Mitigating the Risk of Bacterial Contamination of Platelets - Recent Developments

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Disclosures

Grants	bioMerieux Charles River Labs Fenwal Gambro Genprime Hemosystem Immunetics Pall Verax
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Advisory Board	Verax
Scientific Advisor (uncompensated)	BioSense Technologies Lynntech, Inc. Blood Systems Inc.
Other	Member of the Bacterial Contamination Task Force of AABB Member of the Bacterial Contamination Task Force of International Society for Blood Transfusion

Mitigating the Risk of Bacterial Contamination of Platelets - Recent Developments

The latest developments and the recommendations in the FDA Final Guidance published September 2019 will be reviewed. This new guidance will define how blood collection centers and hospital blood banks and transfusion services will need to operate moving forward.

Objectives:

- Characterize the extent and nature of this risk
- Review FDA Final guidance and the options for addressing this risk and their implications
- Review the role of rapid testing in satisfying guidance
- Present data on recent advances in rapid testing technology for bacteria in platelets

Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion. *Guidance for Industry*. *September 2019*
https://www.fda.gov/media/123448/download

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Bacterial Contamination of Platelets (BCP) in the US

- BCP is a major problem due to room temperature storage
- Primary culture of apheresis collections was introduced in 2004
- Numerous studies show apheresis BCP of 300-400 per million **primary culture negative** units at time of use or outdate
- This extrapolates to **500-700 apheresis BCP** transfused per year in the US (based on current annual pathogen reduction use on 250,000 units)
- Septic reactions and fatalities from BCP continue to be reported

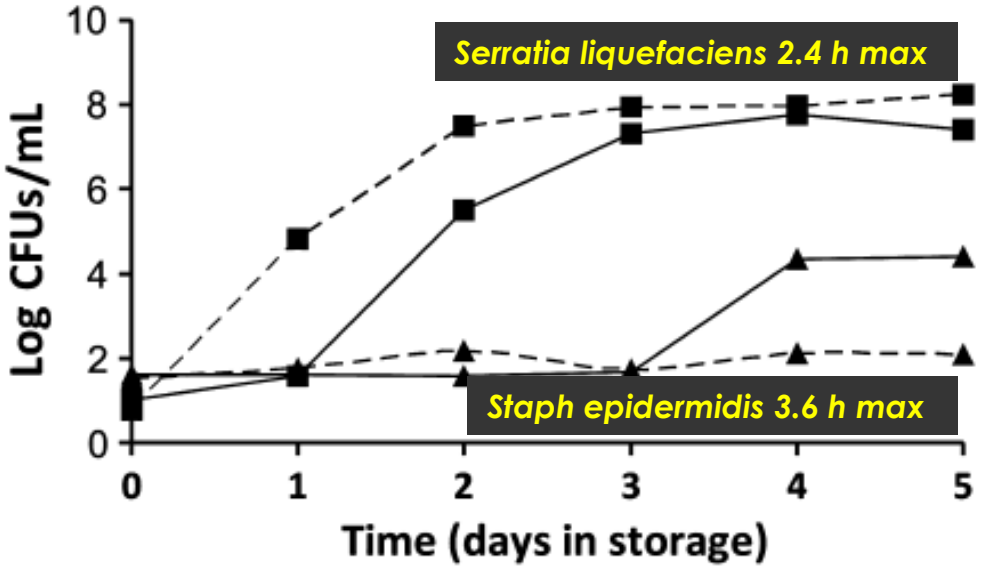


Fig. 3. Growth of *S. liquefaciens* (■) and *S. epidermidis* (▲) in either PLT-poor plasma (—) or PAS containing 30% plasma (– – –). Means ± SD of three independent experiments are shown.

Greco, et al. *Transfusion* 2010, Nov;50(11):2344-52

Jacobs MR. BPAC Presentation, July 18, 2018 Downloads/BPAC-Transcript-071818%20(1).pdf
Fatalities Reported to FDA Following Blood Collection and Transfusion Annual Summary for FY2017
https://www.fda.gov/vaccines-blood-biologics/report-problem-center-biologics-evaluation-research/transfusiondonation-fatalities

Recent US CDC National Healthcare Safety Network Hemovigilance and FDA Data

- CDC NHSN Hemovigilance **2010-2016**
  - Included 195 institutions with surveillance of 1.54 million platelet transfusions
  - Report documented 30 septic reactions to platelets - 14 severe, 5 life-threatening and 3 fatal
  - 26 were associated with apheresis and 4 with WBD platelets

- FDA annual reports of transfusion associated fatalities **2013-2017**
  - Bacterially contaminated platelets accounted for 10 fatalities
  - 9 were associated with apheresis and 1 with WBD platelets

Haass KA et al. Transfusion Medicine Reviews 2019, 33:84-91 https://doi.org/10.1016/j.tmrv.2019.01.001
Fatalities Reported to FDA Following Blood Collection and Transfusion Annual Summary for FY2017
https://www.fda.gov/vaccines-blood-biologics/report-problem-center-biologics-evaluation-research/transfusiondonation-fatalities

Active surveillance for Bacterial Contamination of Platelets, University Hospitals Cleveland, 1991-2013:

