MCM Pediatric Dose Selection – Case Presentation

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Outline

- Pediatric dose scaling based on allometry
- Levofloxacin pediatric dose for anthrax/plague
- Raxibacumab pediatric dose for inhalational anthrax
- Summary and moving forward

Pediatric Dose Scaling Based on Allometry

$$AUC_{Adult}=\frac{Dose_{Adult}*Bioavailability_{Adult}}{Clearance_{Adult}} \equiv AUC_{Children}=\frac{Dose_{Children}*Bioavailability_{Children}}{Clearance_{Children}}$$

$$Dose_{Children} = Dose_{Adult} * \frac{Clearance_{Children}/Bioavailability_{Children}}{Clearance_{Adult}/Bioavailabiluty_{Adult}}$$

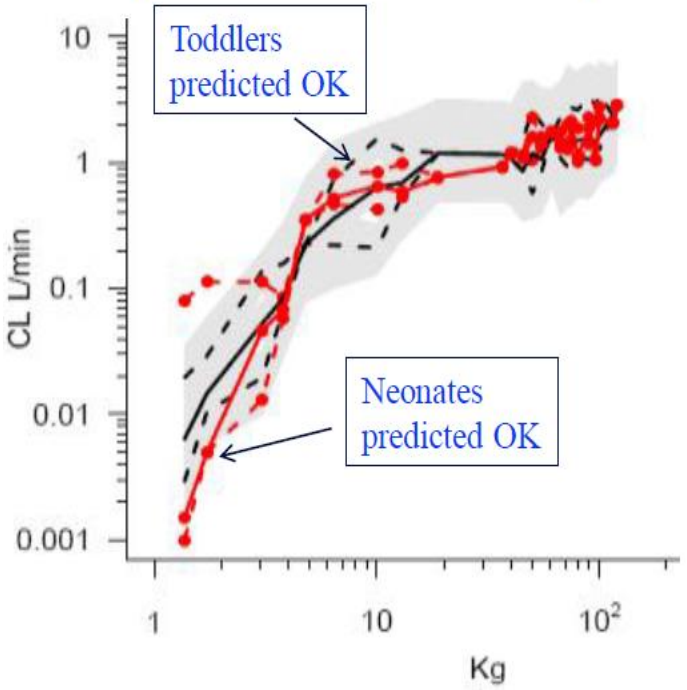
$$CL_{PREDICTED} = CL_{STD} \cdot \left(\frac{WT}{WT_{STD}}\right)^{3/4} \cdot MF \cdot OF$$

Organ Function

Size

Maturation

¾ Allometry + Maturation explains 80% of CL variability



http://holford.fmhs.auckland.ac.nz/docs/tips-and-traps-in-pediatric-PKPD.pdf

Propofol clearance

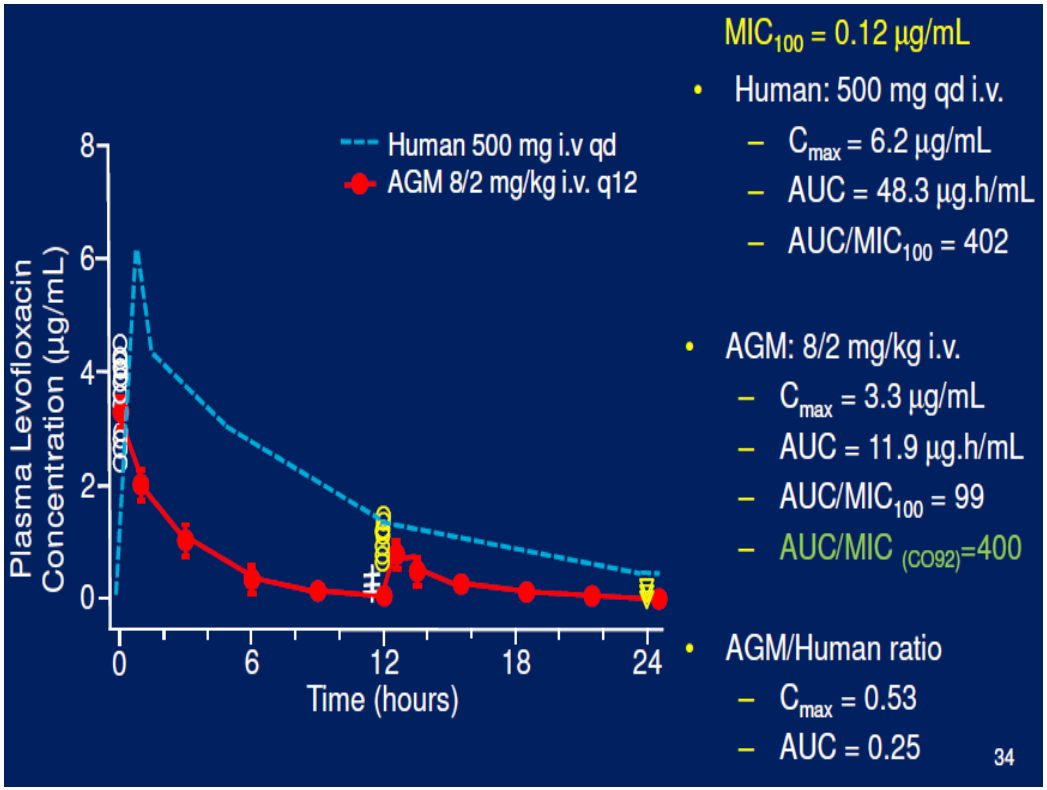
Case Study 1:
Levofloxacin for Pneumonic Plague

