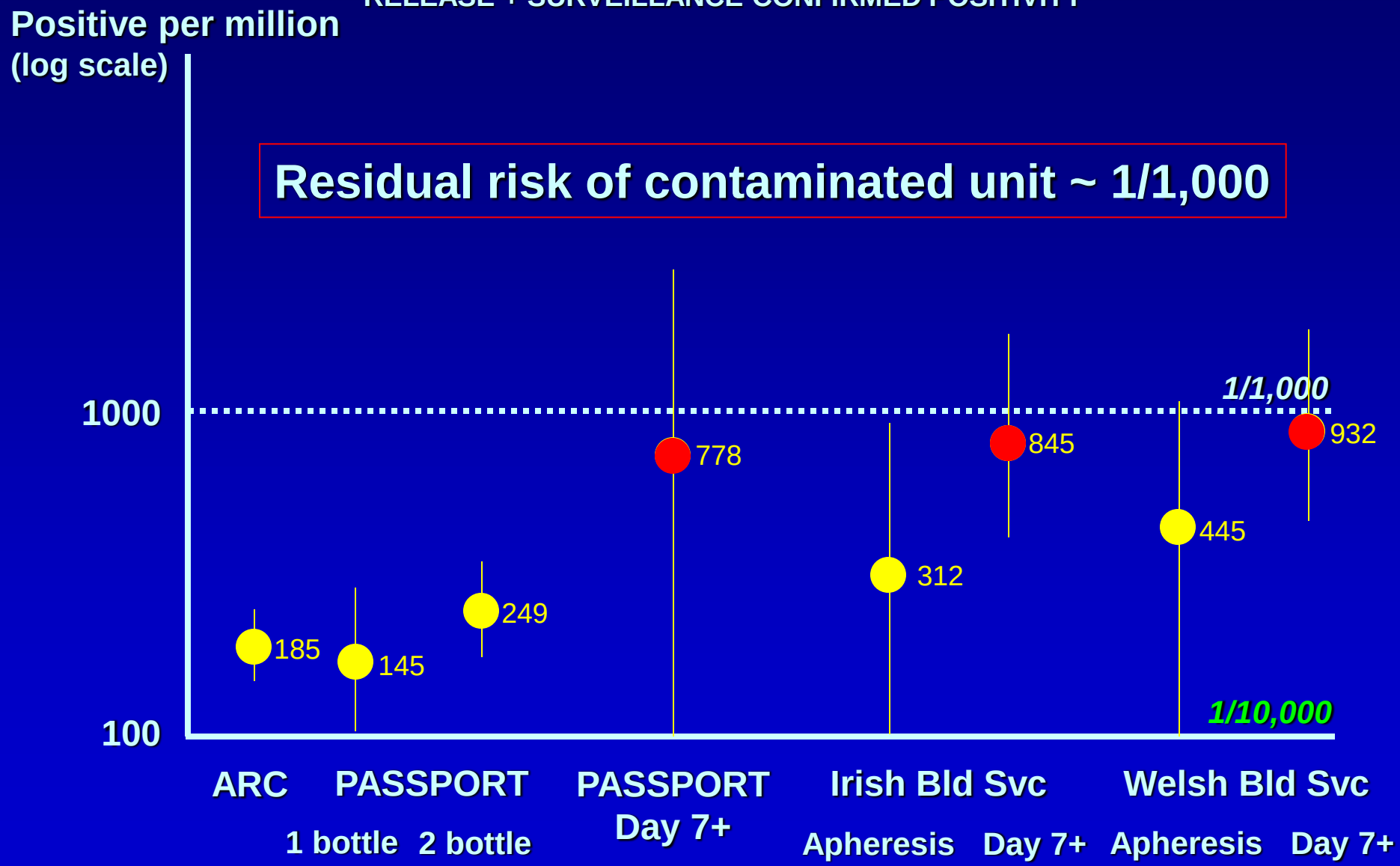
1/3,100

Residual Risk: 1/605
Sensitivity of initial culture: 29%

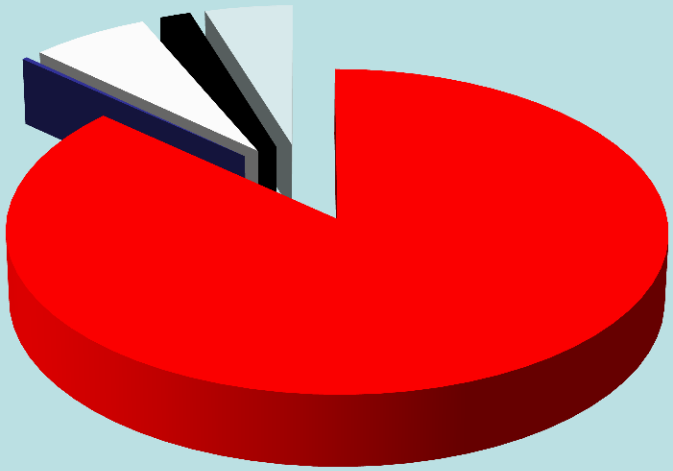
Murphy WG *et al. Vox Sang* 2008

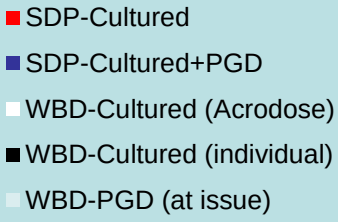
Where are we now?

