Developmental and environmental considerations in analysis of “Big Data” in pediatrics

Jennifer Goldman MD, MS

ADEPT4

September 19, 2017

Children's Mercy KANSAS CITY

UMKC School of Medicine

BEST CHILDREN'S HOSPITALS U.S.News & WORLD REPORT RANKED IN 10 SPECIALTIES 2016-17

MAGNET RECOGNIZED AMERICAN NURSES CREDENTIALING CENTER

Disclosures

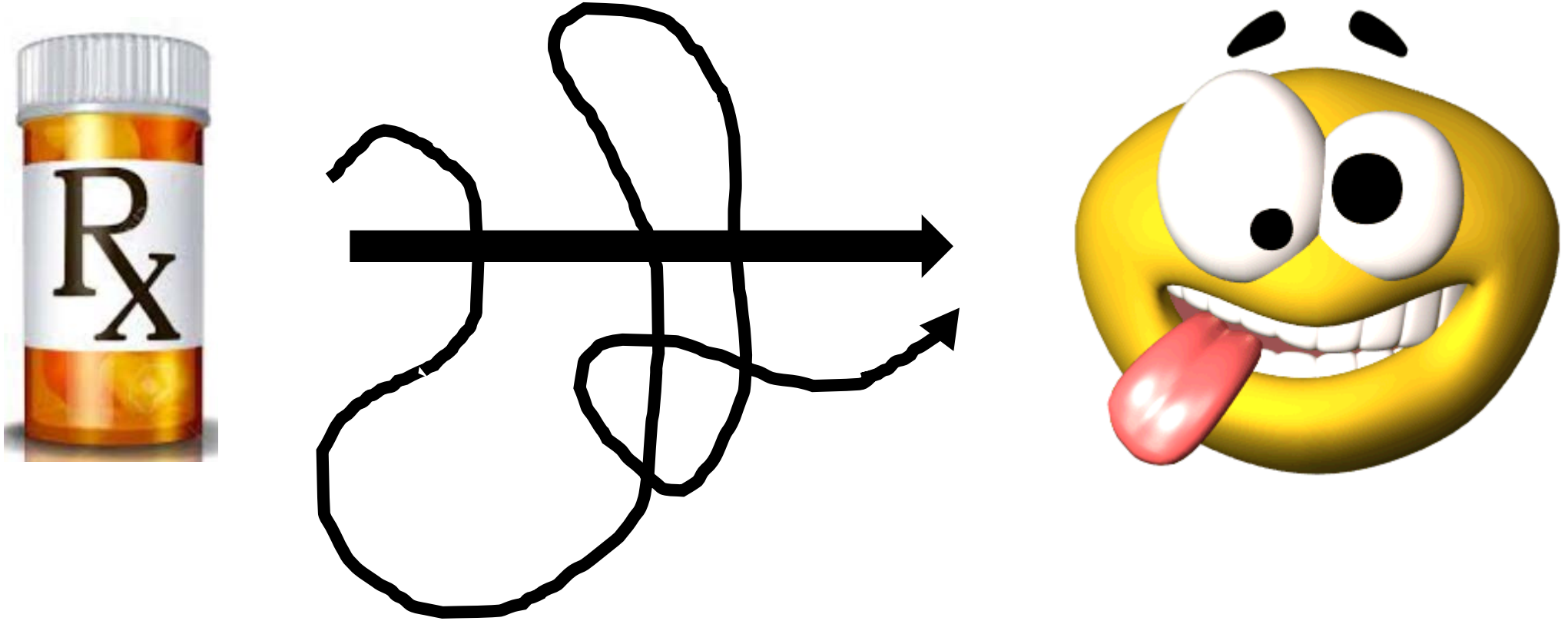
In the past 12 months, I have no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or providers of commercial services discussed in this presentation.

Children's Mercy KANSAS CITY

Objectives

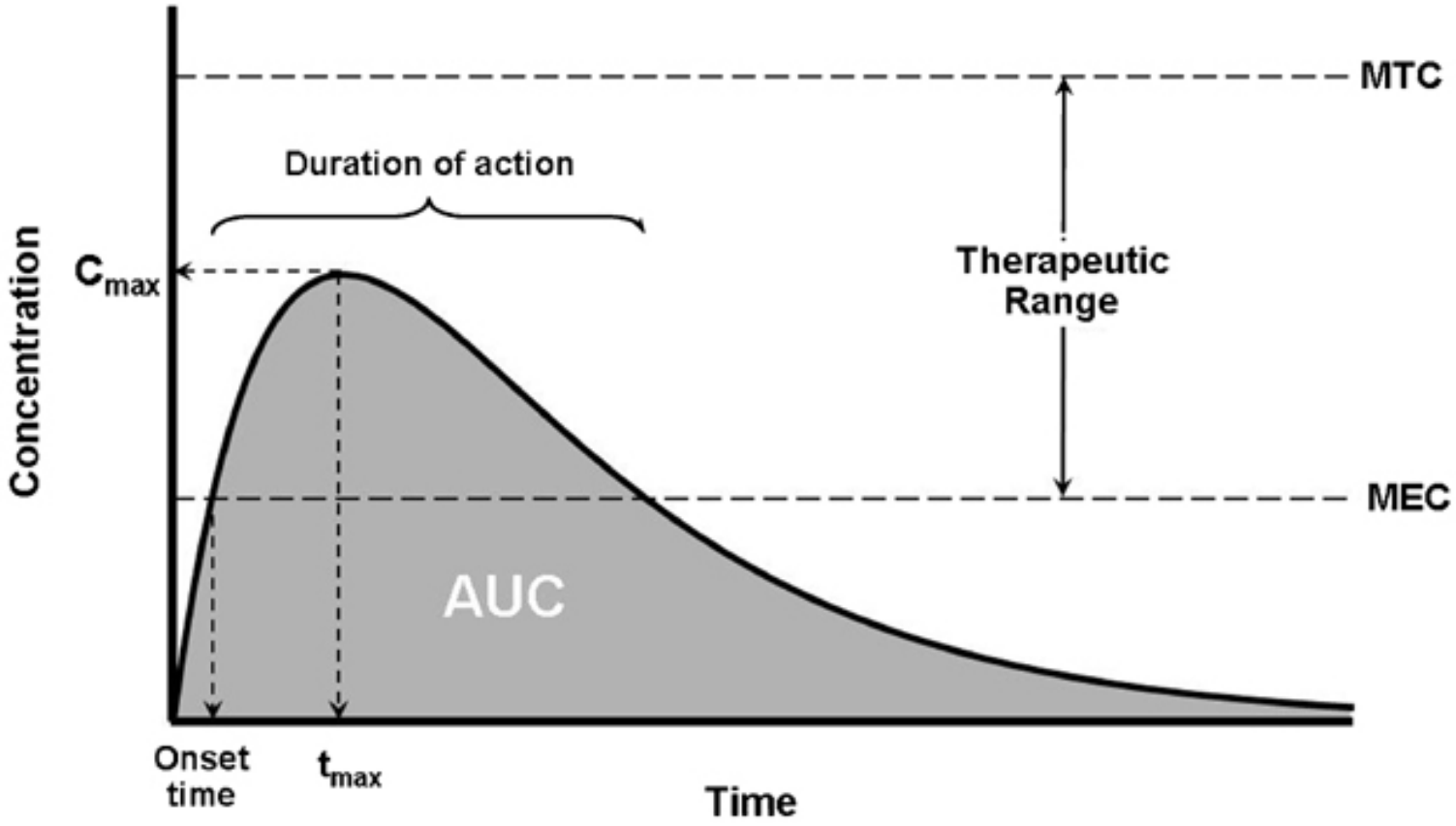
- Highlight key differences in pediatric exposures as compared to adults
- Discuss factors that may influence the interpretation of big data in pediatrics
- Recognize information that is important when evaluating pediatric drug exposure but is not readily available in big data