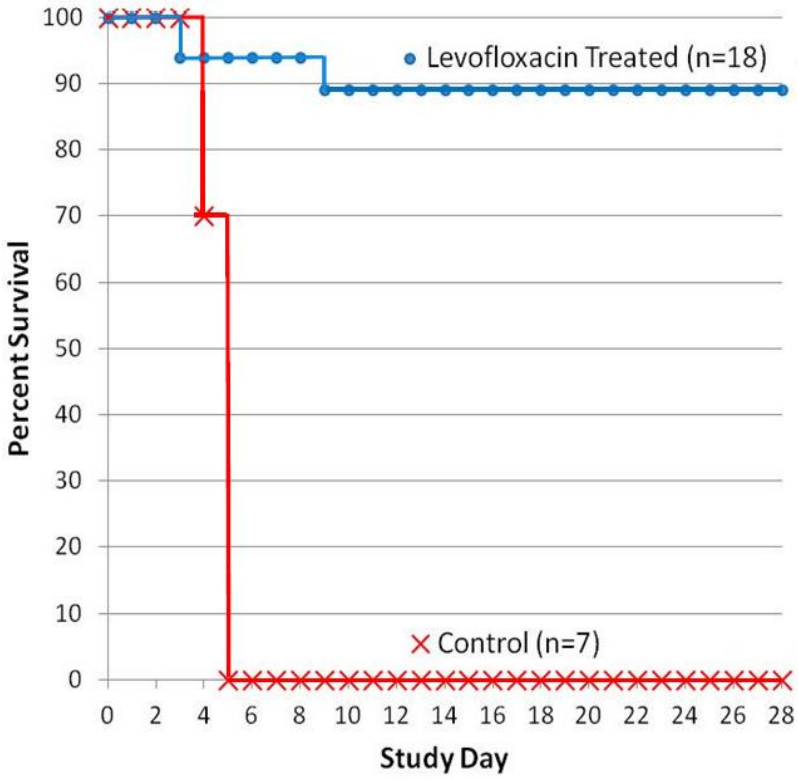
Levofloxacin

- First approved in 1996
- Indications:
  - ✓ Various bacterial infection
  - ✓ Inhalational anthrax, post exposure (2004, 2008 pediatric)
  - ✓ Plague (2012)
- Dose Ranges
  - ✓ 250mg QD x 3 days (UTI)
  - ✓ 500mg/750mg QD x 5 -14 days (CAP)
  - ✓ 750mgQD x 7 - 14 days (noscomial pneumonia)
  - ✓ 500mg QD x 60 days (anthrax)