Detection of septic reactions 10-fold lower by passive surveillance

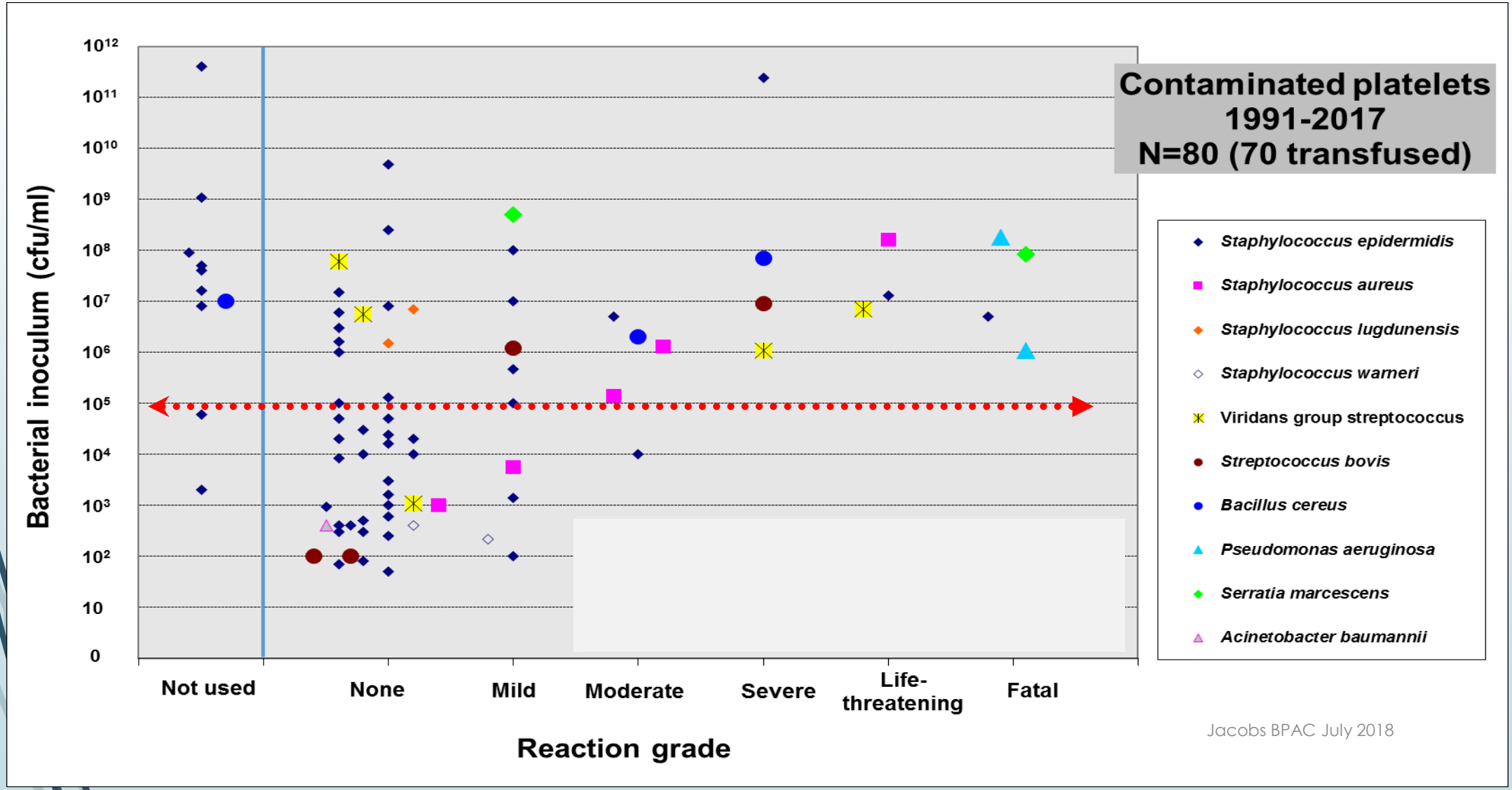
Period	1991-2006 (1)			2007-2013 (2)
Surveillance	**Active (n=102,998)**	**Passive (n=135,885)**	**Odds Ratio (95% C.I.)**	**Active (n=51,440)**
Bacterial contamination	50 485/mill	2 15/mill	32.0 (8.0-135.0)	20 389/mill
Sepsis	16 155/mill	2 15/mill	10.6 (2.4-45.9)	5* 97/mill
Death	1 10/mill	1 7/mill	1.3 (0.01-21.1)	1* 19/mill

*None detected by passive surveillance

1. Jacobs MR, Yomtovian R CID 2008; 46:1217

2. Hong H et al. Blood 2016, 127(4):496-502

Transfusion reactions are associated with platelets contaminated with bacterial loads of >10^5 cfu/mL



Jacobs BPAC July 2018

Current methods to limit BCP

- Collection: Enhanced skin prep, diversion of first part of collection
- Prepooling of WBD units
- Primary culture of apheresis collections and prepooled WBD units
- Secondary testing of apheresis and prepooled WBD units by rapid test or culture
- Pathogen reduction

Recent fatal transfusion reactions 2017

Morbidity and Mortality Weekly Report

Fatal Sepsis Associated with Bacterial Contamination of Platelets — Utah and California, August 2017

Roberta Z. Horth, PhD[1,2,3]; Jefferson M. Jones, MD[4]; Janice J. Kim, MD[5]; Bert K. Lopansri, MD[6]; Sarah J. Ilstrup, MD[6]; Joy Fridey, MD[7]; Walter E. Kelley, DO[8]; Susan L. Stramer, PhD[9]; Ashok Nambiar, MD[10]; Lynn Ramirez-Avila, MD[10]; Amy Nichols, MBA[10]; Wendy Garcia[11]; Kelly F. Oakeson, PhD[12]; Nicholas Vlachos, MS[4]; Gillian McAllister[4]; Robert Hunter, MS[5]; Allyn K. Nakashima, MD[3]; Sridhar V. Basavaraju, MD[4]

- During August 2017, two separate clusters of platelet transfusion–associated bacterial sepsis were reported in Utah and California.
- In Utah, **two patients died** after platelet transfusions from the same donation.
- ***Clostridium perfringens*** isolates from one patient's blood, the other patient's platelet bag, and donor skin swabs were highly related by whole genome sequencing
- In California, **one patient died** after a platelet transfusion contaminated with ***Klebsiella pneumoniae***

MMWR / June 29, 2018 / Vol. 67 / No. 25 / p 718-722

Four severe septic reactions from three apheresis platelet collections 2018

- Platelets were apheresis units collected and manufactured by different facilities, staff, and equipment
- Platelet units included one **pathogen reduced** unit (with negative co-component), one **apheresis** unit (with negative co-component) and two **apheresis** units from the same collection
- Interventions to mitigate risk of contamination included primary culture, pathogen reduction and rapid testing
- ***Acinetobacter baumannii*** isolated from all 4 patients, ***Staphylococcus saprophyticus*** from 2 patients
- All 4 patients developed severe septic reactions, with one being fatal
- ***Acinetobacter baumannii*** cultured from Blood Bank environment in one case
- CDC investigation suggests a common (but unknown) source of both organisms

Jones, SA, Jones JM, et al. Sepsis attributed to bacterial contamination of platelets associated with a potential common source – Multiple states. MMWR, July 14, 2019. 519-523

What has this experience taught us?

- **Bacterial contamination** is real and continues to the present; additional measures are needed to address this
- **Active bacterial surveillance** by culture of platelets at time of issue is the key to understanding the extent of the problem and **the effect of interventions**
- **Primary culture** was effective in removing many of the fastest-growing, most virulent bacterial species but not in eliminating septic reactions and fatalities
- **Recognition and reporting of septic reactions is poor**, so **assessment of the value of interventions based on septic reaction reports is of limited value**
- **Clinical features of septic reactions changed after introduction of primary culture:** frequently delayed, less severe and more difficult to differentiate from other transfusion reactions