Making the link between drug exposure and an adverse reaction



Children's Mercy KANSAS CITY

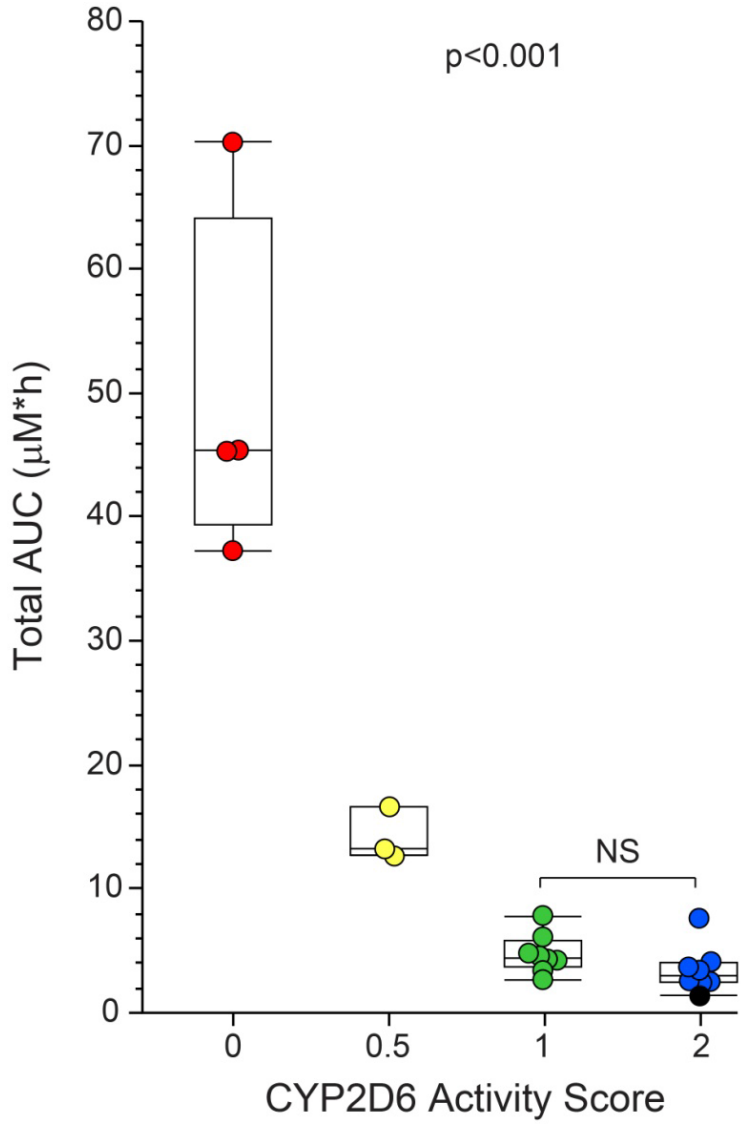
Textbook Drug Exposure



Children's Mercy KANSAS CITY

Courtesy Steve Leeder ADEPT 2016

Reality as related to exposure



- Dose 0.5 mg/kg
- Mean AUC differs **14.2-fold** between PM and EM2 groups
- **50-fold** absolute range in AUC values

Children's Mercy KANSAS CITY

Brown JT et al. Clin Pharmacol Ther. 2016 June ; 99(6): 642–650.

Reality as related to exposure

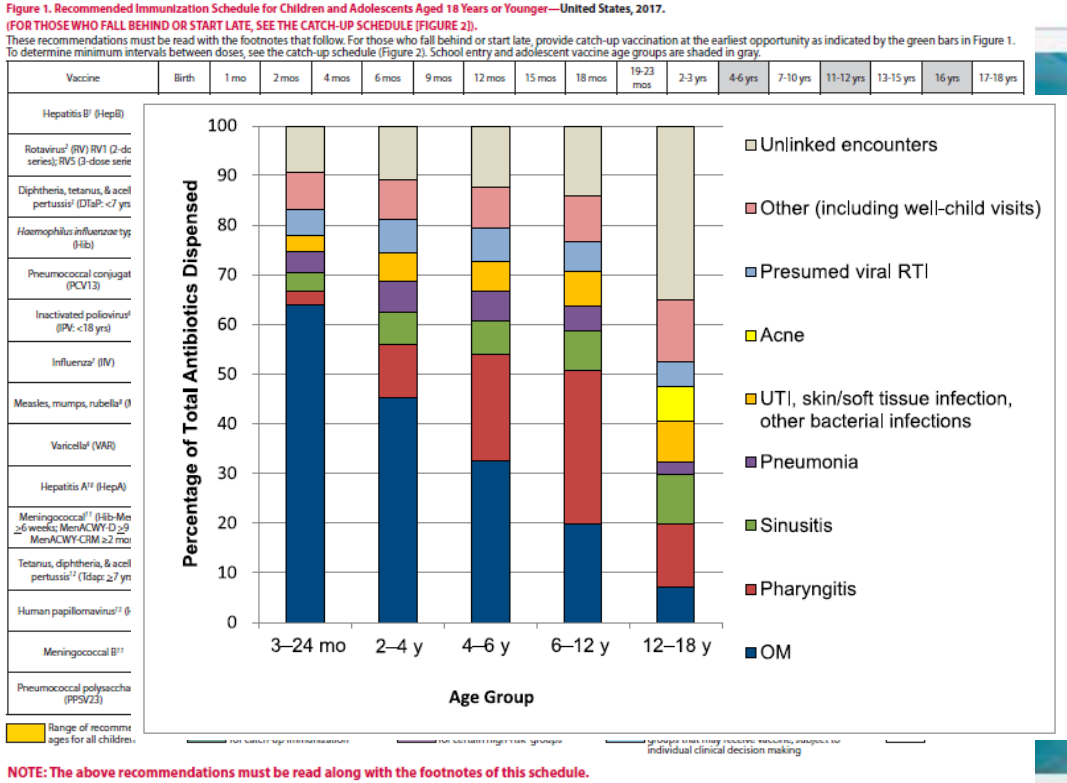


Figure 1. Recommended immunization schedule for adults aged 19 years or older by age group, United States, 2017

Vaccine	19–21 years	22–26 years	27–59 years	60–64 years	≥ 65 years
Influenza[1]	1 dose annually				
Td/Tdap[2]	Substitute Tdap for Td once, then Td booster every 10 yrs				
MMR[3]	1 or 2 doses depending on indication				
VAR[4]	2 doses				
HZV[5]				1 dose	
HPV–Female[6]	3 doses				
HPV–Male[6]	3 doses				
PCV13[7]	1 dose				
PPSV23[7]	1 or 2 doses depending on indication				1 dose
HepA[8]	2 or 3 doses depending on vaccine				
HepB[9]	3 doses				
MenACWY or MPSV4[10]	1 or more doses depending on indication				
MenB[10]	2 or 3 doses depending on vaccine				
Hib[11]	1 or 3 doses depending on indication				

Recommended for adults who meet the age requirement, lack documentation of vaccination, or lack evidence of past infection

Recommended for adults with additional medical conditions or other indications

No recommendation

Four Vs

- Volume
- Velocity
- Variety
- Variability

Children's Mercy KANSAS CITY

Gilmore RO. WIREs Cogn Sci 2016, 7:112–126.

Four Vs

- **Volume**
- Velocity
- Variety
- Variability

Children's Mercy KANSAS CITY

Volume

Number of participants or data points

Volume

- Fewer drug exposures in pediatrics
- Fewer ADRs identified/reported
    - ADR hospital admission rate
        - Pediatrics 4.1% (IQR 0.16-5.3%)
        - Adults 6.3% (lQR 3.9-9.0%)
        - Elderly 10.7% (lQR 9.6-13.3%)
- Under recognized?

Children's Mercy KANSAS CITY

Kongkaew C et al. The Annals of Pharmacotherapy. 2008;42:1017-25.

