A framework for drug pharmacokinetics during cardiopulmonary bypass

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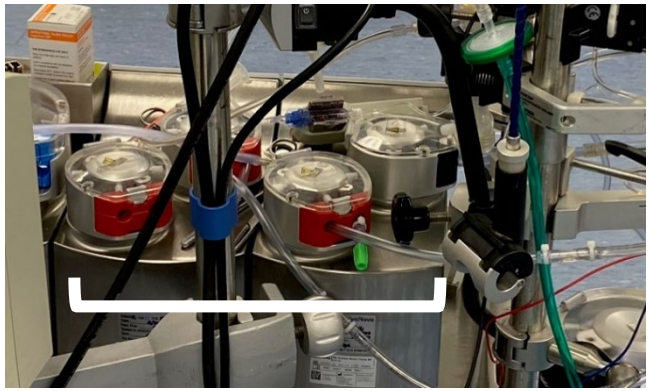
CPB device – complex

Front view

Rear view

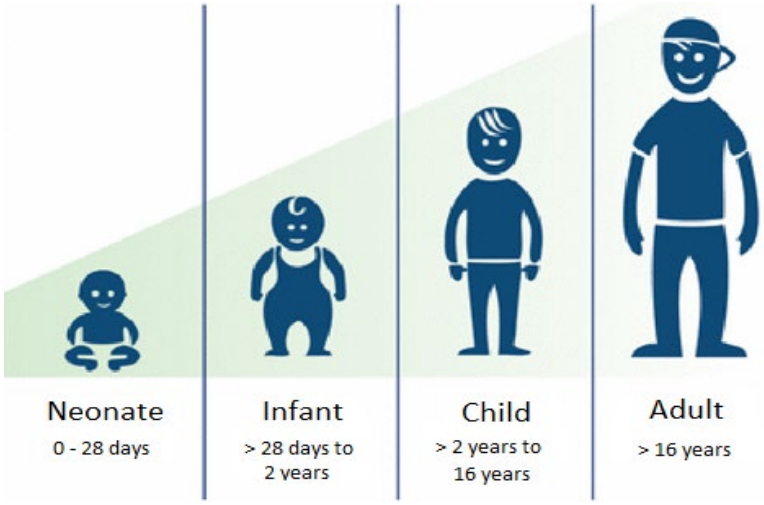


Cardiac surgery and CPB

- Cefazolin is a β-lactam antibiotic that is administered for prophylaxis against bacterial infections during cardiac surgery
  - IV administration
  - Renally eliminated
  - Highly bound to albumin (~90%)

- Patient dosed with cefazolin and also dosed into the CPB device

- CPB device factors
  - Different sizes
  - Different coatings



Aims

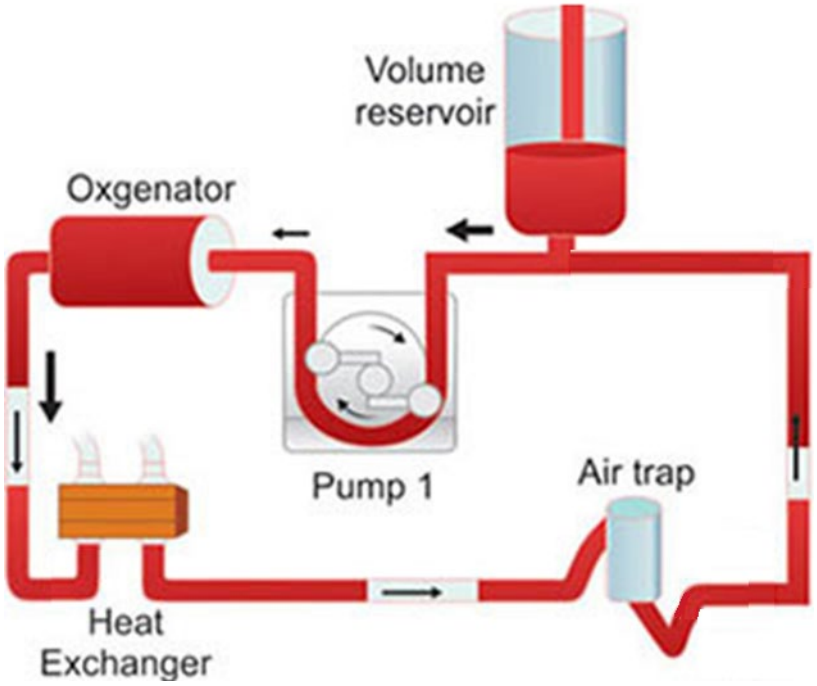
1. Population PK model for cefazolin in neonates, infants and children undergoing cardiac surgery supported by CPB
   - Does CPB impact population PK?
   - Is change clinically relevant?

