Dosing Anti-Infectives in the Obese Pediatric Patient

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Disclosures

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Objectives

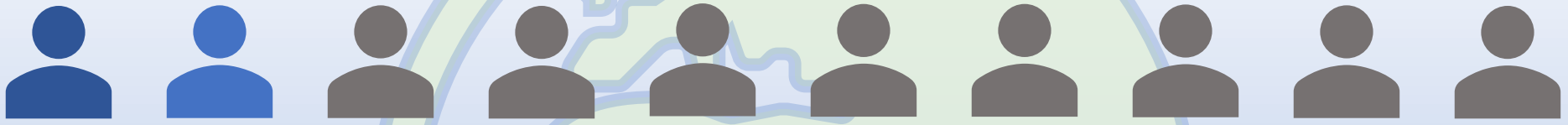
- Review epidemiology and impact of obesity on infections in children
- Understand relevant physiological changes associated with obesity
- NOT look at a complex dosing table
- Become familiar with the state of the art
- Summarize strategies to guide dosing and advance the field

Definitions

- Age, sex-specific
- Uses CDC growth charts revised in 2000, based on data up to 1994

Category	BMI%	BMI z-Score
Lean	<85	<1.04
Overweight	85 to <95	1.04 to 1.64
Obese	≥95	>1.64

Burden of pediatric obesity

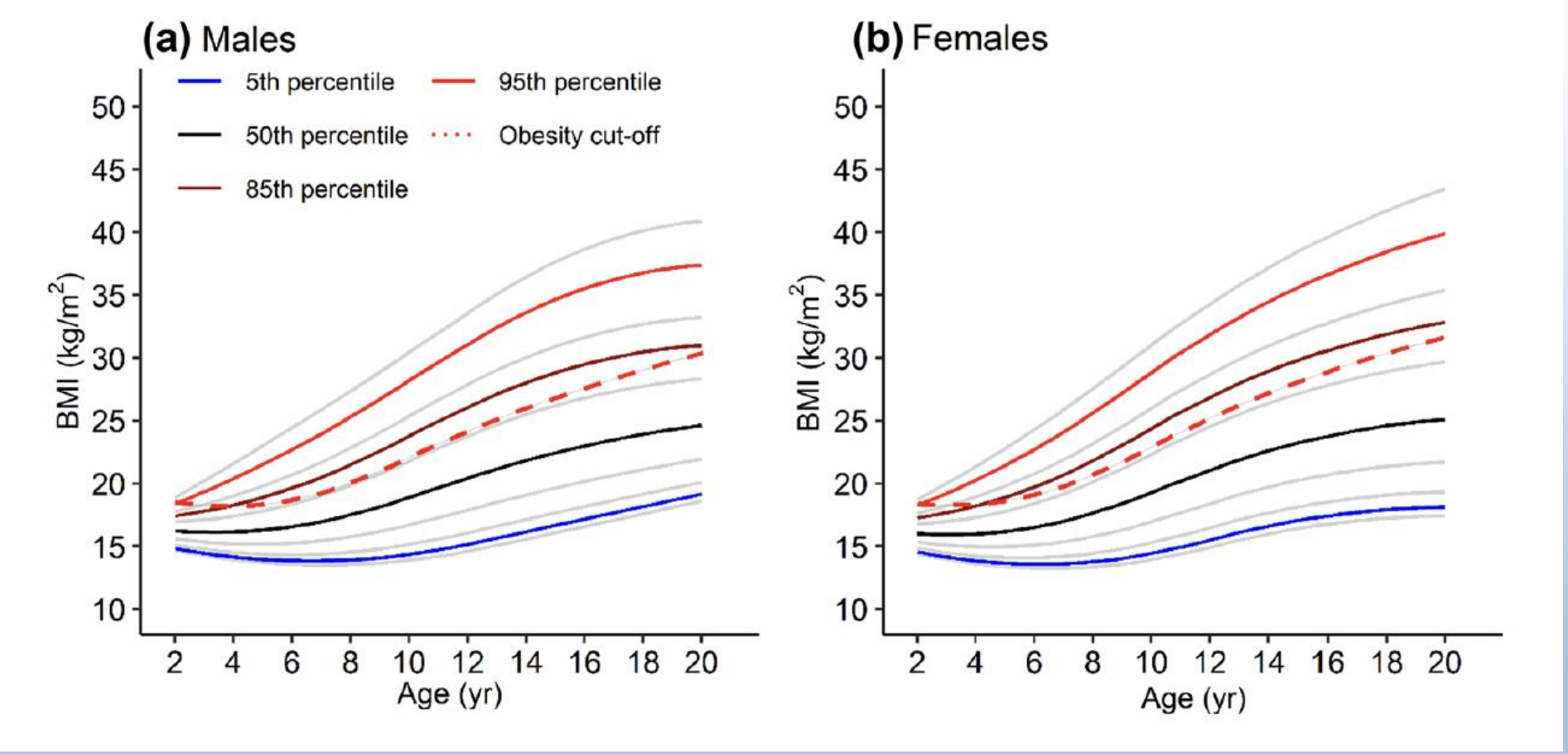


>380 Million

WHO, 2021

Burden of pediatric obesity

Shifting demographic



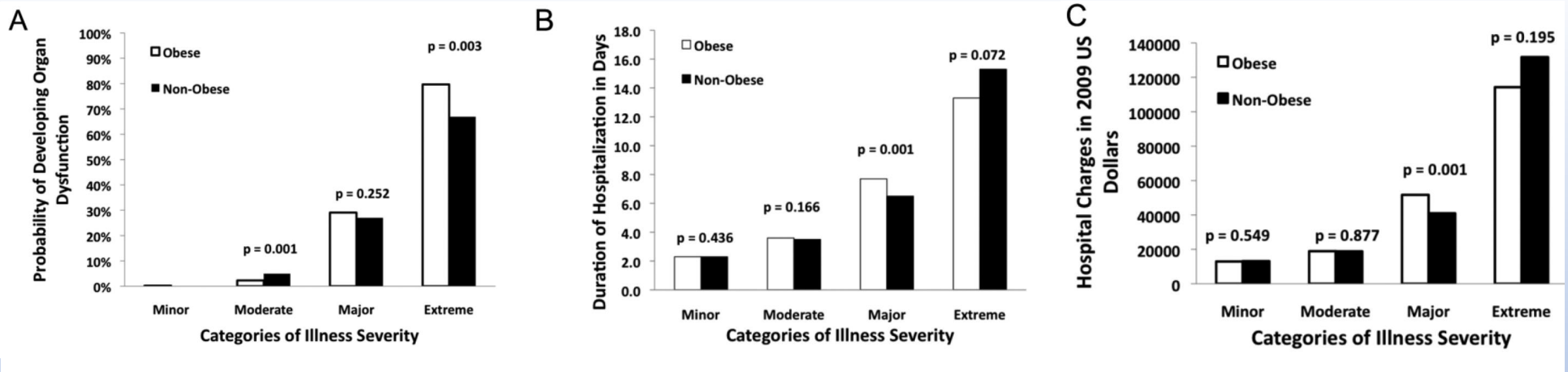
Gerhart et al, 2022

Clinical difference?

Infectious outcomes in obese children

- Osteomyelitis (Kyler et al, 2021)
  - ~ double risk of surgical procedures
  - 1 day longer hospitalization
- Post-surgical infections (Bechard et al, 2013)
  - +/- increased rate of infections
- Sepsis (Maley et al, 2017)
  - Increased organ dysfunction
  - 0.6 days longer hospitalization
  - Increased hospital charges

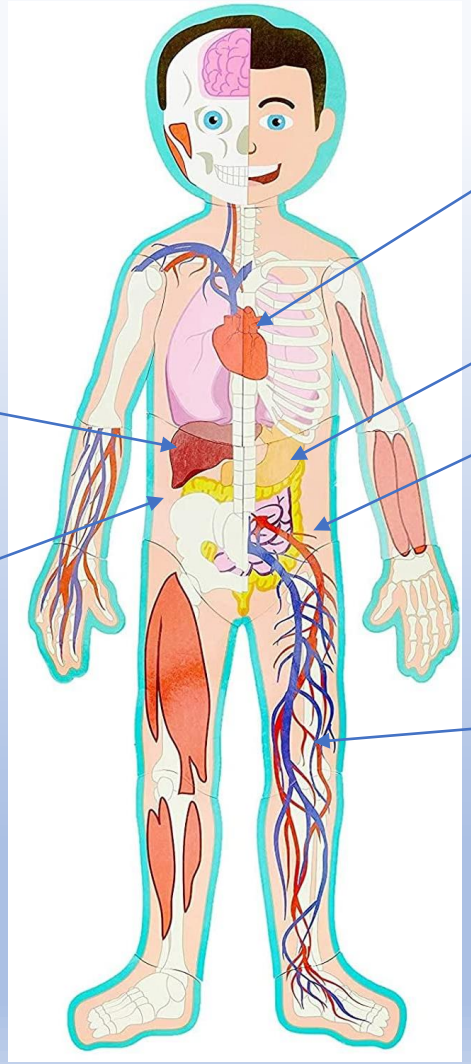
Sepsis outcomes



357,701 pediatric hospitalizations for infection
5,685 in obese children

Maley et al, 2017

Physiologic changes in pediatric obesity



Cardiac output +10-20% (L/min)

