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PRODUCING 2 PATHOGEN INACTIVATED PLATELET CONCENTRATES FROM 8 RANDOMLY PICKED BUFFY COATS - IN SILICO EVALUATION AND PILOT STUDY

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Introduction

In the area of Zurich, demand for red blood cells has declined by almost 30% since 2011. Consequently, the amount of whole blood (WB) donations collected also dropped, resulting in fewer buffy coats (BCs) available to make platelet concentrates (PCs). On the other hand, demand for PCs, routinely pathogen inactivated (PI), didn't drop. This development is a potential threat to the supply with PCs. An approach to mitigate the situation is pooling less BCs to get 1 PC. Pooling 4 instead of 5 BCs would theoretically allow making 25% more PCs. Since reducing the platelet (plt) content of a PC doesn't decrease its effectiveness to the same extent, pooling less BCs to get more PCs actually improves supply. However, pools of 4 BCs show too much variability to meet Swiss QC specifications (spec) for PI-PCs (≥ 2.4 E11 plts in ≥ 90%) *(Fig 1)*. Since variability decreases if pool size increases, a concept of pooling 8 BCs to produce 2 PI-PCs was evaluated in silico followed by a pilot study. For convenience, AB0 but not RhD identity was considered when pooling BCs.

Figure 1: Platelet Concentrates Made from 4 or 5 Buffy Coats

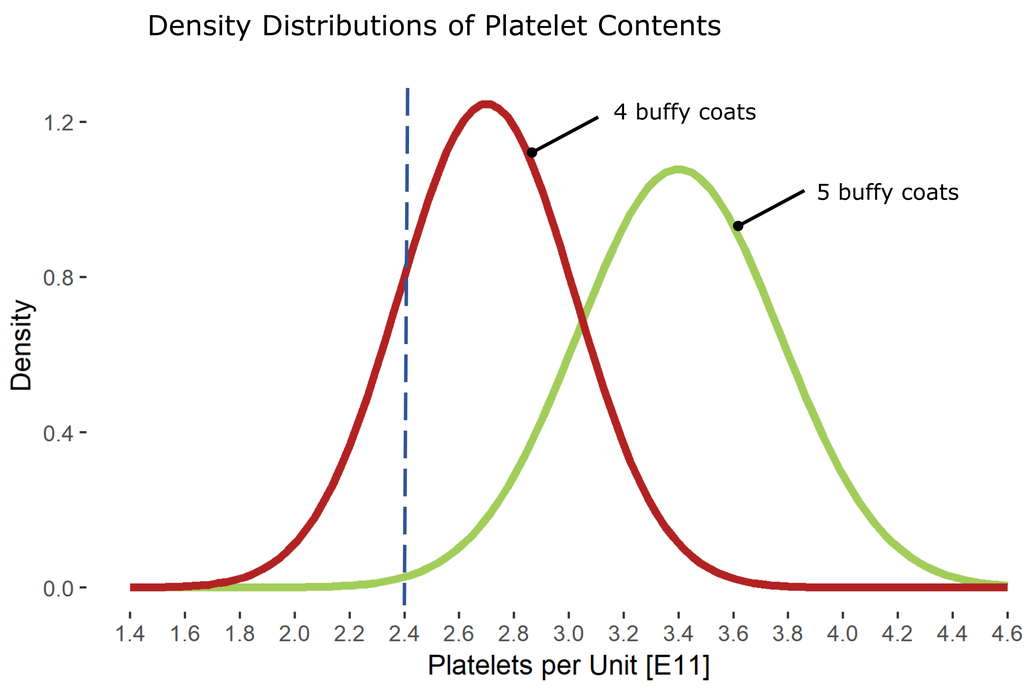


Figure 1 : Simulated density distributions of platelet concentrates made from:
- ***5 buffy coats** (**green**; av = 3.4 and sdv = 0.37 E11 plts/unit; 0.3% < 2.4 E11 plt/unit)*
- ***4 buffy coats** (**red**; av = 2.7 and sdv = 0.32 E11 plts/unit; 18.9% < 2.4 E11 plt/unit)*

