Slide 1

New Insights into the Pharmacokinetics of Gentamicin, Amikacin and Vancomycin – from Neonates to Adults

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Slide 2

The GAVamycin Project 2007 – 2023

Holford, N. H. G. (2017)

- Gentamicin
- Amikacin
- Vancomycin

- Three similar antibiotics
- Eliminated primarily by the renal route
- Used extensively in neonates
- Standard size and maturation model approach

Holford, N. H. G. (2017). "Systems Pharmacology – Learning from GAVamycin." PAGANZ 2017 https://www.paganz.org/abstracts/systems-pharmacology-application-to-gavamycin/ Accessed 28 Jan 2023 https://www.paganz.org/wp-content/uploads/2017/02/systems-biology-and-pk-of-GAVamycin.pdf

Slide 3

Locations and Data

Source	Drug	Location	Source	Drug	Location
1	Vancomycin	Leuven, Belgium	10	Vancomycin	Dunedin, New Zealand
2	Vancomycin	Coimbra, Portugal	11	Vancomycin	Paris, France
3	Vancomycin	Marseille, France	12	Gentamicin	Salt Lake City, UT, USA
4	Vancomycin	Kuala Lumpur, Malaysia	13	Vancomycin	Salt Lake City, UT, USA
5	Vancomycin	Glasgow, Scotland	14	Amikacin	Salt Lake City, UT, USA
6	Amikacin	Dunedin, New Zealand	15	Gentamicin	Brisbane, Australia
7	Amikacin	Leuven, Belgium	16	Gentamicin	Brisbane, Australia
8	Gentamicin	Dunedin, New Zealand	17	Vancomycin	Boston, MA, USA
9	Gentamicin	Dunedin, New Zealand	18	Gentamicin	Christchurch, New Zealand

Drug	Number of patients	Number of observations
Gentamicin	5970	8878
Amikacin	737	2106
Vancomycin	3233	16357
Total	**9940**	**27341**

Slide 4

Methods: Consistent Covariates

- Fat Free Mass (FFM)
  - Premature Neonates to Adults
- Estimated Creatinine Clearance (eGFR)
  - New formula for Creatinine Production Rate (CPR)
- Normal Glomerular Filtration Rate (nGFR)
  - Update of Rhodin (2009)
  - GFR_{STD}=6.96 L/h/70kg TBM male
- Renal Function (RF)
  - eGFR/nGFR
  - Size, body composition, age independent metric
  - RF=1 if kidney function is normal

O'Hanlon, C. J., N. Holford, A. Sumpter and H. S. Al-Sallami (2023). "Consistent Methods for Fat Free Mass, Creatinine Clearance and Glomerular Filtration Rate to describe Renal Function from Neonates to Adults." CPT Pharmacometrics Syst Pharmacol (Accepted)

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Methods: PK Covariate Effects

- Theory Based Allometric Size Scaling
  - Normal Fat Mass (NFM)
- Clearance Maturation
  - Post-Menstrual Age symmetrical sigmoidal (PMA)
  - Post-Natal Transition asymptotic exponential (PNA)
- Volume Maturation
  - Two exponential decline processes (PNA)

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Methods: Clearance Matthews (2004)

- Clearance described by two components

  1. CLcr Clearance (CLRF)

  $$CLRFgrp = POP_{CL} \times F_{CLRF} \times {Clcr}/{6\ L/h}$$

  2. Non-CLcr Clearance (CLNRF)

  $$CLNRF_{grp} = POP_{CL} \times (1 - F_{CLRF})$$

- Total Clearance = CLRF + CLNRF

Matthews, I., C. Kirkpatrick and N. Holford (2004). "Quantitative justification for target concentration intervention--parameter variability and predictive performance using population pharmacokinetic models for aminoglycosides." Br J Clin Pharmacol **58(1): 8-19.**

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Slide 7

Methods: Clearance Holford (2023)

- Clearance described by two components

  1. GFR Clearance (CLGFR)

  $$CLGFRgrp = FGFR_{drug} \times nGFR \times asymmetrical\ sigmoid\ function(RF)$$