Organ volume +15%

GFR +30%

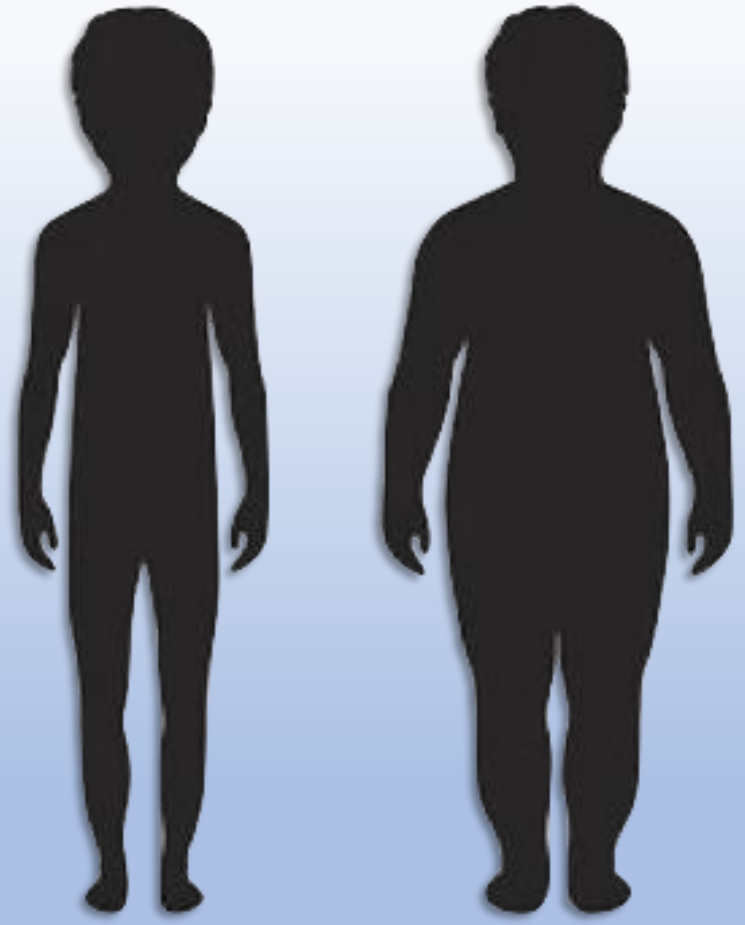
DME/Transporters

Adipose (kg) =
f(age, wt, BMI, sex)

Hematocrit
Protein binding
Organ blood flow (ml/min/kg)

