

Clinical Development of Systemic Antifungal Drugs in Pediatrics – Achievements and Challenges

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Invasive Fungal Diseases in Pediatric Patients

- **Relative to adults, children and adolescents are similarly vulnerable**
- **However, differences exist as to:**
 - **Populations at risk**
 - **Epidemiology**
 - **Usefulness of newer diagnostic tools**
 - **Pharmacology of antifungal agents**

Pediatric Populations at Risk for Invasive Fungal Diseases

- **AML, ALL during prolonged steroid treatment**
 - **Recurrent leukemias**
 - **Hematopoietic stem cell transplantation**
 - During granulocytopenia until engraftment
 - During augmented immunosuppression for GVHD
 - **Very low and extremely low birth weight infants**
 - **Children with life-threatening problems in the ICU**
- ... chronic granulomatous disease; lung and heart/lung, liver, and pancreas transplantation; metabolic diseases

Antifungal Pharmacology and Pediatric Drug Development

Dosage / Dosage Interval



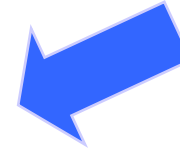
**Disease-
related
Factors**



Pharmacokinetics

Absorption
Distribution
Metabolization
Elimination

**Growth and
Development**



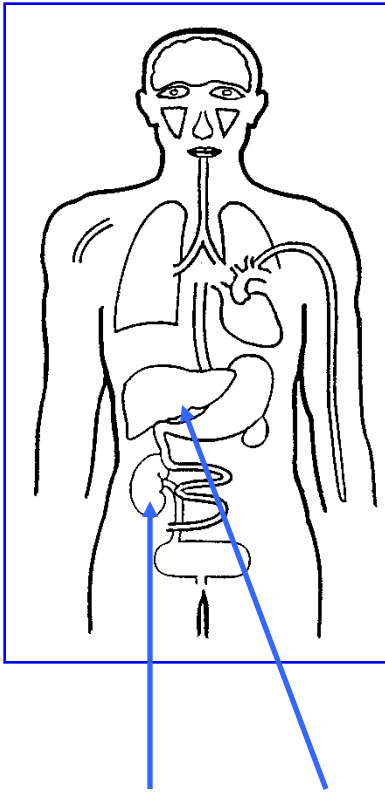
Concentration at Target Site



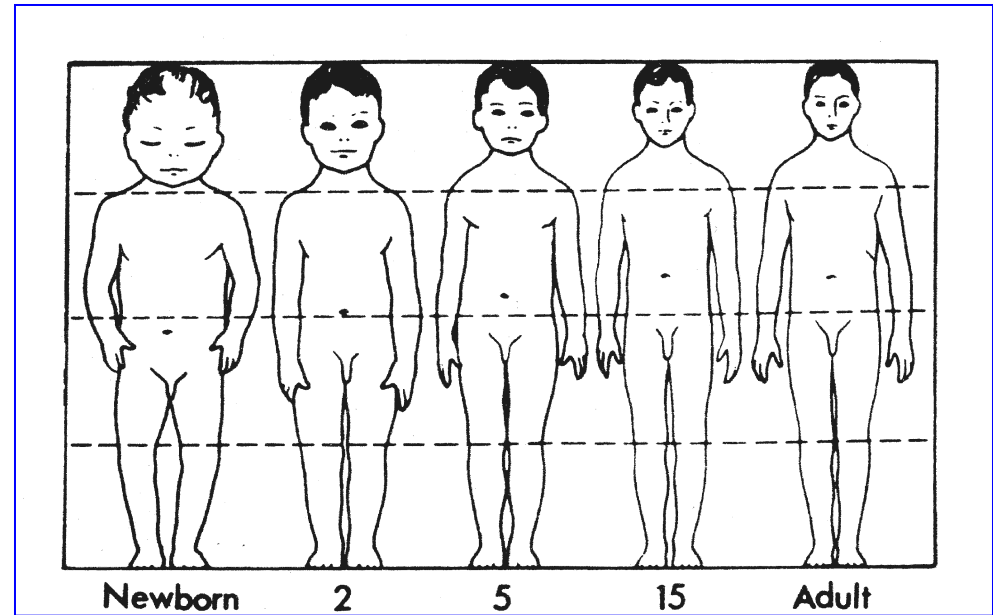
Pharmacological Effects

Efficacy
Toxicity

Changes in body mass and body composition



**Maturation processes
of excretory organs**



**Scaling of dosing regimens based on body weight
or body surface area generally inappropriate**

PK Challenges in Pediatric Patients

- **Distribution: larger V_d**
- **Metabolism/elimination: greater CI**
- **Oral Bioavailability/Absorption:**
 - development of a palatable oral solution may be a major challenge to providing oral delivery of an antifungal compound
- ***Particular challenge: premature neonates***

EMA Guidance for Pediatric Drug Development

- clinical studies on pharmacokinetics, safety and tolerance are prerequisite
- if underlying conditions, cause of targeted disease and expected response are similar

 data generated in adults can be used to support documentation of efficacy

However, the regulations stress the importance of post-marketing surveillance to increase the pediatric database