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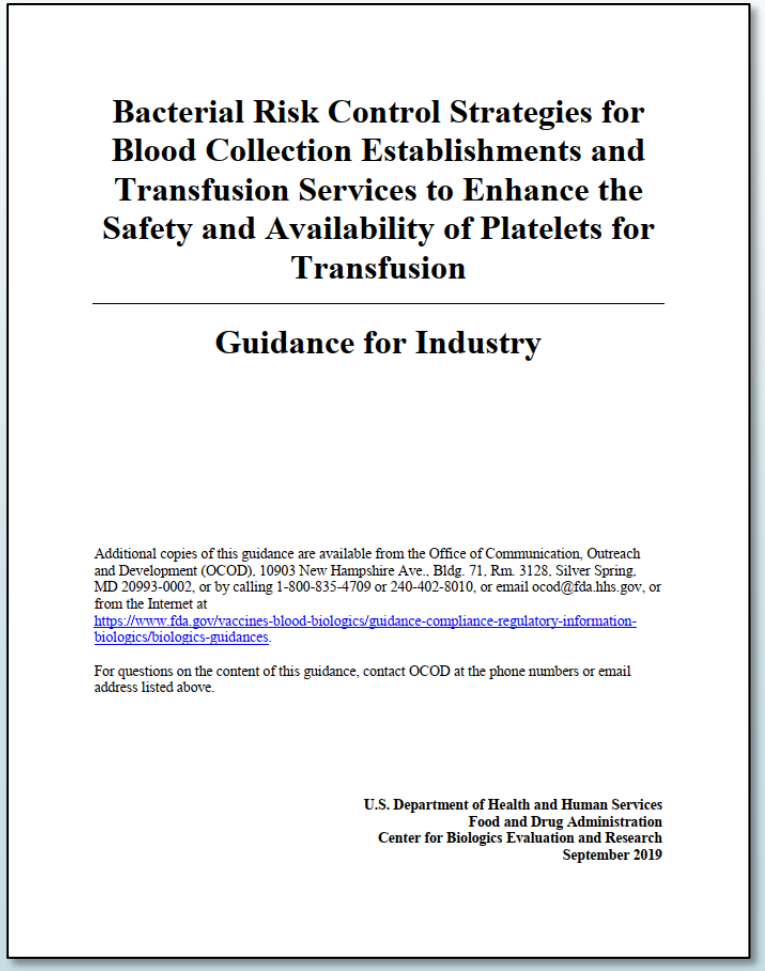
- Review the role of rapid testing in satisfying guidance
- Present data on recent advances in rapid testing technology for bacteria in platelets

Final Guidance has been published by the FDA

Published September 30, 2019

- 18 month recommended compliance period (by March 2021)
- Applies to all blood collection establishments and transfusion services
- Makes numerous recommendations
- Must use FDA-cleared or approved products in order to comply
- Use of these products must be consistent with their instructions for use



Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion

Guidance for Industry

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-8010, or email ocod@fda.hhs.gov, or from the Internet at https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances.

For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
September 2019

Guidance overview

Key FDA clarifications in the guidance

- Products may ship during recommended culture incubations provided that control of the product is maintained during the incubation period

and

- Platelets that have been identified as bacterially contaminated may not be released for transfusion

Guidance Appendix A

APPENDIX A: BACTERIAL RISK CONTROL STRATEGIES ASSOCIATED WITH SPECIFIC PLATELET STORAGE DURATION AND TYPE OF PLATELET UNIT

Storage duration	Types of Units: Apheresis	Pre-storage pools of WBD platelets	Single units of WBD platelets	Post-storage pools of WBD
5 days	LVDS ≥ 36 hours	LVDS ≥ 36 hours	Rapid testing	Rapid testing
	Pathogen reduction	Primary culture ≥ 24 hours + secondary culture ≥ day 3	Primary culture ≥ 24 hours	
	Primary culture ≥ 24 hours + secondary culture ≥ day 3	Primary culture ≥ 24 hours + secondary rapid testing	Primary culture ≥ 36 hours	
	Primary culture ≥ 24 hours + secondary rapid testing			
7 days	LVDS ≥ 48 hours	N/A	N/A	N/A
	LVDS ≥ 36 hours + secondary rapid testing			
	LVDS ≥ 36 hours + secondary culture ≥ day 4			
	Primary culture ≥ 24 hours + secondary culture ≥ day 4			
	Primary culture ≥ 24 hours + secondary rapid testing			

LVDS=large volume (16 mL), delayed sampling

Guidance Appendix B

APPENDIX B: SUMMARY OF BACTERIAL RISK CONTROL STRATEGIES FOR APHERESIS AND PRE-STORAGE POOLS OF WBD DERIVED PLATELETS

Strategy		Applicable Components[1]	Time Performed	Volume Sampled[2]	Product to be Sampled	Growth Conditions	Recommended Incubation Period	Expiry
Single-step Strategies								
LVDS ≥36 hours		Apheresis and pre-storage pools	No sooner than 36 hours from the time of collection	≥16 mL total	Each apheresis split unit or pre-storage pool	Aerobic and anaerobic	Minimum of 12 hours	Day 5[3]
LVDS ≥48 hours		Apheresis	No sooner than 48 hours from the time of collection	≥16 mL total	Each apheresis split unit	Aerobic and anaerobic	Minimum of 12 hours	Day 7[4]
Pathogen Reduction		Per device instructions for use	Per device instructions for use	N/A	Per device instructions for use	N/A	N/A	Per device instructions for use
Two-step Strategies								
Step 1	**Primary culture ≥24 hours**	Apheresis and pre-storage pools	No sooner than 24 hours from time of collection	≥ 16 mL total	Main collection ("mother bag"), each apheresis split unit, or pre-storage pool	Aerobic and anaerobic	Minimum of 12 hours	See note[5]
	or							
	LVDS ≥36 hours	Apheresis and pre-storage pools	No sooner than 36 hours from the time of collection	≥16 mL total	Each apheresis split unit or pre-storage pool	Aerobic and anaerobic	Minimum of 12 hours	Day 5[6]
and								
Step 2	**Secondary culture**	Apheresis and pre-storage pools	No sooner than day 3	≥8 mL	Each split unit or pre-storage pool	At least aerobic	Establish a minimum incubation time period in SOPs	Day 5
	or							
		Apheresis	No sooner than day 4	≥16mL total	Each split unit	Aerobic and anaerobic	Minimum of 12 hours	Day 7[7]
	or							
	Secondary rapid testing	Apheresis and pre-storage pools	Per device instructions for use	Per device instructions for use	Each apheresis split unit or pre-storage pool	N/A	N/A	Per device instructions for use (up to day 7[8])

[1] This table applies only to apheresis platelets and pre-storage pools of whole blood derived (WBD) platelets. For post-storage pooled products and single units of WBD platelets, see section III.C. and Appendix C of the guidance.
[2] When aerobic and anaerobic cultures are performed, sampled volumes should be split evenly between aerobic and anaerobic culture bottles.
[3] The storage of platelets tested by LVDS no sooner than 36 hours may be extended by secondary testing methods. See Step 1 of 'Two-step strategies', and footnote 4 of Appendix B.
[4] Platelets may only be stored beyond day 5 and up to day 7 if each component is tested using a bacterial detection device cleared by FDA and labeled for use as a "safety measure" according to its instructions for use, and if the platelet storage container has been cleared or approved for 7-day storage.
[5] Following primary culture performed no sooner than 24 hours, apheresis and pre-storage pooled platelet components should not be transfused after day 3 unless appropriate secondary testing (culture or rapid testing) has been performed to assure that the risk of bacterial contamination has been adequately controlled. See section III.B.2 of the guidance for additional details.
[6] The storage of platelets tested by LVDS no sooner than 36 hours may be extended by secondary testing methods. See footnote 4 of Appendix B.
[7] See footnote 4 of Appendix B.
[8] See footnote 4 of Appendix B.

