Pharmacokinetic-Pharmacodynamic (PKPD) modelling to inform efficacy in paediatric antimicrobial trials

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Overview

- Scaling PKPD
- Study design
- Data analysis
- Future perspectives
- Conclusion

Scaling PK

- Antimicrobial efficacy often extrapolated from PK
  - e.g. $fT > MIC$, AUC/MIC, C_{max}/MIC
- Generally know adult PK
- Most interested in clearance (CL) because:
  - $AUC = DOSE/CL$
  - $C_{ss} = DOSE\ RATE/CL$
- CL tends to scale with $weight^{0.75}$

Lamivudine, Burger 2007

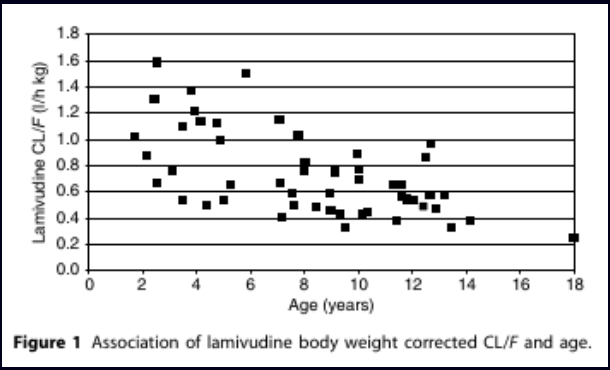


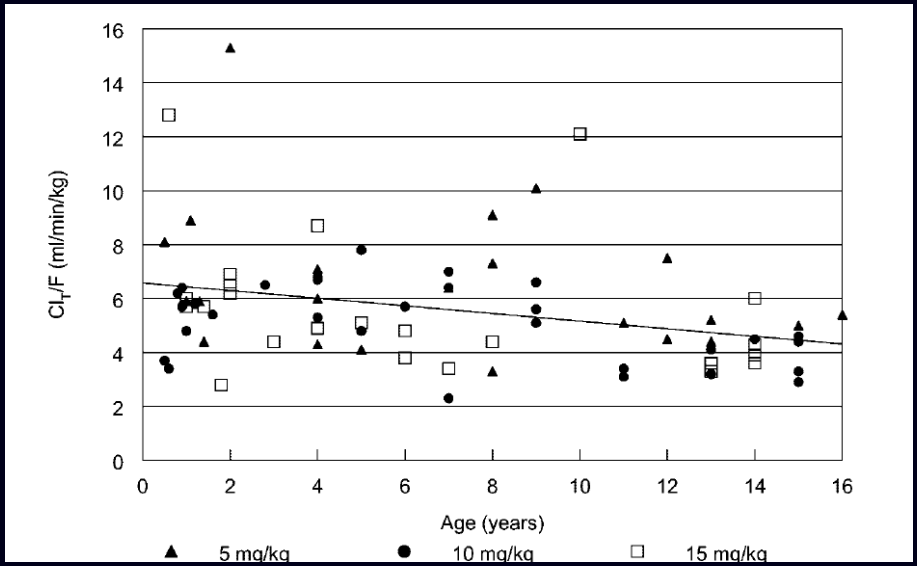
Figure 1 Association of lamivudine body weight corrected CL/*F* and age.

- 4 year old CL $\approx$ 1 L/h/kg
- 12 year old CL $\approx$ 0.7 L/h/kg
- These PK studies changed ART dosing, why???

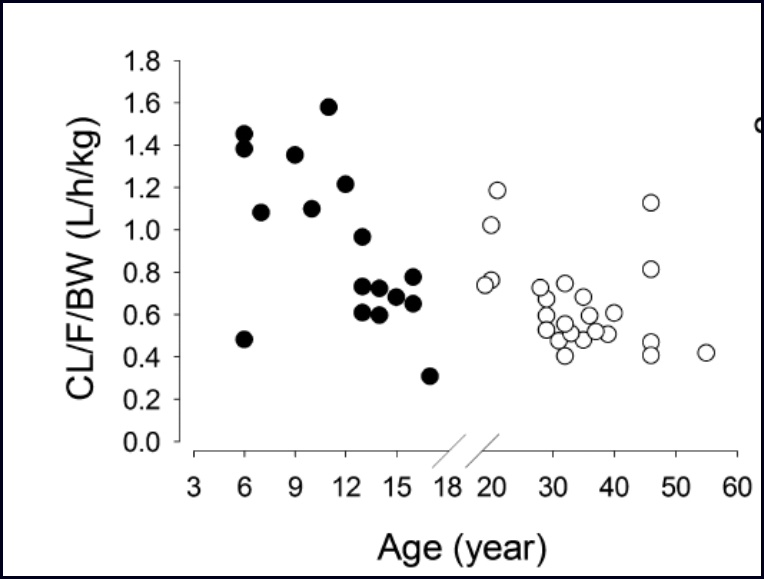
Underdosing of antiretrovirals in UK and Irish children with HIV as an example of problems in prescribing medicines to children, 1997-2005: cohort study