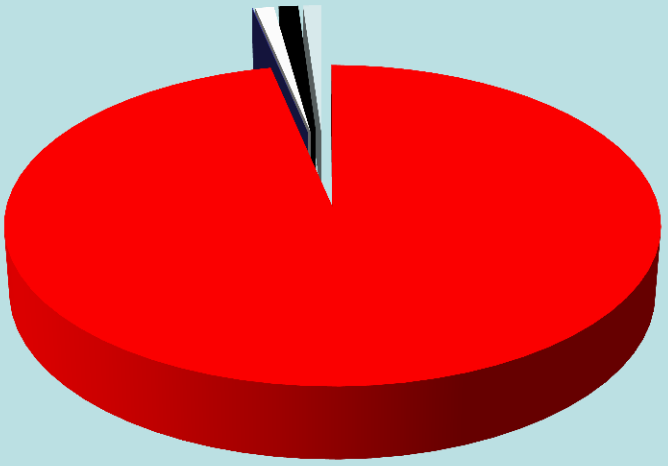
RELEASE + SURVEILLANCE CONFIRMED POSITIVITY



US: Current Status of Platelet Transfusions



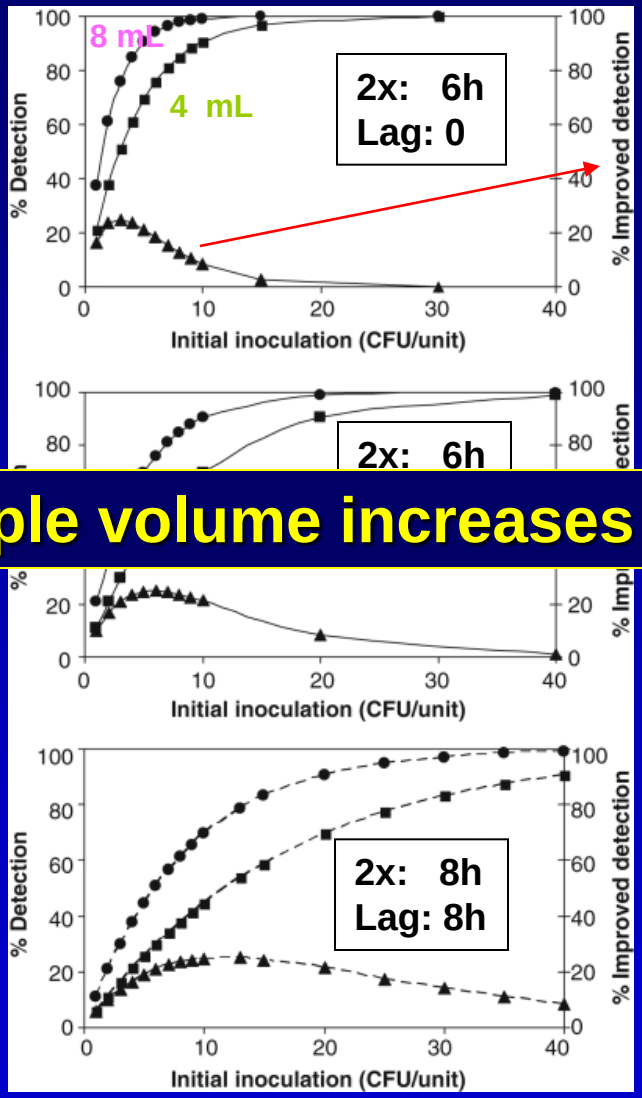




≈ 2 million platelet doses

≈ 510 contaminated transfusions

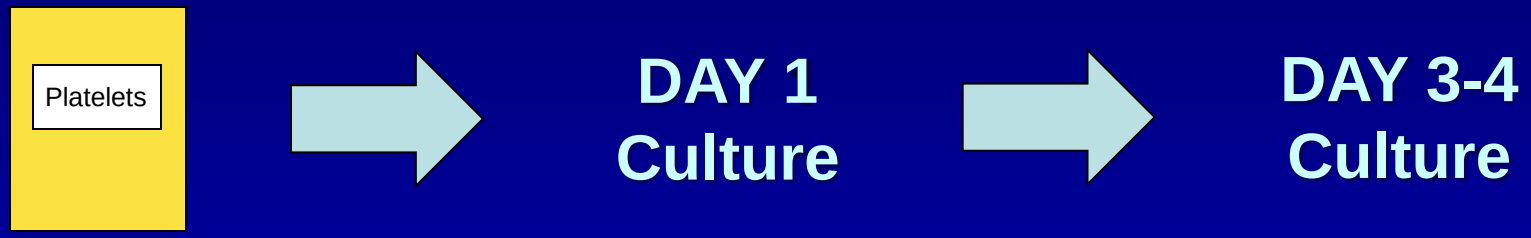
Effect of Increased Sample Volume



Doubling the sample volume increases sensitivity ~25%

Wagner SJ, Eder AF. *Transfusion* 2007;47:430-3.

Another Option: Repeat Culture

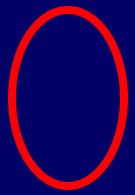


Challenges: Logistics
Outdating

Sereis W *et al. Vox Sang* 2011:101:191-9.
Vollmer T et al. Vox Sang 2012:102:365

You have to look for it!

	Active Surveillance (CULTURE ON RELEASE)	Passive Surveillance (REPORTING)
Units transfused	102,998	135,985
Contaminated units	485	15/million

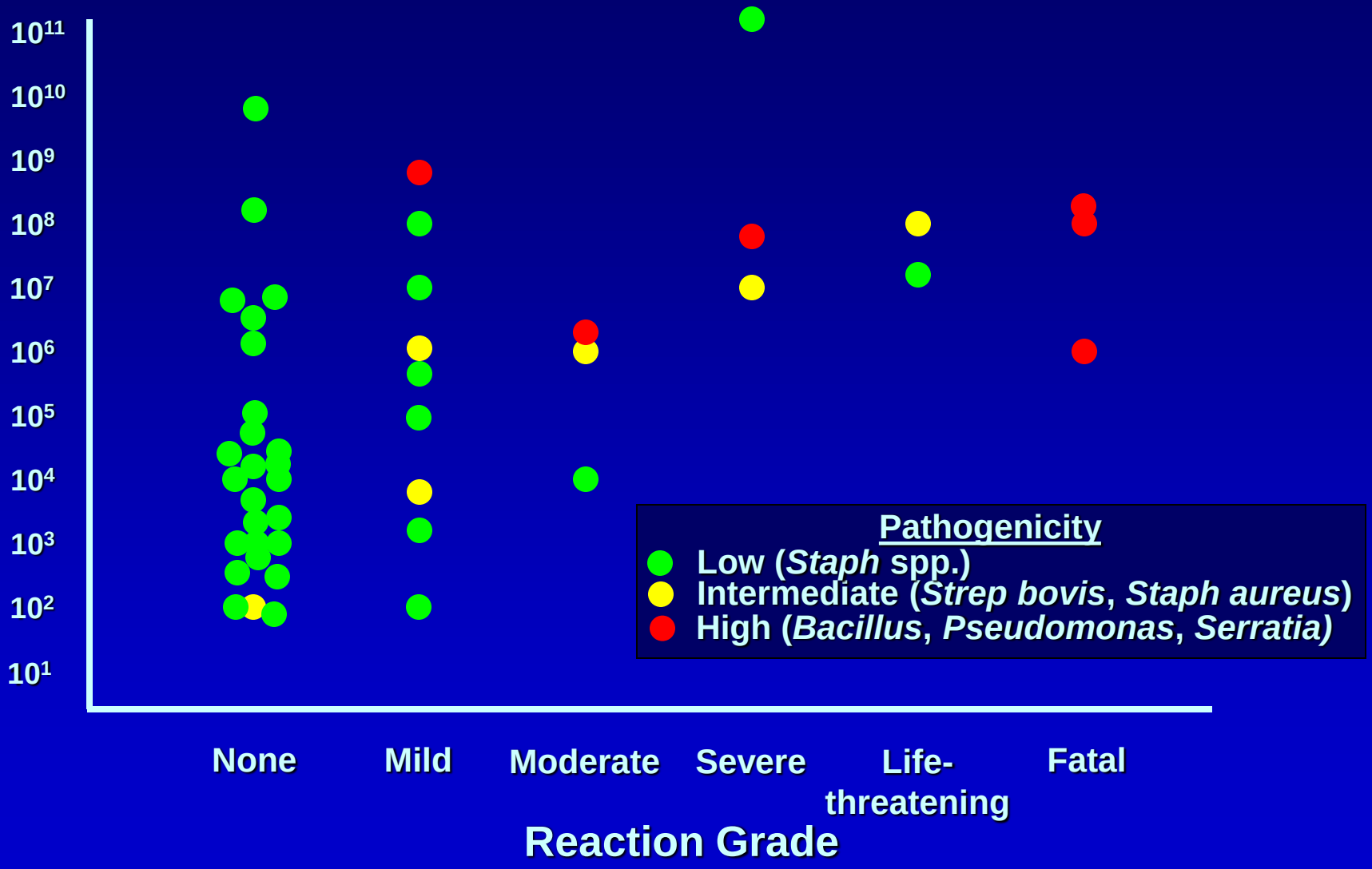


What was important?

- Organism virulence
- Inoculum ($\geq 10^5$ CFU/mL)