Four Vs

- Volume
- **Velocity**
- Variety
- Variability

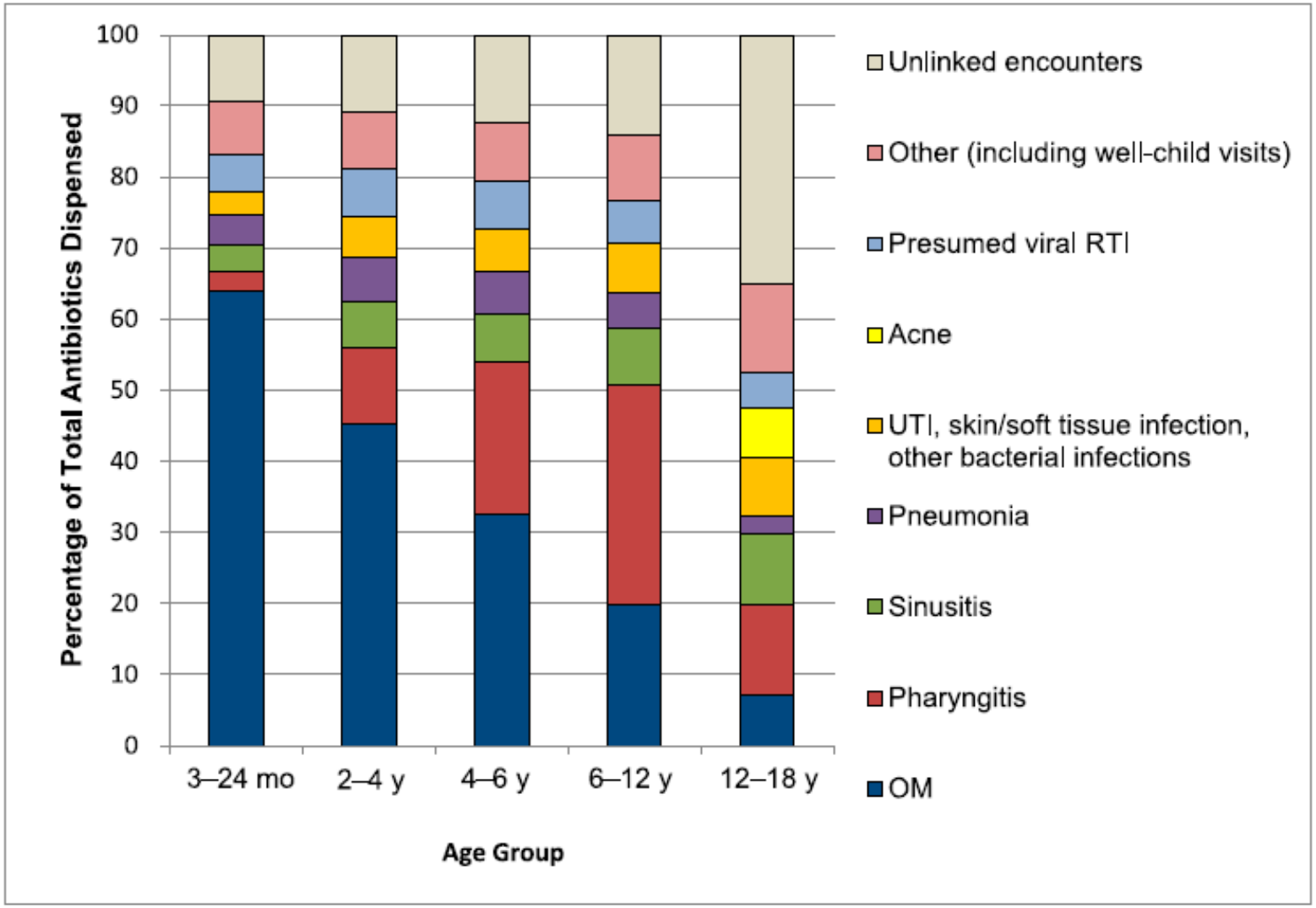
Children's Mercy KANSAS CITY

Velocity

Estimation of trends within and between people across time

Children's Mercy KANSAS CITY

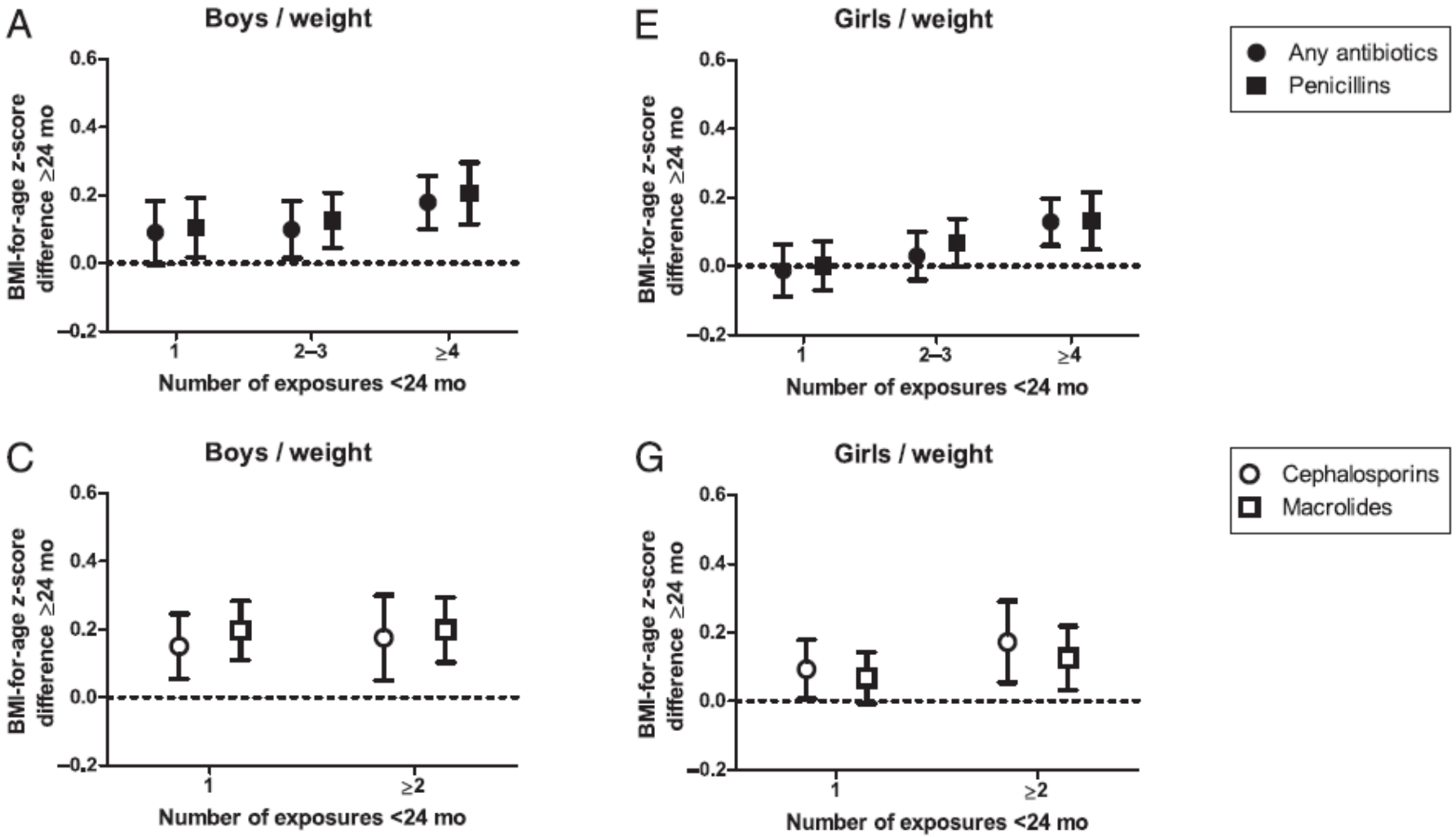
Antibiotic Exposure By Age



Children's Mercy KANSAS CITY

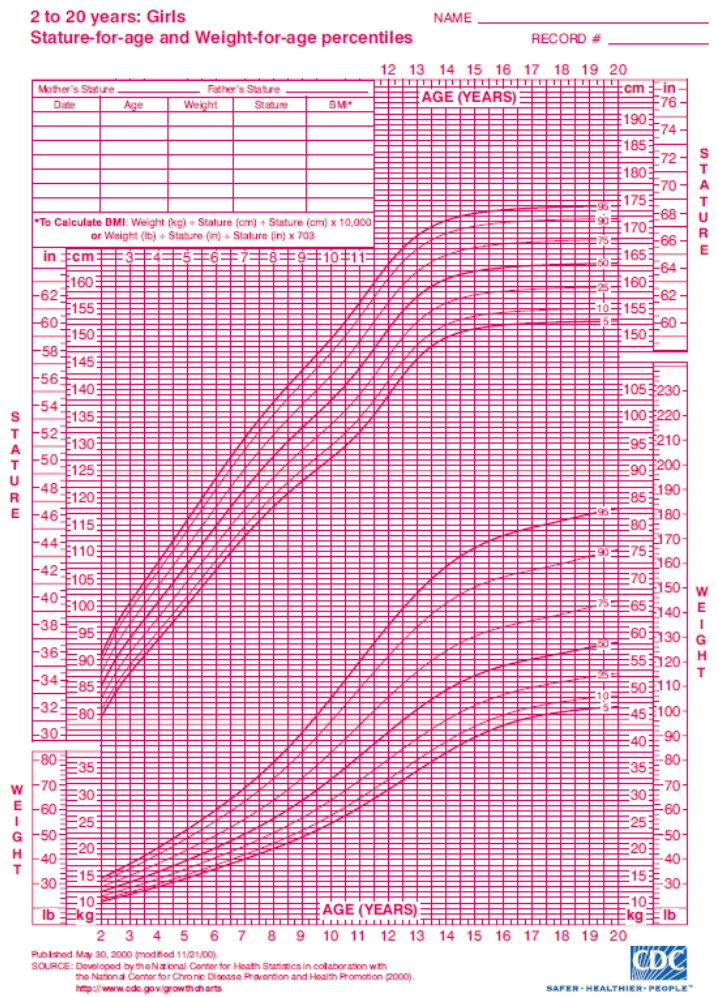
Vaz LE et al. Pediatrics 2014;133:1–11.

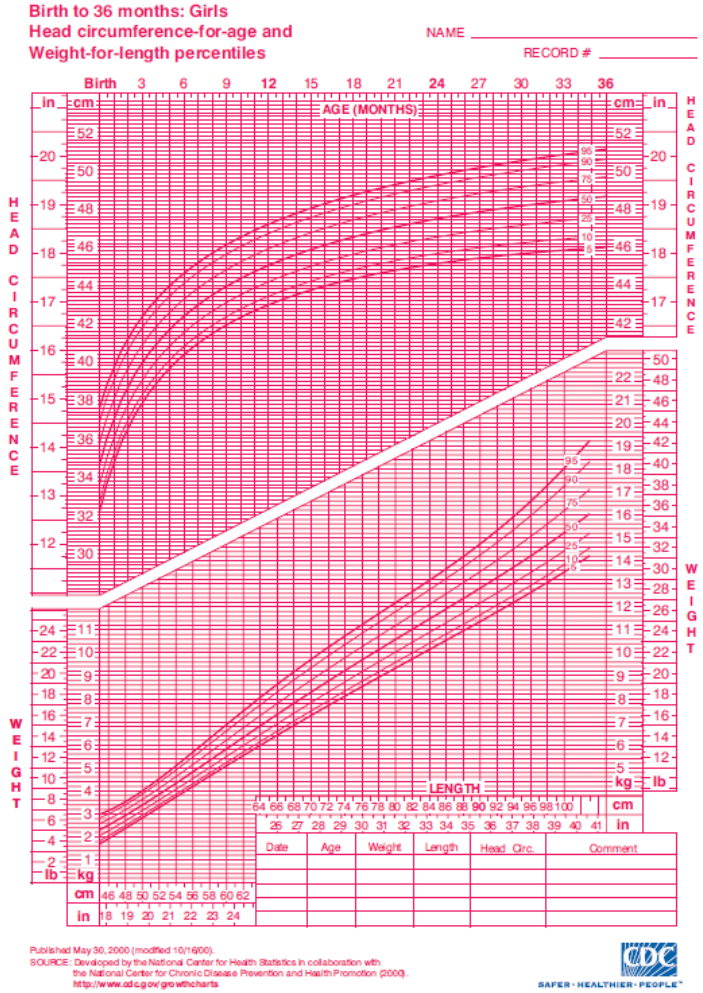
Antibiotic Exposure in Infancy and Risk of Being Overweight in the First 24 Months of Life



Saari A et al. Pediatrics.135 (4) 2015.