2. Quantify cefazolin adsorption to CPB devices
   - How much is bound to CPB device?
   - Is adsorption clinically relevant?

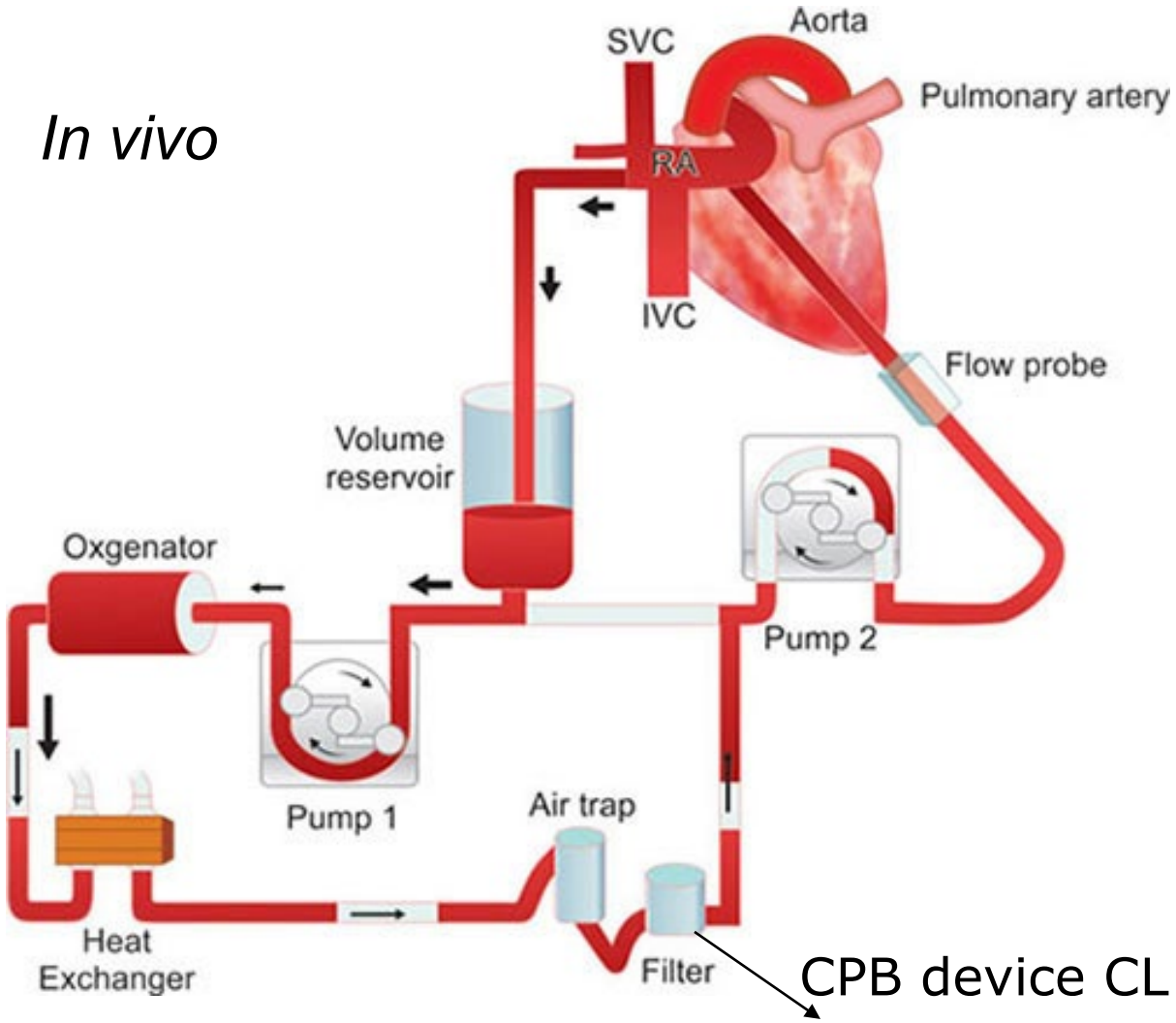
3. Can findings be generalised to other drugs?
   - Application to vancomycin