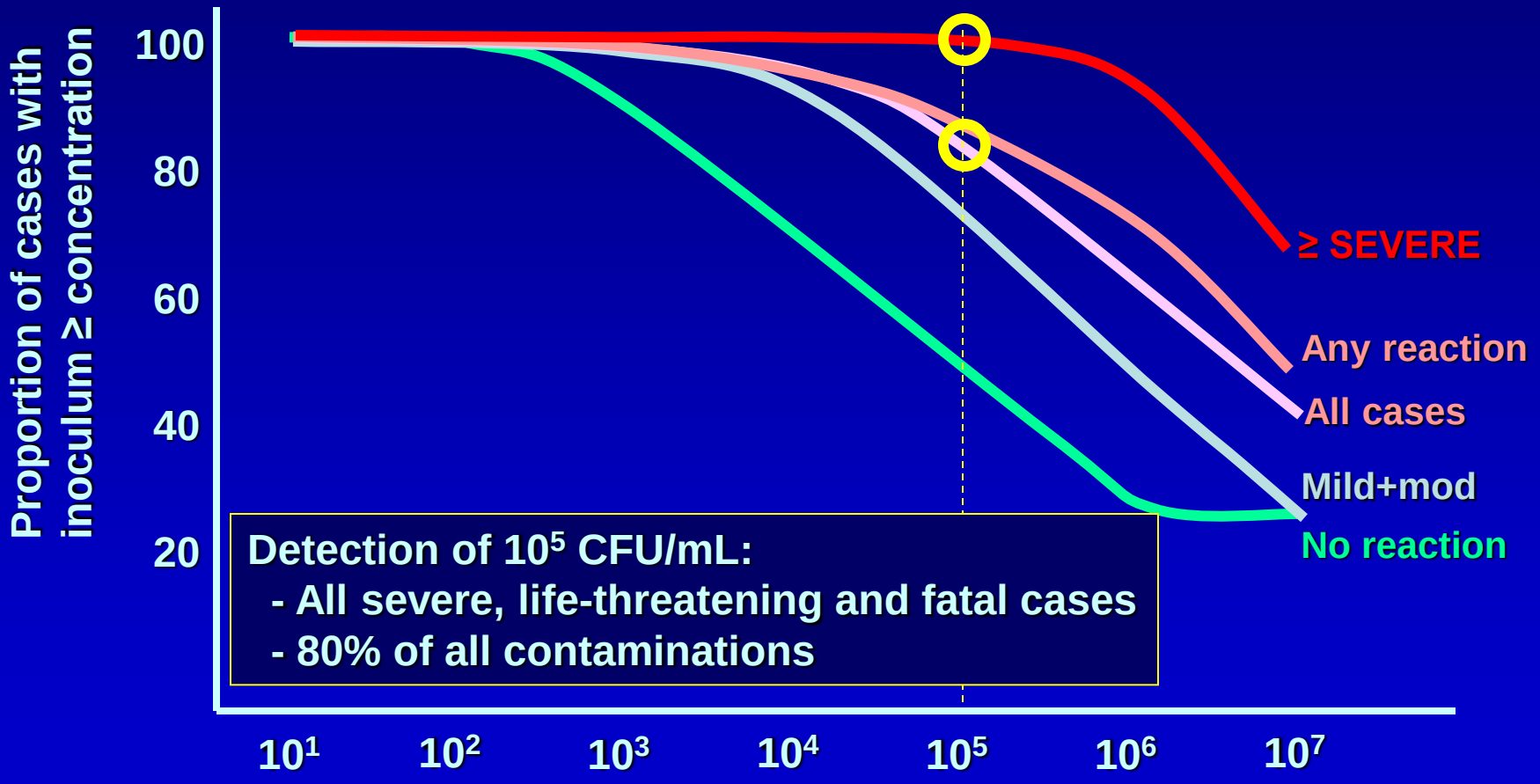
Jacobs M *et al. Transfusion* 2007;47:36A.

Predicting the Outcome



Jacobs M *et al. Transfusion* 2007;47:36A.
Jacobs M *et al. Clin Infect Dis* 2008;46:1214-20.

Predicting the Outcome



Jacobs M *et al. Transfusion* 2007;47:36A.
Jacobs M *et al. Clin Infect Dis* in press.

Where Are We Now?

Far from perfect!

- but an improvement

Reported cases of

post-transfusion sepsis: 1/75,100
fatality: 1/638,000

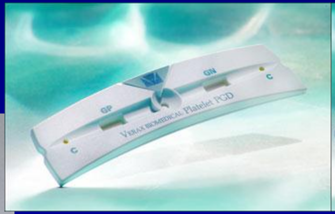
(passive reporting)

Te Boekhorst *et al. Transfusion* 2005;45:514-9.
MMWR 2005;54:167-9.
Benjamin *et al. Transfusion* 2005;45:1832
Fang *et al. Transfusion* 2005;45:1845-52.
Ede *et al. Transfusion* 2006;46:1A.

Platelets

What Should We Do?

INTERCEPT BLOOD SYSTEM



- or -

Day 1

Day 3

At “issue”

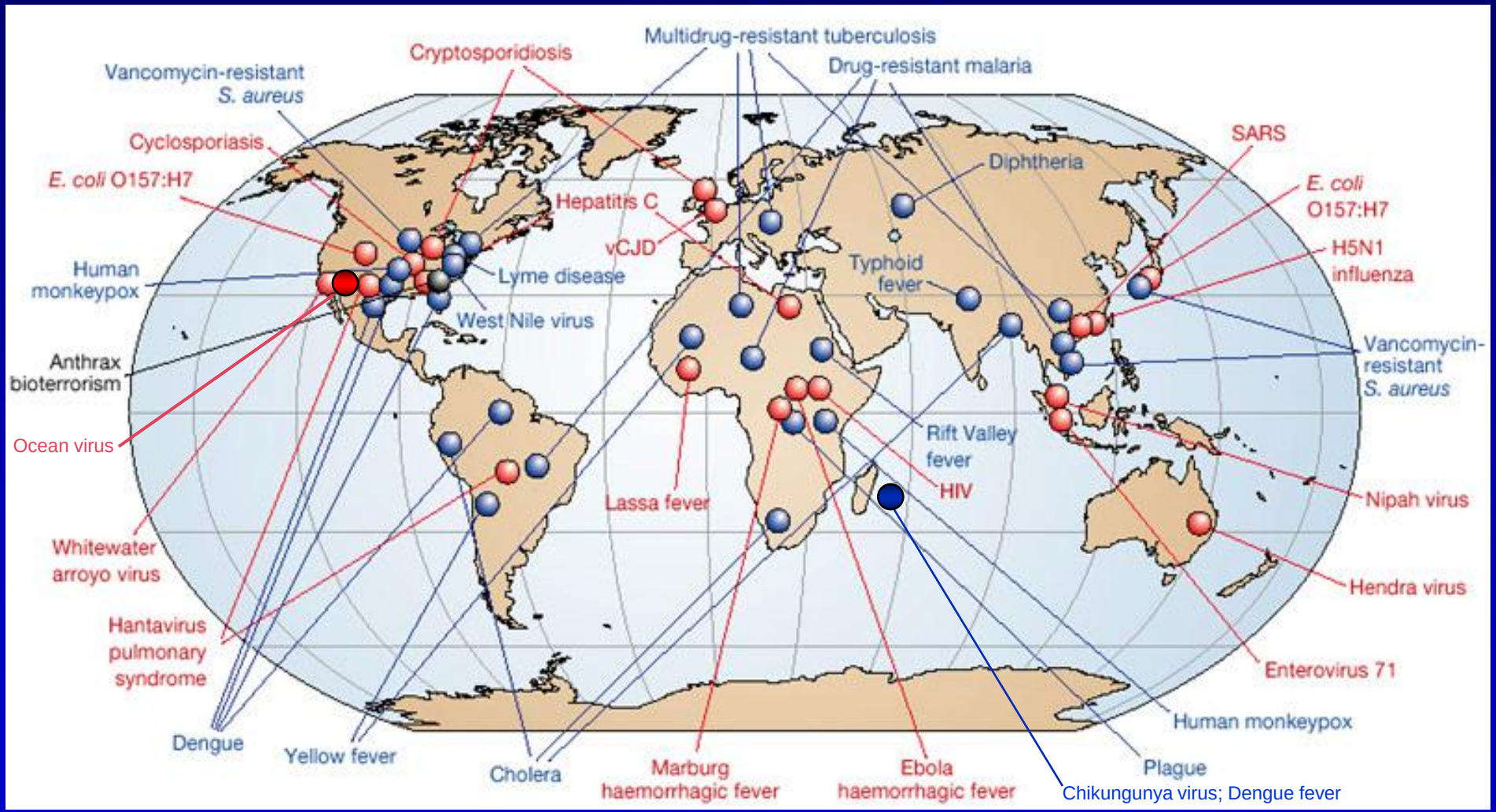
Cost

Hospitals qualifying units for transfusion (Logistics)

Logistics

Pathogen Inactivation Technologies

“Emerging” Pathogens



Modified from: Morens DM *et al. Nature* 2004;430:242-9.