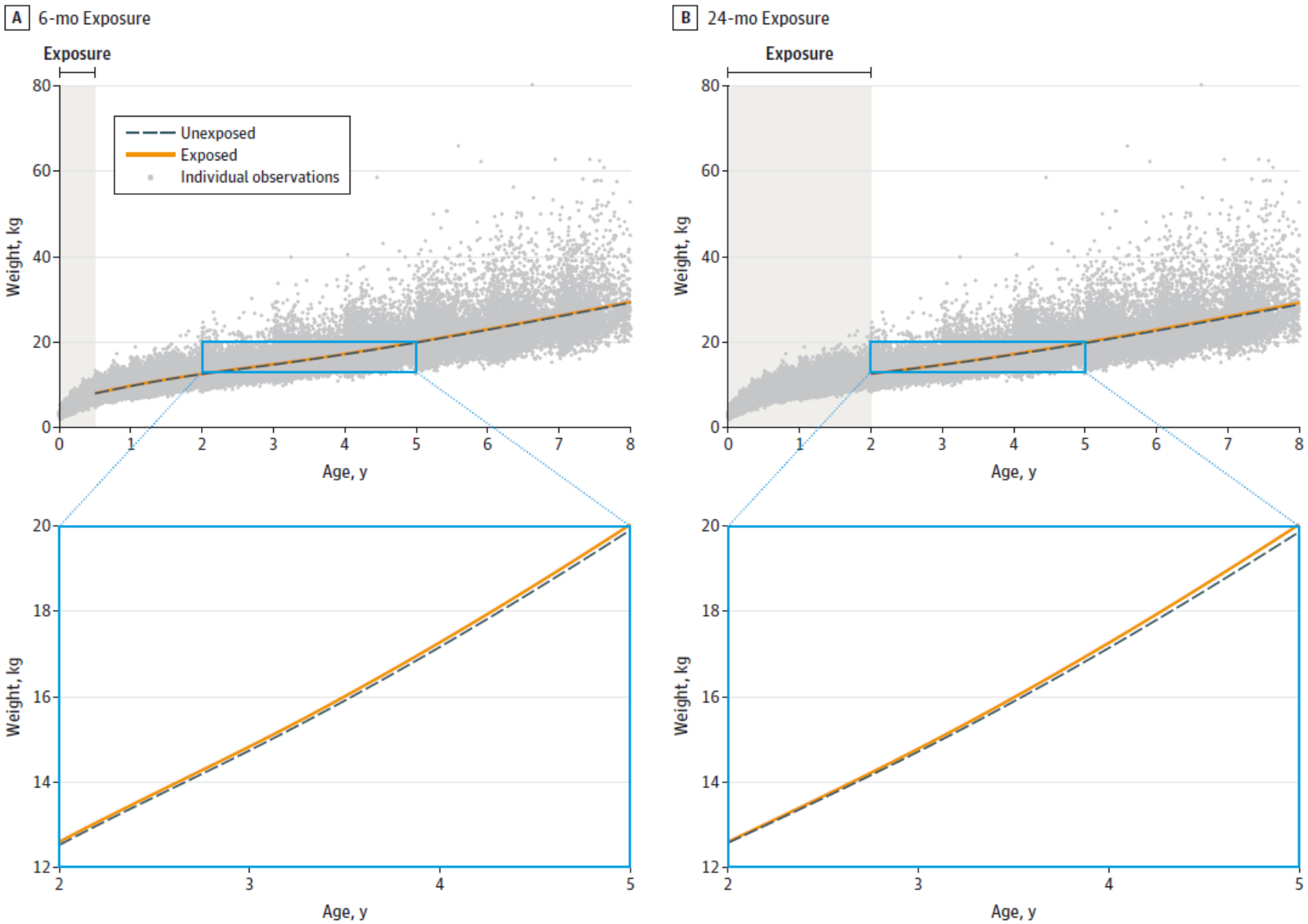
Velocity





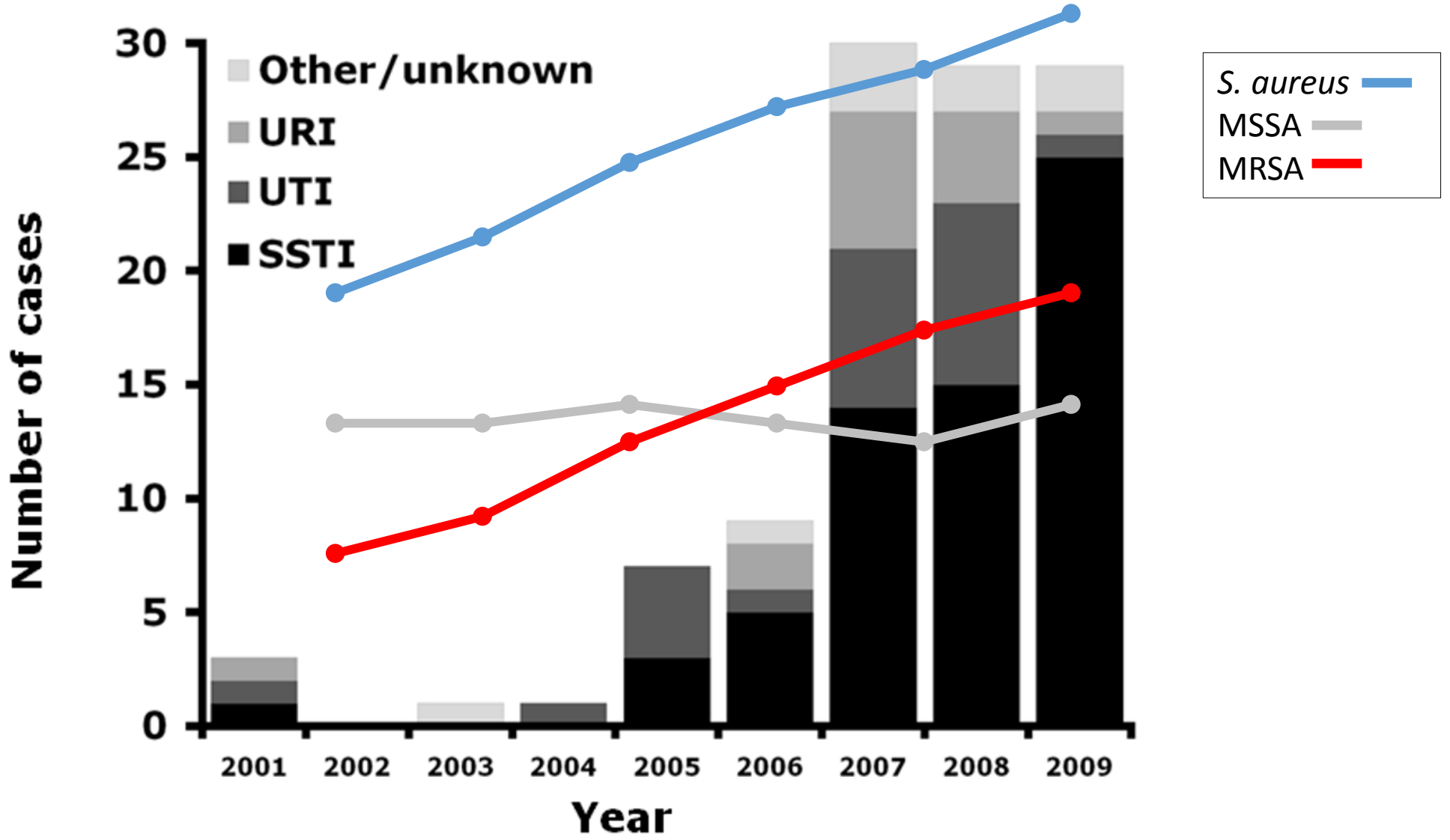
Children's Mercy KANSAS CITY

Antibiotic Exposure During the First 6 months of Life and Weight Gain During Childhood