CPB *ex vivo* and *in vivo* studies

Ex vivo



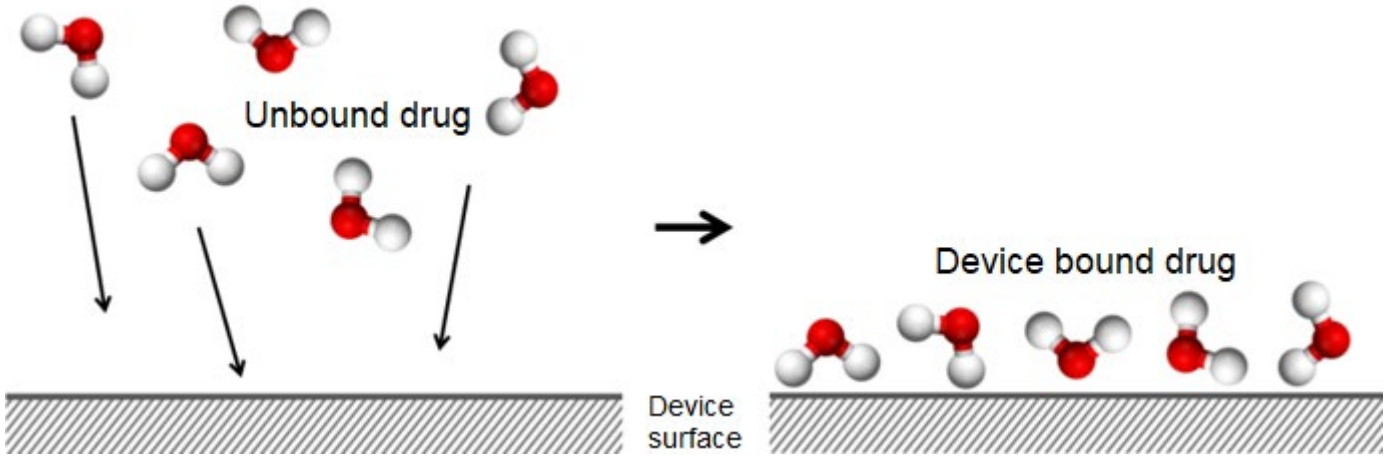
In vivo



CPB device adsorption

- Drug is adsorbed to central reservoir, tubing and oxygenator

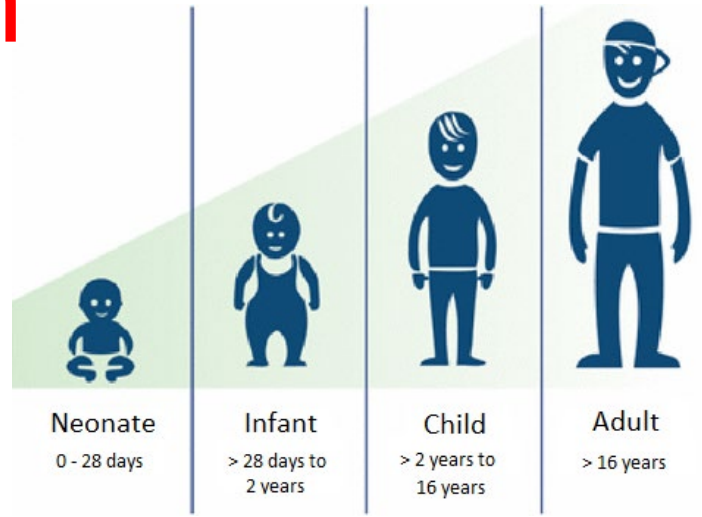
- Drugs that are highly plasma-protein bound have shown greater adsorption to CPB devices[1]



1. Shekar K, Roberts JA, Mcdonald CI, Ghassabian S, Anstey C, Wallis SC, Mullany DV, Fung YL, Fraser JF. Protein-bound drugs are prone to sequestration in the extracorporeal membrane oxygenation circuit: results from an ex vivo study. Critical Care. 2015 Dec;19(1):1-8.