  2. Non-GFR Clearance (CLNGFR)

  $$CLNGFR_{grp} = POP_{CLNGFR,drug} \times Fmat_{CLNGFR} \times RF$$

- Total Clearance = CLGFR + CLNGFR

Holford, N., C. J. O'Hanlon, K. Allegaert, A. Falcao, N. Simon, Y. L. Lo, A. Thompson, C. Sherwin, E. Aigrain, C. Llanos-Paez, L. Mockas and C. Kirkpatrick (2023). "New Insights into the Pharmacokinetics of Gentamicin, Amikacin and Vancomycin - from Premature Neonates to Adults." In Preparation

Slide 8

Results: Model Selection

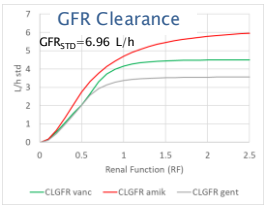
Description	dOFV	df	p
MATV VC,VP T2neo for each drug separately	-0.4	2	0.799
MATV VC,VP separate, T2neo same for each drug	0.0	0	Final
MATV Vss separate, T2neo same for each drug	37.2	-3	4E-08
MATV Va,Vb separate, T2neo same for each drug	76.5	0	.
FFM Al-Sallami 2015	195.3	-7	1E-38
No maturation of volumes (MATV)	440.6	-8	4E-90
No RF on CLNGFR	814.5	-2	1E-177
Linear RF on CLGFR instead of asym. sigmoid	1447.0	-9	5E-306
No maturation of CLNGFR	2891.6	-4	~0.

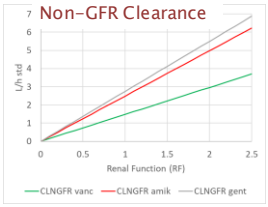
dOFV=change in objective function value from final model
df=degrees of freedom (number of parameters less than final model), p=Chi square(dOFV,df)

T2neo=half-life of exponential decrease from birth
MATV=maturation of volumes , VC=central volume, VP=peripheral volume
Vss=VC+VP, Va and Vb are intercepts for biexponential decrease

Slide 9

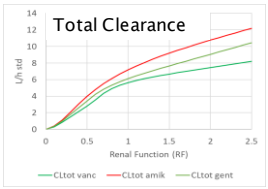
Results: Clearance and RF





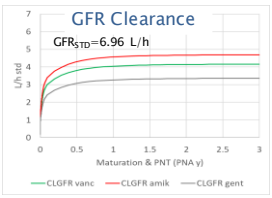
FCL_VANC	Vancomycin fraction GFR$_{STD}$	0.648
FCL_AMIK	Amikacin clearance GFR$_{STD}$	0.909
FCL_GENT	Gentamicin clearance GFR$_{STD}$	0.513

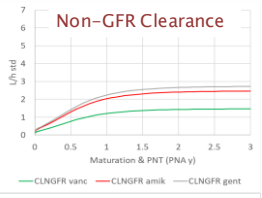
CLNGFR_VANC	Vancomycin non-GFR clearance	L/h std	1.48
CLNGFR_AMIK	Amikacin non-GFR clearance	L/h std	2.49
CLNGFR_GENT	Gentamicin non-GFR clearance	L/h std	2.75



Slide 10

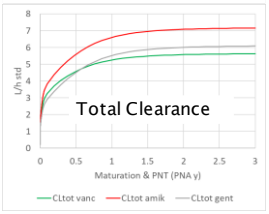
Results: Clearance and Age





GFR_TM50	Maturation half-time	33.6	PMA week
GFR_HILL	Maturation steepness	3.49	.
GFR_PNTmax	PNT maximum	0.588	.
GFR_PNTthalf	PNT half-life	6.94	PNA day

CLNGFR_TM50	Maturation half-time	64.8	PMA week
CLNGFR_HILL	Maturation steepness	4.23	.
CLNGFR_PNTmax	PNT maximum	0.617	.
CLNGFR_PNTthalf	PNT half-life	3.81	PNA day



PNT=post natal transition

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Results: Body Composition

$$NFM = FFM + (TBM - FFM) \times Ffat$$

Fraction of fat mass (Ffat)	Estimate
GFR	0
CPR	0
CLNGFR vanc	0.26
CLNGFR amik	1.2
CLNGFR gent	3.4
VC vanc	0.28
VC amil	1.4
VC gent	1.2
VP vanc	6.3
VP amik	1.8
VP gent	7.0
Q vanc	3.0
Q amik	-0.28
Q gent	0.99