Amotosalen Efficacy

HIV	
Cell-free	**>6.2 $\log_{10}$**
Cell-associated	**>6.1 $\log_{10}$**
Integrated pro-virus	**(BEYOND DETECTION)**
HCV	**>4.5 $\log_{10}$**
HBV surrogates	**5-6 $\log_{10}$**
CMV	**>5.9 $\log_{10}$**
Parvovirus B19	**>4 $\log_{10}$**
Blue tongue virus *(NE)*	**6.1 $\log_{10}$**
Calicivirus *(NE)*	**1.7 $\log_{10}$**
T. cruzi	**>4.6 $\log_{10}$**
Bacteria	**>6 $\log_{10}$**
Spore-forming bacteria	**(REQUIRES VEGETATIVE PHASE)**

PI Platelets: The Similarities

Some loss of platelets through process (small; manageable)

UV light ➔ *Identifiable platelet damage*

Increased metabolic rate

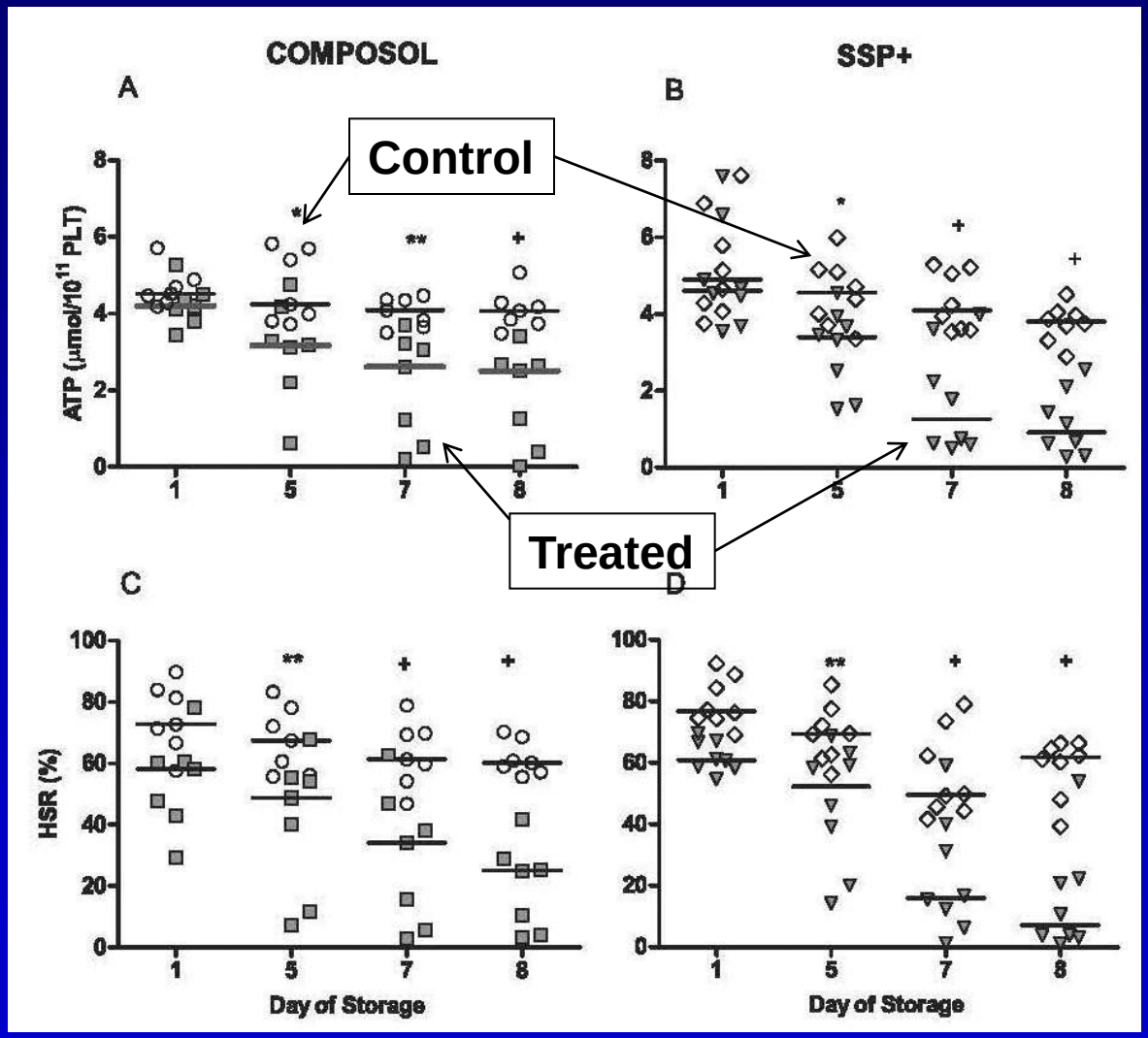
Increased activation during storage

Reduced recovery

Reduced survival

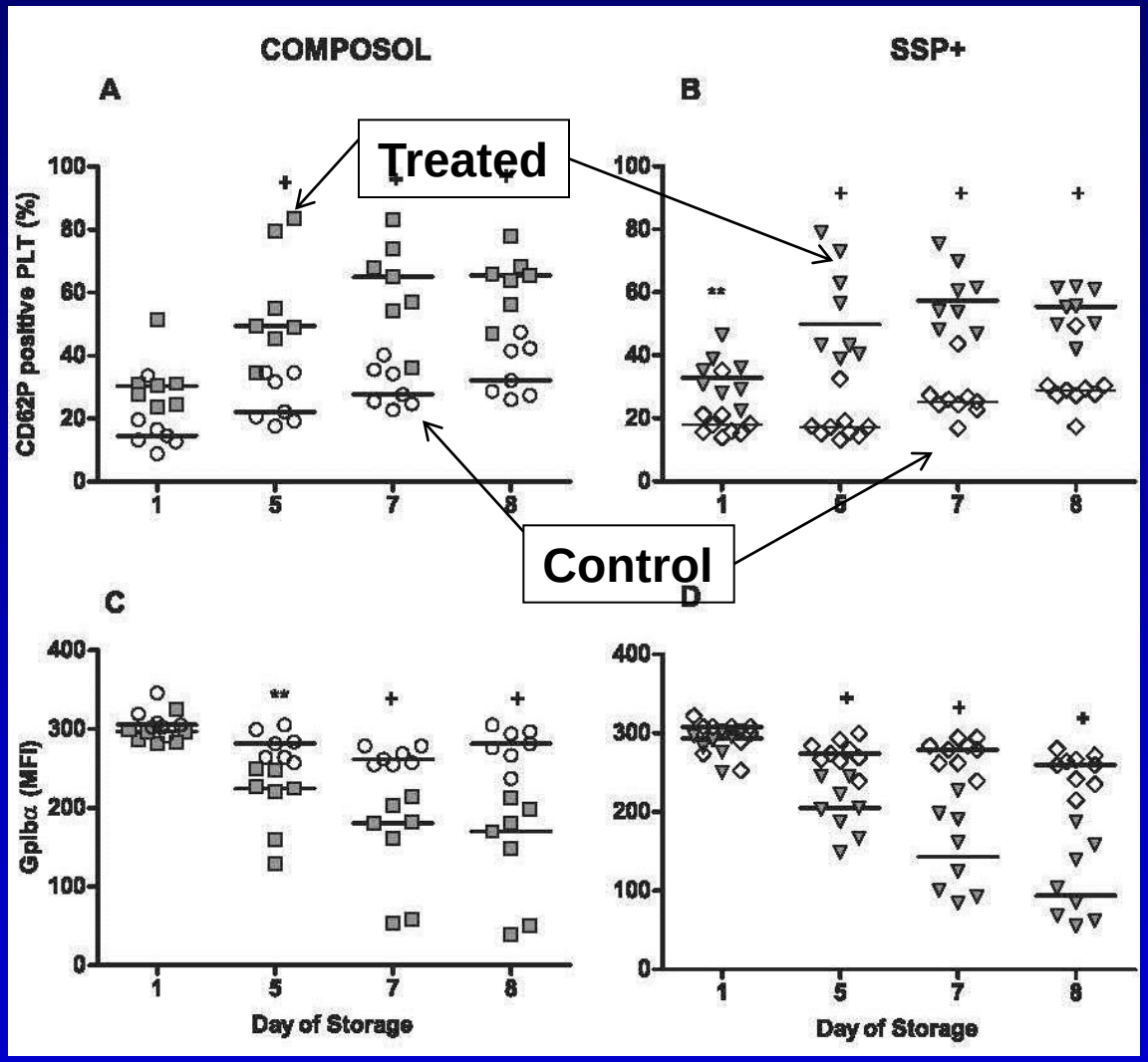
} **15-25%**

Metabolic Changes: Treatment and Storage



Cookson P *et al. Transfusion* 2012;52:983-94.

