Current Status of Bacterial Contamination in Transfusion Safety

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Objectives

- Platelet Transfusion Bacterial Risk
- US Food and Drug Administration (FDA) Guidance
- Bacterial Risk Control Strategies
- Implementation at Northwell Health

Platelet Transfusion Bacterial Risk

- Bacterial contamination of platelets is the leading cause of transfusion transmitted infections due to room temperature storage
- 1: 5000 platelet units estimated to have bacterial contamination
- Depending on the source and surveillance method, 1:10,000 to 1:100,000 transfusion-transmitted septic reactions
- Highest risk of transfusion transmitted infections are in platelets that are on days 4 or 5 of shelf-life, with majority of septic transfusion reactions and fatalities occurring on those days
- Risk has persisted despite the implementation of single unit culture ≥24 hours and preventive measures (collection technique, diversion of 1st part of collection) and **fatal transfusion reactions** from undetected contaminated platelets continue to occur.

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Fatalities Reported to FDA - Annual Summary for FY2018

Table 3: Transfusion-Associated Fatalities by Complication, FY2014 – FY2018

Complication	FY14 No.	FY14 %	FY15 No.	FY15 %	FY16 No.	FY16 %	FY17 No.	FY17 %	FY18 No.	FY18 %	Total No.	Total %
Anaphylaxis	2	7%	2	5%	5	12%	3	8%	2	6%	**14**	**8%**
Contamination	1	3%	5	14%	5	12%	7	19%	7	23%	**25**	**14%**
HTR (ABO)	4	13%	2	5%	4	9%	1	3%	2	6%	**13**	**7%**
HTR (non-ABO)	4	13%	4	11%	1	2%	6	16%	4	13%	**19**	**11%**
Hypotensive Reaction	1	3%	1	3%	1	2%	0	0%	0	0%	**3**	**2%**
TACO	5	17%	11	30%	19	44%	11	30%	12	39%	**58**	**32%**
TRALI*	13	43%	12	32%	8	19%	9	24%	4	13%	**46**	**26%**

Platelet

- Bacterial contamination of platelets accounted for 72% of fatalities from microbial contamination in 2014-2018
- Both aerobic and anaerobic bacteria implicated

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Active vs Passive Surveillance of Bacterial Contamination of Platelets

Period	1991-2006			2007-2013
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

Jacobs MR CID 2008
Hong H Blood 2016

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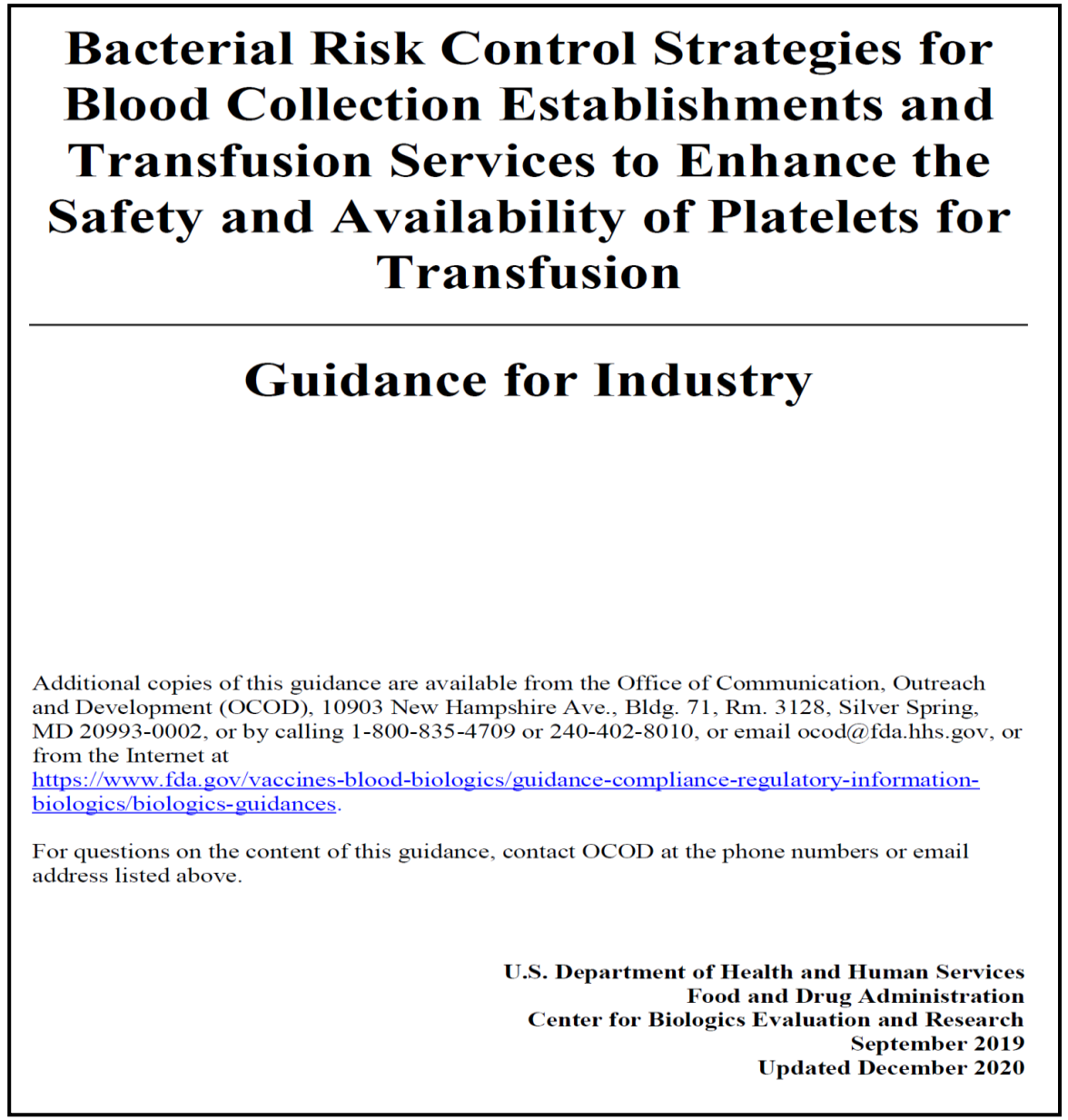
Implementation of FDA Guidance to Enhance Safety of Platelets

- Final guidance published in September 2019 with target implementation date of March 31, 2021
- Implementation delayed to October 1, 2021 due to COVID-19 pandemic



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

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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
Updated December 2020

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Three Types of Bacterial Risk Reduction Strategies

- Primary testing: Direct testing for infectious agents: Large Volume Delayed Sampling (LVDS)
- Secondary testing by culture or bacterial detection with an FDA-approved “rapid test”
- Pathogen reduction technology (PRT)

FDA Guidance: Bacterial Testing of Platelets

Single-Step Strategies:

1- Large Volume, Delayed Sampling (LVDS) ≥ 36 hours (5-day expiration)

2- Large Volume, Delayed Sampling (LVDS) ≥ 48 hours (7-day expiration)

3- Pathogen Reduction (5-day expiration)

Two-Step Strategies:

Step 1: Primary Culture ≥ 24 hours (secondary testing ≥ day 3 or ≥ day 4)

-or-

Large Volume, Delayed Sampling (LVDS) ≥ 36 hours (secondary testing ≥ day 4)

Step 2: Secondary Culture (extend to 5- or 7-day expiration)

-or-

Secondary “rapid resting” (extend to 5- or 7-day expiration)

Limiting factors: Shelf-life, cost, availability, logistics of implementation

FDA Guidance: Bacterial Risk Control Strategies– Apheresis and WBD Platelets

	Apheresis	Pre-storage pools of WBD Platelets	Single unit 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 ≥3 days	Primary culture ≥24 hours + secondary rapid testing	Primary culture ≥ 36 hours	
	Primary culture ≥24 hours + secondary rapid testing			

Rapid testing within 4 hours of transfusion for single unit WBD or post-storage WBD pooled platelets