Factors influencing adsorption

- Sizes
  - Affect area for adsorption (neonate, infant, child, adult)



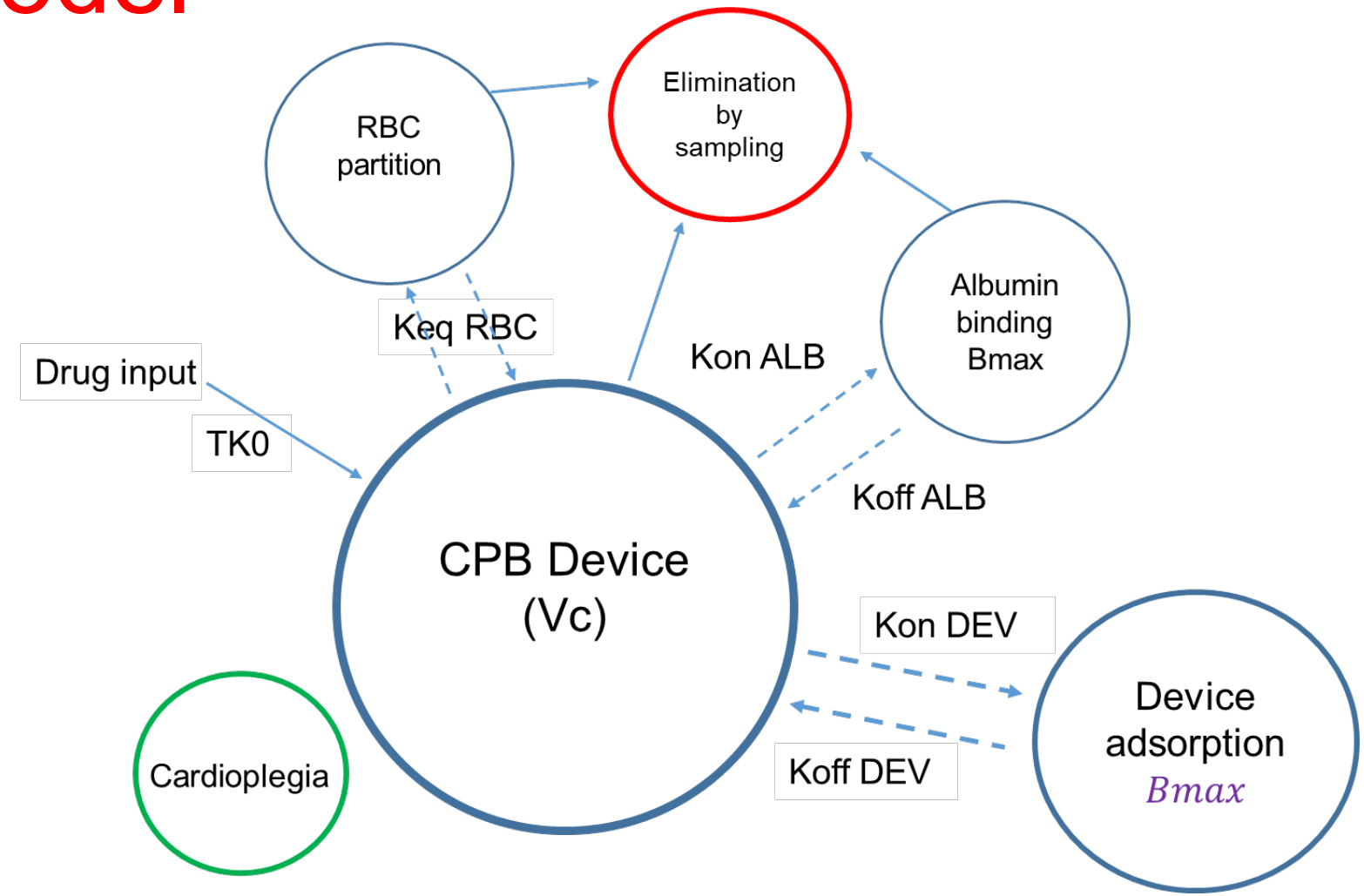
- Coatings designed to decrease adsorption e.g.
  - Xcoating™ (poly-2-methoxy-ethyl-acrylate coating)
  - Rheoparin® (heparin type coating)
  - PH.I.S.I.O (phosphorlycholine coating)

- Matrices
  - Plasmalyte or blood based (not expected to affect adsorption)