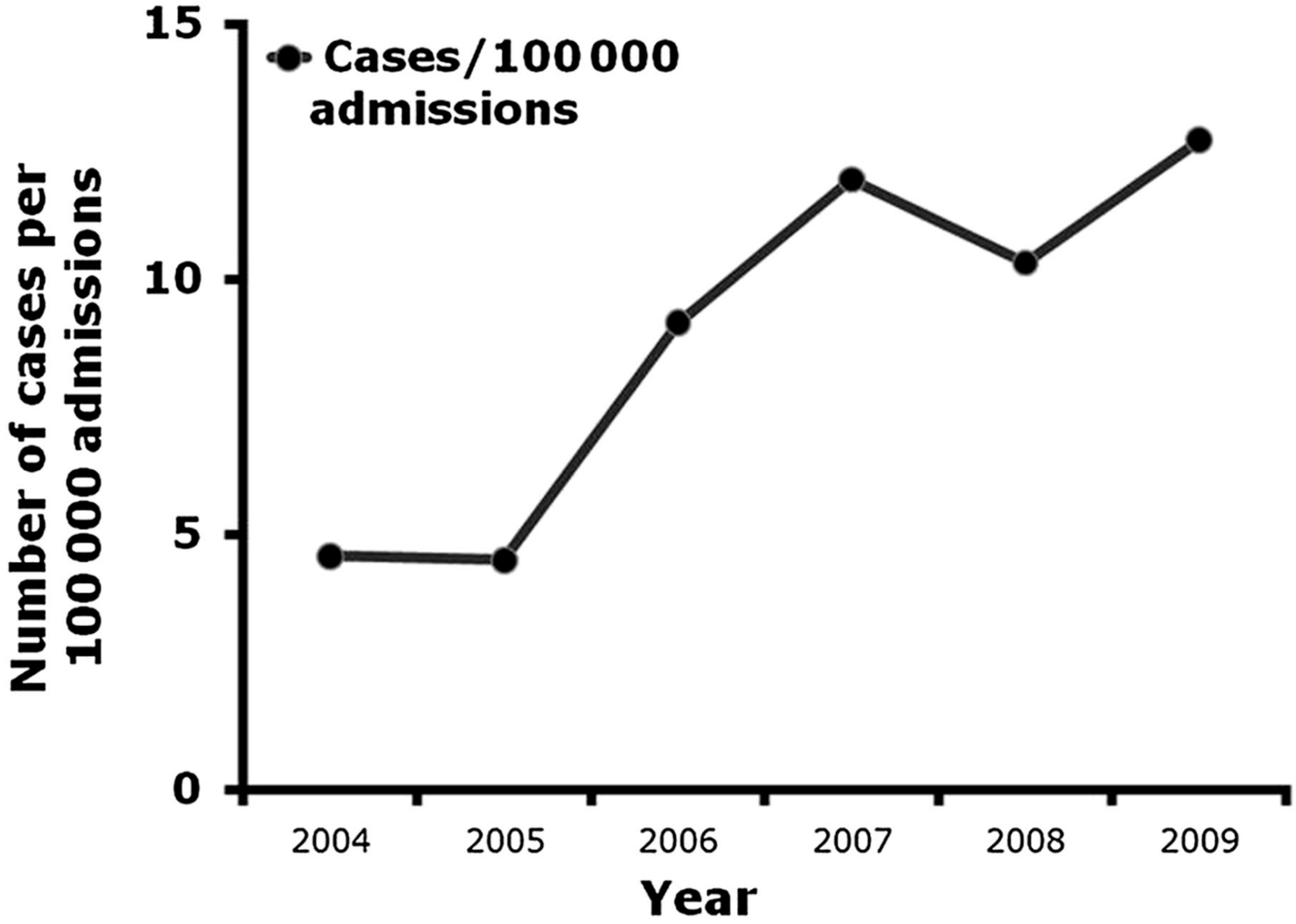
Gerber JS et al. JAMA. 2016;315(12):1258-1265.

Children Experiencing TMP-SMX ADRs



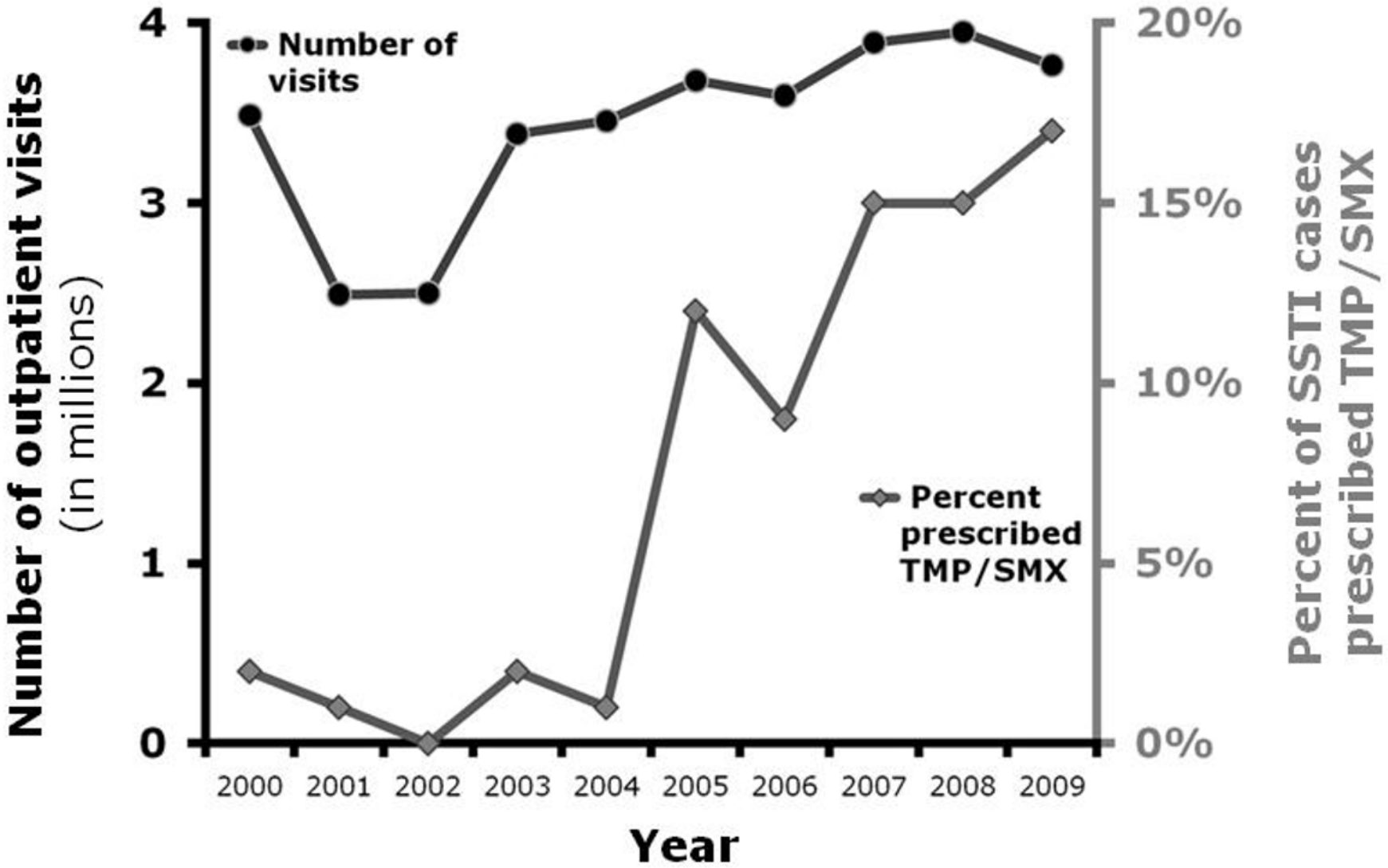
Goldman et al., Pediatrics, 2013. 131(1): p. e103-8.
Gerber et al. Clin Infect Dis. 2009 July 1; 49(1): 65–71

Number of cases of TMP-SMX ADRs in hospitalized children



Goldman, JL et al., Pediatrics, 2013. 131(1): p. e103-8.

Outpatient Prescribing of TMP-SMX



Goldman, JL et al., Pediatrics, 2013. 131(1): p. e103-8.

Four Vs

- Volume
- Velocity
- **Variety**
- Variability

Children's Mercy KANSAS CITY

Variety

Range of measurement types employed across developmental spectrum

What is normal?

Alkaline Phosphatase
0-3 yrs = 110-320 U/L
3-10 yrs = 140-400
10-12 yrs = 140-560
12-14 yrs = 105-420
14-16 yrs = 70-230
>16 yrs = 50-130

Alanine aminotransferase (ALT)
0-1wk = 10-100 U//L
1wk-2yrs = 20-77
>2 yrs = 12-50

Aspartate aminotransferase (AST)
0-1wk = 10-100 U/L
1wk-2yrs = 20-77 U/L
> 2 yrs = 12-50 U/L

Gamma-glutamyl transferase (GGT)
0-3 months: 27-210 U/L
3months - 1yr: 10-115
>1yr: 10-78

Bilirubin, total
0 - 1 mo: 0.6 - 11.1 mg/dL
> 1 mo: 0.0 - 1.2 mg/dL
Critical Value: >20.0 mg/dL

Protein, serum
0-1day = 4.0-6.8 g/dL
1day-2mos = 5.4-7.4
2mos-2yrs = 6.2-8.3
>2yrs = 6.5-8.3

Albumin
0-2mos = 2.0-5.3 g/dL
2mos-1yrs = 2.7-5.6 g/dL
1-12yrs = 2.9-5.1 g/dL
>12yrs = 3.0-5.1 g/dL

Children's Mercy KANSAS CITY

Examples of commonly utilized laboratory tests with age-dependent reference ranges

Hematology
- Factors V and IX
- Hemoglobin
- Partial thromboplastin time
- Prothrombin time

Endocrine
- IGF-1
- Follicle-stimulating hormone
- Luteinizing hormone
- Thyroxine

Immunology/renal
- White blood cell count
- Immunoglobulins (IgA, IgM, IgG and IgE)
- Complement C3 and C4
- Creatinine

Children's Mercy KANSAS CITY

Biomark Med. 2011 December ; 5(6): 781–794.