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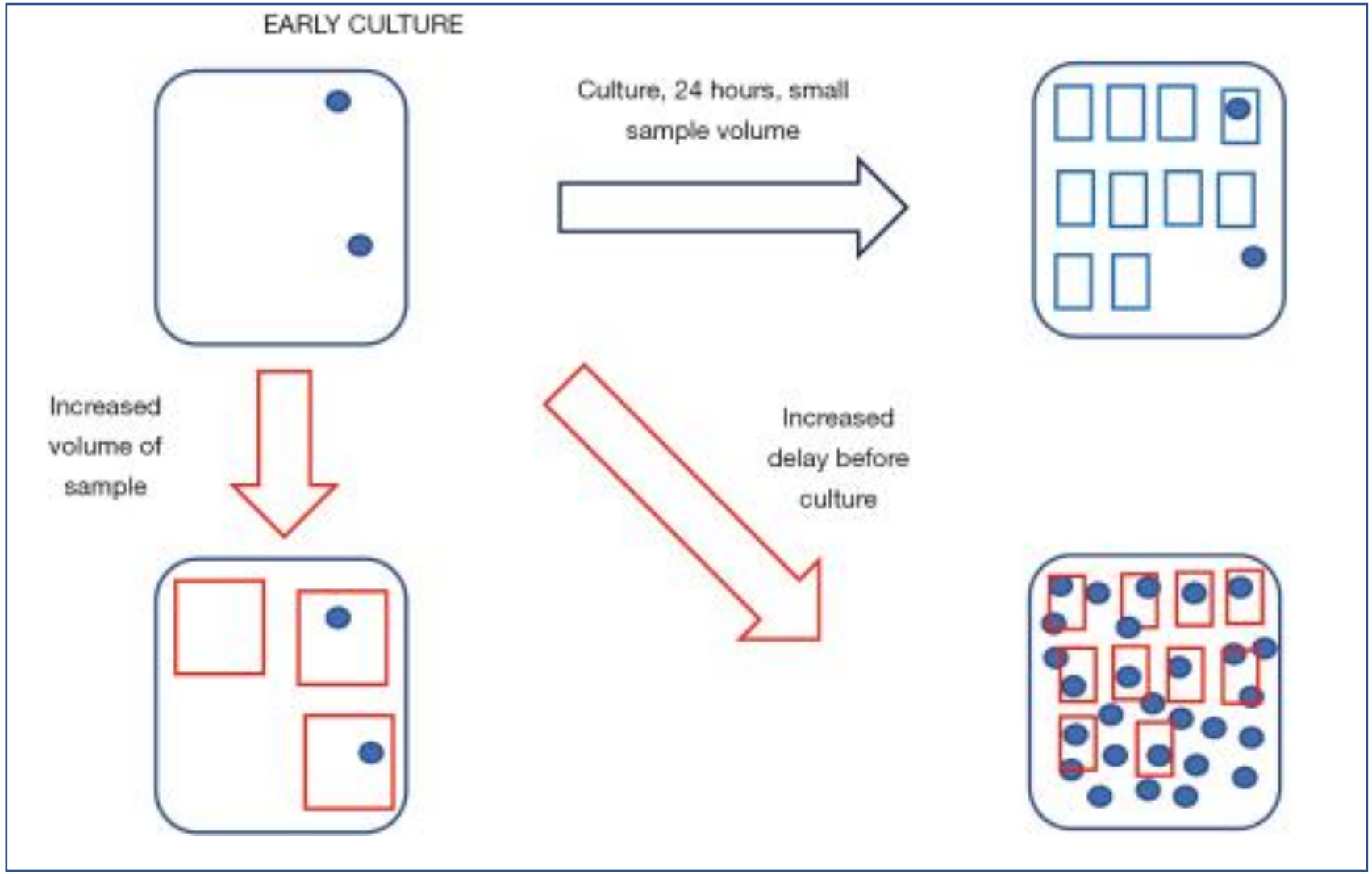
Impact of Increased Volume and Delayed Sampling on Capacity to Detect Bacterial Contamination



A 16ml sample is taken from each bag of platelets 36-48 hours after collection. If sample is negative for bacterial contamination after 12 hours, product can be used for transfusion

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Large Volume Delayed Sampling

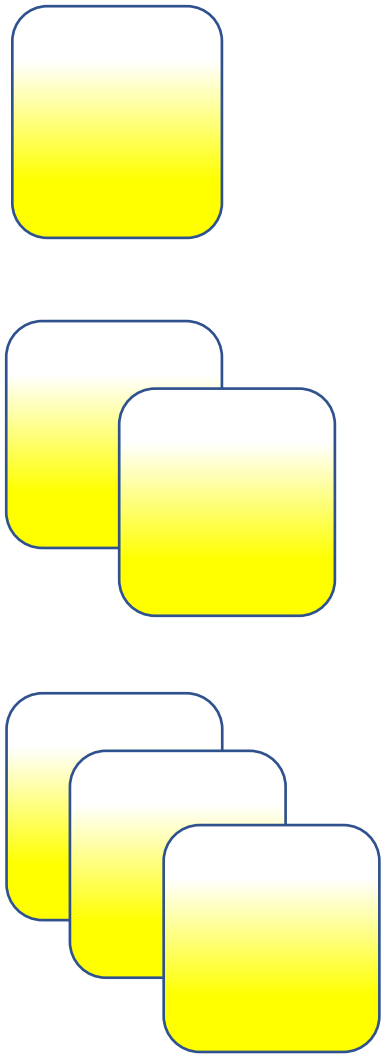
Previous practice:

Aerobic 8 mL from mother bag at 24 hours

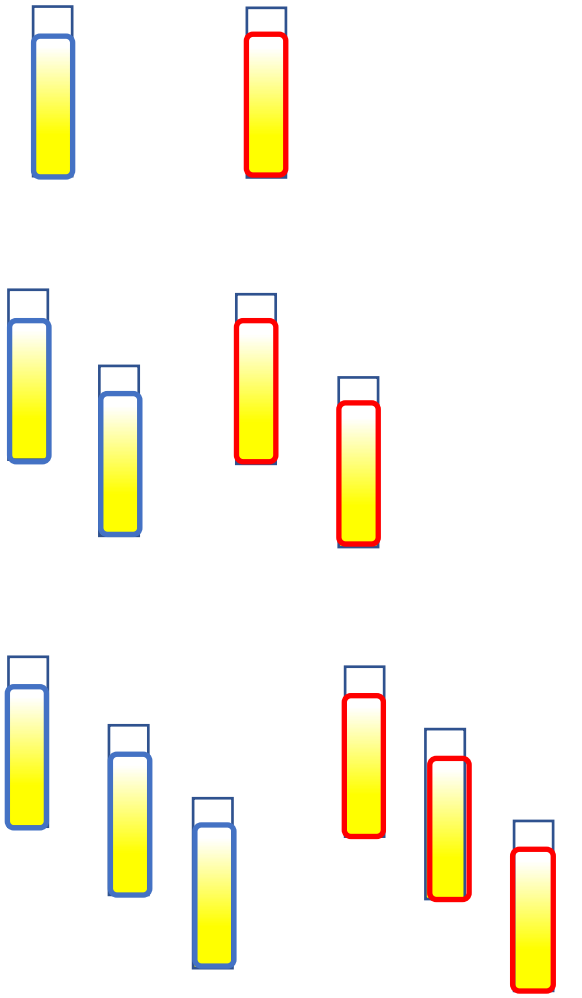
Single

Double

Triple



Aerobic and Anaerobic 8ml sample each



Take sample 36-48 hours after collection from each bag in collection

16 ml Single

32 ml Double

48 ml triple

12-hour minimum incubation

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LVDS 36 or 48

LVDS 36

- Sampled no sooner than 36 hours after collection
- Minimum 16ml from each component (also splits)
- Inoculate aerobic and anaerobic bottles
- Minimum 12-hour incubation before release (48 hours)
- 5-day expiration (shelf-life can be extended with 2 step strategy
- ~2 ½ day usable shelf-life

LVDS 48

- Sampled no sooner than 48 hours after collection
- Minimum 16ml from each component (also splits)
- Inoculate aerobic and anaerobic bottles
- Minimum 12-hour incubation before release (60 hours)
- 7-day expiration
- ~4-day usable shelf-life

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LVDS- Platelet Discard Rate % Before & After Implementation of 7-day PCs

	Canadian Blood Services	Hospitals	Combined
June 2015-August 2017 (before 7-d PCs)			
Apheresis PCs	1.6%	14.7%	16.3%
Pooled PCs	3.7%	16.3%	20.0%
Overall			18.9%
September 2017-December 2019 (after 7-d PCs)			
Apheresis PCs	0.8%	10.1%	10.9%
Pooled PCs	3.0%	10.9%	13.8%
Overall			13.1%

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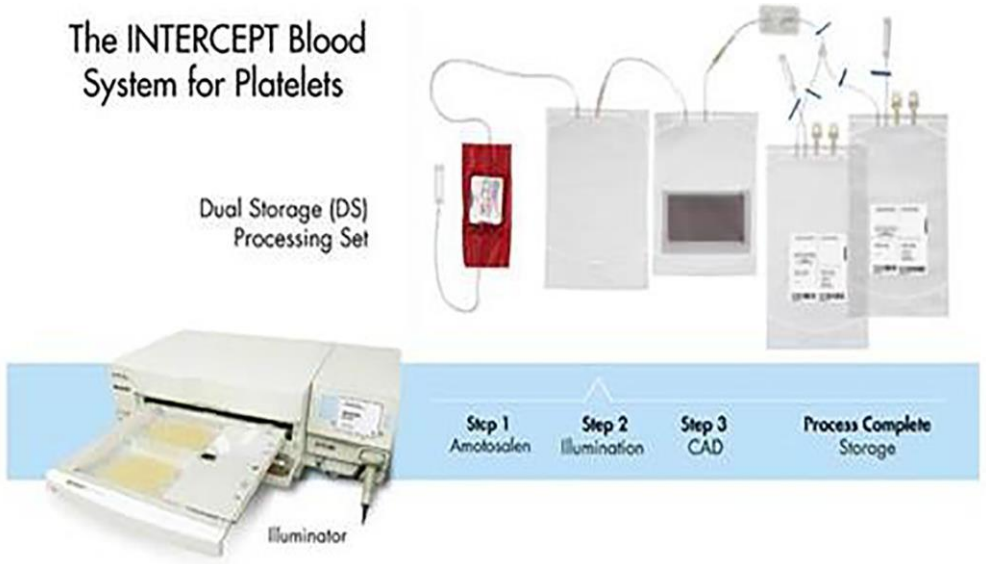
Ramirez-Arcos Transfusion 2020

