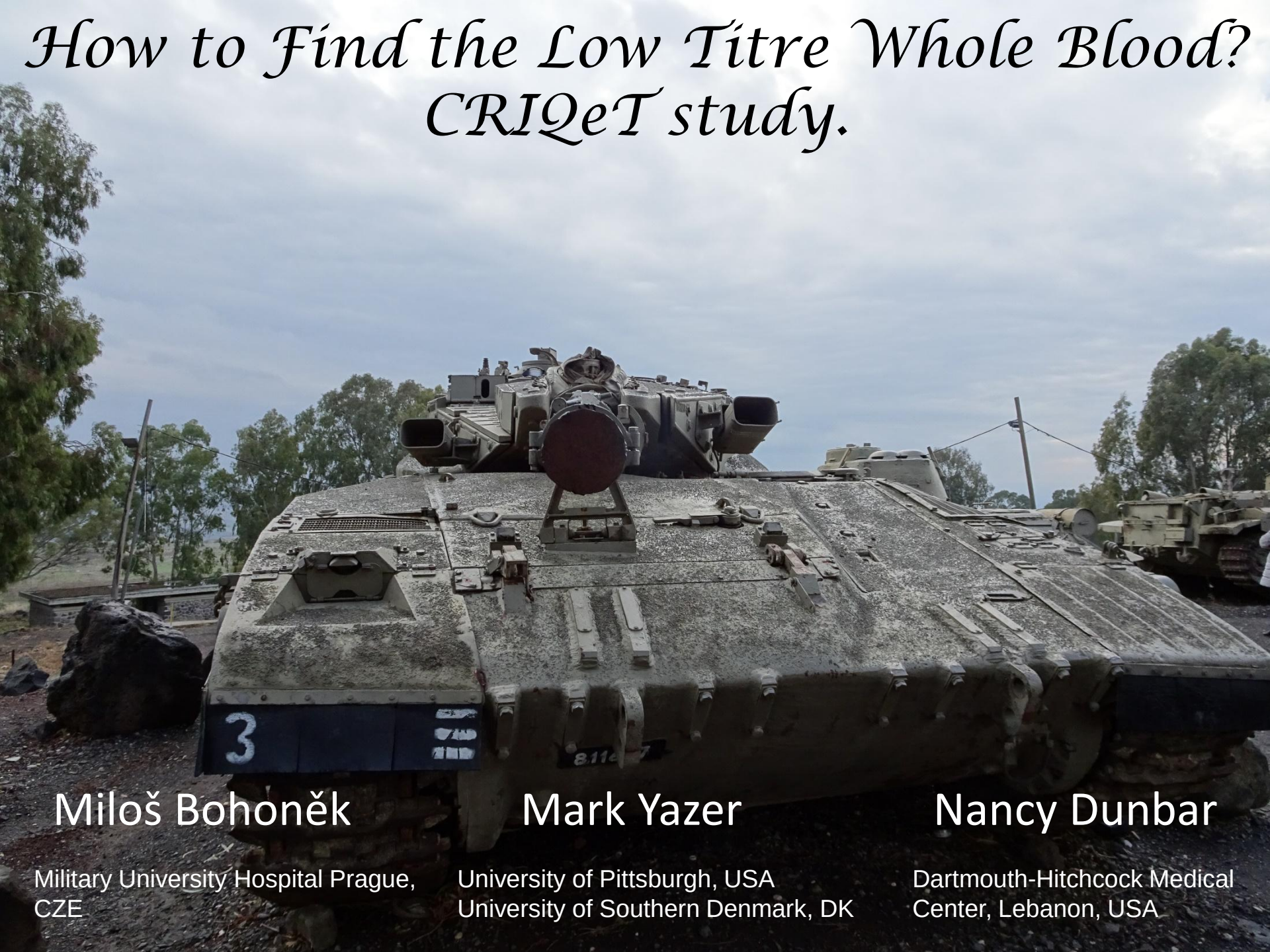
How to Find the Low Titre Whole Blood? CRIQeT study.