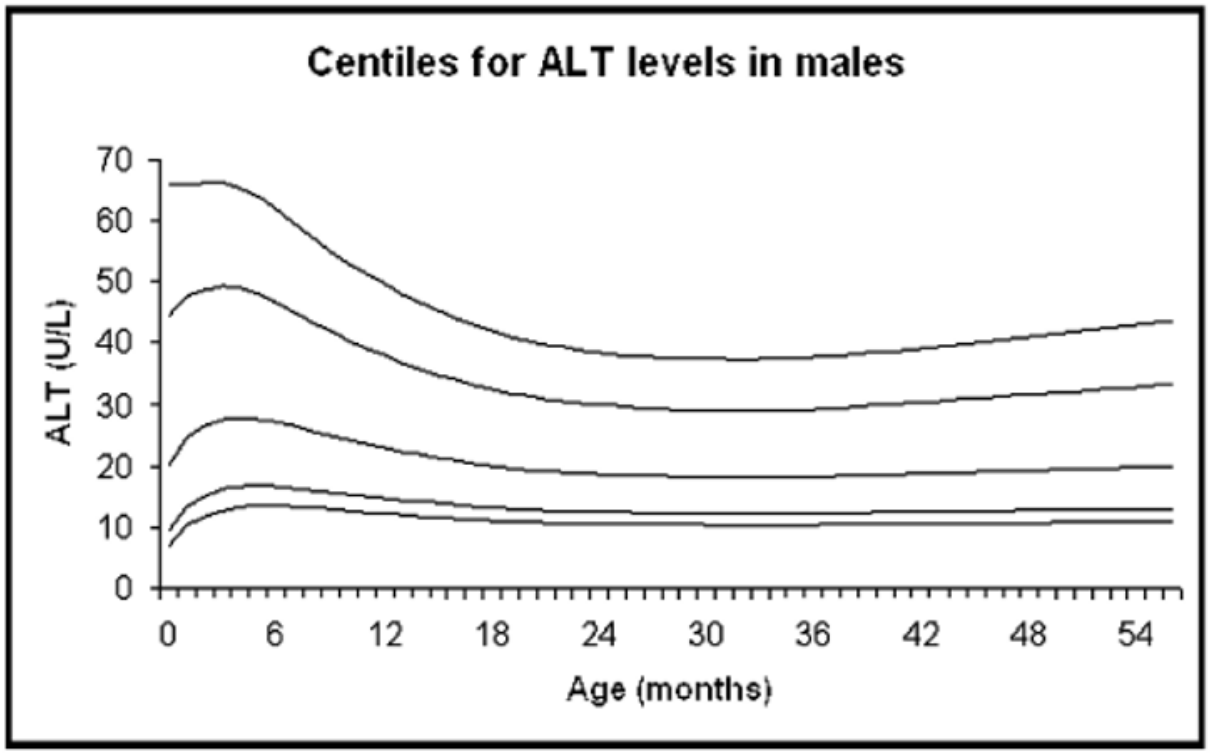
Age- and Sex-related Reference Ranges of Alanine Aminotransferase Levels in Children: European Paediatric HCV Network

- 1,293 hepatitis C virus-uninfected children
  - ALT levels peaked between 6 and 18 months of age
  - decreased with increasing age
  - lower in girls compared to boys
  - increased with increasing weight for age (*z* scores)

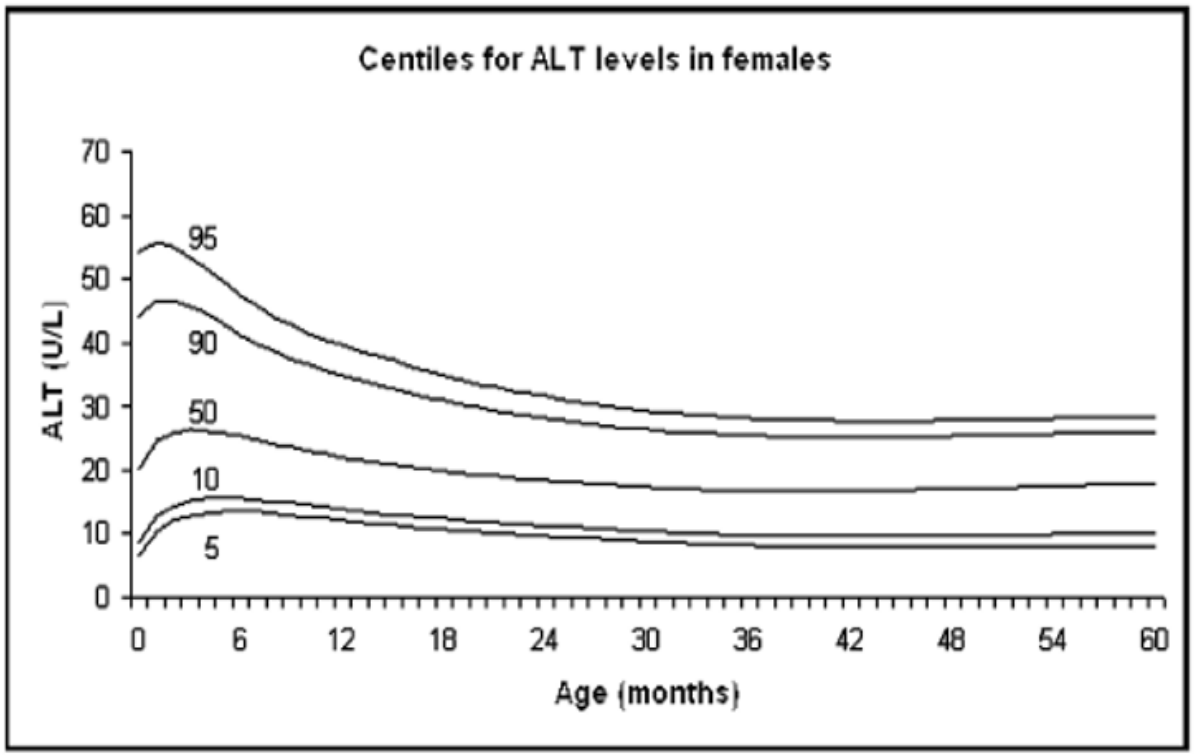
Children's Mercy KANSAS CITY

England K. et al. JPGN. 49:71–77, 2009.

A



B



Children's Mercy KANSAS CITY

England K. et al. JPGN. 49:71–77, 2009.

Clinical chemistry criteria for drug-induced liver injury

- Increase in alanine aminotransferase (ALT) 5 times above the upper limit of normal or baseline value
- Alkaline phosphatase 2 times above the upper limit of normal
- Combination of ALT 3 times above the upper limit of normal and bilirubin 2 times above the upper limit of normal

Children's Mercy KANSAS CITY

Shehu AI et al. Clin Liver Dis 21 (2017) 35–54
Aithal GP et al. Clin Pharmacol Ther. 2011 Jun;89(6):806-15