Adult Dose for Plague

500 mg QD *(greater exposure than those with 8/2 mg/kg q12 in AGMs)*



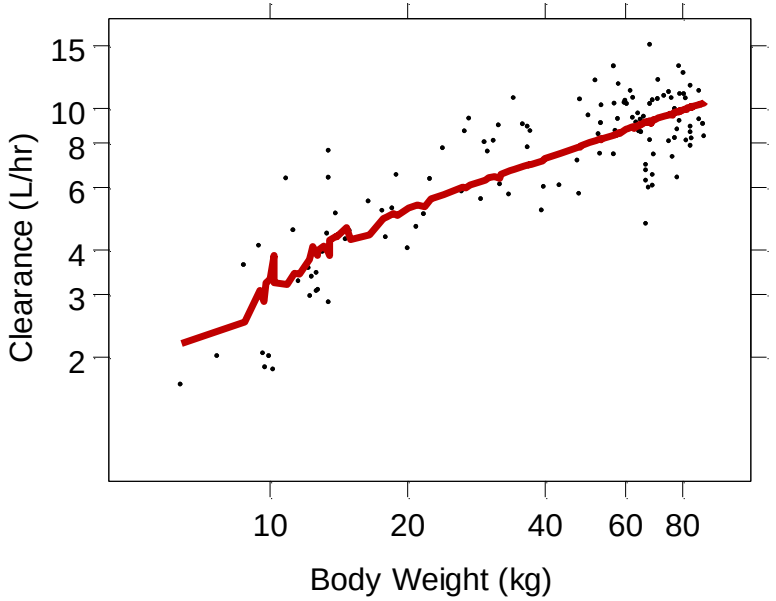


http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM299775.pdf

Pediatric Dose for Anthrax/Plague

Derived from modeling and simulation based on PK data from both pediatrics and adults

$$CL = \alpha \cdot WT^{\beta} \cdot [Age/(Age+A_{50})] \cdot \exp(\eta)$$



Patients < 50 kg: 8 mg/kg BID (up to 250 mg/dose)

Patients > 50 kg: 500 mg QD

Age	PK parameter		
	$AUC_{0\text{-}24,ss}$ (μg.h.ml)	$C_{max,ss}$ (μg/ml)	$C_{min,ss}$ (μg/ml)
6 mo to < 2 yr	51.7 (26.8–75)	5.6 (3.2–7.3)	0.6 (0.26–1.2)
2 to <5 yr	50 (41.7–65.2)	5.4 (4.2–6.6)	0.6 (0.25–1.1)
5 to <10 yr	55.6 (46.9–83.3)	5.4 (3.7–7.1)	0.9 (0.38–1.6)
10 to 18 yr	55.7 (42.0–83.5)	6.3 (4.6–8.1)	0.6 (0.2–1.4)
Adult[b]	47.7 (41.8–55.1)	5.5 (5.0–6.8)	0.4 (0.3–0.55)

Case Study 2:
Raxibacumab for Inhalational Anthrax

Raxibacumab

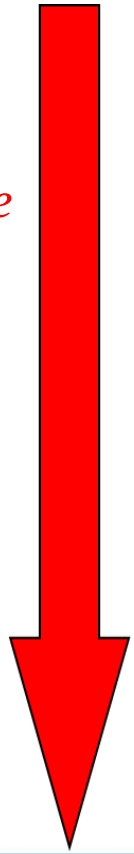
- First biologics approved based on the Animal Rule
- Antitoxin agent – mAb binds to the *Protective Antigen (PA)* of anthrax bacterium
- Dose (infusion over 2 hours and 15 minutes)
  - ✓Adults: 40 mg/kg
  - ✓Pediatrics > 50 kg: 40 mg/kg
  - ✓Pediatrics > 15 and ≤ 50 kg: 60 mg/kg
  - ✓Pediatrics ≤ 15 kg: 80 mg/kg

  No studies in the pediatric population. Dosing in pediatric patients was derived from a population PK approach.

Determination of Pediatric Dose

40 mg/kg regimen for adult patients based on animal efficacy studies and human PK/safety studies