Pediatric Antifungal Arsenal

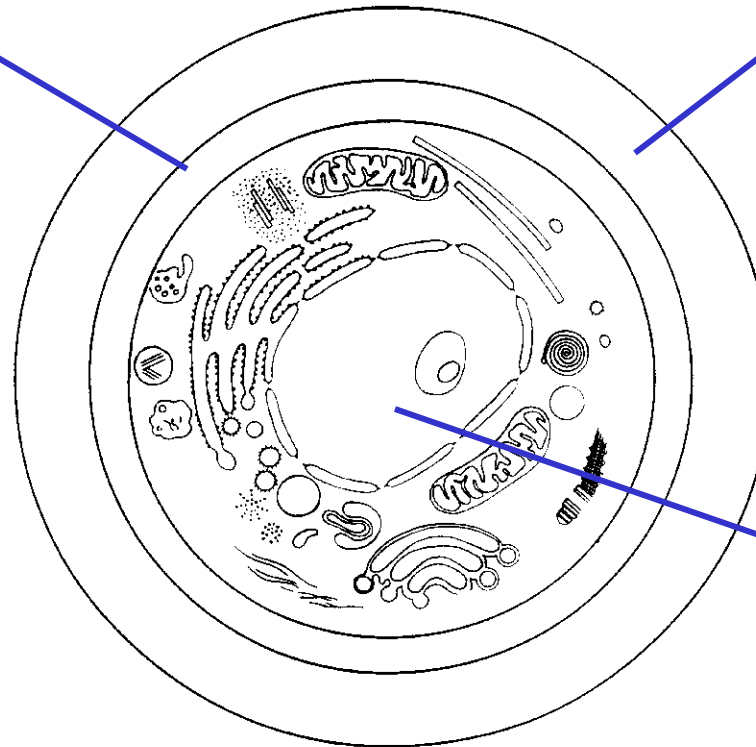
Cell membrane

- Polyenes

- > DAMB
- > LAMB
- > ABLC

- Triazoles

- > Fluconazole
- > Itraconazole
- > Voriconazole
- > Posaconazole



Cell wall

- Echinocandins

- > Caspofungin
- > Micafungin
- > Anidulafungin

Nucleic acid synthesis

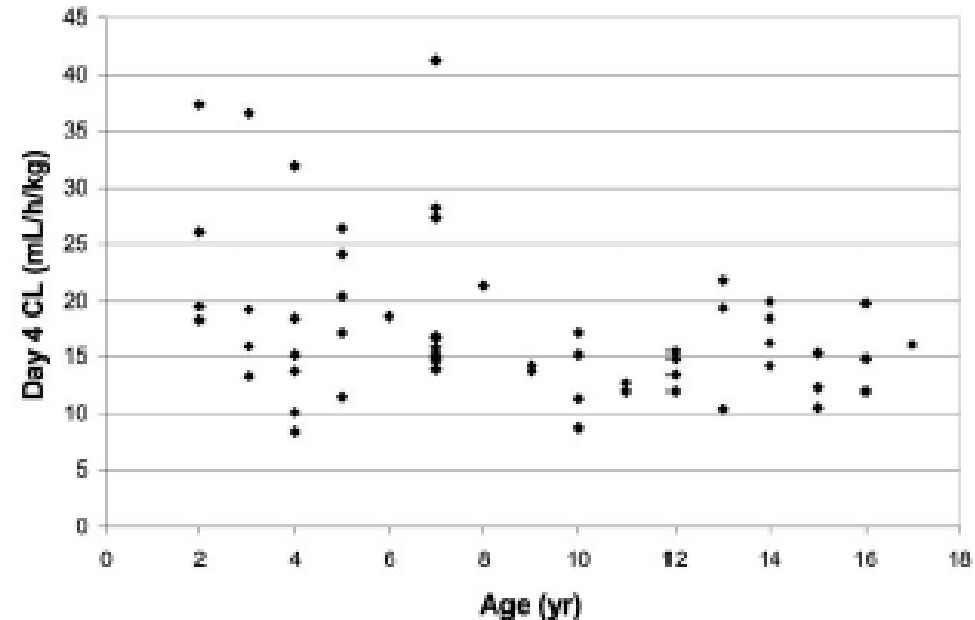
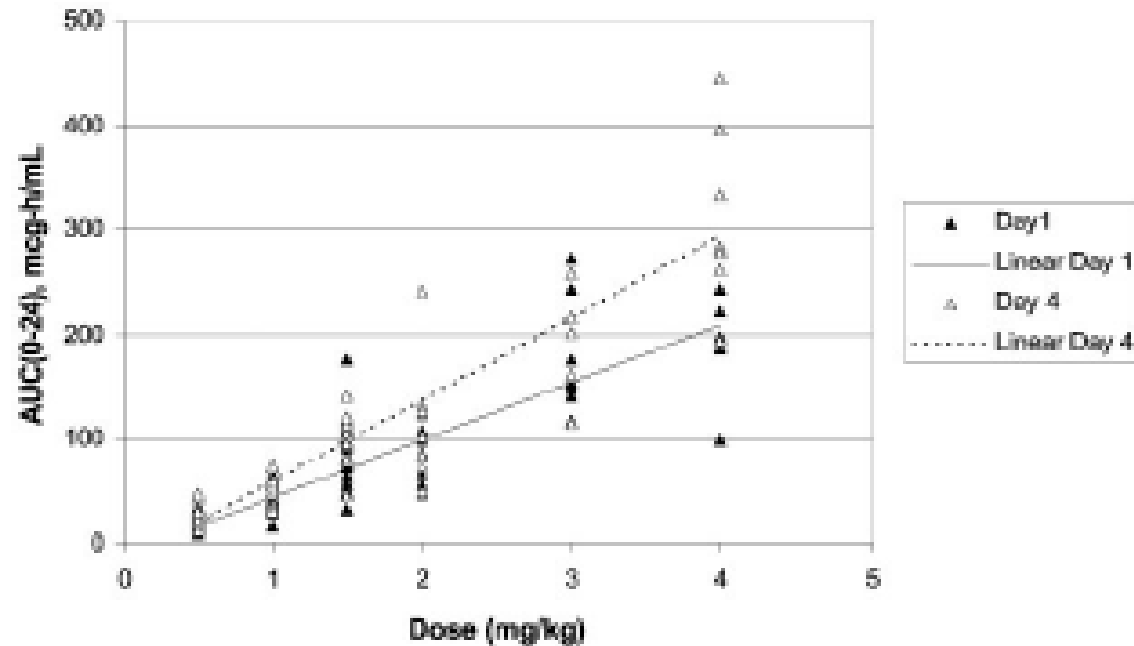
- > Flucytosine

Micafungin

Micafungin: Pk-Study in in Children 2-17 Years

- **Open-label, sequential, dose-escalation study in 78 patients with neutropenia requiring antifungal therapy**
 - **Six dose levels of MICA (0.5–4.0 mg/kg); 1-hour infusion once daily**
 - **Two age groups (2–12 and 13–17 years)**
 - **Samples for PK analysis taken on d 1 and 4**