Esse N Menson, A Sarah Walker, Mike Sharland, Carole Wells, Gareth Tudor-Williams, F Andrew I Riordan, E G Hermione Lyall, Diana M Gibb, for the collaborative HIV paediatric study steering committee

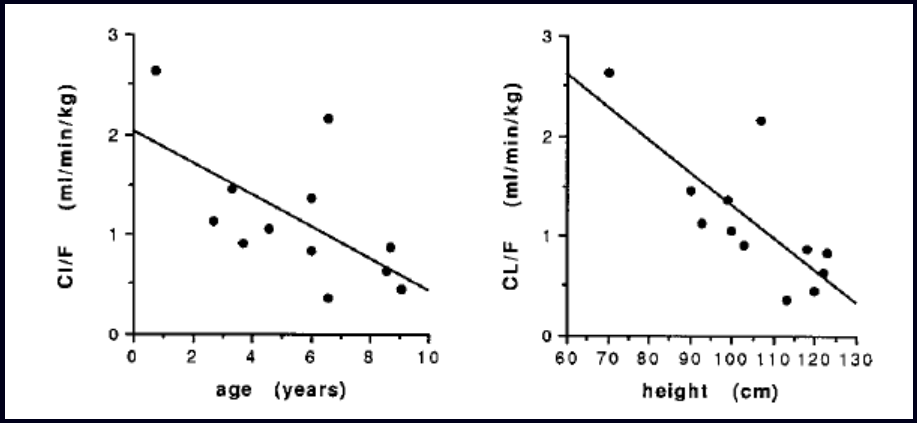
Gatifloxacin, Caparelli 2005



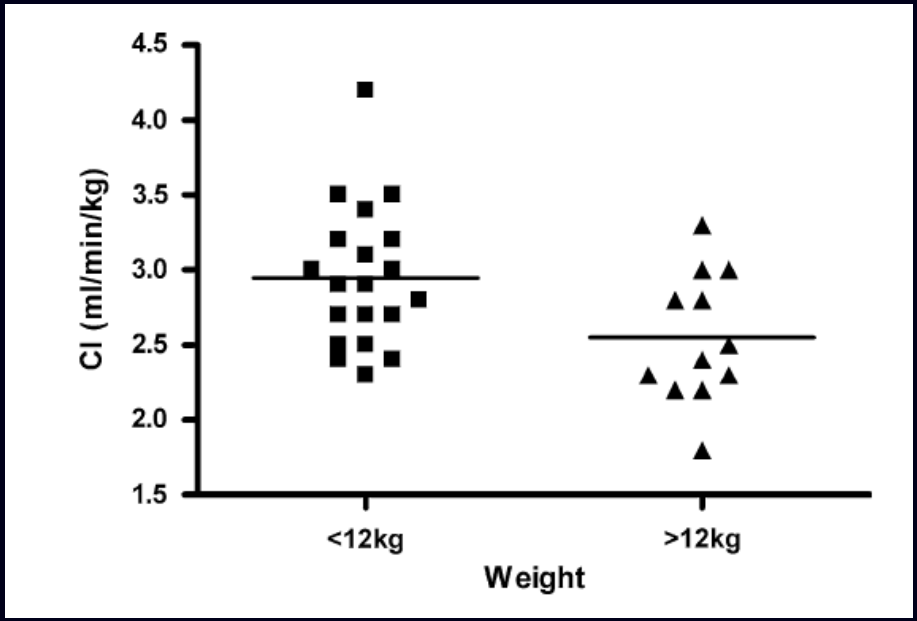