Workflow to Determine the Pediatric Dose

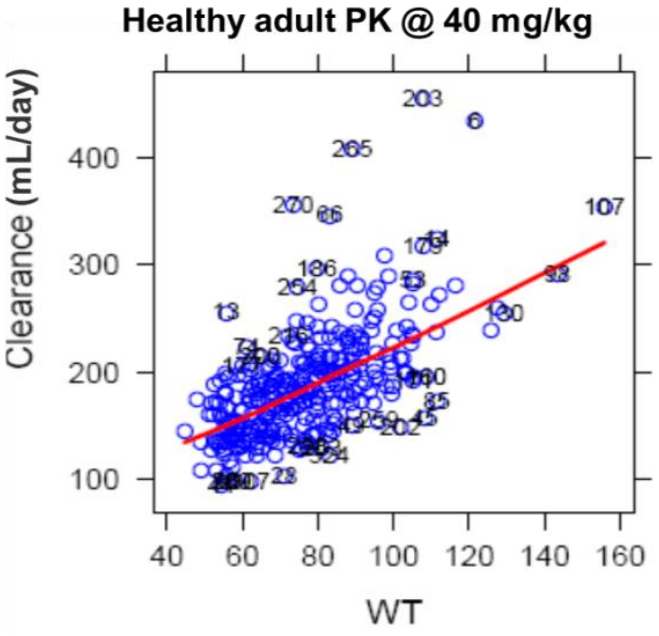


- **Learn** from adult population PK analysis
  - The relationship between PK parameters *vs* body weight
  - Inter-subject variability
  - Residual variability

- **Simulate** pediatric PK profiles using different dosing regimens
  - Various combinations of dose and body weight band

- **Select** a pediatric dosing regimen
  - Match the exposure (e.g., AUC) observed in adults at 40 mg/kg
  - Simple to implement

Learn from Adult Population PK



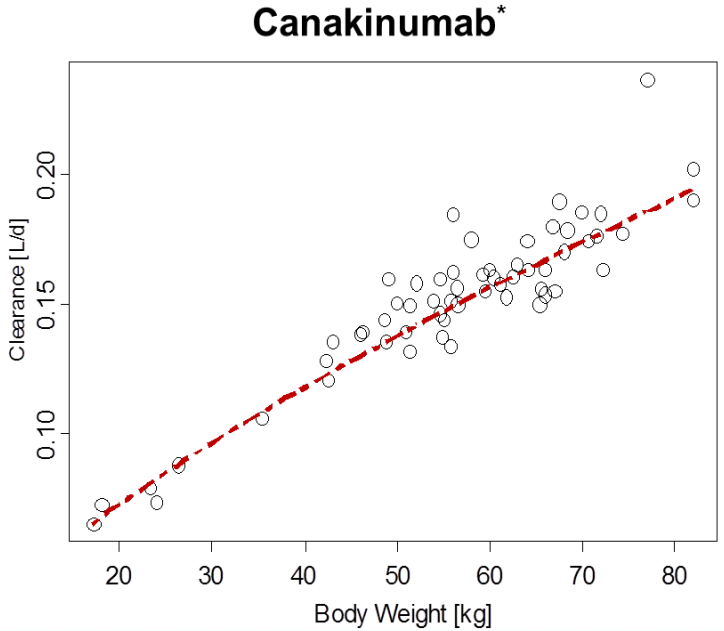
Population PK modeling

$$\hat{CL} = \theta 1 * (WT / 70)^{\theta 2}$$

θ2 (Exponent): 0.796

Assuming the same PK-BW relationship is applicable to the pediatric population

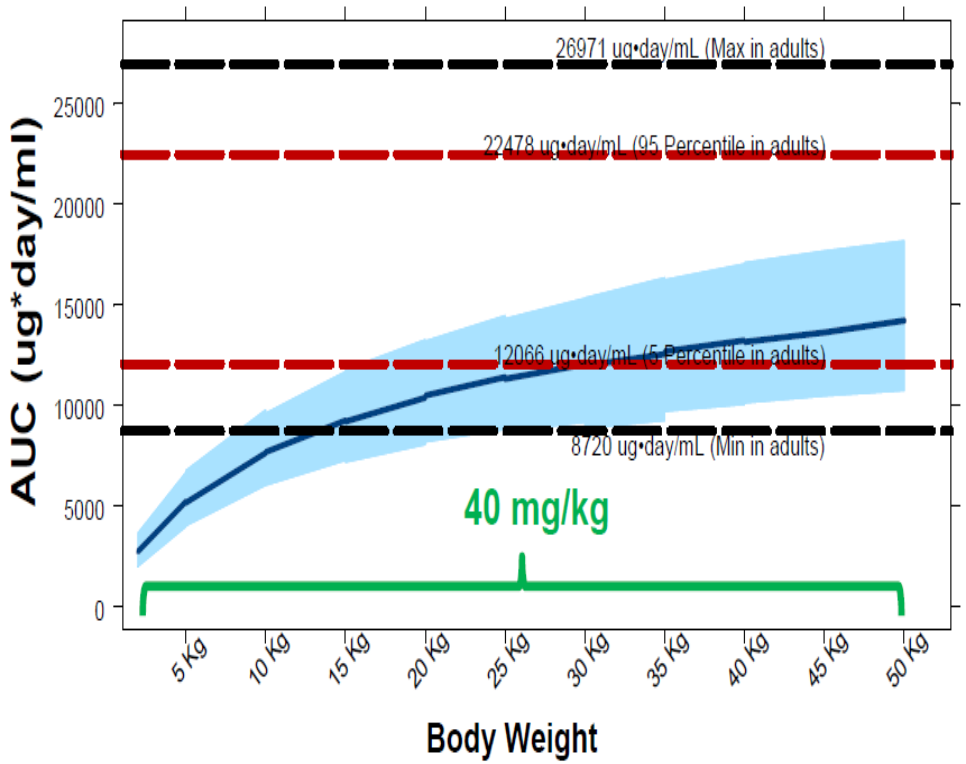
- Eliminated by non-specific proteolysis (minimal effect of maturation for <2 yrs on mAb PK)
- Similar phenomenon: Canakinumab, Infliximab, certolizumab, basiliximab