Gerhart et al, 2022

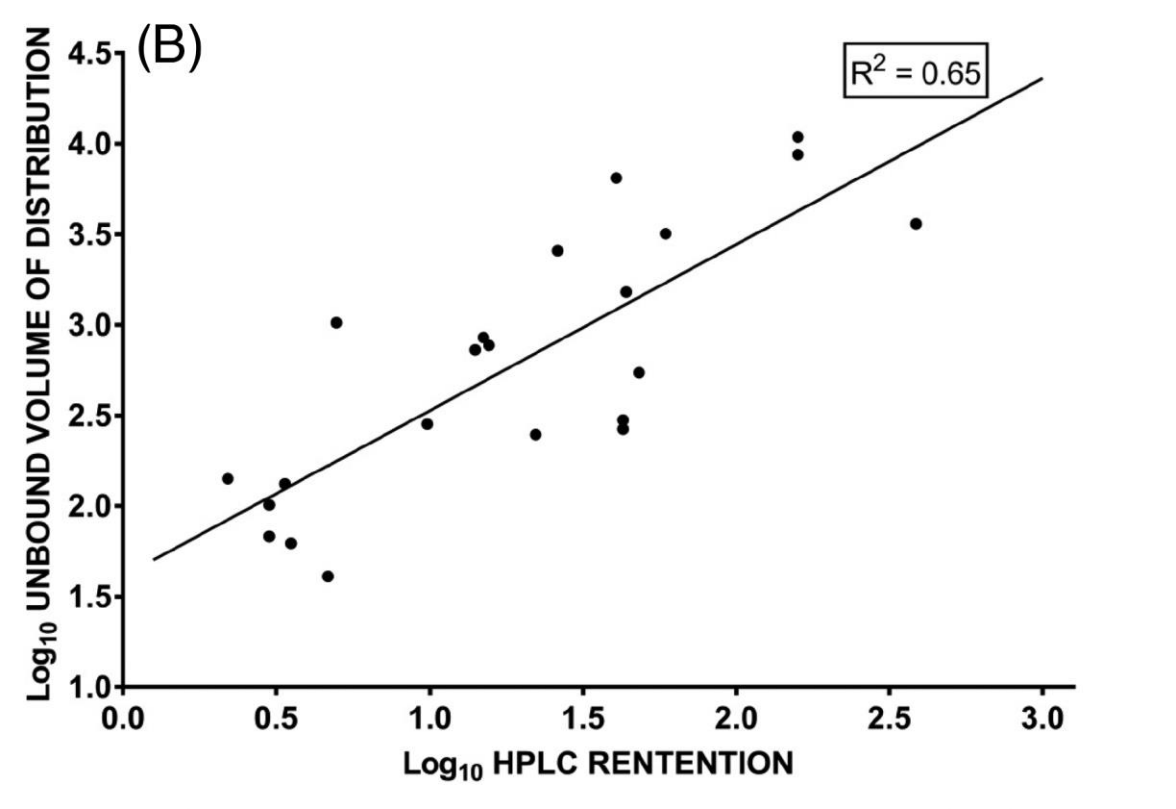
Effect of increased adipose on drug PK

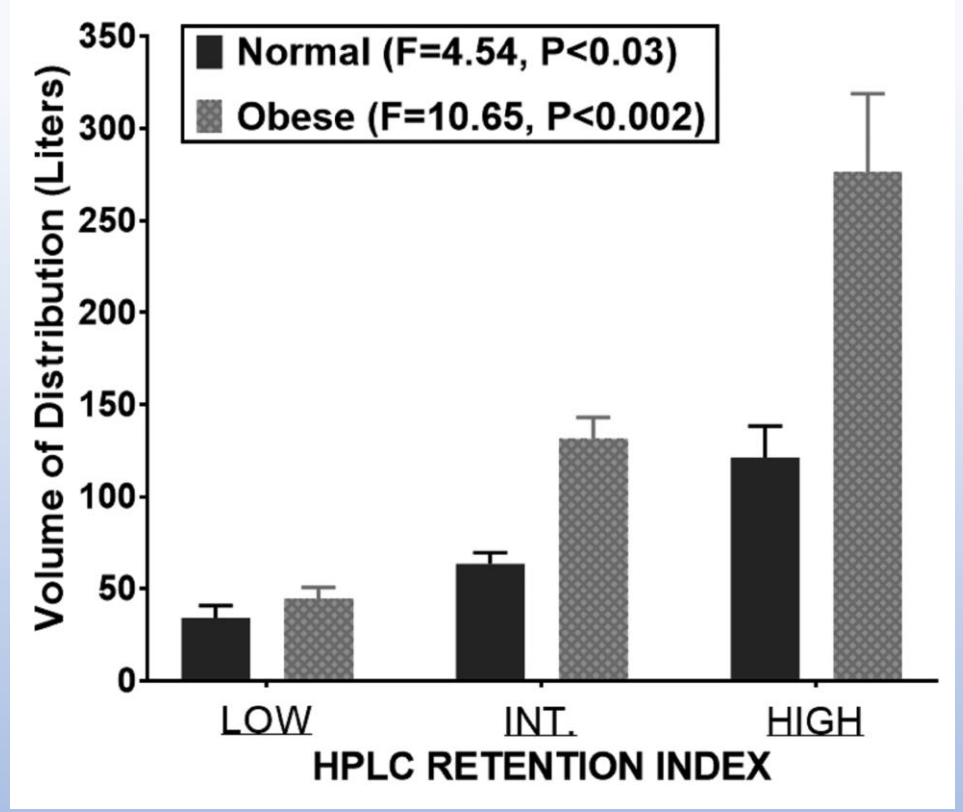


Lipophilic drug = Increased Vd

Lipophilic drug = Variable CL

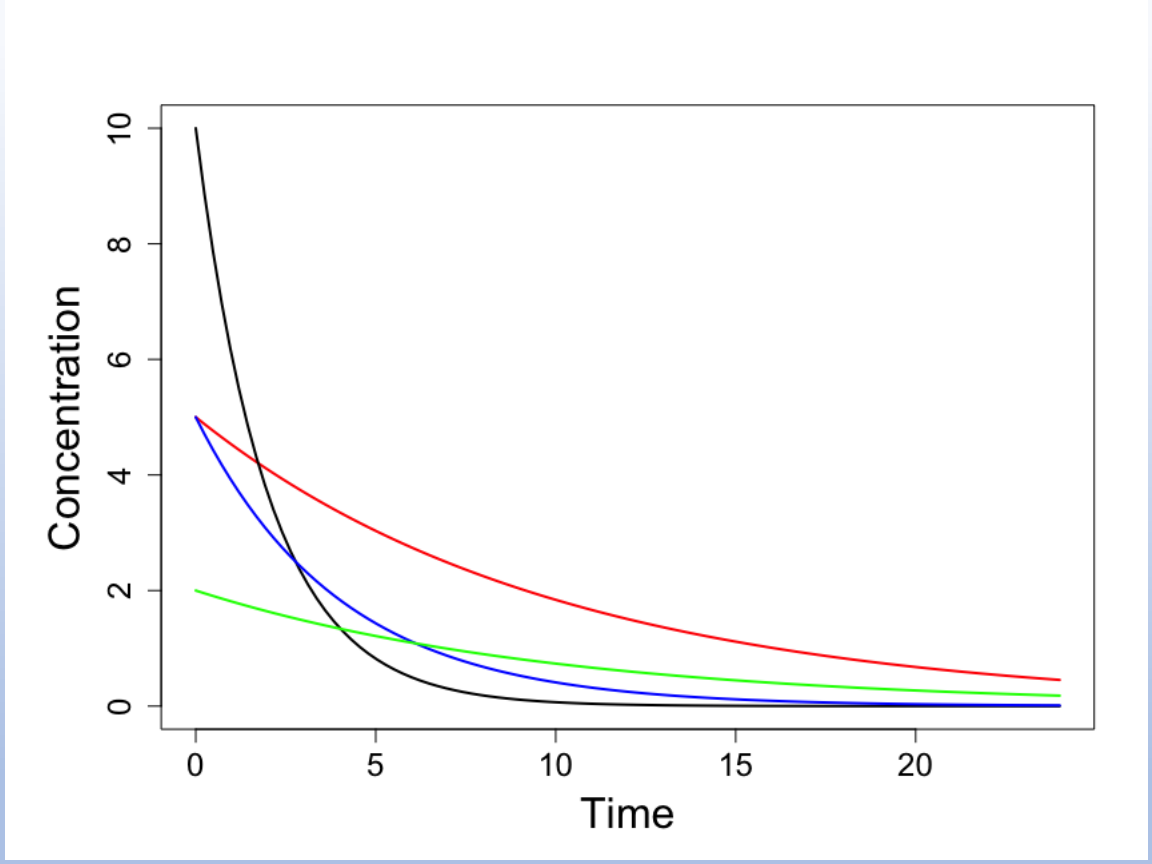
Lipophilicity and Vd





Bruno et al, 2020

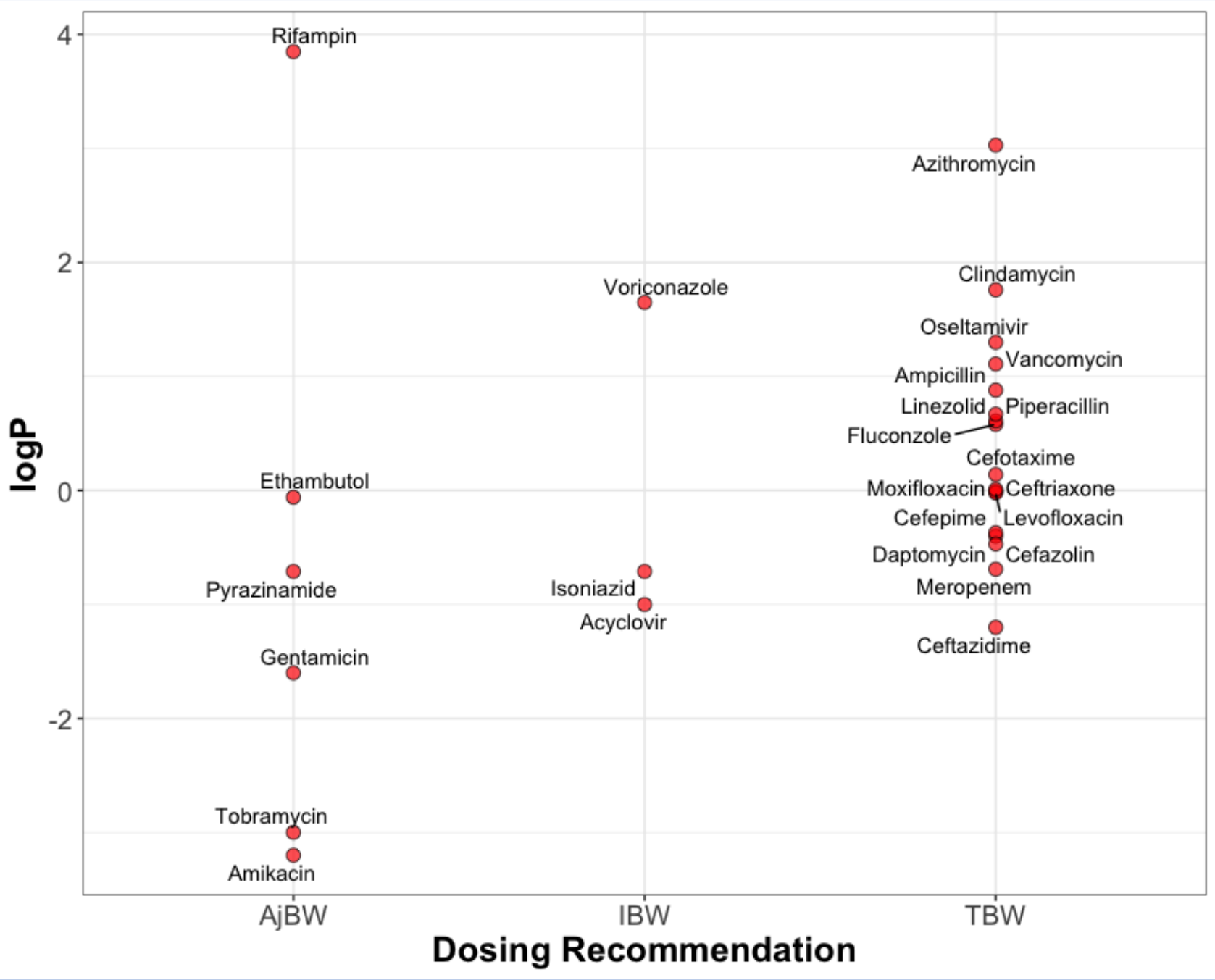
Myopia



Dose	AUC	CL	Cmax	Cmin
100	50	2	5	0.45
100	20	5	10	0.00
100	20	5	5	0.01
100	20	5	2	0.18

Basic PK

- $AUC = \frac{dose}{CL}$
- $t_{1/2} = \frac{\log(2) * V_d}{CL}$



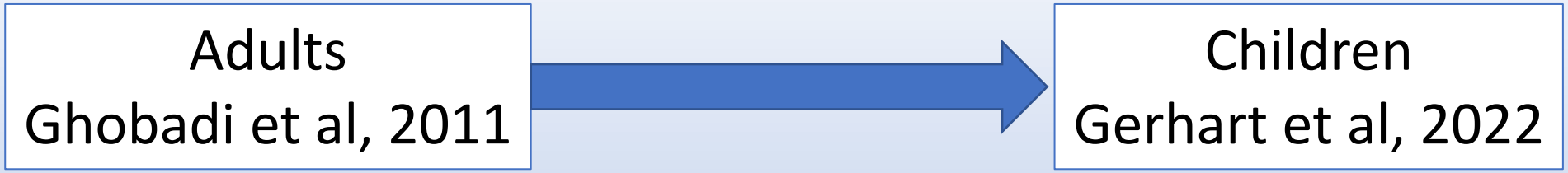
$$\text{IBW} = \frac{cm^2 * 1.65}{1000}$$

$$\text{AjBW} = IBW + 0.4 * (TBW - IBW)$$

Hall, 2015
Ross et al, 2015
Natale et al, 2017
Srinivas, 2018
Kyler et al, 2019
Takahashi et al, 2020
Smit et al, 2021