Four Vs

- Volume
- Velocity
- Variety
- **Variability**

Children's Mercy KANSAS CITY

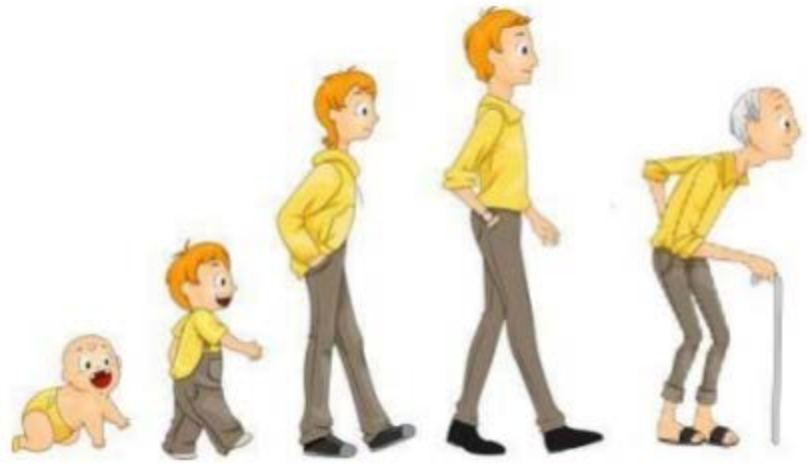
Variability

Intra-individual variability and complexity

Variability

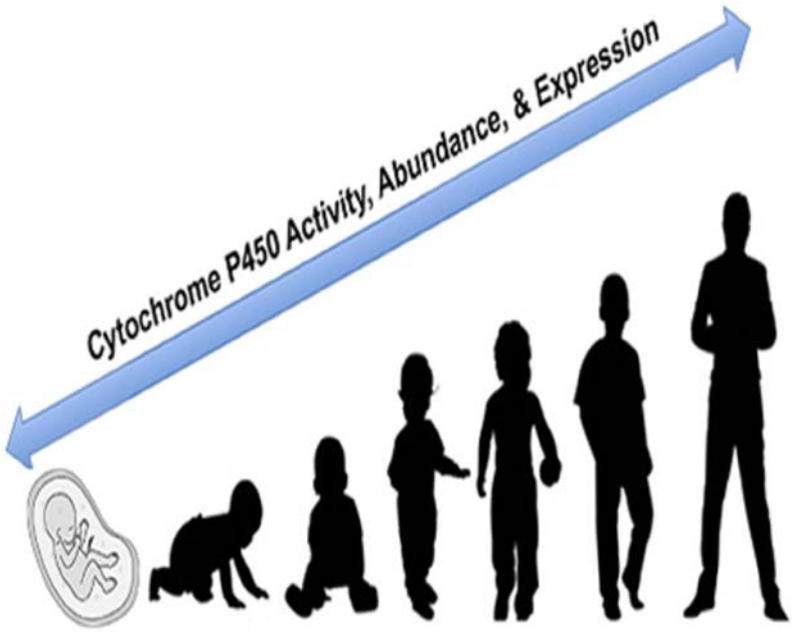
- Ontogeny
- Genetic variation

Neonate ⟶ Infant ⟶ Toddler ⟶ Child ⟶ Adolescent

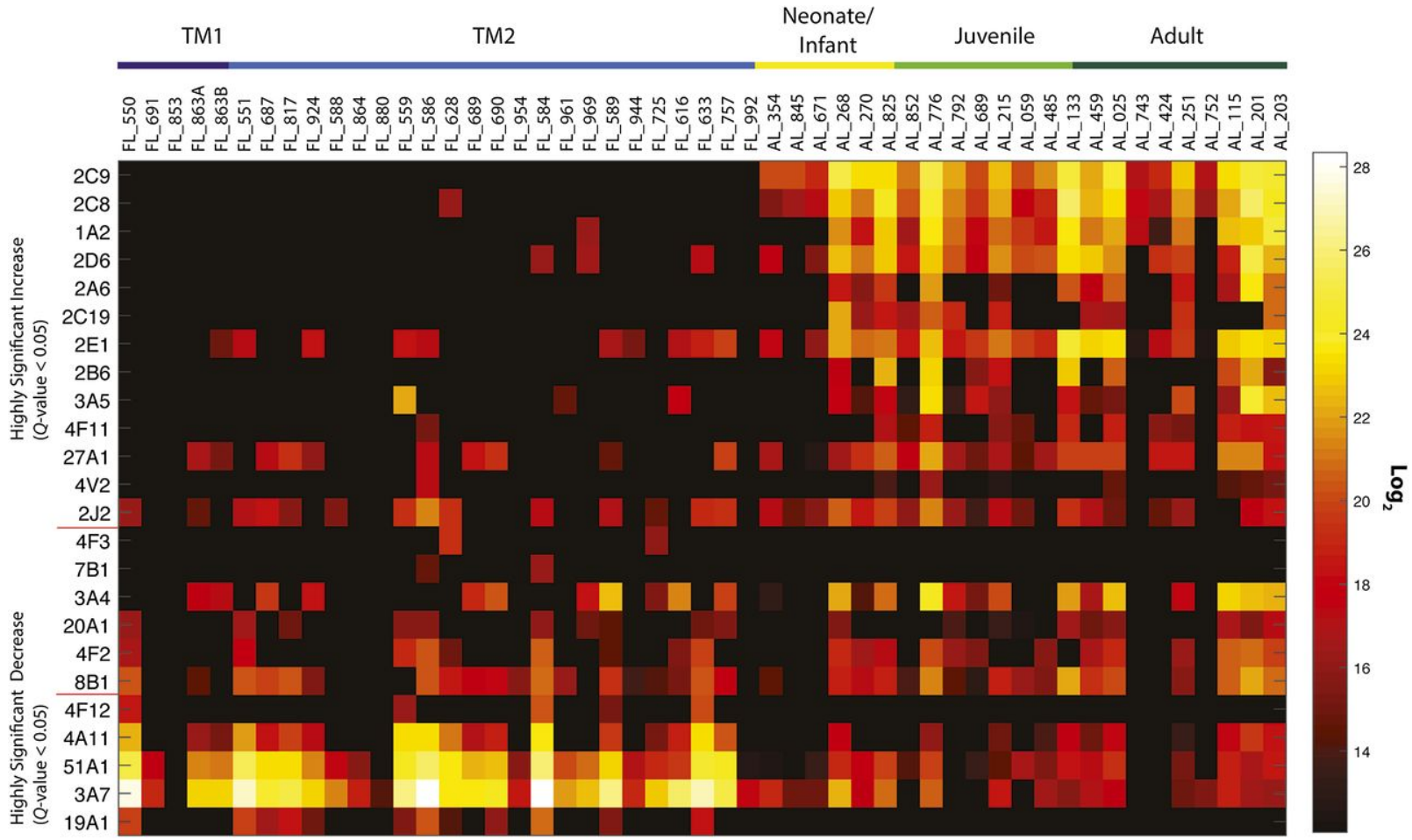


Children's Mercy KANSAS CITY

Variability



Activity-based protein profiling of P450 enzymes

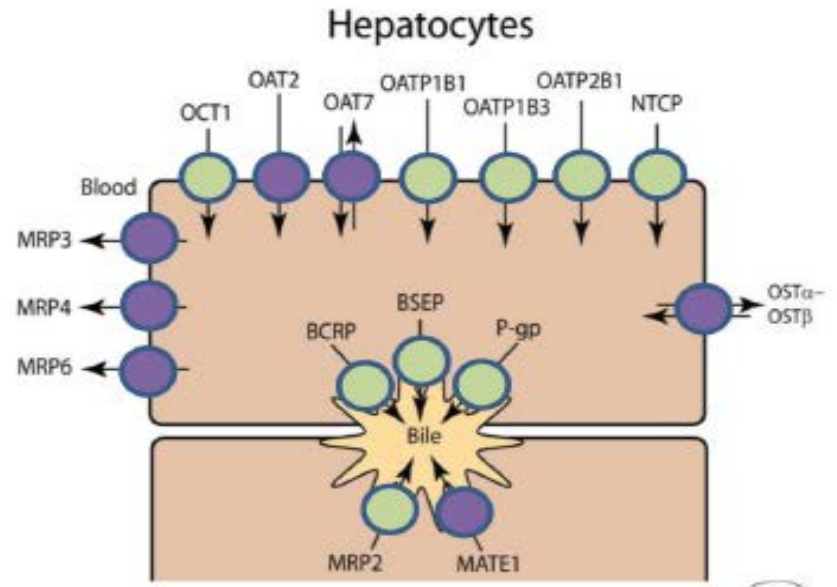


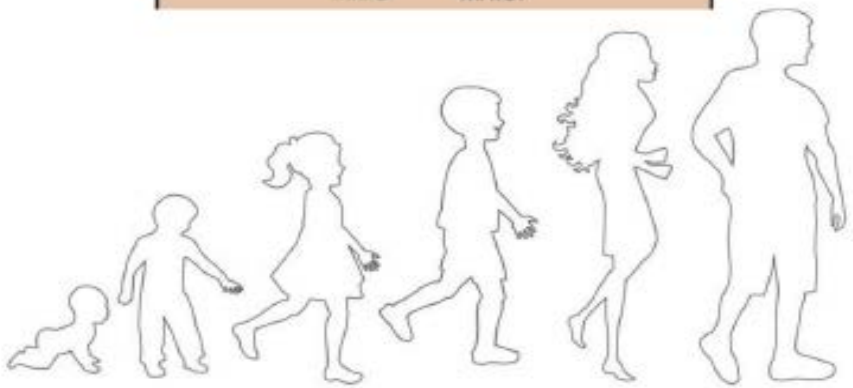
Children's Mercy KANSAS CITY

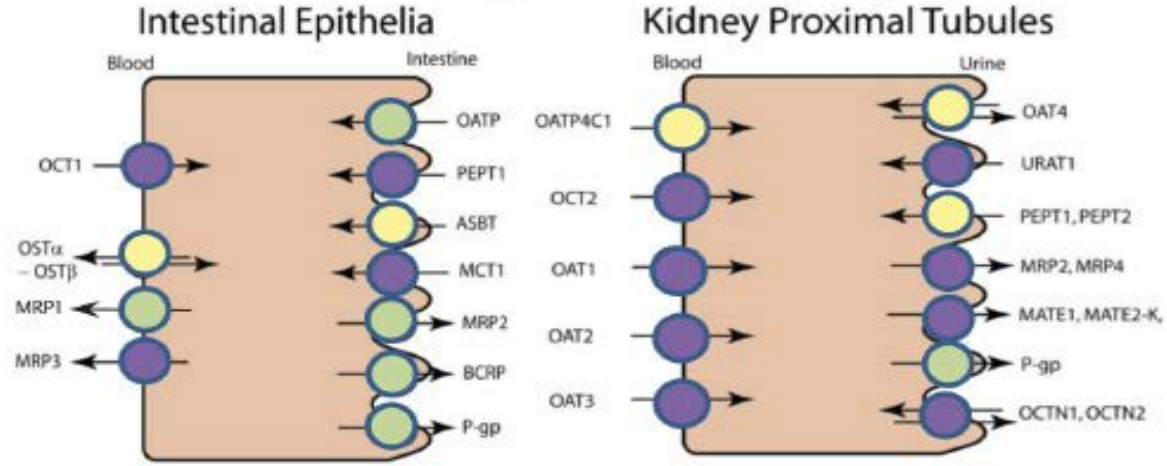
Sadler NC et al. Drug Metab Dispos 2016;44:984-991

Human Transport Proteins for Drugs and Endogenous Substances

Brouwer KL. Clin Pharmacol Ther. 2015; 98(3): 266–287.