Hydrocodone, Liu 2015



Dapsone, Gatti 1995



Carboplatin, Veal 2010



Busulfan, Tran 2004

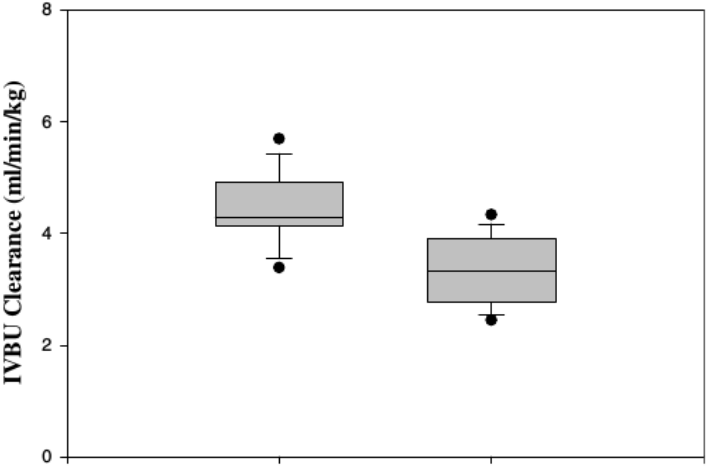
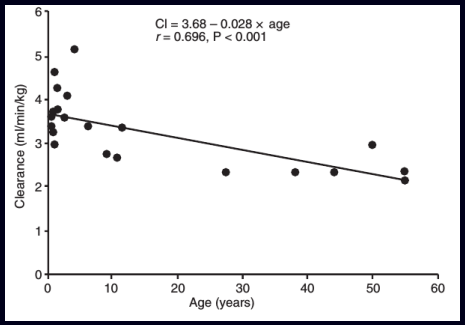
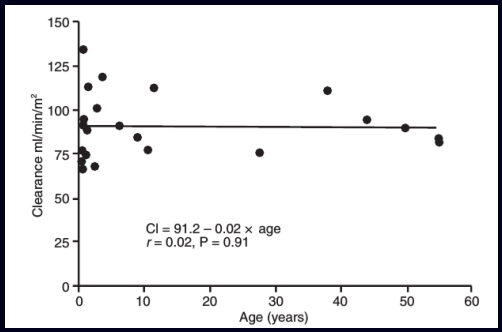


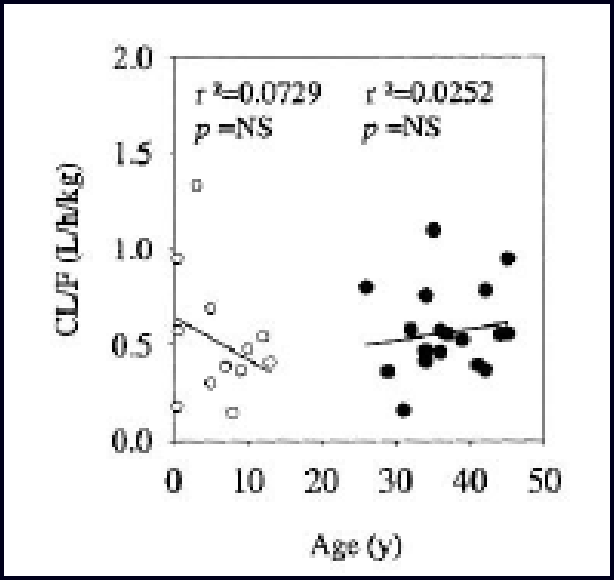
Figure 1. IBVU clearance by age group. Comparison of final clear-