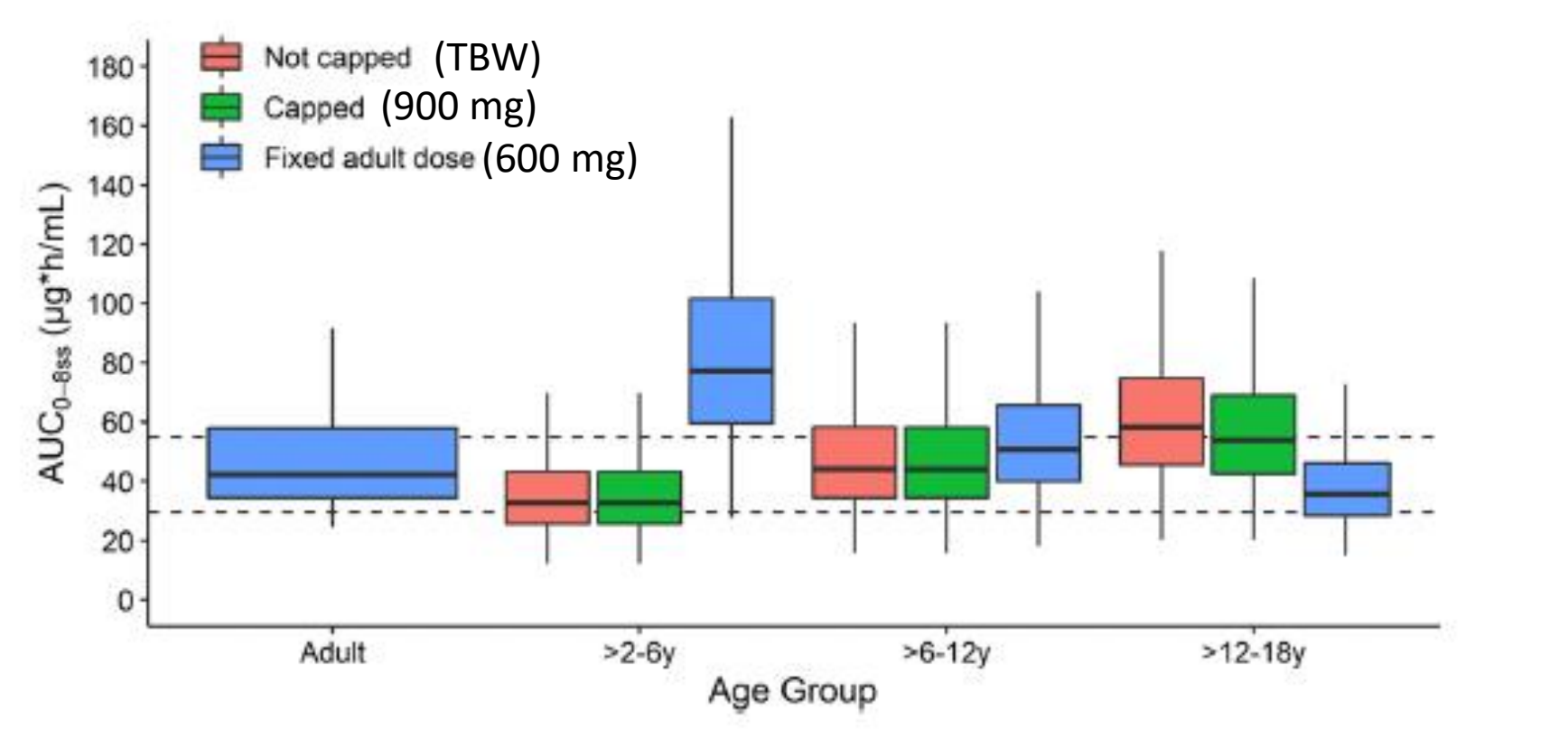
State of the Art

PBPK



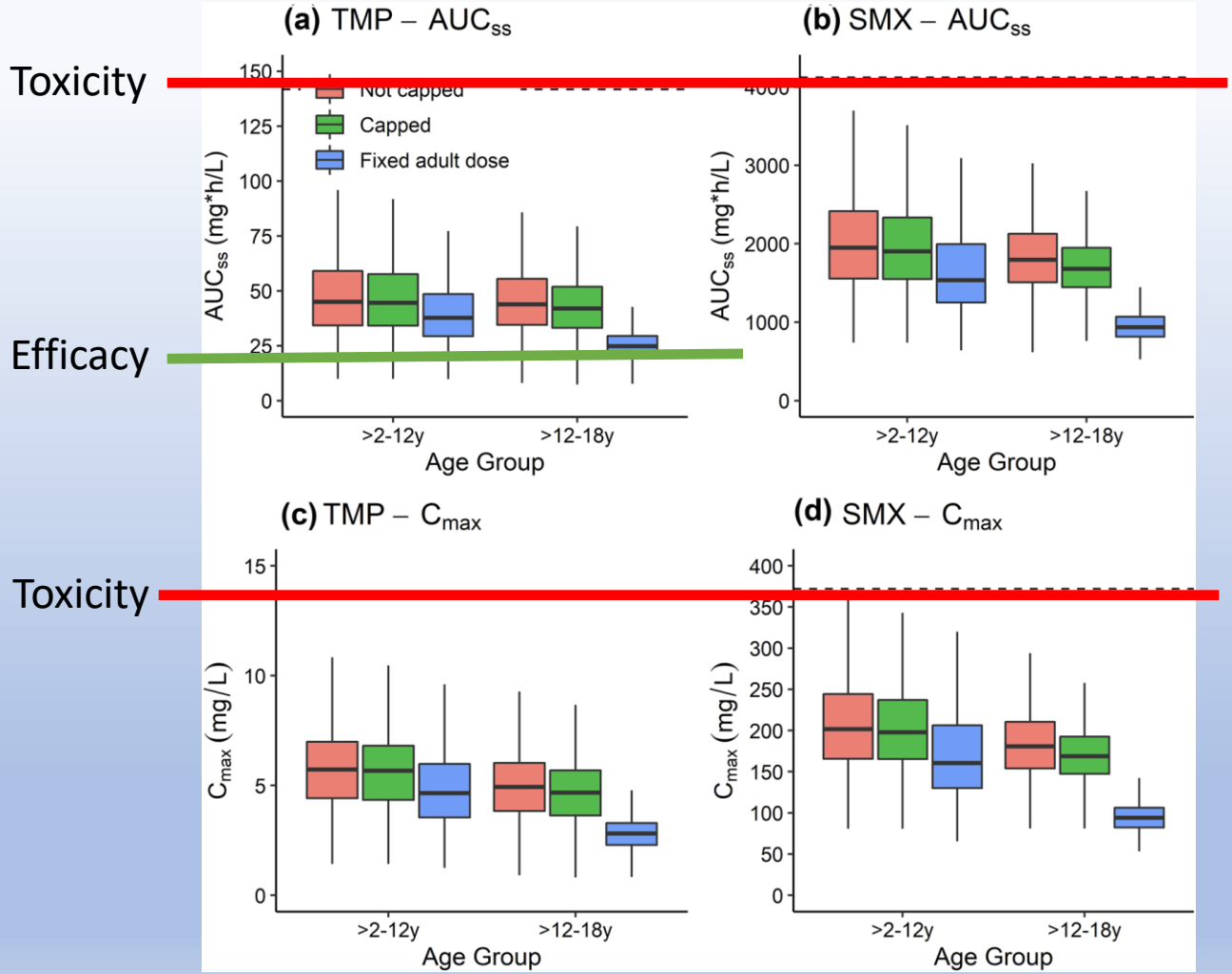
Commentary
Neely et al, 2011

Clindamycin PBPK



Gerhart et al, 2022

TMP/SMX PBPK



Gerhart et al, 2022

DNR PK in obese pediatric patients: PBPK

	PK-SIM host model			
Real population*	Standard	Standard+	Obese *(Gerhart et al, 2022)*	Obese+
Lean (n=38)	1.02 (0.84 – 1.24)	0.71 (0.59 – 0.87)	—	—
Overweight (n=17)	1.53 (1.24 – 1.88)	1.12 (0.90 – 1.38)	1.47 (1.20 – 1.80)	1.12 (0.92 – 1.37)