Large Volume Delayed Sampling

- Increased false positive culture result mostly from anaerobic culture bottles
- Cost and platelet availability implications
  - Cost of additional cultures in bottles, hardware and labor
  - Reduced split collection rates due to larger sample size
- Larger sampling volumes results in smaller product volume, which may result in about 20% of platelet units having **up to 10% reduction** in platelet content as compared to previous platelet units

Pathogen Reduction Technology

- Prevent pathogen replication through irreversible damage to nucleic acids
  - INTERCEPT: P*soralen +UVA*
  - MIROSOL: Riboflavin + UVA or UVB
- Apheresis platelets stored in plasma or platelet additive solution (PAS) or pre-pooled WBD platelets
- Intercept system approved in the US for Apheresis platelets (no triple collections)



- Treatment within 24 hours of collection- No holding period or incubation delays before use. Usable shelf-life ~4 days
- May result in **up to 10% reduction** in platelet content as compared to previous platelet units

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Rapid testing- PGD Prime

- Simple, rapid, single use, lateral flow immunoassay for the detection of GN and GP aerobic and anaerobic bacteria
- 150uL sample from apheresis platelets collected in plasma or platelet additive solution (PAS) or WBD single unit or pre/post storage pools
- May be used as secondary testing to extend shelf-life of apheresis platelets to 5 or 7 days
- Single step or 2 step strategy for WBD platelets
- Testing within 24 hours of transfusion (4 hours for post-storage WBD pools or single WBD platelets)

- Limit of detection is 10^3- 10^5 CFU/mL
- False neg/pos. results
- Need for QC, proficiency testing and competency

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Impact of Various Testing Strategies on Platelet Yield and Cost

Method	Impact on Platelet Yield	Relative Cost
Primary Culture >24hours	None	$
LVDS	Low yield platelets may account for up to 20% of inventory	$$
Pathogen reduced (Intercept)	May lower platelet yield	$$$
Rapid testing (PGDPrime)	None	$

Cold-Stored Platelets

- Cold Storage may reduce risk of bacterial contamination of platelets
- Better preserved hemostatic function than room temperature platelets which may be best for actively bleeding patients
- FDA approved for
  - Resuscitation of bleeding patients (3-day shelf-life, no agitation, 1-6C)
  - Supplemental approval: treatment of actively bleeding patients when conventional platelets not available (14-day shelf-life, no agitation, 1-6C)

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- 23 hospitals, with 14 transfusion services
- Blood/Platelet providers: NYBC (90%)
- NYBC Platelet distributions to Northwell Health:
  - 2019 – 13,967
  - 2020 – 14,157
  - 2021 – 15,711
- Conversion to **7-day LVDS 48** (both LVDS and low yield LVDS) in April 2021
  - **Pathogen-reduced platelets** supplied when LVDS not available

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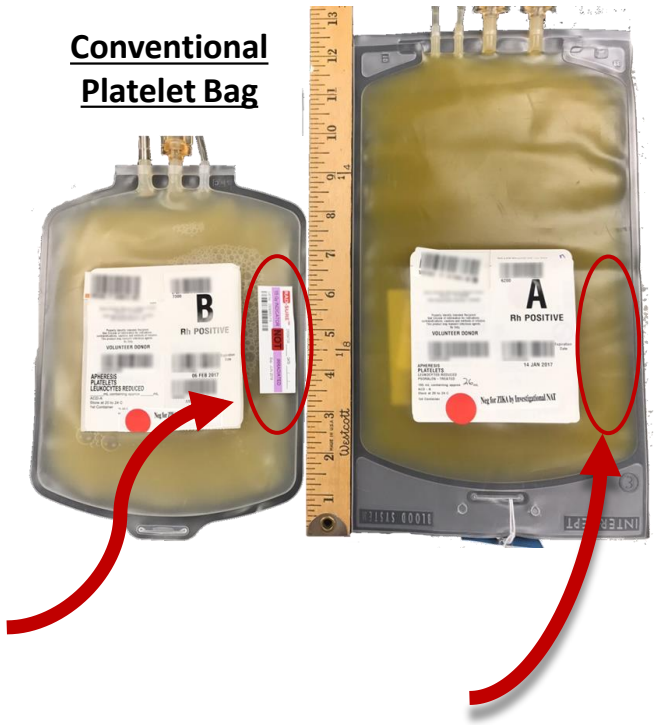
Large Volume Delayed Sampling (LVDS) Platelets

Pathogen Reduced (Psoralen-Treated) Platelets

Pathogen Reduced Platelet Bag Size

Conventional Platelet Bag



No irradiation Sticker on Pathogen Reduced Platelets

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Round Robin - Platelet-sharing Program Between 14 Transfusion Services

Platelet and RBC Standing Orders are packed by Blood Center

Blood Center driver arrives at Community Hospital

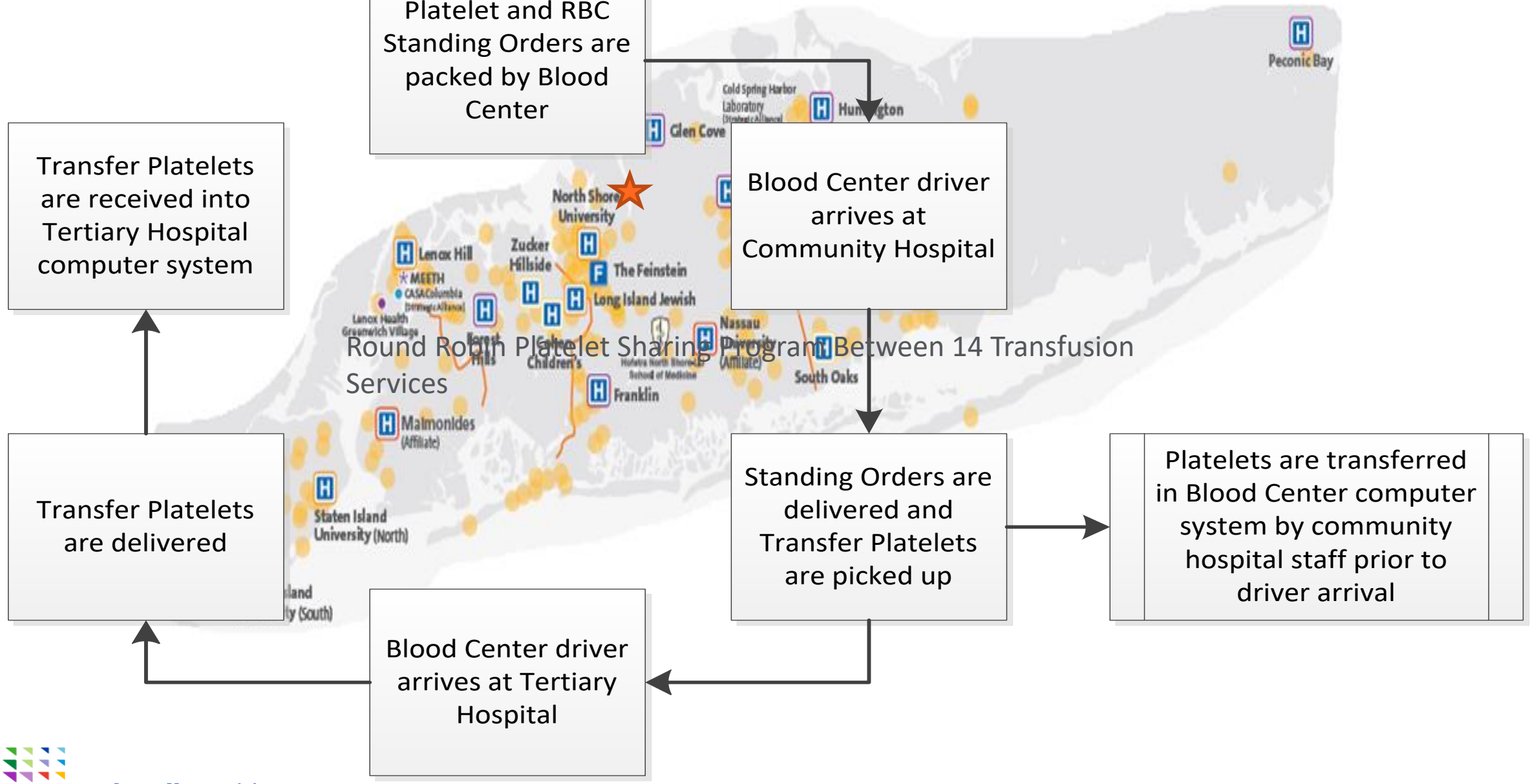
Standing Orders are delivered and Transfer Platelets are picked up

Platelets are transferred in Blood Center computer system by community hospital staff prior to driver arrival

Blood Center driver arrives at Tertiary Hospital

Transfer Platelets are delivered

Transfer Platelets are received into Tertiary Hospital computer system



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North Shore University Hospital (NSUH)