Metabolic Changes: Treatment and Storage



↑ Metabolism
↑ Activation

in plasma or PAS

Cookson P *et al. Transfusion* 2012;52:983-94.

Clinical Trial: Amotosalen-Treated Platelets

The euroSPRITE Trial

	Treated	Control	
Units transfused/patient	7.5±5.8	5.6±5.5	p > 0.05
Count increment (10^9/L):			
1h post-transfusion	27.6±13.3	35.8±23.3	p < 0.02
24h post-transfusion	16.4±9.5	24.7±17.6	p = 0.004
Corrected count increments:			
1h post-transfusion	13,100±5400	14,900±6200	p = 0.11
24h post-transfusion	7300±5400	10,600±7100	p = 0.02

Van Rhenen D *et al. Blood* 2000;96:819a.

Clinical Trial: Amotosalen-Treated Platelets

The SPRINT Trial

WHO Grade 2, 3 or 4 bleeding: No difference between groups
Platelet content of treated units: 7.5% less
Post-transfusion counts: 22-26% lower in treated group
Comparison by dose:
Equivalent effect from similar dose

French/Belgian experience: No increase in usage
Loss: 8%

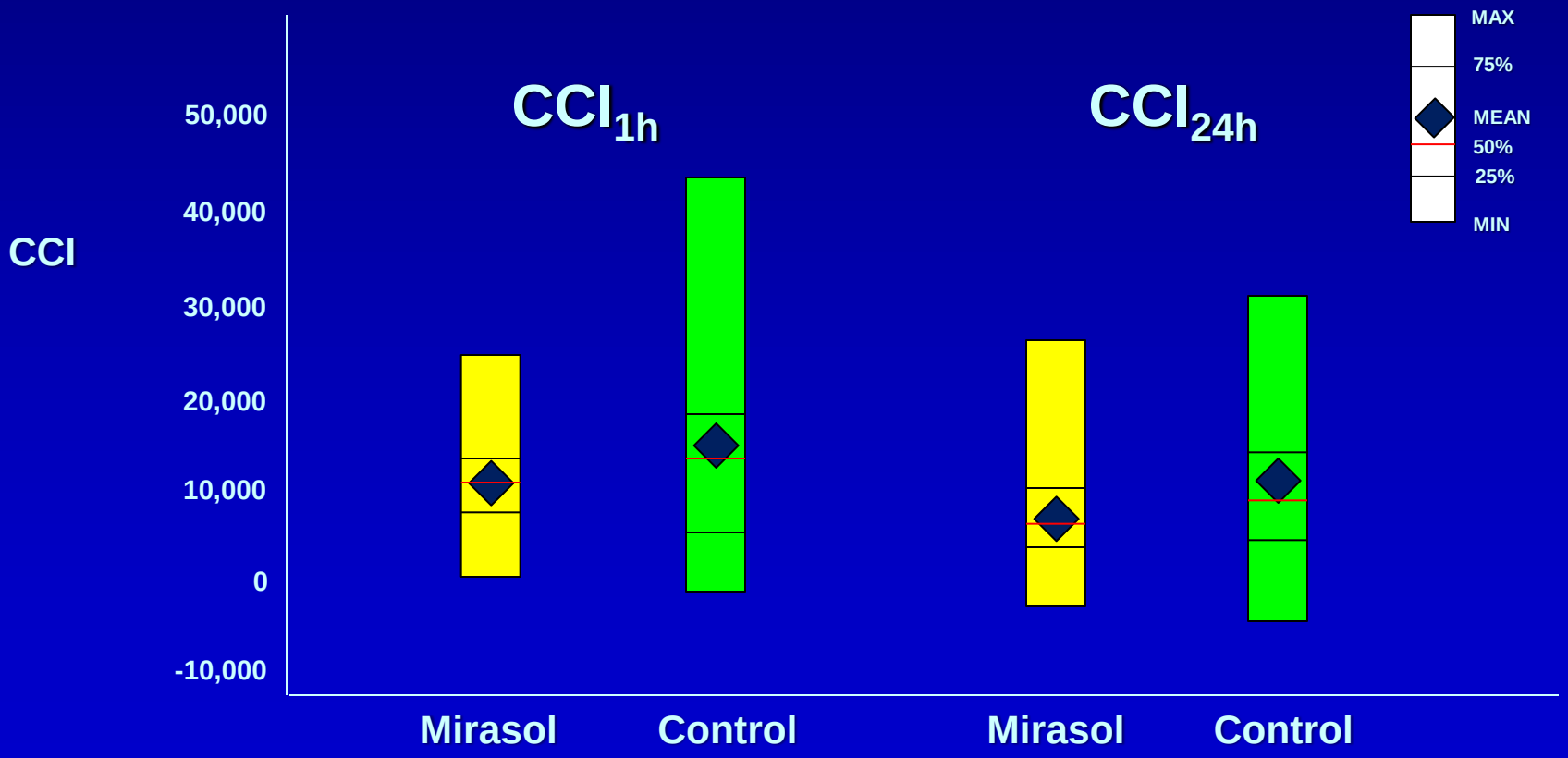
McCullough J *et al. Blood* 2001;98:450a.
Murphy S *et al. Transfusion* 2006;46:24-33.

Clinical Trial: Riboflavin-Treated Platelets

The MIRACLE Trial

n = 110

CCI_{1h}: 31% decrease (primary outcome measure)



Transfusion 2010;50:2362-75.

Clinical Trial: Riboflavin-Treated Platelets

The MIRACLE Trial

n = 110

CCI_{1h}: 31% decrease (primary outcome measure)

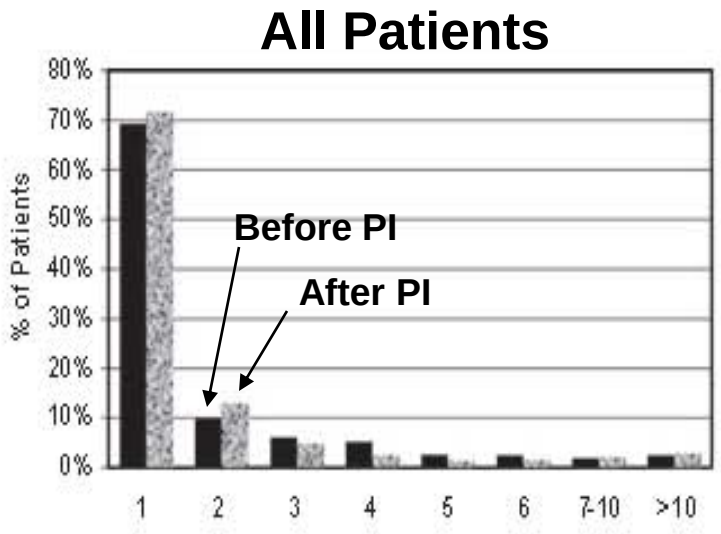
<u>No differences observed</u>

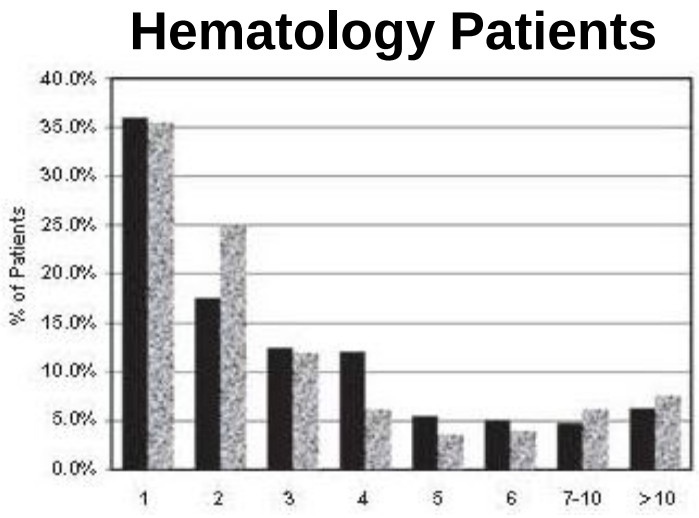
Clinical bleeding assessment

Inter-transfusion interval

***Transfusion* 2010;50:2362-75.**

Impact of Conversion to PI Platelets





Platelet Transfusions Required

Osselaer JC *et al. Transfusion* 2009;49:1412-22.