Micafungin: Pk in Children 2-17 Years



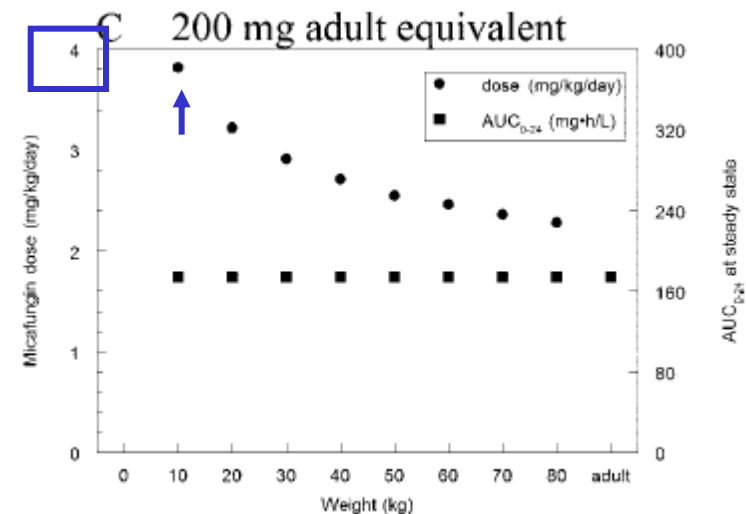
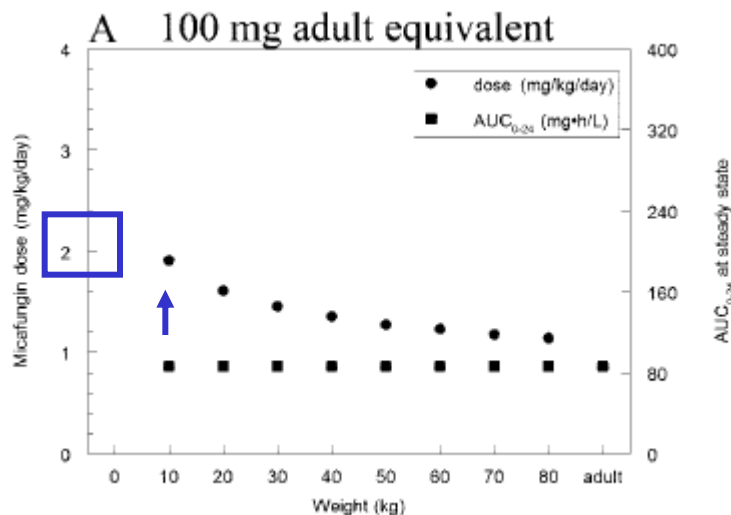
➔ 1) linear PK; 2) age-dependent weight-normalized CL

Micafungin: PK Study in Children 2-17 Years

	Pediatric pts (2-17 yr)			Adults	
Dosage	1 mg/kg	2 mg/kg	4 mg/kg	50 mg	100 mg
C _{max} (ug/mL)	10.8	15.3	30.3	3.6	7.1
AUC 0-24h (ugxh/mL)	40.3	83.0	191.4	33.9	59.9
T _{1/2} beta (h)	12.5	13.2	11.6	12.5	13.0
CL (L/h/kg)	0.021	0.020	0.017	0.017	0.018
VD _{ss} [L/kg]	0.33	0.31	0.28	0.31	0.32

Micafungin: Population Pk in Children 2-17 Years

- Allometric power model: *Clearance in smaller children is higher than predicted on the basis of weight alone, requiring a relative dosage increase to ensure exposure comparable to older children*



Monte Carlo simulations in 9,999 simulated pts showing micafungin dosages in children 10 to 80 kg required to produce a mean AUC 0-24 equivalent to the AUC0–24 observed in adults receiving 100 mg (A) and 200 mg (C) at s/s

Micafungin Pediatric Program

Pediatric PK Study in Adolescents or Older Children 2-17 Years Old (n = 77)

Dose selection

**P III *Candida*
(n = 52)**

**P III Prophylaxis
(n = 39)**

**P II *Candida*
(n = 53)**

**P II *Aspergillus*
(n = 70)**

**Pediatric PK Studies in Premature Neonates
(≤ 40 weeks, ≥ 500 g) (n = 23)**

Micafungin: Pk-study in Premature Infants

- Phase I, single-dose, multicenter, open-label trial
 - Post-gestational age ≤ 40 weeks and body weight ≥ 500 g
 - MICA doses of **0.75, 1.5 and 3.0 mg/kg**; single 30-minute infusion
- A total of 23 patients were included; five weighed 500–1000 g, 18 weighed >1000 g
- Micafungin safe and well tolerated
- No serious drug-related AEs