CPB *ex vivo* model

- Kinetic binding model with saturable binding ($Bmax$), parameterised by K_d (dissociation constant) and $T2_{off}$ (half-life of dissociation)

$$T2_{off} = \frac{\ln(2)}{K_{off}} \qquad K_d = \frac{K_{off}}{K_{on}}$$



RBC – red blood cell, Keq – equilibration rate constant, Kon – rate constant for association, Koff – rate constant for dissociation, ALB – albumin, DEV – device, TK0 – constant rate infusion

CPB *ex vivo* – results

- Device size ($Bmax$) and device coating (K_d, $T2_{off}$) are factors describing rate and extent of adsorption

Parameter	Units	Estimate	RSE %
$Bmax$			
Neonate	mg	**40**	30%
Infant	mg	**49**	33%
Child	mg	**78**	16%
Adult	mg	**196**	1%
K_d			
Xcoating™	mg/L	**114**	20%
PH.I.S.I.O/ Rheoparin®	mg/L	**0.17**	68%
$T2_{off}$			
Xcoating™	min	**71**	8%
PH.I.S.I.O/ Rheoparin®	min	**1**	66%

Ex vivo model evaluation with vancomycin

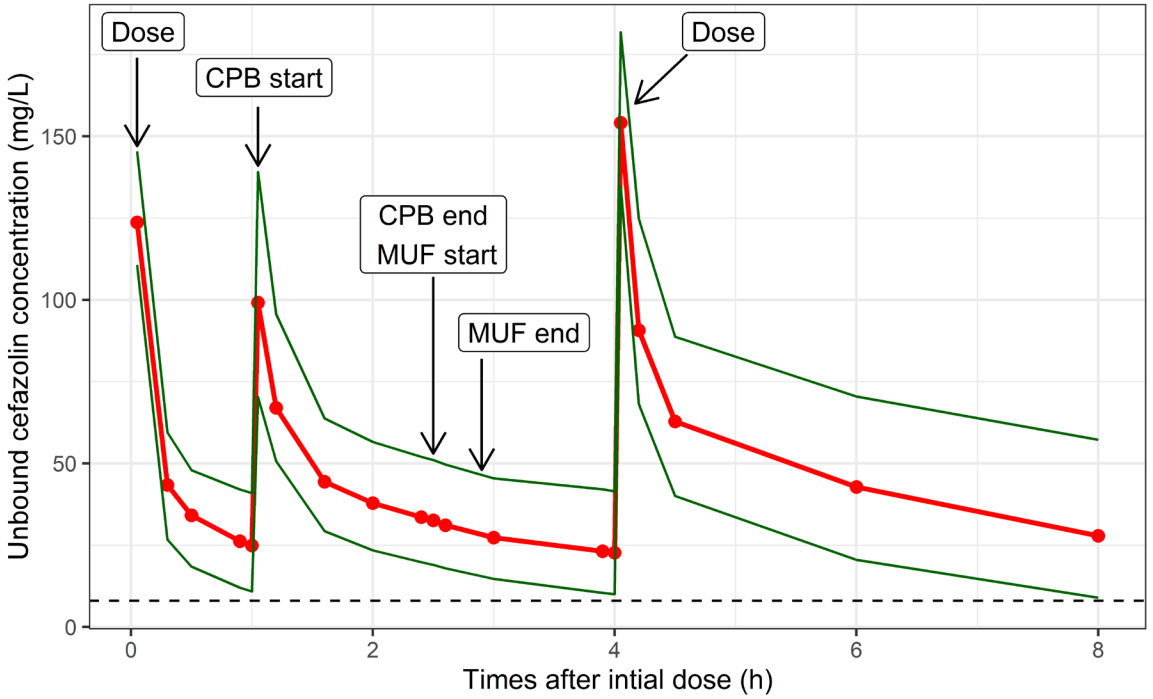
- Vancomycin administered for surgical antimicrobial prophylaxis
  - Moderately protein bound (~50%)

- The *ex vivo* model described the vancomycin data with no changes except for estimation of vancomycin specific binding parameters

Parameter	Units	Cefazolin	Vancomycin
$Bmax$			
Neonate	mg	**40**	**5**
Child	mg	**78**	**8**
Adult	mg	**196**	**13**
K_d PH.I.S.I.O	mg/L	**0.17**	**0.01**
$T2_{off}$ PH.I.S.I.O	min	**1**	**0.7**