Pathogen-Inactivated Platelets in Routine Use

3 yr before ➔ 3 yr after adoption of INTERCEPT platelets

(Used in place of bacterial detection and gamma irradiation)

	Before	After
Patients	690	756
Transfusions	6829	7538
Transfusions/patient	9.9	10.0
Platelets collected/unit	6.6×10^{11}	6.7×10^{11}
Storage period	5d	7d
Outdating	9.1%	1.2%

Osselaer JC *et al. Transfusion* 2007;47:19A.

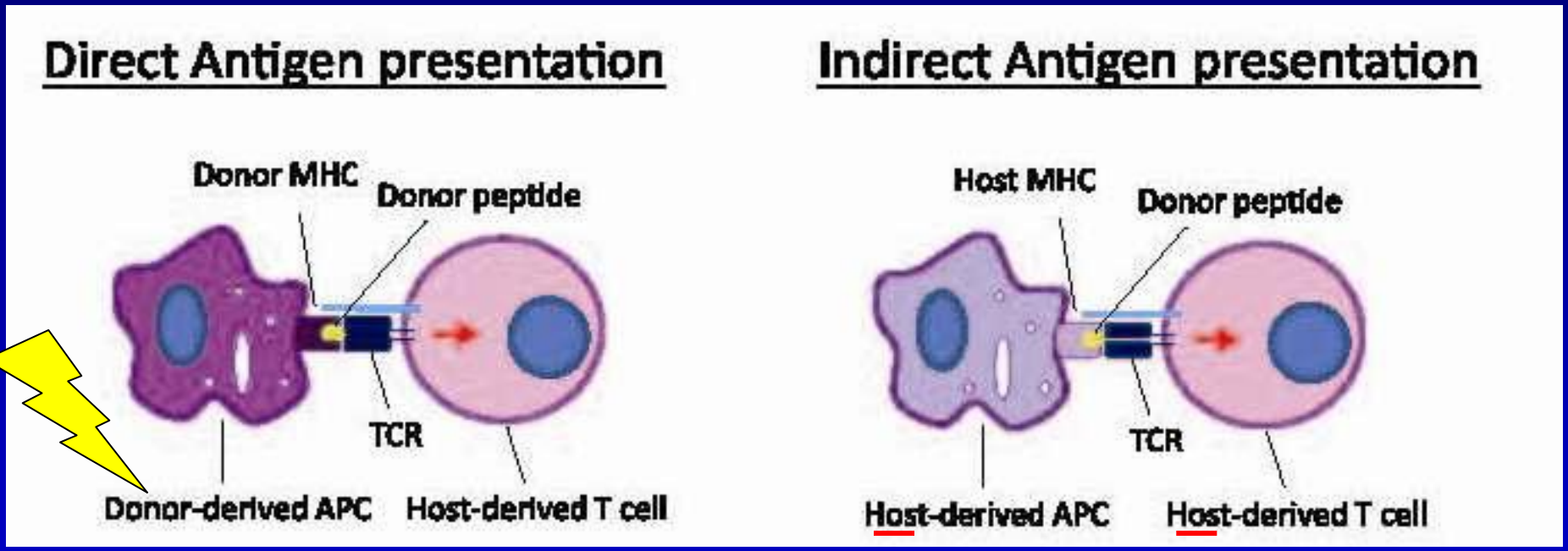
PI Platelets: The Similarities

Some loss of platelets through process (small; manageable)

UV light ➔ *Identifiable platelet damage*
- Increased metabolic rate
- Increased activation during storage
- Reduced recovery
- Reduced survival

Interaction with leukocytes' DNA ➔
- Reduction in alloimmunization
- Consideration of replacement of γ-irradiation

Prevention of Alloimmunization



MECHANISM INHIBITED BY PHOTINACTIVATED PI

MECHANISM *NOT* INHIBITED BY PHOTINACTIVATED PI

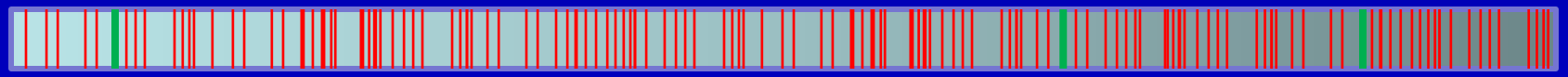
Marschner S *et al. Transfusion* 2010;50:2489-98.

Prevention of Graft versus Host Disease

Adducts:

Amotosalen + UV	1/83 base pairs
Gamma irradiation	1/37,000 base pairs

Prevention of GvHD in murine model
Inhibition of APC function
Inhibition of cytokine production



R Dodd *Vox Sang* 2002;83(Suppl 1):267-70.
Osselaer JC et al. Blood 2007;110:849a.

PI Platelets: Concerns

SPRINT Trial (FDA)

Respiratory distress: **5** test vs. 0 control (n=671)

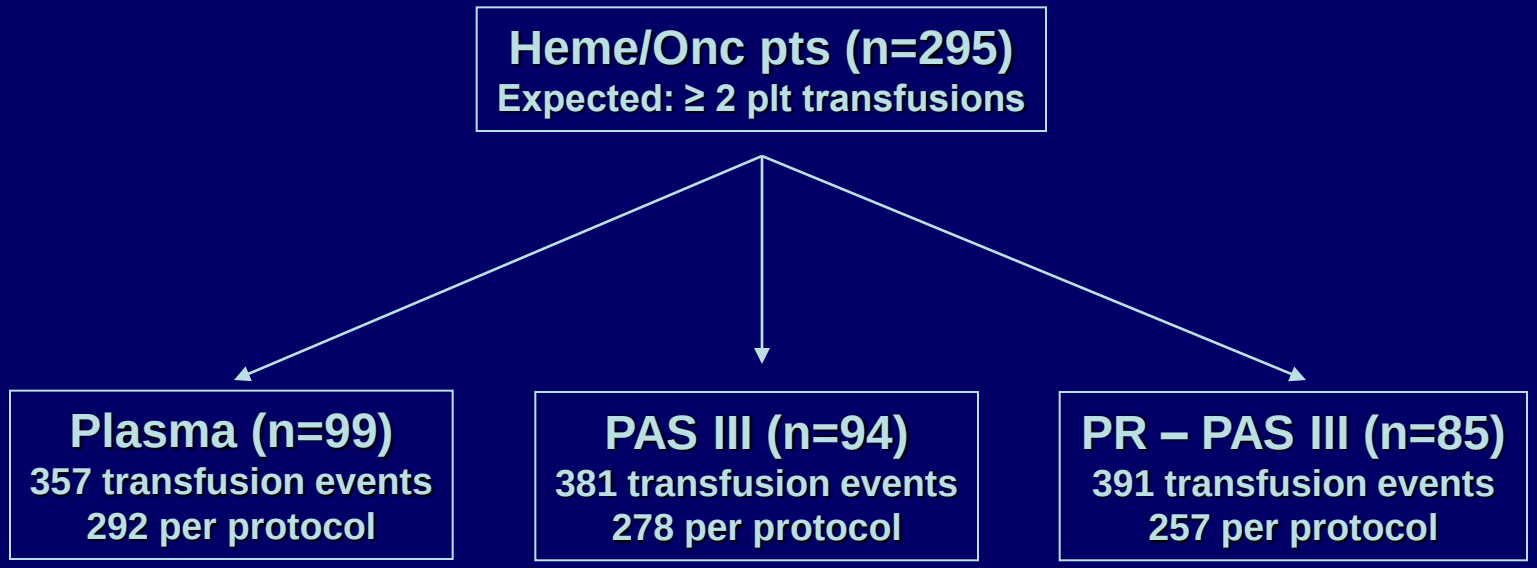
Independent, blinded review of all (148) pulmonary events

➔ No association with PI platelets

Corash L *et al. Blood* 2011;117:1014-20.