Micafungin: Pk-study in Premature Infants

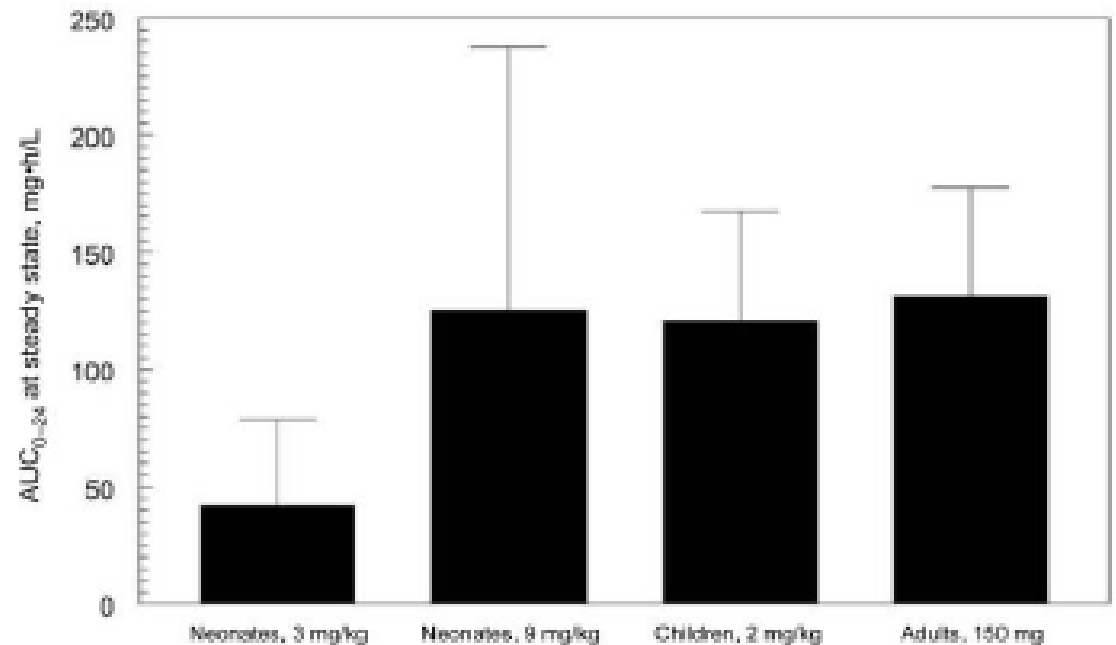
Population	$t_{1/2}$ (h)	K_e (1/h)	Vd_{ss} (L/kg)	Cl (mL/h/kg)
Neonates >1000 g (n = 15)				
Mean	8.8	0.088	0.435	38.9
SD	1.8	0.02	0.111	12.1
95% CI	7.4–9.2	0.08–0.1	0.378–0.491	32.8–45.0
Children 2–8 years old (n = 33) ¹⁴				
Mean	11.5	0.064	0.335	22.5
SD	2.9	0.016	0.16	8.6
95% CI	10.5–12.4	0.059–0.069	0.28–0.39	19.6–25.4
Children 9–17 years old (n = 32) ¹⁴				
Mean	13.4	0.056	0.243	15.1
SD	3.8	0.018	0.074	6.3
95% CI	12.1–14.7	0.05–0.062	0.216–0.271	12.87–17.24
Adults (n = 48) ⁸				
Mean	13.1	0.055	0.256	14.6
SD	3.0	0.01	0.052	3.4
95% CI	12.2–13.9	0.052–0.058	0.241–0.271	13.6–15.5

$t_{1/2}$ indicates half-life; K_e , elimination rate constant; Vd_{ss} , steady-state volume of distribution; Cl, clearance; SD, standard deviation; 95% CI, 95% confidence interval.

Micafungin: Population Pk in Premature Neonates

Population PK modeling of the neonatal PK data and Monte Carlo Simulation:

- a larger neonatal dose is required to produce drug exposure comparable to those predicted on the basis of weight in children and adults
- Additional population PK based on open label PK studies with doses of 7- 15 mg/kg/d support the use of 10 mg/kg for neonates



age-dependent serum protein binding – 8-fold higher unbound fraction ($f(u)$) in neonatal serum

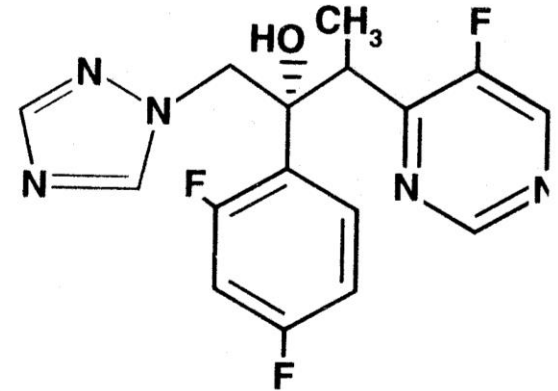
Micafungin: Antimicrobial Bridging

- **Characterization of pharmacokinetics and pharmacodynamics of micafungin in a rabbit model of neonatal hematogenous *Candida* meningoencephalitis**
 - **Bridging of the results to neonates by use of population pharmacokinetics and Monte Carlo simulation**
- ➔ An experimental dose–microbiological response relationship was apparent in the brain, and near-maximal effect was apparent with doses of 8 mg/kg**
- ➔ Monte Carlo simulations revealed that near-maximal antifungal effect was attained at human neonatal doses of 12–15 mg/kg**

Voriconazole

Voriconazole

- ***Non-linear pharmacokinetics***
- ***Complex hepatic metabolism***
 - Substrate/inhibitor of CYP2C9, 3A4, 2C19
 - ***Genetic polymorphisms of CYP2C19***
- ***Number of relevant pharmacokinetic interactions***
- ***Toxicity issues with link to exposure***



Voriconazole: Pediatric Development

- **Two phase II studies investigating the PK of IV VCZ in children 2-12 years at dosages of 2x3 and 2x4 mg/kg**
- **355 plasma samples in 35 patients**
- ➡ **High interindividual variability**
- ➡ **faster clearance / linear pharmacokinetics**

Voriconazole: Dosage in children 2 to 11 yrs (1)

1.3 -fold dosage

Medians	3mg/kg		4mg/kg	
	*Paed.	**Adults	*Paed.	**Adults
C_{ave} (ng/ml)	889	1155	1186	3217
AUC_{τ} (ng·h /ml)	10, 670	13, 855	14, 227	38, 605