Busulfan, Hassan 2002

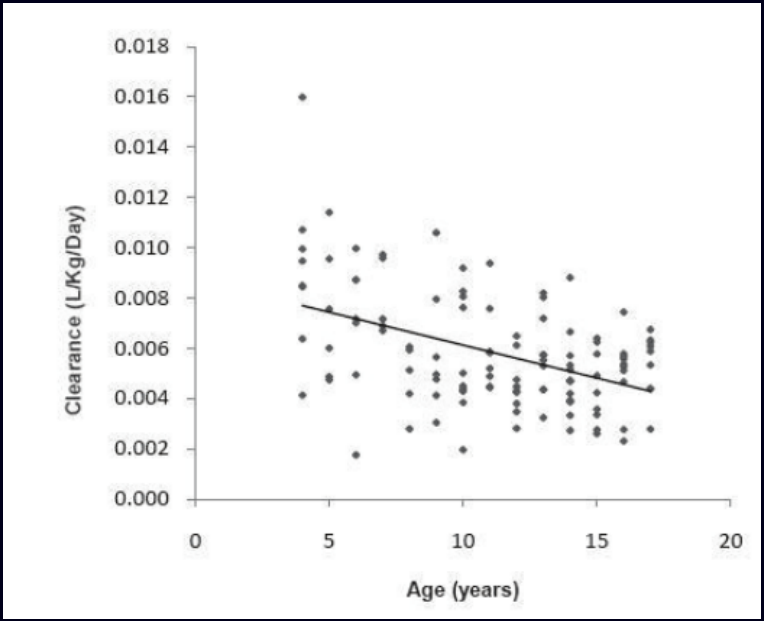




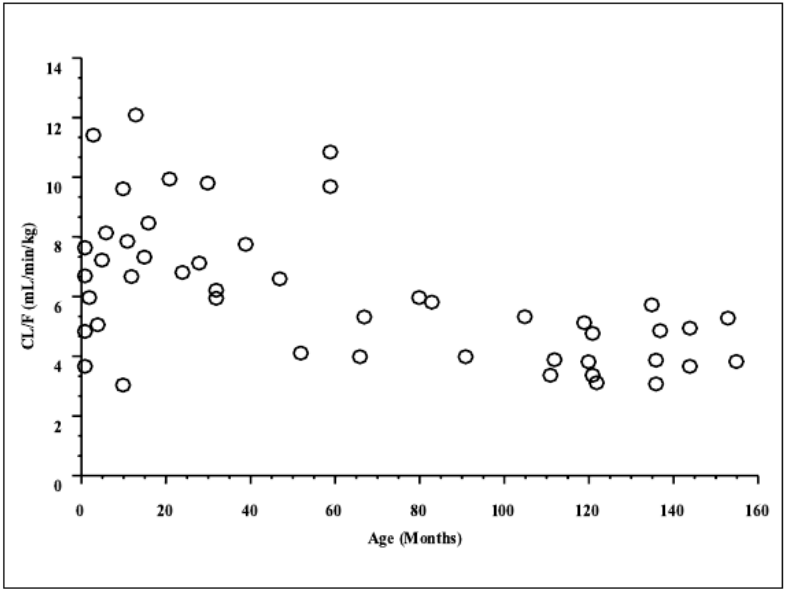
Omeprazole, Marier 2004



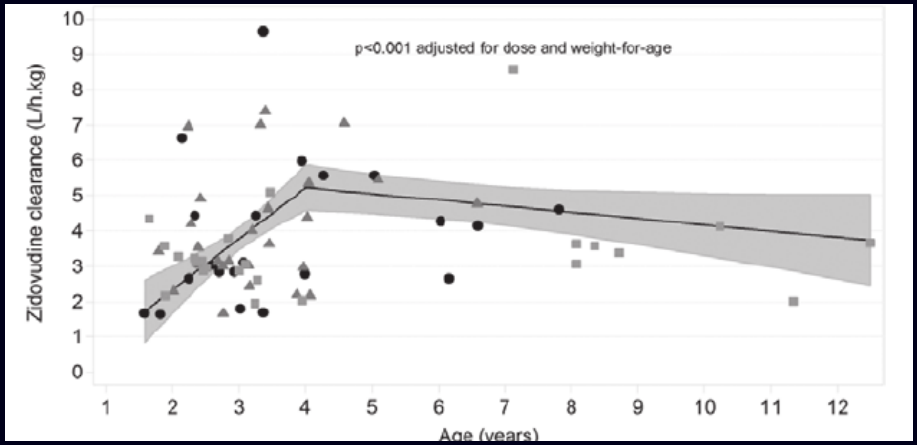
Infliximab, Goldman 2012



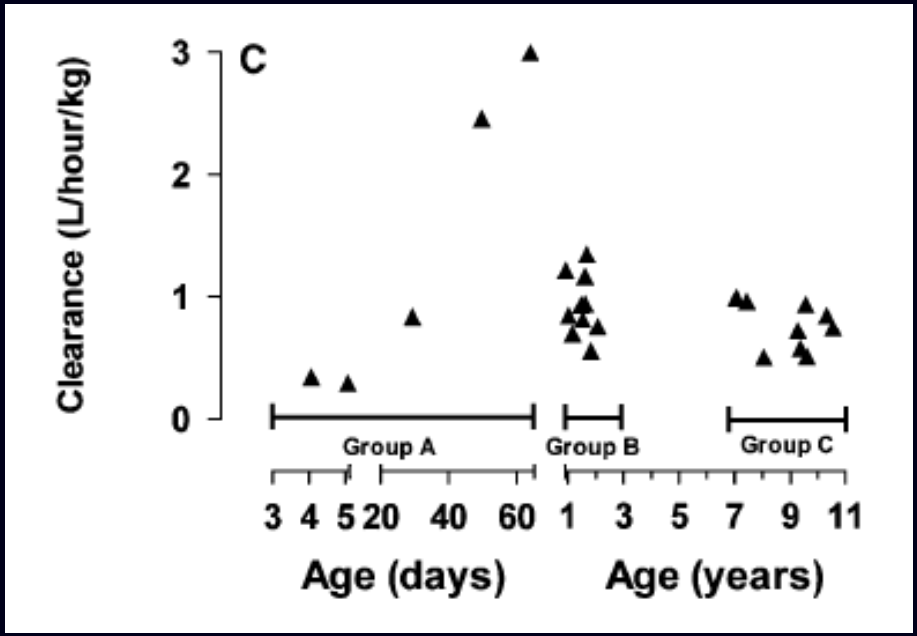
Gabapentin, Haig 2001



Zidovudine, Fillekes 2014



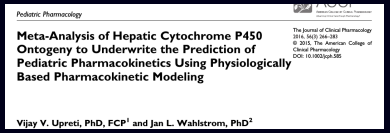
Ketobemidone, Lundeberg 2009



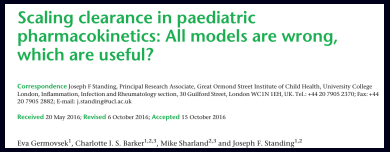
CL scaling

Biological "priors" on PK scaling:

- liver size scales with weight$^{0.78}$ (Johnson 2005); glomerular filtration scales with weight$^{0.63}$ (Rhodin 2009)
- understanding maturation: e.g. Upreti 2016 shows how; Calvier 2017 explores why (with PBPK):



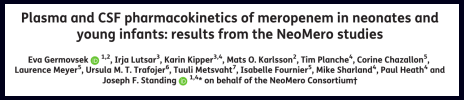
- Standardised parameterisation is beneficial (Germovsek 2017 and 2018):



CL scaling: post natal *versus* gestational age

Need to stratify by gestational and postnatal age?

- Some studies found no effect beyond postmenstual age



Plasma and CSF pharmacokinetics of meropenem in neonates and young infants: results from the NeoMero studies