Guidance Appendix C

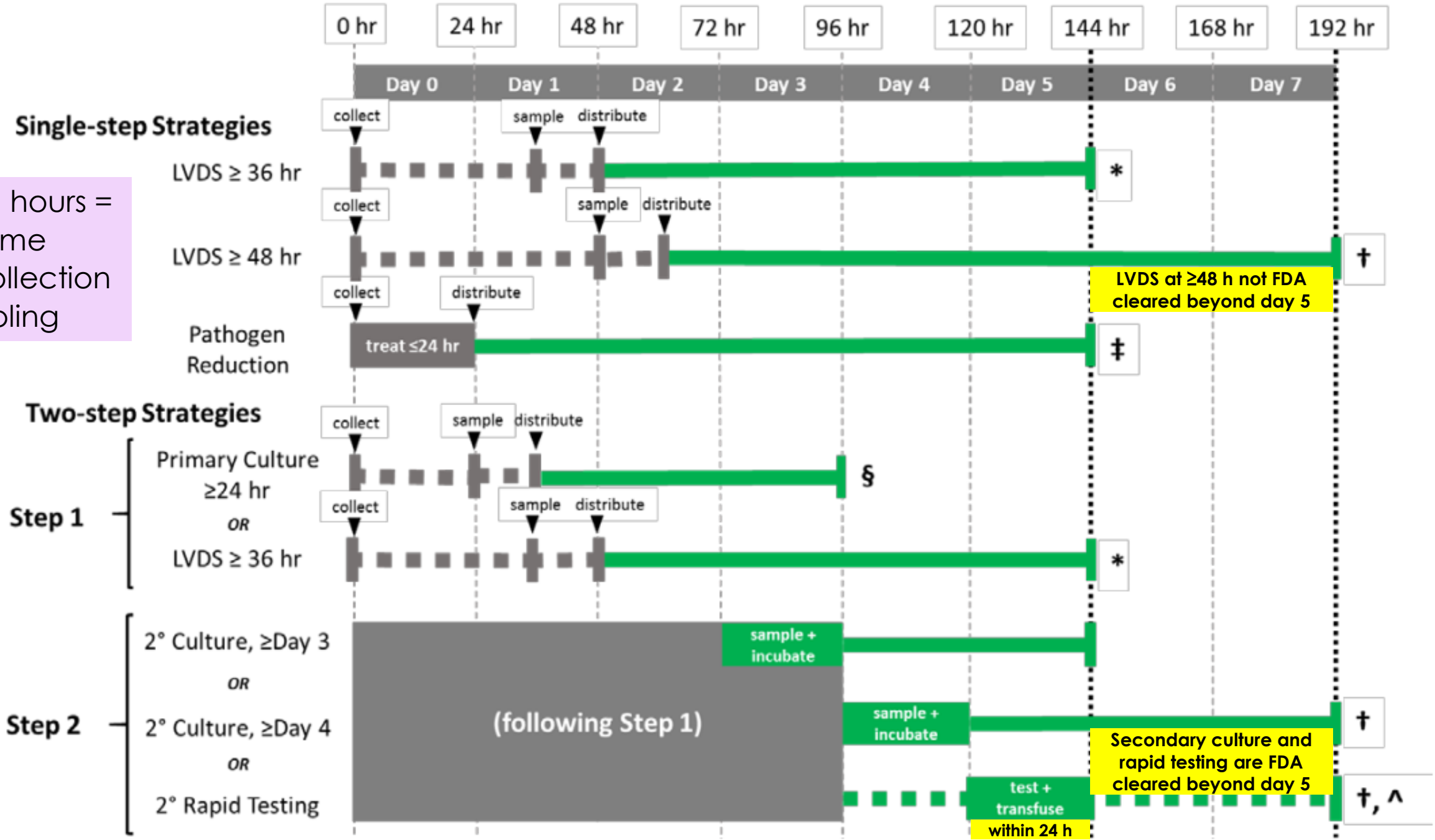
APPENDIX C: SUMMARY OF BACTERIAL RISK CONTROL STRATEGIES FOR SINGLE UNIT WBD PLATELETS AND POST-STORAGE POOLS OF WBD PLATELETS

Strategy	Applicable Components	Time Performed	Volume Sampled	Growth Conditions	Recommended Incubation Period	Expiry
Single-step Strategies						
Rapid testing	Single unit or post-storage pool	Per device instructions for use	Per device instructions for use	N/A	N/A	Per device instructions for use (up to day 5)[1]
Single culture	Single unit	No sooner than 36 hours from time of collection **or** No sooner than 24 hours from time of collection	Largest practical volume within the range permitted by the device instructions for use	At least aerobic	Minimum of 12 hours	Day 5[2]

[1] Based on currently available storage systems, storage of these products is limited to 5 days.
[2] Following primary culture performed no sooner than 24 hours, for transfusion after day 3 of storage, secondary rapid testing may be considered.

APPENDIX D: EXAMPLE TIMELINES OF BACTERIAL RISK CONTROL STRATEGIES FOR APHERESIS PLATELETS

Times in hours = exact time after collection or sampling



Current methods

	Time after collection (hours)	Incubation time before release (hours)	Shelf life (days)	FDA status
Current practices under AABB standard and FDA regulations				
Apheresis and pre-storage pooled WBD: Culture at ≥24 h after collection of 8 mL in an aerobic bottle per apheresis **collection** or whole-blood derived **pool**	≥24	~12	5	Cleared
Secondary testing of apheresis platelet **units** in plasma with FDA cleared Safety Measure rapid test within 24 hours of transfusion **OR** Culture of apheresis **units** on day 4 or later in both aerobic and anaerobic bottles with 8-10 mL per bottle	NA ≥Day 4	NA Not specified	Up to 7	Cleared with Safety Measure for BacT/ALERT and PGD test
Rapid test on single unit WBD or post storage WBD pools within 4 hours of transfusion	NA	NA	5	Cleared
Pathogen reduction of apheresis **units** performed within 24 h of collection	≤24	NA	5	Cleared