- 800 beds, tertiary care hospital, flagship hospital at Northwell Health
- Care in all medical and surgical specialties
  - Level I trauma center
  - Cardiovascular services
  - Cancer Center
  - Hematopoietic and solid organ transplant services
  - Maternal-fetal medicine and women's health
  - Orthopedics
  - Gastroenterology
- NYBC Platelet distributions to NSUH
    - 2019 – 6246
    - 2020 – 5570
    - 2021 – 7645

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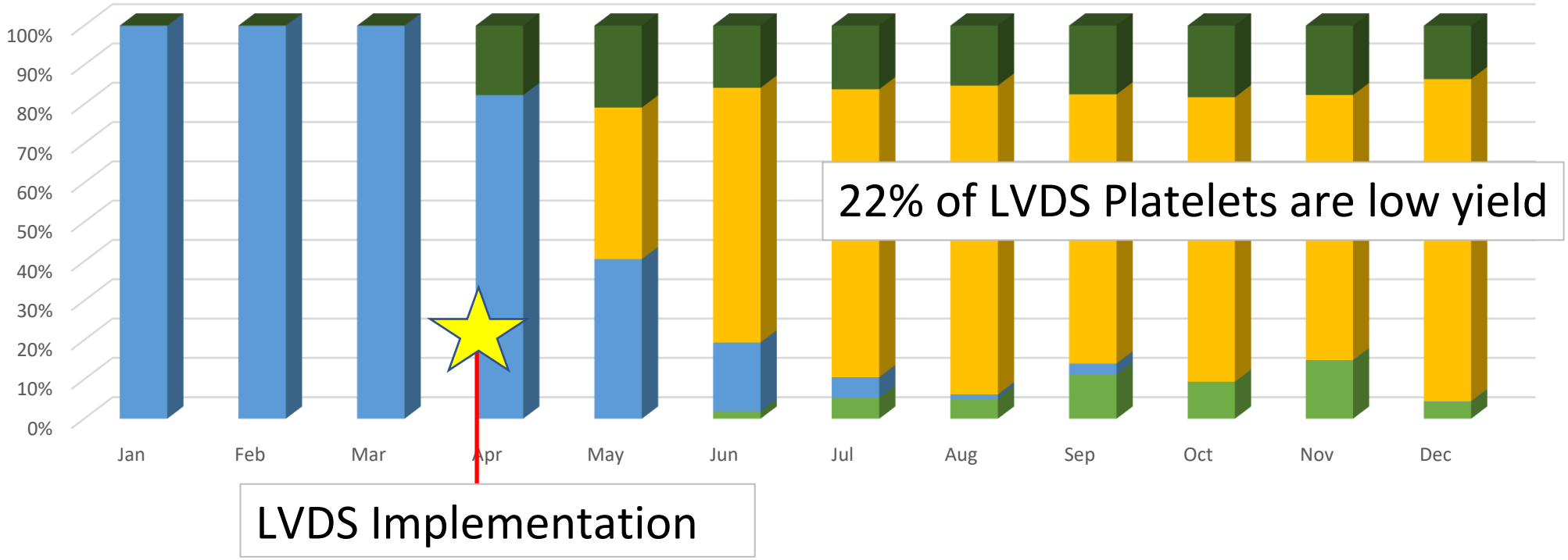
2021 Platelet Transfusions- North Shore University Hospital



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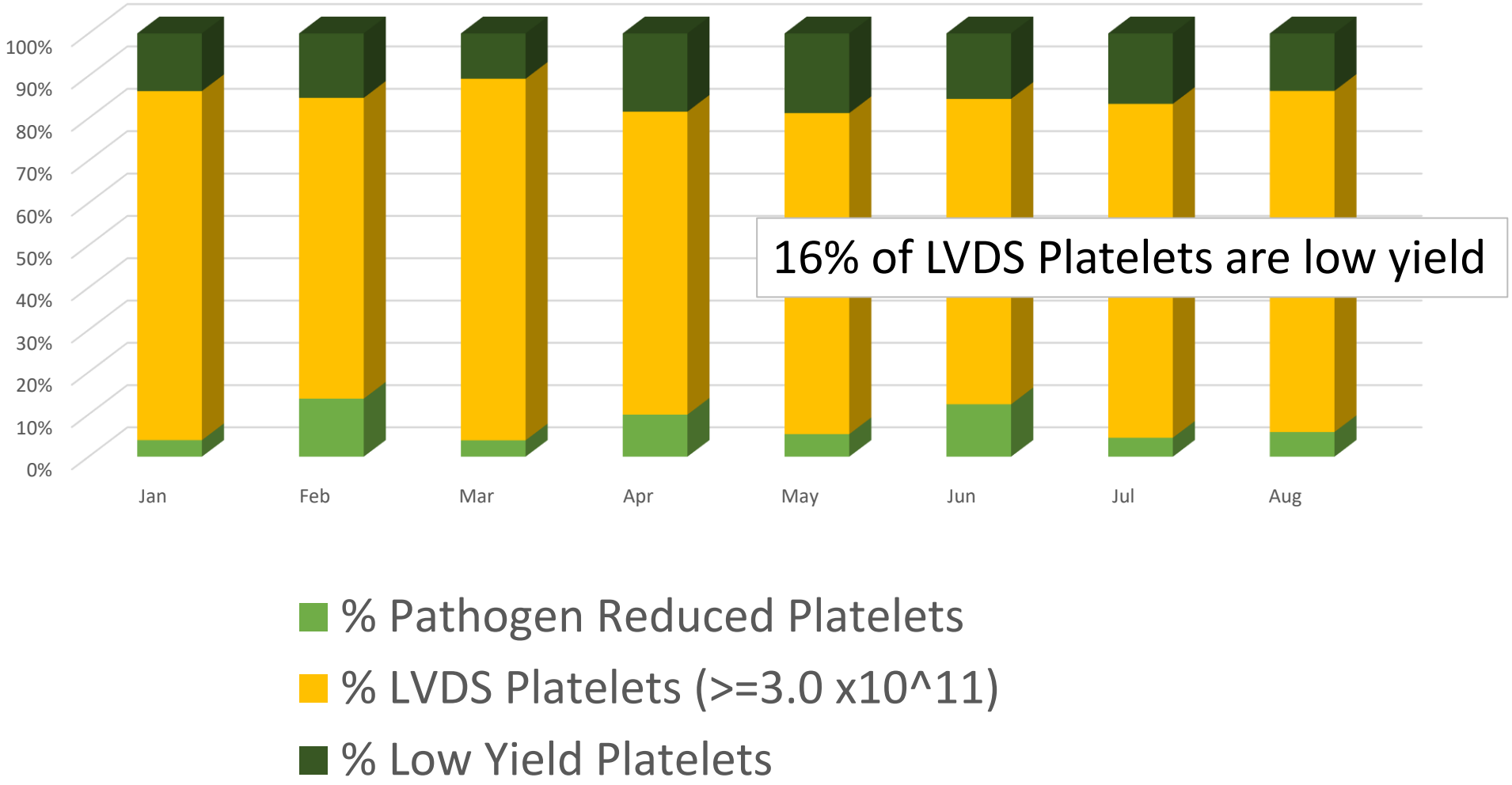
Platelet Transfusions - North Shore University Hospital
January- August 2022



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Platelet Bacterial Contamination Recalls from NYBC at Northwell Health

	Total recall #	Transfused #	Discarded#	STR #
2020	0	0	0	0
2021 Pre-LVDS	2	0	2	0
2021 Post-LVDS	18	9	9	0
2022 to date	13	8	5	0

- 17 Transfused units since 7-day LVDS implementation:
- 11 products – Cutibacterium acnes (from 8 collections)
- 2 products – Dietzia papillomatosis (from 1 collection)
- 4 products – False positive (from 2 collections)
- No septic transfusion reactions

