# Scaling Renal Function in Neonates and Infants to Describe the Pharmacodynamics of Antibiotic Nephrotoxicity

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# Outline

- What does Scaling of Pharmacodynamics mean?
- What is GAVamycin?
- Creatinine Production Rate
- Glomerular Filtration Rate
- Renal Function
  - Disease Progression
  - PD of Gavamycin

# Scaling, Maturation, Disease Progression

- Scaling
  - Body mass used to predict body structure and body function differences
  - Allometric theory
- Maturation
  - Describing maturation of structure and function using biological age
  - Applied with allometric theory to account for body mass
- Disease Progression
  - Description of changes in disease status with time
  - Pharmacodynamics may change disease progress

# Pharmacodynamic Scaling and Maturation

- Effect Scale (Emax, Slope)

  No scaling possible when effect is not related to size

  e.g. EEG effects, analgesia, antibiotic action, anti-depressant effect, ..

- Receptor Affinity (C50)
  - Maturation using biological age to young adult values
  - Ageing changes in older adults (probably no real change in affinity – changes more likely related to age associated changes in body function)

# GAVamycin

- Gentamicin
- Amikacin
- Vancomycin

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

Holford N, Heo YA, Anderson B. A pharmacokinetic standard for babies and adults. J Pharm Sci. 2013;102(9):2941-52.
Germovsek E, Barker CIS, Sharland M, Standing JF. Scaling clearance in paediatric pharmacokinetics: All models are wrong, which are useful? Br J Clin Pharmacol. 2017;83(4):777-90.

# Data and Key Question

| Study | Description | Location | Principal Investigator | Patients |
|---|---|---|---|---|
| ALL | Pooled gentamicin, amikacin, vancomycin, GFR | International | Holford & Sherwin | 6055 |
| STDY4 | Glomerular filtration rate | International | Rhodin et al. (2009) | 108 |
| STDY14 | Gentamicin | Salt Lake City | | 3209 |
| STDY15 | Vancomycin | Salt Lake City | | 2655 |
| STDY16 | Amikacin | Salt Lake City | | 83 |

Can this large data set be used to demonstrate adverse pharmacodynamics effects of these antibiotics on renal function?