NFM=normal fat mass
FFM=fat free mass
TBM=total body mass
Ffat=fraction of fat mass contributing to NFM

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Body Composition During Growth – Water and Fat

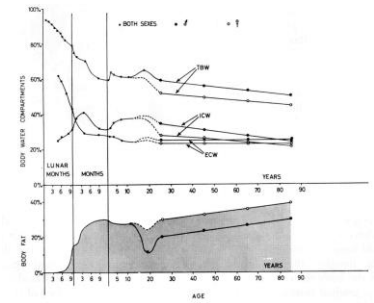

FIG. 4. Changes in TBW, ICW, ECW and the fat content of the body from early fetal life to old age[1]

Friis-Hansen, B. (1971). "Body composition during growth. In vivo measurements and biochemical data correlated to differential anatomical growth." Pediatrics 47(1): 264-274.

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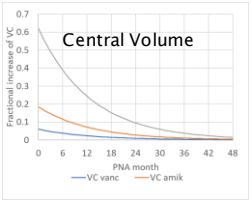
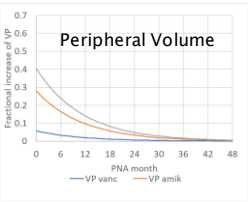
Results: Maturation of Volumes of Distribution





Volume maturation reached 5% of adult values by 3.2 years (central volume) and 2.9 years (peripheral volume)

Vancomycin percent increase of VC at birth	6%
Amikacin percent increase of VC at birth	18%
Gentamicin percent increase of VC at birth	62%
Half-life of loss of neonatal VC PNA	38.6 weeks

Vancomycin percent increase of VP at birth	6%
Amikacin percent increase of VP at birth	28%
Gentamicin percent increase of VP at birth	40%
Half-life of loss of neonatal VP PNA	34.3 weeks

The maturation half-lives of central and peripheral volume are similar to the GFR maturation half-life of 33.6 weeks

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Slide 14

The Fat Lady Is About to Sing …

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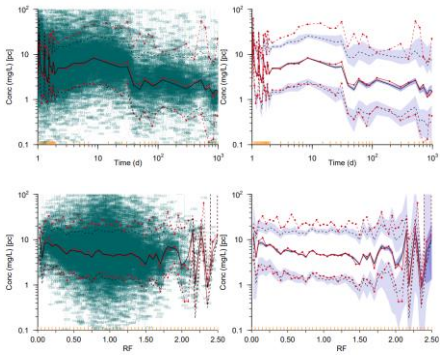
Slide 15

Results: VPC Time and RF



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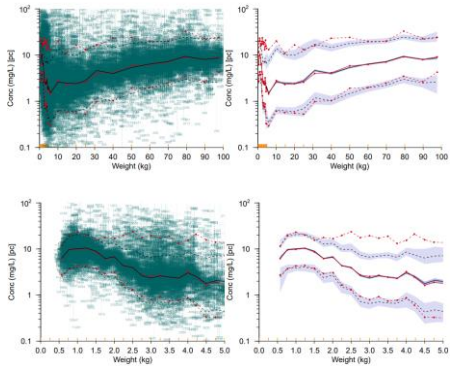
Results: VPC Weight



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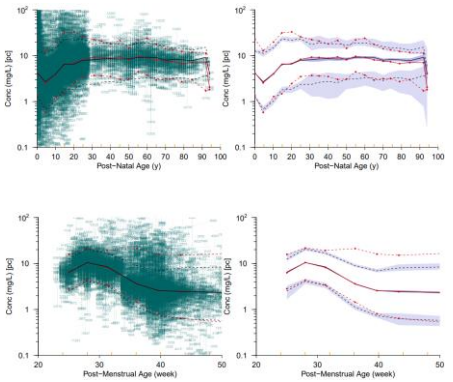
Results: VPC PNA and PMA



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Slide 18

Summary

- Description of clearance across human age, weight and renal function required a new approach based on GFR and RF
- Body composition association with fat mass unexpectedly high
- Maturation of volumes of distribution consistent with changes in body water over first few years of life

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Slide 19

Acknowledgements

Conor O'Hanlon[1], Karel Allegaert[2], Brian Anderson[3], Amilcar Falcão[4], Nicolas Simon[5], Lin Lo[6], Alison Thomson[7], Catherine Sherwin[8], Evelyne Jacqz-Aigrain[9], Carolina Llanos-Paez[10],Stefanie Hennig[11] , Linas Mockus[12], Carl Kirkpatrick[13]