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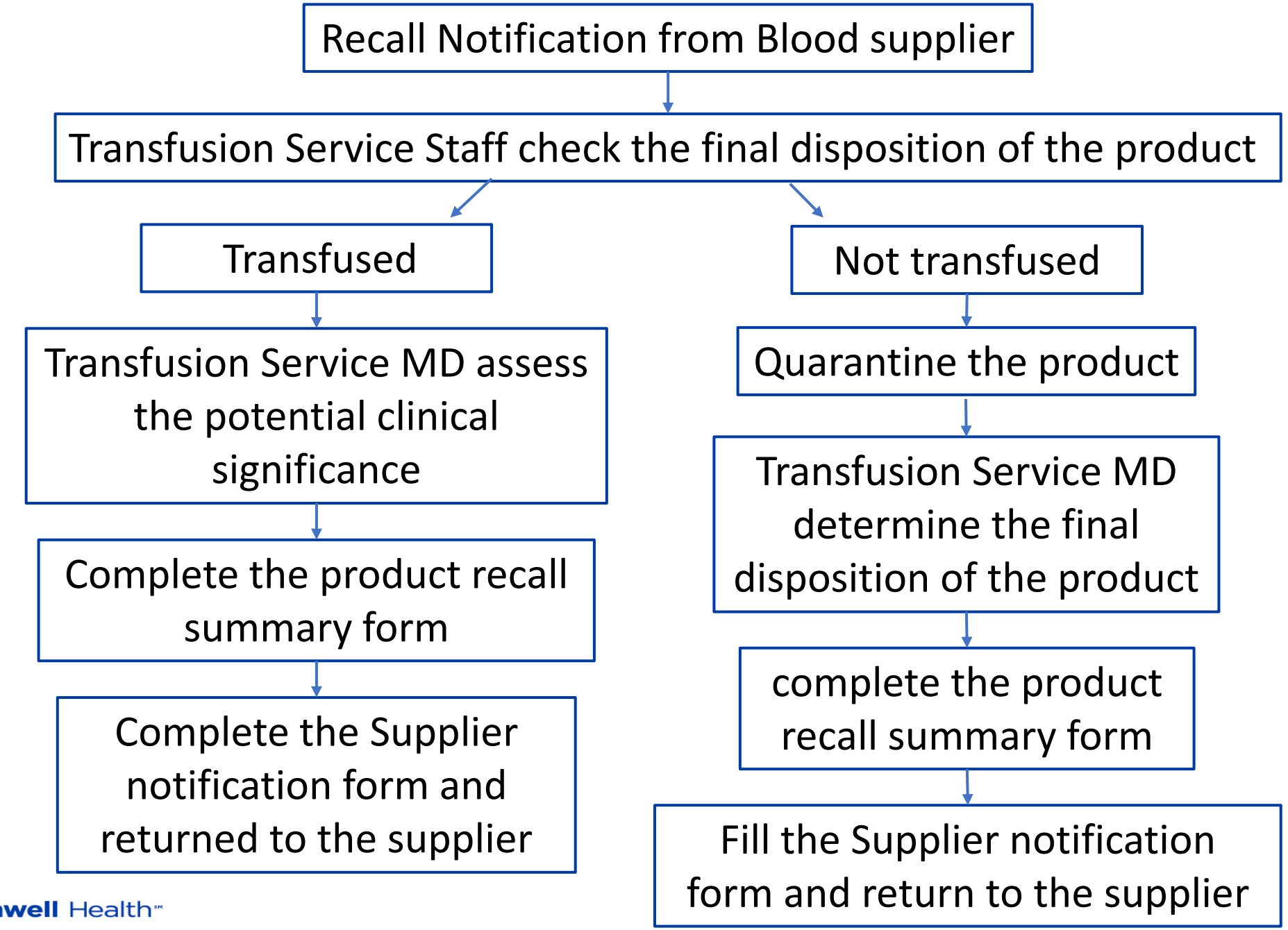

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Platelet Bacterial Contamination Recalls – Northshore University Hospital

	Total recall #	Transfused #	Discarded#	STR #
2020	0	0	0	0
2021 Pre-LVDS	0	0	0	0
2021 Post-LVDS	4	2	2	0
2022 to date	2	2	0	0

- 5 recalls from main blood supplier, 1 recall from secondary supplier

- 2 products transfused – Cutibacterium acnes
- 2 products transfused – no growth
- No septic transfusion reactions

- 1 product discarded – Gram positive Coccobacilli
- 1 product discarded – Positive blood culture

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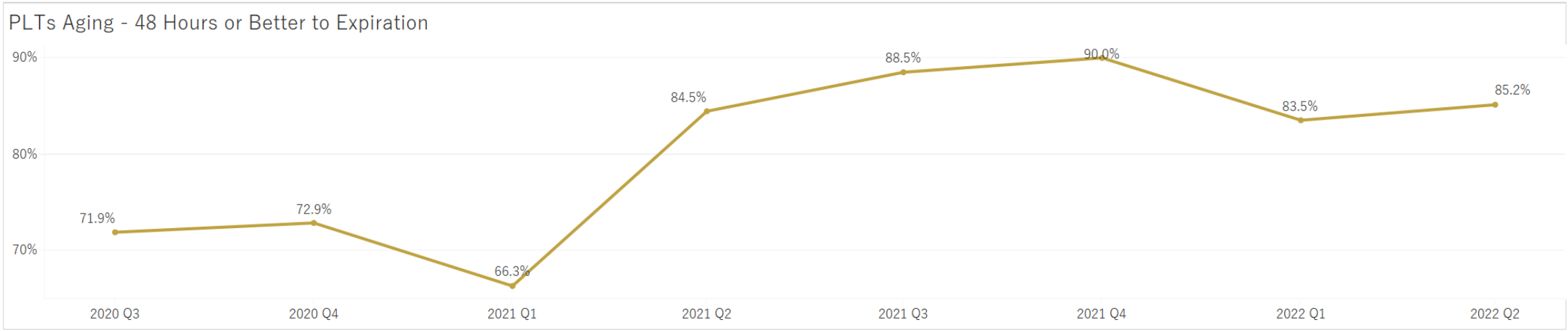
Percentage of LVDS Platelets with >48 Hours Shelf-life



	2020		2021				2022	
	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2
Glen Cove Hospital	90.5%	81.8%	95.8%	92.6%	93.1%	96.3%	100.0%	91.3%
Huntington Hospital	90.8%	88.0%	86.6%	92.2%	97.4%	97.4%	96.3%	95.8%
John T. Mather Memorial Hospital	86.2%	90.7%	83.9%	92.7%	94.9%	95.2%	97.0%	96.4%
Lenox Hill Hospital	79.1%	85.1%	71.9%	89.6%	87.6%	90.3%	88.9%	83.9%
Long Island Jewish Forest Hills	95.7%	91.1%	92.3%	98.5%	92.9%	92.1%	92.6%	88.8%
Long Island Jewish MC	87.5%	86.6%	80.2%	92.7%	95.4%	95.1%	73.6%	75.4%
Long Island Jewish Valley Stream	91.2%	76.2%	93.2%	94.7%	96.6%	90.6%	95.2%	94.4%
Nassau University MC	86.8%	91.8%	84.3%	98.2%	99.2%	96.1%	89.0%	84.8%
North Shore University Hospital	46.0%	48.4%	40.7%	71.2%	79.7%	82.4%	77.7%	83.4%
Northern Westchester Hospital Center			100.0%	100.0%				
Peconic Bay MC	76.1%	82.6%	76.4%	95.8%	100.0%	94.4%	93.9%	97.4%
Phelps Memorial Hospital								100.0%
Plainview Hospital	97.5%	98.1%	84.4%	100.0%	100.0%	98.3%	100.0%	97.7%
South Shore University Hospital BLD	78.0%	77.2%	72.4%	90.8%	98.2%	98.6%	99.6%	94.0%
Staten Island University Hospital North	88.0%	89.2%	79.3%	92.3%	94.7%	97.5%	94.5%	93.7%
Staten Island University Hospital South	44.4%	64.3%	66.7%	53.8%	66.7%	55.6%	77.8%	47.4%
Syosset Hospital	100.0%	90.0%	90.0%	100.0%	100.0%	100.0%	100.0%	100.0%
Grand Total	**71.9%**	**72.9%**	**66.3%**	**84.5%**	**88.5%**	**90.0%**	**83.5%**	**85.2%**

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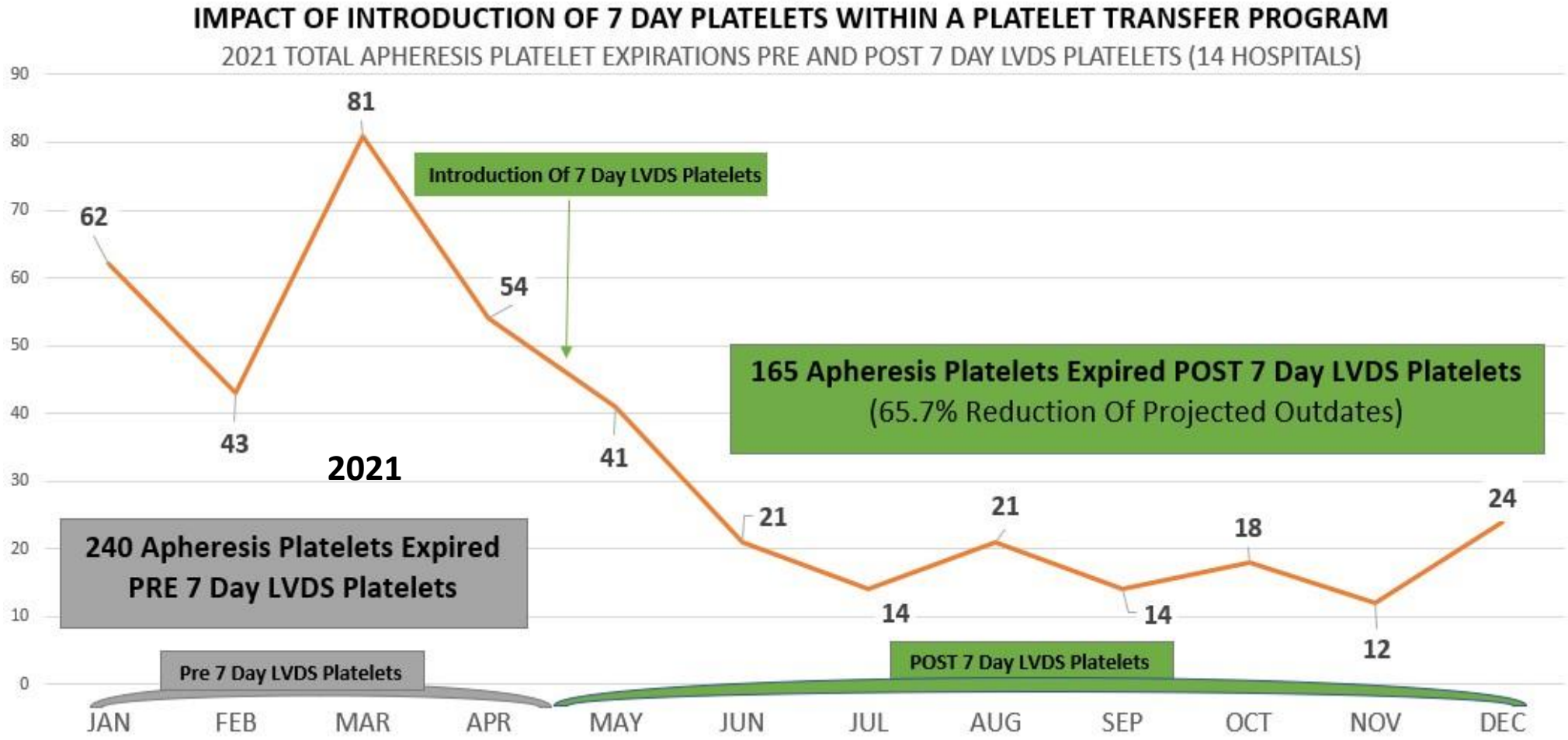
Platelet Outdates at Northwell Health