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Disclosures

- Grífols: Honoraria & SAB
- Macopharma: Scientific advisory board
- Octapharma: Scientific advisory board
- Terumo: Honoraria
- Haemonetics: Honoraria
- Cook Biotech: Scientific advisory board
- Verax Biomedical: Scientific advisory board
- New Health Sciences: Scientific advisory board

The puzzle of incompatible plasma

- Ideally everything would be ABO compatible, I guess
- Not practical, especially for platelets
  - Maybe with 7 day PLTs the supply will be better
- Group AB donors are rare and their plasma is precious
  - A bad trauma can really deplete the city's inventory
- Is there an alternative for massively bleeding patients?

ABO incompatible plasma? Seriously?

Yes!

- Begs some questions that need to be answered:
  - What is a safe titer threshold?
  - How often should donors be titered?
  - How should donors be titered?

Hemolysis happens primarily at high titer

Author, Year	Recipient		Platelet Product		Isohemagglutinin Titer		
	Age	ABO group	Type	ABO group	Saline	AHG	Hemoglobin Drop (%)
Zoes, 1977[25]	44	AB	Random donor pool	O	anti-A: 256 anti-B: 64	NR	NR
McLeod, 1982[26]	45	A	Apheresis	O	1,280	10,240	42.8
Conway, 1984[27]	15	A	Apheresis	O	8,192	NR	NR
Pierce, 1985[28]	2.5	A	Apheresis	O	512	32,000	50.4*
	58	B	Random donor	O	512	16,384	42.6
Ferguson, 1988[29]	66	A	Random donor	O	256	> 4,000	26 g/L
Reis, 1989[30]	56	B	Apheresis	O	NR	4,096	53.9
Murphy, 1990[31]	30	A	Apheresis	O	256	1,024	47.3
Mair, 1998[32]	28	A	Apheresis	O	128	NR	30.9
MacManigal, 1999[33]	72	AB	Apheresis	O	NR	NR	NR
Larsson, 2000[34]	44	A	Apheresis	O	16,384	NR	29.8†
Valbonesi, 2000[35]	51	A	Apheresis (dry platelet)	O	> 8,000	NR	37.2
	16	A					39.7*
Anonymous, 2002[36]	36	A	Apheresis	O	NR	2,048	22.5
	45	A	Apheresis	O	NR	4,096	15.3

Lozano and Cid *TMR* 2003;17:57-68

Examples of titer thresholds

Product	Source	Method	Critical titer: Direct agglutination, indirect agglutination
Group O Apheresis platelets	Josephson et al.[41]	Gel	≥64, ≥256
	Cooling et al.[6]	Gel	NT, ≥128
	Quillen et al.[42]	Gel	≥250, NT
	Karafin et al.[19]	Gel	≥512
	Pittsburgh, USA[16]	Tube	≥100, NT
	UK national guidance[43]	Automated Tube	≥100, NT ≥128, NT
	Scottish National Blood Transfusion Service[29]	Automated	≥50, NT
	Italy[44]	Gel	≥64, 256
	Germany[44]	Tube	≥64, NT
	Norway[44]	Gel	NT, ≥250
	Sweden[44]	Tube	≥100, ≥400
	Japan[44]	Gel	NT, ≥512
Group A Plasma	STAT study[7] 3 centers 1 center 13 centers	 Tube Tube NT	 ≥50, NT ≥100, NT
Whole Blood	Mayo Clinic, USA[33]	Tube	≥200, NT
	Pittsburgh, USA[34]	Tube	≥50, NT

Yazer et al. *Transfusion* 2018;58:532-538

Examples of titer thresholds for LTOWB in USA

<50	4 (17)
<100	2 (9)
<200	13 (57)
<256	3 (13)
Other	1 (4)

Yazer and Spinella *Transfusion* in press

What is a safe titer threshold?

- I don’t know
- Probably doesn’t exist
- Question really is – below what titer threshold is hemolysis *unlikely*
- Risk is always there

Balance of safety and inventory management

- Lots of variability between high titer rates and methods
- Group A plasma…

Center	# Units Tested	# Units Failed anti-B	Fail Rate	p
Tube <50	1068	84	8%	index
Tube <50	1297	105	8%	0.88
Tube <50	2816	359	13%	<0.0001
Tube <100	37,106	5,060	14%	<0.0001

Harm and Yazer et al. *Transfusion* in press

Balance of safety and inventory management

- Group O whole blood…

Titer method	High titer -A rate	High titer -B rate	High titer -A & -B rate	High titer rate (overall)
Tube 50 N=2980	11.78%	2.92%	5.87%	20.57%
Tube 50 N=94	25.53%	4.26%	12.77%	42.55%
Tube 200 N=172	6.40%	n/a	n/a	6.40%

Harm and Yazer et al. *Transfusion* in press

How often should donors be titered?