1.3 -fold

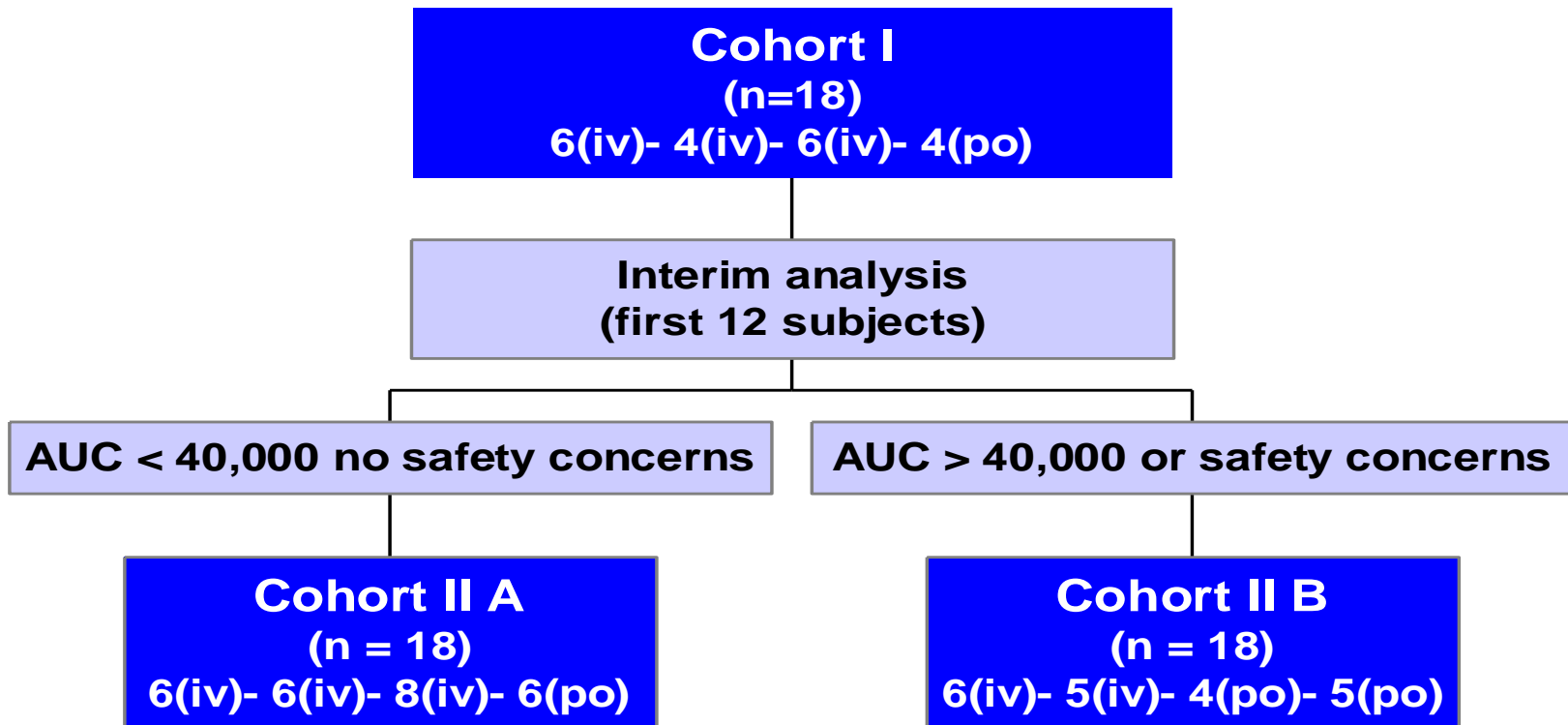
2.8 -fold

* 35 subjects from SD and MD PK studies

** 236 healthy volunteers from SD and MD PK studies

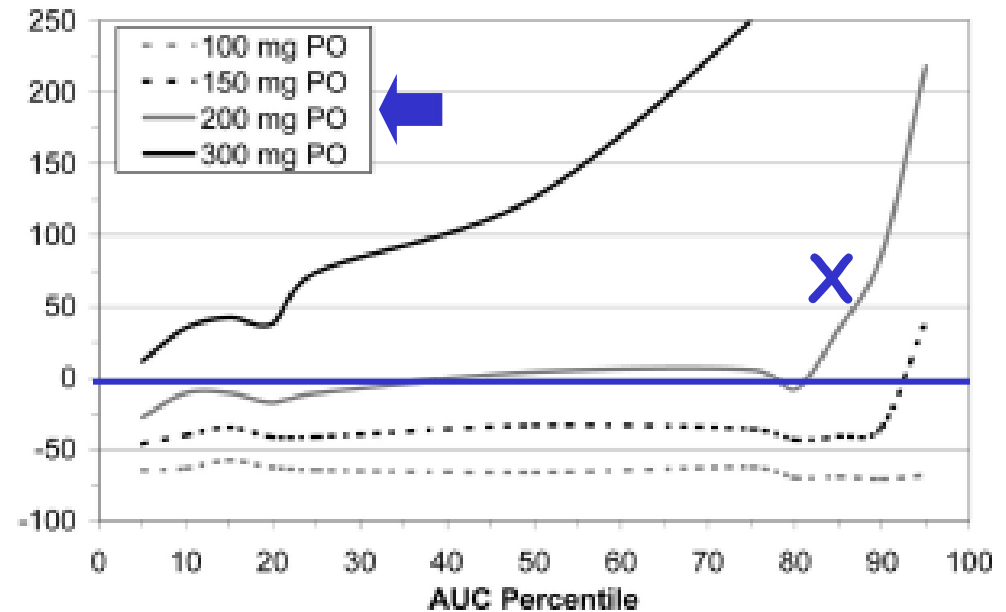
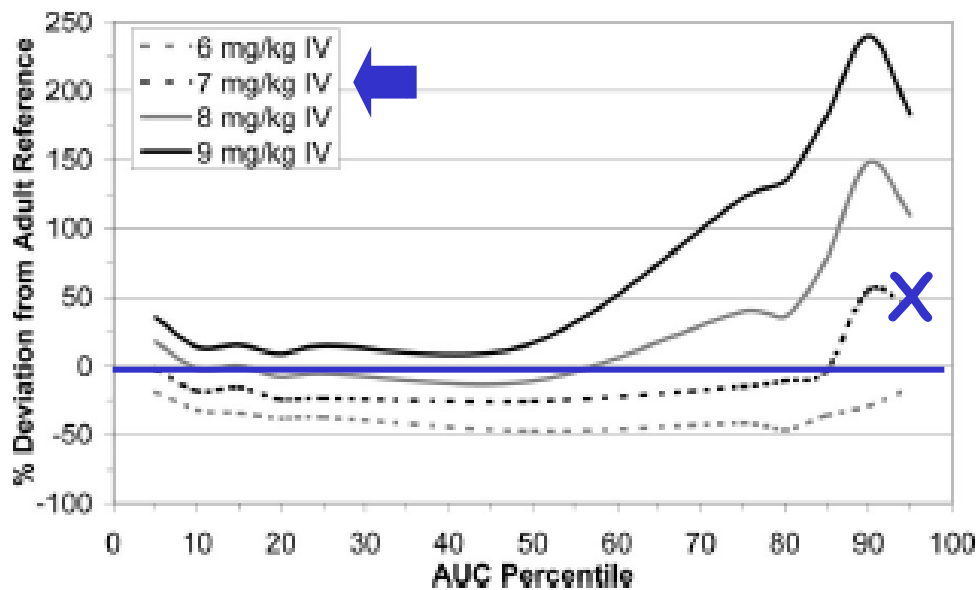
VCZ in children 2-11 yrs: A 1501037