n=10,000 iterations *each.*

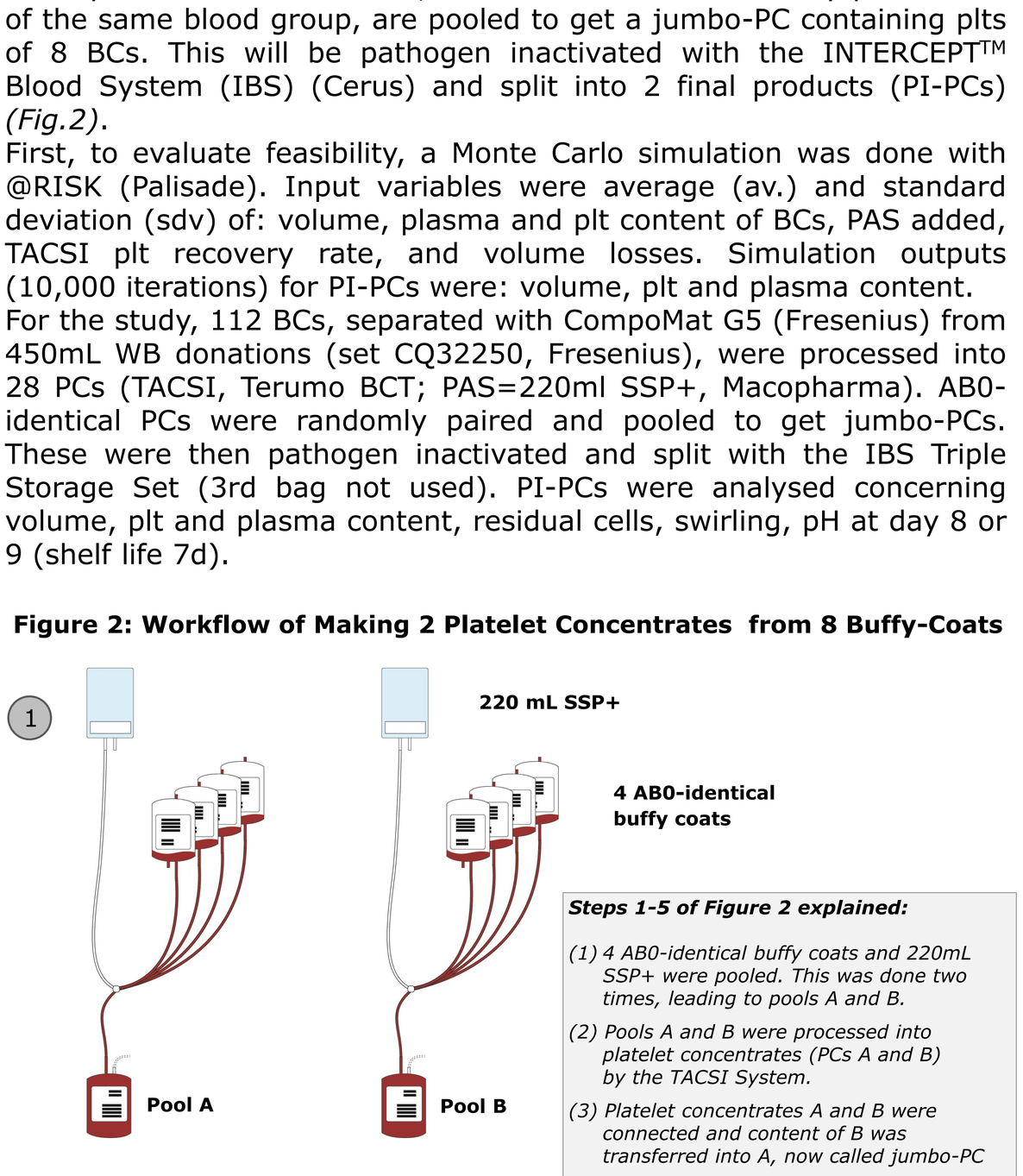
Methods

Concept: 2 AB0-identical PCs, each made from 4 randomly picked BCs of the same blood group, are pooled to get a jumbo-PC containing plts of 8 BCs. This will be pathogen inactivated with the INTERCEPT™ Blood System (IBS) (Cerus) and split into 2 final products (PI-PCs) *(Fig.2)*.