# Renal Function

GFR=**FCLcr***CLcr=**FCLcr***CPR/Scr ; Actual GFR but FClcr unknown

aGFR=**aCPR**/Scr ; Apparent GFR with FCLcr=1

**GFR**=**STDGFR***$\mathbf{FSZ}_{\mathbf{GFR}}$*$\mathbf{FMAT}_{\mathbf{GFR}}$ ; Normal GFR Size and maturation

Renal function (RF) defined as ratio of apparent GFR to normal **GFR**

$$RF=aGFR/\mathbf{GFR}$$

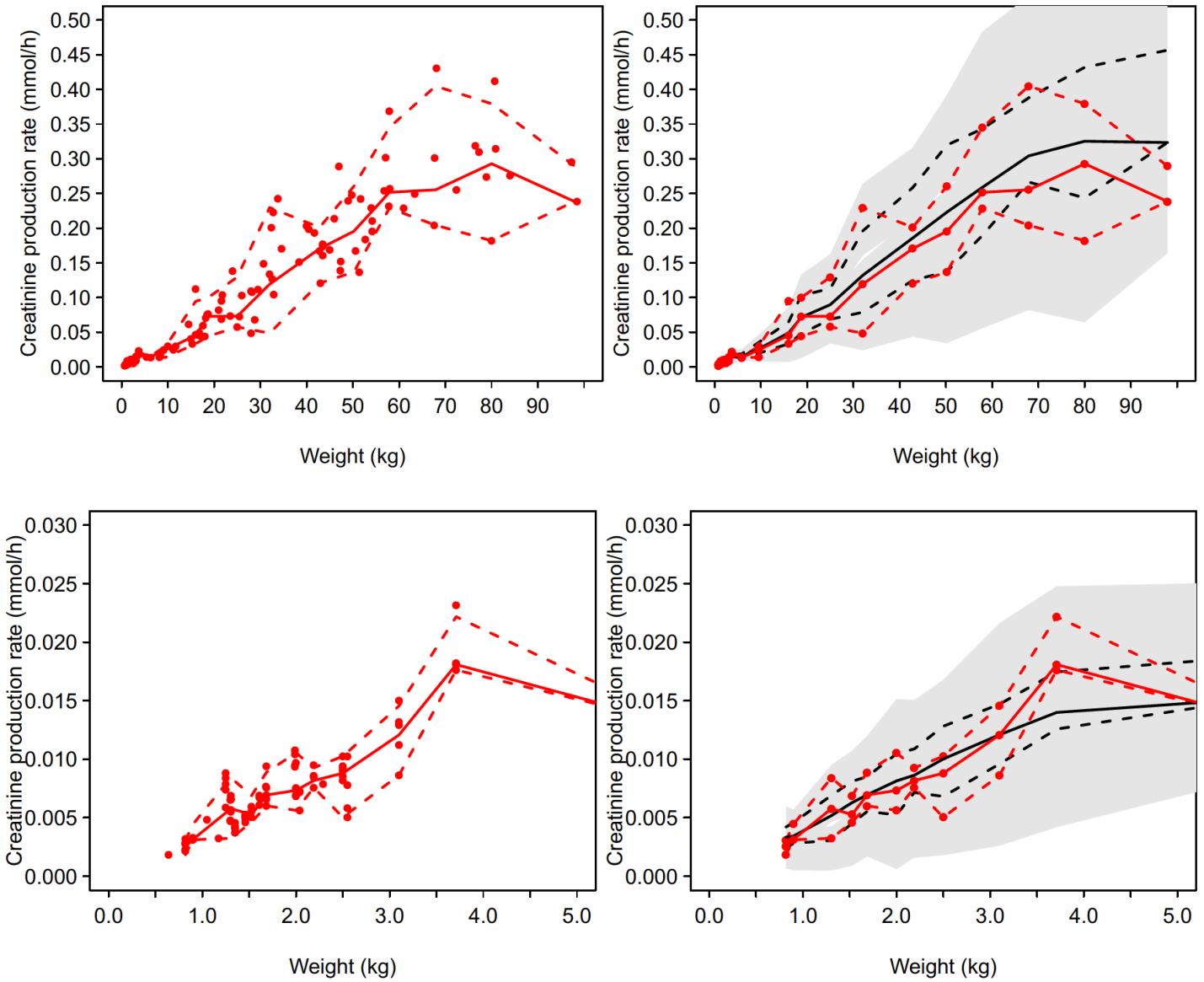
**aCPR**=apparent creatinine production rate estimated by assuming CLcr=GFR

**STDGFR** =6.8 L/h (119 mL/min) from Rhodin et al (2009) updated with neonatal and child FFM predicted using data from Sumpter & Holford (2012)