Eva Germovsek [1,2], Irja Lutsar[3], Karin Kipper[3,4], Mats O. Karlsson[2], Tim Planche[4], Corine Chazallon[5], Laurence Meyer[5], Ursula M. T. Trafojer[6], Tuuli Metsvaht[7], Isabelle Fournier[5], Mike Sharland[4], Paul Heath[4] and Joseph F. Standing [1,4]* on behalf of the NeoMero Consortium†

Pharmacokinetics of Penicillin G in Preterm and Term Neonates

Helgi Padari,[a] Tuuli Metsvaht,[a] Eva Germovsek,[b] Charlotte I. Barker,[b,c] Karin Kipper,[c,d] Koit Herodes,[d] Joseph F. Standing,[b] Kersti Oselin,[a] Tõnis Tasa,[f] Hiie Soeorg,[g] Irja Lutsar[a]

- In NeoGent postnatal effect 50% complete by day 2 of life, 80% by day 7

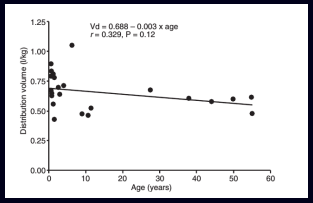
Development and Evaluation of a Gentamicin Pharmacokinetic Model That Facilitates Opportunistic Gentamicin Therapeutic Drug Monitoring in Neonates and Infants

Eva Germovsek,[a] Alison Kent,[b] Tuuli Metsvaht,[c] Irja Lutsar,[c] Nigel Klein,[a] Mark A. Turner,[d] Mike Sharland,[b] Elisabet I. Nielsen,[e] Paul T. Heath,[b] Joseph F. Standing,[a] on behalf of the neoGent Collaboration

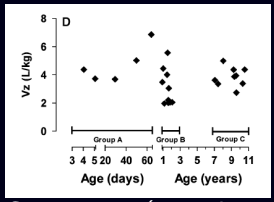
- Conclusion: Recruit range of post menstrual age, no need for stratification by post-natal age unless very narrow therapeutic index

Volume (generally) linear (Price 2003)