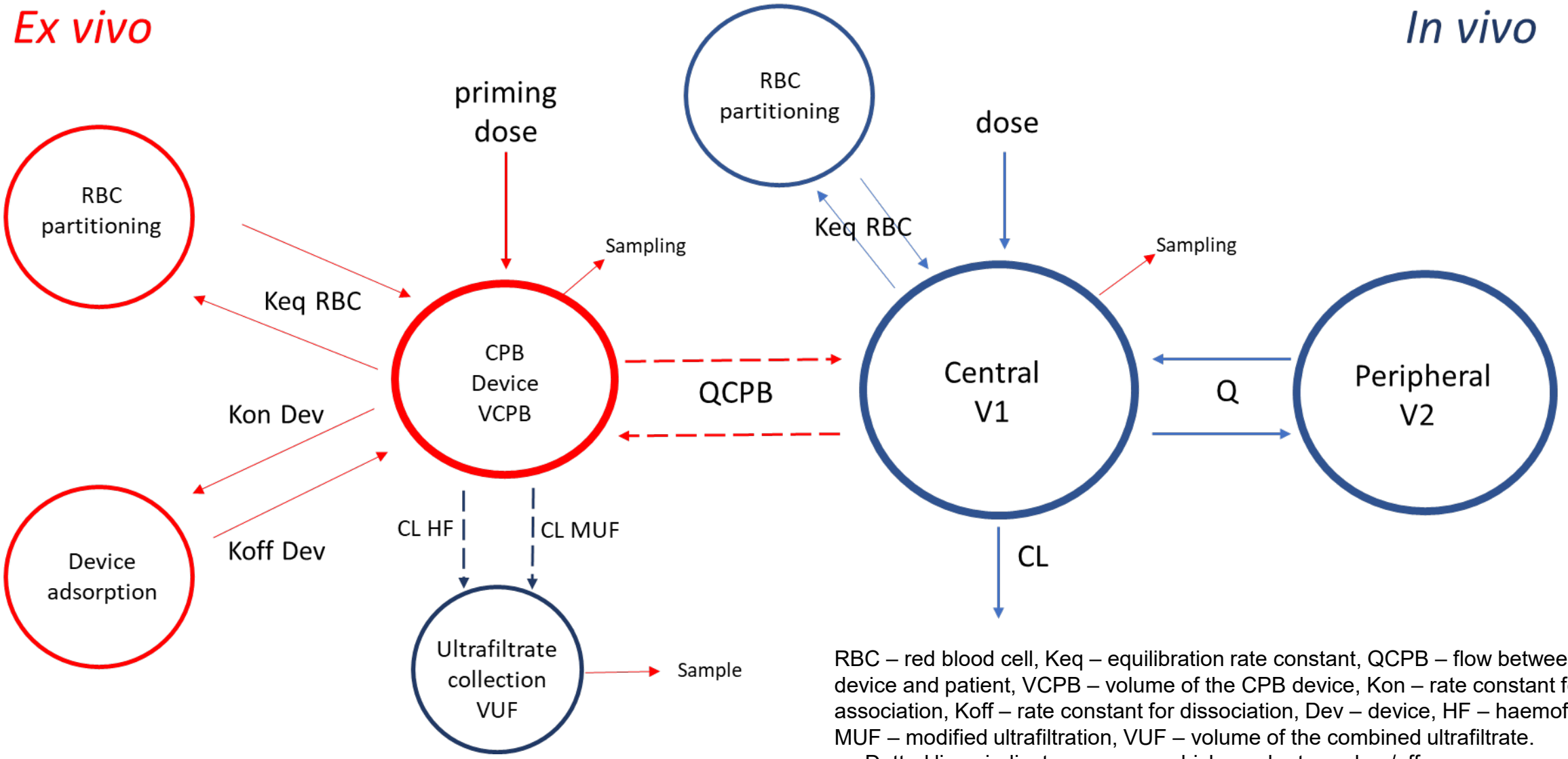
CPB *in vivo* setting and participants

- 50 neonates, infants, children undergoing cardiac surgery supported by CPB at Starship Children's Hospital, Auckland, New Zealand
  - 3 days to 14 years Post Natal Age (PNA)
  - Between 11 – 22 samples taken per patient



- Unbound (n=678) and total (n=622) and concentrations quantified using HPLC-UV and LCMS
  - Unbound concentrations used to estimate PK parameters
  - Total concentrations used to estimate binding parameters

Structural model



RBC – red blood cell, Keq – equilibration rate constant, QCPB – flow between CPB device and patient, VCPB – volume of the CPB device, Kon – rate constant for association, Koff – rate constant for dissociation, Dev – device, HF – haemofiltration, MUF – modified ultrafiltration, VUF – volume of the combined ultrafiltrate.
···· Dotted lines indicate a process which can be turned on/off.