First, to evaluate feasibility, a Monte Carlo simulation was done with @RISK (Palisade). Input variables were average (av.) and standard deviation (sdv) of: volume, plasma and plt content of BCs, PAS added, TACSI plt recovery rate, and volume losses. Simulation outputs (10,000 iterations) for PI-PCs were: volume, plt and plasma content.

For the study, 112 BCs, separated with CompoMat G5 (Fresenius) from 450mL WB donations (set CQ32250, Fresenius), were processed into 28 PCs (TACSI, Terumo BCT; PAS=220ml SSP+, Macopharma). AB0-identical PCs were randomly paired and pooled to get jumbo-PCs. These were then pathogen inactivated and split with the IBS Triple Storage Set (3rd bag not used). PI-PCs were analysed concerning volume, plt and plasma content, residual cells, swirling, pH at day 8 or 9 (shelf life 7d).

Figure 2: Workflow of Making 2 Platelet Concentrates from 8 Buffy-Coats



Steps 1-5 of Figure 2 explained:

(1) 4 AB0-identical buffy coats and 220mL SSP+ were pooled. This was done two times, leading to pools A and B.

(2) Pools A and B were processed into platelet concentrates (PCs A and B) by the TACSI System.

(3) Platelet concentrates A and B were connected and content of B was transferred into A, now called jumbo-PC

(4) The jumbo-PC was connect to the IBS triple storage set for pathogen inactivation.

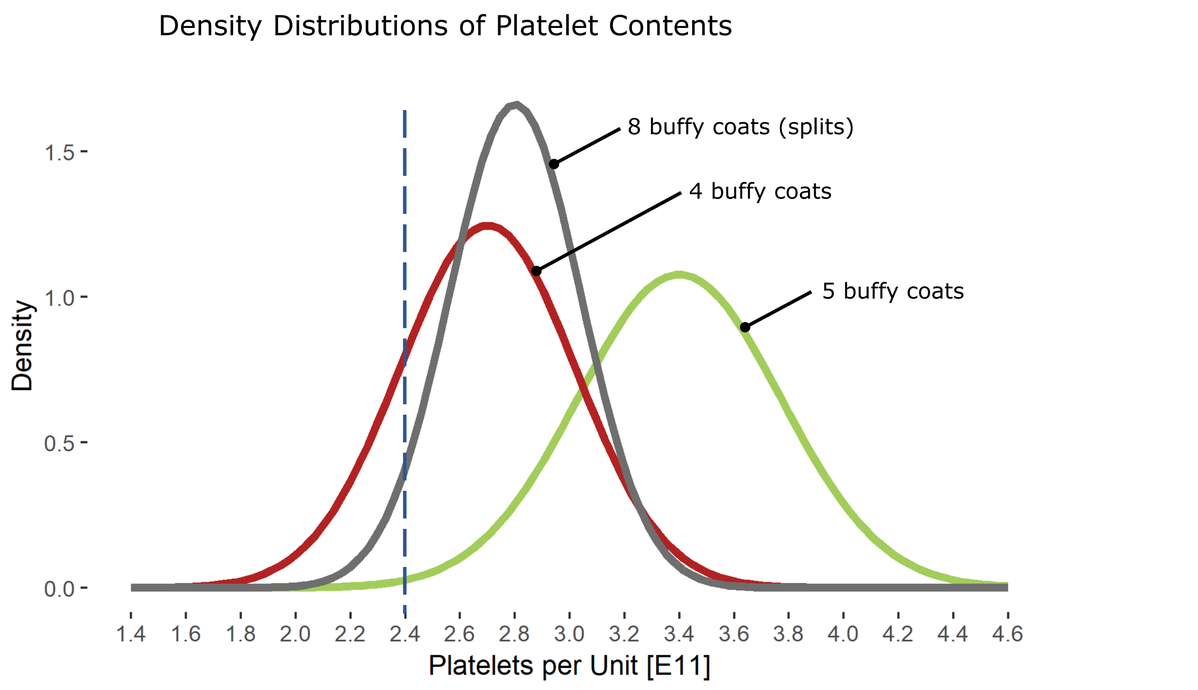
(5) Pathogen inactivation was performed and afterwards the jumbo-PC was split into two of the three bags of the IBS set (3rd bag not used ✖)