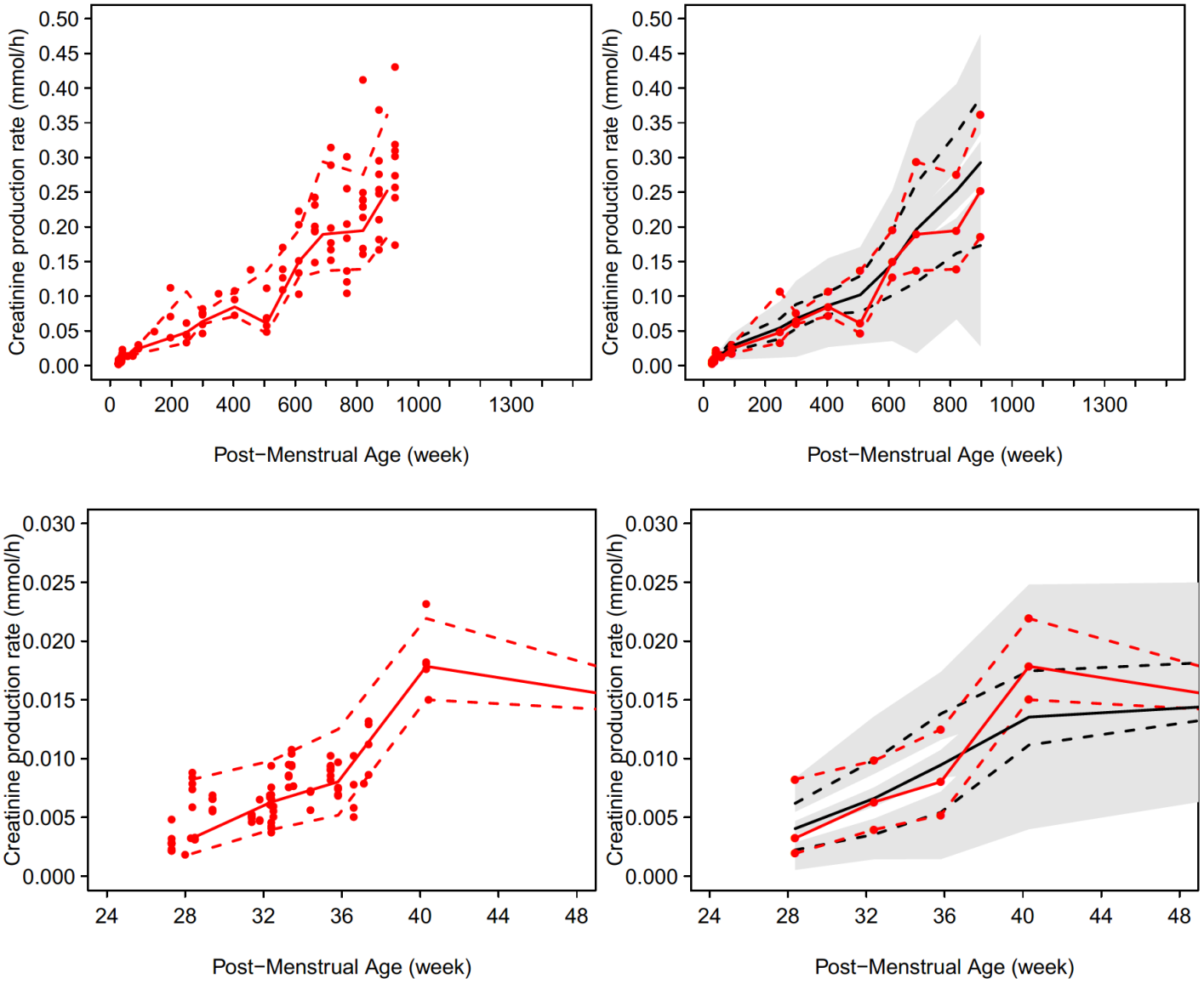
# Computational Methods

- NONMEM 7.4.1
- gfortran 64 bit
- Wings for NONMEM 742
- R to create WFN VPC

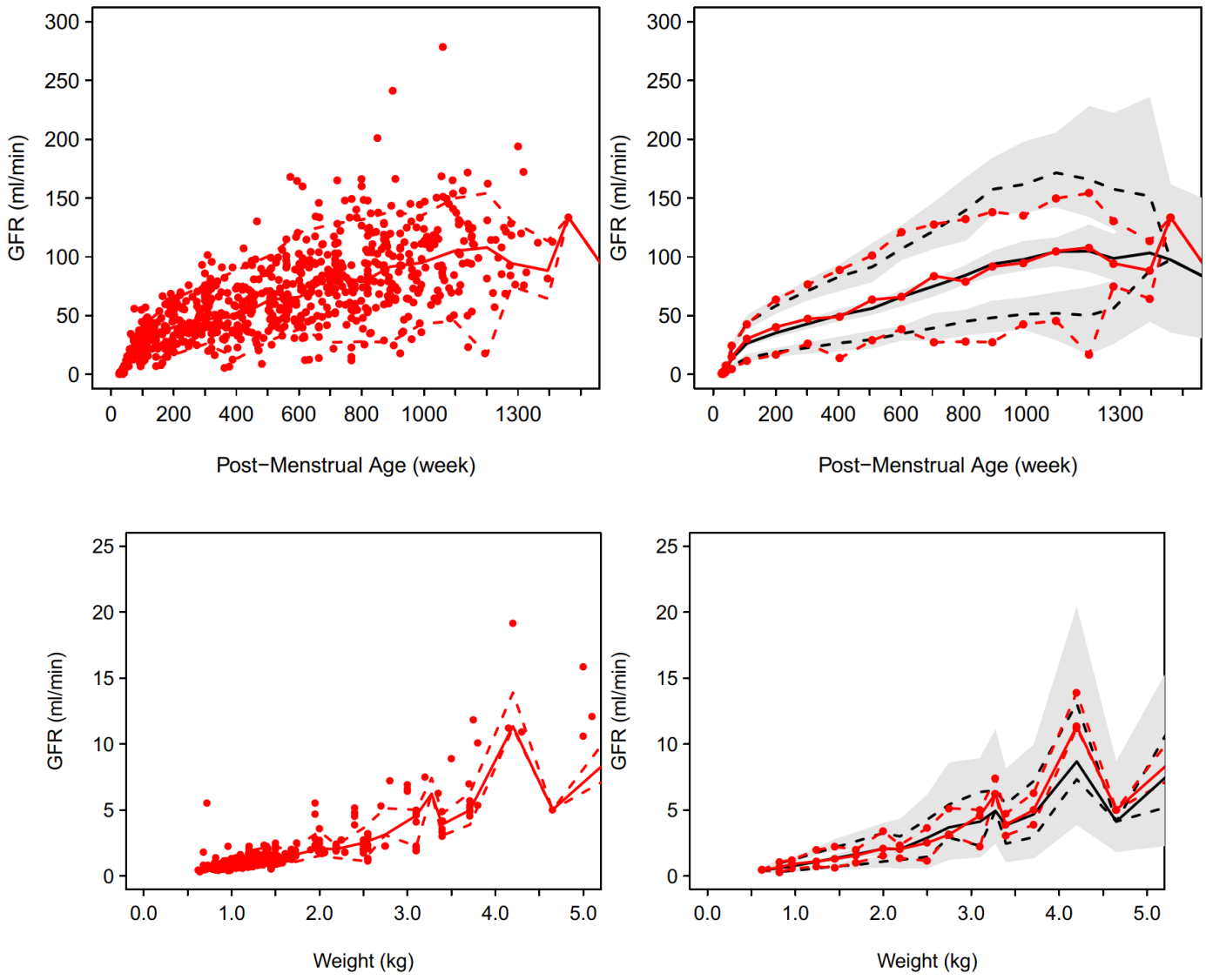
# Creatinine Production Rate Size



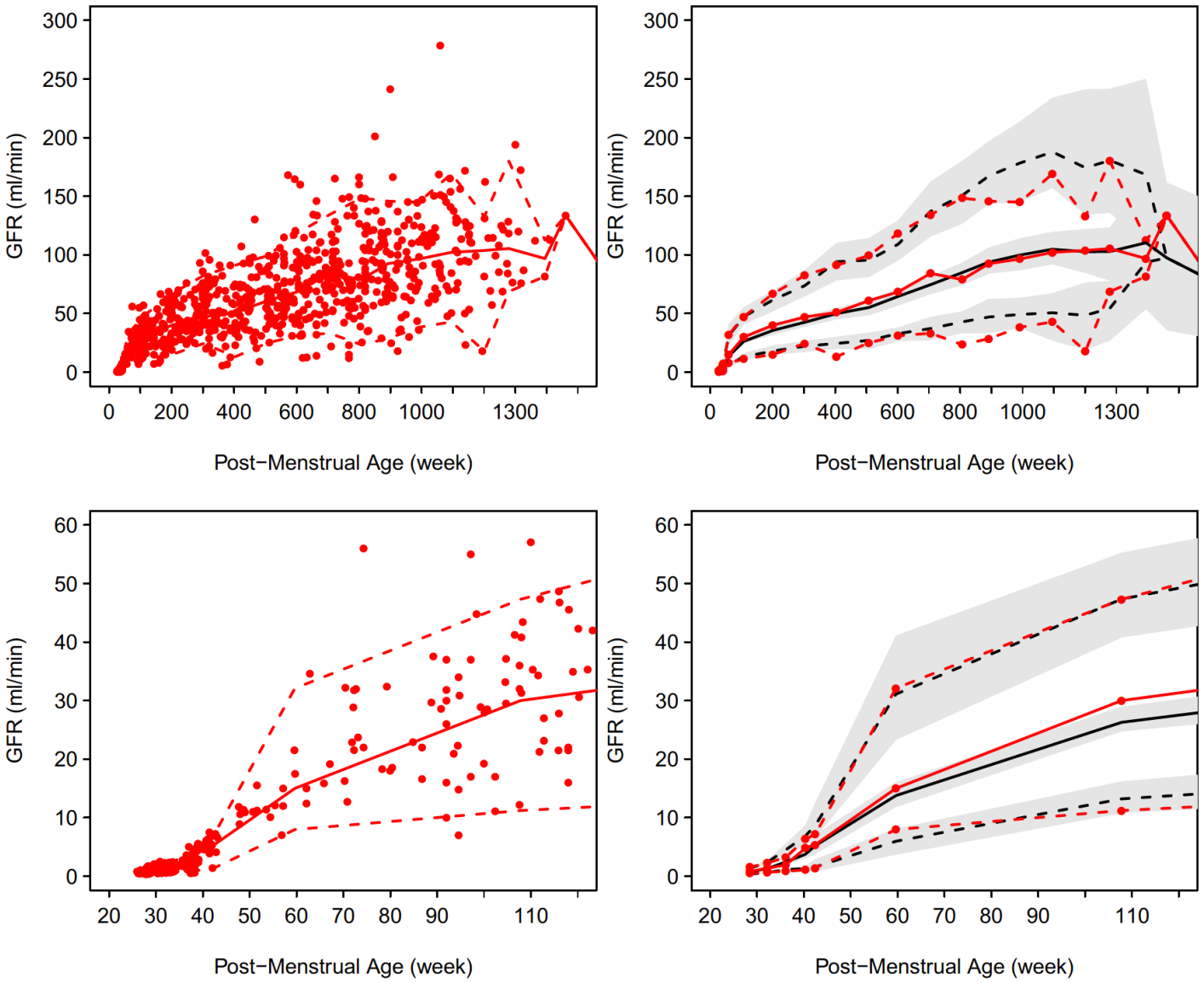