Summary of new FDA guidance

Specific timing definitions: Times in hours = exact time after collection or sampling Times in days = any time on day specified	Time after collection (hours)	Incubation time before release (hours)	Shelf life (days)	FDA status
Final Guidance: 1 Single-step strategies				
a Culture at ≥36 h after collection of 16 mL (8 mL in an aerobic bottle and 8 mL in an anaerobic bottle) per split apheresis **unit** or whole-blood derived **pool**	≥36	≥12	5	Cleared
b Culture at ≥48 h after collection of 16 mL (8 mL in an aerobic bottle and 8 mL in an anaerobic bottle) per split apheresis **unit**	≥48	≥12	7	Needs "safety measure" label for 7d*
c Pathogen reduction of apheresis **units** performed within 24 h of collection	≤24	NA	5	Cleared
Final Guidance: 2 Two-step strategies				
Step 1: Culture at ≥24 h after collection of 16 mL (8 mL in an aerobic and 8 mL in an anaerobic bottle) per apheresis **collection** (mother bag), apheresis split **unit** or whole-blood derived pool **OR** Culture as in 1a above (≥36 h with 16 mL cultured)	≥24 ≥36	≥12	3* 5*	Cleared
Step 2: To extend Step 1 shelf life, three options are available:				
a Secondary culture of each unit of 8 mL in aerobic bottle on **≥Day 3**		Set by user	5	Cleared
b Secondary culture of each unit of 16 mL as in step 1a on **≥Day 4**		≥12	7	Cleared
c Rapid testing of each unit within 24 hours of transfusion **≥Day 3** - device with Safety Measure claim allows 7 day dating of apheresis platelets in plasma		NA	5 or 7	Cleared for 5 d with BacTx and for 7 d with Safety Measure for PGD test

***Culture of 25,000-50,000 apheresis units at time of use or at outdate is needed to determine the performance of this method (Jacobs MR, BPAC presentation 2018)**

Implications for blood centers and hospitals?

Three technology choices

- **Culture**
  - LVDS for 5 or 7 Day dating of apheresis platelets in plasma – not yet FDA cleared for 7 d
  - Secondary culture for 5 day dating of apheresis platelets or pre storage pools
  - Secondary culture for 7 day dating of apheresis platelets
  - Single WBDs for 5 day dating
- **Pathogen Reduction for 5 day dating**
  - Applies to leukoreduced apheresis platelets in PAS or plasma
- **Rapid Testing for 5 or 7 day dating**
  - Applies to leukoreduced apheresis in plasma (LRAPs) for 7 day dating or LRAPs in plasma or PAS, pre-storage pooled WBDs for 5 day dating and single units and post storage pools of WBDs

Large Volume Delayed Sampling (LVDS)

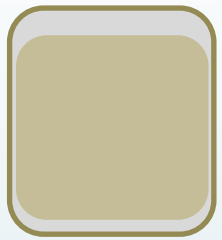
Increased sample size and delayed platelet release

Current Practice

Aerobic 8 mL from Mother Bag at 24 Hours

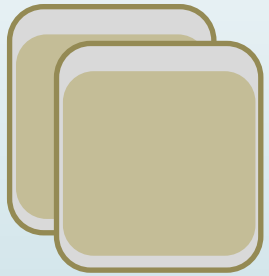
On collection of any size

Single

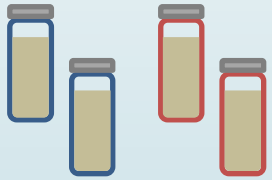


Aerobic and Anaerobic 8 mL sample in each

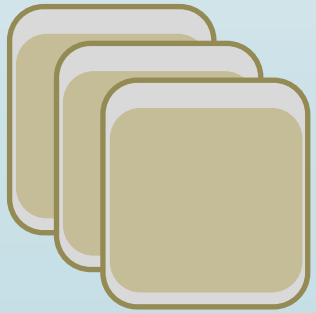
Double



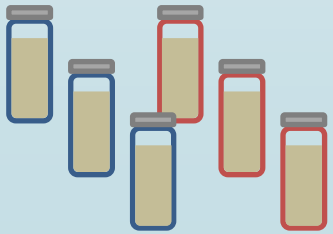
Aerobic and Anaerobic 8 mL sample in each



Triple



Aerobic and Anaerobic 8 mL sample in each



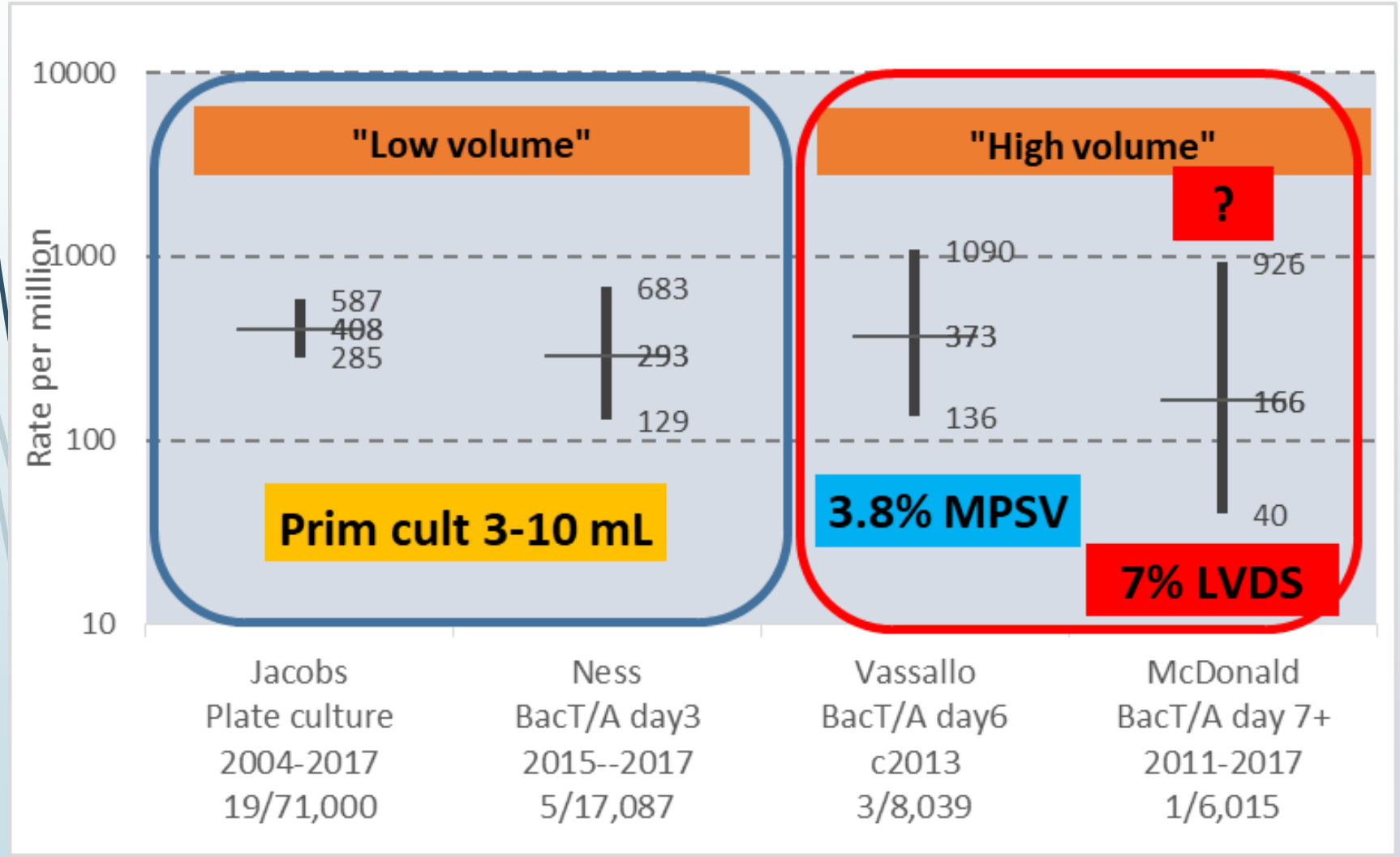
- Take sample 36-48 hours after collection from each bag in the collection
- 16 mL for a single
- 32 mL for a double
- 48 mL for a triple
- Inoculate Aerobic & Anaerobic bottles
- 12 hour minimum incubation
- Monitor until expiration (up to Day 7)