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7. Strathdyde Institute of Pharmacy and Biomedical Sciences, Scotland
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12. Purdue University, USA
13. Centre for Medicine Use and Safety, University of Monash, Australia

Slide 20

Backup

Slide 21

Fat Free Mass (1)

The dependent variable for the fractional FFM (FRFFM) model, was calculated using observations of FFM from the study data ($FFM_{observed}$) and predictions of FFM from Janmahasatian, Duffull (3) (FFM_{adult}), using TBM, height and sex (Equation 5).

$$FRFFM = \frac{FFM_{observed}}{FFM_{adult}} \quad \text{Equation 5}$$

FRFFM is then a fraction of FFM predicted from the adult model (3), relative to the observed FFM. The FRFFM model (see Figure 1 and Equation 6) predicts the value of FRFFM by combining a baseline (FFMIN), a component for neonates and infants (FFNEO) and a component for children (FFKID), using postmenstrual age and sex.

$$FRFFM = FFMIN + FFNEO + FFKID \quad \text{Equation 6}$$

The baseline, FFMIN, is obtained from FMAT_PRE, a parameter describing FRFFM in a 24-week premature neonate and FMAT_MAX, the asymptotic estimate of FFM_{adult} (Equation 7).

$$FFMIN = FMAT\_PRE \times FMAT\_MAX \quad \text{Equation 7}$$

O'Hanlon, C. J., N. Holford, A. Sumpter and H. S. Al-Sallami (2023). "Consistent Methods for Fat Free Mass, Creatinine Clearance and Glomerular Filtration Rate to describe Renal Function from Neonates to Adults." CPT Pharmacometrics Syst Pharmacol (Accepted)

Slide 22

Fat Free Mass (2)

The neonatal component, FFNEO, describes the exponential drop in FFM fraction from FMAT_PRE towards FFMIN. TFF_PRE is the half-life of decrease of FFNEO and PMAY is PMA in years (Equation 8).

$$FFNEO = (FMAT\_PRE - FFMIN) \times e^{\frac{-\log(2)}{TFF\_PRE \times \left(PMAY - \frac{24}{52}\right)}} \quad \text{Equation 8}$$

The child component, $FFKID$, is an asymmetrical sigmoid Emax model. $FFKID$ rises as PMA approaches adult values ($FMAT\_MAX$) from baseline ($FFMIN$). $A50$ is the PMAY when $FFKID$ is 50% of the adult FRFFM. The $HILL$ exponent has a different value when younger (HILL_Y) or equal to or older (HILL_O) than $A50$ (Equation 9).

$$FFKID = \frac{FMAT\_MAX - FFMIN}{1 + \left(\frac{PMAY}{A50}\right)^{-HILL}} \quad \text{Equation 9}$$

O'Hanlon, C. J., N. Holford, A. Sumpter and H. S. Al-Sallami (2023). "Consistent Methods for Fat Free Mass, Creatinine Clearance and Glomerular Filtration Rate to describe Renal Function from Neonates to Adults." CPT Pharmacometrics Syst Pharmacol (Accepted)

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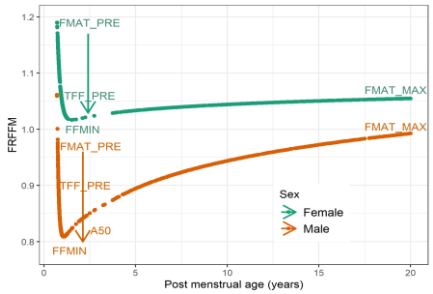
Slide 23

Maturation of Fat Free Mass



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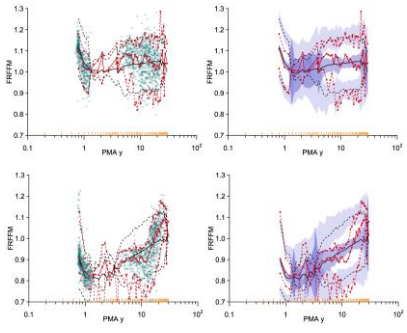
VPC Fat Free Mass