Results

Simulated PI-PCs had an av. plt yield of 2.8 E11 (sdv 0.24 E11) and 4.2% contained < 2.4 E11 plts (range 1.8 – 3.8 E11) *(Fig. 3)*. Av. volume was 290mL and plasma content ranged 34 – 38% (spec 32 – 47%).

PI-PCs of the study contained in av. also 2.8 E11 plts (sdv split 1= 0.14 and split 2= 0.17 E11, p>0.05). None contained < 2.4 E11 plts (range 2.4 – 3.0 E11) but the probability density function forecasts 1.0%. Av. volume was 287mL and plasma content ranged 35 – 37%. Residual cells and swirling passed but one pH value didn't (spec >6.4, range 6.4 – 7.1, av. 6.8) *(Fig. 4)*.

Figure 3: Platelet Concentrates Made from 4, 5 or 8 Buffy Coats



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- ***8 buffy coats** and then splitted (**grey**; av. 2.8 and sdv = 0.24 E11 plts/unit; 4.2% < 2.4 E11 plt/unit)*

n=10,000 iterations *each.*

Figure 4: Results Pilot Study

Parameters Checked	Average	Sdv	(Range)	Specification	Fraction Passed
Volume [mL]	287	6.8	(275 - 297)	> 150	100%
WBC [E6/Unit]	0.13	n.s.	(0.04 - 0.19)	< 1	100%
RBC [E6/mL]	0.50	n.s.	(0.27 - 0.94)	< 4	100%
Plts [E11/Unit]	2.8	0.16	(2.4 - 3.0)	≥ 2.4*	100%
Plasma Content [%]	36	0.41	(35 - 37)	32 - 47	100%
pH after shelf life	6.80	0.16	(6.4 - 7.1)	> 6.4	96%
Swirling	n.a.	n.a.	all passed	well visible	100%

Figure 4: Results pilot study: Results of splits1 and 2 pooled; *n=28;* Volume losses due to sampling were calculatory compensated; *WBC=White Blood Cells; RBC=Red Blood Cells; plts=platelets; n.s. = "not shown" (because normal distribution can't be assumed); n.a.=not applicable; Specifications according to Swiss requirements for platelet concentrates; * at least 90% of QC samples have to fulful; all parameters passed except 1 pH value after shelf life.*