PI Platelets: Concerns

HOVON Trial



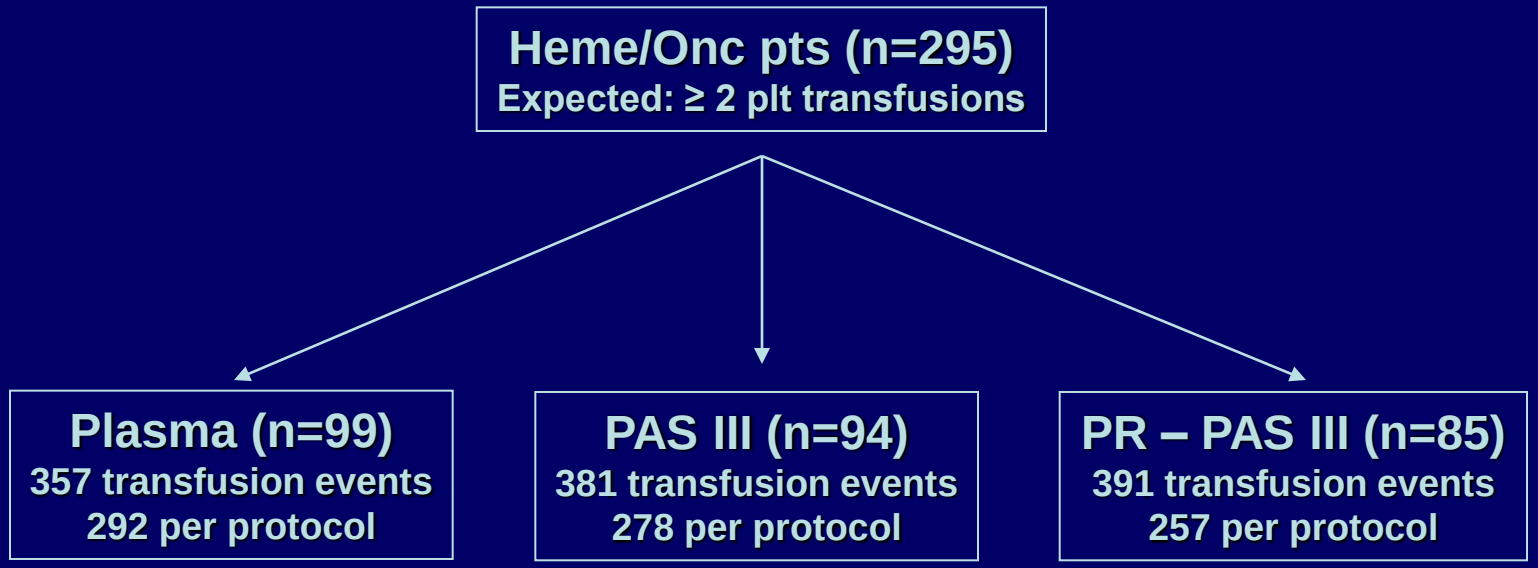
Primary endpoint: CCI_{1hr}

Secondary endpoints: CCI_{24hr}, bleeding, transfusion needs and intervals, reactions

Kerkoffs J-LH *et al. BJH* 2010150:209-17.

PI Platelets: Concerns

HOVON Trial



SPONTANEOUSLY REPORTED; UNBLINDED TRIAL

Primary endpoint: CCI_{1hr}

Secondary endpoints: CCI_{24hr}, bleeding, transfusion needs and intervals, reactions

Kerkoffs J-LH *et al. BJH* 2010150:209-17.

PI Platelets: Concerns

Maximum grade of bleeding (%)

	Plasma	PAS III	PR – PAS III
Grade 1	12%	11%	19%
Grade 2	6%	4%	7%
Grade 3	1%	0	6%

APPROPRIATE TO COMBINE?

Kerkoffs J-LH *et al. BJH* 2010.

VoxSanguinis
The International Journal of Transfusion Medicine
ISBT International Society of Blood Transfusion
Vox Sanguinis (2012)

ORIGINAL PAPER

DOI: 10.1111/j.1423-0410.2012.01614.x

Therapeutic efficacy of platelet components treated with amotosalen and ultraviolet A pathogen inactivation method: results of a meta-analysis of randomized controlled trials

J. Cid, G. Escolar & M. Lozano

Department of Hemotherapy and Hemostasis, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Hospital Clínic, University of Barcelona, Barcelona, Spain

VoxSanguinis
The International Journal of Transfusion Medicine
ISBT International Society of Blood Transfusion
Vox Sanguinis (2012) **102**, 302–316

ORIGINAL PAPER

DOI: 10.1111/j.1423-0410.2011.01555.x

Meta-analysis of the studies of bleeding complications of platelets pathogen-reduced with the Intercept system

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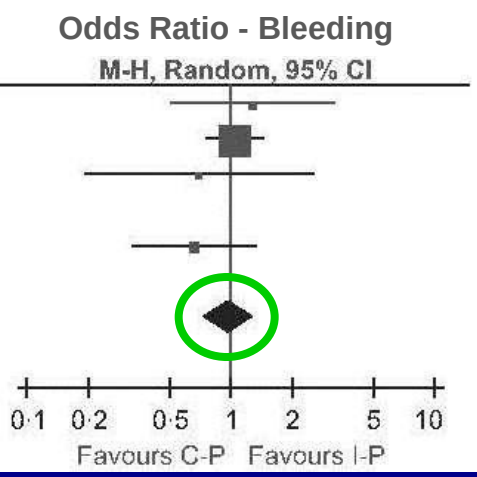
Department of Pathology and Laboratory Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, USA

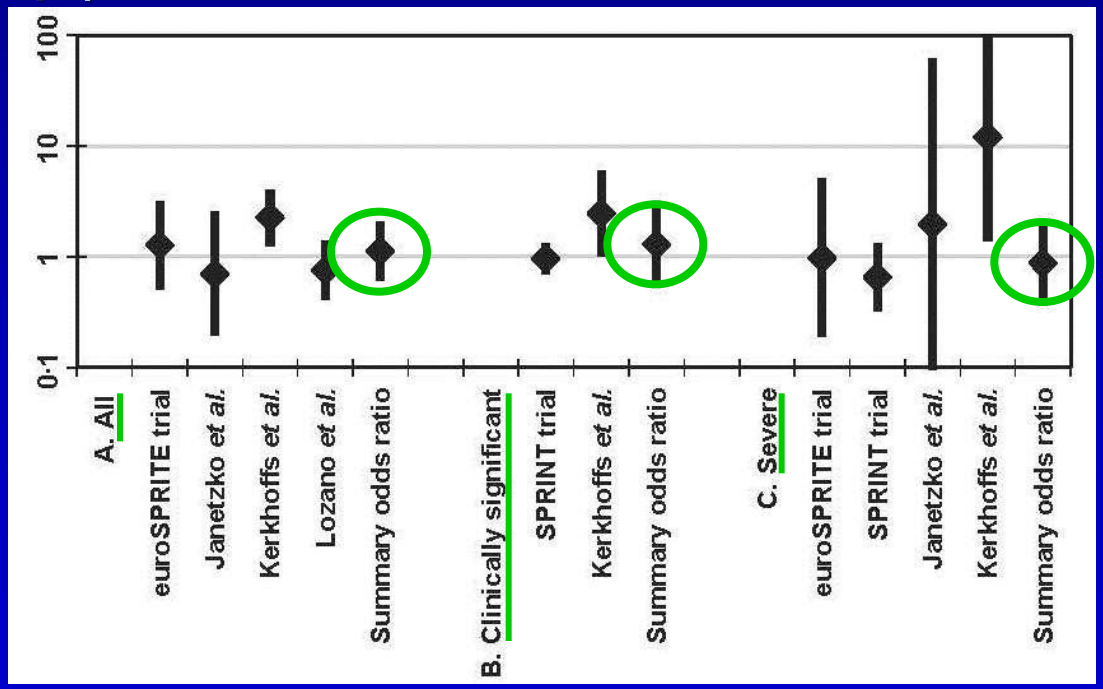
Study or Subgroup	I-P Events	I-P Total	C-P Events	C-P Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
EuroSPRITE[17]	41	52	38	51	8·4%	1·28 [0·51, 3·19]	2003
SPRINT[18]	186	318	188	327	72·4%	1·04 [0·76, 1·42]	2004
Janetzko[19]	14	22	15	21	4·3%	0·70 [0·19, 2·53]	2005
Kerkhoffs[20]	27	85	14	94	0·0%	2·66 [1·28, 5·51]	2010
Lozano[21]	17	105	24	106	14·9%	0·66 [0·33, 1·32]	2011
Total (95% CI)		497		505	100·0%	0·97 [0·75, 1·27]	
Total events	258		265				