Geometric mean ratio (GMR) of the simulated : observed AUCs and the 90% confidence interval (CI) of the GMR

**Thompson et al, 2014*

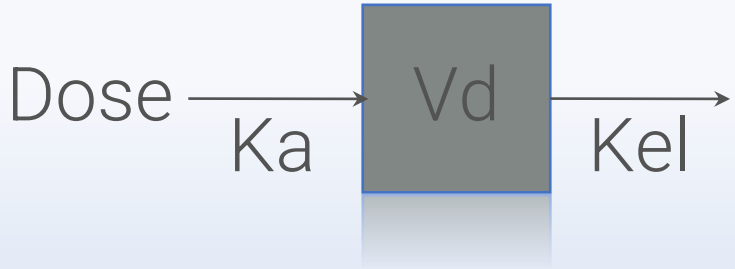
Parkikh et al, ACoP, 2022

Enzyme activity in adipose tissue

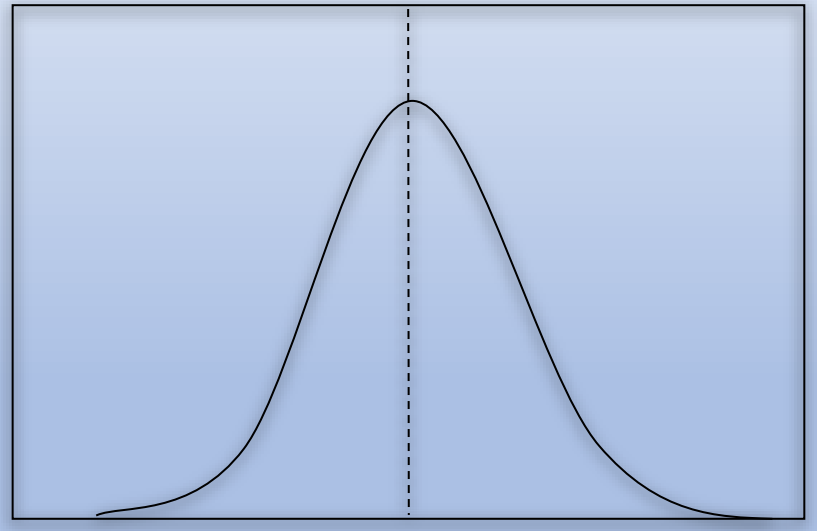
	CBR1	AKR1C1	AKR1C2	AKR1C3
Lean	1.14 (0.77 – 1.51)	1.58 (1.33 – 1.83)	0.46 (0.32 – 0.60)	0.61 (0.34 – 0.88)
Obese	1.33 (1.25 – 1.41)	2.11 (1.87 – 2.35)	0.90 (0.66 – 1.14)	1.09 (0.97 – 1.21)
P-value	0.37	**0.02**	**0.02**	**0.02**