# Creatinine Production Rate Maturation



# Glomerular Filtration Rate Size



# Glomerular Filtration Rate Maturation

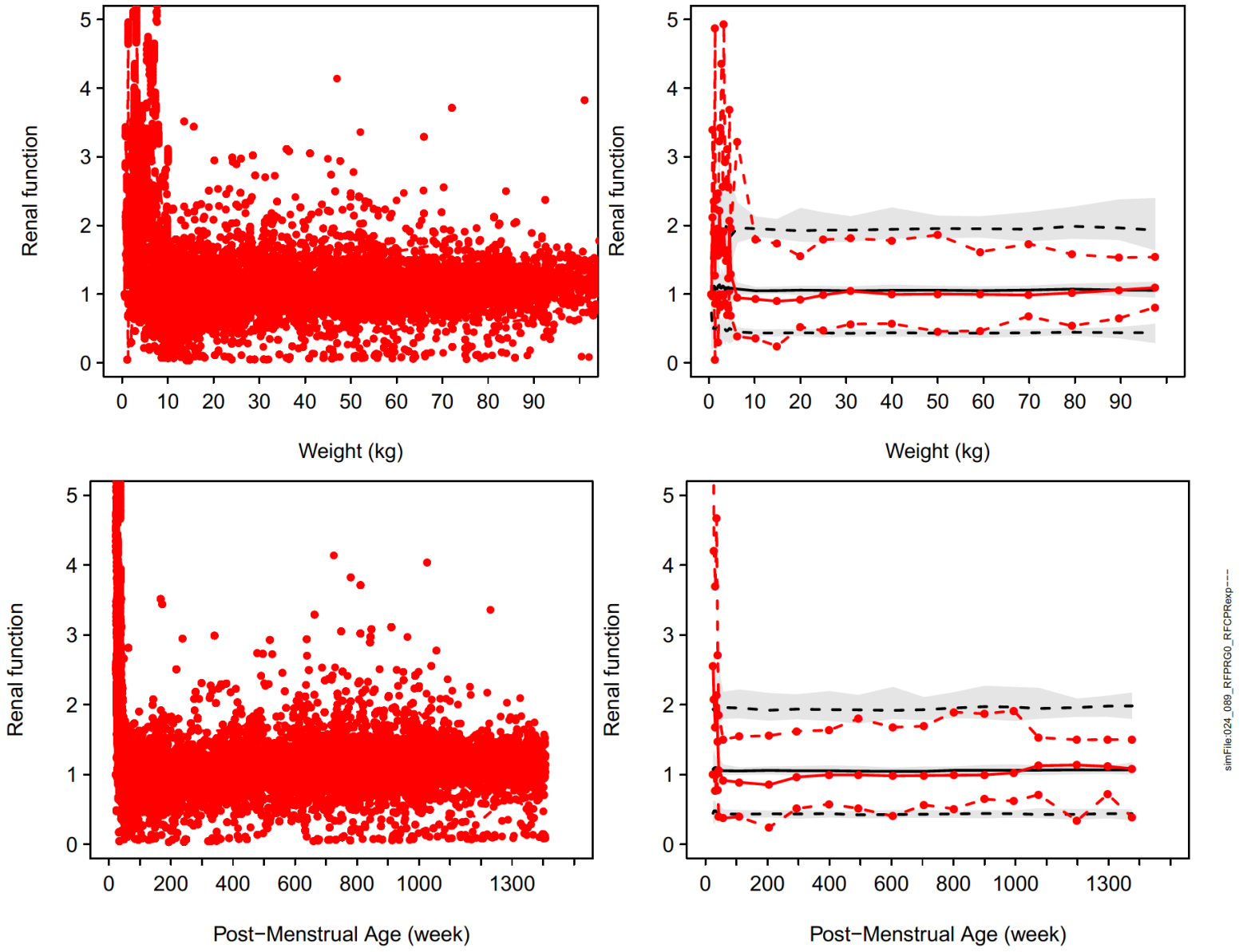


# Results CPR and GFR

- **Creatinine Production Rate**
  - Allometric size exponent=1, Ffat=0 (size fat free mass).