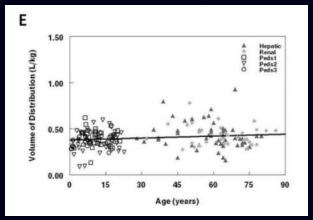
Busulfan, Hassan 2002



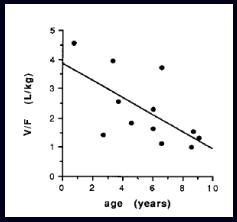
Ketobemidone, Lundeberg 2009



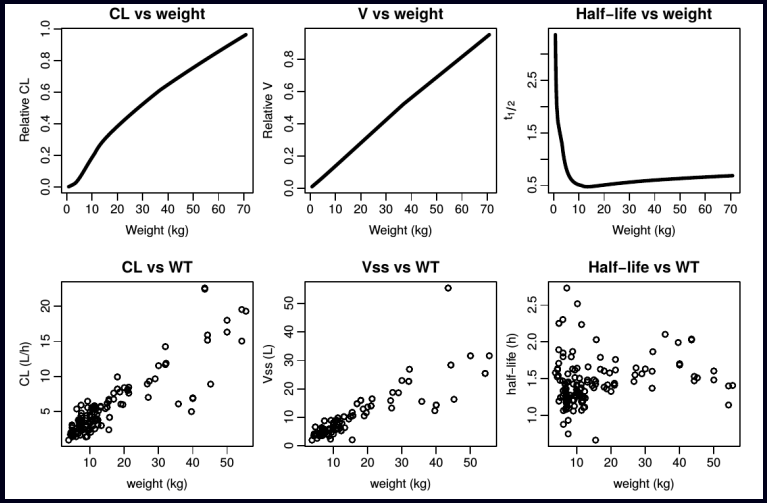
Oxaliplatin, Nikanjam 2015



Dapsone, Gatti 1995 (not always)



PK scaling reality (treosulfan)



PD scaling

Clinical response in antibiotic trials:

- Often no known source of infection, but resistance rates similar (Bielicki 2015)
- Standardisation of clinical endpoints?

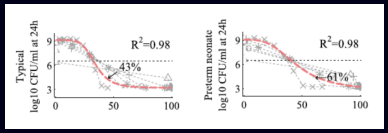
Biological prior:

- Neutrophil, macrophage and dentritic function ?impaired (Cuenca 2013)
- $\downarrow$ age $\rightarrow \uparrow$ lymphocyte counts, but more naive

PK indices:

- PKPD based on *in vitro* MIC often used: ft>MIC, AUC/MIC, C_{max}/MIC, changing PK profile shape may change most appropriate index (Nielsen 2011)
- Neonates need higher ft>MIC based on *in vitro* (Kristoffersson 2016)

Simulation setting	Benzylpenicillin				
	R^2			$fT_{>MIC}$	
	fC_{max}/MIC	fAUC/MIC	$fT_{>MIC}$	B_{stat} (%)	B_{eid} (%)
Default	0.54	0.84	0.93*	29	38
i *(a)* Reduced CL	0.73	0.94*	0.93	25	33
(b) PK neonate	0.86	0.98*	0.91	24	32



Overview

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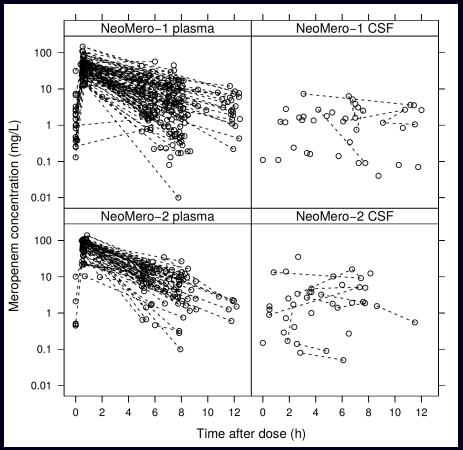
Choice of sampling times

Three main approaches

- Optimal design
- Simulation-estimation studies
- Empirical:
  - based on experience
  - opportunistic and scavenged sampling

NeoMero optimal sampling times

- Used PopED software for ED-optimal design
- Optimal times: Peak, 5-6 hours, trough
- 109 patients had full sampling schedule



Choice of sampling times: Simulation-estimation

- Simulate from proposed model with proposed sampling schedule
- Estimate model parameters from simulations
- Compare precision under competing designs

Example:

- neofosfo iv/oral antimicrobial neonatal PK
- Took adult models and scaled for age and size
- Simulated with various sampling designs and looked at precision on CL, V and F

Drawback of OD and simulation-estimation:

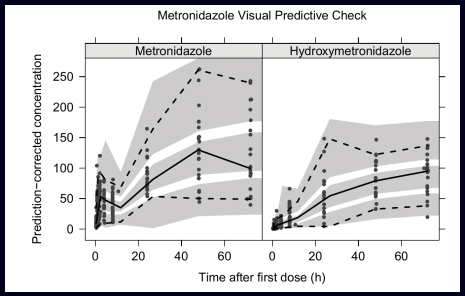
- Need to know the model

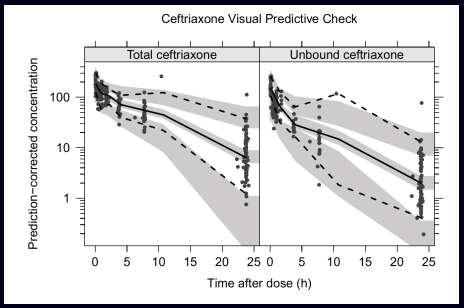
Choice of sampling times: Design by experience