Large Volume Delayed Sampling

- Significant cost and platelet availability implications:
  - Reduced split collection rates due to larger sample size
  - Cost of additional cultures in bottles, hardware and labor
  - Need for additional collections / recruiting to offset split rate impact
- Nine secondary culture or testing studies of apheresis contaminants missed by primary culture showed contamination rates that were 1) not statistically significantly different and 2) independent of volume cultured, time of testing and test method

Jacobs MR, BPAC presentation 2018

Increasing volume and delaying testing of apheresis units does NOT decrease residual contamination rate



No statistically significant differences between MPSV, LVDS* and current primary culture

*Culture of 25,000-50,000 apheresis units at time of use or at outdate is needed to determine the performance of this method (Jacobs MR, BPAC presentation 2018)

Secondary culture for 5 or 7 day dating

- Significant cost and logistics implications:
  - Quarantine time and logistics of returning to BCs for retesting
  - Cost of additional cultures in bottles, hardware and labor
  - Not all units may qualify for 7 day option given large sample volume required
  - Lower cost than pathogen reduction

	Primary culture*	Pathogen reduction	Primary culture* + secondary rapid test	Primary culture + secondary culture*
Total cost per transfused unit**	$719.48	$914.53	$728.65	$738.50
Increase in cost per unit		+$195.05	+$9.17	+$19.02

*Primary and secondary cultures using aerobic bottles only in these calculations
**Includes costs of platelet unit, secondary testing, administration, complications and expired units

Kacker S, Bloch EM, Ness PM, Gehrie EA, Marshall CE, Lokhandwala PM, Tobian AAR. Financial impact of alternative approaches to reduce bacterial contamination of platelet transfusions. Transfusion. 2019 Apr; 59(4):1291-1299. Epub 2019 Jan 8.

Pathogen Reduction

Apheresis platelets for 5 day dating

- FDA cleared treatment sets available for singles and doubles but not triples
- Not FDA cleared for pre-storage pools, single WBDs or post storage WBD pools
- No holding period or incubation delays before use
- Significant cost and platelet availability implications:
  - Reduced split collection rates due to reduced processing yield
  - Need for additional collections / recruiting to offset split rate impact
  - Cost estimated to be around $200 more than testing an apheresis unit with PGD rapid test for 7 Day dating*

*Li JW et al. Transfusion 2017, 57:2321
Kacker S et al. Transfusion. 2019 59:1291

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Summary of new FDA guidance: Culture of apheresis collection at 24h plus rapid test

Specific timing definitions: Times in hours = exact time after collection or sampling Times in days = any time on day specified	Time after collection (hours)	Incubation time before release (hours)	Shelf life (days)	FDA status
Final Guidance: 1 Single-step strategies				
a Culture at ≥36 h after collection of 16 mL (8 mL in an aerobic bottle and 8 mL in an anaerobic bottle) per split apheresis **unit** or whole-blood derived **pool**	≥36	≥12	5	Cleared
b Culture at ≥48 h after collection of 16 mL (8 mL in an aerobic bottle and 8 mL in an anaerobic bottle) per split apheresis **unit**	≥48	≥12	5 7	Cleared for 5 d Needs "safety measure" label for 7d
c Pathogen reduction of apheresis **units** performed within 24 h of collection	≤24	NA	5	Cleared
Final Guidance: 2 Two-step strategies				
Step 1: Culture at ≥24 h after collection of 16 mL (8 mL in an aerobic and 8 mL in an anaerobic bottle) per apheresis **collection** (mother bag), apheresis split **unit** or whole-blood derived pool **OR**	≥24	≥12	3*	Cleared
Culture as in 1a above (≥36 h with 16 mL cultured)	≥36		5*	
Step 2: To extend Step 1 shelf life, three options are available:				
a Secondary culture of each unit of 8 mL in aerobic bottle on **≥Day 3**		Set by user	5	Cleared
b Secondary culture of each unit of 16 mL as in step 1a on **≥Day 4**		≥12	7	Cleared
c Rapid testing of each unit within 24 hours of transfusion **≥Day 3** - device with Safety Measure claim allows 7 day dating of apheresis platelets in plasma		NA	5 or 7	Cleared for 5 d with BacTx and for 7 d with Safety Measure for PGD test

Rapid testing: for 5 or 7 day dating

- Apheresis platelets in plasma, PAS or pre-storage WBD pools
  - 500 µL sample for any unit type previously tested by early culture
  - Use PGD Test within 24 hours of transfusion (Day 3+ post-collection for optimal performance) for 5 day dating
  - Use PGD Test on apheresis platelets in plasma within 24 hours of transfusion (Day 3+ post-collection for optimal performance) for 7 day dating
- 1:3,069 detection rate in a culture negative apheresis inventory*
- Overall Specificity of 99.9%*

* Platelet PGD Test package Insert, Rev J

Rapid testing: for 5 or 7 day dating

- Typical users implement with daily batch testing and do not require additional staff

Doses Tested Annually	Batches	Total Time Required	Attended Time Required
2,000	of 6	40 min, 37 sec	17 min, 30 sec
4,000	of 12	61 min	35 min
6,000	3 of 6	122 min	53 min
8,000	2 of 12	122 min	70 min

PGD Batch Testing time motion study

Rapid testing: for 5 or 7 day dating

Economic implications: Survey of 16 blood collection centers and 66 hospitals

- 7 day dating of LRAPs can fully fund all testing and save money
- No impact on split rates due to small sample size, with reduced need for donor recruiting with 7 day dating

Survey of blood collection centers and hospitals that use PGD Test to extend dating to 7 days		
	Blood collection Centers (N=16)	Hospitals (N=66)
Mean outdate reduction	**69%**	**74%**
Annual mean cost savings	**$415,000**	**$176,803**

Mintz PD. Seven-day platelet storage: Outdate reduction and cost savings (abstract). Ann Clin Lab Sci 2019;49(3):414. Presented at the Association of Clinical Scientists Annual Meeting. Hershey PA. May 2019.