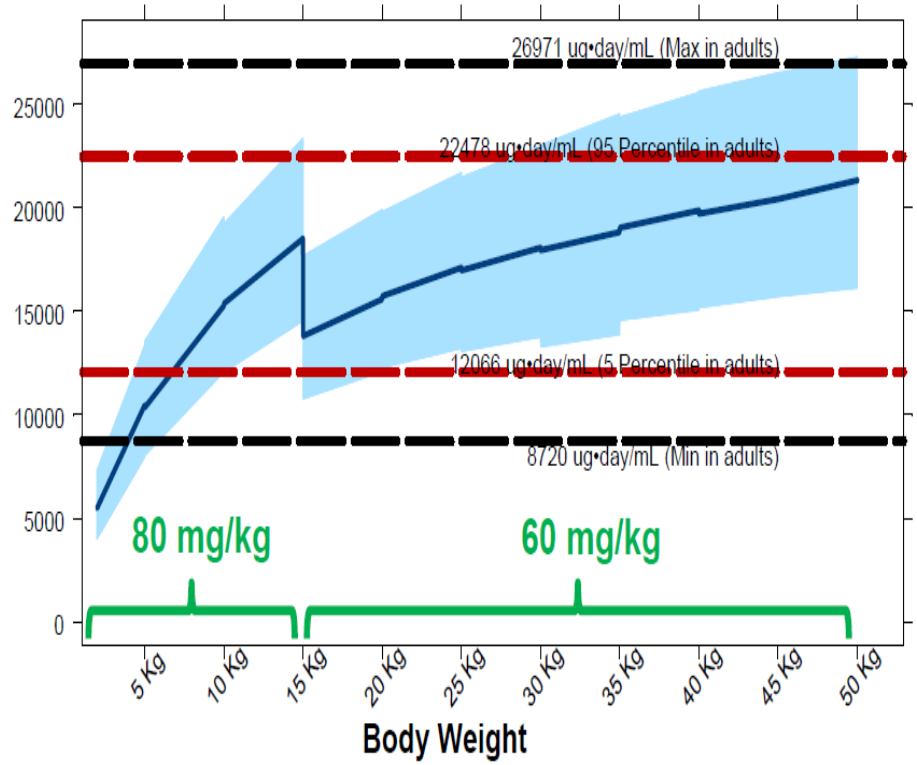


Simulation and Pediatric Dose Selection

Following adult dose of 40 mg/kg

- ✓ Pediatrics > 50 kg: 40 mg/kg
- ✓ Pediatrics > 15 and ≤ 50 kg: 60 mg/kg
- ✓ Pediatrics ≤ 15 kg: 80 mg/kg





Summary and Moving Forward

Modeling and simulation is critical for MCM pediatric dose selection

- Dosing selection is mainly based on PK matching to adults
- Current experience mainly based on allometric scaling from adults
  - Levofloxacin
    - PK/Safety information in pediatrics
    - Organ function/maturation is important for children < 2 yrs
  - Raxibacumab
    - Purely derived from modeling and simulation
    - Maturation seems less important for mAb
- *Moving forward: Role of PK/PD and PBPK(/PD)?*

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