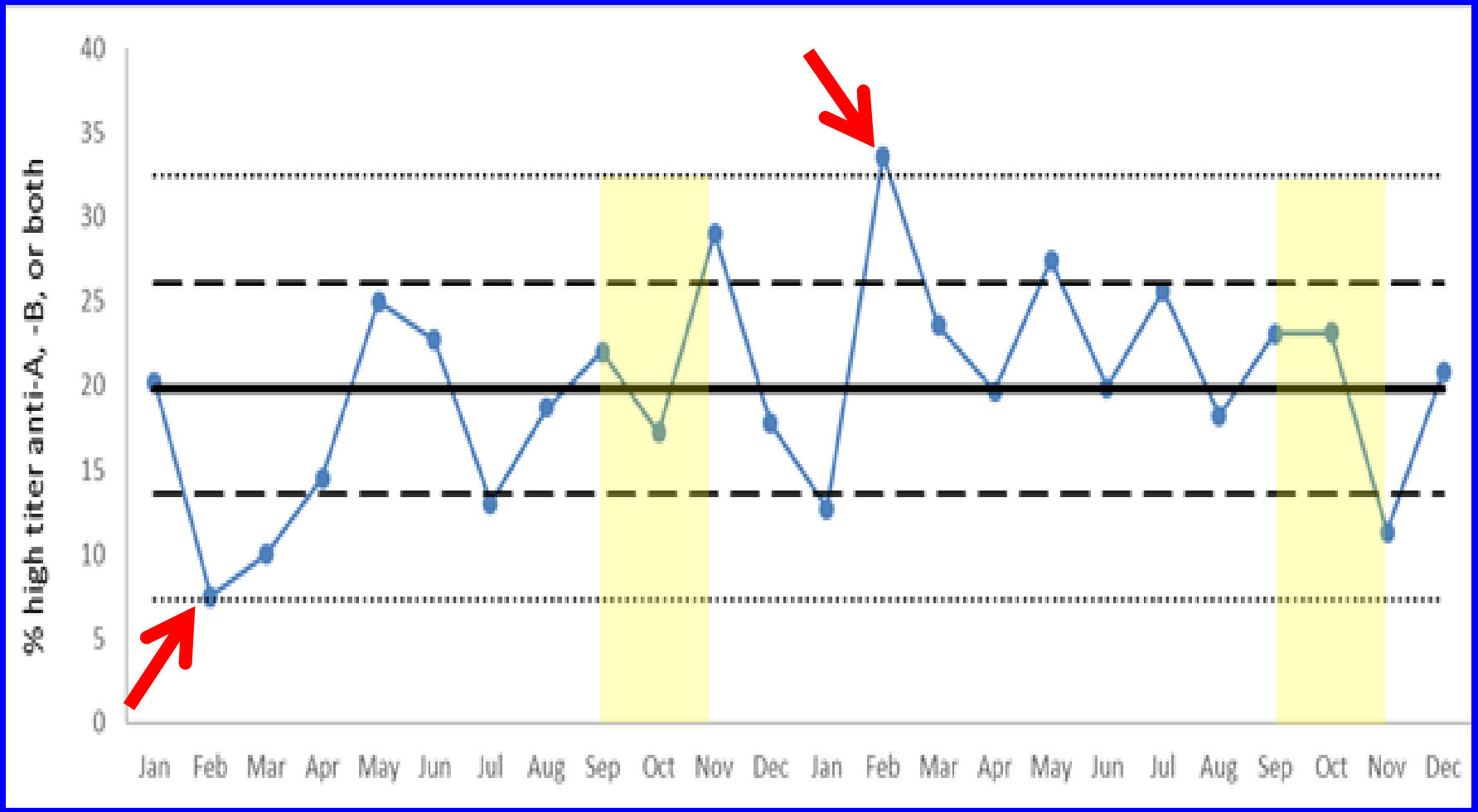
- Measured anti-A and/or –B in 56 healthy Danish people every 3 months for a year
- Solid phase, automated method
  - (Immucor NEO)
- Expressed as $\log_2$ titer steps
  - Titer 32 = 5 titer steps