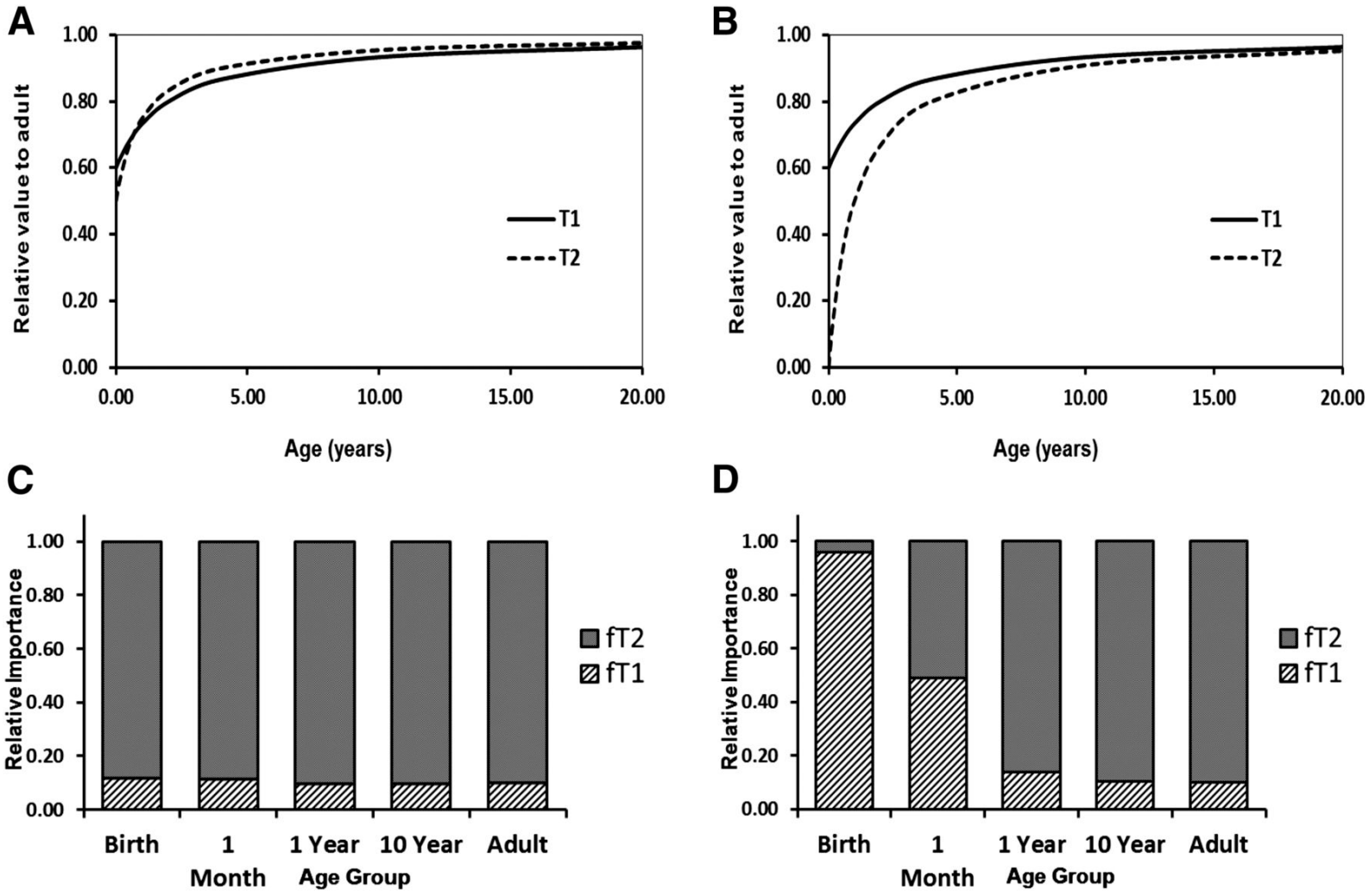




Children's Mercy KANSAS CITY

Variability

The relative abundance values (A) and (B), and the age-related changes in the relative importance of two transporters T1 (C) and T2 (D) in different age groups.



Elmorsi Y et al. Drug Metab Dispos 2016;44:992-998

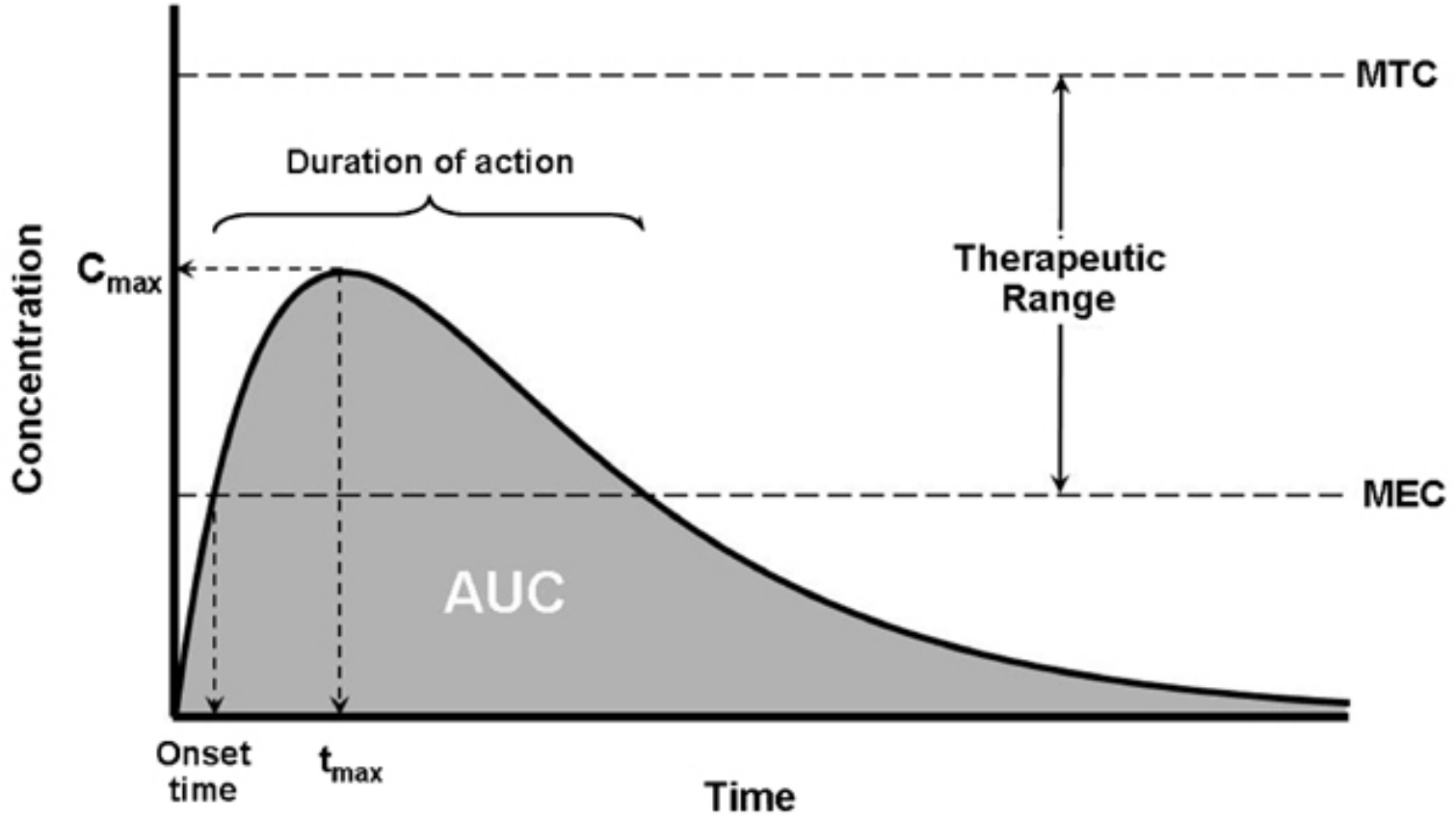
Textbook Drug Exposure

Volume

Velocity

Variety

Variability



Children's Mercy KANSAS CITY

Conclusions

- Changes during human development influence drug exposure (both AUC and types of exposure)
- Development and environment must be considered when using big data in pediatrics
- While many variables important in pediatrics can be captured in large data sets, data related to developmental changes may be overlooked or unavailable

Children's Mercy KANSAS CITY