  - Constant up to 44 weeks PMA then linear maturation to 20 years using data of Rhodin et al (2009).
- **Glomerular Filtration Rate**
  - Update of Rhodin et al (2009) with better prediction of fat free mass in neonates, infants and children.
  - GFR predicted best by fat free mass. No effect of fat mass.

PMA=Post Menstrual Age (estimate of post conception age)

# Renal Function Size and Maturation

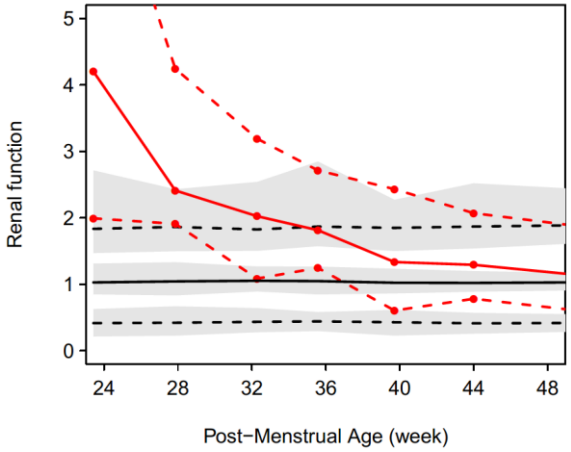


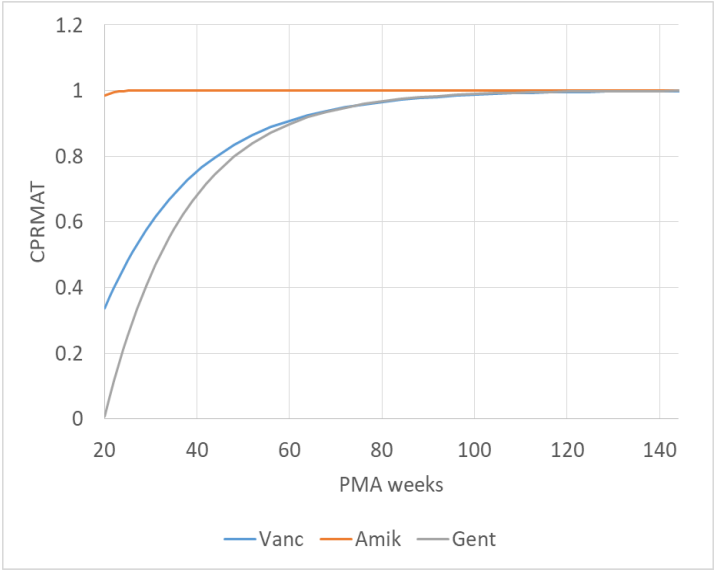
# Neonatal Renal Function Maturation by Drug