No.	Volunteers	Anti-A, IgM	Anti-A, IgG	Anti-B, IgM	Anti-B, IgG
O	19	4.7 (0.45)	4.9 (0.39)	4.3 (0.50)	3.5 (0.30)
A	27			3.5 (0.41)	0.1 (0.31)
B	10	4.0 (0.37)	0.3 (0.58)		
Overall	56	0.42 (n = 29, 0.87)	0.47 (n = 29, 0.96)	0.45 (n = 46, 0.91)	0.30 (n = 46, 0.62)

- Maximum titer step variation was 1.5 (IgG anti-A) and 1 (all 3 others)

Sprogøe U et al. *JTACS* 2017;82:S87-S90

No periodicity of high titer whole blood units



Harm and Yazer et al. *Transfusion* in press

Periodicity found in US Army Rangers

- 58% higher chance of being low titer if tested in Fall

	Low Titer (<256) Donor Status	
Variables	AOR (95% CI)	p value
Season		
Winter (ref)	--	--
Spring	0.83 (0.57,1.23)	0.36
Summer	1.16 (0.90,1.51)	0.25
Fall	1.58 (1.22,2.04)	0.001

Bailey et al. *Transfusion* in press

So how should we perform antibody titer testing?

*Conco**R**dance*
*I**n** Q**uantifying*
*T**iters* (CRIQeT) study

Mark H. Yazer, Nancy M. Dunbar, Carolina Bonet Bub, Brittany E. Condict, Robyn Dunn, Miloslava Janoušková, Jose Kutner, Ludmila Landová, Hana Lejdarová, Božena Nesvačilová, Rita Pacasová, Renata Procházková, Lenka Řehořová, Jay S. Raval, Alyssa Ziman, and Miloš Bohoněk

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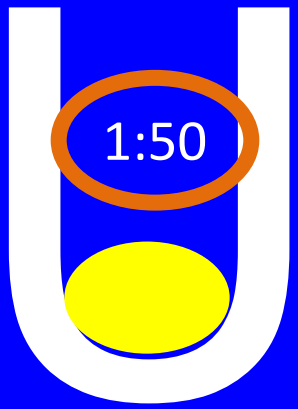
CRIQeT study protocol



Routine 1-dilution method, no incubation

Positive?

Negative?

CRIQeT study results

- Many different products tested

Blood products / titer thresholds		Manual tube	Manual and automated buffered gel card	Automated microplate
Number of plasma-containing blood products tested		374	206	49
Number of antibodies tested		698	412	98
Type of blood product tested	Group O WB	289 (77.3)	168 (81.6)	49 (100)
	Group O SDP	28 (7.5)	31 (15)	0 (0)
	Group O plasma	7 (1.9)	7 (3.4)	0 (0)
	Group A plasma	50 (13.4)	0 (0)	0 (0)
Titer threshold	1:50	374 (100)	184 (89.3)	49 (100)
	1:64	0 (0)	22 (10.7)	0 (0)

Yazer et al. *Transfusion* in press

CRIQeT study results

- Some variability of testing results between methods

	Manual tube	Manual and automated buffered gel card	Automated microplate
Sensitivity (95% CI)	0.88 (0.83-0.92)	0.95 (0.91-0.98)	0.76 (0.71-0.93)
Specificity (95% CI)	1.00 (0.98-1.00)	0.87 (0.81-0.91)	0.96 (0.92-0.99)
Positive Predictive Value (95% CI)	0.99 (0.97-0.99)	0.85 (0.79-0.89)	0.88 (0.80-0.98)
Negative Predictive Value (95% CI)	0.93 (0.90-0.95)	0.96 (0.92-0.98)	0.90 (0.88-0.97)
Accuracy (95% CI)	0.95 (0.93-0.97)	0.90 (0.87-0.93)	0.90 (0.82-0.95)

Yazer et al. *Transfusion* in press

CRIQeT study conclusion

The IS 1-dilution titer test without an incubation period is suitable for the identification of high titer units, thereby eliminating the need for the transfusion service or blood center to perform an extended incubation during titer testing

Yazer et al. *Transfusion* in press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