Example:

- Ceftriaxone and oral metronidazole in malnourished infants
- Only 3 post-dose samples feasible
- Need to capture:
  - Ceftriaxone C_{max}
  - Metronidazole absorption
  - Ceftriaxone concentration-dependent protein binding
  - Accumulation of metronidazole and hydroxymetronidazole
- SOLUTION: Randomise patients to different combinations of early, middle and late samples

Choice of sampling times: Design by experience





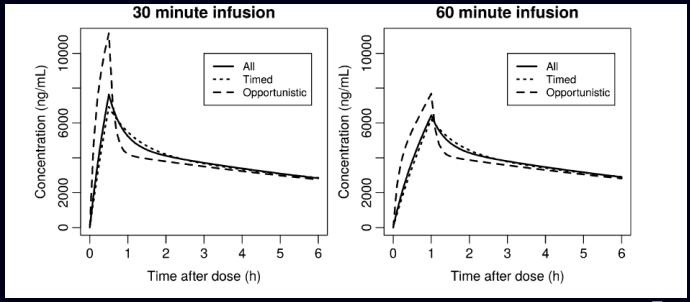
(Standing 2018)

Choice of sampling times: Opportunistic and scavenged sampling

- Can lead to problems: Leroux *et al* compared model derived parameters from samples taken at designed times (C_{max}, trough ...) with opportunistic samples in same study

> *Conclusion* Blood samples scavenged in the course of caring for neonates can be used to estimate ciprofloxacin pharmacokinetic parameters and therapeutic dose requirements.

- Results do not entirely support this:



How many patients to recruit?

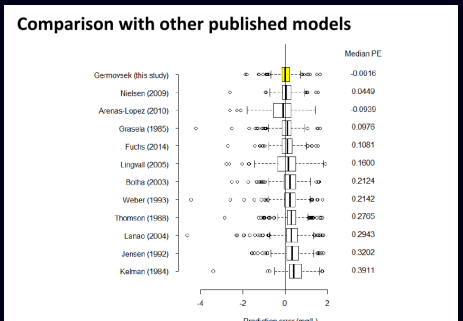
- Can also be answered with optimal design
- Simulation-estimation used for parameter precision, see:

TUTORIAL

Use of Modeling and Simulation in the Design and Conduct of Pediatric Clinical Trials and the Optimization of Individualized Dosing Regimens

C Stockmann[1], JS Barrett[2], JK Roberts[1] and CMT Sherwin[1]*

- Rule of thumb: ≥ 50 patients required to identify covariates (Ribbing 2004)
- Law of diminishing returns (more noisy data $\neq$ better predictions) (Germovsek 2016):



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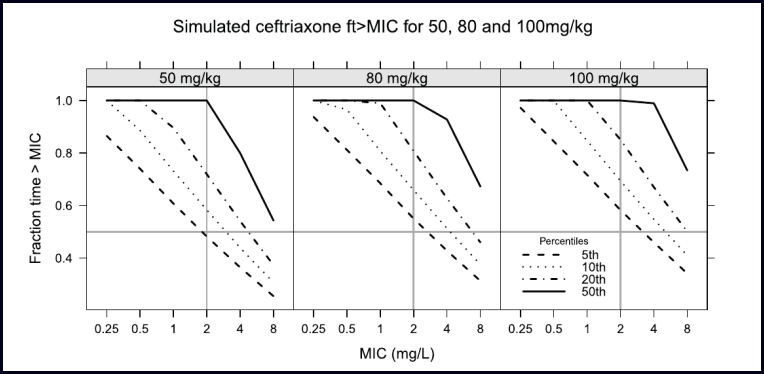
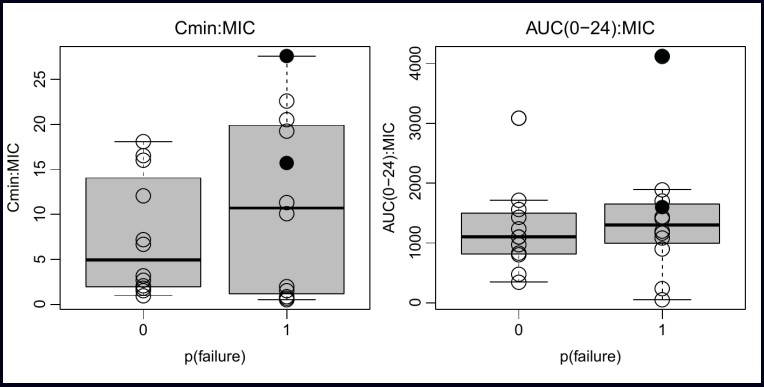
Data Analysis: PTA Curve