Rapid testing: post-storage WBD pools and single WBDs

- Single units and post-storage pools
  - Test within 4 hours of use
  - 5 day dating
- Cost and workflow implications:
  - Only practical test given small sample size and one test per pool

Mitigating the Risk of Bacterial Contamination of Platelets - Recent Developments

Objectives:

- Characterize the extent and nature of this risk
- Review FDA Final guidance and the options for addressing this risk and their implications
- Review the role of rapid testing in satisfying guidance
- **Present data on recent advances in rapid testing technology for bacteria in platelets**

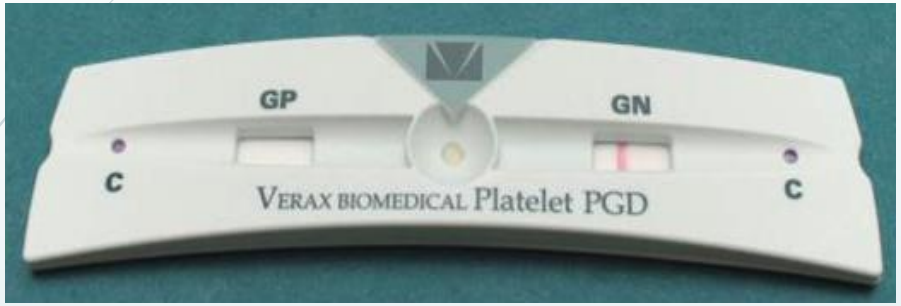
Updated Platelet PGD Test Significantly increased specificity

- An 18 hospital study of the original Platelet PGD Test demonstrated overall specificity for apheresis platelets in plasma of 99.5%
- A manufacturing change to Line 1 of the test strip was made to address this issue
- 5,410 platelet units were tested side by side with the updated and current versions of the PGD test at 3 sites and their performance was compared

Platelet Type	# of Platelet Doses Tested	Observed Specificity (LCL*)	
		Original PGD Test	Updated PGD Test
Leukoreduced Apheresis in plasma	3303	99.4% (99.1%)	99.9% (99.8%)
Non-Leukoreduced WBD	498	98.8% (97.7%)	99.4% (98.5%)
Apheresis In Platelet Additive Solution	416	99.8% (98.9%)	99.8% (98.9%)
Pre-Storage Pools (Acrodose™)	1193	99.7% (99.4%)	99.9% (99.6%)

Platelet PGD Test package Insert, Rev J

PGD*prime* Test – the next update to PGD



PGD Procedure

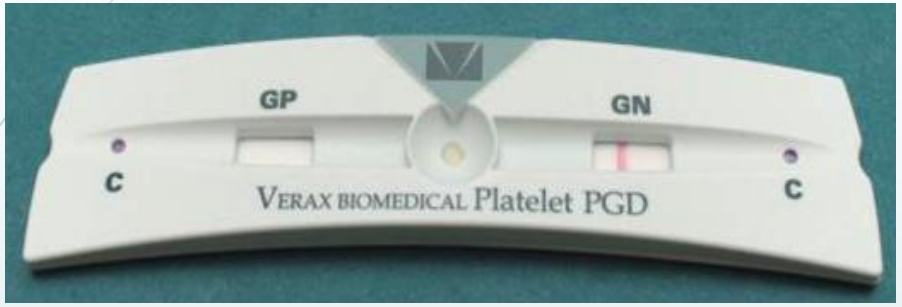
1. Add Reagent 1 (lysing agent) to platelet sample
2. Centrifuge
3. Decant supernatant
4. Add Reagent 2 (base) to pellet
5. Disrupt pellet and mix
6. Add Reagent 3 (neutralizer) and vortex
7. Transfer to PGD test device.

Validation of the Specificity of the PGD*prime*® Test for Bacteria in Platelets with Commercial Scale Lots

Lisa Shinefeld, Nancy Hornbaker, Pat Rasmusson, Nancy Best, Willa Lee, Gary Tambolleo, Michael Pelak, Johny Lisitu, Remo Vallejo

Verax Biomedical Incorporated, Marlborough, MA

PGD*prime* Test – the next update to PGD



PGD Procedure

1. Add Reagent 1 (lysing agent) to platelet sample
2. Centrifuge
3. Decant supernatant
4. Add Reagent 2 (base) to pellet
5. Disrupt pellet and mix
6. Add Reagent 3 (neutralizer) and vortex
7. Transfer to PGD test device.

PGD*prime* Procedure

1. Add Reagent 1A (base) to platelet sample. Invert to mix.
2. Add Reagent 1B (neutralizer) to sample. Invert to mix.
3. Transfer to test device.
4. Add Chase buffer (Reagent 2).

- No centrifuge is required.

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Conclusions

- New FDA guidance on mitigating the risk of bacterial contamination of platelets was published in September 2019, with a recommended implementation date within 18 months (by March 2021)
- This guidance includes multiple options
  - Pathogen reduction with a 5-day shelf life
  - Primary culture of **apheresis collections**, **apheresis units** and **WBD pools** ≥24 h to ≥48 h of **actual** time of collection, with minimum volume of platelets cultured of **16 mL**, split between **aerobic and anaerobic** culture bottles, with shelf life of **3-7 days**
  - Secondary testing using culture or rapid method with Safety Measure label to extend shelf life to **4-7 days**
- Implementation of the new guidance will have significant logistic and economic challenges
- Primary testing of apheresis **collections** 24 h after collection with a secondary rapid test on **units** on days 4-7 offers an approach that is least disruptive to the platelet supply and will result in cost savings instead of increased costs with other approaches