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Normal Fat Mass

Normal Fat Mass (NFM) (1) is used as the descriptor for body size in the FFM, CPR and nGFR models described in this work. NFM is an extension of the concept of predicted normal weight (18) and is a size metric derived from TBM, FFM and theory based allometric concepts. NFM is calculated from FFM and TBM with an additional parameter; Ffat (Equation 2).

$$NFM = FFM + Ffat \times (TBM - FFM) \quad \text{Equation 2}$$

The influence of fat mass (TBM - FFM) combined with FFM as a predictor of theory based allometric size is described by Ffat. The basis of NFM is to estimate the value of Ffat which is specific to the biological structure or function parameter being described. For example, if Ffat is estimated to be 0 then FFM alone may be used to predict size, whereas if Ffat is 1 then TBM may be used to predict size. A standard value for NFM (NFM_{std}) may be calculated for a male with a TBM of 70 kg, a FFM of 56.1 kg, a height of 1.76 m and the drug parameter specific value of Ffat (Equation 3).

$$NFM_{std} = 56.1 + Ffat \times (70 - 56.1) \quad \text{Equation 3}$$

A size factor, F_{size}, can be obtained from NFM, NFM_{std} and a theory based allometric exponent WBE (Equation 4). WBE is obtained from the West, Brown and Enquist theory which predicts an allometric exponent of 1 for structural properties (e.g. V) and ¾ for functional properties (e.g. CL) (19). NFM allows for body composition to be included in the meaning of relative size.

$$F_{size} = \left(\frac{NFM_i}{NFM_{std}}\right)^{WBE} \quad \text{Equation 4}$$

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Creatinine Production Rate (1)

Measurements of GFR and Scr from Rhodin, Anderson (16) were used to construct the model for CPR. One hundred and eight subjects had measurements of both GFR (not indexed to BSA) and Scr, 95th%ile PMA interval [27.8, 872] weeks. Covariate distributions for these subjects are shown in Figure S2. By assuming CLcr is equal to GFR, CPR can be calculated using Equation 11.

$$CPR = GFR \times Scr \quad \text{Equation 11}$$

CPR can be predicted using a population standard for CPR, size and age. The model for CPR based on these factors is shown in Equation 13.

$$CPR = CPR_{std} \times F_{size} \times F_{MAT.CPR} \quad \text{Equation 13}$$

CPR_{std} is the standard enzymatic equivalent CPR for a 40 year old male based on the estimate for a male with 70 kg TBM (0.386 mmol/h/70kg = 0.516 mmol/h/70 kg x F_{SCr}) (8). Size is scaled using FFM because Ffat was estimated to be close to 0. The allometric exponent for CPR uses the theory-based value of 1 as CPR comes from muscle mass which is a structural rather than a functional property. An empirical maturation function ($F_{MAT.CPR}$) based on PMA was used to describe the maturation of CPR from premature neonates to young adults. This function has 3 segments depending on PMA (Equation 14, Equation 15, and Equation 16).

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Creatinine Production Rate (2)

After accounting for body size, when PMA is less than or equal to 37 weeks, the CPR does not seem to increase and is described by the constant CPR_{int} (Equation 14).

$$F_{MAT.CPR} = CPR_{int} \quad \text{Equation 14}$$

From infants to adults (PMA > 37 to 1080 weeks PMA_{adult} /20 years postnatal age (PNA)) the CPR maturation function is describable by a linear function (CPR_{slope}) (Equation 15). Both the CPR_{int} and CPR_{slope} parameters are sex specific.

$$F_{MAT.CPR} = 1 + \frac{CPR_{slope} \times (PMA_{adult} - PMA)}{100} \quad \text{Equation 15}$$

For adults (> 20 years PNA), CPR is calculated using the Matthews, Kirkpatrick (8) modification of the Cockcroft and Gault model (Equation 16).

$$F_{MAT.CPR} = \frac{112 - AGE}{(112 - 40)} (\times 0.82 \text{ if female}) \quad \text{Equation 16}$$

O'Hanlon, C. J., N. Holford, A. Sumpter and H. S. Al-Sallami (2023). "Consistent Methods for Fat Free Mass, Creatinine Clearance and Glomerular Filtration Rate to describe Renal Function from Neonates to Adults." CPT Pharmacometrics Syst Pharmacol (Accepted)