	Pre 7 Day LVDS (Actual)	Post 7 Day LVDS (Projected)	Post 7 Day LVDS (Actual)
# Outdated Units	240	480	165
# Units Acquired	4,877		10,834
Rate of Outdates	4.9%		1.5%

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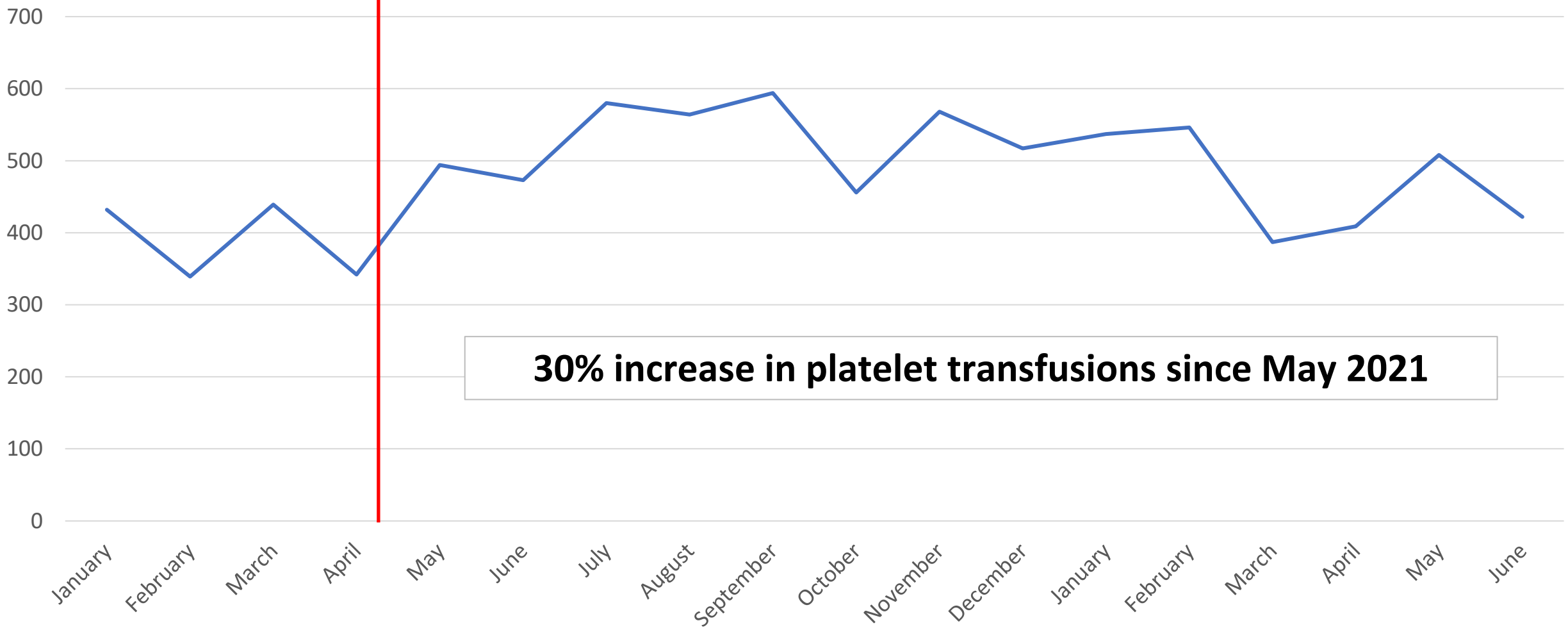
January 2021- June 2022 NSUH Platelet Transfusion- Hematology

January	February	March	April	May	June	July	August	September	October	November	December	January	February	March	April	May	June
432	339	439	342	494	473	580	564	594	456	568	517	537	546	387	409	508	422
Average = 388				Average = 530								Average = 468					
Per patient usage = 9.9				Per patient usage = 17.5								Per patient usage = 16.8					



30% increase in platelet transfusions since May 2021

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Summary

- Bacterial contamination of platelets is recognized as a serious risk of transfusion
- Multiple strategies have been introduced to mitigate the risk of bacterial contamination of platelets including large volume delayed sampling (LVDS), pathogen reduction technology, and secondary testing
- Shelf-life, Cost, logistics, and availability impact implementation decisions
- Implementation of LVDS platelets at Northwell has led to increased bacterial detection rate and decrease in platelet outdates
- The impact of low yield and older platelets on the increasing number of platelet transfusions since implementation of 7-day platelets is being evaluated

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- Thank you

sshariama@northwell.edu

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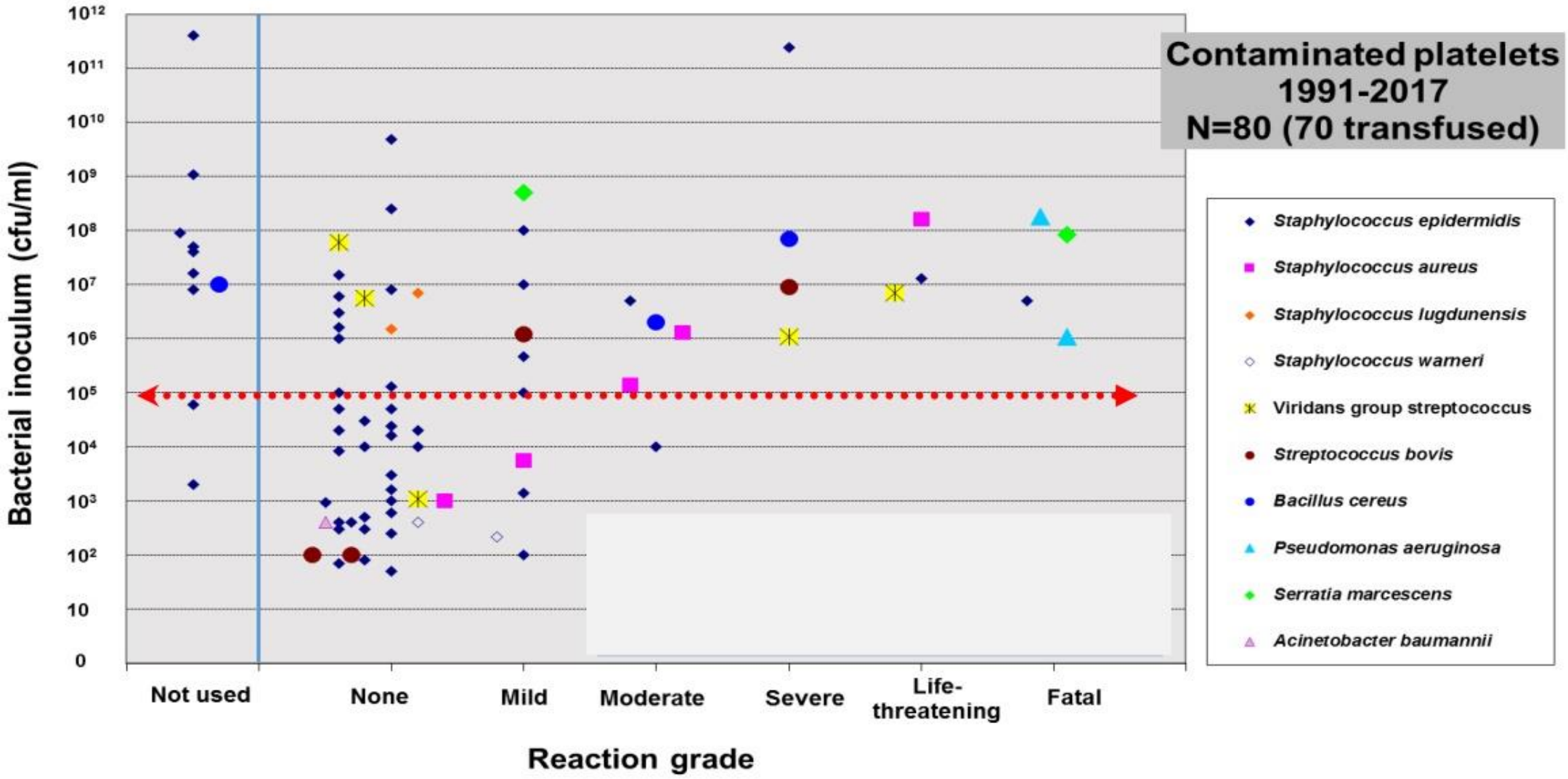
Transfusion reactions are associated with platelets contaminated with a bacterial loads of ≥10^5 CFU/ml