Figure 5: Histogram of Platelet Contents – Pilot Study vs Simulation

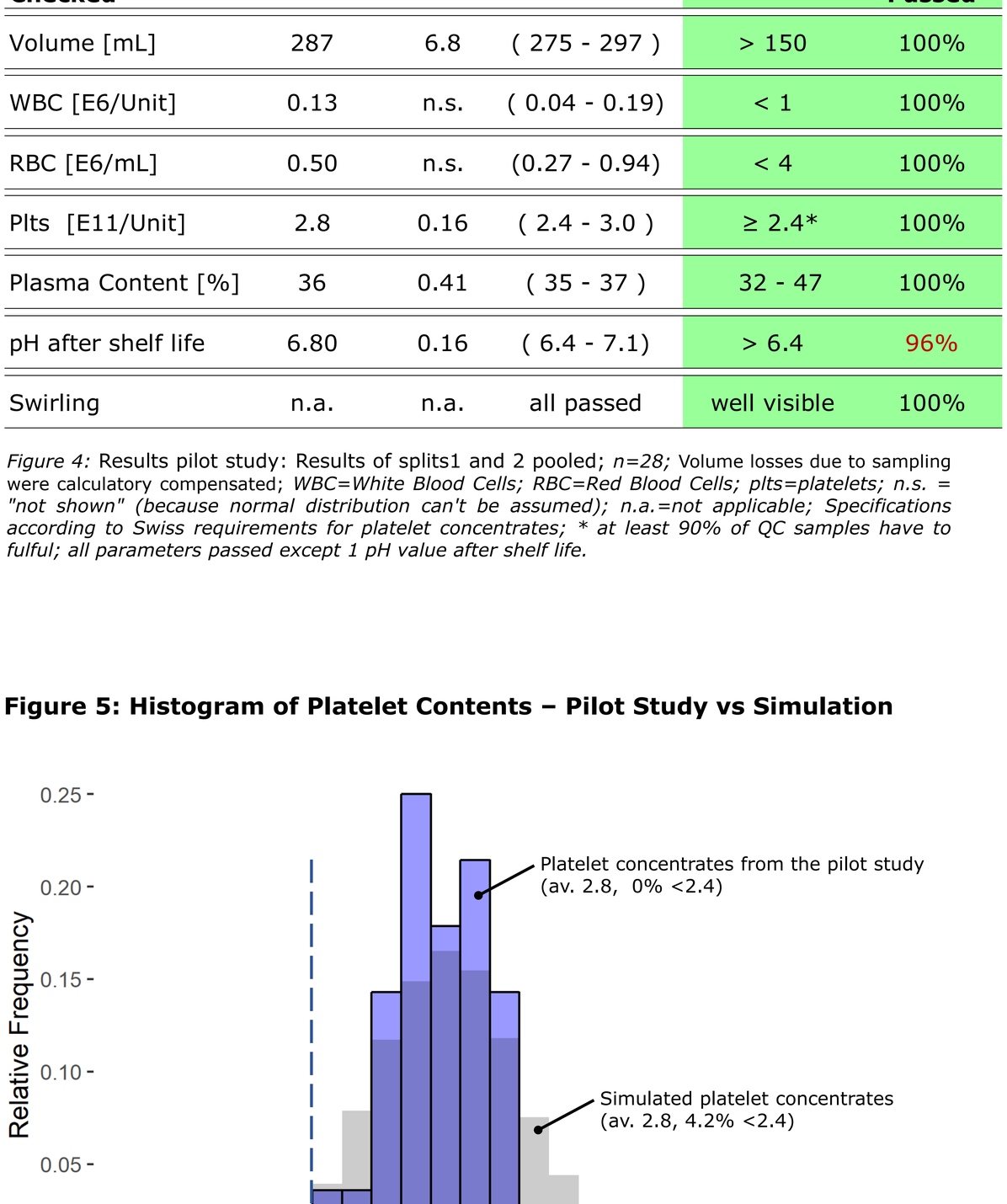

*Figure 5:*Histograms of platelet contents resulting from the pilot study (**blue,** n=28) and from the simulation (**grey**, n=10,000): Av. plt content is 2.8 E11/unit in both cases; Sdv is 0.16 in the pilot study (results of splits1 and 2 pooled) and 0.24 E11/unit according to the simulation.

Conclusion

With the concept, 2 PI-PCs passing Swiss spec for ptl content can be made from 8 random BCs. However, one pH value was low, which needs further investigation. Simulated av. values showed good matches with the study but variabilities were somewhat higher *(*e.g. plt contents, *Fig. 5)*. Probably because rare events didn't occur in the small study, showing one of the simulation's strengths: estimating long-term performance.