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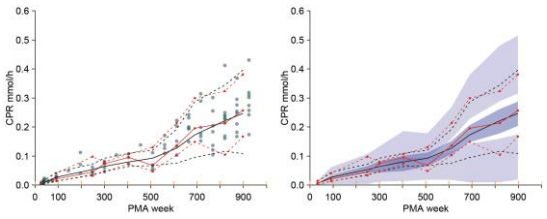
VPC Creatinine Production Rate (CPR)



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Slide 29

Glomerular Filtration Rate (1)

The Rhodin, Anderson (16) model describing GFR was updated using FFM as a measure of size from the FRFFM model described above, and the addition of a PNA maturation function which describes a birth effect (Equation 21). nGFR describes GFR predicted under the assumption of normal kidney function. nGFR changes rapidly after birth due to increasing body size (growth) and increasing age (maturation) (27). Theory based allometry and maturation models can be used to describe the impact of these processes on GFR using Equation 19.

$$nGFR = GFR_{std} \times F_{size} \times F_{mat.PMA} \times F_{mat.PNA} \quad \text{Equation 19}$$

GFR_{std} is the mature population estimate for GFR of a male with TBM 70 kg and height of 176cm. NFM, specific for GFR, was used to predict F_{size} (Equation 4). A sigmoid Emax model was used to describe the maturation of GFR with respect to PMA. To account for maturation of GFR and the impact of birth, two maturation fractions were combined based on postmenstrual age ($F_{mat.PMA}$ weeks) and postnatal age ($F_{mat.PNA}$ days). $F_{mat.PMA}$ is defined in terms of TM_{50}, the maturation half time i.e. the PMA (weeks) at 50% of the fully mature value of 1, and HILL, a parameter that describes the steepness of the maturation curve (Equation 20).

O'Hanlon, C. J., N. Holford, A. Sumpter and H. S. Al-Sallami (2023). "Consistent Methods for Fat Free Mass, Creatinine Clearance and Glomerular Filtration Rate to describe Renal Function from Neonates to Adults." CPT Pharmacometrics Syst Pharmacol (Accepted)

Slide 30

Glomerular Filtration Rate (2)

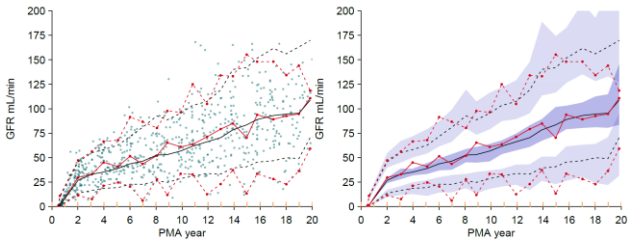
$$F_{mat.PMA} = \frac{1}{1 + \left(\frac{PMA}{TM_{50}}\right)^{-HILL}} \quad \text{Equation 20}$$

Transition from the intrauterine to the extrauterine environment is associated with major changes in blood flow and oxygenation. This can cause changes in GFR, kidney function and drug metabolism (28, 29). Therefore $F_{mat.PNA}$ (postnatal age maturation) was used to describe changes in addition to those predicted from PMA alone (Equation 21).

$$F_{mat.PNA} = 1 - PNA_{max} + PNA_{max} \times \left(1 - e^{\frac{-\ln(2) \times PNAD}{PNAT50}}\right) \quad \text{Equation 21}$$

PNA_{max} is the fractional increase relative to the completion of the birth associated component of maturation, $PNAT_{50}$ is the half time required to achieve 50% of this maturational change and PNAD is postnatal age in days. $F_{mat.PMA}$ and $F_{mat.PNA}$ approach an asymptote of 1 signifying completion of these maturational processes.

O'Hanlon, C. J., N. Holford, A. Sumpter and H. S. Al-Sallami (2023). "Consistent Methods for Fat Free Mass, Creatinine Clearance and Glomerular Filtration Rate to describe Renal Function from Neonates to Adults." CPT Pharmacometrics Syst Pharmacol (Accepted)

Slide 31	 VPC Maturation of GFR  O'Hanlon, C. J., N. Holford, A. Sumpter and H. S. Al-Sallami (2023). "Consistent Methods for Fat Free Mass, Creatinine Clearance and Glomerular Filtration Rate to describe Renal Function from Neonates to Adults." CPT Pharmacometrics Syst Pharmacol (Accepted) Auckland Pharmacometrics Group	