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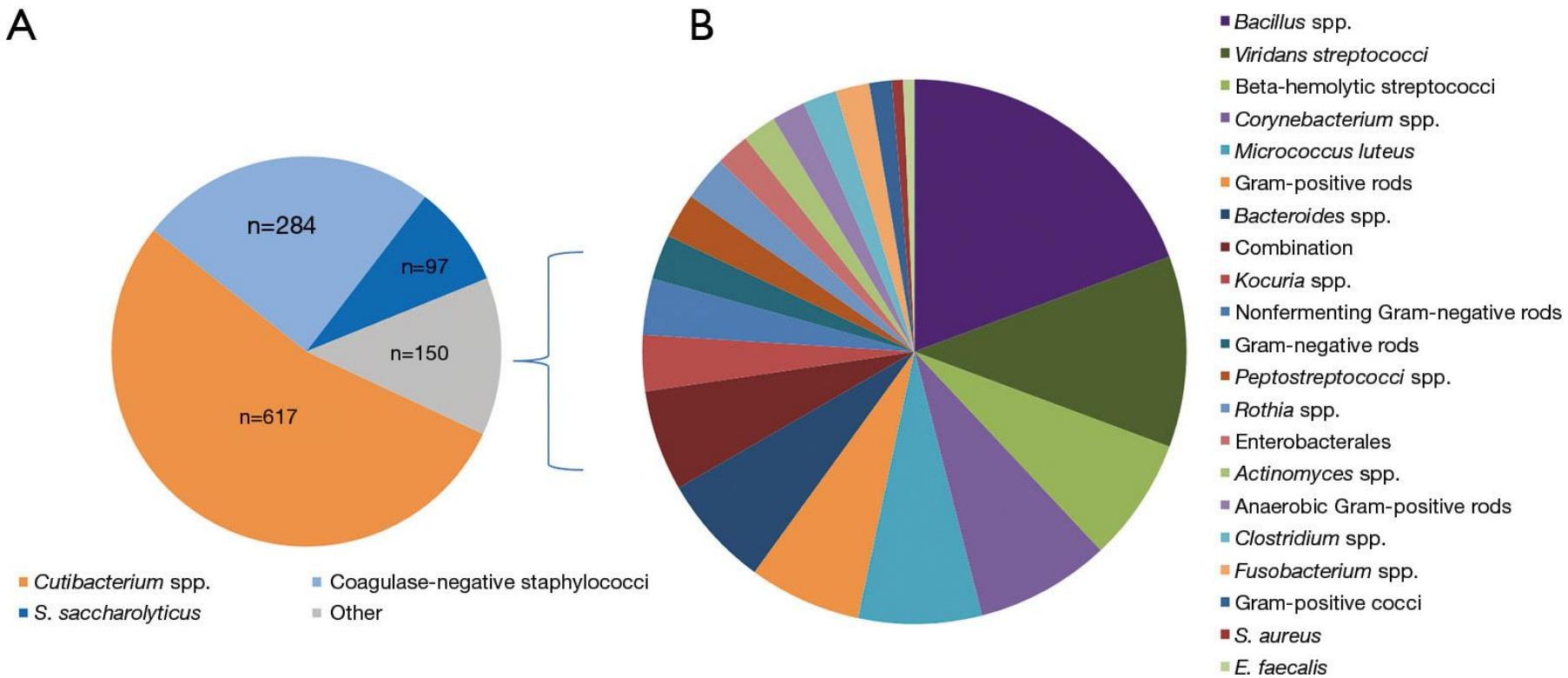
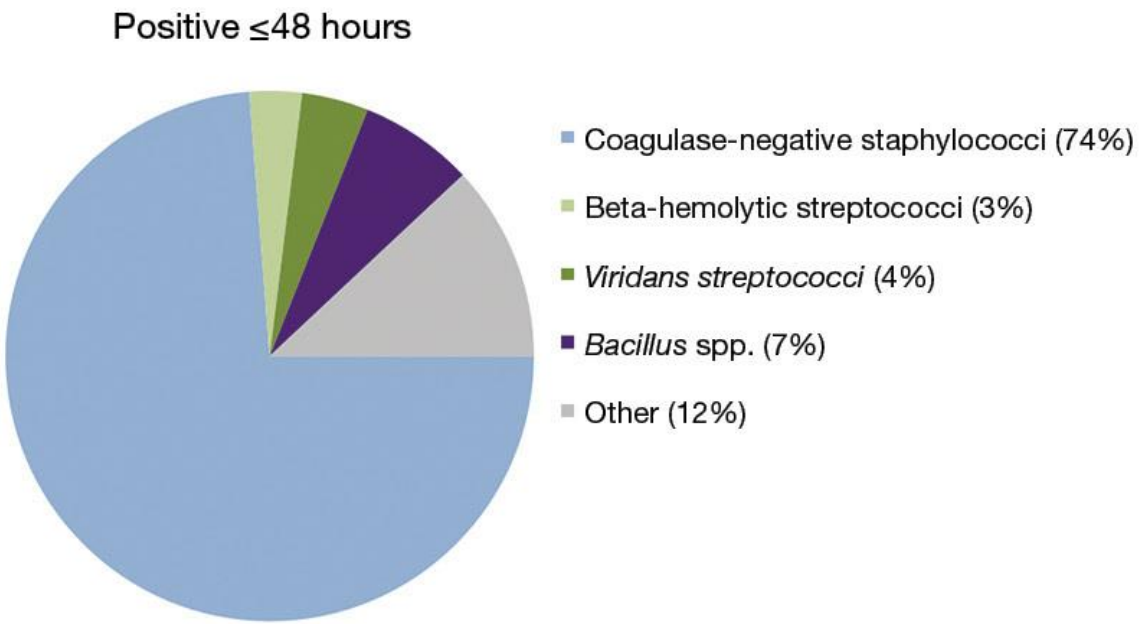
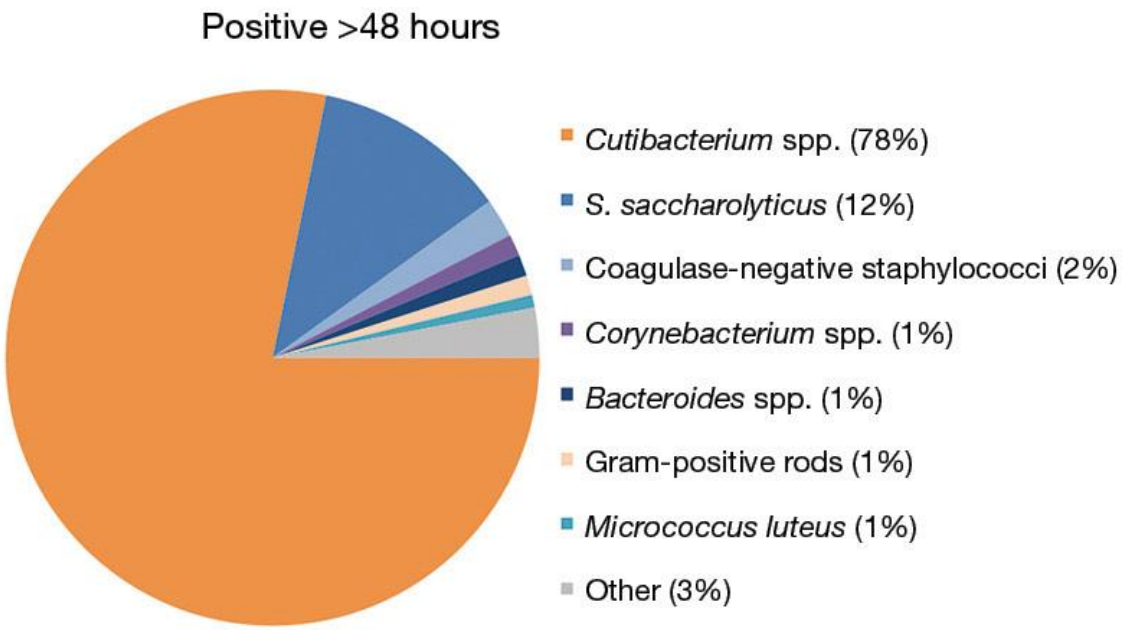
Jacobs MR BPAC 2018

Distribution of bacterial species in confirmed positive BacT/ALERT® screening of pooled BC derived platelets [2013–2019]. The proportions and absolute numbers of bacterial species are shown in (A), and the composition of species in the group “Other” (n=150) is shown in (B). BC, Buffy coats