Chart Title



VCZ in children 2-11 yrs: A 1501037 Pop-PK Analysis

Percent deviations from the reference adult population
AUC distribution (4 mg/kg BID IV; 200 mg BID PO)



Voriconazole: Initial Pediatric Dose

Dose recommendation for pediatric patients *2 to 11 yrs*

- 2x7 mg/kg IV without loading
- 2x200 mg PO without loading

Dosage for adolescents ≥ 12 yrs

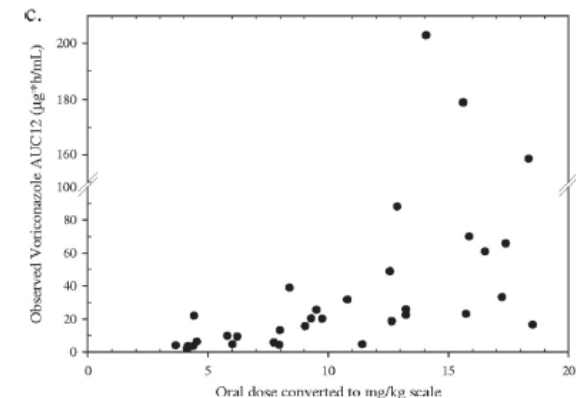
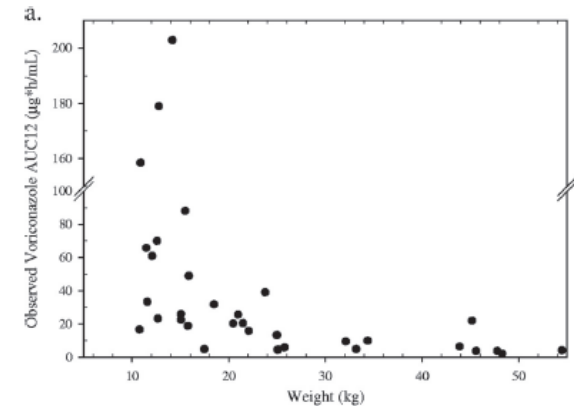
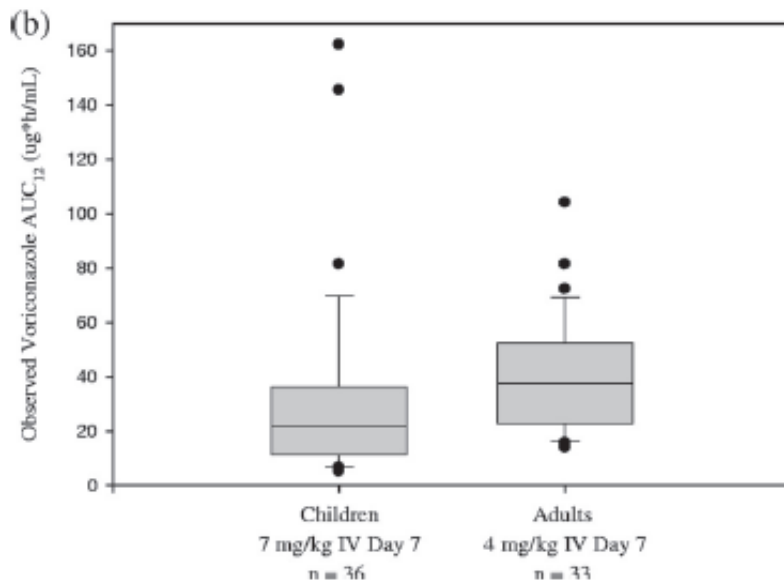
- 2x4 mg/kg IV (2x6 mg day 1)
- 2x200 mg PO (2x400 mg day 1)



*Dosage validation (exposure and safety)
in two subsequent pediatric PK trials*

Voriconazole: Pediatric Dose Finding

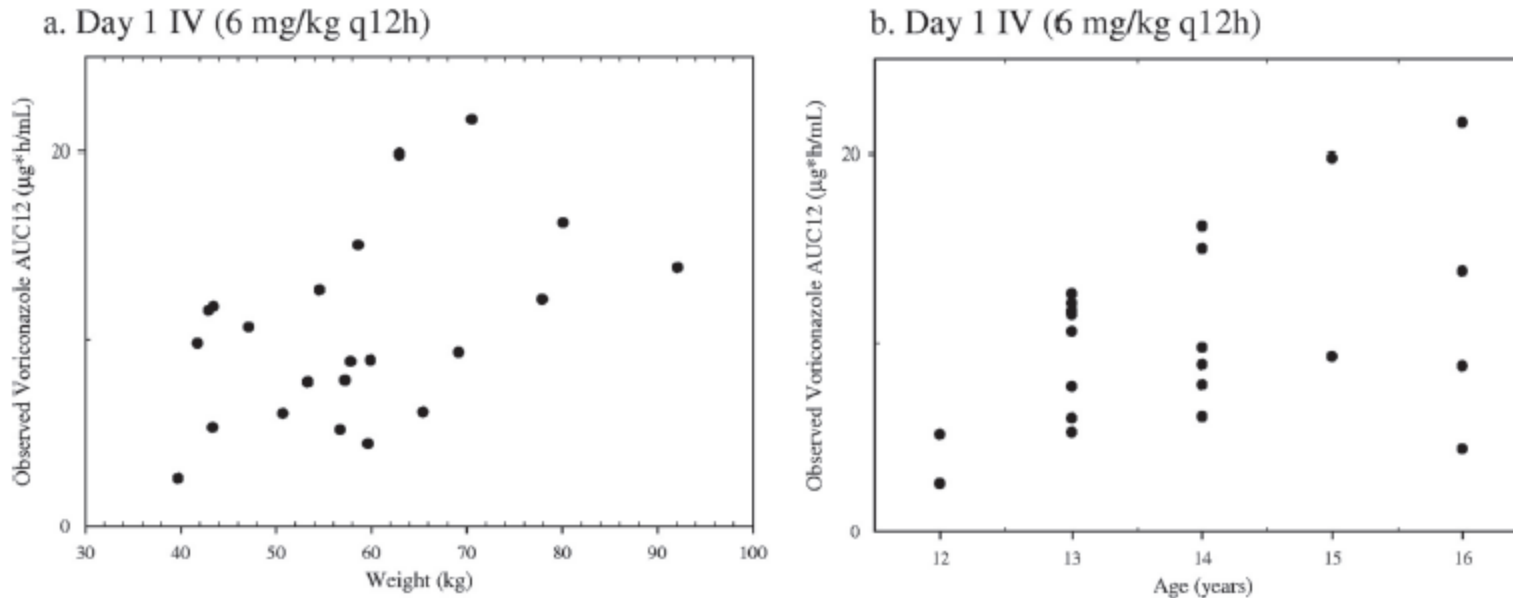
40 immunocompromised children 2 to <12 ,
7 mg/kg IV BID, switched to 200 mg PO BID