- Probability of Target Attainment (PTA) often used
- Deal with uncertainty in target by presenting PKPD index with associated percentiles e.g. (Standing 2018):



Data Analysis: PKPD index *vs* outcome NeoMero example

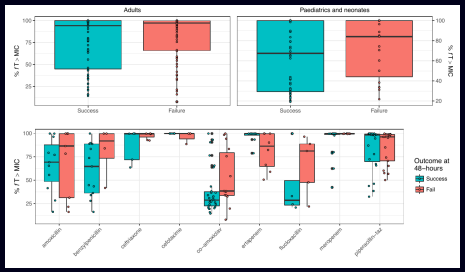
- 24/123 had Gram negative BSI with MIC
- Failure defined as death or treatment modification at ToC



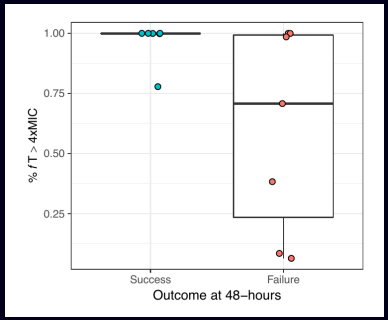
(Germovsek 2018)

Data Analysis: PKPD index *vs* outcome ABDose example

- Prospective observational PKPD on NICU, PICU and ICU, 230 patients aged 1 day (24 week GA) to 90 years, top 10 antibiotics
- Failure defined as: requirement for further antimicrobials or death; SOFA (disease severity score) most significant predictor on multivariable analysis
- 13 had sterile site organisms with MIC



(Lonsdale 2018 PhD thesis)



Data Analysis: PKPD index *vs* outcome Vancomycin GOSH example

- 102/785 had Gram positive BSI with MIC, 80 were CoNS
- Failure defined as death, re-infection or re-treatment following Lodise 2014
- Results:
  - Median (range) AUC/MIC ratios: 320 (50-2755) mg.h/L
  - No correlation with PKPD and efficacy outcome
  - Change in renal function significantly associated with duration of exposure

(Kloprogge 2018 manuscript in preparation)

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Future perspectives

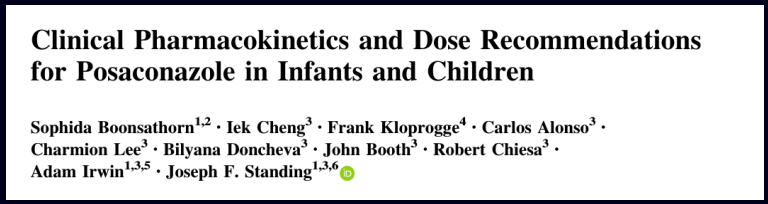
Prospective multi-centre PK studies, open to multiple drugs

- Neonatal and Paediatric Pharmacokinetics of Antimicrobials Study (NAPPA) ClinicalTrials.gov Identifier: NCT01975493
- 428 participants, 2 - 8 PK samples, 6 penicillins

(Barker PhD thesis in preparation)

Use Electronic Health Records (EHR) to leverage routine data

- At GOSH data now biobanked (17/LO/0008 Use of routine GOSH data for research)
- Can run large PK studies in few centres
- e.g. posaconazole 117 patients, 105 of whom $\leq$ 12 (Boonsathorn 2018):



Clinical Pharmacokinetics and Dose Recommendations for Posaconazole in Infants and Children

Sophida Boonsathorn[1,2] · Iek Cheng[3] · Frank Kloprogge[4] · Carlos Alonso[3] · Charmion Lee[3] · Bilyana Doncheva[3] · John Booth[3] · Robert Chiesa[3] · Adam Irwin[1,3,5] · Joseph F. Standing[1,3,6]

- Plans to look at sepsis/infection biomarkers with time

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Conclusions

- PK scaling and extrapolation is known
- PTA targets in young (neonates mainly) patients may need to be considered
- Prospective trials with culture-positive children huge challenge (6-20% in our experience)
- Basis for clinically-derived targets - we have not managed to replicate in 3 studies, often finding opposite direction of relationship
- Much information can be leveraged from EHR - can it be reliably and systematically be collated?

Acknowledgements

Main collaborators on work presented here: Mike Sharland (SGUL), Irja Lutsar (Tartu), Paul Heath (SGUL), Tuuli Mehtsvart (Tartu), Adam Irwin (GOSH/UQ), Nigel Klein (UCL/GOSH), Jay Berkley (Oxford/KEMRI), neoMero consortium, London Pharmacometrics Interest Group

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