Heterogeneity: $Tau^2 = 0·00$; $Chi^2 = 1·98$, df = 3 (P = 0·58); $I^2 = 0\%$

Test for overall effect: Z = 0·20 (P = 0·84)



… (Intercept) was not associated with differences in bleeding



Treatment with Intercept may increase the risk of all and clinically significant (albeit not severe) bleeding complications.

Bacterial Reduction by Antimicrobial Peptides

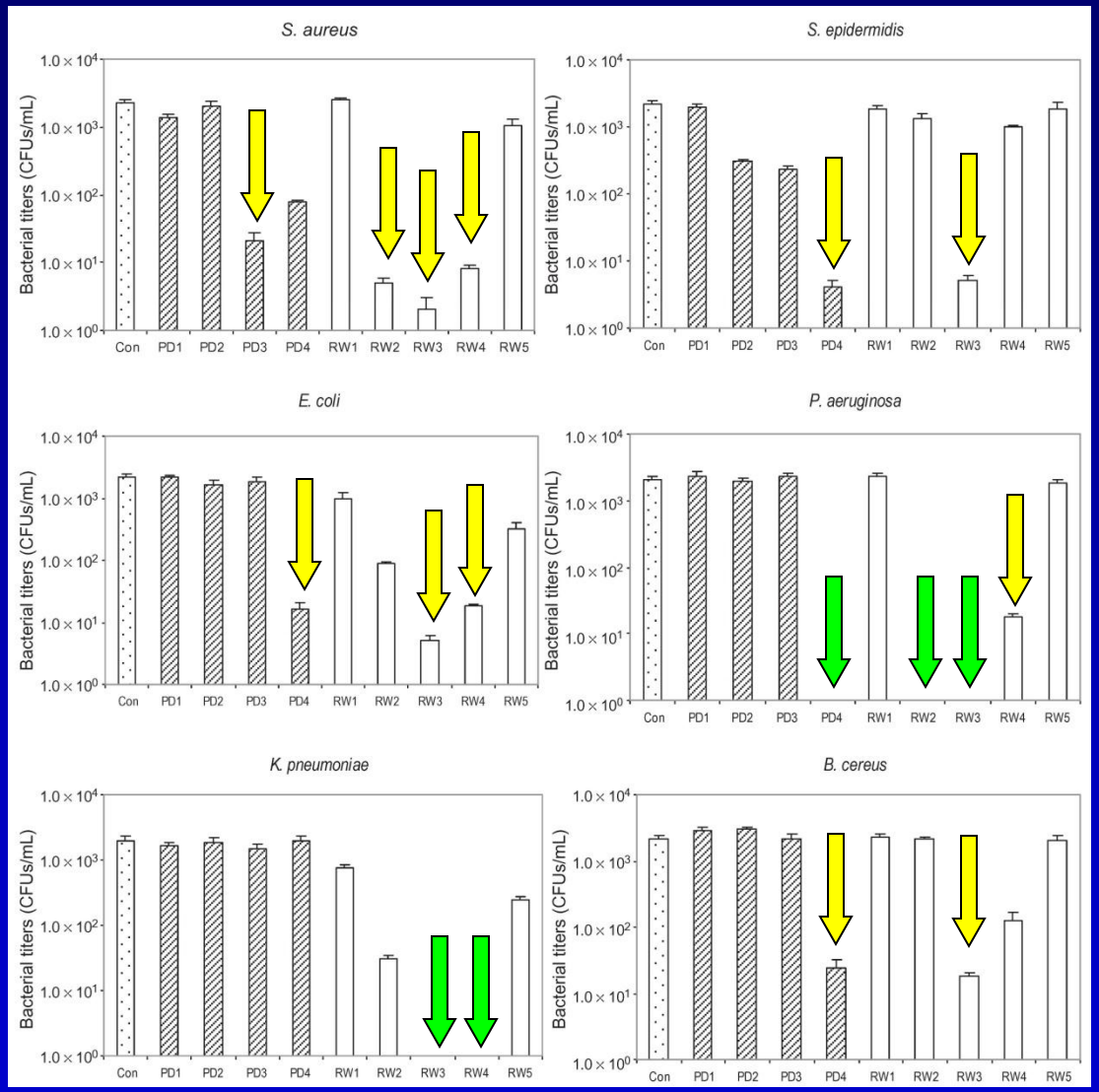
Antimicrobial Peptides Studied

Peptide type	Peptides	Sequence
PMP-derived peptides	PD1	^{1}SDDPKESEGDLHCVC^{15}
	PD2	^{13}CVCVKTTSLVRPRHI^{27}
	PD3	^{49}KNGRKLCLDLQAALY^{63}
	PD4	^{60}AALYKKKIIKKLLES^{74}
RW series peptides	RW1	RW
	RW2	RWRW
	RW3	RWRWRW
	RW4	RWRWRWRW
	RW5	RWRWRWRWRW

* Peptides PD1-4 are PLT microbicidal protein (PMP)-derived peptides and superscript numbers on each peptide sequence indicate amino acid position on the PMP sequence.

Mohan KVK *et al. Transfusion* 2010;50:166-73.

Bacterial Reduction by Antimicrobial Peptides



Mohan KVK *et al. Transfusion* 2010;50:166-73.

“If someone says it’s not about the money, it’s about money!”

Intercept Platelet conversion experience - Strasbourg

Kit cost: 75€/apheresis unit
Personnel time: 3€

Costs avoided:
Bacterial detection: 30€
Per new test: 10€

For France: Cost neutral with apheresis proportion 85% ➔ 55%

Cazenave JP *et al. Vox Sang* 2007; 93(suppl 1):51-2.

Reduction of Economic Impact

TREATED APHERESIS PLATELET

TREATED APHERESIS PLATELET

WHOLE BLOOD

Plt

Plt Plt

DOUBLE POOL

TREATED POOLED PLTS

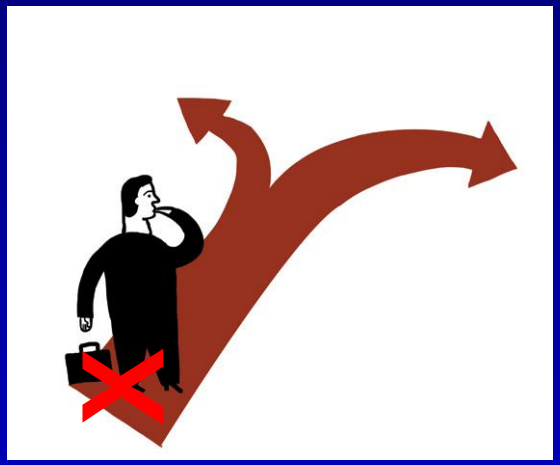
TREATED POOLED PLTS

Pathogen Inactivation Technologies

An opportunity to improve patient safety
and
simplify blood banking.

Beating the Bugs

Exploring Options to Improve Platelet Transfusions



When you come to a fork in the road, take it.

Are *you* satisfied yet?