IV doses higher than 7 mg/kg are needed to closely match adult exposures, and a weight-based oral dose may be more appropriate

Voriconazole: Pediatric Dose Finding

26 immunocompromised **adolescents 12 to <17 years**, IV to PO switch, 6 mg/kg IV BID (d1), then 4 mg/kg IV BID, then 300 mg PO



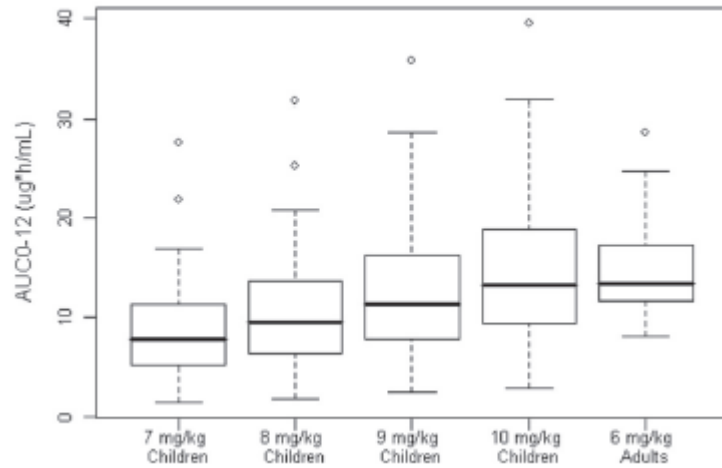
Exposures in adolescents overall comparable to those in adults. **Young adolescents 12-14 with low body weight may need higher doses**

VCZ in pediatric patients 2-17 years: Population PK Analysis

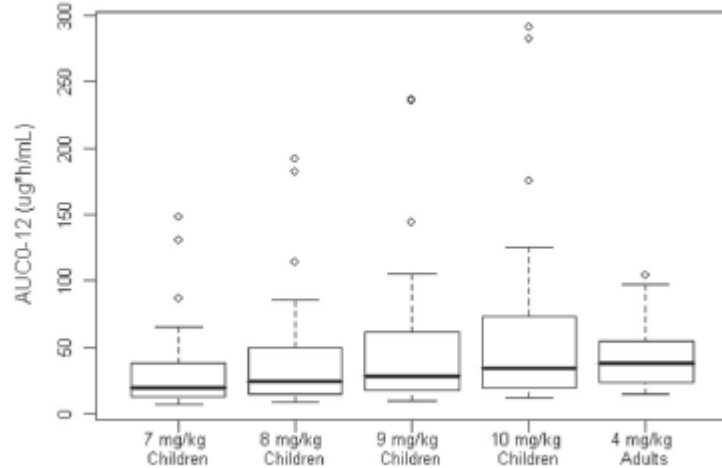
- Pooled data from 112 immunocompr. children (2 to <12 yrs), 26 immunocompr. adolescents (12 to <17 yrs), and 35 healthy adults
 - Different maintenance doses (i.e., 3, 4, 6, 7, and 8 mg/kg BID IV ; 4 mg/kg, 6 mg/kg, and 200 mg BID PO) evaluated in the *children*
 - The adult dosing regimens (6 mg/kg i.v. BID on day 1, followed by 4 mg/kg BID, and 300 mg orally BID) evaluated in the *adolescents*
- Two-compartment model with first-order absorption and mixed linear and nonlinear (Michaelis-Menten) elimination developed
- Deterministic simulations based on individual parameter estimates from the final model to derive dosage

VCZ in children 2-11 yrs: Predicted comparative exposures

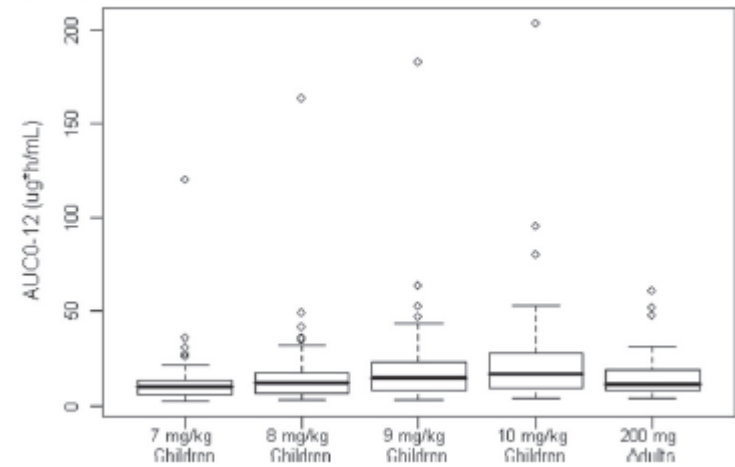
a) Day 1 IV



b) Day 7 IV (Steady State)