Bayesian Control

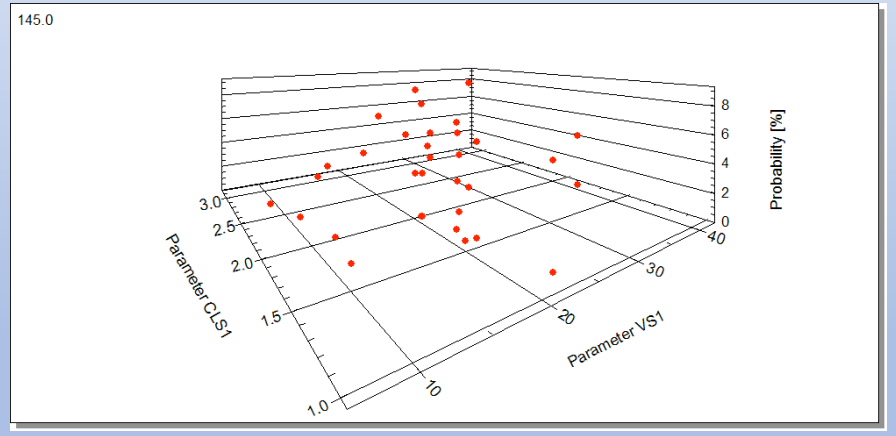
Begin with a model



Parametric

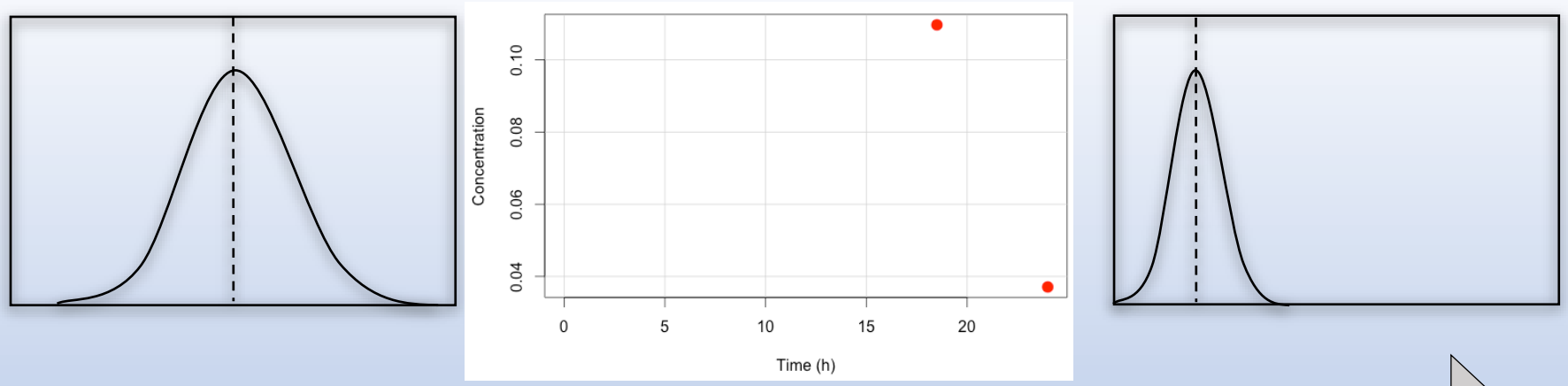


Nonparametric



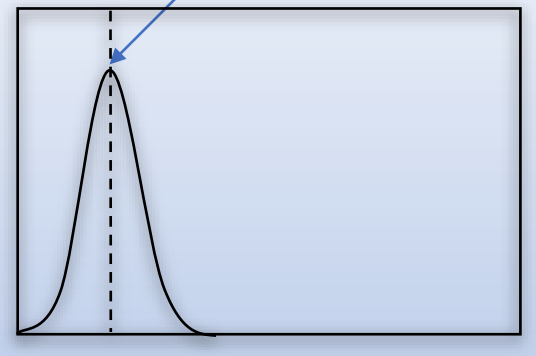
Use the model

The parametric approach



MAP-Bayesian Parametric model

Maximum **a** **p**osteriori Bayesian probability



One version of the patient

Shrinkage towards population mean with sparse sampling

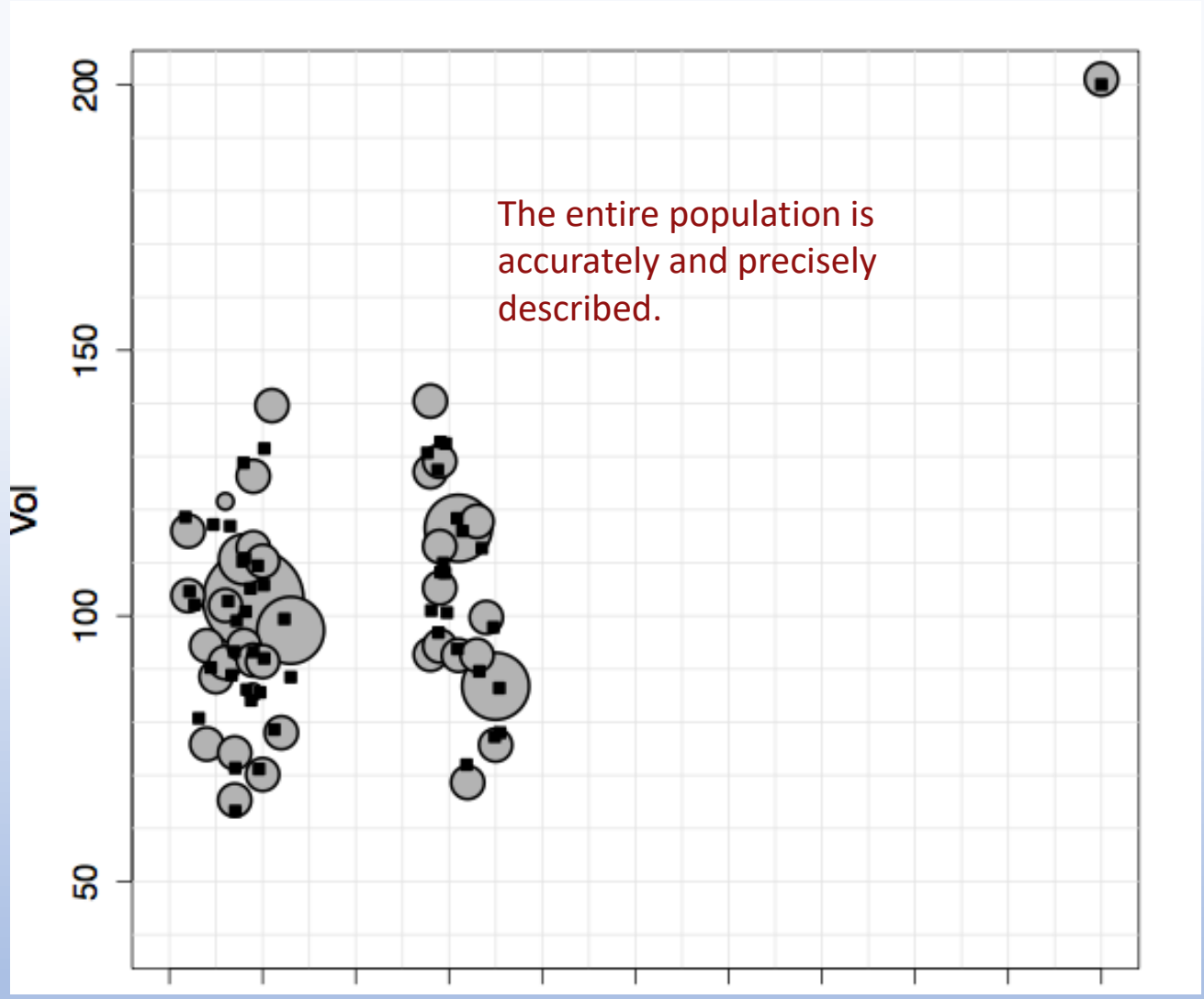
No probability of future success vs. failure

Non-Normal Populations

Simulated population (■)

Non-parametric estimation of population values (●)