Backup info

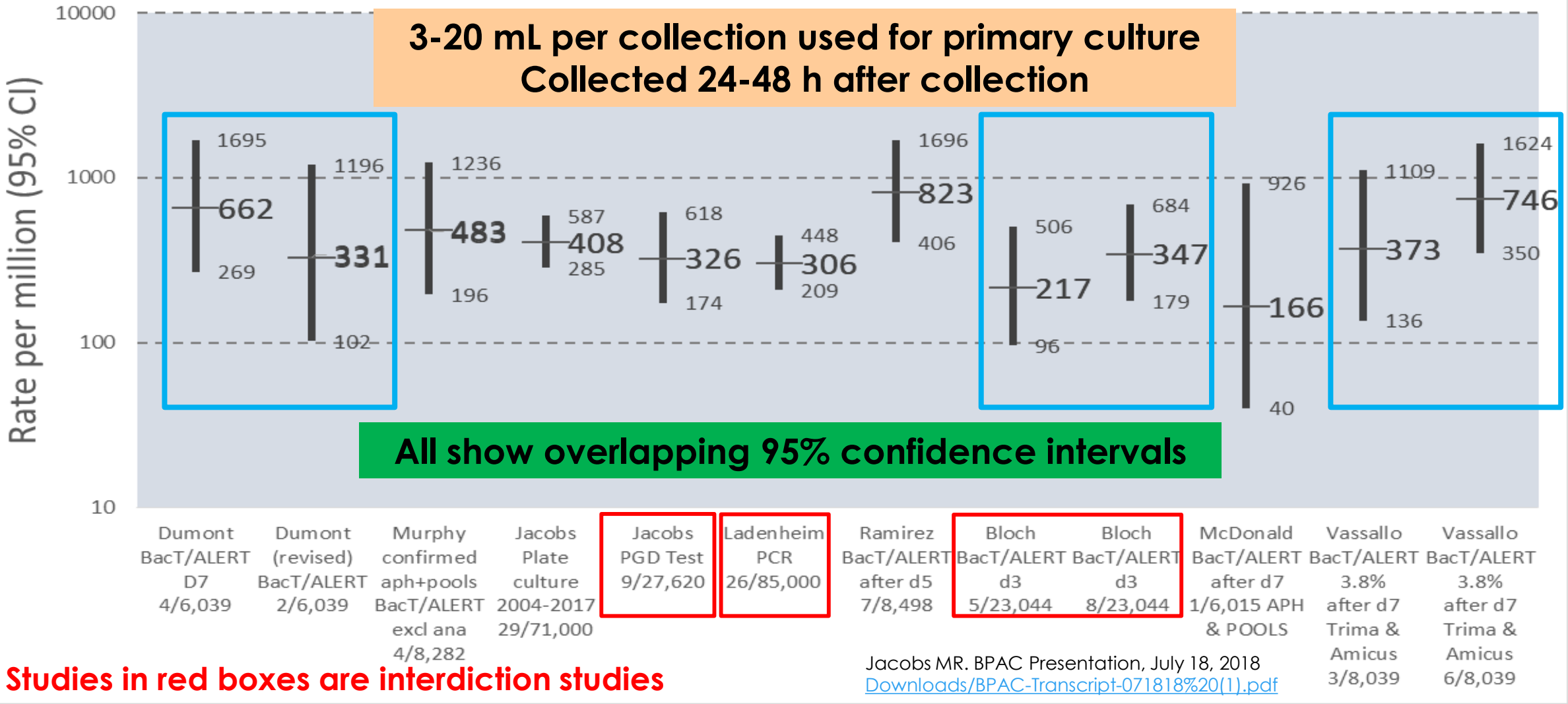
Data sources for slide on contamination rates at issue or outdate

Contaminants missed by primary culture: Independent of volume or time of testing

	Period	Primary test method	Time tested after collection	Volume tested primary method	Secondary test method	Time tested	Contam rate at secondary test	Contam rate per million
Dumont 2010	2005-2008	BacT/ALERT BPA and BPN	24-36 h	4-5 mL X 2	BacT/ALERT BPA and BPN	Day 8	4/6,039	662
Dumont 2010 (revised)	2005-2008	BacT/ALERT BPA and BPN	24-36 h	4-5 mL X 2	BacT/ALERT BPA and BPN	Day 8	2/6,039	331
Murphy 2008 aph+pools	2005-2007	BacT/ALERT BPA and BPN	36 h	7.5-10 mL X 2	BacT/ALERT BPA and BPN	Day 7	4/8,282 (excl. ana)	483
Jacobs 2018	2004-2017	BacT/ALERT BPA or eBDS	24-36 h	BPA: 8-10 mL eBDS: 3-4 mL	Plate culture 0.1 mL	Day 4-6	29/71,000	408
Jacobs 2011	2008-2010	BacT/ALERT BPA	24-36 h	8-10 mL	PGD Test	Day 2-5	9/27,620	326
Ladenheim 2012	2004-2011	BacT/ALERT BPA	24-36 h	8-10 mL	PCR	Day 3-5	26/85,000	306
Ramirez 2017	2010-2016	BacT/ALERT BPA	24 h	8-10 mL	BacT/ALERT BPA and BPN	Day 6	7/8,498 (excl. ana)	823
Bloch 2018	2016-2017	BacT/ALERT BPA	24-36 h	8-10 mL	BacT/ALERT BPA	Day 3	5/23,044	217
Bloch 2018	2016-2017	BacT/ALERT BPA	24-36 h	8-10 mL	BacT/ALERT BPA	Day 3	8/23,044	347
McDonald 2018	2011-2017	BacT/ALERT BPA and BPN	36-48 h	16 ml per split (~7% of collection)	BacT/ALERT BPA and BPN	Day 8	1/6,015 (APH + pools)	166
Vasallo 2018	2013	BacT/ALERT BPA	24-36 h	3.8% of collection	BacT/ALERT BPA	Day 6	3/8,039	373
Vasallo 2018	2013	BacT/ALERT BPA	24-36 h	3.8% of collection	BacT/ALERT BPA	Day 6	6/8,039	746

Studies in red are interdiction studies

Nine secondary culture or testing studies of apheresis contaminants missed by primary culture: Independent of volume, time of testing and test method



Studies in red boxes are interdiction studies

Jacobs MR. BPAC Presentation, July 18, 2018
Downloads/BPAC-Transcript-071818%20(1).pdf

Cost comparison

TABLE 3. Probabilistic sensitivity analysis results.

	Baseline	Pathogen reduction	Point-of-release testing	Secondary culture
Unit costs (US$): mean (SD)				
Acquisition	557.91 (0.14)	748.95 (11.64)	557.91 (0.14)	557.91 (0.14)
Testing/manipulation	13.58 (0.01)	0.00 (0.00)	45.4 (3.71)	30.83 (1.79)
Transfusion	78.83 (4.40)	78.83 (4.40)	82.02 (1.79)	78.80 (4.49)
Complications	0.91 (2.09)	0.00 (0.00)	0.75 (1.89)	0.61 (1.73)
Total	651.23 (4.92)	827.78 (12.38)	686.23 (4.76)	668.16 (5.09)
Unit disposition (%)				
Uncontaminated transfusion	90.48%	90.51%	94.16%	90.46%
Contaminated transfusion	0.04%	0.00%	0.02%	0.01%
Disposed	0.00%	0.00%	0.77%	0.04%
Expired	9.49%	9.49%	5.06%	9.49%
Total cost per transfused unit (US$): mean (SD)	719.48 (40.49)	914.53 (52.79)	728.65 (16.72)	738.50 (42.43)
Annual costs (million US$): mean (SD)	14.39 (0.81)	18.29 (1.06)	14.57 (0.33)	14.77 (0.85)

Financial and clinical impact of baseline strategy and three alternative risk reduction approaches, varying input parameters simultaneously. Unit costs are expressed per "effective" unit received by a hospital transfusion service from a blood collection agency. Annual costs assume 20,000 transfused units per year.

Primary and secondary cultures using aerobic bottles only in these calculations
Costs includes costs of platelet unit, secondary testing, transfusion, complications and expired units

Kacker S, Bloch EM, Ness PM, Gehrie EA, Marshall CE, Lokhandwala PM, Tobian AAR. Financial impact of alternative approaches to reduce bacterial contamination of platelet transfusions. Transfusion. 2019 Apr; 59(4):1291-1299. Epub 2019 Jan 8.