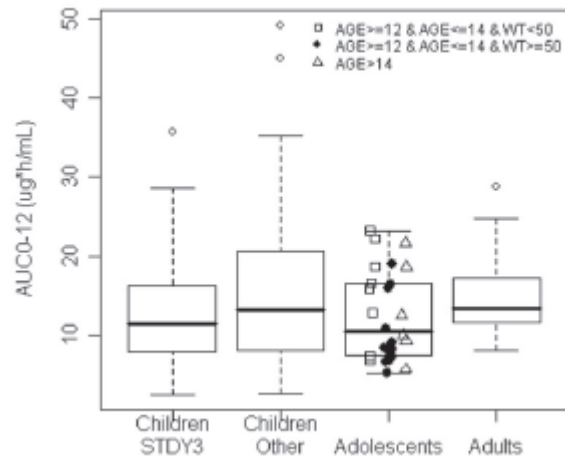


c) Day 7 Oral (Steady State)

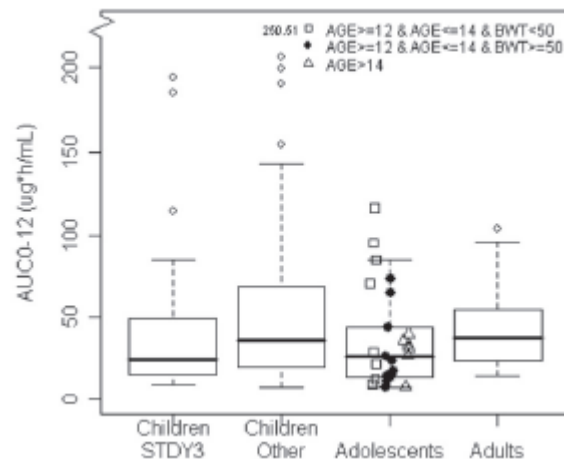


VCZ in adolescents: Predicted comparative exposures

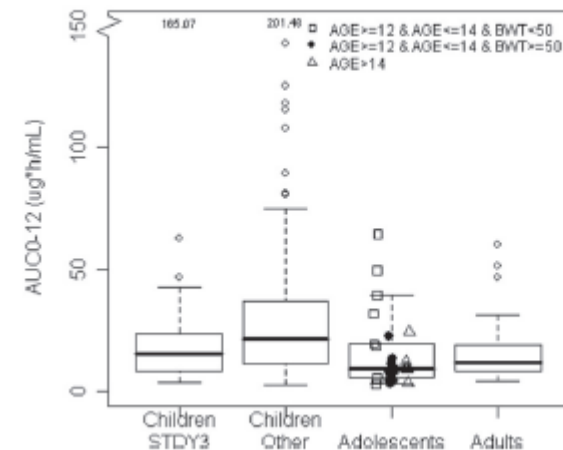
a) Day 1 IV – 9 or 6 mg/kg



b) Day 7 IV (Steady State) – 8 or 4 mg/kg



c) Day 7 Oral (Steady State) – 200 mg or 9 mg/kg (max of 350 mg)



Voriconazole:

Current dosage recommendation

Children 2 to 11 years and adolescents 12-14 years and <50 kg

- 2x8 mg/kg IV (day 1: 2x9 mg/kg)
- 2x9 mg/kg PO (max: 2x350mg)

Adolescents ≥ 12 to 14 years and > 50 kg and those 15 years and beyond:

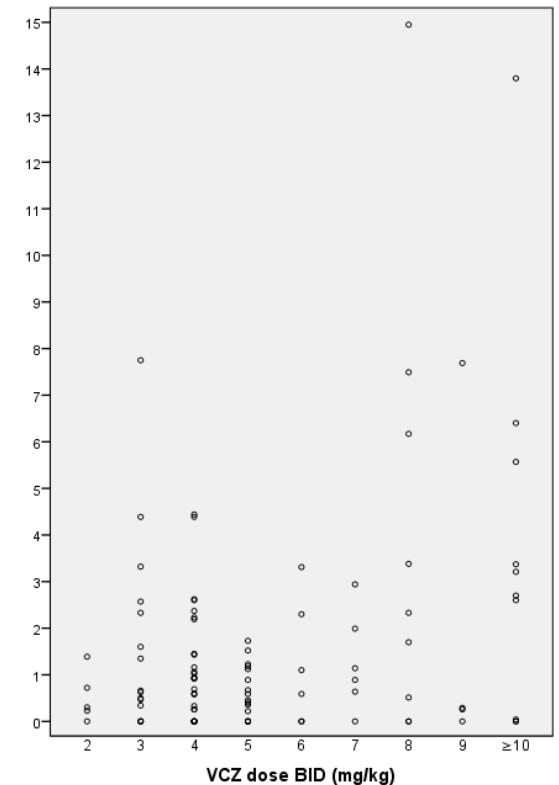
- 2x4 mg/kg IV (2x6 mg day 1)
- 2x200 mg PO (2x400 mg day 1) (adult dose)

VCZ TDM in Immunocompromised Pediatric Patients

74 pts (0.2-18y; mean: 10.2y) / 101 courses of VCZ IV (4) and (15)/or (82) PO at median of 4.8 mg/kg BID (r, 2.2-17.4) for a median of 40 days (r, 6-1002)

Voriconazole trough [mg/L]	No. (%) of samples
< 0.2	56 (22.3)
0.2 – 0.5	50 (19.9)
> 0.5 – 1.0	39 (15.5)
> 1.0 – 2.0	36 (14.3)
> 2.0 – 5.0	50 (19.9)
> 5.0	20 (8.0)

- *no predictable dose-concentration relationships*
- *TDM recommended in guidelines (not in SPC)*



Conclusions

Pharmacological Challenges



- **Much has been achieved in the field of pediatric antifungal pharmacology**
 - **Drug- and age-dependent differences in plasma pharmacokinetics and dosing**
 - **No apparent differences in safety and tolerance relative to adults**
- **Increasing number of population PK studies to guide dose finding**
 - **work well for drugs with robust PK, less well for more complex drugs**
- **Still very limited number of phase II and IV pediatric validation studies**