Size proportional to probability

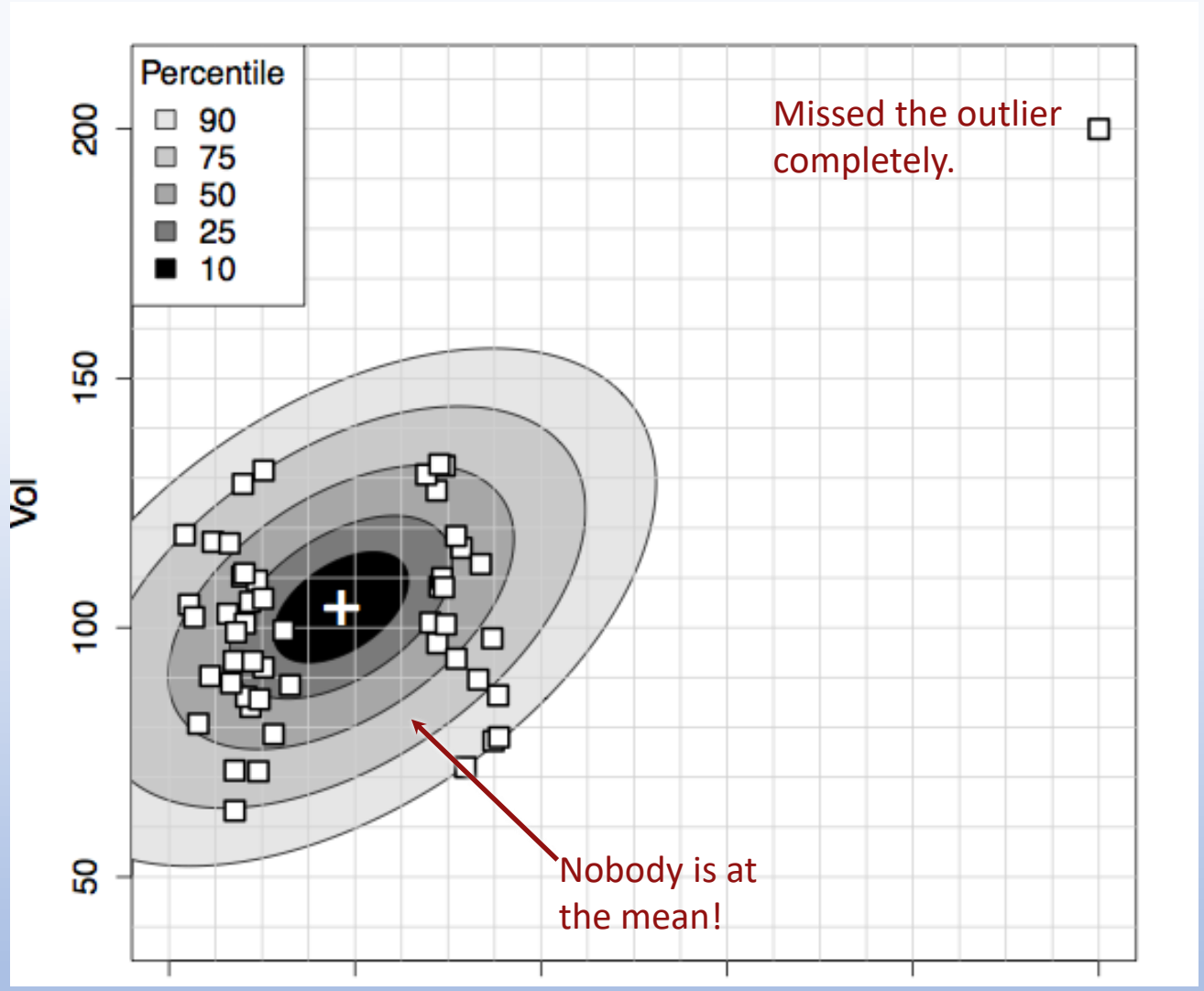


Neely et al, 2012

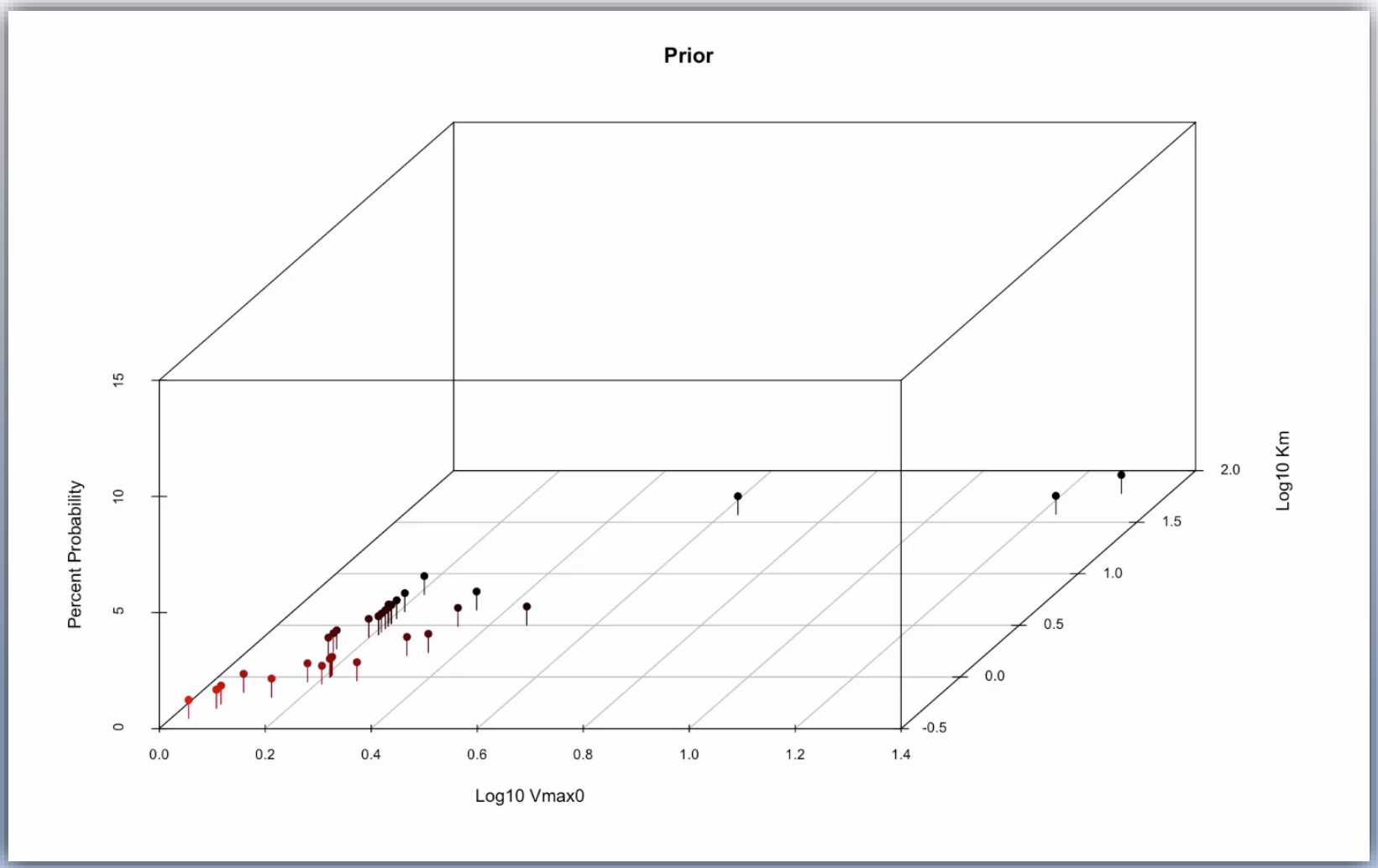
Non-Normal Populations

Simulated population (□)

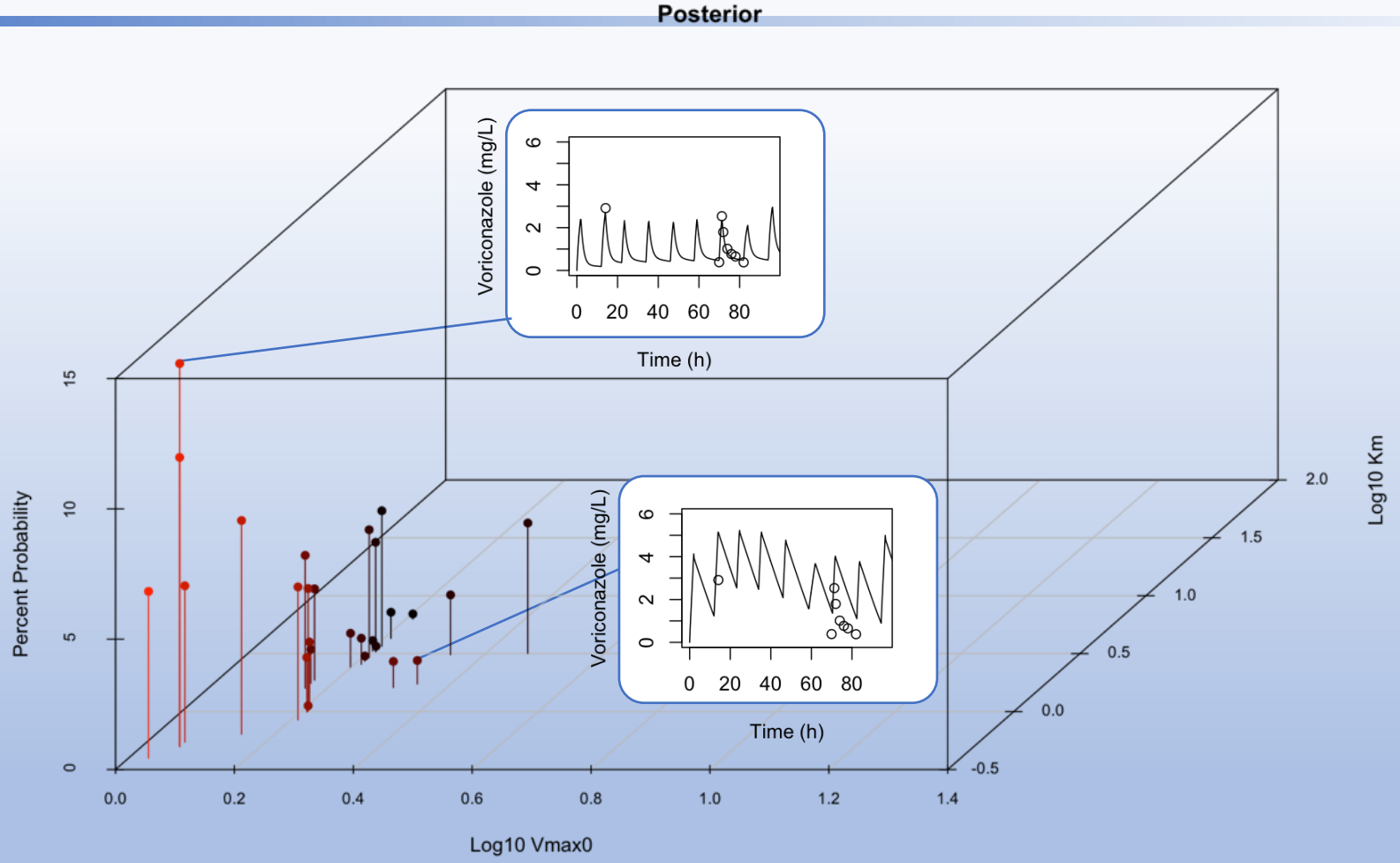
Mean (+) and percentile distributions of parametric population parameter estimates