Pharmacokinetic covariate model

- Size (including Normal Fat Mass (*NFM*))[1], maturation and renal function (*RF*)[2] and an effect of CPB (F_{CPB}) were covariates for *CL*
  - $CL_{pre} = CL_{POP} \times \left(\frac{NFM}{NFM_{STD}}\right)^{\frac{3}{4}} \times \frac{1}{1+\left(\frac{PMA}{TM_{50}}\right)^{-HILL}} \times RF$
  - $CL_{during/post} = CL_{pre} \times F_{CPB}$

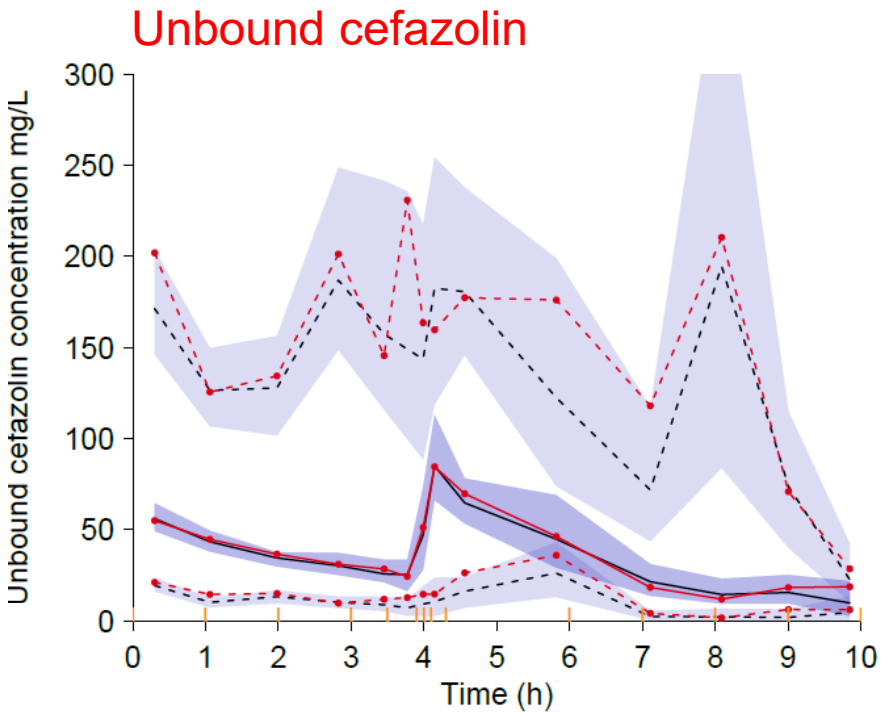
- Size (with *NFM*) and an effect of CPB were covariates on V1, V2 and Q, e.g.
  - $V1 = V1_{POP} \times \left(\frac{NFM}{NFM_{STD}}\right)^{1} \times F_{CPB}$