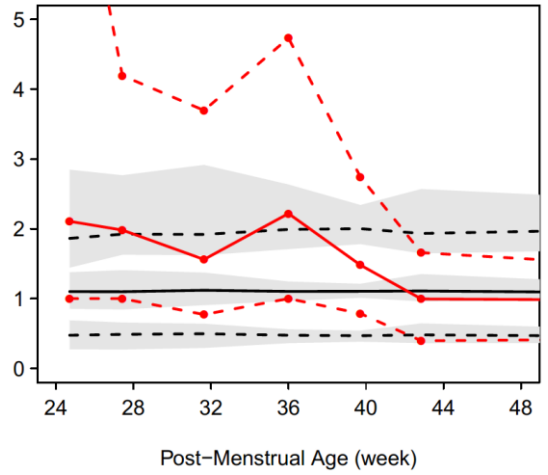
Gentamicin

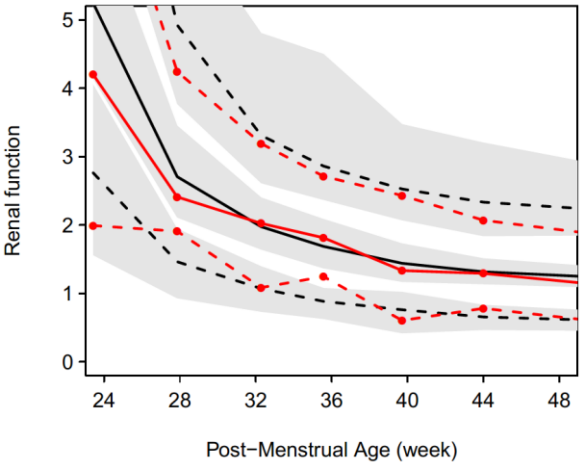
CPRMAT=CPR20+(1-CPR20)*(1-exp(-T2CPR*(PMA-20))

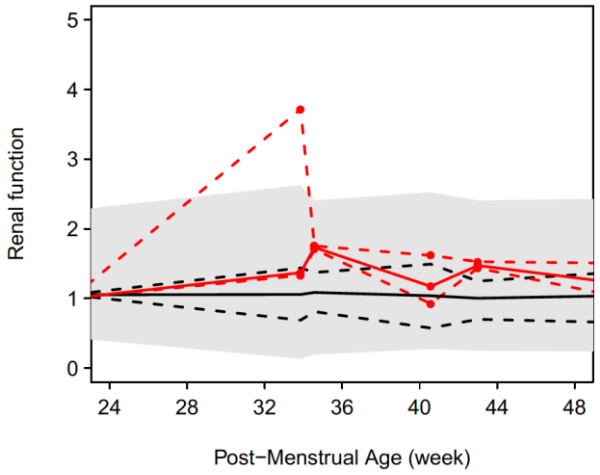
Vancomycin

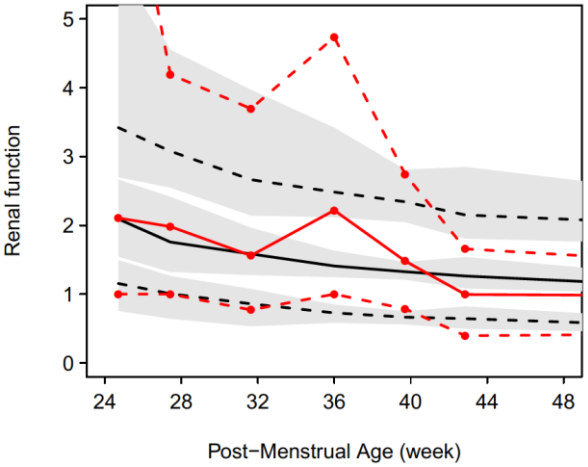



RF=RFDRUG/CPRMAT

# Results Renal Function

- Renal Function
  - Renal function (median) close to 1 from infancy to adult (30 y).
  - Unexpectedly high renal function in premature neonates can be explained by adding an additional maturation function for CPR.
- Disease Progress
  - No systematic change in renal function with time.
- Pharmacodynamics
  - No slope effect of exposure (Dose/CL) on progression.
  - No offset effect of exposure relative to baseline renal function.

# Conclusion

- Creatinine production rate from premature neonates up to young adults can be calculated using fat free mass and post-menstrual age.
- Maturation of CPR increases rapidly in premature neonates approaching an asymptote at 44 weeks PMA then increases linearly to young adulthood.
- Renal function in patients treated with vancomycin, amikacin or gentamicin is close to 100% at all ages.
- No pharmacodynamic effect of antibiotic exposure (AUC) on renal function progression was detectable.
- Current clinical practice is not associated with a population trend for nephrotoxicity.