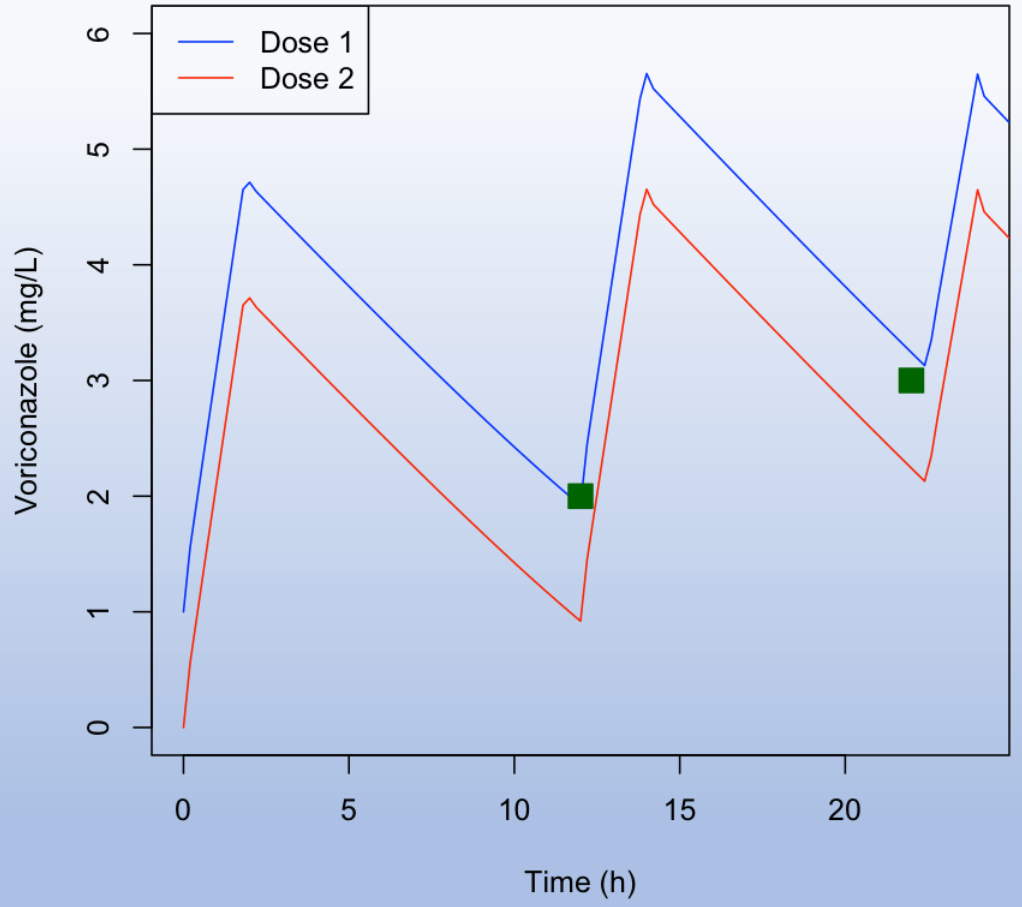
NP MM Approach



Multiple Models



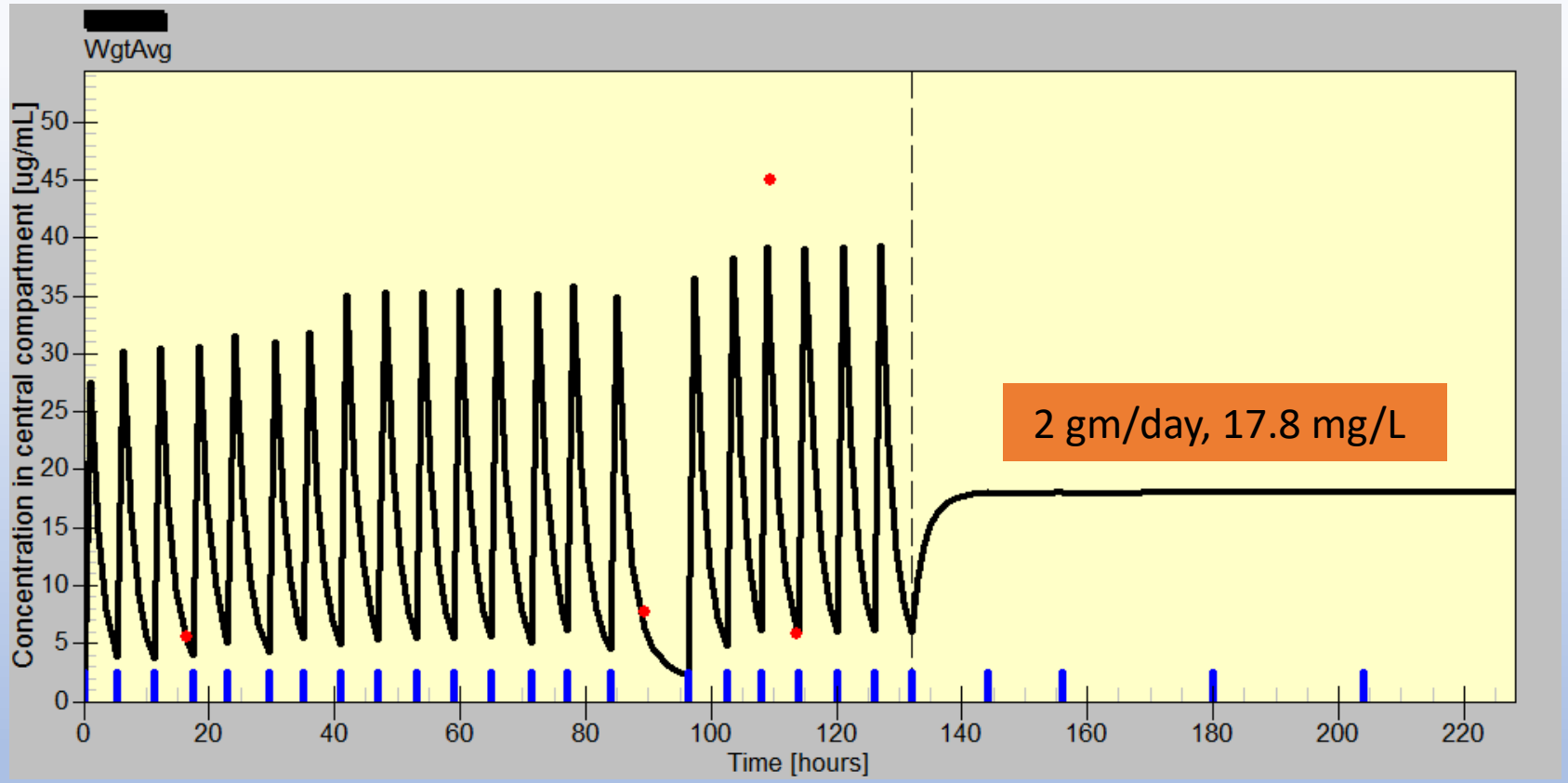
Multiple Models



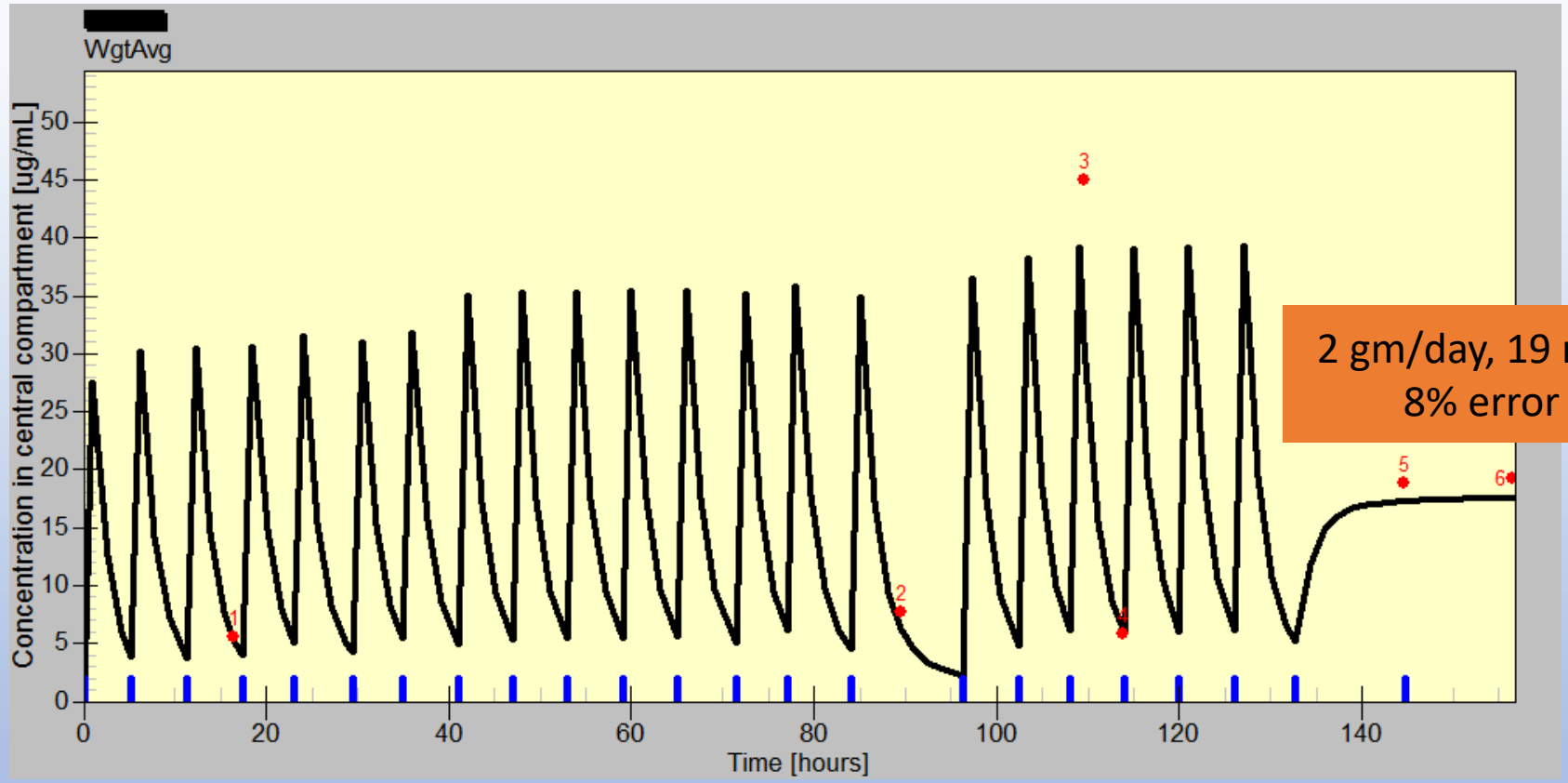
A real patient

- 7 y/o who had a cerebellar brain tumor resected
- 25 kg, BMI 18.3 (92%), z-score 1.38 → overweight/borderline obese
- Developed an infection of the cavity with MRSA (vancomycin MIC 0.5 mg/L)
- Repeatedly culture positive and continually febrile for a week
- Primary team dosing vancomycin up to 80 mg/kg/day divided every 6 hours (500 mg/dose)
- Typical doses are 40-60 mg/kg/day
- Highest trough was 7.7 mg/L. Target was 15-20 mg/L

Fit and plan


WgtAvg
Concentration in central compartment [ug/mL]
0
5
10
15
20
25
30
35
40
45
50
0
20
40
60
80
100
120
140
160
180
200
220
Time [hours]
2 gm/day, 17.8 mg/L

Results



2 gm/day, 19 mg/L
8% error

Summary

- Lipophilicity is not predictive of needed dosing modifications
- PBPK for drug development and general dosing guidance
  - More work needed on physiologic changes associated with obesity
- Pop PK with individual Bayesian control for patient care

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*Current