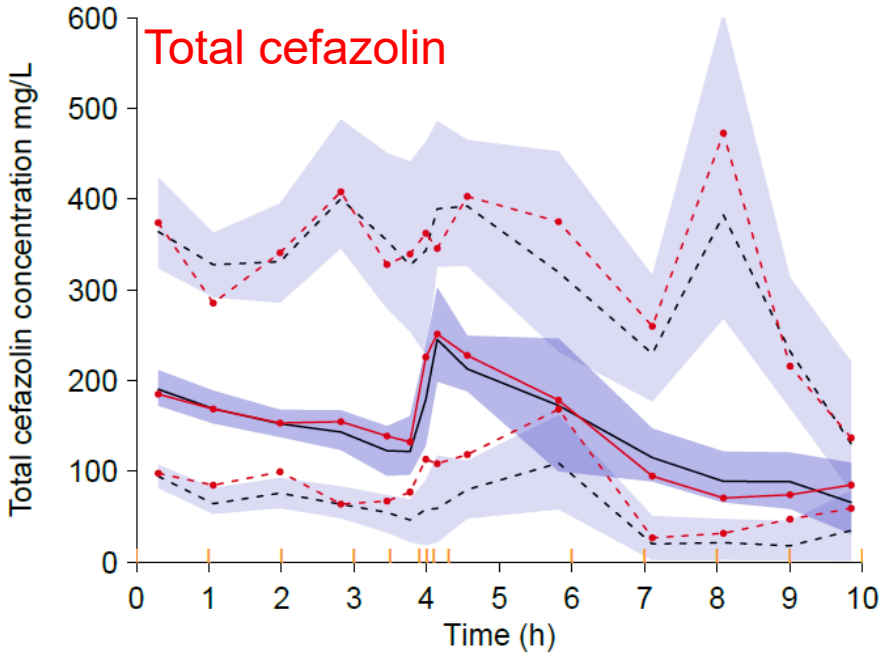
1. Holford NH, Anderson BJ. Allometric size: the scientific theory and extension to normal fat mass. European Journal of Pharmaceutical Sciences. 2017 Nov 15;109:S59-64.
2. O'Hanlon CJ, Holford N, Sumpter A, Al-Sallami HS. Consistent methods for fat-free mass, creatinine clearance, and glomerular filtration rate to describe renal function from neonates to adults. CPT: Pharmacometrics & Systems Pharmacology. 2023 Mar;12(3):401-12.

Parameter estimates

PK Parameters	Units	Estimate (RSE)	FCPB (RSE)
$CL_{Pre\text{-}bypass}$ $CL_{During/post}$	L/h/70 kg	20 (8%) ***13***	**0.66** (13%)
$V1_{Pre\text{-}bypass}$ $V1_{During/post}$	L/70 kg	11 (23%) *12*	1.1 (33%)
$Q_{Pre\text{-}bypass}$ $Q_{During/post}$	L/h/70 kg	41 (21%) *35*	0.85 (41%)
$V2_{Prebyass}$ $V2_{During/post}$	L/70 kg	24 (15%) *29*	1.2 (12%)
Factors for cardiopulmonary bypass (FCPB): $CL_{during/post} = CL_{pre} \times F_{CPB}$			

Binding Parameters			Size and maturation
Bmax Albumin	mg/L	208 (6%)	*Ffat* CL = 0 *Ffat* V = 1 TM50 = 47.7 weeks HILL = 3.4
Kd Albumin	mg/L	29 (9%)	
$C_{total} = \frac{Bmax \times C_{unbound}}{K_d + C_{unbound}} + C_{unbound}$			





Clinical relevance of CPB adsorption

- How much of the total cefazolin dose (patient and CPB device) is adsorbed to the device at the end of the CPB ?

Size	Coating	Typical total dose	% of dose adsorbed after CPB of 2 h
Neonate	Xcoating™	200 mg	2.5%
Infant	Rheoparin®	600 mg	8%
Child	Xcoating™	1200 mg	1%
Adult	PH.I.S.I.O	3000 mg	6%

Typical CPB duration 120 min

- Duration not important for Rheoparin® or PH.I.S.I.O because they equilibrate rapidly ($T2_{off}$ 1 min)
- Duration is important for Xcoating™ with slow dissociation ($T2_{off}$ 71 min)

Typical unbound cefazolin concentration 37 mg/L

- Both Rheoparin® and PH.I.S.I.O saturate rapidly (K_d 0.17 mg/L)
- Concentration time course of patient important for Xcoating™ (K_d 114 mg/L)

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Conclusion

- CPB impacts cefazolin PK
  - Reduced CL (34%) - **Clinically important? Duration unknown**
  - Increased V1 (10%) and V2 (20%)

- Device adsorption determined by size ($Bmax$) and coating (K_d, $T2_{off}$)
  - Bmax small relative to patient dose to clinically unimportant for all device types
  - 8% adsorbed to adult (PH.I.S.I.O) and 6% mg to infant (Rheoparin®) devices
    - Saturable, independent of dose at clinically relevant doses
  - Adsorption to Xcoating™ depends on patient conc-time course

- Vancomycin adsorption described with same framework
  - Framework could be extended to other PK studies involving CPB

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