Bacterial species in BacT/ALERT® screening of pooled BC derived platelets positive before (A) and after (B) 48 hours [2013–2019]. BC, Buffy coats





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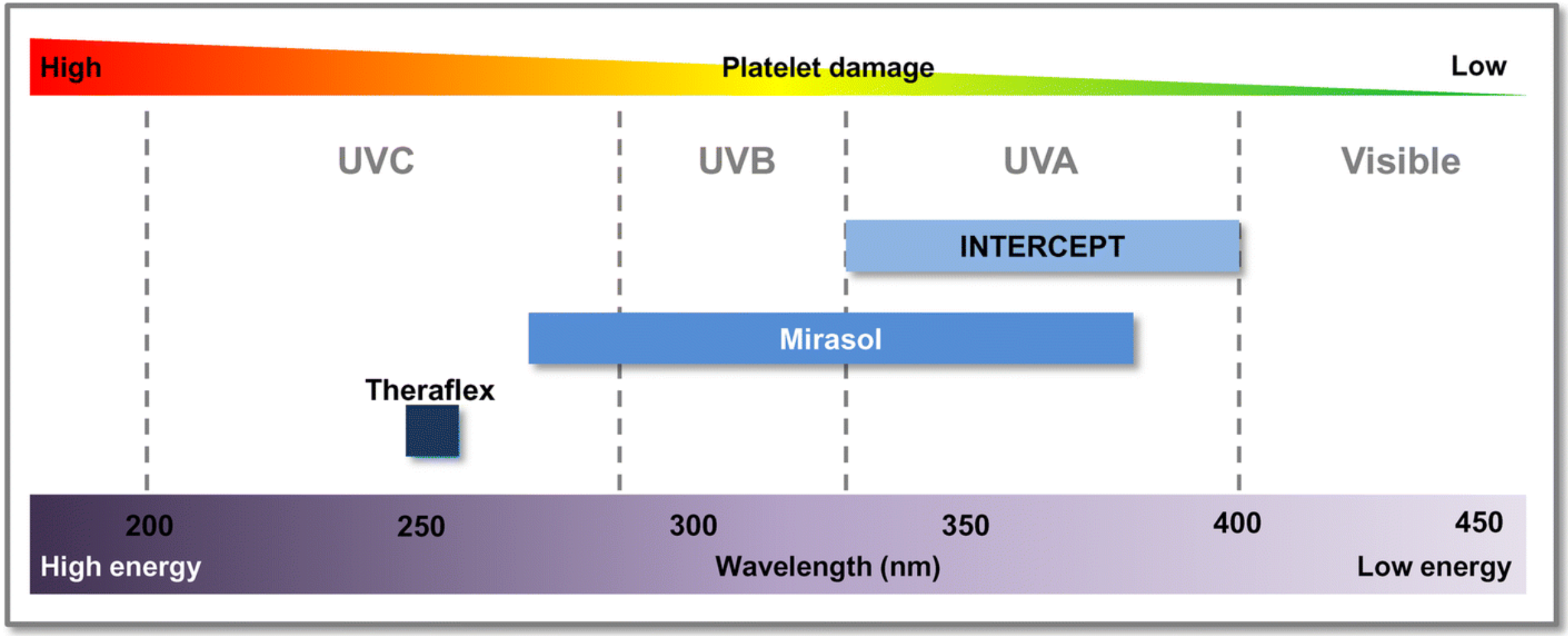
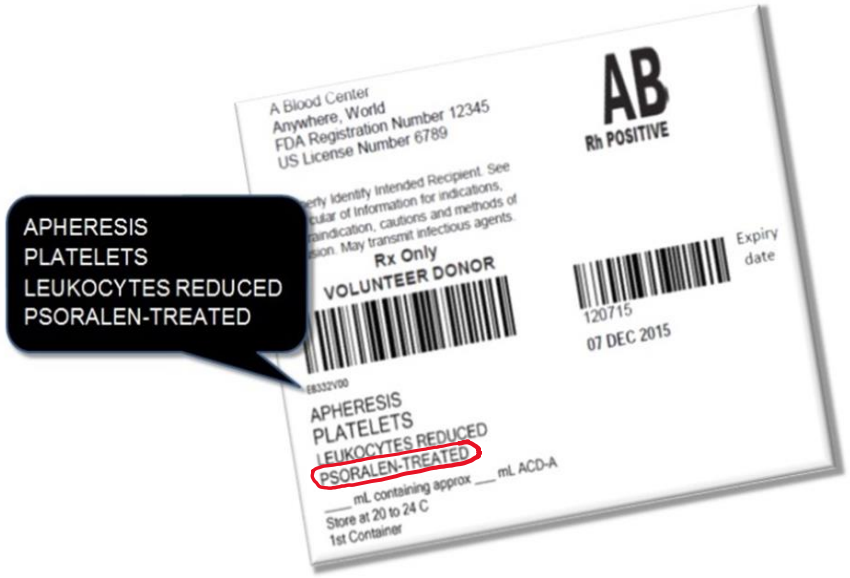
	Apheresis	Pre-storage pools of WBD Platelets	Single unit of WBD platelets	Post storage pools of WBD
7 days	LVDS ≥48 hours	NA	NA	NA
	LVDS ≥36 + secondary rapid testing	NA	NA	NA
	LVDS ≥36 + secondary culture ≥4 days	NA	NA	NA
	Primary culture ≥24 hours + secondary culture ≥4 days		NA	NA
	Primary culture ≥24 hours + secondary rapid testing			



Wavelength, energy, and dose for pathogen reduction/inactivation technologies compatible with platelets. Irradiation doses for each technology are 3 J/cm² (INTERCEPT), 6.2 J/mL (Mirasol), and 0.2–0.3 J/cm² (THERAFLEX)

Pathogen Reduced Platelet Labeling



- Labeled as: APHERESIS PLATELETS LEUKOCYTES REDUCED
- *Note new wording added to label:* PSORALEN-TREATED

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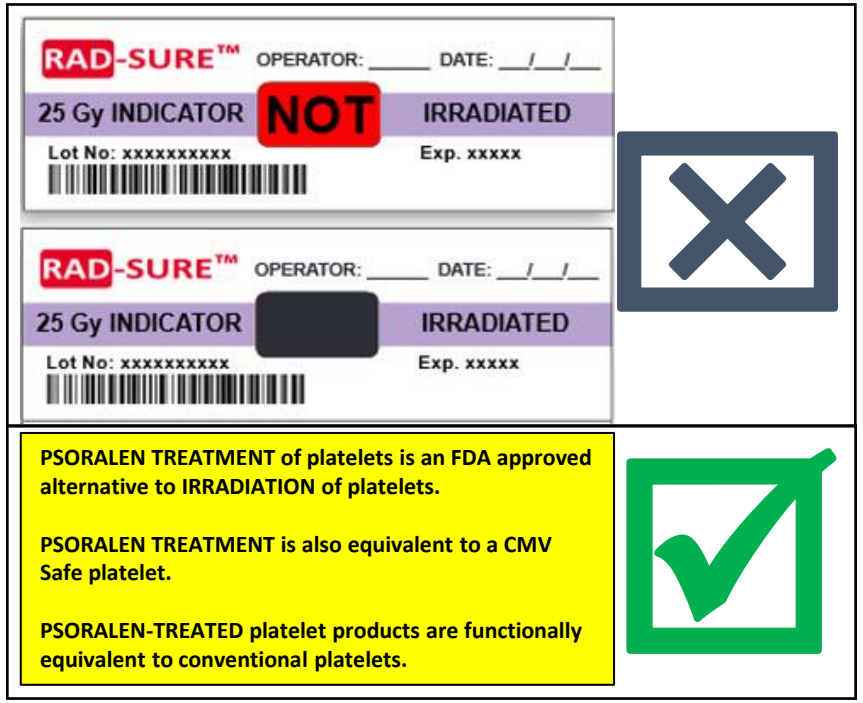
Irradiated VS. Pathogen Reduced Platelet Labeling

- PSORALEN TREATMENT (Pathogen Reduced) or IRRADIATION ARE BOTH FDA APPROVED METHODS to prevent Transfusion Associated Graft vs. Host Disease (TA-GVHD)

- The bag will not contain the Rad Sure irradiated sticker:
  - A yellow auxiliary sticker or tag as pictured id added to a PSORALEN-TREATED PLATELET.



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What are the benefits of PI technology to patients?

✓	✓	✓
Reduce the risk of transfusion-transmitted infections for patients	Eliminate the need for serologic testing for cytomegalovirus (CMV) and production of CMV-reduced-risk components	Eliminate the need for irradiation to prevent transfusion-associated graft-vs-host disease (TA-GVHD).

✓ No holding period or incubation delays before use- treatment within 24 hours of collection

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Phototherapy and Psoralens

- **USA INTERCEPT Package Insert**
  - *Contraindicated for preparation of platelet components intended for neonatal patients treated with phototherapy devices that **emit a peak energy wavelength less than 425 nm, or have a lower bound of the emission bandwidth <375 nm,** due to the potential for erythema resulting from interaction between ultraviolet light and amotosalen.*

- **Most, if not all phototherapy devices used on neonates in the US emit a peak wavelength ≥ 425 nm and none have a lower bound of the emission bandwidth < 375 nm.**